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THE DEVELOPMENT OF PHOTOCROSSLINKABLE HYDROXETHYLCELLULOSE MEMBRANES FOR SUSTAINED RELEASE PHARMACEUTICAL PREPARATIONS

Gary Van Savage
University of Rhode Island

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CROSSLINKED HYDROXYETHYLCELLULOSE FILMS

THE DEVELOPMENT OF PHOTOCROSSLINKABLE HYDROXETHYLCELLULOSE MEMBRANES FOR SUSTAINED RELEASE PHARMACEUTICAL PREPARATIONS

BY

GARY VAN SAVAGE

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GARY VAN SAVAGE

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ABSTRACT

Strict anti-pollution laws have drastically changed how pharmaceutical manufacturers operate. Increased environmental awareness has forced changes in the way that sustained release pharmaceuticals are manufactured. Coatings which were once applied from organic solutions have been reformulated into water based polymeric dispersions that, although effective, cannot equal the performance of their predecessors. Research has led to updated coatings composed of three time tested polymers; cellulose acetate, ethylcellulose and methacrylic acid copolymer. Additionally, new coatings have been manufactured from custom polymers which provide excellent sustained release. Unfortunately, their development has not progressed beyond the laboratory since regulatory bodies worldwide are reluctant to approve new polymers for use *in vivo*. Clearly there exists a need for new coating materials that are "environmentally friendly, " approvable for *in vivo* use, and effective. An attempt was made to identify materials which, in addition to imparting sustained release, could be used safely, without organic solvents. The crosslinking of a water soluble polymer was decided to be the most feasible means of achieving that goal. Hence hydroxyethylcellulose (HEC), a water soluble, GRAS (generally recognized as safe) polymer was identified and evaluated under various conditions. The ability to insolubilize films of HEC was demonstrated when films containing riboflavin-5'-phosphate were exposed to visible or ultraviolet light. The drug release controlling potential of those films was demonstrated by their application to tablets containing model drugs, and their subsequent insolubilization via visible light exposure. Release rates of tablets with crosslinked coatings were determined *in vitro* and found to be nearly zero order and well controlled, in both water and 0.1 N HCl. The

shortcomings of this technique lie in the difficulties in quantitatively assaying the crosslinked polymer. Since the crosslinked polymer is largely water and organo-insoluble, attempts were made to differentiate between crosslinked and uncrosslinked polymer. To date none of the techniques evaluated provides a means to differentiate between the HEC's. While analysis of the crosslinked polymer has proven difficult, a system capable of providing for the sustained release, composed entirely of GRAS materials and not requiring organic solvents, has been realized.

ACKNOWLEDGMENTS

This work represents the culmination of a five year journey of discovery. As in any journey, the road is not always what it was believed to be, and often unexpected route changes must be taken to reach one's destination.

The story of this work, and all research, is that of perseverance. Through my two and a half year association with this project I have learned that nearly any hurdle may be overcome provided that one is willing to try. During that time I have found myself faced with seemingly unanswerable questions, lacking equipment, funding, a laboratory, and even a place to live. This document is my proof that perseverance has it's rewards.

Although this dissertation bears my name as both author and principle researcher it would not be here before you, it's reader, without the encouragement, support, and guidance of the many people who saw in me someone whom I did not. While my most sincere gratitude goes out to each of the innumerable people whose actions have led me to my current achievements, there are few special people whose contributions cannot remain anonymous.

I wish to thank the following: Professor Dr. Christopher T. Rhodes, for serving as my mentor and academic advisor. For his undaunting support, generousity, and ability to show me "the big picture" when my view was at best, myopic I am truly grateful. Dr. George Lukas and Ciba - Geigy Pharmaceuticals for their generous funding and patience. Without Dr. Lukas' stewardship this project would have faltered in it's infancy and never been realized to the extent it has. Dr. James Clevenger and Mr. Augie Bruno for helping me wade through

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PREFACE

This work has been prepared in accordance with the manuscript format option for dissertation preparation, as outlined in section 11-3 of The Graduate Manual of the University of Rhode Island. Contained within is a body of work divided in to three sections.

Included within Section I is Manuscript 1, a historical review, which provides the reader with an introduction to the subject of this dissertation, a statement of the hypothesis tested herein, and the specific objectives of my research.

Section II is comprised of three manuscripts, contain the findings of the research which comprises this dissertation. These three manuscripts, as well as the one found in Section I are presented in the format required by the journal to which they will, or have been, submitted. Also included in Section II is a compilation of the primary conclusions drawn from this research.

Section III contains three appendices containing, ancillary data (information essential to, but not usually included in published manuscripts) and other details pertinent to the understanding of the concepts presented in Section II. Note that within the graphical representations of data presented in this dissertation there may be "T" shaped error bars which depict the standard deviation of that data from it's respective mean. This dissertation closes with a complete listing of all the works cited in this dissertation, arranged in alphabetically by the author's last name.

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Manuscript I

THE SUSTAINED RELEASE COATING OF SOLID DOSAGE FORMS: A HISTORICAL REVIEW

THE SUSTAINED RELEASE COATING OF SOLID DOSAGE FORMS: A HISTORICAL REVIEW

ABSTRACT

The continued development of sustained release technology over the past forty years has provided countless ways of producing long acting dosage forms. Of all the methods proposed, coating has proven to be one of the most enduring. Although many have attempted to introduce new sustained release coatings to the marketplace, only three have been widely accepted. This paper seeks to provide the reader with a historical review of sustained release coating and examine the reasons why three materials, cellulose acetate, ethylcellulose and methacrylic acid copolymer have dominated this technology.

INTRODUCTION

The coating of tablets, granules, and other dosage forms has provided manufacturers with a means to extend the utility of an active ingredient which may have physical or biopharmaceutical shortcomings. Usually, great changes in the *in vivo* performance of a problematic, yet effective drug can be imparted by applying the proper coating to it. Some of these changes, hiding an unpleasant odor for example, may seem insignificant when looked at from a biopharmaceutical standpoint. However, it is rather easy to comprehend the benefits of applying a thin, acid resistant coating to protect an acid labile drug from the low pH of the stomach.

Several authors (1,2,3) have published reviews of pharmaceutical coating which pay close attention to the techniques and equipment employed for solid dosage forms. These reviews are an invaluable tool to the formulator as they contain in depth descriptions of the most common coating processes, including individual advantages and disadvantages. An added benefit to these reviews is their near timelessness. While it is true that the science of coating has evolved over the years, it is also true that the coating equipment which we employ today is not much different than that which was used twenty or even forty years ago.

The evolution of coating equipment has not proceeded rapidly, largely due to the limited ways in which large amounts of material can be handled efficiently. A similar evolutionary trend is evident for coating materials.

Although progresses in polymer chemistry have allowed the development of specialized polymer systems which provide any number of desired properties, the conservative nature of the pharmaceutical industry has, until recently, allowed for the widespread usage of only a few. Yet the introduction and popularity of these engineered materials is largely responsible for transforming pharmaceutical coating from an artform, guarded by a few skilled individuals, to a science which can be readily duplicated, tailored to specific needs and transferred between manufacturing sites.

Many contemporary sustained release coatings are really the direct descendants of those that were first introduced in the 1950's. While many attempts have been made to introduce new coatings to the industry, those systems which applied new technologies to extant polymers have proven most successful. This paper seeks to provide the reader with a concise overview of the coatings employed for sustained release, providing a brief history of the most popular coating techniques, an examination of the reasons why products are coated, and provide a historical review of sustained release coatings in the pharmaceutical industry.

REASONS FOR COATING SOLID DOSAGE FORMS

To the layman, tablet coatings may appear as mere decoration added to make tablets more attractive to the eye and pleasing to the palate. However, just as the sugar coating on some chocolate candies keeps the chocolate from melting in your hand, coatings on tablets provide a means to improve the stability and performance of the drugs held within them. Of course coatings are

not just a cosmetic placed on tablets to make them more inviting, although they may be used as such. Sometimes an opaque coating is used to mask a mottled or discolored tablet but, more frequently, coatings are used to modify the biopharmaceutical properties of a drug or to compensate for physico-chemical shortcomings which it may possess.

It is possible to remedy certain problems encountered in tabletting by applying some type of coating. The nature of the problem is what ultimately determines which type of coating is applied. Therefore, coatings can be loosely placed into one of three categories, grouped by the shortcomings which they are intended to overcome. There are coatings which can alter the biopharmaceutical profile of a drug and others which help counteract the physical incompatibilities of some drugs. Lastly, there are coatings which are used for purely cosmetic purposes.

Many authors have posed many reasons for coating tablets. The remainder of this section shall present those reasons which are still relevant today and some others which are of historical interest.

Tablets and other solid dosage forms may be coated to:

* Mask unpleasant tastes and odors
* Hide mottled or discolored tablet surfaces
* Prevent freshly prepared pills and troches from adhering to one another (4)
* Protect from gastric fluids those drugs which are destroyed by acid i.e. erythromycin (5)

* Prevent nausea , vomiting, or ulceration due to irritation (6)
* Impart a delayed action component for repeat action tablets (4)
* Protect a drug from oxygen, carbon dioxide, water, and light (5)
* Prevent incompatibilities between medicaments in a combination tablet (6)
* Provide a semipermeable membrane which limits the release of a drug from it's respective dosage form

TABLET COATING: A HISTORICAL PERSPECTIVE

Modern coating can be traced to rather humble origins in the kitchens of 19th century confectioners who had perfected the "art" of pan coating (4). In the confectioner's kitchen, methods were developed to cover sticky, sweet candies with a bright layer of colored, sometimes flavored sugar, thus rendering them non-sticking, easily transportable, and as pleasing to the eye as they are to the palate. One might speculate that pharmacists, often faced with preparations that were difficult to handle, would welcome such a novel and useful tool to their trade. Unfortunately, during most of the 19th century, nearly all prescriptions were prepared by extemporaneous compounding. A considerable amount of the pharmacist's time was spent preparing the individual prescription so little could be devoted to a process as time consuming as sugar coating. In fact, when necessary, most pill coating was performed by simple techniques which provided a suitable means of keeping the pills from sticking together or hiding their bad taste. Large batches of pills (and later, tablets) were uncommon.

However, the 19th century pharmacist did find it necessary to apply some sort of coating to many of his products especially massed pills, troches, lozenges, and tablets. The methods employed may seem quite primitive today, but were an effective means of resolving some problems and had the advantage of being easy and efficient to use with small amounts of material.

Perhaps the simplest of these coating methods was the application of a small amount of finely divided chalk or confectioner's sugar to the moistened surface of pills (4). This was accomplished with two pilling tiles, one sprinkled with finely divided dusting powder, the other with a thin layer of gum arabic or tragacanth mucilage through which the pills could be continually rolled until a thin white coating was obtained. Color could be added by incorporating a small amount of dye into the dusting powder. A variation of this method suggests that the pills be moistened with an etherial solution of tolu balsam. The principle advantage to this variation is that the pills would dry much more quickly due to the rapid evaporation of the ether (4). Yet another adaptation of "dusting" was Furley's process, which was quite popular in 19th century England. The principal difference between the two was the ingredients of the coating. Tragacanth and sugar were used in place of dusting powder as the solid portion while albumen, obtained from a fresh egg replaced gum arabic as the binder. Other coating methods employed at the time varied in complexity ranging from the simple (i.e. "gilding") to more complex methods including gelatin and sugar coating. In most cases "complexity" meant the need for specialized equipment.

Of all the early coating methods "gilding" has been subject to the most scrutiny. Today it seems somewhat absurd to cover a medicament with a metal

which could severely retard or completely prevent it's release in invivo. However, at the time it was one of the most elegant and readily available methods to coat small quantities of pills. Another advantage to this method is the excellent compatibility of gold with other chemicals. Detailed instructions for gilding pills are published in many of the earlier all inclusive pharmaceutical texts. Parrishes, 4th ed. 1874, describes several methods for gilding and cautions the pharmacist to use only pure gold and limit the amount applied. A point of interest in this nearly 120 year old work is the concern about dosage form's "solubility" (a reference to bioavailability). It states "The former belief that a coating with metallic leaf, if sufficient to hide the taste and smell of the pills, would interfere with their solubility, has been very much modified by recent experience" (4). Indicating, if only on the most rudimentary level, that pills coated with gold leaf could effectively release their medication in the gastrointestinal tract.

While successful in their own right, "dusting" and "gilding" were gradually replaced by "dipping" and pan coating. Dipping, a process once nearly forgotten, but recently resurrected in a refined form for several OTC preparations (Tylenol Gelcaps), is mentioned briefly in Parrishes and is discussed at great length in Remington's 3rd ed. 1894 (7). Similar coverage of sugar coating a technique whose popularity was ever growing at the turn of the century, can also be found in these works.

Generally, pills were dip coated in one of three materials gelatin, keratin and salol. Of these three, gelatin was the most popular and versatile, while keratin and salol were reserved for enteric coatings (8). This fairly simple and

effective process for coating involved the placement of freshly prepared pills onto long pins which were then dipped, several times, into a hot solution of gelatin. After hardening, the pins were removed and the hole which they left behind was filled with additional gelatin. This efficient process was well suited for the extemporaneous compounding of pills and many machines which improved the process were patented.

"Dip Coating" of pills was quite effective, regardless of the few shortcomings of the method, however it was impossible to coat compressed tablets in this manner because they could not be easily pierced with a needle. A remedy to this problem and a better way to coat pills was invented by J.B. Russell and later adopted by Parke, Davis & Co (7). This apparatus replaced the pins, previously used to hold pills, with a suction device which covered one half of the tablet. Tablets were still dipped in the gelatin solution and allowed to cool. Once cool, another set of tubes with vacuum was applied to the opposite side of the tablet while the first set was removed. Again the tablets were dipped and allowed to cool. The result was a gelatin coated tablet or pill that did not require further processing.

As the turn of the century approached, sugar coating in rotating pans was becoming the coating standard in large pharmaceutical houses. In a large company, product batches were of sufficient size to warrant the use of pan coating. Many thousand pills or tablets could be economically coated by relatively few employees. The era of modern pharmaceutical coating had begun.

During the first half of this century, tablet coating evolved into the processes with which we are familiar today. Sugar coating pans have changed little in the last one hundred years. Copper pans, a leftover from confections, have been replaced by stainless steel. The source of drying air has progressed from charcoal fires (4) to steam and finally, the forced hot air systems in use today. Lastly, the coater's ladle has been replaced by a spray nozzle to better control the application of coating solutions.

While the art of sugar coating had reached near perfection in the early 1950's its shortcomings (9) would lead to its overshadowing by a more efficient and versatile technology. The introduction of film coating (Abbott Laboratories, 1953) to the pharmaceutical industry allowed for great changes in the way formulators perceived tablets. No longer were they bound to the use of featureless, nearly spherical tablets as the newer polymeric coatings allowed for tablets of many shapes. Even embossed tablets could be coated in an efficient and aesthetically pleasing manner. These new coatings although versatile, were not well suited for use in existing coating equipment. At about the same time as the development of the new polymeric coatings, two advances in coating technology were introduced. Both of which have become essential to the modern pharmaceutical industry.

The addition of many small holes and it's enclosure within a sealed cabinet were modifications of the conventional coating pan which led to the "perforated" pan. Perforated pans (i.e. Thomas Engineering's Accela Coater and others) allow for the passage of great volumes of air across the tablet bed

and controlled temperatures which are necessary to meet the demands of polymeric film coatings.

The second of these innovations, the air suspension coater was an entirely different approach to coating (10). Unlike coating pans, the mechanics of the suspension coater caused tablets to continually rise and fall in a stream of gas while the coating solution is sprayed onto them from below. Since it's inception, the "fluid bed" coater has undergone continual modification leading to a very versatile tool capable of coating tablets, pellets, and even very small granules in a timely fashion. While capable of many things, perhaps the greatest advantage of this apparatus lies in its ability to function in a "closed loop" thereby facilitating the recovery of organic solvents and increasing the level of occupational and environmental safety.

Further advances in coating technology have been less monumental yet have served to enhance the existing technology. After all, the coating machinery and methods most commonly employed are well suited to the types of coating that is performed in today's industry. Likewise, progress in coating machinery will most likely accompany, or follow, the development of new types of coatings. Unfortunately, this is the age of cost containment and conservative formulation strategies within the industry. The chance of an entirely new approach to tablet coating coming into large scale usage in the near future is rather small unless it proves vastly superior to existing methods.

SUSTAINED RELEASE COATINGS: A HISTORICAL SURVEY

In the preceding section, an attempt was made to provide the reader with an overview of the methods and technologies employed in the coating of solid dosage forms during the past century. The majority of the methods described were simple, developed by pharmacists for use within the pharmacy, primarily for the purpose of making distasteful drugs more palatable. Later, coating would evolve into a science which allowed the formulator to selectively alter, or improve, the biopharmaceutical behavior of the products to which they were applied.

Although there are many ways to obtain the sustained release of medication (11,12), coatings applied to tablets, pellets, or granules are perhaps the most popular. According to USP XXII (13) there are three classes of coating commonly employed in the manufacture of solid dosage forms. The oldest of these, the "Plain Coatings" (USP XXII), are those used to alter the taste and appearance of tablets or to protect them from the detrimental effects light and moisture. Plain coatings, perhaps best exemplified by sugar and hydroxypropylmethylcellulose, are not intended to alter the biopharmaceutical performance of the drug contained within them. The second group of coatings, dubbed "Delayed Release" by USP, are more commonly known as "enteric". The enteric coatings (i.e. cellulose acetate phthalate), due to their poor solubility in acidic media, serve to protect acid labile drugs from the low pH of the stomach by delaying their release until the tablet has reached the intestinal tract. Sustained release coatings ("extended-release" USP XXII), those which have been designed to meter the amount of drug released from a dosage form, complete the list.

Until this point, the discussion of sustained release film coatings has been oversimplified, implying that the coating is a single, pure entity. Rather, film coatings are a mixture of several components which result in a continuous film with desirable properties. Generally, a film coating solution will contain four basic components; film former, solvent, plasticizer, and colorant (3). These components, both alone and in conjunction with one another have been the subject of numerous studies and several lengthy reviews. While not the focus of this paper, general reviews of film coating have been presented by Banker (14), Conrad and Robinson (15), and Seitz et. al. (1).

Pharmaceutical film coatings is a broad terminology which encompasses several types of film. These films modify the release of medicaments via three basic mechanisms; erosion (polyethylene glycol), gel formation (hydroxyethylcellulose) and diffusion (ethylcellulose). Those coatings which provide release through diffusion have a reputation of being predictable, easy to apply and are probably the most common sustained release coatings employed today. Yet the majority of today's sustained release coatings are ones, or descendants of ones, first used in the 1950's. Generally, the evolutionary path of these coatings began with polymers dissolved in organic solvents. Later, in response to many factors, attempts were made to prepare entirely or partially aqueous coating solutions. Throughout the past forty years other coating techniques have also been attempted, none of which has received the acceptance of coating from solution.

The vast body of literature published on the subject of coating would lead an investigator to believe that there are hundreds of coatings and

methodologies employed today. A closer examination reveals the contrary. The current United States Pharmacopeia only lists three sustained release coatings that function as a rate controlling membrane; cellulose acetate, ethylcellulose, and methacrylic acid copolymer. Although other coatings exist, these three remain the most popular, undergoing continual modification to withstand the challenges of time and changing regulatory climates. As the previous sentence suggests, the evolution of sustained release coatings was not one that was purely driven by the quest for better performance. Other issues, including safety (occupational and environmental) and cost have played an equally important role in the development of suitable coatings.

At the time film coating was introduced to the marketplace (Abbott Laboratories 1953) researchers were searching for economical and more versatile alternatives to sugar coating (9). The use of polymeric film formers in conjunction with organic solvents was perhaps the most important advance in dosage form development of that era. Their introduction provided researchers with new avenues to explore in the quest for controlled drug delivery and has led to the invention of many of the technologies which are so important today.

Many of the early commentaries touted the benefits of organo-soluble polymers as coating agents while they remained quite apprehensive about the use of aqueous solutions (9,17). The fear of dilute aqueous solutions was largely based on experience gained from sugar coating where the high water contents of coating solutions were implicated as the cause of stability problems and long processing times. The principle benefits of solvent usage were the considerable reduction in processing times and the removal of water from the

process, thereby reducing the loss of active ingredient through hydrolysis. Yet another advantage of organic solvents was their ability to completely dissolve the polymeric film formers thereby allowing for smooth, continuous coatings which were capable of protecting medicaments from environmental stresses and making tablets more distinctive.

An early patent for a sustained release tablet is recognized as the first to make use of a polymeric membrane to control the release rate of a drug substance. Assigned to Consolazio in 1949 (US patent # 2,478,182), this patent described the manufacture of a tablet composed of granules of sodium chloride coated with cellulose acetate or cellulose nitrate that was designed to eliminate the gastrointestinal upset caused by the localized deposition of medicaments.. Consolazio claimed that the invention delayed the solution time of sodium chloride some 60 to 80 minutes by the gradual leaching of drug through and the subsequent bursting of the cellulosic membrane (11). Unbeknownst to Consolazio at the time, was the semipermeable nature of cellulose acetate. His results might have been quite different if a larger organic molecule had been used since, due to their size, many drugs will not pass through cellulose acetate membranes. Although larger organic molecules are retained, water will still enter the tablet leading to the eventual bursting of the membrane and subsequent "dumping" of the medication within. A similar approach to sustained release was undertaken by Rosenthal (US patent # 2,895,880 issued 1959) that substituted any one of a number of prolamines for cellulose acetate. The principal difference between this approach and that of Consolazio was the digestibility of prolamines which would ensure the release of medication into the GI tract.

By 1958 ethylcellulose had joined cellulose acetate as a polymeric membrane for sustained release. A patent issued to Lowey (US patent 2,853,420) made use of granules of an inert material that were coated with a solution of ethylcellulose and drug. Once ingested, the drug entrapped within the ethylcellulose membrane would slowly diffuse out from the membrane and be absorbed. Knowledge of the mechanics of diffusion allowed the release rate to be "programmed" by blending together granules of differing film thicknesses.

It is interesting to note that the three polymers most commonly used today as sustained release membranes were introduced to the industry before 1962. Cellulose acetate and ethylcellulose, both mentioned previously, were introduced before 1958. The third polymer (really a class of polymers) Methacrylic acid copolymer, was first used in a 1961 matrix formulation patented by Levesques (US patent # 2,987,445). Levesques designed a matrix tablet which contained drug and soluble pore formers dispersed in a matrix of polyethylmethylmethacrylate or copolymers of methylmethacrylate and alkylacrylate that allowed for the slow leaching of drug into the gastrointestinal tract.

The fact that only three polymers which provide sustained release through membrane diffusion are listed in USP should not be construed as a lack of research in this area. Several researchers of the 1960's sought to find other polymeric materials that would exhibit suitable sustained release properties (18, 19, 20, 21). Much of their work was focused on various combinations of other vinyl, acrylic, and cellulosic polymers and provided a battery of screening tests

by which the suitability of a candidate polymer system could be judged. However, what these studies had failed to do was develop a new organo-soluble coating system which would be widely accepted by the industry. Possible reasons for this are many but perhaps the two most significant ones are the risks associated with organic solvent usage and the emergence of a newer hybrid technology, the pseudolatex coating.

Near the end of sixties, new, improved methacraylate derivatives had been introduced to the industry for use as diffusion controlled membranes (22). Although they performed well, these copolymer systems represented the end of an evolutionary pathway. Stricter environmental legislation in conjunction with the high cost of controlling organic solvent emissions forced researchers to find alternative, "environmentally friendly" coating systems. An early, and now widely known, product of this search was the pseudolatex dispersion.

Research has shown that pseudolatex dispersions, finely divided colloidal dispersions of water insoluble polymers in aqueous media, can be prepared from many water insoluble polymers. These preparations possess several properties which made them the most popular possible replacements for organic solvent based coatings including; no need for organic solvents, high solids concentration with low viscosity, shorter drying times through increased solids concentration, and lower water vapor permeability than comparable films from organic solution (23).

The use of latex dispersions invivo could be traced back to their listing in the U.S. Federal Register (1961) as a food additive (23). Later, after perfecting

acrylate pseudolatexes for other pharmaceutical coatings, at least two researchers had developed systems which would provide diffusion controlled drug release (24, 25). The commercial acceptance of acrylate pseudolatexes for diffusion controlled membranes (Eudragit (26)) led to the development of ethylcellulose pseudolatexes (Aquacoat (27) and Surelease (28)) and more recently, those made form cellulose acetate (FMC corporation (27)).

Pseudolatex technology has received such considerable attention from both academic and industrial researchers that an in depth discussion would be redundant and beyond the scope of this paper. If interested in the science and application of these coatings the reader should start by consulting the chapters by Lehman and Steurnagel in *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms* (22,23) as they provide comprehensive reviews of the subject.

While the pseudolatex coatings mentioned previously have been proven effective in many pharmaceutical applications, one somewhat disturbing fact remains. The extensive research on, and the wide acceptance of this technology is a largely due to the fact that the same three, well accepted polymers which had been historically used for sustained release were used in a new manner. In fact, it is only recently that another, completely different polymer has begun to gain acceptance. In 1989 Li and Peck (29) introduced sustained release tablets that were coated with a silicone elastomer latex (Dow Chemical (30)). Although it was yet another latex type coating, the use of a silicone elastomer represented a departure from the use of methacrylate and cellulosic polymers.

Unlike the existing latexes, those made of silicone are completely impermeable to water and require the use of a pore forming agent, usually polyethylene glycol, and an anti-tack agent, fumed silica. The amount of polyethylene glycol in the film ultimately determines its porosity and subsequent drug release rate. Li and Peck demonstrated the ability of silicone elastomers to provide the apparent zero order release of potassium chloride from coated tablets for greater than 12 hours with 20 percent PEG 8000 (29). Faster release could be gained by increasing the percentage of PEG. Other factors which were believed to have an effect on the release rate from silicone elastomer films include; the weight of coating applied, heat treatment and pH of the dissolution media have been confirmed by Dahl and Sue (31)

The silicone elastomer latex represents an adaptation of existing pharmaceutical technology to a new type of polymer. Although not yet approved for use in pharmaceutical formulations, silicone elastomers are used for medical applications and are a representative of a trend which has developed within the industry. The manufacturers of pharmaceutical excipients are well aware of the difficulties that are encountered when new excipients are submitted for FDA approval. The fact that only three polymers that provide diffusion controlled sustained release are listed in the Pharmacopeia is due, not to a lack of research, but due to the difficulty with which a prospective polymer would gain approval. It seems that contemporary research has taken this into consideration and has focussed it's effort on materials which are already approved for invivo usage.

Recent studies of sustained release film formers appear to be embarking on yet another major trend in pharmaceutical coating. Remember that sustained release coatings began as organic solutions and evolved to aqueous dispersions in response to changing safety and environmental regulations. Much of the sustained release film research during the 60's and 70's was centered on updating the polymers which had been used previously with a few noteworthy exceptions.

One of these attempts was is described in a patent issued to Seiyaku in 1967 (British patent #1,075,404) which described the "electrostatic" coating of tablets. In its truest form, electrostatic coating allows for the deposition of thin polymeric films without the need for any solvent. Films are formed when a charged particle is attracted to a substrate of opposite charge. Seiyaku's invention was not really a true electrostatic coating as it still required the use of a solvent which had to be removed after coating (32). Another earlier attempt by Endicott and later marketed by Abbott as "Gradumet" is a forerunner of some of the more interesting attempts of recent years (11). The Gradumet was a matrix tablet composed of drug and a plastic carrier which, after manufacture, was exposed to acetone vapors causing a the plastic to coalesce into a continuous network. The coalesced plastic provided a tortuous matrix which delayed the release of the drug held within it.

Recent studies of sustained release coatings appear to be branching out onto two pathways. While some determined researchers are experimenting with polymeric materials which have not yet gained FDA approval, others are

looking at ways to modify other preapproved polymers to provide sustained release membranes.

Perhaps the most promising attempt to make use of an already approved polymer lies in the crosslinking of alginic acid salts. The sodium salt of alginic acid is a hydrophillic, water soluble polymer which has traditionally been used in tablet manufacture as a binder and disintegrant. On the other hand, the calcium salt, although hydrophillic, is insoluble in water. Julian and colleagues studied the ability of free films of calcium alginate to control the release rate of drugs (33). Later, several researchers studied coating methods which converted sodium alginate to calcium alginate on the surface of the tablet or pellet (34,35). Bhagat et. al. describe a method in which guiafenisen tablets containing calcium chloride are dipped into a solution of sodium alginate. Immediately after immersion, insoluble calcium alginate begins to form on the tablet surface. Throughout the immersion calcium chloride, and unfortunately some drug, leach out of the calcium alginate membrane thereby maintaining the conversion of polymer at the surface. The thickness of the coating is controlled by the time of immersion in the sodium alginate solution. Through the use of this method Bhagat was able to produce tablets with an approximate film thickness of 2 mm that were able to provide the sustained release of guiafenesin for four hours. This technique, although promising, is not without its shortcomings. Perhaps the most difficult of these are the loss of drug during film formation and the rather thick films required for reasonable release rates.

Abletshauser and co-workers, dissatisfied with the immersion method used by Bhagat, adapted the sodium to calcium alginate crosslinking process

for use in a fluid bed coater (35). In their study pellets of indomethcin and acetaminophen were coated in a specially modified fluid bed that contained two spray guns. One gun sprayed a sodium alginate solution, while the other sprayed calcium chloride in alternating cycles. Drug release from these pellets with a 100 micron thick coating was extended over periods of three and eight hours for acetaminophen and indomethacin respectively. Although this method eliminated the drug loss of Bhagat's technique, it required considerable processing times due to the large amount of water in the coating solutions.

While aqueous coatings have eliminated many of the problems found in solvent coating, the removal of water remains a problem. Some recent attempts at novel sustained release coating have sought to develop systems which do not require any solvent. Yoshida and co-workers reported the sustained release of potassium chloride from beads of gamma radiation crosslinked methacrylates (36). The production of the beads was accomplished by dropping a liquid mixture of drug and monomer into an extremely cold quenching bath and then exposing the frozen globules to gamma rays. The extent of crosslinking was so complete and impermeable that the addition of PEG 600 was necessary to facilitate diffusion.

A similar approach to coating is currently under study by Wang and Bogner who have been experimenting with the photocrosslinking of several siloxane prepolymers (37,38). Unlike that of Yoshida, their method employs the use of high intensity UV light in conjunction with a suitable photoinitiator (Benzoin Methyl Ether) that has been adapted for use in a fluid bed coater. Within the coater, the liquid prepolymer and photocatalyst can be sprayed onto

pellets and exposed to the UV light. Upon exposure to the UV light the polymer will begin to crosslink, thereby increasing in viscosity until a solid, insoluble coating is obtained.

Radiation crosslinking offers a novel and economical way to produce sustained release coatings in the future. Unfortunately, current academic research must overcome several problems if it is to be accepted for invivo usage in the future. Firstly, both of the radiation crosslinked methods mentioned previously make use of prepolymeric monomers which pose serious health risks if they remain unpolymerized. Additionally, some of the methods require catalysts which may also prove toxic. Still another possible problem lies in use of radiation as an energy source. Remember that ultraviolet light has long been known as a cause of drug degradation. Yet, if a system can be developed which makes use of materials which are approved, or approvable, for invivo usage it will open up many new opportunities for improved pharmaceutical coatings.

CONCLUSIONS

Coating, in one form or another, remains an integral part of the pharmaceutical industry. Yet to fully understand its future, investigators must be aware of the vast body of work which precedes them and make use of the information contained within it. The past forty years have provided the pharmaceutical industry with several lessons which have been, and will remain valuable. While it is true that the equipment and materials used in the manufacture of coated, sustained release dosage forms has not changed

drastically in the last forty years, it has evolved. Countless materials have been screened for use as release rate controlling membranes yet, until recently only three have been widely used. The same three polymers which were once deposited from organic solution, have been continually updated to comply with ever changing pharmaceutical, safety, and environmental regulations.

As researchers continue to develop new types of sustained release coatings, they must remember that those which have been successful in the past have been so, not only due to their performance, but also because of their prior approval for invivo usage. Future investigators should not regard this observation as a warning to avoid new, unapproved materials. Rather, it should serve to impress upon them the realities of the pharmaceutical industry. While there have been many good ideas, greater attention should be given to those systems which are ultimately approvable.

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HYPOTHESIS TESTED HEREIN

It should be possible to develop an entirely water soluble polymeric coating system for solid, pharmaceutical dosage forms, which will provide adequate dissolution control and have the potential for commercial application, when such a system is produced via controlled exposure to radiation.

SPECIFIC OBJECTIVES of RESEARCH

I. Search literature for:
   a. Polymers that may be crosslinkable and have been demonstrated to be safe for usage *in vivo*.
   b. Prior examples of radiation induced crosslinking in pharmaceutical preparations.

II. Evaluate the potential of radiation induced crosslinking in the manufacture of pharmaceutical dosage forms.

III. Explore the nature of radiation induced crosslinking of hydroxyethylcellulose under different experimental conditions (radiation source, molecular weight of polymer, catalyst concentration, etc.).

IV. Examine the effect of crosslinked films on drug dissolution control.

V. Explore the possible physico - chemical changes which hydroxyethylcellulose may undergo as a result of the crosslinking conditions selected.

SECTION II

- Manuscript II "Photocrosslinked Hydroxyethylcellulose Membranes as Sustained Release Coatings: A Feasibility Study."

- Manuscript III "Photocrosslinked Hydroxyethylcellulose Membranes as Sustained Release Coatings: Assessment of Performance *In Vitro*."

- Manuscript IV "Photocrosslinked Hydroxyethylcellulose Membranes as Sustained Release Coatings: Problems Associated with and Possible Solutions for the Characterization of Crosslinked Materials."

- Primary conclusions drawn from this investigation.

Manuscript II

PHOTOCROSSLINKED HYDROXYETHYLCELLULOSE MEMBRANES AS SUSTAINED RELEASE COATINGS: A FEASIBILITY STUDY

PHOTOCROSSLINKED HYDROXYETHYLCELLULOSE
MEMBRANES AS SUSTAINED RELEASE COATINGS: A FEASIBILITY STUDY

ABSTRACT

Photocrosslinkable films which provide prolonged drug release have been developed as possible alternatives to traditional organo - soluble polymeric coatings. Unfortunately, the utility of many of these systems may never be realized due to concerns over the *in vivo* safety of one or more of their components. This study explores the feasibility of producing photocrosslinkable films that lessen or eliminate safety concerns through the use materials which have prior approval for use in pharmaceutical preparations. Through the careful selection of polymer and photocatalyst, films have been produced that readily crosslink upon exposure to an appropriate light source. Once crosslinked the polymer, hydroxyethylcellulose, is no longer readily soluble in aqueous media. Possible advantages of this system as a possible pharmaceutical coating, lie in the regulatory acceptance of each of its components and its ability to crosslink when exposed to visible light.

KEYWORDS

Hydroxyethylcellulose, Riboflavin 5' phosphate, Photocrosslinked, Sustained Release, Sustained Release Coating, Visible Light, Ultraviolet Light

INTRODUCTION

The introduction of the sustained release (SR) coating to solid dosage form manufacture during the 1950's had revolutionized oral drug delivery and opened up many new research paths for pharmaceutical scientists. A review of the coating literature might lead contemporary formulators to believe that there are dozens of different sustained release coatings at their disposal. Closer examination reveals that nearly all of the coatings in use today have been derived from one of three, time tested polymers (cellulose acetate, ethylcellulose, and methacrylic acid copolymer) that have been in use since the 1950's.

The reasons why today, some forty years since the introduction of sustained release coatings only three polymers have been widely accepted, surely cannot be blamed on a lack of research. Since the 1950's, many authors have published studies which sought additional polymers that could meet this need (1-5). While they were successful in their searches, their candidates were nonetheless unacceptable for *in vivo* use. The failure of so many of those early, second generation polymers to gain acceptance by regulatory bodies may be summed up by one word, safety.

The safety of cellulose acetate, ethylcellulose, and methacrylic acid had been proven by many years of use prior to the adoption of strict safety legislation. Because of increased concerns over product safety, many possible successors to the aforementioned polymers did not, nor likely ever would, gain such approval.

While the concern over safety *in vivo* remained an important criteria to judge possible SR coatings, the heightened environmental awareness of the 1970's introduced additional criteria which played an equally important role in their fate. Prior to the 1970's most SR coatings were applied from organic solutions providing for elegant and effective coatings that were both easy and economical to apply. Economical, until The Clean Air Act of 1970 and the increased awareness of the health risks associated with prolonged organic solvent exposure placed restrictions on their use (6).

During the late 1960's aqueous derivatives of the traditional organic solvent coatings were developed with the hope that they might someday eliminate the need for the organic solvents (7). Although these pseudolatex coatings have proven useful, they too have limitations. Consequently, the search for new coatings continues with much of the effort being spent on alternate formulations of the same three, time tested polymers. While it makes sense to try to modify extant techniques, there are always alternative techniques which should be investigated.

One possible avenue of investigation is the insolubilization of water soluble cellulose derivatives with a suitable crosslinking agent (i.e. divinylsulphone, dimethylurea and glyoxal) (8-10). The application of such technology to pharmaceuticals appears quite feasible at first. However, the toxic potential of the crosslinking agents and the harsh conditions required for their reaction makes the use of these techniques nearly impossible in pharmaceutical manufacturing, unless a less destructive, less toxic system can be developed.

Uehara and Sakata report that hydroxyethylcellulose (HEC) may be rendered insoluble, without the use of an external crosslinker, by exposing the polymer to a gas plasma (corona treatment) (11). Other researchers have reported the insolubilization of cellulose ethers by exposure to ultraviolet light in the presence of a photosensitizer (i.e. chrome or azo dyes) (12). While several azo dyes are approved as colorants for pharmaceuticals, many are under scrutiny by regulatory agencies and their future as pharmaceutical excipients is in question.

This paper seeks to determine the feasibility of producing a purely aqueous sustained release coating, containing a polymer and photocatalyst that may be deposited, by conventional means, onto the surface of a tablet and rendered water insoluble by exposure to light. While others have attempted similar radiation crosslinked coatings (13,14), their methods are such that the source of radiation may cause extensive drug degradation or pose serious health risks due to the toxicities of the photocatalysts or monomers employed (15).

It should be possible to circumvent the shortcomings of the aforementioned radiation cured coatings through the careful selection of coating components. The system discussed in this paper has been prepared entirely from FDA approved components and employs an insolubilizing technique which is less likely to be detrimental to the dosage form.

MATERIALS AND METHODS

Materials

Natrosol 250 L, M, and H pharmaceutical grade hydroxyethylcellulose was provided by the Aqualon Corporation (Wilmington, DE). The viscosity

averaged molecular weights of the different grades of polymer were reported (by the manufacturer) to be 90,000, 720,000 and 1,000,000. Riboflavin and Riboflavin-5'-phosphate sodium were purchased from Sigma Chemical (St. Louis, MO) while FD&C Red #3, FD&C Red #40, FD&C Blue #1, FD&C Blue #2, FD&C Green #3, FD&C Yellow #5 and FD&C Yellow #6 were provided by Warner Jenkinson (St. Louis, MO). Methanol, Urea, Acetone, HCl (0.1N) and NaOH (0.1N) were purchased from Fisher Scientific (Springfield, NJ). Simulated Gastric Fluid with enzyme was prepared as per USP XXII.

Screening of Possible Catalysts

Hydroxyethylcellulose is readily water soluble when its molecular weight is less than 1.3×10^6. Therefore, films prepared for this study were expected to be readily soluble unless some degree of crosslinking had occurred.

For the initial photocatalyst screening studies, aqueous solutions of each candidate dye (6 mg/mL) were prepared. A 1.0 mL aliquot of each dye was added to 9.0 mL of a 3.0 % $^{w}/_{w}$ solution of Natrosol 250 L (90,000 mw) and mixed thoroughly yielding a final dye concentration of (0.6 mg/ml). A small amount of each solution was then poured onto individual glass plates, spread to a thickness of 12 mils (0.305 mm) and subsequently dried at 50°C resulting in a film with a 2.0 % dye concentration based on total solids content.

After drying the films were placed on to a conveyor belt moving at 30 feet per minute and exposed to 600 watts of ultraviolet light from two mercury arc lamps placed six inches overhead. The amount of UV exposure was controlled by limiting the number of times which a sample film was passed under the light source at a speed of 2 seconds per pass. Samples were exposed for 0, 3, 6, or 9 passes. Following UV exposure, equal amounts of exposed and control films

were stripped from their glass substrates and placed into 20 mL of water and shaken vigorously. After one hour of mixing, the samples were compared amongst one another. A qualitative comparison was used to determine which dye produced the most insoluble HEC.

Determination of Optimum Polymer - Photocatalyst Ratios

Experimental Design

In order to determine the optimum combination of polymer, catalyst and light exposure, a 2x3x6 full factorial design with three replicates was used. In the original design, each of the two different grades of polymer designated M and H were to be combined with six concentrations of catalyst (0,2,4,6,8 and 10% w/w based on weight of polymer) and three levels of ultraviolet light exposure (0, 5 and 10 passes under UV lamp at a speed of 2 sec./pass).

After the preceding study had been completed, further experimentation revealed that visible light may, in fact provide a better yield of insoluble material than UV light. Consequently, a new study with 2 polymer grades (M and H), 3 levels of visible light exposure (0, 24 and 120 hours), 3 levels of catalyst (0, 2, and 4% w/w based on weight of polymer), and three replicates was performed. The number of catalyst concentrations had been reduced after studying preliminary data from the ultraviolet light study.

Data from each study was fitted to an analysis of variance model using PROC GLM on the SAS statistical software (Release 5.18, SAS Institute Inc., Cary, NC). All factors and all possible interactions were considered.

Preparation of Films

Stock solutions of HEC, M & H grade, were prepared by incorporating 9.0 g of polymer into 542.5 g distilled water with the aid of a homogenizer (Silverson L4R UK) run at low speed. After preparation the stock solutions were kept in a dark refrigerator and allowed to deaerate. The solutions were prepared so that a 90 mL aliquot would yield a final polymer concentration of 1.5 % $^{w}/_{w}$ when brought up to a volume of 100ml with one of several riboflavin-5'-phosphate solutions.

To obtain the necessary concentrations of riboflavin-5'-phosphate, a 15 mg/mL stock solution of the catalyst was prepared and protected from light. Aliquots of 0, 2, 4, 6, 8, and 10 mL of the riboflavin-5'-phosphate stock solution were then pipetted into 10 mL volumetric flasks and brought to volume with distilled water. The diluted riboflavin solutions were then added to the 90 mL aliquots of the polymer, thoroughly mixed, and allowed to deaerate in a darkened refrigerator.

Prior to film casting, the solutions were warmed to room temperature and divided into three equal portions. The portions were then individually poured onto preheated (60^{o}C) plates of untreated window glass (4 x 8 inches) and spread into thin films with the aid of a film casting table (RK Print-Coat Instruments, UK) equipped with a # 8 casting rod. The wet film thickness was 0.040 inch (1.016 mm). After casting the films were dried in a darkened 60^{o}C oven for 24 hours, removed and then stored in darkness until needed.

Later, the dried films were exposed to either visible or UV light to initiate the "crosslinking" reaction. Films kept in darkness were used as controls through the study. Ultraviolet light exposure was provided by a Fusion Systems (Rockville, Md) F300-6 electrodeless UV curing system equipped with a mercury "H" bulb and a conveyor belt operating at 30 feet per minute. The

amount of UV exposure was controlled by the number of times (0, 5 &10 at a speed of 2 sec./pass) that the plates were passed under the UV lamp. Visible light exposure was accomplished with the aid of a Hotpack environmental chamber (model 352642, 600 ft. can., 25^{o}C). Films were exposed to the lamps for either one or five days and immediately tested upon removal from the chamber.

Percent Insoluble Determination

The amount of insoluble material was determined by a method adapted from that of Geurden (9). A sample of each film was stripped from the glass substrate and accurately weighed (approximately 150 to 250 mg per sample). The weighed samples were then placed into 100 ml of distilled water and stirred for two hours. After stirring the samples were decanted into a fritted glass funnel containing a piece of pre-dried, pre-tared filter paper (Whatman #2) and rinsed with 200 mls of distilled water. Excess solvent was removed by vacuum filtration and the samples were dried for 24 hours at 65 ^{o}C. Samples were removed from the oven and immediately weighed. The percentage of insoluble HEC was determined by the following equation: *(weight of paper & soaked film - weight of paper)/ initial weight of film x 100*. Each solvent/film combination was repeated in triplicate.

Solubility Evaluation

The solubilities of control and visible light exposed films were evaluated in several different solvents in an attempt to understand the changes, if any, that the HEC molecule undergoes as a result of the insolubilizing procedure. Additionally, several of the test solvents were chosen so that a prediction could

be made as to how the crosslinked films would withstand the rigors of the gastrointestinal tract.

Films were prepared from a solution containing 1.5 % $^{w}/_{w}$ hydroxyethylcellulose, 0.03 % $^{w}/_{w}$ Riboflavin-5'-phosphate, and 98.47 % distilled water which was prepared in a manner that was consistent with previous film casting solutions. The solution was then stored in a dark refrigerator until needed.

Films were cast in a manner that was consistent with the procedure mentioned previously. Immediately after casting, the wet films were transferred to a dark oven and dried, overnight at 65^{o}C. Once dry, the films were divided into two groups, one kept in darkness and the other in a lighted stability cabinet (Forma Scientific model 3890, 1000 ft. can., 25^{o}C) for seven days.

Afterwards, 2.5 x 4.0 cm pieces of each of the films were cut with a razor blade, removed from the glass plates and accurately weighed (approximately 50 mg/piece). After weighing, the film samples were transferred to an erhlenmeyer flask containing 100 mL of either of the following solvents; distilled water, 0.1 **N** HCl, 0.1**N** NaOH, Acetone, Urea (10 % aqueous), Methanol and Simulated Gastric Fluid with Enzyme USP. The flasks were immediately sealed and shaken gently for 24 hours. Later, the samples were decanted into a fritted glass funnel containing a piece of pre-dried, pre-tared filter paper (Whatman #2) and dried for an additional 24 hours. Once dry, the remaining film and filter paper were quickly weighed. The percent of insoluble film was determined by the following equation; *(weight of paper & soaked film - weight of paper)/ initial weight of film x 100.* Each solvent/film combination was repeated in triplicate.

Microscopic Analysis of Film Samples

Microscopic analysis was used to determine if any gross physical changes to the surfaces of the HEC films were evident as a result of the UV or visible light exposure, as surface changes may be indicative of destruction of the film components. Scanning electron microscopy was used to examine the surfaces of film samples before and after exposure to UV and visible light sources (Leica (Cambridge) Stereoscan S-360). Samples were prepared for study by mounting them onto aluminum SEM stubs with double faced tape and sputter coating them with gold (Poloron E5100, 1 min. @ 25 Kv).

RESULTS and DISCUSSION

Screening of possible catalysts

Those films which had not been subjected to UV light behaved as expected, dissolving quickly and completely when immersed in water. A simple physical mixture of polymer and dye did appear to decrease the solubility of the polymer. However, upon exposure to UV light, each of the dye / polymer combinations produced some amount of insoluble HEC although the amount was not quantified. Additionally, small amounts of insoluble polymer were obtained from neat films of HEC which had been exposed to UV light. It is unlikely however, that these particles were formed through crosslinking rather their insolubility is more likely a result of UV induced degradation of the cellulose molecules (16).

Preliminary observation of films which had been immersed in water proved discouraging as the films, once wet, rapidly disintegrated yielding small insoluble particulates. However, magnification of the particulate HEC revealed that the particles were in fact, thin sheets of film which had coiled about themselves thus forming fibers of different lengths dependent on the dye used.

The relative length of the fibers was used as an indicator of the integrity of the film. It, in conjunction with the overall quantity of insoluble material produced was used to determine the "best" dye for future crosslinking studies.

FD&C Red #40 produced the longest, most continuous fibers of all the FD&C dyes tested yet, riboflavin, having an apparently greater yield and wide acceptance as a dietary supplement (vitamin B2) was chosen to be the catalyst for future investigations. The relatively poor water solubility of riboflavin made it difficult to produce a transparent, homogeneous film at required catalyst concentrations. A water soluble derivative, riboflavin-5'-phosphate sodium was substituted with favorable results.

Determination of Optimum Polymer - Photocatalyst Ratios

The effects of polymer molecular weight, catalyst concentration and light source are presented in figures 1 - 4. Generally, exposure to light produced high yields of insoluble material from films containing catalyst, while those films that had not been exposed or lacked catalyst produced little, if any insoluble HEC. It should be noted that the apparent production of insoluble HEC in the films which lacked catalyst or light exposure is largely due to the inherent viscosity of the polymer. The gelled polymer was retained on the filter during assay and once dry, did not show evidence of film formation. Also noted was the tendency of the riboflavin-5'-phosphate to reduce the gelling tendency of films that had not been exposed to light perhaps due to some degree of acid hydrolysis (16).

Table 1 lists the p-values for the main effects and all possible interactions for those films exposed to UV and visible light. Analysis of the data from the UV study revealed that each of the main effects and their interactions were

significant at level of 0.05 (ANOVA). However, individual examination of each polymer grade revealed that the amount of UV exposure and catalyst concentration were not significant factors for the M grade polymer (p values 0.149 and 0.074 respectively) but were clearly significant for the H grade (p values 0.038 and 0.0004).

Generally, films of the M grade HEC produced similar amounts of insoluble polymer, allowing for quite a variation in amount of catalyst and UV exposure while the yield of the "H" films appeared to be catalyst concentration dependant. This apparent dependency may be due in part to a decreased accessibility of reactive functional groups on the HEC molecule due to the larger molecular size of the "H" grade. If that is the case, the lower intra-sample variability of the M grade could be explained as its functional groups would be more readily accessible to the catalyst.

The effect of visible light on the HEC - riboflavin-5'-phosphate films was also studied but on a scale smaller than that of the UV light study. The results of this investigation are presented in figures 3 and 4. Consistent with the UV study, films prepared without catalyst tended to form gels that were retained on the filter paper and erroneously reported as insoluble. Unlike the UV films, the neat films of HEC exposed to visible light continued to form viscous gels after prolonged light exposure. However, as in the case of the UV films, the addition of riboflavin-5'-phosphate suppressed gelling in films that received no light exposure.

Visible light treatment of the HEC - Riboflavin-5'-phosphate films produced the highest yield of insoluble material. Statistical analysis of the data revealed that the grade of polymer chosen and all of the interactions containing polymer were not significant (see table 1). Figures 3 and 4 show that the

average percentage of insoluble HEC obtained from films that contained catalyst and had been exposed to visible light was routinely in excess of eighty percent and quite reproducible.

Solubility Evaluation

This study was undertaken to gain a general understanding of how photocrosslinked HEC would behave when exposed to different solvents. Since the data gathered was not intended to provide an absolute measure of solubility, the relative solubilities of the films have been graded on a scale of 1 to 10 where 1 represents a solubility less than 10% and 10, a solubility greater than 90 %. Results are presented in table 2.

Water, HCl, NaOH, and Simulated Gastric Fluid USP were chosen to simulate conditions encountered *in vivo*, while acetone and methanol were used to determine the behavior of the films in organic media. Additionally, the films were subjected to an aqueous urea solution, as urea is a known decoupler of hydrogen bonds (11). Therefore, a greater solubility in aqueous urea than in water would be evident of hydrogen bonding and not chemical crosslinking.

The control films were quite soluble in aqueous media, although the amount of insoluble material obtained from the urea solution was somewhat greater. While no detectable remnants of film could be found on the filter, it is possible that some polymer may have been retained within the filter paper thereby, yielding a slightly higher value for films soaked in the urea solution. Those uncrosslinked films exposed to organic media remained continuous and largely insoluble as predicted.

The crosslinking process allowed for great changes in the aqueous solubility of the HEC films. Films that were freely soluble prior to crosslinking,

were poorly soluble afterwards. Values obtained from crosslinked films in water are consistent with those presented earlier and similar to those of films soaked in simulated gastric fluid or aqueous urea. Any apparent difference in the values obtained for the three media in table 2, is small although somewhat exaggerated since they fall on either side of the 90 % cutoff. Slightly lower values were obtained for films soaked in HCl and NaOH. These lower values may be due, in part, to some breakdown of the polymer by acid hydrolysis or oxidative degradation (12).

Finally, there were no great changes in the solubilities of the control and crosslinked films that were soaked in organic solvents. Any apparent difference between them in table 2 is somewhat exaggerated due to the actual values falling on either side of the 90 percent cutoff.

Microscopic Analysis of Film Samples

Representative micrographs of the HEC/riboflavin-5'-phosphate films are presented in figure 5. Figure 5a, depicts a film sample which had not received any light exposure (control sample). The surface of this film is essentially smooth and continuous, confirming that it is possible to produce suitable films with the method employed. Visible light exposure (7 days @ 1000 ft. can.) did not appear to alter the film surface (5b). A sample of the film depicted in figure 6 was soaked in water and dried prior to examination (5c). The micrograph of the soaked film confirms that the film remained continuous and nearly indistinguishable from the control, except for the appearance of small depressions (approx. 20 microns diameter) which do not appear to pass through the film.

Figures 5d and 5e depict film samples which had been exposed to different amounts of UV light (5 and 30 passes, mercury H bulb 600 watts/inch). The surface of these films appear to have been altered by the UV exposure as small, somewhat circular, areas of different texture appear. The frequency of these areas appears to increase with greater amounts of UV exposure.

Conclusions

The ability of light, from both visible and ultraviolet sources, to alter the aqueous solubility of hydroxyethylcellulose (HEC),irradiated in the presence of a photosensitive dye, has been demonstrated. While the exact mechanism of the insolubilization has not been determined, it is believed that the changes in HEC solubility are a result of crosslinking facilitated by the dyestuff.

Visible light curing of HEC films that include riboflavin-5'-phosphate as the photosensitizer offers the most consistent and reproducible method to alter solubility, however long cure times are necessary. Shorter cure times (minutes vs. days) are possible when UV light is employed, but the yield of insoluble HEC is less consistent and the nature of the light source has a greater potential to cause degradation of the film components.

While there have been other radiation cured coatings, the combination of HEC and riboflavin is unique in that it exploits the interaction of two compounds which have prior FDA approval for *in vivo* usage. Prior approval, although not a necessity for a prospective new coating, should facilitate its approval provided that no new, unknown chemical species have been produced as a result of the photocuring process.

The initial success of this feasibility study warrants further investigation of photocured HEC/riboflavin-5'-phosphate films as sustained release coatings. It

is hoped that future studies of photocured HEC films shall demonstrate their ability to facilitate the prolonged, and consistent release of drugs and other bioactive molecules which have been coated in this manner.

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TABLE 1

Statistical analysis of Optimum HEC Insolubilization Parameters

	p - Values	
Main Effects & Interactions	**UV Light**	**Visible Light**
Polymer MW (P)	< 0.001 *	0.161
# Light Exposure (L)	< 0.001 *	< 0.001 *
# Catalyst (C)	< 0.001 *	< 0.001 *
P x L	< 0.001 *	0.867
P x C	0.0015 *	0.054
L x C	< 0.001 *	< 0.001 *
P x L x C	0.039 *	0.567

* denotes significance at 0.05 level

TABLE 2

Relative solubility of control and visible light cured (7 days @ 1000 footcandles) HEC films containing riboflavin-5'-phosphate in various solvents. Numerical values in table denote the average amount of insoluble material obtained from three separate trials. A value of 1 represents 0 to 10 % insoluble, 2 represents 11 to 20 %, 3 represents 21 to 30 % etc..

	Insolubility of HEC Films	
Solvent	**Unexposed**	**Exposed**
DI Water	1	10
HCL 0.1 N	1	9
NaOH 0.1 N	1	8
Sim. Gastric	1	9
Urea 10% aq.	2	9
Acetone	9	10
Methanol	9	10

FIGURE 1

The effect of visible light exposure and riboflavin-5'-phosphate concentration on the aqueous solubility of films prepared from M grade HEC

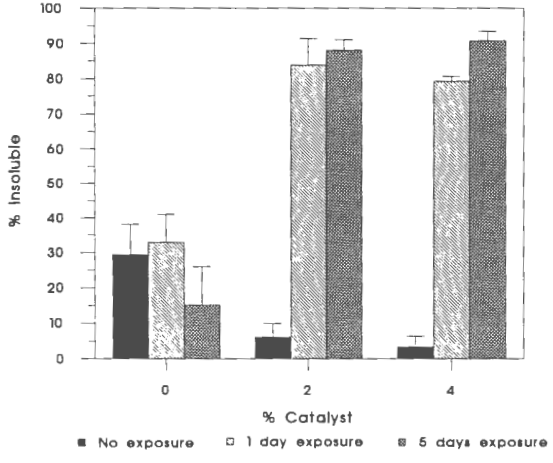


FIGURE 2

The effect of visible light exposure and riboflavin-5'-phosphate concentration on the aqueous solubility of films prepared from H grade HEC

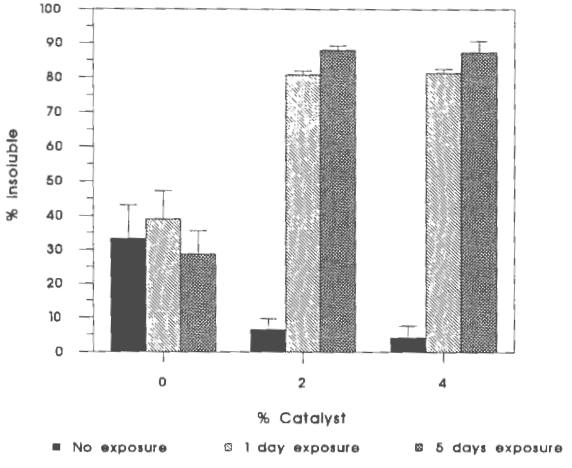


FIGURE 3

The effect of UV light exposure and riboflavin-5'-phosphate concentration on the aqueous solubility of films prepared from M grade HEC

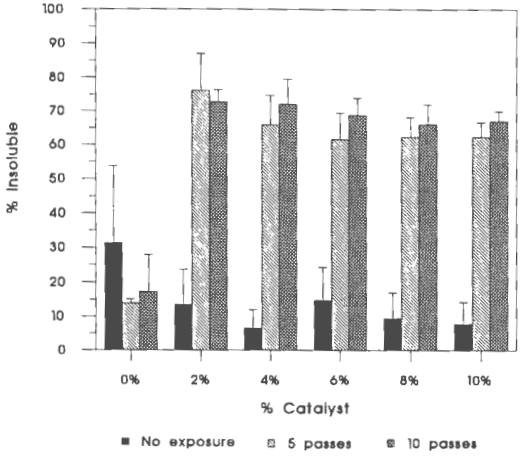


FIGURE 4

The effect of UV light exposure and riboflavin-5'-phosphate concentration on the aqueous solubility of films prepared from H grade HEC

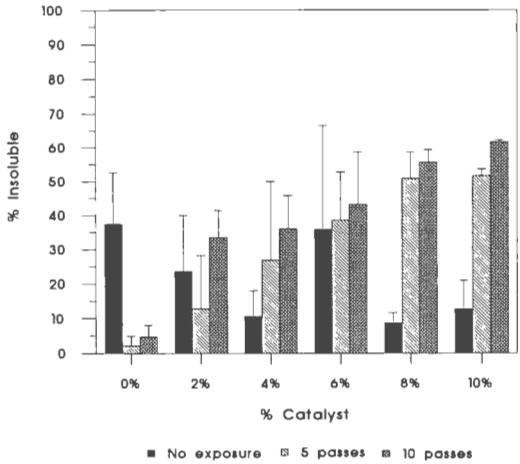


FIGURE 5

Scanning electron micrographs depicting surface characteristics of photocrosslinkable HEC films containing riboflavin-5'-phosphate: (a) Untreated film, (b) Exposed to visible light (1000 ft. can. x 7 days), (c) Exposed to visible light (1000 ft. can. x 7 days), soaked in water (24 hrs.) and dried (24 hrs.@ 65 ^{o}C), (d) Exposed to UV light (600 watts/in. for 10 seconds), (e) Exposed to UV light (600 watts/in. for 60 seconds)

FIGURE 5 a

Scanning Electron Micrograph of an Untreated Film

FIGURE 5 b

Scanning Electron Micrograph of a Film Exposed to Visible Light

FIGURE 5 c

Scanning Electron Micrograph of a Film Exposed to Visible Light and Washed with Water

FIGURE 5 d

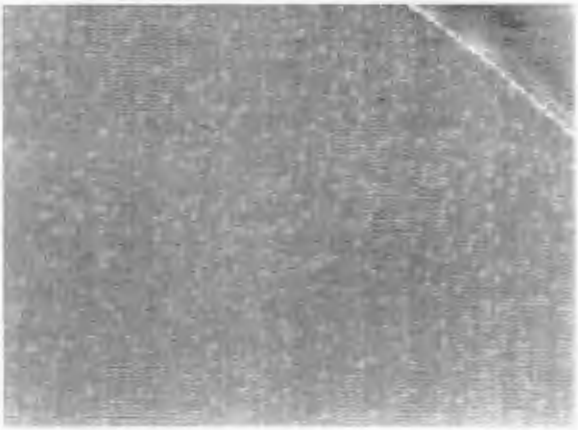
Scanning Electron Micrograph of a Film Exposed to Ultraviolet Light

(10 Second Exposure)

FIGURE 5 e

Scanning Electron Micrograph of a Film Exposed to Ultraviolet Light

(60 Second Exposure)



Manuscript III

PHOTOCROSSLINKED HYDROXYETHYLCELLULOSE MEMBRANES AS SUSTAINED RELEASE COATINGS: ASSESMENT OF PERFORMANCE *IN VITRO*

PHOTOCROSSLINKED HYDROXYETHYLCELLULOSE MEMBRANES AS SUSTAINED RELEASE COATINGS: ASSESSMENT OF PERFORMANCE IN VITRO

ABSTRACT

A water insoluble membrane is obtained when films of hydroxyethylcellulose (HEC) containing riboflavin-5'-phosphate (R5P) are crosslinked via exposure to an appropriate light source. Unlike other photocrosslinkable coatings which have been considered for pharmaceutical applications, the system presented herein is unique in that it is composed entirely of compendial materials. Tablets that had been designed to function as oral osmotic delivery systems when coated with cellulose acetate, containing either metoprolol fumarate or dextromethorphan HBr, were coated with the experimental materials. Successful coating of the tablets and crosslinking of the experimental coatings warranted the determination of drug release rates *in vitro*. Dissolution of tablets with crosslinked coatings was less rapid and considerably better controlled than control tablets whose coatings had not been crosslinked. The time to 80 percent of tablet label claim released was approximately five hours for metoprolol fumarate and slightly greater than 3 hours for dextromethorphan HBr upon successful membrane crosslinking. Comparatively, uncoated tablets of metoprolol and dextromethorphan each achieved complete dissolution 1.5 and 0.5 hours, respectively. In both cases dissolution in 0.1 N HCl was more rapid than in water, yet most of this effect may be attributed to the increased solubility of the drugs in acid.

KEYWORDS

Hydroxyethylcellulose, Riboflavin-5'-phosphate, Photocrosslinking, Sustained Release, Tablets, Visible Light, Ultraviolet Light

INTRODUCTION

The Clean Air Act of 1970 and recent, more stringent legislation have made the use of large quantities of organic solvents in manufacturing prohibitively expensive (1, 2). As the problems associated with organic solvent usage have continued to increase, pharmaceutical manufacturers have turned their attention to the various water based coatings which are currently available. While the aforementioned coatings offer one possible alternative to those requiring organic solvents, there are other options currently under development.

Recent research provides examples of what appears to be a new trend in the development of sustained release solid dosage forms, the in situ insolubilized coating (3-6). Coatings of this type exploit materials that, once deposited onto the surface of a dosage form, may be converted into durable, water insoluble coatings through polymerization and/or crosslinking reactions.

Generally, these coatings may be divided into two groups. The first of these, as exemplified by Wang and Bogner (7) and Yoshida et. al. (5) relies on the radiation induced polymerization of monomeric materials to form continuous water insoluble coatings. The second, including the methods developed by Ishikawa et. al.(6) and Abletshauser et. al.(3) exploits the ability of certain polymeric materials to undergo drastic changes in solubility when crosslinked. Although each of the aforementioned methods has been demonstrated to impart sustained release, the possibility of any of them obtaining regulatory approval is rather limited.

The work of Abletshauser and colleagues may be the exception, as calcium alginate is currently included in the French Pharmacopeia, a fact which might facilitate its acceptance elsewhere (8). Nonetheless, it is doubtful that the alginates are the only GRAS polymers capable of being rendered water

insoluble in situ. Rather it is quite possible that other polymers which equal, if not exceed the desired properties of the alginates lie listed in some GRAS list awaiting our attention.

Previously, we had demonstrated that a practically water insoluble film could be obtained from water soluble components (HEC/R5P) crosslinked by exposure to visible light (9,10). The coating studied herein is similar to others which rely on changes in solubility of the coating components yet, it is unique in that it is composed entirely of excipients that are included in the current USP NF (11). An attempt has been made to assess the sustained release potential of this system when applied to tablets that function as oral osmotic drug delivery systems. Tablets of this type were chosen for their ability to generate internal pressures great enough to challenge the mechanical strength of the test coating, a good measure of a films durability, and the fact that osmotic tablet coating remains heavily dependent on organo soluble film formers. Model drugs were chosen for this study that had different degrees of aqueous solubility. Metoprolol fumarate is representative of those drugs that are quite water soluble, while dextromethorphan HBr represents those drugs that are sparingly soluble.

MATERIALS AND METHODS

Materials

The following materials were obtained from commercial sources and used without further purification: Natrosol 250 M pharmaceutical grade hydroxyethylcellulose, molecular weight 720,000 (Aqualon Corporation, Wilmington, DE), riboflavin-5'-phosphate sodium (Sigma Chemical, St. Louis, MO), acetonitrile, HPLC grade (EM Science, Gibbstown, NJ), triethylamine (J.T.

Baker, Phillipsburg, NJ), hydrochloric acid, acetic acid and ammonium hydroxide, all reagent grade (Fisher Scientific, Fairlawn, NJ), docusate sodium and ammonium nitrate, all reagent grade (Aldrich Chemical, Milwaukee, WI).

Additionally, uncoated metoprolol fumarate (190 mg) and dextromethorphan HBr (20 mg) tablets were provided by Ciba - Geigy.

Processing

Coating solution preparation

Tablets were coated with a solution consisting of the following: Natrosol 250M (pharma. grade) 1.5% w/w, riboflavin-5'-phosphate 0.031% w/w, and distilled water 98.47%. Both the polymer and riboflavin were dissolved in water with a propeller mixer (Lightnin' TSR 1516, 1000 rpm). After several minutes of mixing, any agglomerated polymer was dispersed with a homogenizer (Silverson L4R, England) run at a low speed so any untoward effects to the polymer may be minimized. Once free of undissolved polymer, the coating solution was transferred to a darkened refrigerator and allowed to deaerate overnight. Solutions were warmed to room temperature prior to coating.

Tablet coating

On separate occasions, 1 kilogram of metoprolol fumarate and 1.25 kilograms of dextromethorphan HBr tablets were charged into a Glatt GC 300 coating pan (Glatt AG, Switzerland) and preheated to 45^{o}C. The following coating parameters were used throughout the study: pan speed = 10 rpm, atomizing air = 1.25 bar, inlet air temperature = 55^{o}C, outlet air temperature = 40 - 45^{o}C, air volume 180 m^{3}/hr. The coating solution was delivered to the pan with a peristaltic pump (Masterflex #7526-00) and sprayed through a 0.8 mm nozzle tip at an initial rate of four milliliters per minute. Spray rate was gradually

increased to, and later maintained, at 10 ml per minute. After a sufficient amount of the coating solution had been applied, the pan speed was reduced to 5 rpm and the tablets were dried for thirty minutes.

Crosslinking

Once coated, tablets were arranged on clear glass plates and exposed to 600 footcandles of visible light within a Hotpack environmental chamber (model 352642, 25^{o}C) for three or seven day periods. Three day exposed dextromethorphan tablets were exposed to 1000 footcandles of visible light. Periodically the position and orientation of each tablet, with regard to the lamps, was changed to ensure complete exposure to the light source. Once tablets had been exposed for their prescribed times, they were removed and stored in darkness in sealed containers.

Release Portal

A release portal was drilled in those tablets requiring one with a high speed mechanical drill (Servo Products Corp. model 7000). Portals were drilled so that they completely pierced the tablet coating, but did not penetrate the tablet cores to any significant depth. The portal sizes used for the metoprolol fumarate and dextromethorphan HBr were: 0.6 and 0.25 mm, respectively.

Dissolution Testing

Metoprolol Fumarate

The release of metoprolol fumarate from HEC/R5P coated tablets was studied by USP method I (basket), 100 rpm, 900 ml water, 37^{o}C, n = 6. The release rate of metoprolol fumarate in water was determined from tablets in

various stages of the coating process including: uncoated tablets (n = 3), coated yet uncrosslinked tablets (n = 3), coated and exposed for three days with and without a release portal, and coated and exposed for seven days with and without a release portal. Additionally, those tablets with crosslinked coatings were tested in 0.1 N HCl.

One milliliter samples were drawn according to the following regimen: 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, & 12 hours with an automated dissolution sampling system (Hanson Research model 75 - 400). Samples were assayed upon completion of the dissolution test.

Dextromethorphan HBr

The release of dextromethorphan HBr from HEC/R5P coated tablets was studied under the same conditions as metoprolol fumarate except the run time was shortened to eight hours. Samples were drawn according to the following schedule; 0.08, 0.25, 0.5, 1, 2, 3, 4, 5, 6, and 8 hours.

Assay

Metoprolol Fumarate

Interference by riboflavin-5'-phosphate at the analytical wavelength necessitated the use of HPLC. Consequently, an HPLC method was developed to separate riboflavin-5'-phosphate from metoprolol fumarate. The following system was employed: Column: Shodex RSpack D18 - 613 (15 cm), Autoinjector: Waters Wisp 712D (injection volume: 30 microliters), Pump: Shimadzu LC10AS (flow rate: 1.0 ml/min.), Column heater: Eppendorf CH30 (45^{o}C), Detector: Shimadzu SPD6AV (l 272 nm, 0.02 AUFS), Integrator: Waters 840 chromatographic data station.

A mobile phase consisting of ammonium hydroxide (0.61 % solution) 64.9% w/w, acetonitrile 33.4% and triethylamine 1.7% adjusted to a pH of 11.0 with acetic acid, was prepared fresh prior to each dissolution run.

The retention time of metoprolol fumarate was approximately 6.1 minutes. The percentage of metoprolol released was determined by comparing the peak area of the sample to that of the mean peak area of bracketed standards that represented 190 mg of metoprolol fumarate.

Dextromethorphan HBr

As in the case of metoprolol fumarate, interference by riboflavin-5'-phosphate at the analytical wavelength necessitated the use of HPLC. The chromatographic system was identical to that mentioned previously except a Waters Microbondpack C18 column (10m particle size 3.9 x 300 mm) was used at ambient conditions. Other changes included an analytical wavelength of 280 nm and an injection volume of 50 microliters.

The mobile phase for this assay was prepared in the following manner. For each liter of mobile phase 700 ml of acetonitrile and 300 ml of distilled water were combined. Docusate sodium (2.21 g) and Ammonium nitrate (400.3 mg) were added to the mixture which was subsequently adjusted to a pH of 3.05 with glacial acetic acid, filtered (0.5 micron), and degassed.

The retention time of dextromethorphan HBr was approximately 5.2 minutes at a flow rate of 1.25 ml/min.. The percentage of dextromethorphan HBr released was calculated by comparing the peak area of the sample to that of the mean peak area of bracketed standards which represented 20 mg of dextromethorphan HBr.

Scanning Electron Microscopy

Microscopic analysis of HEC/R5P coated metoprolol fumarate tablets was used to determine the integrity and continuity of the coating both before and after dissolution testing. Micrographs of tablets that had been mounted onto aluminum SEM stubs and subsequently sputter coated with gold (Poloron E5100, 1 min. @ 25Kv) were obtained with a Leica Stereoscan S - 360 scanning electron microscope.

RESULTS AND DISCUSSION

Background

Throughout this study, tablets that had been coated with the HEC/R5P and crosslinked were compared to both uncrosslinked tablets and uncoated core tablets to illustrate the release rate limiting potential of the crosslinked coating. The time required to attain the release of 80 percent of the tablet label claim (T80%), 190 mg for metoprolol fumarate and 20 mg for dextromethorphan, was used as a comparative measure of the dissolution profiles obtained from the various tablets tested.

Figures 2,3,5 and 6 contain the dissolution profiles of tablets to which a release portal has been added in order to gain some understanding of the relative permeability of crosslinked HEC films. Both the metoprolol and dextromethorphan tablets used in this study had originally been designed to function as osmotic delivery systems when coated with cellulose acetate. In those systems cellulose acetate acts as a semipermeable membrane allowing the influx of water and small ions but not larger molecules (drugs). As water enters the membrane the internal osmotic pressure rises. The rising pressure then either causes the rupture of the rigid membrane (undrilled tablet) or

initiates the "pumping" of drug through the release portal. The bursting of the undrilled membranes during dissolution testing and a gradual near zero order release from drilled tablets was assumed to be preliminary evidence of a semipermeable membrane.

Metoprolol fumarate

Figure 1 compares the dissolution profiles of uncoated metoprolol fumarate tablets with those that had been coated with the HEC/R5P coating (approx. 16 mg per tablet) and either exposed to visible light (3 or 7 days at 600 foot candles) or kept in darkness (control). Dissolution of the core tablets (n=3) was rapid and variable, yielding a T80% of 30 minutes. Complete dissolution was reached in two hours.

The addition of an HEC/R5P coating to the tablets resulted in prolonged drug release, regardless of any post coating treatment. Drug release from the control tablets, although prolonged, yielded a T80% of three hours while those tablets that had been crosslinked yielded T80%'s of approximately five hours.

Crosslinked tablets, irrespective of the duration of light exposure, produced the most consistent rate and longest duration of metoprolol fumarate release (Table 1). Following a brief lag time (15 min), the tablets with crosslinked coatings exhibited near zero order release for nearly four hours. In comparison, release from the control tablets was less predictable, exhibiting a longer lag time (30 min) followed by rapid and irregular drug release. Closer examination of the control tablets shows that their release profile, although spread out over a longer period, is similar to that of the core tablets. It is interesting to note that the release profile of the control tablets is quite similar to that of the core tablets if the lag time is disregarded. The similarity between

core and control tablets and the marked difference between their release profiles and those of the crosslinked tablets may be indicative of two distinct mechanisms of release.

Clearly, release from the core tablets is dictated by erosion. As the tablet is wetted, its outermost layers dissolve in the dissolution media thereby releasing the drug contained within them. This process continues, assuming sink conditions, until all of the drug has gone into solution. Much the same is true for the control tablets except drug release is further governed by the presence of the uncrosslinked HEC/R5P coating. (Remember that HEC is a hydrophillic water soluble polymer and the 16 mg present on each tablet is readily soluble in 900 ml of dissolution media.). The lag time exhibited by these tablets is most probably a result of delayed core wetting due to the hydration of the HEC coating. Once the coating has hydrated, release from the system is believed to be determined by a complex mixture of drug release from an eroding tablet core that is encased within a swollen, progressively dissolving film. Much of the last ten percent of drug release stems from the delay in tablet core dissolution affected by the gradual dissolution of the HEC/R5P membrane. Once the membrane has dissolved, dissolution of the core tablet, previously delayed by the HEC film, proceeds until the entire tablet dissolves and complete drug release is obtained.

Unlike the control tablets, those tablets with crosslinked coatings did not completely dissolve during dissolution testing. Empty, swollen, yet continuous membranes were recovered from the dissolution vessels after testing of the crosslinked tablets was completed. Occasionally, these "shells" were recovered intact but with a tear along one side. While the coating may have burst during testing, the low inter-tablet standard deviation obtained from each test of

crosslinked tablets suggests that these tears had either a very small effect on dissolution rate or, more likely, occurred after the final sample was drawn. The recovery of the intact crosslinked HEC/R5P shells in conjunction with the rather consistent release obtained from tablets with crosslinked coatings indicates membrane controlled diffusion as the principal mechanism of drug release. Oddly there was little, if any difference in the dissolution profiles of the three and seven day exposed tablets. This may be indicative of a "crosslinking maximum" that, once achieved, is not affected by further light exposure.

As mentioned previously, an attempt was made to ascertain the permeability of the crosslinked HEC/R5P membrane by testing the ability of drilled tablets to function as osmotic delivery systems. Figure 2 compares the release profiles of crosslinked HEC coated tablets with those to which a 0.6 mm release portal had been added. The addition of a release portal served to increase the average amount of metoprolol fumarate released from three day exposed tablets by nearly 10 percent. The release from drilled seven day exposed tablets was also faster, although the overall difference between tablets with and without a release portal was not as prominent. This indicates that the crosslinked HEC/R5P membranes are not semipermeable yet they do serve to mediate drug release in a controlled and consistent manner.

Lastly, in addition to distilled water, the dissolution rate of crosslinked tablets (7 day exposure, with and without release portal) was determined in 0.1 N HCl. Although the insolubility of crosslinked HEC in acid was determined previously (9), no predictions could be made as to the effects, if any, that the acidic media might have on drug release from tablets with crosslinked coatings. The release profiles of tablets tested in water and 0.1 N HCl are presented in figure 3.

In each case, the release of drug in water is slower than that in acid. When dissolution was carried out in acid, the time to T80% ranged from 3.0 hours for tablets with a release portal to 3.75 hours for those without. By comparison, drug release from water was slower, yielding a T80% of 5 hours in each case, although the tablets with a portal appeared to release somewhat faster in the early part of the dissolution test. This result was not unexpected as the solubility of metoprolol fumarate is greater in acid (12). However, the differences between water and acid are greater than ten percent at the three and four hour time points. Given the rather narrow standard deviation of the data, it is possible that the film may be subject to a greater degree of swelling in acid, thereby facilitating diffusion and a more rapid release of drug.

Dextromethorphan HBr

The dissolution profiles of Dextromethorphan HBr tablets both with and without an HEC/R5P coating (7.9 mg/tab) and subjected to different amounts of visible light exposure are presented in figure 4. Initially it was hoped that all crosslinking could be performed under identical conditions, however a malfunction of the 600 footcandle light cabinet necessitated the use of a substitute lightsource (1000 footcandles). Due to the different levels of light exposure, no direct comparison of the three and seven day exposed tablets was made.

Presented in figure 4 are the dissolution profiles obtained from the various dextromethorphan tablets tested. As one might predict, based on the previous discussion of metoprolol dissolution, release from the core tablets was rapid, yielding a T80% of 15 minutes and complete dissolution within 30 minutes. Likewise, release from the control tablets was prolonged (T80% of

approx. 1.6 hours), although erratic due to the simultaneous swelling and solvation of the uncrosslinked HEC/R5P membrane and the tablet core.

Crosslinking of the membrane, as in the case of metoprolol, produced dextromethorphan tablets which provided rather consistent and considerably prolonged release over a several hour period. The T80% for the 3 day, 1000 footcandle and 7 day, 600 footcandle exposed tablets were approximately 2.8 and 3.2 hours, respectively. Additionally, near zero order release was obtained from the 7 day exposed tablets for nearly four hours while that of the three day exposed tablets continued for nearly three (Table 1).

Figure 5 includes dissolution profiles from dextromethorphan tablets with crosslinked HEC/R5P membranes tested both with and without a 0.25 mm release portal. It appears that the addition of a release portal had a very little effect on the dissolution rate of the dextromethorphan tablets. This observation is further supported by the dissolution profiles presented in figure 6.

A comparison of the dissolution rates of dextromethorphan tablets with crosslinked HEC/R5P membranes may be found in figure 6. As in the case of metoprolol fumarate, the release of dextromethorphan was more rapid in acidic media than in water (T80% of 2.5 hours vs. 3.15 hours). Yet unlike the metoprolol tablets, and consistent with the profiles in figure 5, the addition of a release portal had little effect on the dissolution rate of dextromethorphan in either media. While no definite explanation of this occurrence is proposed, we postulate that the portal placed in the dextromethorphan tablets was too small and thus readily susceptible to blockage by uncrosslinked HEC or other components of the core tablets.

Electron Microscopy

Micrographs depicting the surface of the metoprolol fumarate tablets both before and after dissolution testing in water are presented in figures 7 and 8. In each figure, micrographs designated "a" represent a tablet photographed prior to dissolution testing while those designated "b" represent what remains of a tablet after the completion of testing.

Figure 7 reveals both the disappointing fact that the coating contains many small holes ranging in diameter from about 0.6 to 0.12 mm. Certainly we had hoped to form a continuous membrane and not a microporous one. Fortunately, observation of the tablets in the dissolution bath revealed that the shell actually swelled, and maintained a considerable internal pressure during the course of testing. It is doubtful that this could have occurred if the film remained microporous, therefor we postulate that it was possible for the holes to be sealed, perhaps by a combination of uncrosslinked polymer and swelling of the crosslinked coating. To some extent this idea is supported by figure 7b which depicts the remains of a tablet after testing. Drying had caused the shell to shrink to 80 percent of its original size. Additionally, it appears that the coating contained a far fewer amount of the large, deeply penetrating holes (figure 8). At this time it is not known whether the disappearance of the holes is an actuality or a remnant of the drying process. Irrespective of that fact, when the tablets are recovered from the dissolution media they are swollen, almost spherical and able to withhold the osmotic pressure generated by the core tablet. Clearly, this observation suggests that the holes may not penetrate the coating entirely, or have been sealed upon hydration.

CONCLUSIONS

The idea of an *in situ* crosslinkable tablet coating, made entirely of materials with current regulatory approval has been realized. Through prolonged exposure of prototype HEC/R5P films to visible light we have demonstrated that an water insoluble film may be obtained from entirely water soluble starting materials. The practicality of this technology lies in it's use of conventional coating techniques and a simple, and safe source of radiation. Although this crosslinking process must still be optimized, this study has shown that it is indeed possible to obtain consistent and controlled drug release from tablets that have been coated with crosslinkable HEC.

Indirect evidence has indicated that the crosslinked films in their present state, do not provide a semipermeable membrane, although membrane mediated diffusion is the most probable method of release. While not a reality at this time, a semipermeable membrane might be possible if the coating process can be optimized to obtain a more continuous and dense coating. Another option may be the addition of a plasticizer to the system although the effects of a plasticizer on the "crosslinkability" of the system are not yet known.

While this paper has illustrated the potential of crosslinked HEC/R5P membranes, the photocrosslinking techniques used herein are somewhat rudimentary. Obviously if techniques such as this are to become commercially viable for drug manufacturing, greater effort must be placed on the characterization of the products and processes of crosslinking and the determination of the mechanism(s) by which the reactions occur. An understanding of the physico-chemical nature of this system, in conjunction with positive, rather than inferred proof of the safety of the crosslinked material could lead to the regulatory acceptance of this or a similar coating for use *in vivo*

thereby offering the industry a class of coatings which behave quite similarly to organo soluble coatings but without the need for organic solvents.

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Table 1

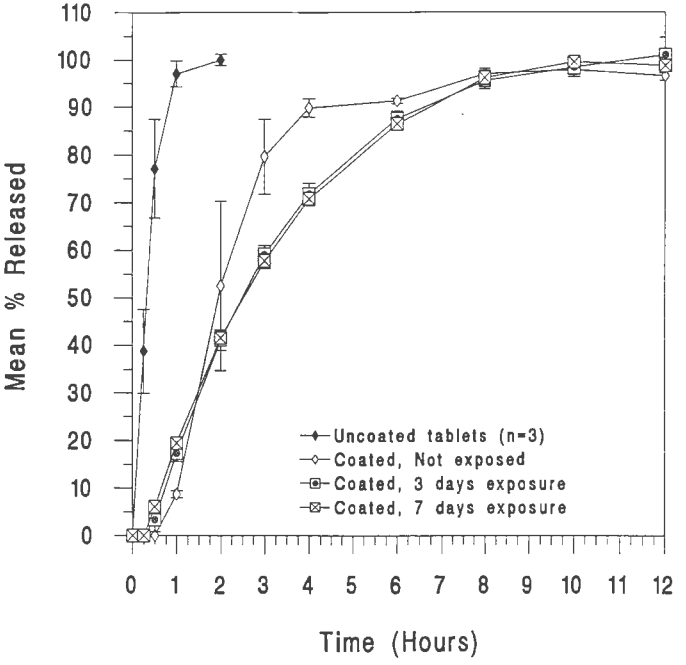
Photocrosslinked HEC/R5P Membrane Dissolution Studies:
PERCENT LABEL CLAIM RELEASED PER HOUR

	Metoprolol Fumarate					Dextromethorphan HBr				
		Three Days		Seven Days			Three Days		Seven Days	
Time (hours)	Control	No Hole	Hole	No Hole	Hole	Control	No Hole	Hole	No Hole	Hole
1	8.7	17.3	25.9	19.5	22.9	54.2	30.7	29.6	27.3	29.1
2	43.9	23.9	24.6	22.2	23.1	42.0	29.7	26.7	28.4	28.1
3	27.2	18.0	16.9	16.2	16.6	4.3	22.4	21.3	22.7	22.7
4	10.2	12.8	11.5	13.1	10.2		12.2	15.6	16.0	14.1
5	***0.7***	***7.9***	***6.6***	***7.8***	***6.8***		6.8	5.4	3.5	4.5
6	***0.7***	***7.9***	***6.6***	***7.8***	***6.8***					
7		***4.0***	***2.1***	***4.8***	***3.3***					
8		***4.0***	***2.1***	***4.8***	***3.3***					
9		***1.4***	***0.4***	***1.6***	***1.0***					
10		***1.4***	***0.4***	***1.6***	***1.0***					
11		***1.3***	***0.2***		***1.1***					
12		***1.3***	***0.2***		***1.1***					

Note: Bolded values represent the mean hourly percent of drug released as samples were drawn at two hour intervals

Figure 1

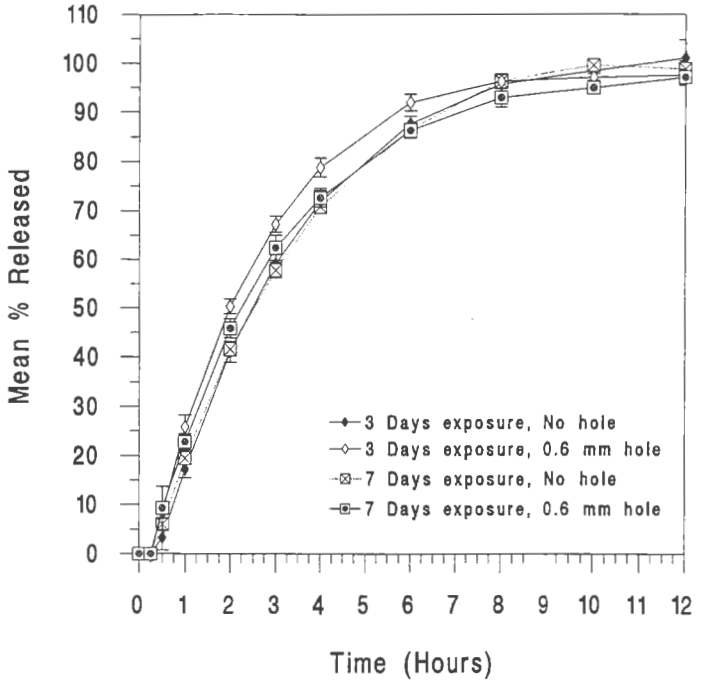
Comparison of Dissolution Profiles: Metoprolol Fumarate Osmotic Tablets (190 mg) with and without HEC/R5'P coating



Note: Exposed tablets were subjected to 600 footcandles of visible light. Dissolution media was Water USP.

Figure 2

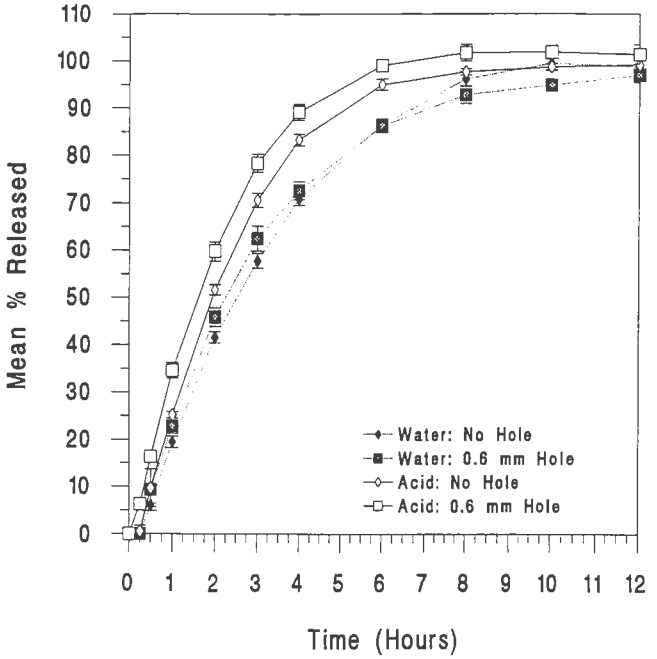
Comparison of Dissolution Profiles: Metoprolol Fumarate Osmotic Tablets (190 mg) coated with HEC/R5P with and without 0.6 mm hole



Note: Tablets were exposed to 600 footcandles of visible light for a period of 3 or 7 days. Dissolution media was Water USP.

Figure 3

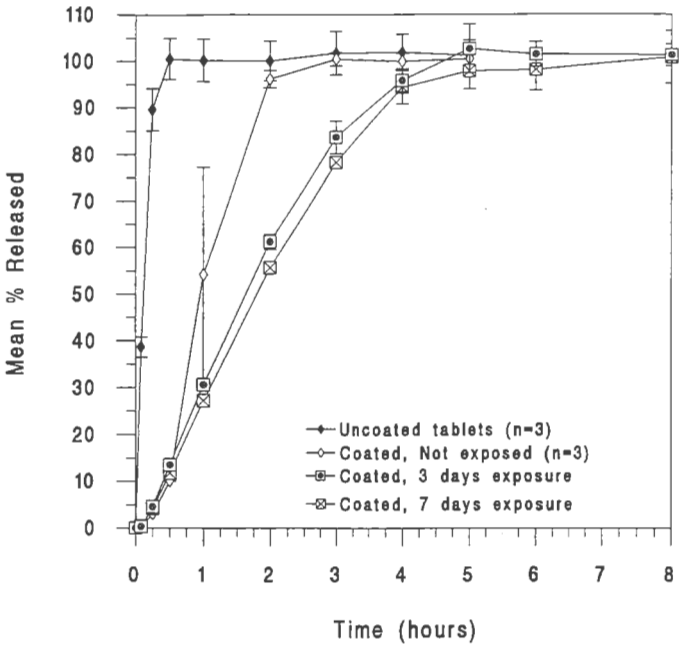
Comparison of Dissolution Profiles: HEC/R5P coated Metoprolol Fumarate Osmotic Tablets (190 mg) in water and 0.1 N HCl



Note: All tablets exposed to 600 footcandles of visible light for 7 days.

Figure 4

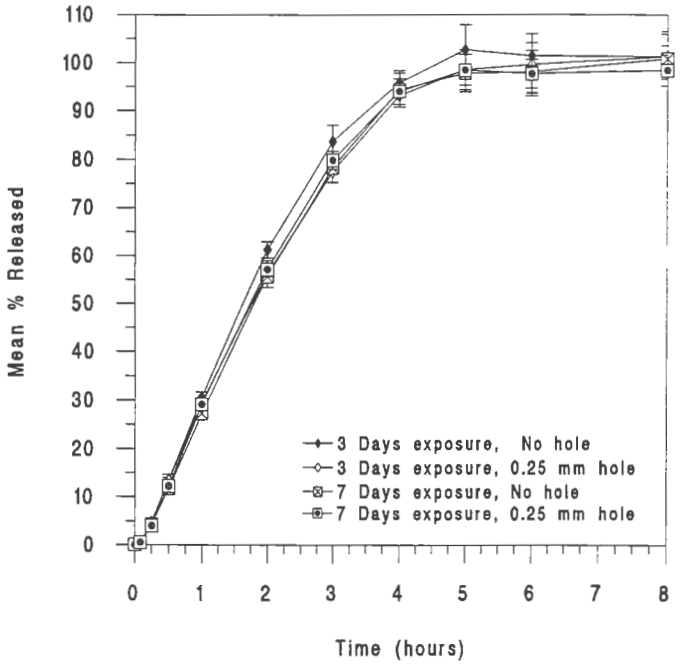
Comparison of Dissolution Profiles: Dextromethorphan HBr Tablets (20 mg) with and without HEC/R5P coating in Water



Note: Tablets were exposed to 600 or 1000 footcandles of visible light for 7 or 3 days, respectively.

Figure 5

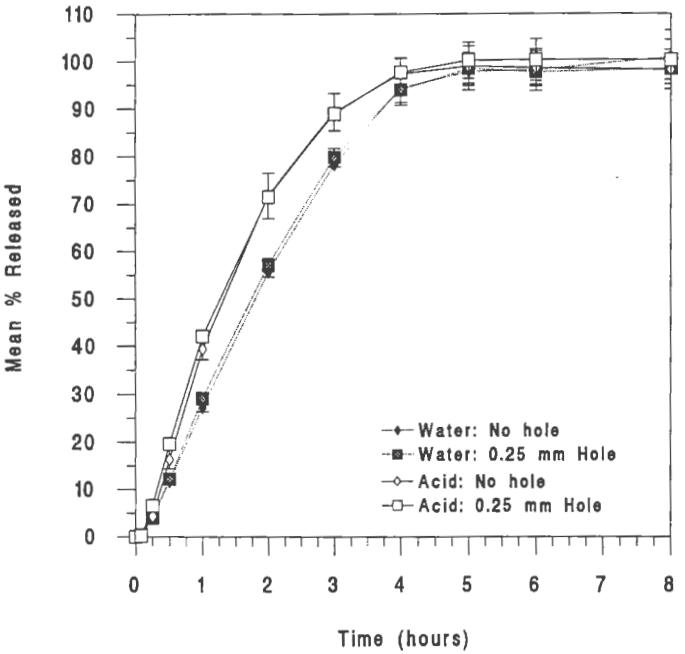
Comparison of Dissolution Profiles:
Dextromethorphan HBr Tablets (20 mg) coated with HEC/R5P with and without 0.25 mm hole



Note: Tablets were exposed to either 600 or 1000 footcandles of visible light for a period of 7 or 3 days, respectively. Dissolution media was Water USP.

Figure 6

Comparison of Dissolution Profiles: HEC/R5P coated Dextromethorphan HBr Tablets (20 mg) in water and 0.1 N HCl

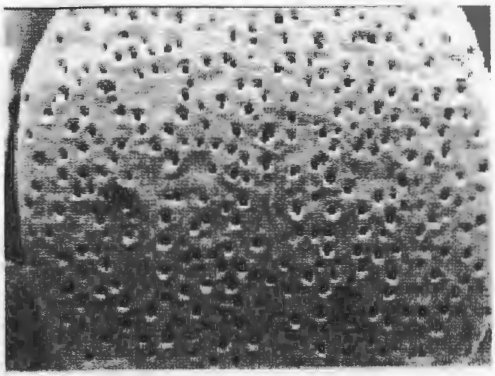


Note: Tablets exposed to 600 footcandles visible light for 7 days.

Figure 7

Scanning Electron Micrographs of Crosslinked HEC/R5P Coated Metoprolol Fumarate Tablets before (7a) and after (7b) Dissolution Testing
Magnification 16.5 X

7a



7b

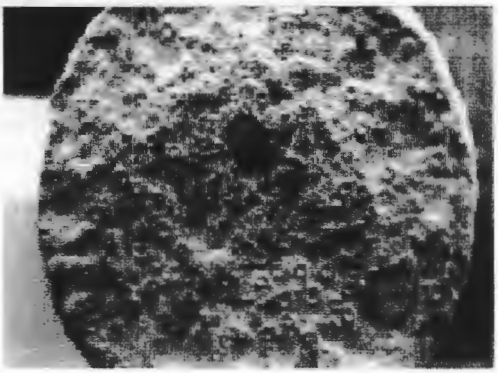
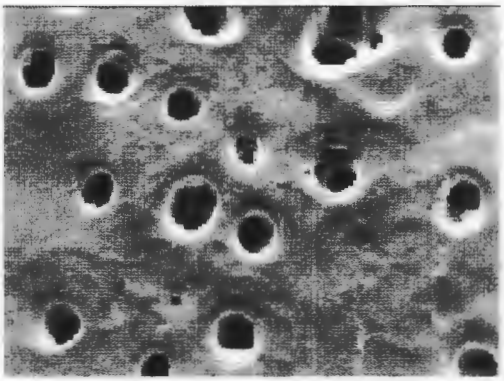


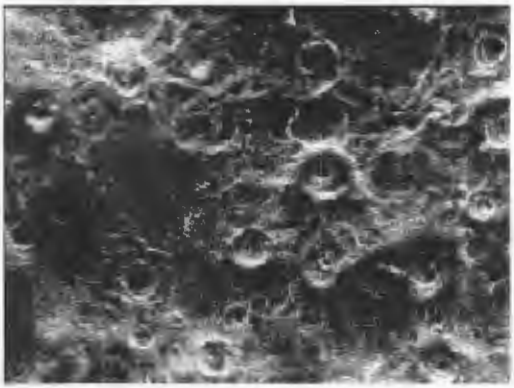
Figure 8

Scanning Electron Micrographs of Crosslinked HEC/R5P Coated Metoprolol Fumarate Tablets before (8a) and after (8b) Dissolution Testing
Magnification 75 X

8a



8b



Manuscript IV

PHOTOCROSSLINKED HYDROXYETHYLCELLULOSE MEMBRANES AS SUSTAINED RELEASE COATINGS: PROBLEMS ASSOCIATED WITH AND POSSIBLE SOLUTIONS FOR THE CHARACTERIZATION OF CROSSLINKED MATERIALS

PHOTOCROSSLINKED HYDROXYETHYLCELLULOSE MEMBRANES AS SUSTAINED RELEASE COATINGS: PROBLEMS ASSOCIATED WITH AND POSSIBLE SOLUTIONS FOR THE CHARACTERIZATION OF CROSSLINKED MATERIALS

ABSTRACT

A method by which films of water soluble hydroxyethylcellulose may be rendered insoluble, after deposition onto the surface of pharmaceutical solids, has been developed. While the application of such a technology is rather simple and offers promise as a substitute for organic solvent usage, the development of meaningful analytical methodology, by which the crosslinking process may be monitored and understood has proven rather difficult. Attempts have been made to understand and quantify changes occurring to the polymer as a result of the crosslinking reaction. Unfortunately many have proven inconclusive. Much of the complexity of this problem lies in the insolubility of the crosslinked polymer in common aqueous and organic solvents. Therefore considerable attention has been paid to analytical techniques which may be performed on materials in their solid state. The functional relevance of such techniques, as well as others included in our previous work to large scale production is considered herein. Additionally included is discussion of alternative techniques which, although not tested with this system, may provided useful information about the crosslinking process and provided recommendations for other ways to evaluate the crosslinked product should instrumental methods fall short of their intended goals.

KEYWORDS

Hydroxyethylcellulose, Riboflavin-5'-phosphate, Crosslinking, Oxygen Permeability, Tablet Coating, Polymer

INTRODUCTION

In previous papers we describe a process by which hydroxyethylcellulose (HEC), a water soluble, nonionic polymer may be rendered water insoluble through exposure to visible light when in the presence of riboflavin-5'-phosphate (1). While the insolubilization of HEC has been demonstrated previously, we believe our method is unique in that insoluble HEC may be obtained through reaction with a photosensitizer that is currently approved for use *in vivo* (2-4). The development of a system containing only GRAS components which may be cured with visible light is notable in that previous attempts at radiation cured coatings for pharmaceutical solids have suffered the shortcomings of unapproved raw materials and the untoward effects of ionizing radiation (5,6). In addition to the development of the HEC crosslinking process, (which may circumvent the problems associated with unapproved materials) we have demonstrated the potential of photocrosslinked HEC as a sustained release tablet coating *in vitro* (7).

While we are confident that it is possible to alter the aqueous solubility of HEC films applied to tablets and prolong the release of the drugs contained within those films, our experience with this process has left us with many unanswered questions. Simply put, there are aspects of this system that would be difficult to characterize, let alone gain an understanding of the nature of the chemical changes that have taken place. Fortunately, a complete understanding of this system is not a prerequisite to its successful application. Still, there exists a need for some reliable indicator of the extent of the crosslinking process (quality control).

Generally, polymeric materials, especially those derived from natural sources, are difficult to characterize. HEC is no exception having no conjugated

bonds, thereby ruling out ultraviolet spectroscopy, very poor organosolubility and poor water solubility, once crosslinked (1,8).

Official methods, both compendial (USP/NF) and ASTM, have been developed for the identification of, and to set raw material acceptance criteria specifications for, HEC (8,9). Unfortunately, these tests do not provide any information about the chemical changes that may have taken place as a result of the crosslinking reaction. Another official ASTM method which determines the ethoxyl substitution of cellulose ethers may provide useful information about the polymer if its level of ethoxyl substitution changes as a result of crosslinking (10). Unfortunately, the utility of this method remains questionable since the chemical changes that may be caused by crosslinking have yet to be determined.

This paper seeks to gain insight into the nature of the crosslinking of HEC through common instrumental methods that could be used routinely in a quality control setting. The methods included within this work were chosen in the hope that they could elucidate any physico-chemical differences between crosslinked and control samples of HEC without the need for complex testing regimens. While this work has been concentrated on the characterization of free films, it is hoped that the methods employed here for films may be readily adaptable to coated tablets.

MATERIALS AND METHODS

Materials

Natrosol 250 M pharmaceutical grade hydroxyethylcellulose, molecular weight 720,000 was supplied by The Aqualon Corporation (Wilmington, DE) while riboflavin-5'-phosphate sodium was purchased from Sigma Chemical

Corp. (St. Louis, MO). All materials were used, as received from their respective manufacturers without further purification.

Film Preparation

All films evaluated in this study were prepared in the following manner.

Formulation:

Natrosol 250 M Pharma	1.50 % w/w
Riboflavin-5'-phosphate	0.03
Water USP	98.47
	100.00

The Natrosol and riboflavin-5'-phosphate were weighed and slowly added to the vortex of a propeller type mixer (Lightnin' Labmaster TSR 1516) operating at 1000 rpm. Any undissolved polymer, which remained after several minutes of mixing was dispersed with the aid of a "lab scale" homogenizer (Silverson L4R, UK) run at a slow speed so to lessen the possibility of reducing the molecular weight of the polymer. Once free of any undissolved polymer, the solution was transferred to a darkened refrigerator and allowed to deaerate overnight. Prior to film casting, the polymer solution was allowed to warm to room temperature.

Once at room temperature, a suitable portion of the solution was poured onto a preheated glass plate (60^{o}C) and spread into a thin film (1.016 mm, wet thickness) with the aid of a film casting table (RK Print - Coat Instruments, UK) equipped with a # 8 casting rod. Once cast, the films were placed into a darkened 60^{o}C oven and dried for 24 hours.

Those films used for oxygen permeability testing were placed into an environmental cabinet (Forma Scientific) previously calibrated to deliver 1000 footcandles of visible light at 25^{o}C. Films were exposed to visible light for a

period of 4, 8, 16, 24, or 168 hours, removed from the cabinet, and subsequently stored in darkness until required.

Films that were evaluated by DSC, TGA, and IR spectroscopy were subjected to either 600 footcandles of visible light for a period of 24 hours (Hotpack environmental cabinet, model 352642, 25^{o}C) or evaluated without prior light exposure.

OXYGEN TRANSMISSIBILITY (Dk)

A Dk1000 Oxygen Permeability Apparatus (JDF Company, Norcross, GA) was used for all oxygen transmissibility determinations. Testing was performed in accordance with ASTM method 3985 (11)

Prior to testing each film sample was immersed in ultra pure water until fully hydrated. Once hydrated, the films were cut into 1.5 x 1.5 cm squares, and reimmersed in water until needed for testing. The thickness of each individual square was measured prior to its placement into the diffusion cell (0.35 cm^2 exposed area).

The test cell of the Dk 1000 was then filled with ultra pure water, sealed and subsequently purged with an inert carrier gas (2% H2 and 98% N2) until a stable baseline was attained. Once stable, a humidified gas mixture containing oxygen and nitrogen (79 and 21% , respectively) was introduced into the cell. Gradually, if the film is permeable, oxygen will diffuse through it and be carried to the detector by the carrier gas. At the detector, an electrical current is generated and converted to a signal that is directly proportional to the oxygen flux through the film (12).

Wherever possible, Dk measurements were performed in triplicate.

IR SPECTROSCOPY

Infrared spectra of HEC, R5P, and films representative of the different stages of the crosslinking process were obtained with the aid of a Nicolet Magna 550 FT-IR (Nicolet Instrument Corp. Madison, WI) operated under normal conditions. Film samples were run, as received without any further preparation while powder samples were finely ground, mixed with KBr and compressed into pellets (40 ft./lb. compression force). Prior to testing, excess water and CO_2 were purged from the sample chamber with nitrogen. After purging, each sample was scanned 100 times and its spectra plotted as percent transmittance vs. frequency (4000 - 600 cm^{-1}). Background spectra were gathered each day prior to sample assay.

DSC, TGA

Differential scanning calorimetry (DSC) and thermogravimetric analyses (TGA) were performed on samples of HEC which had been subjected to different amounts of preparation. Films samples, prepared in a manner consistent with those mentioned previously, were tested both before and after 6 days of exposure to 600 watts of visible light and compared to profiles obtained for HEC powder tested "as received".

Calorimetry was performed, in duplicate under nitrogen, with the aid of a Perkin Elmer DSC-7 (Perkin Elmer, Norwalk, CT). Samples were heated at a rate of 10 ^{o}C/min over a temperature range of -60 to 125 ^{o}C.

TGA analyses of HEC samples similar to those evaluated by DSC were performed with a Mettler TA 2000 C Thermogravimetric Analyzer (Mettler Instruments, Switzerland) under both air and nitrogen. In each case heating was maintained at a rate of 4 ^{o}C/min over a range of 25 to 600 degrees.

RESULTS AND DISCUSSION

Oxygen Transmissibility

The oxygen transmissibility (Dk) of hydrogels is largely dependent upon two factors, the material itself and the amount of water which it contains. While the materials which make up a hydrogel (water excluded) may add a small contribution to its overall Dk, its water content appears to have the greatest influence on its Dk (12, 13). HEC will readily form hydrogels, a characteristic which has been exploited for the creation of sustained release matrices (14). Matrices of this type gradually swell, once hydrated, and continue to do so until all of the polymer has dissolved. Much the same can be said for uncrosslinked films of HEC/R5P.

However once crosslinked, HEC/R5P films become insoluble, the degree of which is dependent on the amount of crosslinking which has occurred. Therefore, based on the statements of the previous paragraph, the Dk of HEC/R5P films should decrease as their degree of crosslinking increases. This was indeed the case in this study.

Table 2 displays the effect of different durations of visible light exposure on the oxygen permeability of HEC/R5P films. From previous solubility studies of crosslinked HEC/R5P films we have learned that the majority of the crosslinking which will occur does so within the first 24 hours of exposure, although additional exposure beyond 24 hours allows for additional crosslinking. Samples that were exposed for 4 and 8 hour periods, although largely insoluble in water, were difficult to handle due to their overall weakness when hydrated. Because of these difficulties only two tests could be completed for those films exposed for 4 hours.

Statistical analysis of the oxygen permeability (Table 3) revealed significant differences between the mean Dk's of the 168 hour exposed films and the remainder of the group except the 8 hour films whose mean had proved to be marginally insignificant at an a of 0.05. The outcomes of the t-tests, although they must be viewed cautiously because of small sample sizes, confirm our observations. The extent of crosslinking of the 4 and 8 hour samples is much more variable than that of films exposed for longer periods of time.

Inconsistent crosslinking would allow portions of the HEC film to behave in a manner more consistent with that of an uncrosslinked film. Areas of low crosslink density would readily absorb large volumes of water and swell considerably thereby forming a loose polymeric network which would readily allow for the passage of oxygen and other, larger molecules. Conversely, those films with relatively high crosslink densities although hydrophilic, resist swelling and maintain much of their mechanical strength when hydrated.

IR Spectroscopy

Spectra representing various combinations of HEC, R5P and visible light exposure are presented in figure 1. A listing of the spectra presented in figure 1 may be found in table 1. Spectra of neat samples of HEC and R5P have been included as controls by which the spectra of crosslinked films may be judged.

Examination of figures 1b through 1f reveals no distinct differences between the various conditions of exposure below 1500 and above 2500 wavenumbers. Much of the difference in spectra between 2500 and 1500 wavenumbers may in fact be due to physical differences in the film samples and not any distinct chemical change. Of course the addition of R5P to an HEC film

causes a change in the appearance of the spectrum. Yet the presence, or absence of peaks which correspond to those used for the identification of R5P (1728, 1648, 1623 and 1578 cm^{-1}) gives some insight to the role which R5P has in the changes in HEC solubility encountered upon its exposure to visible light (15).

Within figures 1d and 1f the benchmark peaks for R5P are clearly evident, however they are no longer visible once the crosslinked film has been washed with an excess amount of water (Figure 1f). The absence of R5P in figure 1f is most encouraging as it leads to the assumption that R5P, or its remnants have acted as true catalysts or photosensitizers, facilitating a chemical reaction while remaining as separate moieties which may be readily removed after accomplishing their intended task. Although a mechanism for this reaction has not been determined, Holmstrom has suggested that riboflavin is reduced upon exposure to light of sufficient energy (16). While the mechanism proposed is beyond the scope of this discussion, it would be safe to postulate that the reduced riboflavin has extracted a proton form the most readily accessible source, in this case the HEC molecules which constitute the majority of the film.

The ease by which R5P may be extracted from visible light exposed HEC films, in conjunction with the notable differences in the aqueous solubilities of visible light exposed films with and without R5P (1) leads to the assumption that a crosslinking reaction has occurred, facilitated by the presence of a photosensitizer. However the lack of significant changes in the infrared spectra of the crosslinked films leads us to believe that the crosslinks achieved are few, yet numerous enough to have a drastic effect on the polymer solubility.

DSC, TGA

Thermograms of the three HEC samples evaluated are presented in figure 2. Little, if any change in the thermal properties of HEC and the HEC/R5P mixtures is evident, especially when one takes note that the heat flows expressed on the y axis are less than 1mW overall. Therefore, any apparent differences between the respective samples is exaggerated by the scale on which they are presented.

The outcomes of TGA experiments, performed in air and nitrogen, are presented in figures 3 and 4 respectively. Detectable mass loss commences at about 210^{o}C for samples tested in air and about 225^{o}C for samples tested under nitrogen. Both of these values are consistent with the 205 to 210 degree "browning range" provided in the manufacturers technical literature (14). Unfortunately, differences between polymer samples apparent in the TGA plots are small and do not allow for the meaningful interpretation of the changes imparted to the HEC as a result of the crosslinking reaction.

CONCLUSIONS

Although a process by which HEC may be crosslinked through visible light exposure has been realized, a determination of what changes, if any, may have occurred to the polymer has proven to be most difficult. While a detailed mechanistic determination of the reaction between HEC, R5P and visible light may be beyond the intended goals of this research, there exists a need for analytical techniques by which the success and efficiency of this technique may be monitored. Of the three analytical techniques discussed in this work, none has provided direct proof of significant chemical changes to the polymer as a result of crosslinking. Yet each of them, in some way, has provided insight into

the those changes which have taken place. Much of the data gathered, while not conclusive of drastic changes imparted by light exposure, is nonetheless suggestive of the nature of the few changes which must have occurred to effect the alterations in solubility observed and are therefore, invaluable. The real value of three of the methods which we had investigated lay in the "circumstantial", and not the direct evidence which were gathered from them.

IR spectroscopy has revealed that no gross changes in the chemical structure of HEC were effected as a result of the crosslinking reaction. Yet, our attempt to "wash out" the R5P from the crosslinked films revealed that it may indeed function as a true catalyst for crosslinking, acting only to facilitate changes in the polymer without becoming chemically bound to it. Similarly, DSC and TGA investigations demonstrated the similarities, and not differences between the crosslinked and control HEC films.

Circumstantial evidence has led us to postulate that water insoluble HEC films are comprised of a weakly crosslinked polymeric network to which chemical changes have been effected that are great enough in number to impart drastic changes in aqueous solubility, yet few enough to not cause significant changes in the polymer's thermal and infrared characteristics. This effect may be largely due to the far greater contribution of polymeric inter-chain interactions to the mechanical and thermal properties of HEC films, when tested in a dry state, than those of the actual crosslinks created through visible light exposure (17).

Unlike the circumstantial data proved by IR spectroscopy and thermal analyses, oxygen transmissibility testing yielded data which provided a quantitative, although quite preliminary, difference between films which had been manufactured via different amounts of light exposure. The positive initial

result of oxygen permeability testing has demonstrated it's potential value as a test method to characterize crosslinked systems and provided hope that future research may correlate, quantitatively, amount of crosslinking incurred as a result of the dose of light applied. The success of this method is due to the fact that measurements are performed on hydrated films. Hydration causes HEC to swell considerably. Like other hydrogels, prolonged exposure of uncrosslinked HEC to excess water leads to it's eventual solvation. Crosslinking locks polymer molecules into fixed structures whose degree of swelling is determined by the crosslink density. Therefore, the more crosslinked a polymeric film, the less it can swell thereby resulting in a lower overall permeability.

While we have demonstrated the potential use of oxygen transmissibility testing to differentiate between films of differing crosslink densities, the utility of this technique for crosslinked tablet coatings remains questionable as it requires the use of "free" films. Additionally, time might pose another hurdle since at least 2 hours are required to run one sample.

Although the data gathered from oxygen transmissibility exhibits quantitative differences between film samples subjected to different test conditions, this test may not prove readily adaptable to an often performed quality control procedure as would be required for the manufacture of crosslinked tablet coatings. Likewise, the circumstantial evidence derived from IR spectroscopy and thermal methods is rarely the basis for a system of quality control. Clearly there exists a need for alternative test procedures capable of distinguishing the changes that may occur within a photocrosslinkable coating system while remaining efficient in both time and cost.

At present, the only test which we have found to be both indicative of crosslinking and feasible in respect to its use a quality control regimen is the rather subjective determination of a film's aqueous solubility. This type of testing is similar to the "acid bath" tests routinely employed for the evaluation of the efficiency of enteric coatings. In the case of crosslinked HEC films, finished tablets would be immersed in water and judged by the number of tablets whose of coatings fail within a specified time period. Failure of a particular lot of tablets would serve to indicate insufficient crosslinking and the subsequent need for additional processing.

Although a solubility test similar to the one previously discussed is a reasonable idea, in its' present form it is at best qualitative, and may not be capable of discerning the subtle differences in the amount of crosslinking incurred by a batch of tablets which may lead to failure of the coating *in vivo*. Surely there are other techniques which, although as of yet untested, may assist in the characterization of crosslinked HEC and other polymeric materials. In the search for such tests one must remember that some test procedures may provide information which may assist in the physico-chemical characterization of a polymer, yet have no functional relevance to the performance of a crosslinked system containing that polymer. Tests of this type are most useful to the theoretical scientist wishes to understand the underlying mechanism by which such a crosslinking reaction to occurs. The applied scientist's needs are more simple. What he, or she, requires is a battery of test methods which are indicative of if, and not necessarily descriptive of the manner in which a suitable amount of crosslinking has occurred.

Ideally the tests needed to monitor the processing of the type of crosslinked coatings explored herein would be those which require minimal sample preparation while allowing for the timely testing of many samples. Unfortunately such methods may be unattainable. While the search for suitable process monitoring assays continues, other actions may be taken to characterize the crosslinking process so that reasonable process "end points" may be determined. Future studies of photocrosslinked HEC coatings require that investigators seek empirical tests which are clearly indicative off the extent to which the reaction has occurred. If a simple testing regimen is not readily forthcoming, validation of the irradiation process in conjunction with the determination of meaningful process limits may offer a suitable means of controlling the outcome of the crosslinking process.

The *in situ* crosslinked tablet coating technology which we have investigated in this, and previous papers, offers promise as a new means of creating sustained release pharmaceuticals, yet the technology remains in its' infancy. Future investigations need to find meaningful analytical techniques for the crosslinked HEC and attempt to define the limits of the irradiation process. If these needs are met, and regulatory agencies agree with the assumption that a coating made from GRAS materials is itself a GRAS material, pharmaceutical formulators may soon have a new sustained release technology at their disposal.

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ACKNOWLEDGMENTS

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Table 1

Combinations of hydroxyethylcellulose and riboflavin-5'-phosphate studied by infrared spectroscopy and presented in Figure 1

Figure	Composition	Physical State	Visible Light Exposure
1a	Riboflavin-5'-phosphate	KBr Pellet	None
1b	Hydroxyethylcellulose 250 M	Film	None
1c	Hydroxyethylcellulose 250 M	Film	7 days @ 600 ft. cand.
1d	HEC 250 M and 2 % R5P	Film	7 days @ 600 ft. cand.
1e	HEC 250 M and 2 % R5P	Film	7 days @ 600 ft. cand.
1f	HEC 250 M and 2 % R5P	Film	(H20 washed)7 days @ 600 ft. cand.

Figure 1 a

Infrared Spectrum of Riboflavin-5'-phosphate (Obtained from KBr Pellet)

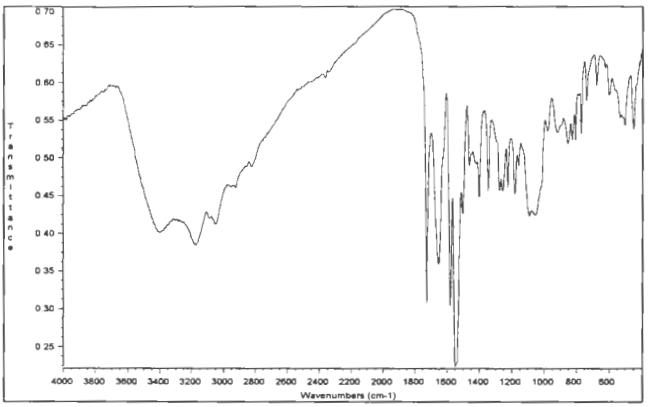


Figure 1 b

Infrared Spectrum of Hydroxyethylcellulose (Natrosol 250 M) Free Film

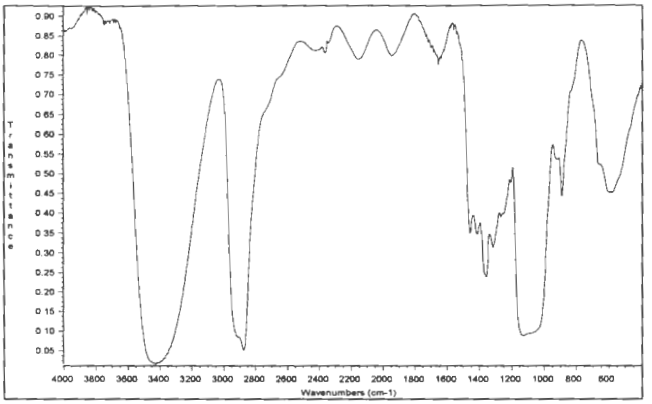


Figure 1 c

Infrared Spectrum of Hydroxyethylcellulose (Natrosol 250 M) Exposed to Visible Light (600 footcandles) for 7 Days, Free Film

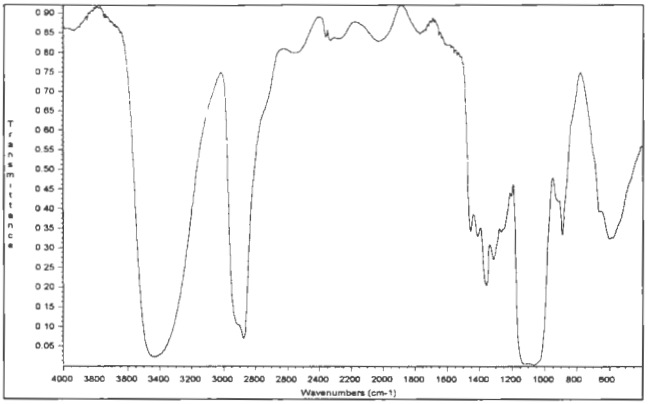


Figure 1 d

Infrared Spectrum of Free Film containing Hydroxyethylcellulose and Riboflavin-5'-phosphate (2% w/w), No Light Exposure

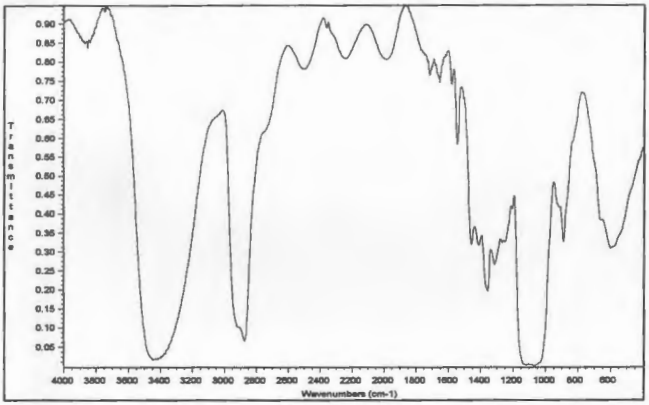


Figure 1 e

Infrared Spectrum of Free Film containing Hydroxyethylcellulose and Riboflavin-5'-phosphate (2% w/w), Exposed to Visible Light (600 footcandles) for 7 Days

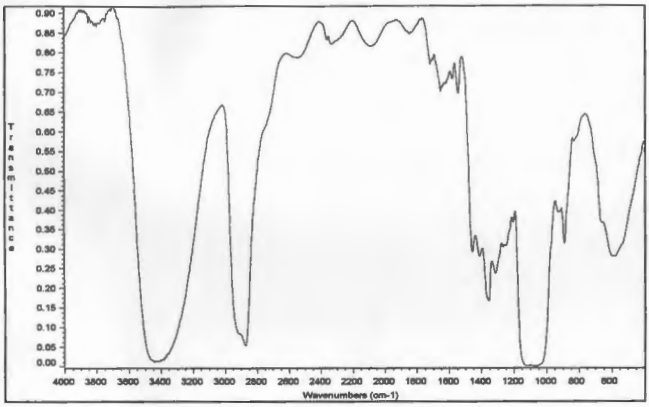


Figure 1 f

Infrared Spectrum of Free Film containing Hydroxyethylcellulose and Riboflavin-5'-phosphate (2% w/w), Exposed to Visible Light (600 footcandles) for 7 Days and Subsequently Washed with Distilled Water

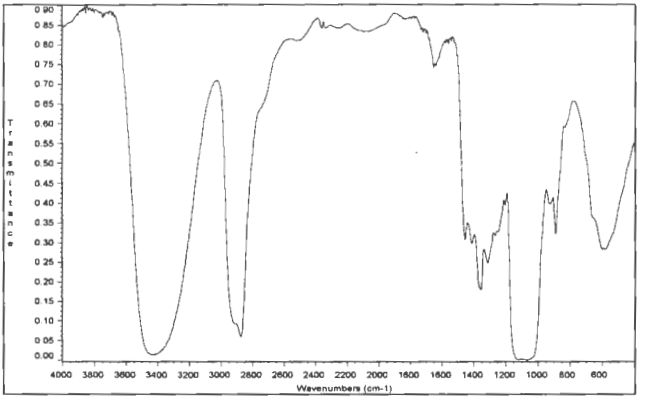


Figure 2

Thermograms of Selected Hydroxyethylcellulose Samples: Reference: Hydroxyethylcellulose 250 M Powder, Film Sample 1: Film containing HEC 250 M and 2 % w/w Riboflavin 5' Phosphate following exposure to Visible Light (600 footcandles, 6 days), Film Sample 2: Film containing HEC 250 M and 2 % w/w Riboflavin 5' Phosphate , No light exposure. Note: Samples were heated from -60 to 125 degrees centigrade (run 1), cooled and subsequently reheated (run 2).

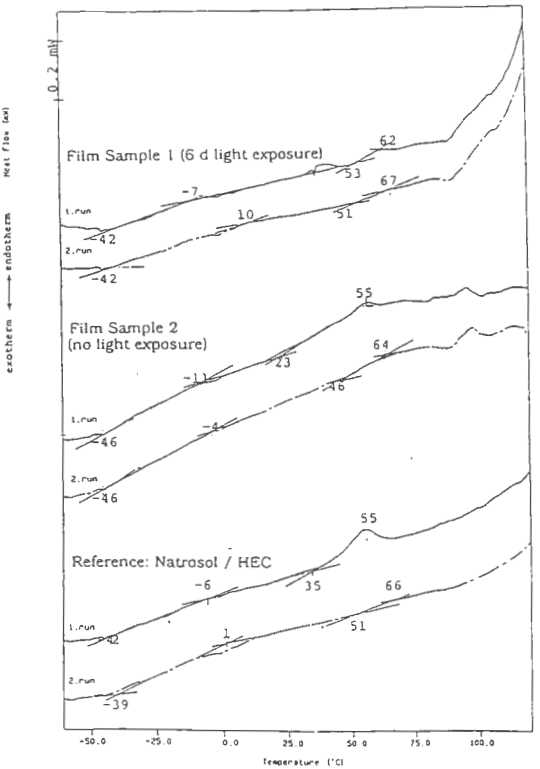


Figure 3

Thermogravimetric analysis of various Hydroxyethylcellulose samples tested in air; Reference: Hydroxyethylcellulose 250 M Powder (solid line), Film Sample 1: HEC 250 M and 2 % w/w Riboflavin 5' Phosphate following exposure to 600 footcandles of Visible Light for 6 days (dashed line) Sample 2: Film containing HEC 250 M and 2 % w/w Riboflavin 5' Phosphate , No light exposure (dotted line).

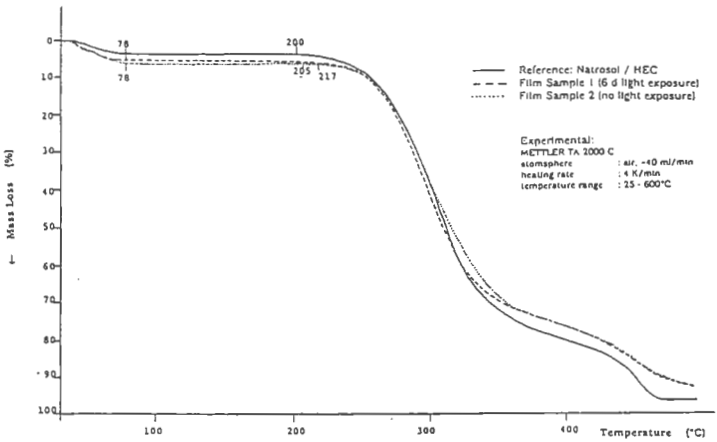


Figure 4

Thermogravimetric analysis of various Hydroxyethylcellulose samples tested under nitrogen; Reference: Hydroxyethylcellulose 250 M Powder (solid line), Film Sample 1: HEC 250 M and 2 % w/w Riboflavin 5' Phosphate following exposure to 600 footcandles of Visible Light for 6 days (dashed line) Sample 2: Film containing HEC 250 M and 2 % w/w Riboflavin 5' Phosphate , No light exposure (dotted line).

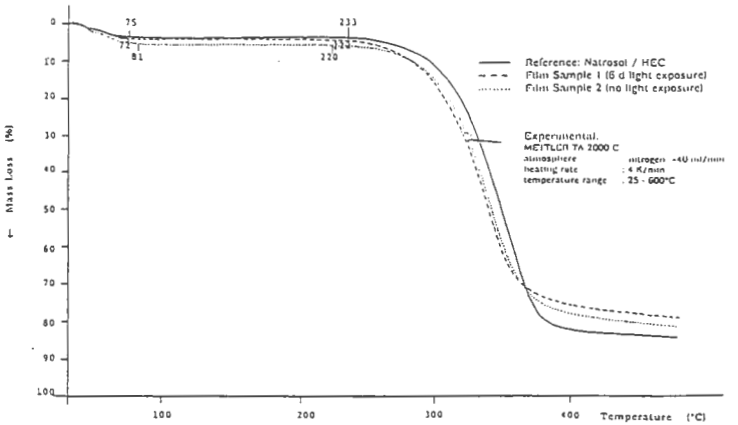


TABLE 2

The Effect of Visible Light Exposure on the Oxygen Permeability (Dk) of Hydroxyethylcellulose Films

Exposure time	4 hours	8 hours	16 hours	24 hours	168 hours
Trial 1	8.20E-10	9.80E-10	7.90E-10	6.70E-10	5.90E-10
Trial 2	1.06E-09	1.48E-09	7.60E-10	7.80E-10	5.60E-10
Trial 3	-	8.40E-10	6.80E-10	7.80E-10	6.10E-10
Mean Dk	9.40E-10	1.10E-09	7.43E-10	7.43E-10	5.87E-10
Standard Deviation	1.70E-10	3.37E-10	5.69E-11	6.35E-11	2.52E-11

Note: Dk expressed in cc $O_2/cm^2/sec/mm$ Hg

TABLE 3

Statistical Analysis Comparing the Effect of Visible Light Exposure Duration on the Oxygen Permeability (Dk) of Hydroxyethylcellulose Films

Results of Two Tailed T-Tests

	4 hours	**8 hours**	**16 hours**	**24 hours**
8 hours	0.601			
16 hours	1.987	1.810		
24 hours	1.943	1.804	0	
168 hours	3.866T	2.635	4.363T	3.972T

T Denotes significant difference at a = 0.05.

Note: For comparisons vs. 4 hours, where n=2, total degrees of freedom = 3. In all other cases, degrees of freedom = 4. Critical t values for d.f. = 3 and 4 were 3.18245 and 2.7765, respectively at a = 0.05 for a two-tailed t-test assuming equal variances.

GENERAL CONCLUSIONS

- Within the modern pharmaceutical industry there is a need for new coating materials which can prolong the release of medicaments from their respective dosage forms. However, due to regulatory constraints the chance of a new coating not composed of materials which are "generally regarded as safe," ever entering the marketplace is rather small.

- Hydroxyethylcellulose (HEC), a readily water soluble polymer, may be rendered water insoluble through exposure to light, visible or ultraviolet, when in the presence of riboflavin 5' phosphate.

- Visible light exposure of Hydroxyethylcellulose films containing riboflavin 5' phosphate provides for superior yeilds of insoluble polymer than does irradiation with ultraviolet light under the test conditions studied.

- Once crosslinked, HEC is practically insoluble in water, acidic and basic media (0.1 N), acetone, methanol, and aqueous urea. As urea is a known decoupler of hydrogen bonds, hydrogen bonding is believed not to be a significant cause of the polymer's change in solubility.

- The idea of an *in situ* crosslinkable tablet coating for the sustained release of mediaction has been realized. Such a coating may be applied with extant technologies and be rendered insoluble via exposure to visible light.

- The ability of crosslinked HEC membranes to prolong and control the release of both metoprolol fumarate and dextromethorphan HBr has

been demonstrated *in vitro*. The mechanism of release does not appear to be that of a semipermeable mebrane but rather membrane mediated diffusion.

- Although the crosslinking of HEC has been facilitated, analysis of the crosslinked product has proven to be most difficult. Aside from relatively qualitative solubility and swelling tests which can demostrate the differences between samples which had been subject to different test conditions, more quantitative techniques have proven elusive.

- Data gathered from infrared spectroscopy, differential scanning calorimetry, and thermo gravimetric analysis has proven to be largely circumstantial in nature. While no direct changes to the polymer are observed, their lack leads to the assumption that what changes have occurred are too small in number to be detected by these methods, yet numerous enough to drastically alter the solubility of HEC.

SECTION III

- Appendices 1, 2, and 3.
- Complete listing of references cited.

APPENDICES

1. ASSAY VALIDATION: METOPROLOL FUMARATE
2. ASSAY VALIDATION: DEXTROMETHORPHAN HBr
3. UNITED STATES PATENT APPLICATION: "RADIATION CURED DRUG RELEASE CONTROLLING MEMBRANE"

Appendix 1

Assay validation report for metoprolol fumarate samples in water and in 0.1 N HCl

Appendix 1

Assay validation report for metoprolol fumarate samples in water and in 0.1 N HCl

ASSAY VALIDATION:
METOPROLOL FUMARATE TABLETS COATED WITH PHOTOCROSSLINKED HYDROXYETHYLCELLULOSE

1. SOURCE of STANDARD:

Metoprolol fumarate, Lot # S-2-92-24, was prepared by the Chemical Development Department, Ciba - Geigy Pharmaceuticals, Summit, NJ and subsequently assayed and released for use as a reference standard by the Physical and Analytical Chemistry Department, Ciba - Geigy Pharmaceuticals, Suffern, NY (attachment 1).

2. ASSAY:

System:

Pump:	Shimadzu LC10AS
Injector:	Waters WISP 712D
Column Heater:	Eppendorf CH30
Column:	Shodex RS Pack D18-613 (15 cm)
Detector:	Shimadzu SPD6AV, UV/VIS
Integrator:	Waters 840 Chromatographic Data Station

Parameters:

Flow Rate:	1.0 ml/min.
Injection Volume:	30 µL
Temperature:	45° C
Detector:	λ 272 nm, 0.02 AUFS

Solutions:

Ammonium Hydroxide (0.61 %)
Add 22 ml of ammonium hydroxide to approximately 500 ml distilled water in a 1 liter volumetric flask, mix well, and dilute to volume with distilled water.

Mobile Phase:
In a suitable flask combine 340 ml of acetonitrile, 660 ml of ammonium hydroxide (0.61%), and 34 ml of triethylamine. Mix well and degas under vacuum for 10 minutes. Adjust pH to 11.0 with acetic acid and filter through a 0.5 µ Millipore filter, or equivalent, before use.

3. REPRESENTATIVE CHROMATOGRAMS:

The chromatograms presented in figures 1 through 9 represent the various components present in the final, coated dosage form. They are as follows:

Figure #	Description	Concentration (mg/ml)
1	Water Blank	n/a
2	Metoprolol Fumarate in Water	$2.412x10^{-1}$
3	Riboflavin 5' Phosphate in Water	$4.038x10^{-4}$
4	Metoprolol Tablet (Uncoated) Water	$2.11x10^{-1}$ (drug)
5	Metoprolol Tablet (Coated)	$2.11x10^{-1}$ (drug)
6	HCl Blank	0.1 N
7	Metoprolol Fumarate in HCl	$2.423x10^{-1}$
8	Riboflavin 5' Phosphate in HCl	$4.038x10^{-4}$
9	Metoprolol Tablet (Uncoated) HCl	$2.11x10^{-1}$ (drug)

The retention time of metoprolol fumarate was approximately 6.0 minutes when assayed by this method.

4. LINEARITY:

The linearity of metoprolol fumarate in both distilled water and 0.1 N HCl was determined by simple linear regression ("Cricket Graph" graphing software, Computer Associates International, Inc. Islandia, NY). In each case, seven separate concentrations of metoprolol fumarate were used to generate the standard curve. Figure 10 depicts the standard curve, and linear regression of metoprolol fumarate in water while figure 11 depicts that of metoprolol fumarate in 0.1 N HCl.

The following concentrations were used for each linearity determination:

Solution #	Conc. in Water (mg/ml)	Conc. in 0.1 N HCl (mg/ml)
1	$2.412x10^{-1}$	$2.423x10^{-1}$
2	$2.171x10^{-1}$	$2.180x10^{-1}$
3	$1.447x10^{-1}$	$1.454x10^{-1}$
4	$9.648x10^{-2}$	$9.692x10^{-2}$
5	$4.824x10^{-2}$	$4.846x10^{-2}$
6	$1.929x10^{-2}$	$1.938x10^{-2}$
7	$4.824x10^{-3}$	$4.846x10^{-3}$

Suitable linearity was obtained in each case. Correllation coefficients for linearity determinations in water and 0.1 N HCl were $9.995x10^{-1}$ and $9.997x10^{-1}$, respectively.

5. PRECISION:

Assay precision was determined by plotting the peak areas of triplicate injections of metoprolol fumarate samples of known concentration against the standard curves generated in the previous section. The mean %

difference between the actual concentration of the samples and that determined by the standard curve did not exceed 2.0% for any of the individual concentrations/injections tested (see below). Plots of each individual injection vs. their corresponding standard curve are presented in figures 12 and 13.

Equation 1. Linearity of metoprolol fumarate in water:

Conc. metoprolol fumarate = $5.4435 \times 10^{-3} + 3.1563 \times 10^{-7}$ x PEAK AREA

Sample #	Conc. (actual) (mg/ml)	Conc. (by Eq. 1) (mg/ml)	% Difference (conc.actual vs. by eq. 1)
1a	1.998×10^{-1}	2.034×10^{-1}	1.80
1b	1.998×10^{-1}	1.999×10^{-1}	0.05
1c	1.998×10^{-1}	2.045×10^{-1}	2.35
2a	9.999×10^{-2}	1.004×10^{-1}	0.41
2b	9.999×10^{-2}	1.005×10^{-1}	0.58
2c	9.999×10^{-2}	1.005×10^{-1}	0.58
3a	4.995×10^{-2}	5.017×10^{-2}	0.44
3b	4.995×10^{-2}	5.068×10^{-2}	1.46
3c	4.995×10^{-2}	5.178×10^{-2}	3.67

Equation 2. Linearity of metoprolol fumarate in 0.1 N HCl:

Conc. metoprolol fumarate = $3.8207 \times 10^{-3} + 3.2073 \times 10^{-7}$ x PEAK AREA

Sample #	Conc. (actual) (mg/ml)	Conc. (by Eq. 1) (mg/ml)	% Difference (conc.actual vs. by eq. 1)
1a	2.039×10^{-1}	2.057×10^{-1}	0.85
1b	2.039×10^{-1}	2.083×10^{-1}	2.13
1c	2.039×10^{-1}	2.077×10^{-1}	1.83
2a	1.019×10^{-1}	1.006×10^{-1}	1.35
2b	1.019×10^{-1}	1.016×10^{-1}	0.37
2c	1.019×10^{-1}	1.025×10^{-1}	0.51
3a	5.099×10^{-2}	5.048×10^{-2}	1.00
3b	5.099×10^{-2}	4.997×10^{-2}	2.00
3c	5.099×10^{-2}	5.003×10^{-2}	1.88

6. SYSTEM SUITABILITY

System suitability tests were performed prior to each dissolution run according to the specifications set forth in USP XXII. In each case,the mean peak area and standard deviation of six replicate injections of a

metoprolol fumarate standard solution were determined. Rejection was made if the peak area standard deviation was found to be in excess of 2.0 percent.

Historical system suitability data is presented in attachment 2.

Figure 1

Chromatogram of Distilled Water

42194 21-Apr-94 14:32:55

Printed on 21-Apr-94 at 15:21:22

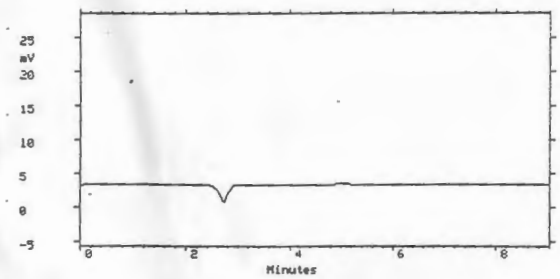
Acquisition method	loporos	Quantitation method	loporos
Units		System number	1
Channel	1	Vial	1
Injection	1	Total injections	1
Run time	9.00 min	Sample rate	1.00 per sec
Injection volume	30 uL	Mode	Calibration
Acquisition version	6.21	Quantitation version	6.21

uv/vis

HPLC METHOD VALIDATION
METOPROLOL FUMARATE IN RIBOFLAVIN 5P04 COATED TABS

water blank

Chromatogram of 42194



Peak Name	Ret time	Area	Height	Type	Response	Deviation	Intercept	Slope
lopressor	5.80	-	-	NF	-	-	-	-

Figure 2

Chromatogram of Metoprolol Fumarate in Distilled Water

42194 21-Apr-94 14:43:32

Printed on 21-Apr-94 at 15:23:22

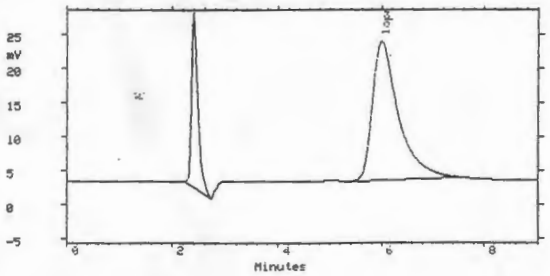
Acquisition method	loporos	Quantitation method	loporos
Units		System number	1
Channel	1	Vial	2
Injection	1	Total injections	1
Run time	9.00 min	Sample rate	1.00 per sec
Injection volume	30 uL	Mode	Calibration
Acquisition version	6.21	Quantitation version	6.21

uv/vis

HPLC METHOD VALIDATION
METOPROLOL FUMARATE IN RIBOFLAVIN 5PO4 COATED TABS

MET FUM in WATER

Chromatogram of 42194



Peak Name	Ret time	Area	Height	Type	Response	Deviation	Intercept	Slope
UNKNOWN	2.40	211057	25911	BB	-	-	-	-
lopressor	6.00	741023	20484	BB	7.41023e+05	3.9567e+03	0.000e+00	3.922e+03

Figure 3

Chromatogram of Riboflavin 5' Phosphate in Distilled Water

42294 22-Apr-94 13:16:57

Printed on 22-Apr-94 at 13:50:09

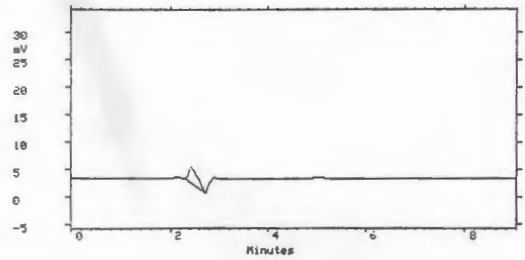
Acquisition method	loporos	Quantitation method	loporos
Units		System number	1
Channel	1	Vial	5
Injection	1	Total injections	1
Run time	9.00 min	Sample rate	1.00 per sec
Injection volume	30 uL	Mode	Calibration
Acquisition version	6.21	Quantitation version	6.21

uv/vis

HPLC METHOD VALIDATION
METOPROLOL FUMARATE IN RIBOFLAVIN 5PO4 COATED TABS

RIBO 5PO4 in WATER

Chromatogram of 42294



Peak Name	Ret time	Area	Height	Type	Response	Deviation	Intercept	Slope
UNKNOWN	2.43	39862	2907	BB	-	-	-	-
lopressor	5.80	-	-	MF	-	-	-	-

Figure 4

Chromatogram of Metoprolol Fumarate Tablet (uncoated)
in Distilled Water

42294 25-Apr-94 10:11:20

Printed on 25-Apr-94 at 13:45:54

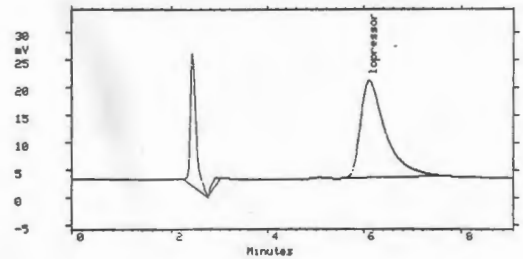
Acquisition method	loporos	Quantitation method	loporos
Units		System number	1
Channel	1	Vial	7
Injection	1	Total injections	1
Run time	9.00 min	Sample rate	1.00 per sec
Injection volume	30 uL	Mode	Calibration
Acquisition version	6.21	Quantitation version	6.21

uv/vis

HPLC METHOD VALIDATION
METOPROLOL FUMARATE IN RIBOFLAVIN 5PO4 COATED TABS

MET FUM CORE in H2O

Chromatogram of 42294



Peak Name	Ret time	Area	Height	Type	Response	Deviation	Intercept	Slope
UNKNOWN	2.43	199544	24097	BB	-	-	-	-
UNKNOWN	2.92	13624	1363	BB	-	-	-	-
lopressor	6.12	640984	17726	BB	6.40984e+05	5.6006e+04	0.000e+00	3.588e+03

Figure 5

Chromatogram of Metoprolol Fumarate Tablet (coated)
in Distilled Water

tab2 17-Nov-93 12:17:34

Printed on 15-Jun-94 at 13:55:51

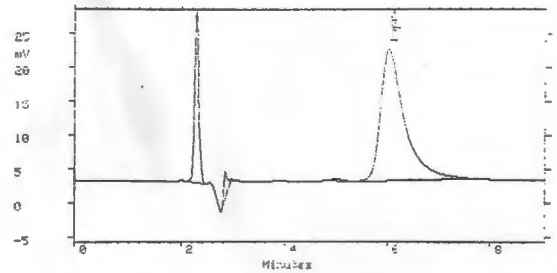
Acquisition method	ioporos	Quantitation method	loporos
Units		System number	1
Channel	1	Vial	75
Injection	1	Total injections	1
Run time	9.00 min	Sample rate	1.00 per sec
Injection volume	30 uL	Mode	Analysis
Acquisition version	6.21	Quantitation version	6.21

uv/vis

HPLC Analysis of LOPRESSOR OROS PHOTO COATED TABS
USING SHODEX c18-6163 colum 34% ACN 66% nh4oh pH 11
6 days @ 600 ft can #456 no hole
no exposure/hole #123

12h 4

Chromatogram of tab2



Peak Name	Ret time	Area	Height	Type	Amount	Intercept	Slope	Response
UNKNOWN	2.28	137462	25971	BB	-	-	-	-
UNKNOWN	2.84	18869	3871	BB	-	-	-	-
UNKNOWN	4.97	4163	340	BB	-	-	-	-
lopressor	6.03	628270	19372	BB	233.070	0.000e+00	2.696e+03	6.28270e+05

Figure 6

Chromatogram of 0.1 N HCl

42194 21-Apr-94 14:54:10

Printed on 21-Apr-94 at 15:26:23

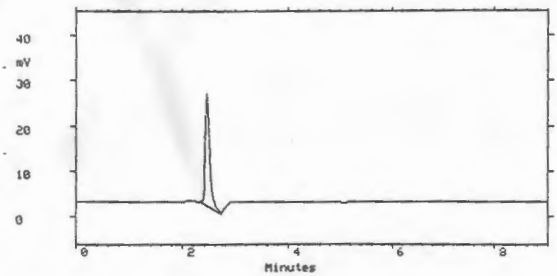
Acquisition method	loporos	Quantitation method	loporos
Units		System number	1
Channel	1	Vial	3
Injection	1	Total injections	1
Run time	9.00 min	Sample rate	1.00 per sec
Injection volume	30 uL	Mode	Calibration
Acquisition version	6.21	Quantitation version	6.21

uv/vis

HPLC METHOD VALIDATION
METOPROLOL FUMARATE IN RIBOFLAVIN 5PO4 COATED TABS

0.1 N HCL blank

Chromatogram of 42194



Peak Name	Ret time	Area	Height	Type	Response	Deviation	Intercept	Slope
UNKNOWN	2.45	143521	24823	BB	-	-	-	-
lopressor	5.80	-	-	BF	-	-	-	-

Figure 7

Chromatogram of Metoprolol Fumarate in 0.1 N HCl

42294 25-Apr-94 10:21:59

Printed on 25-Apr-94 at 13:50:31

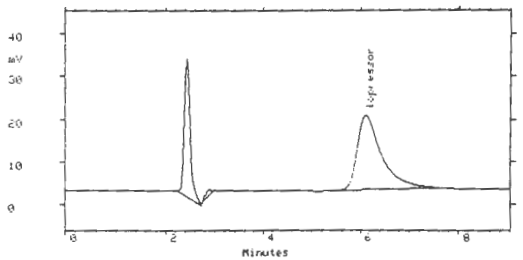
Acquisition method	loporos	Quantitation method	loporos
Units		System number	1
Channel	1	Vial	8
Injection	1	Total injections	1
Run time	9.00 min	Sample rate	1.00 per sec
Injection volume	30 uL	Mode	Calibration
Acquisition version	6.21	Quantitation version	6.21

uv/vis

HPLC METHOD VALIDATION
METOPROLOL FUMARATE IN RIBOFLAVIN 5PO4 COATED TABS

MET FUM CORE in 0.1 NHCL

Chromatogram of 42294



Peak Name	Ret time	Area	Height	Type	Response	Deviation	Intercept	Slope
UNKNOWN	2.43	274191	32082	BB	-	-	-	-
UNKNOWN	2.90	11330	1178	BB	-	-	-	-
lopressor	6.11	625793	17550	BB	6.25793e+05	5.5819e+04	0.000e+00	3.565e+03

Figure 8

Chromatogram of Riboflavin 5' Phosphate 0.1 N HCl

42294 22-Apr-94 13:27:41

Printed on 22-Apr-94 at 13:55:21

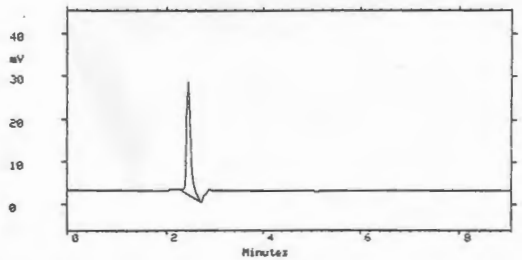
Acquisition method	loporos	Quantitation method	loporos
Units		System number	1
Channel	1	Vial	6
Injection	1	Total injections	1
Run time	9.00 min	Sample rate	1.00 per sec
Injection volume	30 uL	Mode	Calibration
Acquisition version	6.21	Quantitation version	6.21

uv/vis

HPLC METHOD VALIDATION
METOPROLOL FUMARATE IN RIBOFLAVIN 5PO4 COATED TABS

RIBO 5PO$ in 0.1 N HCl

Chromatogram of 42294



Peak Name	Ret time	Area	Height	Type	Response	Deviation	Intercept	Slope
UNKNOWN	2.45	163599	26638	BB	-	-	-	-
lopressor	5.80	-	-	BF	-	-	-	-

Figure 9

Chromatogram of Metoprolol Fumarate Tablet (uncoated)
in 0.1 N HCl

42194 21-Apr-94 15:04:50

Printed on 21-Apr-94 at 15:28:24

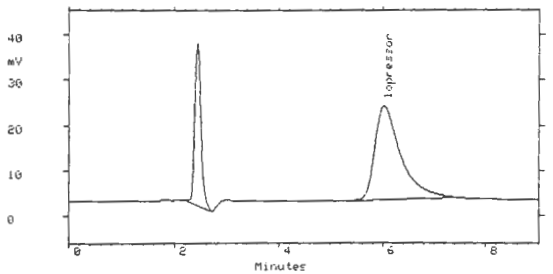
Acquisition method	loporos	Quantitation method	loporos
Units		System number	1
Channel	1	Vial	4
Injection	1	Total injections	1
Run time	9.00 min	Sample rate	1.00 per sec
Injection volume	30 uL	Mode	Calibration
Acquisition version	6.21	Quantitation version	6.21

uv/vis

HPLC METHOD VALIDATION
METOPROLOL FUMARATE IN RIBOFLAVIN 5PO4 COATED TABS

MET FUM in 0.1 N HCl

Chromatogram of 42194



Peak Name	Ret time	Area	Height	Type	Response	Deviation	Intercept	Slope
UNKNOWN	2.44	304415	35870	BB	-	-	-	-
lopressor	6.02	743006	20859	BB	7.43006e+05	3.5713e+03	0.000e+00	3.920e+03

Figure 10

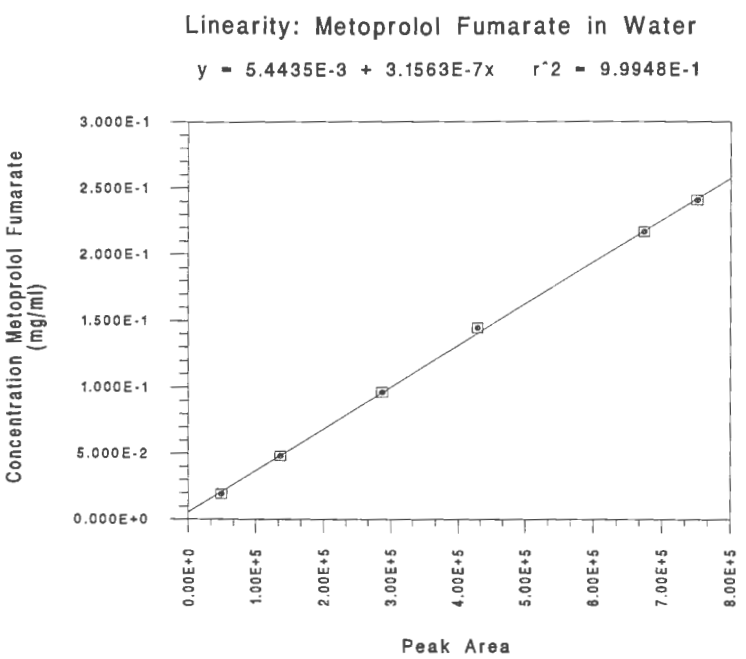

Linearity: Metoprolol Fumarate in Water
y = 5.4435E-3 + 3.1563E-7x r^2 = 9.9948E-1
Concentration Metoprolol Fumarate (mg/ml)
3.000E-1
2.500E-1
2.000E-1
1.500E-1
1.000E-1
5.000E-2
0.000E+0
0.00E+0
1.00E+5
2.00E+5
3.00E+5
4.00E+5
5.00E+5
6.00E+5
7.00E+5
8.00E+5
Peak Area

Figure 11

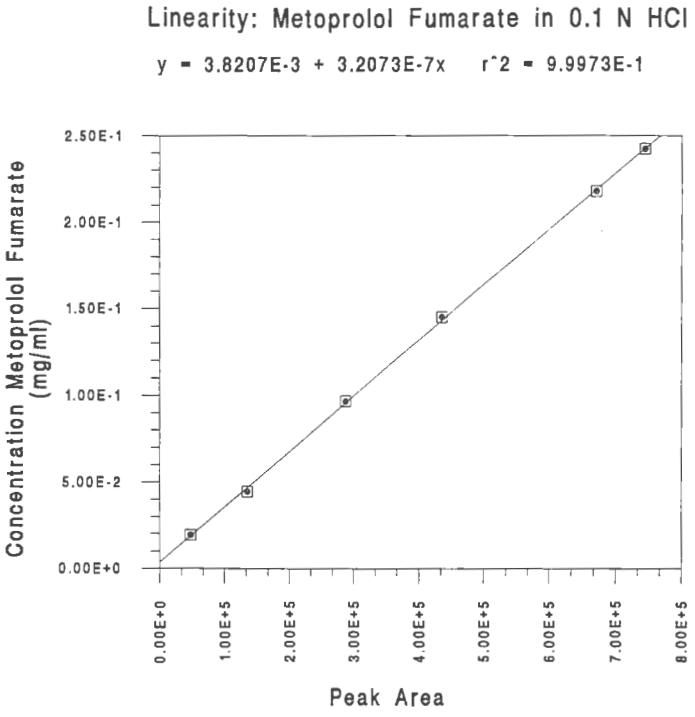

Linearity: Metoprolol Fumarate in 0.1 N HCl
y = 3.8207E-3 + 3.2073E-7x r^2 = 9.9973E-1
Concentration Metoprolol Fumarate (mg/ml)
2.50E-1
2.00E-1
1.50E-1
1.00E-1
5.00E-2
0.00E+0
0.00E+0
1.00E+5
2.00E+5
3.00E+5
4.00E+5
5.00E+5
6.00E+5
7.00E+5
8.00E+5
Peak Area

Figure 12

Precision: Metoprolol Fumarate Samples vs. Standard Curve in Water

Note: Three injections for each concentration

Metoprolol Concentration = 5.4435E-3 + 3.1563E-7*Peak Area
r^2 = 9.9948E-1

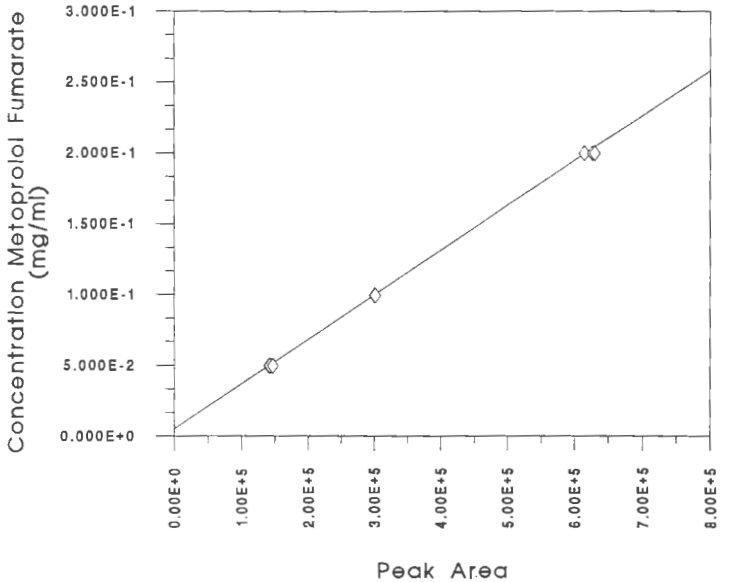
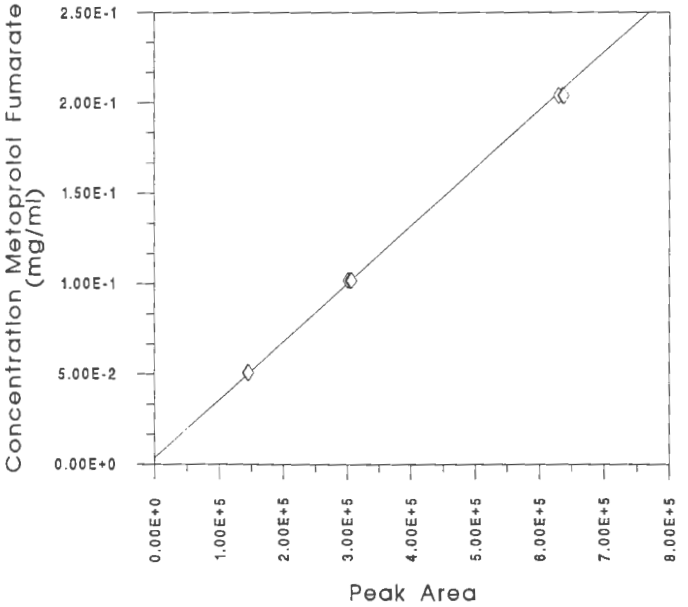


Figure 13

Precision: Metoprolol Fumarate Samples vs. Standard Curve in 0.1 N HCl

Note: Three injections for each concentration

Metoprolol Concentration = 3.8207E-3 + 3.2073E-7*Peak Area
r^2 = 9.9973E-1



CIBA-GEIGY, CORPORATION

Physical and Analytical Chemistry
(Reference Standard)

METOPROLOL FUMARATE
1-Isopropylamino-3-[p-(2-methoxyethyl)phenoxyl]-2-propanol (2:1)
Fumarate Salt

Reference Standard No.: S-2-92-24 (Reassay of S-2-87-20)

Source: Chemical Development, Summit

Sample Designation: CDF 2232 (Sample No. 83-695)

Amount Available: 299 grams

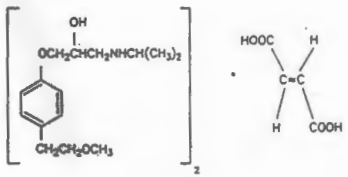
Date: May 27, 1992

Reassay Date: May, 1997

Recommended Storage Condition: Store in an amber glass bottle at room temperature.

Recommended Dispensing Instructions: Dispense approximately 5 grams per bottle.

Structure:



Molecular Weight: 650.79 Empirical Formula: $C_{34}H_{54}N_2O_{10}$

TESTS

1. Description:

Clean, white crystalline powder.

2. Spectroscopy:

Infrared Spectrum

The infrared spectrum, obtained as a nujol mull, is comparable to the previous metoprolol fumarate reference standard S-2-87-20. The following assignments are consistent with the structure of metoprolol fumarate.

Wavenumber (cm^{-1})	Assignments
1612	Aromatic ring, carboxylate ion
1517	Aromatic ring
1244	Aromatic ether
1195	Isopropyl group
1113	Aliphatic ether, secondary alcohol
1051	1-4 Disubstituted benzene
990	C=C
812	1-4 Disubstituted benzene

3. Chromatographic Impurities - Liquid Chromatography/Thin Layer Chromatography:

a. Thin-Layer Chromatography:

$CHCl_3$ [under NH_3 atmosphere], Silica Gel GF 254, 250 μm layer: At the 200 μg level. Total impurities detected less than 0.1%.

b. Liquid Chromatography:

LC % impurities = 0.1% (by percent area normalization)
LC + TLC total impurities = 0.2%

Column:	μBondapak C_{18} (Waters Associates, 30 cm x 3.9 mm ID)
Mobile Phase:	Acetonitrile/water (380 mL/1620 mL) containing 7.8 gm of ammonium acetate, 4.0 mL of triethylamine, 20 mL of glacial acetic acid, and 6.0 mL of phosphoric acid.
Detection:	Ultraviolet detector (275 nm)
Sensitivity:	0.01 AUFS
Flow Rate:	1 mL/minute
Temperature:	40°C

4. Loss on Drying - Dry at 60°C under vacuum for four hours:

0.02%

5. Assay - Nonaqueous titration ($HClO_4$):

99.5% (dried basis)

This material is suitable for use as a reference standard for Lopressor.

Reference: NB-132 RK #67/130

R. Katimy P.D.

RK:ap

Attachment 2

SYSTEM SUITABILITY DATA
Metoprolol Fumarate Assay
Acceptance Criteria: rsd > 2.0%

Run Date	11/3/93	11/12/93	11/16/93	11/17/94	5/4/94	5/6/94
Mg Eq. Standard	188.64	194.81	194.81	188.17	180.81	180.81
Injection #	Peak area	Peak area	Peak area	Peak area	Peak area	Peak area
1	633962	641233	696370	649744	617486	625682
2	628092	640588	708284	645780	619004	610162
3	629994	647129	713181	640102	616919	618400
4	627219	642045	707666	641716	619151	618656
5	623836	640102	727169	639494	623214	622584
6	627351	647397	721446	634094	622220	616304
Mean Peak Area	628409.00	643082.33	712352.67	641821.67	619665.67	618631.33
Standard Dev.	3079.40	3016.40	9973.82	4941.91	2313.48	4874.01
Rsd %	0.490	0.469	1.400	0.770	0.373	0.788
Run Date	5/8/94	5/10/94	5/13/94	5/16/94	5/17/94	5/20/94
Mg Eq. Standard	180.81	190.00	190.00	197.86	197.86	190.03
Injection #	Peak area	Peak area	Peak area	Peak area	Peak area	Peak area
1	649420	664148	669201	694088	697328	670669
2	628946	661572	663634	693349	698670	690437
3	643949	654365	662022	685917	701430	673783
4	634409	661266	662251	696255	701116	661335
5	629780	660908	661826	692735	692355	665846
6	663134	656475	661153	689348	705019	656580
Mean Peak Area	641606.33	659789.00	663347.83	691948.67	699319.67	669775.00
Standard Dev.	12123.87	3317.03	2721.38	3387.35	3938.23	10836.36
Rsd %	1.890	0.503	0.410	0.490	0.563	1.618

Appendix 2

Assay validation report for dextromethorphan HBr samples in water and in 0.1 N HCl

ASSAY VALIDATION:
DEXTROMETHORPHAN HBR TABLETS COATED WITH PHOTOCROSSLINKED HYDROXYETHYLCELLULOSE

1. SOURCE of STANDARD:

Dextromethorphan HBr, Lot # S-1-90-17, was prepared by the Chemical Development Department, Ciba - Geigy Pharmaceuticals, Summit, NJ and subsequently assayed and released for use as a reference standard by the Physical and Analytical Chemistry Department, Ciba - Geigy Pharmaceuticals, Suffern, NY (attachment 1).

2. ASSAY:

System:

Pump:	Shimadzu LC10AS
Injector:	Waters WISP 712D
Column:	Whatman Partisil 5 ODS - 3 (15 cm)
Detector:	Shimadzu SPD6AV, UV/VIS
Integrator:	Waters 840 Chromatographic Data Station

Parameters:

Flow Rate:	1.25 ml/min.
Injection Volume:	50 µL
Temperature:	Ambient
Detector:	λ 280 nm, 0.01 AUFS

Solutions:
Mobile Phase:
In a suitable flask combine 700 ml of acetonitrile, 300 ml of distilled water, 2.21 g docusate sodium and 400.3 mg ammonium nitrate. Mix well and degas under vacuum for 10 minutes. Adjust pH to 3.05 with acetic acid and filter through a 0.5 µ Millipore filter, or equivalent, before use. Discard after twenty four hours.

3. REPRESENTATIVE CHROMATOGRAMS:

The chromatograms presented in figures 1 through 9 represent the various components present in the final, coated dosage form. They are as follows:

Figure #	Description	Concentration (mg/ml)
1	Water Blank	n/a
2	Dextromethorphan HBr in Water	4.0×10^{-2}

3	Riboflavin 5' Phosphate in Water	4.038×10^{-4}
4	Dextromethorphan Tablet (Uncoated) Water	4.0×10^{-2} (drug)
5	Dextromethorphan Tablet (Coated)	4.0×10^{-2} (drug)
6	HCl Blank	0.1 N
7	Dextromethorphan HBr in HCl	4.01×10^{-2}
8	Riboflavin 5' Phosphate in HCl	4.038×10^{-4}
9	Dextromethorphan Tablet (Uncoated) HCl	4.0×10^{-2} (drug)

The retention time of Dextromethorphan HBr was approximately 5.1 minutes when assayed by this method.

4. LINEARITY:

The linearity of Dextromethorphan HBr in both distilled water and 0.1 N HCl was determined by simple linear regression ("Cricket Graph" graphing software, Computer Associates International, Inc. Islandia, NY). In each case, seven separate concentrations of Dextromethorphan HBr were used to generate the standard curve. Figure 10 depicts the standard curve, and linear regression of Dextromethorphan HBr in water while figure 11 depicts that of Dextromethorphan HBr in 0.1 N HCl.

The following concentrations were used for each linearity determination:

Solution #	Conc. in Water (mg/ml)	Conc. in 0.1 N HCl (mg/ml)
1	7.946×10^{-2}	8.012×10^{-2}
2	3.973×10^{-2}	4.006×10^{-2}
3	3.178×10^{-2}	3.205×10^{-2}
4	2.543×10^{-2}	2.564×10^{-2}
5	1.589×10^{-2}	1.602×10^{-2}
6	7.946×10^{-3}	8.012×10^{-3}
7	2.384×10^{-3}	2.404×10^{-3}

Suitable linearity was obtained in each case. Correllation coefficients for linearity determinations in water and 0.1 N HCl were 9.995×10^{-1} and 9.997×10^{-1}, respectively.

5. PRECISION:

Assay precision was determined by plotting the peak areas of triplicate injections of Dextromethorphan HBr samples of known concentration against the standard curves generated in the previous section. The mean % difference between the actual concentration of the samples and that determined by the standard curve did not exceed 4.4% (mean % differences: 2.11 for water and 1.62 for 0.1 N HCl) for any of the individual concentrations/injections tested (see below). Plots of each individual

injection vs. their corresponding standard curve are presented in figures 12 and 13.

Equation 1. Linearity of Dextromethorphan HBr in water:

Conc. Dextromethorphan HBr = $2.8207 \times 10^{-4} + 7.9307 \times 10^{-8}$ x PEAK AREA

Sample #	Conc. (actual) (mg/ml)	Conc. (by Eq. 1) (mg/ml)	% Difference (conc.actual vs. by eq. 1)
1a	2.861×10^{-2}	2.935×10^{-2}	2.59
1b	2.861×10^{-2}	2.987×10^{-2}	4.40
1c	2.861×10^{-2}	2.955×10^{-2}	3.29
2a	1.907×10^{-2}	1.951×10^{-2}	2.31
2b	1.907×10^{-2}	1.954×10^{-2}	2.46
2c	1.907×10^{-2}	1.928×10^{-2}	1.10
3a	4.768×10^{-3}	4.787×10^{-3}	0.40
3b	4.768×10^{-3}	4.837×10^{-3}	1.45
3c	4.768×10^{-3}	4.721×10^{-3}	0.98

Equation 2. Linearity of Dextromethorphan HBr in 0.1 N HCl:

Conc. Dextromethorphan HBr = $2.0129 \times 10^{-4} + 7.75535 \times 10^{-8}$ x PEAK AREA

Sample #	Conc. (actual) (mg/ml)	Conc. (by Eq. 1) (mg/ml)	% Difference (conc.actual vs. by eq. 1)
1a	2.884×10^{-2}	2.927×10^{-2}	1.49
1b	2.884×10^{-2}	2.960×10^{-2}	2.64
1c	2.884×10^{-2}	2.957×10^{-2}	2.53
2a	1.923×10^{-2}	1.957×10^{-2}	1.77
2b	1.923×10^{-2}	1.951×10^{-2}	1.46
2c	1.923×10^{-2}	1.935×10^{-2}	0.62
3a	3.205×10^{-3}	3.186×10^{-3}	0.59
3b	3.205×10^{-3}	3.295×10^{-3}	2.81
3c	3.205×10^{-3}	3.226×10^{-3}	0.65

6. SYSTEM SUITABILITY

System suitability tests were performed prior to each dissolution run according to the specifications set forth in USP XXII. In each case,the mean peak area and standard deviation of six replicate injections of a Dextromethorphan HBr standard solution were determined. Rejection was made if the peak area standard deviation was found to be in excess of 2.0 percent.

Historical system suitability data is presented in attachment 2.

Figure 1

Chromatogram of Distilled Water

VAILID 24-May-94 12:37:58

Printed on 24-May-94 at 15:19:34

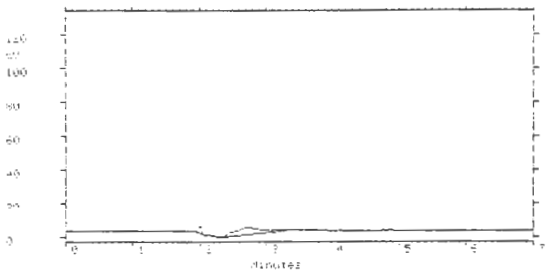
Acquisition method	DEXTRO	Quantitation method	DEXTRO
Units		System number	1
Channel	1	Vial	90
Injection	1	Total injections	1
Run time	7.00 min	Sample rate	1.00 per sec
Injection volume	50 uL	Mode	Calibration
Acquisition version	6.21	Quantitation version	6.21

UV/VIS

HPLC analysis PHOTOCOATED DEXTRO HBR TABS 20 MG
MEDIA: WATER

WATER BLANK

Chromatogram of VAILID



Peak Name	Ret time	Area	Height	Type	Response	Deviation	Intercept	Slope
DEXTROMETHORPHAN	5.15	-	-	MF	-	-	-	-

Figure 2

Chromatogram of Dextromethorphan HBr in Distilled Water

VAILID 24-May-94 12:47:07

Printed on 24-May-94 at 15:22:05

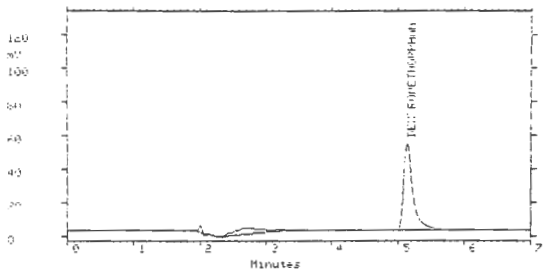
Acquisition method	DEXTRO	Quantitation method	DEXTRO
Units		System number	1
Channel	1	Vial	91
Injection	1	Total injections	1
Run time	7.00 min	Sample rate	1.00 per sec
Injection volume	50 uL	Mode	Calibration
Acquisition version	6.21	Quantitation version	6.21

UV/VIS

HPLC analysis PHOTOCOATED DEXTRO HBR TABS 20 MG
MEDIA: WATER

DEXTRO in WATER

Chromatogram of VAILID



Peak Name	Ret time	Area	Height	Type	Response	Deviation	Intercept	Slope
DEXTROMETHORPHAN	5.14	511667	52020	BB	5.11667e+05	3.1702e+05	0.000e+00	2.099e+04

Figure 3

Chromatogram of Riboflavin 5' Phosphate in Distilled Water

VALID 25-May-94 8:05:30

Printed on 25-May-94 at 8:15:03

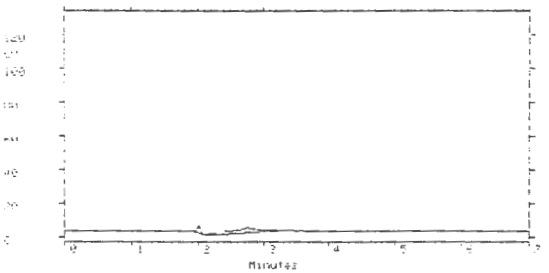
Acquisition method	DEXTRO	Quantitation method	DEXTRO
Units		System number	1
Channel	1	Vial	65
Injection	1	Total injections	1
Run time	7.00 min	Sample rate	1.00 per sec
Injection volume	50 uL	Mode	Calibration
Acquisition version	6.21	Quantitation version	6.21

UV/VIS

HPLC analysis PHOTOCOATED DEXTRO NBR TABS 20 MG

RIBOFLAVIN IN WATER 4.0 E-4 MG/ML

Chromatogram of VALID



Peak Name	Ret time	Area	Height	Type	Response	Deviation	Intercept	Slope
DEXTROMETHORPHAN	5.15	-	-	MF	-	-	-	-

Figure 4

Chromatogram of Dextromethorphan HBr Tablet (uncoated) in Distilled Water

VAILID 24-May-94 12:55:59

Printed on 24-May-94 at 15:24:48

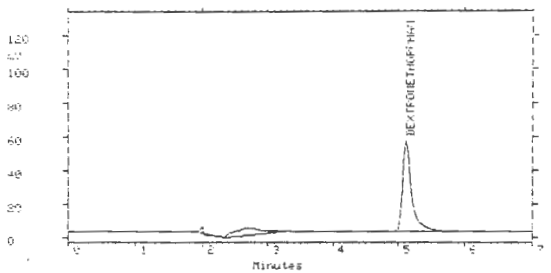
Acquisition method	DEXTRO	Quantitation method	DEXTRO
Units		System number	1
Channel	1	Vial	92
Injection	1	Total injections	1
Run time	7.00 min	Sample rate	1.00 per sec
Injection volume	50 uL	Mode	Calibration
Acquisition version	6.21	Quantitation version	6.21

UV/VIS

HPLC analysis PHOTOCOATED DEXTRO HBR TABS 20 MG
MEDIA: WATER

TAB in WATER

Chromatogram of VAILID



Peak Name	Ret time	Area	Height	Type	Response	Deviation	Intercept	Slope
DEXTROMETHORPHAN	5.12	524680	53586	BB	5.24680e+05	3.1152e+05	0.000e+00	2.119e+04

Figure 5

Chromatogram of Dextromethorphan HBr Tablet (coated) in Distilled Water

SYSSUIT 26-May-94 17:59:36

Printed on 26-May-94 at 18:09:02

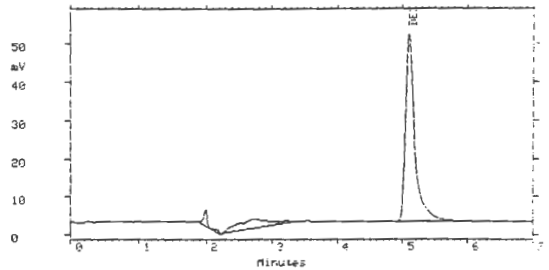
Acquisition method	DEXTRO	Quantitation method	DEXTRO
Units		System number	1
Channel	1	Vial	61
Injection	1	Total injections	1
Run time	7.00 min	Sample rate	1.00 per sec
Injection volume	50 uL	Mode	Calibration
Acquisition version	6.21	Quantitation version	6.21

UV/VIS

HPLC analysis PHOTOCOATED DEXTRO HBR TABS 20 MG
DISSOLUTION OF CORES AND COATED, UNTREATED TABS 3 EACH
MEDIA: WATER

6 HR

Chromatogram of SYSSUIT



Peak Name	Ret time	Area	Height	Type	Response	Deviation	Intercept	Slope
DEXTROMETHORPHAN	5.10	485486	49277	BB	4.85486e+05	2.2635e+05	0.000e+00	1.918e+04

Figure 6

Chromatogram of 0.1 N HCl

VAILID 24-May-94 13:04:55

Printed on 24-May-94 at 15:27:46

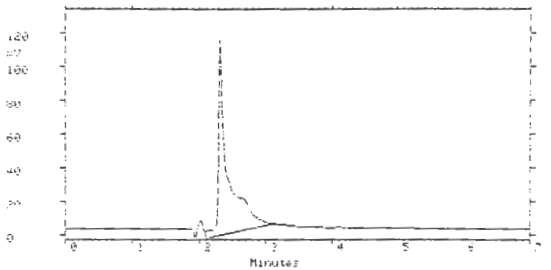
Acquisition method	DEXTRO	Quantitation method	DEXTRO
Units		System number	1
Channel	1	Vial	93
Injection	1	Total injections	1
Run time	7.00 min	Sample rate	1.00 per sec
Injection volume	50 uL	Mode	Calibration
Acquisition version	6.21	Quantitation version	6.21

UV/VIS

HPLC analysis PHOTOCOATED DEXTRO HBR TABS 20 MG

0.1 N HCL

Chromatogram of VAILID



Peak Name	Ret time	Area	Height	Type	Response	Deviation	Intercept	Slope
DEXTROMETHORPHAN	5.15	-	-	BF	-	-	-	-

Figure 7

Chromatogram of Dextromethorphan HBr in 0.1 N HCl

LINEARITY 24-May-94 14:05:30

Printed on 24-May-94 at 14:14:53

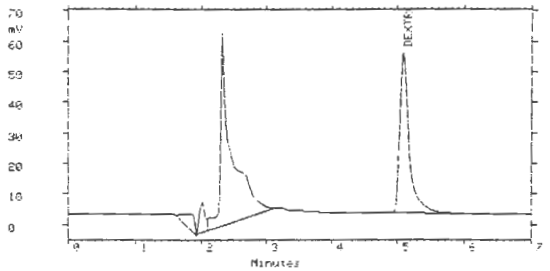
Acquisition method	DEXTRO	Quantitation method	DEXTRO
Units		System number	1
Channel	1	Vial	2
Injection	1	Total injections	1
Run time	7.00 min	Sample rate	1.00 per sec
Injection volume	50 uL	Mode	Calibration
Acquisition version	6.21	Quantitation version	6.21

UV/VIS

HPLC analysis PHOTOCOATED DEXTRO HBR TABS 20 MG
MEDIA: 0.1 N HCL

LINEARITY 2 4.006 E-2

Chromatogram of LINEARITY



Peak Name	Ret Time	Area	Height	Type	Response	Deviation	Intercept	Slope
DEXTROMETHORPHAN	5.09	517589	52584	BB	5.17589e+05	3.3636e+05	0.000e+00	2.334e+04

Figure 8

Chromatogram of Riboflavin 5' Phosphate 0.1 N HCl

VALID 25-May-94 8:14:42

Printed on 25-May-94 at 8:23:39

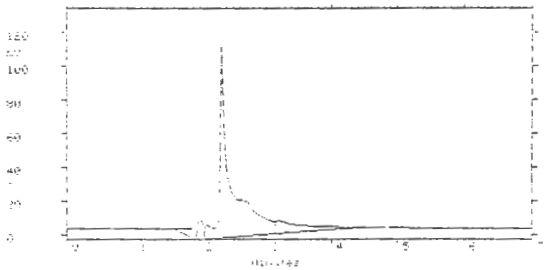
Acquisition method	DEXTRO	Quantitation method	DEXTRO
Units		System number	1
Channel	1	Vial	86
Injection	1	Total injections	1
Run time	7.00 min	Sample rate	1.00 per sec
Injection volume	50 uL	Mode	Calibration
Acquisition version	6.21	Quantitation version	6.21

UV/VIS

HPLC analysis PHOTOCOATED DEXTRO HBR TABS 20 MG
MEDIA: 0.1 N HCL

RIBOFLAVIN IN 0.1 N HCL 4.0 E-4 MG/ML

Chromatogram of VALID



Peak Name	Ret time	Area	Height	Type	Response	Deviation	Intercept	Slope
DEXTROMETHORPHAN	5.15	-	-	NF	-	-	-	-

Figure 9

Chromatogram of Dextromethorphan HBr Tablet (uncoated) in 0.1 N HCl

VAILID 24-May-94 13:13:48

Printed on 24-May-94 at 15:30:18

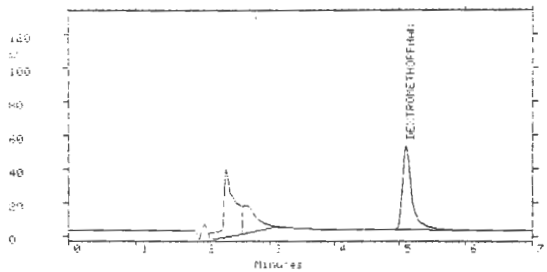
Acquisition method	DEXTRO	Quantitation method	DEXTRO
Units		System number	1
Channel	1	Vial	94
Injection	1	Total injections	1
Run time	7.00 min	Sample rate	1.00 per sec
Injection volume	50 uL	Mode	Calibration
Acquisition version	6.21	Quantitation version	6.21

UV/VIS

HPLC analysis PHOTOCOATED DEXTRO HBR TABS 20 MG
MEDIA: WATER

TAB in HCL

Chromatogram of VAILID



Peak Name	Ret time	Area	Height	Type	Response	Deviation	Intercept	Slope
DEXTROMETHORPHAN	5.10	490167	49938	BB	4.90167e+05	3.0595e+05	0.000e+00	2.131e+04

Figure 10

Linearity: Dextromethorphan HBr in Water

y= 2.8207E-4 + 7.9307E-8x r^2 = 9.9946E-1

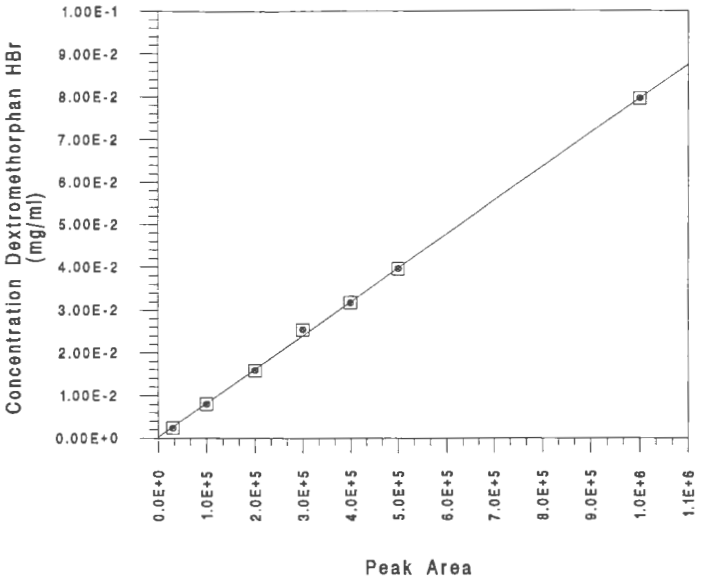


Figure 11

Linearity: Dextromethorphan HBr in 0.1 N HCl

y = 2.0129E-4 + 7.7535E-8x r^2 = 9.9986E-1

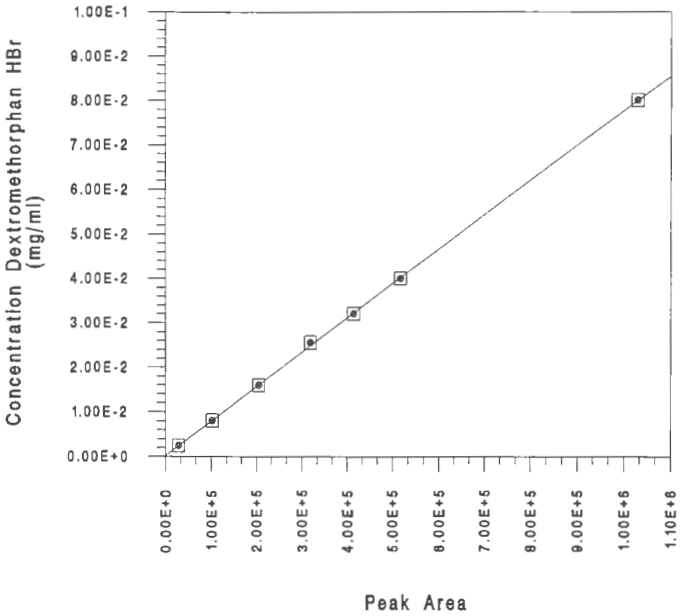


Figure 12

Precision: Dextromethorphan HBr Samples vs. Standard Curve in Water

Note: Three injections at each concentration

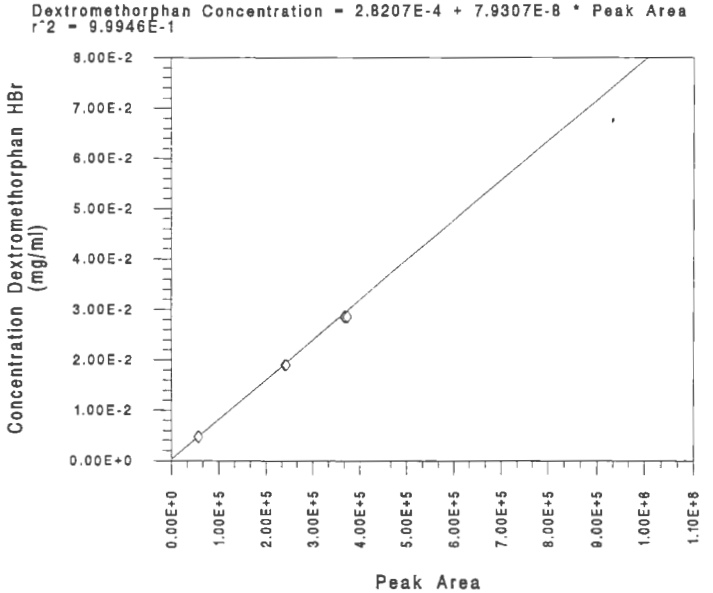
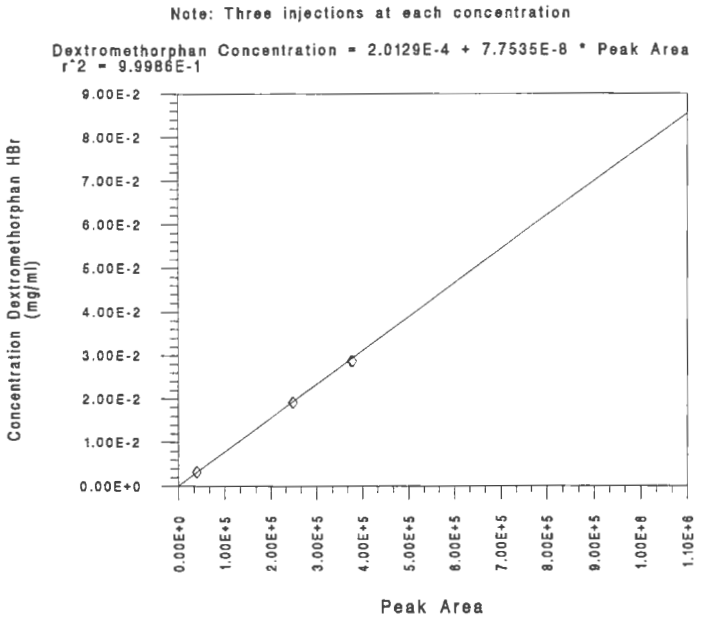


Figure 13

Precision: Dextromethorphan HBr Samples vs. Standard Curve in 0.1 N HCl



Attachment 1

CIBA-GEIGY CORPORATION

Physical and Analytical Chemistry
(Reference Standard)

Dextromethorphan Hydrobromide

Reference Standard No.: S-1-90-17 (Reassay of S-1-85-21)

Source: Chemical Development, Summit

Sample Designation: Batch No. NA-1-97

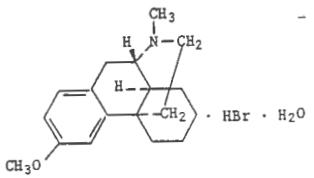
Amount Available: 971 g

Date: June 1, 1990

Reassay Date: June, 1995

Recommended Storage Conditions: Store in a tight, light-resistant container

Structure:



Molecular Weight: 370.33 Empirical Formula: $C_{18}H_{25}NO \cdot HBr \cdot H_2O$

TESTS

1. Description:

White crystalline powder.

2. Infrared Spectroscopy:

The spectrum is consistent with the structure indicated.

Wavenumber (cm^{-1})	Assignments
3283	C-H stretching
2926,2857	$-CH_2$ bending
1616	H-O stretching
1576,1498	C=C stretching, aromatic ring
1463	$-CH_3$ bending
1281,1170	C-N stretching, tertiary amine
1244,1071,1042	$-OCH_3$ stretching
867,775,727,693	C-C out-of-plane bending, aromatic ring

3. Liquid Chromatography:

Column:	μBondapak C_{18} (Waters) 30 cm x 3.9 mm ID, or equivalent
Mobile Phase:	Dissolve 3.1 g of docusate sodium in 1000 mL of acetonitrile/water (70:30), add 560.4 mg of ammonium nitrate, adjust the pH to 3.4 with acetic acid, mix and filter the solution through a 0.45 μm Millipore FH filter (or equivalent). Degas the mobile phase before use.
Detector:	UV - 280 nm
Flow Rate:	1 mL/minute
Sensitivity:	0.1 AUFS
Temperature:	Ambient
Assay:	99.6%, anhydrous basis (external standard method)

4. Identification:

4.1 Infrared Absorption:
Conforms to previous reference standard.

4.2 Ultraviolet Absorption:
Conforms to previous reference standard.
Absorptivity of sample vs. USP reference standard = 0.78% (anhydrous basis)

4.3 Bromide:
Positive

5. pH (1 in 100):

5.5

6. Water Content:

4.72%

This sample is suitable for use as a reference standard in testing of Dextromethorphan Hydrobromide.

Reference: MB #94/52

M. Bordun

MB:ap

Attachment 2

SYSTEM SUITABILITY DATA
Dextromethorphan HBr Assay
Acceptance Criteria: rsd > 2.0%

Run Date	5/26/94	5/27/94	5/31/94	6/1/94	6/2/94	6/7/94
Mg Eq. Standard	20.67	20.67	20.88	20.68	20.68	19.86
Injection #	Peak area	Peak area	Peak area	Peak area	Peak area	Peak area
1	537812	535713	541428	529917	541938	438031
2	538292	536078	544172	531170	542156	437841
3	538087	530820	540179	533341	539409	437693
4	537131	518856	542329	534753	540720	435689
5	533114	521248	539765	536848	539939	435679
6	529696	518993	544293	530106	543389	435608
Mean Peak Area	535688.67	526951.33	542027.67	532689.17	541258.50	436756.83
Standard Dev.	3205.70	7488.07	1766.24	2537.90	1369.79	1102.81
Rsd %	0.598	1.421	0.326	0.476	0.253	0.252

Run Date	6/10/94	6/12/94	6/14/94
Mg Eq. Standard	19.86	19.57	19.57
Injection #	Peak area	Peak area	Peak area
1	519894	519673	513199
2	523396	520254	515779
3	524883	516610	516325
4	527527	521182	512937
5	519913	522027	516220
6	505843	519322	518435
Mean Peak Area	520242.67	519844.67	515482.50
Standard Dev.	6977.56	1707.06	1904.07
Rsd %	1.341	0.328	0.369

Appendix 3

United States Patent Application entitled: "Radiation Cured Drug Release Controlling Membrane" and documents concerning its receipt by U.S. Patent Office.

CGC 1740

RADIATION CURED DRUG RELEASE CONTROLLING MEMBRANE

Inventor: Gary Van Savage, residing at 10 Flanders Way, Bridgewater, New Jersey 08807, a citizen of the United States of America; and James Merl Clevenger, residing at 432 Little Brook Road, Glen Gardner, New Jersey 08826, a citizen of the United States of America.

Prepared by: Karen G. Kaiser, Esq.
Patent Department
Ciba - Geigy Corp.

Background of the Invention

This invention relates to cross-linked hydrophilic polymeric films, the process of making such films, and their use in applications where strength of the polymer article and high permeability to water are required simultaneously. In particular, these films are suitable for use as a carrier for biologically active agents, such as pharmaceuticals, both human and veterinary, insecticides, and fertilizers; as hydrophilic membranes for separation processes; as bandages for wound treatment; as body implants or as coatings for such implants; and as coatings on glass, metal, wood or ceramics.

Such films, particularly when used as biological carriers, should not only be able to entrap the biological agent, but should also be biocompatible; that is, both mild and non-cytotoxic to living organisms. Additionally, they should be chemically and mechanically stable.

Cross-linked polymeric films have been made. For example, U.S. Patent Nos. 2,976,576 and 3,220,960 disclose cross-linked hydrophilic polymers which are produced by polymerizing a hydrophilic monomer in the presence of a cross-linking agent; U.S. Patent No. 3,520,94 discloses hydrophilic cross-linked polymers which are produced by admixing a water-soluble polymerizable hydroxyalkyl monoester of a mono-olefinic monocarboxylic acid and a polymerizable diester of a mono-olefinic monocarboxylic acid in the presence of a linear polyamide; and U.S. Patent Nos. 4,192,827 and 4,277,582 disclose cross-linked polymers which are produced from a polymer of mono-olefinic monomers or copolymers of mono-olefinic monomers which is cross-linked with

a terminal diolefinic hydrophobic macromer. However, the use of monomers is disadvantageous in the pharmaceutical industry due to the potential cytotoxicity of unreacted monomers.

Other cross-linked polymeric films have been made from polymers, thereby overcoming the problem of unreacted monomers. For example, WO 93/09176 discloses cross-linking of polysaccharides, polycations and lipids with polymerizable acrylate in the presence of a radical initiator by using certain sources of energy; U.S. Patent No. 3,077,468 discloses the method of cross-linking water-soluble hydroxyalkyl polysaccharide ethers by reacting them with an insolubilizing agent selected from unsaturated dibasic aliphatic acids and their anhydrides and the water-soluble derivatives of said acids and their anhydrides; and U.S. Patent No. 3,272,640 discloses cross-linking water-soluble polymers by reacting them with a hydrophobic film former.

Summary of the Invention

It is accordingly an object to the present invention to provide cross-linked, hydrophilic polymeric films which are suitable for use as a carrier for biologically active agents, such as pharmaceuticals, both human and veterinary, insecticides, and fertilizers; as hydrophilic membranes for separation processes; as bandages for wound treatment; as body implants or as coatings for such implants; and as coatings on glass, metal, wood or ceramics.

It is another object of this invention to provide such a film which is essentially insoluble in aqueous and non-aqueous solutions.

It is yet another object of this invention to provide a cross-linked hydrophilic polymeric film which can be prepared without the use of organic solvents.

It is still another object of this invention to provide a cross-linked hydrophilic polymeric film which is safe for in vivo usage.

These, and other objects apparent to those skilled in the art from the following detailed description, are accomplished by the present invention which pertains to cross-linked hydrophilic polymeric films, the process of making such films, and their use. These films are produced by the application of an aqueous solution of a water-soluble polymer and a photosensitive or light degradable catalyst to a suitable substrate, optionally drying said solution, and exposing the resultant film to a suitably interacting energy source.

Detailed Description of the Invention

This invention pertains to cross-linked hydrophilic polymeric films, the process of making such films, and their use. These films are produced by the application of an aqueous solution of a water-soluble polymer and a photosensitive or light degradable catalyst to a suitable substrate, optionally drying said solution, and exposing the resultant film to a suitably interacting energy source.

Appropriate polymers are those which are water-soluble and possess a structure which, in the presence of a suitable catalyst or cross-linking agent, may bond to additional molecules, thus yielding a macromolecule of said polymer which, due to its increased molecular weight, is no longer readily soluble in an aqueous medium. These polymers include, but are not limited to, water-soluble polyvinyl

alcohols, poly(hydroxyethyl methacrylates), and polysaccharides, particularly hydroxyalkyl polysaccharide ethers, more particularly cellulose ethers such as hydroxyethyl cellulose and hydroxypropyl methylcellulose. Polymers which have low viscosities are preferred; those which have viscosities which approach that of water are most preferred.

The amount of polymer used is that which can be solubilized in water and still remains free-flowing. A solution with a viscosity near that of water is preferred. Particularly, from about 1.0 to about 30% (w/w), more particularly from about 1.0 to about 6.0% (w/w) of the polymer is used.

Appropriate catalysts include those which are photosensitive or light degradable, such as azo dyes and riboflavin. The catalysts include, but are not limited to, riboflavin and its derivatives, Congo red, Evans blue, chlorazodin, erythrosine (FD&C Red #3), FD&C Red #40, tartrazine (FD&C Yellow #5), fast green FCF (FD&C Green #3), sunset yellow FCF (FD&C Yellow #6), brilliant blue FCF (FD&C Blue #1), and indigotine (FD&C Blue #2). In particular, the catalyst is a flavin. More particularly, the catalyst is riboflavin or a riboflavin derivative, preferably water soluble riboflavin derivatives, including, but not limited to, riboflavin-5'-phosphate or a salt thereof, riboflavin-5'-adenosine diphosphate, 6-hydroxyriboflavin, 8-nor-8-hydroxyriboflavin, roseoflavin, 5-deazariboflavin, 8a-(N1-histidyl)flavin, 8a-(N3-histidyl)flavin, 8a-S-cysteinylflavin, 6-S-cysteinylflavin, lumiflavin, and lumichrome. Most particularly the catalyst is riboflavin-5'-phosphate sodium.

Typically 0.1 to 10% (w/w), more particularly from about 1.0 to about 4% (w/w) of the catalyst is used, based on the total weight of the solids (polymer plus

catalyst) in solution. Before forming the film, the solution of polymer plus catalyst may be deaerated so as to decrease the amount of air trapped within the final product. Deaeration may be accomplished by allowing the solution to stand, particularly in a darkened, refrigerated room, ie. overnight, or by conventional methods known in the art. Although it is not necessary, deaeration generally improves the quality of the resultant film.

To form the film, the polymer is applied to a substrate. If the film is to be formed separately, as opposed to being coated onto an object, the substrate should be a smooth, non-reactive surface, ie. glass. Application may be by any conventional method known in the art.

The film is preferably allowed to dry before exposure to the energy source. Although this will occur at ambient temperatures, heat and or vacuum may be applied to decrease drying time. The film is preferably allowed to dry to a water content of no more than 30%, more narrowly to one of no more than 10%. However, as the film is hydrophilic, it is common for it to pick up water, thus rehydrating to some extent.

The energy source used to cure the polymer may be any type of electromagnetic radiation, such as actinic light, x-rays, or gamma radiation. Light sources, particularly those within the ultraviolet or visible range, are preferred, particularly those with wavelengths of from approximately 200 to approximately 800 nanometers, more particularly those with wavelengths of from approximately 300 to approximately 700 nanometers. When the polymer is to be used as a carrier for a biologically active agent, particularly pharmaceuticals, it has been found that light within the visible range is most preferred because of the potential for

degradation of the active agent outside of this range. The wavelength most suited to use in any particular curing will depend upon the catalyst chosen.

The film should be exposed to the energy source for such time as is necessary to achieve the desired amount of cross-linking of the polymer, particularly for such time as is necessary to ensure that the film is no longer freely soluble in an aqueous medium. The exposure time is dependent upon the intensity and type of energy source used as well as the type of polymer and thickness of the film. Sufficient exposure is generally indicated by a change in film color due to the catalyst. For example, the film turns from a bright yellow to a yellow-brown color when riboflavin or a derivative thereof is used as the catalyst.

Surprisingly, the instant reaction will occur in the presence of oxygen unlike many others in which free radical scavenging inhibits the reaction. In addition, when the energy source used is light, the reaction is substantially temperature independent within the range of 0-100°C though ambient conditions are considered to be best. The reaction may proceed without organic solvents. Whenever organic solvents are used in a pharmaceutical process, measures need to be taken to protect the operators who produce the dosage forms and the environment from overexposure to the hazardous, often teratogenic and carcinogenic, materials. Additional precautions are necessary to protect equipment and facilities from harm. Further, despite all precautions, it is still likely for detectable levels of residual solvent to remain in the finished dosage form. Not only is the instant process advantageously safer, but the resultant film is safer in that it does not contain residual organic solvents. Thus, the present reaction, which may proceed without organic solvents, is advantageous, especially in the pharmaceutical industry.

Another safety advantage in the pharmaceutical industry is that since polymeric, not monomeric, materials are used, the cytotoxic potential of unreacted monomers is eliminated. Further, the film may be made with ingredients which are "generally regarded as safe" (GRAS) by the Food and Drug Administration.

The cured polymer may be applied using any conventional coating technique including, but not limited to, spray coating, dip coating, and fluidized bed coating. The resultant film is substantially water insoluble and hydrophilic. Further, it tends to be insoluble in both acidic and alkaline solutions. The film is not appreciably elastic, but is flexible and continuous.

The possible film thickness is dependent upon the light penetration. If thicker films are desired, however, multiple layers may be applied successively, each layer being cured before the next layer is deposited. This is especially useful in coating processes, for example coating of a pharmaceutical dosage form.

The resultant film can be used, inter alia, as a carrier for biologically active agents, particularly pharmaceutically active agents. The term "pharmaceutically active agent," as used herein, refers to any composition of matter which will produce a pharmacological or biological response, including pharmaceuticals which are used to treat the body topically as well as systemically. Suitable mixtures of such active agents can be dispensed with equal facility as with single component systems. Furthermore, derivatives of these pharmaceutically active agents, eg. ethers, esters, amides, etc., which are easily hydrolyzed within the body can be employed as can various forms of the active agents, eg. salts, acids, complexes, etc.

Pharmaceutically active agents useful in the present invention include, but are not limited to, proteins and peptides, antiasthmatics, antianginals, corticosteroids, 5-lipoxygenase inhibitors, antihypertensives, and leukotriene B4 receptor antagonists. Proteins and peptides include, but are not limited to, transforming growth factors (TGF), immunoglobulin E (IgE) binding factors, interleukins, interferons (IFN), insulin-like growth factors (IGF), milk growth factors, anticoagulants, anabolics, analgesics, androgens, antibiotics, androgens, antidepressants, antidiabetics, anticonvulsants, antihistamines, antihypertensives, antiinfectives, antiparasistics, antiparkinson agents, antiphlogistics, antitussives, appetite depressants, bronchodilators, coronary dilators, corticoids, cytostatics, diuretics, hypnotics, neuroleptics, psycho-analeptics, tranquilizers, uricosurics, vasodilators, and parathyroid hormones (PTH). Specific active agents include, but are not limited to IGF-I, PTH (1-34) and analogues thereof, TGF_{α},$TGF_{\beta 1}$, $TGF_{\beta 2}$,$TGF_{\beta 3}$, IFN_{α}, hybrid IFN_{α}, IFN_{γ}, hirudin, heparin, calcitonin, 5-aminosalicylic acid, CGS 23885, CGS 25019C, CGS 26529, Zileuton, ONO-LB 457, beclomethasone dipropionate, betamethasone-17-valerate, prednisolone metasulfobenzoate, tixocortol pivalate, budesonide, fluticasone, metoprolol fumarate, metoprolol tartrate, tetrahydroaminoacridine (THA), galanthamine, theophylline, ursodiol, clomipramine hydrochloride, terbutaline sulfate, aminoglutethimide, deferoxamine mesylate, estradiol, isoniazid, metyrapone, methandrostenolone, acetylsalicylic acid, phenylbutazone, methadone, methyltestosterone, imipramine, maprotiline, phenformin, carbamazepine, tripelennamine, hydralazine, trimethoprim, nifurtimox, levodopa, naproxen, benzonatate, mazindol, fenoterol, fenalcomine, dexamethasone, floxuridine, hydrochlorothizide, glutethimide, reserpine, methylphenidate, diazepam,

sulfinpyrazone, isoproterenol, and rifampin.

As used herein, the active agents CGS 23885, 25019C, CGS 26529, Zileuton, ONO-LB 457 are defined as follows: CGS 23885 refers to N-hydroxy-N-((6-phenoxy-2H-1-benzopyran-3-yl)methyl)- urea; CGS 25019C refers to 4-[5-[4-(aminoiminomethyl)phenoxy] pentoxy]-3-methoxy-N,N-bis(1-methylethyl)benzamide (Z)-2-butenedioate; CGS 26529 refers to N-[2-[[2-[[4-(4-fluorophenyl)phenyl]methyl]-1,2,3,4-tetrahydro- 1-oxo-6-isoquinolinyl]oxy]ethyl]-N-hydroxyurea; Zileuton refers to 1-(1-benzo[b]thien-2-ylethyl)-1-hydroxyurea; ONO-LB 457 refers to 5-[2-(2-carboxyethyl)-3-{6-(para-methoxyphenyl)-5E-hexenyl} oxyphenoxy] valeric acid.

Incorporation of the biologically active agent into the polymeric film may be accomplished by dissolution or dispersion into the polymer solution prior to curing or by diffusion into the finished article after cross-linking has occurred. In the alternative, the polymeric film can be hydrated in a solution of the active agent to be delivered and the solvent is then evaporated, leaving the agent within the film.

The biologically active agent may also be incorporated by techniques known in the art, for example microcapsules could be formulated by air-jet droplet generation, co-axial extrusion, or by emulsification. Incorporation may also be accomplished by coating the agent, either alone or admixed with acceptable excipients, using coating techniques known in the art, for example spray-coating or fluidized bed coating.

A pharmaceutical dosage form, such as a tablet or capsule, may alternatively be

coated by admixing the polymer and catalyst, compression coating said mixture onto the pharmaceutical dosage form, and then exposing the compression coated form to the energy source. In this manner, the film is formed without any solvents. Techniques known in the art may be used to optimize this process; for example, the polymer/catalyst mixture may be ground to an appropriate particle size or acceptable tabletting agents may be added to the mixture.

The amount of the biologically active agent incorporated within the film may vary widely depending upon the particular agent, the desired therapeutic effect, and the time span of release.

As a carrier, the film may be used as a semi-permeable membrane for controlled release delivery systems. The film may be used to coat products for controlled sustained release of their contents as is or the coated product may be further outfitted with an orifice for release of active agent. In this latter embodiment, the coated product functions in a manner similar to those utilizing the oral osmotic technology known under the Alza tradename OROS/. This product permits passage of water and certain dissolved materials, but retains others, thus allowing active agent to be emitted at a controlled rate. The films of this invention however differ from the typical semipermeable membrane used in an OROS-type system in that a release orifice is optional, not necessary.

An additional advantage is that these polymeric films are easily removable before cross-linking as the polymer will readily form a viscous gel upon exposure to humidified environments. The gel-like film can then be easily removed by mechanical intervention. This is especially important in the field of pharmaceuticals as the film can be separated from the active agent after the

delivery device has been made. This separation allows for recovery of expensive pharmaceutical active agents.

Examples

Example 1 -

2% (w/w) Hydroxyethylcellulose with a viscosity averaged molecular weight of 720,000 and 0.031% (w/w based on total solids) riboflavin-5'-phosphate are dissolved in distilled water. The resultant solution is allowed to deaerate in a dark refrigerator overnight. The deaerated solution is poured onto a glass plate and spread to a thickness of 12 mils (0.305 mm) and subsequently dried in a conventional oven at 50°C to a moisture content of less than 10%. The film is then exposed to a visible light source rated at 600 footcandles (Hotpack environmental cabinet) for twenty-four hours. The resultant film is greater than 90% insoluble in water at ambient conditions.

Example 2 -

Three grams of hydroxyethylcellulose with a viscosity averaged molecular weight of 90,000 and a degree of substitution of 2.5 (ie. Natrosol 250L) and 60 mg of FD&C Blue #2 are dissolved in 100 ml of distilled water. The resultant solution is poured onto glass plates and spread to a thickness of 12 mils (0.305 mm) and subsequently dried in a conventional oven at 50°C to a moisture content of less than 10%. The film is then exposed to a high intensity ultraviolet lightsource (Mercury "H" bulb, 600 Watts/inch) for approximately 30 seconds. The resultant film is crosslinked and is insoluble, but swellable in water.

Example 3 -

The process of Example 2 is repeated with the exception that the catalyst used is riboflavin-5'-phosphate.

Example 4 -

2% (w/w) Hydroxyethylcellulose with a viscosity averaged molecular weight of 720,000 and a degree of substitution of 2.5 (grade M) and 2% (w/w based on total solids) riboflavin-5'-phosphate are dissolved in distilled water using a homogenizer. The resultant solution is deaerated overnight in a dark refrigerator. The deaerated solution is poured onto a glass plate which had been preheated to 60°C and spread to a wet thickness of 0.040 inches (approximately 1.0 mm). The film is subsequently dried in a conventional oven at 60°C overnight. The film is then exposed to a high intensity ultraviolet lightsource (Mercury "H" bulb, 600 Watts/inch) for 30 seconds. The resultant film is approximately 75% insoluble in water at ambient conditions.

Example 5 -

The process of Example 4 is repeated with the exception that the energy source used is visible light rated at 600 footcandles (Hotpack environmental cabinet) and exposure is for twenty-four hours. The resultant film is in excess of 80% insoluble in water at ambient conditions.

Example 6 -

1.5% (w/w) Hydroxyethylcellulose which has a viscosity averaged molecular weight of 720,000 and a degree of substitution of 2.5 (Natrosol 250M) and 0.031% (w/w) riboflavin-5'-phosphate are dissolved in distilled water using a conventional mixer. The solution is deaerated overnight in a darkened refrigerator.

10.5 Kg of this solution is used to coat 1.25 Kg of 75 mg tablets containing dextromethorphan using conventional spraying in a pharmaceutical coating pan. The resultant coated tablets each contain 6.1 mg coating.

Example 7 -

The process of Example 6 is repeated except that the coated tablets are then exposed to ultraviolet light (Mercury "H" bulb, 600 Watts/inch) on all sides for approximately 60 seconds.

Example 8 -

A standard USP dissolution test in water USP is used to compare the coated tablets of Examples 6 and 7. Exposure of the coated tablets to ultraviolet light significantly decreased the dissolution rate. Eighty percent release occurred at 30 minutes for the tablets of Example 6, but did not occur until 150 minutes for the tablets of Example 7, a five-fold difference.

Example 9 -

The process of Example 7 is repeated except that the coating weight of each tablet is 7.9 mg and the energy source is visible light rated at 600 footcandles (Hotpack environmental cabinet) with exposure for 7 days.

Example 10 -

The process of Example 9 is repeated except that each tablet is pierced with a single hole measuring 0.025 inches (approximately 0.635 mm) in diameter to form a release orifice.

Example 11 -

A standard USP dissolution test in water USP is used to compare the coated tablets of Examples 9 and 10. Eighty percent release occurred at 3 hours for the tablets of Example 9, but did not occur until 4.1 hours for the tablets of Example 10.

Example 12 -

1.5% (w/w) Hydroxyethylcellulose which has a viscosity averaged molecular weight of 720,000 and a degree of substitution of 2.5 (Natrosol 250M) and 0.031% (w/w) riboflavin-5'-phosphate are dissolved in distilled water using a conventional mixer. The solution is deaerated overnight in a darkened refrigerator. 10.5 Kg of this solution is used to coat 1.25 Kg of 215 mg tablets containing metoprolol fumarate using conventional spraying in a pharmaceutical coating pan. The resultant coated tablets each contain 18 mg coating.

Example 13 -

The process of Example 12 is repeated except the coated tablets were exposed to 600 foot-candles of visible light for 6 days.

Example 14 -

A standard USP dissolution test in water USP is used to compare the coated tablets of Examples 12 and 13. Eighty percent release occurred at 3 hours for the tablets of Example 13, but did not occur until 6 hours for the tablets of Example 12.

The above description is for the purpose of teaching the person of ordinary skill in the art how to practice the present invention and it is not intended to detail all

those obvious modifications and variations of it which will become apparent to the skilled worker upon reading the description. It is intended, however, that all such obvious modifications and variations be included within the scope of the present invention and by the following claims.

Claims

What is claimed is:

1. A method of preparing a hydrophilic cross-linked polymer which comprises solubilizing a water-soluble polymer containing an effective amount of a photosensitive or light degradable catalyst and exposing the solution to an electromagnetic energy source.

2. The method of claim 1, wherein the water-soluble polymer is selected from the group consisting of the water-soluble polysaccharides, polyvinyl alcohols, and poly(hydroxyethyl methacrylates).

3. The method of claim 2, wherein the polymer is selected from the group consisting of hydroxyethyl cellulose and hydroxypropyl methylcellulose.

4. The method of claim 1, wherein the amount of polymer used is from about 1.0% to about 30% by weight of the solution.

5. The method of claim 1, wherein the catalyst is selected from the group consisting of flavins, Congo red, Evans blue, chlorazodin, erythrosine (FD&C Red #3), FD&C Red #40, tartrazine (FD&C Yellow #5), fast green FCF (FD&C Green #3), sunset yellow FCF (FD&C Yellow #6), brilliant blue

FCF (FD&C Blue #1), and indigotine (FD&C Blue #2).

6. The method of claim 5, wherein the flavinoid catalyst is selected from the group consisting of riboflavin and riboflavin derivatives.

7. The method of claim 5, wherein the flavinoid catalyst is riboflavin-5'-phosphate or a salt thereof.

8. The method of claim 1, wherein the amount of catalyst used is from about 0.1 to about 10% of the combined weight of the polymer and catalyst.

9. The method of claim 1, wherein the energy source is light.

10. The method of claim 9, wherein the light is visible or ultraviolet.

11. The method of claim 10, wherein the light is in the range of from approximately 400 to approximately 700 nanometers.

12. The method of claim 1, which further comprises drying the solution before exposing it to the energy source.

13. A hydrophilic crosslinked polymeric film prepared by the method of claim 1.

14. A pharmaceutical delivery system comprising the film of claim 13 and at least one pharmaceutically acceptable active agent.

15. A method of coating a pharmaceutical dosage form with a hydrophilic

cross-linked polymer which comprises: admixing a water-soluble polymer and an effective amount of a photosensitive or light degradable catalyst to form a mixture; compression coating said mixture over a pharmaceutical dosage form; and exposing the coated dosage form to an electromagnetic energy source.

Abstract

This invention pertains to cross-linked hydrophilic polymeric films, the process of making such films, and their use. The films of this invention are produced by solubilizing a water-soluble polymer with a photosensitive or light degradable catalyst, optionally drying said solution, and exposing the solution to an energy source, particularly light. These films are suitable for use as a carrier for biologically active agents, such as pharmaceuticals, both human and veterinary, insecticides, and fertilizers; as hydrophilic membranes for separation processes; as bandages for wound treatment; as body implants or as coatings for such implants; and as coatings on glass, metal, wood or ceramics.

Memo from K. Kaiser, Esq. acknowledging receipt of application by U.S. Patent Office

CIBA-GEIGY Corporation Intraoffice Correspondence

CIBA-GEIGY

Date: May 25th, 1994

To: G. Van Savage (SU)

From: K.G. Kaiser

Location Patents(SU/D-3059)

Subject: CGC 1740

Enclosed is copy of Serial Card received from the Patent Office today, 08/238,115 is the Serial Number which will be used for your patent application.

Sincerely,

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