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# ENHANCEMENT OF CARBAMZEPINE SOLUBILITY USING SELECTED WATER SOLUBLE POLYMERS AND A SOLID DISPERSION TECHNIQUE

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# ENHANCEMENT OF CARBAMZEPINE SOLUBILTY USING SELECTED WATER SOLUBLE POLYMERS AND A SOLID DISPERSION TECHNIQUE

BY

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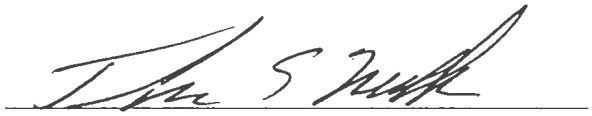

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## ABSTRACT

With the recent advent of combinatorial chemistry and high throughput screening of potentially therapeutic agents, the number of poorly soluble drug candidate has risen sharply and the formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenge to formulation scientists in the pharmaceutical industry. There are certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. And one of these drugs is carbamazepine. In the literature, solid dispersions have shown tremendous potential for improving drug solubility and dissolution.

In this study the main objective was to enhance the solubility of carbamazepine using selected water-soluble polymers and a solid dispersion technique. The solid dispersions were prepared by fusion method, using water-soluble polymers as carriers, namely Solutol HS, Vitamin E TPGS, Poloxamer 188 and Lipocol C 10 at a fixed ratio of 9:1 (drug:carrier) was used. Physical and recrystallized mixtures of the same ratios were also prepared for comparison purpose. Solubility studies were carried out in distilled water for a period of 48 hours with sample analysis at nine time intervals. The drug concentration was measured using a spectrophotometer at 285 nm. Differential Scanning Calorimetry (DSC) and powder X-ray diffraction (XRD) were used to characterize all the preparations. Optimized ratios of the solid dispersions were determined and used for dissolution studies by comparing $D_{10}$ (dissolution rate at 10 min) values for each ratio. A USP dissolution apparatus II using 900 ml of simulated gastric fluid at 50 rpm was used.

Microfluidization studies were also conducted to determine the effects of shear stress on the solubility of solid dispersions.

The solubility and dissolution rate of carbamazepine improved considerably with solid dispersions for all the selected polymers as compared to physical mixtures and recrystallized mixtures. Statistical analysis showed that both polymer and process had a significant effect on the solubility of the carbamazepine. Microfluidization studies initially showed a spike in drug solubility then a rapid drop back to equilibrium solubility. There was no significant effect of shear stress on the equilibrium solubility of solid dispersions of carbamazepine. Solid dispersions prepared with Vitamin E TPGS show maximum solubility as compared to solid dispersion prepared with other water-soluble polymers. It has also been seen that dissolution rate is enhanced to greater extent for solid dispersion prepared with Vitamin E TPGS compared to solid dispersion prepared with other water soluble polymers.

In general, solubility increase as well as dissolution rate enhancement was greater in solid dispersions than in physical mixtures and recrystallized mixture.

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## PREFACE

This document has been prepared in the format of a manuscript plan in accordance to section 11-3 of the graduate manual at the University of Rhode Island. This Thesis has been divided into three sections.

Section I contains the introduction, the statement of the problem and a brief introduction to the objectives of this research. Section II forms the central part of this thesis and is composed of one manuscript written in the format prescribed by the scientific journal to which it has been or will be submitted for publication. This Section follows appendices that include the list of publications and experimental details useful for a clearer understanding of the results described in the preceding manuscripts. A general summary of conclusions and bibliography for the entire thesis follows this section.

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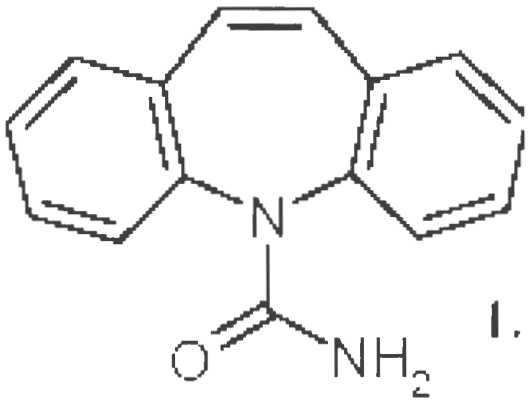
# SECTION 1

## 1.1 Background:

The advent of high throughput screening (HTS) for search of model drugs during the 1989-1991-time period made it feasible to screen for in-vitro activity across hundreds of thousands of compounds (1). Combinatorial chemistry soon began and allowed automated synthesis of massive numbers of compounds for screening using new HTS screens. Since HTS is trying to maximize receptor site affinity and since hydrophobic molecules tend to provide better interaction at the receptor site, the resultant compounds are relatively high molecular weight and highly lipophilic. These kinds of molecules show poor solubility in water and in turn poor bioavailability. The enhancement of the solubility of poorly soluble drugs for better bioavailability poses one of the most challenging aspects of drug development (2).

One of the drugs that pose challenges for better bioavailability due to poor water solubility is Carbamazepine. Carbamazepine is classified as an anticonvulsant. It has a chemical composition of $C_{15}H_{12}N_2O$ and molecular weight of 236.27. Its chemical name is 5H–Dibenz (b,f) azepine-5-carboxamide and its structural formula is as follows (3). It is a specific analgesic for trigeminal neuralgia. It is also indicated for the epilepsy, bipolar disorder and acute mania (4).

Carbamazepine is a white to off-white powder, practically insoluble in water, soluble in alcohol and acetone. It is available as chewable tablets of 100 mg, 200 mg, as extended release tablets of 100 mg, 200 mg, 300 mg, 400 mg, and a suspension of 100 mg/5 ml (5). The melting point of Carbamazepine is in the range of 190-193$^{o}$ C.




1.

**FIGURE 1. STRUCTURAL FORMULA OF CARBAMAZEPINE**

Carbamazepine is characterized by low and erratic absorption. Carbamazepine induces its own metabolism and that's why it has variable half-life. Autoinduction is completed after 3-5 weeks of fixed dosing regimen. Initially half-life values range from 26-65 hours, decreasing to 12-17 hours after repeated doses. Carbamazepine is metabolized in liver. Cytochrome P450 3AA was identified as the major isoform responsible for the formation of Carbamazepine-10,11-epoxide. After oral administration, 72% is eliminated in the urine and 28% in the feces. Carbamazepine has at least four polymorphic forms and a dihydrate (6).

## 1.2 Methods to Improve Solubility of a Drug

Together with permeability, the solubility behavior of a drug is a key determinant of its bioavailability. Consideration of the modified Noyes-Whitney equation (7) provides an indication as to how the dissolution rate of even poorly soluble compounds might be improved so that the limitations of oral availability can be minimized:

$$\frac{dc}{dt} = \frac{AD\,(Cs - C)}{h}$$

Where, ***dc/dt*** is the rate of dissolution, ***A*** is the surface area available for dissolution, ***D*** is the diffusion coefficient of the compound, ***Cs*** is the solubility of the compound in the dissolution medium, ***C*** is the concentration of the medium at time ***t*** and ***h*** is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

The main possibilities for improving dissolution according to this analysis are to increase the surface area available for dissolution by decreasing the particle size of the solid compounds, to decrease the boundary layer thickness, and last not but least, to improve the apparent solubility of the drug under physiologically relevant conditions. Of these possibilities, the most attractive option for increasing the release rate is the improvement of the solubility through formulation approaches. Table 1 summarizes the various formulation and chemical approaches that may be used to improve the solubility or to increase the available surface area for dissolution.

**TABLE 1: APPROACHES TO IMPROVE THE SOLUBILITY OR TO INCREASE THE AVAILABLE SURFACE AREA FOR DISSOLUTION (12)**

| *I. Physical Modifications* | *II. Chemical Modifications* |
|---|---|
| Particle size | Soluble prodrugs |
| Micronization | Salts |
| Nanosuspensions | |
| Modification of the crystal habit | |
| Polymorphs | |
| Pseudopolymorphs | |
| Complexation/ Solubilization | |
| Use of surfactant | |
| Use of acceptable cyclodextrins | |
| Drug dispersion in carriers | |
| Eutectic mixtures | |
| Solid dispersions (non-molecular) | |
| Solid solutions | |

Of the physical approaches, the use of polymorphs (8), the amorphous form of the drug (9) and complexation (10, 11) has been widely reviewed. Decreasing the particle size of the compound by milling the drug powder theoretically results in an increase in the surface area for dissolution. However in those cases where the micronized powder agglomerates, is negating the advantages of the milling procedure. Presenting the molecular dispersion of a drug in a water soluble polymer, on the other hand, combines the benefits of a subsequent increase in the solubility by maximizing the surface area of the compound that comes in contact with the dissolution medium as the carrier dissolves.

### 1.3 Solid dispersions

The term solid dispersion has been utilized to describe a family of dosage forms whereby the drug is dispensed in a biologically inert matrix, usually with a view to enhancing oral bioavailability. Sekiguchi and Obi introduced the concept of solid dispersion in 1961 (13). They proposed formation of a eutectic mixture of a poorly soluble drug with a physiologically inert, easily soluble carrier. The eutectic mixture was prepared by melting the physical mixture of the drug and the carrier, followed by rapid solidification procedure. Upon exposure to aqueous fluids, the active drug released into the fluids are fine, dispersed particles because of the fine dispersion of the drug and rapid dissolution of the soluble matrix.

The advantage of solid dispersion, compared with conventional capsule and tablet formulations, is shown schematically in Figure 2. (14)

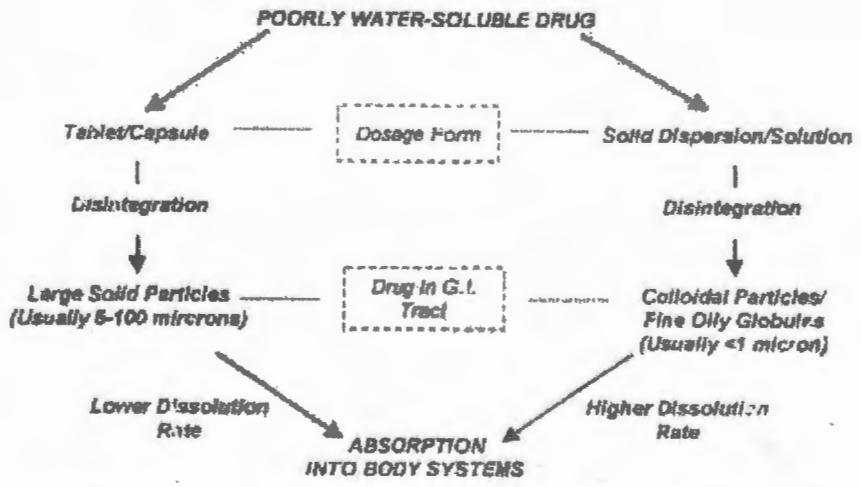



**FIGURE 2. SCHEMATIC REPRESENTATION OF THE BIOAVAILABILITY ENHANCEMENT OF POORLY WATER-SOLUBLE DRUG BY SOLID DISPERSION COMPARED WITH CONVENTIONAL TABLET OR CAPSULE (14)**

Chiou and Riegelman, (15) in their early classic review, defined these systems as " a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting (fusion), solvent or melting-solvent methods". The formulation prepared by any of these processes, classified as solid dispersions but simple mechanical mixes are not considered to be solid dispersions.

Corrigan (16) suggested the definition of solid dispersion as being a ' product formed by converting a fluid drug-carrier combination to solid state'. In practice, these dosage forms have been traditionally regarded as being synonymous with systems whereby the in vitro release of the drug is enhanced compared to conventional dosage forms, with concomitant implications for in vivo release. Furthermore, the carrier used has, again traditionally, been a water-soluble or water miscible polymer such as polyethylene glycol (PEG) or polyvinylpyrolidone (PVP) or low molecular weight materials such as sugars. However, the proliferation of research in the area since the first solid dispersions were described has led to a broadening of these definitions to include water insoluble matrices such as Gelucires® and Eudragits® that may yield either slow or rapid release and absorption. The latest review publication by Serajuddin (1999) (14) gives details of some more recent approaches such as the use of surface active carriers and the use of melt extrusion of PVP dispersions as a means of manufacturing viable dosage forms using this technology.

Solid solutions are comparable to liquid solutions, consisting of just one phase irrespective of the number of components, and are made up of a solid solute dissolved in a solid solvent. It is often called a mixed crystal because the two components crystallize together in a homogenous one-phase system (17). Solid solutions containing

a poorly water soluble drug dissolved in a carrier with relatively good aqueous solubility achieve a faster dissolution rate because the particle size of the drug in the solid solution is reduced to a minimum state, i.e., its molecular size, and the dissolution rate is determined by the dissolution rate of the carrier (18). By judicious selection of a carrier, the dissolution rate of the drug can be increased by up to several orders of magnitude.

In addition to the reduction of the crystalline size, the following factors may contribute to the faster dissolution rate of a drug dispersed in these systems (19),

a) An increase in drug solubility may occur if the majority of its solid crystallites are extremely small (20).

b) A solubilization effect by the carrier may operate the microenvironment (diffusion layer) immediately surrounding the drug particle in early stages of dissolution since the carrier completely dissolves in a short time. This was demonstrated by the faster dissolution rate of acetaminophen from its physical mixtures with urea than that of the pure compound with comparable particle size (21).

c) The absence of aggregation and agglomeration between fine crystallites of the pure hydrophobic drug may play a far more important role in increasing rates of dissolution and absorption than is presently recognized. Serious drawbacks of aggregation and agglomeration and lumping in the dissolution medium between pure drug particles are, however, rarely present in most solid dispersion systems because the individually dispersed particles are surrounded in a matrix of carrier particles. It be must emphasized that the aggregation and agglomeration of the solid dispersion powder may not significantly affect the dissolution of the drug, which can still

disintegrate quickly due to more rapid dissolution of the soluble carrier. This advantage of solid dispersion systems was demonstrated in vivo (22) for griseofulvin that was dispersed in polyethylene glycol 6000 (10% w/w) and compressed into a hard tablet. The dissolution rate of the dispersed drug was found to be 25 times that of the pure drug.

d) Excellent wettability and dispersibility of a drug from those systems, prepared with a water-soluble matrix results in an increased dissolution rate for the drug in aqueous media. This is due to the fact that each single crystallite of the drug is very intimately encircled by the soluble matrix, which can readily dissolve and cause the water to contact and wet the drug particle. As a consequence, a fine homogenous suspension of a drug can be easily obtained with minimum stirring (13).

### 1.4 Analytical methods used to characterize solid dispersions

In order to differentiate between solid dispersions and solid solutions and physical mixtures of the drug in a carrier following methods are used to characterize.

1) Solubility and dissolution testing
2) Thermoanalytical methods: differential thermo analysis and hot stage microscopy
3) X-ray diffraction
4) Surface properties studies
5) Spectroscopic methods such as FT-IR spectroscopy
6) Microscopic methods including polarization microscopy and scanning electron microscopy.

Among these, the most important methods are Thermoanalytical, X-ray diffraction and measurement of the release rate of the drug. It is difficult to differentiate precisely between molecularly dispersed and not molecularly dispersed systems.

Since it is usually assumed that the dispersions in which no crystallinity can be detected are molecularly dispersed and the absence of crystallinity is used as criterion to differentiate between solid solutions and solid dispersions (12).

#### 1.4.1 Differential scanning calorimetry (DSC):

Thermoanalytical methods include an examination of system properties as a function of temperature. Most thermodynamic events are accompanied by a loss of heat or require addition of heat from an external source in order to proceed. Each of these occurrences can be followed thermodynamically by noting either change of temperature of the sample under study or energy changes of the sample with respect to time. Thermal

analysis includes thermogravimetry (thermogravimtric analysis, TGA), differential thermal analysis (DTA) and differential scanning calorimetry (DSC). DSC is frequently a preferred thermal analytical technique because of its ability to provide detailed information about both the physical and energetic properties of a substance (23). DSC is very closely related to TGA, but differs only in that the sample and reference container are not contagious, but are heated separately by individual coils that are heated (or cooled) at the same rate. Platinum resistance thermometers monitor the temperature of the sample and the reference holders and electronically maintain the temperature of the two holders constant. If a thermodynamic event occurs which is either endothermic or exothermic, the power requirements for the coils maintaining the constant temperature will differ. This power difference is plotted as a function of the temperature recorded by the programming device. Unlike DTA, in DSC the amount of heat put into the system is exactly equivalent to the amount of heat absorbed or liberated during a specific transition (transition energy). Melting of a drug is one of the examples of the endothermic transition. Exothermic transitions, such as conversion from one polymorph to a more stable polymorph, can also be detected. Lack of a melting peak in the DSC of a solid dispersion indicates that the drug present in amorphous rather than crystalline form.

### 1.4.2 X-ray diffraction:

Powder X-ray diffraction analysis is employed in the characterization of crystalline structure. X-rays are high-energy electromagnetic radiations of short wavelength. Diffraction is the scattering of x-rays in a few specific directions by the crystals. The

scattering and diffraction is caused by the interaction with electrons. When an X- ray beam hits a crystal surface at angle O, a portion of it is scattered by the layers of atoms at the surface. The unscattered portion of the beam penetrates to the second layer of atoms where again a fraction is scattered, and remainder passes on the third layer.

In powder X-ray diffraction analysis the crystallinity of the sample is reflected by a characteristic fingerprint region in the diffraction pattern. Owing to specificity of the finger print region, crystallinity of the drug can be separately identified from that of the carrier. However, crystallinities of fewer than 5-10% cannot be determined with X-ray diffraction (23).

### 1.4.3 Solubility and Dissolution studies:

Solubility and dissolution studies are of prime importance in accessing the success of these approaches. As the goal of preparing solid dispersions is to improve solubility and consequently, dissolution of poorly water-soluble drugs, the release rate experiment results are very important. Dissolution studies help in understanding the rate of dissolution differences between drug, physical mixture, solid dispersions and solid solutions. Comparison of results with those for pure drug powder and a physical mixture of the drug in a carrier can help indicate the mechanism by which the carrier improves dissolution.

## 1.5 Solutol HS ®

Solutol HS is a Polyethylene glycol 660 12-hydroxystearate. It is a yellowish white paste at room temperature that becomes liquid at 30° C. It consists of polyglycol mono and di-esters of 12-hydroxy-stearic acid (lipophilic part) and about 30% of free polyethylene glycol (hydrophilic part) (24). It dissolves in water, ethanol and 2-propanol to form a clear solutions. Its solubility in water decreases with increasing temperature. It has high chemical stability.

It is useful for the manufacture of aqueous parenteral preparations with vitamin A, D, E, K and a number of other lipophilic pharmaceutical active ingredients (25). It has been also used to increase the solubility and consequevently bioavailability of Cyclosporin A (26). It has been utilized to improve the stability of parenteral emulsions too (27).

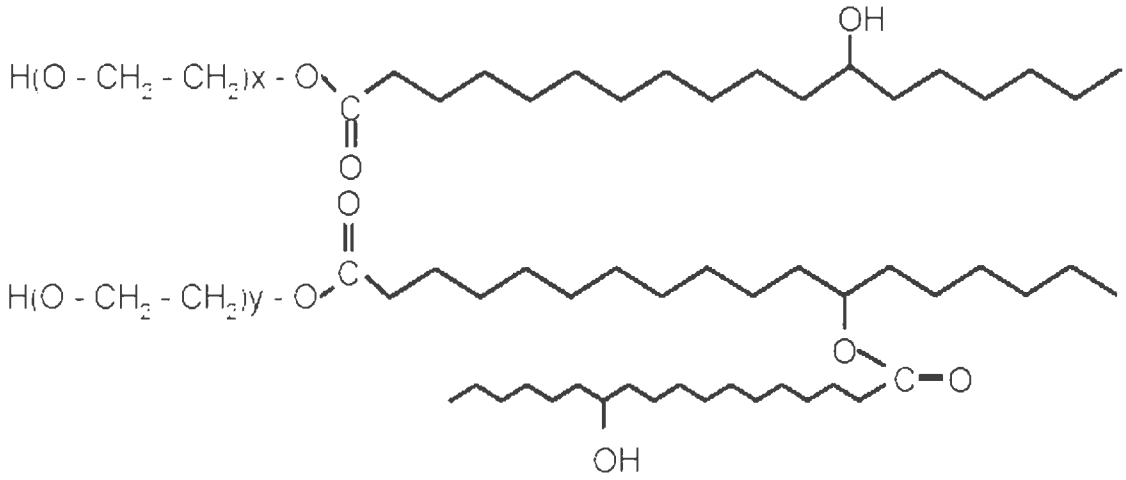



**FIGURE 3: CHEMICAL STRUCTURE OF SOLUTOL HS**

### 1.6 Vitamin E TPGS ®

Vitamin E TPGS is prepared by the etherification of polyethylene glycol 1000 to the acid group of crystalline d-α tocopheryl acid succinate. It is also called as d-α tocopheryl polyethylene glycol 1000 succinate. The molecular weight of Vitamin E TPGS is approximately 1513. It is practically tasteless and is a yellowish to off-white solid. It is mainly used to absorb Vitamin E easily from the gastrointestinal tract (28). Vitamin E TPGS is water-soluble while other forms of Vitamin E are fat-soluble.

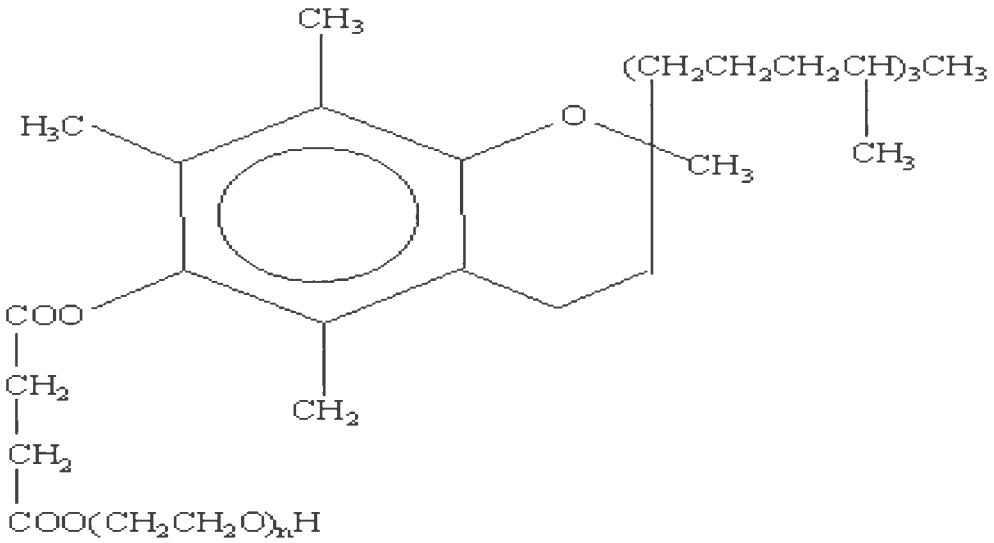
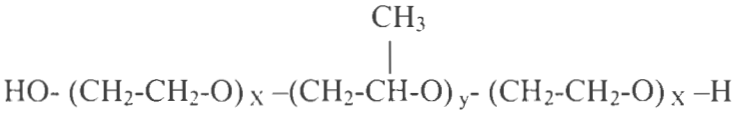



**FIGURE 4: CHEMICAL STRUCTURE OF VITAMIN E TPGS**

Along with assisting in vitamin E absorption, the water solubility of Vitamin E TPGS results in a product, which is quite stable and does not hydrolyze under normal conditions (29). It is used in the preparation of nanospheres (30) of paclitaxel, for enhancement of intestinal absorption of vancomycin (31), to increase solubility of cyclosporin (32), and to form hot-melt extrudates with selected drugs (33).

### 1.7 Poloxamer 188 NF ® (Pluronic F68)

Poloxamer 188 is water-soluble block copolymer of the general formula,



Where x = approx. 79 and y = approx. 28

**FIGURE 5: STRUCTURAL FORMULA OF POLOXAMER 188**

It contains approximately 80% Polyoxyethylene block and its average molecular weight is 8250. It is a white to slightly yellowish waxy substance in the form of micropearls having slight odor (34). It is readily soluble in ethanol and water. It has widespread industrial application in detergency, dispersion stabilization, foaming, emulsification, lubrication, etc. In addition, they are used in specialized applications such as for the solubilization and controlled release of drugs.

Poloxamer 188 NF is useful in improving the dissolution rate of many hydrophobic drugs such as digitoxin and digoxin (35), nifedipine (36). Also, Its solubilizing effect does not depend on the formation of micelles.

### 1.8 Lipocol C 10

Lipocol C 10 is a white waxy solid and has a characteristics bland odor. It has a chemical structure of $[(CH_3)_3(CH_2)_{14}CH_2(OCH_2CH_2)nOH]$. It has a HLB value near to

Vitamin E TPGS i.e. 12.9. It is used to deduce the effect of surfactant property of Vitamin E TPGS in this study.

### 1.9 Microfluidization

Microfluidization is a process largely used to prepare microemulsions (37) and liposomes (38). Microfluidization is used to study the effect of shear stress on the properties of a solid dispersion. It employs a the submerged jet principle in which two fluidized streams interact at ultrahigh velocities in precisely defined microchannels within the interaction chambers.

**Statement of Problem:**

According to Biopharmaceutical classification of system (BCS), Carbamazepine is Class II drug. The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and gastro-intestinal permeability. Carbamazepine falls under Class II category that means it has high permeability but solubility is low and as a result absorption may be low, also.

It has also been shown that carbamazepine is characterized by low and erratic absorption from the gut. The conventional carbamazepine tablet yields peak plasma concentration varying from 4 to 32 hours. This irregular and delayed absorption of carbamazepine is attributed to slow dissolution. Thus, dissolution is the main rate-limiting step for the absorption of carbamazepine. If the solubility of carbamazepine is enhanced then dissolution rate would also increase and subsequently bioavailability too.

**Objective of study:**

Carbamazepine is used for epilepsy, trigeminal neuralgia and bipolar disorder. It is neutral and lipid soluble in nature, with very poor water solubility and dissolution rate. In order to increase its solubility and dissolution, solid dispersions will be prepared using Solutol HS, Vitamin E TPGS, Poloxamer 188 and Lipocol C 10 respectively. The solid dispersion will be prepared by the melt or fusion method. For comparison purposes, physical mixtures of the same ratios will be prepared by simple mixing. The solvent evaporation process will be also utilized to study varied effect on the solid-state

of the drug. All preparations will be characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (XRD), solubility and dissolution studies. The solubility studies will be carried out in distilled water and solubility measurements will be done utilizing an UV-visible spectrophotometer. A USP dissolution apparatus II will be used to perform dissolution studies.

There may be some positive effect of shear stress on the solubility of carbamazepine in presence of polymer. To ascertain this fact, the Microfluidizer will be used to study the effect of shear stress on the solid dispersions.

The objectives of this research project, therefore, can be summarized as:

A) To enhance the solubility of the carbamazepine using selected water-soluble polymers and a solid dispersion technique. Also, to analyze the effect of solubility on the dissolution rate of Carbamazepine.

B) To evaluate the effect of microfluidization of the solid dispersion of drug on its solubility.

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## SECTION II

### Manuscript I

### Enhancement of Carbamazepine Solubility using selected water-soluble polymers and a solid dispersion technique

**Abstract:**

Solubility of any drug in the gastrointestinal tract has profound a effect on the bioavailability of that particular drug in the body. Carbamazepine is a drug of choice in the treatment of epilepsy, trigeminal neuralgia, bipolar disorder and acute mania. According to Biopharmaceutical Classification System (BCS), it is a Class II drug, which means it has low solubility and high permeability. It is hydrophobic in nature and has a poor dissolution rate. It has been shown that conventional Carbamazepine tablets show variable peak plasma concentrations from 4–32 hours, which in turn gives variable Bioavailability. In order to increase its water solubility and the dissolution rate, solid dispersions were prepared using water-soluble polymers namely Solutol HS, Vitamin E TPGS, Poloxamer 188 and Lipocol C 10. Solid dispersions with these polymers were prepared by the fusion method. For solubility studies, a fixed ratio of 900 mg:100 mg (drug: carrier) was used. Physical mixtures and recrystallized mixtures of the same ratio were also used for comparison purpose. For dissolution studies, optimized ratios of solid dispersions were used. All preparations were characterized by Differential Scanning Colorimetry (DSC) and powder X–ray diffraction studies. Microfluidization studies were also conducted to determine the effects of shear stress on the solubility of the solid dispersions. The Solubility of

Carbamazepine improved considerably with the solid dispersions for all the selected polymers as compared to physical mixtures and recrystallized mixtures. Microfluidization studies showed initial spike in the solubility, then, rapid decline back to equilibrium solubility. It showed no significant effect of shear stress on the equilibrium solubility of solid dispersions of Carbamazepine. The dissolution rate of the drug was also improved with the solid dispersions as compared to physical mixtures. DSC and X-ray diffraction studies showed no significant change in the crystallinity of the drug at a ratio of 900 mg:100 mg. However, an increased ratio of polymer (20:80) showed significant change in the crystallinity of the drug. Vitamin E TPGS was found to be best polymer of all the polymers used to increase the solubility as well as dissolution rate of the Carbamazepine. The improved solubility may be attributed deagglomeration of fine particles, and presence of carbamazepine as very small crystallites within the dispersion. Water-soluble polymers might have formed a complex with Carbamazepine, which is enough to inhibit the conversion of Carbamazepine anhydrous to dihydrate, which is the sole reason for low solubility of Carbamazepine.

## 2.1 Introduction:

The important requirement to achieve absorption of a poorly water-soluble drug from the GI tract and achieve a desired bioavailability is that the drug should be in solution in the GI tract. A poorly water-soluble drug is the one whose dissolution in the GI fluid under normal conditions takes a longer time than its transition through the absorption sites in the GI tract (1). The solubility enhancement of such a poorly water-soluble drug and in turn increasing its oral bioavailability drugs poses one of the most challenging aspects of the drug development. Although salt formation, decreasing particle size and other methods are commonly used to increase the solubility of the drugs, there are practical limitations with these techniques and thus, the desired bioavailability enhancement may not always be achieved (2). Today among the many methods available, a solid dispersion system in which drug is dispersed in water-soluble matrices either molecularly or as fine particles has gained attention in recent years. It has shown promising results in increasing the dissolution as well as bioavailability of many poorly water-soluble drugs (3).

Although a search of the literature revealed that many articles on solid dispersions, very few research articles are available on the utilization of solid dispersions to enhance the solubility of carbamazepine and subsequently dissolution and bioavailability. Attia and Habib, 1985 (4) prepared solid dispersions with sugars to enhance the dissolution as well as bioavailability of carbamazepine. Different classes of nonionic surfactants as well as bile salts were used by Samaha and Gadalla, 1987 (5) to study their solubilization effect on carbamazepine and found a marked increase in solubility with all eight nonionic surfactants used. They also found that increasing

the concentration of the bile salts increased the solubilized amount of carbamazepine. Luthala, S., 1990 (6) studied the effect of benzalkonium chloride, a cationic surfactant, on the growth of carbamazepine crystals in aqueous suspensions and also the effect of this surfactant on the solubility of carbamazepine in water. The growth of carbamazepine crystals, which is initiated by a transition from the anhydrous form to a dihydrate, is caused by the differences in the solubilities of the two forms with the anhydrate demonstrating at least 2.4 times greater solubility than the dihydrate. Benzalkonium chloride was found to increase the apparent solubility of carbamazepine in the system. Habib et al., 1993 (7) studied the development of a carbamazepine and phospholipid solid dispersion formulation to improve dissolution characteristics of carbamazepine. Al-Meshal et al., 1993 (8) formed complexes of carbamazepine with cyclodextrins and found the inclusion complex to augment the bioavailability of carbamazepine. Zerrouk et al., 2001 (9) investigated the effects of solid dispersion on the solubility, the dissolution rate and the pharmacokinetic profile of carbamazepine. They found that solubility studies showed a linear increase in carbamazepine solubility with increasing PEG 6000 concentration.

The objective of this study was to increase the water solubility of carbamazepine by preparing solid dispersions using Solutol HS, Vitamin E TPGS, Poloxamer 188 or Lipocol C 10. These studies include preparation and characterization of the solid dispersions and evaluation of the effect of the shear stress of the solid dispersions on the solubility of Carbamazepine. A microfluidizer is used to assess the effect of shear stress on the solubility of solid dispersions. Also, to know exact mechanism of

solubility enhancement, solid dispersions are prepared with Lipocol C 10 are prepared and analyzed in the same manner.

## 2.2 Materials:

### 2.2.1 Chemicals

Hi-Tech Pharmacal, NY, provided micronized Carbamazepine. Solutol HS and Pluronic F68 (Poloxamer 188 NF) were obtained from BASF Corporation (Mount olive, NJ). Vitamin E TPGS and Lipocol C 10 were purchased from Eastman Chemicals (Kingsport, TN) and Lipo Chemicals (NJ) respectively. Sodium chloride (Fisher Scientific, Fair Lawn) and hydrochloric acid (Fisher Scientific, Fair Lawn) were used to prepare simulated gastric fluid dissolution medium. Methanol and acetone were used to recrystallize the mixture of carbamazepine with various polymers. Purified de-ionized water was prepared using Milli Q50 (Millipore, Bedford, MA) purification system. All chemicals used were of analytical grade.

### 2.2.2 Instruments

The analysis of all the samples was performed using HP 8451A Diode Array Spectrophotometer. Microfluidization studies were conducted using M-110S Microfluidizer® Processor (Microfluidics Corporation). Dissolution studies were conducted using USP Dissolution Apparatus II (Vankel Dissolution System model). Differential Scanning Calorimetry (DSC); (TA Instruments Q100), Microchip based Powder X-ray Diffraction instrument is used for X-ray diffraction studies.

## 2.3 Methods:

### 2.3.1 Preparation of physical mixtures

The drug and carriers were passed through a 40-mesh screen and mixed thoroughly in a mortar and pestle. For solubility studies, a fixed ratio of drug and carrier was used (900 mg:100 mg). For the microfluidization studies, a drug to carrier ratio of 20:80 was used. For dissolution studies, various ratios were prepared depending on the results of the optimization study of the solid dispersions.

### 2.3.2 Preparation of Solid dispersions

The respective polymer was heated at about $60^{o}$ C in an oven, until it melted completely. The drug was added to the molten polymer and mixed thoroughly. The mixture was cooled to ambient conditions, milled and passed through a 40-mesh screen. The same ratios used for the physical mixtures, were used for the preparation of the solid dispersions.

### 2.3.3 Preparation of Recrystallized Mixtures

The drug and polymer were weighed (900 mg:100 mg) and dissolved by sonication in 10 ml of a 1:1 mixture of acetone and methanol. The solution was filtered under vacuum and then transferred to an evaporating dish. The solvents were allowed to evaporate at room temperature under the vacuum hood and then the samples were transferred to a dessicator and further dried for 24 hours or until no further loss in weight occurred.

### 2.3.4 Preparation of Microfluidized Mixtures.

The respective polymer was heated to 60° C in an oven, until it melted completely. The drug was added to the molten polymer and mixed thoroughly. The mixture was then passed through the microfluidizer preheated at 60° C. Microfluidizer was operated at pressure gauge set to 40 psi. The solution was then passed through the equipment for 10 strokes of the pump and collected from the outlet.

**2.4 Solubility Measurements:**

Solubility studies of Carbamazepine were performed in water, for a period of 48 hours with sample analysis at nine time intervals according to the method of Connors and Higuchi (10). The 48-hour time duration was selected since it allowed the drug to reach equilibrium solubility. An excess amount of the drug in the medium ensured equilibrium during the 48-hour period. The studies were conducted at room temperature (25° C). The solution was filtered through a 0.45 μ pore size filter. The solution concentration was measured using UV-Visible spectrophotometer at 285 nm.

**2.5 Dissolution Studies:**

Dissolution was studied using a USP Dissolution Apparatus II with 900 ml of simulated Gastric Fluid without pepsin at pH 1.3 ± 0.05 as a dissolution medium at 37° C and a paddle speed of 50 RPM. Accurately weighed amounts of the solid dispersions or physical mixtures, corresponding to 20 mg of carbamazepine, were added to the dissolution media. As per guidance given in FDA dissolution manual, the samples were placed into an AAA size gelatin capsule. Samples were drawn at different time intervals and assayed for drug content using UV/VIS spectrophotometer with reference to a suitably constructed standard plot at 285 nm. The withdrawn volume of sample media was replaced with a fresh media. The studies were conducted at room temperature (25° C).

### 2.6 Differential Scanning Calorimetry analysis

A Differential Scanning Calorimeter (DSC) equipped with a liquid nitrogen-cooling accessory was used. Samples (5-10mg) were prepared in hermitically sealed pans. The pans were crimped with the instrument sealer for the solid samples. The samples were scanned at a heating rate of $10^{o}$ C/min. from $0^{o}$ C to $220^{o}$ C. Data were treated mathematically using DSC TA universal analysis program.

### 2.7 Powder X-ray Diffraction (XRD):

Various samples were analyzed by Powder X-ray diffraction using Fe anode to determine the crystalline state of the drug in the solid dispersions. The XRD pattern was collected in the angular range of $6 < 2\theta < 76^{o}$in step scan mode. A current of 10 miliamperes and a voltage used of 34 kW was used. The scans are conducted at room temperature and pyrolytic graphite is used as a filter.

### 2.8 Statistical Analysis

A two factorial design is used to study the effect of the different processes and polymers on the solubility of the drug. In this study, we have used a 4 x 3 factorial design, that is, we have 2 factors, one with 4 levels and the other with 3 levels. The two factors are polymer ($C_1$) and process ($C_2$) with 4 and 3 levels respectively. The two independent variables, their levels and their values are summarized in Table 2. Therefore, the number of treatment groups would be 4 x 3 = 12 groups (Table 3). Data for each representative group is generated in triplicates; hence, we have 36 observations. Solubility was the response parameter. All the statistical and regression

analysis procedures in the response parameters were performed using the Minitab ® software package. Statistical analysis was carried out which includes the analysis of variance (ANOVA) to determine the significance of each independent variable (process, polymer), two-way interactions (process-polymer) (10). The general linear model used for the experimental design was:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2$$

The Student-Newman-Keuls Test with SAS software was performed to determine the best polymer process combination that would give the best possible results to enhance the solubility.

## 2.9 Results and Discussion:

### 2.9.1 Solubility Measurements:

The solubility determinations were carried out using an excess amount of a drug at a fixed ratio of drug to polymer of 900 mg:100 mg with three replications according to the method of Connors and Higuchi (11). Solutol HS, Vitamin E TPGS, Poloxamer 188 and Lipocol C 10 were used for this study. In solubility determinations the concentration in solution depends on the drug's solubility. Excess drug accounts for any loss that may occur in solution, whereby more drug is released from the suspended particles so that the amount of dissolved drug remains constant. This concentration is the drug's equilibrium solubility in a particular solvent at a particular temperature (12). The initial rate of solubilization of the drug varies hyperbolically with time. During the initial time period, the drug goes into solution continuously, increasing the concentration of drug linearly. As the time increases, more and more drug goes into solution, until the solution is saturated with the drug, and equilibrium solubility is observed.

Physical mixtures, solid dispersions and recrystallized mixtures were prepared as per the methods described. Accurately weighed quantity of each sample were weighed and transferred to glass vials. Added 10 ml of water into the vials and vials were allowed to shake for 48 hours on a Burrell wrist shaker. 2ml of samples were collected at 10, 30, 45, 60, 120, 360, 720, 1440, and 2880 minutes with the replacement of 2ml fresh water. Samples were filtered and analyzed using UV-Visible spectrophotometer at 285 nm after dilution. The solubility profile of the untreated drug, physical mixtures, solid dispersions and recrystallized mixtures were examined. The solubility profiles of

Carbamazepine with Solutol HS, Vitamin E TPGS, Poloxamer 188 and Lipocol C 10 are shown in Figures 6, 7, 8, & 9 respectively. The physical mixtures of the drug and the three polymers were tested for any positive effect on the solubility of the drug in the presence of polymers. A look at solubility profiles shows a 10-50 μg/ml increase in solubility for all the physical mixtures as compared to the solubility of carbamazepine alone at any given time point. However, this was not a significant increase in solubility and hence can be considered equivalent to untreated drug for all practical purposes. All the polymers increase the solubility of carbamazepine when they were incorporated as Solid dispersions. It is evident that Vitamin E TPGS when used in the solid dispersions shows greater increase in solubility as compared to other three polymers (Figure 10). There is an approximate 500% increase in solubility with the use of Vitamin E TPGS, and 200-400%-fold increases with the use of Solutol HS, Poloxamer 188 and Lipocol C 10, which is shown in Table 2.

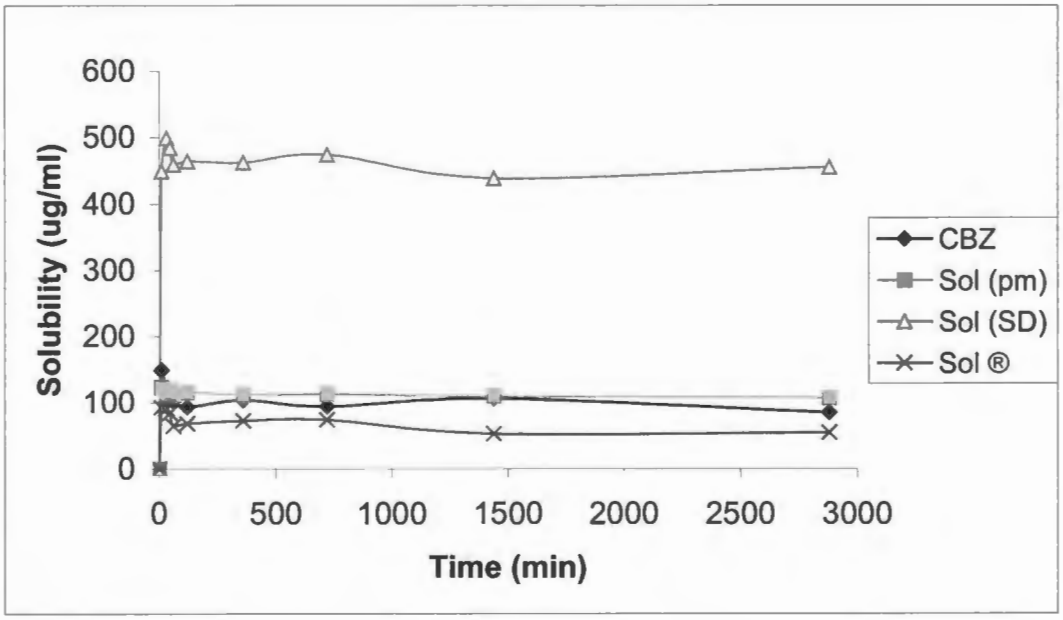



**FIGURE 6: SOLUBILITY PROFILE OF CARBAMAZEPINE AND ITS PHYSICAL MIXTURE, SOLID DISPERSION AND RECRYSTALLIZED MIXTURE WITH SOLUTOL HS (90:10)**

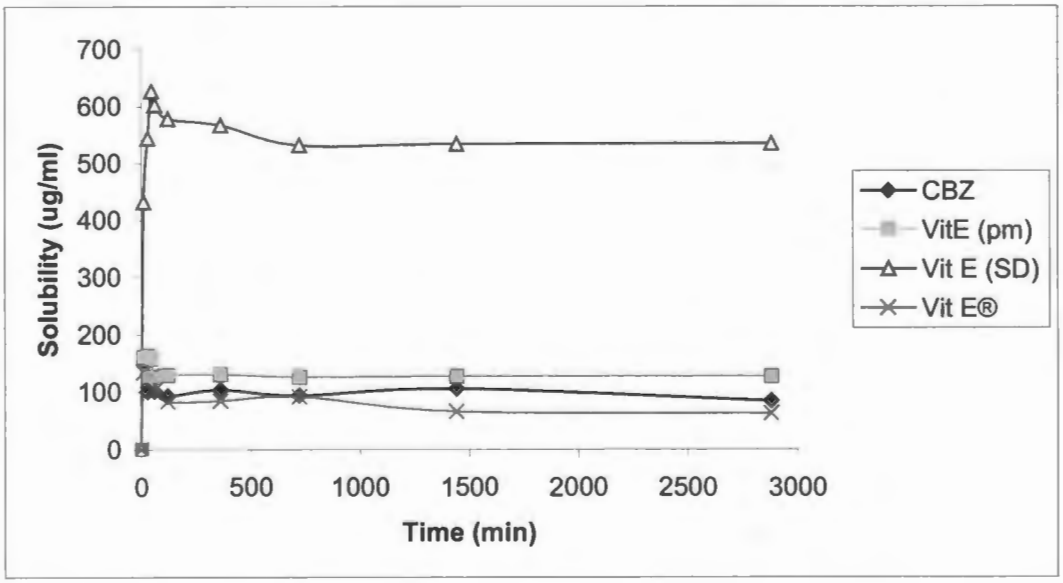



**FIGURE 7: SOLUBILTY PROFILE OF CARBAMAZEPINE AND ITS PHYSICAL MIXTURE, SOLID DISPERSION AND RECRYSTALLIZED MIXTURE WITH VITAMIN E TPGS (90:10)**

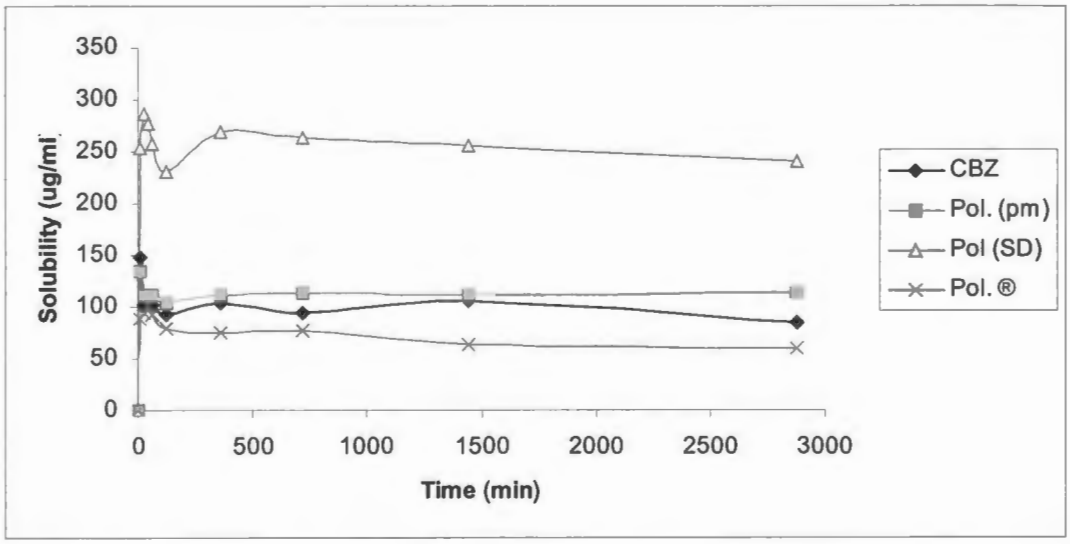



**FIGURE 8: SOLUBILTY PROFILE OF CARBAMAZEPINE AND ITS PHYSICAL MIXTURE, SOLID DISPERSION AND RECRYSTALLIZED MIXTURE WITH POLOXAMER 188 (90:10)**

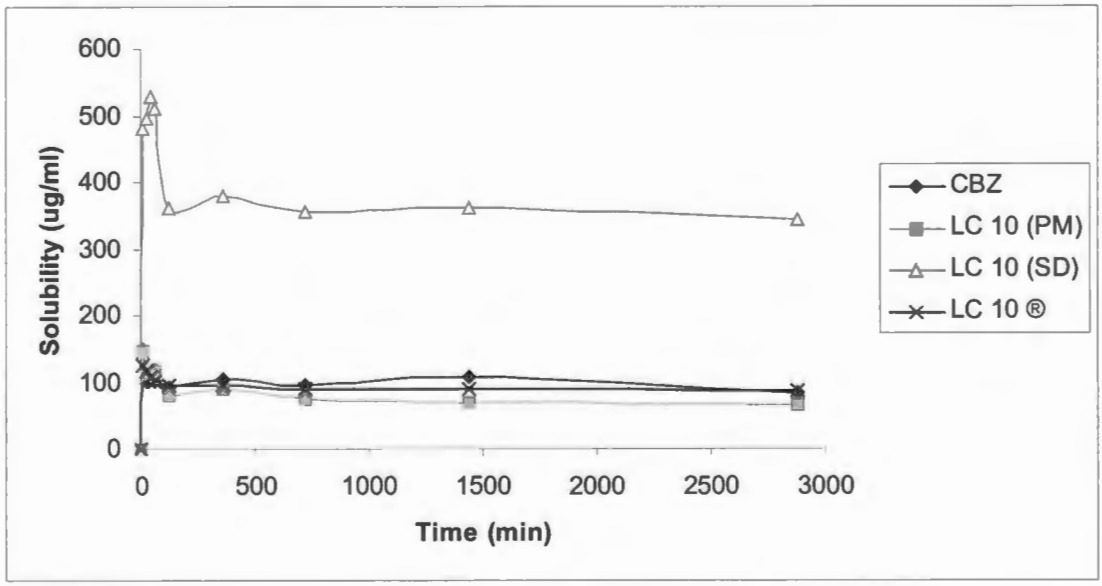



**FIGURE 9: SOLUBILTY PROFILE OF CARBAMAZEPINE AND ITS PHYSICAL MIXTURE, SOLID DISPERSION AND RECRYSTALLIZED MIXTURE WITH LIPOCOL C 10 (90:10)**

**TABLE 2: COMPARISON OF SOLID DISPERSIONS OF CARBAMAZEPINE WITH SOLUTOL HS, VITAMIN E TPGS, POLOXAMER 188, AND LIPOCOL C 10 (90:10)**

| Time (min) | CBZ (ug/ml) | Sol (SD) (ug/ml) | Vit. E (SD) (ug/ml) | Pol. (SD) (ug/ml) | LC (SD) (ug/ml) |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 |
| 10 | 149.00 | 449.22 | 432.40 | 253.37 | 481.50 |
| 30 | 100.97 | 499.13 | 544.73 | 286.69 | 494.95 |
| 45 | 106.39 | 484.35 | 627.34 | 277.27 | 527.35 |
| 60 | 101.82 | 459.43 | 603.69 | 258.08 | 509.30 |
| 120 | 93.05 | 464.80 | 578.62 | 231.38 | 361.20 |
| 360 | 103.83 | 462.77 | 567.84 | 269.12 | 380.15 |
| 720 | 94.15 | 474.10 | 532.68 | 262.54 | 355.80 |
| 1440 | 106.28 | 438.62 | 534.78 | 255.96 | 360.60 |
| 2880 | 85.00 | 454.87 | 535.89 | 241.00 | 344.65 |

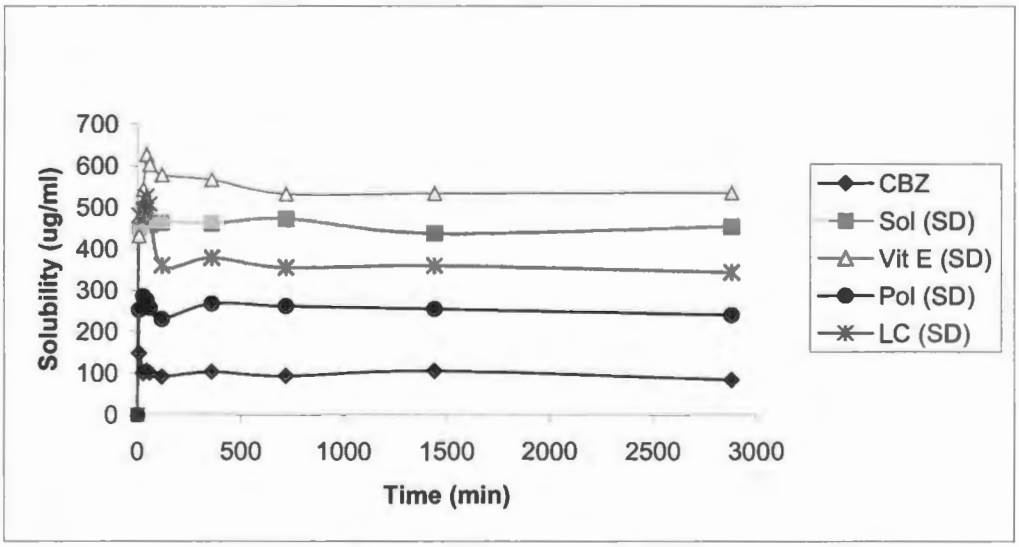



**FIGURE 10: SOLUBILTY PROFILE OF CARBAMAZEPINE AND ITS SOLID DISPERSION WITH SOLUTOL HS, VITAMIN E TPGS, POLOXAMER 188 AND LIPOCOL C 10 (90:10)**

DSC scan of the Carbamazepine represented in Figure 11 shows a distinct melting endotherm at around 192° C. Pure carbamazepine shows a small melting endotherm at 176° C followed by second endotherm at around 192° C. These two endotherms correspond to form III and I of Carbamazepine respectively. DSC scans of Solutol HS, Vitamin E TPGS, Poloxamer 188 and Lipocol C 10 with characteristic endotherm for each of the polymers are depicted in Figures 12 - 15. The DSC data carried out on the physical mixtures (Figures 16 - 19) does not show any changes in the melting endotherms of the mixture, from that of the untreated drug. Distinct endotherms for drug as well as for the polymers can be seen in those scans. Thus, we can safely conclude that there is no form of chemical interaction between the drug and any of the polymers in their physical mixtures.

The DSC scans carried out for solid dispersions of the carbamazepine with each polymers also shows the same pattern of endotherms as that of physical mixture (Figures 20 - 23).

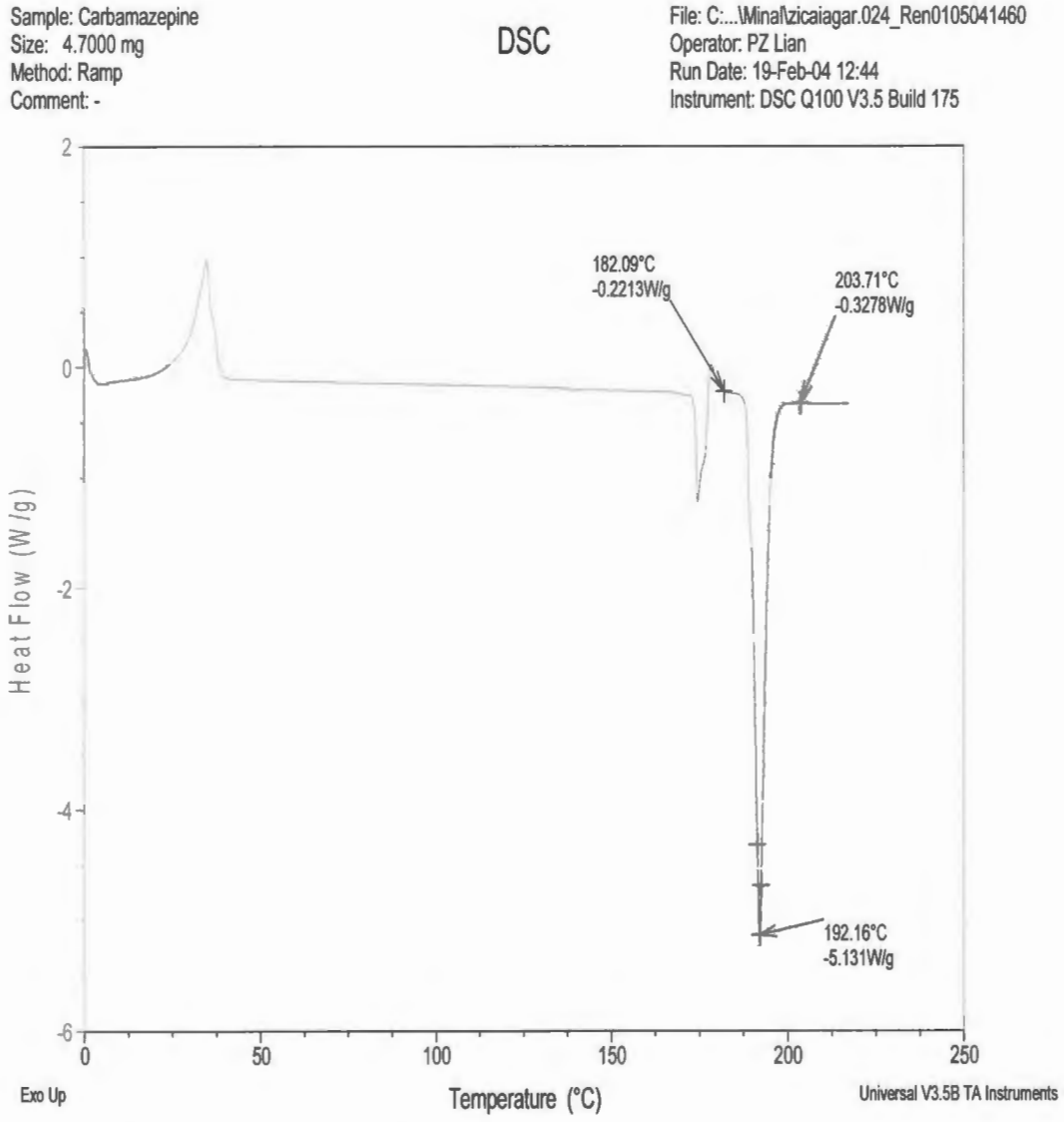



**FIGURE 11: REPRESENTATIVE THERMOGRAM SHOWING MELTING ENDOTHERM OF CARBAMAZEPINE**

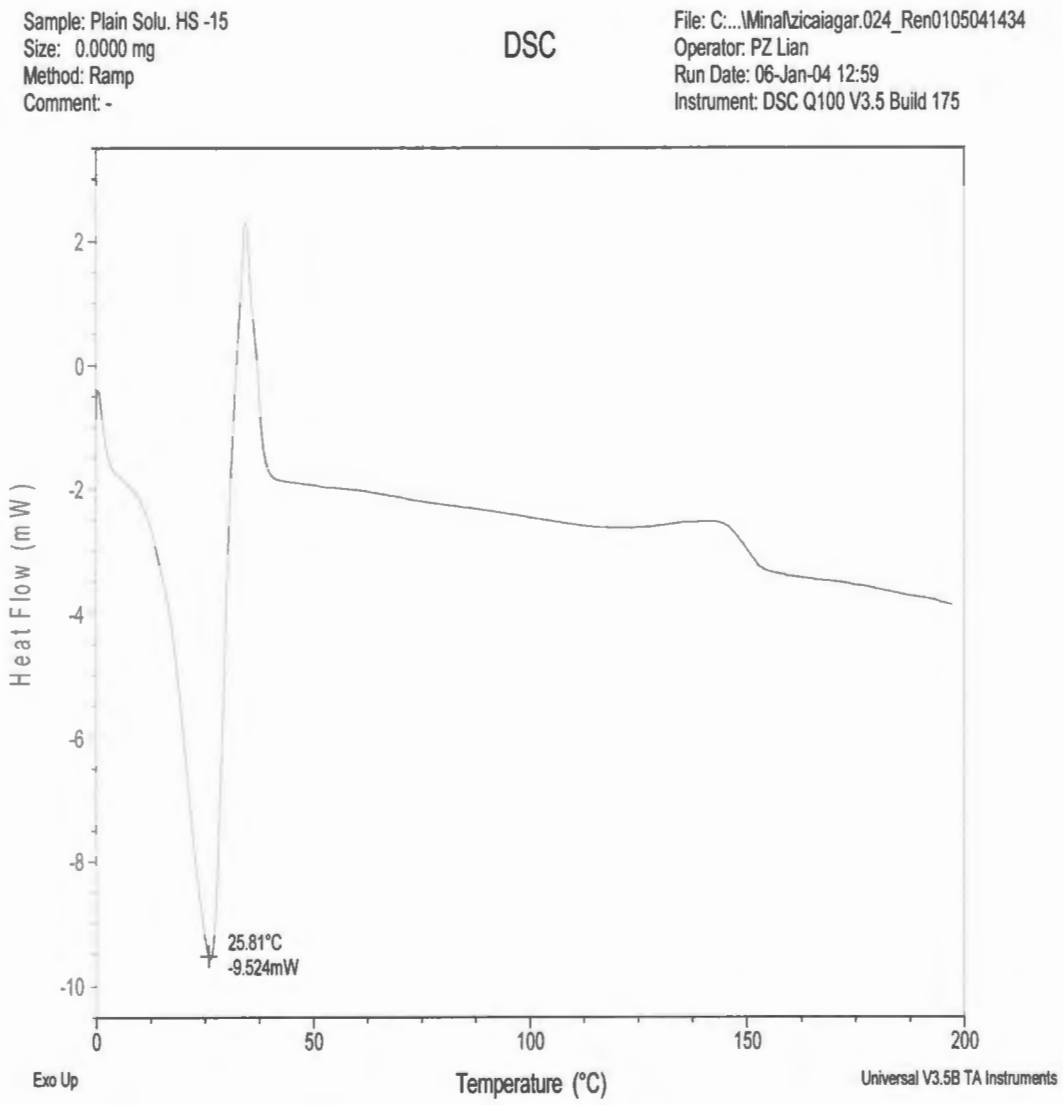



**FIGURE 12: REPRESENTATIVE THERMOGRAM SHOWING MELTING ENDOTHERM OF SOLUTOL HS**

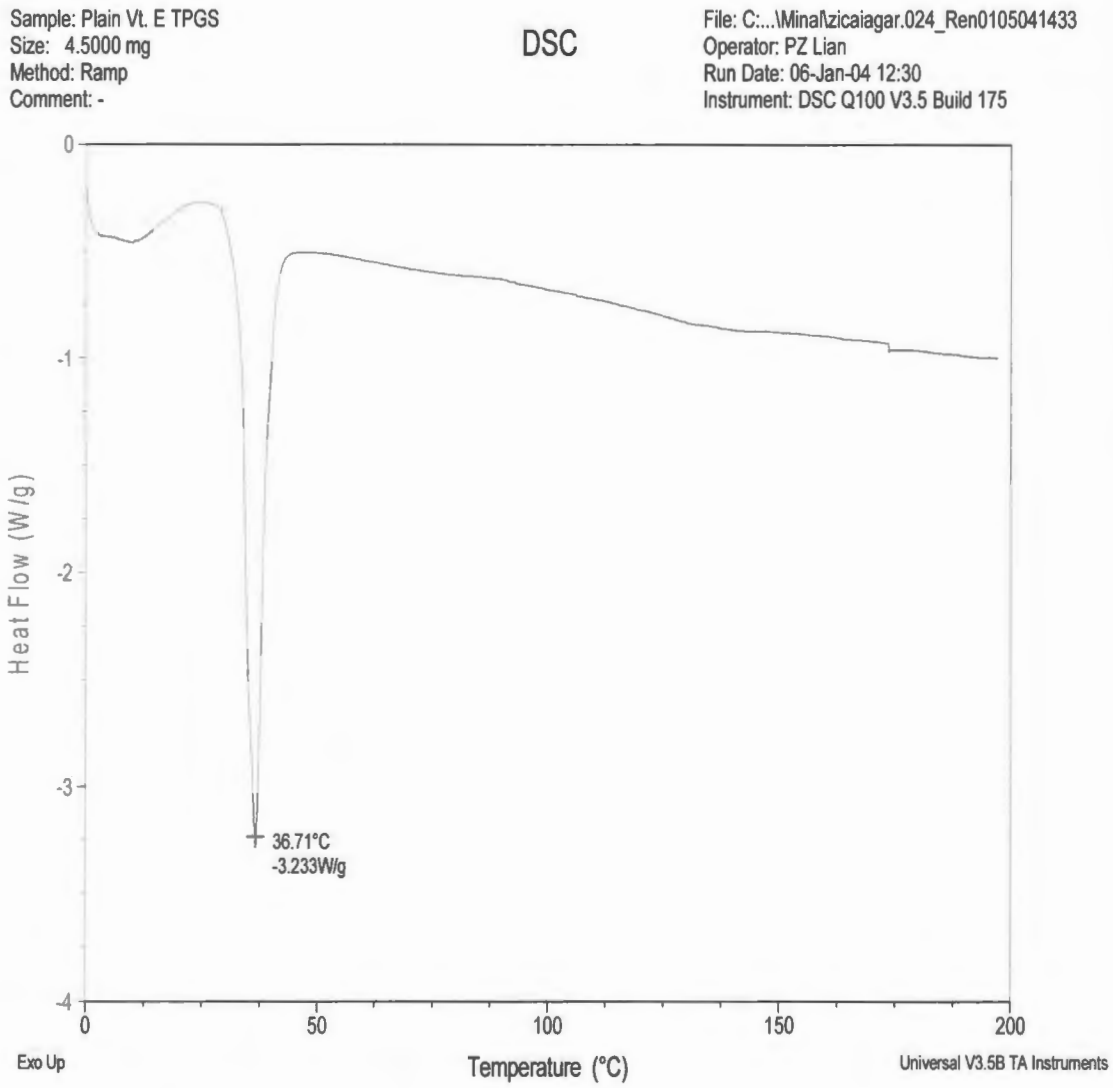



**FIGURE 13: REPRESENTATIVE THERMOGRAM SHOWING MELTING ENDOTHERM OF VITAMIN E TPGS**

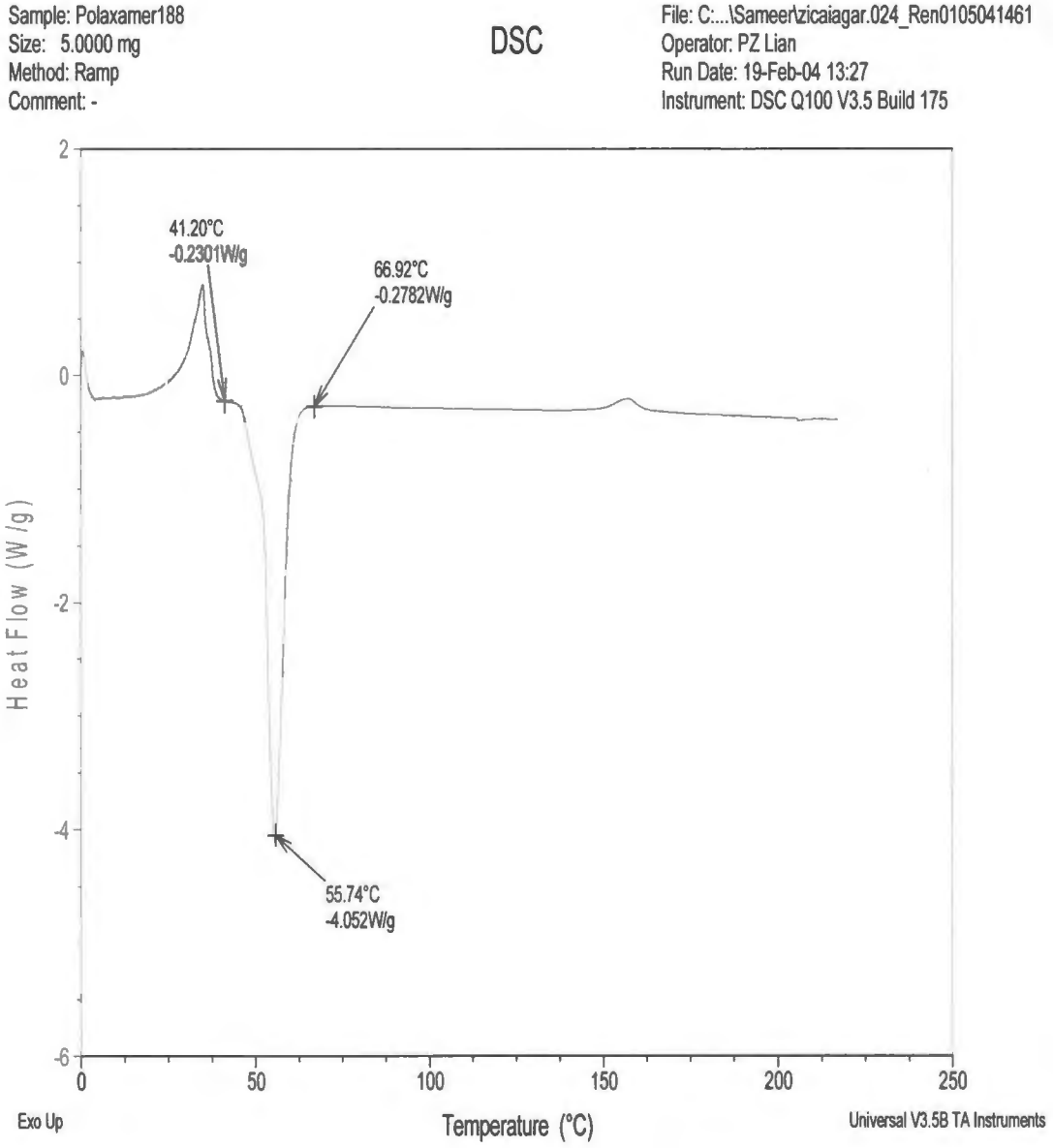



**FIGURE 14: REPRESENTATIVE THERMOGRAM SHOWING MELTING ENDOTHERM OF POLOXAMER 188**

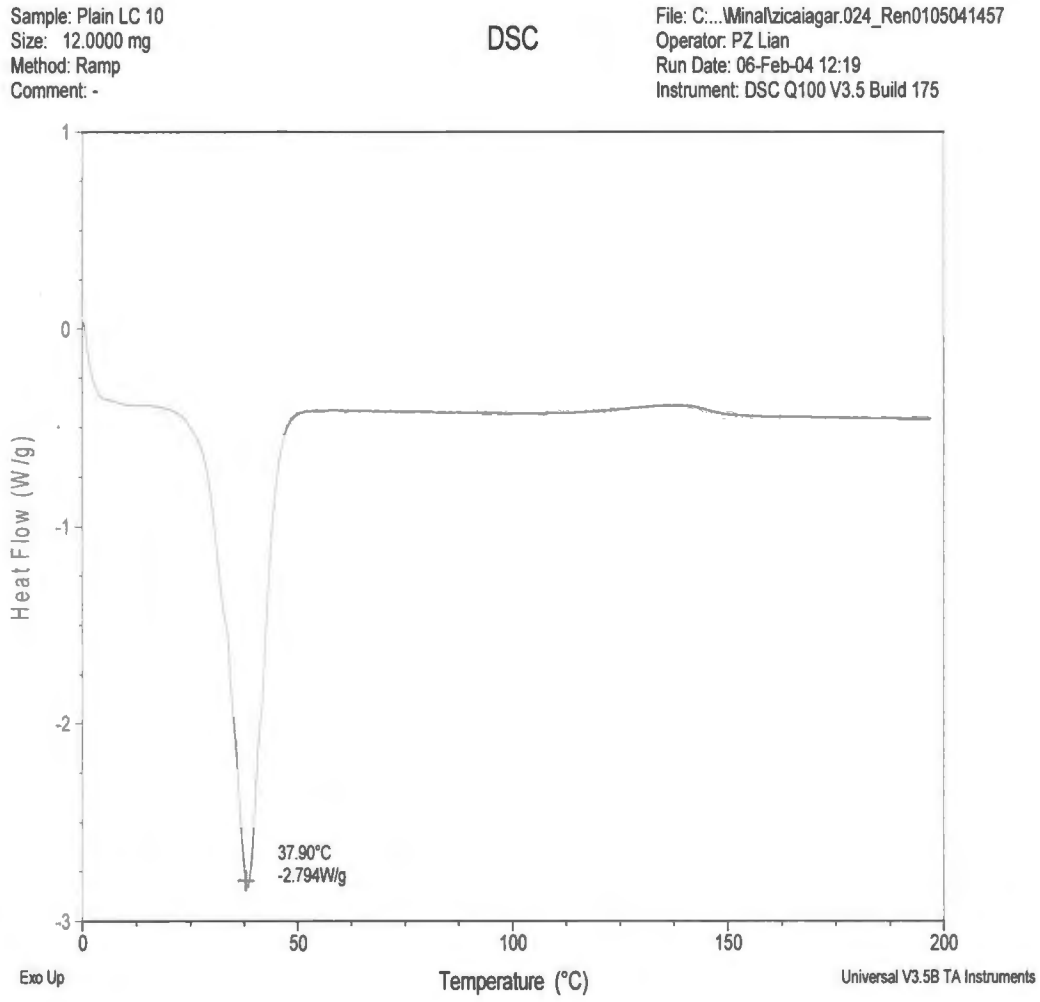



**FIGURE 15: REPRESENTATIVE THERMOGRAM SHOWING MELTING ENDOTHERM OF LIPOCOL C 10**

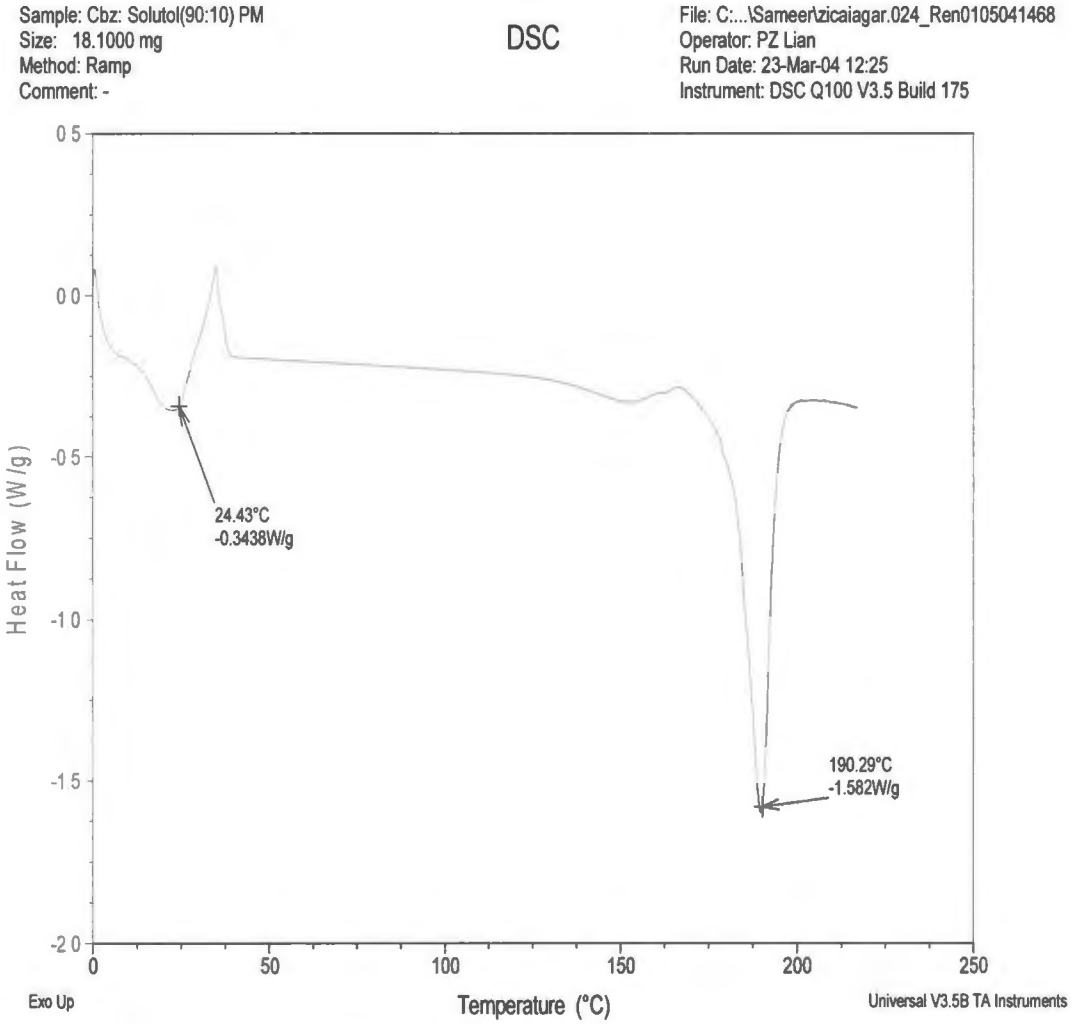



**FIGURE 16: REPRESENTATIVE THERMOGRAM OF PHYSICAL MIXTURE OF CARBAMAZEPINE AND SOLUTOL HS (90: 10)**

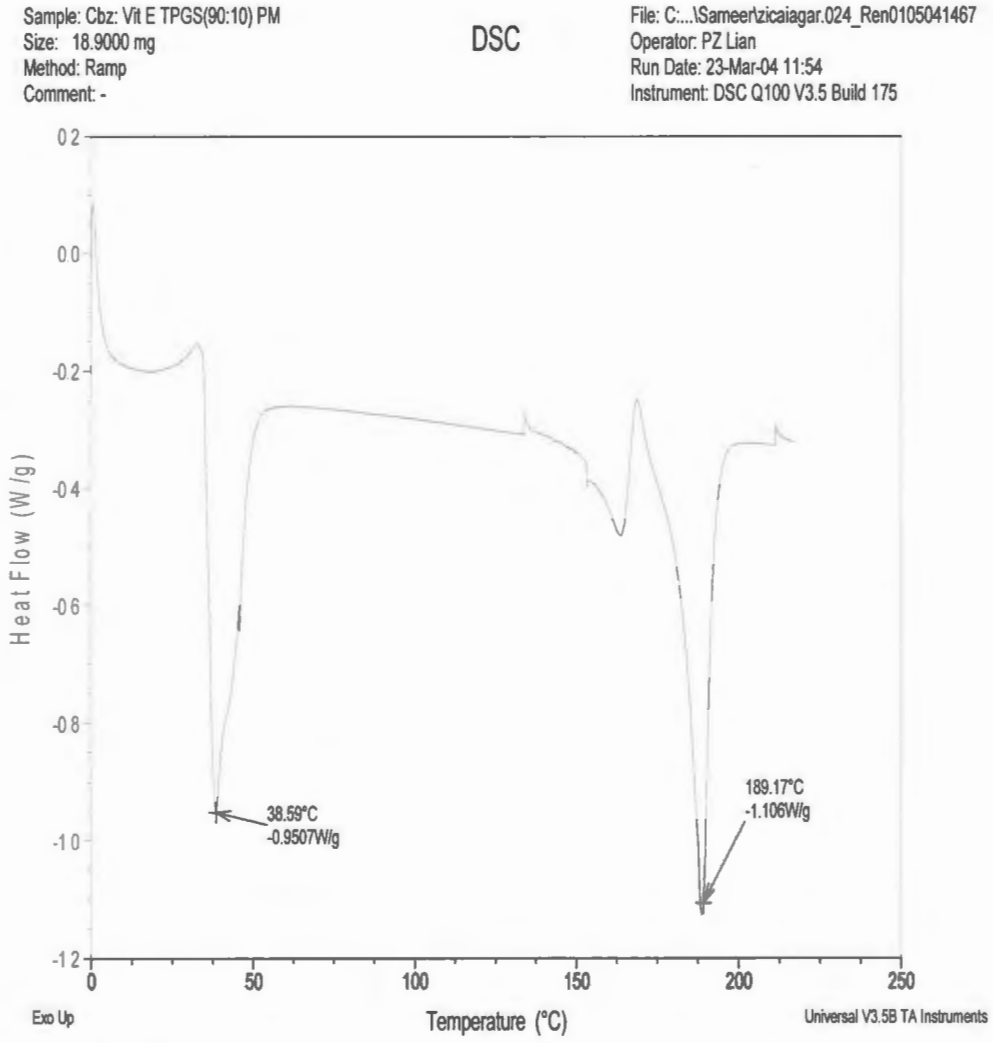



**FIGURE 17: REPRESENTATIVE THERMOGRAM OF PHYSICAL MIXTURE OF CARBAMAZEPINE AND VITAMIN E TPGS (90: 10)**

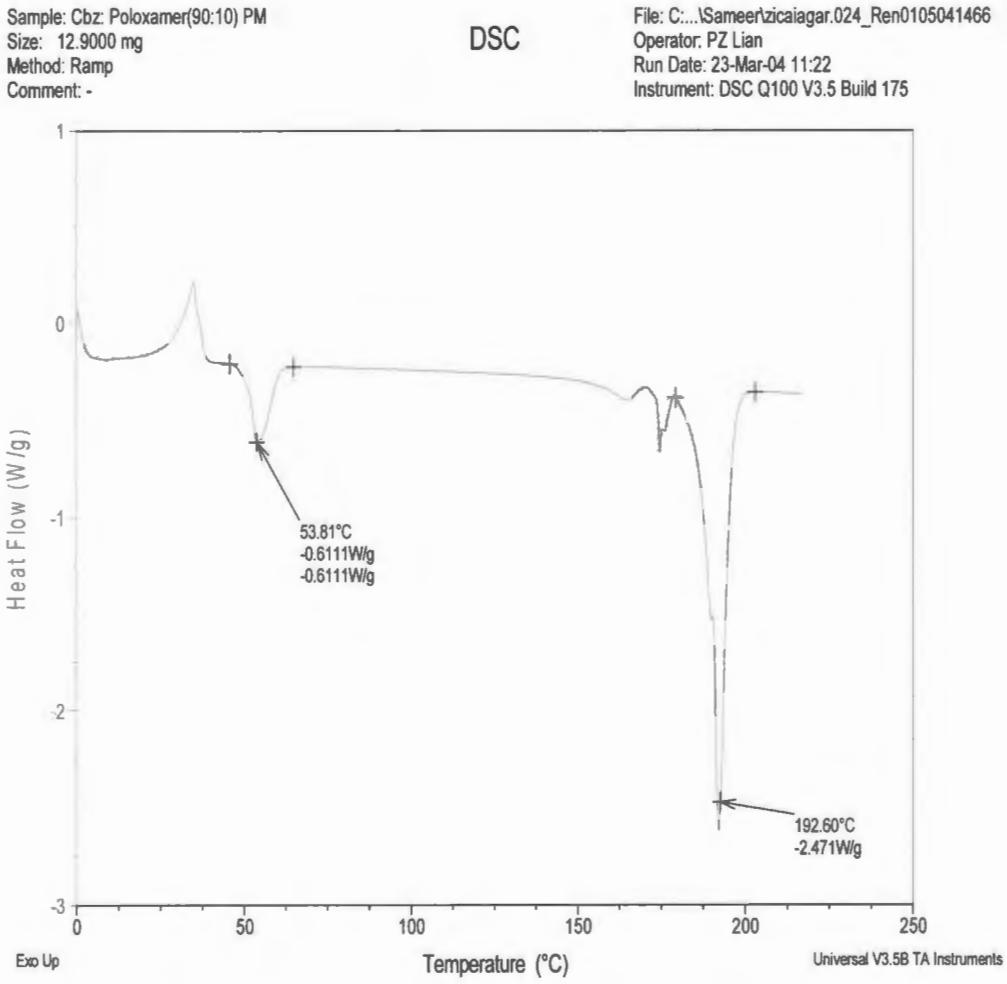



**FIGURE 18: REPRESENTATIVE THERMOGRAM OF PHYSICAL MIXTURE OF CARBAMAZEPINE AND POLOXAMER 188 (90: 10)**

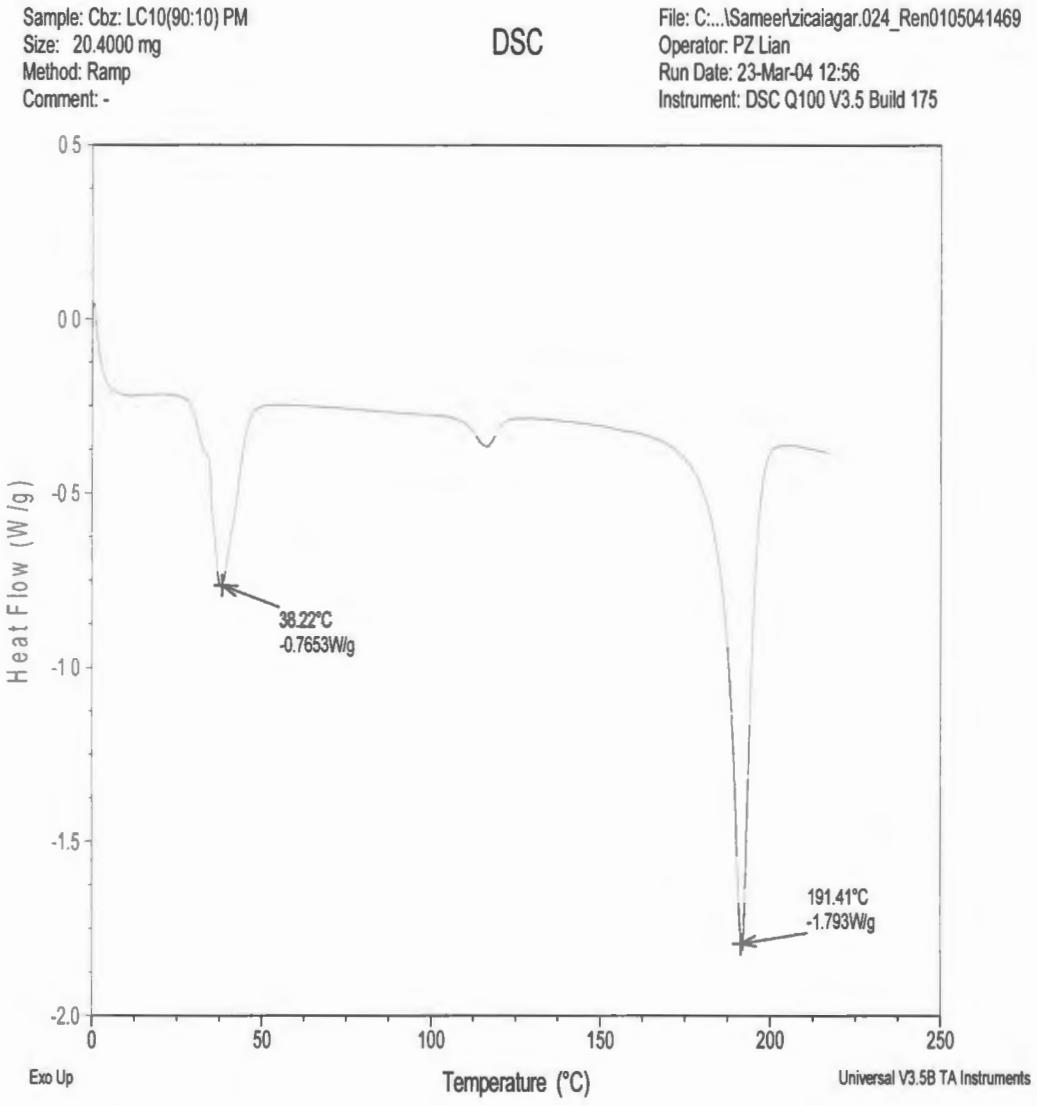



**FIGURE 19: REPRESENTATIVE THERMOGRAM OF PHYSICAL MIXTURE OF CARBAMAZEPINE AND LIPOCOL C 10 (90: 10)**

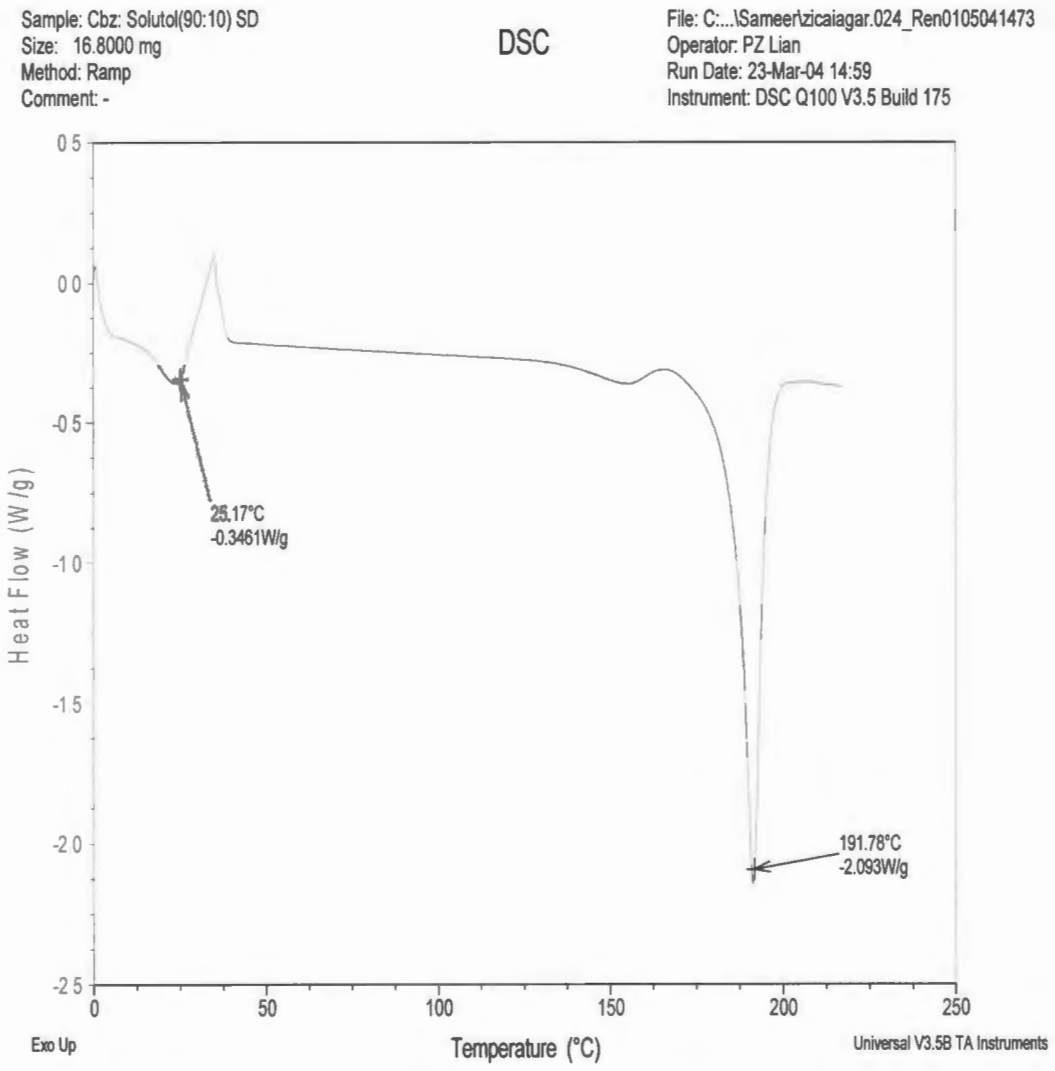



**FIGURE 20: REPRESENTATIVE THERMOGRAM OF SOLID DISPERSION OF CARBAMAZEPINE AND SOLUTOL HS (90: 10)**

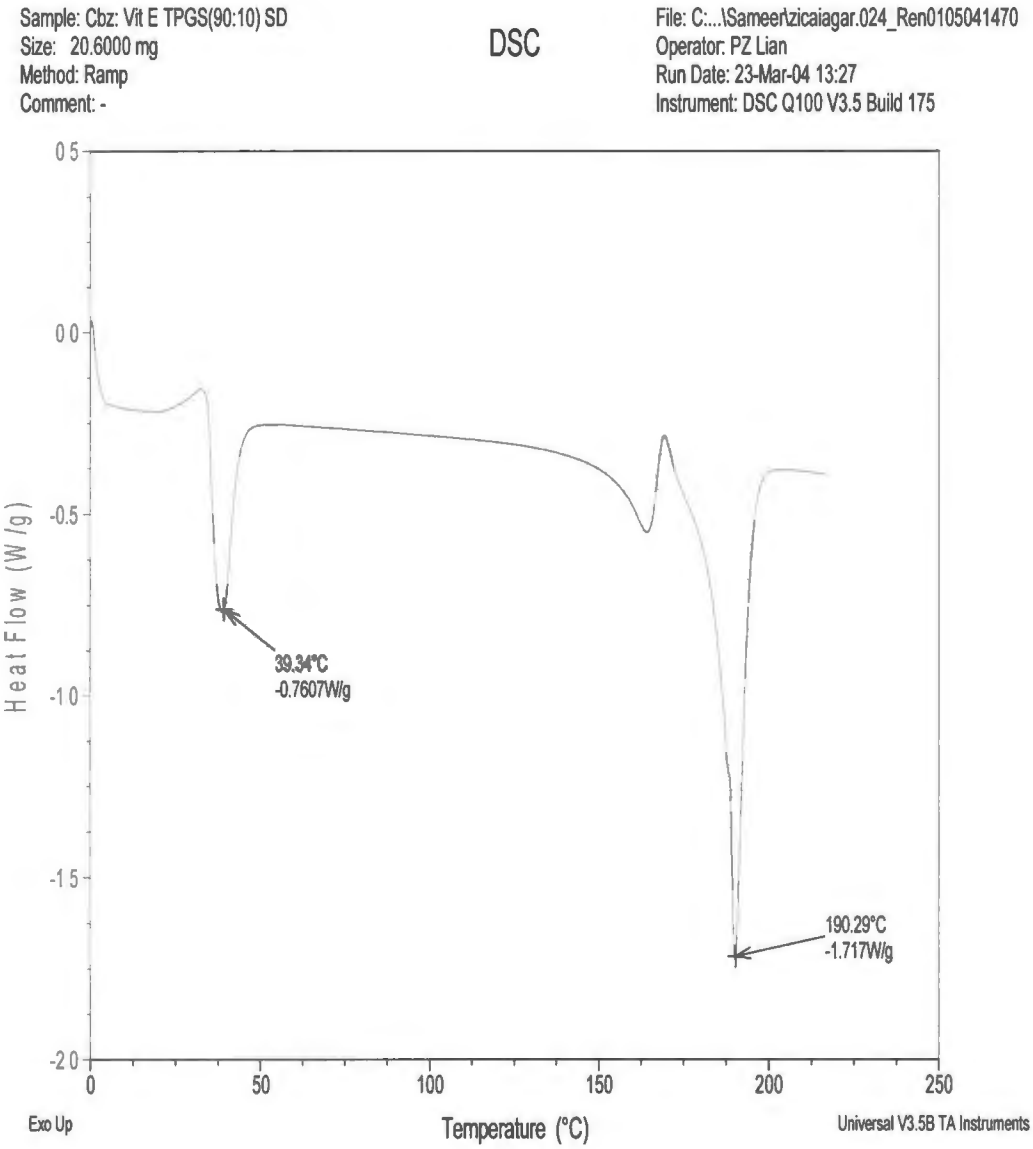



**FIGURE 21: REPRESENTATIVE THERMOGRAM ENDOTHERM OF SOLID DISPERSION OF CARBAMAZEPINE AND VITAMIN E TPGS (90: 10)**

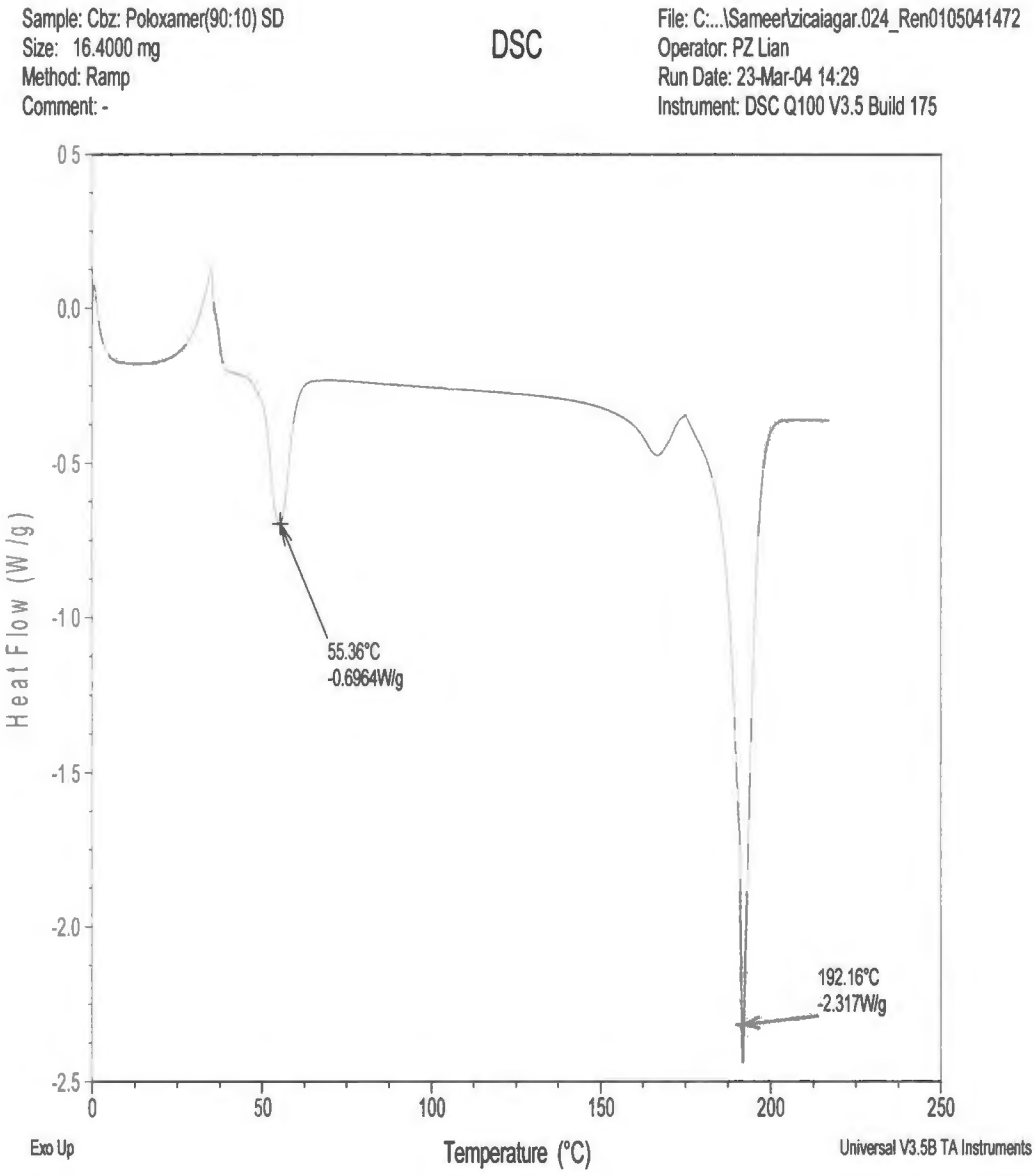



**FIGURE 22: REPRESENTATIVE THERMOGRAM OF SOLID DISPERSION OF CARBAMAZEPINE AND POLOXAMER 188 (90: 10)**

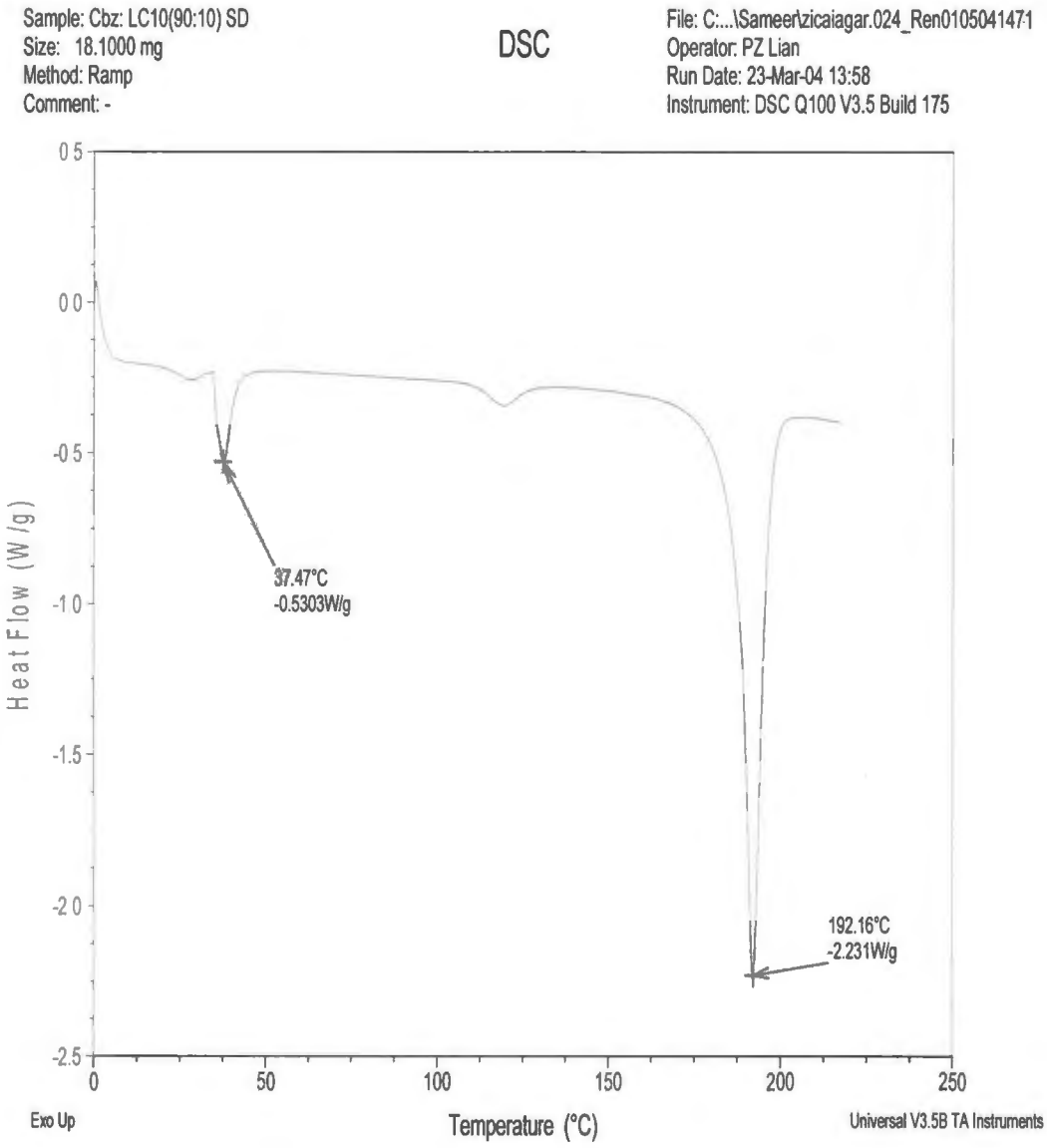



**FIGURE 23: REPRESENTATIVE THERMOGRAM OF SOLID DISPERSION OF CARBAMAZEPINE AND LIPOCOL C 10 (90: 10)**

X-Ray Diffraction studies can confirm the physical state of carbamazepine in physical mixtures as well as in solid dispersions too. All the solid dispersions and physical mixtures show the presence of distinct peaks characteristics of crystallinity. Pure carbamazepine shows peaks at the region from 150-500 on the X-ray scan represented in Figure 24. Solutol HS, Vitamin E TPGS, Poloxamer 188 and Lipocol C 10 show distinct peaks in the region from 250-500 on the X-ray Scan (Figures 25 - 28). The characteristics peaks of carbamazepine were also evident in all the physical mixtures (Figures 29 - 32). Thus, simply mixing of the drug and polymers did not change the physical state of either of the components. Figures 33 - 36 show X-ray diffraction pattern of carbamazepine solid dispersions. Solid dispersions of carbamazepine show characteristics peaks of carbamazepine. We can conclude that solid dispersion also did not change the physical state of either of the components.

From the DSC and X-ray data we can safely conclude that there is no change in crystallinity pattern of either of the components.

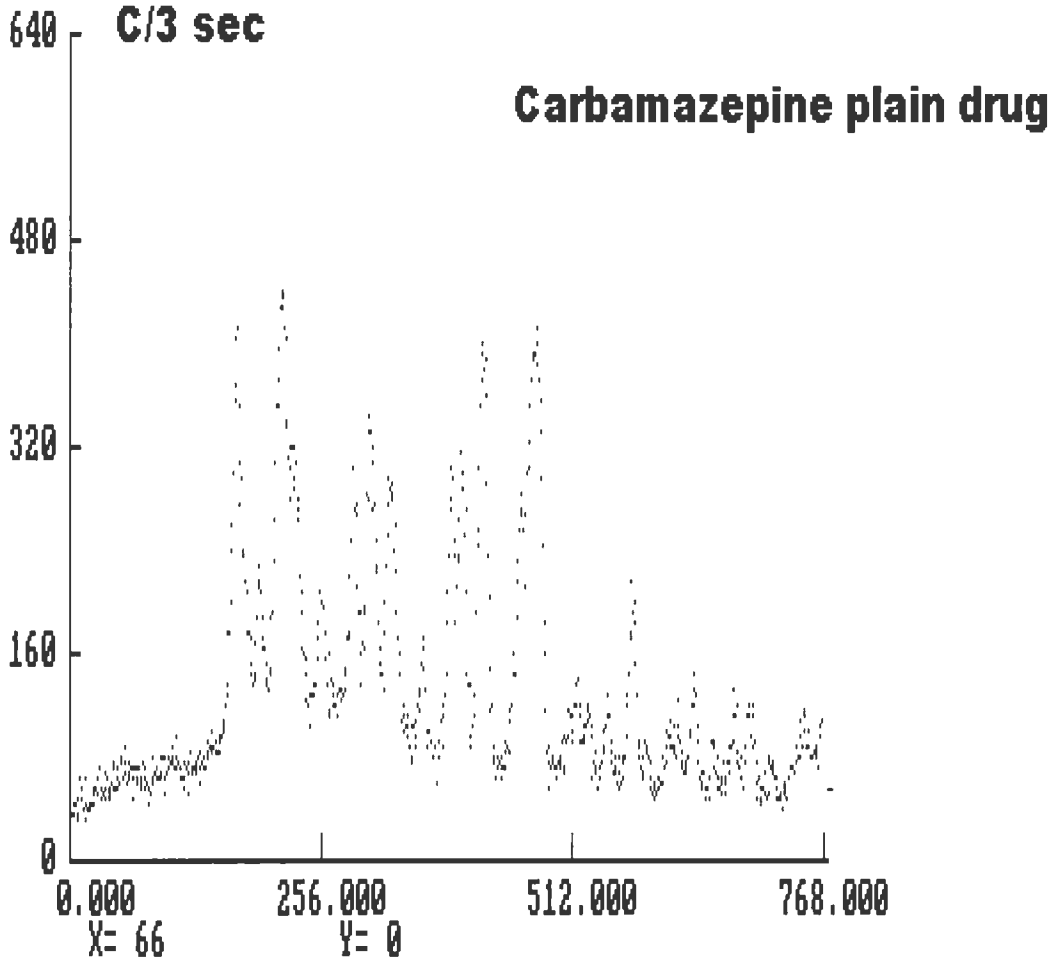



**FIGURE 24: XRD SCAN OF THE SAMPLE OF CARBAMAZEPINE**

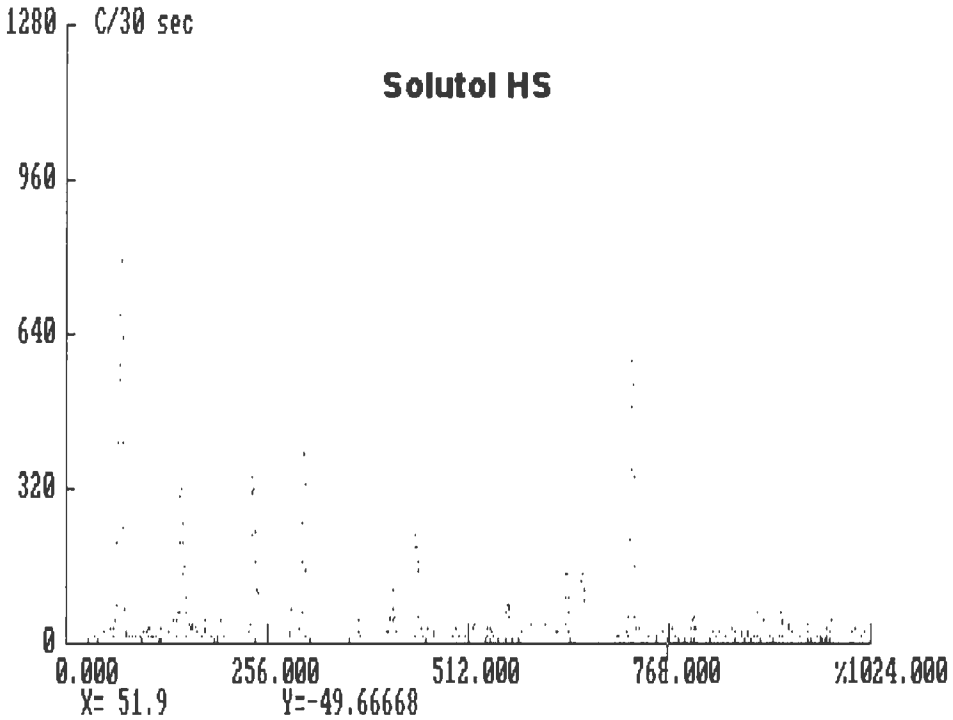



**FIGURE 25: XRD SCAN OF SAMPE OF SOLUTOL HS**

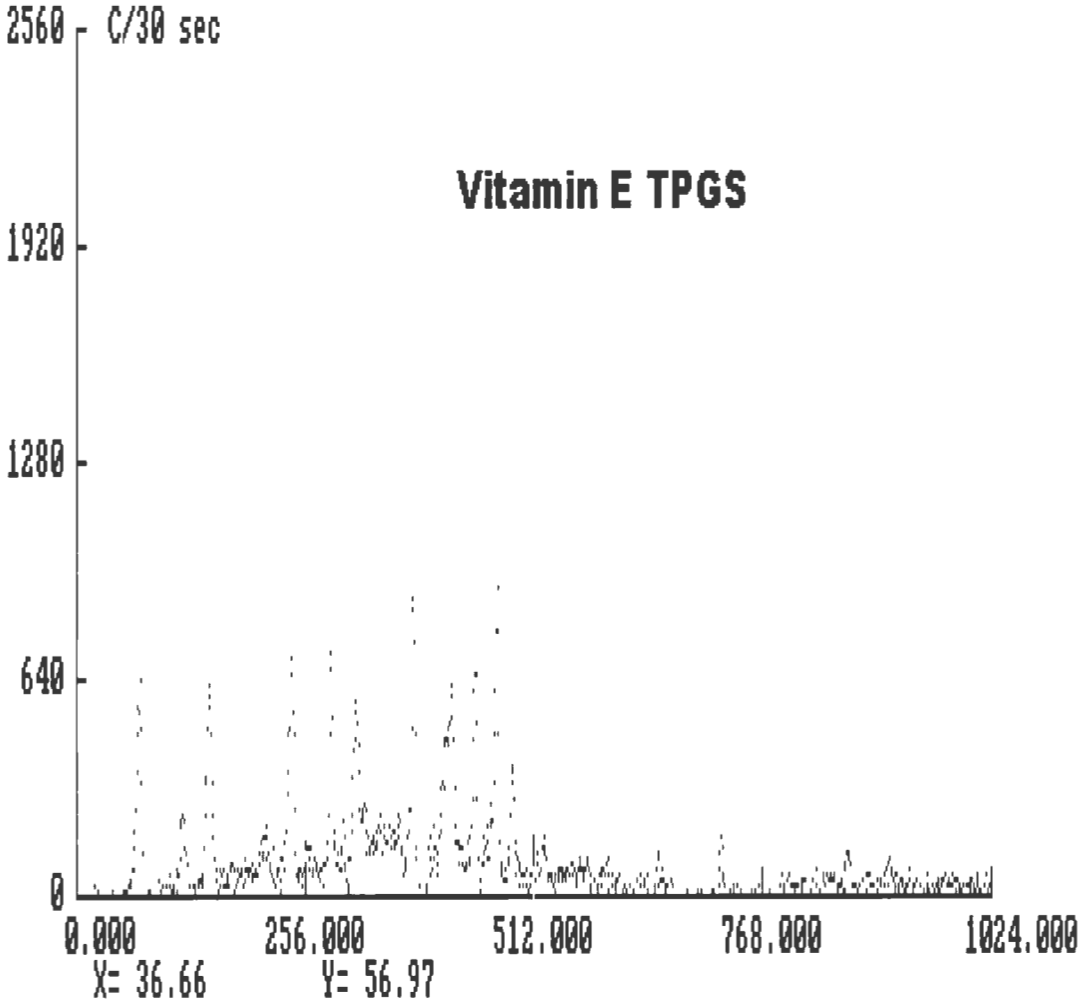



**FIGURE 26: XRD SCAN OF THE SAMPLE OF VITAMIN E TPGS**

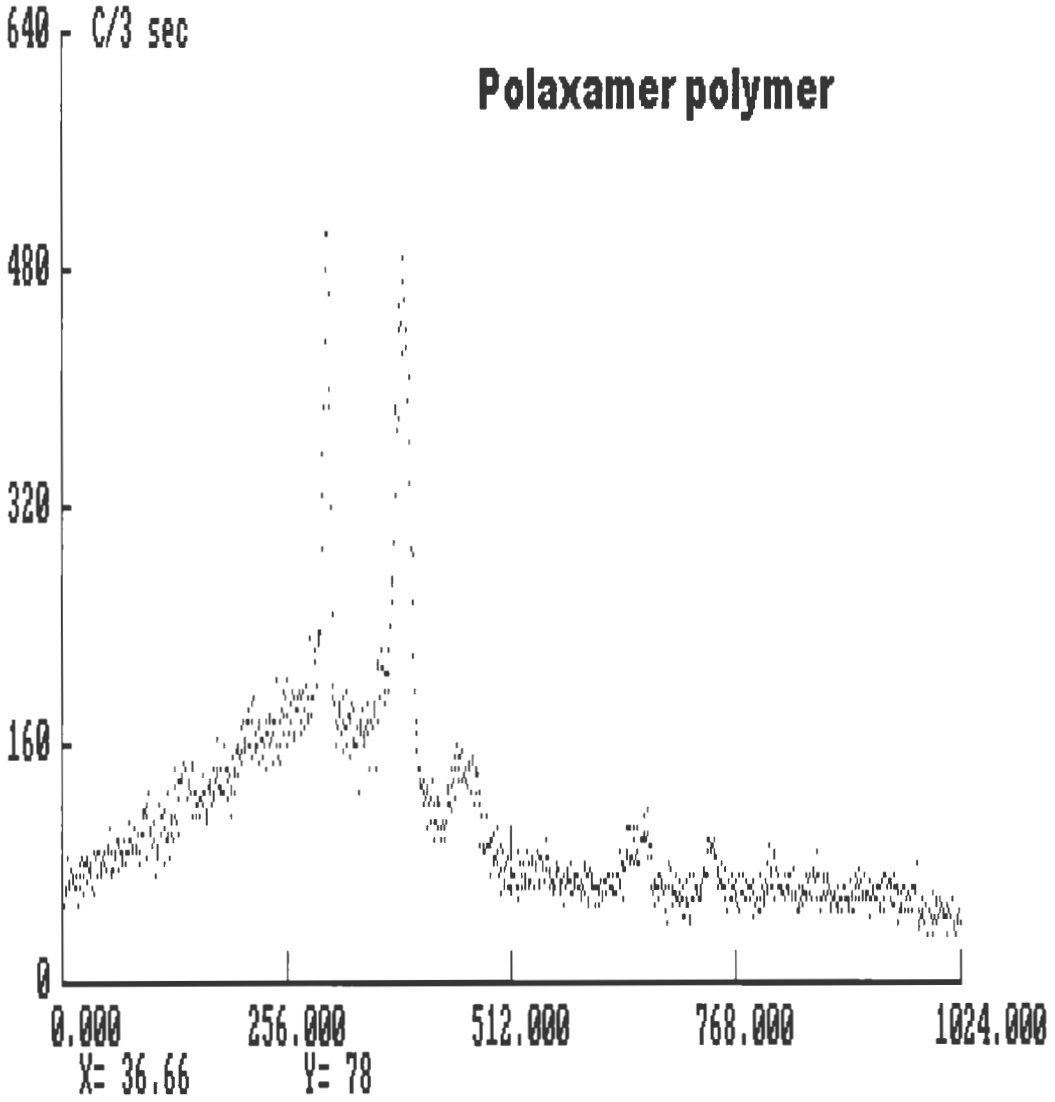



**FIGURE 27: XRD SCAN OF THE SAMPLE OF POLOXAMER 188**

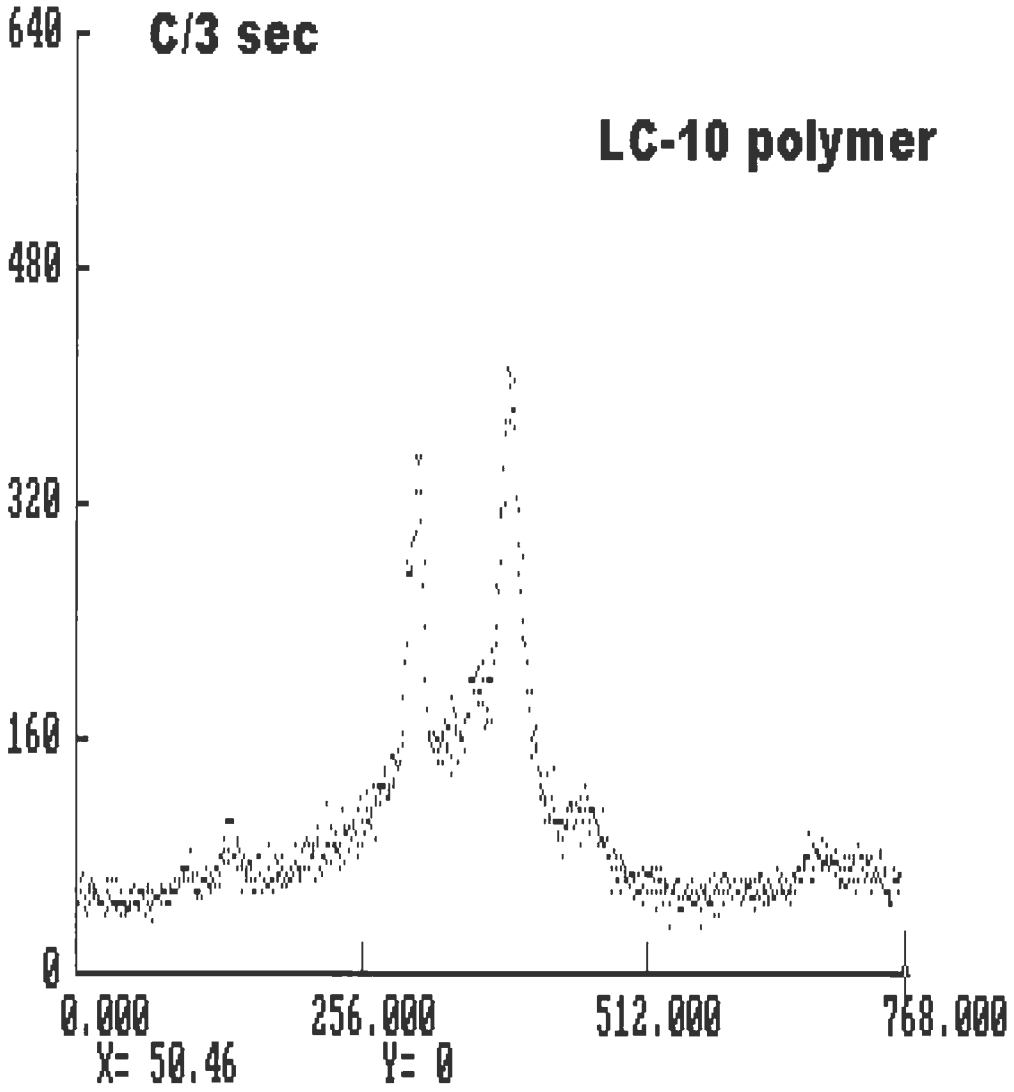



**FIGURE 28: XRD SCAN OF SAMPE OF LIPOCOL C 10**

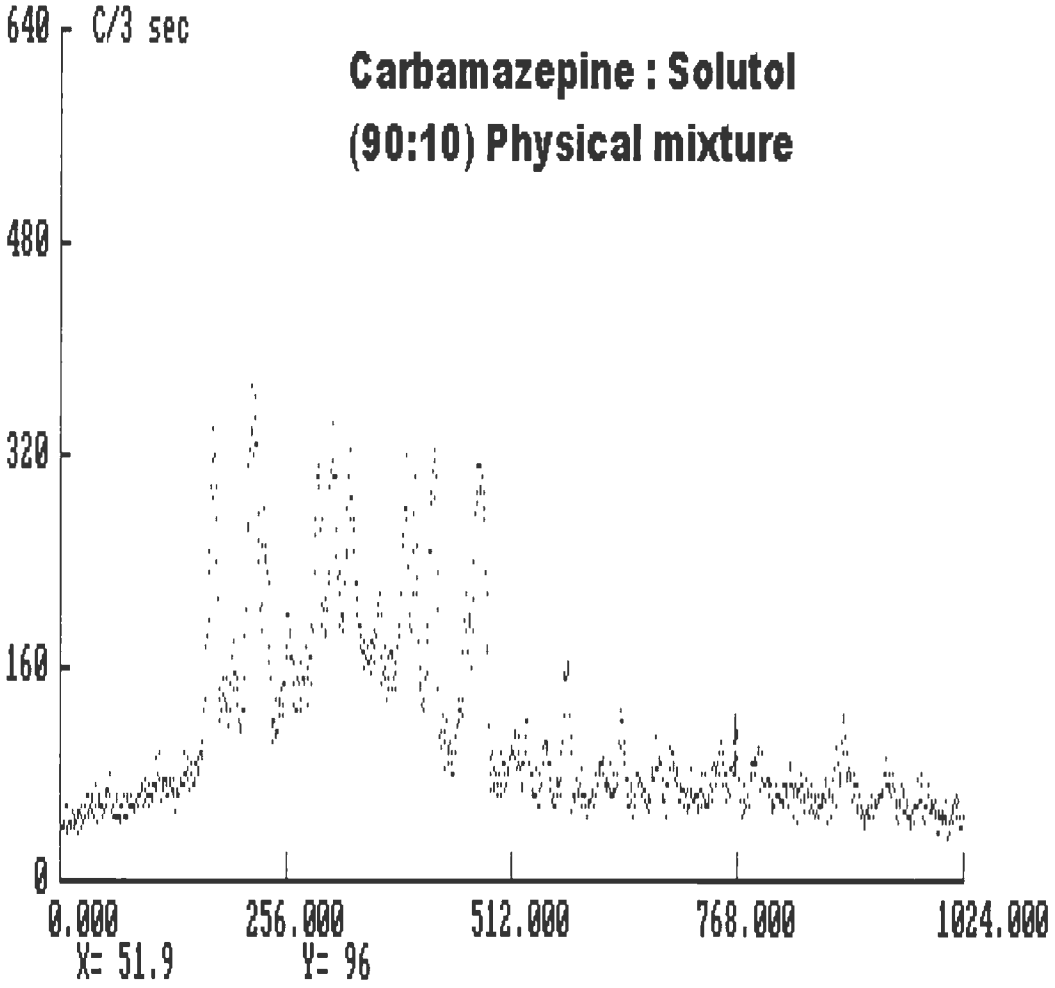



**FIGURE 29: XRD SCAN OF PHYSICAL MIXTURE OF CARBAMAZEPINE AND SOLUTOL (90:10)**

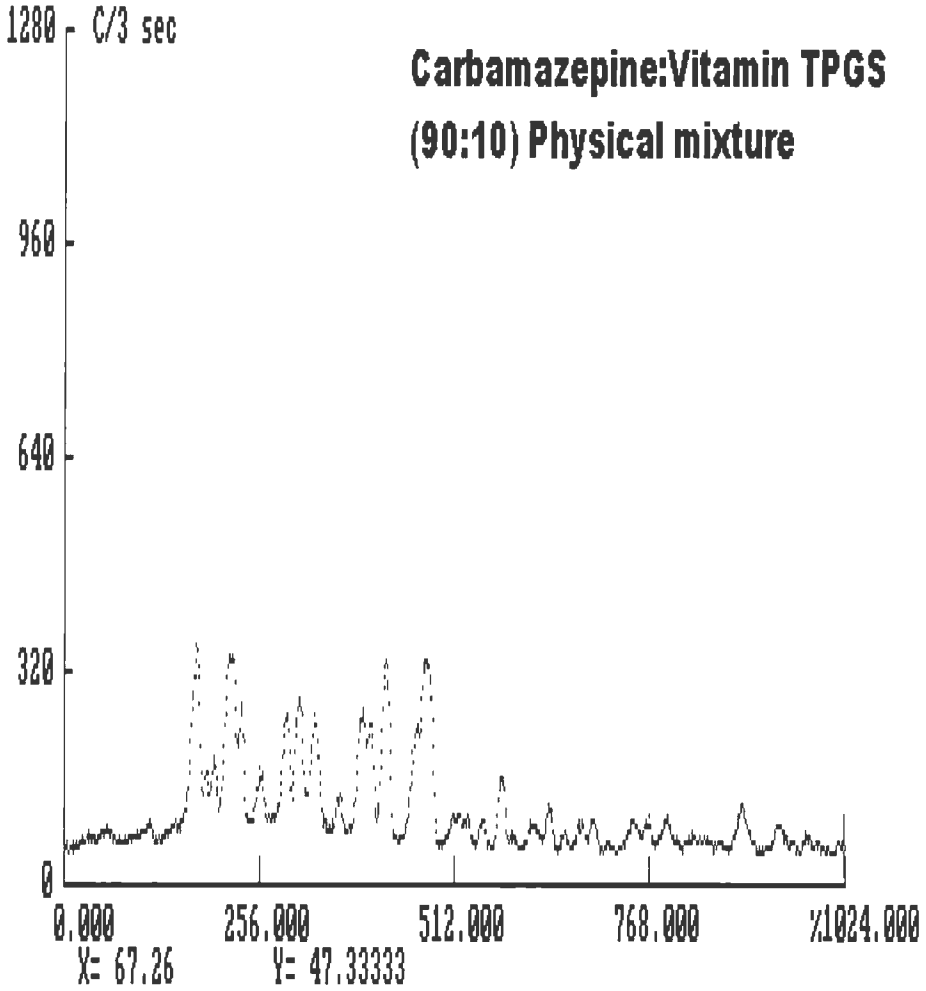



**FIGURE 30: XRD SCAN OF PHYSICAL MIXTURE OF CARBAMAZEPINE AND VITAMIN E TPGS (90:10)**

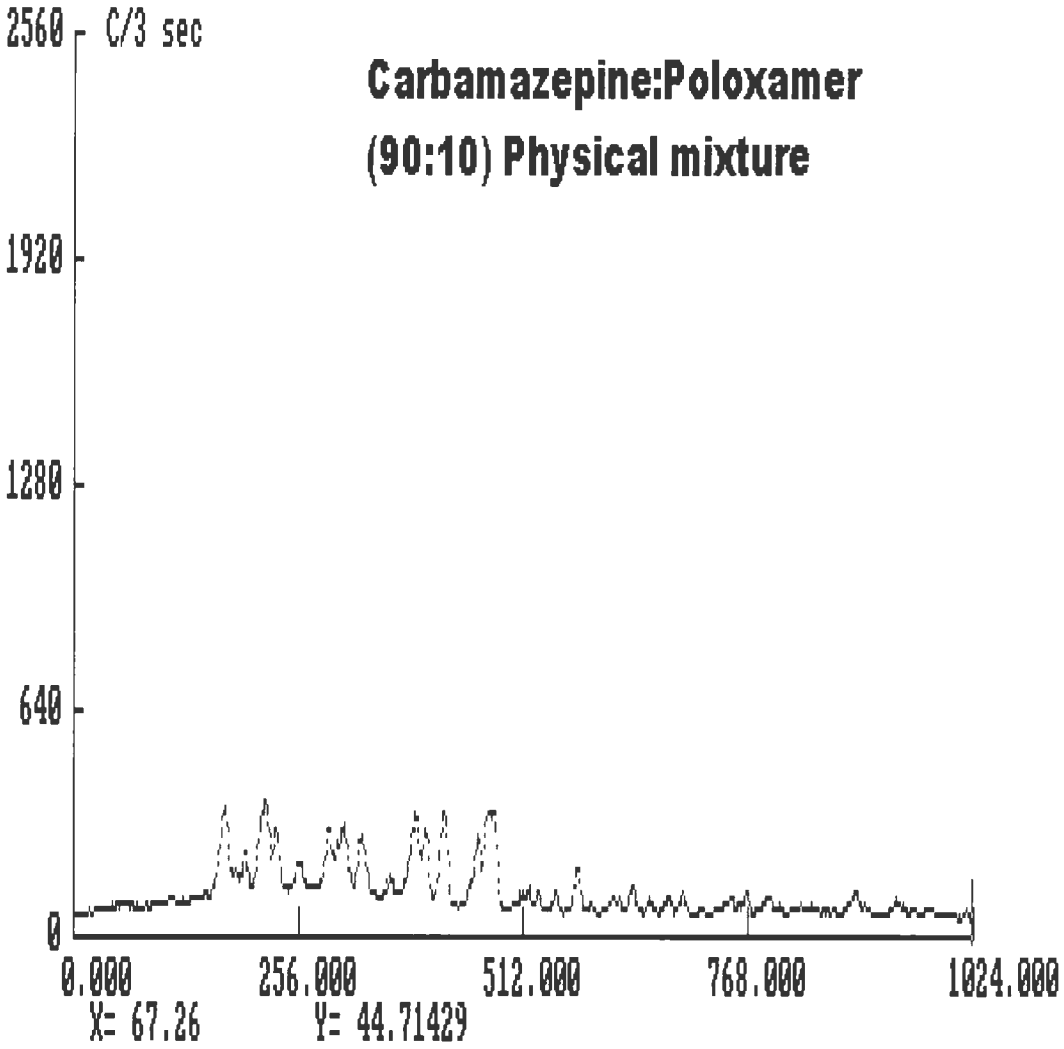



**FIGURE 31: XRD SCAN OF PHYSICAL MIXTURE OF CARBAMAZEPINE AND POLOXAMER (90:10)**

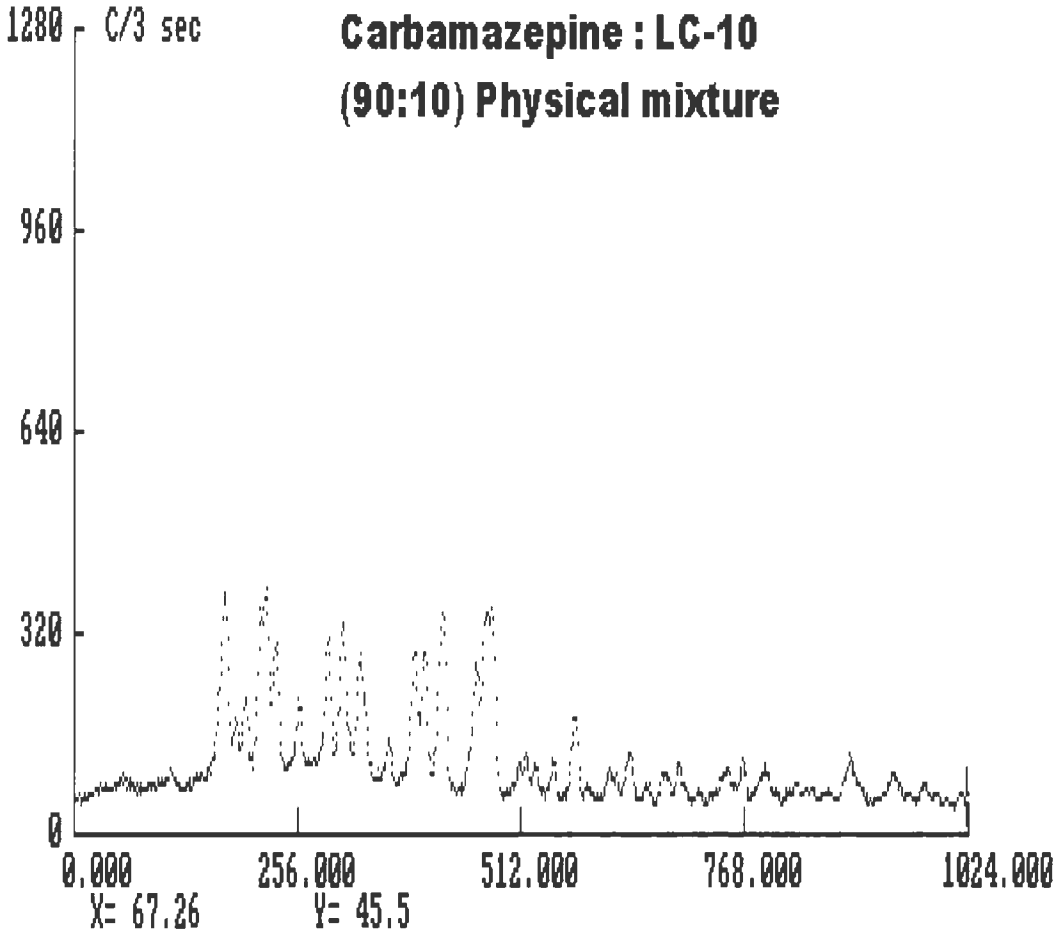



**FIGURE 32: XRD SCAN OF PHYSICAL MIXTURE OF CARBAMAZEPINE AND LIPOCOL C 10 (90:10)**

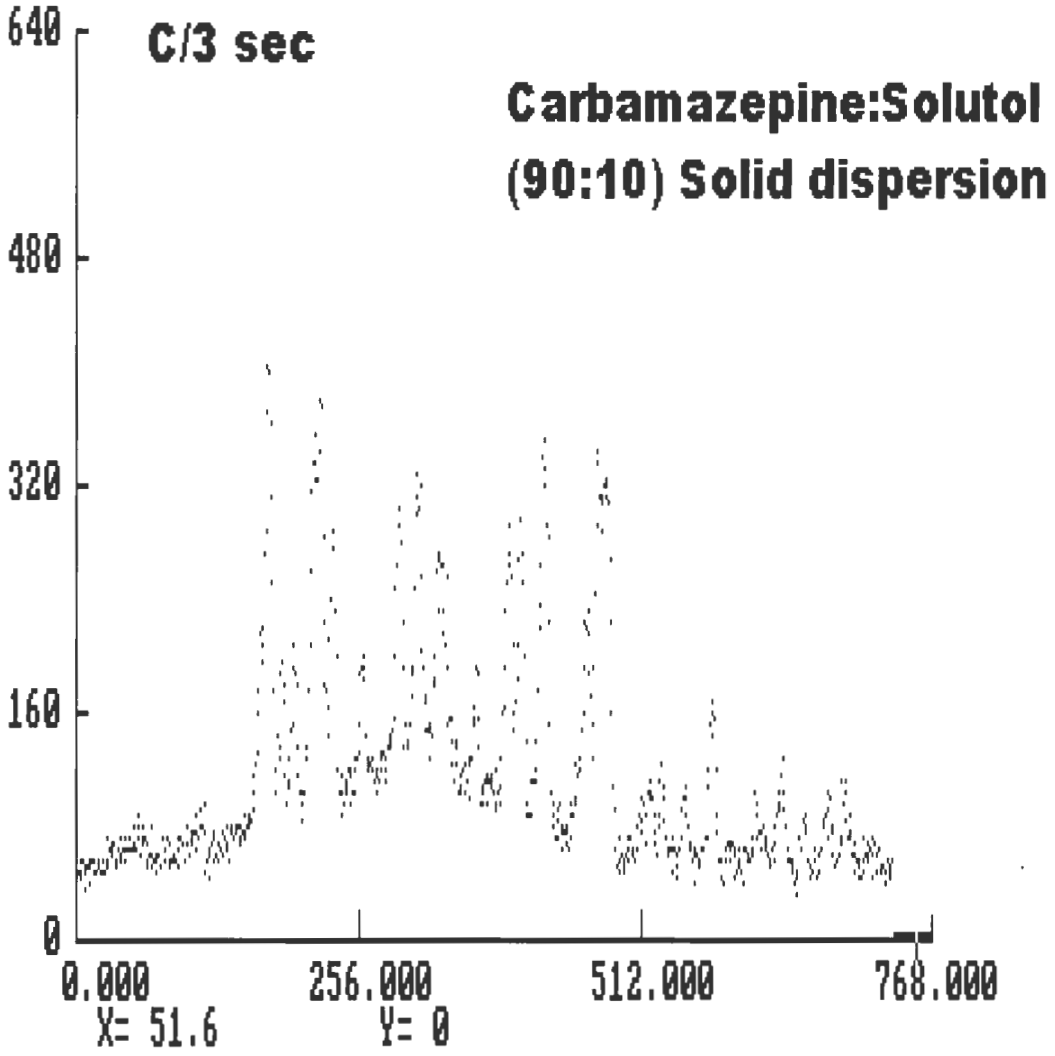



**FIGURE 33: XRD SCAN OF SOLID DISPERSION OF CARBAMAZEPINE AND SOLUTOL HS (90:10)**

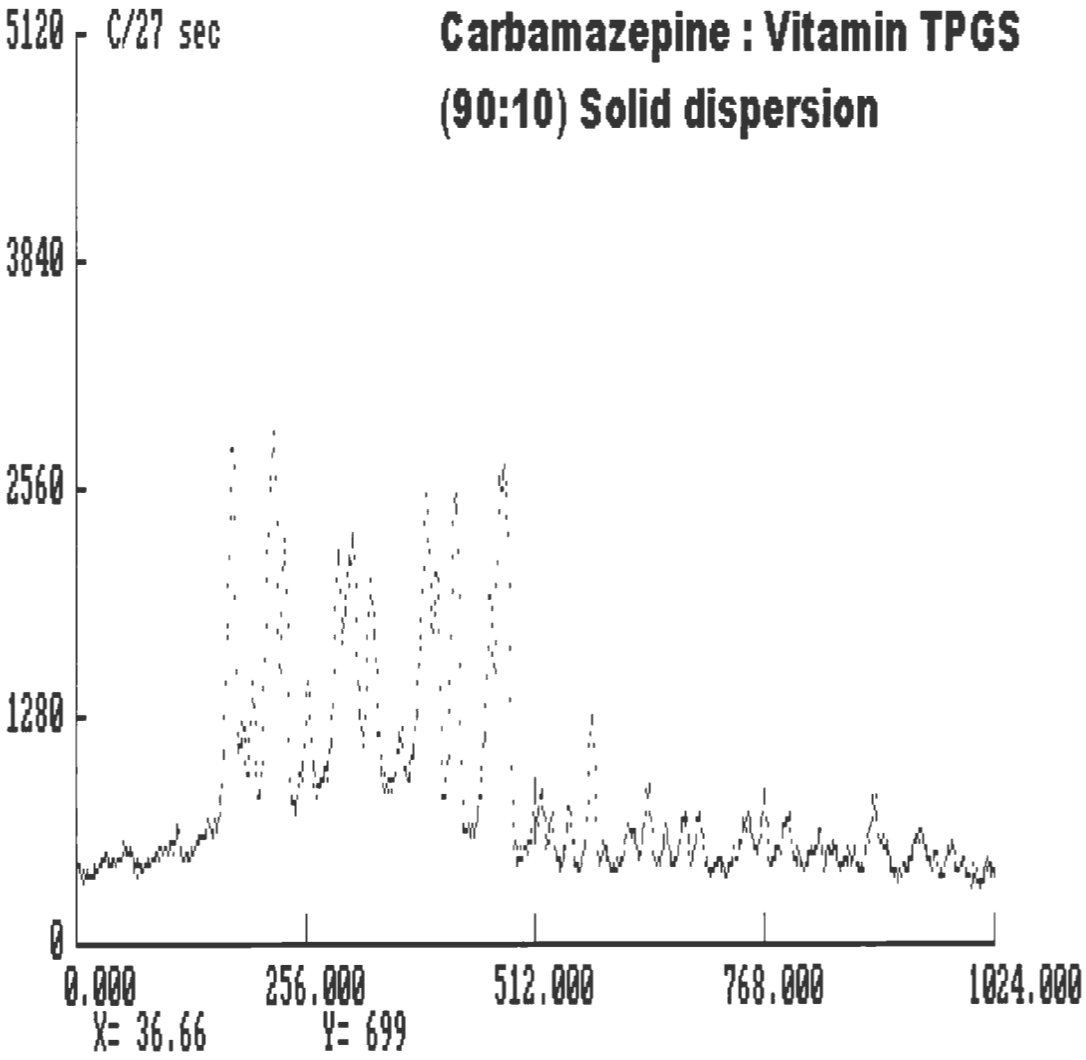



**FIGURE 34: XRD SCAN OF SOLID DISPERSIONS OF CARBAMAZEPINE AND VITAMIN E TPGS (90:10)**

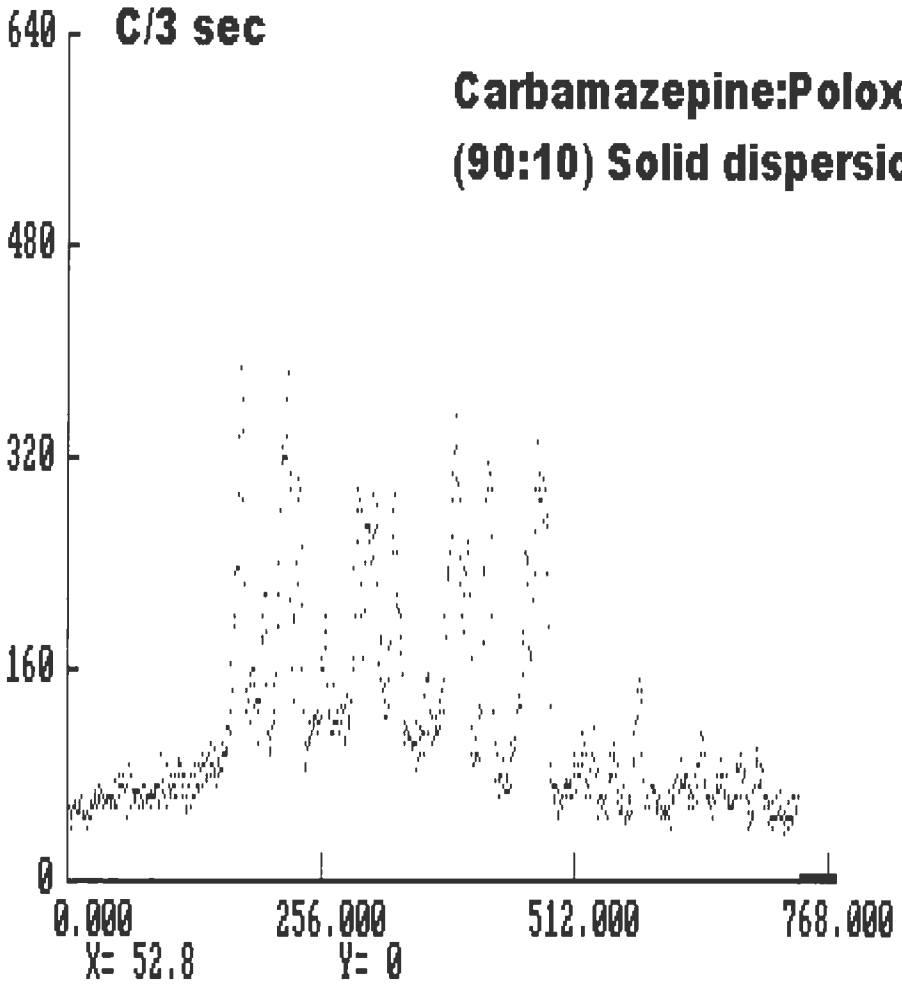



**FIGURE 35: XRD SCAN OF SOLID DISPERSION OF CARBAMAZEPINE AND POLOXAMER 188 (90:10)**

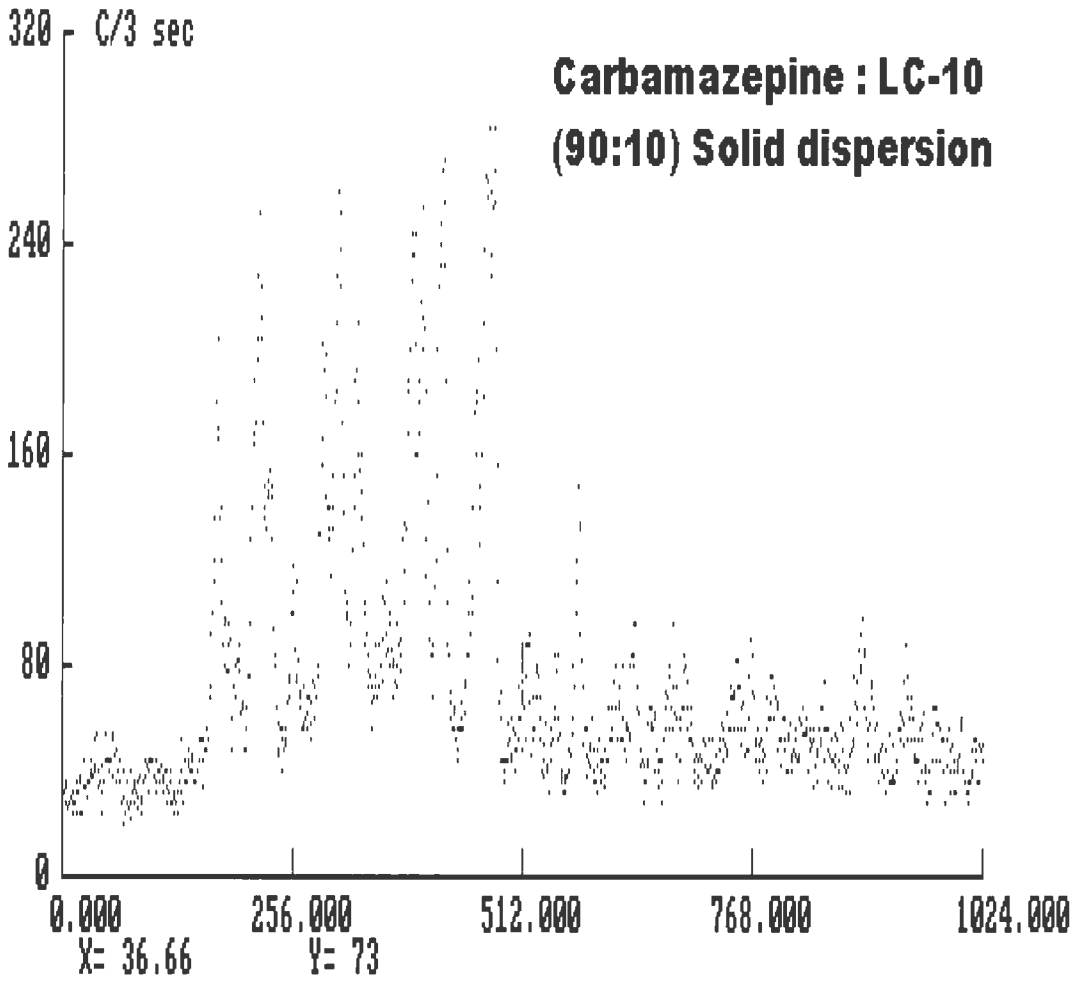



**FIGURE 36: XRD SCAN OF SOLID DISPERSION OF CARBAMAZEPINE AND LIPOCOL C 10 (90:10)**

One of the major reasons for the poor solubility of carbamazepine is conversion of anhydrous form to the dihydrate form when it comes into contact with water (13,14). The solubility of anhydrous carbamazepine is approximately twice that of it dihydrate (15). Polymers have got polar and non-polar ends in their structure and they can interact with the polar and non-polar group present in the carbamazepine structure. This way they can prevent the formation of dihydrate in aqueous solutions. It has been shown that some surfactants and polymers prevent the dihydrate formation of carbamazepine by micelle formation and also increase solubility to considerable extent (8). The presence of hydroxypropyl methylcelluose in sustained released tablets also has been shown to affect the dissolution of the drug due to its inhibitory effect on dihydrate formation (16). Recently, it was shown that hydroxypropyl cellulose inhibited the dihydrate formation of carbamazepine (17). Also, it has been show that solid dispersions with polyethylene glycol (PEG) have an inhibitory effect on dihydrate formation and an enhanced effect on the solubility of carbamazepine (18).

In the present study, enhancement of solubility of carbamazepine can be attributed to different factors like wetting effect, the formation of amorphous carbamazepine, and presence of carbamazepine as very small crystallites within the dispersion, and inhibitory effect of polymers on the conversion of anhydrous to dihydrate carbamazepine. In physical mixtures of carbamazepine with all the polymers (Figures 6 - 9), there is not a significant increase in solubility, which indicates that there is very low wetting effect of the polymers on the solubility enhancement of carbamazepine. The DSC scans (Figures 20 - 23) and X-ray scans (Figures 33 - 36) of solid dispersion of carbamazepine with different polymers are similar to the DSC (Figures 16 - 19) and

X-ray scans (Figures 29 - 32) of physical mixtures of carbamazepine with different polymers. This tells us that there is less possibility of formation of amorphous carbamazepine as there is no change in melting endotherms or no change in crystallinity pattern. But increasing the polymer content showed formation of amorphous carbamazepine. This may tell us that there may be presence of carbamazepine as very small crystallites of carbamazepine within the mixture at low content of polymer. Lipocol C 10 is used in this study to try to determine mechanism of solubility enhancement. Lipocol C 10 is a surfactant with hydrophilic lipophilic balance (HLB) value of 13.0, which has the same HLB value as that of Vitamin E TPGS (13.2). A physical mixture of Lipocol C 10 confirms that there is no significant wetting effect to enhance the solubility of carbamazepine. A solid dispersion of carbamazepine and Lipocol C 10 gives nearly a 4-fold increase in solubility profile of carbamazepine. So it can be confirmed that the drug may be forming a micellar solubilization when it is incorporated into solid dispersions which has confirmed by Luthala et al. Physical mixtures do not show any positive effect on the enhancement of the solubility of carbamazepine. DSC and X-ray diffraction scans do not show formation of amorphous carbamazepine within the system. But the solubility profiles of solid dispersions (Figures 6 - 9) show great enhancement of the solubility of carbamazepine. The only other possible reason that we can postulate for this enhancement of solubility of carbamazepine would be inhibitory effect of polymers on the conversion of anhydrous to dihydrate carbamazepine this can further be further proved from the literature (18). Also, there is greater solubilization observed with Vitamin E TPGS than Lipocol C 10, which can be attributed to individual inhibitory

effect of respective polymers for the conversion of anhydrous to dihydrate carbamazepine. Therefore, enhancement of solubility of carbamazepine may be largely attributed to presence of very small crystallites within the dispersion and individual inhibitory effect of respective polymers for the conversion of anhydrous to dihydrate carbamazepine.

The ANOVA table (Table 5) summarizes the statistical analyses conducted. From the table we can see that the P-values for the polymer, process and the polymer-process interaction are lower than the $\alpha$-value (0.05). Hence we can conclude that these three factors have a significant effect on solubility of the drug.

The Student-Newman-Keuls Test Table analyses all the results according to statistically significant differences. It can be seen that solid dispersion with Vitamin E TPGS is statistically significantly different than that of all other results. Hence we can conclude that solid dispersion with Vitamin E TPGS gives higher enhancement of solubility as compared with other polymers

**TABLE 3: LIST OF FACTORS, THEIR LEVELS AND VALUES**

| FACTOR | TYPE | LEVELS | VALUES |
|---|---|---|---|
| Polymer | Fixed | 4 | 1 2 3 4 |
| Process | Fixed | 3 | 1 2 3 |

POLYMER

1 SOLUTOL HS

2 VITAMIN E TPGS

3 POLOXAMER 188

4 LIPOCOL C 10

PROCESS

1 PHYSICAL MIXTURE

2 SOLID DISPERSION

3 RECRYSTALLIZATION

**TABLE 4: 4 x 3 (2- FACTOR) FULL FACTORIAL DESIGN**

| NO | C1<br>Polymer | C2<br>Process |
|---|---|---|
| 1 | 1 | 1 |
| 2 | 1 | 2 |
| 3 | 1 | 3 |
| 4 | 2 | 1 |
| 5 | 2 | 2 |
| 6 | 2 | 3 |
| 7 | 3 | 1 |
| 8 | 3 | 2 |
| 9 | 3 | 3 |
| 10 | 4 | 1 |
| 11 | 4 | 2 |
| 12 | 4 | 3 |

## TABLE 5: ANOVA TABLE SUMMARIZING THE STATISTICAL ANALYSES

General Linear Model: Solubility versus Polymer, Process

| Factor | Type | Levels | Values |
|---|---|---|---|
| Polymer | fixed | 4 | 1 2 3 4 |
| Process | fixed | 3 | 1 2 3 |

Analysis of Variance for Solubility, using Adjusted SS for Tests

| Source | DF | Seq SS | Adj SS | Adj MS | F | P |
|---|---|---|---|---|---|---|
| Polymer | 3 | 216859 | 216859 | 72286 | 543.12 | 0.000 |
| Process | 2 | 1226825 | 1226825 | 613412 | 4608.85 | 0.000 |
| Polymer*Process | 6 | 119052 | 119052 | 19842 | 149.08 | 0.000 |
| Error | 24 | 3194 | 3194 | 133 | | |
| Total | 35 | 1565930 | | | | |

## TABLE 6: STUDENT –NEWMAN-KEULS TEST ANALYSES

The SAS System 13:52 Saturday, March 27, 2004 1

The GLM Procedure

Class Level Information

| Class | Levels | Values |
|---|---|---|
| x | 13 | 1 2 3 4 5 6 7 8 9 10 11 12 13 |

Number of observations 130

**TABLE 6: STUDENT –NEWMAN-KEULS TEST ANALYSES (contd.)**

The SAS System 13:52 Saturday, March 27, 2004 2

The GLM Procedure

Dependent Variable: y

| Source | DF | Sum of Squares | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| Model | 12 | 2724402.364 | 227033.530 | 30.32 | <.0001 |
| Error | 117 | 876170.308 | 7488.635 | | |
| Corrected Total | 129 | 3600572.672 | | | |

| R-Square | Coeff Var | Root MSE | y Mean |
|---|---|---|---|
| 0.756658 | 47.72989 | 86.53690 | 181.3055 |

| Source | DF | Type I SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| x | 12 | 2724402.364 | 227033.530 | 30.32 | <.0001 |

| Source | DF | Type III SS | Mean Square | F Value | Pr > F |
|---|---|---|---|---|---|
| x | 12 | 2724402.364 | 227033.530 | 30.32 | <.0001 |

## TABLE 6: STUDENT –NEWMAN-KEULS TEST ANALYSES (contd.)



The GLM Procedure

Student-Newman-Keuls Test for y

NOTE: This test controls the Type I experiment wise error rate under the complete null hypothesis but not under partial null hypotheses.

| | |
|---|---|
| Alpha | 0.05 |
| Error Degrees of Freedom | 117 |
| Error Mean Square | 7488.635 |

| Number of Means | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Critical Range | 76.6442 | 91.8725 | 100.866 | 107.2304 | 112.1348 | 116.1123 |

| Number of Means | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|
| Critical Range | 119.4499 | 122.3200 | 124.8342 | 127.0685 | 129.0772 | 130.9005 |

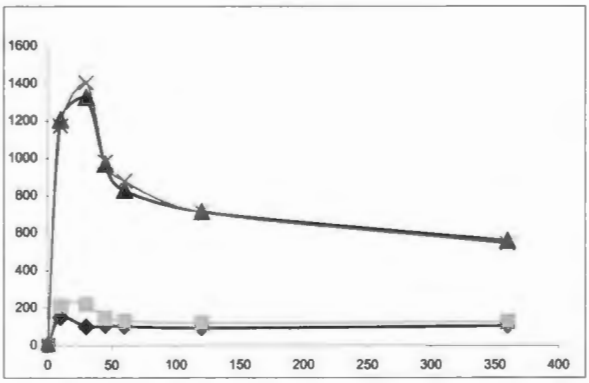
Means with the same letter are not significantly different.

| SNK Grouping | Mean | N | x |
|---|---|---|---|
| A | 495.79 | 10 | 9 |
| B | 418.73 | 10 | 6 |
| B | | | |
| B | 381.55 | 10 | 3 |
| C | 233.54 | 10 | 12 |
| D | 125.50 | 10 | 8 |
| | D | | |
| D | 102.43 | 10 | 11 |
| | D | | |
| D | 101.78 | 10 | 5 |
| | D | | |
| D | 94.05 | 10 | 1 |
| | D | | |
| D | 90.60 | 10 | 4 |
| | D | | |
| D | 87.63 | 10 | 10 |
| | D | | |
| D | 87.10 | 10 | 2 |
| | D | | |
| D | 72.86 | 10 | 13 |
| | D | | |
| D | 65.41 | 10 | 7 |

### 2.9.2 Microfluidization Study

In this study, the process of microfluidization has been used to assist in evaluation of the effect of shear stress on the solubility of the solid dispersions of the carbamazepine. The solubility profile of physical mixtures, solid dispersions and microfluidized solid dispersions were examined. For this study, a ratio used was 20:80 (drug:polymer) as there may be problem of blockage of instrument if we use large amounts of drug. As seen in figure (Figures 37 and 38), both solid dispersions and microfluidized solid dispersions bring about an increase in the solubility of carbamazepine at the same level. However, microfluidized solid dispersions show an initial spike in the solubility at around 30 minutes. It also shows there is a rapid decline in solubility till 6 hours, reducing the amount of drug dissolved to the solubility of carbamazepine after 48 hours. This indicates that there must be rapid conversion of the amorphous (high solubility) form to its crystalline (low solubility) form due to high pressure and the high temperature generated during microfluidization. The solid dispersions are not showing a rapid conversion of amorphous form to crystalline form as compared to the microfluidized solid dispersions. The DSC scans (Figures 40 - 44) for the solid dispersions and microfluidized solid dispersions show an absence of the endotherms. This fact is further proved by XRD (Figures 46, & 47) data. A lack of a drug melting endotherm in solid dispersions usually suggests the presence of the drug in an amorphous form within the dispersions. The DSC scan and X-ray scan data indicate that the higher solubility is due to the conversion of carbamazepine to its amorphous form. In the case of microfluidized solid dispersions, carbamazepine loses its amorphous form on prolonged exposure to medium, as indicated by the downward

slope of the solubility curve (Figures 37, & 38). However, the solid dispersions show only a gradual decrease in the solubility indicating a greater resistance to conversion to its original form. Pharmaceutical solids, as we know them, rarely exist as 100% crystalline or 100% amorphous phases (19). The presence of domains of one phase in another can act as a focal point for spontaneous phase transitions such as crystallization (20 - 22). The solid dispersions is likely to have reduced the number of such domains, thereby decreasing initiation sites for crystallization and preventing rapid conversion to the crystalline form as compared to the microfluidized solid dispersions. This study also proves that when higher proportion of polymer is used to make solid dispersions of carbamazepine they tend to amorphous carbamazepine with the solid dispersion. This fact is very useful which also suggests that at small proportion they tend to form small crystallites with the respective solid dispersion.



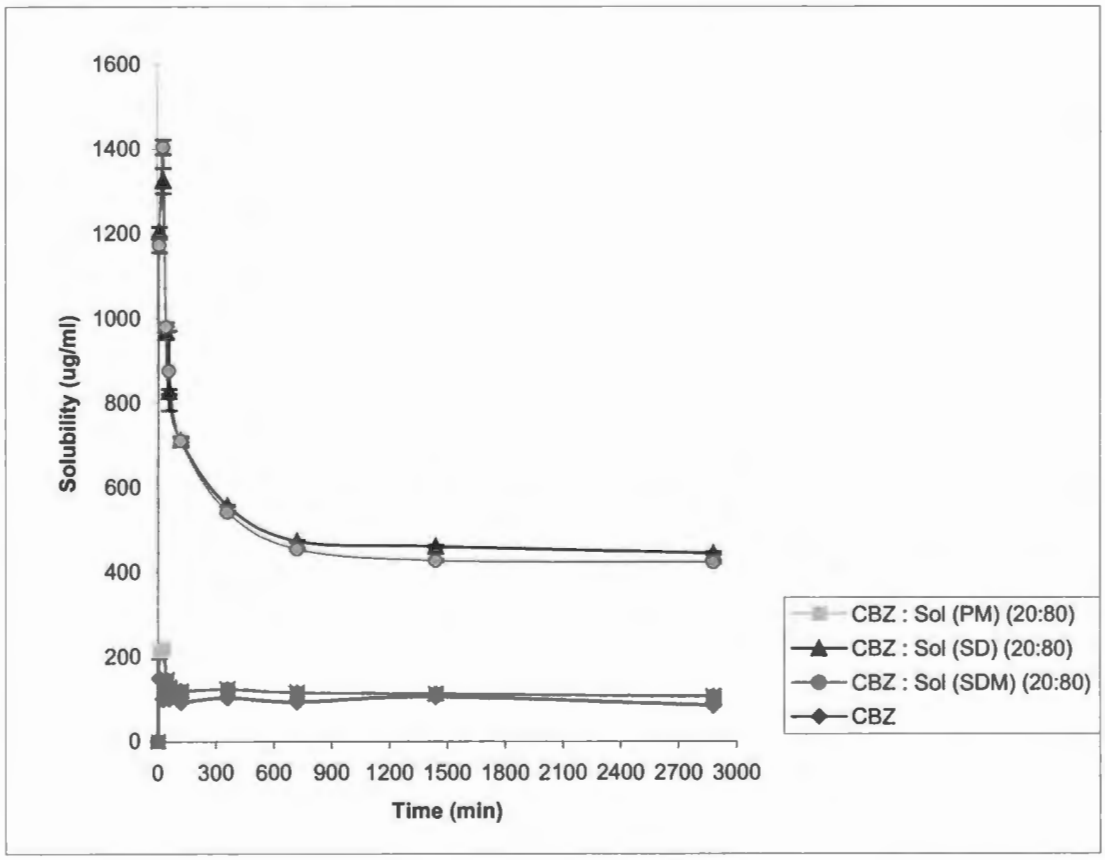
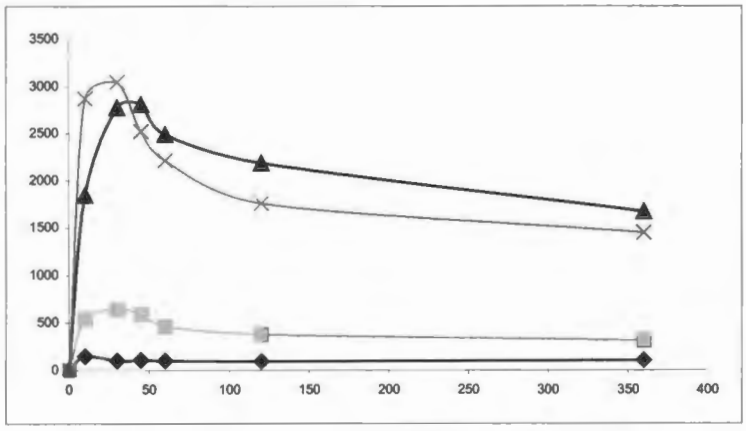




**FIGURE 37: SOLUBILITY PROFILE OF CARBAMAZEPINE, ITS PHYSICAL MIXTURE, SOLID DISPERSION AND MICROFLUIDISED SOLID DISPERSION WITH SOLUTOL HS (20:80)**



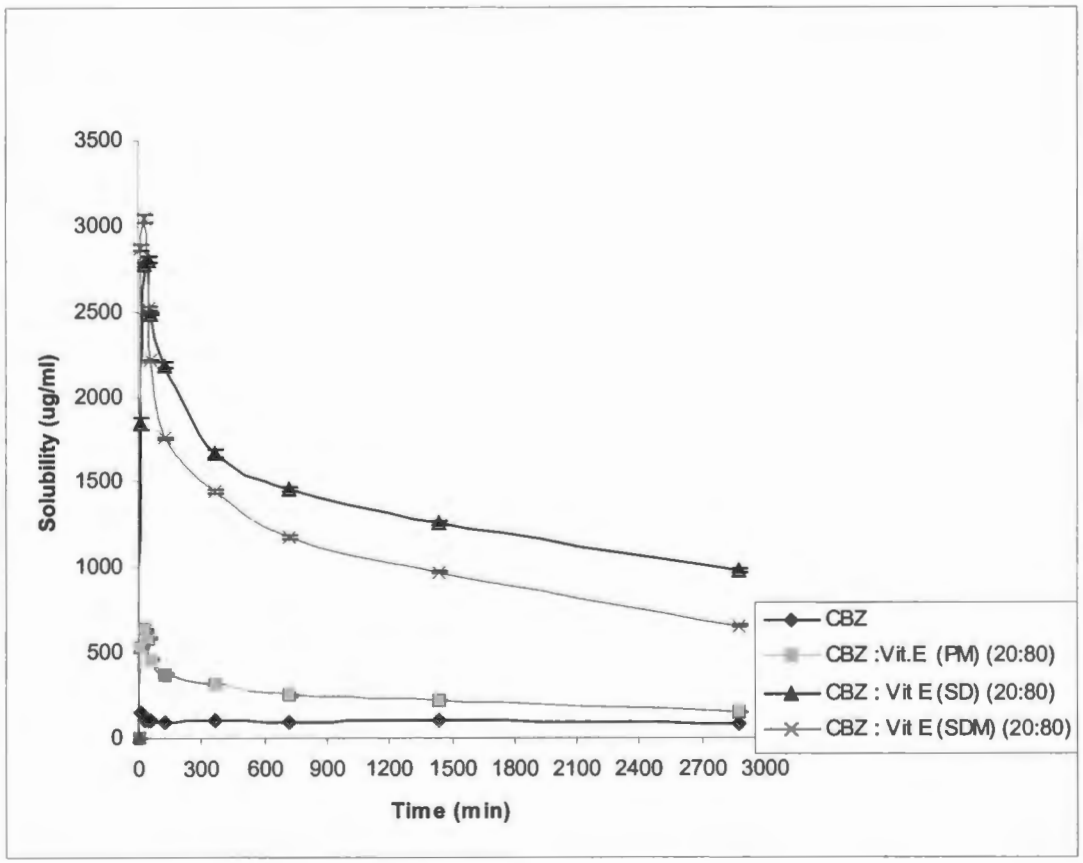




**FIGURE 38: SOLUBILITY PROFILE OF CARBAMAZEPINE, ITS PHYSICAL MIXTURE, SOLID DISPERSION AND MICROFLUIDISED SOLID DISPERSION WITH VITAMIN E TPGS (20:80)**

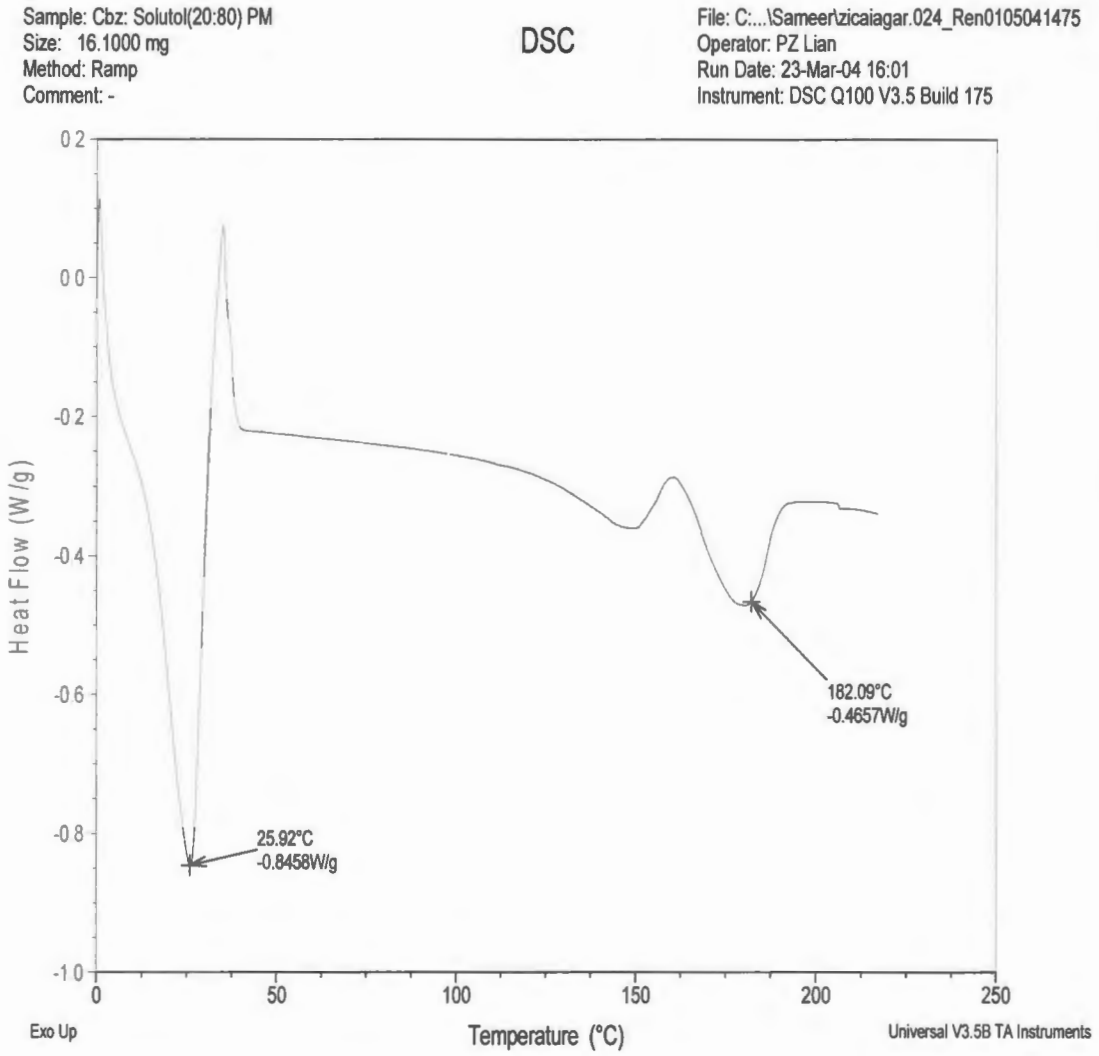



**FIGURE 39: REPRESENTATIVE THERMOGRAM OF PHYSICAL MIXTURE OF CARBAMAZEPINE AND SOLUTOL HS (20:80)**

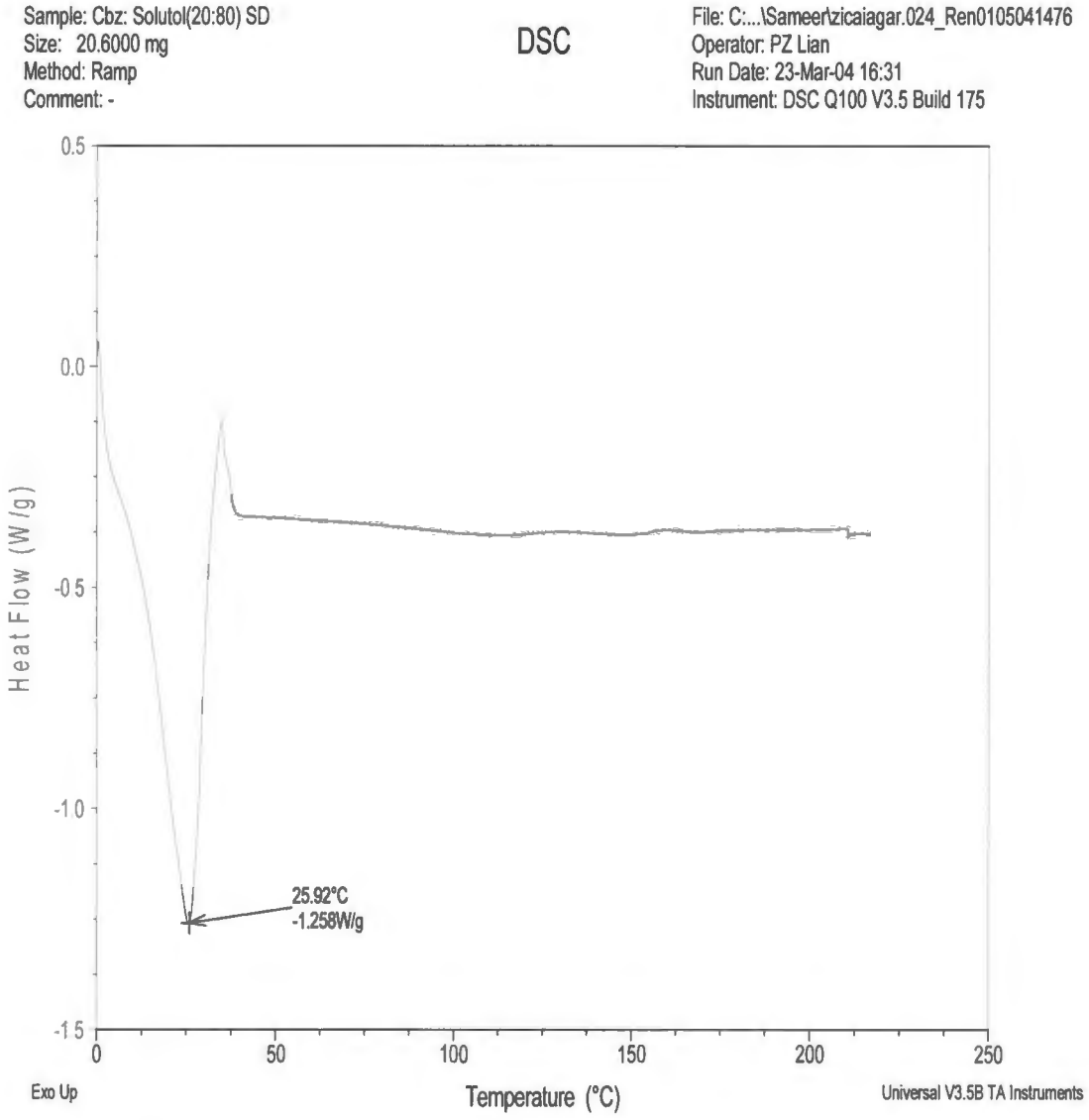



**FIGURE 40: REPRESENTATIVE THERMOGRAM SOLID DISPERSION OF CARBAMAZEPINE AND SOLUTOL HS (20: 80)**

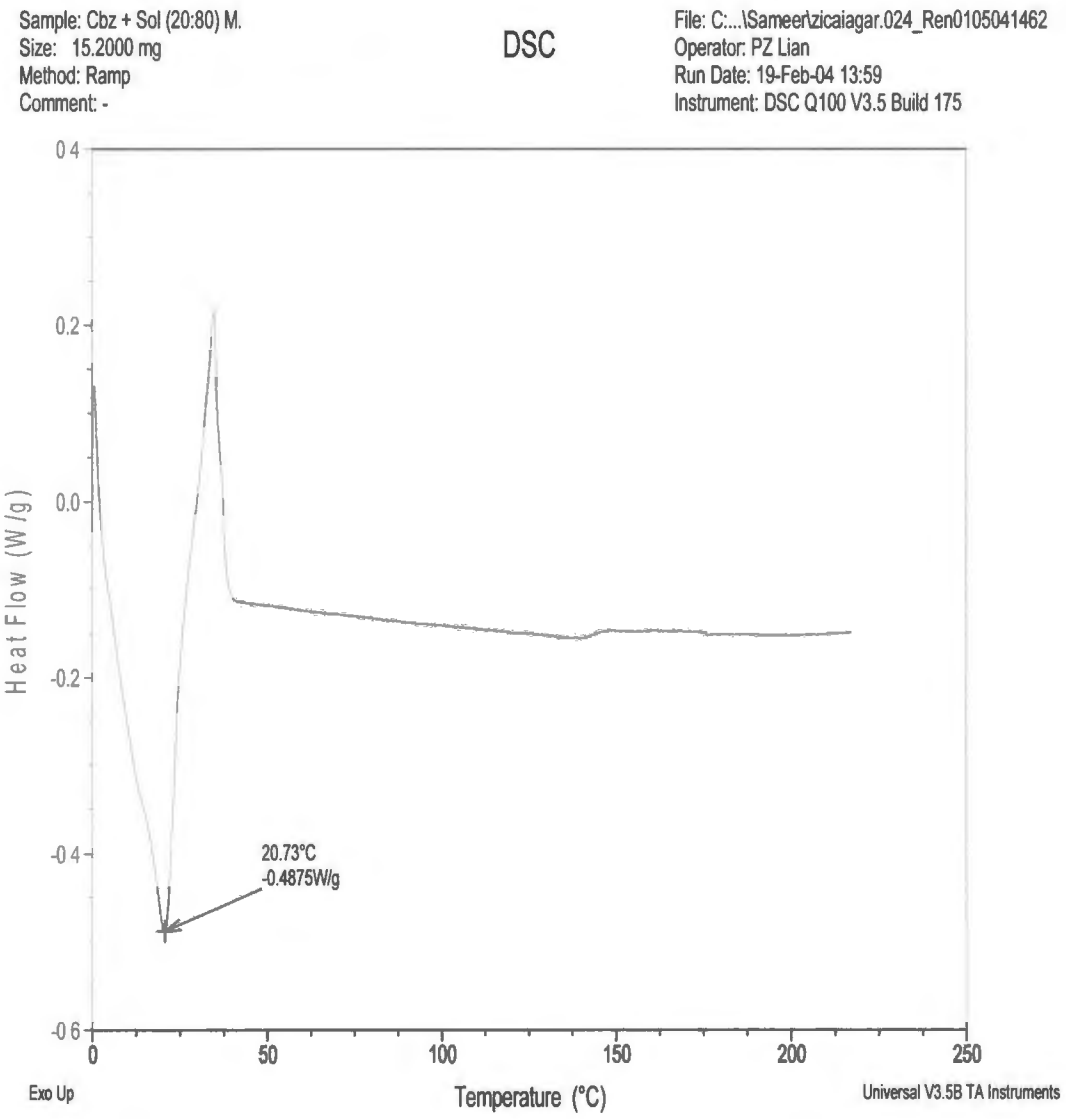



**FIGURE 41: REPRESENTATIVE THERMOGRAM OF MICROFLUIDIZED SOLID DISPERSION OF CARBAMAZEPINE AND SOLUTOL HS (20:80)**

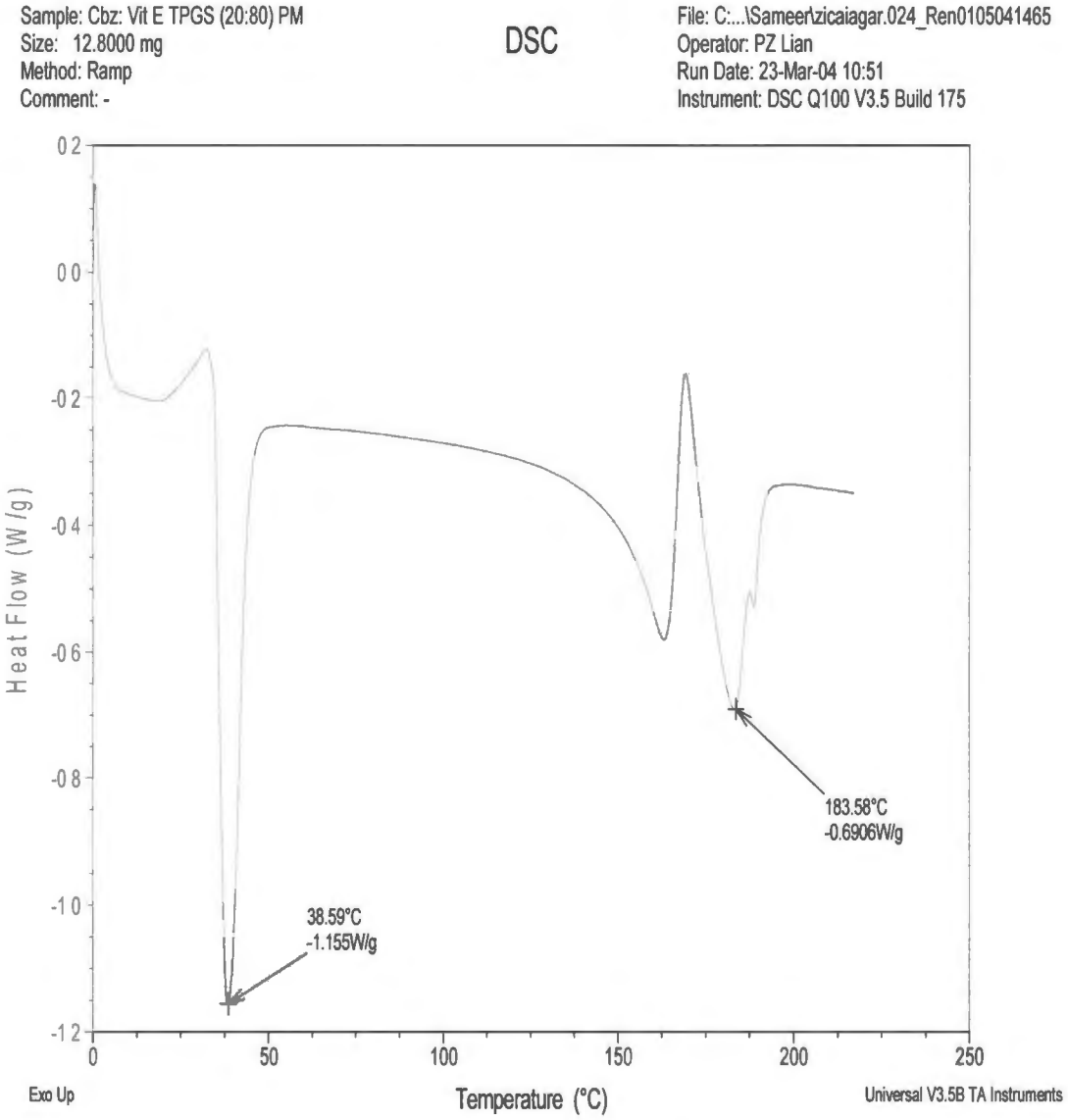



**FIGURE 42: REPRESENTATIVE THEROMOGRAM OF PHYSICAL MIXTURE OF CARBAMAZEPINE AND VITAMIN E TPGS (20:80)**

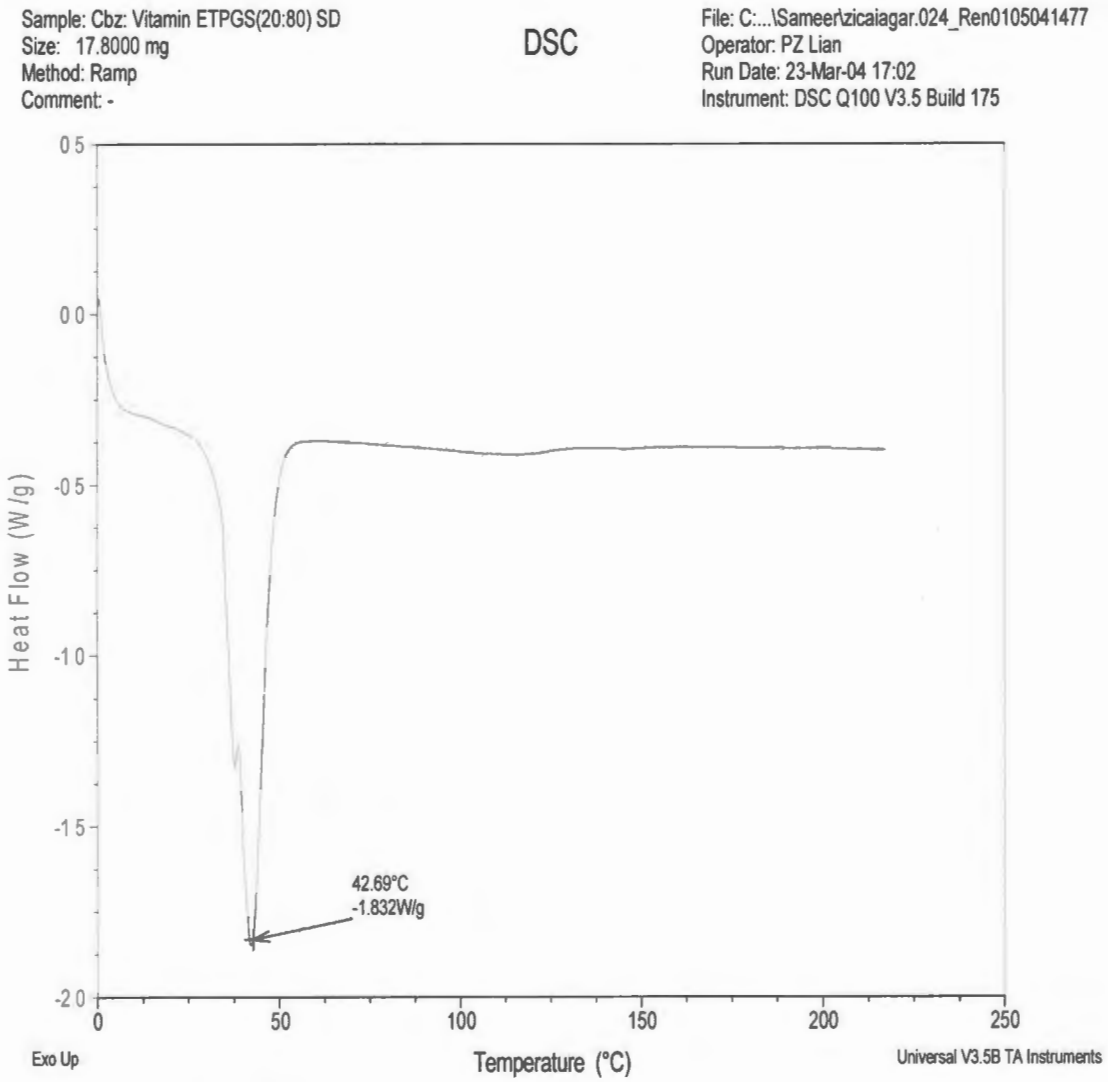



**FIGURE 43: REPRESENTATIVE THERMOGRAM OF SOLID DISPERSION OF CARBAMAZEPINE AND VITAMIN E TPGS (20:80)**

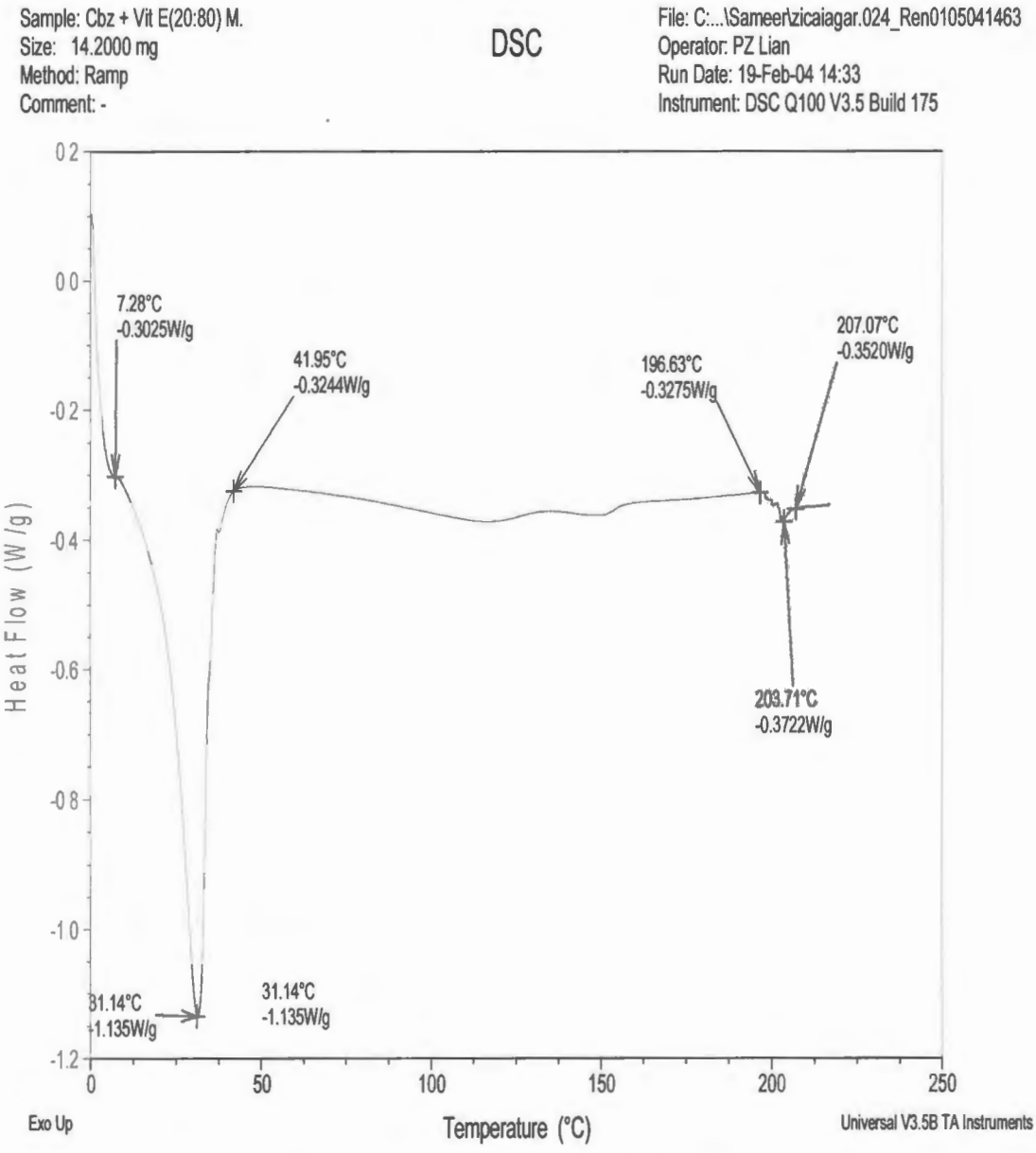



**FIGURE 44: REPRESENTATIVE THERMOGRAM OF MICROFLUIDIZED SOLID DISPERSION OF CARBAMAZEPINE AND VITAMIN E TPGS (20:80)**

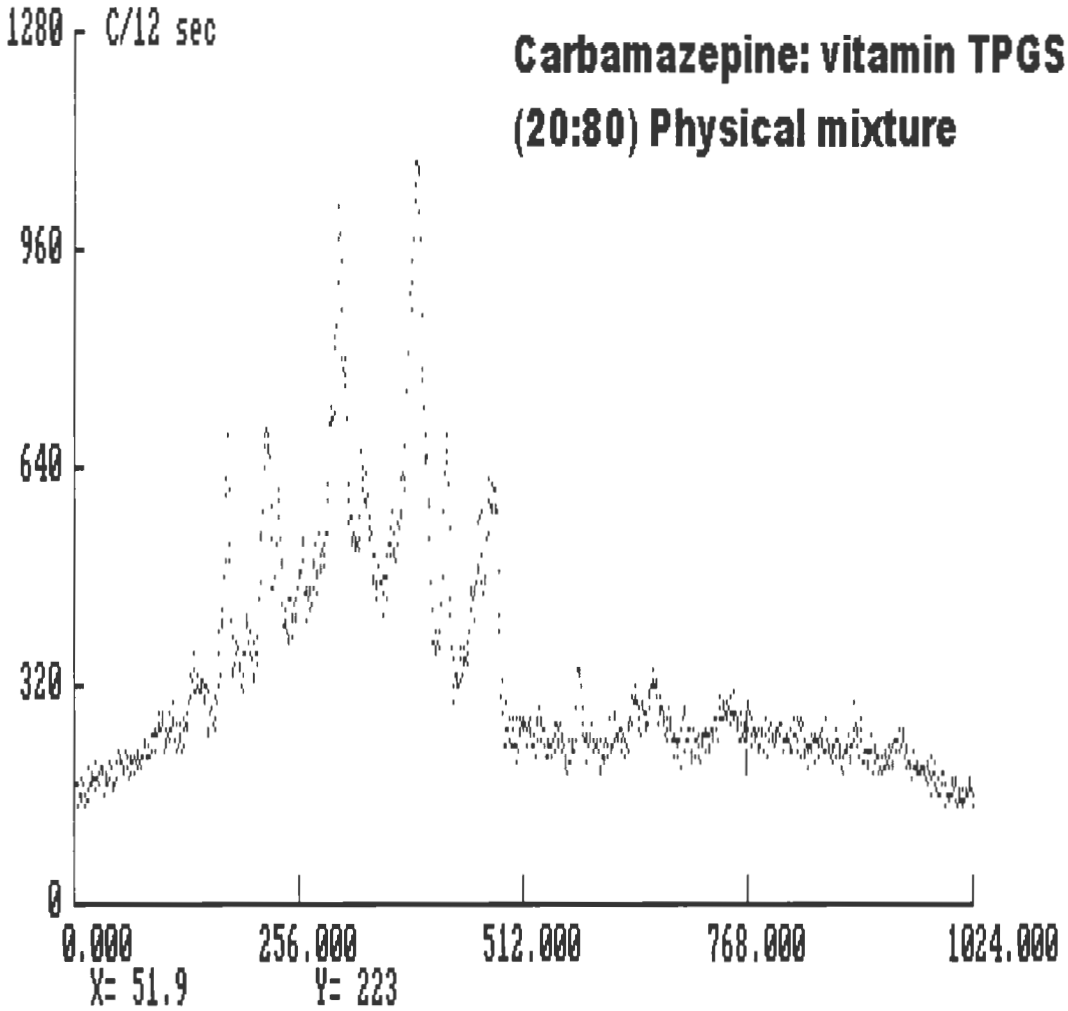



**FIGURE 45: XRD SCAN OF PHYSICAL MIXTURE OF CARBAMAZEPINE AND VITAMIN E TPGS (20:80)**

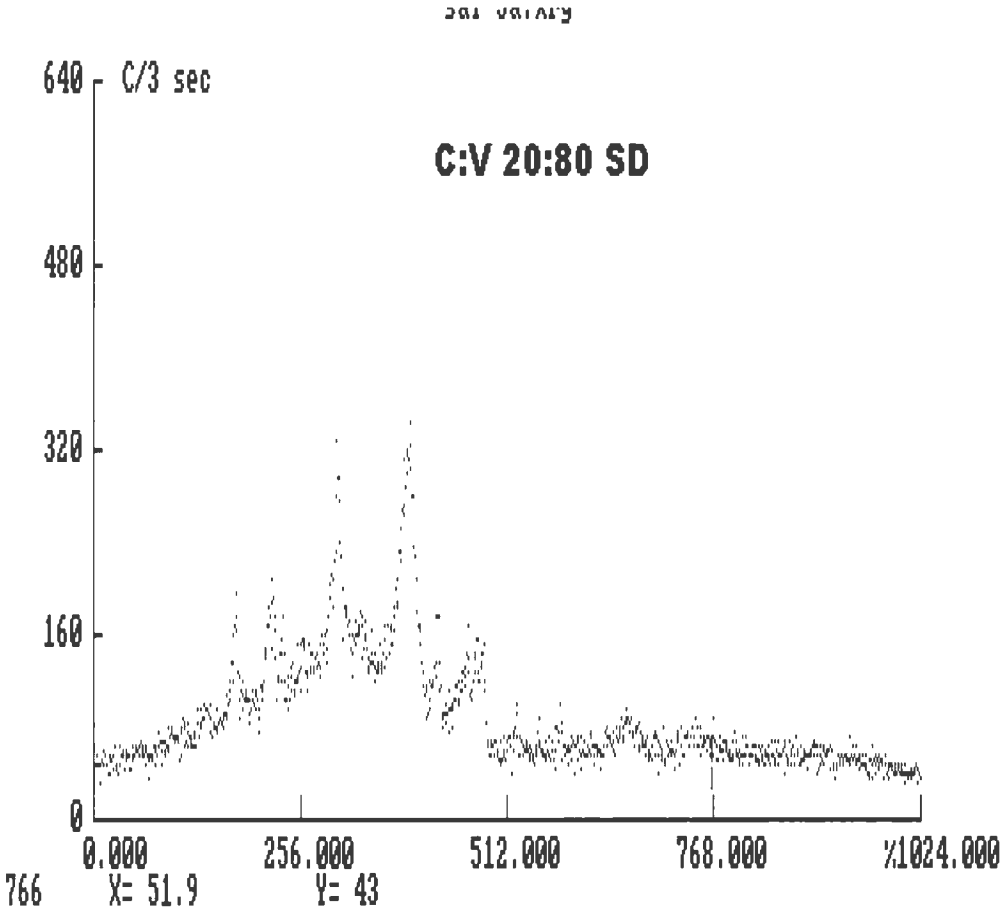



**FIGURE 46: XRD SCAN OF SOLID DISPERSION OF CARBAMAZEPINE AND VITAMIN E TPGS (20:80)**

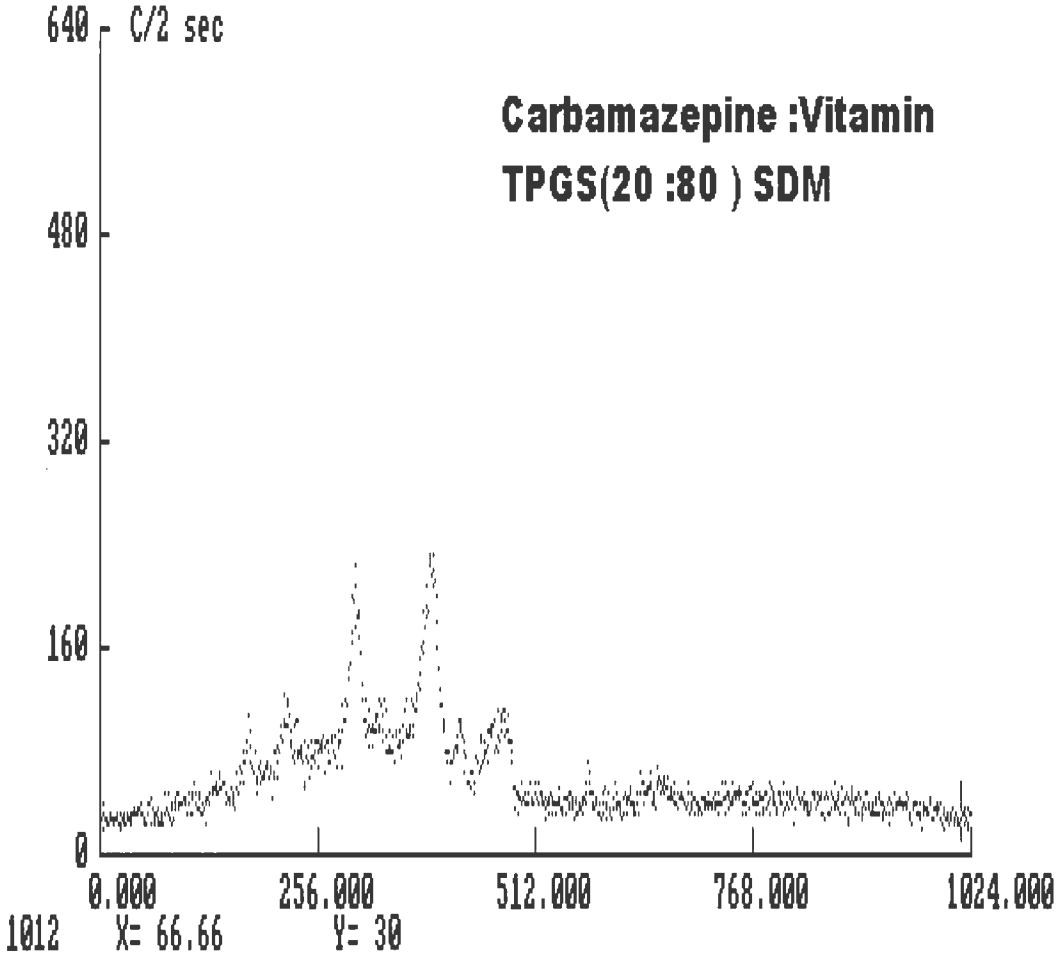



**FIGURE 47: XRD SCAN OF MICROFLUIDIZED SOLID DISPERSION OF CARBAMAZEPINE AND VITAMIN E TPGS (20:80)**

### 2.9.3 Dissolution studies

Dissolution studies aid in understanding the solubility differences between the drug, physical mixtures, and solid dispersions. In vitro dissolution is used to characterize the release behavior of different formulations. Dissolution rate data can be expressed using Noyes Whitney equation (23) as shown below:

$$\frac{dC}{dt} = \frac{AD\,(Cs - C)}{h}$$

where dC/dt is the rate of dissolution, A is the surface area available for dissolution, D is the diffusion coefficient of the compound, Cs is the solubility of the drug in the dissolution medium, C is the concentration of drug in the medium at time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

Dissolution profiles of different ratios of drug and polymer of physical mixtures and solid dispersions with Solutol HS are shown in Figures 48 and 49. The dissolution profile of physical mixtures and solid dispersions with Vitamin E TPGS were shown in Figures 50 and 51. Similarly, dissolution profile of Poloxamer 188 physical mixtures and solid dispersions are shown in Figures 52 and 53. For dissolution studies, optimum ratios that were determined using optimization study were used. To find out the optimum ratio for the respective polymer $D_{10}$ values (dissolution rate at 10 min) was compared with different ratios of the respective polymer. Dissolution profile of physical mixtures showed that with increase in amount of polymer, dissolution rate increases. This trend remains same for the solid dispersions. Comparing the drug, physical mixtures with each respective polymer and solid dispersions with each

respective polymer, the solid dispersions gave a higher dissolution rate. Increase in the dissolution rate can be attributed to increased wetting of the hydrophobic drug, as there is increase in the dissolution rate in physical mixtures too. They also showed partial amorphous nature for solid dispersions, which may be another reason for the enhancement of dissolution rate.

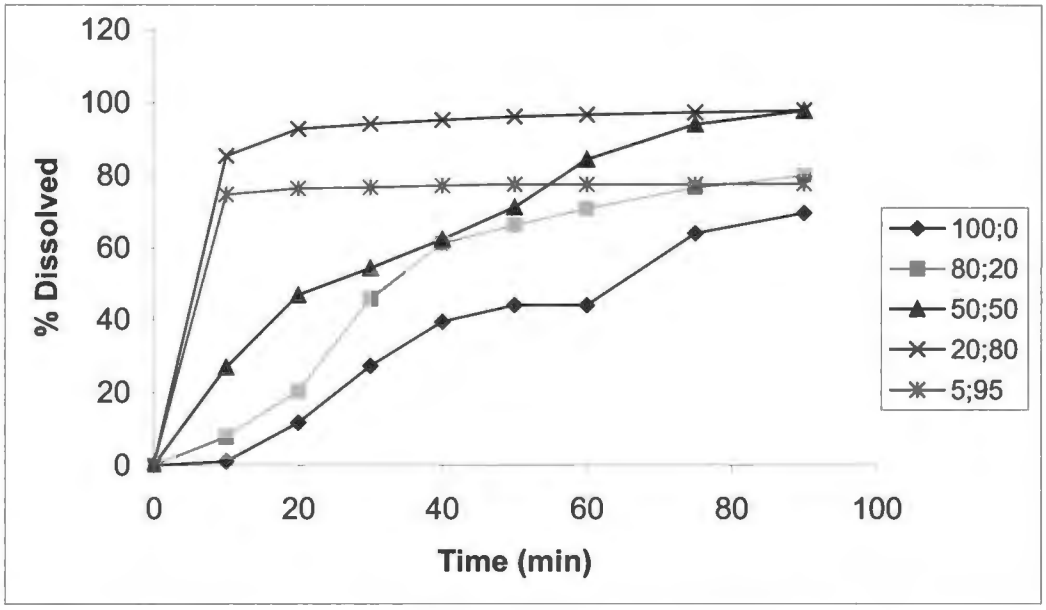



**FIGURE 48: DISSOLUTION PROFILE OF PHYSICAL MIXTURES OF CARBAMAZEPINE WITH SOLUTOL HS**

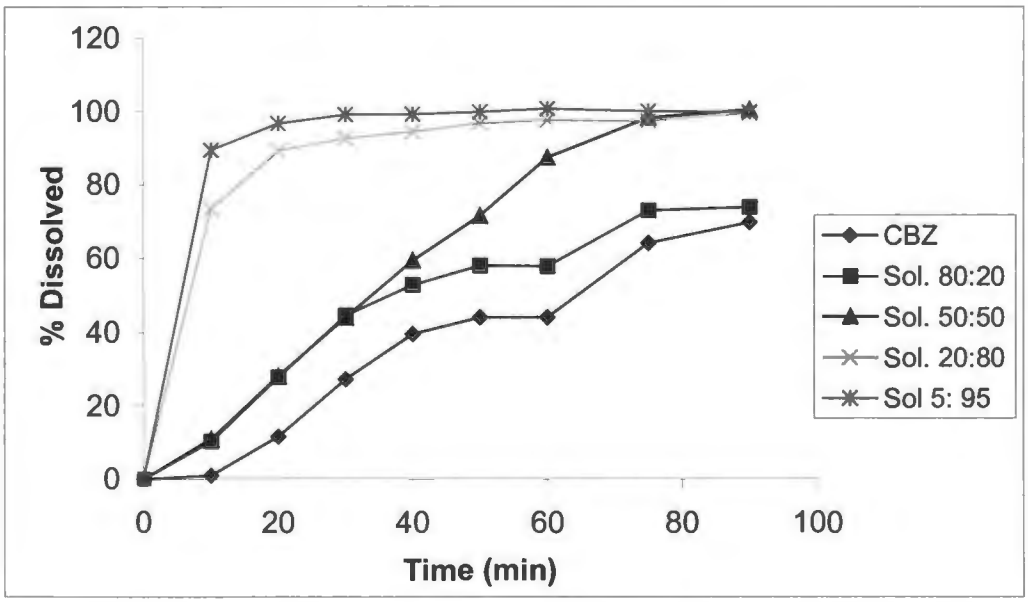



**FIGURE 49: DISSOLUTION PROFILE OF SOLID DISPERSIONS OF CARBAMAZEPINE WITH SOLUTOL HS**

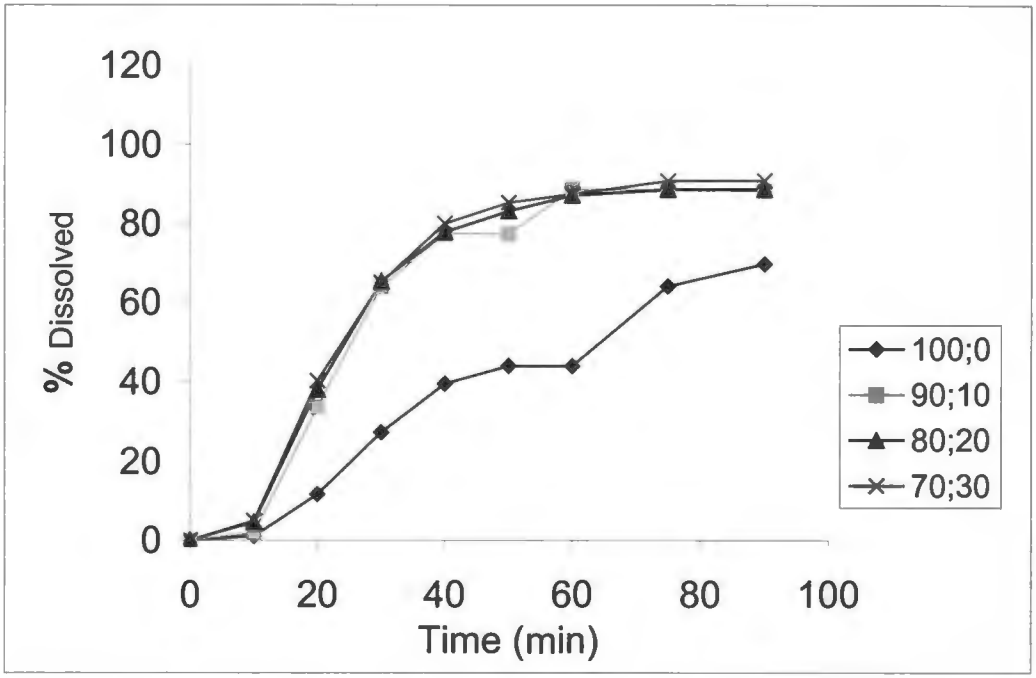



**FIGURE 50: DISSOLUTION PROFILE OF PHYSICAL MIXTURES OF CARBAMAZEPINE WITH VITAMIN E TPGS**

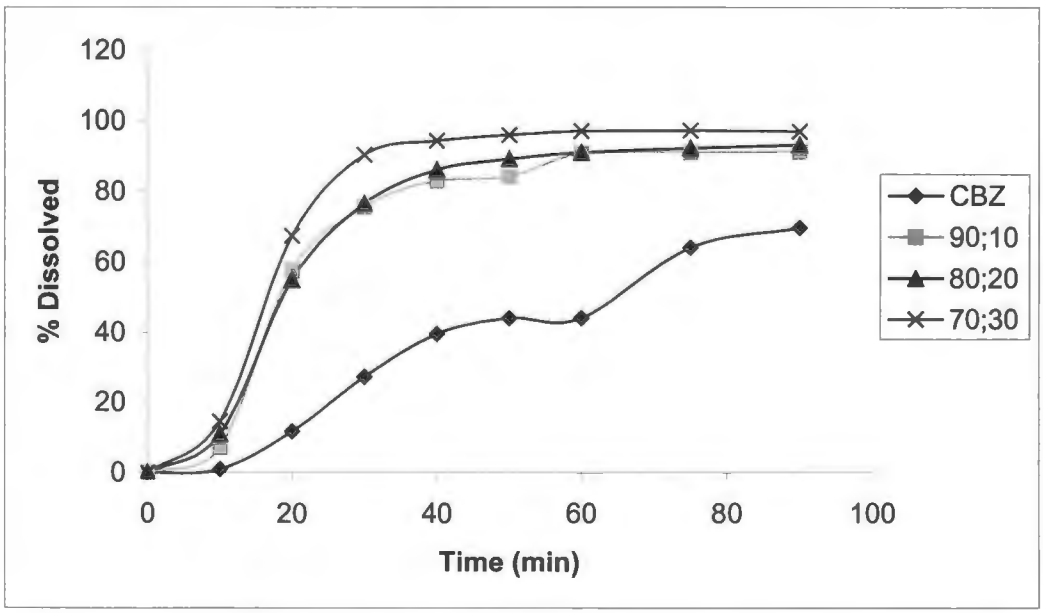



**FIGURE 51: DISSOLUTION PROFILE OF SOLID DISPERSIONS OF CARBAMAZEPINE WITH VITAMIN E TPGS**

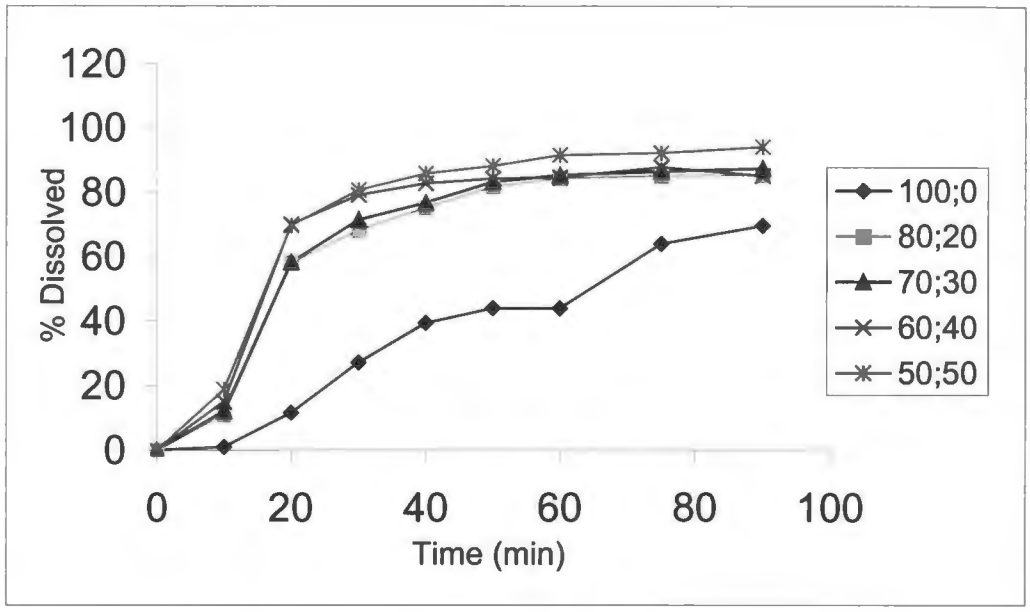



**FIGURE 52: DISSOLUTION PROFILE OF PHYSICAL MIXTURES OF CARBAMAZEPINE WITH POLOXAMER 188**

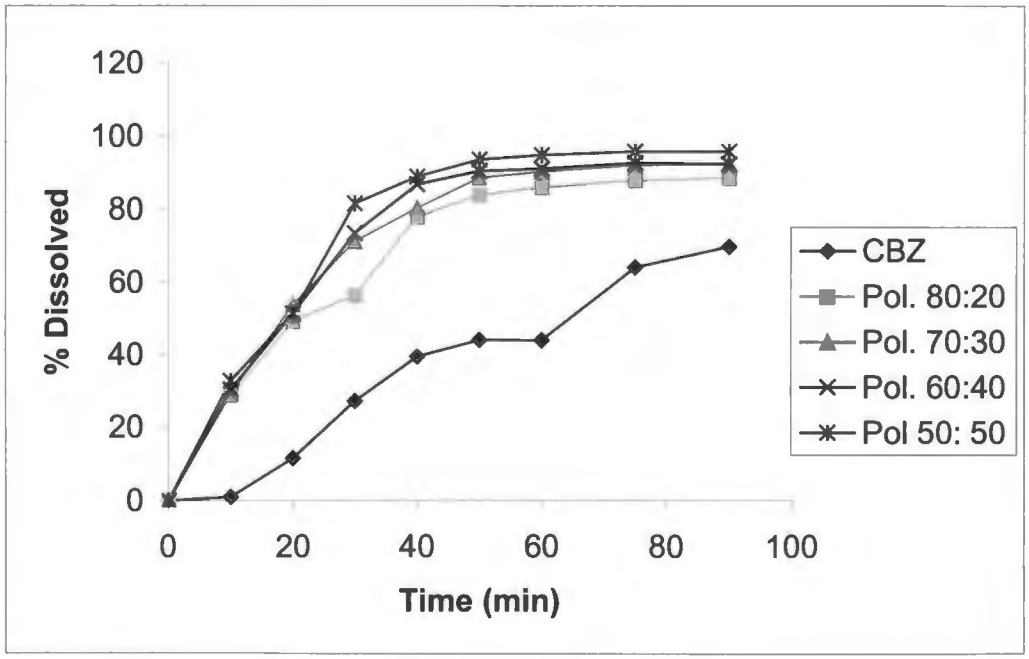



**FIGURE 53: DISSOLUTION PROFILE OF SOLID DISPERSIONS OF CARBAMAZEPINE WITH POLOXAMER 188**

**TABLE 7: DISSOLUTION PROFILE OF CARBAMAZEPINE WITH DIFFERENT POLYMERS AT 80:20 (DRUG: POLYMER)**

| | 80;20 | | | |
|---|---|---|---|---|
| Time (min) | CBZ | Solutol | Vit. E TI | Pol.188 |
| 0 | 0 | 0 | 0 | 0 |
| 10 | 1.03 | 10.34 | 11.01 | 28.83 |
| 20 | 11.67 | 27.87 | 54.95 | 49.09 |
| 30 | 27.27 | 44.6 | 76.62 | 56.11 |
| 40 | 39.5 | 52.77 | 86.06 | 77.84 |
| 50 | 44.06 | 58.03 | 89.21 | 83.68 |
| 60 | 44.04 | 57.83 | 90.96 | 85.88 |
| 75 | 64.06 | 72.88 | 92.29 | 87.69 |
| 90 | 69.7 | 73.87 | 93.16 | 88.35 |

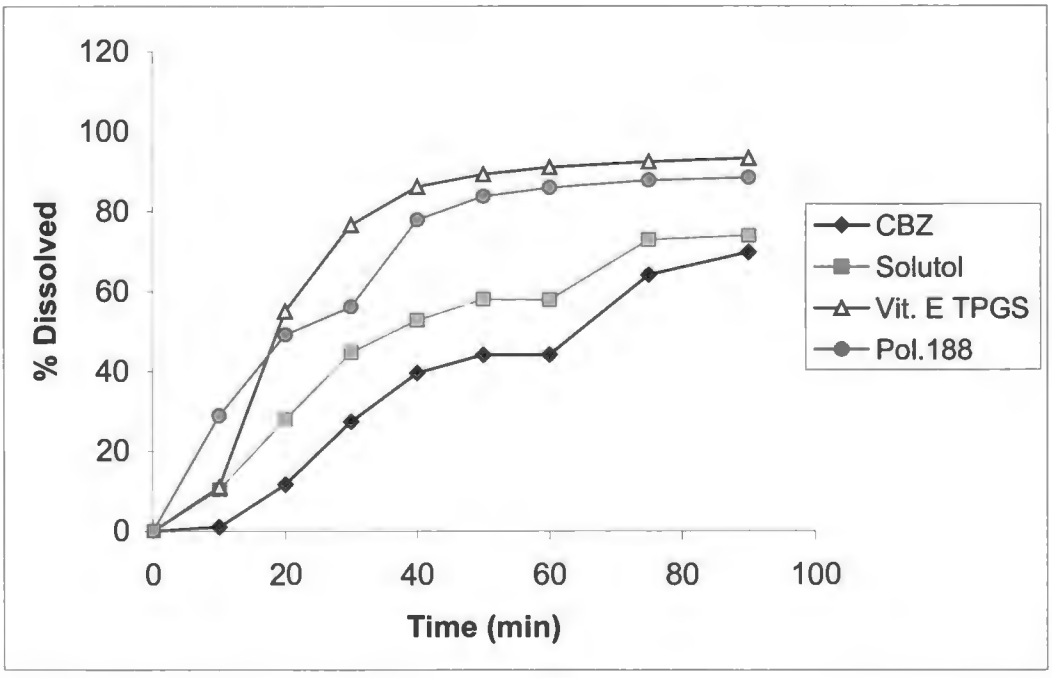



**FIGURE 54: DISSOLUTION PROFILE OF CARBAMAZEPINE WITH DIFFERENT POLYMERS AT 80:20 (DRUG: POLYMER)**

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## SUMMARY OF CONCLUSIONS

The solid dispersions of carbamazepine with Solutol HS, Vitamin E TPGS and Poloxamer 188 showed enhancement in the solubility of the carbamazepine. Solid dispersions of carbamazepine with all the polymers increased the solubility of carbamazepine by different mechanisms. Physical mixtures of carbamazepine with different polymers showed no significant increase in solubility. From it we can conclude that wetting effect of surfactant is not the factor responsible for the enhancement of solubility. At lower content of polymer, there is no change in melting endotherms and crystalline patterns for solid dispersions, but higher ratios of polymer content showed changes in melting endotherms and crystalline patterns. This indicates that there may be presence of carbamazepine as very small crystallites within the dispersion. Lipocol C 10 which is having same HLB value as that of Vitamin E TPGS showed 4 times increase in solubility as compared to carbamazepine. Vitamin E TPGS solid dispersions showed 5 times increase in the solubility of carbamazepine. The varied enhancement of Lipocol C 10 and Vitamin E TPGS also suggest that they tend to inhibit the conversion of anhydrous carbamazepine into dihydrate form, which is the sole reason for lower solubility of carbamazepine when comes in contact with water. Microfluidization study is used to observe the effect of shear stress on the solubility of the solid dispersions. It showed an initial spike in solubility due to conversion of drug into amorphous form. But it showed rapid decline in the solubility back to equilibrium solubility, which is equivalent to the solubility of the carbamazepine solid dispersions.

It showed that shear stress has no effect on the solubility of solid dispersions. Dissolution studies also showed significant increase with different polymers at different ratios. The statistical model selected was adequate and unbiased. The results of Student-Newman-Keuls Test clearly show that if solid dispersion process and Vitamin E TPGS polymer is used to enhance the solubility of carbamazepine, gives significantly higher results as compared to other polymers.

Physical mixtures and recrystallized mixtures showed no significant of enhancement of solubility. The ANOVA table showed that all the three-selected process and polymer variable had a significant effect on the solubility of carbamazepine.

# APPENDIX A

List of Publication

The following is the journal in which the manuscript will be submitted for publication

Manuscript I: Solubility Enhancement of Carbamazepine Using Selected Water-Soluble Polymers and a Solid Dispersion Technique.

Journal: Journal of Pharmaceutical Sciences

## APPENDIX B

**Determination of Lambda max of Carbamazepine.**

For quantitative analysis of Carbamazepine in the solubility studies as well as in the dissolution studies, an ultraviolet (UV) spectrophotometer was used. A solution of carbamazepine in distilled water and simulated gastric fluid was scanned for ultraviolet absorbance between 200 and 400 nm on a Hewlett Packard 8451 A Diode Array Spectrophotometer. The Lambda max was found to be 284 nm.

**Construction of the Calibration curve of Carbamazepine in distilled water and simulated gastric fluid.**

Stock Solution: Dissolve 25.08 mg of Carbamazepine in 25 ml of methanol and sonicated till it gets dissolved. The concentration of solution is approximately 1 mg/ml. This solution is then stored at a cool and dry place.

For calibration curve in distilled water, serial concentrations of Carbamazepine in distilled water using stock solutions having concentrations from 10-50 µg/ml were prepared. The absorbance of the prepared solutions was measured spectrophotometrically at $\lambda_{max}$ 284 nm. The absorbance was plotted against the concentration. The regression lines were calculated.

For calibration curve in simulated gastric fluid, serial concentrations of Carbamazepine in simulated gastric fluid using stock solutions having concentrations from 05-30 µg/ml were prepared. The absorbance of the prepared solutions was measured spectrophotometrically at $\lambda_{max}$ 284 nm. The absorbance was plotted against the concentration. The regression lines were calculated.

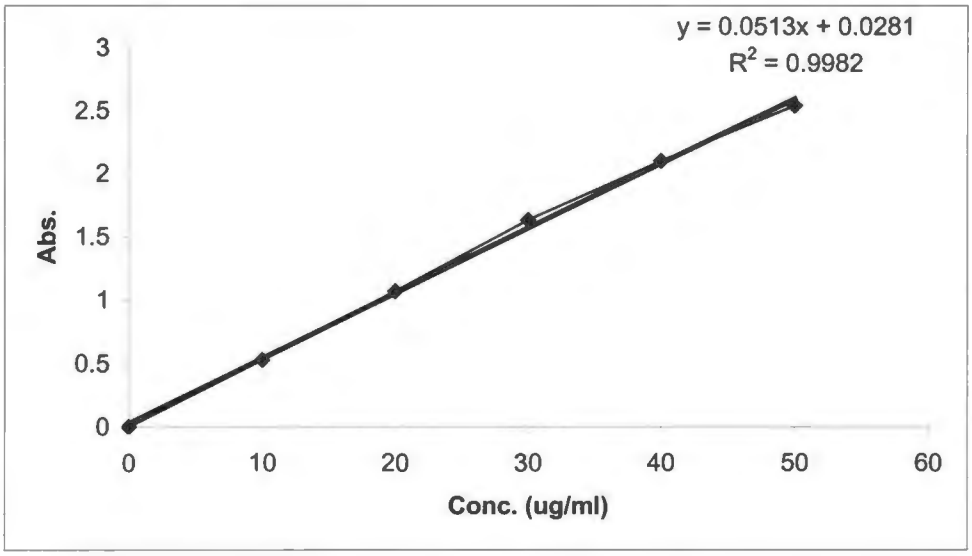


**FIGURE 55: CALIBRATION CURVE OF CARBAMAZEPINE IN DISTILLED WATER**

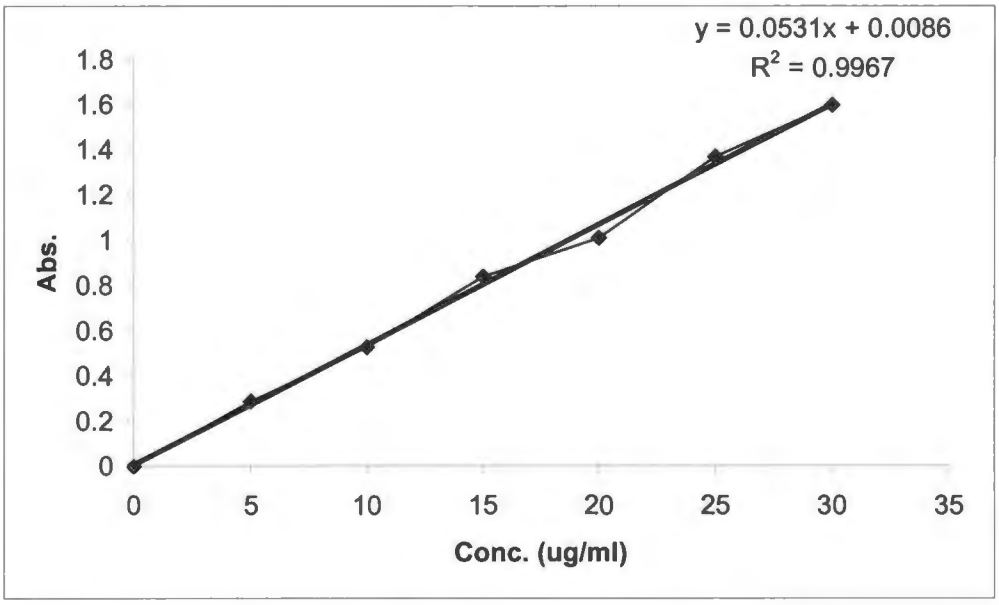


**FIGURE 56: CALIBRATION CRUVE OF CARBAMAZEPINE IN SIMULATED GASTRIC FLUID**

**TABLE 8: GROUPS FOR STUDENT-NEWMAN-KEULS TEST**

| No. | GROUP |
|---|---|
| 1 | Carbamazepine |
| 2 | Carbamazepine:Solutol HS (90:10) PM |
| 3 | Carbamazepine:Solutol HS (90:10) SD |
| 4 | Carbamazepine:Solutol HS (90:10) RE |
| 5 | Carbamazepine:Vitamin E TPGS (90:10) PM |
| 6 | Carbamazepine:Vitamin E TPGS (90:10) SD |
| 7 | Carbamazepine: Vitamin E TPGS (90:10) RE |
| 8 | Carbamazepine:Poloxamer 188 (90:10) PM |
| 9 | Carbamazepine:Poloxamer 188 (90:10) SD |
| 10 | Carbamazepine:Poloxamer 188 (90:10) RE |
| 11 | Carbamazepine:Lipocol C 10 (90:10) PM |
| 12 | Carbamazepine:Lipocol C 10 (90:10) SD |
| 13 | Carbamazepine:Lipocol C 10 (90:10) RE |

**Biopharmaceutical Classification System (BCS) of Drug classification**

The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, that BCS takes into a account three major factors that governs the rate and extent of drug absorption from solid oral dosage forms, dissolution, solubility and intestinal permeability.

BCS answers - Is the dissolution rate-limiting step for absorption

- Is the gastric emptying time limiting step for absorption
- Is the permeability rate limiting step for absorption
- Is the absorption process depends on pH conditions

It has four classes,

Class I - High solubility + High permeability

Class II – Low solubility + High permeability

Class III – High solubility + Low permeability

Class IV – Low solubility + Low permeability

**Optimization Study**

To obtain the maximal dissolution rate of the drug from solid dispersions, an optimal weight fraction of the polymer was needed. Simonelli et al obtained similar findings with sulphathiazole/PVP solid dispersion. To explain this behavior, they postulated that the formation of a PVP outer layer (at optimal weight fraction), which controlled the drug, release. If a large difference exists between the solubilities of the carrier and the drug, the range of weight fractions over which the dissolution is controlled by the carrier is very small, and occurs only at high carrier weight fractions. When Solid dispersions containing weight fraction over optimum were added to the surface of dissolution medium, gel formation was observed. Thus, the drug particles were trapped inside the gel and release rate was reduced.

To determine optimum ratio for dissolution studies, dissolution rate at 10 min for each drug:polymer ratio was determined. For further dissolution studies ratios below optimum ratio were selected.

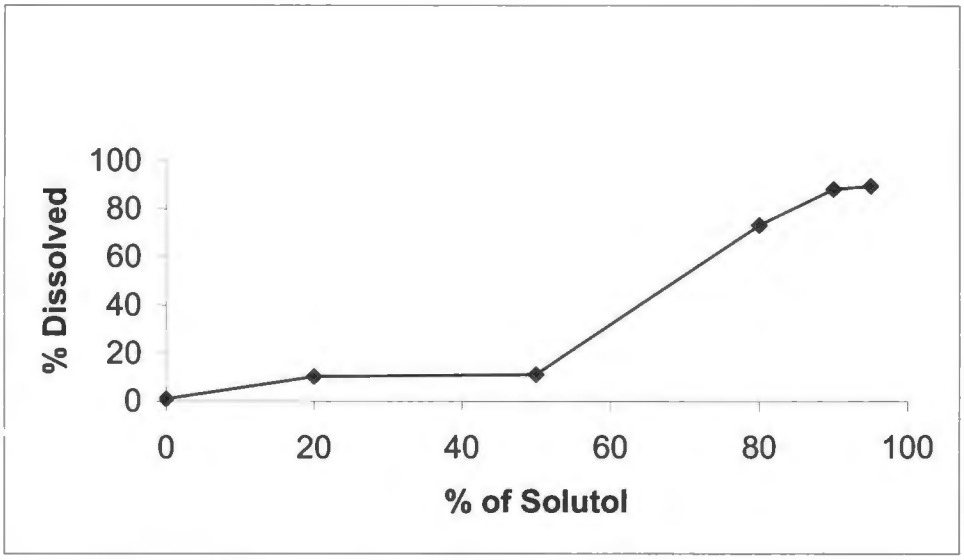


**FIGURE 57: OPTIMIZATION STUDY FOR SOLID DISPERSIONS OF CARBAMAZEPINE AND SOLUTOL HS**

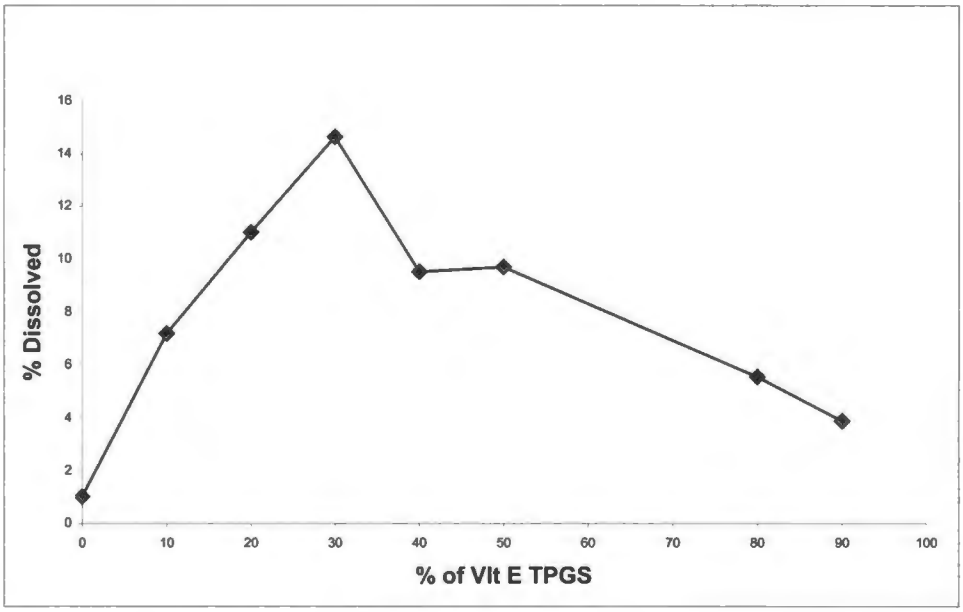


**FIGURE 58: OPTIMIZATION STUDY FOR SOLID DISPERSIONS OF CARBAMAZEPINE AND VITAMIN E TPGS**

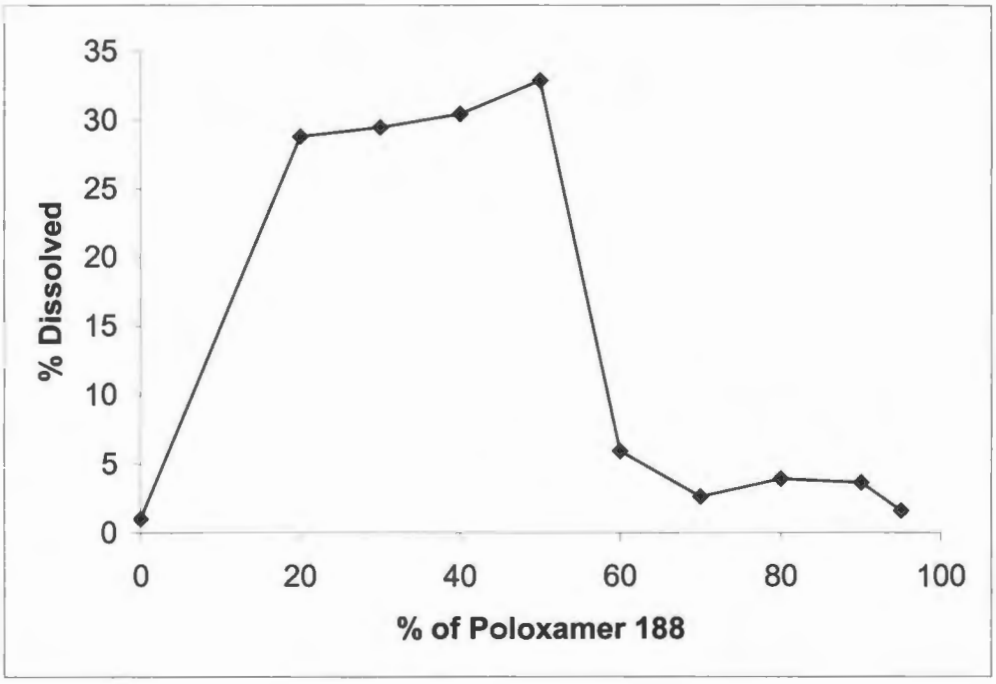


**FIGURE 59: OPTIMIZATION STUDY FOR SOLID DISPERSIONS OF CARBAMAZEPINE AND POLOXAMER 188**

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