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MOISTURE INTERACTIONS WITH PHARMACEUTICALPOL YMERJC FILM COATINGS

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MOISTURE INTERACTIONS WITH PHARMACEUTICAL POLYMERIC FILM COATINGS

BY

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MASTER OF SCIENCE THESIS
OF
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ABSTRACT

It is a well-known fact that water can act as a detrimental variable in performance of pharmaceutical dosage forms. Derivatives of various starches and cellulose are widely used as excepients, generally in high proportions to the total amount making up the dosage form. A complete understanding of the uptake of moisture by cellulose polymers is important because moisture-polymer interaction affects various properties such as compressibility and stability. In this study 1) hydroxypropyl methylcellulose (HPMC), 2) modified HPMC (SEPPIC®), 3) microcrystaline cellulose containing carrageenan (Lusterclear®) were used for studies of moisture polymer interaction. The interaction of moisture with these polymers was assessed using a simple and precise sorption system, which allows a rapid measure of uptake and loss of moisture. The effect of temperature on the sorption behavior of the film was also examined. All the three excepient films displayed sorption isotherms that were classified as type II (Langmuir) and demonstrated hysteresis during desorption. The BET model could be used restrictively but the GAB model fitted the data over the entire range of water activity under study. The Young & Nelson model was successful in modeling hysteresis phenomenon but did not offer any mechanistic details.

Thermodynamic analysis of water-excepient film system has also been performed to understand the mechanistic details of moisture-excepient interactions. Partial molal free energies, enthalpies and entropies were calculated for the three polymeric films. Results from the theoretical methods are useful for the predictive purpose where as thermodynamic studies offered mechanistic details of water-excepient interaction. A comparative study of the theoretical models and thermodynamic studies showed that the results from both the approaches were not always analogues to each other. In conclusion, 1) dynamic vapor sorption is very useful in investigation of water-excepient interaction 2) it is necessary to apply both theoretical models and thermodynamic concepts for complete understanding of water-excepient interactions.

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PREFACE

This document has been prepared in the format of the 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 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 if three manuscripts written in the format prescribed by the scientific journal to which they have been or will be submitted for publication. Section III contains appendices that include the list of publications and experimental details useful for 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 I

INTRODUCTION

Pharmaceutical solids as raw materials or dosage forms often come in contact with water during processes like wet granulation, crystallization and/or during storage i.e. because of exposure upon handling and storage to an atmosphere containing water vapor. Water associated with solids used pharmaceutically can significantly influence important physical, chemical and pharmaceutical properties such as dissolution, temperature, glass transition, compaction, powder flow and stability (1-3). Many precautions such as reduced contact with atmosphere or control of the relative humidity of atmosphere can be taken when water is perceived to be a problem, which add expense to the process. They also do not guarantee that there will be no further problems associated with moisture during the life of the product. So it is important to know as much as possible about the interaction of water with solids before planning to use them.

Derivatives of starch and cellulose are commonly employed as excepients for various purposes i.e., binders, adhesives, disintegrates and coating materials to provide physical and chemical protection to drugs. The quantity of moisture in excepients used pharmaceutically can greatly influence the appearance and performance of dosage form. (3). As these excepients are commonly employed in large amounts and known to take up and retain significant amount of moisture, it is important to understand moisture interactions of these excepients. In this context it is important to know some of the critical aspects concerning water-solid interaction like a) total amount of water present b) how much of water will be sorbed or desorbed at a given relative humidity and temperature c) what is the thermodynamic state of water associated with solids at various levels of moisture content and d) what are the kinetics of moisture. uptake/loss. It is an objective of this thesis to develop a methodology and evaluate an data analysis techniques to answer above questions for films of pharmaceutical excepients that can form moisture barrier coatings. It is interesting to note that despite the extensive use of film coatings in pharmaceuticals, a detailed examination of interaction of water with excepient film has been not reported.

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2) Achanta A.S., "Hot melt coating:Water sorption behaviour of excipient films" pg 31, M.S thesis, Univ. of Rhode Island, USA (1999)

3) George Zografi and Mark. Kontny, "The Interaction of water with Cellulose- and Starch- Derived Pharmaceutical Excepients" Pharmaceutical Research, vol 3, No. 4, 1986

4) Labuza T.P., " Sorption phenomena in foods", *Food Technology*, 22: 263-272 (1968).

OBJECTIVES

The salient objectives of this study have been listed below:

1) Develop a method to construct sorption/desorption isotherm for excepient film using dynamic vapor sorption technique (DVST). This includes optimization of sample preparation and handling, sample size, defining threshold value for reaching equilibrium and exposure time at each water activity.
2) Complete analysis of Isotherm using Langmuir, BET and GAB models. Evaluate hysteresis and distribution of moisture using Young and Nelson model.
3) Study influence of temperature on sorption/desorption behavior of excepient film. Estimate microrate constants for sorption and desorption and examine their variation with temperature.
4) Generate smoothed adsorption data from isotherms and use the data for complete thermodynamic analysis of water-excepient film systems. Perform a comparative evaluation of the results obtained from application of established models and thermodynamic analysis.

SECTION II

MANUSCRIPT I

REVIEW: The Interaction of Moisture with Cellulose- and Starch-Derived Pharmaceutical Excipients

1) Introduction:

Pharmaceutical solids as dosage forms often may come in contact with water during storage i.e. because of exposure upon handling and storage in an atmosphere containing water vapor. Water associated with solids used pharmaceutically can significantly influence important physical, chemical and pharmaceutical properties such as dissolution, temperature, glass transition, compaction, powder flow and stability (1,2). Many precautions such as reduced contact with atmosphere or control of the relative humidity of the atmosphere can be taken when water is perceived to be a problem, which add expense to the process. They also do not guarantee that there will be no further problems associated with moisture during the life of the product (3). So it is important to know as much as possible about the interaction of water with solids before planning to use them.

Derivatives of starch and cellulose are commonly employed as excepients for various purposes i.e., binders, adhesives, disintegrants and coating materials, to provide physical and chemical protection to drugs (4). As these excepients are commonly employed and known to take up significant amount of moisture, it is important to understand moisture interactions of these excepients. In this context it is important to know some of the critical aspects concerning water-solid interaction like a) total amount of water present, b) how much of water will be sorbed or desorbed at a given relative humidity and temperature, c) what is the thermodynamic state of water associated with solids at various levels of moisture content and d) what are the kinetics of moisture uptake/loss. This importance only increases when the excepient function is to form a film that acts as a barrier to moisture ingress.

The literature reveals extensive work concerning sorption and desorption of water vapor in various fields such as paper (5), textiles (6), food (7). It is interesting to note that despite the extensive use of film coatings in pharmaceuticals, a detailed examination of the interaction of water with excepient film has been rarely reported. This review was compiled mainly focusing on cellulose and starch owing to their widespread usage in film coating.

2) GENERAL PROPERTIES OF CELLULOSE AND STARCH

Over the years volumes of studies have been reported regarding the physical and chemical properties of starch and cellulose. So overviews of physical and chemical properties that aid in understanding the nature of moisture interactions are reviewed below.

STARCH: Starch is a high molecular weight carbohydrate composed of 10-20% of amylose and 80-90% amylopectin. The glucose residues are in the form of branched chains in amylopectin and are arranged in linear fashion in amylose. The chief linkages of glucose units in starch, which gives starch structure and integrity of the system, are hydrogen bonds (8). Starch obtained from corn, which contains about 75% of dry weight of starch, is widely used as pharmaceutical excepient (9). Starch occurs as irregular, angular, white masses and contains polygonal or rounded grains from 3to 35 microns in diameter.

CELLULOSE: Cellulose is anhydrides of β-glucose, possibly existing as long unbranched chains, consisting of 100 to 200 β-glucose units. These chains are cross-linked by hydrogen bonds to produce supporting structure to cell walls of plants. X-ray diffraction studies have revealed that the crystalline regions have lengths of 600 A and width of about 50-150 A (10). In cellulose from higher plants crystalline units can be 2-3 in nm length containing 15 chains. The percentage of crystallinity for cellulose obtained from woods and cotton is about 70% (11).

Microcrystalline Cellulose: Microcrystalline cellulose (MCC) is a purified, partially depolymerized cellulose prepared by treating alpha cellulose with mineral acid.

This is generally obtained from wood pulp. The specific surface area is in the range of 1-2 m^2/g (11).

Hydroxypropyl Methylcellulose: Hydroxypropyl methylcellulose (HPMC) is a propylene glycol ether of methylcellulose. It contains a substitution of 19-24%of methoxyl groups (OCH_3) and 4-12% of hydroxypropyl groups (OC_3H_6OH). It is a white, fibrous or granular powder. (9)

3) <u>SORPTION ISOTHERMS</u>:

The sorption isotherm is best described as a plot of mass of water taken up per unit mass of dry solid as a function of water vapor pressure P, or water activity, P/P_o. where P_o is the vapor pressure of pure liquid water (12).Sorption is best studied starting with dried sample and exposing it to known relative humidity and desorption by starting with system containing sorbed water and reducing the relative humidity (3). Generally, moisture content at a particular relative humidity should be same, whether determined from sorption or desorption measurements. But, sorption-desorption isotherms commonly show hysteresis for certain type of systems such as microporous solids. Hysteresis generally is observed as the amount of water associated with solid on desorption is greater than the amount of originally sorbed water at a given relative humidity. A typical sorption isotherm for hydroxypropyl methylcellulose shows classical sigmoidal shape.

3.1) Langmuir Model

The classical approach in analyzing isotherms has been that of Langmuir. Langmuir's equation is based on the theory that molecules of gas or vapor are adsorbed on active sites and forms a monolayer when adsorbed onto the surface of solids (12,13). The Langmuir isotherm is given by the equation

$$y=y_m bp/1+bp$$

where y = mass of the gas adsorbed per gram of adsorbent at pressure p and constant temperature

y_m = mass of the gas that 1gm of adsorbent can absorb when the monolayer is complete $b = k1/k2$ where k1 and k2 are the constants that govern rate of adsorption and desorption respectively

A plot of p/y Vs p, a straight line results, the slope of which equals to y_m. Thus the mass of gas that one gram of adsorbent can adsorb when the monolayer is complete can be easily computed. In case of starches and cellulose, Langmuir model is useful for understanding the cursory nature of k1 and k2, but this model does not fit most of the isotherms because of the following assumptions:

a) The adsorption possible is more than just a monolayer

b) There are possible lateral interactions between the adsorbed molecules, whereas the model assumes no interactions.

c) The surface is composed of many varying sites with different attractions for water.

3.2) Brunauer, Emmett, and Teller Equation

Brunauer, Emmett, and Teller put forth the model most commonly used to describe the sigmoidal shaped isotherms. The BET model assumes that the first vapor molecule is adsorbed onto the adsorption site of the solid and is tightly bound where as the molecules beyond the first layer are assumed to behave like bulk liquid (7). The BET equation is

$$W= C_B W_M(P/P_o)/[1-(P/P_o)][1-(P/P_o)+C_B(P/P_o)]$$

W is the mass of vapor adsorbed per gram of dry solid at a relative pressure of P/P_o, W_M is the quantity of vapor adsorbed when each adsorption site has one molecule adsorbed to it, and C_B is a constant related to H_1,the heat of adsorption of the first vapor molecule adsorbed to a site, and H_L, the heat of condensation of bulk adsorbate.

In general, the BET equation fits the adsorption data of starches and cellulose quite well over the range of relative pressure range of 0.3 to 0.4, but at higher relative pressures it predicts more adsorption than is practically observed. This can be explained on the basis of assumptions made by this model which are:

a) Sorption occurs only on specific sites

b) Infinite number of layers are adsorbed at a relative pressure of unity

c) The heat of sorption (Q_l) for first layer is constant and Q_l for layers above monolayer is equal to the heat of vaporization (ΔH_V).

In case of simple monolayer adsorption the BET equation reduces to Langmuir equation. In case of starches and cellulose where adsorbed moisture forms multilayers on the surface of solid is not a case of classical BET model. The BET equation is probably useful in predicting monolayer value and heat of adsorption.

There have been many attempts to modify the BET equation so that it would describe the sorption of water vapor over the entire range of relative pressure. Many of the modified BET models incorporated at least one fitting parameter that makes the computer fittings necessary. The meaning of the values obtained from these analyses often do not help in understanding the mechanisms of sorption from molecular viewpoint.

3.3) Guggenheim, Anderson, and deBoer Equation

The model developed by Guggenheim, Anderson, and deBoer, which is an extension BET model, fit the data over the entire range of relative pressure. The GAB model accounts for the intermediate state of water between the tightly bound molecules at the adsorption site and the condensed molecules in free state (1). The GAB equation is given as

$$W=[W_M C_G K(P/P_o)]/ [(1-K(P/P_o))(1-K(P/P_o)+C_G K(P/P_o))]$$

Where P, Po, W, and W_M are the same parameters used in BET equation, and K,C_G are defined as

$$K = B \exp [H_L\text{-}H_M/RT] \text{ and } C = D \exp [H_1\text{-}H_M/RT]$$

Where B, D are constants, H_M is the heat of adsorption of intermediately bound layer, H_1 is the heat of adsorption of the first vapor molecule adsorbed to a site, and H_L is the heat of condensation of bulk adsorbate. However, the BET and GAB models do not give an insight to the nature of the water molecules binding to the primary binding sites of starch and cellulose (14).

3.4) Young and Nelson Equation (YNM)

The sorption isotherms of starch and cellulose usually show hysteresis. There are numerous theories that have been proposed to explain this phenomenon. The most extensively used model is the one proposed by Young and Nelson. The YNM was developed for the biological material in an attempts to relate equilibrium water vapor sorption to relative humidity (15). YNM differentiates three types of water: a bound monolayer, external water and absorbed or internal water. YNM is based on the assumption that the water bound on the outer surface determines movement of water to and from the biological cells (15). The mathematical equations describing YNM are:

$$\theta = a_W/ (a_W+(1-a_W)E)$$

$$\varphi = a_W(\theta)$$

$$\alpha = -(a_W.E)/(E-((E-1).\ a_W))+(E2/(E-1))\ln(E-((E-1).\ a_W)/E)-(E+1)\ln(1- a_W)$$

$$M_S = A(\theta + \alpha) + B\varphi$$

$$M_d = A(\theta + \alpha) + B\theta\, a_{Wmax}$$

where M_s and M_d are the moisture contents of the material during sorption and desorption conditions, θ is the fraction of surface covered by a monomolecular layer, φ is the fraction of the surface covered by multimolecular surface, α total amount of moisture in a multilayer,a $_{wmax}$ is the maximum water activity condition and A, B and E are the parameters unique to each substance. $A.\theta$ is the amount of monomolecular layer of water on surface, $A(\theta+\alpha)$ multimolecular layer of moisture and $B.\varphi$ is the amount of moisture sorbed internally.

The parameters A, B, E have to be carefully interpreted because YNM presume the material under consideration to be a biological cell. So the terms outer sorbed and inner absorbed has to be clearly understood.

4) CONCLUSIONS

Although, it is well established that the moisture associated with excepients significantly effect the physical and chemical properties of the drug, the mode of transfer of water from excepient to drug is not clear. A complete knowledge of sorption isotherms of all the ingredients will allow one to identify the amount of water that is equilibrating with other ingredients in vapor state. It was seen that the model which accounts for the for the water in three states: tightly bound outer layer, intermediate or less tightly bound layer and bulk water, can explain the sorption/desorption data for cellulose and starch materials. The hysteresis could be modeled using YNM model, although physical interpretation of models is not definite. Though the model described here are successful in interpreting the data they do not give any insight to the mechanistic details of moisture-excepient interaction.

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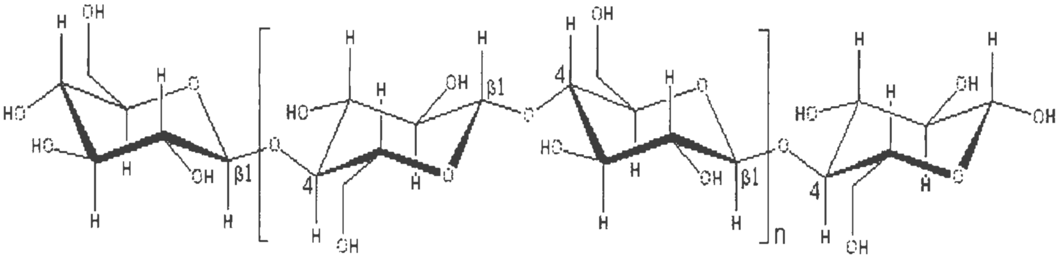
FIG1: Structure of cellulose



MANUSCRIPT II
Water Sorption Behavior of Excipient Films

ABSTRACT

Information on the interaction between moisture and polymers is indispensable for manufacturing of many solid dosage forms since water polymer interaction affects various properties such as compressibility and stability. In this study 1)hydroxypropyl methylcellulose (HPMC), 2)modified HPMC(SEPPIC®), and 3) microcrystaline cellulose containing carrageenan gum (Lusterclear®) were used for studies of moisture polymer interaction. The interaction of moisture with these polymers was assessed using a fully automated gravimetric sorption system, which allows a rapid measure of uptake and loss of moisture. The effect of temperature on the sorption behavior of the film was also examined. All the three excepient films displayed sorption isotherms that were classified as type II (Langmuir) and demonstrated hysteresis during desorption. Detailed analysis of the data shows some departure from simple Langmuir type behavior. The BET model could be used restrictively but the GAB model fitted the data over the entire range of water activity under study. Thermodynamic analysis of water-excepient film system has also been performed to elucidated the mechanistic details of moisture-excepient interactions. Partial molal free energies, enthalpies and entropies were calculated for the three polymeric films. A comparative study of the theoretical models and the experimental thermodynamic studies showed that the results from the two approaches were not always in agreement.

Introduction

The physiochemical properties of pharmaceutical solids are critically dependent on the presence of moisture (1). Pharmaceutical solids as dosage form most often are exposed to water during storage. One method to protect drug products from moisture is to coat them with polymers that act as barrier to moisture ingress. The quantity of moisture in excepients used pharmaceutically can greatly influence appearance and performance of dosage form (2). So it is important to understand interaction of water with excepient films before making strategies to use them. From literature review, hydroxypropyl methylcellulose (HPMC) was a found to be suitable excepient, which acts as barrier to moisture ingress, and included in this study. Novel formulation of HPMC and microcrystalline cellulose (MCC) that are being commercially promoted as moisture protective film coating excepients are also used.

The traditional pharmaceutical method use to determine moisture sorption properties i.e., storing the sample in chambers of various relative humidities and removing them to measure weight gained or lost, is both tedious and imprecise and involves prolonged periods of time (3). So a new technique, the Dynamic Vapor Sorption technique (DVST), reported by Achanta et al. (4) was used to measure uptake and loss of moisture. The Dynamic Vapor Sorption apparatus (DVS) consists of two programmable constant humidity chambers and an ultra sensitive microbalance in a temperature-controlled oven. The material specimen was suspended from the microbalance and a carrier gas was passed over the sample at specific relative humidity. DVS suite software records the change in mass with time data.

It is the objective of this study was to characterize the sorption/desorption behavior of the excepient films and to study the nature of their interaction with water as function of temperature. Established theoretical models were employed for this purpose. A second objective of this study is to investigate thermodynamics water-excepient systems that will elucidate the process of water sorption/ desorption.

2) Materials and methods

Hydroxypropyl methylcellulose (Methocel®, Lot # OA14012N22) was obtained from Dow chemical company, Midland, Michigan. Hydroxypropyl methyl cellulose with a hydrophobic plasticizer, stearic acid, (Seppic®, Lot # 11651) and microcrystalline cellulose containing carrageenan gum (Lusterclear®, Lot # XN118) were obtained from Seppic Inc, 75, Quiad'orsay-75321, Paris and FMC biopolymer, Newark, DE respectively. To cast films 10% w/w dispersions were prepared in deionized water for all the three polymers. 5gm of this dispersion was taken in a flat, circular aluminum pan normally used for loss on drying determinations and dried in an oven at 333 K for 4 hours.

A DVST method using DVS-2000 (Surface Measurements Systems Limited, N.A., Coopersburg, USA) was used to study the moisture interactions of these films. The humidity probes were calibrated as prescribed by manufacturer to cover a water activity (a_w) of 0.00, 0.17, 0.34, 0.51, 0.68 and 0.85.The balance was calibrated before each use.

3) Results and discussion

3.1 Construction of isotherms

Rectangular specimens of each polymeric film prepared were taken and attached to microbalance using paper clip. Paper clips are used instead of normal glass pans to hold the sample to expose maximum surface area to water activity. The conditions for reaching equilibrium is predefined using the DVS analysis suite, as the percent change in mass per minute computed over any consecutive ten minutes fall below the defined threshold value. A threshold value of 0.002%/min was define for the three films, where as USP suggests that weighing should be continued until consecutive readings show a mass change of 0.25%/hour for equilibrium moisture determinations. Using the change in mass with time data recorded by DVS analysis suite the isotherms are constructed for the three polymeric films at T=293, 303 and 313 K. The isotherms constructed by plotting the equilibrium moisture content vs. water activity are shown in figures 1,2 and 3. The isotherms show sigmoidal shapes, which suggests that they come under type II isotherms according to Martin (5). Martin stated that the BET constant (C_{BET}) for type II isotherms should be greater than 2 and this type of isotherms occur when gases are adsorbed onto nonporous solids to form a monolayer followed by multilayer formation.

3.2) Estimation of micro rate constants

Sorption micro rate constant (k_1) and desorption micro rate constant (k_2) were described by Langmuir as governing the sorption and desorption process respectively (6). A plot of mass versus time was constructed at each water activity and the slope of tangent drawn to the initial portion of this plot gives the estimate of these constants. The estimated values of k_1 and k_2 for HPMC, modified HPMC, and MCC are tabulated in tables 1, 2, and 3.

Estimated values of k_1 and k_2 are of the same order for the three polymeric films. The data for both the micro rate constants increased with increasing water activity for the three polymeric films. The estimates for MCC followed fashion that is more orderly and increased with increase in temperature. The Langmuir model does not fit the data of the three polymeric films.This can be explained on the basis of underlying assumptions of the model. Moreover, it is not correct to calculate desorption micro rate constants as explained when the data shows hysteresis. The objective of these calculations is to understand the cursory nature of microrate constants.

3.3) BET and GAB analysis

The isotherms of HPMC, modified HPMC and MCC at T=293, 303and 313 K were analyzed using both BET and GAB models. The BET model satisfactorily fits the data of HPMC, modified HPMC and MCC at three temperatures, over a restricted range of water activity (a_W)(0.17 to 0.51) but does not satisfactorily define data of the three polymeric films at other water activities. The BET constants are grater than 2 for all the three polymers, as stated by Martin. The BET constant (C_{BET}), the constants due to site interaction (H_S) and monolayer values (V_m) are shown in table 4.

The GAB model, which is an extension of BET model, takes into account an extra layer of sorbed vapor intermediate to the monolayer and the bulk water using an additional parameter K. The GAB model fits the data for all the three polymeric films at all the three temperatures over the entire range of water activity understudy. To calculate various parameters of GAB model i.e., K, C_{GAB}, $V_{M,}$ a plot between reciprocal of equilibrium moisture content and water activity was constructed and analyzed using nonlinear regression analysis software (Sigma plot, version 4.0, SPSS Inc., Chicago, USA). The results of this non-linear regression are provided in table 5.

The monolayer values predicted using GAB model for the three polymeric films are almost the same and appear to be temperature independent. The monolayer values obtained from GAB model are in agreement with the values of monolayer obtained from BET model.

3.4) Analysis of hysteresis

The Young and Nelson model (YNM) is the extensively used model to analyze hysteresis. Young and Nelson correlated the equilibrium moisture sorption and desorption of biological material to relative humidity. They distinguished three basic mechanisms of water uptake 1) monomolecular layer of water on surface 2) multimolecular layer of external water 3) moisture absorbed. The total water sorption can be explained by YNM using the two equations:

$M_S = A (\theta + \alpha) + B\varphi$

$M_d = A (\theta + \alpha) + B\theta \, a_{Wmax}$

$\theta = a_W / (a_W + (1 - a_W)E)$

$\varphi = a_W(\theta)$

$\alpha = -(a_W.E)/(E-((E-1). a_W))+(E2/(E-1))\ln(E-((E-1). a_W)/E)-(E+1)\ln(1- a_W)$

where M_s and M_d are the moisture contents of the material during sorption and desorption conditions, θ is the fraction of surface covered by a monomolecular layer, φ is the fraction of the surface covered by multimolecular surface, α total amount of moisture in a multilayer,$a_{w\max}$ is the maximum water activity condition and A, B and E are the parameters unique to each substance. $A.\theta$ is the amount of monomolecular layer of water on surface, $A(\theta+\alpha)$ multimolecular layer of moisture and $B.\varphi$ is the amount of moisture sorbed internally(7). A nonlinear regression analysis procedure was developed to fit the sorption and desorption data of three polymeric films and also to calculate the A, B and E parameters. The SAS statistical software (Version6.12, SAS Institute Inc., Cary , USA) was used for this purpose. The estimated parameters for HPMC, modified HPMC and MCC at various temperatures are given in table 6.

In almost all the cases the YNM predicted showed an excellent fit to the actual data. The parameters A, B of HPMC and modified HPMC are almost same suggesting that the hydrophobic plasticizer added to HPMC did not affect the amount of monolayer moisture or the internally sorbed moisture. The term “internally absorbed” moisture has to be carefully understood in the current situation. As the YNM is basically proposed for biological material, internally sorbed moisture meant the moisture that crossed the cell wall. But in the present situation it perhaps be interpreted as the water that formed some sort of chemical bonds with the adsorbate molecules. Further, YNM offers only a analytical solution to the hysteresis phenomenon, but not the mechanistic solutions.

Therefore the physical significance of the parameters is subjected to further evaluation.

3.5) Free energy changes

The relative partial molal free energy change of water (ΔG_2) for HPMC, modified HPMC and microcrystaline cellulose are shown in figuers5, 6, and 7 respectively. It can be seen that the ΔG_2 is larger for dry excepient films as might be expected. For all the three polymeric films, a point of inflection can be observed at almost all the temperatures. For HPMC at 303 K it can be observed between 0.35 and 0.4 moles of water per 100 g of film. Other than the point of inflection we can see a monotonous curve. This point of inflection perhaps suggests the completion of monolayer formation.

The free energies of adsorption (ΔG), weighted relative partial molal free energy change of water ($n_2\Delta G_2$) and excepient film ($n_1\Delta G_1$) of the three polymers are shown on figures 8, 9, and 10. The value of $n_2\Delta G_2$ gives the contribution of water to the overall free energy change associated with adsorption and $n_1\Delta G_1$ shows the contribution of the excepient film. For all the three films $n_2\Delta G_2$ curves can be divided into three regions: region 1 represents the decreasing part, region 2 represents the plateau region followed by region 3 where the values of $n_2\Delta G_2$ increase. These three regions may represent completion of monolayer, formation of intermediate layers and formation of bulk layer of water respectively. Also, in region 1 the film surface is believed to be restructured due to the interaction with water and this restructured surface serves as substrate for subsequent adsorption. The minima of this region indicate the affinity of excepient to water.

Weighted relative partial molal free energy change of excepient film ($n_1\Delta G_1$) for all the three-excepient films showed almost a linear decrease with increase in water activity. It has been shown that this perturbation becomes evident after saturation of certain sites (8,9). Thus it can be concluded that the excepient films are not inert. For the three polymeric films ΔG showed a monotonic decrease without any inflections. The smooth decrease in the curve indicate the importance of individual examination of relative contributions of water and excepient films.

3.6) Isostearic heats of adsorption

The relative partial molal enthalpies of adsorbed water (ΔH_2) for all the three films are in figures 11,12, and 13. At T=313K for HPMC and modified HPMC, 6 exothermic maximas can be observed where as at T=303 K both of them showed 5 exothermic maximas. The first exothermic maxima of about 20 KJ/mol at T=313 K for HPMC suggests that each water molecule is involved in two hydrogen bonds (10). MCC at both temperatures showed less exothermic maximum than the other excepient films. Exothermic maxima indicate the completion of monolayer. Integral enthalpy of adsorption (ΔH) and weighed relative partial molal enthalpies of excepient film ($n_1\Delta H_1$) and water ($n_2\Delta H_2$) are calculated and figures 14, 15 and 16 present these functions for HPMC, modified HPMC and MCC respectively at T=313 K. The ΔH function is smooth and shows a decrease, while $n_1\Delta H_1$ and $n_2\Delta H_2$ are more informative because of the inflection points. For HPMC at 303 K $n_2\Delta H_2$ function attains a minima and a progressive decrease is seen up to n_2=0.4 mol/100g of film and then increases rapidly. The $n_1\Delta H_1$ first attains maxima and a gradual decrease is observed from then. A similar pattern is seen for HPMC at 313 K.

3.7) Entropy changes

Relative partial molal entropies (ΔS_2) has been calculated for HPMC, modified HPMC and MCC and shown in figures 17, 18 and 19. The initial decrease in the curves for all the three polymeric films suggests lack of mobility of water as the water is tightly bound to the adsorbate molecules. As more water is sorbed, water molecules form cluster around the tightly bound water, which increases the mobility of water. The entropy profiles are comparable to the enthalpies discussed earlier. This can be justified as the $\Delta G2$ curve seen earlier shown a monotonus decrease with only very few inflection points on the top and then flattened out.

3.8) Comparative evaluation:

The comparative study of theoretical model and thermodynamic model was conducted to understand clearly the mechanism of moisture interaction and to verify the nature of data obtained from these methods. Although the theoretical models described above are successful in analytically fitting the data, thermodynamic analysis of the data is very useful in clarifying the water-film interactions at molecular level (10). The theoretical models assumed that the excepient film is inert in the sorption/desorption process that is proven wrong by the thermodynamic methods. GAB model satisfactorily fits the data of all the three polymeric films, which proposes the presence of three types of water, has been confirmed by the thermodynamic studies. The hypothesis of hydrogen bond formation between water and adsorbate molecules and the energy values corresponding to exothermic maximas, which aid in the calculation of number of hydrogen bonds, confirm the hysteresis phenomenon.

4) Conclusions

DVST has proven to be a useful instrument for fast, convenient and accurate determination of moisture interactions of excepients. Results from both the theoretical models as well as thermodynamic methods shown the presence of three different forms of water: monolayer, intermediate less tightly bound water and the bulk water. It has been shown that the hysteresis, which is formed due to hydrogen bonding between water and adsorbate molecules, can be modeled using YNM. The assumption of theoretical models that the excepients are inert in vapor sorption processis of dubious validity for the system reported in this paper. Theoretical models can be used for the predictive and analytical purpose whereas thermodynamic studies help in understanding mechanistic details of moisture interactions with excepient films.

Acknowledgements

The generous financial support, access to laboratory, library and computer facilities of Glaxo SmithKline Consumer Healthcare was gratefully acknowledged.

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Table1: Estimates of microrate constants for sorption (k_1) and desorption (k_2) processes assuming Langmuir behaviour for hydroxyprpyl methylcellulose film

Sorption microrate constants (k_1 X 10^5 in g/min)						
	T=293K		T=303K		T=313K	
Water activity	Mean (n=3)	SD	Mean (n=3)	SD	Mean (n=3)	SD
0.17	3.05	0.99	7.88	1.33	6.54	2.59
0.34	2.91	1.01	7.57	1.15	6.05	2.98
0.51	3.30	1.40	9.00	0.97	7.50	2.78
0.68	3.91	1.61	11.1	1.19	9.32	2.71
0.85	5.31	0.72	15.0	1.35	14.9	4.10
Desorption micro rate constant (k_2X 10^5 in g/min)						
	T=293K		T=303K		T=313K	
Water activity	Mean (n=3)	SD	Mean (n=3)	SD	Mean (n=3)	SD
0.17	3.51	1.61	8.09	0.98	7.89	3.01
0.34	4.36	2.08	9.53	1.33	8.89	3.94
0.51	5.00	1.70	10.7	0.89	10.5	3.77
0.68	7.15	1.92	12.1	0.02	18.6	6.41

Table2: Estimates of microrate constants for sorption (k_1) and desorption (k_2) processes assuming Langmuir behaviour for modified hydroxyprpyl methylcellulose film

Sorption microrate constants (k_1 X 10^5 in g/min)						
	T=293K		T=303K		T=313K	
Water activity	Mean (n=3)	SD	Mean (n=3)	SD	Mean (n=3)	SD
0.17	3.44	3.93	4.93	1.68	4.88	1.03
0.34	3.38	3.66	4.87	1.69	4.48	1.41
0.51	3.95	4.03	5.87	2.00	5.68	1.50
0.68	4.15	4.15	7.19	2.31	6.81	1.66
0.85	4.01	4.61	8.79	2.28	10.4	2.84
Desorption micro rate constant (k_2X 10^5 in g/min)						
	T=293K		T=303K		T=313K	
Water activity	Mean (n=3)	SD	Mean (n=3)	SD	Mean (n=3)	SD
0.17	2.72	2.87	6.07	4.21	5.66	1.49
0.34	3.51	3.38	7.38	3.46	7.44	1.68
0.51	4.22	4.15	8.72	2.60	9.05	2.31
0.68	4.88	5.14	10.1	2.53	14.7	4.24

Table3: Estimates of microrate constants for sorption (k_1) and desorption (k_2) processes assuming Langmuir behaviour for microcrystaline cellulose film

Sorption microrate constants (k_1 X 10^5 in g/min)						
	T=293K		T=303K		T=313K	
Water activity	Mean (n=3)	SD	Mean (n=3)	SD	Mean (n=3)	SD
0.17	1.75	1.11	2.59	0.72	3.32	1.23
0.34	2.12	1.07	3.03	0.65	4.13	1.26
0.51	3.62	1.52	5.23	1.24	7.43	2.27
0.68	6.61	3.24	9.28	1.96	12.2	3.50
0.85	13.3	11.5	18.2	7.63	21.7	5.67
Desorption micro rate constant (k_2X 10^5 in g/min)						
	T=293K		T=303K		T=313K	
Water activity	Mean (n=3)	SD	Mean (n=3)	SD	Mean (n=3)	SD
0.17	2.37	0.45	2.82	2.59	4.38	1.21
0.34	4.48	0.82	5.71	1.36	7.86	2.68
0.51	7.19	1.06	10.2	0.48	17.6	3.28
0.68	11.8	3.13	18.5	0.41	26.6	3.55

Table 4: Results of BET model fits for films of a) hydroxypropyl methylcellulose, b) modified hydroxypropyl methylcellulose, and c) microcrystaline cellulose. BET results are valid for 0.17 $\leq a_W \leq 0.51$

a)			
Temp(K)	C_{BET}	V_m(g of water/g of film	H_s(J/mole)
293	3.00	0.04	2635.71
303	2.94	0.03	2712.10
313	2.86	0.03	2729.40
b)			
293	3.53	0.03	3065.98
303	3.28	0.03	2972.16
313	3.49	0.03	3249.92
c)			
293	3.07	0.03	2415.98
303	2.60	0.05	1981.06
313	4.08	0.03	3655.01

Table 5: Results of GAB model fits for films of a) hydroxypropyl methylcellulose, b) modified hydroxypropyl methylcellulose, and c)microcrystaline cellulose at varying temperatures

a)			
T (K)	K	C_{GAB}	V_m(g of water/g of film
293	0.87	2.28	0.03
303	0.89	2.48	0.03
313	0.93	2.68	0.04
b)			
293	0.91	3.11	0.04
303	0.89	2.86	0.03
313	0.90	3.16	0.03
c)			
293	1.01	2.67	0.03
303	0.90	2.25	0.03
313	1.07	2.28	0.03

Table 6: Estimates of Young and Nelson model parameters A, B and E used to describe hysterisis in sorption data for films of a) hydroxypropyl methylcellulose, b) modified hydroxypropyl methylcellulose, and c) microcrystaline cellulose

a)			
T(K)	A	B	E
293	0.03	0.04	0.77
303	0.04	0.07	1.03
313	0.04	0.03	0.77
b)			
293	0.03	0.07	0.89
303	0.03	0.04	0.71
313	0.04	0.02	0.72
c)			
293	0.04	0.11	2.44
303	0.07	0.04	2.11
313	0.16	0.5	14.5

Figure1: Schematic representation of the dynamic vapor sorption technique apparatus

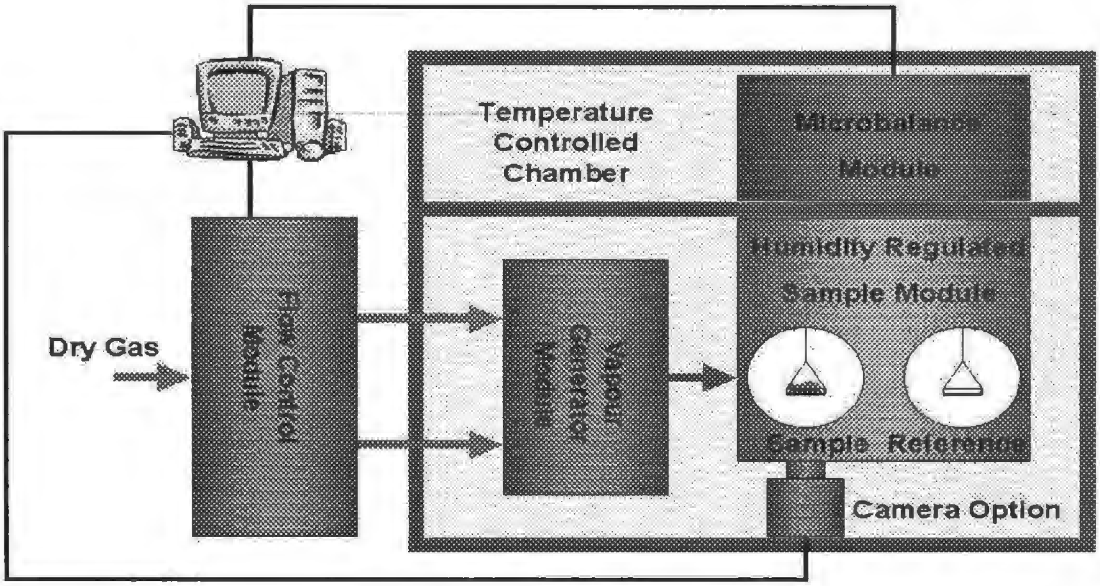


Figure 2: Sorption isotherms for hydroxypropyl methylcellulose (HPMC) film. Values of equilibrium moisture content (V) are mean of n=3

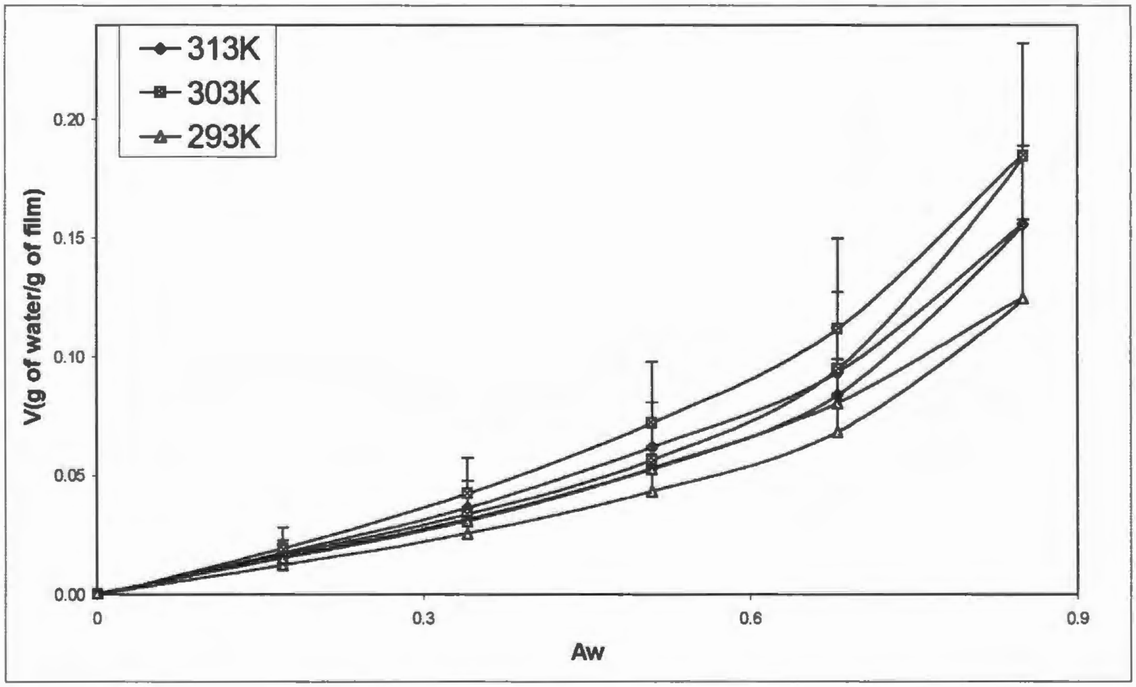


Figure 3: Sorption isotherms for modified hydroxypropyl methylcellulose films. Values of equilibrium moisture content (V) are mean of n=3

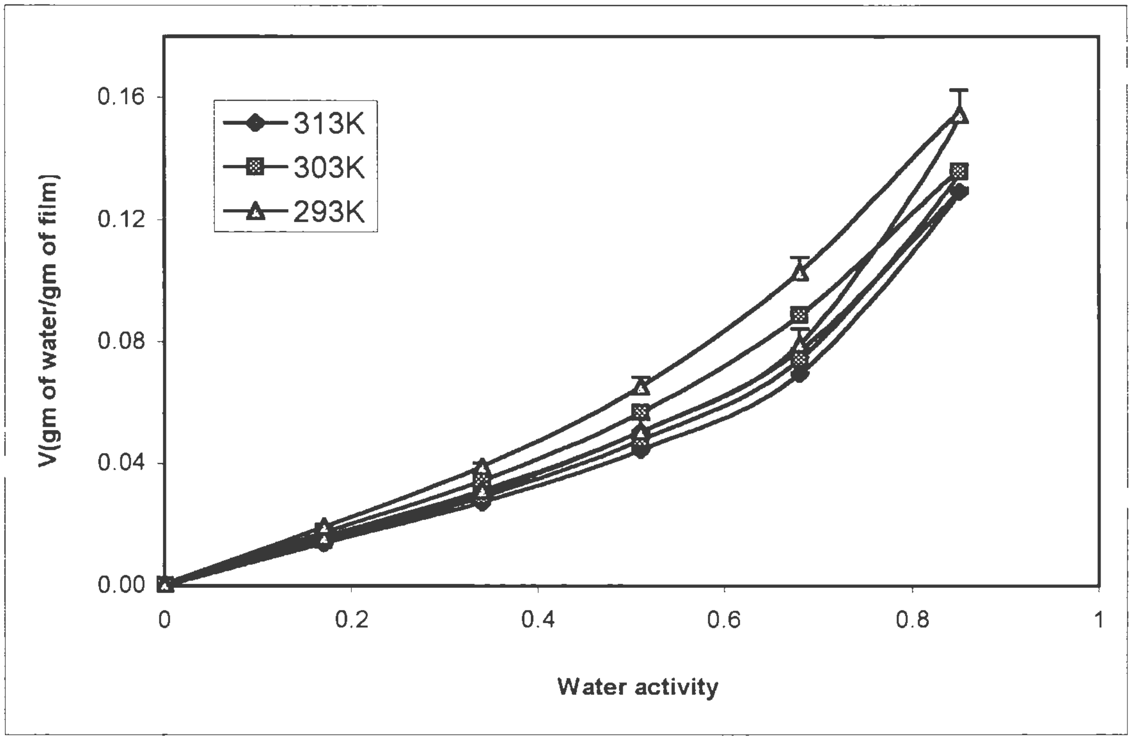


Figure 4: Sorption isotherms for microcrystaline cellulose (MCC) films. Values of equilibrium moisture content (V) are mean of n=3

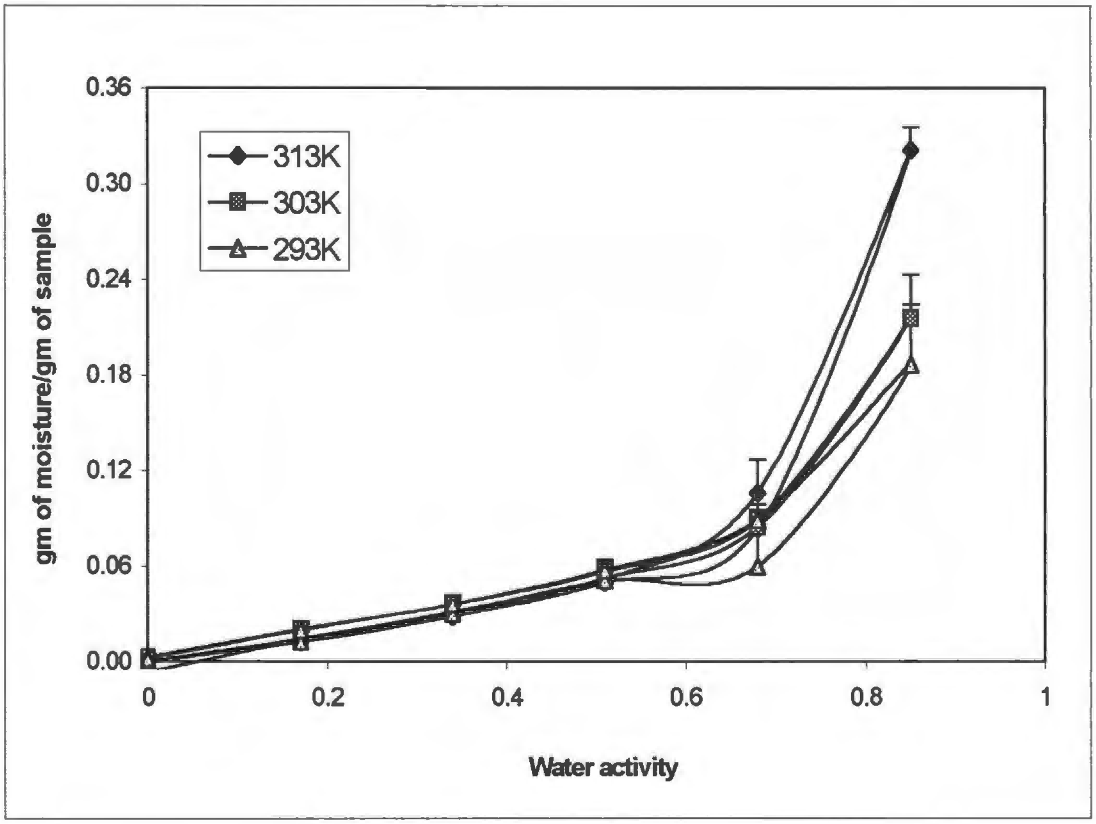


Figure 5:Fit of sorption data using GAB model for hydroxypropyl methylcellulose (HPMC) at T = 303K, • indicates actual data and —represents the fitted data obtained by nonlinear regression (n=3)

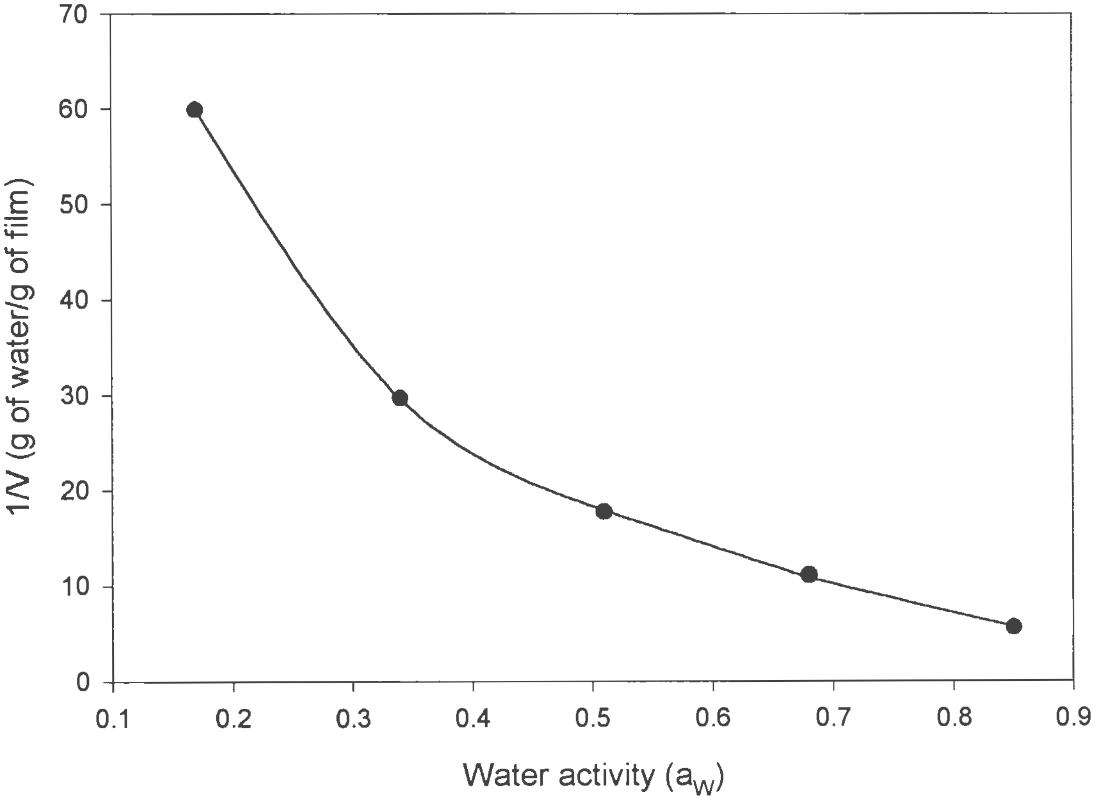


Figure6: Relative partial molal free energy (ΔG_2 in KJ/mol) of adsorbed water on HPMC

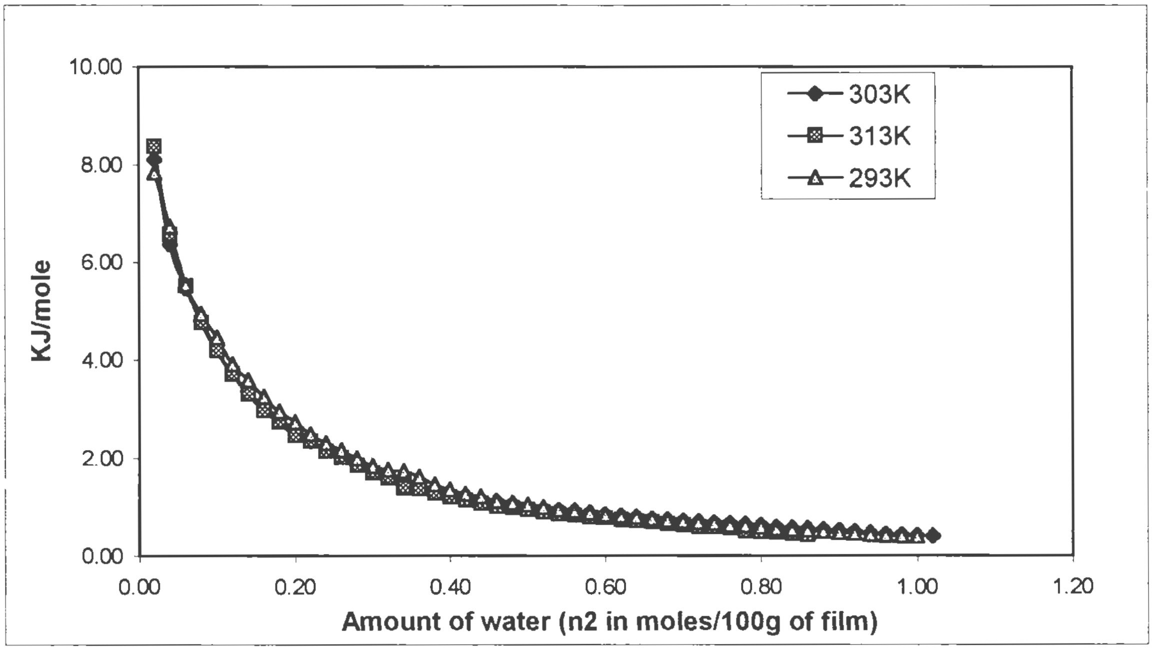


Figure 7:Relative partial molal free energy (ΔG_2 in KJ/mol) of adsorbed water on modified HPMC .

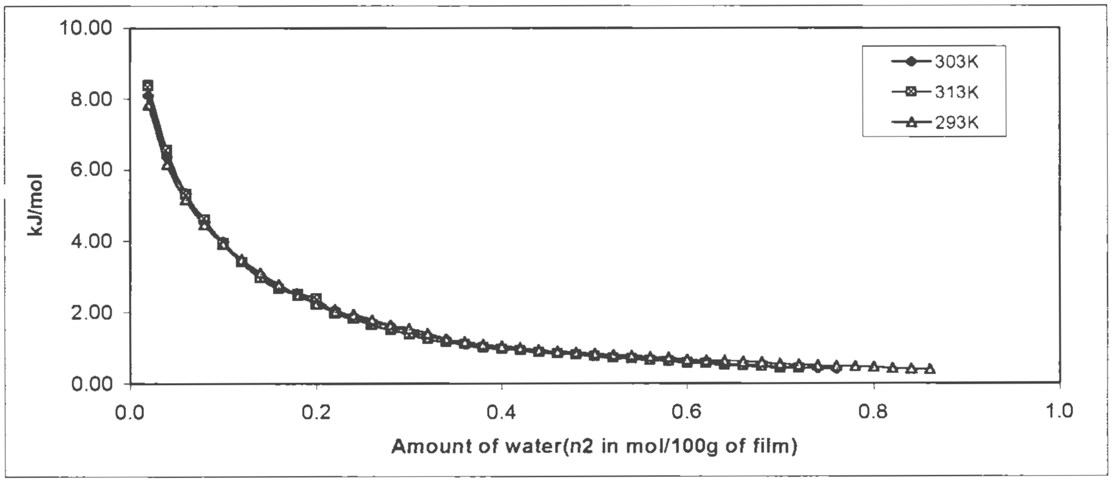


Figure 8: Relative partial molal free energy (ΔG_2 in KJ/mol) of adsorbed water on micro crystaline cellulose .

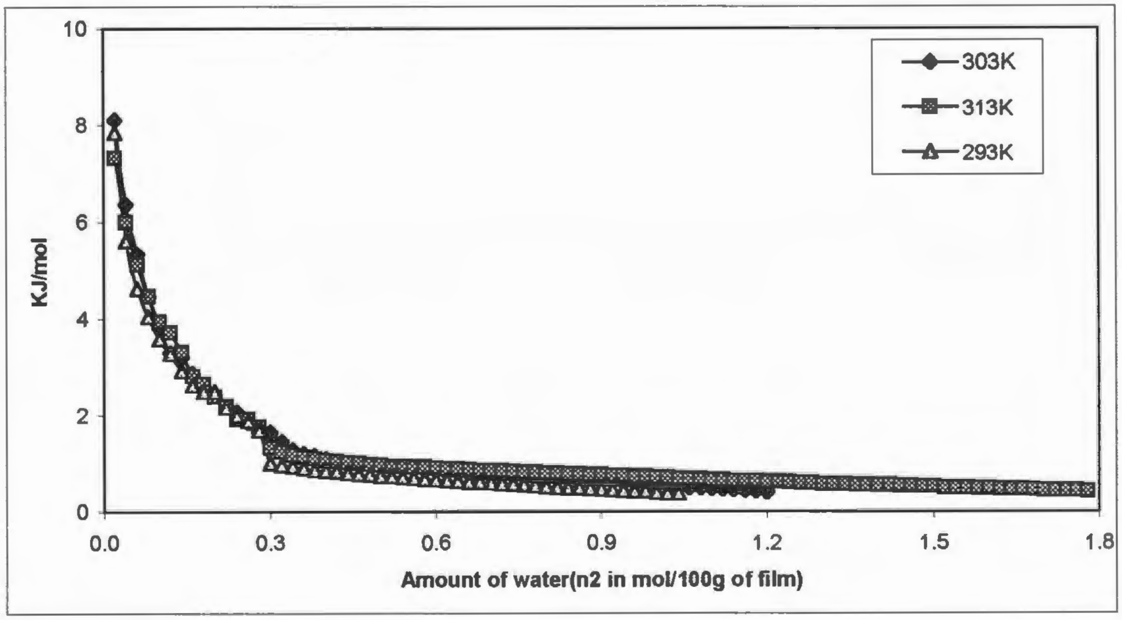


Figure 9: Integral free energy of adsorption (ΔG) and weighted relative partial molal free enegies of excipients film($n_1\Delta G_1$) and water ($n_2\Delta G_2$)for water-Hpmc film at 303 k

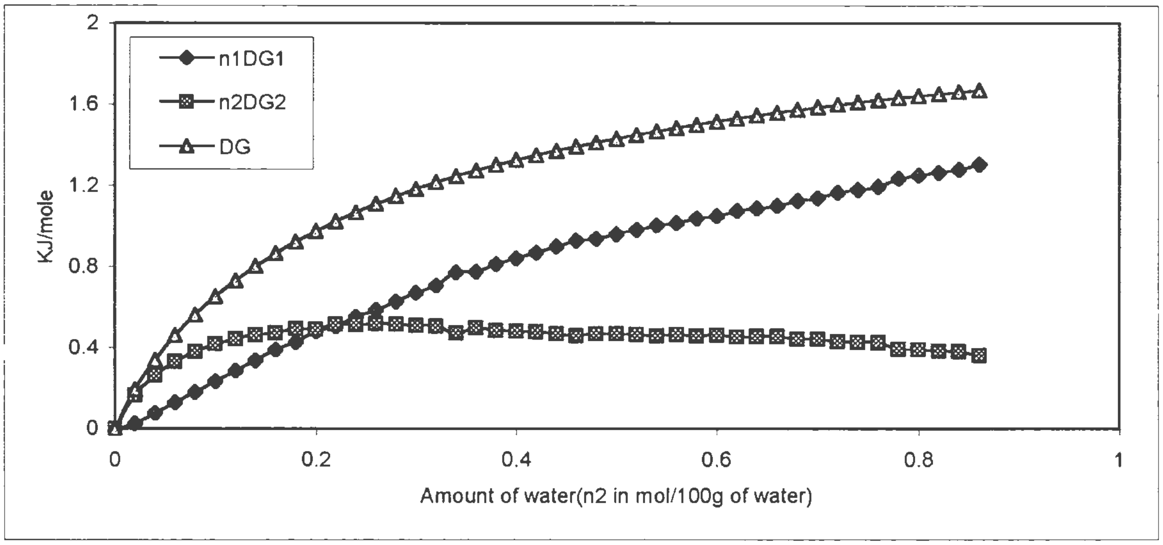


Figure 10: Integral free energy of adsorption (ΔG) and weighted relative partial molal free enegies of excipients film($n_1\Delta G_1$) and water ($n_2\Delta G_2$)for water- modified Hpmc film at 303 K

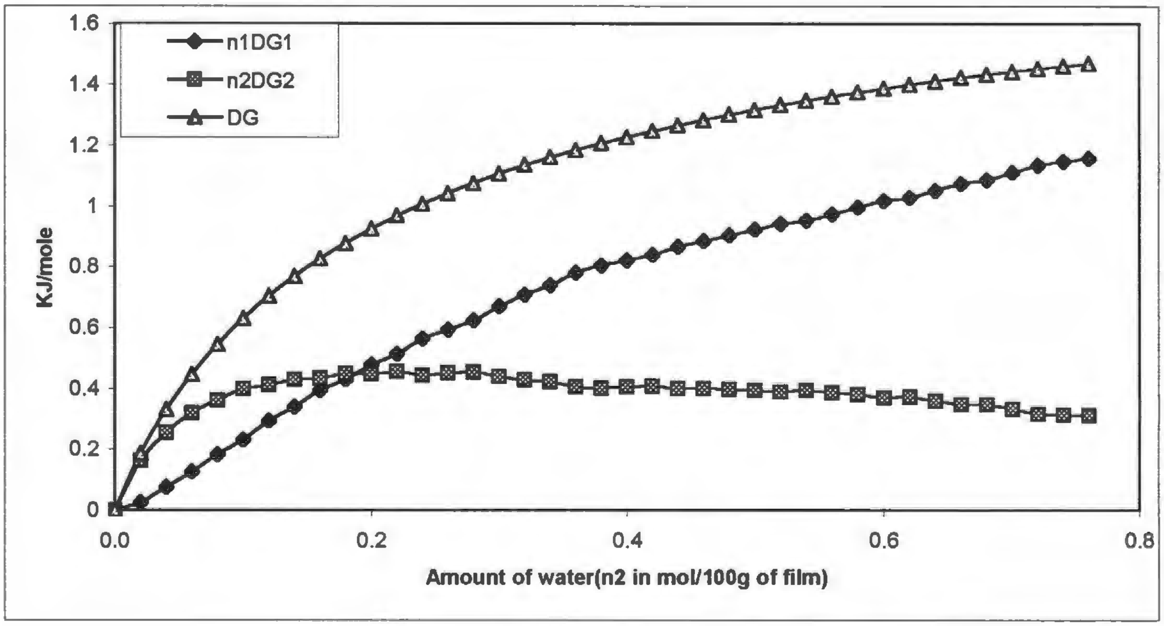


Figure 11: Integral free energy of adsorption (ΔG) and weighted relative partial molal free enegies of excipients film($n_1\Delta G_1$) and water ($n_2\Delta G_2$)for water-microcrystaline cellulose film at 303 k

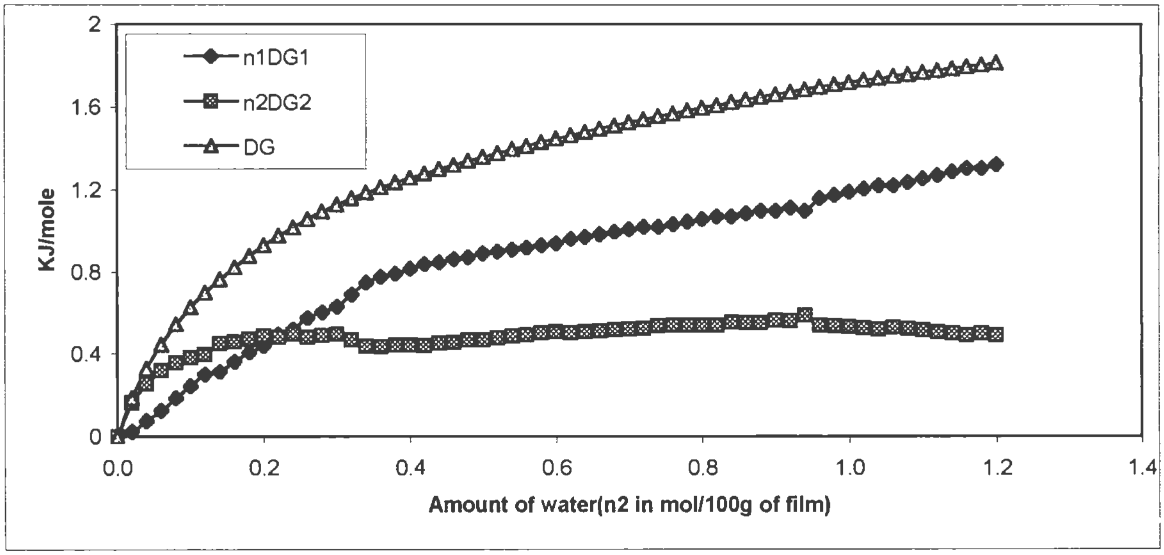


Figure 12: Relative partial molal enthalpy(ΔH_2) of adsorbed water on HPMC film

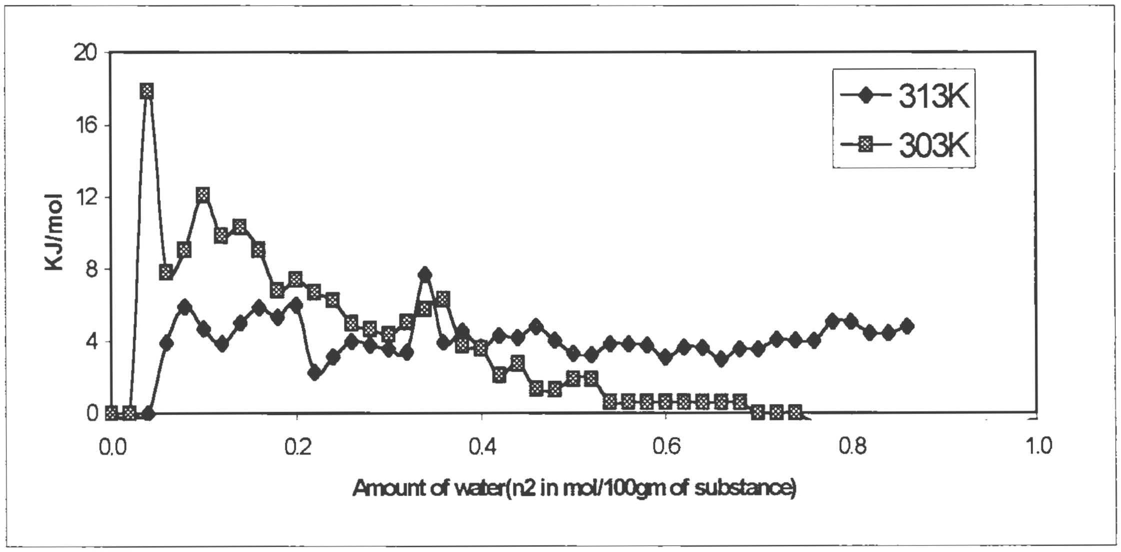


Figure 13: Relative partial molal enthalpy(ΔH_2) of adsorbed water on modified HPMC film

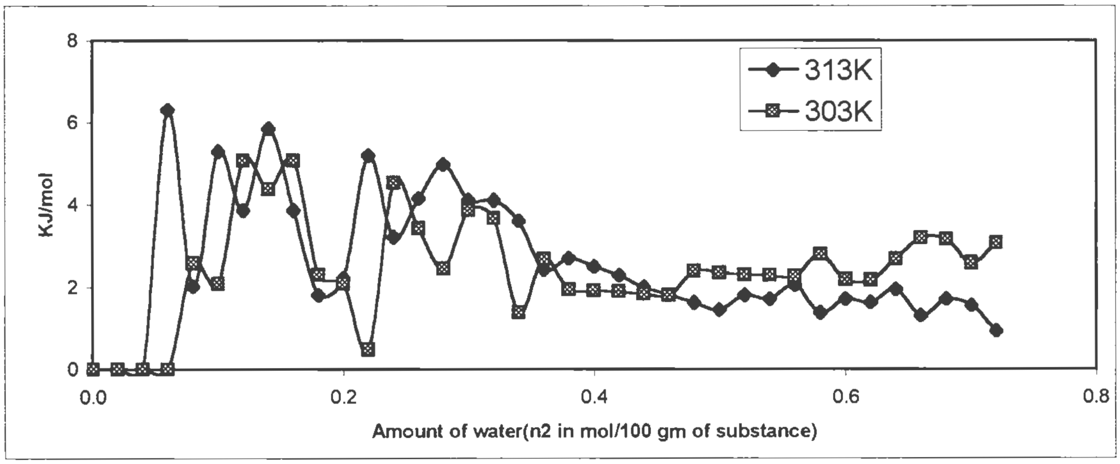


Figure 14: Relative partial molal enthalpy (ΔH_2) of adsorbed water on microcrystaline cellulose film

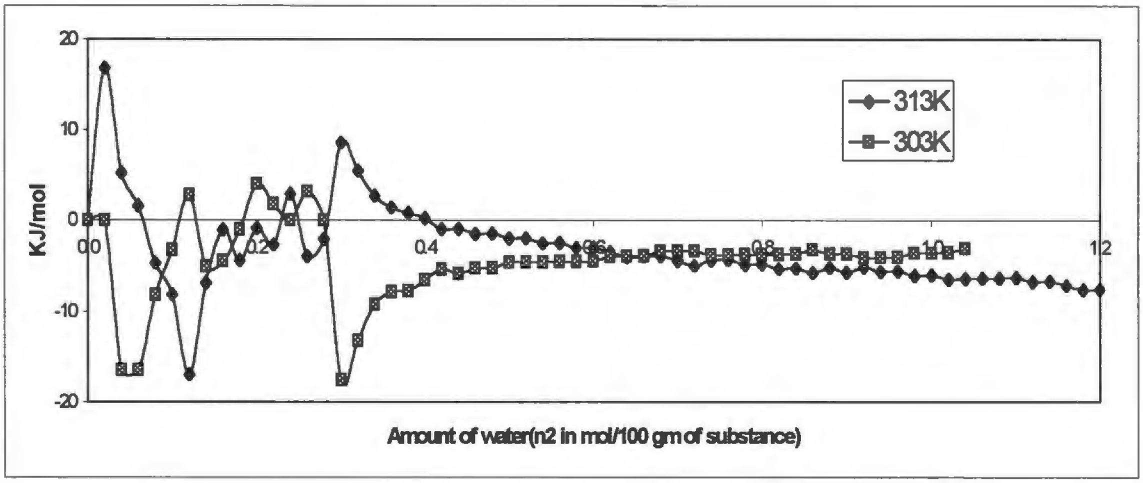


Figure 15: Integral enthalpy of adsorption (ΔH) and weighted relative partial molal enthalpies of excipients film($n_1\Delta H_1$) and water ($n_2\Delta h_2$)for water-Hpmc film at 303 k

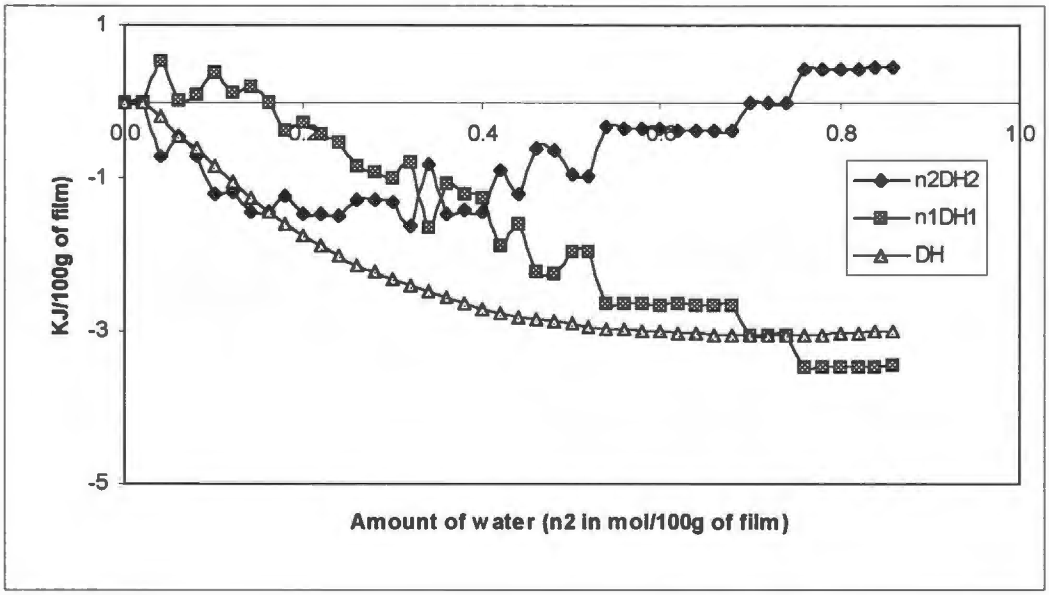


Figure 16: Integral enthalpy of adsorption (ΔH) and weighted relative partial molal enthalpies of excipients film($n_1\Delta H_1$) and water ($n_2\Delta H_2$)for water-modified HPMC film at 303 k

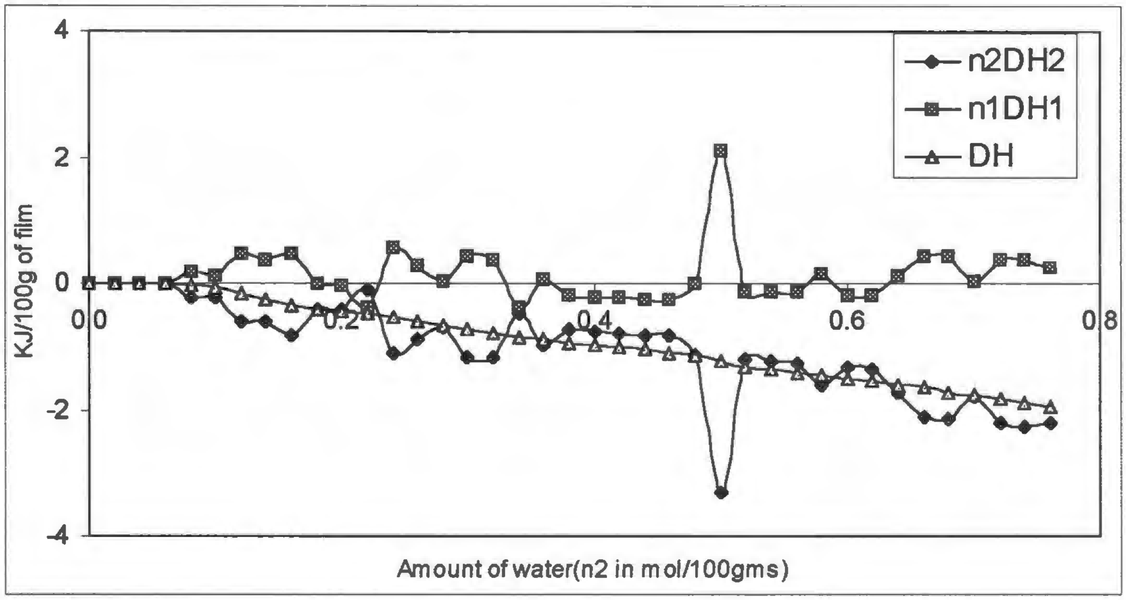


Figure 17: Integral enthalpy of adsorption (ΔH) and weighted relative partial molal enthalpies of excipients film($n_1\Delta H_1$) and water ($n_2\Delta H_2$)for water-MCC film at 303 k

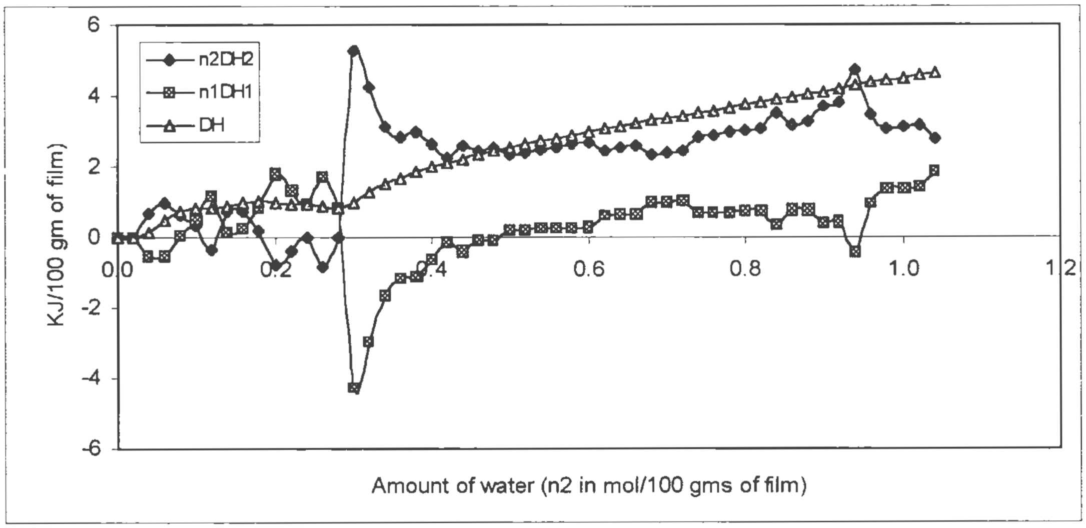


Figure 18: Relative partial molal entropy (ΔS_2) of absorbed water on HPMC film

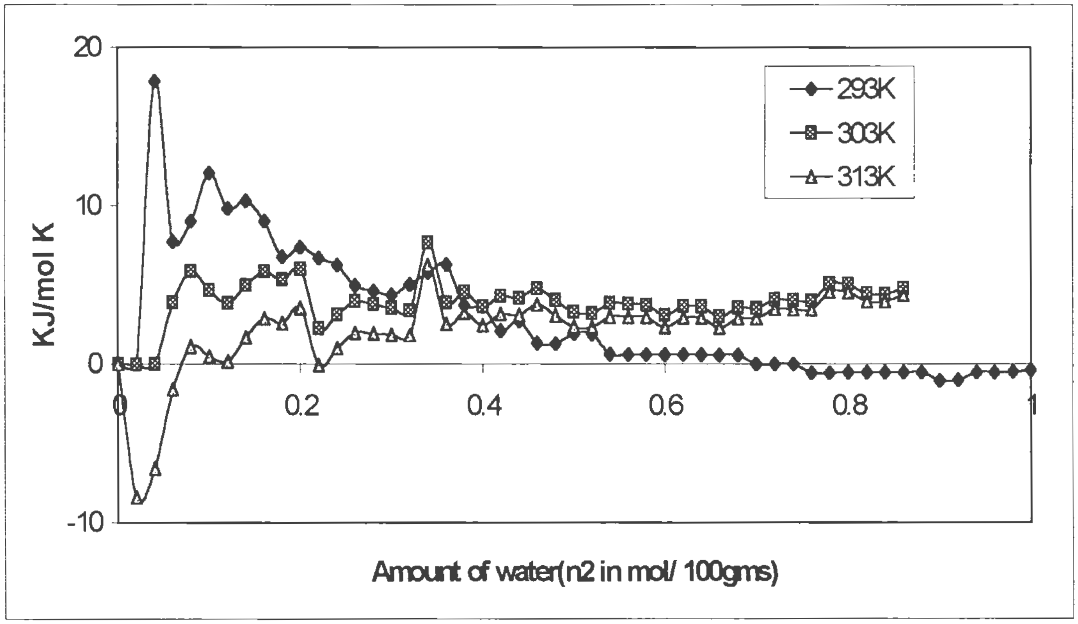


Figure 19: Relative partial molal entropy (ΔS_2) of absorbed water on modified HPMC film

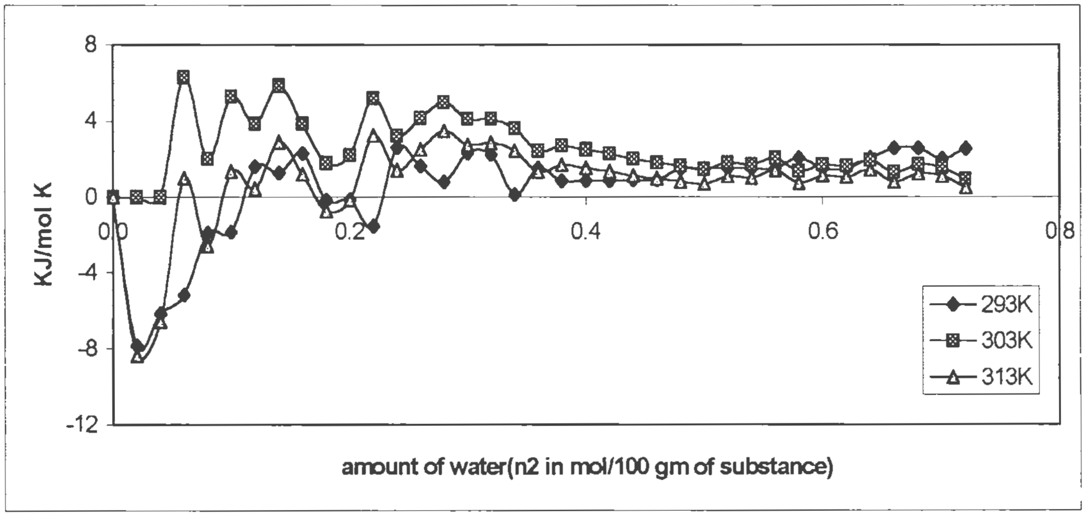
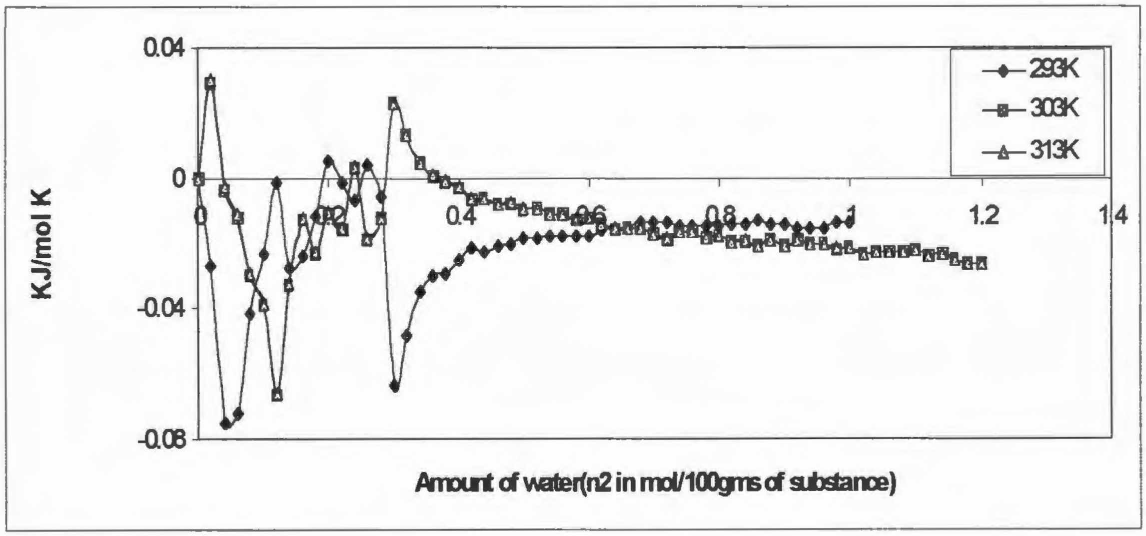


Figure 20: Relative partial molal entropy (ΔS_2) of absorbed water on microcrystaline cellulose film



SECTION III

APPENDIX A

LIST OF PUBLICATIONS

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

Manuscript II: Water Sorption Behavior of Excipient Films

To be submitted for publication in European Journal of Pharmaceutical Sciences

APPENDIX B

DETAILS OF REGRESSION FOR GAB MODEL FITTING

The following illustrates the nonlinear regression routine used along with the regression report generated by Sigma Plot using adsorption data for hydroxypropyl methylcellulose film at T = 303K

```
Nonlinear Regression

[Variables]
a= col (1)
y= col (2)
[Parameters]
K=0.5
C=0.5
W=0.3
[Equations]
f=((1-(K*a))*((1-(K*a))+(C*K*a)))/(C*K*a*W)
fit f to y
[Constraints]
W<0.15
[Options]
tolerance=0.0001
stepsize=100
iterations=100

R = 0.99997065   Rsqr = 0.99994130          Adj Rsqr = 0.99988261

Standard Error of Estimate = 0.2338

            Coefficient  Std. Error      t              P
K           0.9245       0.0146          63.1118        0.0003
C           2.7436       0.1017          26.9713        0.0014
W           0.0416       0.0015          27.4311        0.0013

Analysis of Variance:
            DF           SS              MS             F               P
Regression  2            1861.7989       930.8995       17035.7035      <0.0001
Residual    2            0.1093          0.0546
Total       4            1861.9082       465.4771

PRESS = 0.4205

Durbin-Watson Statistic = 3.3822

Normality Test:   Passed   (P = 0.6394)

Constant Variance Test:    Passed   (P = 0.0500)
```

```
Power of performed test with alpha = 0.0500: 1.0000

Regression Diagnostics:
Row     Predicted   Residual    Std. Res.   Stud. Res.   Stud. Del. Res.
1       59.8763     -0.0010     -0.0041     -0.0305      -0.0216
2       29.5943     0.0461      0.1973      0.2959       0.2139
3       17.8993     -0.1904     -0.8146     -1.0460      -1.0990
4       10.8511     0.2463      1.0538      1.2649       2.0000
5       5.6616      -0.1011     -0.4324     -0.8888      -0.8080

Influence Diagnostics:
Row     Cook's Dist. Leverage   DFFITS
1       0.0170      0.9821      -0.1598
2       0.0364      0.5552      0.2390
3       0.2365      0.3934      -0.8851
4       0.2351      0.3060      1.3280
5       0.8493      0.7633      -1.4510

95% Confidence
Row     Predicted   Regression 5%  Regression 95% Population 5%  Population 95%
1       59.8763     58.8796        60.8730        58.4603        61.2923
2       29.5943     28.8449        30.3437        28.3400        30.8486
3       17.8993     17.2685        18.5302        16.7121        19.0866
4       10.8511     10.2948        11.4075        9.7017         12.0005
5       5.6616      4.7829         6.5404         4.3260         6.9972
```

APPENDIX C

DETAILS OF REGRESSION FOR YOUNG&NELSON MODEL FITTING

The following describes the segmented nonlinear regression routine used

by SAS using data for hydroxypropyl methylcellulose at T = 303 K

```
ptions pageno = 1 number date;
data test;
input col water moist1 moist2 moist3;
cards;
1     0          0.00000 0.00000      0.00000
2     0.17  0.01670      0.01656      0.01656
3     0.34  0.03374      0.03368      0.03368
4     0.51  0.05647      0.05673      0.05673
5     0.68  0.09011      0.09726      0.09726
6     0.85  0.17984      0.18738      0.18738
7     0.68  0.10928      0.11306      0.11306
8     0.51  0.07116      0.07278      0.07278
9     0.34  0.04206      0.04262      0.04262
10    0.17  0.01979      0.01935      0.01935
11    0          0.00002 -0.00062 -0.00062
;
run;
%macro donlin(var,title);
title1 "&title";
proc nlin data=test;
parm a=.1 b=.1 E=.1;

p= water/(water+(1-water)*e);
q= p*water;
r=(-E*water/(E-(E-1)*water))-((E+1)*log(1-water));
s=(E**2/(E-1))*log((E-(E-1)*water)/E);
t=r+s;

if col le 6 then do;
model &var = a*(p+t)+(b*q);
bounds a > 0;
bounds b > 0;
bounds E > 0;
end;

if col ge 6 then do;
model &var = a*(p+t)+(b*p*(.85));
bounds a > 0;
bounds b > 0;
bounds E > 0;
```

```
end;

output out=forplot;
run;

%mend donlin;

%donlin(moist1,Hpmc -T=303K);

proc plot data=forplot;
     plot moist1*water;
run;

%donlin(moist2,Hpmc -T=303K);

proc plot data=forplot;
     plot moist2*water;
run;

%donlin(moist3,Hpmc -T=303K);

proc plot data=forplot;
     plot moist3*water;
run;
```

SUMMARY OF CONCLUSIONS

1) Dynamic vapor sorption technique is proven to be a simple, fast and convenient method for investigation of sorption and desorption behavior of excepient films of pharmaceutical significance. Films of hydroxypropyl methylcellulose, modified hydroxypropyl methylcellulose, microcrystaline cellulose have been used to examine the effect of temperature on moisture sorption/desorption studies.
2) All the three excepients showed type II isotherms and also hysteresis during desorption.
3) The sorption data of all three excepient films did not follow the simple Langmuir model
4) The BET model could be used restrictively.
5) The GAB, which is an extension of BET model, successfully described the data for all the three films at all water activities.
6) The hysteresis shown by all the three films could be modeled accurately using the Young and Nelson model, but meaningful interpretation of the model's parameters was not possible.
7) A complete thermodynamic analysis of water-excepient film interaction was performed. Partial molal free energies, enthalpies and entropies were computed for water-excepient film systems.
8) A comparative evaluation of the results of theoretical models and thermodynamic studies have shown that the results are not always complementary to each other,

emphasizing the need to perform both analyses for complete characterization of water-excepient film systems.

9) It is also possible that the different states of water present can affect the functionality of the excepient. Water within the particles can strongly influence the compaction properties by affecting the degree of viscoelasticity.

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