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Preparation of a novel type of controlled-release carrier and evaluation of drug release from the matrix tablet and its physical properties

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Summary

Solved mixtures of hydrogels (SMH), composed of hydroxypropylcellulose (HPC), a pseudo-hydrogel, and ethylcellulose, a water-insoluble polymer, were prepared by solvent evaporation. Phenylpropanolamine hydrochloride was used as a model drug. The amount of drug released from a matrix tablet containing SMH powder and the drug increased with decreasing weight fraction of HPC (WFH) in SMH. SMH showed improved properties compared to HPC alone, for example, flowability and hydroscopicity. These properties increased with decreasing WFH. The sorption apparatus described in this study is capable of an immediate, sensitive and accurate response to initial moisture sorption. The kinetics of moisture sorption measurement using this apparatus is useful for a preliminary study.

Introduction

Controlled release systems have been developed for the purpose of maintaining a therapeutically effective concentration of drug in the systemic circulation for a long period of time and reducing the side effects. A number of methods and techniques have been used in the manufacture of oral controlled release dosage forms. One of the more common methods of fabricating controlled-release dosage forms is by incorporating the drug substance into a matrix containing a hydrogel. Generally, modulation of their release rate is achieved using different grades of polymers (Nakano et al., 1983), different types of polymers (Baveja et al., 1987), soluble fillers (Ford et al., 1987), or insoluble fillers (Rao et al., 1990).

Hydroxypropylcellulose (HPC) and ethylcellulose (EC) have already been pharmaceutically approved for oral use, and when a mixture of HPC and EC is compressed into a tablet with a drug, the release rate of the drug from the matrix may change.

A direct compression technique after mixing a drug and hydrogels is a simple technique for formulating controlled release dosage forms (Mura et al., 1989), even though one disadvantage

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of direct compression in comparison with wet granulation is the limitation in production of tablets containing a high percentage of drug substance. It is desirable for directly compressed fillers to have good flowability and binding properties. Hydrogels can absorb and retain large amounts of water in their amorphous portions when exposed to water vapor at various relative humidities (Zografi, 1988). This absorbed water can influence the flowability of the powder (Hiestand, 1966) during the manufacturing process or storage. At high relative humidities the flowability of the hydrogel powders deteriorates in relation to the gradual moisture uptake in the hydrogels.

In recent years, there has been active research in generating new materials from known polymers by polymerization or blending so as to improve the properties of known polymers in the field of engineering plastic. The new materials (polymer blends) are called 'polymer alloys'. HPC forms a pseudo-hydrogel upon contact with aqueous medium and thus exhibits controlled-release properties (Nakano et al., 1983). Ethylcellulose (EC), a water-insoluble polymer, is used as a controlled-release carrier (Shaikh et al., 1987). HPC and EC can dissolve in alcoholic medium, and blend easily in alcoholic solution. Polymer blends can be obtained by removing the alcoholic medium. To achieve release rate modulation and to improve the hydroscopicity and flowability of hydrogels, we attempted to blend a water-insoluble polymer with a pseudo-hydrogel by the technique of solvent evaporation.

The objectives of this study were to develop a new type of hydrogel so as to perform release rate modulation, and to improve the inferior properties of known pseudo-hydrogels as well as to evaluate the physical properties, flowability, and hygroscopicity.

Materials and Methods

Materials

Phenylpropanolamine HCl (PPA) was obtained from ALPS Pharmaceutical Ind. (Gifu, Japan). Hydroxypropylcellulose 2320 mPa s (cps) viscosity grade (HPC-H, Nihonsoda, Tokyo, Japan), ethylcellulose (EC, viscosity 10 cps, Dow Chemical, U.S.A.) and ethanol (Wako Pure Chemicals Industries, Tokyo, Japan) were used. Magnesium nitrate, sodium chloride, potassium chloride and potassium dihydrogen phosphate (Wako Pure Chemicals Industries, Tokyo, Japan) were used to prepare saturated salt solutions to provide relative humidities of 52.8, 75.3, 84.3, and 96.6% at 25°C, respectively (Nyqvist, 1983 and Polymer society, polymer and water sorption committee, 1968). HPLC grade acetonitrile was used in the preparation of the HPLC mobile phase. All other chemicals used were reagent grade.

Preparation of experimental powders

A 5% (w/w) ethanolic solution of HPC-H, and a 10% (w/w) ethanolic solution of EC were prepared. These solutions were mixed in the following HPC-H-to-EC weight ratios: 9:1, 4:1, 2:1, 1:1, 1:2 and 1:4, where the weight fractions of HPC-H (WFH) were 0.9, 0.8, 0.67, 0.5, 0.33 and 0.2, respectively. The ethanol was then evaporated from the mixed solution at 60°C in a tray drier (DAE-70 type, Sanwakakouki-kougyo, Japan), and a solved mixture of hydrogel (SMH) flakes was obtained. The SMH flakes were pulverized by a hammer mill (opening size: 0.5 mm, K2-1 type, Fujipowdal, Tokyo, Japan) with liquid nitrogen, to yield the SMH powder. The SMH powder was then dried for 2 days at 60°C. The final product was used for the present experiments.

HPC-H powder was prepared using a 5% (w/w) ethanolic solution of HPC-H by the same method as that used in the preparation of SMH powders.

Preparation of matrix tablets

Several kinds of matrix tablets were prepared to contain 40 mg PPA in a tablet. PPA and various SMHs (1:5) were thoroughly blended using a stationary mixer (Kyouriturikou, Tokyo, Japan), and the tablets were directly compressed on a compression instrument (Autograph IS-5000, Shimadzu, Kyoto, Japan) using 7.98 mm diameter flat-faced punches. The tablets were produced at a compression pressure of 196 MPa.

Dissolution studies

The matrix tablets were subjected to dissolution using a JP11 paddle apparatus (DT-600 dissolution tester, Freund-Jusco, Tokyo, Japan) in 900 ml of distilled water maintained at 37 ± 0.5°C, with the paddle rotating at 100 rpm. At each sampling interval, an aliquot of the dissolution medium was drawn off. The volume of the solution was kept constant by replacing the sample volume with an equal volume of dissolution medium. Measurements of drug release were performed by HPLC (LC-6A instrument, Shimadzu Corp., Kyoto, Japan) with UV detection at 220 nm. The mobile phase used was acetonitrile : 0.05 N potassium dihydrogen phosphate aqueous solution (5 : 95) at a flow rate of 1.5 ml/min through a C18 column (YMC-Pack FL-ODS3 column, 5 cm × 4.6 mm, 3 μm, Yamamura Chemical Lab., Kyoto, Japan).

Measurement of micromeritics on the SMH powders

The angle of repose was determined using an angle of repose measurement apparatus (Powder tester, type PT-D, Hosokawa Micromeritics Lab., Osaka, Japan). A funnel was positioned centrally over a shallow circular dish of known radius, r, and the powder system was poured evenly through the funnel until the cone of the powder made contact with the circumference of the dish. The length of the side of the cone, h, was measured using calipers and the angle of repose, θ, was calculated from the equation $\cos\theta = h/r$.

Flow rate of the test powders was determined in triplicate using the orifice method. The flow rate (g/min) of the test powders, through a circular orifice of diameter 8 mm, was measured by using an orifice diameter measurement apparatus (Konishi Seisakusyo, Osaka, Japan).

Bulk density was determined as follows: Test powders, which had previously been passed through a JIS no. 20 sieve were carefully introduced into a 30 cm^3 cylinder. The powder at the top of the cylinder was levelled by rubbing with a spatula. The bulk density was then determined by dividing the weight of the test powder contained in the cylinder in g by the volume in cm^3.

Mean particle diameter was evaluated by sieve analysis. Sieve analysis was carried out on the test powder using JIS standard sieves vibrating on a sieve analysis apparatus (Tsutsui-rikagaku, Tokyo, Japan) for 60 min. The mean particle diameter was taken as 50% of the value of the cumulative percent undersize.

The circularity of particles was determined by photographic analysis. Circularity was calculated by dividing the circumference of a circle having a Heywood's diameter, d, by the projected outward length of the particle, L, as expressed in Eqn 1:

$$\text{circularity} = \pi d/L \qquad (1)$$

Thus, the circularity value ranges from zero to unity.

Measurement of the mean particle diameter of EC dispersed in SMH powder was performed by the photosedimentation technique or sieve analysis.

Photosedimentation This technique was performed as follows: 1 g of SMH powder was dispersed in 900 ml of water, and stirred until the HPC-H dissolved. The EC dispersed in this solution was then separated by centrifugation (model KN-30F, Kubota, Tokyo, Japan) at 3000 rpm for 120 min. The supernatant was decanted and the EC particles were resuspended in 30 ml of water, followed by separation again by means of centrifugation under the same conditions. This procedure was performed three times, thus yielding an EC suspension. The EC suspension was used to determine the mean particle diameter by means of an instrument (CAPA-700, Horiba, Kyoto, Japan) that applies centrifugal sedimentation. The mean particle diameter was expressed as the mean surface diameter of 50% of the value of the cumulative percent undersize.

Sieve analysis This procedure was performed according to the following protocol. 10 g of SMH powder was used to prepare an EC suspension as described in the preceding section. The final EC suspension was then collected, and the supernatant was decanted. The sedimented EC was dried at 80°C for 12 h. The particle size distribu-

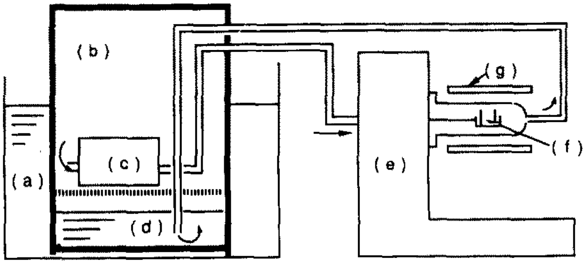

Fig. 1. Sorption apparatus: (a) water bath, (b) chamber, (c) pump, (d) saturated salt solution, (e) TG-DTA apparatus, (f) aluminum pan, (g) temperature-controlled unit.

tion was determined by using a sieve, and the mean particle diameter was evaluated, being expressed as 50% of the value of cumulative percent undersize.

Design of water uptake apparatus

A thermogravimetry differential thermal analysis apparatus (TG-DTA) connected to a container maintained at relative humidities of 52.8, 75.3, 84.3 and 96.6% by introducing saturated salt solutions was employed to measure the rate of moisture uptake of solids. This apparatus was designed in order to measure weight percent gain with microgravimetric accuracy and sensitivity, at constant relative humidities. Fig. 1 shows a schematic drawing of the modified thermogravimetric analysis apparatus (TGA, SSC-5000 series, Seiko, Tokyo, Japan). Before carrying out the measurement, the relative humidity in the TGA system was fixed at a constant value by circulation of air using a pump (flow rate 675 ml/min, Suishin SP-2, Tokyo, Japan).

Measurement of moisture uptake

The amount of powder was accurately weighed into an aluminum pan (diameter 5 mm), the pan being placed on a microbalance which was one of the components of the TGA equipment. Moisture uptake was measured by TGA under the conditions of 25 ± 1°C and constant relative humidity at a flow rate of 675 ml/min. At precise time intervals, weight data were collected in the memory of the computer. At the end of the measurement, the amount of water uptake was calculated and plotted as a function of time.

In this study, the influence of each of the following three factors (i–iii) was investigated experimentally:

(i) Quantity of powder: powder fractionated particle size range of 46–149 μm was used, and moisture uptake was measured at 75% relative humidity.

(ii) Particle size of the powder: HPC powder and 0.5 WFH powder were sieved into different fractions: 37–46, 46–74, 74–105, 105–149, 149–177 and 177–250 μm, of which the mean particle sizes were 41.5, 60, 89.5, 127, 163 and 213.5 μm, respectively. The fractionated powder was accurately weighed in the range of 10.5 ± 0.5 mg, and moisture uptake was measured at 75% relative humidity.

(iii) Relative humidity: the amount of powder, except EC, of which the particle size range was 46–149 μm was accurately weighed in the range of 10.5 ± 0.5 mg. The EC used was passed through a 150 mesh (105 μm) sieve. Evaluation of moisture uptake was performed at 52.8, 75.3, 84.3, and 96.6% relative humidity.

Kinetics of moisture uptake

Moisture sorption rate was estimated from the slope of the initial portion of the water uptake vs time curve by extrapolation of the linear part. An initial rate of uptake was expressed as weight percent gain per unit time, W_i, as proposed by Zografi et al. (1980).

Moisture sorption isotherms

Before measuring moisture sorption isotherms, loss on drying (LOD) was measured according to the JP method.

1 g of powder was placed in a weighing bottle and exposed to four different relative humidities in desiccators, i.e., 52.8, 75.3, 84.3 and 96.6%, achieved by introduction of saturated salt solution. The temperature was maintained at 25 ± 1°C throughout the investigation. The bottles containing the powders were periodically removed from the humidity chambers at specified intervals and accurately weighed to determine any changes in weights of the powders. The samples were assumed to be at equilibrium when the sample weight change from the previous measurement

was no greater than 10 mg/g. The equilibrium moisture sorption (EMS) value was determined in triplicate, and equilibrium moisture content (EMC) was calculated according to Eqn 2:

$$\mathrm{EMC} = \frac{\mathrm{EMS}}{1 - \mathrm{LOD}} \times 100 \qquad (2)$$

Results and Discussion

The experimentally measured percentages of drugs released through the matrices of polymer blends are plotted vs the square root of time in Fig. 2. In every case, the release of drug follows a pattern clearly in accordance with the $t^{1/2}$ model of Higuchi (1963). The absence of positive deviation indicates that the drug is released primarily by diffusion and that the contribution of attrition is negligible (Lapidus and Lordi, 1968). The drug release rate tended to decrease with increasing WFH, in particular, when WFH in the matrix was less than 66.7%, the release profiles were quite different. It appears that the modulation of the release rate was achieved by varying WFH in the matrix tablet.

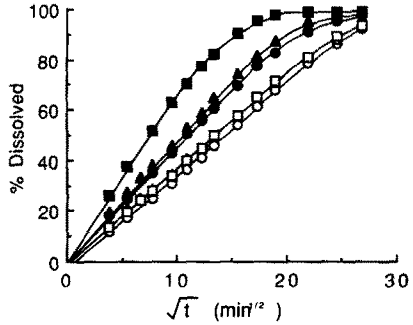

Fig. 2. Effect of WFH in the matrix tablet on PPA release profiles. (○) 0.9; (△) 0.8; (□) 0.67; (●) 0.5; (▲) 0.33; (■) 0.2.

The results obtained on analysis of the physical properties of the experimental powders are listed in Table 1. A detailed knowledge of these phase structures in polymer blends is essential and it is convenient to distinguish three categories corresponding to the mean particle sizes at room temperature. The properties of polymer blends may depend largely on their dispersion structures irrespective of whether they have homogeneous or microheterogeneous phase structures (Akiyama and MacKnight, 1986). With increase in WFH, the mean particle diameter of EC dispersed in SMH was observed to decrease. At WFH ≥ 0.5, the mean particle diameter of the dispersed EC was 1–6 μm. In comparison, at WFH < 0.5, the mean particle diameter of EC dispersed in SMH almost coincided with that of SMH powder. Differential scanning calorimetry, infrared spectrophotometry and X-ray diffraction

TABLE 1

Micromeritics of SMH powders

WFH [a]	Angle of repose (°)	Flow rate from orifice (g/s) [b]	Apparent density (g/ml)	Mean diameter (μm)	Mean diameter of dispersed EC (μm) [c]	Circularity
1	54	no flow	0.244	66	–	0.783
0.9	41	2.21	0.433	89	0.69 [d]	0.808
0.8	41	2.59	0.471	135	1.06 [d]	0.815
0.67	38	3.16	0.475	131	1.51 [d]	0.825
0.5	38	2.13	0.420	120	5.59 [d]	0.864
0.33	38	2.93	0.456	145	147 [e]	0.880
0.2	35	3.82	0.491	170	165 [e]	0.857

[a] Weight fraction of HPC-H in SMH powder. 1 refers to HPC-H only.
[b] Flow rate of powder particles through a circular orifice of diameter 8 mm.
[c] Mean diameter of EC dispersed in SMH powder.
[d] Measured by photosedimentation.
[e] Measured by sieve analysis.

were carried out with SMH powder and physical mixtures, simply mixed with HPC-H and EC powder. No differences between SMH powder and physical mixtures were found. The results indicate that HPC-H and EC in SMH powders do not interact with each other. It was assumed that in SMH powders, in the case where WFH is greater than 0.5, EC particles are dispersed in HPC-H, whereas at WFH below 0.5, HPC-H is dispersed in EC.

The key factor governing the flowability of the powders is considered to be particle-particle interaction and friction. The inherent properties of the powders affecting powder flow are particle size, shape, porosity, density, moisture content, and surface texture (Martin et al., 1970). The angle of repose, flow rate through an orifice, and circularity were selected as indices to determine the flowability of powders.

With increasing WFH, the circularity was observed to decrease while the angle of respose displayed an increase (Table 1). Ridgeway and Rupp (1969) found that with increasing departure from the spherical particle, the angle of respose increased, whilst the bulk density and flowability decreased. Fonner et al. (1966) reported that the angle of repose was primarily a function of surface roughness and that geometrical form and shape on a volume basis were inversely proportional to bulk volume. In the present study, increasing WFH appeared to lead to an increase in angle of repose and a decrease in the bulk density. With decreasing WFH, flowability tended to improve, although the addition of EC to HPC-H did not markedly affect the flowability of the blended powder.

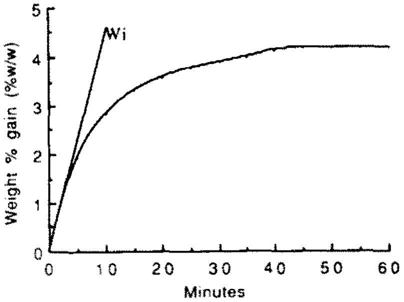

Fig. 3. Selected curve illustrating sorption of moisture by SMH powder at 75.3% relative humidity.

The flow rate was determined by measuring the weight (mg) per s of powder passing through an orifice of diameter 8 mm. HPC-H alone did not flow through the aforementioned orifice. The bulk density of SMH powders was found to be proportional to the flow rate through the orifice, and the flow rate through the orifice increased with increasing bulk density. Thus, the flow rate of SMH powder was found to be improved compared with HPC-H alone. It was concluded that the flowability of SMH powder increased with decreasing WFH; however, no marked effect on flow rate of powder was observed.

The results of moisture uptake measurements are illustrated by the curve plotted in Fig. 3. The moisture sorption rate was determined from the initial rate of uptake, i.e., the slope, by extrapolation of the linear portion as demonstrated in Fig. 3. HPC has an amorphous solid structure (Zografi, 1988) and can take up and retain large amounts of water in amorphous portions when exposed to moisture at various relative humidities (Oksanen and Zografi, 1990). On the other hand, EC has been reported to adsorb water (Dubernet et al., 1990). It was presumed that moist air flowed through the gaps in the powder and that the moisture was absorbed by adhering to a solid surface or diffusing through an amorphous portion. The moisture sorption rate is known to be influenced by the velocity of movement of moist air (Zografi et al., 1980). The flow rate of moist air (675 ml/min) should lead to more rapid absorption of moisture by the powder, and should require a shorter duration to reach equilibrium than an experiment under static conditions.

The relationship between the quantity of powder and weight gain from the rate of moisture absorption per unit time derived from the initial portion of the water uptake curve at 75% relative humidity is shown in Fig. 4. It is presumed that the moisture adsorbed onto solids formed a monolayer followed by multilayers or absorption into the amorphous portion of the solid. If the rate of moisture sorption into the powder is uniform, a close correlation should exist between the quantity of powder and the moisture gain. Even

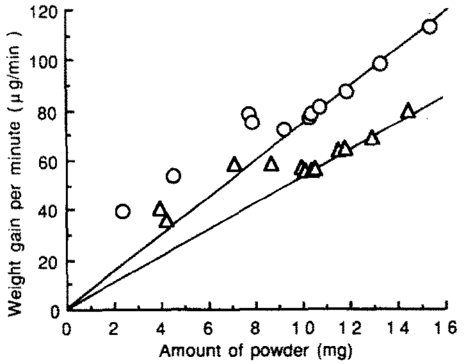

Fig. 4. Relationship between the amount of powder and weight gain per min. (○) HPC-H alone; (△) 0.5 WFH.

in the case where the quantity of powder is small (less than 9 mg), it is presumed that monolayer adsorption saturates rapidly and is followed by multilayer formation or absorption into the amorphous portion of the solid. With small amounts of powder, the correlation between the quantity of powder and weight gain by sorption deviated from linearity (Fig. 4). W_i increased with lower quantities of powder (Fig. 5), whereas in the case where more than 10 mg powder was used, the relationship between the amount of powder and weight gain was observed to conform closely to linear behavior (Fig. 4).

In order to gain insight into the mechanism of moisture sorption, the data on moisture sorption were plotted as a function of the square root of time. In the case of a linear plot, sorption is considered to follow Fickian behavior whereas a sigmoidal curve indicates the process of sorption to be in conformity with Case II transport (Enscore et al., 1977). The above relationships are expressed according to Eqn 3:

$$M_t/M_\infty = k_r t^{1/2} \qquad (3)$$

where M_t denotes the weight sorbed at time t, M_∞ is the equilibrium sorption weight, and k_r represents a constant.

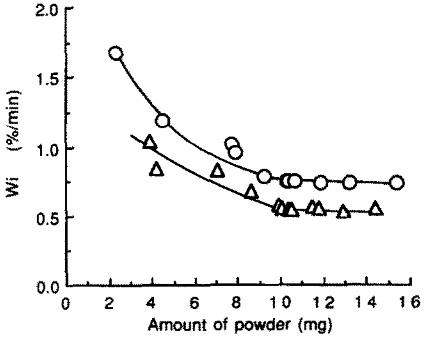

Fig. 5. Effect of the amount of powder on moisture sorption rate at 75.3% relative humidity. (○) HPC-H alone; (△) 0.5 WFH.

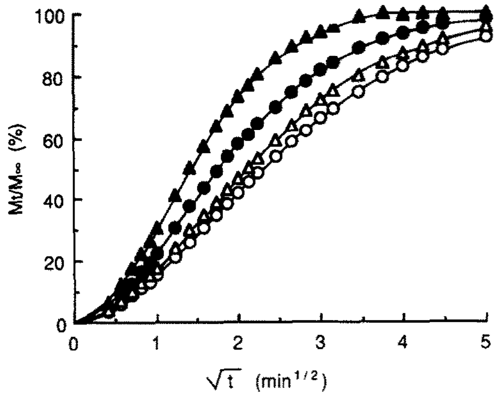

Fig. 6. Sorption curve plotted as a function of the square root of time. (○) 10.38 mg of HPC-H; (△) 10.53 mg of 0.5 WFH; (●) 4.51 mg of HPC-H; (▲) 4.24 mg of 0.5 WFH.

The plot of moisture sorption vs square root of time is sigmoidal (Fig 6). This demonstrates that, irrespective of the amount of powder, the process of moisture sorption for this powder is governed by Case II transport. Approx. 4.5 mg of powder gave the curve to the left of that for about 10.5 mg (Fig. 6). The former quantity of powder should absorb a greater amount of moisture than 10.5 mg of the powder during the initial part of the curve.

The effective surface area of the powder was found to be related to the particle diameter of the powder. With increasing particle diameter, the effective surface area of the powder demonstrated a decrease. The relationship between the particle diameter, d, and surface area of the powder is given by Eqn 4 (Martin et al., 1970). Here, the assumptions were made that the particle can be approximated by a sphere, with particle diameter sieved into fractions of the same

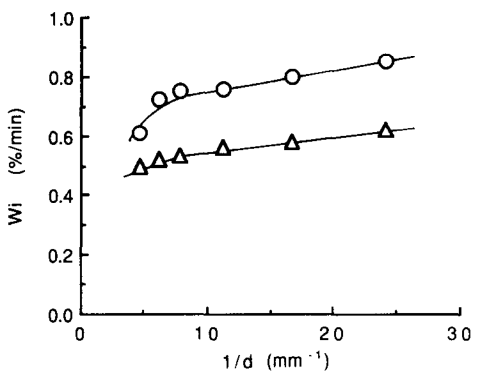

Fig. 7. Effect of reciprocal of particle size on moisture sorption rate. (○) HPC-H alone; (△) 0.5 WFH.

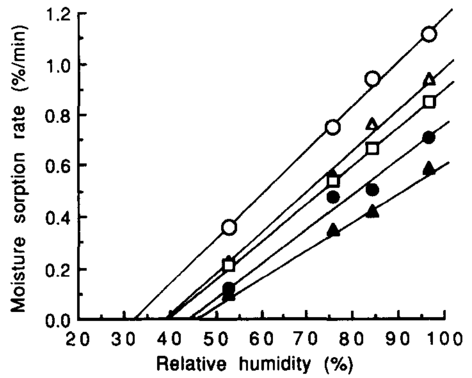

Fig. 8. Relationship between moisture sorption rate and relative humidity for powders containing various WFH. (○) HPC-H alone; (△) 0.8; (□) 0.5, (●) 0.2; (▲) EC alone.

size, and that the density of a particle is constant (which are of course gross approximations):

$$S = \frac{6}{\rho} \cdot \frac{1}{d} \tag{4}$$

where S is the surface area of the powder, ρ represents the density, and d is the diameter of the particle. It was observed that with increase in the reciprocal particle size, the rate of moisture sorption increased at 75% relative humidity (Fig. 7). It was assumed that the rate of moisture sorption was dependent on the surface area of the powder, and that W_i increased with greater surface area of the powder. Deviation from linearity of the plot between W_i and surface area of the powder was observed at lower values of the surface area (Fig. 7). Enscore et al. (1977) reported that the mechanism of moisture sorption is affected by the particle size of the powder. Such deviations are presumed to be correlated with the mechanism of sorption.

The rate of moisture sorption per unit time during the initial period, W_i, was determined at relative humidities of 52.8, 75.3, 84.3, and 96.6%. Carstensen (1977) obtained the working relationship;

$$W_i = k_i A_s P_0 (\mathrm{RH}_i - \mathrm{RH}_c) \tag{5}$$

where k_i denotes the intrinsic material constant, A_s is the specific surface area of the sample, P_0 represents the vapor pressure of pure water at the given temperature, RH_i is the relative humidity of the atmosphere during the course of the experiment, and RH_c denotes the critical relative humidity.

At $\mathrm{RH}_i = \mathrm{RH}_c$, the rate of moisture uptake should be zero. Therefore, in Fig. 8, a straight line should result, the x-intercept of which corresponds to RH_c. With increasing WFH, the RH_c values as determined from the x-intercepts decreased.

Fig. 9 depicts EWC in SMH and EC powders as a function of relative humidity. With increasing WFH, EMC was found to increase. Analyses of moisture uptake isotherms can generally be represented by the BET equation for gas adsorp-

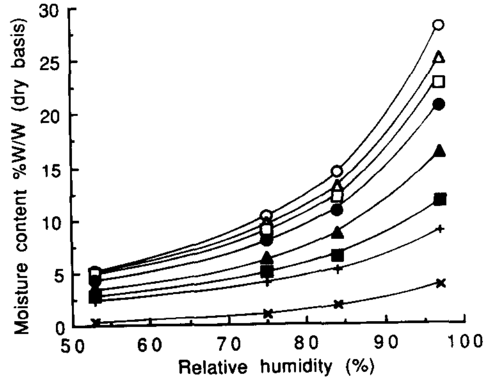

Fig. 9. Moisture sorption isotherms at 25°C for powders containing various WFH. (○) HPC-H alone; (△) 0.9; (□) 0.8; (●) 0.67; (▲) 0.5; (■) 0.33; (+) 0.2; (×) EC alone.

tion or other related expressions (Zografi and Kontny, 1986). The starting point for most analyses is the BET equation (Eqn 6):

$$W=\frac{C_gW_m(P/P_0)}{[1-(P/P_0)][1-(P/P_0)+C_g(P/P_0)]} \tag{6}$$

where W denotes the weight sorbed per unit weight of dry solid at a relative pressure of P/P_0, W_m is the weight sorbed corresponding to one water molecule per sorption site on the solid, and C_g is a variable parameter dependent on the gas and the temperature. However, the BET equation is only valid up to relative pressures (P/P_0) of about 0.35 (Zografi, 1988). The GAB equation, an extension of the BET equation, can be used to fit water sorption data over the entire range of relative pressures (Zografi and Kontny, 1986). The GAB model introduced a third state of sorbed species, intermediate between the tightly bound and free states. The GAB equation is expressed as follows:

$$W=\{C_gW_m(P/P_0)\}\{[1-K(P/P_0)] \times[1-K(P/P_0)+C_gK(P/P_0)]\}^{-1} \tag{7}$$

where P, P_0, W, C_g and W_m are identical to the corresponding parameters in the BET equations and a second equilibrium constant, K, is introduced in order to account for the intermediate state. W_m was determined by fitting Eqn 9 to the sorption isotherms.

The relationship between the W_m values obtained from fitting the sorption data to the equation and the slopes evaluated from Fig. 8 was illustrated by plotting W_m vs slope (min^{-1}, $K_iA_sP_0$) for all the experimental data except for those of EC (Fig. 10). A linear relationship was obtained which is expressed as follows:

$$W_m=5.678K_iA_sP_0-0.0614 \quad (r=0.9833)$$

where W_m denotes the mass of gas corresponding to monolayer coverage or to possible binding sites having been saturated. The vapor pressure of pure water at the given temperature, P_0, remained constant under the above experimental conditions. A close correlation between W_m and K_iA_s was observed. This demonstrates that the slopes determined from Fig. 8 represent the mass of gas corresponding to monolayer coverage or relate to the possibility of saturated binding sites. The slopes from Fig. 8 became less steep with decreasing WFH. Taking the decrease in WFH into consideration, it should lead to a reduction in the mass of saturated moisture sorbed to possible binding sites. Hence, with decreasing WFH, $\mathrm{RH_c}$ should increase while the mass of saturated moisture sorbed to possible binding sites should decrease, i.e., the degree of hygroscopicity should decrease with lower values of WFH. On appraisal of the preliminary data obtained via TGA analysis of the kinetics of water sorption, the present results provide sufficient evidence to warrant further investigations of the sorption kinetics of hygroscopic compounds.

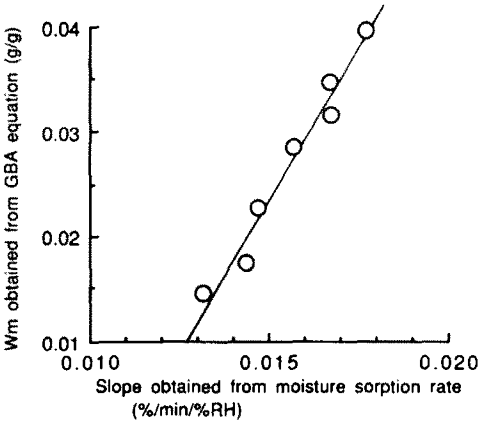

Fig. 10. Relationship between W_m obtained from GBA equation and the slope obtained from moisture sorption rate.

Controlled-release tablets were prepared via direct compression after mixing the drug and SMH powder. The rate of drug release from the matrix tablet tended to decrease with increasing WFH, whereas the flowability and hygroscopicity increased with decreasing WFH. A lower WFH in SMH powder would be desirable for a controlled-release carrier as a result of the good flowability and lower hygroscopicity, although a higher WFH value in SMH can still sustain the release of drug. Selection of the particular WFH should be made in SMH in order to achieve the desired profile for drug release.

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