Physical Properties of Fast-Release Nonreverting Hydrochlorothiazide Solid Dispersions

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INTRODUCTION

Solid dispersion was defined by Chiou and Riegelman as a dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by melting (fusion), solvent, or melting solvent (1). Solid dispersion was used to enhance the dissolution rate of poorly soluble drugs (2–4). However, the improvement in drug dissolution rate was dependent on the drug–carrier ratios (2–4). Simonelli *et al.* (3) and Doherty and York (4) reported that the coprecipitates containing a high concentration of drugs (more than 40%, w/w) show an initial rapid dissolution rate followed by a slow rate which is equal to that of the pure crystalline drug. These changes in dissolution rate may result from the reversion of drugs from the amorphous to the crystalline form during the dissolution process (3). On the other hand, the coprecipitates containing a low concentration (less than 40%, w/w) of drug exhibited an overall rapid dissolution rate and showed no reversion. The reversion process of the coprecipitates may lead to a decrease in drug dissolution rate, and consequently the drug availability will be retarded compared to that in the nonreverting system. Formulation of nonreverting solid dispersions requires high ratios of polymers, which are usually very hygroscopic and/or not easily compressible.

Hydrochlorothiazide (HCT) is a water-insoluble diuretic and its dissolution rate from solid dispersions was affected largely by the polymer concentrations (2,5). The objective of this work was to prepare a nonreverting (HCT)/PVP solid dispersion containing a low concentration of the polymer. For this purpose hydroxypropylmethylcellulose (HPMC), a gel-forming material (6), was tested as a reversion inhibitor.

EXPERIMENTAL

Materials. Hydrochlorothiazide (HCT) was from Sigma Chemical Co., polyvinylpyrrolidone (PVP), MW 10,000, from GAF Corporation, and hydroxypropylmethylcellulose (HPMC) from Aldrich Chemical Co. All chemicals were used without further purification.

Solubility of HCT in HPMC Solutions. The solubility of HCT in different solutions of HPMC was performed using the method of Higuchi and Connors (7).

Preparation of Solid Dispersions. Five grams of either the pure drug or the binary solid dispersions at HCT/PVP and HCT/HPMC ratios of 2:1, 3:2, and 1:1 were accurately weighed and dissolved in 95% ethanol. The solvent was evaporated under reduced pressure in a flash evaporator at 60°C. The residual solids were pulverized and kept in a desiccator until examined. Similarly, 5 g of the different ratios of HCT:PVP:HPMC containing from 50 to 66.7% (w/w) drug was prepared.

Infrared Studies. The infrared (IR) spectra were determined on a Perkin–Elmer 283 spectrophotometer. The IR spectra of pure HCT, pure HPMC, and 2:1 and 1:1 HCT/HPMC solid dispersions were run in Nujol mull oil from 200 to 400 cm^{-1}.

Powder X-Ray Diffraction. The X-ray diffraction patterns of the powder mixtures were determined before and after dissolution runs with an X-ray diffractometer (Rigaku Geigerflex Model D-2 with Ni-filtered Cu–K α radiation). The latter was accomplished by running the dissolution rate of the tablet for 30 min, then scratching its surface and drying the wet mass at 60°C in an oven, followed by grinding.

Dissolution Studies. The drug dissolution from constant-surface tablets was performed using the method reported by Simonelli *et al.* (3). Three hundred milliliters of 0.1 *N* HCl at 37°C was used as the dissolution medium and stirred at 60 rpm. One-milliliter samples were removed at appropriate time intervals, suitably diluted, and analyzed at 272 nm.

RESULTS AND DISCUSSION

Solubility Study. It was observed that the solubility phase diagram of HCT at different concentrations [0, 0,25, 0.5, 1.0, 1.5, and 2% (w/v)] of HPMC is similar to that for the type A_L system described by Higuchi and Conners (7). This result indicates that the drug forms a soluble first-order (1:1) complex. It has been reported (8) that HCT forms complexes of 1:1 and 1:2 with PVP.

IR Analysis. The IR spectra in Fig. 1 shows that the HCT bands at 3370, 3270, and 3170 cm^{-1}, corresponding to NH and NH_2, and those at 1335, 1320, 1165, and 1150 cm^{-1}, corresponding to SO_2 (9), were absent in 2:1 and 1:1 drug/HPMC solid dispersions. These changes indicated that a hydrogen bond (10) was formed between HCT and the polymer during the process of preparation. Similar interactions of HCT with PVP have been reported (8).

Powder X-Ray Diffraction and Dissolution Studies. Figures 2 and 3 show that the results of both X-ray diffraction and dissolution studies are compatible. HPMC inhibited crystal formation during preparation of all drug:polymer ratios studied, with the result of a higher initial dissolution rate compared with that for the drug alone (Fig. 3A). This high initial rate might be due to the colloidal (1) and/or amorphous nature of the drug. Similar findings have been reported previously for HCT and PVP and the results were explained (8).

It is obvious from Fig. 3A that a break took place in the dissolution profile of the binary systems whether they were

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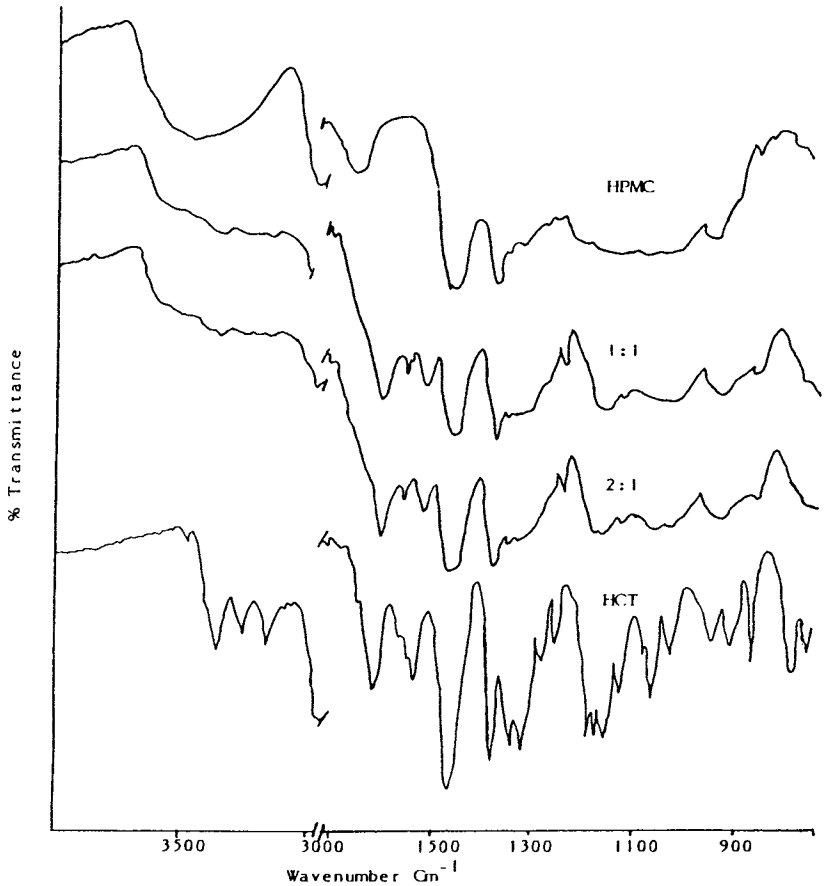

Fig. 1. IR spectra of HCT, HPMC, and 2:1 and 1:1 drug/HPMC solid dispersions.

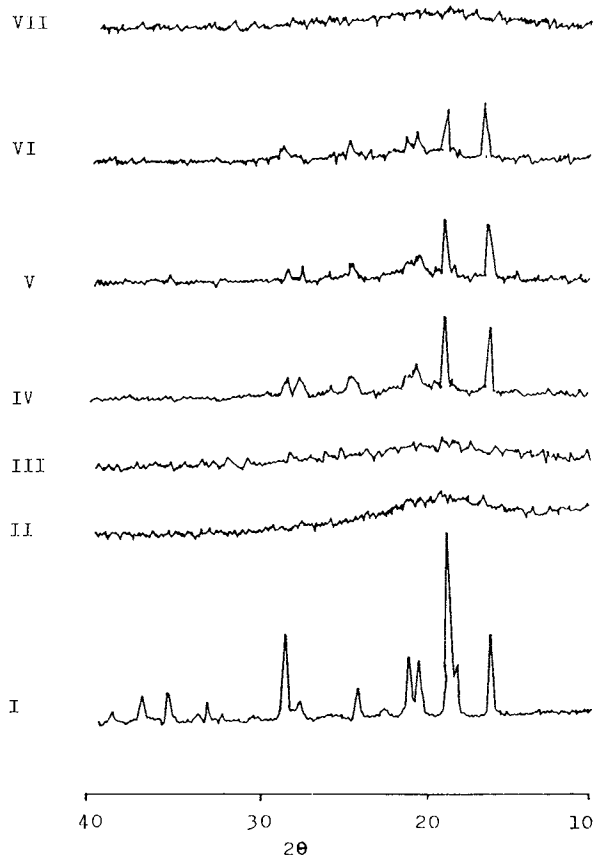

Fig. 2. X-ray diffractograms of pure HCT, pure HPMC, and different ratios of binary and ternary solid dispersions before and after 30 min of dissolution. (I) Pure drug; (II) pure HPMC; (III) 2:1 drug/HPMC before dissolution; (IV) 2:1 drug/HPMC after dissolution; (V, VI, VII) 3:0.5:1.5, 3:1:1, and 1:0.5:0.5 drug:PVP:HPMC, respectively.

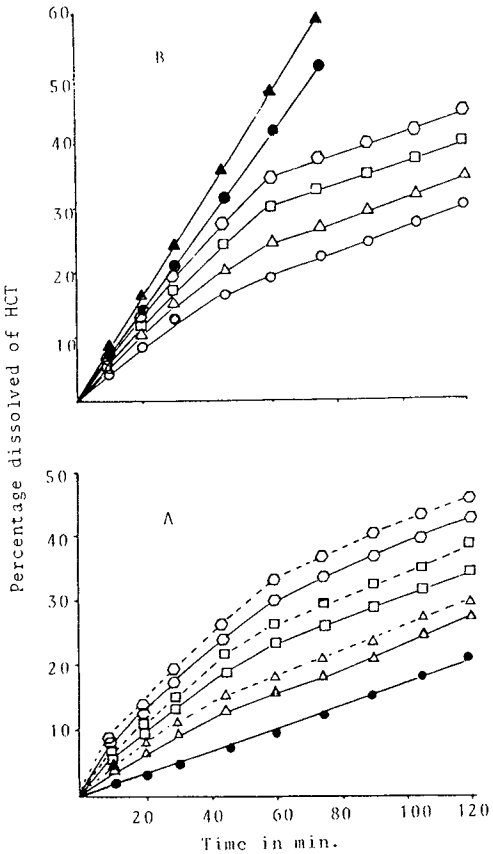

Fig. 3. Dissolution profile of HCT from different ratios of solid dispersions. (A) ●——●, pure drug; △——△, 2:1; □——□, 3:2; ⬡——⬡, 1:1; ·····, drug/PVP; ——, drug/HPMC. (B) HCT:PVP:HPMC: ○——○, 4:1:1; △——△, 3:0.5:1.5; □——□, 3:1:1; ⬡——⬡, 3:1.5:0.5; ●——●, 1:0.5:0.5; ▲——▲, 1:0.75:0.25.

prepared with PVP or HPMC even at a 1:1 drug:polymer ratio. At the break, which was nearly 30 min at the beginning of dissolution, the X-ray pattern confirmed the reversion (Figs. 2 and 3A). On the other hand, the ternary systems revealed different results. When the total ratios of both polymers were equal to that of the drug (1:0.5:0.5 drug: PVP:HPMC), reversion was inhibited and the dissolution profile was linear (Figs. 2 and 3B). It is probable that HPMC, with its high viscosity at the surface of the tablet, augmented by the solubilizing effect of the two polymers, prevents reversion. Since the ternary system 3:1:1 HCT:PVP:HPMC reverted during dissolution, with the result of a break in the profile (Figs. 2 and 3B), it follows that equal ratios of both polymers were not a must to prevent reversion, but rather the sums of the ratios of the two polymers must be either equal to or greater than that of the drug.

REFERENCES

1. W. L. Chiou and S. Riegelman. Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.* 60:1281–1302 (1971).
2. H. M. El-Bana, A. Z. El-Gholmy, and Y. Hammouda. Phase diagram and dissolution-rate studies on hydrochlorothiazide-urea solid dispersions. *Pharm. Acta Helv.* 55:244–248 (1980).
3. A. P. Simonelli, S. C. Metha, and W. I. Higuchi. Dissolution rates of high energy polyvinylpyrrolidone (PVP)-sulphathiazole coprecipitates. *J. Pharm. Sci.* 58:538–549 (1969).
4. C. Doherty and P. York. Mechanisms of dissolution of frusemide-PVP solid dispersions. *Int. J. Pharm.* 34:197–205 (1987).
5. O. I. Corrigan, R. F. Timoney, and M. J. Whelan. The influence of polyvinylpyrrolidone on the dissolution and bioavailability of hydrochlorothiazide. *J. Pharm. Pharmacol.* 28:703–706 (1976).
6. *Handbook of Pharmaceutical Excipients,* American Pharmaceutical Association and Pharmaceutical Society of Great Britain, 1986.
7. T. Higuchi and K. S. Connors. In C. N. Reilly (ed.), *Advances in Analytical Chemistry and Instrumentations, Vol. 4,* Interscience, New York, 1965, p. 117.
8. K. E. Gabr. *Pharmaceutical Study on Some Insoluble Drug-Polymer Combinations,* Ph.D. thesis, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt, 1989.
9. H. P. Deppeler. In K. Florey (ed.), *Analytical Profiles of Drug Substances,* Academic Press, New York, 1981, Vol. 10, p. 405.
10. A. A. Kassem, S. A. Zaki, N. M. Mursi, and S. A. Tayel. T.L.C. and I.R. studies of interaction between macromolecular polymers and chloramphenical in solid dispersions. *Pharm. Ind.* 41:1220–1223 (1979).