AAPS PharmSciTech, Vol. 12, No. 4, December 2011 (© 2011)
DOI: 10.1208/s12249-011-9697-8

Research Article

Dissolution and Solid-State Characterization of Poorly Water-Soluble Drugs in the Presence of a Hydrophilic Carrier

Rahmat Talukder,[1,4] Chase Reed,[1] Thomas Dürig,[2] and Muhammad Hussain[3]

Received 20 April 2011; accepted 12 September 2011; published online 20 September 2011

Abstract. The aim of this study was to investigate the effects of a hydrophilic carrier on the solid-state and dissolution characteristics of poorly water-soluble drugs. Three poorly water-soluble drugs, ibuprofen, carbamazepine, and nifedipine, were studied in combination with hydroxypropyl cellulose (HPC), a low molecular weight hydrophilic polymer, without the use of solvent. A 1:1 drug–polymer ratio was used to evaluate the percent drug release, crystallinity, and wettability. A drug–polymer ratio of 1:4 was also used in co-grinding process to evaluate the effect of polymer levels on drug release. Dissolution studies were carried out in deionized water. Mean dissolution time (MDT) was calculated, and statistical analysis of MDTs was done following a single factor one-way analysis of variance. The dissolution rate of the drugs was enhanced by several folds by the simple process of co-grinding with HPC. X-ray diffraction studies were done to investigate the effects of physical and co-ground mix with HPC on the crystallinity of the drugs, which indicated a partial loss in crystallinity upon grinding. Differential scanning calorimetry studies were performed in order to identify possible solid-state interactions between the respective drugs and HPC. Wettability of the drugs by a 0.5% aqueous HPC solution was compared with that of water and *n*-hexane using the "Washburn method." Increased wetting and hydrophilization of the drugs by HPC, enlarged surface area due to particle size reduction, and a decrease in the degree of crystallinity were identified as the likely contributors to dissolution rate enhancement.

KEY WORDS: dissolution enhancement; HPC; hydrophilic carrier; wettability.

INTRODUCTION

Improvement of the oral bioavailability of poorly water-soluble drugs is one of the most challenging tasks for formulation scientists. The dissolution rate of BCS class II drugs in gastrointestinal fluid is the rate limiting step in their oral absorption (1–3). This phenomenon often results in their low and unpredictable oral bioavailability. Various methods involving chemical and physical modifications have been reported to enhance the bioavailability of poorly water-soluble drugs. In chemical modification, formation of soluble salt is the most commonly used one. Particle size reduction, crystal habit modification, and the use of surfactants and solid dispersions are the common methods used in physical modification.

Solid dispersion for poorly water-soluble drugs provides an efficient method to improve the dissolution rate (4–8). Solid dispersions are usually developed as monolithic systems where drug substance is homogenously dispersed in an inert hydrophilic polymeric matrix. In solid dispersions, the drug substance may remain in the amorphous or crystalline or microcrystalline forms in the polymer matrices (9). Because of its high energy content, amorphous form of the drug is thermodynamically unstable. Most of the amorphous form, however, tends to recrystallize on storage (10). On the other hand, the crystalline drugs in solid dispersions do not pose this type of physical stability problem (11–13). The fabrication techniques of solid dispersions include co-dissolution in an appropriate solvent, co-fusion, or combination of both (14). In the case of co-fusion method, non-homogeneity may result due to high viscosity of the polymeric carrier in the molten state. In this method, thermally unstable drugs can be degraded by the applied heat. In the case of co-dissolution, subtle changes in solvent evaporation condition may result in unpredictable changes in product performances (12,15).

Micronization of drug powders results in higher surface area and higher dissolution rate. Various techniques have been reported in obtaining micronized particles by disruption of large crystals (16). The process may, however, develop cohesive powders with higher surface energy resulting in poor flow properties (17). Moreover, increased cohesivity leads to particle agglomeration and reduced effective surface area (18). Dry or wet co-grinding of poorly water-soluble drugs with hydrophilic carriers develops stable micronized particles. Numerous works have been published on the use of this technique for enhancement of dissolution rate (19–22). Poly-

[1] College of Pharmacy, Southwestern Oklahoma State University, Weatherford, Oklahoma 73096, USA.
[2] Ashland-Aqualon Functional Ingredients, Wilmington, Delaware, USA.
[3] College of Pharmacy, Texas A&M Health Science Center, Kingsville, Texas, USA.
[4] To whom correspondence should be addressed. (e-mail: rahmat.talukder@swosu.edu)

ethylene glycol, hydroxypropyl methylcellulose, partially hydrolyzed gelatin, and polyvinylpyrrolidone have been commonly employed to enhance dissolution rate of various drugs. When used as a carrier, hydroxypropyl cellulose (HPC), a nonionic water-soluble polymer, has been reported to improve anthelmintic activity of mebendazole (23).

The objective of this study is to investigate the effects of a hydrophilic carrier, HPC, on the solid-state, wetting, and dissolution characteristics of poorly water-soluble drugs. Our hypothesis is that the wettability and hydrophilization of the drug by aqueous media are increased in the presence of HPC and thereby enhances the dissolution of the drug. Three poorly water-soluble drugs, ibuprofen with p*K*a of 5.2, carbamazepine (CBZ) with p*K*a of 13, and nifedipine with p*K*a of 7.0, were studied as a physical and co-ground mixture with HPC without the use of solvent or heat.

MATERIALS AND METHODS

Ibuprofen, carbamazepine, nifedipine, and hydroxypropyl cellulose were provided by Aqualon, a Business Unit of Hercules Incorporated, Wilmington, DE. All chemicals used were of analytical grade.

Preparation of Physical and Co-ground Mixtures

Drug and HPC, at a ratio of 1:1, were dry blended by tumble mixing in a V-blender and by co-grinding in a mortar and pestle for about 5 min (the batch size was 20 tablets). Tablet matrices were made from drug powder alone and from the physical and co-ground mixtures in a single punch Carver Press at 1,500 psi using a 6-mm flat-faced die and punch. In order to evaluate the effects of higher polymer levels, separate batches of tablets of drug–polymer at a ratio of 1:4 were made by co-grinding method. The tablet weights in all batches were about 100 mg, and the tablet thickness was about 2 mm.

Dissolution Studies

Dissolution studies were carried out in USP Apparatus II (VK 7010, Vankel Industries, Cary, NC) at 100 rpm in 900 ml deionized water (pH 5.7) at 37°C ($n=6$). The apparatus was equipped with an eight channel peristaltic pump and a UV spectrophotometer for determination of the drug concentration and for return of sample to the dissolution vessel. Nifedipine was protected from light to avoid photodegradation of the drug during experiments.

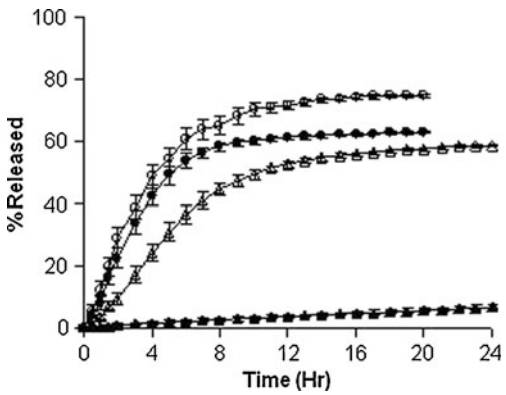

Fig. 1. Dissolution profiles in deionized water for tablets ($n=6$) comprising of nifedipine alone (*filled triangle*), nifedipine–HPC (1:1) physical mixture (*triangle*), nifedipine–HPC (1:1) co-ground mixtures (*filled circle*), nifedipine–HPC (1:4) co-ground mixtures (*circle*)

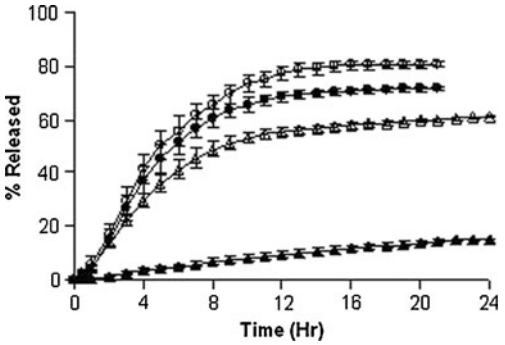

Fig. 2. Dissolution profiles in deionized water for tablets ($n=6$) comprising of ibuprofen alone (*filled triangle*), ibuprofen–HPC (1:1) physical mixture (*triangle*), ibuprofen–HPC (1:1) co-ground mixtures (*filled circle*), ibuprofen–HPC (1:4) co-ground mixtures (*circle*)

Mean Dissolution Time

Mean dissolution time (MDT) was calculated to determine the average time required to dissolve 50% of the drug. Equation 1 was used in calculating MDT (24).

$$\mathrm{MDT} = \frac{\sum_{i=1}^{n} t_{\mathrm{mid}} \Delta M}{\sum_{i=1}^{n} \Delta M} \tag{1}$$

Where i is the dissolution sample number, n is number of dissolution sample times, t_{mid} is the time at the midpoint between t_i and t_{i-1}, and ΔM is the amount of drug dissolved between t_i and t_{i-1}.

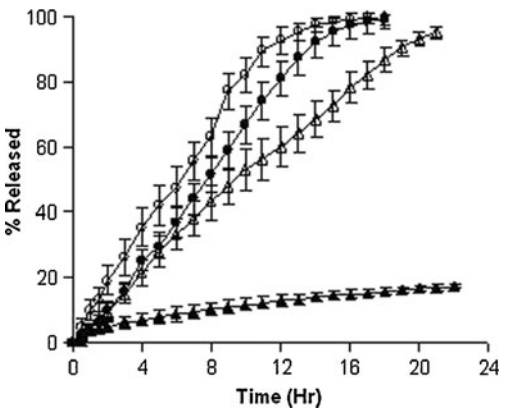

Fig. 3. Dissolution profiles in deionized water for tablets ($n=6$) comprising of carbamazepine alone (*filled triangle*), carbamazepine–HPC (1:1) physical mixture (*triangle*), carbamazepine–HPC (1:1) co-ground mixtures (*filled circle*), carbamazepine–HPC (1:4) co-ground mixtures (*circle*)

Table I. Comparison of Percent Drug Released from Tablets made from Drug Alone, Physical Mix, and Co-ground Mix with Polymer (n=6; SD<7.3% of the Mean)

	Nifedipine		Ibuprofen		Carbamazepine	
Dissolution time (h)	2	4	2	4	2	4
Drug alone	1.0	1.7	1.5	3.5	5.0	7.1
Physical mix (1:1)	9.4	24.2	14.1	29.5	9.6	21.5
Co-ground mix (1:1)	22.6	42.6	15.3	36.9	9.8	22.8
Co-ground mix (1:4)	29.1	48.8	16.8	41.2	19.2	35.4

Statistical Treatment of MDT Data

Differences in mean dissolution times of various formulations were statistically analyzed by one-way analysis of variance (ANOVA) using Sigma Plot (Systat Software, Inc., San Jose, CA). Statistically significant differences between MDT of formulations were defined as $p<0.05$.

Powder X-ray Diffraction

X-ray powder diffraction (XRD) analysis of pure drug, physical mixtures, and ground mixtures were carried out using a Miniflex Tabletop XRD system (Rigaku/MSC, The Woodlands, TX) from 5° to 55° of 2 θ with steps of 0.1°, and the measuring time was 1.0 s/step. The powder samples were illuminated using CuKα radiation (λ=1.54056 Å) at 30 kV and 15 mA. A nickel filter was used to reduce the Kβ contribution to the X-ray signal, and a scintillation counter was used for detection. Background reduction, Kα2 stripping, and data analysis were performed using the MDI Jade 5.0 software (Materials Data Inc, Liverpool, CA).

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) thermograms were obtained using a DSC 2920 Modulated DSC (TA Instruments, New Castle, DE). The temperature axis and cell constant of the DSC cell were calibrated with 10 mg of indium (99.99% pure, melting point 156.60°C, heat of fusion 28.40 J/g). Samples (0.5–0.8 mg) were used in each run. The samples were equilibrated at 25°C and heated to 250°C at a heating rate of 5°C/min under continuous nitrogen flow at a rate of 50 ml/min. The results were analyzed by using the TA instruments universal analysis software. All samples were analyzed in triplicate.

Wetting Studies

Wettability of the drugs by a 0.5% aqueous HPC solution was compared with that of water and n-hexane using the "Washburn method." In this approach, a Krüss tensiometer (Krüss Gmbh, Hamburg, Germany) system for measurement of porous solids was used. According to the Washburn theory, liquid uptake into the pores of a powder bed by capillary action can be described by the Eq. 2 as follows (25):

$$t = Am^2 \text{ and } A = \eta / C\rho^2\sigma\cos\theta \quad (2)$$

Where t is the time after the solid and the liquid are brought into contact, m is the mass of the liquid drawn into the solid, A is a constant dependent on the liquid properties (viscosity, η, density, ρ, and surface tension, σ) and the solid/liquid contact angle, θ, and C is a material constant dependent on the porous architecture of the powder bed. To determine C, the wetting experiment was performed using n-hexane, which has a very low surface tension and is assumed to have a contact angle of zero on all known substrates. Viscosities of the wetting liquids were measured on a Brookfield viscometer using the Ultra Low Spindle set.

RESULTS AND DISCUSSIONS

Dissolution

Figures 1, 2, and 3 represent the dissolution behaviors of nifedipine, ibuprofen, and carbamazepine tablets, respectively. In all cases, the overall dissolution of drugs from the tablets made from co-ground mixture is the highest, while the dissolution from the tablets containing drug alone is the lowest. In the first 4 h, the extent of release of nifedipine from physical mixture tablets was about 14-fold higher than that from the tablets containing drug alone; while the release was 25- and 28-fold higher from co-ground mixture tablets

Table II. Mean Dissolution Time (h) for the Various Tablet Formulations (n=6; SD<8.7% of the Average)

Drug	Drug alone	Physical mix (1:1)	Co-ground mix (1:1)	Co-ground mix (1:4)
Nifedipine	>24	5.5*	3.6**	3.2*·**·***
Ibuprofen	>24	5.2*	4.1**	3.8*·**·***
Carbamazepine	>24	7.7*	6.1**	5.8*·**·***

*$p<0.05$, significantly different than the drug alone; **$p<0.05$, significantly different than the physical mix; ***$p>0.05$, not significantly different than the co-ground mix (1:1)

containing drug–polymer at 1:1 and 1:4 ratio, respectively (Table I). For ibuprofen and carbamazepine tablets, there are substantial increases in dissolution in the first 4 h in presence of HPC. Similar rank order, as found in nifedipine, was observed when MDT were calculated. In the case of nifedipine and ibuprofen, MDT for tablets containing drug alone was about 2-fold higher than the MDT for tablets comprising of drug–polymer physical mix at 1:1 ratio. The MDT of drug–polymer at a ratio of 1:1 physical mix was higher than that of the polymer–drug co-ground mix (Table II). From the single factor ANOVA output, it is evident that the MDTs of all formulations containing 1:1 physical mix, and 1:1 and 1:4 co-ground mixtures are significantly different ($p<0.05$). MDTs of formulation containing 1:1 and 1:4 co-ground mixtures, however, are not significantly different ($p>0.05$), although the overall drug released in 4 h for 1:4 co-ground mix is higher than the drug released from 1:1 co-ground mix for all three drugs (about 15% in case of nifedipine, about 12% in ibuprofen, and about 38% in carbamazepine). This indicates that grinding has significant effects on dissolution rate improvement due to possible particle size reduction (26,27). Grinding of drug may, however, develop cohesive powders with higher surface energy resulting in poor flow properties. Co-grinding of drug with hydrophilic polymer (19) like HPC develops stable micronized particles. Moreover, HPC has significant effect on dissolution rate enhancement of poorly water-soluble drugs, but the dissolution rates do not change proportionately with the change in HPC level in the matrix. It is, therefore, concluded that blending drug with HPC enhanced dissolution; and co-grinding of the drug–polymer mix added further benefits by ensuring intimate mixture of drug particle with the hydrophilic polymer particle and particle size reduction.

The pH of the dissolution media was measured before and after the dissolution. The pH before dissolution was 5.7. Nifedipine and carbamazepine did not appreciably change the pH, while ibuprofen has changed the pH considerably. After dissolution, the pH values of carbamazepine, nifedipine, and ibuprofen were measured at 5.6 (±0.2), 6.0 (±0.3), and 4.3 (±0.2), respectively.

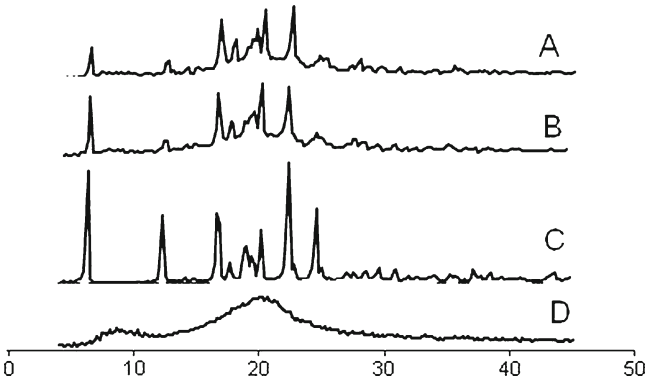

Fig. 5. Powder X-ray diffraction patterns of HPC, ibuprofen, binary physical mixture, and co-ground mixture. *A* Co-ground mix, 1:1. *B* Physical mix, 1:1. *C* Ibuprofen. *D* HPC

X-Ray Diffraction

X-ray diffraction studies were done to investigate the effects of physical and co-ground mix with HPC on the crystallinity of the drugs. The presence of multiple peaks in the diffraction of nifedipine, ibuprofen, and carbamazepine (Figs. 4, 5, and 6) indicates those drugs' high degree of crystallinity. Representative peaks were observed at 8° and 16° for nifedipine, 12° and 24° for ibuprofen, and 12° and 16° for carbamazepine. In contrast, HPC exhibited a very low degree of crystallinity as evidenced by the prominent amorphous "halo" diffraction pattern (10). The characteristic peaks of co-ground mixtures of all drugs were lower in intensity, indicating a partial loss in crystallinity upon grinding. The partial "activation" due to mechanical treatment may thus explain the enhanced dissolution rate of co-ground mixtures as compared to the physical blends of HPC and drug. Moreover, in Fig. 6, there are additional changes evident in the diffraction pattern for HPC–carbamazepine blends. There are distinct changes relative to pure carbamazepine in the ranges of 10–12° of 2 θ, 16–22° of 2 θ and 25–30° of 2 θ indicating that blending with HPC appears to trigger changes in the solid-state structure of carbamazepine.

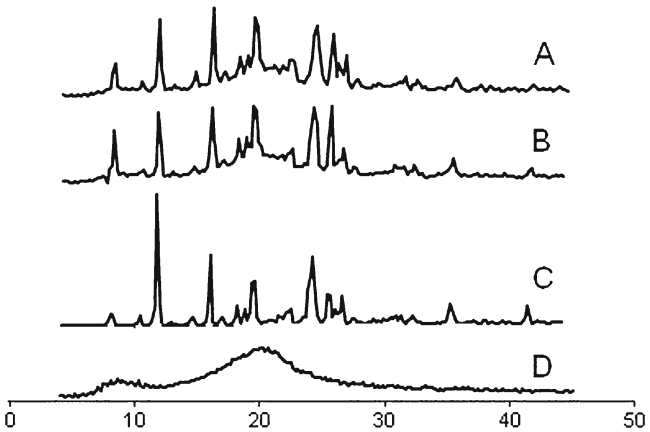

Fig. 4. Powder X-ray diffraction patterns of HPC, nifedipine, physical binary mixture, and co-ground mixture. *A* Co-ground mix, 1:1. *B* Physical mix, 1:1. *C* Nifedipine. *D* HPC

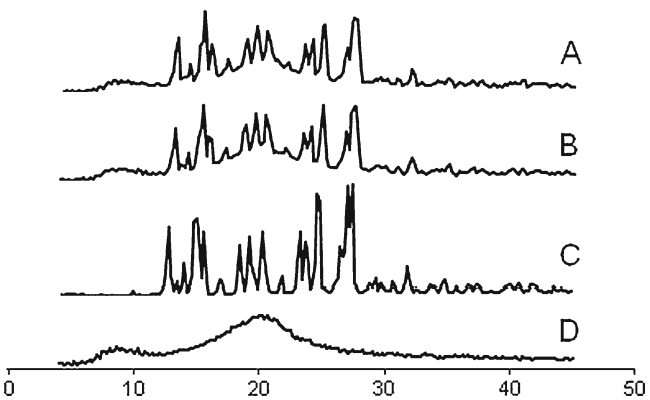

Fig. 6. Powder X-ray diffraction patterns of HPC, carbamazepine, binary physical mixture, and co-ground mixture. *A* Co-ground mix, 1:1. *B* Physical mix, 1:1. *C* Carbamazepine. *D* HPC

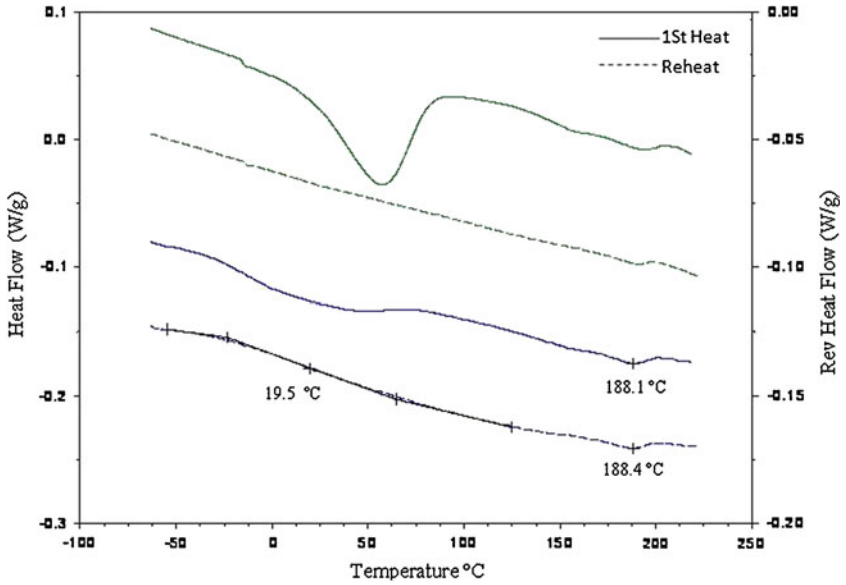

Fig. 7. DSC thermogram of low molecular weight HPC (*top line* represents total heat flow on first heating, *second line* is reversible heat flow curve on first heating, *third line* is total heat flow on second heating, and the *bottom line* is the reversible heat flow on second heating)

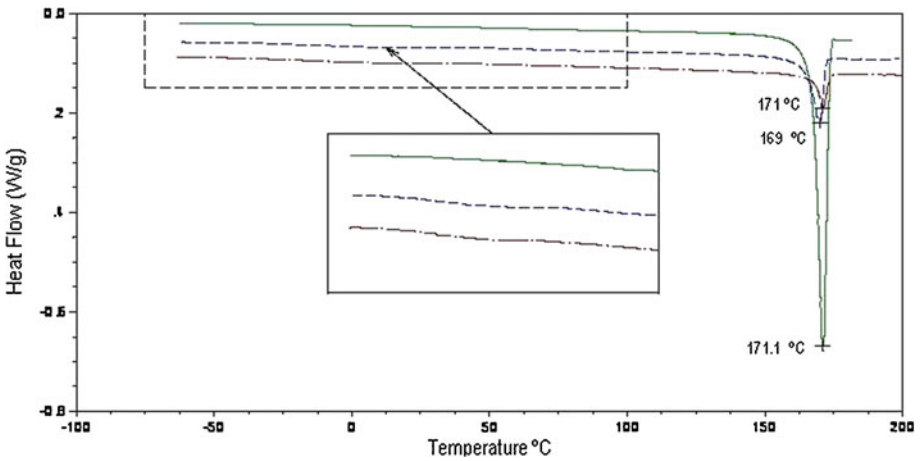

Fig. 8. DSC thermogram of pure nifedipine (*top line*), nifedipine–HPC (1:1) physical mix (*middle line*), and (1:1) co-ground mix (*bottom line*)

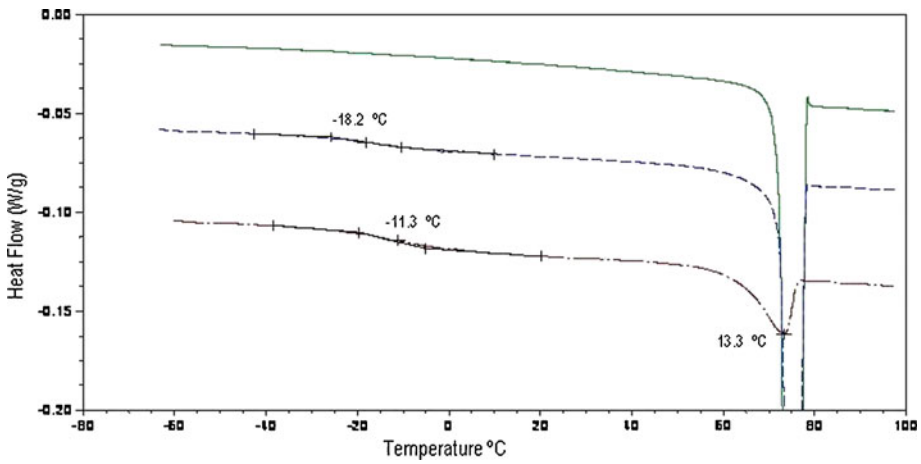

Fig. 9. DSC thermogram of pure ibuprofen (*top line*), ibuprofen–HPC (1:1) physical mix (*middle line*), and (1:1) co-ground mix (*bottom line*)

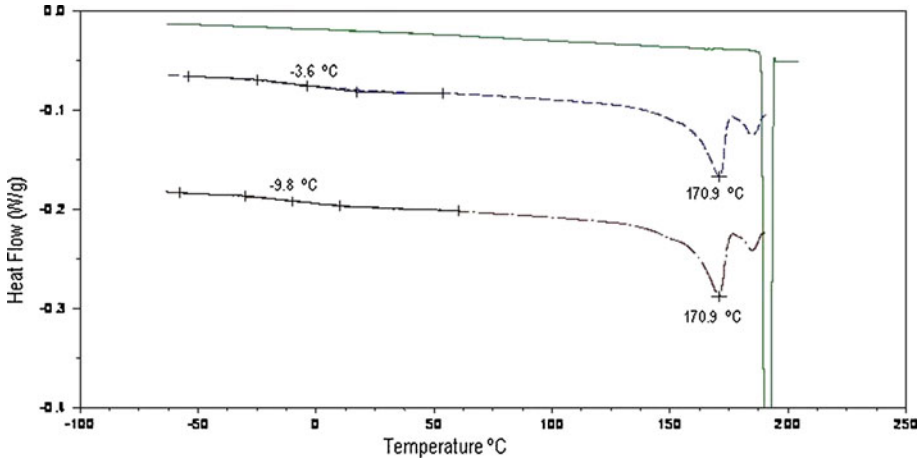

Fig. 10. DSC thermogram of pure carbamazepine (*top line*), carbamazepine–HPC (1:1) physical mix (*midddle line*), and (1:1) co-ground mix (*bottom line*)

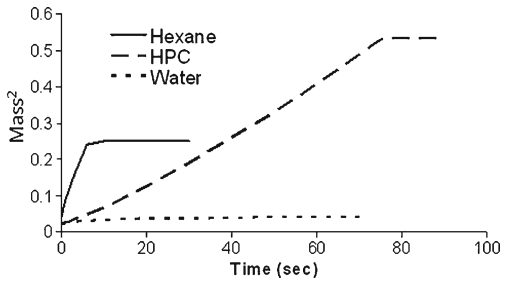

Fig. 11. Liquid uptake (mass^2 *vs* time) into ibuprofen bed

Differential Scanning Calorimetry

DSC studies were performed on the individual ingredients and the HPC–drug mixtures in order to identify possible solid-state interactions between the respective drugs and HPC. As shown in Fig. 7, the DSC thermogram of pure HPC shows a peak at 50°C due to the evaporation of surface moisture (about 3–4%). A very small melting peak is discernable at 188°C, which confirms the low degree of crystallinity (less than 10%) observed by X-ray diffraction. DSC thermograms of nifedipine (Fig. 8) exhibit a sharp distinct melting peak of the drug at 171°C. Due to sample dilution, the melting peaks for the drug–HPC mixtures were smaller than that of the pure drug. Apart from size, the melting peaks for the physical and the co-ground mixtures with HPC were essentially similar to the pure drug, indicating no significant physical interaction due to blending or co-grinding of HPC and nifedipine. Figure 9 shows a distinct melting peak at 75°C for ibuprofen. In the mixtures with HPC, the ibuprofen peak is smaller and slightly lower at 73°C, which is attributed to sample dilution as indicated earlier. Additionally, the T_g midpoint for HPC is seen at −18°C, indicating that ibuprofen may be plasticizing HPC. Pure CBZ underwent a melting transition with a peak temperature of 191°C (Fig. 10). Supporting earlier X-ray observations, blending with HPC appears to have triggered a polymorphic transition in carbamazepine. In the HPC blend, the metastable form of carbamazepine melts at 170.9°C with subsequent recrystallization and remelting at approximately 180°C. The T_g midpoint of HPC is seen in the range of −3°C to −10°C, indicating a possible mild plasticizing effect of carbamazepine. There is strong evidence that carbamazepine and HPC can undergo physical interaction, which could lead to a more soluble metastable state. In addition, grinding with HPC has partially reduced the degree of crystallinity of CBZ.

Wetting Studies

Figure 11 shows the mass uptake of a 0.5% aqueous solution of HPC, *n*-hexane, and water into a porous ibuprofen powder bed. Water fails to wet ibuprofen, and no mass is adsorbed as a function of time. Conversely, the HPC solution rapidly wets ibuprofen as indicated by the fast rate of adsorption. Using the slope of the uptake lines, viscosities, densities, and surface tension of the liquids, the contact angles were calculated (Table III). With all three drugs, the contact

Table III. Wetting Characteristics of Water, 0.5% HPC Aqueous Solution, and *n*-hexane on Different Drugs (n=3; SD<2.4% of the Mean)

Wetting liquid	Contact angle on nifedipine	Contact angle on ibuprofen	Contact angle on carbamazepine	Surface tension (mN/m)	Viscosity (Cp)
Water	84	88	80	72	1
0.5% HPC	65	68	71	40	2.3
n-Hexane	0	0	0	18.4	0.3

angle reduced appreciably. For nifedipine and ibuprofen, in the presence of 0.5% HPC, the contact angle is reduced by over 21% while that is reduced by about 12% for carbamazepine indicating improved drug surface wetting when HPC is introduced into the aqueous phase. This is also supported by the surface tension of the HPC solutions. The surface tension for HPC solution is 40 mN/m, while for water it is72 mN/m. It is, therefore, concluded that besides other factors, improved wetting by HPC has significantly contributed to the enhancement of dissolution rates of poorly water-soluble drugs.

CONCLUSION

The dissolution rate and extent of three poorly water-soluble compounds were enhanced by the simple process of blending or co-grinding with HPC. Various mechanisms are involved in the overall enhancement of dissolution rates. In the case of carbamazepine, a specific interaction with HPC, resulting in formation of a metastable state may contribute to the increased dissolution. Apart from the intimate mixture of HPC and drug particles and enlarged surface area due to particle size reduction, a decrease in the degree of crystallinity is also a likely contributor to dissolution rate enhancement on co-grinding mixture. The major mechanism for enhanced dissolution appears to be the improved wettability of the hydrophobic surfaces in the presence of HPC. The relatively non-polar nature of HPC allows a significant reduction in surface tension of aqueous media and also allows contact between the polymer and the low energy surfaces resulting in enhanced dissolution rates of poorly water-soluble drugs.

REFERENCES

1. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of *in-vitro* drug product dissolution and *in vivo* bioavailability. Pharm Res. 1995;12:413–20.
2. Horter D, Dressman JB. Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract. Adv Drug Deliv Rev. 1997;25:3–14.
3. Lobenberg R, Amidon GL. Modern bioavailability, bioequivalence and biopharmaceutic classification system: new scientific approach to international regulatory standards. Eur J Pharm Biopharm. 2000;50:3–12.
4. Palanisamy M, Khanam J. Solid dispersion of prednisolone: solid state characterization and improvement of dissolution profile. Drug Dev Ind Pharm. 2011;37(4):373–86.
5. Sinha S, Ali M, Baboota S, Ahuja A, Kumar A, Ali J. Solid dispersion as an approach for bioavailability enhancement of poorly water-soluble drug ritonavir. AAPSPharmSciTech. 2010;11(2):518–27. doi:10.1208/s12249-010-9404-1.
6. Rane Y, Mashru R, Sankalia M, Sankalia J. Effect of hydrophilic swellable polymers on dissolution enhancement of carbamazepine solid dispersions studied using response surface methodology. AAPS PharmSciTech. 2007;8(2). doi:10.1208/pt0802027.
7. Patel RP, Patel MM. Physicochemical characterization and dissolution study of solid dispersions of lovastatin with polyethylene glycol 4000 and polyvinylpyrrolidone K30. Pharm Dev Technol. 2007;12(1):21–33.
8. Al-Obaidi H, Buckton G. Evaluation of griseofulvin binary and ternary solid dispersions with HPMCAS. AAPS PharmSciTech. 2009;10(4):1172–77. doi:10.1208/s12249-009-9319-x.
9. Sekiguchi K, Obi N. New solid state dispersions for increasing dissolution rates. Chem Pharm Bull. 1961;29:866–7.
10. Hilden LR, Morris KR. Physics of amorphous solids. J Pharm Sci. 2004;93(1):3–12.
11. Goldberg AH, Gibaldi M, Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures. II—experimental evaluation of eutectic mixtures: urea–acetaminophen system. J Pharm Sci. 1966;55:482–7.
12. Leuner C, Dressman JB. Improving drug solubility for oral delivery using solid solutions. Eur J Pharm Biopharm. 2000;50:47–60.
13. Chokshi RJ, Zia H, Sandhu HK, Shah NH, Malik WA. Improving the dissolution rate of poorly water soluble drug by solid dispersion and solid solution—pros and cons. Drug Deliv. 2007;14:33–45.
14. Habib MJ. Pharmaceutical solid dispersion technology. Lancaster: Technomic Publishing Co.; 2001. p. 20–5.
15. Moneghini M, Carcano A, Zingone G, Perissutti B. Studies in dissolution enhancement of atenolol. Part I. Int J Pharm. 1998;175:177–83.
16. Rasenack N, Hartenhauer H, Muller BW. Microcrystals for dissolution rate enhancement of poorly water-soluble drugs. Int J Pharm. 2003;254:137–45.
17. Feeley JC, York P, Sumby BS, Dicks H. Determination of surface properties and flow characteristics of salbutamol sulphate, before and after micronization. Int J Pharm. 1998;172:89–96.
18. Mura P, Faucci MT, Maestrlli F, Furlanetto S, Pinzauti S. Characterization of physicochemical properties of naproxen systems with amorphous cyclodextrin–epichlorohydrin polymers. J Pharm Biomed Anal. 2002;29(6):1015–24.
19. Yamamoto K, Nakano M, Arita T, Takayama Y, Nakai Y. Dissolution behavior and bioavailability of phenytoin from a ground mixture with microcrystalline cellulose. J Pharm Sci. 1976;55(10):1484–8.
20. Mura P, Faucci MT, Parrini PL. Effects of grinding with microcrystalline cellulose and cyclodextrins on ketoprofen physicochemical properties. Drug Dev Ind Pharm. 2001;27(2):119–28.
21. Sugimoto M, Okagaki T, Narisawa S, Koida Y, Nakajima K. Improvement of dissolution characteristics and bioavailability of poorly water soluble drugs by a novel co-grinding method using water soluble polymers. Int J Pharm. 1998;160:11–9.
22. Kim E, Chun M, Jang J, Lee I, Lee K, Choi H. Preparation of a solid dispersion of felodipine using a solvent wetting method. Eur J Pharm Biopharm. 2006;64:200–5.
23. Garcia-Rodriguea JJ, Torre-Iglesias PM, Vegas-Sanchez MC, Torrado-Duran S, *et al.* Changed crystallinity of mebendazole solid dispersion: improved anthelmintic activity. Int J Pharm. 2011;403:23–8.
24. El-Zein H, Riad L, El-Bary AA. Enhancement of carbamazepine dissolution: *in vitro* and *in vivo* evaluation. Int J Pharm. 1998;168(2):209–20.
25. Hamraoui A, Nylander T. Analytical approach for the Lucas–Washburn equation. J Colloid Interface Sci. 2002;250:415–21.
26. Babu GV, Kumar NR, Sankar SH, *et al. In vitro* evaluation of modified gum karaya as a carrier for improving the oral bioavailability of a poorly water soluble drug, nimodipine. AAPSPharmSciTech. 2002;3(2):1–9.
27. Vadher AH, Parikh JR, Parikh RH, Solanki AB. Preparation and characterization of co-grinded mixtures of aceclofenac and neusilin US2 for dissolution enhancement of aceclofenac. AAPSPharmSciTech. 2009;10(2):606–14.