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Solvent change co-precipitation with hydroxypropyl methylcellulose phthalate to improve dissolution characteristics of a poorly water-soluble drug

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Abstract

Research compound GWX belongs to biopharmaceutical classification system type II, and hence shows dissolution-rate-limited absorption. To improve its dissolution performance, GWX was formulated as a co-precipitate with hydroxypropyl methylcellulose phthalate (HPMCP). Co-precipitates with various drug–HPMCP ratios were prepared and characterised using modulated differential scanning calorimetry (MDSC), X-ray powder diffraction, HPLC and dissolution testing. Co-precipitates with 1:9 and 2:8 drug–HPMCP ratios showed the highest extent of dissolution after both 5 and 90 min, followed by 3:7, 4:6, and 5:5 drug–HPMCP co-precipitates, in respective order. Co-precipitates with drug–HPMCP ratios of 6:4 and greater showed no significant improvement in dissolution over crystalline drug alone. The amounts of crystalline and amorphous drug in co-precipitates, as determined by MDSC, and HPLC quantification of the total amount of drug in co-precipitates were used to determine the amount of drug incorporated into solid solution. It was found that dissolution rate and extent was correlated to the amount of drug incorporated into amorphous solid solution for the 1:9 to 5:5 drug–HPMCP ratio co-precipitates. Amorphous drug alone and physical mixtures of drug and HPMCP showed very little and no significant improvement in dissolution rate or extent, respectively, above crystalline drug alone. Amorphous drug alone re-crystallized to a large extent within 1 min of contact with the dissolution medium, whereas 4:6 drug–HPMCP co-precipitate showed a lower degree of re-crystallization and 2:8 drug–HPMCP co-precipitate showed very little re-crystallization. It was concluded that the likely mechanisms of improved dissolution of low drug–HPMCP ratio co-precipitates were improved wetting or increased surface area for mass transfer, thermodynamically enhanced dissolution of a higher energy amorphous form and inhibition of re-crystallization, when drug was incorporated into solid solution.

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Introduction

The bioavailability of poorly water-soluble drugs is frequently limited or rate-controlled by dissolution (Martin 1993). Incorporation of such drugs into solid dispersions is one way to improve dissolution.

The dispersion of drug into a freely aqueous-soluble carrier has been reported to considerably increase the dissolution rate of several drugs (Sekiguchi & Obi 1961; Kozo et al 1982; Miralles et al 1982; Ntawukulilyayo et al 1993). Dispersion in such a manner may decrease drug particle size, increasing the surface area available for mass transfer, while the carrier may act as a solubilizer for the drug, or physically prevent particle agglomeration during dissolution.

A related mechanism that may increase the rate of dissolution is improvement in wettability of the drug (Chiou & Riegelman 1971). The smaller the drug particles dispersed within the readily wetted carrier, the more significant this effect is likely to be.

The increase in the rate of dissolution due to the above effects is predicted by the modified Noyes-Whitney equation (Noyes & Whitney 1897):

$$dC/dt = AD(C_s - C)/h \quad (1)$$

in which dC/dt represents the rate of dissolution, A is the surface area available for dissolution, D is the diffusion coefficient of the compound, C_s is the solubility of the

compound in the dissolution medium, C is the concentration of drug in the medium at time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

If the solid dispersion is an amorphous solid solution, not only is the drug particle size decreased to the molecular level, but drug molecules will also be in a higher energy (less stable) form. It is likely that there will be a decrease in the enthalpy required to separate drug molecules from each other, or from the carrier molecules, compared with the energy required within a crystalline structure. The free energy of mixing or solution, may decrease as a result (Martin 1993), according to equation 2:

$$\Delta G_m = \Delta H_m - T\Delta S_m \quad (2)$$

in which G_m, H_m, and S_m represent free energy, enthalpy, and entropy, of mixing or solution, respectively, and Δ indicates the difference in these system parameters before and after dissolution. All other factors being equal, the more negative ΔG_m is, the more readily dissolution will occur.

Methods for preparing solid solutions have been classified by Leuner & Dressman (2000) into the hot-melt and the solvent methods. Solvent methods used for solid dispersion manufacture allow for less exposure to heat, and include co-evaporation (Tachibana & Nakamura 1965) and co-precipitation (Simonelli et al 1969; Kislalioglu et al 1991). These techniques may introduce ecological constraints due to their usage of organic solvents, and residual solvent toxicity issues.

Co-precipitation is a technique wherein a drug and a carrier are dissolved in a solvent, and this solution is then added to an anti-solvent. The drug and polymer then precipitate out simultaneously in the anti-solvent, as a solid dispersion. Co-precipitation may be advantageous to co-evaporation techniques such as spray drying, for the following reasons: equipment and energy requirements may be less; high temperature degradation need not occur; solvents can be less volatile and may be required in smaller amounts; and washing can be used to help remove solvents from the product.

The enteric polymer hydroxypropyl methylcellulose phthalate (HPMCP) degrades at temperatures below the melting point of many drugs (Kibbe 2000), and therefore the techniques by which it can be incorporated into solid dispersions are limited to the solvent methods. HPMCP has been used as a carrier in solid dispersions formed by co-evaporation, to successfully improve bioavailability of drugs (Kondo et al 1994; Kai et al 1996).

In this study, the physical characteristics and dissolution of solid dispersions of research compound GWX and HPMCP, made by solvent change co-precipitation, have been investigated. GWX satisfies the structural criteria (rule of 5) proposed by Lipinski et al (1997) in that it does not have: more than 5 hydrogen-bond donor moieties; molecular weight >500; $\log P > 5$; more than 10 hydrogen-bond acceptor moieties.

GWX belongs to biopharmaceutical classification system (BCS) type II (low aqueous solubility, high permeability) (Amidon et al 1995).

Materials and Methods

Materials

GWX powdered drug substance was synthesised by the Chemical Development Department of GlaxoSmithKline, Stevenage, UK. Hydroxypropyl methylcellulose phthalate (HPMCP, HP-55F) was obtained from Shin-Etsu Chemical Industry Co. Ltd, Tokyo, Japan. All reagents were analytical grade and used without further purification. All water used was purified by reverse osmosis.

Determination of GWX solubility in acetone

Four samples of 125 mg GWX in 2 mL acetone were shaken for 12 h in glass flasks (significant residual solid was seen after shaking). The mixtures were centrifuged at 2000 *g* for 5 min, and the supernatant filtered through 0.22-μm filters. A 100-μL portion from each sample was diluted with acetonitrile to 100 mL, and analysed by HPLC.

Preparation of amorphous GWX

Drug (5 g), contained in an 80-mm diameter stainless-steel beaker, was heated in an oven to 190°C. The beaker containing molten drug was then immediately placed on an aluminium block bathed in liquid nitrogen, and allowed to cool under a stream of nitrogen gas. The average rate of quench cooling of the molten drug to 20°C was 6°C s^{-1}, as measured by a Digitron 2022T Type K thermocouple thermometer (Digitron Instrumentation Ltd, Hertford, UK). Quench-cooled drug was removed from the beaker, ground gently with a mortar and pestle and stored with desiccant in amber glass jars until immediately before use in experiments.

Preparation of solid dispersion systems

Drug–HPMCP mixtures (1 g) in ratios of 9:1 to 1:9, as well as HPMCP alone and drug alone, were completely dissolved in a minimum volume of acetone, according to the drug solubility in acetone (35 g L^{-1}, see above), or in 10 mL of acetone (HPMCP).

Each 10 mL of drug and HPMCP in acetone solution was added drop-wise to 70 mL 0.1 M HCl (aq.), in a 250-mL glass round-bottomed flask, while stirring with a magnetic stirrer. Resulting co-precipitates were filtered under vacuum using Whatman No. 54 filter paper.

Filtered co-precipitates were dried under vacuum at 40°C, −800 mbar, for 24 h. The dried co-precipitates were milled in a Pulverisette 7 ball-mill (Fritsch, Idar-Oberstein, Germany), for three 3-min intervals at 400 rev min^{-1}, with a pause of 5 min between each interval. Four 15-mm zirconium oxide balls were used as grinding media in a 40-mm diameter, 45-mL zirconium oxide cylindrical milling chamber.

Samples were prepared in triplicate for each drug–HPMCP ratio, and the resulting powder from the 3 samples mixed with a spatula to make one sample of sufficient size for sieving.

X-ray analysis

X-ray powder diffractometry (XRPD) was carried out with a Philips X'Pert MPD powder diffractometer (Philips Electronics, Eindhoven, Netherlands), employing a CuK_α source operating at 40 kV, 55 mA. Scanning rates used were 0.02°2θ s^{-1}, and 0.04°2θ s^{-1} (fast scan), with step size 0.02°2θ.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) and modulated differential scanning calorimetry (MDSC) were carried out using a TA Instruments DSC 2920 Modulated DSC scanning calorimeter (TA Instruments Inc., DE). Samples, 5–6 mg, were heated in aluminium pans with pin-holed lids, under a 20 mL min^{-1} stream of nitrogen gas. DSC was carried out, heating from room temperature, at 10°C min^{-1}, to the final temperature. MDSC was carried out using the following heating program: firstly, heating to 60°C at 20°C min^{-1} from ambient temperature; secondly, isothermal for 5 min at 60°C with modulation amplitude $\pm$0.25°C, and period 50 s; thirdly, heating to 200°C at 2°C min^{-1} with the same modulation parameters as above. Lissajous plots (Hill et al 1999) of pre-event sections of sample thermograms were made, to check that the calorimeter measured heat flow and modulated the temperature of samples in a controlled manner.

Universal Analysis (version 2.5) software (TA Instruments Inc., DE) was used to detect and analyse thermogram events.

Thermo-gravimetric analysis

Analysis of residual solvent in co-precipitates was determined by thermo-gravimetric analysis (TGA) using a TA Instruments Hi-Res TGA 2950 Thermogravimetric Analyzer (TA Instruments Inc., DE). Samples, 10–15 mg, were heated at a rate of 10°C min^{-1} in aluminium pans. The percent by weight of residual solvent was taken to be the percentage weight change of the sample occurring between ambient temperature and 100°C.

Sieving

Milled co-precipitates were sieved for 15 min using a Gilsonic GA1 vibrating auto-siever (Gilson Co. Inc., Worthington, USA), and the size fraction between 45 and 125 μm was retained. A Malvern Mastersizer X laser diffraction particle sizer (Malvern Instruments Ltd, Worcester, UK), was used to analyse sonicated dispersions of the sieved particles in water, to verify that the mean size of particles which were sieved lay within the size fraction 45–125 μm.

Particulate dissolution

Dissolution experiments were carried out on particle size fractions between 45 and 125 μm, using the USP II paddle method (75 rev min^{-1}, 37°C). Samples containing 25 mg of drug substance were wetted with 5 mL water, before undergoing dissolution in 500 mL of 0.2 M sodium phosphate buffer, pH 6.8, containing 0.1% w/v sodium dodecyl sulphate (SDS). This dissolution medium was chosen because it mimicked intestinal pH, and contained a concentration of SDS that showed sufficiently discriminating dissolution for test materials. Samples taken periodically from the dissolution medium were filtered through 0.45-μm filters, and diluted with an equal volume of acetonitrile before analysis by HPLC.

Drug concentration

Drug concentration in dissolution studies, and the drug content of co-precipitates were determined by HPLC. A Hewlett Packard HP1090A liquid chromatograph attached to an HP series 1100 UV detector (Hewlett Packard, Waldbronn, Germany), detecting absorbance at 270 nm was used. The system was run in reversed phase, with a Hypurity 3 μm C-18 column, 3 mm i.d. $\times$ 100 mm (Hypersil, Cheshire, UK) at room temperature. The mobile phase, 40:60 acetonitrile–0.05 M sodium phosphate buffer, pH 7, was pumped through the column at a flow rate of 0.75 mL min^{-1}. The injection volume was 20 μL. HPMCP concentration for dissolution studies was measured as above, except the absorbance wavelength was set at 220 nm.

Density measurement

The density of amorphous (quench-cooled) GWX, and HPMCP precipitated from acetone, were measured with an Accupyc 1330 pycnometer (Micromeritics, Norcross, USA). Measurements were made in triplicate on materials in powder form, utilizing helium gas as the displacing fluid.

Statistical analysis

One-way analysis of variance, followed by a Tukey's multiple-range test was used to detect whether or not statistically significant differences existed between various formulations (α = 5%) for the following comparisons: extent of dissolution for each formulation prepared, at both t = 5 min and t = 90 min; percentage of drug which is incorporated into solid solution, between co-precipitates with different drug-to-polymer ratios.

The same method was used to compare differences in crystalline and amorphous drug content of various size fractions of a 5:5 drug–polymer ratio co-precipitate after sieving.

Results and Discussion

Characterisation of co-precipitate powder

The co-precipitates investigated with low drug content (10–40%) consisted of an agglutinated mass, whereas higher drug–polymer ratio co-precipitates were finer particles. Recovery of drug and HPMCP weighed into the co-precipitation process was in the range 85–93%.

Milling of dried co-precipitates, drug, and HPMCP yielded fine powders, which were sieved. The weight per-

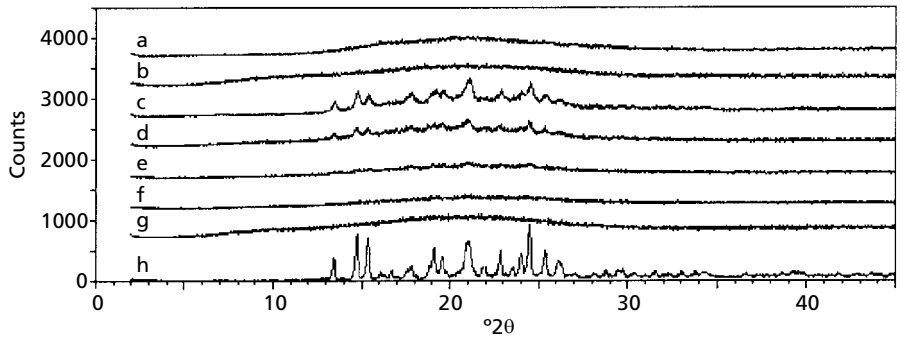

Figure 1 X-ray powder diffractograms of amorphous GWX (a); HPMCP (b); 9:1 (c); 8:2 (d); 5:5 (e); 2:8 (f) and 1:9 (g) drug–HPMCP ratio co-precipitates; and of crystalline GWX (h).

centage residual solvent of co-precipitates (single measurements by TGA) were in the range 0.8–3.5% for 9:1 to 1:9 drug–polymer co-precipitates, respectively. This solvent was thought to consist mainly of water, due to the shape of the TGA thermograms that showed no sign of acetone evaporation at 56.5°C. HPMCP and crystalline drug alone which had been precipitated, and then dried, contained 3.5 and $< 0.1\%$ residual solvent, respectively. Amorphous drug alone made by quench cooling of a melt contained $< 0.1\%$ residual solvent.

XRPD was used to qualitatively detect crystallinity, and ensure absence of polymorphism. Diffractograms of amorphous and crystalline drug, and HPMCP and co-precipitates, are shown in Figure 1. More pronounced crystalline peak intensities were seen as the concentration of the drug in co-precipitates increased.

Quantitation of crystalline and amorphous phases in co-precipitates was carried out using modulated DSC. DSC thermograms of amorphous GWX and HPMCP are shown in Figure 2.

The melting endotherms of crystalline drug in drug–HPMCP physical mixtures were measured for duplicate samples. A resulting calibration curve of % w/w crystalline drug in HPMCP vs crystalline melting endotherm area was linear with a slope of 0.67 and an intercept of 1.36 (R^2 = 0.99). The limit of detection and the limit of quantitation, estimated on the basis of standard deviation of baseline signal (*US Pharmacopeia* 23 1994; Miller & Miller 2000) (n = 5), are 1% (3 s.d.) and 4% w/w (10 s.d.) of crystalline GWX, respectively.

Quench-cooled GWX powder was determined by XRPD to be completely amorphous. Re-crystallization exotherms of physical mixtures of amorphous GWX in HPMCP, and in crystalline GWX, were also measured. Measurements made on duplicate samples from both sets of data were combined to create a composite calibration curve of re-crystallization enthalpy vs amorphous drug content of physical mixtures. This linear curve had a slope of 0.51 and an intercept of 0.25 (R^2 = 0.99). The limit of detection and the limit of quantitation, estimated on the basis of standard deviation of baseline signals (n = 5), are 1% (3 s.d.) and 3% (10 s.d.) w/w of amorphous GWX, respectively.

It was observed that the subsequent melting endotherm

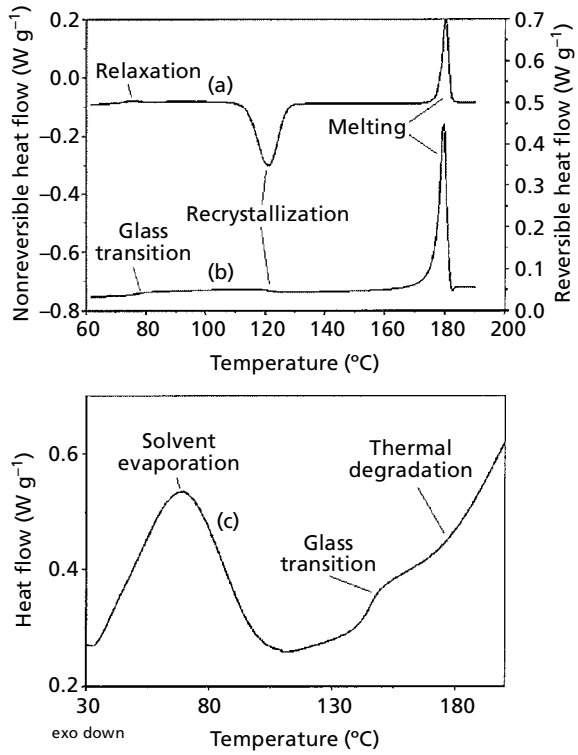

Figure 2 MDSC heating thermograms showing amorphous GWX non-reversible heat flow (a); amorphous GWX reversible heat flow (b) and HPMCP total heat flow (c).

of re-crystallized GWX corresponded to the amount of amorphous GWX weighed into the physical mixture (i.e., amorphous drug alone completely re-crystallized and melted on heating in the DSC pan).

Determination of the amount of drug incorporated into solid solution

Since the total drug content of the co-precipitate can be determined using HPLC and TGA, a mass balance of drug present in 3 phases (crystalline drug, amorphous drug and drug incorporated into solid solution) is possible. Crystalline drug can be quantified from melting endotherm

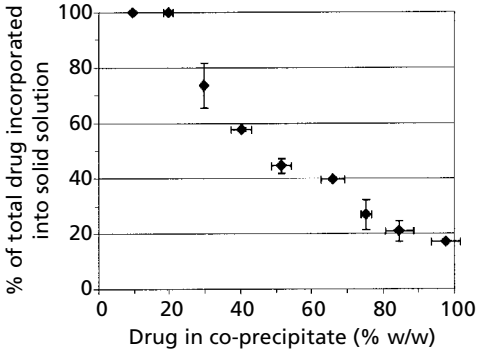

Figure 3 Percentage of total drug incorporated into solid solution, for GWX–HPMCP co-precipitates. Error bars indicate mean ± s.d.

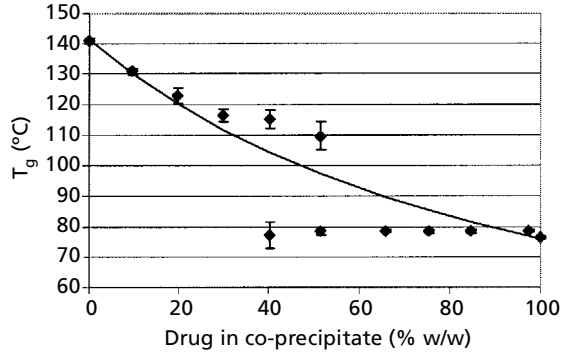

Figure 5 Glass transition temperatures (T_g) detected in co-precipitated material, as a function of drug content. The continuous line is a plot calculated using equations 3 and 4. Error bars indicate mean ± s.d.

energies, and amorphous drug can be quantified from recrystallization exotherm energies. The difference between the two gives the original amount of crystalline drug before heating. The total amount of drug, less original amounts of crystalline and amorphous drug, gives by difference, the amount of drug incorporated into solid solution.

Figure 3 shows the proportion of drug incorporated into solid solution, for the co-precipitates manufactured, as determined by the above mass balance. Drug–polymer ratio-precipitates 1:9 and 2:8 have all of their drug content incorporated into solid solution. The 3:7, 4:6, 5:5 and 6:4 drug–HPMCP ratio co-precipitates then show a statistically significant rank order, having decreasing percentages of drug incorporated into solid solution, as total drug content increases. Although the trend appears to continue in Figure 3, the 7:3, 8:2 and 9:1 drug–polymer ratio co-precipitates do not show significant differences in the percentages of drug incorporated into solid solution.

Glass transition detection

Glass transitions, detected as points of inflection on the reversible MDSC thermograms of co-precipitates, are shown in Figure 4. A downward shift in the higher T_g can be seen as co-precipitates become more drug rich. This is evidence of drug being incorporated into solid solutions with HPMCP. The lower T_g at about 76°C corresponds to amorphous drug alone, and is seen in the co-precipitates with high drug content. The T_g of HPMCP occurs at about 141°C.

A modified form of the Gordon-Taylor equation (3) can be used to estimate glass transition temperatures of amorphous materials containing two components (Gordon & Taylor 1952; Hancock & Zografi 1997):

$$T_{g12} \approx (w_1 T_{g1} + w_2 K T_{g2})/(w_1 + K w_2) \quad (3)$$

where T_g and w are the glass transition temperature and the weight fraction, respectively, of the components represented by subscripts, and

$$K = \rho_1 T_{g1}/\rho_2 T_{g2} \quad (4)$$

in which ρ is density. Density values for quench-cooled GWX, and precipitated HPMCP, determined by gas pycnometry to be 1.31 and 1.37 g cm^{-3}, respectively, were utilized to calculate K and estimate T_{g12} in equations 3 and 4.

Equation 3 has been plotted in Figure 5, and can be used to identify which T_gs are likely to be associated with solid solution phases, and which are due to individual components. The 4:6 and 5:5 drug–polymer co-precipitates show 2 weak glass transitions, indicating the presence of two amorphous phases: drug–HPMCP solid solution, and amorphous drug alone. Glass transitions due to solid solution phases were not detectable in co-precipitates with drug–HPMCP ratios above 5:5, and only the T_g corresponding to amorphous drug alone was seen. The T_g of HPMCP is not seen in any of the co-precipitates, implying that HPMCP does not occur in appreciable amounts as a solitary phase.

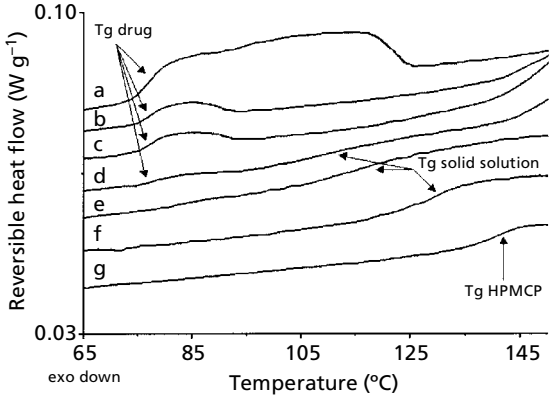

Figure 4 MDSC reversing heat flow thermograms showing glass transitions of quench-cooled GWX (a); 9:1 (b); 7:3 (c); 5:5 (d); 3:7 (e) and 1:9 (f) drug–HMPCP co-precipitates; and of HPMCP (g).

Effect of sieving on homogeneity of co-precipitated material

It was decided to measure the amounts of amorphous and crystalline material in each of the size fractions obtained, after sieving of the 5:5 drug–HPMCP co-precipitate. Four

samples from each of the $< 45\,\mu$m, 45–125 μm and $> 125\,\mu$m sieve fractions were taken. The average amorphous drug content in each size fraction was 5.1, 5.4 and 5.0% w/w, respectively. The average crystalline drug content in each size fraction was 22.9, 22.7 and 20.0% w/w, respectively. One-way analysis of variance performed on data indicated that there were no significant differences between size fractions, in the percentage of crystalline or amorphous material present.

Dissolution testing

The dissolution profiles of co-precipitates in 0.1% SDS in pH 6.8 phosphate buffer are shown in Figure 6. Co-precipitates with drug–HPMCP ratios of 1:9 and 2:8, in which all drug was incorporated into solid solution, showed levels of dissolution at t = 5 min (Q_5) and t = 90 min (Q_{90}), approximately ten fold and three fold that of controls, respectively, but showed no significant difference in dissolution to each other. Below these, a statistically significant rank order at both Q_5 and Q_{90} also existed, decreasing from 3:7 to 4:6 to 5:5 co-precipitates. Dissolution of the remaining higher drug content co-precipitates did not show any statistically significant improvement above drug alone. These results indicate that a greater extent of dissolution appears to be associated with a higher proportion of drug incorporated into solid solution (see Figure 3).

Solubilization effects were investigated by performing dissolution tests on 1:9, 3:7, 5:5, 8:2 and 9:1 crystalline drug–HPMCP physical mixtures. Results showed no significant difference at Q_5 and Q_{90} between physical mixtures and crystalline drug alone, confirming no significant solubilization of GWX by HPMCP in the dissolution medium used.

Dissolution experiments, on HPMCP alone and on amorphous GWX made by quench cooling were also performed to look for possible mechanisms of improved dissolution. Results (Figure 6) and statistical analysis indicate that amorphous GWX by itself shows no significant difference and only a slight significant difference, in Q_5 and Q_{90} respectively, compared with crystalline drug. HPMCP alone, on the other hand, showed a rate and extent of dissolution significantly greater than all the formulations, reaching $> 95\%$ dissolution within 5 min.

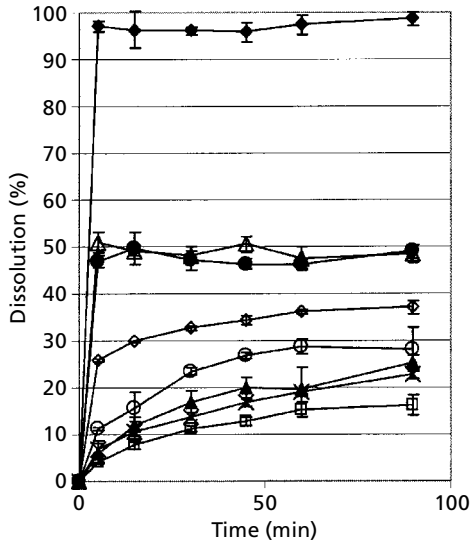

Figure 6 Dissolution profiles of HPMCP (◆), and 1:9 (△), 2:8 (●), 3:7 (◇), 4:6 (○), 5:5 (▲) drug–HPMCP ratio co-precipitates, and of amorphous drug (x) and crystalline drug (□). Error bars indicate mean ± s.d.

Re-crystallization after contact with dissolution medium

To investigate why amorphous drug did not show improved dissolution, amorphous drug was added to stirred dissolution medium as in the dissolution testing. After one minute, the resulting suspension was filtered, and the resulting filter cake was analysed using fast-scan-rate XRPD. Results are shown in Figure 7.

The 2:8 and 4:6 drug–polymer co-precipitates were treated in the same manner as a comparison. The X-ray diffractograms show that amorphous drug alone and the

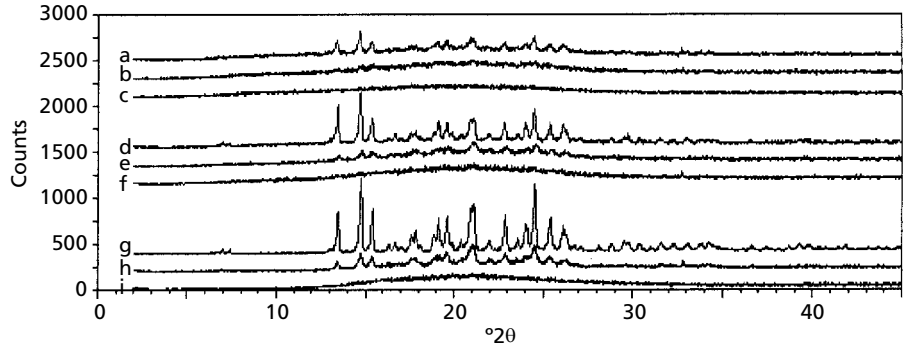

Figure 7 X-ray diffractograms of 2:8 and 4:6 drug–HPMCP co-precipitates, and quench-cooled GWX before (c, f, i) and after (b, e, h) addition to dissolution medium for 1 min, respectively; and of the corresponding 2:8 and 4:6 physical mixtures (a, d) of crystalline drug in HPMCP, respectively; and of crystalline drug (g).

4:6 co-precipitate re-crystallized considerably, whereas the 2:8 co-precipitate re-crystallized only slightly.

This X-ray data indicates that prevention of recrystallization by HPMCP may be a mechanism involved in improving the dissolution rate and extent of the low drug–polymer co-precipitates (drug–polymer ratio $\leqslant 4:6$), in which the majority of drug is in the amorphous solid solution phase.

Conclusions

It appears that the mechanisms by which incorporation of drug into solid solution improves the dissolution performance of the co-precipitates investigated may include improving wetting or increasing surface area, facilitating mass transfer and inhibiting re-crystallization, allowing thermodynamically enhanced dissolution from a higher-energy amorphous form.

Incorporation of drug into solid solution also increases T_g values. This may potentially enhance physical stability, by preventing re-crystallization of the drug during storage (Hancock & Zografi 1997).

The dissolution and stability advantages of the low drug–polymer ratio co-precipitates may, however, be offset by cost, possible toxicological issues and mechanical properties less suitable for handling or comminution, due to the high polymer loading. Co-precipitation in the manner used may therefore be more suitable for high-potency (low-dose) drugs.

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