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Factors affecting incorporation of drug into solid solution with HPMCP during solvent change co-precipitation

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Abstract

Drug–hydroxypropyl methylcellulose phthalate (HPMCP) mixtures were completely dissolved in acetone, and the resulting solution was added drop-wise into $HCl_{(aq)}$. Resulting co-precipitates were filtered, and then dried under vacuum at 45 °C, −800 mbar for 24 h. Modulated differential scanning calorimetry, thermogravimetric analysis, X-ray powder diffraction and HPLC were used to detect and quantify different phases present in co-precipitates. A 1/8 factorial study followed by a circumscribed central composite (CCC) study of significant factors, were used to detect and quantify respectively, the effects that processing factors had on the percentage of drug present in co-precipitates which was incorporated into solid solution (the response). Robustness of the model obtained from the CCC study was tested. Statistically significant factors were found to be the percentage of drug added into solvent, stirrer speed, and antisolvent pH. The statistically significant mathematical model obtained from the CCC study predicted that the dominant factor influencing the response is the percentage of drug added into solvent. The effect of stirrer speed on the response includes a local maximum at stirrer speed $\approx$700 rpm. Both stirrer speed and antisolvent pH showed interactions with the percentage of drug added into solvent. The model obtained from this study indicated the possibility of two opposing phenomena influencing the response: crystallization inhibition by HPMCP, and solvent–antisolvent plasticization. Testing of this model using eight experimentally determined points showed reasonable robustness, with six out of eight points lying inside 95% prediction intervals.

Keywords: Co-precipitation; Solvent change; Amorphous solid solution; Poorly soluble drug; HPMCP; Factorial study

1. Introduction

Incorporation into solid dispersions is one way to improve the dissolution of poorly water-soluble drugs. This approach frequently improves bioavailability that is limited or rate-controlled by dissolution (Martin, 1993). Dispersion in freely

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aqueous-soluble carriers has been reported to considerably increase the dissolution rate of several drugs (Ntawukulilyayo et al., 1993; Kai et al., 1996; Shin and Cho, 1997; Okimoto et al., 1997; Chiou, 1997; Nagarsenker and Garad, 1998).

If the solid dispersion is an amorphous solid solution, not only is particle size of drug decreased to the molecular level, but there could be improvement in wettability of the drug (Craig, 2002) if the carrier is readily wetted. Both these effects increase the surface area available for mass transfer, and can enhance dissolution rate according to the modified Noyes–Whitney equation (Proudfoot, 1988).

Furthermore, there may be a decrease in the enthalpy required to separate drug molecules from each other, or from the carrier molecules, compared to the energy required to separate drug molecules within a crystalline structure. Gibbs free energy of dissolution is likely to decrease as a result, enhancing solubility (Aulton, 1994). Amorphous drugs by themselves also have this solubility advantage, but many tend to rapidly revert to the crystalline state upon exposure to small quantities of plasticizers such as water (Hancock and Parks, 2000).

The solubility advantage of amorphous drugs by themselves is thus offset by poor physical stability, due to high internal energy and corresponding thermodynamic metastability, relative to the crystalline form (Hancock and Zografi, 1997). Existence of amorphous materials is thought to rely on slow kinetics of conversion to a thermodynamically more stable crystalline form (Ediger et al., 1996). Incorporation of drugs into drug-carrier solid solutions can retard drug crystallization (Yoshioka and Zografi, 1995; Kachrimanis and Malamataris, 1999; Khouzag and Clas, 2000). This is more likely when the glass transition temperature (T_g) of the solid solution in question is higher than that of the amorphous drug by itself (Hancock and Zografi, 1997). Although a thermodynamic driving force will still exist for drug molecules to rearrange and form crystals, this transformation to a local free energy minimum may occur at a rate too slow to be practically significant (Ediger et al., 1996).

Plasticizers such as water will decrease T_g (Hancock and Zografi, 1994), and increase the probability of crystallization at any given temperature. They must therefore be kept at minimal levels to maintain physical stability.

One method to form drug-carrier solid solutions is by co-precipitation, a technique in which a drug and carrier are dissolved in a solvent, and this solution is then added to an antisolvent. The drug and polymer then precipitate out simultaneously in the antisolvent. Co-precipitation may be advantageous to other solid dispersion formation techniques such as spray drying, for the following reasons:

- elevated temperatures need not cause degradation of carrier or drug,
- equipment and energy requirements may be less,
- solvents can be less volatile and may be required in lower amounts,
- washing can be used to help remove solvents from the product.

However, as the precipitation process occurs in a solvent and antisolvent mixture, plasticization and resulting high molecular mobility may allow molecular rearrangement including crystallization (Ahlneck and Zografi, 1990). Crystallization may have deleterious effects on dissolution performance of the resultant solid dispersion.

High molecular mobility may exist for a longer time in co-precipitation than in processes such as co-evaporation (Matsumoto and Zografi, 1999; Nagarsenker et al., 2000), in which solvents more volatile than water are generally used, and co-melting, for which very fast cooling may be applied (Leuner and Dressman, 2000).

The experimental drug GW406381X, an aromatic nitrogen heterocycle with aryl substituents, satisfies the "rule of 5" structural criteria proposed by Lipinski et al. (1997), i.e. it does not have:

- more than five H-bond donor moieties,
- molecular weight > 500,
- $\log P > 5$,
- more than ten H-bond acceptor moieties.

GW406381X belongs to biopharmaceutical classification system (BCS) type II (low aqueous solubility, high permeability) (Amidon et al., 1995).

In a preliminary study (Sertsou et al., 2002), GW406381X was co-precipitated with the enteric polymer hydroxypropyl methylcellulose phthalate (HPMCP). It was found that co-precipitates with high percentage of drug incorporated into solid solution were associated with a high rate and extent of drug dissolution. In this study, an attempt has been made to identify factors affecting incorporation of GW406381X into solid solution with HPMCP, during solvent change co-precipitation.

2. Materials and methods

2.1. Materials

GW406381X-powdered drug substance was synthesised by the Chemical Development Department of GlaxoSmithKline (Stevenage, UK). 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.

2.2. Determination of GW406381X solubility in acetone

Four samples of 125 mg GW406381X 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 was filtered through 0.22 μm filters. 100 μl from each sample was diluted with acetonitrile to 100 ml, and analysed using HPLC (see below).

2.3. Preparation of amorphous GW406381X

5 g of drug 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, 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.

2.4. Co-precipitation

The pH of aqueous HCl antisolvent was measured using a Mettler Delta 340 pH meter (Mettler-Toledo Ltd, Halstead, UK). The antisolvent was maintained at the required temperature in a 250 ml glass-jacketed reaction vessel (Radley's, Essex, UK), using water heated/cooled by a Grant Ltd 6 temperature controller (Grant Instruments Ltd, Cambridge, UK). Contents of the reaction vessel were mixed using a PTFE shaft stirrer (6 mm diameter, 500 mm length shaft; 40 mm diameter screw propeller blade) (Radley's), powered by an Ika Eurostar digital overhead stirrer (Ika-Werke GmbH & Co-KG, Staufen, Germany).

Drug–HPMCP mixtures were completely dissolved in acetone, and the resulting solution was pumped through silicone rubber tubing using a Gilson Minipuls 2 peristaltic pump (Gilson, Villiers, France). The solution was then flowed dropwise into the antisolvent from a Volac D810 1 mm tip 150 mm Pasteur pipette (John Poulten Ltd,

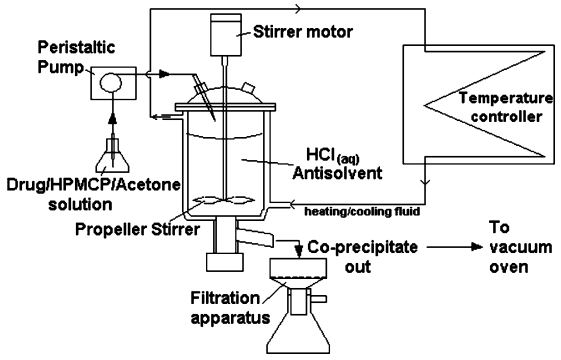

Fig. 1. Schematic of solvent change co-precipitation process.

Essex, UK), attached to the end of the tubing. Fig. 1 is a schematic of the process.

The total volume of the drug–HPMCP–solvent and antisolvent mixtures was kept between 200 and 300 ml, in an attempt to minimise hydrodynamic differences due to volume (Green, 1984), using the aforementioned stirrer and vessel combination.

Immediately after addition of all the drug–HPMCP–solvent solution to the antisolvent, resulting co-precipitates were filtered under vacuum using Whatman® No. 54 filter paper, and then dried under vacuum at 45 °C, −800 mbar for 24 h.

2.5. X-ray analysis

X-ray powder diffractometry (XRPD) was carried out with a Philips X'Pert MPD powder diffractometer (Philips Electronics, Einhoven, Netherlands), employing a CuKα source operating at 40 kV, 55 mA. Scanning rate used was 0.02°2θ/s, with step size 0.02°2θ.

2.6. Differential scanning calorimetry (DSC)

DSC and modulated differential scanning calorimetry (MTDSC) were carried out using a TA Instruments DSC 2920 Modulated DSC scanning calorimeter (TA Instruments Inc., New Castle, DE, USA). 5–6 mg samples were heated in aluminium pans with pin holed lids, under a 20 ml/min stream of nitrogen gas. DSC was carried out heating the samples from room temperature, at 10 °C/min, to 200 °C. MTDSC was carried out using the following heating program:

1) Heating to 60 °C at 20 °C/min from ambient temperature.
2) Isothermal for 5 min at 60 °C with modulation amplitude ±0.25 °C, and period 50 s.
3) Heating to 200 °C at 2 °C/min with the same modulation parameters as above.

The calorimeter was calibrated using indium and sapphire for temperature and heat capacity calibration respectively. Additionally, Lissajous plots (Hill et al., 1999) of pre-event sections of sample MTDSC thermograms were made, to check that the calorimeter measured heat flow and modulated the temperature of samples in a controlled manner.

2.7. Thermogravimetric analysis (TGA)

Analysis of residual solvent in co-precipitates was determined by TGA using a TA Instruments Hi-Res TGA 2950 Thermogravimetric Analyzer (TA Instruments Inc.). Samples weighing 10–15 mg were heated at a rate of 10 °C/min 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.

2.8. Drug quantification by HPLC

The drug content of co-precipitates and solubility study samples were determined by HPLC. A Hewlett Packard HP1090A liquid chromatograph attached to a 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. × 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, and was used to dissolve samples. Injection volume was 20 μl.

2.9. Preparation of physical mixtures

Physical mixtures were prepared immediately prior to analysis. 300 mg of a drug and polymer powder mixture of the appropriate composition was weighed out, and the powders were then mixed with a spatula in a pestle for 3 min.

2.10. Factorial studies

2.10.1. Fractional factorial

An orthogonal, randomised 1/8 fractional seven factor factorial study, with three centre points, was carried out to identify significant factors, the levels of which are shown in Table 1.

Table 1
Factors and corresponding levels used in fractional factorial study

Factor code	Factor	Levels (low, high)
A	Antisolvent to solvent ratio	(6, 8)
B	% drug in drug–HPMCP mixture added to solvent	(25, 75)
C	Fraction of drug solubility in solvent	(0.7, 0.9)
D	Antisolvent temperature (°C)	(5, 45)
E	Stirrer speed (rpm)	(100, 600)
F	Antisolvent pH	(1, 5)
G	Drug–HPMCP–solvent solution addition rate (ml/min)	(2, 8)

The response which was tested for, X, was the percentage of drug present in the co-precipitate, which was incorporated into solid solution, as described above.

2.10.2. Central composite design

Factors found to be significant from the fractional factorial study were used in a circumscribed central composite (CCC) design (Tranter, 2000), with new high and low values. The design consisted of a full factorial cube part, a star design for quantifying main and quadratic effects (axes length = 1.682), and six centre points to estimate precision and goodness of fit. The response factor tested for, X, was as described above.

Design and analysis of fractional and CCC designs were carried out using DESIGN EXPERT 5 software (Stat-Ease Corporation, Minneapolis, MN).

3. Results and discussion

Quantification of crystalline and amorphous phases in co-precipitates was carried out using MTDSC. MTDSC thermograms of amorphous GW406381X and HPMCP are shown in Fig. 2.

The melting endotherms of crystalline drug in drug–HPMCP physical mixtures are shown in Fig. 3, and were measured for duplicate samples.

A resulting calibration curve of % w/w crystalline drug in HPMCP versus specific crystalline melting enthalpy is shown in Fig. 4a. The limit of

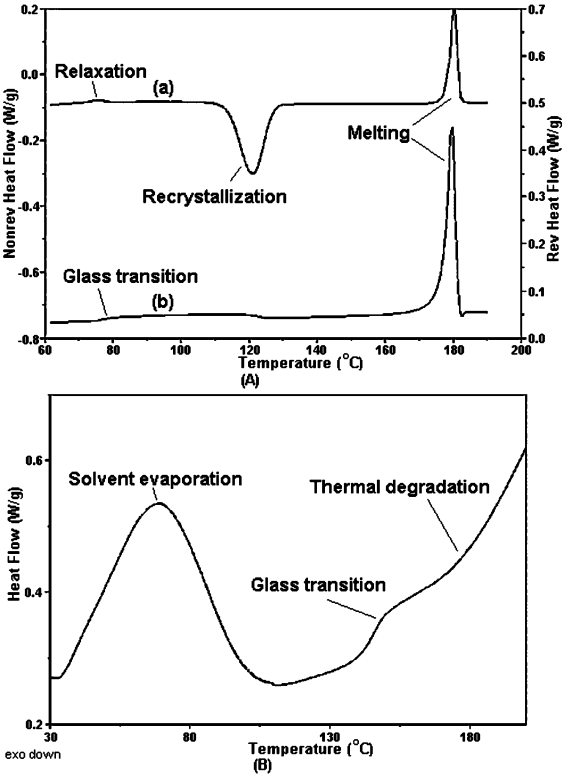

Fig. 2. (a) MTDSC thermogram showing: (i) non-reversible, (ii) reversible thermal events detected when heating amorphous GW406381X. (b) MTDSC thermogram of HPMCP showing total heat flow thermal events detected on heating.

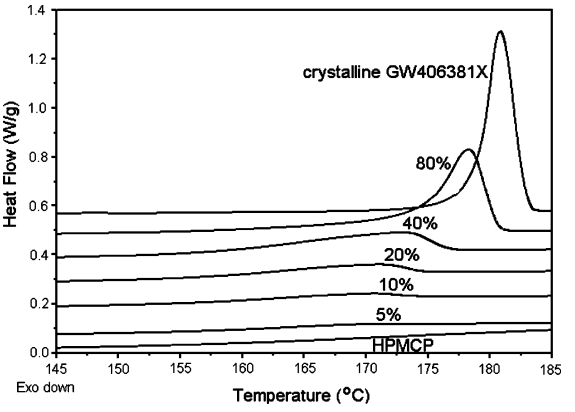

Fig. 3. DSC thermograms of crystalline GW406381X–HPMCP physical mixtures.

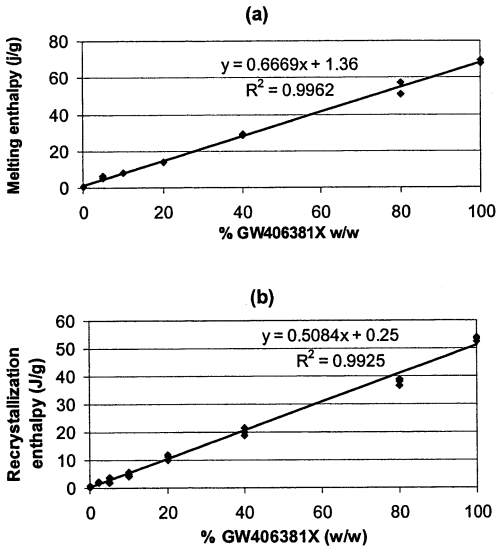

Fig. 4. (a) Calibration curve of total heat flow melting endotherm area versus concentration of crystalline drug in physical mixture. (b) Composite re-crystallization enthalpy calibration curve for physical mixtures of amorphous GW406381X in HPMCP, and in crystalline GW406381X.

detection and the limit of quantitation, estimated on the basis of standard deviation of baseline signal (US Pharmacopeia 23, 1994; Miller and Miller, 2000) ($n = 5$), are 1% (3 SD) and 4% (10 SD) w/w of crystalline GW406381X respectively.

Quench-cooled GW406381X powder showed no evidence of crystallinity by XRPD. Re-crystallization exotherms of physical mixtures of amorphous GW406381X in HPMCP, and in crystalline GW406381X, were also measured and are shown in Fig. 5a and b respectively. Measurements were made on duplicate samples, and the specific re-crystallization enthalpy from both sets of data was combined to create a composite calibration curve (Fig. 4b).

The limit of detection and the limit of quantitation, estimated on the basis of standard deviation of baseline signals ($n = 5$), are 1% (3 SD) and 3% (10 SD) w/w of amorphous GW406381X respectively.

It was observed that the subsequent melting endotherm of re-crystallized GW406381X, corresponded to the amount of amorphous GW406381X weighed into the physical mixture, i.e. amorphous drug alone completely re-crystallized and melted on heating in the DSC pan. HPLC was used to determine the drug content of amorphous material made by quench-cooling. Chromatograms showed no peaks with different retention times or changes in peak area, compared to as received drug, indicating no evidence of chemical degradation during the melting and quench-cooling process.

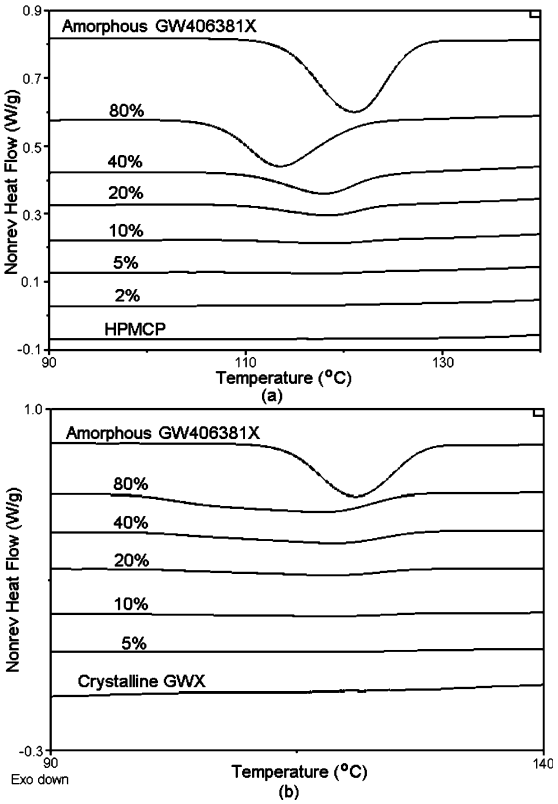

Fig. 5. (a) MTDSC thermograms showing re-crystallization peaks of various % w/w amorphous GW406381X–HPMCP physical mixtures. (b) MTDSC thermograms showing re-crystallization peaks of various % w/w amorphous GW406381X–crystalline GW406381X physical mixtures.

3.1. Determination of the amount of drug incorporated into solid solution

Since the total drug content of the co-precipitate can be determined using HPLC, a mass balance of drug present in three phases (crystalline drug, amorphous drug, and drug incorporated into solid solution) is possible. Crystalline drug, for which no

evidence of polymorphism was seen by XRPD, can be quantified from melting endotherms (Fig. 4a), and amorphous drug can be quantified from recrystallization exotherms (Fig. 4b). The difference between the two gives the original amount of crystalline drug before heating. The total amount of drug, less original amount of crystalline and amorphous drug, gives by difference, the amount of drug incorporated into solid solution, which was the response X, used in factorial and CCC studies.

TGA was used to correct moisture content in calibration curves used for HPLC analysis, and for determination of amorphous and crystalline drug content.

Moisture content determined by TGA for crystalline and amorphous GW406381X, and HPMCP were <0.1, <0.1 and 3.5% w/w respectively. The moisture content for freshly prepared co-precipitates ranged between 0.2 and 3% w/w.

HPLC chromatograms of co-precipitates did not show any peaks with different retention times to those of as received drug and HPMCP alone, indicating no evidence of chemical instability of drug or HPMCP during the co-precipitation process.

3.2. Fractional factorial study

The experimental runs and observed responses are shown in Table 2.

Factors having statistically significant effects ($\alpha = 0.05$) on the response X, were B, E, F, and an A–G interaction:

$$X = 190.27 - 11.78A - 1.20B + 0.02E - 7.00F - 17.50G + 2.67AG \quad (1)$$

A and G by themselves are included only to preserve model hierarchy (DESIGN EXPERT 5 software, 1996).

The fraction of the total variation of the response that is explained by this model, $R^2 = 0.94$. Plots of studentized residuals versus predicted responses, as well as residuals versus run number showed randomly scattered points with no outliers, indicating no requirement for data transformation, no run order effects, and an acceptable model for screening purposes.

Table 2
Factor levels and observed response for the fractional factorial study

Run	A	B	C	D	E	F	G	X
1	6	25	0.9	5	600	5	8	66.2
2	6	75	0.9	5	100	1	8	13.9
3	6	25	0.9	45	600	1	2	95.3
4	7	50	0.8	25	350	3	5	11.9
5	8	25	0.7	45	600	5	2	56.3
6	7	50	0.8	25	350	3	5	13.9
7	8	75	0.9	5	600	1	2	16.7
8	7	50	0.8	25	350	3	5	13.1
9	8	75	0.7	5	100	5	8	15.4
10	6	75	0.7	5	600	5	2	0.0
11	8	75	0.9	45	600	5	8	0.0
12	6	75	0.9	45	100	5	2	0.0
13	6	75	0.7	45	600	1	8	23.0
14	8	25	0.9	5	100	5	2	36.1
15	8	25	0.7	5	600	1	8	99.1
16	8	25	0.9	45	100	1	8	97.5
17	8	75	0.7	45	100	1	2	9.6
18	6	25	0.7	45	100	5	8	32.1
19	6	25	0.7	5	100	1	2	74.9

Factors B, E, and F were carried through into a quantitative central composite study described below.

3.3. Central composite design

The experimental runs and observed responses of the central composite design are shown in Table 3.

DESIGN EXPERT software was used to fit an equation with significant factors ($\alpha = 0.05$) to the above data, which is as follows:

$$X = 83.31 - 0.8B - 0.23E + 9.90F + 3.898\times10^{-3}B^2 + 6.790\times10^{-4}E^2 - 9.672\times10^{-4}BE - 0.09BF - 4.627\times10^{-7}E^3 \quad (2)$$

Although the E^2 term is not significant, it has been kept in the model to preserve hierarchy, and allow translation of the model into actual units. The R^2 value for this model is 0.99, and the prediction R^2, the fraction of the total variation of the response that can be predicted in the model (Lundstedt et

Table 3
Factor levels and observed response for the central composite study

Run	B	E	F	X
1	25	250	1.5	43.9
2	50	80	3.0	53.5
3	75	250	4.5	20.2
4	50	500	3.0	42.6
5	50	500	0.5	29.6
6	75	750	4.5	12.7
7	50	500	3.0	40.5
8	25	250	4.5	70.7
9	50	500	5.5	54.8
10	50	500	3.0	38.3
11	50	500	3.0	40.4
12	50	500	3.0	38.1
13	75	750	1.5	8.8
14	25	750	1.5	69.9
15	75	250	1.5	3.6
16	92	500	3.0	0.0
17	50	920	3.0	27.4
18	25	750	4.5	90.7
19	50	500	3.0	43.8
20	8	500	3.0	100.0

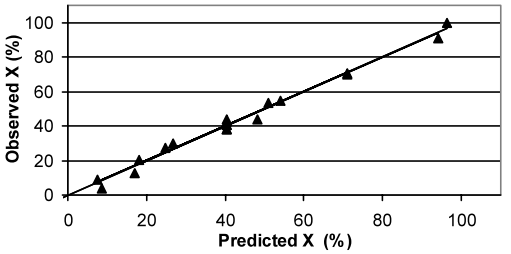

Fig. 6. Fitted versus observed response values for the CCC model.

al., 1998), is 0.88. Fig. 6 shows predicted versus observed values for the CCC model obtained.

The CCC model predicts that B is the dominant factor compared to E and F. It also predicts that a solid solution can be attained with a drug:HPMCP ratio of not much greater than 20%, and this varies only slightly due to E and F.

The predicted response to E shows a local maximum at E ≈ 700 rpm (see Fig. 7), which extends across the pH range, but disappears as B increases. The local maximum may possibly be

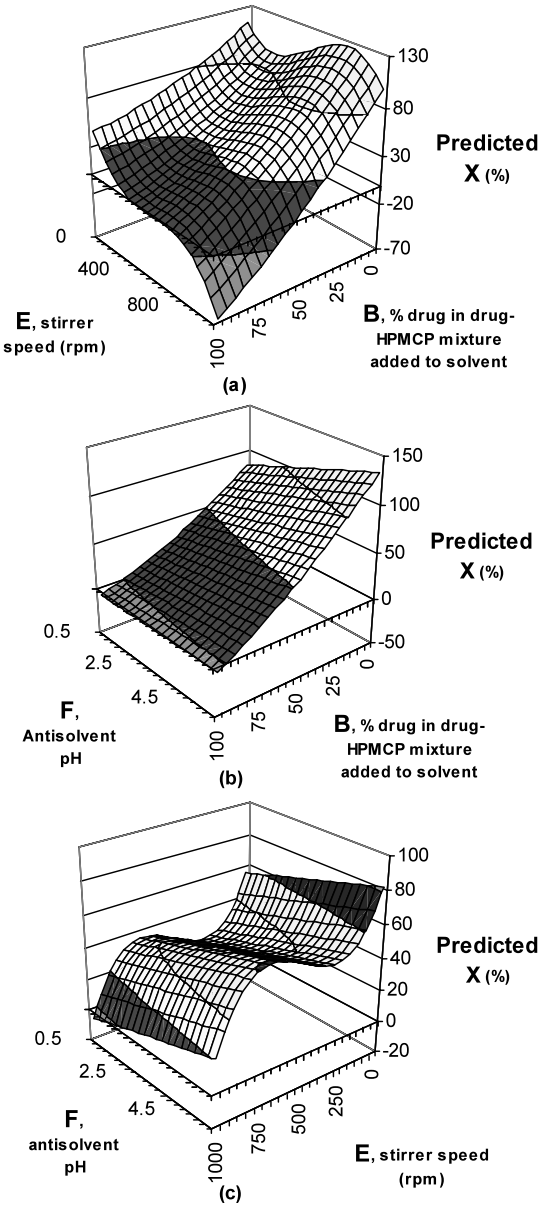

Fig. 7. Plots showing the effect of factors B, E and F on the response surface X, the percentage of drug present in the co-precipitate that is incorporated into solid solution.

explained by two opposing influences on the response:

1) Faster co-precipitation with higher stirrer speed, and earlier prevention of drug crystallization by HPMCP.

2) Increasing mass transfer with higher stirrer speed, leading to a greater degree of plasticization, and loss of drug in solid solution to crystalline or amorphous phases.

In this case, influence 2 dominates when stirrer speed is above about 700 rpm. Support for existence of influence 1 lies in the observation that as B increases, and there is less HPMCP to prevent drug coming out of solid solution, the local maximum disappears. An interaction is also seen with the positive response to increasing F, only when B is low (see Fig. 7). Interactions between B and F, and B and E, are seen as "twists", in the response surfaces.

3.4. Robustness testing of model obtained from central composite design

Eight points were chosen to test robustness of the CCC model obtained above. The points lie on the edges of the design space cube (as in a Box–Behnken design (Karnachi and Khan, 1996), see Fig. 8), and are not close to any centre points, corner points or star points (Tranter, 2000) used to generate the CCC model. These points are therefore likely to have a relatively high amount of prediction error associated with them, and challenge the robustness of the model reasonably well.

The predicted versus observed values from the robustness challenge are shown in Fig. 9.

There is some disagreement between the observed and predicted points, with two out of eight

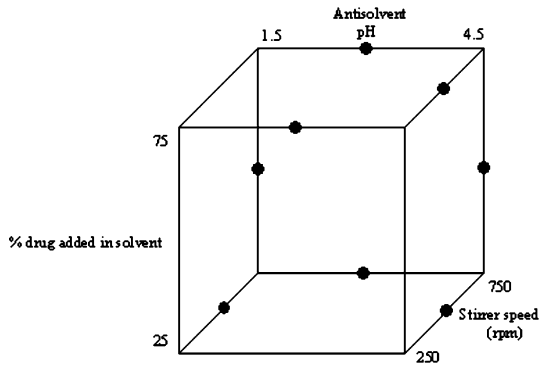

Fig. 8. Positions of robustness testing points in the CCC design space.

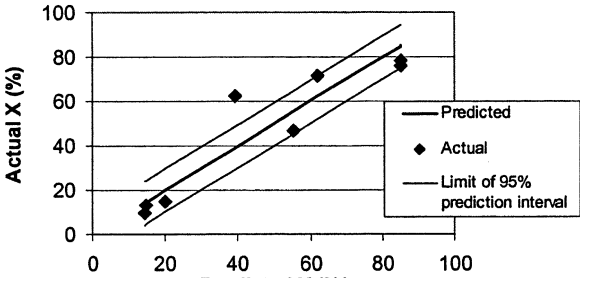

Fig. 9. Actual ersus predicted responses with 95% prediction interals for robustness testing of CCC model.

points lying outside 95% prediction intervals. This may be a result of some over-fitting of the model (Tranter, 2000), due to the low number of experimental design points used in the CCC study. The two outliers however, are close to the prediction intervals, and considering the positioning of robustness testing points within the design space, the model seems to have performed acceptably.

Apart from statistical validity constraints, a shortfall of the CCC model generated, is that it is continuous and does not recognize numerical constraints to quantities such as valid percentages, pH ranges, and stirrer speeds, and so it is important to stay within or close to the design space. Other constraints that are not taken into account by the model, and which may be important include dissolution of HPMCP above about pH 5.5, and the possibility of chemical degradation at very high HCl concentrations.

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References

Ahlneck, C., Zografi, G., 1990. The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state. Int. J. Pharm. 62, 87–95.

Amidon, G.L., Lennernas, H., Shah, V.P., Crison, J.R., 1995. A theoretical basis for a biopharmaceutic drug classification:

the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res. 12, 413–420.

Aulton, M.E., 1994. Pharmaceutics: The Science of Dosage Form and Design. Churchill Livingstone, London, pp. 62–63.

Chiou, W.L., 1997. Pharmaceutical applications of solid dispersion systems: X-ray diffraction and aqueous solubility studies on griseofulvin–polyethylene glycol 6000 systems. J. Pharm. Sci. 66, 989–991.

Craig, D.Q.M., 2002. The mechanisms of drug release from solid dispersions in water soluble polymers. Int. J. Pharm. 231, 131–144.

DESIGN EXPERT 5 software (version 5.0.5), 1996. Stat-Ease Corporation, Minneapolis, MN.

Ediger, M.D., Angell, C.A., Nagel, S.R., 1996. Supercooled liquids and glasses. J. Phys. Chem. 100, 13200–13212.

Green, D.W. (Ed.). Perry's Chemical Engineer's Handbook, 6th ed., McGraw-Hill, New York 1984, pp. 21–60.

Hancock, B.C., Parks, M., 2000. What is the true solubility advantage for amorphous pharmaceuticals? Pharm. Res. 17, 397–404.

Hancock, B.C., Zografi, G., 1994. The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids. Pharm. Res. 11, 471–477.

Hancock, B.C., Zografi, G., 1997. Characteristics and significance of the amorphous state in pharmaceutical systems. J. Pharm. Sci. 86, 1–12.

Hill, V.M., Craig, D.Q.M., Feely, L.C., 1999. The effects of experimental parameters and calibration on MTDSC data. Int. J. Pharm., 21–32.

Kachrimanis, K., Malamataris, S., 1999. Crystallization of paracetamol from ethanol–water solutions in the presence of polymers. J. Pharm. Pharmacol. 51, 1219–1227.

Kai, T., Akiyama, Y., Nomura, S., Sato, M., 1996. Oral absorption improvement of poorly soluble drug using solid dispersion technique. Chem. Pharm. Bull. 44, 569–571.

Karnachi, A.A., Khan, M.A., 1996. Box–Behnken design for the optimization of formulation variables of indomethacin coprecipitates with polymer mixtures. Int. J. Pharm. 131, 9–17.

Khouzag, K., Clas, S.D., 2000. Crystallization inhibition in solid dispersions of MK-0591 and poly(vinylpyrrolidone) polymers. J. Pharm. Sci. 89, 1325–1334.

Leuner, C., Dressman, J., 2000. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm. 50, 47–60.

Lipinski, C.A., Lombardo, F., Dominy, B.W., Feeney, P.J., 1997. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Deliv. Rev. 23, 3–25.

Lundstedt, T., Seifert, E., Abramo, L., Thelin, B., Nystrom, A., Pettersen, J., Bergman, R., 1998. Experimental design and optimization. Chemom. Intell. Lab. Syst. 42, 3–40.

Martin, A., 1993. Physical Pharmacy, 4th ed.. Lea & Febiger, Philadelphia, PA, p. 331.

Matsumoto, T., Zografi, G., 1999. Physical properties of solid molecular dispersions of indomethacin with poly(vinylpyrrolidone) and poly(vinylpyrrolidone-co-vinyl-acetate) in relation to indomethacin crystallization. Pharm. Res. 16, 1722–1728.

Miller, J.N., Miller, J.C., 2000. Statistics and Chemometrics for Analytical Chemistry, 4th ed.. Prentice Hall, London, pp. 121–122.

Nagarsenker, M., Garad, S., 1998. Physical characterization and optimization of dissolution parameters of prochlorperazine maleate coevaporates. Int. J. Pharm. 160, 251–255.

Nagarsenker, M., Garad, S., Ramprakash, G., 2000. Design, optimization and evaluation of domperidone coevaporates. J. Control. Release 63, 31–39.

Ntawukulilyayo, J.D., Bouckaert, S., Remon, J.P., 1993. Enhancement of dissolution rate of nifedipine using sucrose ester coprecipitates. Int. J. Pharm. 93, 209–214.

Okimoto, K., Miyake, M., Ibiki, R., Yasumura, M., Ohnishi, N., Nakai, T., 1997. Dissolution mechanism and rate of solid dispersion particles of nilvadipine with hydroxypropylmethylcellulose. Int. J. Pharm. 159, 85–93.

Proudfoot, S.G., 1988. Introduction to biopharmaceutics. In: Aulton, M.E. (Ed.), Pharmaceutics: The Science of Dosage Form Design. Churchill Livingstone, London, p. 131.

Sertsou, G., Butler, J., Hempenstall, J., Rades, T. 2002. Solvent change co-precipitation with hydroxypropyl methylcellulose phthalate, to improve dissolution characteristics of a poorly water-soluble drug. Proceedings of the Twenty ninth Annual Meeting on Controlled Release Society, Seoul, p. 658.

Shin, S.C., Cho, C.W., 1997. Physicochemical characterizations of piroxicam–poloxamer solid dispersion. Pharm. Dev. Technol. 2, 403–407.

Tranter, R.L., 2000. Design and Analysis in Chemical Research. Sheffield Academic Press, Sheffield, UK, pp. 237–278.

US Pharmacopeia 23. United States Pharmacopeial Convention Inc., Rockville, MD 1994, p. 1984.

Yoshioka, M., Hancock, B.C., Zografi, G., 1995. Inhibition of indomethacin crystallization in poly(vinylpyrrolidone) coprecipitates. J. Pharm. Sci. 84, 983–986.