Stochiometrically governed molecular interactions in drug: Poloxamer solid dispersions

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ABSTRACT

This study probes the molecular interactions between model drugs and poloxamers that facilitate dissolution rate improvements using solid dispersions. Ibuprofen and ketoprofen solid dispersions were prepared at different mole ratios using poloxamers 407 and 188. The carbonyl stretching vibration of the ibuprofen dimer shifted to higher wavenumber in the infrared spectra of 2:1 drug:carrier mole ratio solid dispersions, indicating disruption of the ibuprofen dimer concomitant with hydrogen bond formation between the drug and carrier. Solid dispersions with mole ratios >2:1 drug:carrier (up to 29:1) showed both ibuprofen hydrogen-bonded to the poloxamer, and excess drug present as dimers. X-ray diffraction studies confirmed these findings with no evidence of crystalline drug in 2:1 mole ratio systems whereas higher drug loadings retained crystalline ibuprofen. Similar results were found with ketoprofen-poloxamer solid dispersions. Thermal analysis of ibuprofen-poloxamer 407 solid dispersions and their resultant phase diagram suggested solid solutions and a eutectic system were formed, depending on drug loading. Dissolution studies showed fastest release from the solid solutions; dissolution rates from solid solutions were 12-fold greater than the dissolution of ibuprofen powder whereas the eutectic system gave a 6-fold improvement over the powder. When designing solid dispersions to improve the delivery of poorly-water soluble drugs, the nature of drug:carrier interactions, which are governed by the stochiometry of the composition, can affect the dissolution rate improvement.

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1. Introduction

Solid dispersions can improve the dissolution rates and hence the predicted bioavailability of poorly-water soluble BCS class II drugs. A combination of factors can act to enhance the dissolution of drugs from solid dispersions including particle size reduction, reduced agglomeration, improved wettability and solubility, or dispersion of the drug as either micro-fine crystals, amorphous materials or in a molecular form (Craig, 2002). Different types of carriers and methods are used to prepare solid dispersions (Leuner and Dressman, 2000) and, depending on the physical state of both the drug and carrier, solid dispersions can be classified as eutectic mixtures, solid solutions, amorphous precipitations in a crystalline carrier, glass solutions and glass suspensions, or compound or complex systems. Molecular dispersions can occur when a drug and carrier are miscible in both molten and solid states (Greenhalgh et al., 1999), but these solid solutions are typically only formed at low drug concentrations (Ford, 1986). In addition, solid dispersions

may contain a complex combination of more than one of the above forms.

Ibuprofen and ketoprofen were chosen as model poorly-water soluble drugs which are difficult to wet. Initial experiments used ibuprofen with the structurally related ketoprofen employed to test proposed mechanisms of interaction. The poor-water solubility of ibuprofen (less than 1 mg/ml at 25 °C) necessitates the addition of a surfactant and/or the use of techniques to overcome solubility related dissolution problems. However, excipient selection can be problematic due to, for example, possible esterification of the carboxylic group of ibuprofen (Tedesco et al., 2002).

Intermolecular hydrogen bonds cause ibuprofen to exist as dimers (McConnell, 1974). Thus in a molecular dispersion, these intermolecular bonds need to be broken before a new bond between ibuprofen and the carrier can form. Although ibuprofen exists as a dimer in both solid and liquid states, drug:carrier hydrogen bond formation has been investigated in several studies. Ibuprofen and, to a lesser extent, ketoprofen have both been used as model compounds in solid dispersions with a range of carriers including polyethylene glycols (Shakhtshneider et al., 1996; Khan and Jiabi, 1998) and polyvinylpyrrolidone (Lu et al., 2005; Xu et al., 2007). Typically the focus of these studies is on the production of amorphous or microcrystalline dispersions and consequent improvements in dissolution rate.

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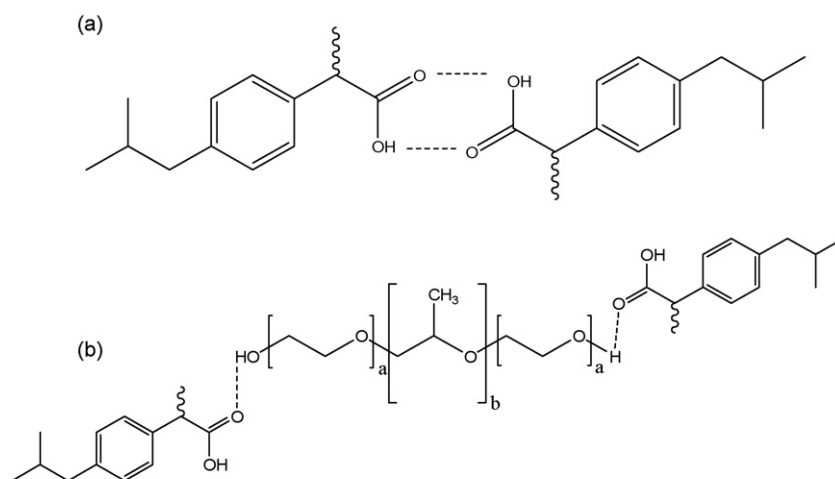
Fig. 1. Schematic representation of (a) hydrogen bonding within the ibuprofen dimer and (b) proposed ibuprofen:poloxamer interaction.

Recently, Rawlinson et al. (2007) explored molecular associations in ibuprofen:polyvinylpyrrolidone dispersions and demonstrated the importance of hydrogen bonding between the hydroxyl moiety of the drug and carboxylic groups in the carrier, and the role of hydrophobic interactions to improve dissolution rates of the drug. These findings were subsequently confirmed by Yu et al. (2009), and by Nakayama et al. (2009) who suggested that hydrogen bonds within ibuprofen crystals converted to ones between ibuprofen and hydroxypropylcellulose in a nanocomposite gel.

Likewise, interactions of ketoprofen with carriers through their carboxylic groups have been studied. Schachter et al. (2003) found that strong intermolecular interactions between ketoprofen and polyethylene oxide 200,000 resulted in disruption of the ketoprofen crystalline lattice and solid solution formation. Martino et al. (2004) and Manna et al. (2007) reported molecular interactions and the formation of an amorphous solid solution of ketoprofen through hydrogen bonding with polyvinylpyrrolidone. Gupta et al. (2002) found that enhanced ketoprofen dissolution from solid dispersion granules was related to ketoprofen hydrogen bonding with silanol groups of an adsorbent (magnesium aluminosilicate) during storage.

Poloxamers (commonly known by their trade names Pluronics®, or Lutrols®) are non-ionic triblock copolymer of polyoxyethylene–polyoxypropylene–polyoxyethylene which have surfactant properties. They are attractive as solid dispersion carriers since they offer improved wettability in addition to molecular dispersion. Passerini et al. (2002) and Newa et al. (2007, 2008) produced dispersions containing 10% ibuprofen in different poloxamers. Whilst these systems improved dissolution rates, molecular interactions and the effects of drug loadings were not explored. The importance of drug loading was shown by Chan and Kazarian (2006); for an ibuprofen/PEG 1500 system in which crystallization of ibuprofen could be avoided, the molar ratio of ibuprofen to PEG could not exceed 2:1, since at this ratio the carbonyl groups of ibuprofen interact stochiometrically with hydroxyl group available at each end of the PEG chain.

In this study, we examine the molecular basis for dispersion formation between ibuprofen or ketoprofen with poloxamers 188 or 407; various mole ratios were selected to range from stoichiometric hydrogen bond formation (2 ibuprofen molecules per 1 poloxamer which carries 2 hydroxyl groups) through to a eutectic composition (Fig. 1). Tammann's diagrams have been used to determine the eutectic composition of ibuprofen with cetyl alcohol (Schmid et al., 2000), stearic acid (Lerdkanchanaporn et al., 2001) and poloxamer 188 (Passerini et al., 2002). Here we use both Tammann diagrams and phase diagrams not only to investigate the composition of eutectic systems but also to determine the limits of solid solutions formation in ibuprofen/poloxamer 407 systems. The influence of these different structures and associations on dissolution rates of the drug was probed.

2. Materials and methods

2.1. Materials

Ibuprofen (BASF) and ketoprofen (Sigma Chemical Company, UK) were used as received; identities were confirmed by DSC peak maxima (melting point 77 °C, and 97 °C respectively). Potassium dihydrogen orthophosphate was from BDH, sodium hydroxide was obtained from Fisher Scientific, and poloxamers 407 and 188, supplied as Lutrol®F127 and Lutrol®F68 and were gifts from BASF, Ludwigshafen, Germany.

2.2. Preparation of solid dispersions and physical mix

Solid dispersions of varying molar compositions were prepared by a melt method; drug was added to molten carrier at 60 °C, with continuous stirring for 15 min until a homogenous dispersion was formed. The dispersion was allowed to solidify at room temperature and then pulverized and sieved; the 355–180 μm fraction was used for all testing. To allow comparison with literature reports, dispersions are reported as both molar ratios and as % (w/w) (see Table 1). In addition, control physical mixtures of 2:1 and 6:1 ibuprofen:poloxamers and 2:1 ketoprofen:poloxamers were prepared by lightly mixing the two components.

2.3. Fourier transform infrared spectroscopy

Fourier Transform infrared spectra were obtained using a Perkin Elmer Spectrum RX1 FTIR spectrometer. Samples of ~2 mg were lightly ground and mixed with dry potassium bromide and then compressed at 12 tonnes in a hydraulic press for 5 min to form discs. Samples were analysed from 4000 cm^{-1} to 400 cm^{-1} and each disc was scanned 10 times at a resolution of 2 cm^{-1}.

Table 1
Mole ratio and their equivalent (%, w/w) concentration of solid dispersions prepared in this study.

Mole ratio of ibuprofen:poloxamer 407	Concentration of ibuprofen (%, w/w)
2:1	3
6:1	10
10:1	15
15:1	20
20:1	25
29:1	33
40:1	40
60:1	50
116:1	66
238:1	80
Mole ratio of ibuprofen:poloxamer 188	**Concentration of ibuprofen (%, w/w)**
2:1	5
6:1	12
28:1	40

2.4. Differential scanning calorimetry

DSC analyses were performed on a Perkin Elmer DSC 7 series calorimeter. The instrument was calibrated using indium, and samples were heated from 20 °C to 100 °C at 10 °C/min under a nitrogen purge at 20 ml/min. Enthalpies of fusion and melting temperatures were measured and used to construct relevant phase diagram.

2.5. Powder X-ray diffractometry

Powder X-ray diffraction patterns were collected using a Bruker D8 advance diffractometer with Cu-Kα radiation ($\lambda = 1.5$ A°) over 5–55° 2θ with a step size of 0.017° 2θ; the time for each step was 0.4 s, and total collection time was 20 min, at 40 mV, 30 mA. Samples were rotated at 30 rpm.

2.6. In vitro dissolution study

Dissolution of pure ibuprofen powder, solid dispersions and physical mixtures was studied using dissolution apparatus II (USP, paddles) with 900 ml of pH 5.0 phosphate buffer at 37 ± 0.5 °C stirred at 50 rpm; the buffer was selected to slow drug dissolution and allow greater discrimination between the formulations. Dissolution was performed under sink conditions using samples containing 10 mg ibuprofen, equivalent to <10% of its solubility in the buffer. Ibuprofen released was assayed by UV spectrophotometry (Varian 50 Bio) at 222 nm and quantified using a calibration curve in the same media. 5 ml samples were removed from the dissolution medium and filtered (Millipore, 0.45 μm) before analysis and an equal volume of fresh buffer, maintained at 37 °C, was added to the dissolution medium to maintain sink conditions.

3. Results and discussion

All solid dispersions were homogenous; independent assays of three samples taken from any dispersion showed even drug distribution within each system.

Solid dispersions of ibuprofen prepared with poloxamer 407 were analysed using FTIR spectroscopy, and compared with ibuprofen powder. The pure drug showed a characteristic absorption band at 1720 cm^{-1}, assigned as the carbonyl stretching vibration of dimerised ibuprofen resultant from hydrogen bonding between two ibuprofen molecules. Similar spectra were seen for solid dispersions with drug:carrier mole ratios > 29:1 (Fig. 2) indicating that crystalline ibuprofen is preserved in these systems despite the apparent complete miscibility of ibuprofen with poloxamer in the molten state. In addition, characteristic absorption bands of polox-
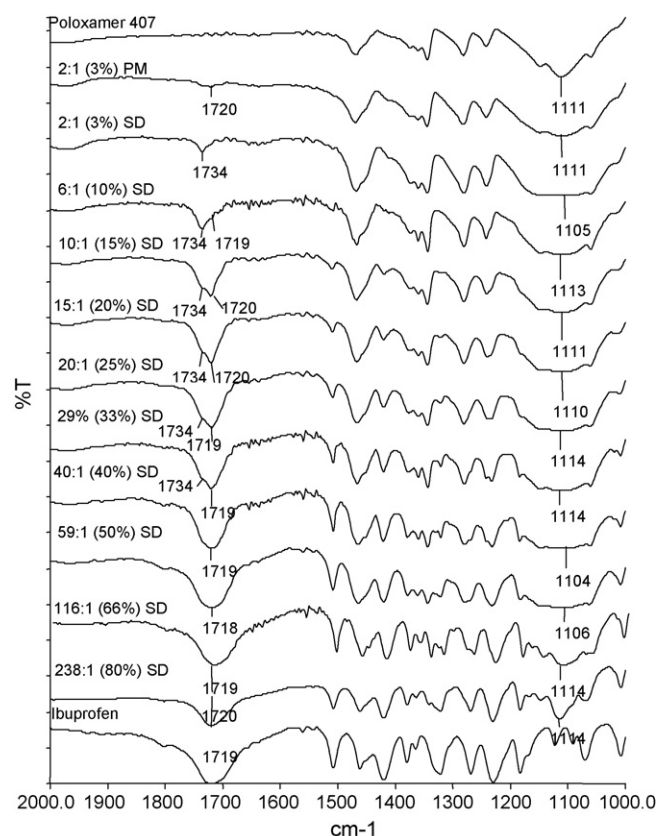

Fig. 2. FTIR spectra for poloxamer 407, ibuprofen, 3% physical mixture (PM) and solid dispersions (SD) containing high drug loadings showing the ibuprofen dimerised hydrogen bond at ~1720 cm^{-1} and low drug loadings showing drug:poloxamer hydrogen bonding at 1734 cm^{-1}.

amer 407 at around 2887 cm^{-1} and 1110 cm^{-1} from C–H and C–O stretching vibrations respectively were unchanged in these systems.

As the ibuprofen:poloxamer mole ratio decreased, a new peak at 1734 cm^{-1} (as a shoulder on the 1720 cm^{-1} feature) was observed in the spectra of the 29:1 drug:poloxamer mole ratio system and the intensity of the 1720 cm^{-1} ibuprofen dimer peak decreased. This new feature strengthened as the mole ratio decreased, and became the predominant peak at a 2:1 mole ratio where the 1720 cm^{-1} ibuprofen dimer absorption was essentially lost, as shown in Fig. 2. This shift in the carbonyl stretching vibration for the 2:1 ratio (equivalent to 3% (w/w) drug load), indicates complete disruption of ibuprofen dimer hydrogen bonds, replaced by ibuprofen:poloxamer bonding.

Clearly hydrogen bonding between ibuprofen and poloxamer was present in all systems that displayed the absorption band at 1734 cm^{-1}, and indeed was probably present in the drug:carrier compositions > 29:1, but was masked by the very strong drug:drug carbonyl stretching mode. At 3% drug loading, the mole ratio of drug:poloxamer 407 is 2:1. Since the poloxamer possesses two terminal OH groups it is expected that 2 ibuprofen molecules will hydrogen bond with one poloxamer molecule. As the concentration of drug increased, the excess ibuprofen above this stochiometry forms dimers, shown by the relative intensity of the 1734 cm^{-1} mode to the 1720 cm^{-1} dimer mode decreasing with increasing drug concentration; beyond the 2:1 drug loading, hydrogen bonding of ibuprofen with poloxamer was constant and the additional drug added to the dispersions was present as drug:drug dimers. These observations are consistent with those of Ozeki et al. (1997) who detected hydrogen bond formation in solid disper-
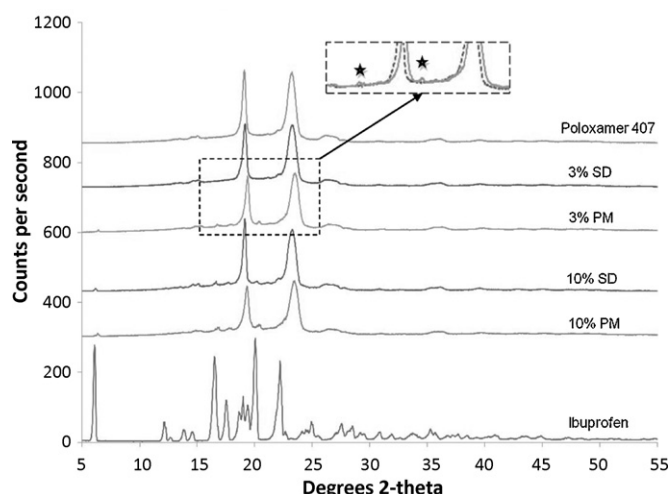
Fig. 3. X-ray diffractograms of poloxamer 407, ibuprofen, physical mixture (PM), solid dispersion (SD) of 3%, and 10% ibuprofen:poloxamer systems, equivalent to 2:1 and 6:1 mole ratios respectively. Enlargement shows the loss of ibuprofen crystalline diffraction peaks in the 2:1 solid dispersion compared to the presence of these features in the physical mix of the same mole ratio.

sions between flurbiprofen and the carriers polyethylene glycol or hydroxypropyl cellulose.

A physical mixture of 3% ibuprofen with 97% poloxamer 407 showed predominantly the dimerised ibuprofen peak indicating that light mixing for short periods of time is not enough to disrupt the dimerised ibuprofen to form hydrogen bonds between the drug and poloxamer and also demonstrates that, if present, low levels of crystalline ibuprofen would be detected in our solid dispersions.

The molecular and crystalline nature of ibuprofen in our solid dispersions was also examined by X-ray diffractometry of 2:1 and 6:1 mole ratio systems, and using physical mixtures of the same mole ratio as well as the drug and carrier alone.

Ibuprofen showed numerous strong diffraction peaks, including at ~6°, 12°, 13.5°, 16°, 17°, 18°, 19°, 20°, 20.5°, 22°, and 22.5° 2θ. Poloxamer 407 showed only two prominent peaks at ~19°, and 23° 2θ, with additionally a broad halo indicative of crystalline domains within the amorphous polymeric material. The 2:1 mole ratio (3% ibuprofen load) solid dispersion showed only the poloxamer 407 diffraction peaks, whereas the diffractograms of the physical mixture at the same mole ratio shows the typical diffraction peaks of ibuprofen, as shown in Fig. 3. The 6:1 mole ratio (10% drug loading) dispersion and physical mixture both show the diffraction peaks of ibuprofen in addition to the poloxamer features. These observations again show loss of ibuprofen crystals in the 2:1 mole ratio dispersion.

Thermal analysis of 3% ibuprofen/poloxamer 407 solid dispersions showed a single endothermic peak from the poloxamer melting; this melting point is depressed as the concentration of ibuprofen increases (Fig. 4). The presence of only a single endothermic peak in the thermograms of solid dispersions has been attributed to either dissolution of drug in the molten carrier during analysis, drug distribution in an amorphous form or the formation of a solid solution (Shah et al., 2007; Liu et al., 2006; Ahuja et al., 2007). Consistent with our infrared data and X-ray analysis, the single melting peak in our DSC studies shows that, at 3% drug loading, our dispersion was predominantly a solid solution. The thermogram of the 10% system also showed only a single clear endothermic peak from the poloxamer but the melting point was further depressed and a small shoulder appeared to be developing on the melting peak. As the concentration of ibuprofen increased to 15%, a second small melting peak developed at around 45 °C, which became more prominent at 20% drug content. This melting
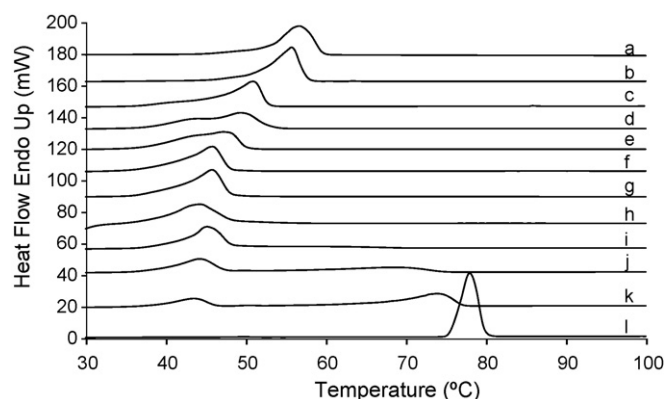

Fig. 4. DSC thermograms of (a) poloxamer 407, and solid dispersions containing ibuprofen at varying drug loads; (b) 3%, (c) 10%, (d) 15%, (e) 20%, (f) 25%, (g) 33%, (h) 40%, (i) 50%, (j) 66%, (k) 80% and (l) ibuprofen powder.

temperature is appreciably lower than that of pure ibuprofen or poloxamer 407, suggesting that it relates to a eutectic system. Dispersions with 25–40% drug loads showed only the eutectic melt and any excess ibuprofen or poloxamer beyond the eutectic composition could not be detected due to the limits of DSC sensitivity. However between 50% and 80% ibuprofen loads, two endothermic peaks, of the eutectic system and that of excess ibuprofen, were easily detected, (Fig. 4), though the excess ibuprofen melted at a lower temperature than pure ibuprofen since the poloxamer acts as an impurity to depress the melting point of the pure drug.

The eutectic composition was determined utilizing a Tammann's diagram; plotting enthalpies of fusion of the eutectic melt versus the concentration of drug in the systems, the eutectic composition was found to be at ~33% drug loading, as shown in Fig. 5. Several studies have reported eutectic systems formed between ibuprofen and carriers, typically with ibuprofen contents between 30 and 35% (Shakhtshneider et al., 1996; Passerini et al., 2002; Newa et al., 2007, 2008; Ho et al., 2008), which are consistent with the results obtained in this study.
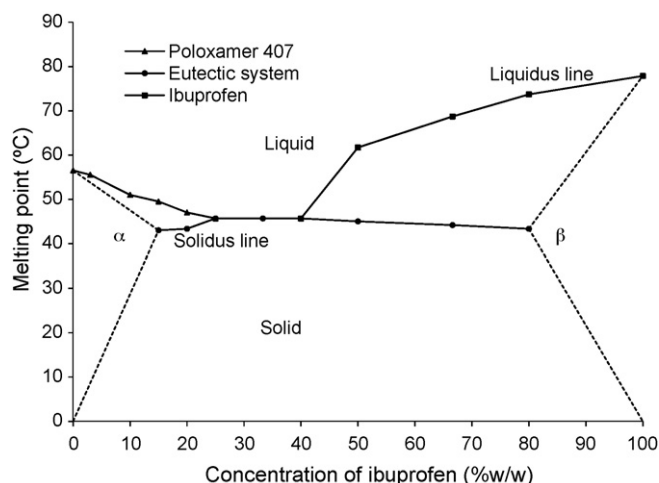
From our data, a phase diagram of ibuprofen:poloxamer 407 was constructed by plotting melting peaks from thermograms of ibuprofen powder, poloxamer 407, and solid dispersions versus % (w/w) drug load (Fig. 6).

The phase diagram shows the limits of solid solution and eutectic mixture formation in the system, in addition to the regions of
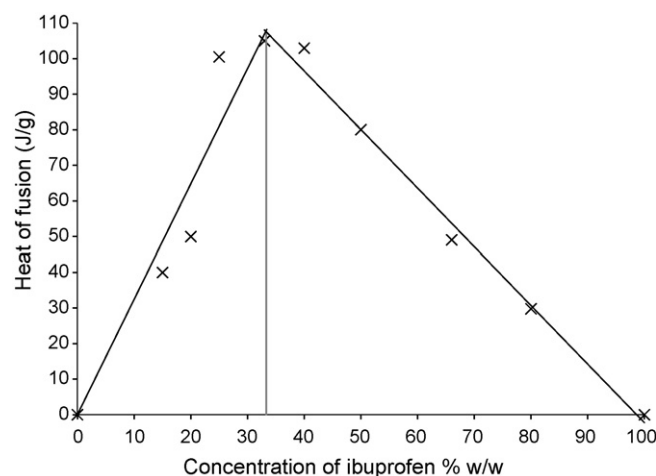
Fig. 5. Tammann's diagram for ibuprofen:poloxamer 407 solid dispersion systems from which the eutectic composition is shown to be approximately 33% ibuprofen in the carrier.

Fig. 6. Phase diagram of ibuprofen:poloxamer 407 systems showing the regions containing solid solutions of ibuprofen in the carrier (α) and of the carrier in ibuprofen (β).

Table 2
Initial dissolution rate constants (K, 0–5 min) for ibuprofen powder, 3% physical mixture of ibuprofen in poloxamer 407, eutectic and solid solution systems.

System	K initial (min)$^{-1}$
Ibuprofen	0.025 ± 0.0045
Eutectic composition	0.142 ± 0.016
Solid solution	0.292 ± 0.064
Physical mixture	0.035 ± 0.0086

liquid and solid phases. The liquidus line results from ibuprofen melting and, on the other side the boundary (solidus line), all systems solidify. Ibuprofen and poloxamer 407 form solid solutions with either a low ibuprofen load (α, ibuprofen in poloxamer), or a high load (β, poloxamer in ibuprofen). In this study only systems from the α region were used, since the β region systems were problematic to prepare.

We explored the effects that different molecular associations within solid dispersions (i.e. solid solutions and eutectic composition) had on ibuprofen dissolution; all solid dispersions with drug loads varying from 3 to 80% improved the dissolution rate of the drug compared with the starting powder. Focusing on drug release from the solid solution and the eutectic composition, Fig. 7 shows dissolution curves of these systems which contain 3% (2:1 mole ratio), and 33% (29:1 mole ratio) ibuprofen respectively and, for comparison, dissolution of a physical mixture of 3% ibuprofen in poloxamer 407 and ibuprofen powder alone. There are clear differences in drug release from the two different types of solid dispersion, especially in the initial stage of dissolution; 59% and 32% of the ibuprofen was released during the first 2 min from solid solution and eutectic systems respectively, whilst only 11.5 and 8% release was obtained from the physical mix and ibuprofen powder

Fig. 7. Dissolution profiles of (a) ibuprofen powder, (b) physical mix containing 3% drug, (c) 33% drug:carrier dispersion (eutectic composition), and (d) 3% drug:carrier dispersion (2:1 mole ratio) in pH 5.0 phosphate buffer. Values are mean $\pm$SD, $n = 3$.

respectively. It is also evident that the overall dissolution rate of the ibuprofen powder was slow, with only 42% dissolved within 60 min compared with near complete dissolution from both solid dispersion systems over the same period. The improved dissolution from the dispersions was not simply due to enhanced wetting of the drug in the presence of the poloxamer since the physical mix containing 3% ibuprofen showed a relatively minor improvement in drug dissolution compared with that obtained from the solid dispersion with the same drug and carrier content. Thus, the loss of crystallinity demonstrated by infrared and X-ray analyses in the 2:1 dispersion results in an enhanced drug dissolution rate.

Dissolution kinetics were calculated for ibuprofen powder, the physical mixture and solid dispersions applying the first order model; initial dissolution rate constants are from drug release during the first 5 min (Table 2). From these values, release rates of ibuprofen were always higher from the solid dispersions compared with pure drug or the physical mix, with the eutectic composition providing a 6-fold increase in the initial dissolution rate whereas the rate for the solid solution was 12-fold greater than the drug powder. This fast initial rate for the solid solution is attributable to the hydrogen bonding between ibuprofen and poloxamer 407, which breaks relatively easily during dissolution compared with the ibuprofen dimer present in the eutectic systems or pure drug. For the eutectic composition, two mechanisms operate sequentially and explain the biphasic release pattern of this system; initial rapid release results from the molecularly distributed drug (as in the solid solution) followed by release of the remaining microcrystalline drug. Dissolution enhancement from solid dispersions prepared with poloxamers has previously been attributed to a reduction in crystalline drug particle size (Passerini et al., 2002; Shah et al., 2007; Newa et al., 2007). Several factors beside particle size reduction are well known to improve dissolution of various drugs from solid dispersions, including improved wetting through intimate contact between a hydrophilic carrier and the drug (Sekiguchi and Obi, 1961; Serajuddin et al., 1988; Ahuja et al., 2007). Our studies show that, in addition to these factors, different molecular associations impact significantly on drug release from solid dispersions, and that wetting by the poloxamer had a minimal effect on drug release, consistent with the literature (Passerini et al., 2002). Dissolution from the physical mix showed only a 1.4-fold improvement in the initial release rate of ibuprofen. This result is simply explained by solubility studies where ibuprofen solubility increased 1.4- and 1.3-fold when the equivalent amount of poloxamer was added to the buffer or water respectively.

To explore further these molecular interactions, poloxamer 188 which has a lower molecular weight than 407, (poloxamer 188 of average molecular weight 8500 compared with average molecular weight of 12600 for poloxamer 407) was used. Thus, the 2:1 mole ratio ibuprofen:poloxamer 188 system contained 5% drug, whereas the equivalent system with poloxamer 407 required only 3% drug. Despite the difference in drug content, the FTIR spectrum of the 2:1 mole ratio ibuprofen:poloxamer 188 dispersion was similar to that with poloxamer 407 and again shows the hydrogen-bonded drug:carrier carbonyl stretching mode at 1734 cm^{-1} (Fig. 8). On increasing the drug content in the system, the ibuprofen dimer feature at 1720 cm^{-1} again develops, initially as a small shoulder in
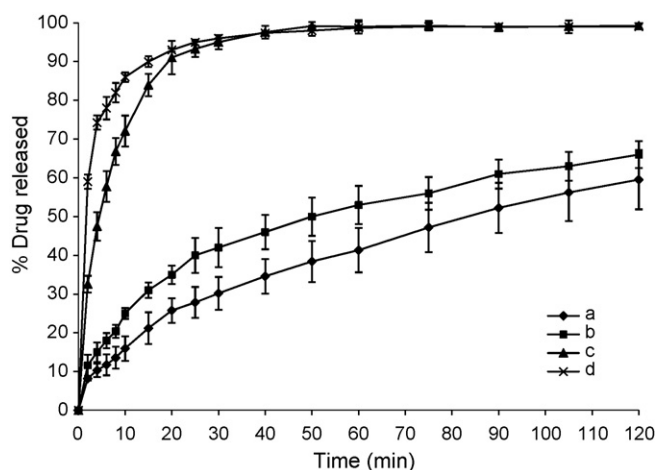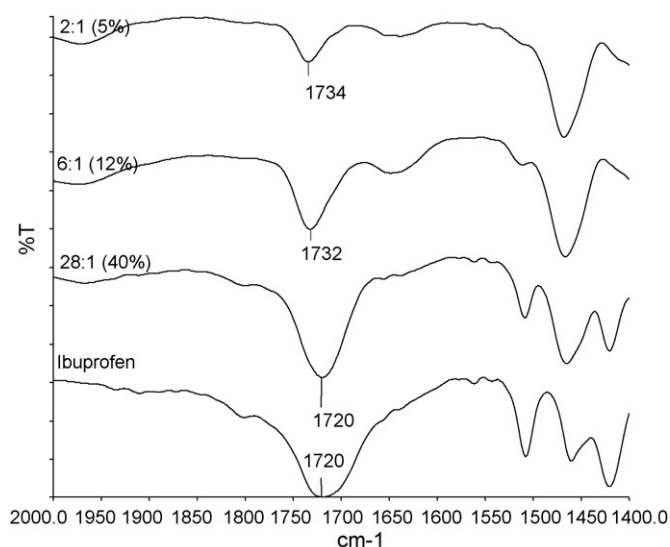
Fig. 8. FTIR spectra of ibuprofen and solid dispersions of 2:1, 6:1 and 28:1 mole ratio ibuprofen in poloxamer 188.

the spectrum of the 6:1 (12% drug content) system and then as the major peak at higher drug loads (e.g. 28:1, 40% drug content). As previously discussed, it is probable that the drug:carrier bonded fraction of these higher loaded dispersions is masked by the strong ibuprofen dimer carbonyl stretching modes. Clearly these findings demonstrate that drug loading *per se* is of limited value when developing solid solutions, rather the stochiometry of the composition drives the nature of the solid dispersion formed and explains literature observations of crystalline ibuprofen in solid dispersions (Passerini et al., 2002; Newa et al., 2007, 2008).

Further solid dispersions were prepared using ketoprofen with both poloxamers; ketoprofen (MW 254) is a larger molecule that ibuprofen (MW 206) and so the 2:1 ketoprofen compositions have higher drug loadings (i.e. 4% and 6%) than the corresponding ibuprofen dispersions (3% and 5%). Ketoprofen again exists in a dimerised form (Manna et al., 2007) shown by a strong FTIR carbonyl stretching mode at around 1696 cm^{-1}. The 2:1 dispersions, with either

poloxamer, (4% or 6%) lost this spectral feature which was replaced by a drug:carrier hydrogen bond carbonyl band at 1734 cm^{-1}, again consistent with the same mode in the ibuprofen dispersions (Fig. 9). As before, these infrared studies were complemented by X-ray powder diffractometry. No crystalline diffraction peaks for ketoprofen were detected in 2:1 dispersions with either poloxamer whereas the physical mixes at the same composition clearly demonstrated peaks resulting from the crystalline drug. Thus the interactions described above are not a specific feature of ibuprofen, but apply to other carboxylic acids which are capable of interacting with the terminal hydroxyl modes on the poloxamers, and supports a "one drug molecule per poloxamer end group" model for solid solution formation.

4. Conclusions

Solid dispersions have been produced using poloxamers 188 and 407 as carriers for ibuprofen and ketoprofen. By altering the ratio of drug:carrier, different forms of solid dispersions were generated with the 2:1 mole ratio compositions producing solid solutions for all drug:poloxamer combinations employed. At higher drug contents, other forms of solid dispersions co-exist with the solid solutions, including eutectic systems and microcrystalline drug in the carriers, depending on the ratio of drug to carrier. All our dispersions improved the dissolution rate of ibuprofen compared to drug alone or in a physical mix with the poloxamer, but the solid solution systems provided the fastest release whereas the eutectic composition also offered a dissolution rate improvement, but to a lesser extent than the solid solution system. Our results demonstrate that, whilst solid dispersions can be produced using various drug loadings, it is the stochiometry of the composition which affects the molecular interactions within these systems, and that this impacts on the dissolution properties seen from solid dispersions.

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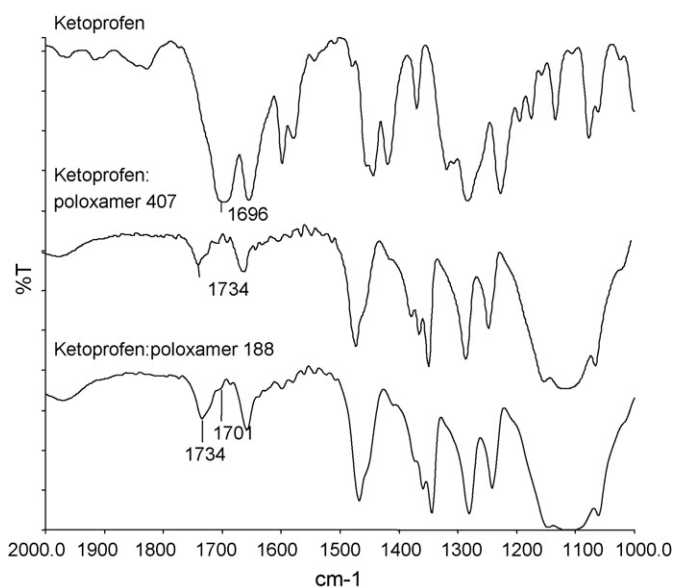
Fig. 9. FTIR spectra of ketoprofen and 2:1 mole ratio solid dispersions of ketoprofen:poloxamer 407 and ketoprofen:poloxamer 188 (equivalent to 4% and 6% (w/w) ketoprofen loads respectively).

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