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Drug-fatty acid salt with wax-like properties employed as binder in melt granulation

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Abstract

The tacky and deformable properties of a wax-like drug-fatty acid salt, propranolol oleate (POA), make particle size reduction and separation challenging. The aim of this study was to investigate the use of POA as binder in a melt granulation procedure to improve processing properties. POA is a suitable candidate for binder phase in melt granulation with a melting temperature of 50–56°C. Small batches (ca 30 g) were manufactured using a high shear mixer with lactose monohydrate as the substrate phase. Optimum uniformity of drug content and minimum friability were found at 10% w/w POA binder concentration. POA melt granules exhibited a >10-fold increase in the rate of in vitro dissolution at pH 7.4 with 0.2% w/v sodium lauryl sulphate compared with raw POA. The increased drug surface area in granular form was thought to be responsible for the change in dissolution behaviour. This study has demonstrated that melt granulation using POA as binder is a viable process which leads to beneficial changes in dissolution behaviour for the lipophilic drug-fatty acid salt.

Keywords: Oleic acid; Drug-fatty acid salt; Melt granulation; Low melting point binder; In vitro dissolution

1. Introduction

The bioavailability of orally administered drugs can be improved by formulation with lipids (Charman et al., 1997). The mechanism of such lipid effects may be biological (e.g. altered gastrointestinal transit time, increased lymphatic drug uptake), physical (e.g. solubilisation into, or partitioning between, oil and water phases) or chemical (e.g. complex formation). An understanding of the biological, physical and chemical properties of lipids and lipid-based formulations is essential for the successful pharmaceutical application of such systems.

Co-formulation of the β-blocker drug propranolol and oleic acid led to an improvement in oral drug bioavailability in humans compared with both immediate and sustained release formulations (Barnwell et al., 1996). Hypotheses abound

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as to the mechanism of bioavailability change, notably reduced first-pass metabolism due to lymphatic drug transport (White et al., 1991; Barnwell et al., 1996) or gut and/or liver isoenzyme saturation (Tucker, 1993). Formation of a drug-fatty acid salt, propranolol oleate (POA), has been demonstrated in propranolol/oleic acid binary mixtures, presenting a possible chemical mechanism of bioavailability change (Crowley et al., 1999). POA has a low melting temperature in the region of 50–56°C and exists as a conformationally disordered mesophase at room temperature (Crowley et al., 1999, 2000). The tacky and deformable properties of POA which draw comparison to waxes make particle size control difficult. The current work was undertaken in order to prepare a POA-containing oral dosage for investigation of the effect of oleate salt formation on propranolol bioavailability in vivo. Our objectives were two-fold — to investigate a means of overcoming the poor particle size control of POA, and to maintain or improve the dissolution properties of POA.

A common approach to improving particle size control is granule formation. Granulation also enables the formulator to prepare particles that possess the desired shape and surface properties, allowing other pharmaceutical properties to be manipulated. Examples include reduction of segregation in polydisperse powders, and improvement of powder flow and compression properties (Summers, 1988). The most commonly used granulation methods are wet and dry granulation. Wet granulation involves the incorporation of liquid binder phase into a powder substrate, followed by solvent removal. An aqueous binder phase is usually employed, often leading to lengthy and costly drying. The possibility of physical or chemical changes resulting from the presence of water is a further drawback of this method (Ghebre-Sellassie, 1989). Dry granulation uses mechanical force alone to bring about particle agglomeration into large slugs or sheets which are milled to the desired granule size. Substrate stability under high compression forces is clearly needed.

Another granulation method that is encountered less frequently in pharmaceutical sciences is melt granulation, whereby a molten binder is introduced to the powder substrate followed by a cooling stage. Though similar to wet granulation in terms of the number of phases and equipment employed, fundamental differences between melt and wet granulation exist. For instance, the absence of an ex vivo liquid phase in melt granulation results in different ratios of liquid binder to solid substrate. Melt granule porosity is also likely to be different as no solvent is removed in the melt granulation process. Thomsen et al. (1994) proposed that materials melting in the range 45–100°C are suitable binder materials for melt granulation. Examples of binders used in the pharmaceutical literature include polyethylene glycol (PEG), microcrystalline wax and a range of lipids (e.g. stearic acid, glyceryl-stearate, -monostearate, -palmitostearate) (Rubinstein and Musikabhumma, 1980; Schæfer et al., 1990; El-Shanawany, 1993; Thomsen et al., 1994; Zhou et al., 1996). With its low melting temperature, POA qualifies as a potential binder for melt granulation.

In this study, the use of POA as a melt granulation binder phase was evaluated. A range of POA binder concentrations was investigated, using the uniformity of binder distribution and granule friability as tests for optimum binder concentration. In vitro dissolution data are presented and the biopharmaceutical implications of formulating a drug-fatty acid salt in melt granular form are discussed.

2. Materials and methods

2.1. Materials

Propranolol base, prepared as described by Crowley et al. (1999), and oleic acid of approximately 94% purity (Croda Oleochemicals, Hull) were used to manufacture propranolol oleate (POA). Equimolar quantities of base and acid were dissolved in chloroform followed by solvent evaporation under vacuum at 25°C for 24 h. The waxy solid product was confirmed as POA using differential scanning calorimetry (Perkin–Elmer DSC-7, Beaconsfield, Buckinghamshire) with ex-

trapolated onset temperature and enthalpy of melting values of 50.2°C (σ_{n-1} 0.7, $n=6$) and 71.6 J/g (σ_{n-1} 2.3, $n=6$) obtained. These data were significantly lower than the corresponding values presented by Crowley et al. (1999), due to the use of a lower grade of oleic acid in the current work. However, no differences were found in the X-ray diffractograms or Fourier-transform infrared spectra for POA prepared from different grades of oleic acid.

Difficulties were encountered when trying to isolate a narrow size fraction of POA due to its waxy nature. Gentle grinding of POA using a pestle and mortar was found to be the only viable method of particle size reduction, though the yield was low. Following repeated grinding, a 420–1000-μm sieve size fraction was isolated of sufficient quantity for use in dissolution studies.

Melt granulation substrate material was lactose monohydrate (90–125 μm, DMV, Holland) as it is stable during such processing at 70°C (Schæfer et al., 1990). Sodium lauryl sulphate (SLS) of approximately 95% purity (Sigma, Poole, Dorset) was used in the in vitro dissolution test medium with an SLS grade of $>99\%$ purity (BDH, Poole, Dorset) used in the high performance liquid chromatography (HPLC) mobile phase. Solvents used in the HPLC mobile phase and for POA preparation were of AnalaR grade (BHD, Poole, Dorset). Water was deionised and double distilled using a Fi-Streem still (Fisons, UK).

2.2. Melt granulation methodology

Melt granulation was carried out in a jacketed high shear mixer, the mixer torque rheometer (MTR, Caleva, Sturminster Newton, Dorset), consisting of two 90/180 geometry blades with metal surfaces coated with polytetrafluoroethylene. The MTR accommodates small batch sizes in the range 20–40 g, so is suited to small-scale pilot studies. In addition, rheological information recorded via a torque arm attached to a mixing blade can be used for formulation and process optimisation (Parker et al., 1990). Mean torque was measured for 30 s at 1-min intervals with a blade speed of 60 rpm. Experimental mean torque values were calculated by subtracting the measured output from a baseline value collected for heated substrate material without binder.

Batches were prepared with binder concentrations ranging from 5 to 15% w/w POA, maintaining a total batch weight of 31 g. Lactose monohydrate substrate was heated to 65–70°C in the MTR operating at a mixing speed of 60 rpm. Temperature was controlled by pumping water from a water bath maintained at 70°C around the body of the MTR. POA binder was heated separately to 70°C and then poured onto the substrate as mixing continued. After 4-min mixing, the heated wet mass was transferred to an oven maintained at 70°C and passed through a 1410-μm mesh sieve to disrupt large aggregates. Finally, the wet mass was spread onto grease proof paper at room temperature and allowed to cool under ambient conditions. A 355–500-μm size fraction was separated by 20-min shaking on a $\sqrt{2}$ sieve stack (Endecotts, London) and stored in amber bottles under ambient conditions for further analysis.

2.3. Measurement of granule binder distribution

Samples (2 mg) of the 355–500-μm granule size fraction were dissolved in 100 ml phosphate buffer, pH 7.4, containing 0.2% w/v SLS and the concentration of drug in solution was measured by HPLC. The mass of POA per granule sample was calculated for six samples. HPLC was carried out on an Integral 4000 automated system (Perkin–Elmer), measuring propranolol concentration in solution by UV detection at 288 nm. A 50-μl sample was injected onto a Zorbax 3 μm ODS column of dimensions 250 × 4.6 mm (i.d.) (Jones Chromatography, Mid Glamorgan). The mobile phase of 60/40 acetonitrile/0.05 M phosphate buffer pH 3, with 4 mM SLS produced a propranolol retention time of 4.7 min when operating at a flow rate of 1.4 ml/min. A calibration curve was constructed in the range 1–100 μM using six standard propranolol solutions (linear regression consistently gave $R^2>0.998$).

2.4. *Measurement of granule friability*

A 3-g sample of the 355–500-μm granule size-fraction was subjected to 5-min agitation at 90 rpm in a Roche friabilator (Copley Instruments, Nottingham) followed by 5-min shaking on a $\sqrt{2}$ sieve stack (Endecotts). The percentage weight of the 355–500-μm size fraction intact, and percentage oversize and undersize, were calculated.

2.5. *Scanning electron microscopy*

Lactose monohydrate and POA melt granule samples were fixed to metal stubs and coated with gold under vacuum, followed by SEM analysis using a Hitachi S-520 (Tokyo, Japan).

2.6. *In vitro dissolution testing*

In vitro dissolution testing was carried out in accordance with the USP XXIII monograph specifications (apparatus 2, paddle method) using the Caleva Model 7ST (Sturminster Newton). The test medium comprised 900 ml pH 7.4 ± 0.05 phosphate buffer containing 0.2% w/v SLS. Paddle rotation speed was 75 rpm and the temperature was maintained at 37 ± 0.5°C. POA samples (20–40 mg, in raw form or an equivalent POA dose in granular form) were poured onto the media surface at time zero. Aliquots (5 ml) of dissolution medium were removed via stainless steel tubes to plastic syringes at time zero and at regular intervals through the test duration. Following sampling, an equal volume of test media was returned to the vessel. Sampling tube tips with 70-μm PE line prefilters (Sigma Techware, Poole, Dorset) were positioned approximately halfway between the media surface and base and within 1 cm of the vessel wall. Samples of dissolution medium were passed through a 0.2-μm cellulose nitrate membrane filter (Whatman, Maidstone, Kent) and propranolol concentration in solution was determined using the HPLC method described in Section 2.3. The in vitro dissolution test was performed on four occasions for each material.

3. Results

3.1. *Mean torque measurement during POA melt granulation*

Mean torque is plotted against time for POA binder concentrations 5–15% w/w POA in Fig. 1. At the lowest binder concentration, 5% w/w POA, a slight increase in mean torque was found on mixing, reaching 0.013 N m after 4 min. Mean torque increased rapidly with time at all other binder concentrations, reaching a maximum value after 2–3 min. The maximum values of mean torque did not differ greatly for 10, 12.5 and 15% w/w POA, ranging from 0.079 to 0.092 N m. However, substantial visual differences in the massing properties at these compositions were observed, notably pronounced overwetting at 15% w/w POA.

3.2. *Uniformity of binder distribution in POA melt granules*

The mean binder concentration, standard deviation and coefficient of variation for melt granulation batches prepared using 5–15% w/w POA are given in Table 1. The lowest coefficient of variation, and thus optimum dose uniformity, was obtained at 10% w/w POA.

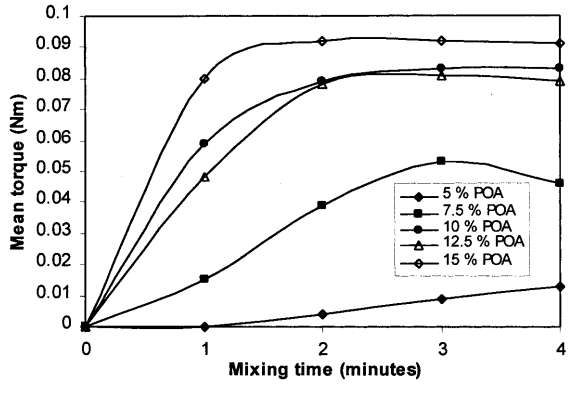

Fig. 1. Mean torque vs. time profiles obtained using the mixer torque rheometer (MTR). Data given for melt granulation systems containing 5–15% w/w POA as melt binder.

Table 1
Summary of dose uniformity and friability measurements for melt granulation batches containing 5–15% w/w POA as melt binder[a]

Dose uniformity				Friability		
POA concentration (% w/w)	Measured concentration (% w/w)	S.D. (σ_{n-1})	Coefficient of variation	<355 μm (%)	355–500 μm (%)	>500 μm (%)
5.0	3.97	0.27	6.7	56	41	3
7.5	7.27	0.31	4.2	47	50	3
10.0	9.66	0.23	2.4	19	73	8
12.5	11.10	0.41	3.7	62	35	3
15.0	12.86	0.56	4.4	12	60	28

[a] Six replicate injections of 1.34 μM propranolol solution (approximately equivalent to 5% w/w POA in 100 ml solution) demonstrated the following accuracy and precision, mean, 1.28 μM; S.D., 0.0139; coefficient of variation, 1.09.

3.3. Friability of POA melt granules

The percentage weight of 355–500-μm sieve fraction intact following friability testing along with percentage over- and undersize are given for melt granulations of composition 5–15% w/w POA in Table 1. Substantial differences in granule friability were found in the range of binder compositions studied. Granule friability was lowest at 10% w/w POA, for which 73% w/w of the 355–500-μm sieve fraction was retained. POA melt granules were found to be fragile even at the optimum binder concentration of 10% w/w POA, so would be prone to particle size change during rigorous processing. The 15% w/w POA granulation yielded a high percentage oversize of 28% w/w, indicating pronounced adhesive/cohesive properties. The unctuous behaviour of POA appeared to predominate at 15% w/w POA, providing additional evidence of overwetting at the highest binder concentration.

3.4. Scanning electron microscopy

The morphology and surface properties of 10% w/w POA melt granules were visualised using SEM. Melt granule micrographs are presented at two magnifications in Fig. 2a and b along with a lactose substrate particle micrograph in Fig. 2c. The high concentration of POA binder in the regions of close substrate particle contact is evident in Fig. 2a and b. Substrate particle surfaces appear smoother in these micrographs in comparison to the coarse surface of lactose substrate before granulation (Fig. 2c). This observation suggests that POA is thinly distributed throughout the whole granule surface, in which case, POA will have a large surface area in melt granule form. An extensive distribution of POA on the granule surface would explain the adhesive and cohesive nature of 15% w/w POA melt granules noted to in the previous section.

3.5. In vitro dissolution testing of raw POA and 10% w/w POA melt granules

Preliminary dissolution testing demonstrated that the propranolol oleate ion pair of POA dissociates in solution at pH 1.2 (Crowley, 1999). POA instability at this pH would be predicted on consideration of the pK_a values of 9.5 and 5.0 for propranolol and oleic acid, respectively (Pharmaceutical Codex, 1994; Alvarez-Núñez and Yalkowski, 1997). As the pharmaceutical advantages of a drug-fatty acid salt would be lost on POA breakdown at low pH, it is essential that a POA drug delivery system ensures intestinal release.

In vitro dissolution testing was carried out at 37°C using pH 7.4. In the absence of surfactant, an immiscible liquid phase formed that was shown to contain high concentrations of intact POA (Crowley, 1999). Drug concentrations in the bulk medium were substantially reduced as a consequence, so it was necessary to modify the test medium by inclusion of a surfactant. SLS (0.2%

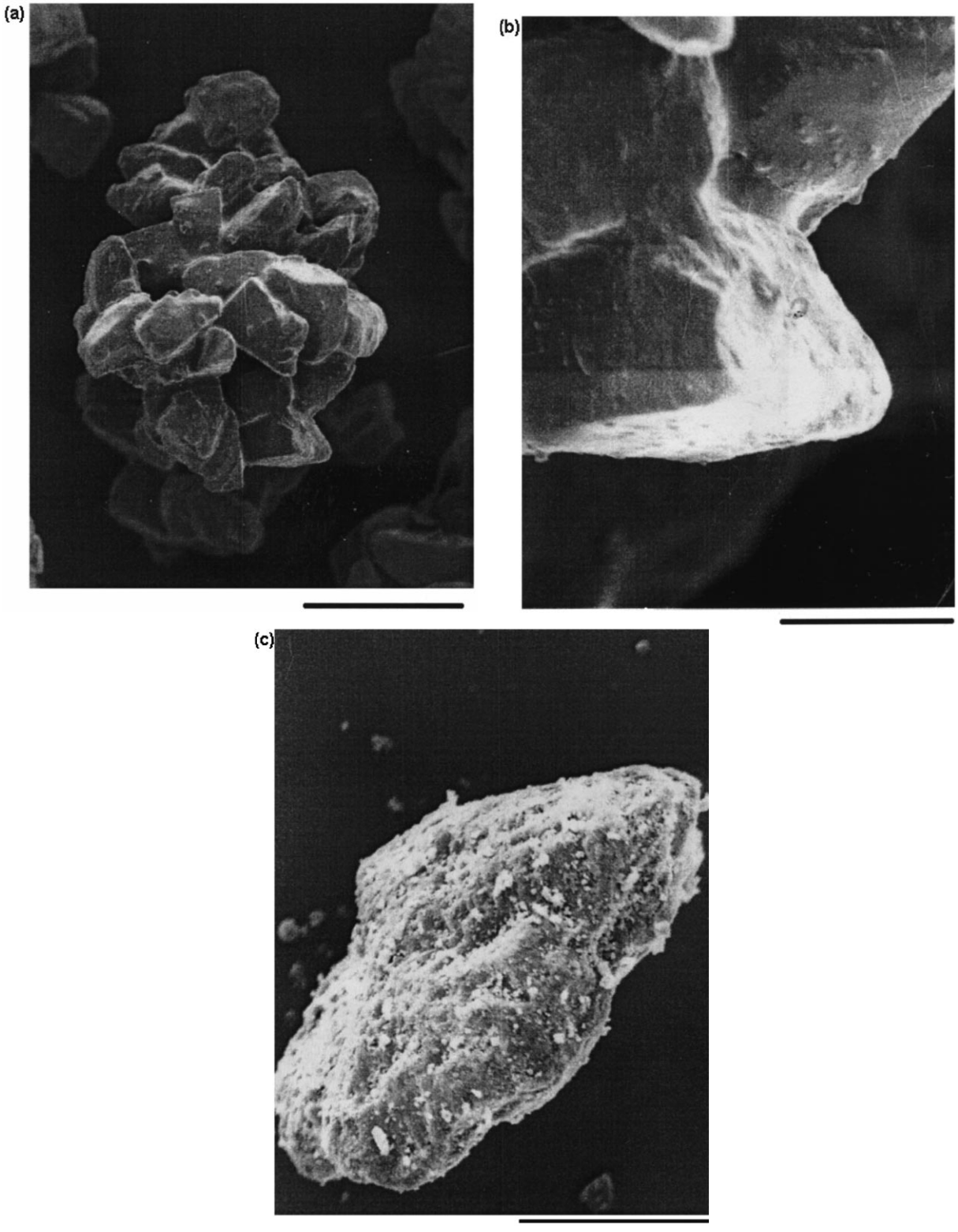

Fig. 2. Scanning electron microscopy (SEM) images of 10% w/w POA melt granules (a and b) and lactose monohydrate substrate particle (c). Scale bar represents (a) 188; (b) 43; (c) 43 μm.

w/w) was found to solubilise the immiscible liquid phase, so these conditions were deemed appropriate for in vitro dissolution testing of POA. Dissolution profiles for raw POA and 10% w/w POA melt granules are presented in Fig. 3. Dissolution was appreciably faster for POA in granular form compared with the raw material. The average time taken to reach 90% w/v drug in solution was 2 min for granulated POA and 25 min for raw POA.

4. Discussion

In this study, the low melting temperature of POA was utilised to prepare a narrow sieve size fraction of POA granules using a melt granulation method. Melt granules containing 10% w/w POA exhibited optimum dose uniformity and minimum friability. However, only 73% w/w of 355–500 μm 10% w/w POA granules remained intact following friability testing, indicating that the melt granules would be susceptible to particle size change on further processing.

There is considerable scope for optimisation of the POA melt granulation process to improve granule strength further. Variables such as impeller speed, mixing time and binder viscosity have significant effects on the properties of melt granules prepared using PEG as molten binder

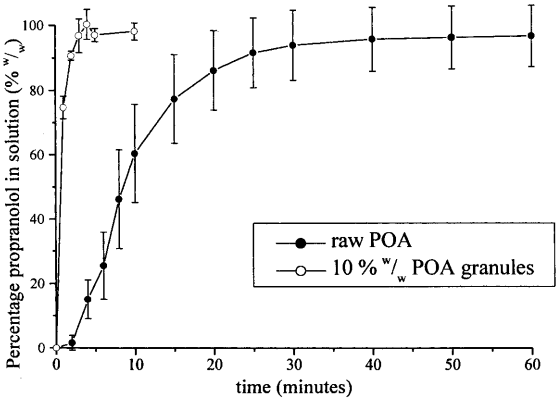

Fig. 3. In vitro dissolution profiles for 10% w/w POA melt granules (open circles) and raw POA (closed circles) in pH 7.4 medium with 0.2% w/v SLS at 37°C. Error bars represent the S.D. (σ_{n-1}) calculated from four experiments.

(Schæfer and Mathiesen, 1996; Schæfer et al., 1990; Johansen et al., 1999). These authors used the heat generated by high shear mixing to melt binder and not an external heat source as in the current study. Another process variable in melt granulation studies is to continue mixing during the cooling stage as binder solidification proceeds (El-Shanawany, 1993; Zhou et al., 1996).

The majority of melt granulation literature reports with wax or lipid binders have focussed on the tableting properties and sustained release potential of granules. A notable exception was presented by Thomsen et al. (1994) who found that there was no relationship between viscosity and binding performance for a range of lipid and wax binders. It has since been shown that different lipid binders exhibit different electrostatic charging behaviour during melt granulation, suggesting that this phenomenon may be a major determinant of successful granulation (Eliasen et al., 1999). These authors explored the use of lipid blends to improve binding capability, a measure that could be used to improve melt granulation of POA.

Wakiyama et al. (1993) investigated the physicochemical properties of lactose granules containing 10% w/w lipid as binder prepared by wet granulation. Granule bonding forces were not related to substrate/binder interactions but correlated with the visco-elastic strength of the binder material. Assuming that similar interactions are present in dried granules prepared by both the methods, it is possible that the deformable nature of POA contributed to the poor strength of POA melt granules. Caking of 10% w/w POA granules was observed on standing. This behaviour was also found for the lipid granules investigated by Wakiyama et al. (1992, 1993, 1994) and could be reduced by decreasing carrier particle size or remelting lipid with further heat treatment to consolidate granules. Evidently, there is considerable scope for optimisation of the POA melt granulation process.

The MTR is a useful tool for optimisation of the wet granulation process. Early findings presented by Parker et al. (1990) for water/lactose and 5% polyvinyl pyrrolidone aqueous solution/microcrystalline cellulose model systems gave

mean torque values of 0.4–0.5 N m. In contrast, MTR melt granulation profiles presented in Fig. 1 recorded maximum mean torque values of no greater than 0.092 N m for systems containing 5–15% w/w POA. MTR data for the overwet 15% w/w POA melt granulation system did not contain grossly elevated mean torque values at early mixing times. This was in contrast to overwet wet granulation model systems which exhibited raised mean torque at early time points proceeded by a marked decrease in mean torque on further mixing (Parker et al., 1990). These data suggest a large difference in the rheological properties of the POA/lactose melt granulation system compared with the model wet granulation systems cited above. The massing properties of a range of lactose/PEG melt granulations were investigated using the MTR by Johansen et al. (1999), reporting maximum mean torque values greater than those given by Parker et al. (1990). In the lactose/PEG melt granulation study, much higher binder concentrations and massing times were employed than in the current work. Nevertheless, it is important to note that melt agglomeration behaviour in a high shear mixer did not correlate with MTR predictions (Johansen et al., 1999). At present, mixer torque rheometry allows optimisation of the melt granulation process on a small scale, but its suitability for technology transfer and scale up of a melt granulation is uncertain.

Melt granulation formulations containing lipid or wax binders are generally prepared with the aim of prolonging drug dissolution time (El-Shanawany, 1993; Thomsen et al., 1994; Zhou et al., 1996). However, the 10% w/w POA melt granulation produced a large increase in the rate of POA dissolution in comparison to raw POA. Drug material does not appear to have been used as binder phase in a melt granulation process previously. A similar system was investigated by Ford and Rubinstein (1980), using a drug-polymer solid dispersion (indomethacin/PEG 6000) as melt binder. These authors found that tablets prepared from melt granules exhibited faster dissolution compared with tablets produced following wet granulation. Unfortunately, it was not possible to assess the relative contributions of melt granule formation, solid dispersion formation and changes in compression properties on the modified dissolution properties reported by Ford and Rubinstein (1980). In the current work, SEM data in Fig. 2 demonstrated a large surface area of POA in granular form. It is proposed that the marked increase in POA dissolution rate resulted from the increased surface area of POA binder in granular form. The high aqueous solubility of lactose monohydrate carrier particles was also likely to have contributed to the fast in vitro dissolution of POA in granular form. Rapid dissolution of carrier particles further increased the surface area of POA in the dissolution medium.

The increased dissolution rate of POA in melt granular form is advantageous from the biopharmaceutical standpoint. Rapid intestinal release of oleic acid was shown to be a critical factor in improving propranolol bioavailability by Barnwell et al. (1996). High oleic acid concentrations in the small intestine are required to stimulate increased triglyceride content and flow of lymphatic fluid, two factors that determine the magnitude of lymphatic drug transport (Charman and Stella, 1991). An alternative mechanism of propranolol oral bioavailability change when administered with oleic acid is saturation of first-pass metabolism. Again, rapid drug-fatty acid salt release into solution will maximise any potential enzyme saturation in the small intestine and/or liver. Increased propranolol oral bioavailability has been demonstrated when administered with excess oleic acid (Barnwell et al., 1996) but the oral bioavailability of the oleate salt (POA) has not been investigated. Melt granulated POA provides an appropriate form for such a study, although additional formulation will be required to provide enteric protection and thus avoid dissociation of POA at low pH.

5. Conclusion

The drug-fatty acid salt POA was successfully employed as binder to prepare melt granules. Optimum dose uniformity was found at a binder concentration of 10% w/w POA. Friability was at the minimum at this binder concentration but an appreciable decrease in granule size was found

during testing. Further work is needed to prepare POA melt granules that will not be prone to particle size change when subject to physical stresses during any further processing. In vitro dissolution testing of 10% w/w POA granules demonstrated rapid dissolution in comparison to raw POA. Thus, melt granulation is a viable method for preparing a narrow size distribution of POA that produces favourable changes in dissolution for this lipophilic drug-fatty acid salt.

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