International Journal of Pharmaceutics, 59 (1990) 115–119
Elsevier

IJP 01998

The filling of molten ibuprofen into hard gelatin capsules

A. Smith, J.F. Lampard, K.M. Carruthers and P. Regan

Pharmaceutical Division, The Boots Company PLC, Nottingham (U.K.)

(Received 28 August 1989)
(Accepted 27 September 1989)

Key words: Ibuprofen; Melt-filled capsule; Dissolution rate; Rheological properties

Summary

The dissolution rate of melt-filled ibuprofen capsules is markedly affected by low (10% or less) levels of a variety of excipients. Thus, a high fill weight can be achieved and virtually any in vitro dissolution profile obtained. For any particular system of interest the effect of processing conditions can be readily determined.

Introduction

It is widely accepted that molten or thixotropic liquids and pastes may be filled into hard gelatin capsule shells (Walker et al., 1980a,b; Cuine and Francois, 1981; Djimbo and Moes, 1984). Such techniques facilitate the processing of liquid or low melting point materials into capsule form but also offer other potential advantages. These include improved chemical stability, excellent homogeneity and content uniformity, the elimination of dust or cross-contamination and easy modification of drug release rate (Djimbo and Moes, 1984; McTaggart et al., 1984; Bowtle et al., 1988). We report a new aspect of liquid-paste filling whereby a high fill weight of a low-melting thermostable drug (ibuprofen) can be attained using low levels of excipient whilst preserving the facility to obtain a wide range of drug release rates.

Correspondence: A. Smith, Pharmaceutical Division, The Boots Company PLC, Nottingham, U.K.

Materials and Methods

Ibuprofen and all other materials were of compendial or pharmaceutical grade. White two-piece hard gelatin capsule shells of the necessary sizes were provided by Elanco.

Ibuprofen together with any other miscible ingredients was warmed in a stainless-steel vessel. Additional liquid or suspendable excipients were added to the stirred mass when molten. The mixture was adjusted to 70–80 °C before filling into suitably sized capsules by means of a pipette or single Hi-Bar pump (Harro-Hofliger), rejecting any capsules outside ± 5% of the target fill.

In order to obtain information on the likely release mechanism for ibuprofen, capsules were agitated in a BP disintegration apparatus for up to 3 h in pH 2.2 and 7.2 buffers. The time taken for total disintegration was recorded.

Dissolution rate was assessed using a six-station USP XXI Apparatus in Mode II with 900 ml of pH 7.2 buffer at 37 °C and a paddle speed of 50 rpm. Filtered dissolution medium was sampled

TABLE 1

Attainable fill weight of ibuprofen for alternative capsule sizes

Size	Approximate fill (mg)
1	450
0	605
0 elongated	680
00	825

sequentially from each flask and assayed spectrophotometrically.

The rheological behaviour of selected mixtures was examined and compared with that of ibuprofen alone at 70 °C using the Contraves Rheomat 15 fitted with concentric cylinders.

Results

The molten feed did not cause distortion or other adverse effects on the capsule shell. The maximum fill weight of alternative capsule sizes, when filled with ibuprofen alone, is given in Table 1.

TABLE 2

Apparent viscosity of mixtures at 70 °C as measured using Contraves Rheomat 15

Excipient	%	Viscosity (cP)	Shear rate (s^{-1})
None		27	196
Beeswax	5	27	196
Aerosil 200	1	28	196
	2	35	196
	3	60	196
	4	1258	137
	5	2123	196
Aerosil R972	4	900	137

The addition of excipients had little effect on the melting point of the mass and, with the exception of Aerosil had no significant effect on viscosity or processing at the levels studied. A marked thickening was noted between 3 and 4% Aerosil 200 (Table 2). The rheological behaviour of selected mixtures containing Aerosil is shown in Fig. 1. At the 1% level, the rheological properties were virtually identical to those of ibuprofen alone.

All the formulae examined set to form solid plugs with similar overall appearance although

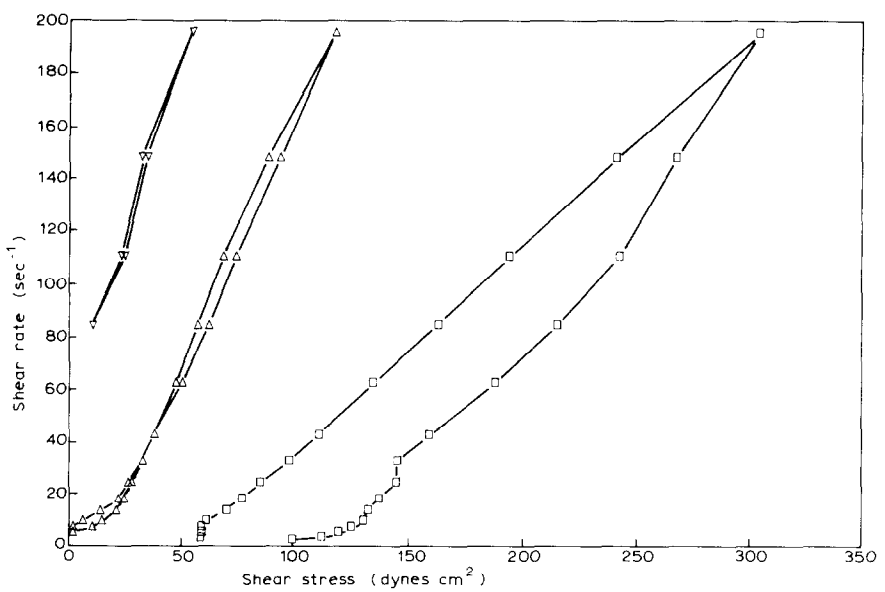

Fig. 1. Rheological behaviour of selected mixtures containing Aerosil 200. (□) Aerosil 5%, (△) Aerosil 3%, (▽) Aerosil 1%.

TABLE 3

Dissolution performance of ibuprofen 600 mg melt-filled capsules at pH 7.2

Excipient	%	T_{50} (h)	Excipient	%	T_{50} (h)
None	–	2.9	Arachis oil	10	4.1
PEG 400	10	3.5			
4000	10	3.3	Liquid paraffin	10	4.8
6000	10	4.2			
			Aerosil 200	1	4.7
Maize starch	1	3.5		3	6.6
	5	1.6		5	10.0
	10	0.2			
			Aerosil R972	1	5.9
Explotab	1	1.8		5	20.5
	5	0.3			
			Stearic acid	1	4.2
AcDiSol	1	0.4		5	7.8
	2.5	0.1		10	> 24
Crospovidone	10	4.0	Stearyl alcohol	1	10.0
				5	14.0
Pluronic F68	5	3.0		10	> 24
Gelucire 50/13	5	3.0	Beeswax	10	> 24

variations in surface area arose occasionally from 'holing', especially if capsules were disturbed during solidification. The crushing strength of plugs was investigated (Schleuniger apparatus) after removal of the capsule shell. Values for ibuprofen plugs ranged from 5.1 to 8.8 kp (mean 6.4 kp; $n = 10$) and were not affected markedly by low levels (up to 10%) of excipient.

Capsules formulated with 5% AcDiSol disintegrated in under 1 h even at pH 2.2. The dispersion of capsules containing Explotab, starch or lower levels of AcDiSol showed a dependence upon the level of excipient and was not complete after 3 h. All other capsules did not disintegrate but dissolved or eroded from the surface.

Preliminary studies revealed that the dissolution rate depended on neither stirring speed of the

TABLE 4

Effect of various excipient mixtures containing Aerosil on the dissolution of ibuprofen 600 mg melt-filled capsules at pH 7.2

Excipient	%,%	T_{50} (h)
Aerosil 200, AcDiSol	1,1	1.0
	3,1	6.0
	3,5	0.7
	1,5	0.3
Aerosil 200, stearic acid	1,1	11.7
Aerosil R972, stearic acid	1,1	9.8
Aerosil R972, stearyl alcohol	1,1	15.0
Aerosil R972, beeswax	1,1	15.0

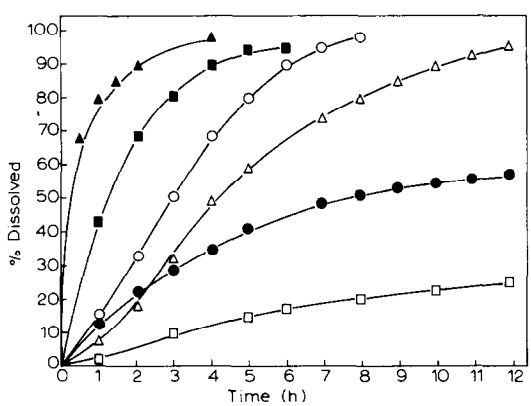

Fig. 2. Dissolution of ibuprofen 600 mg melt-filled capsules. (○) Ibuprofen, (▲) AcDiSol 2.5%, (■) maize starch 5%, (△) arachis oil 10%, (●) stearic acid 5%, (□) beeswax 10%.

melt nor cooling rate and, whilst more prolonged stirring did exert an effect upon release rate, capsule filling could be carried out over several hours without noticeable change occurring. Typical dissolution data for a range of ibuprofen 600 mg formulations are represented as the mean time taken for 50% dissolution (T_{50}) in Tables 3 and 4 and given fully in Fig. 2.

Discussion

Ibuprofen can be filled into capsules in molten form. Current production scale equipment utilises a pumping system whose operation will clearly be affected by the rheological properties and surface tension of the fill material. Tests on the single Hi-Bar pump suggest that the viscosity and/or surface tension of ibuprofen alone is too low for optimum filling. Nevertheless, the results indicate that rheological properties are readily modified (see below). Furthermore, McTaggart et al. (1984) reported that a similar pumping system could dose materials of widely differing viscosity and flow properties with great precision.

The type and amounts of excipients are easily varied to produce changes in the release behaviour giving virtually any desired in vitro dissolution rate (Table 3 and Fig. 2), although the effect of any particular excipient cannot necessarily be predicted. Unexpected effects have also been reported for excipients in solid dispersion systems (Ford, 1986; Bloch and Speiser, 1987).

Prolonged drug release is facilitated by the addition of hydrophobic materials, particularly oils and waxes whilst the dissolution rates of capsules containing disintegrants were increased (Table 3). Disintegrant effects are in general agreement with those in compressed systems except that crospovidone is relatively inactive after melt filling. This is presumably related to an observed difference in 'wetting' of crospovidone by molten ibuprofen. Workers have previously found disintegrants to be ineffective in melt-filled systems except at high concentration (Djimbo and Moes, 1984). This difference in behaviour may be due to the high proportion of carriers previously employed.

Polyethylene glycols are known to promote wetting and dissolution from solid dispersions (Chiou and Riegelman, 1971) and have been used for this purpose in liquid (Walker et al., 1980b; Ganley et al., 1984) and paste (Djimbo and Moes, 1984; Djimbo et al., 1984) filled capsules. Surprisingly, polyethylene glycols caused a slight prolongation of release in the present study. Five percent of a surfactant poloxamer (Pluronic F68) or the glyceride-poly-glycide Gelucire 50/13 had little influence on release although it is highly probable that different grades and concentrations of these and other surfactants will have demonstrable effects.

The majority of mixtures exhibited Newtonian flow or only slight shear thinning. The effect on rheology exhibited by increasing the Aerosil 200 content is indicative of increased structure in the melt arising from chains of silicon dioxide particles. Plots of shear stress vs. shear rate (Fig. 1) are linear up to 1% Aerosil 200 but as the level of excipient was raised above 3%, mixtures exhibited increasing thixotropy.

Combinations of excipients can be used to refine further the processing characteristics and/or performance of the product. As an example, consider the use of Aerosil (Table 4). In combination with hydrophobic excipients fine adjustment to prolong in vitro dissolution behaviour can be made. Alternatively, by the inclusion of AcDiSol to accelerate dissolution, beneficial viscosity and surface tension effects can be derived from Aerosil without a concomitant lengthening of the release period.

According to Bloch and Speiser (1987), the major problems arising in the development of solid dispersion systems are related to processing/scale-up and instability due to changes in crystallinity on storage. Our preliminary studies on ibuprofen melt-filled capsules have shown dissolution rate to be dependent upon neither the stirring speed of the melt nor cooling rate. It has been further suggested that stability problems are exacerbated by the use of low levels of carriers (Ford, 1986). In a limited study no significant changes in either the solid state or dissolution properties have been found for ibuprofen or ibuprofen-excipient mixtures after storage for 3

months at $20 \pm 2°C$. At 40 and 50 °C, changes in dissolution were induced which resembled, at least qualitatively, stirring the melt for very prolonged periods.

References

Bloch, D.W. and Speiser, P.P., Solid dispersions – fundamentals and examples. *Pharm. Acta Helv.*, 62 (1987) 23–27.

Bowtle, W.J., Barker, N.J. and Woodhams, J., A new approach to vancomycin formulation using filling technology for semisolid matrix capsules. *Pharm. Technol.*, June (1988) 86–97.

Chiou, W.L. and Riegelman, S., Absorption characteristics of solid dispersed and micronised griseofulvin in man. *J. Pharm. Sci.*, 60 (1971) 1376–1379.

Cuine, A. and Francois, D., Thixotropic filling medium for hard gelatin capsules. *British Patent* 1,590,864 (1981).

Djimbo, M. and Moes, A.J., Release of drugs formulated as hard pastes filled into hard gelatin capsules. 1. Physical properties and in vitro testing. *J. Pharm. Belg.*, 39 (1984) 36–42.

Djimbo, M., Fell, J.T., Kaus, L. and Moes, A.J., Release of drugs formulated as hard pastes filled into hard gelatin capsules. 2. In vivo studies. *J. Pharm. Belg.*, 39 (1984) 43–49.

Ford, J.L., The current status of solid dispersions. *Pharm. Acta Helv.*, 61 (1986) 69–88.

Ganley, J.A., McEwen, J., Calvert, R.T. and Barker, M.C.J., The effect of in vivo dispersion and gastric emptying on glibenclamide absorption from a novel, rapidly dissolving capsule formulation. *J. Pharm. Pharmacol.*, 36 (1984) 734–739.

McTaggart, C., Wood, R., Bedford, K. and Walker, S.E., The evaluation of an automatic system for filling liquids into hard gelatin capsules. *J. Pharm. Pharmacol.*, 36 (1984) 119–121.

Walker, S.E., Bedford, K. and Eaves, T., Improvements in and relating to pharmaceutical preparations in solid unit dosage form. *British Patent*, 1,572,226 (1980a).

Walker, S.E., Ganley, J.A., Bedford, K. and Eaves, T., The filling of molten and thixotropic formulations into hard gelatin capsules. *J. Pharm. Pharmacol.*, 32 (1980b) 389–393.