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The filling of molten and thixotropic formulations into hard gelatin capsules

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Problems in the formulation and manufacture of conventional solid dose form products include the variation of fill weight and drug content, dissolution control of poorly water soluble drugs and dust generated during manufacture giving rise to cross contamination. We have examined the application of a liquid filling technique for the manufacture of hard gelatin capsules as a means of overcoming some of these. Filling materials are based on water-soluble hot melt polymers such as polyethylene glycol or water-dispersible thixotropic systems of pharmaceutical oils with thixotropic additives. A Zanasi LZ64 capsule filling machine was adapted to fill liquids using a liquid filling pump. No dust is generated during filling and 20 μg doses of drug can be accurately filled without extensive processing. The formulations are simple and do not require specialist ingredients such as lubricants, binders, disintegrants and flow aids. The method of manufacture is reduced to a simple mixing and direct filling operation. The system may be applied to promote the dissolution of poorly water soluble drugs using solid solutions or solid dispersions. Slow release formulations are also available using suitable retard excipients.

The use of solid solutions and solid dispersions has been widely advocated as a means of overcoming dissolution problems of poorly water soluble drugs, for instance, tolbutamide (Salib et al 1976), griseofulvin, cardiac glycosides and steroids (Chiou & Riegelman 1971) and riboflavine (El-Gindy & El-Khawas 1977). Few conventional dosage forms have exploited these advantages, probably because of the poor processing properties of solid solution systems, which tend to be wax-like materials difficult to handle on high speed tableting and capsule filling machinery (Wells et al 1975). Many solid solution systems require pulverization before they can be filled into capsules (Chiou & Smith 1971).

We have evaluated a means of filling liquids into hard gelatin capsules as a way of reducing the problems of conventional pharmaceutical processing methods (Walker et al 1977).

Many excipients are claimed to be suitable for use in capsule filling of thixotropic or molten liquids (Cuiné et al 1978a, 1978b) and the control of viscosity, melting point and dissolution properties are possible by the selection of appropriate raw materials.

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MATERIALS AND METHODS

Capsule filling machine modifications

An automatic capsule filling machine (Model Zanasi LZ64, ACM Machinery Ltd.) was adapted to fill liquids instead of powders by replacing the powder hopper and dosator tubes by a liquid filling pump (Precision Shot Dispenser, Model PKM 161, Kent Moore).

Synchronization of the filling operation with the positioning of an empty capsule body at the filling station is achieved by a microswitch located at Turntable station G (Fig. 1). The microswitch is activated by the capsule body holding bush as it comes to rest at station G during the intermittent cycle of operation. Actuation of the microswitch opens the valve of the dispenser and a controlled shot of liquid is delivered to the capsule body at the filling station via the filling nozzle. The dispenser is operated by compressed air and controlled by an electrical timer. The volume dispensed may be adjusted by varying the compressed air pressure, which alters both the pressure exerted on the plunger in the reservoir and the speed of operation of the valve and also by the timer which adjusts the period during which the valve remains open. The dispenser is equipped with a 'snuff-back' device which ensures a clean break in the issuing stream by sucking back slightly when the valve closes. This reduces tailing and prevents excess droplets of liquid falling into the

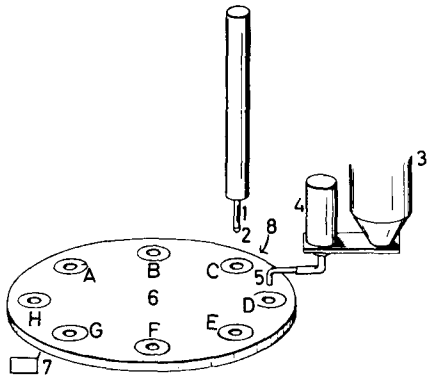

FIG. 1. Diagrammatic representation of capsule filling machine modifications. 1, Locating bar; 2, Light emitting diode; 3, Dispenser reservoir; 4, Dispenser valve; 5, Dispenser nozzle; 6, Zanasi LZ64 turntable; 7, Microswitch; 8, Light detector. Turntable locations: A, Empty capsule shell feeding; B, Separation of cap and body; C, Location of body in bush and detection of absence of capsule shell; D, Filling station; E, Transfer station only; F, Transfer station only; G, Ejection of filled capsules; H, Vacuum cleaning of turntable.

capsule body. A detector system (Fig. 2) to stop the filling cycle if a capsule body is not present avoids the soiling of the turntable by the liquid.

The detector is mounted below the turntable and a light emitting diode is placed on the capsule locating bar which also engages the capsule shells firmly in the turntable bush. In normal operation with opaque capsule shells light from the diode does not reach the detector. If for any reason it does, operation of the filling machine is halted.

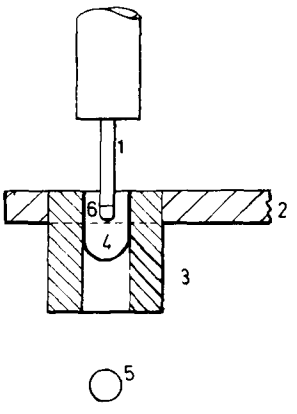

FIG. 2. Detail of turntable station C. 1, Locating bar; 2, Turntable; 3, Capsule body holding bush; 4, Capsule body; 5, Detector; 6, Light emitting diode.

Filling system evaluation

The modified capsule filling system was evaluated by assessing fill weight variation in size 1 hard gelatin capsules at fill weights between 290 and 620 mg and at machine speeds of 1800 and 3600 capsules h^{-1}. Fill weight was determined on intact capsules by subtracting the average capsule shell weight.

The formulations used were:

I. Liquid paraffin B.P. 90, beeswax B.P. 10% w/w were mixed whilst warming to 65 °C and kept molten in the reservoir of the filling machine by heating tapes. II. Aerosil 200 5% w/w was dispersed in Miglyol oil 95% w/w at room temperature using a Silverson mixer and poured into the unheated reservoir. III. Thixcin R (hydrogenated castor oil) 3% w/w and Aerosil 200 2% w/w were dispersed at room temperature in liquid paraffin 95% w/w using an ultrasonic homogenizer and poured into the unheated reservoir. IV. Polyethylene glycol 1500 100% w/w was heated to 50 °C on a steam bath and poured into the heated reservoir.

Formulations I and IV are 'hot melt' systems and were filled at 75° and 60 °C respectively. Formulations II and III are thixotropic systems and were consequently filled at room temperature. The shearing action associated with passage of the gel through the dispensing nozzle was adequate for liquefying the thixotropic systems and no stirring within the reservoir was necessary. The mean fill weight and its variation were calculated from the individual weights of 20 filled capsules.

Preparation of capsules containing low doses

Capsules containing low doses of a model drug were prepared using both the liquid-fill technique and a conventional powder-fill method. Fill weight and content variations of the two batches of capsules were then determined. Triamterene B.P. was used as its strong absorbance enables simple and accurate determination of the drug content per capsule.

The liquid-fill batch was prepared as follows: polyethylene glycol 1500, 400 g, was heated and stirred on a steam bath and triamterene 21 mg was added and mixed thoroughly using a Silverson mixer. The hot melt was filled into size 1 capsule shells using the modified Zanasi LZ64 capsule filling machine at a fill weight of 406 mg per capsule, i.e. a dose of 20 μg triamterene at a speed of 3600 capsules h^{-1}. The reservoir and filling line of the Precision Shot Dispenser were kept at approximately 10 °C above the melting point of the mix, electrically. After filling, the capsules were allowed to cool to room temperature so that the melt solidified.

The conventional powder-fill capsules were prepared by mixing triamterene 60 mg with a lactose, starch, Avicel capsule filling mix 100 g followed by ball milling for 24 h. The premix was diluted with the remaining filling material and mixed for 10 min in a planetary mixer. Magnesium stearate was then added and the whole (810 g) mixed for a further 5 min. The material was then filled into size 1 gelatin capsules using the standard powder fill attachments of the Zanasi at a fill weight of 270 mg/capsule and a speed of 3600 capsules h^{-1}.

Samples were taken every 10 min throughout both 60 min filling runs and were combined before testing. The capsules were evaluated for fill weight and fill weight variation and the triamterene content was determined spectrophotometrically after extraction into methanolic 0·1 M hydrochloric acid. A tangent baseline correction was performed to correct the absorbance at the wavelength of maximum absorbance (at approximately 350 nm) for interference.

Preparation of capsules with sustained release properties

Polyethylene glycol 1500, 80·6 g, was melted as before, and 6·0 g polyvinyl acetate (Gelva C3V10K, Monsanto) was incorporated with stirring until fully dissolved. Nomifensine hydrogen maleate 13·4 g was added and stirring was continued to ensure a thorough dispersion. The hot melt was then filled into the size 1 hard gelatin capsules, to give a drug content of 75 mg in a total fill weight of 560 mg. Capsules were filled by hand using a refillable syringe.

The dissolution rate of the capsules was determined using the Desaga flow-through dissolution apparatus at a flow rate of 100 ml h^{-1}. The dissolution fluid was changed during the test to increase the pH of the test medium as the dissolution test progressed. For the first period of the test pH 1·2 HCl/NaCl solution at 37 °C was used as dissolution fluid and this was changed to pH 5·5 phosphate buffer after $1\frac{1}{4}$ h. After a further hour the dissolution fluid was changed to a pH 7·5 phosphate buffer which was then used for the remainder of the test.

The nomifensine content of the dissolution medium was determined by a colourimetric assay based on diazotization of the drug and coupling of the resulting diazonium salt with naphthylethylenediamine to give a red colour. The absorbance of the final solution was measured at 530 nm in 1 cm cells and compared with that of a standard drug solution subjected to the diazotization/colour development procedure concurrently with the sample solutions.

Two further batches of capsules were then prepared containing 2 and 4% w/v polyvinyl acetate, and evaluated identically.

Preparation of capsules with enhanced dissolution properties

To demonstrate the possible enhancement of in vitro dissolution properties, liquid-fill capsules of triamterene (50 mg) were compared with those of a conventional commercially available capsule (Dytac 50 mg capsules, Smith, Kline and French).

Polyethylene glycol 1500, 350 g, was melted as before and triamterene B.P. 50 g was incorporated using a Silverson mixer. Size 1 capsule shells were filled using the liquid-fill attachment of the Zanasi LZ64 to give a dose of triamterene of 50 mg in a total fill of 400 mg. Capsules were filled at a rate of 1600 h^{-1}.

The in vitro dissolution rates of both the liquid-fill and the conventional capsules were determined in triplicate using the U.S.P. dissolution apparatus with 0·1M hydrochloric acid at 37 °C as dissolution fluid and a rotation speed of 100 rev min^{-1}. Samples were taken for analysis at 15, 30, 240 and 360 min.

The content of triamterene was determined spectrophotometrically, after suitable dilution with 0·1M hydrochloric acid if necessary, in 1 cm cells at the wavelength of maximum absorbance (approximately 360 nm). Results were calculated by comparison with the absorbance of a concurrently measured standard triamterene solution.

RESULTS AND DISCUSSION

Filling system evaluation

The results in Table 1 illustrate that the uniformity of fill weight using the Precision Shot Dispenser with both thixotropic and hot melt liquid-fill systems, is equivalent to that achieved in conventional powder filling. Fill weight variation decreases with increasing fill weight and with decreasing filling rates.

The liquid-fill system as described is capable of clean trouble-free operation using a variety of media at laboratory scale. Although fill weight uniformity is acceptable, improvements could be expected using purpose-built pumps on a production scale.

Content uniformity

Content uniformity in pharmaceutical manufacture is dependent on fill weight reproducibility and homogeneity of the filling material. Fill weight reproducibility in conventional capsule manufacture is dependent on bulk density uniformity and flow properties of the filling mix, as well as on machine

Table 1. Fill weight variation of thixotropic (T) and hot melt (HM) systems using the Precision Shot Dispenser at several different fill weights.

System		Type	Machine speed (caps h^{-1})	Mean fill (mg)	Relative s.d. of fill weight (%)
I	Liquid paraffin + 10% Beeswax	HM	1800	342	2·0
II	Miglyol & 5% Aerosil	T	1800	355	2·7
III	Liquid paraffin/Thixcin/ Aerosil	T	1800	290	2·8
				345	2·0
				620	1·4
IV	PEG 1500 melt	HM	1800	406	1·0
		HM	3600	411	2·7

variables such as machine speed and variability of tooling. Homogeneity of the filling material is dependent on the efficiency of mixing which has taken place throughout the processing stages and on the extent of segregation which has occurred in the machine hopper during capsule filling.

Table 2 shows that satisfactory content uniformity can be achieved by the liquid-fill system even at doses as low as 20 μg. The improved relative standard deviation of fill weight compared with the conventional capsules may be attributed to the greater fill weight which is possible with the higher density liquid-fill systems. The relative standard deviations of drug contents reflect the fill-weight values although there is evidence of a greater variation in the uniformity of the filling material for the conventional capsules than for the liquid-fill capsules. This is evident even though a time-consuming ball-milling step was included in the conventional process and there was no stirring of the contents of the liquid-fill reservoir. It is clear that the liquid-fill system is capable of giving improved content uniformity with minimal precautions.

Table 2. Fill weight and content uniformity for triamterene 20 μg capsules prepared by the liquid-fill and powder-fill techniques.

	Powder-fill	Liquid-fill
Average fill weight (mg)	269·2	405·9
s.d. of fill weight (mg)	5·4	4·1
Relative s.d. of fill weight (%)	2·0	1·0
Triamterene average content (μg)	16·4	18·9
Relative s.d. of content (%)	3·1	1·8
Excipient dilution (total wt ÷ dose)	1 : 13,460	1 : 20,295

Sustained release

Fig. 3 demonstrates the close control of the dissolution profile that can be achieved using a typical liquid-fill capsule formulation. The sustained release principle uses polyvinyl acetate in a water soluble matrix. The water soluble polyethylene glycol 1500 matrix solidifies on cooling to form a stable plug. On contact with water there is a rapid initial release of drug and polyethylene glycol 1500 from the outer surface of the plug. The water then slowly penetrates

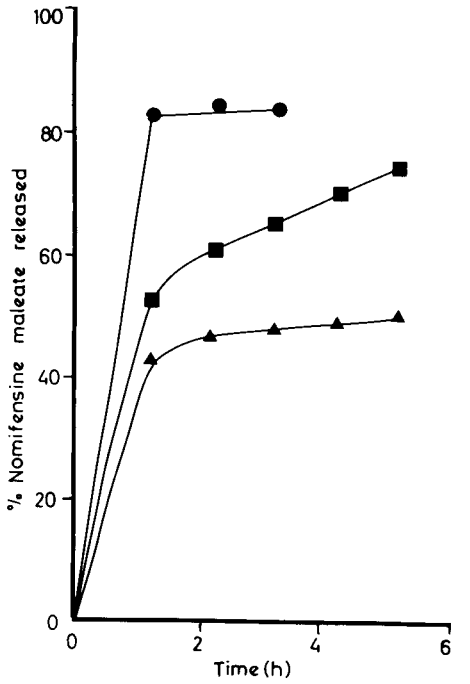

FIG. 3. In vitro dissolution rate of nomifensine hydrogen maleate 75 mg capsules from liquid-fill formulations containing 2% (●), 4% (■) and 6% (▲) polyvinyl acetate.

the plug, dissolving the polyethylene glycol and precipitating the polyvinyl acetate so that subsequent release is dependent on diffusion through water in the pores within the sponge-like polyvinyl acetate matrix. The rate and extent of the initial rapid release phase is reduced by increasing the polyvinyl acetate content and the slow release phase is prolonged. This two stage release profile may have advantages in vivo as it provides an initial phase to establish a therapeutic blood level rapidly, followed by a slower release profile to maintain the level over a prolonged period. Altering the polyvinyl acetate content from 2 to 6% w/w changed the retard profile by reducing the rate and extent of the rapid initial phase and modifying the rate of release of the slower phase.

Dissolution enhancement

Fig. 4 illustrates that a liquid-fill capsule can be used to achieve dissolution enhancement over conventional pharmaceutical processing techniques, using a simple molten formulation filled directly into

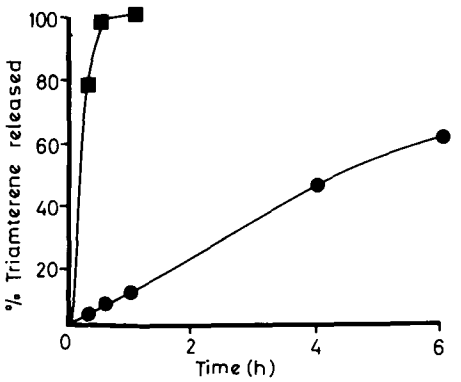

FIG. 4. In vitro dissolution rate of Triamterene from 50 mg liquid-fill capsules (■) and 50 mg conventional powder-fill capsulses (●).

capsule shells with no other processing steps before filling. There was a high rapid initial drug release and dissolution was complete within 60 min.

Rapid dissolution of the drug may be promoted by several factors in the solid dispersion system. (i) Rapid disintegration of the water soluble matrix. (ii) Improved wetting properties of the drug. (iii) Increased drug surface area due to the absence of crystal aggregates, which may exist in the dry powder mix. (iv) Rapid dissolution of material which exists in a solid solution or a fine solid dispersion form.

The advantages of solid solution and solid dispersion systems in dissolution enhancement have, of course, been well documented. However, most investigations have been of limited application to manufacturing, because of the processing problems of the wax-like sticky masses that result from the use of hydrophilic compounds such as polyethylene glycol. Often the solidified mass requires milling and screening before use, and applications have therefore been restricted to hand filling of capsules or small scale tableting. The liquid-fill approach to solid solutions and solid dispersions may offer a simple answer to these manufacturing difficulties.

Conclusion

The filling of molten or thixotropic liquids into hard gelatin capsules may be used to overcome a number of problems which are frequently associated with the development and manufacture of conventional pharmaceutical capsules. The potential of the technique to improve content uniformity, to impart sustained release properties and to enhance the dissolution of poorly water soluble drugs has been demonstrated.

The method of manufacture enables a dust-free environment to be maintained and thereby reduces the dangers of cross contamination and operator exposure.

The formulations are simple and use a small number of standard excipients which are able to provide the combined functions of diluent, disintegrant and lubricant. As a result, the number of unit operations required is less than those for conventional solid dose form manufacture.

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