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FEASIBILITY OF MANUFACTURING A SOLID DOSAGE FORM USING A LIQUID NONVOLATILE DRUG CARRIER: A PHYSICO-CHEMICAL CHARACTERIZATION

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ABSTRACT

Experiments were performed to determine the formulation and manufacturing feasibility of three model solid capsule formulations using a spray-on liquid drug carrier. Methylparaben was used as a model low-dose drug in the liquid drug carrier. Formulations containing different amounts of liquid drug carrier were successfully encapsulated on the H&K 400 capsule filling machine. The formulations contained varying ratios of liquid (methylparaben-propylene carbonate solution) to solid (compressible sugar, NF), which ranged from 10.0 - 20.0 µL/450 mg. Physical characteristics (i.e. weight variation, dissolution, etc.) of the filled capsules were evaluated. The 20.0 µL liquid/450 mg solid ratio was found to be the best hard gelatin capsule formulation based upon its rapid dissolution profile and was equivalent to all other formulations tested with respect to weight variation and content uniformity.

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INTRODUCTION

Content uniformity for dosage forms is a critical parameter (1), especially for potent drugs in low dose dosage forms. A theoretical treatment to ensure adequate content uniformity has been derived using statistical principles (2) and several theories have been summarized (3). As a result, several manufacturing methods have therefore been used to prevent poor content uniformity. Ordered mixing was used by Hersey (4) and McGinity, et. al. (5) to distribute relatively small quantities of drug substance, however Egermann and his coworkers (6,7) dispute the validity of this technology. Tawashi and Speiser (8) evaluated the effects of using extremely long mixing times to obtain acceptable levels of content uniformity. A newer technology, which could be used to obtain adequate content uniformity and is somewhat similar to the method we evaluated in the present report, is the use of carrier granulation (9). Our method is a modified version of moisture-activated dry granulation technology (10). However, those technologies evaporate the granulating solvent from the powder bed.

Complexities such as poor chemical stability and high potency of some new drug entities, necessitate the use of nonconventional methods to stabilize and deliver these agents. Liquid filled, soft elastic gelatin capsules are one possible solution to these delivery problems; however, they require a very specialized technology. Another possibility is the use of a hard gelatin capsule containing the drug substance dissolved in a nonvolatile liquid carrier, which has been sprayed onto a solid substrate. It was the purpose of our study to evaluate the feasibility of developing novel a solid dosage form which would be similar in content uniformity and other capsule parameters to a soft elastic gelatin capsule form. In this study, methylparaben was used as a model drug substance, propylene carbonate as a nonvolatile, stabilizing liquid carrier, and compressible

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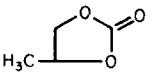
TABLE 1

PHYSICAL AND CHEMICAL CHARACTERISTICS OF PROPYLENE CARBONATE, NF

Characteristics	
Chemical name	4-methyl-1,3-dioxolan-2-one
Structure	
Density (20°C)	1.189
Boiling point (C°)	240

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sugar the solid support. The latter two components were chosen because they were previously identified as the only compatible excipients with the therapeutic agent of interest.

EXPERIMENTAL

Materials

Propylene carbonate, NF (Hüls, West Germany), compressible sugar, NF (Amstar Sugar Corp, New York, NY) methylparaben, NF (Sigma, St.Louis, MO), and magnesium stearate, NF (Mallinckrodt, St. Louis, MO) were all used as received. Some properties (11) of propylene carbonate, NF are listed in Table 1.

Granulation Process

The appropriate amount of methylparaben, NF was dissolved in propylene carbonate (pc), NF to prepare solutions of 1.75, 2.33, and 3.50 mg/ml.

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These solutions were sprayed onto compressible sugar, NF using a peristaltic pump (Cole Parmer Instruments, Chicago, IL).

Mixing Process

Ten percent of the required compressible sugar, NF was mixed with magnesium stearate, NF for three minutes in a 16 quart V-blender (Patterson-Kelley, East Stroudsburg, PA). The methylparaben-pc solution was sprayed onto the remaining compressible sugar in a 1.8 cubic feet high shear mixer (Littleford-Lödige, Florence, KY). Both the mixing and chopping blades were turned on and the solution sprayed onto the compressible sugar, NF.

After all the solution was added, the mixing was stopped and the compressible sugar-magnesium stearate preblend was added. All components were then mixed for an additional three minutes in the high shear mixer. The total batch weight was 18.144 kg.

Encapsulation

All blends (Table 2) were encapsulated on a high speed capsule filling machine (H&K 400; Hofliger-Kargg, West Germany). Four hundred and fifty milligrams of the blend containing approximately 35 µg of methylparaben was filled into size #0 hard gelatin capsules (HGC) at maximum machine speed. Weight variation was monitored every 10-15 minutes on an average of 20 capsules throughout the run and at the end of the run. Tamping pins were inspected for powder sticking after each batch was encapsulated.

Content Uniformity

Twenty capsules were chosen at random and assayed for methylparaben content by reversed-phase HPLC. The contents of one capsule were emptied into a 10 ml volumetric flask, dissolved with the addition of 5 ml of distilled water and diluted to 10 ml with methanol. The volumetric flask

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TABLE 2

EXPERIMENTAL HARD GELATIN CAPSULE POWDER BLEND FORMULATIONS

Formulation	Ingredient	% w/w
A	Methylparaben-Propylene Carbonate Solution 3.5 mg/ml	2.64
	Magnesium Stearate, NF	0.50
	Compressible Sugar, NF[1]	96.86
B	Methylparaben-Propylene Carbonate Solution 2.33 mg/ml	3.97
	Magnesium Stearate, NF	0.50
	Compressible Sugar, NF[1]	95.54
C	Methylparaben-Propylene Carbonate Solution 1.75 mg/ml	5.28
	Magnesium Stearate, NF	0.50
	Compressible Sugar, NF[1]	94.22

[1]Trade name is Dipac®.

was shaken and an aliquot was filtered and injected onto the column. A C_{18} column was used in conjunction with a mobile phase of 60:40 methanol-water. Methylparaben was monitored at a wavelength of 254 nm.

Disintegration

The USP XXI disintegration method for hard gelatin capsules was used (12).

Dissolution

The USP XXI paddle method was used (12). One capsule was added to each of six vessels (Hanson Research, Northridge, CA) containing 400 ml of

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distilled water maintained at 37° + 2°C. The decreased volume was used to accommodate the sensitivity of the HPLC assay due to the low dose of methylparaben. The paddles were rotated at 50 rpm. Five milliliter samples were removed from each vessel every 15 minutes and immediately replaced with five milliliters of distilled water. Each sample was then assayed by HPLC for methylparaben. When the capsule shell was dissolved and the solution injected onto the HPLC column, a peak was eluted at a similar time to the methylparaben peak. This peak, which may be from the preservatives in the capsule shell, comprises approximately 7-8% of the total area of the methylparaben peak. Even so, this experiment still gives a good indication of the dissolution of methylparaben from the three formulations. Either a new HPLC method or methylparaben free HGC shells would have to be used for better quantitation of future samples.

RESULTS AND DISCUSSION

Encapsulation

All three batches manufactured on the capsule filling machine ran without difficulty. Each run lasted approximately two hours. The batch manufactured from Formulation A had an in-process average capsule fill weight of 452.1 $\pm$ 3.6 mg (n=9 time points) and a coefficient of variation of 0.8%. Batches manufactured from Formulations B and C had in-process average capsule fill weights of 451.0 $\pm$ 5.5 mg (n=11) and 450.7 $\pm$ 3.9 mg (n=12), respectively. Their coefficients of variation were 1.2% and 0.9%, respectively. The final release values for weight variation, average fill weight and standard deviation are given in Table 3.

A small amount of sticking was noticed with all three batches. Sticking was observed only on the pins of the first tamping station for Formulations A and B. Sticking was seen on the pins of the first and second tamping stations for Formulation C. There was less sticking seen on

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TABLE 3

PHYSICAL AND CHEMICAL PROPERTIES OF FILLED HARD GELATIN CAPSULES

	Final Weight Variation			Content Uniformity			
Formulation	Average Fill Weight (mg)	S.D.	C.V. (%)	Average Methylparaben Content (mcg)	Percent Label Strength	S.D.	C.V. (%)
A	452	4.2	0.9	37.95	108.4	0.6	1.7
B	447	5.6	1.3	36.66	104.7	0.6	1.7
C	445	6.1	1.4	36.54	104.4	0.6	1.7

the second station than the first station. Additionally, this blend stuck to the side of the hopper where the force feed could not scrape. Geometric alterations to the present hopper could be designed to alleviate this occurrence. This powder was easily removed from the hopper sides with a spatula, force fed down the hopper and encapsulated.

Sticking was not a major problem since the powder could be easily removed from the end of the pins with a light touch. The sticking was due to the wetness of the powder and did not affect the filling process as evidenced by consistently good in-process capsule weight variation checks. The sticking could be further eliminated by lining the tamping pins with teflon.

The average methylparaben content and percent label strength (Table 3) were higher than the target value because the required solution volume for spraying was measured in a 1000 ml graduated cylinder. However, the coefficient of variation was less than 2% for all three batches. All three

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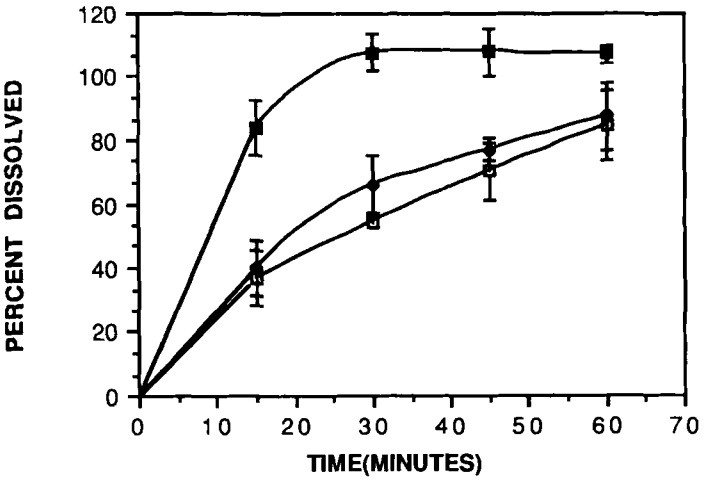

Figure 1.

Effect of propylene carbonate volume on in vitro dissolution of methylparaben from hard gelatin capsules: Key: (⊡) Formulation A containing 10.0 µl/capsule, (◆) Formulation B containing 15.0 µl/capsule, and (■) Formulation C containing 20.0 µl/capsule.

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formulations passed the USP XXI uniformity of dosage specifications by the content uniformity method.

Disintegration

Capsules filled with Formulation A, B, and C disintegrated in 5.3, 5.6 and 6.5 minutes, respectively, by the USP XXI hard gelatin capsule disintegration method.

Dissolution

As shown in Figure 1, one hundred percent release was not achieved in 60 minutes with formulations A and B. Only formulation C showed rapid dissolution, even though all three formulations maintained a plug when the

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compressible sugar was wetted by the dissolution medium. The plug of formulation C, having the highest ratio of liquid to solid (20.0 µL/450 mg fill), broke up quickly and completely released the methylparaben within 30 minutes. The plugs containing 15.0 µL of the 2.33 mg/mL methylparaben solution (Formulation B) and 10.0 µL of the 3.50 mg/ml methylparaben solution (Formulation A) capsules did not break apart completely after 60 minutes resulting in incomplete release of methylparaben. These dissolution results are not without possible consequence as has been retrospectively shown by Yan and Meyer (13). They showed that general correlations can be made between in vitro and in vivo parameters.

Upon wetting and disintegration of the HGC, the capsule contents show a plug which is the result of the capsule filling process. The volume of methylparaben-pc solution appears to affect the formation and cohesiveness of the plug. As the ratio of methylparaben-pc solution to solid decreased it appears the ability for the plug to break apart decreases. This prevents wetting of the inside of the plug and results in a slower and incomplete release of methylparaben.

CONCLUSIONS

All three formulations are equal based on in-process and final capsule weight variation, content uniformity and disintegration. However, dissolution is only acceptable for Formulation C. This formulation has the highest liquid to solid ratio (20.0 µL/450 mg) and it can be run at maximum speed on the H&K 400 capsule filling machine for at least 2 hours with good in-process capsule fill weight variation. Formulation C passed USP XXI uniformity of dosage specification, disintegrated within 10 minutes and demonstrated complete dissolution within 30 minutes.

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