Studies on the Micromeritic Properties of Ibuprofen Microcapsules.

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ABSTRACT

Ibuprofen microcapsules were prepared by complex coacervation phase separation technique using gelatin and grewia gum as coating materials. Gelatin-acacia gum was used to microencapsulate ibuprofen as standard for comparison. Microcapsules were prepared with the ratio of 1:1 core: wall. Micromeritic studies of the two batches of ibuprofen microcapsules were carried out. The flow rate, angle of repose, bulk density, tapped density, true density, Carr's index, Hausner ratio, and mean particle size of each of the batches of microcapsules were studied. The studies showed that the microcapsules prepared using gelatin-grewia gum gave excellent flowability, and smaller particle size in comparison to that of gelatin-acacia gum microcapsules.

(Keywords: Grewia, gelatin, acacia, complex coacervation, microcapsules, micromeritic)

INTRODUCTION

Ibuprofen is a non-steroidal anti-inflammatory drug which also has analgesic and antipyretic activities (Mycek *et al*., 2000). The drug is practically very slightly soluble, but it is readily absorbed from the gastrointestinal tract. This drug causes irritation of gastric mucous membrane. It is also unstable to light. Hence, microencapsulation of the drug in a polymeric shell would be of advantage to these drawbacks.

The use of new natural hydrophilic polymers as drug carriers has received considerable attention in recent decades (Remunan-Lopez and Bodmeier, 1996). Grewia gum is a polysaccharide gum derived from the inner stem bark of edible plant *Grewia mollis* Juss. (Family Tiliaceae). The plant is a shrub abundant in the savannah region of West Africa. The leaves and bark of the plant contain gum. In Nigeria, the dried and pulverized inner stem bark of the plants is used as a thickening agent in some local dishes (Okafor and Chukwu, 2003).

Grewia gum is one of the gums that have potential application in pharmaceutical formulations. The gum is reported to be compatible with many drugs and excipients (Okafor *et al*., 2001). The isolation, chemical contents, physicochemical and rheological properties of the gum has been reported elsewhere (Okafor *et al.*, 2001). Also the binding property, mechanical properties, water vapor permeability of the gum film as well as the influence of granulating solvents on drug release from tablets containing grewia gum have been reported (Okafor *et al.*, 2003; Okafor *et al.*, 2004). But, no report had been given on the application of the gum in microencapsulation.

Several kinds of preparations such as tablets, capsules and coated pellets have been suggested for use as oral extended release formulations. In order to formulate drug powder into these dosage forms, it is very important to assess its flow properties. The physical, chemical and pharmacologic properties of a drug are affected by the size, surface area and surface to volume ratio of a drug particle. Particle size of material used in formulation of suspension, emulsions and tablets is of great importance. Also, the dissolution rate of drug powders and its stability is greatly affected by the particle size distribution (Ozyazici, 1996).

The aim of this work is to investigate the effect of microencapsulation process on the compressibility and compactibility of ibuprofen powder using gelatin-grewia gum in comparison to that of gelatin-acacia gum. Hence, the flow rate, angle of repose, bulk density, tapped density, true density and mean particle size of the microcapsules were determined. The sustained release dosage forms can be obtained by either

tableting the microcapsules or filling these microcapsules into hard gelatin capsules. Therefore, the Carr's (consolidation) index and Hausner ratio of microcapsules were calculated in order to determine the flow ability of the microcapsules.

MATERIALS

In this experiment we utilized the following: Gelatin bloom 275 (granular) type A (Fisher Scientific Company, Chemical Manufacturing Division USA), grewia gum (processed in our laboratory) distilled water, 10% acetic acid, sodium hydroxide, 95% ethanol (BDH Chemicals, England), formaldehyde 37% (Sigma Aldreich Ltd., England), acacia gum (processed in our laboratory), and ibuprofen (Mallinckrodt Chemicals Inc. USA).

METHODS

Preparation of Ibuprofen Microcapsules

The method of Palmieri *et al.* (1996) was adapted. A certain amount of the ibuprofen powder was incorporated into a 2%w/v Grewia gum solution at 40°C. Then an equal volume of 8% w/v gelatin solution at 40°C was added to the suspension and the system was continually stirred. The final ratio between the drug and the two polymers was 1:1. This new suspension was then diluted with pre-warmed (40°C) distilled water. Afterward, the pH of the system was adjusted with 2% sodium hydroxide to give a pH of 4.5 with continuous stirring for 30 mins. at 40°C. 4 ml formaldehyde (37% w/v) was added with continuous stirring for 30 mins. The system was then cooled rapidly to 4-5°C by submerging the beaker containing the microcapsules in an ice bath. The supernatant was decanted and the microcapsules were filtered and freeze- dried.

Freeze-drying

An SB4 freeze-drying machine (Crawley, England) was used for this process. The coacervate was filtered and shared into Petri dishes. These Petri dishes were placed in the specimen chamber of the SBA machine. To freeze the products, the specimen chamber refrigeration button was pressed on the control panel. When the products were frozen to the desired temperature (-47 to 22°C), the specimen chamber refrigeration was switched off, leaving only the condenser refrigeration running. Once the condenser chamber temperature was below -30°C, the vacuum pump was switched on. As vapor went off from the products, it formed as frost on the sides of the condenser chamber. Heat going into the product caused the ice to sublimate or vaporize. All the ice in the products eventually boiled off. The dried product was then collected and analyzed.

Micromeritic Studies

The bulk density as well as the tapped density of each of the batches of microcapsules were determined using a measuring cylinder; while the true density was determined using a liquid pycnometer with kerosene as the displacement fluid. The flowability of the microcapsules was indicated by the angles of repose, Carr's (consolidation) index and Hausner ratio. The flow rate of the microcapsules was determined using an Erweka flow meter, while the angle of repose was evaluated using the fixed height method. Furthermore, Carr's index was calculated using the equation:

$$Carr's\ Index = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} X\ 100 \qquad (1)$$

While Hausner's ratio was calculated using the equation:

$$Hausner's\ ratio = \frac{Tapped\ density}{Bulk\ density} \qquad (2)$$

The Student t-test was used to analyze the results obtained.

Particle Size Analysis

Particle size analysis was carried out to determine the granulometric distribution and mean particle size of the microcapsules. A certain amount of the microcapsules was weighed into Endecotts stainless steel test sieves of the following aperture size (expressed in micrometers) 1800, 1000, 710, 500, 325, 180, 150, 106, and 90 micrometer apertures.

RESULTS AND DISCUSSION

The micromeritic properties of the microcapsules are shown in Table 1.

Table 1: Micromeritic Properties of Ibuprofen Microcapsules.

Properties	Grewia/Gelatin Ibuprofen Microcapsules	Acacia/ Gelatin Ibuprofen Microcapsules
Flow rate (g/sec)	2.8460 ± 0.021	1.5170± 0.090
Angle of repose (degrees)	33.00 ± 0.132	28.33 ± 0.653
Bulk density (g/cm^3)	0.1787 ± 0.007	0.1670 ± 0.001
Tapped density (g/cm^3)	0.1984 ± 0.005	0.1709 ± 0.002
True density (g/cm^3)	1.0423 ± 0.013	1.0388 ± 0.040
Carr's index	9.93	2.29
Hausner ratio	1.11	1.02
Mean particle size	790	1200

The micromeritic properties of microcapsules presented above indicate that the microcapsules produced using 2% w/v grewia gum and 8% w/v gelatin as well as 1% w/v acacia, and 1% w/v gelatin as coating material yielded microcapsules with good flow properties due to the fact that their angle of repose were 33^o and 28.33^o, respectively. As a general rule, powder with angle of repose greater than 50^o has unsatisfactory flow properties (Aulton, 1999). Usually, the particle size of microcapsules is larger than that of raw materials; hence the flow property of the drug is improved by microencapsulating it. However, in order to assess whether this improvement would be enough for producing gelatin capsules and tablets from the microcapsules with the necessary amounts, the Carr's (consolidation) index and Hausner ratio of the microcapsules should be examined.

Microcapsules containing grewia gum and gelatin possessed significantly ($P < 0.05$) higher flow rate than those made with acacia and gelatin.

The values of Hausner's ratio and Carr's compressibility obtained for the microcapsules are in conformity with their flow rates. Both the Carr's index and Hausner's ratio indicate excellent and good flow respectively (Aulton, 1999; Ozyazici, 1996). Usually, the particle size of microcapsules is larger than that of raw materials; hence the flow property of the drug is improved by microencapsulation. The bulk density of ibuprofen microcapsules containing grewia gum and gelatin is $0.1787 g/cm^3$. This is significantly ($P < 0.05$) higher than the bulk density of $0.1670 g/cm^3$ obtained for ibuprofen microcapsules when acacia and gelatin were used.

The coacervating system containing grewia gum and gelatin (2 and 8% w/v) is higher than the system in which acacia and gelatin were used (1% w/v each). This may be responsible for the high bulk density obtained for the drug in the system containing grewia gum and gelatin. So also is the tapped density. Both bulk and tapped densities affect the packing characteristics of powdered material (Aulton, 1999). Increase in tapped density is advantageous in tabletting and encapsulation because of reduced fill volume.

The particle size of materials is another property that affects the packing characteristic of the materials. The mean particle size obtained for ibuprofen microcapsules containing grewia gum and gelatin is 790 µm. The corresponding mean particle size of microcapsules made with acacia and gelatin is 1200 µm. These sizes are within the range of size of microcapsules reported elsewhere (Kumar, 2000). It could be seen that the acacia and gelatin coacervating system produced a higher particle size of the drug than that containing grewia gum and gelatin. Particle size affects flow rates, angle of repose, bulk and tapped densities and the release characteristics of granules, tablets and capsules (Aulton, 1999). The results of the particle size analysis carried out to determine the granulometric distribution and mean particle size of the microcapsules is reflected in the graphs below.

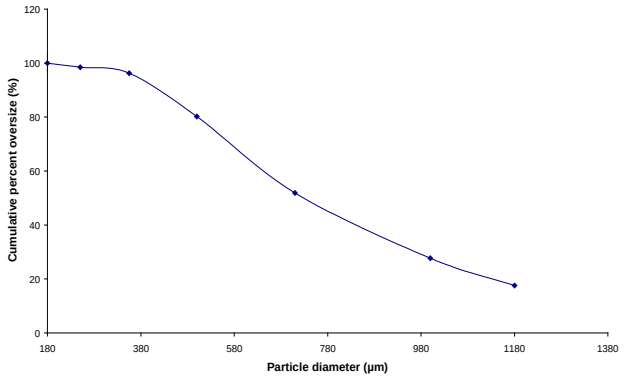

Figure 1: Cumulative Percent Oversize vs. Particle Size for Ibuprofen Microcapsules containing Grewia Gum and Gelatin.

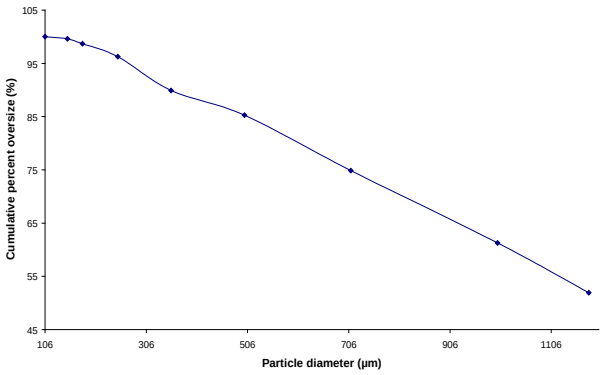

Figure 2: Cumulative Percent Oversize vs. Particle Size for Ibuprofen Microcapsules containing Acacia Gum and Gelatin.

CONCLUSION

The results obtained from this work indicate that Grewia gum which is more economical and readily available compared to acacia would be valuable in micro encapsulation of drugs powders that are intended for preparation of gelatin capsule fill and tablet production. This is due to the fact that similar results were obtained for grewia/gelatin microcapsules as well as acacia/gelatin microcapsules.

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