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Spray Dried Ispaghula Microspheres Loaded with Aspirin: A Report on Unsuccessful Encapsulation.

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ABSTRACT

Aspirin loaded microspheres were prepared by spray drying using ispaghula husk mucilage (IM) and arabinoxylan (AX) as carriers. Aspirin is known for ester hydrolysis, and the degradation rate depends on pH. An attempt is made to encapsulate aspirin using IM and AX at pH of 3 and 7.4. The pH was selected based on the lowest rate of degradation reported on the literature. The yield of microspheres prepared at acid pH was low (less than 5%) and hence discontinued. The yield of microspheres prepared at the alkaline pH was 30-40% and further characterised to study the stability of the encapsulated drug. Scanning electron microscopy revealed spherical and smooth surfaces of drug loaded AX microspheres. In contrast, IM microspheres were non-spherical and shown crystals of degraded drug product on the surface. Particle size analysis of IM and AX microspheres showed an average size of 33.1 and 24.4 µm, respectively. Infra-red spectroscopy and X-ray diffraction analysis of the drug loaded microspheres indicated aspirin degradation. The use of IM/AX as carriers and the spray drying conditions did not prevent aspirin degradation.

Keywords: Arabinoxylan, ispaghula husk, microsphere, spray drying, aspirin.

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INTRODUCTION

Ispaghula (*Plantago ovata*) seed husk contains mucilage, and its alkaline hydrolysis has yielded arabinoxylan [1-3]. Recently; it has received attention in tablet technology as disintegrating agent [4] and release retardant [2]. The intended application was achieved with the ispaghula alone [2, 5] or in combination with other polymers [6]. Due to the hydrophilic nature, it has higher swelling factor [1, 3] of 40-90 %. The purpose of this work to evaluate the formulation of arabinoxylan and ispaghula mucilage microspheres loaded with aspirin by spray drying. Spray drying is one of the methods to enhance dissolution of poorly water soluble drugs [7]. Aspirin is selected as model drug because of its relatively poor solubility in water [8], and many formulations were attempted [9-12] to enhance its dissolution.

EXPERIMENTAL

Materials

Ispaghula (*Plantago ovata*) was purchased from Sidhpur Sat-Isapgol factory, Sidhpur, Gujarat, India. Aspirin (o-acetyl salicylic acid) and all other reagents were purchased from R&M Chemicals, Malaysia.

Methods

Preparation of ispaghula husk mucilage

Ispaghula husk mucilage (IM) is produced by dispersing 2.5 g of ispaghula husk (IH) in 500 ml of phosphate buffer of pH 7.4 at 80 ºC under constant magnetic stirring for 2 h. Then the resulting IM was allowed to cool and filtered through a nylon filter followed by a muslin cloth to get a viscous solution.

Isolation of arabinoxylan

Arabinoxylan (AX) was extracted from the ispaghula husk mucilage was carried out using the method reported by Guo et al. [13]. The gel phase of the IM was separated by centrifugation (L-100XP, Beckman Coulter Ultracentrifuge, USA) at 13200 rpm for 60 min. Later, the gel phase was dissolved in 50 ml 0.5 M of NaOH solution at room temperature and filtered to separate a small amount of residue. The alkaline extract (solution) was neutralized with 2M HCl to produce a large amount of gel-like precipitate. Finally, using centrifugation gel fraction that contains arabinoxylan was collected, washed three times with distilled water and then freeze dried (Labconco Freezone 4.5 Freeze Drier, USA). Freeze dried AX was stored in the freezer until utilized for microsphere formation.

Preparation of aspirin loaded microspheres

To 500 ml of IM, 0.8333 g (25 % w/w of IH) of aspirin was added for encapsulation. The weighed amount of aspirin was triturated with five ml of phosphate buffer pH 7.4 to form a lump-free suspension. Then the suspension was added into the IM and magnetically stirred at room temperature for 2 min to produce a homogenous mixture. While magnetic stirring, the mixture was spray-dried through a one mm nozzle using LabPlant SD-06A Spray Dryer, England. The spray drying conditions were as follows: liquid flow rate of 900 ml/h; the air speed at exhaust is 4.3 m/s; the deblocker was set as fast; the inlet temperature was 130 ºC; outlet temperature was 75-76 ºC. The spray drying process was completed in 20-25 min. Finally, the IM microspheres loaded with aspirin was collected and kept in a desiccator until further use. For AX microspheres, 2 g of freeze dried AX gel was dispersed in 400 ml of phosphate buffer pH 7.4 at 60 ºC under constant overnight magnetic stirring to produce AX solution. To this, 0.6664 g of aspirin (25 % w/w of AX) was added at room temperature and spray dried as explained for IM microspheres. Similarly other batches of IH and AX microspheres were prepared using water and adjusting the pH to three using 1N HCl.

Scanning electron microscopy (SEM)

A Hitachi S-3400N scanning electron microscope was used to study the shape, size and surface morphology of the aspirin and microspheres. Samples were initially coated with a thin layer of platinum using

a Quorum Q150RD SEM sputter coating system before being observed at 50x, 200x and 30,000x magnifications.

Particle size analysis

Microspheres were dispersed in liquid paraffin containing 2% w/w span 80 and sonicated for 30 s before sampling. The particle size was measured by laser diffraction (Malvern Master Sizer-3000, UK) and plotted for size distribution using the software supplied by the manufacturer.

Fourier transform infrared spectroscopy (FT-IR)

Infrared spectra of aspirin and aspirin loaded microspheres were measured between 800 and 2400 cm^{-1} in a Varian 640-IR FT-IR spectrophotometer using attenuated total reflection accessory.

X-ray diffraction

An Olympus InXitu BTXII X-ray diffraction apparatus was used to record the X-ray diffraction patterns of aspirin, unloaded and aspirin loaded microspheres. Each sample was screened through 150 µm sieve and loaded into the apparatus via the sample spinner assembly. The analysis was performed in a Cobalt target X-ray tube operating at 30 kV and 330 µA. A 25 min acquisition produced the diffractograms over a 2θ range.

RESULTS AND DISCUSSION

Preparation of Microspheres

The AX and IM microspheres were prepared by using one mm nozzle to allow continuous spray drying process. As the melting point of aspirin is 135 -139º C [9, 10, 14] the temperature of the spray drying was kept at 130º C with the intention to minimize the degradation of aspirin. The exposure of aspirin to the water during the entire manufacturing kept low as possible (approx. 30 min). The yield of microspheres prepared at acidic condition is very low (less than 5%) and most of the microspheres were adhered on the surface of the cyclone collector. The product was sticky and in rubbery consistency with poor flow properties. We could not improve yield of the microspheres under acidic pH, and the formulation is discontinued. In contrast, the yield of microspheres prepared at pH 7.4 was 30-40%. The freshly prepared microspheres at pH 7.4 were free flowing but shown aggregation due to absorption of moisture during storage. The abosption of moisture could be due to the hydrophilic nature of AX and IM; hence, the microspheres were stored in a desiccator until used.

Scanning Electron Microscopy

The SEM pictures revealed crystalline nature of aspirin (Fig.1A and B) which ranged between 20 to 80 µm. The unloaded AX and IM microspheres were spherical and ranged from 3 to 10 µm with smoother surfaces (Fig. 1 C and D). The drug loaded AX microspheres were spherical with smooth surfaces ranged from 3 to 15 microns (Fig.1 E and F). The SEM pictures also showed a few drug crystals. In contrast, IM microspheres were relatively non spherical, ranged from 4 to 20 microns and shown larger crystals (Fig.1 G and H). Surface of IM microspheres was rough (Fig. 1 H) due to the presence of degraded drug crystals on the surface.

Particle Size Analysis

As shown in Fig. 2, aspirin loaded IM microspheres shown a size distribution from 14 to 300 µm with an average size of 33.1 µm. Whereas, AX microspheres were in the range of 12 to 200 µm with an average size of 24.4 µm. Though SEM pictures shown individual particle of lower size, aggregation of microspheres resulted in higher size ranges. The particle aggregation was also observed in SEM pictures. The aggregation could be due to absorption of water on the surface of microspheres, which resulted in the formation of strong bridges between the particles.

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FT-IR analysis

FT-IR spectra of aspirin, aspirin loaded and unloaded AX microspheres were shown in Fig. 3. A, B and C, respectively. Peaks present at 1750 and 1683 cm^{-1} in the (Fig. 3. A) spectrum of aspirin indicated acetoxyl carbonyl stretching and hydrogen bonded carboxyl carbonyl stretching, respectively [10]. Peaks in the region of 1600-1400 and 1300 -1000 cm^{-1} are due to aromatic C=C and C-O in ester/carboxylic acid of aspirin, respectively [14]. These characteristic aspirin peaks were absent in the FT-IR spectrum of aspirin loaded AX microspheres (Fig. 3. B). Similar effects were also seen in IM microspheres. The FT-IR of unloaded AX microspheres has shown characteristic peaks (Fig. 3. C) of arabinoxylan [15] at 1630 (absorbed water), 1462 (in-plane OH), 1417 (CH_2), 1375 (CH), 1249, 1162 (antisym. bridge oxygen) and 896 (antisym. out of the plan) cm^{-1} and confirms isolation of arabinoxylan from IH mucilage.

XRD

As shown in Fig. 4. A, XRD of aspirin showed several crystalline peaks at 6, 15.5, 16.5, 20.5, 21.5, 22.5, 23.5, 25, 27 and 40.5 degrees. Yan et al. [16] reported similar XRD peaks for aspirin. The XRD patterns of aspirin were absent in the microspheres (Fig. 4. B and C) and shifts of several crystalline peaks were observed. This observation along with FT-IR confirms the degradation of aspirin during spray drying.

Figure 1: SEM pictures of aspirin (A, B), unloaded AX (C) and IH (D) microspheres, aspirin loaded AX (E, F) and IH (G, H) microspheres. Higher crystalline drug observed in IM (G, H) than AX (E, F) microspheres.

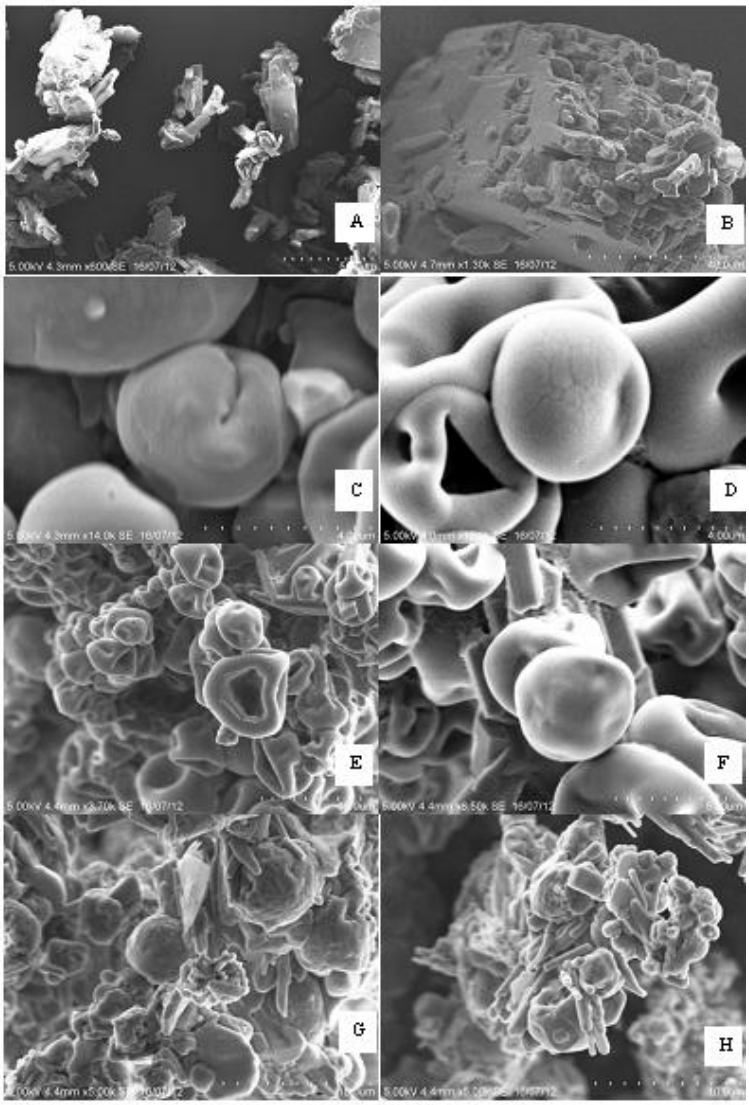

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Figure 2: Particle size analysis of AX (A) and IH (B) microspheres loaded with aspirin.

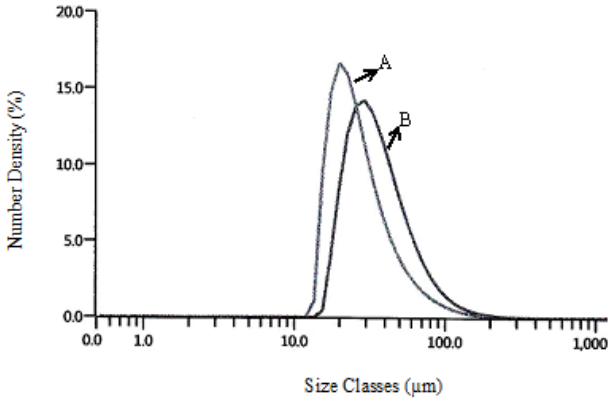


Figure 3: FT-IR spectra of aspirin (A), aspirin loaded (B) and unloaded (C) AX microspheres.

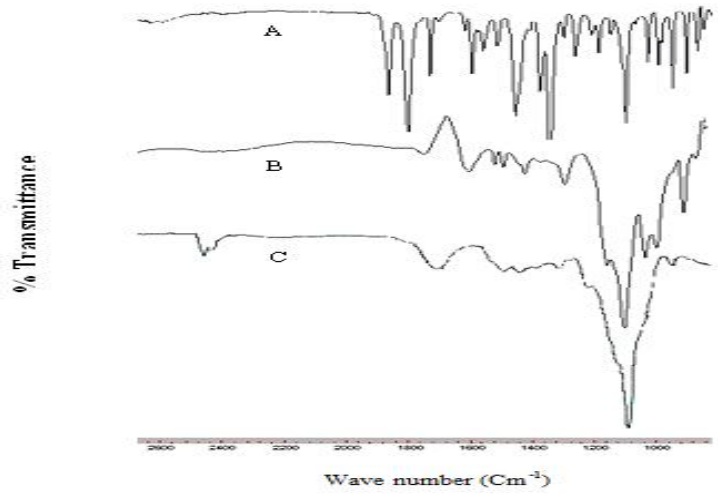
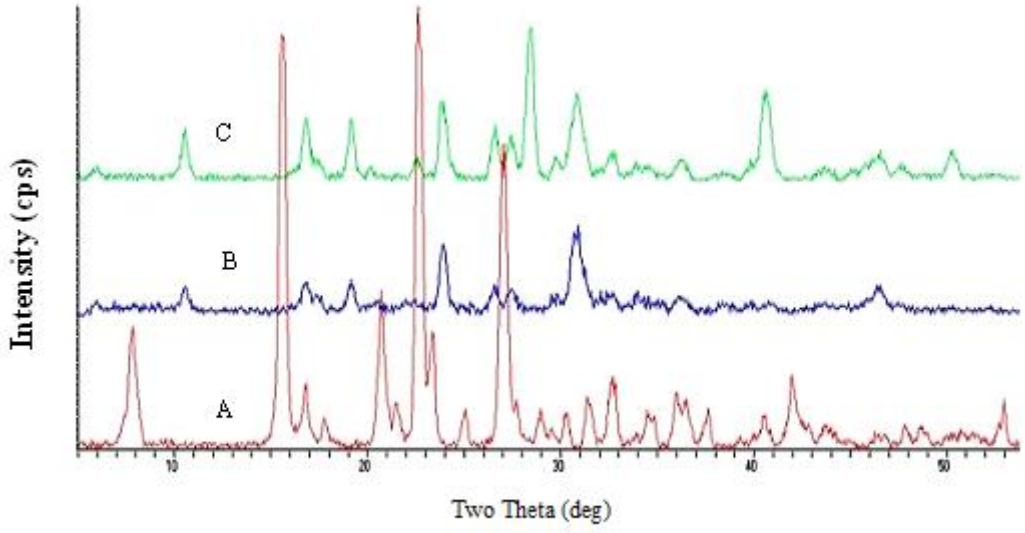


Figure 4: XRD patterns of aspirin (A), AX (B) and IH (C) microspheres loaded with aspirin.



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CONCLUSION

Aspirin is susceptible to pH dependent hydrolytic degradation. The rate of degradation [17] at 17 ºC at pH 3 and 7.4 were 0.027-0.034 and 0.10-0.13 $days^{-1}$. The degradation between pH 5-7.5 is almost same. Extreme acidic and alkaline conditions had shown higher degradation rate. Based on the available degradation data, an attempt was made to spray dry the aspirin at lowest possible degradation pH using IH and AX as the carrier. However, encapsulation of aspirin in arabinoxylan and ispaghula mucilage by spray drying was unsuccessful as neither the carrier nor the spray drying method prevents the hydrolytic degradation of the aspirin.

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