RESEARCH ARTICLE

Preparation and evaluation of sweet potato starch-blended sodium alginate microbeads

Antesh K Jha, A Bhattacharya[1]

Anand College of Pharmacy, (Affiliated to UP Technical University, Lucknow, and Approved by AICTE), AEC Campus, Keetham, Agra - 282 007, [1]Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh, Assam - 786 004, India

The design of effective drug delivery systems has recently become an integral part of the development of new medicines. Hence, research continuously keeps searching for ways to deliver drugs over an extended period of time with a well-controlled release profile. The ionotropic gelation method was used to prepare sweet potato starch-blended controlled release alginate microbeads of ibuprofen. Sweet potato is an important crop in many developing countries. Although sweet potato originated from Central America, its ability to adapt to a wide variety of climatic conditions allows it to grow both in tropical and in moderate temperature regions of Africa, Asia and the Americas. The influence of various formulation factors such as *in vitro* drug release, entrapment efficiency, swelling study and micrometric properties was investigated. Other variables included sweet potato starch concentration, percentage drug loading, curing time, cross-linking agent and stirring speed during the microencapsulation process. The entrapment efficiencies were found in the range of 71.85 ± 2.04 - 94.53 ± 1.02%. The particle sizes were found in the range of 0.82 ± 0.006 - 1.08 ± 0.009 mm. This suggested that the ionotropic gelation method was successful in producing sweet potato starch-blended alginate microbeads.

Key words: *Alginate, ibuprofen, ionotropic gelation technique, sweet potato starch*

INTRODUCTION

Sweet potato (*Ipomea batatas*) is an important crop in many developing countries. Although sweet potato originated from Central America, its ability to adapt to a wide variety of climatic conditions allows it to grow both in tropical and in moderate temperature regions of Africa, Asia and the Americas.[1] Sweet potatoes are rich in starch (6.9 - 30.7% on wet basis)[2] and starch production is the main industrial utilization of sweet potatoes. Sweet potato starch granules are reported as round, oval and polygonal shapes with sizes ranging between 2 and 42 cm.[2,3] Amylose contents of sweet potato starches vary between 8.5 and 38%.[2,4] Swelling and solubility of sweet potato starches are less than those of potato and cassava starches. Both single- and two-stage swelling patterns are found for sweet potato starches of different varieties.[5,6] Gelatinization temperatures of sweet potato starches are reported to be in the range of 58 - 84°C and the gelatinization enthalpy is between 10.0 and 16.3 J/g.[2,7-10] The pasting behaviors of sweet potato starches exhibit a high peak viscosity and they become thinner rapidly with prolonged cooking before thickening on cooling.[2] Sweet potato starches have been reported to retrograde more slowly than wheat and corn starches, but this retrogradation is similar to potato starch.[7,11] Sweet potato amylose appeared to retrograde at the same rate as tapioca amylose but it retrograded more slowly than potato amylase.[7] On the contrary, Rasper[5] showed that sweet potato amylose retrograded at a slower rate than that of tapioca and also that sweet potato amylopectin retrograded at a greater rate than tapioca amylopectin.[5] Alginate is a complex polysaccharide whose composition varies on the basis of the proportions of its monomeric units, namely mannuronic acid and glucuronic acid.[12] In any given alginate preparation, if the occurrence of any one of these monomeric units at a proportion is more than 60% of the alginate composition, that preparation of alginate would be described as high in that particular monomer.[12] Ibuprofen is a non-steroid drug commonly used in the treatment of post-operative, epidural, arthritis, arthragra, dysmenorrhea and dental pain. It is α-aryl propionic acid drug and shows poor water dissolution and tableting behavior due to its hydrophobic-substituted isobutyl benzene. Additionally, its high coalescence results in low flowability and processibility.[13] The drug can be easily absorbed from the gastrointestinal tract and the peak plasma concentrations occur 1-2 h after ingestion.[14] As its duration of action is fairly short,

Address for correspondence:
Dr. Antesh K Jha, Anand College of Pharmacy, AEC Campus, Keetham, Agra - 282 007, India.
E-mail: jha_antesh@rediffmail.com

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repeated administration of the same single dose is necessary during 24 h.[15] In the last two decades, many studies have been undertaken to obtain controlled-release systems for ibuprofen, such as tablets.[16-18] gels,[19,20] osmotic pumps,[21] beads,[22] spherical crystal agglomerates,[23] microspheres and microcapsules[24-27] and nanoparticles.[28] However, serious burst release of ibuprofen was frequently reported.[29] In this study, a series of ibuprofen-loaded microspheres were prepared. It was expected to prolong ibuprofen release and reduce burst release through regulating the composition of the system.

MATERIALS AND METHODS

Materials

Ibuprofen was obtained from Aristo Pharma Ltd. (Mumbai, India). Sweet potato was obtained from local village of Banaras Hindu University, Varanasi (India). Sodium alginate and sodium hydroxide were obtained from LOBA CHEMIE Pvt. Ltd. (Mumbai, India). Calcium chloride, barium chloride, potassium di-hydrogen orthophosphate and aluminum sulfate were obtained from RANKEM, Ranbaxy Fine Chemicals Ltd. (Delhi, India). Tween 80 and Span 80 were obtained from CDH Laboratories, Mumbai (India).

Preparation of microbeads

The ionotropic gelation technique was selected to prepare controlled-release ibuprofen-loaded microbeads due to its simplicity, low cost and its success with poor aqueous soluble drugs and the production of microbeads.[30] The microbeads were prepared by blending pre-gelatinized sweet potato flour with sodium alginate.[31] Sweet potato flour–sodium alginate solutions were prepared by mixing sodium alginate in a pre-gelatinized sweet potato slurry. Ibuprofen was added to the above solution and dispersed thoroughly by stirring on a magnetic stirrer for 15 min. The resulting dispersion was added manually drop wise with a 10 ml syringe (needle) into 100 ml of calcium chloride solution (5, 8 and 12%) or barium chloride solution or aluminum sulfate solution by stirring with a mechanical stirrer. The beads were formed from the outside to the inside. A gelation time of 1 h was allowed to complete the curing reaction and produce spherical and rigid microbeads. The beads so prepared were collected by decantation, washed with distilled water and dried for 6 h, at room temperature, in sunlight and 10 h in a hot air oven at a temperature of 40°C.

Particle size analysis

The particle sizes of the prepared microbeads were determined using the optical microscopy method. It is the most direct method for size distribution measurement. The prepared microbeads were mounted in light liquid paraffin and the diameters of 100 particles were measured by means of an optical microscope equipped with a calibrated ocular micrometer. Then, the mean diameter was calculated.

Entrapment efficiency

About 30 mg of accurately weighed drug-loaded microbeads were crushed in a glass mortar–pestle and added to 50 ml of phosphate buffer, pH 7.4. The resulting mixture was stirred on a magnetic stirrer for 3 h. Then, after the solution was filtered and 1 ml of this solution was appropriately diluted using phosphate buffer, pH 7.4, and analyzed spectrophotometrically at 264 nm using a Hitachi U-2001 (Tokyo, Japan) UV-VIS spectrophotometer, the method was checked for precision and accuracy. The drug entrapment efficiency was calculated as per the following formula:

Entrapment efficiency (E) = (Practical drug content/ Theoretical drug content) $\times 100$

Release study

The drug release behavior of the microbeads was evaluated in phosphate buffer with a pH value 7.4. The paddle method (USP XXI) was used to conduct the dissolution tests and each experiment was performed in triplicate. The paddle position was set at 2.5 cm from the bottom of the flask and the speed was adjusted to 50 rpm. The *in vitro* dissolution studies were carried out in 500 ml of phosphate buffer maintained at 37 ± 0.5°C. Microbeads containing 30 mg of the drug were employed in each case. Aliquots of 5 ml were withdrawn and immediately replaced with 5 ml of the dissolution medium to maintain a constant volume of 900 ml. The samples were taken at the following time intervals: 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 h, respectively. Stirring with the paddles was continued for up to 10 h and the speed was increased to 200 rpm for the last 15 min in order to estimate the 100% release point. The samples were filtered through a Whatman filter paper and the absorbance was determined at 264 nm using a Hitachi-2001(Tokyo, Japan) UV-VIS spectrophotometer against an appropriate buffer as a blank.

Stability study

The drug-loaded microbeads were stored at various storage conditions (room temperature, 40°C) in an airtight container. The drug content of the drug-loaded microbeads was determined as described, at regular intervals of 0, 4, 8, 12, 16, 20, 24 and 28 days.

RESULTS AND DISCUSSION

The effects of various process and formulation parameters on the particle size and drug entrapment efficiency

The effects of various process and formulation parameters on the particle size and entrapment efficiency of the prepared microbeads are shown in Tables 1 and 2. Ibuprofen-containing microbeads were in the size range of 0.82 ± 0.006 - 1.08 ± 0.009. Ibuprofen-loading amount, stirring speed, curing time, polymer concentration and cross-linking agent seemed to affect the values of particle size. It was found that the particle size

Table 1: Formulation table

	Processing parameters					
Formulation code	Sweet potato flour (mg)	Sodium alginate (mg)	Ibuprofen (mg)	Cross-linking agent (% w/v)	Stirring speed (rpm)	Curing time (h)
F1	100	200	100	8*	200	1
F2	200	200	100	8*	200	1
F3	100	200	50	8*	200	1
F4	100	200	150	8*	200	1
F5	100	200	100	5*	200	1
F6	100	200	100	12*	200	1
F7	100	200	100	8**	200	1
F8	100	200	100	8***	200	1
F9	100	200	100	8*	300	1
F10	100	200	100	8*	200	6
F11	100	200	100	8*	200	12

*Calcium chloride; **Barium chloride; ***Aluminum sulfate

Table 2: Effect of various processing parameters on the particle size and drug entrapment efficiency of ibuprofen-loaded microbeads

Formulation code	Mean particle size (mm ± SD)	Entrapment efficiency (%) (± SD, n = 3)
F_1	0.88 ± 0.006	88.36 ± 1.07
F_2	1.08 ± 0.009	93.27 ± 1.04
F_3	0.82 ± 0.006	94.53 ± 1.02
F_4	0.94 ± 0.014	81.18 ± 1.19
F_5	0.82 ± 0.006	81.94 ± 2.07
F_6	0.94 ± 0.008	88.25 ± 1.16
F_7	0.82 ± 0.006	88.88 ± 1.21
F_8	0.82 ± 0.009	71.85 ± 2.04
F_9	0.86 ± 0.012	85.09 ± 1.35
F_{10}	0.82 ± 0.014	84.01 ± 1.84
F_{11}	0.98 ± 0.006	86.35 ± 2.08
F_{12}	1.04 ± 0.014	85.54 ± 0.77

increased significantly by increasing ibuprofen loading. When the ibuprofen loading was high, the proportion of larger particle formed was also high. The viscosity of the polymer solution at such high drug loading was very high and was responsible for the formation of large microbeads. The size of the prepared microbeads could easily be controlled by varying the stirring speed of the system and the concentration of the sweet potato flour to the aqueous medium. At low stirring speed (200 rpm), the mean particle diameter of the prepared microbeads increased significantly. At a stirring speed of 300 rpm (also 400 rpm), the particle changed to a lesser extent. At this higher stirring speed, a vigorous, uniform, increased mechanical shear might have resulted. This suggests that the size of the droplets formed during microencapsulation might, therefore, be closely related to the size of the final microbeads, which increased significantly by decreasing the stirring speed. The increase in the concentration of the cross-linking solution has shown microbeads with a larger particle diameter. This appears to result from the incorporation of a higher amount of the non-shrinkable solids to the polymer skeleton. Furthermore, the viscosity of the polymer solution significantly affected the microbead size distribution. The smallest microbeads were produced when sweet potato flour was used at a low concentration. Low polymer concentration resulted in decreased inner-phase viscosity, which might efficiently promote the break-up of the coacervate droplets and prevent coalescence. The entrapment efficiencies were found in the range of 71.85 ± 2.04 - 94.53 ± 1.02% for ibuprofen-containing microbeads. Good entrapment efficiency was achieved by increasing the polymer concentration. Evaluation of the variation of the polymer concentration showed that ibuprofen was highly entrapped when the polymer concentration was high. A reduction in curing time and stirring speed showed improved entrapment efficiency. The small particle size of the microbeads showed lower entrapment efficiency when compared with the big particle size of the microbeads. The entrapment efficiency was related to the particle size of the ibuprofen-loaded microbeads. On the other hand, the entrapment efficiencies were determined to increase as their mean particle sizes increased. Barium chloride, as a cross-linking agent, was found to improve the drug load. Furthermore, aluminum sulfate, as a cross-linking agent, was found to decrease the drug load as it produced porous microbeads than that of calcium chloride as a cross-linking agent.

Release study

The release pattern observed, as shown in Figures 1 and 2, was biphasic, as characterized by an initial burst effect followed by slow release. Microbeads with smaller diameters showed higher percentages of drug release than bigger particles. The higher and faster drug release displayed by the microbeads with a smaller diameter could be attributed to the decrease of sweet potato flour–sodium alginate matrix density related to the increase in porosity. The smallest-sized microbeads presented a very fast release rate. As the polymer concentration of the prepared microbeads increased, the release rate was decreased. An inverse relationship was

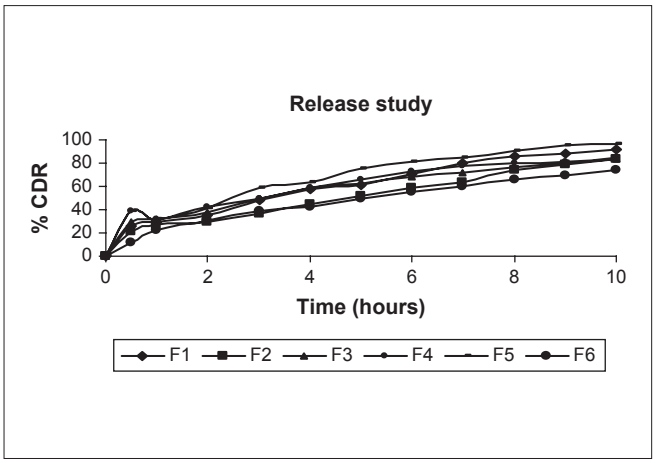

Figure 1: Effect of amount of drug and polymer concentration and concentration of the cross-linking agent

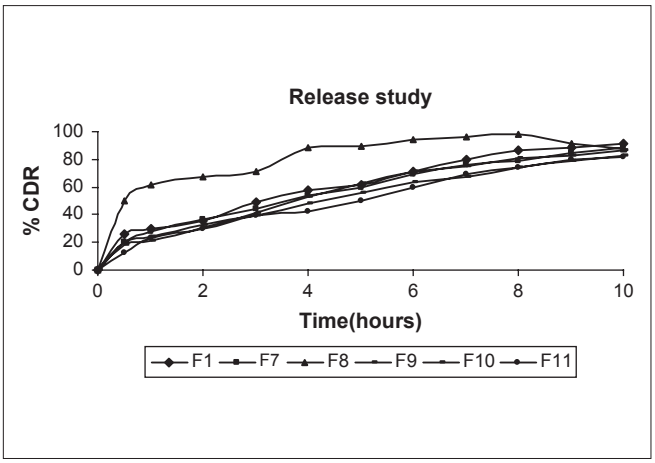

Figure 2: Effect of different cross-linking agents, stirring speed and curing time

observed between the polymer concentration and the drug release from the prepared microbeads. The drug release from microbeads prepared at lower drug–polymer ratios was faster than that of microbeads prepared at higher drug–polymer ratios because of the small size of the microbeads, which produced a larger surface area for faster drug release. This finding is consistent with the general rule (i.e., small size of microspheres provides larger surface area for faster drug release). It was found that aluminum sulfate, as a cross-linking agent, produced a very irregular and non-reproducible release pattern and therefore could not be utilized for the preparation of the sustained release microbeads but calcium chloride, as a cross-linking agent, produced a regular and reproducible release pattern. Therefore, it could be utilized for the preparation of sustained release microbeads. As the concentration of calcium chloride increased, the release rate decreased. Here also, an inverse relationship was observed between the concentration of cross-linking agent (calcium chloride) and drug release from the prepared microbeads. It was also found that as the curing time of the prepared microbeads increased, the release rate decreased. Around 25% of the drug was found to be released in the first 30 min. This result could be due to the loosely bound surface-embedded drug. The subsequent slow release may be because of the release medium being diffused into the polymer matrix, whereby the drug may have diffused out of the microbeads. All these results indicate that release of ibuprofen from sweet potato flour-blended sodium alginate microbeads can be controlled by varying the drug–polymer ratio, polymer concentration, curing time and concentration of the cross-linking agent.

Stability study

Table 3 showed results of drug content for drug-loaded microbeads (F_{11}) at various storage conditions for a period of 28 days. As described in the table, there was no significant change in the drug content of drug-loaded microbeads, stored at room temperature, room temperature and 40°C after 28 days of study.

Table 3: Stability study data of ibuprofen-loaded microbeads at various temperatures

Days	Drug entrapment efficiency at room temperature (°C)	Drug entrapment efficiency at 40°C
0	88.25 ± 1.09	88.22 ± 1.02
4	88.23 ± 2.09	88.19 ± 1.71
8	88.21 ± 2.17	88.07 ± 2.18
12	88.18 ± 2.09	88.07 ± 2.06
16	88.07 ± 1.09	88.04 ± 1.31
20	88.03 ± 1.32	87.93 ± 2.01
24	87.97 ± 3.32	87.95 ± 2.07
28	87.71 ± 1.03	87.85 ± 1.01

CONCLUSION

In conclusion, the present study reveals the characteristics of ibuprofen-loaded sweet potato flour–alginate microbead formulations. The ionotropic gelation can be used in producing ibuprofen-loaded sweet potato flour-blended alginate microbeads. The formulation variables, drug loading, polymer concentration, cross-linking agents, stirring speed and curing time influenced the mean particle size, entrapment efficiency and *in vitro* drug release characteristics of the prepared microbeads. The entrapment efficiencies were not affected when subjected to different stability conditions. The data suggest that sweet potato flour is a potentially useful natural material for making controlled release ibuprofen-loaded microbeads by the ionotropic gelation technique.

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