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Pharmaceutical Utility of Assam Bora Rice for Controlled Drug Delivery

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Abstract: The use of natural polymers in the drug delivery continues to be an area of intensive research despite the advent of several new synthetic polymers. The present study envisages pharmaceutical utility of Assam glutinous rice as natural biopolymeric matrix for microfabricated controlled DDS. Microcarriers were prepared using an industrially feasible ionic gelation method using the blends of proposed new biopolymer alongwith sodium alginate. The microcarriers so prepared were subjected to characterization for particle size analysis, entrapment efficiency, mucoadhesivity, swelling, surface topography and drug release kinetics in an *in vitro* dissolution testing. The prepared microcarriers showed excellent drug entrapment efficiency, having the particle size distribution in range of 0.98 ± 0.008 to 1.12 ± 0.014 mm and exhibited pH dependent drug release in an *in vitro* dissolution test. Scanning electron microscopy revealed the irregular surface of the microcarriers and with varying shapes.

Key words: Drug delivery · Assam glutinous rice · Microcarriers · Biopolymer

INTRODUCTION

Drug delivery is highly innovative in terms of materials to assist delivery, excipients and technology which allow fast or slow release of drugs [1]. DDS (DDS) that can precisely control the release rates of target drugs to a specific body site have had an enormous impact on the health care system. The last two decades in the pharmaceutical industry have witnessed an avant-grade interaction among the field of polymer and pharmaceutical science, resulting in the development of novel DDS [2]. Design of effective DDS has recently become an integral part of the development of new medicines. The goal is to provide drug release in an amount sufficient to maintain the therapeutic drug level over extended period of time, through the predominantly controlled release profiles by special technological construction and design of the system itself [3]. Hence, research continuously keeps on searching for ways to deliver drugs over an extended period of time, with a well-controlled release profile. The market of oral controlled drug delivery alone is expected to grow at 9% more every year. The driving force behind this booming market can be categorized as the patient related factors like patient comfort and compliance, reduction in healthcare cost and reduced toxicity, as well as the market driven factors like regular input of new chemical entity (NME), Govt. incentives for R and D, possibility of repatenting successful drugs [4], coupled with increasing expenses in bringing NMEs to market has been instrumental in generating interest in controlled release DDS as an attractive financial option to pharmaceutical companies in addition to seeking new therapeutic indications to new products [5]. A number of technologic advancements with regard of regulating the rate of drug delivery, sustaining the duration of therapeutic action and /or targeting the drug to specific site or tissue have been made over the recent years. Based on the technologic sophistication, oral CRDDS are categorized as matrix based systems, enteric gels, osmotically controlled systems, microcarriers, submicron DDS, feedback regulated, stimuli sensitive or site targeted DDS [6]. Among the wide spectrum of CRDD technologies, the carrier mediated DDS are one of the most successfully survived technologies offering a number of advantages. The most important function of drug carriers is to regulate the release rate of the drug and thereby to reduce effectively the chance of both underdosing and overdosing, thus provide better use of the active agents. It can also alleviate disadvantages from allergy of some patients [7-9].

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Polymers are large molecules synthesized from smaller molecules called *monomers* [10]. The use of polymers in pharmaceutical preparation dates back to 3000 B.C.E, with references in ancient Indian medical text *'Atharvveda'*. The usefulness of polymers in DDS is well established now, they have become an indispensable part of the DDS, be it be conventional drug delivery or novel drug delivery. The role of polymeric excipients is more unique and active than traditional excipients since not only do they modify the pharmacokinetics of the encapsulated drug, but they also shield the drug from enzymatic attack [11]. They have drastically changed the mode of drug delivery by introducing lot of flexibility. The better polymeric excipients have been continuously in demand to overcome the cost barriers, for better pharmacokinetic profile and to by-pass the patent barriers in the manufacture of certain products by pharmaceutical industries which could have otherwise been protected by patents and require regulatory processes for grant of permission to manufacture from innovator and are huge cost affairs [12]. The application of drug delivery is a valuable, cost-effective life-cycle management resource [13, 14].

With more than 50 patents expired recently and several other in queue, which includes a number of blockbuster drugs, pharmaceutical companies are recognizing drug delivery technology, which is based on the use of polymer, as a powerful strategic marketing tool to differentiate products. This enables them to extend product life cycle and remain competitive in the marketplace [15, 16, 17]. By infusing drugs with new and innovative therapeutic benefits, DDS extend products profitable life cycle, giving pharmaceutical companies competitive and financial advantages and providing patients with improved medications. Therefore in present investigation, pharmaceutical utility of *'Assam Bora rice'*, a variety of glutinous rice cultivated mainly in Assam region and characterized by very high amylopectin content [18], is proposed and examined as biopolymeric matrixing agent for CRDDS.

Experimental

Materials: The *Bora rice* was procured from the local market of Dibrugarh Assam. Drug samples were obtained as gift sample from industrial sources. Sodium alginate (Loba Chemi Pvt. Ltd. Mumbai), Calcium chloride (Qualigens Mumbai, India), Hydroxyl propylmethylcellulose (Loba Chemi Pvt. Ltd. Mumbai), Calcium chloride (Ranbaxy Fine Chemicals, India) and Barium chloride (Ranbaxy Fine Chemicals, India), were procured from the commercial sources. Ibuprofen was kindly gifted by Ms Aristo Pharma Ltd. India. All other reagents were of analytical grade laboratory reagents.

Preparation of Microcarriers: The microparticulate DDS were prepared from the gel blend of pregelatinized *Bora rice* and sodium alginate [19] in varying proportions (Table 1). The rice polysaccharide was gelatinized by thermal gelation by autoclaving the aqueous suspension of known strength of rice flour at 121 °C for 1 hour [20]. Drug was added to *Bora rice* polymer in a calculated amount and ultrasonicated for 30 sec to 1 min. The two gels were then blended and homogenized in a way to obtain suitable rice sodium alginate ratio *viz*. 4:1, 3:1, 2:1. The resulting dispersion was added drop-wise into cross-linking solution ($CaCl_2$, $BaCl_2$, or Al_2SO_4) with constant stirring. Microcarriers were allowed for 35-40 min curring as time and were washed with distilled water, dried in vacuum oven at a temperature below 40 °C and stored in a desiccator for further use.

Table 1: Formulation Table

Processing parameters					
Formulation code	Bora rice (mg)	Sodium alginate (mg)	Ibuprofen (mg)	Cross linking agent (%w/v)	Stirring speed (rpm)
F1	375	125	100	8*	200
F2	500	125	100	8*	200
F3	375	125	50	8*	200
F4	375	125	150	8*	200
F5	375	125	100	5*	200
F6	375	125	100	12*	200
F7	375	125	100	8**	200
F8	375	125	100	8***	200
F9	375	125	100	8*	300
F10	375	125	100	8*	400
F11	375	125	100	8*	200
F12	375	125	100	8*	200

* Calcium chloride, ** Barium chloride, *** Aluminium sulfate

Particle Size Analysis: The particle size and size distribution of prepared microcarriers was studied by the optical microscopy using phase contrast microscope (LaboMed XLR II) and the mean diameter was calculated. The effect of drug concentration, concentration of cross-linking agent and ratio of the two polymers on the average particle size were studied [20].

$$\text{Mean particle size} = \sum n.d / \sum n$$

Entrapment Efficiency: Accurately weighed drug loaded microcarriers equivalent to about 30 mg of drug were crushed in a glass mortar-pestle and added to 50 mL of phosphate buffer, pH 7.4. The resulting mixture was homogenized to leach out the drug and filtered. One mL of this solution was so diluted using phosphate buffer, at pH 7.4 to get an absorbance below 1 when analyzed spectrophotometrically at 264 nm using UV-VIS Spectrophotometer (Hitachi U-2001, Japan). The drug entrapment efficiency was calculated as per the following formula [20]:

$$\text{Entrapment efficiency} = \frac{\text{Estimated percentage drug loading}}{\text{Theoretical percentage drug loading}} (100)$$

$$\text{Percentage drug loading} = \frac{\text{Amount of drug in microspheres}}{\text{Amount of microspheres}} (100)$$

Swelling Studies: The swelling studies were performed gravimetrically in aqueous swelling media with 0.1M HCl, buffer at pH 7.4 and water at 37.5 ± 0.5 °C. The swelling ratio, S_{wt}, was calculated from the following expression [21]:

$$S_{wt} = [(W_t - W_0)/ W_0] \times 100$$

Where Wt and W_0 are the weight of sample swollen at time t and the weight of the original sample, respectively.

Evaluation of Mucoadhesive Property: The mucoadhesive property of the fabricated DDS was evaluated using *in vitro* wash-off test by modifying a tablet disintegration test apparatus, wherein the upper moving cage was removed and moving arm was tagged with a glass using silk thread. A rectangular piece of chicken mucosa was fixed at the side of glass slide using an acrylic adhesive. To this mucosal surface, microspheres were attached moving up and down dipped in aqueous medium to check for how long they will take to detach from mucosal surface. The retention time of the microcarriers to the e xcised mucosa was compared with a non bioadhesive material in different release environments [22].

Water Vapour Uptake Study: The prepared microcarriers were kept in the controlled humidity environments (32%, 52%, 75% and 92%), in contact with saturated salt solutions of Potassium acetate, Magnesium nitrate, Sodium chloride and Potassium nitrate in a closed vessel. The equilibrium moisture content was determined by weight difference attained due to the moisture uptake by the microcarriers [23].

***In vitro* Drug Release Studies:** The drug release behaviour of the microcarriers was evaluated in two different phosphate buffers with pH values of 5.8 and 7.4 respectively using the USP dissolution rate test paddle-type apparatus at 50 rpm, performed in triplicate [24, 25]. Microcarriers equivalent to 30 mg of the drug were used each time for dissolution studies. 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 time intervals of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 hours. The samples withdrawn were filtered through a membrane filter and quantified for drug content spectrophotometrically by measuring absorbance measurments at 264nm using in UV-VIS spectrophotometer (Hitachi-2001, Japan) taking appropriate buffer as blank.

Fourier Transform Infrared Spectroscopy (FTIR): Drug-polymer interactions were studied by FTIR spectroscopy. The spectra were recorded for Ibuprofen, *Bora rice*, sodium alginate, blank microcarriers and drug-loaded microcarriers using JASCO FT-IR 4200. Samples were prepared in KBr disks (2 mg sample in 200 mg KBr).The scanning range was 450-4000 cm^{-1} and the resolution was 4 cm^{-1}.

Scanning Electron Microscopy Analysis (SEM): Scanning electron microscopy (SEM) was carried at an accelerating voltage of 15 kV and 20 kV using scanning electron microscope (JSM-5501LV, Japan). The microcarriers were placed on one side of an adhesive stub and the stub was then coated with conductive gold with sputter coater attached to the instrument.

X-Ray Powder Diffractometry: X-ray powder diffractometry was carried out to investigate the effect of microencapsulation process on crystallinity of the drug.

Powder XRD patterns were recorded on a Carl Zeiss Leo Model 1430 VP. Scanning rate employed was 1° min^{-1} over the 10° to 80° diffraction angle (2è) range. The XRD patterns of Ibuprofen crystals, *Bora rice,* sodium alginate and powdered blank as well as drug-loaded microcarriers were recorded.

Differential Scanning Calorimetry: The DSC analysis of pure drug, *Bora rice*, sodium alginate, blank microcarriers and drug-loaded microcarriers was carried out using Perkin Elmer DSC No 7, to evaluate any possible drug-polymer interaction. Blank microcarriers and drug-loaded microcarriers were triturated to get a finely divided powder and passed through a sieve # 100 before analysis..

Stability Study: The drug-loaded microcarriers were stored at various storage conditions (room temperature, 40° C) in airtight container. The drug content of the drug-loaded microcarriers 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 entrapment efficiency of *Bora rice* microcarriers are shown in Table 2. Ibuprofen containing microcarriers were in the size range of 1.06 ± 0.006 to 1.20 ± 0.014mm. Ibuprofen-loading amount, stirring speed, curring time, polymer concentration and cross-linking agent seemed to affect the particle size and size distribution of microcarriers. It was observed that the particle size increased significantly by increasing polymer: drug ratio. When the Ibuprofen-loading was high, the proportion of larger particle formed was also high. The viscosity of polymer solution at such high drug loading was comparatively higher and therefore might be responsible for the formation of large microcarriers. Furthermore, it was also observed that the particle size was inversely proportional to the percentage of the polymer. The size of the prepared microcarriers could easily be controlled by varying the stirring speed of the system and the concentration of *Bora rice* to the aqueous gel prepared by thermal gelation. At low stirring speed (200 rpm), the mean particle diameter of the prepared microcarriers increased significantly. At a stirring speed of 300 rpm and 400 rpm, particle size change was lesser than variation at higher rage of rpm. The increase in the concentration of the cross-linking solution has shown the microcarriers with larger particle diameter. This appears to be resulted from the incorporation of higher amount of the non-shrinkable solids to the polymer skeleton. The viscosity of the polymer solution significantly affected the microcarriers size distribution. The entrapment efficiency of different batches found ranging from 70.85 ± 2.14% to 93.53±1.12% for Ibuprofen containing microcarriers. Better entrapment efficiency was achieved by increasing polymer concentration. A reduction in curring time and stirring speed also has a positive impact on entrapment efficiency of drug loaded microcarriers. Microcarriers cross-linked with barium chloride have shown better entrapment when compared to the microcarriers produced by calcium chloride and aluminium sulphate cross-linking. This is probably due to the non porous microcarriers produced by barium as revealed in SEM analysis.

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

Serial No.	Formulation code	Mean particle size (mm± SD)	Entrapment efficiency (%) (± SD, n =3)
1	F_1	1.08±0.009	86.56±1.03
2	F_2	1.20±0.014	92.20±1.44
3	F_3	1.06±0.009	93.53±1.12
4	F_4	1.11±0.014	80.18±1.19
5	F_5	1.06±0.010	80.94±2.20
6	F_6	1.11±0.022	87.25±1.56
7	F_7	1.06±0.006	87.88±1.21
8	F_8	1.06±0.021	70.85±2.14
9	F_9	1.07±0.009	84.09±1.35
10	F_{10}	1.06±0.014	83.01±1.84
11	F_{11}	1.13±0.012	85.35±2.08
12	F_{12}	1.19±0.010	84.54±0.77

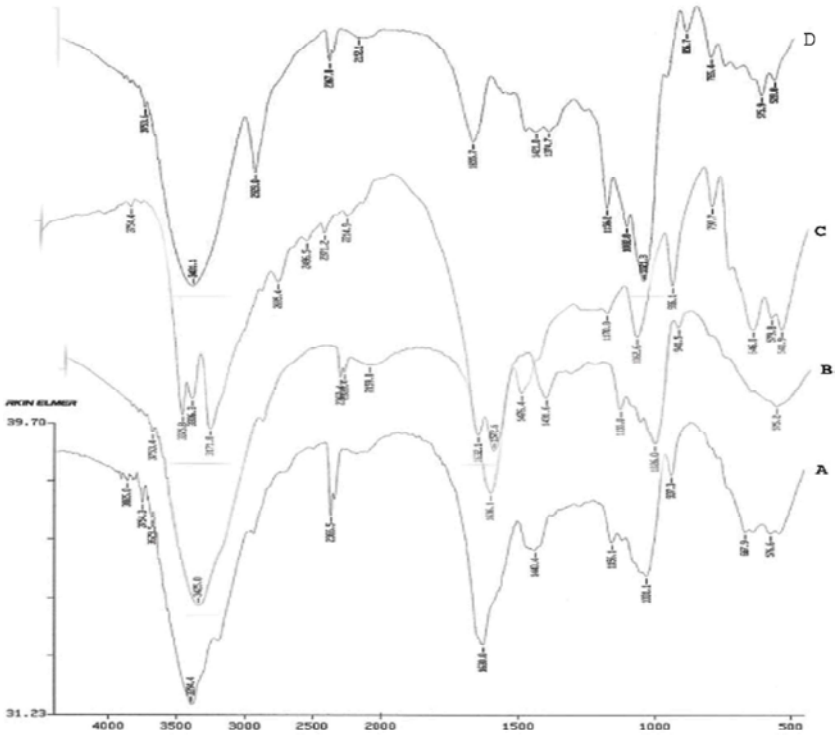

Fig. 1: FTIR Spectra of Microcarriers: (A) Drug loaded microcarriers (B) Placebo (C) Bora rice polysaccharide (D) Pure drug sample

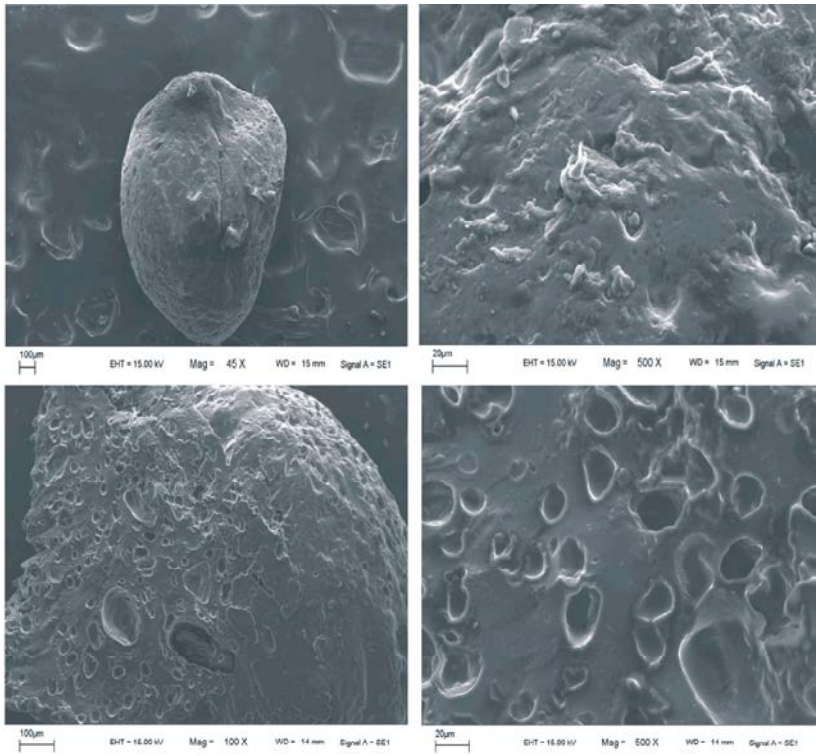

Fig. 2: Scanning electron microscopy image of Ibuprofen loaded *Bora rice* microcarriers before and after dissolution (45 X, 100 X and 500X).

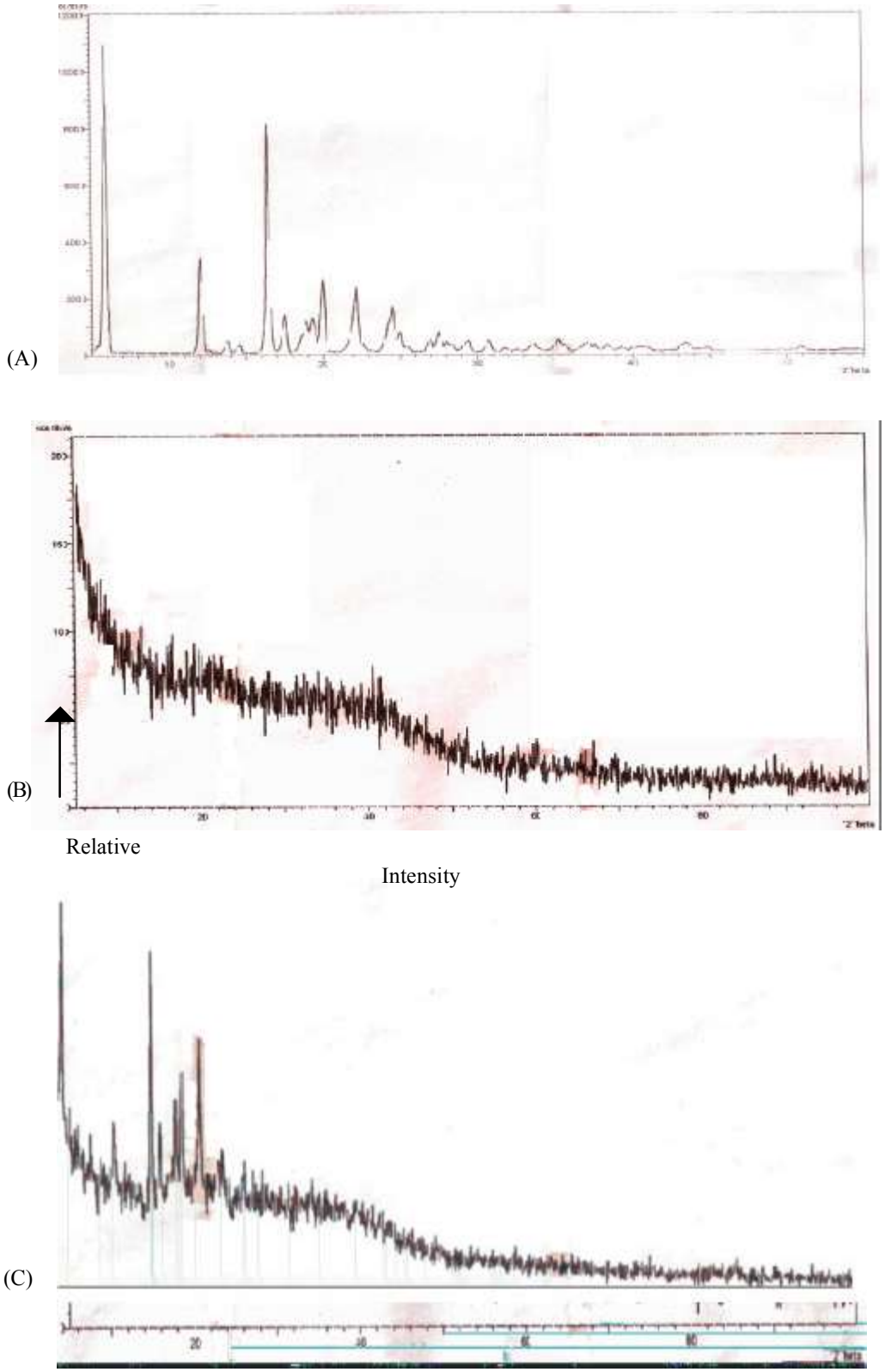

Fig. 3: XRD spectra of (A) Ibuprofen, (B) blank microcarriers, (C) Ibuprofen-loaded microcarriers.

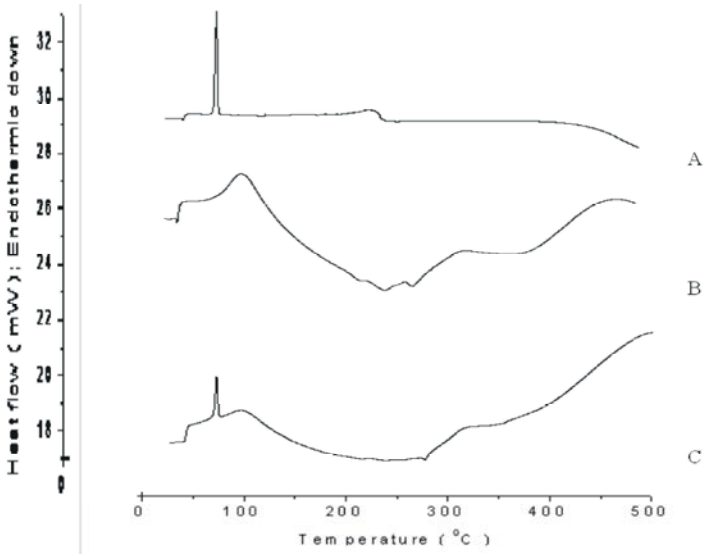

Fig. 4: DSC curves of (A) Ibuprofen, (B) blank microcarriers, (C) Ibuprofen-loaded microcarriers

FTIR spectrum of the drug showed characteristic peaks of Ibuprofen at around 1070 cm^{-1}, 1231 cm^{-1}, 1420 cm^{-1}, 1720 cm^{-1} and 2922 cm^{-1}. Peaks at around 1720 cm^{-1} and 2922 cm^{-1} were due to carbonyl and hydroxyl stretching respectively confirming the identity of drug. From spectra it was found that there was no significant difference in the FTIR spectra of drug and polymers as well as drug loaded microcarriers when compared to the spectra of individual components.

The characteristic carbonyl-stretching band of isopropionic acid group of drug was unchanged in case of microcarriers. The characteristic peaks are retained in drug loaded microcarriers revealing that there is no chemical interaction between the drug and polymeric backbone which is further supported by DSC. The scanning electron microscopy (Fig. 2) revealed the varying shape and irregular surface morphology of the microcarriers under different magnifications *viz.* 45x, 100x, 250x and 500x, for the different batches. Although the fresh microcarriers prepared by Ionic gelation method were in round shape but after air and oven drying the particles get totally deformed in shape. This might be due to the surface pressure and unequal water loss through the surface. The microcarriers coated with HPMC are having smooth surface. Both the coated and uncoated microcarriers after dissolution showed lot of holes and cracks on the surface that depicts drug release from the microcarriers. The X-ray powder diffraction patterns of *Bora rice-alginate* microcarriers along with raw crystals of drug and polymers are shown in figure 3. The Ibuprofen loaded bora rice alginate system, in the form of microcarriers, indicated the presence of the crystalline Ibuprofen but with a dramatic decrease of the intensity of the signal because of both of dilution effect and a decrease in crystallinity of drug. X-ray diffractogram of *Bora rice* also depicts its semi-crystalline nature and the supports the findings of Zhang *et al.* 1993 [24].

The DSC thermograms (Fig. 4) having sharp endotherm observed for Ibuprofen at the temperature corresponding to its melting point. The same thermal behavior of Ibuprofen was observed in Ibuprofen-loaded *Bora rice*-alginate microcarriers showing thermal peak at around melting point of Ibuprofen but lost its sharp appearance. This reveals that that the drug is physically matrixed in the polymer backbone with no chemical reaction with polymer or excipients. The DSC thermogram of *Bora rice* is having two endotherms one corresponding to its glass transition temperature and the another represents melting of amylopectin crystallites.

The drug release pattern observed (Fig. 5) were biphasic, characterized by an initial burst effect followed by slow release. Microcarriers with smaller diameters showed higher percentages of drug release than bigger particles. An inverse relationship was observed between polymers concentration and drug release from the prepared microcarriers, as polymer concentration of the prepared microcarriers increased, the release rate was decreased. Increasing the drug load of microcarriers by higher drug ratio in blend has a little effect on the drug release pattern of microcarriers. Higher drug load in the microcarriers results a comparative faster release pattern. It was found that the aluminium

Table 3: Stability study data of Ibuprofen-loaded microcarriers at various temperatures

S. No.	Days	Drug entrapment efficiency at room Temp.(°C)	Drug entrapment efficiency at 40°C temperature
1	4	85.25 ± 2.09	85.22 ± 3.02
2	8	85.21 ± 2.17	85.17 ± 2.08
3	12	85.18 ± 1.09	85.01 ± 1.06
4	16	85.07 ± 2.01	84.91 ± 2.31
5	20	84.91 ± 1.32	84.73 ± 2.77
6	24	84.87 ± 3.32	84.65 ± 2.97
7	28	84.71 ± 2.03	84.55 ± 2.01

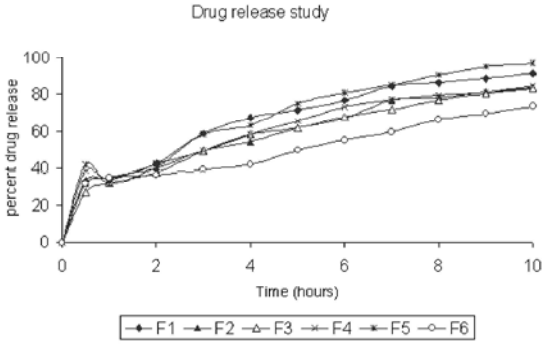

Fig. 5a: Effect of amount of drug and polymer concentration and concentration of cross-linking agent.

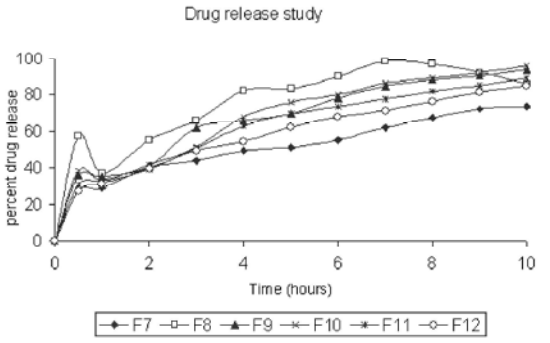

Fig. b: Effect of different cross-linking agents, stirring speed and curring time.

sulfate, as cross-linking agent, produced very much irregular and non-reproducible release pattern as compared to calcium chloride, as cross-linking agent which produced regular and reproducible release. Therefore it is concluded that aluminium sulphate is not suitable for use as cross-linking agent for preparation of sustained release microcarriers by ionic gelation method. Increasing the concentration of cross-linking agent, the release rate was more smooth and controlled and it also increases the drug entrapment efficiency. Therefore an inverse relationship was observed between the concentration of cross-linking agent (calcium chloride) and drug release from the prepared microcarriers. It was also found that as the curring time of the prepared microcarriers increased, the release rate was decreased. The pay-load of drug in the first 30 min was found to be about 32 percent. This result could be due to the loosely bound of surface-embedded drug. The subsequent slow release resulted probably because of the release medium being diffused into the polymer matrix, whereby drug may have diffused out of the microcarriers. All these results indicate that release of Ibuprofen from *Bora rice*-sodium alginate microcarriers can be controlled by varying the drug-polymer ratio, polymer concentration, curring time and concentration of cross-linking agent.

An stability indicating assay as shown in Table 3, reflects drug content for drug-loaded microcarriers (F_{11}) at various storage conditions for a period of 28 days. It shows that there was no significant change in the drug content of drug-loaded microcarriers, stored at room temperature, room temperature and 40°C after 28 days of study.

CONCLUSION

In conclusion, the ionotropic gelation can be used in producing Ibuprofen-loaded *Bora rice*-alginate microcarriers. Results from present investigation reveal the characteristics of Ibuprofen-loaded *Bora rice*-alginate microcarriers with different formulation and process parameters. The data suggest that bora rice is a potentially useful natural material for making controlled release Ibuprofen-loaded microcarriers by the ionotropic gelation technique.

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