Reprinted from

International Journal of Health Research

Peer-reviewed Online Journal

http://www.ijhr.org

Abstracting/Indexing
African Index Medicus, Open-J-Gate, Directory of Open Access Journals (DOAJ), Socolar (China's largest online database), EBSCO, Index Corpenicus

PORACOM
Academic Publishers

e2113p111

International Journal of Health Research

The *International Journal of Health Research* is an online international journal allowing free unlimited access to abstract and full-text of published articles. The journal is devoted to the promotion of health sciences and related disciplines (including medicine, pharmacy, nursing, biotechnology, cell and molecular biology, and related engineering fields). It seeks particularly (but not exclusively) to encourage multidisciplinary research and collaboration among scientists, the industry and the healthcare professionals. It will also provide an international forum for the communication and evaluation of data, methods and findings in health sciences and related disciplines. The journal welcomes original research papers, reviews and case reports on current topics of special interest and relevance. All manuscripts will be subject to rapid peer review. Those of high quality (not previously published and not under consideration for publication) will be published without delay. The maximum length of manuscripts should normally be 10,000 words (20 single-spaced typewritten pages) for review, 6,000 words for research articles, 3,000 for technical notes, case reports, commentaries and short communications.

Submission of Manuscript: The *International Journal of Health Research* uses a journal management software to allow authors track the changes to their submission. All manuscripts must be in MS Word and in English and should be submitted online at http://www.ijhr.org. Authors who do not want to submit online or cannot submit online should send their manuscript by e-mail attachment (in single file) to the editorial office below. Submission of a manuscript is an indication that the content has not been published or under consideration for publication elsewhere. Authors may submit the names of expert reviewers or those they do not want to review their papers.

Enquiries:

The Editorial Office
International Journal of Health Research
Dean's Office, College of Medicine
Madonna University, Elele Campus, Rivers State
E-mail: editor_ijhr@yahoo.com or editor@ijhr.org

PORACOM
Academic Publishers

e2113p112

International Journal of Health Research, March 2009; 2(1): 93-99 (e2112p113-119)

Available at http://www.ijhr.org

Open Access
Online Journal

Original Research Article

Modeling and Characterization of Drug Release from Glutinous Rice Starch Based Hydrogel Beads for Controlled Drug Delivery

Received: 05-Feb-09 **Revised:** 17-Feb-09 **Accepted:** 17-Feb-09

Abstract

Purpose: To identify the potential of *Assam Bora rice* in modulation of drug release from the formulated matrix devices and demonstrate its utility in pharmaceutical drug carrier systems.
Methods: The hydrogel microbeads were prepared by an industrially feasible conventional ionotropic gelation method using the blends of pregelatinized *Bora rice* along with sodium alginate as mucoadhesive backbone. The potential of proposed natural polymer in modulation of drug release from the formulated microbeads was investigated through *in vitro* dissolution test conducted as per SUPAC-MR guidelines provided by FDA. Data obtained from *in vitro* release studies were fitted to various kinetic equations to find out the kinetics and mechanism of drug release from fabricated microbeads.
Results: The microbeads were almost spherical, discreet and free flowing in a size range of about 0.726±0.008 mm to 1.16±0.009 mm. The different formulations had variable correlation with the different kinetic models under the different release environments.
Conclusion: *Assam Bora* can be a promising option for mucoadhesive controlled drug delivery systems as natural substance.

***Keywords*:** Drug delivery, Bora rice starch, Release kinetics, Natural polymer.

Nikhil K Sachan[1]

Bhattacharya A[2]

[1] University Institute of Pharmacy, C.S.J.M. University, Kanpur – 208 024 (U.P.) India

[2] Dept. of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh – 786 004 (Assam) India

For Correspondence:

Tel: +91-9307755497

Email: nikhilsachan@gmail.com

Introduction

Drug delivery technology is one of the frontier areas of research in the field of science and technology. Considerable attention is focused on the development of controlled drug delivery systems offering the advantages of better therapeutic efficacy and easier to comply with than the conventional regimens requiring more frequent dosing[1, 2]. The concept of mucoadhesive drug delivery is to cope the property of mucoadhesion of certain polymers with the sustained release delivery systems in order to circumvent the problem of inability of oral formulations to restrain and localize at the site of absorption in gastrointestinal tract[2]. A number of newer polymers have been investigated in this field but only a few of them have found industrial application. The biocompatibility and cost are the two major limiting factors for the industrial use in practice[4]. Use of natural and modified natural polymers in the drug delivery continues to be an area of intensive research despite the advent of several new synthetic polymers. Natural polymers primarily remain attractive for a number of reasons as they are economical, readily available, capable of modifications, and thereby potentially degradable and compatible due to their natural origin[5, 6].

The pharmaceutical utility of *Bora rice*, a variety of glutinous rice cultivated mainly in Assam region, as novel mucoadhesive biopolymer is proposed and examined in present work. The *Bora rice starch* composed of mainly amylopectin and only traces of amylose[7] (less than 3%); it has the free hydroxyl groups that open up possibility to be cross-linked with other polymers to be used in controlled drug delivery[8]. In this study, the *Bora rice* was used in combination with sodium alginate for the preparation of drug loaded microbeads by micro orifice ionic-gelation technique[9]. Several preformulation trials were undertaken, with varying the drug-polymer ratio, using varying fraction of two polymers, cross-linking with different concentrations of cross-linking agents and with different cross-linking agents, altering the gelatinization conditions for *Bora rice*, altered gel strength, varying the stirring speed, adjusting the curing time and subjecting the product to different drying conditions so as to optimize the product characteristics and release profile of the drug from prepared gel beads. The metformin hydrochloride, an oral antidiabetic drug[10], was used as a model medicament to evaluate the sustained release potential of *Bora rice starch* as a natural polymer.

Experimental

Materials

Bora rice was procured from the village near to Dibrugarh University and was confirmed so by local people. Sodium alginate (Loba Chemi Pvt. Ltd. Mumbai), Calcium chloride (Qualigens Mumbai, India), Glacial acetic acid (Qualigens Mumbai, India), were procured from the commercial sources. Metformin hydrochloride was kindly gifted by Ms Ranbaxy Pharmaceuticals, India. All other reagents were of analytical grade laboratory reagents and were procured from commercial sources.

Preparation of microbeads

The microparticulate drug delivery systems were prepared from the gel blend of pre-gelatinized *Bora rice* and sodium alginate[4]. The rice polymer was gelatinized by thermal gelation by autoclaving the aqueous suspension of known strength of rice flour at 121 ^{o}C for 1 hour[11]. 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. The resulting dispersion was added drop-wise into calcium chloride solution (Figure 1). Beads were allowed 5 – 10 min curring time and were washed with a mixture of ethanol and acetone, then dried in vacuum oven at a temperature below 40 ^{o}C and stored in a desiccator for further use.

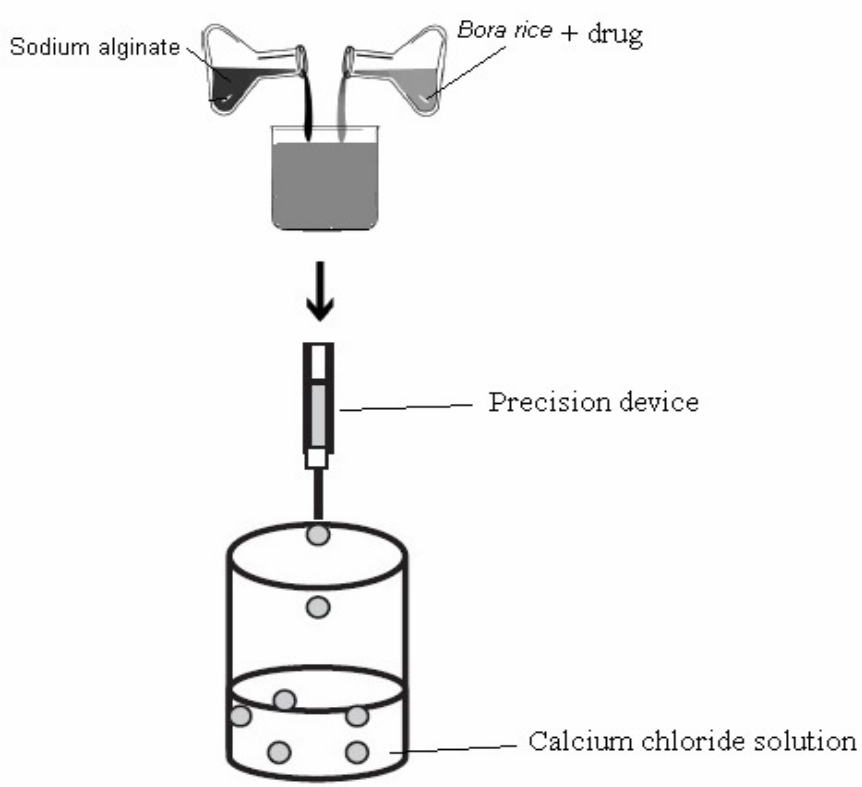

Figure 1: Preparation of microbeads by ionic-gelation method

Optimized beads with *Bora rice* backbone were coated with hydroxyppropylmethyl cellulose (HPMC) using solvent evaporation method[12]. Beads were dispersed in 10% strength of HPMC in acetone and the solvent was evaporated in a rotary evaporator by applying vacuum 300 mmHg and rotation rate was 50 rpm, then vacuum dried in desiccators. All the batches were evaluated on the basis of release study.

Estimation of drug

The content of metformin hydrochloride in microbeads and its release as a function of time was estimated spectrophotometrically using an UV spectrophotometer (U2001 Hitachi, Japan) at 233 nm in aqueous medium taking 798 as the value of *A* (1%, 1 cm)[10,13].

Characterization of prepared beads

The prepared beads were studied for the drug entrapment, size and size distribution, water vapour uptake, mucoadhesion, swelling, surface and mechanistic properties through phase contrast, scanning electron microscopy (SEM), and x-ray diffraction (XRD); after primary screening the selected formulations were taken forward for further investigation of sustained release potential.

In vitro drug release study

The release of metformin hydrochloride from the microbeads was studied in aqueous medium using USP XXVI Dissolution Test apparatus; basket type (Campbell Electronics, Mumbai) at 37± 0.2 ^{o}C with a rotating speed of 50 rpm[13,14]. A sample of microbeads equivalent to 50 mg of metformin hydrochloride was used in each test. At

preset time intervals 5 ml aliquots were withdrawn and replaced by an equal volume of fresh dissolution medium. The samples were withdrawn through a membrane filter (0.45 μm) and were analyzed for metformin hydrochloride content spectrophotometrically at 233nm using the UV-Visible Spectrophotometer (U2001 Hitachi Inc). The *in vitro* dissolution profile studies for characterization of release kinetics were carried as per the SUPAC guidelines for the modified release dosage forms (CDER-FDA) [15].

The concentration of metformin hydrochloride was corrected for sampling effects according to the following equation:

$$C_n = M_n \left\{ \frac{V_T}{V_T - V_S} \right\} \times \left\{ \frac{C_{n-1}}{M_{n-1}} \right\}$$

where, C_n is the corrected concentration of the n^{th} sample, M_n is the measured concentration of the n^{th} sample, V_T is the volume of the dissolution medium, V_S is the volume of the sample withdrawn, C_{n-1} is the corrected concentration of the $(n-1)^{th}$ sample, and M_{n-1} is the measured concentration of the $(n-1)^{th}$ sample.

Data analysis

Each experiment was conducted in triplicate and the mean was taken for further interpretation of release kinetics. Statistical comparison of data was achieved using Student's t-test ($p < 0.05$). The 95 % confidence interval was calculated for the slope of the line when the fraction released was plotted as a function of time in different kinetic models. Results are given as means ± standard errors of the mean (S.E.M.).

For comparison of multiple dissolution profile, similarity testing was also performed using pair wise dissolution data obtained in each individual medium by calculating the similarity factor (*F*) as per the SUPAC guidelines for modified-release dosage forms. This factor is a logarithmic reciprocal of square root transformation of one plus the average mean squared (average sum of squares) differences of drug percent dissolved between the two dissolution profiles over all time points.

$$F = 50 \times \log \left\{ \left[1 + \frac{1}{n} \sum_{J=1}^{n} [R_J - T_J]^2 \right]^{-0.5} \times 100 \right\}$$

where n is the number of dissolution time points and R_J and T_J are the dissolution values of two dissolution profiles at time t. The two dissolution profiles are considered similar when F value is in the range of 50 to 100.

Modeling and comparison of release profiles: Data obtained from *in vitro* release studies were fitted to various kinetic equations to find out the kinetics and mechanism of drug release from fabricated microbeads. The drug release data were treated mathematically to plot the corresponding release graphs for, zero order (% CDR Vs time), first order (log % of drug remaining Vs time), Higuchi squire root law (% CDR Vs squire root of time), Hixson-Crowell cube root model (cube root of % CDR Vs log time) and Korsmeyer's model (log % CDR Vs log time) in order to find out the kinetics of drug release[16]. The model of best fit was identified by comparing the values of correlation coefficients in drug release graphs plotted as above under different release environments.

Results

The formed beads were almost spherical, discreet and free flowing in a size range of about 0.726 ± 0.008 mm to 1.16 ± 0.009 mm as shown in phase contrast and scanning electron microscopy. It was found that particle size distribution of each formulation was within a narrow range. The drug entrapment efficiency of the beads was in range of 19 – 53 % depending upon the drug polymer ratio, stirring speed, curring time, gel strength and medium of microencapsulation. Beads exhibited suitable pharmaco-technical parameters when evaluated for the kinetics of drug release by fitting the *in vitro* drug release data, obtained under the varying release environments, to different mathematical models provided for characteri-

Table 1: Correlation obtained with different kinetic models

Formulation		Zero order plot [R^2]	First order plot [R^2]	Higuchian plot		Korsmeyer's plot [R^2]	Hixson-Crowell plot [R^2]
				Slope (n)	[R^2]		
F_1	In 0.1 M HCl	0.8204	0.9641	3.7748	0.9713	0.9687	0.7799
	In water	0.7166	0.9671	3.6965	0.9072	0.8869	0.3792
	In buffer pH 7.4	0.6225	0.9294	3.6217	0.9063	0.8953	0.4883
F_2	In 0.1 M HCl	0.8009	0.9591	3.8143	0.9590	0.9604	0.8467
	In water	0.7283	0.9347	3.6832	0.9158	0.9302	0.6678
	In buffer pH 7.4	0.6389	0.9541	3.4349	0.8602	0.9166	0.6272
F_9	In 0.1 M HCl	0.9003	0.9565	3.9487	0.9908	0.9920	0.8476
	In water	0.7869	0.9343	3.7277	0.9505	0.9595	0.7338
	In buffer pH 7.4	0.6389	0.9601	3.6217	0.9063	0.9403	0.5819
F_{10}	In 0.1 M HCl	0.6887	0.9269	3.8084	0.8965	0.9112	0.6291
	In water	0.5822	0.9608	3.3579	0.8161	0.8662	0.6092
	In buffer pH 7.4	0.4680	0.9309	4.0269	0.9511	0.9082	0.5784
F_2 coated	In 0.1 M HCl	0.9975	0.7372	3.3079	0.9259	0.9864	0.9281
	In water	0.9706	0.9842	3.7658	0.9387	0.9845	0.8972
	In buffer pH 7.4	0.9468	0.9884	3.3079	0.9259	0.9661	0.8604

Table 2: Models with highest correlation to drug release pattern in particular release environments

FORMULATION CODE	Model (s) with Highest Correlation: Release Environments		
	0.1M HCl	Distilled water	Buffer pH 7.4
F_1	Higuchi model	First order	First order
F_2	Kerseymere's model	First order	First order
F_9	Kerseymere's model	Kerseymere's model	First order
F_{10}	First order	First order release	Higuchi model
F_2 - Coated	Zero order release	Kerseymere's model	First order

zation of release kinetics. The different formulations showed variable correlation with the different kinetic models under the different release environments as depicted in Table 1. The best fit kinetics under the particular release environment, as decided upon by the correlation coefficient calculated from release plots are summarized in Table 2.

Discussion

Excipients play an important role in pharmaceutical formulations as they can affect the overall success of a drug formulation in therapeutics as well as in market affecting the patient compliance, regulatory approval, buyer's/physician's perception and compatibility with the active pharmaceutical ingredients. The kinetics of

drug release from dosage form are important as they influence the dosing interval, bioavailability, overall patient compliance and in many instance the occurrence of side effects or un-toward effects. For a new excipient to be used in drug delivery system, its capability of modulation of drug release is an important and foremost criterion for screening[17]. In the present study, *Bora rice* microspheres are composed of polysaccharide rich plant material generally used as food source and may be classified as 'Generally regarded as safe' (GRAS). Numerous new smart polymers have been created and used to develop environment sensitive drug delivery systems, but none of them have been used in the commercial formulations to date because, for first time use, these polymers required to be labeled as 'GRAS' which is a high cost affair[18].

In this study, the drug entrapment efficiency was initially very low for the metformin hydrochloride because it, being highly water soluble, diffuses out to calcium chloride solution at the time of encapsulation or during curring. This was improved considerably by some changes in the encapsulation process as the drug was thoroughly mixed with pre-gelatinized starch gel to get it to penetrate to the hollow hilum of rice granule that hinders diffusion[4, 8]. A change in solvent system to dilute acetic acid improved drug encapsulation probably due to the reason, that the resultant gel backbone does not swell in acidic medium so the drug can not get out of the matrix easily during curring.

The variable release kinetics are exhibited by the prepared beads under the different release environments which is obvious as the swelling behaviour of matrix is dependent on the surrounding pH and ionic environment. The span of release of medicament from the formulations is prolonged enough to justify the proposed polymer system as a potential drug release modulator for controlled release drug delivery systems. Drug release kinetics from the beads reflects a clue about the effect of identified formulation and process parameters and of drug release environment on to the drug release, that are important parameters for the design of controlled and target retentive systems. The fabricated microdevices in this study, and assessment of physico-chemical parameters pointed out that the *Bora rice* is a potential natural resource with potential use in the drug delivery. Its performance may be better in delivery of drugs with variable solubility.

Conclusion

The prepared microbeads have shown sufficiently prolonged release of medicament justifying the potential of the formulation in modulating drug release at variable pH environments. A particular absorption window can be identified for a drug and knowing the drug release kinetics under that environment, formulation development can be taken forward. This study provides an alternative option for synthetic mucoadhesive polymers in drug delivery than, with proper research efforts, can be comparatively cost effective and an import substitute.

References

1. Majeti N, Ravikumar V. Nano and Micro Particles as Controlled Drug Delivery Devices. J Pharm Pharmacol 2000; 3: 234-254.
2. Sachan NK., Singh B, Rao KR. Controlled drug delivery through microencapsulation. Malaysian J Pharm Sci 2006; 4(1) 65-81.
3. Bernnkop SA. Mucoadhesive systems in oral drug delivery. Drug Discovery Today: Technologies 2005; 2(1): 83-87.
4. Sachan NK, Bhattacharya A. Evaluation of Assam Bora rice starch as a possible natural mucoadhesive polymer in formulation of micro-particulate controlled drug delivery systems. J Assam Sci Soc. 2006; 47: 34-41.
5. Satturwar M. P., Fulzele. V. S., Dorle. A.K. Biodegradation and in vivo Biocompatibility of Rosin: A natural film-forming Polymer. AAPS Pharm SciTec 2003; 4: (4): Article 55.
6. Sachan NK, Singh D. Evaluation of dried pulp from Carica papaya fruits as disintegrating agent in the formulation of metformin hydrochloride dispersible tablets. J Assam Sci Soc 2006; 46: 20-22.

7. Pathak PK, Ahmed T, Sharma KK, Pathak AK. High yielding glutinous rice varieties in Assam. Oryza. 1995; 32: 48 – 50.
8. Kumar N. Fabrication and characterization of hydrogel microbeads of Metformin hydrochloride using Bora rice starch as possible mucoadhesive biopolymer. M.Pharm Thesis, India. Dibrugarh University, Dibrugarh; 2006 Oct. 38p.
9. Kim CK, Lee EJ. The controlled release of blue dextranfrom alginate beads. Int J Pharm 1992; 79: 11-19.
10. British Pharmacopoeia 2003, Stationary office, Her Majesty Publication, London. [Electronic version].
11. Bhattacharya KR. Gelatinization temperature of rice starch and its determination. Proc of Workshop on Chemical aspects of rice grain quality, International Rice Research Institute, Philippines. 1979; 231 – 250p.
12. Paharia A, Yadav AK, Rai G, Jain SK, Pancholi SS, Agrawal GP. Eudragit-coated pectin microspheres of 5-fluorouracil for colon targeting. AAPS PharmSciTech 2007; 8:12.
13. Asarafi M, Chowdhary JA, Reza SM. Controlled Release of Metformin Hydrochloride I. In vitro Release from Physical Mixture Containing Xanthan Gum as Hydrophilic Rate Retarding Polymer. Dhaka University J Pharm Sci 2005; 4(1) Electronic version.
14. Patel RP. et al. Modeling and comparison of dissolution profiles of commercial metformin hydrochloride sustained release tablets. Drug Del 2005;.5(1). Electronic version.
15. FDA Guidance for Industry. SUPAC-MR—Modified Release Solid Oral Dosage Forms: Scale-Up and Post Approval Changes, Center for Drug Evaluation and Research (CDER), Sept 1997.
16. Costa P, Lobo JMS. Modeling and comparison of dissolution profiles. Eur J Pharm Sci 2001; 13: 123-133.
17. DeMerlis CC, Goldring JM, Schoneker DR. New excipient evaluation procedure. Pharm Tech. 2008; 32 (1) 104-105.
18. Rados C. GRAS: Time-Tested, and Trusted, Food Ingredients. FDA Consumer Magazine. 2004 (March-April) Available from: http://www.fda.gov/Fdac/features/2004/204_gras.html