Abdul Baquee Ahmed et al /J. Pharm. Sci. & Res. Vol. 9(7), 2017, 1139-1146

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Development and Evaluation of Assam Bora Rice Starch-Carbopol Based Oral Mucoadhesive Gel of Irinotecan for Mouth Cancer

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Abstract:

Aim: The objective of the present study is to develop and evaluate, mucoadhesive gel of irinotecan using blend of Assam bora rice starch and Carbopol 934 for treatment of mouth cancer.

Methods: The starch was isolated from Assam bora rice and subjected for drug compatibility study by FT-IR and DSC. Gel formulation based on bora rice starch loaded with irinotecan (0.6%) was prepared by trituration method and evaluated for various rheological properties, *ex-vivo* mucoadhesion and *in vitro* drug release study in phosphate buffer pH 6.8.

Results: The results of FT-IR and DSC studies revealed the compatibility of the drug with Assam bora rice starch and Carbopol 934. The F 4 formulation containing blend of starch-carbopol 934 (1:0.05 ratio) was found to have highest mucoadhesive force (46.3±6.79 g) and adhesive strength (18.8±0.46 g). The viscosity of the formulations were ranked as F4>F3>F2>F1>F WS. *In-vitro and ex-vivo* study of F 4 formulation showed 54.07±1.26 % and 51.7±1.03 % drug release respectively after 6 hrs and studied for release kinetics.

Conclusion: From the study, it can be conclude that Assam bora rice starch have a good mucoadhesive potential that can be explored in future as a novel excipient in mucoadhesive drug delivery system.

Keywords: Assam bora rice starch, oral mucoadhesive gel, *ex-vivo* mucoadhesion, *in vitro* drug release.

INTRODUCTION

Now a day one of the leading virulent diseases in the world is cancer that causes abnormal growth of cells spreading to surrounding tissues in the body[1,2]. Despite of lots of breakthrough in cancer treatment there are still some limitations that restrain the efficacy and safety of cancer chemotherapy. The ninth version of the international classification of diseases by the World Health Organization (WHO) classifies oral cancer under lip, tongue, gingiva, floor of the mouth, and other parts of mouth[3]. Oral cancer patients suffer a trouble of life life-frightening illness unlike other cancer patients; they can rarely conceal their affliction from the public view as the treatment of these oral cancer results in dysfunction and disfigurement of the head and neck structures. Patients undergoing management for oral cancer frequently have shown problems with low self-esteem due to a change in self-image. The majority of the oral cancer patients are associated with tobacco and alcohol abuse[4]. In a study conducted by Vora *et al*. about alcohol, tobacco, and paan use and its relation to oral cancer threat among Asian males in Leicester, it was found that 7% of first-generation Hindu males chewed paan containing tobacco that is strongly associated with oral cancer[5].

The major factor of anticancer Drugs is wide distribution capacity in the body and owing to non-selective cytotoxicity of these drugs not only the cancer cells but also healthy cells are killed. But, because of low therapeutic index of anticancer drugs, a rapid increase and subsequent decay of drug concentration in blood is also one of the limitations of cancer therapy. Although in cancer therapy, the intravenous route is more common than the others, it is thought that with recent advances oral chemotherapy will be the breakthrough step in future chemotherapy[6]. By means of oral administration, it is possible to prevent the initial rapid increase and the subsequent decay of drug concentration in blood that occurs via the intravenous route[7,8].

Several approaches have been immersed to prolong the extent of absorption of many drugs and one of these the development of mucoadhesive drug delivery system. In recent times, a huge impact have made in the development of novel drug delivery dosage forms that can control the release rates and target the drugs to a targetted body site. Mucoadhesive dosage forms have been extensively developed for the treatment of oral cavity diseases[9]. The crusial limitation of mucoadhesive tablets that is concerned with the size (thickness must be limited to about 1 mm) and softness, to be acceptable to patients and not cause irritation[10], recommend the use of mucoadhesive films or gels that illustrate an alternative to solid forms as they can offer a larger and softer surface area of release in the buccal area for an extended period of time, due to their viscosity[11,12].

Because of the presence of a smooth and relatively immobile surface for placement of a mucoadhesive dosage form, the buccal region appears to be more suitable for sustained delivery of therapeutic agents using mucoadhesive systems. The buccal and sublingual routes avoid first-pass metabolism. These regions consist of a

non-keratinized epithelium, resulting in a somewhat more permeable tissue than the skin[13].Semisolid mucoadhesive dosage forms, such as gels (or ointments), that represent excellent formulations for several routes of administration, such as topical, vaginal and rectal, may therefore be considered efficient as drug delivery systems in the buccal cavity, covered by a mucus layer: mucoadhesive gels are easily dispersed throughout the oral mucosa, even if drug dosing from these pharmaceutical forms may not be as accurate as from tablets, patches, or films[14,15].

Mucosal adhesives, or mucoadhesives, was introduced into the controlled drug delivery area, have recently gained interest among pharmaceutical scientists as a means of improving drug delivery by promoting dosage form residence time and contact time with the mucous membranes.

The main purpose of this study was to develop gel formulations with better mucoadhesion capability and evaluate its mechanical strength along with its *in vitro* performances for buccal release loaded with irinotecan using Assam bora rice starch as a mucoadhesive agent that prolong the release by increasing the adhering strength. The Bora rice chemically can be characterized by the lack of amylose content and the highest amount of amylopectin. Bora rice also known as sticky rice or glutinous rice and characterized by its sticky texture and also posses a good gelling property [16]. As this selective polysaccharide has its bioadhesive nature, it can be used as a drug delivery system for targeted and optimal drug delivery due to the intimacy and duration of contact[17,18].

MATERIALS AND METHODS

Materials:

Assam Bora Rice was collected from the local market of Kamrup district of Assam, India. Irinotecan was obtained as a gift sample from Emcure Pharmaceuticals Limited (Pune, India). Triethanolamine was procured from Sisco Research Laboratory Pvt. Ltd. (New Mumbai). Carbopol 934P were purchased from Yarrow Chem. Products (Mumbai, India) respectively. Freshly excised goat intestine was obtained from the local butcher shop (Azara, Guwahati). All other chemicals used were of analytical grade.

Method:

Isolation of starch from Assam Bora rice:

The starch granules were isolated from rice flour by wet milling following the method of Syahariza, Li, and Hasjim (2010) with some modifications. 100 gm of rice was mixed in 120 ml of distilled water and subjected for wet milling. The rice flour then homogenized at 10,000 rpm for 10 min and soaked in 0.25 % NaOH solution (100 ml) for 1 h. Suspension was centrifuged at 4,000 rpm for 10 min and the starch layer was collected and washed with 0.25% NaOH solution and recentrifuged (4,000 rpm for 10 min). The supernatant and the surface brown layer were removed and the lower white starch layer was washed with distilled water, followed by centrifugation. Washed starch was subjected for an acid (1M HCl) treatment and allowed to stand for 24 h. Acid treated starch then homogenized at 10,000 rpm for 10 min and the pH was neutralized with 0.2 M NaOH and filtered with Buchner funnel followed by oven drying at 95˚c for 15 min that lead to gelatinized starch. Gelatinized starch was air dried for 2 h and kept in desiccators for one night and again oven dried for 2.5 h at 45˚c and the dried starch powder was collected and kept at room temperature until use[19–22].

Characterization of native starch:

Differential scanning calorimetry (DSC):

DSC thermogram of the bora rice starch was evaluated using a differential scanning calorimeter (Perkin Elmer 4000). About 5mg of the sample were crimped in a standard aluminum pan and heated in a temperature range of 30˚C to 400˚C at a heating rate of 10˚C per minute in nitrogen atmosphere.

Fourier transform infra-red spectroscopy (FT-IR):

Starch was studied for its functional groups in FT-IR spectroscopy in a Fourier–transform infrared spectrophotometer (Bruker, Alpha) in range of 4000–400 cm^{-1}.

Ex-vivo mucoadhesive strength study:

A mucoadhesive strength evaluation of native starch was done by carrying out adhesive tests employing texture analyzer (TA.XT Express, Stable Micro System). The analyser was equipped with different weight load cell. At room temperature, sample compact was placed on the upper probe. Freshly excised goat mucosal tissue was attached to the lower probe as model membrane. During the measurement the probe was lowered at a rate of 0.5 mm/s until a contact with the model membrane at a constant force of 100 g obtained. The force of 100 g was maintained for 5 min and the upper probe was moved upwards at a rate of 5 mm/s. The force required to detach the sample from tissue was considered as an index of mucoadhesive potential [23].

Formulation of oral mucoadhesive gel system -

Oral mucoadhesive gel loaded with irinotecan using bora rice starch in different concentration was prepared. Mucoadhesive property of native starch was further evaluated by formulating gels using irinotecan as the model drug. For gel preparation, Carbopol 934P (0.5%, w/v), as a gelling agent was dispersed in aqueous solution of irinotecan (0.6%, w/v) that contain starch in different proportions as mucoadhesive agent followed by addition of triethanolamine and allowed to hydrate for overnight.

Characterization of prepared gel

Physical appearance

The prepared gel formulations were inspected visually for their color, homogeneity, consistency, grittiness and phase separation.

Gelation study

Phase transition of liquid to gel is considered as the gelation process. In brief, each formulation was transferred into a 10-mL transparent vial containing a magnetic bar and placed on a temperature water bath. Due to gelation when the magnetic bar almost stopped moving considered as the gelation point. The formed gel was analyzed for

consistency by visual inspection and reported. At least three replicates of each preparation were measured[24].

Determination of pH

The pH of prepared formulations was evaluated by using digital pH meter. A specified amount of gel of each formulation has taken in a 100 ml beaker and the pH meter was immersed into the sample and the data of pH meter were recorded. Each formulation was subjected for the same process thrice.

Determination of viscosity

Irinotecan loaded gels containing native starch was studied for viscosity measurment using a Brookfield Viscometer (Brookfield DV-E Viscometer) at a speed of 10 rpm using spindle no. 25 at 25˚c.

Swelling index

The swelling index of prepared oral mucoadhesive gel was determined by taking previously weighed 1 gm of gel on porous aluminum foil and then placed separately in a petridish containing 10 ml 0.1 N NaOH. Then samples were removed from beakers at different time intervals and put it on dry place for some time and reweighed. Swelling index was calculated as follows.

Swelling Index (SW) % = [(Wt – Wo) / Wo] ×100 (1)

Wt = Weight of swollen gel after time t.

Wo = Original weight of gel at zero time.

Drug content Determination

1.6 gm (equivalent to 10 mg of drug) of gel of each formulation was taken and dissolved in 10ml of dimethyl sulfoxide and 100 ml volume was made up by using phosphate buffer pH 6.8 and kept for shaking for a period of 15 min followed by filteration. Further dilutions were made by buffer of prepared concentration. The absorbance was measured at 254 nm by UV-Visible spectrophotometer and drug content was determined.

Adhesive strength analysis

Texture analyzer (TA.XT Express, Stable Micro System) was used to perform the gel adhesiveness. Each formulation was transferred into a beaker and a cylindrical probe was forced down into sample at a defined rate (0.5 mm/s) of and to a defined depth (10mm). Each of the samples was analyzed at least for three times at temperatures 25˚C±0.5˚C and from the force-time plot the adhesiveness (the work necessary to overcome the attractive forces between the surface of the sample and the surface of the probe) was derived.

***Ex-vivo* mucoadhesive potential**

The mucoadhesive potential of each formulation was measured by the means of the force required to detach the formulation from the tissue. In short, the freshly excised goat intestinal tissue was collected and a section of the tissue was attached to lower probe having a surface area of 3.14 cm^2. At the room temperature, fixed amount of sample of each formulation was placed on the upper probe and the probe was lowered down until the sample contacted the surface of the tissue. A particular force of 100 gm was applied for 20 Sec to confirm the intimate contact in between the sample and the tissue and the force to detached the sample from the tissue surface was recorded[25].

***In-vitro* release study**

The *in-vitro* drug release studies were performed using a USP type II dissolution apparatus. A weighed amount (1 g) of formulation was applied in a dialysis membrane[26]. Phosphate buffer pH 6.8 was used as a dissolution media and was maintained at 37±0.5˚C. Dialysis membrane was then immersed in the media that was tied with paddle set at a rotation speed of 100 rpm. Sample (1 ml) was withdrawn at regular time intervals and replaced with same volume of prewarmed medium. The samples were diluted up to 10 ml with same solvent analyzed spectrophotometrically at 254 nm and the cumulative % drug release was calculated.

***Ex-vivo* tissue permeation study**

For *ex-vivo* drug release study goat buccal skin was collected and maintained under standard laboratory conditions (25 ± 1°C and 55 ± 5% relative humidity) until use. The epidermis was attached in a Keshary-chien diffusion keeping the dermis side facing towards the receptor compartment which was filled with phosphate buffer pH 6.8 and the stratum corneum was in direct contact with the gel placed in donor compartment. The system was placed on a magnetic stirrer to maintain the hydriodyanamics of the receptor compartment by continuous stirring. A weighed amount (1 g) of sample was placedin donor compartment and a fixed amount of sample (1 ml) was withdrawn at predetrmined time intervals replacing with equal volume of fresh media and analyzed spectrophotometrically at 254 nm after appropriate dilution. The permeation rate of drug through the skin tissue was measured as a means of flux by measuring the slope of the permeation profile.

RESULTS AND DISCUSSION

Isolation of bora rice starch was done and the collected product was found to be white in colour and soluble in water in presence of some amount of heat. The average yield was amounted to 66 ±3.78% of the utilized amount of the rice. The collected starch was evaluated for compatibility with the drug.

Compatibility study of the bora rice starch:

The physicochemical compatibility study was carried out by infrared spectroscopy and DSC study. IR spectral analysis of irinotecan showed peaks at 1746.64 cm^{-1} (C=O stretching), 1610.61 cm^{-1}(C=C stretching), 1450.43 cm^{-1} (C=C multiple streching), 1189.83 cm^{-1} (CH_2 wagging), 1156.76 cm^{-1} (C-H in plane bending), 1006.33 cm^{-1} (C-C stretching), 849.24 cm^{-1} (CH_2 deformation) confirmed the purity of the drug with standard. The IR spectrum of starch showed different stretch and bend vibrations in respect of the peaks. The spectra of starch displayed a characteristic broad peak at 3301.18 cm^{-1} representing hydroxyl (-OH) groups. Peak at 2930.92 cm^{-1} is associated to C-H stretching of alkanes. Peak at 1151.21 cm^{-1} is due to (C-O-C) stretching. Coupled C-C stretching was confirmed by the peaks at 1001.43 cm^{-1}. The spectrum of Carbopol having a peak at 3177.49 cm-1 is due to O-H stretching of carboxylic acids. The peak appeared at 1717.87 cm^{-1} is associated with carboxylic C=O stretching vibration. Peak at 1244.31 cm^{-1} represented C-O-C stretching of acrylates.

The band at 800.02 cm^{-1} was for the out plane bending of =C-H. While the peak at 605.78 cm^{-1} was assigned with C-H bending of alkynes.

In spectra of physical mixture of drug with Carbopol and starch, the major peaks of irinotecan at 1746.80 cm^{-1} due to C=O stretching, 1611.13 cm^{-1} for C=C stretching and band appeared at 1154.43 cm^{-1} for the presence of C-H in-plane bending was found to be remained at same wave range as in pure drug. The peak at 1006.44 cm^{-1} and 837.74 cm^{-1} represented C-C stretching and CH_2 deformation respectively which further was sufficient to confirm the compatibility of the drug with the starch and Carbopol. Apart from these other additional peaks also have been observed which again could prove the compatibility of drug.

The DSC study of drug alone and along with starch and Carbopol was performed. The DSC analysis of drug alone elicited a peak at 274.44˚C which is close to the reported value of Irinotecan melting point presented in Figure 1A. While the thermogram of the physical mixture of the bora rice starch and Carbopol 934P along with drug showed three different peaks of their own at 81.11˚C, 227.42˚C and 267.44˚C respectively this indicates no interaction between the drug and other excipients.

***Ex-vivo* bioadhesive strength study:**

Ex-vivo bioadhesive strength measurement of starch compact showed in Figure 1B. The maximum force of a detachment of starch compact from the intestinal mucosa under the target force of 100 g was found to be 156.5 ±6.79 g. This high bioadhesive strength of starch alone illustrated its possible exploration as a mucoadhesive agent which further can be evaluated by preparing the gelling system.

Table. 1: Composition of the gel using bora rice starch in different concentration

Ingrediant	Quantity (%)				
	F 1	F 2	F 3	F 4	F WS
Irinotecan	0.6	0.6	0.6	0.6	0.6
Starch	2	5	7	10	-
Carbopol	0.5	0.5	0.5	0.5	0.5
Triethanolamine	q.s.	q.s.	q.s.	q.s.	q.s.
Methyl Paraben	0.04	0.04	0.04	0.04	0.04
Propyyl Paraben	0.012	0.012	0.012	0.012	0.012
Propylene glycol	6	6	6	6	6
Distilled water	q.s.	q.s.	q.s.	q.s.	q.s.

Table 2: Physical appearance of the mucoadhesive gel

Sl. No.	Formulation	Colour and appearance	Phase separation	Grittiness	Homogeneity
1	F 1	Slight off-white	None	None	Homogeneous
2	F 2	Slight off-white	None	None	Homogeneous
3	F 3	Slight off-white	None	None	Homogeneous
4	F 4	Slight off-white	None	None	Homogeneous
5	F WS	Slight off-white	None	None	Homogeneous

Table 3: Evaluation of different physical characteristics of the gel

Formulation	Gelation	pH	Viscosity (cP)	Swelling (%)	Drug content (%)
F 1	++	6.87±0.16	18899±178.23	12.8±0.49	91.23±1.4
F 2	++	6.53±0.08	28940±218.42	13.4±1.82	93.48±0.9
F 3	++	6.98±0.19	33720±356.60	13.1±1.89	89.1±1.43
F 4	++	7.04±0.44	42580±211.42	13.9±1.02	93.75±1.53
F WS	++	6.82±0.89	16129±298.03	13.1±0.95	94.26±0.2

All the values are represented in mean±SD (n=3).

Table 4: Mechanical strength profile of oral mucoadhesive gel

Formulation	Adhesive strength (g)	Mucoadhesive strength (g)
F 1	10.3±0.49	34.6±1.76
F 2	11.3±0.51	37.0±1.08
F 3	13.1±0.72	43.5±2.11
F 4	18.8±0.46	46.3±1.22
F WS	8.5±0.33	30.9±1.52

All the values are represented in mean±SD (n=3).

Table 5: Kinetic modelling and release kinetics of irinotecan from different gel formulations

Model	Parameter	F 1	F 2	F 3	F 4	F WS
In-vitro release study						
Zero order	$R^2_{adjusted}$	0.9852	0.9733	0.9770	0.9760	0.9905
	K_0	0.252	0.230	0.206	0.176	0.280
First order	$R^2_{adjusted}$	0.9752	**0.9888**	**0.9937**	**0.9982**	0.9404
	K_1	0.004	0.003	0.003	0.002	0.005
Higuchi	$R^2_{adjusted}$	0.9161	0.9257	0.9275	0.9387	0.8832
	K_H	3.871	3.554	3.173	2.720	4.283
Korsmeyer-Peppas	$R^2_{adjusted}$	**0.9931**	0.9886	0.9919	0.9960	**0.9958**
	K_{KP}	0.539	0.636	0.555	0.538	0.362
	N	0.862	0.816	0.821	0.798	0.954
Ex-vivo permeation profile						
Zero order	$R^2_{adjusted}$	0.9900	0.9883	**0.9887**	0.9888	0.9845
	K_0	0.192	0.176	0.168	0.148	0.207
First order	$R^2_{adjusted}$	0.9009	0.9027	0.9151	0.9184	0.8610
	K_1	0.003	0.002	0.002	0.002	0.003
Higuchi	$R^2_{adjusted}$	0.9106	0.9071	0.9121	0.9086	0.8945
	K_H	2.883	2.649	2.525	2.228	3.094
Korsmeyer-Peppas	$R^2_{adjusted}$	**0.9918**	**0.9899**	0.9848	**0.9903**	**0.9925**
	K_{KP}	0.031	0.025	0.033	0.023	0.016
	N	1.329	1.349	1.294	1.338	1.464

(n=3)

Characterization of prepared gel

Physical appearance

The mucoadhesive oral gel was found to be white in color with viscous smooth and homogeneous texture.

Gelation study

The bora rice starch mixtures were studied for thermal gelation characteristic by measuring its gel formation temperature (GFT) in the range of 35–40 ◦C. Gelation characteristics was assessed on ordinal scale ranging between − (no gelation), ++ (immediate gelation for fewer duration) and +++ (immediate gelation remains for longer duration). All the formulations showed immediate gelation remains for fewer duration represented in Table 3.

Determination of pH

The pH of the prepared oral gel was measured and reported in Table 3. The pH of different gelling system was found to be in between 6.4 to 7.4 which lie in between normal pH range of oral mucosa hence which may not produce any skin irritation.

Determination of viscosity

The apparent viscosities of all the formulations with and without starch were measured using Brookfield Viscometer (Brookfield DV-E Viscometer). The results represented in the Table 3 showed the formulation F 4 containing highest concentration of starch (10% w/w) existed with the highest viscosity of 42580±211.42 cP. While the formulation F WS containing only Carbopol possess the lower viscosity of 16129±298.03 cP. It was observed that the viscosity increased with the increasing concentration of starch in different formulations. The study revealed that the increased viscosity of the starch based gelling systems could provide a better controlled release of drug from the matrix gelling system.

Swelling index

Swelling study was performed according to the method mentioned above at a temperature of 25 ±0.5 ˚C and represented in Table 3. The gel containing the starch in a concentration of 7 % was found to have a relatively high swelling capacity. The formulations with and without starch existed to possess almost same swelling potency in a range of 12-14 %.

Drug content Determination

Drug content of the prepared gels were evaluated and reported in Table 3. The higher drug content of 94.26 % was found in gel without starch whereas the gel formulation contain 7% of starch possess relatively lower drug content (89.1 %).

Adhesive strength analysis

It is important to study the adhesive strength of any gelling system during preparation as it helps to evaluate its gel stickiness property. The viscosity of the gel controls the adhesiveness. The effect of using bora rice starch in different concentrations on adhesive strength showed in Table 4. The Formulation F 4 exhibited the higher strength of 18.8±0.46 g whereas the only Carbopol based gel found to have a lower adhesion capacity of 8.5±0.33 g (Figure 2).

***Ex-vivo* mucoadhesive potential**

Table 4 represents the ex-vivo bioadhesion of all theformulations following the modified method reported by Martinac et al. However, the mechanically performed adhesive strength of the gelling systems cannot be taken as the true index of the mucoadhesion, it is important to evaluate the appropriate index of mucoadhesivity by using the goat intestinal mucosa as model membrane. It was found that there was increase in mucoadhesive strength of the gel with the increase in the amount of starch. The maximum mucoadhesion (Figure 3) was found for the gelling system containing the highest amount of starch (F 4) and the only carbopol based gel was found to exist the lowest mucoadhesive strength. The formulation F 4 showed almost 1.5 fold better mucoadhesion than the only carbopol based gel. The presence of secondary hydroxyl groups in bora rice starch structure could be illustrated as the prime reason for the mucoadhesion.

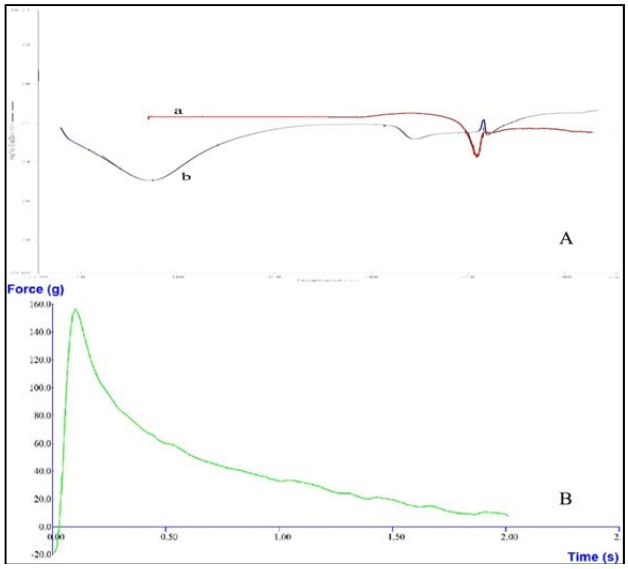

Figure 1: A) DSC thermogram of pure drug(a) and drug along with starch and carbopol(b)
B) *Ex-vivo* bioadhesive strength profile of starch compact

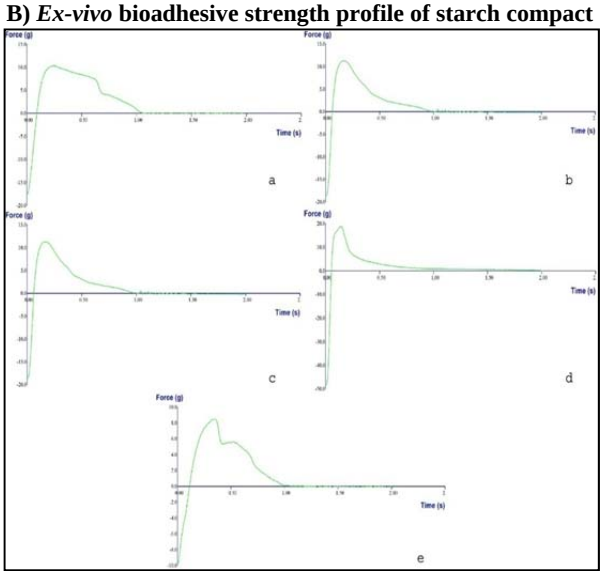

Figure 2: Adhesive strength of the different gels: a) F 1, b) F 2, c) F 3, d) F 4, e) F WS

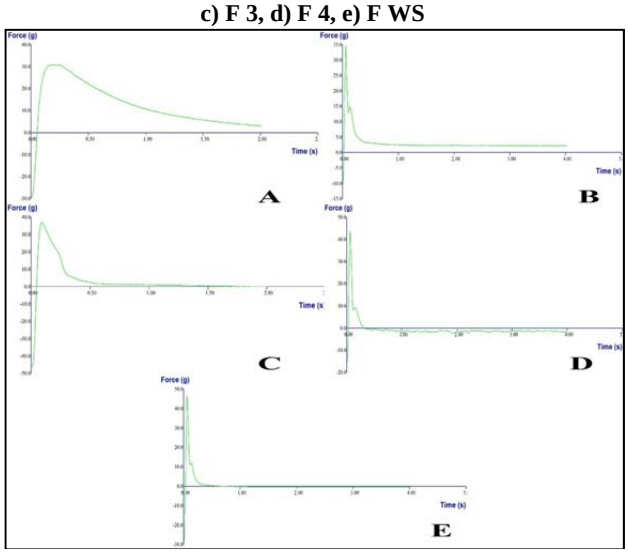

Figure 3: *Ex-vivo* mucoadhesive strength of the different gels: A) F WS, B) F 1, C) F 2, D) F 3, E) F 4

In-vitro release study

In-vitro drug release profile of different formulations was reported in Figure 4A. The release rate of drug from gel depends on the viscosity as well as on the consistency gel matrix. The release data represents the cumulative amount of the drug that was diffused through the cellulose *membrane. The drug release from the formulations significantly decreases as the amount of starch increased from 2% w/ amount of the starch. F WS containing only carbopol provided a faster release followed by the formulation F 1(2% w/w starch), F 2(5% w/w starch), F 3(7% w/w starch) and F 4(10% w/w starch) afforded the slowest release after a release study of 6.5 h. However, the drug release of F 1 and F WS showed no significant difference which could be considered as a result of less viscosity of the formulation. The formulations based upon their time dependent release profile can ranked as F WS>F 1> F 2>F 3>F4. Based on the physicochemical properties and drug release pattern the formulation F 4 was found to be the suitable for controlled release delivery system.

To evaluate the release kinetics and suitable release mechanism the release reports were fitted in different kinetic models. As shown in Table 5, the release profile could be best explained by first order and Korsmeyer-Peppas model as the linearity showed by the plots having far better than other two. The F 2, F 3 and F 4 formulations followed the 1st order release pattern while the F WS and F 1 were best suited in korsmeyer-Peppas equation. The release rate constant from different formulations could be ranked as F 4>F WS>F 3>F 1>F 2. Further study on the release exponent (n) found the value for all the formulations in a range of 0.5 to 1 which indicates a non-Fickian or anomalous diffusion.

Ex-vivo tissue permeation study

Figure 4B showed the *ex-vivo* permeation profile of the irinotecan loaded gels through the goat buccal tissue. The permeation pattern of the *ex-vivo* release was found to be almost similar. By plotting the cumulative drug release and time, a linear relationship [r^2= 0.9 (0.98-0.99)] was obtained which helped to determine that the permeation followed the Korsmeyer-Peppas model of release except the formulation F 3. From F 3 formulation the release of drug followed the zero order kinetics The formulation F WS showed higher percentage of release (74.77%) having no trace of starch. Whereas the formulations F 2, F 3 and F 4 consisting starch in increasing amount represented the better controlled release of irinotecan. But the formulation F 1 showed a release pattern almost similar to F WS. The study on the release exponent (n) of Korsmeyer-Peppas equation revealed that the mechanism of release is super case II transport as the n values for all the formulations are not less than 0.89[27].

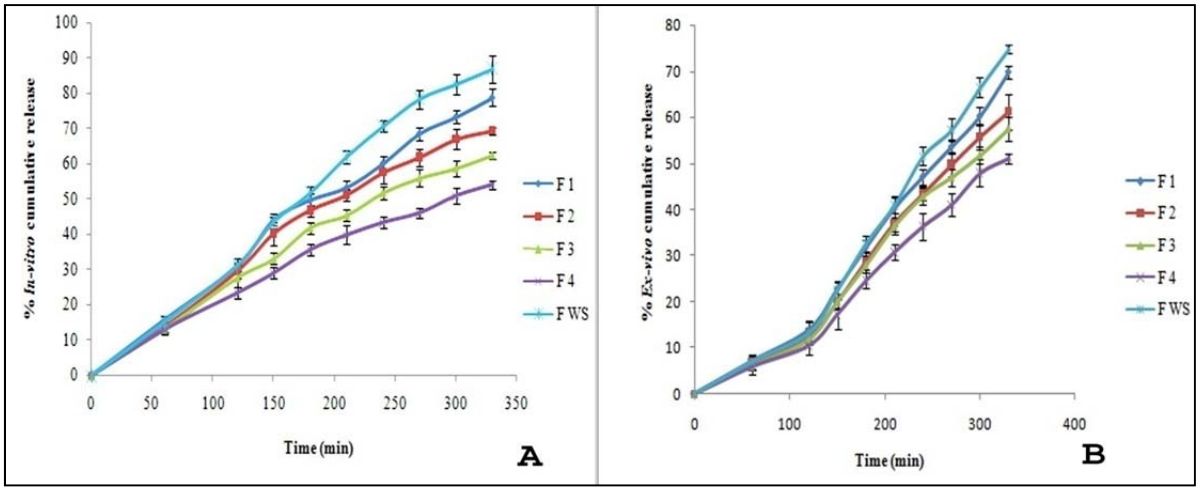

Figure 4: A) % *In-vitro* release and B) % *Ex-vivo* release of irinotecan from various gel formulations

CONCLUSION

The oral mucoadhesive gel of irinotecan using blend of Assam bora rice starch and Carbopol 934 for the treatment of mouth cancer was developed successfully and evaluated for various parameters. The drug, starch and carbopol were subjected for compatibility study which confirmed its compatibility. Formulation F 4 containing 10% starch was found to have the higher degree of mucoadhesion and mechanical strength. The permeation of irinotecan from different gelling systems across the goat buccal tissue was found feasible based on the *ex-vivo* tissue permeation study. Also the *in-vitro* study showed a higher degree of controlled drug release from the starch based gels than carbopol based gels after 6 hrs study in phosphate buffer pH 6.8. On account of this study, it can be concluded that the present study revealed the feasibility of the Assam bora rice starch as a potential mucoadhesive agent to be used in controlled drug delivery system.

ACKNOWLEDGEMENT

The authors would like to thank Emcure Pharmaceuticals Ltd. (Pune, India) for providing Irinotecan as gift sample and the Girijananda Chowdhury Institute of Pharmaceutical Science for providing all the facilities for the study.

DECLARATION

The authors declared no conflict of interest.

AUTHOR CONTRIBUTION

The authors meet the following conditions:

- Authors made valuable contributions to design, and/or acquisition of data, and/or analysis and interpretation of data.
- Authors also participated in drafting the article and revised it extensionally for its appropriate formatting.

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