EVALUATION OF *DELONIX REGIA* ENDOSPERMIC MUCILAGE AS GASTRIC MUCOADHESIVE AGENT

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Summary

Delonix regia is tropical tree found widely in India. Seeds of the Plant contain galactomannan hence the attempt to evaluate the seed mucilage for suitability as gastric mucoadhesive agent. Oral sustained release gastroretentive dosage forms offer many advantages for drugs showing absorption from the upper gastrointestinal tract and improve the bioavailability of medications that are characterized by the narrow absorption window. The mucilage obtained used for preparation of Verapamil Hydrochloride gastric mucoadhesive tablets. The tablets were prepared by direct compression and evaluated for mucoadhesive time; release profile for 12 hours. The results were compared with tablets prepared with Xanthan gum as gastric mucoadhesive agent. Results indicated that endospermic mucilage obtained from *Delonix regia* seeds possess comparable gastric mucoadhesive, swell able and release retardant properties.

Keywords: *Delonix regia*, Seed, Mucilage, Galactomannan, Gastric mucoadhesive agent

Introduction

Delonix regia is an ornamental tree and given the name **Royal Poinciana** or **Gulmohar**. Seeds of the Plant contain galactomannan type polysaccharide hence we attempt to use the seed mucilage for suitability as gastric mucoadhesive agent. Oral route of drug administration is an oldest and safest mode of drug administration. It does not pose the sterility problem and minimal risk of damage at the site of administration. Hydrophilic polymers are widely used in oral controlled drug delivery due to their flexibility to produce desirable drug release profile, cost effectiveness, and broad regulatory acceptance. In the case of oral sustained released dosage form, an effect is for several hours depending upon residence time of formulation in the GIT. Mucoadhesive matrix tablets are among the most popular delivery systems for oral controlled-release dosage forms. Verapamil hydrochloride is a calcium ion influx inhibitor (L-type calcium channel blocker). Verapamil exerts its pharmacological effect by selectively inhibiting the transmembrane influx of ionic calcium into arterial smooth muscle as well as in conductile and contractile myocardial cells without altering serum calcium concentration. Half life of Verapamil is 6 hours and requires multiple daily doses to maintain adequate plasma concentration. The present study was undertaken with an aim to the formulation development and evaluation of Verapamil hydrochloride sustained release mucoadhesive tablet with the aid of different polysaccharides as mucoadhesive agents.

Materials and Method

Materials:
Verapamil Hydrochloride was obtained as gift sample from Glenmark Pharmaceuticals Ltd, Goa. Xanthan gum, DCP, Magnesium Stearate Purchased from Modern Science laboratory. *Delonix regia* gum/mucilage extracted from the seeds.

Authentification of Plant:
The authentification of the plant was done by Dr. P. G. Diwakar, Deputy Director, Botanical Survey of India, Koregaon Road, Pune; identified and authenticated the voucher specimen by comparing morphological features. The voucher specimen has been submitted to B.S.I. repository at Pune, no.SHWDER2 (reference number- BSI/WC/Tech/2009/ SHWDER2.).

Collection of the seeds:
Pods/Fruits of *Delonix regia* were collected from the trees on roadside in Gangapur area, Nasik Maharashtra. The seeds from uninfected brown colored, matured, pods were removed manually. These seeds were processed further for extraction of mucilage from them.

Swelling tests, endosperm extraction, and powder preparation:
The necessary conditions to extract endosperms from swollen seeds were determined by monitoring seed mass during soaking at room temperature over 3 days, or during soaking in boiling water over the course of several hours. Because seeds differed with respect to the efficiency and degree of swelling, endosperm extraction (1,2,3) was done in three steps (a) swelling at room temperature; (b) boiling at 95^{o}C for 5 min followed by room temperature swelling; (c) extended boiling at 95^{o}C and removing swollen seeds at 1 hr intervals. Seeds

consisting of gummy or pasty endosperms or darkened germs after these treatments were tablet discarded. Powder was prepared by pre-cutting the extracted endosperms to a. 1 mm size, then hydrating the extracted endosperms in water, and milling the particles with a rotor mill to pass through 0.2 mm mesh. Powders were dried under room temperature and humidity conditions for several days followed by drying in desiccators. Selected galactomannan were further purified by dissolving the powder at 0.5% (w/w) concentrations in deionised water at room temperature, hydrated for 1 hr, held in a water bath at 85^0C for 10 min and centrifuged to remove insoluble matter(40,000g, 15 min, 25^0C). The supernatant was precipitated into 2 volumes of ethanol, pressed and rewashed for several times with ethanol, air dried overnight in a petridish, and dried in desiccators. Percentage yields of purified galactomannan were about 30%w/w.

Formulation of tablets:

Mucoadhesive tablets of Verapamil hydrochloride were prepared by direct compression. The powder mixture was directly compressed in Rimek multistation tablet compressing machine fitted with flat punches and dies (9 mm diameter). The tablet weight was adjusted to 300 mg and 25 tablets for each batch were prepared. The formula for the different batches is given in the Table 1.

Table 1: Formulation of mucoadhesive tablets of Verapamil HCl

Ingredients in mg/batch	F1	F2	F3	F4	F5	F6	F7	F8	F9
Verapamil HCL	120	120	120	120	120	120	120	120	120
Xanthan gum	60	90	120	-	-	-	30	60	60
***Delonix regia* mucilage**	-	-		60	90	120	60	30	60
Dicalcium phosphate	115	85	55	115	85	55	85	85	55
Mg. stearate	5	5	5	5	5	5	5	5	5
Total	300	300	300	300	300	300	300	300	300

Evauation of Tablets:

The compressed mucoadhesive tablets were evaluated (4) for thickness, weight variation, hardness, adhesion time, swelling index, erosion study, and release study.

Thickness:

The thicknesses of tablet were determined using Vernier Caliper (Kayco, India). Six tablets from each batch of formulation were used and mean thickness value and SD was calculated for each formulation.

Hardness:

For each formulation, the hardness of six tablets was measured using the Pfizer hardness tester (Cadmach, Ahemadabad, India) and mean value and SD was calculated for each formulation.

Weight variation:

To study the weight variation, 20 tablets of each formulation were weighed using an electronic digital balance. The average weight of each tablet was calculated.

Friability:
For each formulation the friability of 6 tablets was determined using Roche Friabilator. (Remi Equipments).

***In vitro* drug release study:**
In vitro dissolution of formulation was studied using the rotating basket method (USP Type I apparatus). In this method, 900 ml of 0.1 N HCl was used as the dissolution media. The rate of stirring was 100 rpm. The tablets were placed in dissolution media maintained at 37 ± 5°C for a period of 12 hours. At appropriate time interval up to 12hrs, 5 ml of each sample was taken and 0.45 membrane filtered. The dissolution media was then replaced by 5 ml of fresh dissolution fluid to maintain a constant volume (sink condition). The drug content in each sample was analyzed after suitable dilution with a Shimadzu2501PC UV/VIS spectrophotometer at 277.8nm. The amount of drug present in the samples was calculated with the help of calibration curve constructed.

***In-vitro* mucoadhesion time:**
Adhesion time (5) of formulations were determined by using USP type VI (rotating cylinder method) apparatus, DISSO 2000 LABINDIA at 37 ± 0.5^0 C at 100 rpm using 0.1N HCl as a medium. The goat gastric mucosa was adhered to the cylinder by using cynoacrylate glue. The tablets were pressed on the mucosa gently with the finger for 1 minute. Time up to which tablet remains adhered to goat gastric mucosa was measured and shown in Table 3.

Swelling study of formulations:
Swelling study (5) of individual polymers and combinations were carried out using USP type I dissolution apparatus (rotating paddle), DISSO 2000 LABINDIA at 100 rpm and 0.1 N HCl was used as medium, temperature was maintained at 37± 0.5^0 C. Weight of individual tablet was taken prior to the swelling study (W1). The tablet was kept in a basket. The weight of tablet was taken at time interval of 4, 8, 12 hours (W2). Percent hydration (swelling index) was calculated as shown in Table 4, using following formula,

% of hydration = (W2-W1) X 100 / W2

Where W1:- initial weight of tablet, W2:- weight of tablet after 12 hours.

Measurement of matrix erosion:
The swollen tablet in swelling study at 12 hours was dried at 60^0 C for in vacuum oven. The tablets were air dried for 7 days and reweighed (W3). Matrix erosion (5) or dissolution was calculated by using following formula,

DS= (W1-W3) X 100 / W1

Where, W1- initial weight of tablet, W3 = Weight of tablet dried at 60^0 C for 12 hrs in vacuum.

Result and Discussion

The **thickness** of all the formulations were varies within ranges from 3.6-4.0 mm. All the formulation showed uniform thickness. The **weight variation** test was carried out as per official method and it was found that all formulation to be within the limit (as per pharmacopoeial standard). The **content uniformity** test was also carried out as per official method and it was found that different batches shown good content uniformity. The tablet **hardness** of all the formulations was determined and it was found sufficient in the range 7.2-7.6 kg/cm^2. Another measure of tablet hardness was the **friability**. A compressed tablet that loses less than 1 % of their weight is generally considered acceptable. For all formulation tried here the weight loss was less than 1 % hence acceptable.

Table 2: Table shows Evaluation of Tablets:

Formulation code	Thickness (mm) (mean ±S.D)	Hardness (Kg/cm2) (mean ±S.D)	Weight Variation (%)	Friability (%) (mean ±S.D)
F1	**3.75 ±0.0034**	**7.3±0.0011**	**2.2**	**0.48±0.0043**
F2	**3.95 ±0.0012**	**7.4±0.0043**	**1.4**	**0.35±0.0023**
F3	**3.90 ±0.0023**	**7.4±0.0022**	**1.5**	**0.40±32**
F4	**4.00 ±0.0014**	**7.3±0.0015**	**1.8**	**0.41±0.0027**
F5	**3.75 ±0.0030**	**7.2±0.0034**	**1.4**	**0.35±0.0028**
F6	**3.87 ±0.0033**	**7.5±0.0020**	**2.5**	**0.42±0.0032**
F7	**3.90 ±0.0024**	**7.4±0.0015**	**1.9**	**0.31±0.0027**
F8	**3.85 ±0.0040**	**7.2±0.0024**	**1.5**	**0.37±0.0028**
F9	**3.77 ±0.0043**	**7.5±0.0030**	**2.1**	**0.32±0.0032**

Table 2: Determination of Ex-vivo mucoadhesion time:

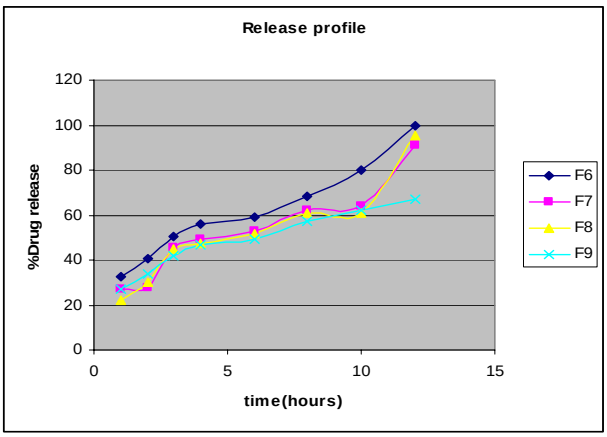
Formulation	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Adhesion time Hours ± SD	9 ± 0.76	10 ± 0.98	10 ± 0.34	10 ± 0.89	11 ± 0.34	12 ± 0.56	10 ± 0.98	9 ± 0.65	11± 0.67

Table 4: Table shows swelling index of tablets:

Formulation	Percent swelling index in hours			%Matrix erosion or dissolution after 12 hours
	4	8	12	
F1	23	39	48	24
F2	29	43	55	27
F3	32	46	61	31
F4	24	40	53	24
F5	31	47	58	29
F6	37	52	69	30
F7	31	45	61	26
F8	31	46	63	24
F9	35	49	66	29

The swelling index (69) and mucoadhesive time (12 hours) of formulation F6 was higher than other formulation, containing *Delonix regia* mucilage 120mg. The tablets, in formulation batch F9, containing *Delonix regia* mucilage and Xanthan gum in the ratio of 1:1 had the maximum swelling index but less adhesion time (11 hours).

Fig.1: Drug Release Profile



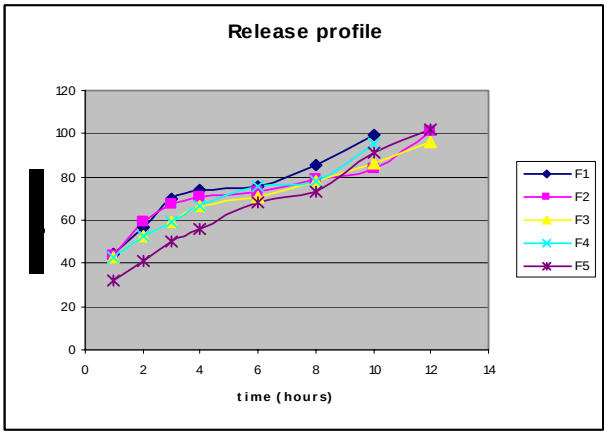
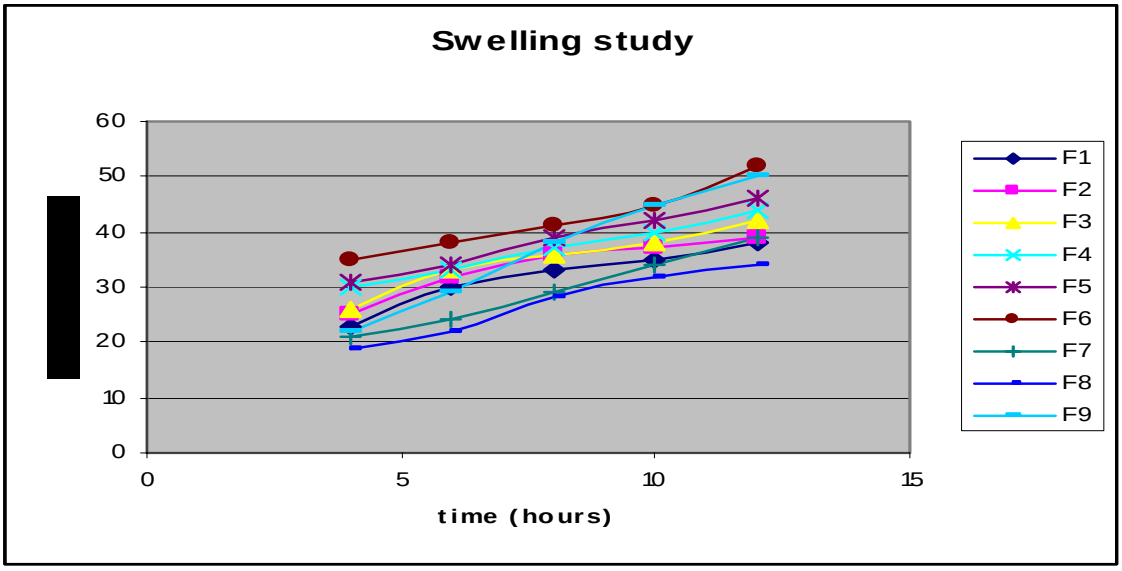


Figure2. Swelling profile:



Conclusion

From the above study it is concluded that as *Delonix regia* mucilage concentration increases swelling as well as mucoadhesive property increases compared to xanthan gum. Formulation contatining *Delonix regia* mucilage and Xanthan gum in ratio (1:1) have higer swelling index but less adhesion time and release of drug is very slow. So Formulation F6 containing (40%) *Delonix regia* mucilage have good adhesion time, swelling index and release of drug up to 12 hours. So *Delonix regia* mucilage may be a good candidate for sustained realease, mucoadhesive drug delivery system.

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