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DEVELOPMENT OF TRANSMUCOSAL DELIVERY SYSTEM FOR PROPRANOLOL HYDROCHLORIDE USING NOVEL NATURAL POLYSACCHARIDE

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ABSTRACT

The objective of the present study was designed to overcome the hepatic first pass metabolism and enhance the bioavailability, as it is the major disadvantage of the oral drug delivery, for that Buccal route of administration is one of the routes of choice for the administration of drugs that undergo extensive first pass metabolism. Natural plant polysaccharides, such as gums and mucilages find a wide variety of applications in pharmaceutical formulations. Commonly they are used as binding agents, disintegrating agents, sustaining agents in matrix tablets, film forming agents, gelling agents, suspending and emulsifying agents, and as coating agents for granule coating and microencapsulation. Tshe gum from Prunusamygdalus exhibited very good mucoadhesive properties. Hence, the objective of the present study was to formulate unidirectional, bilayered, mucoadhesive tablets for buccal delivery of propranolol hydrochloride using Prunusamygdalus. So Different shaped bilayered unidirectional buccal tablets were prepared taking different concentrations of polymer, among these bilayers one is drug containing layer which compressed with drug, polymer, avicel PH 101 and magnesium stearate using KBR pellet machine by maintaining 1 ton pressure another layer was backing layer compressed with ethyl cellulose and evaluated for all possible parameters and also conducted *in vivo* studies using 6 human volunteers. It can be stated that the formulated unidirectional, bilayered, mucoadhesive tablets of propranolol hydrochloride using natural polysaccharide as mucoadhesive polymer were able to bypass the first pass metabolism associated with oral administration and improves the bioavailability of the drug.

Key words: Prunus amygdalus, Direct compression, KBR Pellet machine and Bilayered mucoaddhessice tablets

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INTRODUCTION

Oral administration of drugs and presystemic metabolism[1]

Any drug, to elicit its pharmacological action, has to reach the systemic circulation. To reach systemic circulation, the drug has to be administered through various routes, namely, oral, parenteral or local routes. Among these, oral route is the most natural, uncomplicated, convenient safe and economic route of drug administration. One of the major disadvantages of oral route is metabolism of certain drugs by the enzymes of mucosa, intestinal flora or liver, before they gain access to the systemic circulation.

After oral administration, a drug must pass from the gastrointestinal lumen, through the gut wall, then through the liver, before reaching systemic circulation. This sequence is an anatomic requirement since the blood perfuses the entire length of gastrointestinal tract. With exception of buccal cavity and lower rectum, the blood drains into the liver through hepatic portal vein. Since gut wall and liver are the sites of metabolism, a fraction of the drug absorbed gets metabolized before reaching the blood stream. Hence, a drug administered orally may get completely absorbed, but may not be completely available to the systemic circulation, due to presystemic metabolism.

Liver is the main site of presystemic metabolism, because of its high level of drug metabolizing enzymes, its ability to rapidly metabolize different kinds of drug molecules and its unique anatomic location. This presystemic metabolism by the liver is called as first pass metabolism or first pass effect. A large number of drugs are subject to hepatic presystemic metabolism. Some of the classes of drugs, which are highly susceptible for first pass metabolism are β-blockers, analgesics, antidepressants and antiarrythmics.

Alternative routes to bypass presystemic betabolism[1]

The hepatic first pass effect can be avoided to a great extent by the use of buccal tablets, transdermal preparations, inhalations, and to a lesser extent by use of rectal suppositories. Buccal absorption, transdermal and inhalation routes provide direct access to systemic circulation but not to portal vein.

The disadvantage with transdermal route is less penetration of drug through the skin. It has been estimated that the permeability of the skin is 4-4000 times lesser than that of buccal mucosa[2]. Similarly, from suppositories also, only about 50% of the drug can bypass liver because they tend to move upwards in the rectum, which is connected to superior hemorrhoidal vein that leads to liver. The drugs administered by inhalation bypass the

hepatic first pass metabolism, but lung also serves as a site of first pass loss by excretion and metabolism[3].

Buccal administration of drugs[4]

Buccal cavity provides a highly vascular mucous membrane site for the administration of drug. The epithelial lining of the oral cavity is different both in type and in thickness in different areas and the difference gives rise to regional variation in permeability to drugs. Although some macromolecules have been found to be absorption barriers, the absorption of smaller drug molecules occur more reproducibly and rapidly. The main absorption mechanism is passive diffusion of unionized form of drug. The blood drainage from the mouth enters general circulation directly without first passing through the liver. This feature enhances the bioavailability of certain drugs compared with per oral administration. This route of administration has the following advantages:

- Rapid onset of action
- Quick termination of the drug effect
- Avoidance of first pass metabolism of the drug
- Avoidance of drug degradation in the stomach

Factors influencing drug absorption from oral cavity[4]

The main factors that influence the drug absorption from the oral cavity are the permeability of the oral mucosa to the drug and the physicochemical characteristics of the drug.

Permeability of the oral mucosa[5,6]

The lipid membranes of oral mucosa are resistant to the passage of large macromolecules. However, small, unionized molecules tend to cross the membrane with relative ease. The main mechanism involved in the drug transfer across the oral mucosa is passive diffusion although facilitated diffusion has also been reported to take place, primarily with nutrients. In the passive diffusion, the movement of solute occurs from a region of higher concentration in the mouth, to a region of lower concentration within the buccal tissues. Further diffusion then takes place into the venous capillary system, with the drug eventually reaching the systemic circulation via the jugular vein[7].

Physicochemical characters of drug

The physicochemical characters of drug, which affect its absorption from oral mucosa,

include molecular weight, particle size, surface area, polymorphism and amorphism, salt form, and lipid solubility[8].

Controlled release mucoadhesive drug delivery systems[9]

The basic rationale of controlled drug delivery system is to optimize the biopharmaceutic, Pharmacokinetic and pharmacodynamic properties of a drug in such a way that its utility is maximized through reduction in side effects and care or control of condition in the shortest possible time by using smallest quantity of drug administered by the most suitable route.

Buccal route of drug administration has advantages compared with other routes, including rapid onset of action, high blood levels, avoidance of first pass metabolism and avoidance of exposure of the drug to the GI tract. There is of course, excellent accessibility and the drug can be applied, localized and removed easily. At present, these advantages are relevant for only a limited number of drugs. However, the recent development of new formulations such as mucoadhesive preparations, this number may increase.

A variety of drugs have been shown to be absorbed by mucosal epithelium of oral cavity, mainly by the buccal or sublingual mucosa. Recently, many researchers have focused their attention on the use of bioadhesive hydrophilic polymers to control the delivery of biologically active agents systemically or locally. These bioadhesive systems are useful for the administration of drugs, which are susceptible to extensive degradation in GI tract. Buccalmucoadhesive systems appear to be especially attractive because of the easy accessibility and robust nature of oral mucosa. It is less prone to irritation by a dosage form and hence, it may lead to better patient compliance and acceptance.

Mucoadhesion[10-12]

Mucoadhesion is an interfacial phenomenon in which, two materials are held together by means of interfacial forces. The attachment would be between an artificial material and biological substrate such as the adhesion between polymer and biological membrane. In the case of polymer attached to the mucosal tissue, the term mucoadhesion is employed. From the theoretical stand point, mucoadhesion may lead to the solution of bioavailability problems resulting from a short stay of pharmaceutical dosage form at the absorption site. Several theories, such as electronic theory, absorption theory and diffusion theory, have been proposed to explain the mechanism of adhesion. In a particular system, one or more theories can equally well explain the formation of bioadhesive bonds.

EXPERIMENTAL

Unidirectional, bilayered, buccoadhesive tablets of propranolol hydrochloride using polysaccharide from Prunus amygdalus as mucoadhesive polymer were prepared by double compression technique in a hydraulic press. Initially, a backing layer was made using ethyl cellulose, onto which, the drug containing granules were placed and recompressed to get bilayered tablets. In the formulation of bilayered tablets, propranolol hydrochloride was used as model drug, selected polysaccharide was used as mucoadhesive polymer, pearlitol was used as sweetening agent, magnesium stearate was used as glidant and microcrystalline cellulose (Avicel PH 101) was used as diluent. The backing layer was prepared using ethyl cellulose to make the release from the tablet unidirectional. Based on previous studies carried out in our laboratory, 40 mg of ethyl cellulose was used in the backing layer. Three different permeation enhancers, sodium tauro deoxycholate, sodium glycocholate, and sodium taurocholate were used at three different concentrations, (i.e., 2.5, 5 and 10%) were used in the formulation. The formulae used for the preparation of tablets are given in Table 1.

Table 1: Formulae used for preparation buccoadhesive tablets of propranolol hydrochloride using Prunus Polysaccharide

Ingredient	Quantity per tablet (%)									
	B1	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	**B9**	**B10**
Propranolol hydrochloride	12.12	12.12	12.12	12.12	12.12	12.12	12.12	12.12	12.12	12.12
Prunus polysaccharide	15	15	15	15	15	15	15	15	15	15
Pearlitol	20	20	20	20	20	20	20	20	20	20
Sodium tauro deoxycholate	-	2.5	5	10	-	-	-	-	-	-
Sodium glycocholate	-	-	-	-	2.5	5	10	-	-	-
Sodium taurocholate	-	-	-	-	-	-	-	2.5	5	10
Avicel pH 101 q.s to	100	100	100	100	100	100	100	100	100	100
Magnesium stearate	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Ethylcellulose (mg/tablet)	40.00	40.00	40.00	40.00	40.00	40.00	40.00	40.00	40.00	40.00

Preparation of granules and compression of bilayered tablets

For the preparation of granules, wet granulation method was used. Accurately weighed quantities of the ingredients were mixed in a glass mortar and required quantity of warm water was added to the powder mass and mixed thoroughly. The granules were prepared by passing the wet mass through British Standard Sieve (BSS) No. 16. Wet

granules were dried in a hot air oven for 30 min at 60°C and then passed through BSS No. 22. Finally, required quantity of the drug containing granules were placed on the precompressed backing layer in a hydraulic press and recompressed into tablets of 10 mm diameter. In the previous study carried out in our laboratory, the compression force of 1 ton/cm^2 was found to be ideal and hence, in the present study also, same force of compression was used. In each batch, 20 tablets were compressed.

Effect of permeation enhancers on release profile

The effect of three different permeation enhancers, sodium tauro deoxycholate, sodium glycocholate and sodium taurocholate, at three different concentrations 2.5, 5 and 10% of the total weight of tablets, was studied on release profile of drug from the buccal tablets.

Effect of tablet shape on physicochemical properties and release profile

For determination of effect of tablet shape on physicochemical properties and release behaviour, the formula of ideal batch of round shaped tablets was punched using oval and flower shaped punches. These tablets were also evaluated for physical properties and *in vitro* drug release profiles.

Evaluation of buccoadhesive tablets

All the above batches were evaluated for average thickness, average weight and weight variation, hardness, friability, drug content, swelling index, and *in vitro* drug release profile, using the procedures described below.

Average thickness

The thickness of ten buccal tablets in each batch was determined using a digital vernier calipers. The average thickness and standard deviation were calculated.

Average weight and weight variation

Ten buccoadhesive tablets from each batch were weighed in sartorius digital balance and average weight was determined and standard deviation was calculated.

Hardness

The hardness of a tablet is indication of its strength. It is tested by measuring the force required to break the tablet across the diameter. The force is measured in Kg/cm^2 and the hardness of about 4 Kg/cm^2 is considered to be satisfactory for uncoated tablets.

Monsanto hardness tester was used for this purpose. The hardness of five tablets in each batch was measured and the average hardness was calculated.

Friability

Friability of the tablets was determined using Roche friabilator. From each batch, 10 tablets were weighed accurately and placed in the friabilator and rotated at 25 rpm for 4 min. The percentage friability was determined using the following formula:

$$\text{Friability (\%)} = \frac{\text{Initial weight of 10 tablets - Final weight of 10 tablets}}{\text{Initial weight of 10 tablets}} \text{ x } 100$$

Drug content

The content of propranolol hydrochloride in the prepared buccoadhesive tablets was determined by UV spectrophotometry. Five tablets from each batch were powdered and the powder quantity equivalent to 20 mg of propranolol was transferred into a standard flask containing 50 mL purified water and vigorously shaken and filtered. The absorbance of the filtrate was measured at 289.6 nm in a spectrophotometer. A blank was prepared using dummy tablets in a similar manner. The determination was carried out three times and average was calculated and standard deviation was determined.

Swelling studies

The swelling index of the ideal batch of the mucoadhesive tablets was determined according to the procedure described below. The tablet was weighed accurately (W1) and placed in petri dish containing 4 mL of phosphate buffer of pH 6.8. At the end of 2 h, the tablets were removed from the petri dish and excess surface water was removed carefully using filter paper and the swollen tablets were reweighed (W2). The swelling index was calculated according to the formula:

$$\text{Swelling index} = (W2-W1) / W1$$

***In vitro* diffusion**

USP dissolution apparatus with paddle was used for the *in vitro* diffusion study of buccoadhesive tablets with a simple modification. A two end open glass cylinder of 3 cm diameter and 20 cm length was taken. The prepared buccoadhesive tablet was placed by applying a moderate pressure onto a moistened semi-permeable membrane, having a thickness of ~500 μm and this was tied to one end of the cylinder, taking care to place the tablet inside the cylinder. This cylinder was then placed on the surface of phosphate buffer

of pH 6.8 (900 mL), which was used as dissolution medium. The temperature of the medium was previously set to 37 ± 1°C and stirring was done at 100 rpm. At specified time intervals, 5 mL samples were withdrawn and immediately replaced with equal quantity of fresh buffer. The diffusion study was carried out for a period of 3 h. The drug content was determined in the samples after suitable dilution, by measuring the absorbance at 289.6 nm.

RESULTS AND DISCUSSION

The physicochemical properties of different batches of buccoadhesive tablets are given in Table 2.

Table 2: Physicochemical properties of different batches of buccoadhesive tablets

Batch	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content per tablet (mg)	Swelling index (%)
B1	1.85 ± 0.01	2.67 ± 0.29	0.62 ± 0.03	19.36 ± 0.02	149.10 ± 0.14
B2	1.84 ± 0.01	2.83 ± 0.29	0.61 ± 0.00	19.85 ± 0.03	179.30 ± 0.42
B3	1.85 ± 0.01	3.00 ± 0.00	0.70 ± 0.03	19.89 ± 0.02	189.25 ± 0.35
B4	1.85 ± 0.01	2.83 ± 0.29	0.63 ± 0.03	19.93 ± 0.12	217.28 ± 0.39
B5	1.86 ± 0.01	3.00 ± 0.00	0.90 ± 0.01	19.95 ± 0.18	189.75 ± 0.21
B6	1.84 ± 0.01	2.50 ± 0.00	0.97 ± 0.01	19.63 ± 0.07	231.65 ± 0.49
B7	1.85 ± 0.01	2.83 ± 0.29	0.80 ± 0.01	19.94 ± 0.09	252.75 ± 0.35
B8	1.84 ± 0.01	2.83 ± 0.29	0.73 ± 0.01	19.64 ± 0.01	165.60 ± 0.57
B9	1.85 ± 0.02	3.00 ± 0.00	0.83 ± 0.04	19.60 ± 0.07	162.05 ± 1.06
B10	1.85 ± 0.00	2.83 ± 0.29	0.85 ± 0.01	19.94 ± 0.14	210.50 ± 0.14

The thickness of tablets was found to be within range of 1.84-1.86, which was found to be acceptable and the deviation was very less. The average weight of all the batches of tablets was within specified limits. The hardness of the tablets was little less when compared to the specifications for normal tablets, but, it was found to be suitable because of lesser thickness of the tablets. The friability and drug content values of all the batches of buccal tablets were within acceptable limits. The tablets had swelling indices within the range 149.10-252.75%. The tablets containing 10% of the permeation enhancer exhibited higher swelling when compared to remaining two concentrations. Among them, highest swelling was found with 10% of sodium glycocholate. This swelling might lead to absorption of water and faster release of drug from the buccal tablets.

The *in vitro* diffusion data of all the ten batches of buccal tablets is given in Figs. 1 to 3. The batch of buccal tablets prepared without any permeation enhancer found to release minimum quantity of the drug during the diffusion study. The presence of permeation enhancers increased the release rate. The release of drug from the buccal tablets was found to increase with increase in the concentration of permeation enhancer.

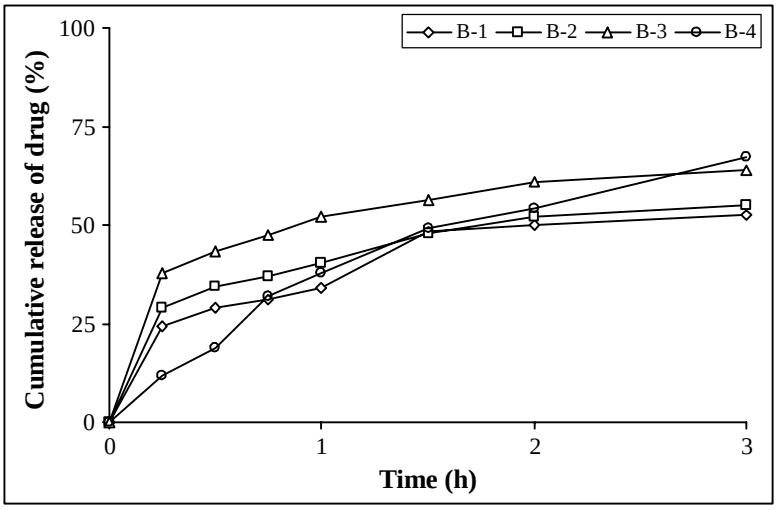


Fig. 1: *In vitro* release profiles of buccal tablets containing sodium tauro deoxycholate as permeation enhancer

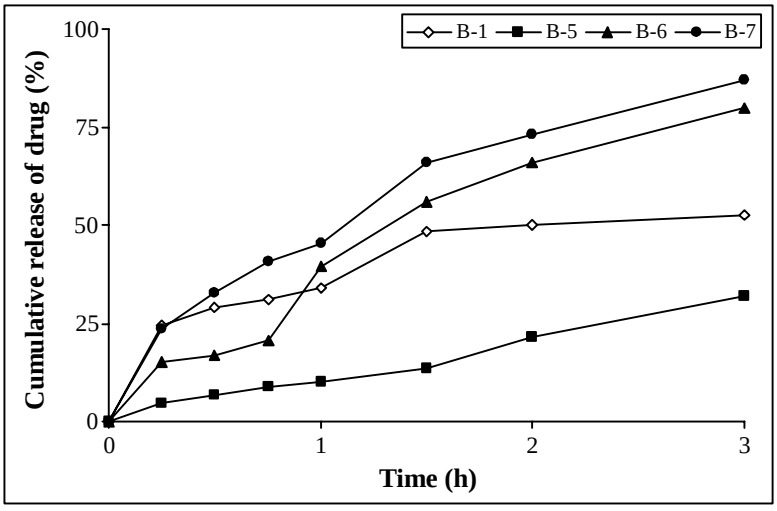


Fig. 2: *In vitro* release profiles of buccal tablets containing sodium glycocholate as permeation enhancer

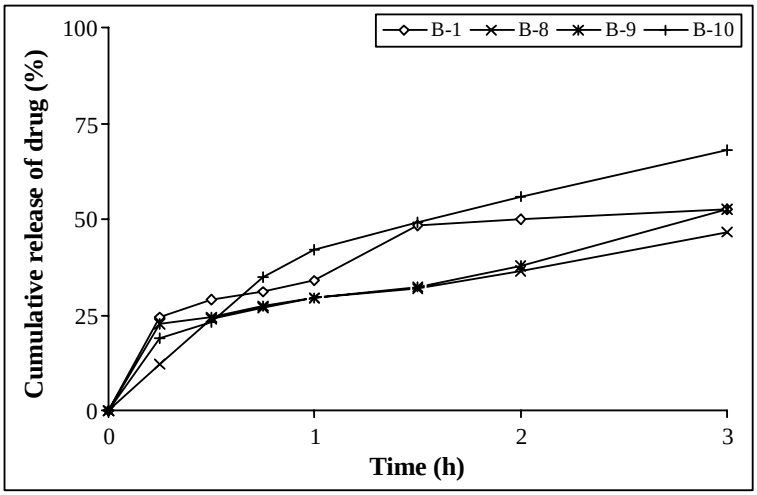


Fig. 3: *In vitro* release profiles of buccal tablets containing sodium taurocholate as permeation enhancer

Among the three permeation enhancers used, sodium glycocholate exhibited maximum release when compared with other two enhancers. At a concentration of 10%, the tablets exhibited a highest release of 86.86% at the end of 3 h. The other two permeation enhancers, sodium tauro deoxycholate and sodium taurocholate exhibited a maximum release of 67.35 and 67.91%, respectively, at the end of 3 h. Hence, the batch of buccal tablets containing 10% sodium glycocholate (B7) was considered as ideal batch and was selected for further study, i.e., effect of tablet shape on physicochemical properties and drug release.

Table 3: *In vitro* release profile of ideal batch of buccal tablets through goat mucous membrane

Time	Cumulative drug release (%)	SD
0.25	20.36	2.47
0.5	29.89	0.32
0.75	35.30	1.31
1.0	42.43	1.82
1.5	45.61	1.33
2.0	50.52	1.65
3.0	66.25	1.47

The values are represented as Mean ± SD; n=6

Table 4: Physicochemical properties of buccal tablets of oval and flower shape

Shape	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content per tablet (mg)
Round (B7)	1.85 ± 0.01	2.83 ± 0.29	0.80 ± 0.01	19.94 ± 0.09
Oval	2.45 ± 0.02	3.33 ± 0.29	1.21 ± 0.50	19.94 ± 0.02
Flower	2.19 ± 0.01	2.83 ± 0.28	2.25 ± 0.62	19.95 ± 0.08

The values are represented as mean ± SD; n = 6

Table 5: *In vitro* release profile of buccal tablets of round, oval and flower shapes

Time (h)	Cumulative release of drug (%)					
	Round (B7)		Oval		Flower	
	Release	SD	Release	SD	Release	SD
0.25	23.50	1.65	4.41	3.29	8.95	0.49
0.5	32.59	0.17	9.79	4.96	17.02	1.32
0.75	40.67	1.65	11.92	3.32	22.42	1.65
1.0	45.37	2.31	18.91	3.31	32.68	0.34
1.5	66.11	1.99	27.44	5.45	45.42	1.15
2.0	72.97	3.63	37.61	3.32	54.68	1.65
3.0	86.86	2.49	56.29	3.18	59.85	1.65

The values are represented as Mean ± SD; n=6

When diffusion study was carried out through biological membrane, there was a little reduction in the release of the drug from the tablet. In the initial stages, the release through biological membrane almost resembled that through artificial membrane. But, at the later stages of diffusion, the release was found to retard through biological membrane. Through artificial membrane, the drug release at the end of 3 h was 86.86%, whereas, through biological membrane, it was only 66.25%. This reduction might be due to uneven surface of biological membrane and its varying thickness.

The results of comparative bioavailability study are shown in Tables 6 and 7, and Fig. 9. Assessment was done for C_{max}, T_{max}, AUC, half-life and elimination rate constant. From the results of comparative *in vivo* bioavailability study, it can be seen that the plasma concentrations of the drug from the buccoadhesive tablet was higher than that of conventional dosage form. T_{max} was found to be lower in buccal tablet, because of higher absorption rate. Similarly, C_{max} was also higher in case of developed buccoadhesive tablet. The AUC_{0-t} of developed tablet was found to be higher than that of the marketed formulation. Also, the plasma half life of the drug was found to improve and the elimination rate constant was found to decrease with buccoadhesive tablet, which indicates better bioavailability for a prolonged period of time. This is also indicated by the higher value of AUC_{0-inf} of the formulated buccoadhesive tablet. This increase in AUC or bioavailability is due to the capacity of the developed buccoadhesive tablet to bypass the first pass effect associated with oral administration

Table 6: Plasma concentration of propranolol hydrochloride in human volunteers

Time (h)	Plasma concentration of drug (μg/mL)			
	Buccoadhesive tablet		Marketed tablet	
	Value	± SD	Value	± SD
0.00	0.0000	0.00	0.0000	0.00
0.50	0.5604	0.12	0.5524	0.17
1.00	0.6185	0.27	0.6379	0.17
1.50	1.0251	0.38	0.6923	0.15
2.00	1.2478	0.57	0.9407	0.24
3.00	1.2054	0.49	0.7857	0.16
4.00	0.6238	0.21	0.7339	0.17
6.00	0.6712	0.13	0.5682	0.01
8.00	0.4181	0.16	0.3881	0.16
12.00	0.1385	0.10	0.0747	0.04

The values are represented as Mean ± SD; n=3

Table 7: Pharmacokinetic parameters for the developed buccoadhesive tablets

Parameter	Buccoadhesive tablet		Marketed tablet	
	Value	± SD	Value	± SD
C_{max}	1.6825	0.27	0.9497	0.22
T_{max}	2.1667	0.76	2.3333	0.58
AUC_{0-t}	7.0526	0.51	5.9834	0.44
K_e	0.2477	0.07	0.2746	0.08
$t_{½}$	2.9501	0.84	2.6850	0.81
AUC_{0-inf}	14.4168	3.57	9.7403	1.97

Effect of tablet shape on physicochemical properties and drug release

To evaluate the effect of tablet shape on physicochemical properties and drug release, three different shapes were selected, namely, round, oval and flower. The composition of ideal batch (B7) was used for compression of oval and flower shaped tablets. The compression force and amount of ethyl cellulose in the backing layer were kept constant and only the shape was changed. The physicochemical properties are given in Table 4, and the physical appearance of all the three shapes are given in Fig. 5.

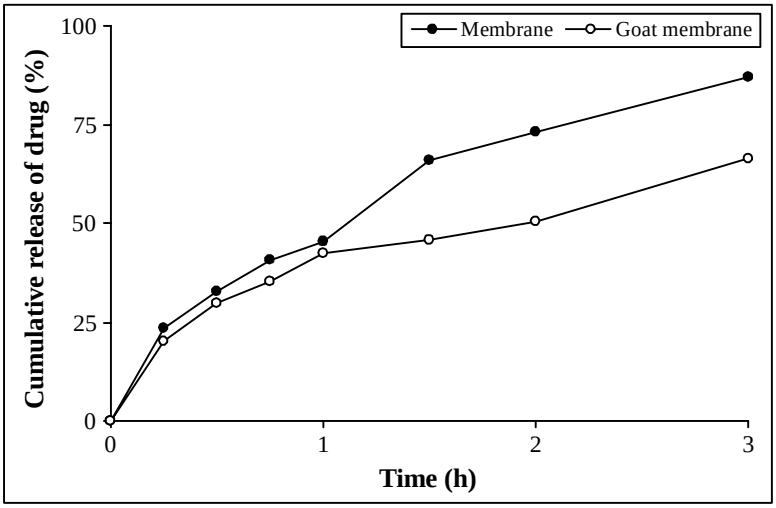
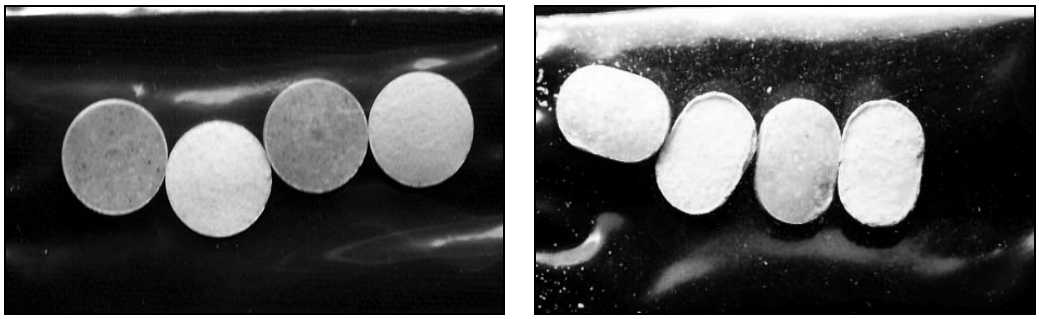
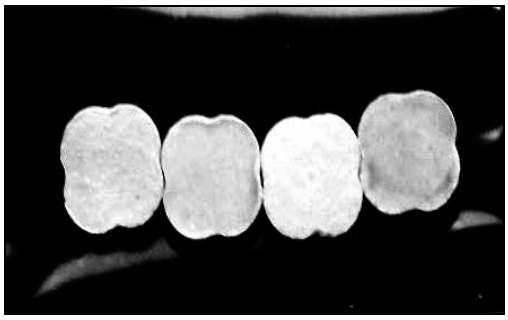


Fig. 4: *In vitro* release profile of ideal batch of buccal tablets through goat mucous membrane



(a) Round shaped buccal tablets (b) Oval shaped buccal tablets



(c) Flower shaped tablets

Fig. 5: Physical appearance of round, oval and flower shaped buccal tablets

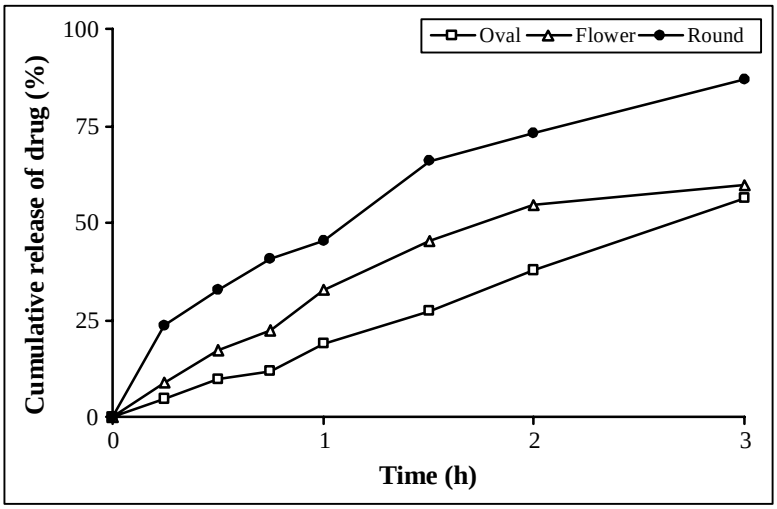


Fig. 6: *In vitro* release profile of buccal tablets of round, oval and flower shapes

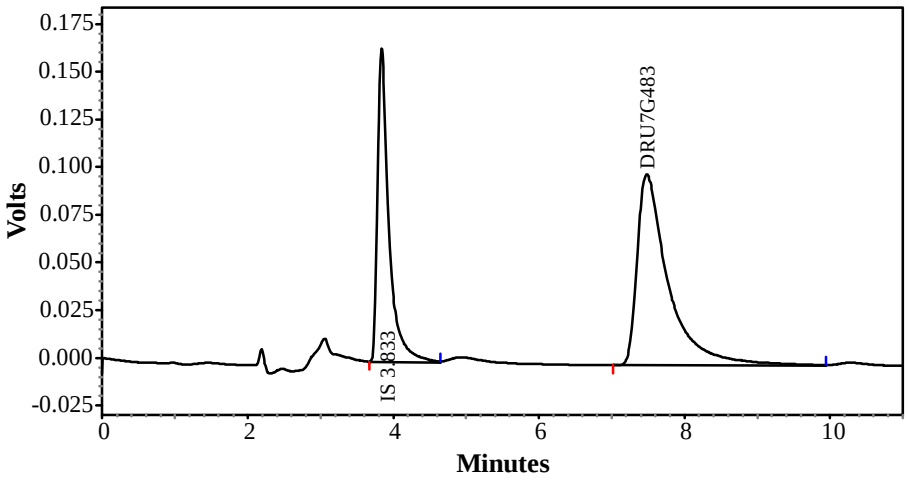


Fig. 7: Typical chromatogram of propranolol hydrochloride standard solution

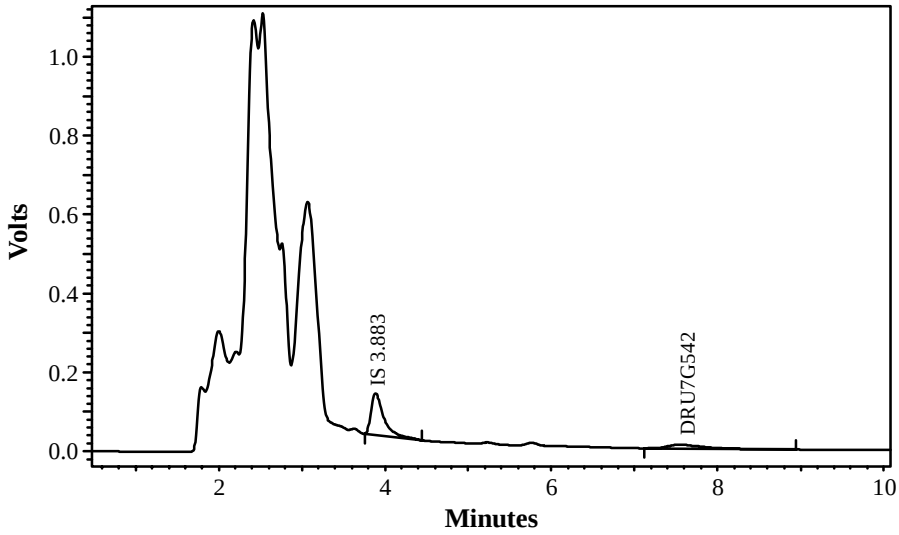


Fig. 8: Typical chromatogram of propranolol hydrochloride sample solution

The oval and flower shaped tablets did not exhibit better physical properties when compared to round tablets. The oval and flower shaped tablets had higher thickness, but, the hardness, average weight and drug content did not change significantly, and were within acceptable limits. The friability was found to be very high in both these shapes and it was more than the USP specified limits. In case of flower shaped tablets, the friability was maximum because of too much whiskers formation at the edges. This was due to the shape of the punch. Due to this, the tablets lost too much of weight when subjected to friability test.

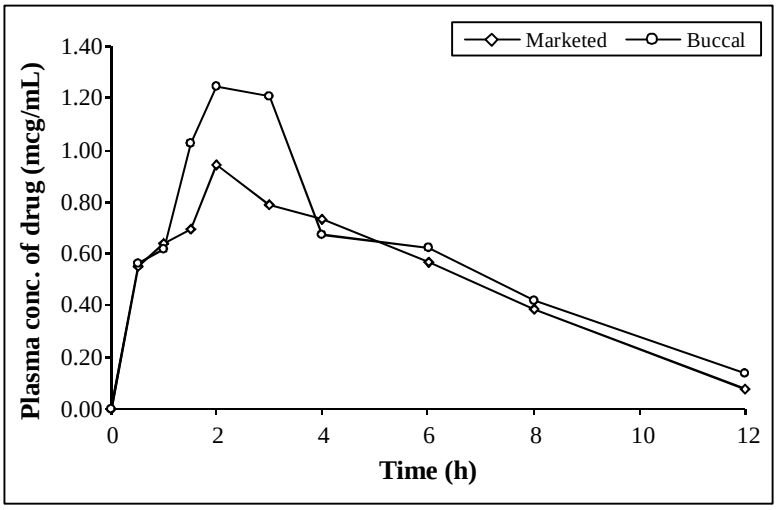


Fig. 9: Plasma concentration-time curve of propranolol hydrochloride for marketed tablet and formulated buccoadhesive tablet

The *in vitro* diffusion data of both the selected shapes is given in Table 3 and Fig. 6. The oval and flower shaped tablets exhibited lower release than the round shaped tablets. This retardation in release might be because of lower surface area of tablet for the given weight. Also, the oval and flower shaped tablets had higher thickness, when compared to round tablets. This increased thickness delays solvent penetration and hence, might be responsible for lower release. Another reason that may be attributed for this lower release is the compression force. Due to increased thickness, the tablet experiences more compression pressure and hence, the particles in the tablet undergo plastic deformation. Because of this, the tablet will take up solvent at a slower rate and hence, the drug release will be lower.

CONCLUSION

In conclusion, it can be stated that the formulated unidirectional, bilayered, mucoadhesive tablets of propranolol hydrochloride using natural polysaccharide as mucoadhesive polymer were able to bypass the first pass metabolism associated with oral administration and improves the bioavailability of the drug. This leads to improvement of therapy and reduction in dose of the drug. Hence, the developed bilayered buccoadhesive tablet dosage form using natural polymer is highly suitable for transmucosal delivery of propranolol hydrochloride. However, long term stability study, testing of bioavailability in more number of human volunteers and suitability study for long-term application are needed to establish the potential of the developed transmucosal delivery system.

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