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DESIGN AND EVALUATION OF BUCCOADHESIVE DRUG DELIVERY SYSTEM OF METOPROLOL TARTRATE

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ABSTRACT: The purpose of the present study was to develop a buccoadhesive drug delivery system of Metoprolol Tartrate (MT) using combination of natural polymers in order to overcome its first pass metabolism which may improve its bioavailability. MT is mainly used in cardiovascular disorders and is well absorbed in gastrointestinal tract. However, its extensive first pass metabolism results in poor bioavailability. The tablets of MT were prepared by using semi-synthetic polymer such as sodium carboxy methyl cellulose and natural polymers such as gum karaya, xanthan gum and locust bean gum. An impermeable backing layer of ethyl cellulose was applied to give unidirectional drug release. Buccal tablets were evaluated by different parameters such as appearance, physical integrity, hardness, *ex vivo* mucoadhesive strength, *in vitro* drug release and *ex vivo* drug permeation. Results revealed that formulation containing combination of xanthan gum and locust bean gum in 2:1 ratio exhibited complete drug release in 45 mins but poor drug permeation. Incorporation of 1% sodium lauryl sulphate improved the drug permeation across the porcine buccal mucosa.

KEY WORDS: Buccoadhesive drug delivery system, xanthan gum, locust bean gum, Metoprolol Tartrate.

INTRODUCTION

Transmucosal routes of drug delivery offers distinct advantages over per oral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the gastrointestinal tract and depending on the particular drug, a better enzymatic flora for drug absorption.[1] Buccal mucosa is relatively permeable with a rich blood supply. The dosage form can be applied, localized, and removed easily. These factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery.[2]

An ideal buccal dosage form must have three properties. It must maintain its position in the mouth for required time period; release drug in a controlled fashion, and provide the drug release in a unidirectional way towards the mucosa. In regard to the first requirement, strong adhesive contact to the mucosa is established by using mucoadhesive polymers as excipients. If the mucoadhesive excipients are able to control drug release, the second requirement can also be achieved. The third objective can be obtained by using bilayerd devices.[3]

Metoprolol Tartrate (MT) is a competitive, β_1-selective (cardioselective) adrenergic antagonist. It is widely used in the treatment of hypertension, angina pectoris, cardiac arrhythmias, myocardial infraction and prophylaxis of migraine. Although it is well absorbed in the gastrointestinal tract, its bioavailability is low (40%-60%) as a result of extensive first-pass metabolism (40-60%). Since the buccal route bypasses the hepatic first pass effect, the dose of MT can be reduced. Its high solubility in water, partition coefficient (1.8)[4] and dose 25 mg makes it suitable candidate for administration by the buccal route.[5]

The aim of present study was to develop an erodible immediate release buccal mucoadhesive drug delivery system of MT having a balance between mucoadhesive strength and drug release to improve its bioavailability. The buccal tablets were evaluated for appearance,

physical integrity, hardness, *ex vivo* mucoadhesive strength, *in vitro* drug release and *ex vivo* drug permeation.

EXPERIMENTAL

MATERIALS:

MT was received as a gift sample from Cipla Ltd. (Mumbai). Sodium carboxy methyl cellulose (SCMC), gum karaya (GK), xanthan gum (XG), locust bean gum (LBG), poly vinyl pyrollidone K-30 (PVP K-30), sodium lauryl sulphate (SLS), talc and magnesium stearate (Mg.St.) were bought from S.D. Fine Chemicals. Ethyl cellulose (EC) was received as a gift sample from Colorcon Asia Pvt. Ltd and Pharmatose DCL 11 from D.M.V. International. All other reagents and chemicals used were of analytical grade.

PREPARATION OF MUCOADHESIVE TABLETS:

Mucoadhesive tablets of MT were prepared by direct compression techniques using different polymers with varying concentration **(Table I-III).** The tablets were prepared using SCMC, XG, GK and LBG as polymers, PVP K-30 as a binder and SLS was used as a penetration enhancer. The tablets were compressed using 9 mm flat circular punch on single station compression machine. For the application of the backing membrane, tablets were transferred to 10 mm die and a layer of EC (60 mg) was compressed on it.

EVALUATION:

The tablets were evaluated for appearance, physical integrity, dimensions, hardness and *ex vivo* mucoadhesion strength. The tablets fulfilling above criteria were subjected to *in vitro* drug release. Further the tablets showing complete drug release in 45 mins were subjected to *ex vivo* permeation studies.

IN VITRO DRUG RELEASE:

The United States Pharmacopoeia (USP) XXIII rotating paddle method was used to study the drug release from the buccal tablets. The dissolution medium consisted of 500 mL of phosphate buffer pH 6.8. The study was performed at 37 ± 0.5^0 C, with rotational speed of 50 rpm for a period of 45 mins. To study the drug release from only one side, the tablets were stuck to the paddle with Ethyl cellulose layer facing to paddle. Samples (5 mL) were withdrawn at 15 mins interval and replaced with the fresh medium. The samples were filtered and analyzed at 274 nm [6] by UV-Vis spectrophotometer (Shimadzu 1601).

EX VIVO MUCOADHESION STRENGTH:

The mucoadhesion strength was determined using modified balance test.[7] Porcine buccal mucosa was obtained from local slaughterhouse and used as the model membrane. The mucosal membrane was excised by removing the underlying connective and adipose tissue and was equilibrated at 37 ± 1^0C for 30 mins in phosphate buffer pH 7.4. The tablet was stuck to the Teflon arm using cyanoacrylate adhesive and lowered into the mucosa under a constant weight of 5 g for a total contact period of 1 min. Mucoadhesion strength was assessed in terms of weight (g) required to detach the tablet from the membrane.

EX VIVO PERMEATION STUDY:

Preparation of porcine buccal tissue [8]: The mucosal membrane was excised by removing the underlying connective and adipose tissue of freshly slaughtered pig and was equilibrated at 37 ± 1.0 ^{0}C for 30 min in phosphate buffer pH 7.4. The buccal epithelium was carefully mounted in between the two compartments of Modified Franz Diffusion Cell. Tablets were stuck to the mucosa in the donor side containing simulated saliva pH 6.8. Receiver medium was 20 ml of phosphate buffer pH 7.4, mimicking the blood pH maintained at 37 ± 0.5 ^{0}C under gentle stirring. Fro the receiver compartment, 2 mL aliquots were collected at predetermined time intervals and replaced by an amount of fresh buffer. The samples removed were filtered, diluted and analyzed at 274 nm using HPLC.

OPTIMISATION:

Formulation which showed good tablet integrity, appearance, hardness, *in vitro* drug release, *ex vivo* mucoadhesion strength and *ex vivo* permeation was optimized using 3^2 factorial design as shown in **Table IV.**

Experimental trials were performed on all possible combinations. Independent variables selected were amount of Xanthan gum (X1) and amount of Locust bean gum (X2) with *in vitro* drug release and mucoadhesion strength as dependent variables. The results obtained were analysed using STAT-EASE Design Expert 7.1 software. The optimized formulation so obtained was further subjected to following evaluation tests.

i. WEIGHT VARIATION:

Twenty tablets were taken and weighed individually. The average weight was found out. Since the average weight is in the range of 80 to 250 mg, the test requirements are met if none of the individual weights are less than 92.5% or more than 107.5% of the average weight.[9]

ii. ASSAY:

Twenty tablets were weighed and powdered. A quantity of the powder containing about 0.100 g of metoprolol tartrate was weighed accurately and transfer to a 100 mL volumetric flask, 75 mL of water was added and shaken for 15 minutes. Then, it was diluted to volume with water, mixed and filtered. Further dilutions were made using phosphate buffer pH 6.8 to get 10µg/mL. Absorbance of the resulting solution at about 274 nm was measured. Concentration of the resulting solution was calculated in comparison with standard plot equation which was calculated previously.

Table I: Batches made with Sodium CMC and Xanthan gum as mucoadhesive polymer

Ingredients	Quantity Per Tablet (mg)								
	A1	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**
MT	25	25	25	25	25	25	25	25	25
Pharmatose DCL 11	57	47	37	62	59.5	57	54.5	52	58.5
SCMC	10	20	30	-	-	-	-	-	-
Xanthan gum	-	-	-	5	7.5	10	12.5	15	7.5
PVP K-30	5	5	5	5	5	5	5	5	5
SLS	-	-	-	-	-	-	-	-	1
Talc	2	2	2	2	2	2	2	2	2
Mg. St.	1	1	1	1	1	1	1	1	1
TOTAL	100	100	100	100	100	100	100	100	100

Table II: Batches made with Gum karaya and Locust bean Gum as mucoadhesive polymer

Ingredients	Quantity Per Tablet (mg)								
	B1	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	**B9**
MT	25	25	25	25	25	25	25	25	25
Pharmatose DCL 11	57	47	37	62	59.5	57	54.5	52	58.5
Gum Karaya	10	20	30	-	-	-	-	-	-
Locust Bean Gum	-	-	-	5	7.5	10	12.5	15	7.5
PVP K-30	5	5	5	5	5	5	5	5	5
SLS	-	-	-	-	-	-	-	-	1
Talc	2	2	2	2	2	2	2	2	2
Mg. St.	1	1	1	1	1	1	1	1	1
TOTAL	100	100	100	100	100	100	100	100	100

Table III: Batches made with Xanthan Gum and Locust Bean Gum as mucoadhesive polymer

Ingredients	Quantity Per Tablet (mg)						
	C1	C2	C3	C4	C5	C6	C7
MT	25	25	25	25	25	25	25
Pharmatose DCL 11	64	63	62	61	60	59	60
Xanthan Gum	1	2	3	4	5	6	4
Locust Bean Gum	2	2	2	2	2	2	2
PVP K-30	5	5	5	5	5	5	5
SLS	-	-	-	-	-	-	1
Talc	2	2	2	2	2	2	2
Mg. St.	1	1	1	1	1	1	1
TOTAL	100	100	100	100	100	100	100

Table IV: 3^2 factorial design

Levels / Ingredients	+1	0	-1
Conc. of Xanthan gum (mg)	5	4	3
Conc. of Locust bean gum (mg)	3	2	1

Table V: Results of Appearance and Physical Integrity of tablets

Batch No.	Appearence	Physical Integrity	Batch No.	Appearence	Physical Integrity
A1	+++	+	B5	+++	+++
A2	+++	+++	B6	+++	+++
A3	+++	+++	B7	+++	+++
A4	+++	++	B8	+++	+++
A5	+++	+++	B9	+++	+++
A6	+++	+++	C1	+++	-
A7	+++	+++	C2	+++	-
A8	+++	+++	C3	+++	+
A9	+++	+++	C4	+++	+++
B1	+	-	C5	+++	+++
B2	+	-	C6	+++	+++
B3	+	-	C7	+++	+++
B4	+++	+			

iii. SURFACE PH:

The method used to determine the surface pH of the formulation was similar to that used by Bottenberg *et al.* [10]a combined glass electrode was used for the purpose. The tablets were allowed to swell by keeping them in contact with 1 mL of distilled water for 2 hrs and pH was noted by bringing the electrode in contact with the surface of tablet and allowing it to equilibrate for 1 min.

iv. *EX VIVO* MUCOADHESION TIME:

The *ex vivo* mucoadhesion time was performed after application of the buccal tablet on freshly prepared porcine buccal mucosa. The fresh buccal mucosa was tied on the glass slide and a mucoadhesive side of each tablet was wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 mL of the phosphate buffer pH 6.8 and was kept at 37ºC ± 1ºC. After 2 mins, a 50 rpm stirring rate was applied to stimulate the buccal cavity environment and tablet adhesion was monitored for 6 hrs. The time for the tablet to detach from the porcine buccal mucosa was reported as the mucoadhesion time.[11]

v. *IN VITRO* RESIDENCE TIME:

The *in vitro* residence time was determined using a locally modified USP disintegration apparatus, based on the apparatus applied by Nakamura *et al.* [12] The disintegration medium was composed of 800 mL pH 6.75 isotonic phosphate buffer (IPB) maintained at 37^0C. A segment of porcine buccal mucosa, 3 cm length, was glued to the surface of a glass slab, vertically attached to the apparatus. The mucoadhesive tablet was hydrated from one surface using 15 µL pH 6.8 IPB and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the tablet was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the tablet from the mucosal surface was recorded (mean of triplicate determinations).

vi. MOISTURE ABSORPTION STUDIES:

Saturated solutions of different salts were prepared and placed into closed chambers. Chambers were allowed to equilibrate with the moisture. This gave different relative humidities (potassium carbonate- 43.2 % RH, sodium chloride- 75.3 % RH, potassium sulphate- 97.3 % RH) in presence of different salt solutions. Mesh of ≈ 1 mm pore size was placed above the surface (≈ 5 mm) of each salt solution. 3 weighed tablets were placed on each mesh and chambers were closed. After specific time intervals the tablets were withdrawn and weighed. Graph of % weight gain with respect to time were plotted.

RESULTS AND DISCUSSION

PHYSICAL CHARACTERIZATION:

The diameter of tablets was found to be 10 mm. The thickness of the tablets ranged from 1.5 to 1.55 mm. All tablets had weight within 160 ± 5 mg.

Appearance and Physical Integrity of tablets is given in **Table V.**

All the batches made of Sodium CMC (A1-A3) showed good appearance. But batch A1 lacked physical integrity. Increasing concentration of polymer improved the physical integrity.

All the batches made of Xanthan Gum (A4-A9) showed good appearance but batch A4 lacked the physical integrity.

Batches B1-B3 made of Gum Karaya showed poor appearance and physical integrity.

Batches containing Locust Bean Gum (B4-B9) showed good appearance, physical integrity of batch B4 was found to be poor.

Batches showing good appearance and physical integrity were evaluated further.

HARDNESS AND MUCOADHESION STRENGTH OF TABLETS:

Hardness and mucoadhesion strength of the tablets are shown in **Table VI.**

Batches A1 and A2 showed good mucoadhesion strength which was increased with polymer concentration of sodium CMC but poor hardness ranging from 1-1.5 Kg/cm^2. This in accoradance with the observations of ozer *et al.*[13] who could achieve hardness around 1.5 Kg/cm^2 using direct compression method for preparation of buccoadhesive pindolol tablet. Tablets containing Xanthan gum (A5-A9), Locust bean gum (B5-B9) and their combination (C4-C7) showed hardness of 2.5-3 Kg/cm^2 and mucoadhesion strength was found to increase with concentration of polymer.

***IN VITRO* DRUG RELEASE:**

Batches containing Gum karaya lacked physical integrity thus these tablets were not further tested for *in vitro* drug release.

Dissolution data of batches made with Sodium CMC are shown in Fig. 1

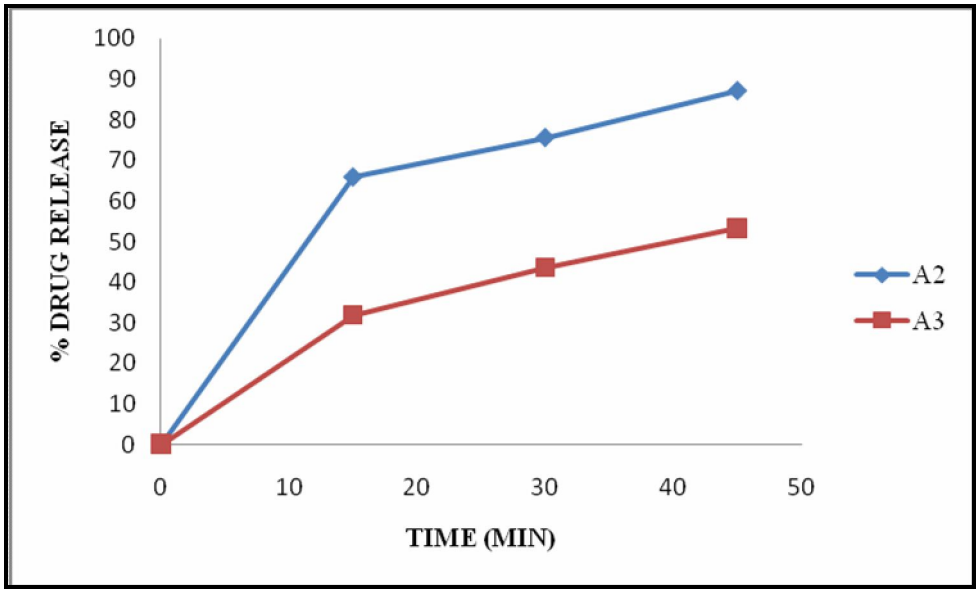

Fig. 1 Dissolution data of batches made with SCMC

Batch A2 containing 20% Sodium CMC showed 87.17% drug release which decreased to 53.26% when amount of Sodium CMC was increased to 30%.

Dissolution data of batches made with XG are shown in Fig. 2

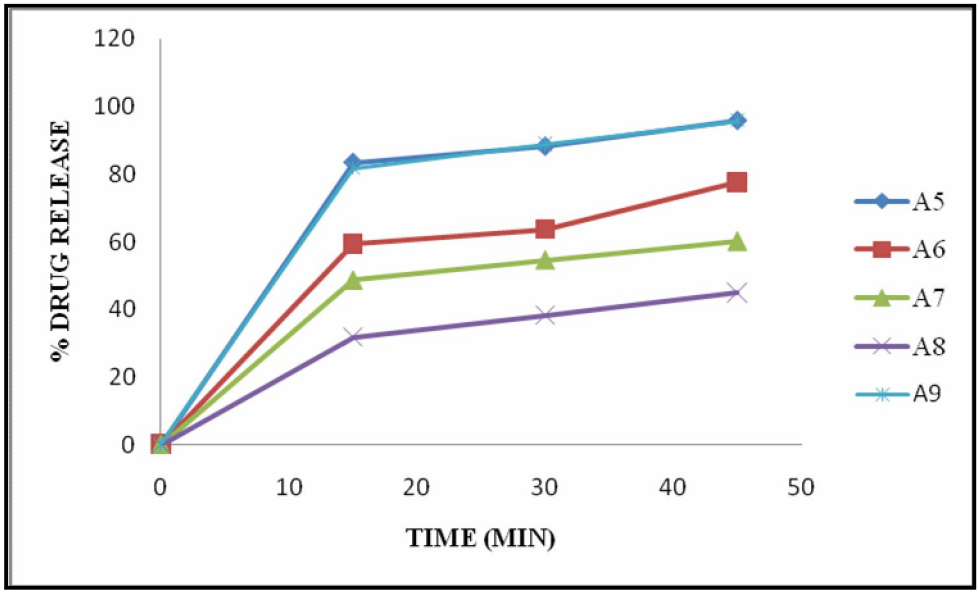

Fig. 2 Dissolution data of batches made with xanthan gum

Batch B5 containing 7.5% XG showed 95.87% drug release which was found to decrease with increase in polymer concentration. A complete drug release in 1 hour using 10% Xanthan Gum has been reported by Park *et al.*[14] They also observed that with further increase in polymer concentration, the drug release was retarded, which is similar to our observation.

Dissolution data of batches made with LBG are shown in Fig. 3

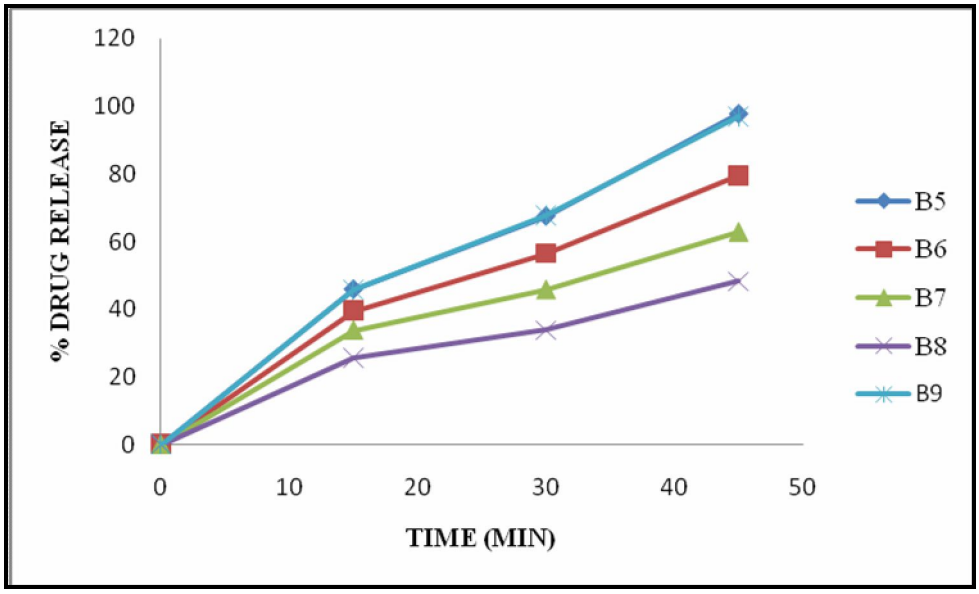

Fig. 3 Dissolution data of batches made with LBG

Batch B5 containing 7.5% of Locust Bean Gum showed drug release of 97.63% which was found to decrease with increase in polymer concentration. Dissolution data of batches made with XG and LBG combination are shown in Fig. 4.

Batches made up of combinations of XG and LBG at low concentration (C1-C3) did not give physical integrity. Batch C4 containing 4% XG and 2% LBG showed drug release 98.21% which was decreased with increasing concentration.

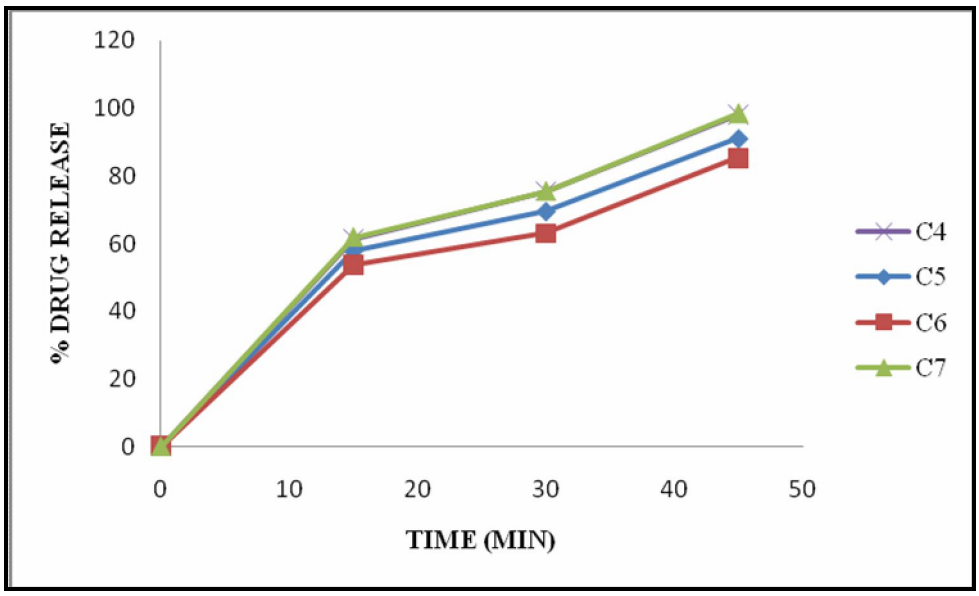

Fig. 4 Dissolution data of batches made with XG and LBG

Table VI: Results of Hardness and Mucoadhesion strength of tablets

Batch No.	Hardness (Kg/cm^2)	Mucoadhesion Strength(g)	Batch No.	Hardness (Kg/cm^2)	Mucoadhesion Strength(g)
A2	1.5	12	B6	2.5	13
A3	2	15	B7	2.5	13.5
A5	2.5	12	B8	3	15
A6	2.5	13	B9	2.5	12.5
A7	2.5	13.5	C4	2.5	12
A8	2.5	14	C5	2.5	12.5
A9	3	12	C6	2.5	12.5
B5	2.5	12.5	C7	2.5	12

***EX VIVO* PERMEATION STUDY:**

Fig. 5 shows *ex vivo* permeation study of the batches which showed complete *in vitro* drug release. Incorporation of 1% SLS as the penetration enhancer (batches A9, B9 and C7) showed increase in the amount of drug permeated as compared to saturated solution of drug and formulations devoid of penetration enhancer (A5, B5 and C4).

2.68 mg of drug was found to be permeated from saturated solution of drug. 2.51 mg and 2.31 mg of drug were found to be permeated from A5 and B5 respectively. Whereas 8.35 mg, 7.18 mg and 8.78 mg of drug were found to be permeated from batches A9, B9 and C7 respectively. Thus incorporation of SLS improved the penetration of drug. SLS has been utilized extensively as a penetration enhancer. [15]

OPTIMIZATION:

Analysis of the results obtained from 3^2 factorial design of formulation C7 concluded that the formulation containing XG 4 mg, LBG 2 mg, SLS 1 mg and PVP K-30 5 mg was devised as optimised formula. The results of the various tests performed on this batch were as given **in Table VII.**

MOISTURE ABSORPTION STUDIES:

Moisture absorption studies showed that the increase in weight at 43.2% RH and 75.3% RH was approximately 1.9% and 2% respectively. Whereas the final weight reached after 24 hrs at 97.3% RH was 6.8%. These studies proved that there was very less uptake of moisture (less than 10%), hence pointing to the fact that the tablets need no special precautions during packaging and storage.

Table VII: Results for optimized batch

Sr. No.	Parameters	Results
1.	Appearance	Good
2.	Dimensions	Diameter -10 mm ± 0.1mm. Thickness – 1.5 mm ± 0.2mm.
3.	Hardness	2.5 ± 0.5 kg/cm^2
4.	Weight variation	Passes
5.	Assay	97.83%
6.	Ex- vivo Mucoadhesion time	More than 3 hrs
7.	Ex-vivo Mucoadhesion strength	12 ± 0.5 g/cm^2
8.	Surface pH	6 – 7
9.	In-vitro residence time	More than 3 hrs
10.	In-vitro drug release	98.39% in 45 mins
11.	Ex vivo permeation study	8.78 mg drug at the end of 120 mins

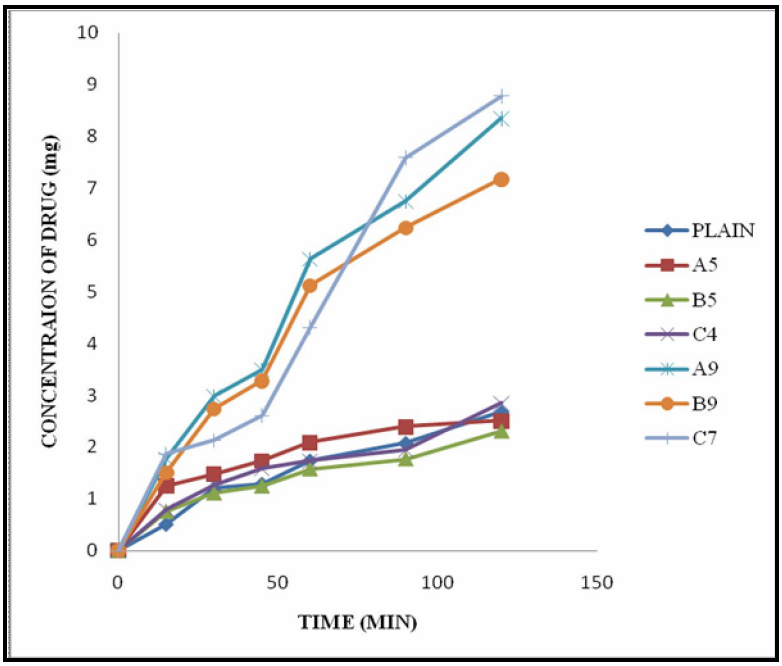

Fig .5 Ex vivo permeation

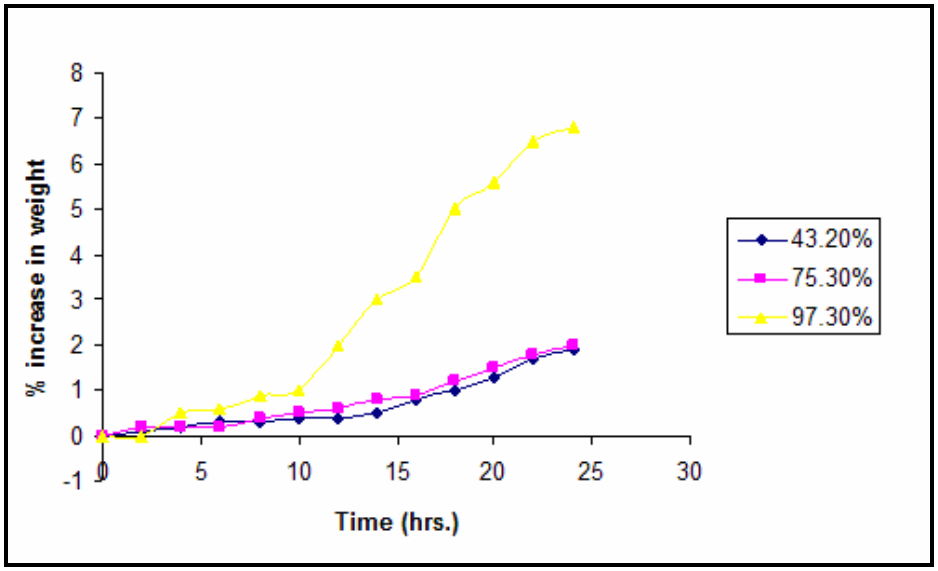

Fig. 6 Results of moisture absorption studies

CONCLUSION

From the above study it can be concluded that Xanthan gum and Locust bean gum can be successfully utilized in erodible immediate release buccal mucoadhesive tablets. This will bypass the hepatic first pass effect and improve bioavailability of MT.

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