Research Article

FORMULATION AND IN VITRO EVALUATION OF BUCCAL TABLETS OF METOPROLOL SUCCINATE

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Abstract: Buccal route is the most preferred route, which can by-pass and allow the drug directly in to systemic circulation. In the present study, buccal mucoadhesive tablets of Metoprolol succinate were prepared by using the polymers like HPMC K4M and Carbopol 974p. By using each polymer, 5 formulations were developed with varying drug : polymer ratio. With HPMC K4M, the five ratios selected were 1:1, 1:2, 1:3, 1:4 and 1:5 whereas with Carbopol 974p, the selected ratios were 1:0.25, 1:0.5, 1:0.75, 1:1 and 1:1.5. From this study it can be concluded that formulation F6 containing 1:0.25 ratio of drug : Carbopol 974p, has shown optimum bioadhesion and in vitro release properties.

Key**words:** Metoprolol succinate, buccal mucoadhesive, bioadhesion

INTRODUCTION

In our pharma market, the most commonly used drug delivery systems are orally administered drug delivery systems. But these oral systems are associated with some inherent problems like drug degradation in gastric medium, decreased bioavailability due to poor absorption and enzymatic metabolism etc[1]. To overcome these problems most of the novel drug delivery systems were put forwarded in pharma research[2].

Depending on the physico-chemical properties, most of the drugs are subjected to pre systemic metabolism in oral route. To prevent this metabolism, other than oral route should be selected for these drugs[3]. In some cases the inherent problems associated with the drug in oral route can be solved by modifying the formulation. For example: reduction of gastric irritation by application of an enteric coating for tablets such as diclofenac sodium sustained release tablets. On the other hand, in most of the cases, the poor bio-availability can only be improved by reforming the drug for delivery via different route. There are other alternate routes which include pulmonary, ocular, nasal, rectal, buccal, sublingual, vaginal, transdermal and transmocosal[3].

Among the various transmucosal routes, buccal mucosa has excellent accessibility, an expense of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage forms. The buccal region of the oral cavity is an attractive target site for administration of the drug of choice. Buccal delivery involves the administration of desired drug through the buccal mucosal membrane which is the lining of the oral cavity[4]. In buccal delivery, the direct access to the systemic circulation through the internal jugular vein bypasses drugs from hepatic first pass metabolism and avoids other problems associated with conventional oral route, there by improving bio-availability. This route offers a great potential for commercial application[5].

Metoprolol succinate is selective beta-1 receptor blocker and chemically it is (RS)-1-(Isopropylamino)-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol. It is subjected to first-pass metabolism and the oral bioavailability has been reported to be 12%. The elimination half life of Metoprolol succinate is about 3 hours[6].

The main objective of this study is to formulate and evaluate buccal mucoadhesive matrix tablets of Metoprolol succinate which is subjected to first-pass effect and having low half life. The present research mainly aimed at studying the effect of drug : polymer ratio on drug release and other bioadhesive properties.

MATERIALS AND METHODS:
Materials

Metoprolol succinate was gifted from Aurabindo Pharma, Hyderabad and HPMC K4M was gifted from Zydus cadila, Ahmedabad and Carbopol 974p was purchased from Himedia Laboratories. The other excipients like Micro crystalline cellulose, Mannitol, Magnesium stearate, Talc, Potassium dihydrogen ortho phosphate, Sodium hydroxide and Agar – agar powder were purchased from Himedia Laboratories.

Methods
1. Preformulation study[8, 9]

Preformulation studies were primarily performed to investigate the physicochemical properties of drug and to establish its compatibility with polymers and other excipients. Fourier Transform Infrared (FTIR) spectrophotometer was used for infrared analysis of samples to interpret the interactions of drug with polymers and other ingredients. The powder sample along with KBr was used for FTIR studies. The IR spectrum of a) pure Metoprolol

succinate, b) physical mixture containing drug, HPMC K4M and other excipients, c) physical mixture containing drug, Carbopol 974p and other excipients, were taken, interpreted and compared with each other.

2. Buccoadhesive tablets preparation[10]

Metoprolol succinate was mixed manually in poly bags with different ratios of HPMC K4M or Carbopol 974p as mucoadhesive polymers and Mannitol, microcrystalline cellulose as diluents for 10 mins. The blend was lubricated with magnesium stearate for 3-5mins and talc was added as glidant. The mixed blend was then compressed into tablets by direct compression method using 9 mm flat faced punches on a twelve station rotary tablet punching machine. Total 10 formulations were prepared and formulation composition is given in the table 1.

Table 1: Formulation composition of Metoprolol succinate buccal tablets

Formulation	D : P	Drug	HPMC K4M	Carbopol 974p	Micro crystalline cellulose	Mannitol	Mg stearate	Talc
F1	1 : 1	6.25mg	6.25mg	-	133.5mg	50mg	2mg	2mg
F2	1 : 2	6.25mg	12.5mg	-	127.5mg	50mg	2mg	2mg
F3	1 : 3	6.25mg	18.75mg	-	121mg	50mg	2mg	2mg
F4	1 : 4	6.25mg	25mg	-	114.75mg	50mg	2mg	2mg
F5	1 : 5	6.25mg	31.25mg	-	108.5mg	50mg	2mg	2mg
F6	1 : 0.25	6.25mg	-	1.56mg	138.1mg	50mg	2mg	2mg
F7	1 : 0.5	6.25mg	-	3.12mg	136.6mg	50mg	2mg	2mg
F8	1 : 0.75	6.25mg	-	4.68mg	135.0mg	50mg	2mg	2mg
F9	1 : 1	6.25mg	-	6.25mg	133.5mg	50mg	2mg	2mg
F10	1 : 1.5	6.25mg	-	9.37mg	130.3mg	50mg	2mg	2mg

3. Evaluation of buccal tablets
A) Characterization of tablets for physicochemical parameters

The prepared Metoprolol succinate buccal tablets were evaluated for their physicochemical parameters like weight variation, hardness, thickness and friability.

B) Assay of Metoprolol succinate[11, 12, 13]

Ten tablets were taken from each formulation and powdered; powder equivalent to one tablet was taken and was allowed to dissolve in 100 ml of pH 6.6 phosphate buffer separately on a rotary shaker overnight. The solution was centrifuged and the supernatant was collected. The absorbance of supernatant was measured using UV-Visible Spectrophotometer at λ_{max} of 205 nm.

C) In vitro release studies

The drug release rate from buccal tablets was studied using the USP type II dissolution test apparatus.

Tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed on the other side of the tablet. The tablet was further fixed to a 2x2 cm glass slide with a solution of cyanoacrylate adhesive. Then it was placed in the dissolution apparatus. Samples of 5 ml were collected at different time intervals up to 10 h and replaced 5 ml of buffer at each collection. Then collected samples were analyzed spectrophotometrically[14, 15]

Dissolution medium   :   pH 6.6 phosphate buffer

Rpm   :   50
Temperature   : 37 ± 0.5˚c

Data of the in vitro release was fitted into different equations to explain the release kinetics and release mechanism of Metoprolol succinate from buccal tablets. The kinetic equations used were zero-order, first-order and the drug release mechanism models used were Higuchi, Korsmeyer- Peppas and Hixson- Crowell.

D) Tissue Isolation[16, 17]

Porcine buccal tissue from domestic pigs was obtained from a local slaughterhouse and used within 2 hours of slaughter. The tissue was stored in pH 6.6 phosphate buffer at 4°C after collection. The epithelium was separated from the underlying connective tissue with a surgical technique and the delipidized membrane was allowed to equilibrate for approximately one hour in receptor buffer to regain lost elasticity.
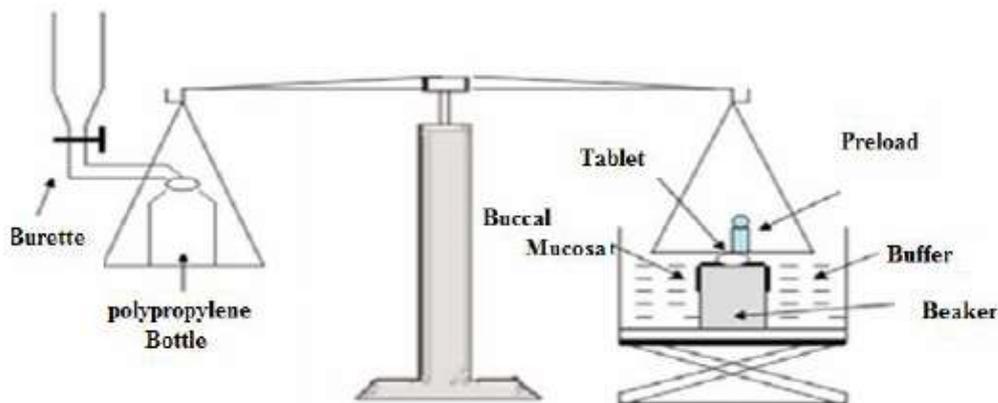
E) In vitro mucoadhesion studies[18]

Mucoadhesive strength of Metoprolol succinate buccal tablets with porcine buccal mucosa was measured using a modified 2-arm balance apparatus. The design of apparatus used while measuring the mucoadhesive strength is shown in fig.1.

Fig. 1: Modified physical balance for measurement of mucoadhesive strength

The experiment was performed within 3 hours of procurement of the mucosa. The porcine buccal mucosa was fixed to a surface with cyanoacrylate adhesive and kept in contact with phosphate buffer of pH 6.6 to maintain buccal mucosal viability during the experiment. The tablet was attached at the middle of lower surface of one of the pans of balance and then the set consisting of mucosa was raised slowly until contact between porcine buccal mucosa and tablet was established.

A constant weight was placed on the pan for 10mins as preload to establish adhesion bonding between the tablet and porcine buccal mucosa. The preload and preload time were kept constant for all the formulations. After completion of preload time, weight was removed from the pan and water was added into the container placed on another pan, with the help of a pipette at a constant rate. The addition of water was stopped when tablet was detached from porcine buccal mucosa. The weight of water required to detach the tablet from buccal mucosa was noted as mucoadhesive strength and the experiment was repeated with fresh mucosa in an identical manner.

F) Moisture absorption study[19]

This study was performed in a solidified agar. Agar (5%, w/v) was dissolved in hot water and transferred into Petri dishes and allowed to solidify. Six buccal tablets from each formulation were placed in a vacuum oven overnight prior to the study to remove moisture, if any and one side of the tablet was laminated with a impermeable backing membrane. They were then weighed and placed on the surface of the solidified agar and incubated at 37 °C for one hour. Then the tablets were removed and reweighed and the percentage of moisture absorption was calculated by using the following formula.

$$\% \text{ moisture absorption} = (\text{final weight} - \text{initial weight} \times 100) / \text{initial weight}$$

G) In vitro retention time study [20]

The adhesive tablet was pressed over excised pig mucosa for 30 sec after previously being secured on glass slab and was immersed in a basket of the dissolution apparatus containing around 750 ml of pH 6.6 phosphate buffer, at 37^{0}C. The paddle of the dissolution apparatus was adjusted at a distance of 5 cm from the tablet and rotated at 25 rpm (fig. 2). The time for complete erosion or detachment from the mucosa was recorded.

Fig. 2: Schematic representation of in vitro retention time study.

H) In vitro drug permeation study[20]

      The test was carried out in the standard Franz diffusion cell with a diffusion area of 6.16 cm^2 and the acceptor compartment volume of 16 ml. A porcine buccal mucosa was clamped between the donor and acceptor compartments. The phosphate buffer of pH 6.6 (37^{0}C) in the acceptor compartment was continuously stirred at 600 rpm using a magnetic stirrer. The tablet was placed into the donor compartment and was wetted with 1ml of phosphate buffer. The amount of drug that permeated through the membrane was determined by removing aliquots from the receptor compartment and replacing the same volume of buffer. Then the samples were analyzed by using UV-Visible spectrophotometer at λ_{max} of 205 nm.

I) Characterization of drug in buccal tablets

      FTIR studies were conducted for characterization of drug in tablets of selected optimized formulation (F6).

The selected buccoadhesive tablets were powdered and the pelletized powder along with KBr was used for FTIR studies. The IR spectra were recorded using Fourier Transform Infrared spectrophotometer. The IR spectra of pure Metoprolol succinate and pelletized powder of tablets were taken, interpreted and compared with each other.

RESULTS AND DISCUSSION
1. Preformulation study

      In IR spectrum of pure Metoprolol succinate, the presence of peaks at 2980.98 cm^{-1} (OH stretching), 1192.24, 1228.06, 1382.83 cm^{-1} (C-N stretching), 1747.39, 1590.63 cm^{-1} (C=O group) 2565.69 cm^{-1} (S-H stretching) were characteristic to that of the pure drug and all of them remained un altered in the IR spectra of physical mixtures containing drug, polymers and other ingredients. IR analysis (fig. 3 and 4) revealed that there was no evidence for chemical interaction of drug with polymers and other ingredients.
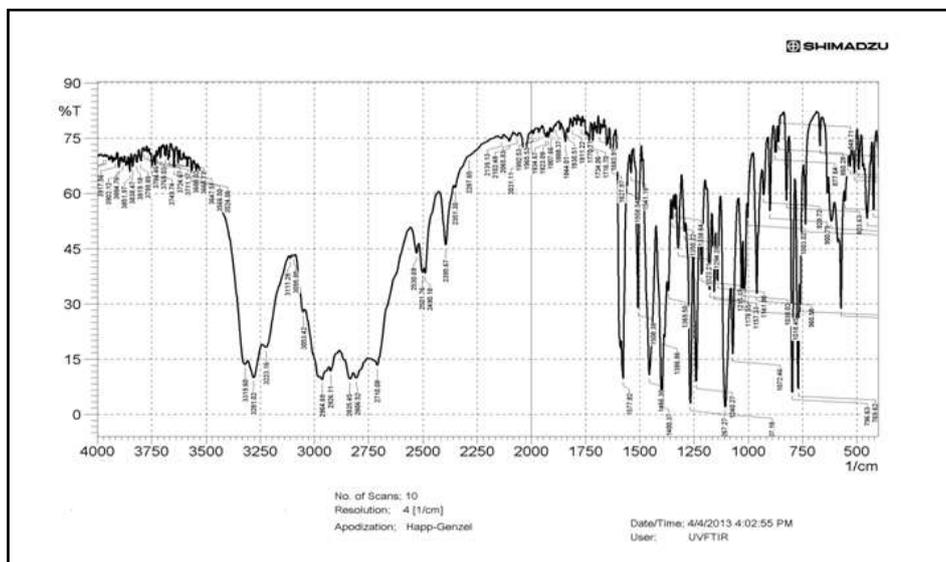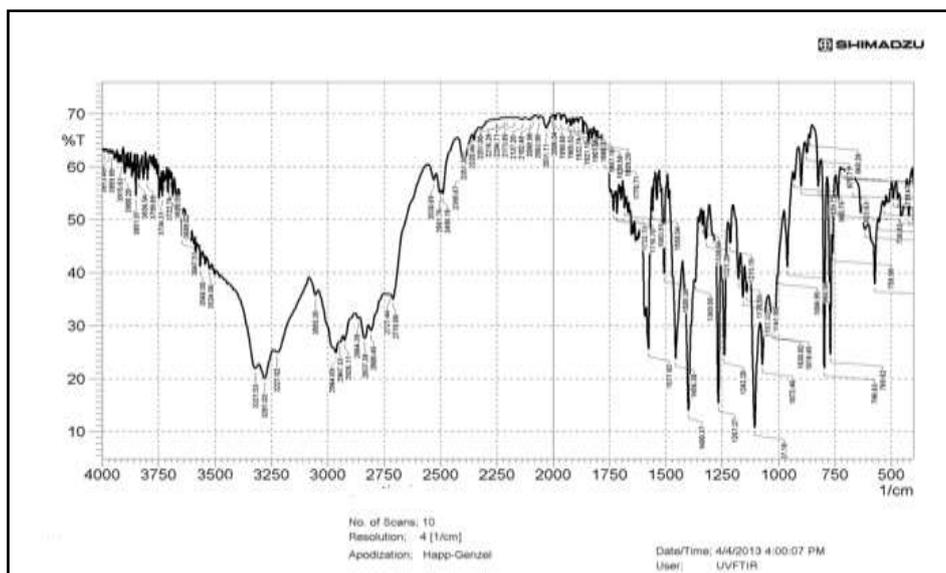

Fig. 3: IR spectrum of pure Metoprolol tartrate

Fig. 4: IR spectra of Physical mixtures of drug with polymers and other ingredients

2. Evaluation of buccal tablets
A) Weight variation, thickness, friability and assay:

The weight variation, thickness, friability and assay of the tablets (Table 2) were within the limits of uniformity. The mass ranged from 196.54 to 199.58 mg with SD values 0.59–1.05. Thickness ranged between 2.18 and 2.41 mm with SD values of 0.02 to 0.04. The mass and thickness of all compressed tablets were within the limits as per USP.

The drug content ranged from 107.5 ± 0.39% in formulation F1 to 108.80 ± 0.58% in formulation F5, 92.13 ± 0.39% in formulation F6 to 107.15 ± 0.45% in formulation F10 and the friability was ranged from 0.27 to 0.98. Friability and assay of all compressed tablets were within the limits as per USP. The hardness of all prepared tablets was in the range of 3.5 to 4 kgs.

Table 2: Weight variations, Thickness, Friability and Assay

Formulation	Mass (mg) Mean ± SD	Thickness (mm) Mean ± SD	Friability (%)	Assay (%)
F1	198.51 ± 1.05	2.24 ± 0.02	0.69	107.50 ± 0.39
F2	196.54 ± 0.60	2.29 ± 0.03	0.98	116.78 ± 0.41
F3	197.53 ± 0.59	2.36 ± 0.03	0.57	112.35 ± 0.61
F4	199.58 ± 0.84	2.39 ± 0.04	0.61	111.05 ± 0.71
F5	196.78 ± 1.01	2.19 ± 0.02	0.73	108.80 ± 0.58
F6	198.68 ± 0.76	2.25 ± 0.03	0.59	92.13 ± 0.39
F7	199.25 ± 0.91	2.20 ± 0.02	0.74	94.26 ± 0.41
F8	198.89 ± 0.79	2.34 ± 0.04	0.32	106.52 ± 0.40
F9	199.32 ± 1.02	2.37 ± 0.03	0.28	104.21 ± 0.38
F10	197.99 ± 0.66	2.28 ± 0.02	0.27	107.15 ± 0.45

B) In vitro drug release

The release of Metoprolol succinate from buccoadhesive tablets (fig. 5 and 6) varied according to the type and ratio of matrix forming polymers. The drug release was governed by the amount of matrix forming polymers and microcrystalline cellulose. Formulation F1 showed good controlled release up to 10 hours, it has given 88.13 ± 0.36% drug release at end of 10 hours. Formulations F2 and F3 given maximum drug release within 10 hours and they showed burst release after 6 hours. Formulations F2 and F3 given almost same drug release pattern within 10 hours. F4 and F5 had given maximum release within 8 hours with burst release pattern after 4 hours. Formulations F6, F7 and F8 have given good controlled release within 10 hours. The formulation F9 showed burst release pattern after 8 hours .Where as formulation F10 showed burst release within 4 hours.

In all the formulations it was observed that with the increasing the concentrations of polymers the controlled property was decreased. This may be due to increased hydrophilicity owing to adsorption property of microcrystalline cellulose, which is present in each formulation as diluent. Due to increased hydrophilicity, formulations containing high concentrations of polymer showed burst release[18, 19 and 20].

Table 3: In vitro release profiles of formulations F1 to F5

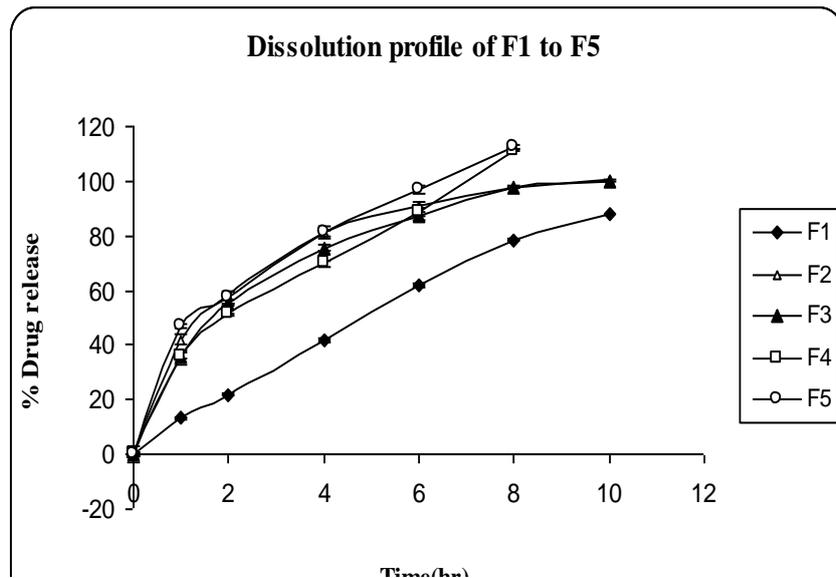| Time (hrs)	F1	F2	F3	F4	F5
0.00	0.00	0.00	0.00	0.00	0.00
1	13.29 ± 0.84	42.08 ± 0.59	36.15 ± 2.74	35.49 ± 0.36	47.14 ± 0.88
2	22.07 ± 0.23	58.06 ± 1.63	54.92 ± 1.36	51.23 ± 2.84	57.33 ± 0.59
4	41.96 ± 0.59	81.30 ± 1.48	75.50 ± 0.23	69.78 ± 0.36	81.05 ± 2.49
6	61.88 ± 0.67	91.26 ± 2.34	87.27 ± 1.28	88.57 ± 1.28	96.63 ± 1.23
8	78.32 ± 0.54	97.77 ± 1.07	97.68 ± 1.29	**111.43 ± 1.51**	**112.81 ± 1.40**
10	**88.13 ±0.36**	**100.83 ± 0.36**	**100.06 ± 0.23**	105.84± 0.71	110.88± 0.84

Fig. 5: Comparative dissolution profile of formulations F1 to F5

Table 4: In vitro release profiles of formulations F6 to F10

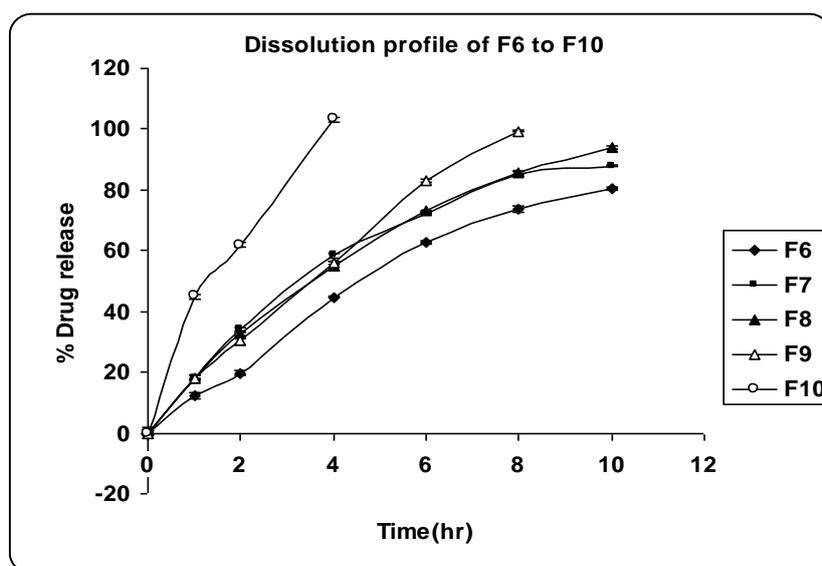| Time (hrs)	F6	F7	F8	F9	F10
0	0	0	0	0	0
1	12.49 ± 1.07	17.82 ± 0.23	18.17 ± 0.94	18.25 ±0.88	44.89 ± 0.75
2	19.80 ± 0.54	34.23 ± 0.62	32.39 ± 0.48	30.30 ±1.23	61.92 ± 0.70
4	44.76 ± 0.36	58.37 ± 0.40	54.87 ± 0.36	55.76 ±0.48	**103.25 ± 0.36**
6	62.70 ± 0.71	72.30 ± 0.36	73.04 ± 0.62	82.98 ±0.54	133.59 ± 0.88
8	73.79 ± 0.48	85.29 ± 0.48	85.73 ± 0.36	**99.31 ±0.48**	123.29 ± 0.84
10	**80.44 ± 1.29**	**87.88 ± 0.23**	**94.05 ± 0.23**	94.37 ±0.48	140.51 ± 0.59

Fig. 6: Comparative dissolution profile of formulations F6 to F10

Kinetics of drug release and mechanism[16, 17, 18, 20]:

The release data of formulations F1 to F5 seem to fit better with the first order kinetics except formulation F1 where as the release data of formulations F6 to F10 seem to fit better with first order kinetics except F9 and F10. Therefore, the release rate in formulations, F2 to F5 and F6 to F8, is dependent of its concentration or amount of drug incorporated, where as in formulations, F1, F9 and F10, it is independent.

The drug release pattern of formulations F1, F2, F3, F5 and F9 seem to fit better with the Peppas model i.e. drug release mechanism depends on value of release exponent (n). As the 'n' values of formulations F2, F3 and F5 are closer to 0.5, the drug release mechanism from these formulations is Fickian diffusion, where as drug release mechanism from F1 and F9 is anomalous or non-Fickian diffusion, because 'n' values for these formulations are in between 0.5 and 1. The release data of formulations F4 and F10 seem to fit better with the Higuchi model i.e. the release mechanism is Fickian diffusion. The R^2 values are very close in Higuchi and Peppas models and it can be concluded that the release rate from all formulations, except from F6, F7 and F8, followed diffusion mechanism. As increasing the concentration of polymers in these formulations, 'n' value decreased i.e. release mechanism turned from non-fickian to fickian. It is clear that the drug release from these formulations was controlled by liquid diffusion into formulation and polymeric chain relaxation. The release data of formulations F6, F7 and F8 seem to fit better with Hixson-Crowell model i.e. the release mechanism is surface erosion.

C) In vitro mucoadhesion strength

In the formulations F1 to F5, as the polymer concentration increased, the mucoadhesion was increased up to F3 and then deceased. In the formulations F6 to F10, as the polymer concentration increased, the mucoadhesion was increased up to F8 and then deceased. The possible reason may be due to increased hydrophilicity that leads to

degradation of tablet integrity in formulations F4, F5 and F9, F10. Buccal tablets formulated with Carbopol 974p showed stronger mucoadhesion (Table 5) than that of with HPMC K4M. Very strong bioadhesion could damage the epithelial lining of the buccal mucosa. Hence Formulation F6 having 11.47 ± 0.15 gm of mucoadhesion was selected as best optimized formulation.

D) Moisture absorption

Moisture absorption was increased from formulations F1 to F5 and F6 to F10. The possible reason may be the increased concentration of polymer from formulations F1 to F5 and F6 to F10. The moisture absorption (Table 5) was more in formulations containing HPMC K4M when compared to formulations containing Carbopol 974p. The order of moisture absorption capacity of polymers used in the preparation can be given as Carbopol 974p < HPMC K4M. This may be due to the more hydrophilic nature of HPMC K4M. This may be attributed to integrity maintenance i.e. formulations with HPMC K4M maintained less integrity due to increased hydrophilicity when compared to formulations with Carbopol 974p[19, 20].

E) In vitro retention time

The in vitro retention time is one of the important physical parameter of buccal mucoadhesive tablets. Formulations F4 and F5 showed less retention time when compared to formulations F1 to F3. And formulations F9 and F10 showed less retention time when compared to formulations F6 to F8. As increasing the concentration of polymer in formulations, the retention time was increased up to certain concentration because of optimum hydrophilicity and adhesion, after that increased concentration leaded to decreased retention time because of degradation of tablet integrity due to increased hydrophilicity. This test reflects the adhesive capacity of polymers used in formulations. Formulations with Carbopol 974p have shown more retention time than that of formulations with HPMC K4M. Based on the results (Table 5), F6 formulation was selected as best formulation.

Table 5: Mucoadhesion strength, Moisture absorption and Retention time of buccal tablets

Formulation	Mucoadhesion strength (gm) Mean ± SD	Moisture absorption (%) Mean ± SD	In vitro retention time
F1	3.29 ± 0.15	12.24 ± 1.22	7 hrs 12 min
F2	4.97 ± 0.16	12.43 ± 1.75	8 hrs 24 min
F3	6.50 ± 0.20	53.80 ±1.63	8 hrs 27 min
F4	2.53 ± 0.17	57.43 ± 1.48	3 hrs 41 min
F5	2.03 ± 0.12	89.95 ± 1.36	2 hrs 11 min
F6	11.47 ± 0.15	8.54 ± 0.07	8 hrs 51 min
F7	13.27 ± 0.12	9.09 ± 0.22	8 hrs 54 min
F8	14.10 ± 0.20	11.00 ± 0.18	8 hrs 59 min
F9	9.80 ± 0.10	13.63 ± 0.22	3 hrs 51 min
F10	8.20 ± 0.10	14.00 ± 0.18	3 hrs 29 min

F) In vitro drug permeation

Based on the *in vitro* drug release, mucoadhesion strength, moisture absorption and *in vitro* retention time of all formulations, the F6 formulation was selected as optimized best formulation and *in vitro* permeation studies were conducted for this formulation. The results of drug permeation from buccal tablets through the porcine buccal mucosa, revealed that Metoprolol succinate was released from the formulation and permeated through the porcine buccal membrane and could possibly permeate through the human buccal membrane. The drug permeation was slow and steady (fig. 7) and $88.81 \pm 0.13\%$ w/w of Metoprolol succinate was permeated through the buccal membrane during 12 hours.
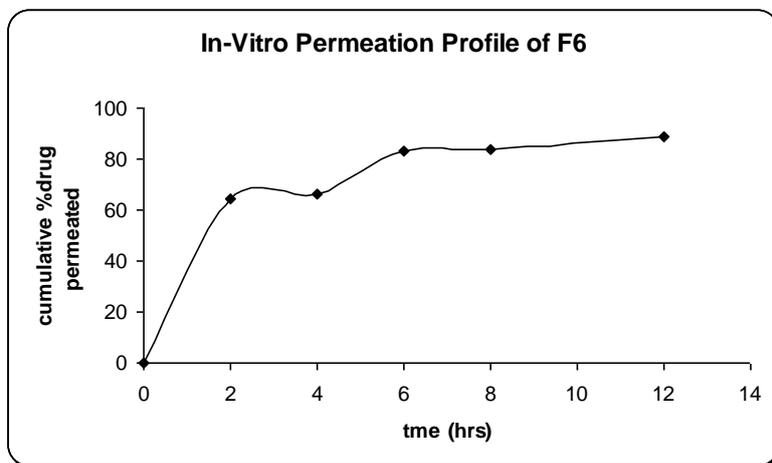

Fig. 7: In vitro permeation of Metoprolol succinate

H) Characterization of drug in buccal tablets

The characteristic peaks in IR spectrum of pure Metoprolol succinate were remained unaltered in the IR spectrum of powder sample of tablets (Formulation F6). IR analysis (fig. 8) revealed that there was no evidence for chemical interaction of drug with polymers and other ingredients in prepared buccal tablets.
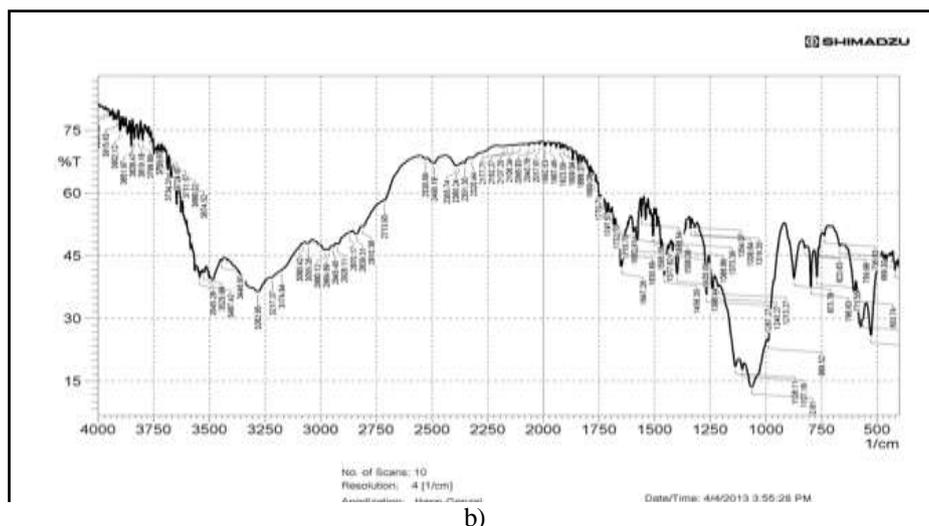

a)
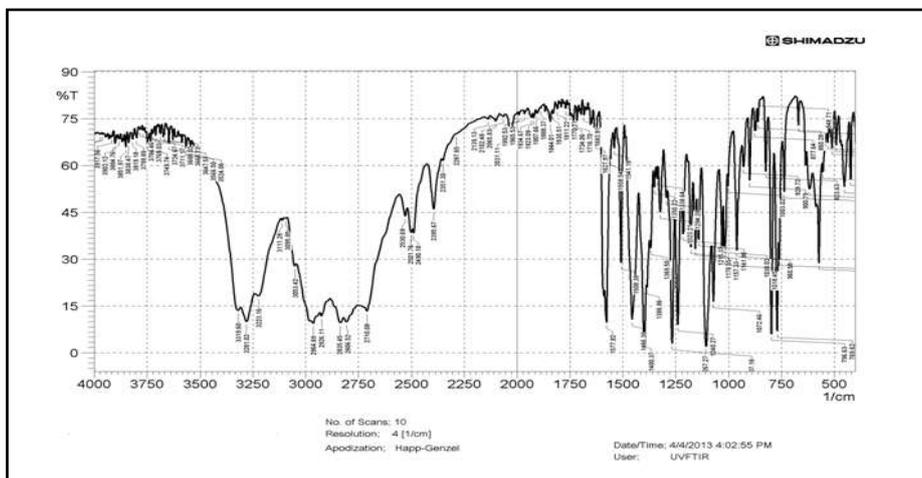
b)
Fig. 8: IR spectra of a) Pure drug b) F6 formulation

CONCLUSION

A new buccoadhesive system for the controlled release of Metoprolol succinate was developed by using HPMC K4M and Carbopol 974p in appropriate ratios. The influence of concentration of polymers on the Metoprolol succinate release from buccal tablets and other bioadhesion properties of tablets were investigated. The results propose the achievement of therapeutic concentration in the site, the decrease of drug side effects and the improvement of patient compliance. It can be concluded that the designed bioadhesive controlled release tablets of optimized formulation F6 containing 1:0.25 ratio of drug : Carbopol 974p can overcome the disadvantage of poor and erratic oral bioavailability of Metoprolol succinate associated with currently marketed oral formulations. Further work in this direction is needed in order to support its efficacy by long term pharmacokinetic and pharmacodynamic studies in human beings.

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