



FORMULATION AND *IN-VITRO* EVALUATION OF BUCCAL TABLETS OF METOPROLOL TARTRATE

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ABSTRACT

The aim of study was to prepare and characterize buccoadhesive tablets of Metoprolol tartrate using different Mucoadhesive polymers such as Carbopol 934, Sodium alginate and HPMC K4M in combination. Ten formulations were prepared with varying concentrations of polymers using combination of two polymers in each formulation. Formulations F1 to F5 were composed of Sodium alginate and HPMC K4M mixture in drug: polymer mixture ratios of 1:0.75 to 1:1.75 where as formulations F6 to F10 were composed of carbopol 934 and HPMC K4M mixture in same drug: polymer mixture ratios. The prepared tablets were evaluated for physicochemical parameters such as hardness, thickness uniformity, weight variation, surface pH, Ex-vivo residence time and moisture absorption studies. The prepared tablets were also evaluated for bioadhesive strength and in vitro drug release. In vitro bioadhesive strength and in vitro release studies showed that formulation F8 containing 1:1.25 ratio of drug and polymer combination showed optimum bioadhesive and exhibited optimum drug release (77.33 ± 0.23). FTIR results showed no evidence of interaction between the drug and polymers.

Keywords: Metoprolol tartrate, buccal tablets, Formulation, Evaluation.

INTRODUCTION

Among the various routes of drug delivery, oral route is the most suitable and most widely accepted one by the patients for the delivery of the therapeutically active drugs. But, after oral drug administration many drugs are subjected to presystemic clearance in liver, which often leads to a lack of correlation between membrane permeability, absorption and bioavailability¹⁻⁴. Within the oral route, the oral cavity is an attractive site for drug delivery due to ease of administration and avoids possible drug degradation in the gastrointestinal tract as well as first pass hepatic metabolism⁵.

In the, oral cavity the delivery of drugs are classified into three categories: 1. Sublingual delivery, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth; 2. buccal delivery it is the drug administration through mucosal membranes lining the cheeks (buccal mucosa); and 3. Local delivery it is the drug delivery into the oral cavity^{6,7}. Among these routes, buccal delivery is suitable for administration of retentive dosage forms because of an excellent accessibility, an expanse of smooth muscle and immobile mucosa. So, buccal delivery of drugs is attractive alternative to the oral route of drug administration⁸⁻¹⁰.

Buccal delivery involves the administration of drug through buccal mucosal membrane (the lining in the oral cavity). Buccal drug delivery is the safer method of drug utilization because; drug absorption is terminated in case of toxicity by removing the dosage form from the buccal cavity. The drug directly reaches to the systemic circulation through the internal jugular vein and bypasses the drugs from the hepatic first pass metabolism, which leads to high bioavailability¹¹. The other advantages of buccal drug delivery include: low enzymatic activity, suitable for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless drug administration, easy drug withdrawal, possible to include the permeation enhancer/enzyme inhibitor or pH modifier in the formulation. A suitable buccal drug delivery system should be flexible and should possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. In addition, it should release the drug in a controlled and predictable manner to elicit the required therapeutic response¹²⁻¹⁴. Various buccal mucosal dosage forms are suggested for oral delivery which includes: buccal tablets, buccal patches and buccal gels^{15,16}.

Metoprolol tartrate is a cardio selective β_1 adrenergic antagonist and widely used in the treatment of hypertension, angina pectoris, cardiac arrhythmias and myocardial infarction. It is rapidly absorbed from oral route but undergoes first pass metabolism, which results in only 38% oral bioavailability. The half life of metoprolol tartrate is approximately 3-4 hours. Metoprolol tartrate was selected as model drug to avoid first pass hepatic metabolism

and to improve the oral bioavailability and to control the release of the drug from the tablets by matrix forming polymers, as the half life of drug is low¹⁷⁻¹⁹.

In this investigation, buccoadhesive tablets of Metoprolol tartrate have been developed using anionic polymers like Sodium alginate, Carbopol 934 and non-ionic polymer Hydroxy propyl methyl cellulose K4M (HPMC K4M), each formulation had combination of anionic and non-ionic polymers. The main objective of this investigation is to study the effect of charge in polymers combination and the effect of drug: polymer ratio on drug release and other bioadhesive properties.

MATERIALS AND METHODS

Materials

Metoprolol tartrate was kindly donated by Aurobindo Pharma, Hyderabad. Hydroxy propyl methyl cellulose (HPMC K4M, non-ionic polymer) was donated by Zyudus Cadila, Ahmedabad and Carbopol 934 (anionic polymer) was purchased from Himedia laboratories and Sodium alginate (anionic polymer) was purchased from CDH. Mannitol was purchased from Universal laboratories. All other chemicals and reagents used were of analytical reagent grade and purchased from CDH and Himedia, Hyderabad.

Buccoadhesive tablets preparation

Metoprolol tartrate was mixed manually in polybags with different ratios of Sodium alginate and Methocel K4M (HPMC K4M) mixture or Carbopol 934 and HPMC K4M mixture as mucoadhesive polymers and mannitol as diluent (table 1) for 10 mins. The blend was lubricated with magnesium stearate for 3-5mins and talc was added as glidant. Then mixed blend was compressed into tablets by direct compression method using 8 mm flat punches in a sixteen station rotary tablet punching machine. Each tablet (220 mg) contains 50 mg of Metoprolol tartrate. The mass of the tablets was determined using a digital balance (Shimadzu) and thickness with digital vernier calipers (Mitutoyo).

Drug content uniformity¹⁸

Three tablets of each formulation were taken in separate 100ml volumetric flask, 100 ml of pH 6.6 phosphate buffer was added and continuously stirred for 24 hours in rotary shaker. Supernatant was collected, diluted suitably and analyzed by using UV Visible Spectrophotometer at λ_{max} of 275 nm. The average of the drug contents of three tablets was taken as final reading.

Table 1: Formulation composition of Metoprolol tartrate buccal tablets

| Formulation | D : P | Drug | Na. alginate | Carbopol 934 | HPMC K4M | Mannitol | Mg. stearate | Talc |
|-------------|----------|------|--------------|--------------|----------|----------|--------------|-------|
| F1 | 1 : 0.75 | 50mg | 25mg | - | 12.5mg | 123.5mg | 4.4mg | 4.4mg |
| F2 | 1 : 1 | 50mg | 25mg | - | 25mg | 111.2mg | 4.4mg | 4.4mg |
| F3 | 1 : 1.25 | 50mg | 25mg | - | 37.5mg | 98.7mg | 4.4mg | 4.4mg |
| F4 | 1 : 1.5 | 50mg | 25mg | - | 50mg | 86.2mg | 4.4mg | 4.4mg |
| F5 | 1 : 1.75 | 50mg | 25mg | - | 62.5mg | 73.7mg | 4.4mg | 4.4mg |
| F6 | 1 : 0.75 | 50mg | - | 25mg | 12.5mg | 123.5mg | 4.4mg | 4.4mg |
| F7 | 1 : 1 | 50mg | - | 25mg | 25mg | 111.2mg | 4.4mg | 4.4mg |
| F8 | 1 : 1.25 | 50mg | - | 25mg | 37.5mg | 98.7mg | 4.4mg | 4.4mg |
| F9 | 1 : 1.5 | 50mg | - | 25mg | 50mg | 86.2mg | 4.4mg | 4.4mg |
| F10 | 1 : 1.75 | 50mg | - | 25mg | 62.5mg | 73.7mg | 4.4mg | 4.4mg |

In vitro release studies¹⁹

The United state pharmacopoeia (USP) type II dissolution apparatus was used to study the release of drug from buccal tablets. 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. In vitro drug release studies were carried out in 500 ml of phosphate buffer solution pH 6.6 for 8 h using a TDT 08L dissolution paddle apparatus (Elico, India) at 50rpm and 37±0.5 °C. At predetermined time intervals samples were withdrawn and replaced with fresh medium. The samples were filtered, diluted suitably and then analyzed spectrometrically at 275 nm. All dissolution studies were performed in triplicate.

Tissue isolation²³

Porcine buccal tissue from domestic pigs was obtained from a local slaughterhouse and used within 3 hours of slaughter. Pigs were 6.5 ± 0.5 months of age at the time of death. The animals were killed by electroshock followed by exsanguinations. The tissue was stored in pH 6.6 phosphate buffer at 4°C after collection. Excesses of connective and adipose tissue were trimmed away until 0.8 ± 0.1 mm thick slides were obtained and allowed to equilibrate for approximately one hour in receptor buffer at room temperature to regain lost elasticity.

Measurement of mucoadhesive strength^{20, 21}

Ex-vivo mucoadhesive strength of Metoprolol tartrate buccal tablets was measured by using modified physical balance using the method described by Kashappa Goud et al. Porcine buccal mucosa was used as the model substrate and phosphate buffer pH 6.6 was used as the moistening fluid. Freshly excised porcine buccal mucosa was obtained from male/female pigs with an average weight of 65 ± 6 kg, from the local slaughterhouse used within three hours of slaughter. The tablet was laid onto the model membrane under constant weight of 50 gm for a total constant period of 5 min. Bioadhesive strength was measured in terms of weight in grams of water required to detach the tablet from the porcine buccal mucosa. 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 *ex-vivo* mucoadhesive strength. Mucoadhesive strength was performed in triplicate and average Mucoadhesive strength was determined. All the measurements were carried out at 37±1°C.

Ex-vivo residence time²¹

The *Ex-vivo* residence time was determined using a modified USP dissolution apparatus. The phosphate buffer of pH 6.6 is used as dissolution medium which is maintained at 37°C ± 2°C. A segment of porcine buccal mucosa each of 4 cm length was glued to the surface of glass slide which was then vertically attached to the apparatus. Three tablets of each formulation were hydrated using 15µl pH 6.6 buffer on one side and hydrated surface was brought into contact with mucosal membrane. The tablets secured on the glass slide were completely immersed in the buffer solution. The paddle of the dissolution apparatus as adjusted at a distance of 5 cm from the

tablet and rotated at 25 rpm the time for complete erosion or detachment from the mucosa was recorded.

Moisture absorption study²⁴

The moisture uptake studies give an indication about the relative moisture absorption capacities of polymers and an idea whether the formulations maintain their integrity after absorption of moisture. The study was carried out as per procedure reported earlier (Velmurugan et al., 2010). Briefly, agar (5 % w/v) was dissolved in hot water, transferred into petriplates and allowed to solidify. Six tablets from each formulation series were placed in vacuum oven overnight prior to the study to remove moisture if any and laminated on one side with water impermeable backing membrane. They were then incubated at 37°C for one hour, removed and reweighed. The percentage moisture absorption was calculated by using the formula

$$\% \text{ moisture absorption} = \frac{(\text{Final weight} - \text{Initial weight}) \times 100}{\text{Initial weight}}$$

Surface pH measurement²²

The buccal tablets of each formulation were allowed to swell for 2 h on the surface of the agar plate. The surface pH was measured by means of pH paper placed on the surface of the swollen tablets. Experiments were performed in triplicate and a mean of three readings was recorded.

Stability of buccal tablet in human saliva²⁰

The human saliva was collected (from human healthy volunteers) and filtered. Stability study was performed for the optimized formulation (F8), selection was based on the results of *in-vitro* drug release, moisture absorption, mucoadhesive strength and *ex vivo* residence time studies. Six tablets from optimized batch were immersed in 5ml of human saliva for 6 h and taken out of saliva at predetermined time intervals. The stability of the metoprolol tartrate buccoadhesive tablet was evaluated by its appearance such as color, shape, collapse of the tablet and metoprolol concentration.

In vitro drug permeation study¹⁶

The *ex vivo* permeation studies of mucoadhesive buccal tablets of drug through excised layer of porcine buccal mucosa were carried out using Franz diffusion cell having 3.14 cm² effective diffusional area. It consists of two compartments one is donor compartment and another is receptor compartment of 20 ml capacity. The cell contents were stirred with a magnetic stirrer and temperature of 37±1°C was maintained throughout the experiment. The separated buccal epithelium was mounted between two chambers and in receptor chamber phosphate buffer of pH 6.6 (37°C) was filled and epithelium was allowed to stabilization for the period of 1 hrs. After stabilization the tablet was placed into the donor compartment and was wetted with 1ml of phosphate buffer. The amount of drug permeated through the membrane was determined by removing samples periodically and same volume fresh medium was replaced. Then the samples were analyzed by using UV-Visible spectrophotometer at λ_{max} of 275 nm.

Drug excipients compatibility study

The pure drug, Metoprolol tartrate and its mixture with the polymer HPMC K4M, Sodium alginate and carbopol 934 powders was mixed separately with IR grade KBr and pellets were prepared by applying a pressure of 10 tons in a hydraulic press. The pellets were scanned over a wavelength range of 400 to 4,000 cm^{-1} using an FTIR 8400S model instrument. Drug-excipient interactions play a vital role in the release of drug from formulations. FTIR techniques have been used to study the physical and chemical interactions between drug and excipients used. DSC studies also performed to investigate the physical state of the drug in the tablets and to know the interactions of drug with polymers in the formulation. Thermal properties of pure drug and the formulation were evaluated by Differential scanning calorimetry (DSC) using a Diamond DSC (Mettler Star SW 8.10). The analysis was performed at a rate $5\text{ }^{\circ}\text{C min}^{-1}$ from $500\text{ }^{\circ}\text{C}$ to $2000\text{ }^{\circ}\text{C}$ temperature range under nitrogen flow of 25 ml min^{-1} .

RESULTS AND DISCUSSION

Weight variation, hardness, thickness and drug uniformity

All the tablets with different proportion of polymer composition were within the weight range of 219.76 mg to 220.75 mg with SD values 0.66-1.08. The tablets thicknesses of the various formulations were observed to be in the range of 3.95mm to 4.01mm with SD values of 0.01-0.03 (Table 2). The mass and thickness of all compressed tablets were within the limit as per USP. The hardness of all the tablets was found to be in the range of 3.5 to 4 kg/cm^2 . The drug content ranged from $100.9 \pm 0.36\%$ in formulation F1 to $100.9 \pm 0.75\%$ in formulation F5, $99.3 \pm 0.36\%$ in formulation F6 to 101.2 ± 0.36 in formulation F10. The results of content uniformity shows all the formulations comply with that prescribed in the Indian pharmacopeia. The loss in total weight of tablets due to friability was in the range of 0.30 to 0.90. Friability for all the formulation shown less than 0.90% which is in the acceptable limits which indicates formulations have good mechanical strength.

Table 2: Mass, thickness, friability and drug content

| Formulation | Weight variation(mg) ^a | Thickness (mm) ^a | Friability (%) ^a | Assay (%) ^a |
|-------------|-----------------------------------|-----------------------------|-----------------------------|------------------------|
| F1 | 220.56 ± 1.05 | 3.95 ± 0.03 | 0.61 | 100.9 ± 0.36 |
| F2 | 220.31 ± 0.66 | 3.95 ± 0.02 | 0.90 | 98.5 ± 0.47 |
| F3 | 220.65 ± 0.69 | 3.96 ± 0.03 | 0.53 | 101.9 ± 0.59 |
| F4 | 220.57 ± 0.79 | 3.96 ± 0.02 | 0.68 | 101.3 ± 1.01 |
| F5 | 220.47 ± 1.04 | 3.96 ± 0.02 | 0.75 | 100.9 ± 0.75 |
| F6 | 220.21 ± 0.89 | 4.01 ± 0.02 | 0.53 | 99.3 ± 0.36 |
| F7 | 220.75 ± 0.85 | 3.99 ± 0.03 | 0.76 | 97.9 ± 0.48 |
| F8 | 220.44 ± 0.99 | 3.97 ± 0.02 | 0.38 | 100.3 ± 0.36 |
| F9 | 219.76 ± 1.08 | 3.98 ± 0.01 | 0.30 | 98.9 ± 0.27 |
| F10 | 220.45 ± 0.72 | 3.97 ± 0.02 | 0.60 | 101.2 ± 0.36 |

Mean ± SD; ^a n = 10

In vitro drug release studies

In order to examine the effect of polymer reaction (concentration & ratio) on the buccal tablets, three different bioadhesive polymers i.e. Sodium alginate, Carbopol 934, HPMC K4 were selected and dosage forms were prepared and their individual drug release profile were evaluated. It is observed that the type of polymers influences the drug release patterns as shown in fig.1 to 2.

Formulation were prepared with batches F1 to F5 containing sodium alginate and HPMC K4M (different ratio) as the matrix forming agent ,where as in batches F6 to F10 containing carbopol 934 and HPMC K4M with 50 mg *Metoprolol tartrate* (Table 1). In polymer mixture of the all formulations HPMC K 4M was increased gradually from F1 to F5 and F6 toF10,where as concentration of sodium alginate and carbopol 934 were maintained constantly in formulations F1 to F5 and F6 to F10 respectively. Formulations F1 and F2 released the drug completely within 5 hours, whereas

formulations F3, F4 and F5 released within 6 hours. The drug release was extended beyond 8 hours in formulations F6 to F10. The most important factor affecting the rate of release from the buccal tablets was the ratio of drug and polymer mixture. The release of Metoprolol tartrate was decreased with increasing concentration of HPMC K4M. The possible reason for observed reduction in total drug release may be the interaction between two oppositely charged bioadhesive polymers i.e. Sodium alginate (anionic) and HPMC K4M (nonionic) in formulations F1 to F5 or Carbopol 934 (anionic) and HPMC K4M in formulations F6 to F10.

It was observed that the matrix formation was more in formulations F6 to F10 when compared to formulations F1 to F5. The possible reason may be because of structure of Carbopol 934. It is a highly cross-linked polymer that swells in water and does not disintegrate upto 24 hours. Because of its structure, the drug dissolution rate from the formulation may delay in comparison with the dissolution rate of the formulation based on the linear polymers.

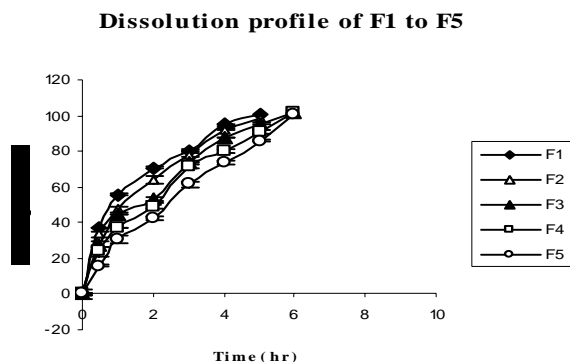


Fig. 1: Dissolution profile of formulations F1 to F5

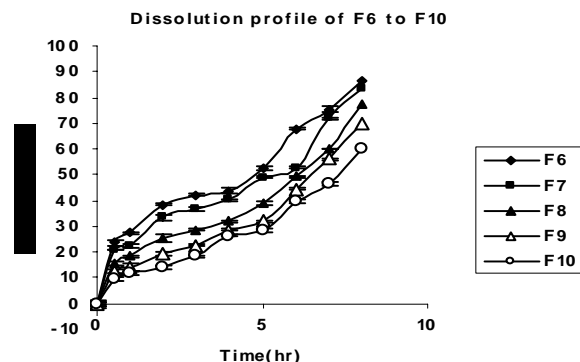


Fig. 2: Dissolution profile of formulations F6 to F10

Kinetics of drug release and mechanism

When the higher R^2 values for zero-order and first order are considered, the release data of formulations F1 to F5 seem to fit better with the first order kinetics where as the release data of formulations F6 to F10 seem to fit better with zero-order kinetics. Therefore, the release rate in formulations, F1 to F5 is dependent on its concentration or amount of drug to be released, where as in formulations, F6 to F10, it is independent.

When the higher R^2 values for Higuchi model, Korsemeyer-Peppas model and Hixson-Crowell model are considered, the release data of

formulations F3, F6 and F7 seem to fit better with the Higuchi model i.e. the release mechanism is Fickian diffusion; the release data of formulations F1, F2, F4, F5 and F8 seem to fit better with Peppas model i.e. drug release mechanism depends on value of release exponent (n); the release data of formulations F9 and F10 seem to fit better with Hixson-Crowell model i.e. the release mechanism is erosion. As the ' n ' values of formulations F1 and F2 are closer to 0.5, the drug release mechanism from these formulations is Fickian diffusion, where as drug release mechanism from F4, F5 and F8 is anomalous or non-Fickian diffusion, because ' n ' value for these formulations are in between 0.5 and 1 (Table 3).

Table 3: Release kinetics of the formulations (R^2 values)

| Formulation | Zero order R^2 | First order R^2 | Higuchi | Peppas | | Hixson-Crowell R^2 |
|-------------|------------------|-------------------|---------|--------|------|----------------------|
| | | | R^2 | R^2 | n | |
| F1 | 0.8581 | 0.9513 | 0.9884 | 0.9892 | 0.42 | 0.9667 |
| F2 | 0.9011 | 0.9409 | 0.9977 | 0.9982 | 0.46 | 0.9879 |
| F3 | 0.9227 | 0.9523 | 0.9922 | 0.9848 | 0.52 | 0.9846 |
| F4 | 0.9481 | 0.9799 | 0.9913 | 0.9929 | 0.58 | 0.9906 |
| F5 | 0.9816 | 0.9759 | 0.974 | 0.9932 | 0.71 | 0.9931 |
| F6 | 0.9412 | 0.9003 | 0.9463 | 0.9203 | 0.44 | 0.9346 |
| F7 | 0.9393 | 0.8605 | 0.9177 | 0.905 | 0.47 | 0.9032 |
| F8 | 0.9448 | 0.8518 | 0.8844 | 0.8976 | 0.53 | 0.8941 |
| F9 | 0.9474 | 0.8759 | 0.8606 | 0.8838 | 0.59 | 0.9059 |
| F10 | 0.9593 | 0.9088 | 0.8687 | 0.8955 | 0.63 | 0.9297 |

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 F9 and F10, followed diffusion mechanism. As increasing the concentration of polymers in these formulations, ' n ' value increased i.e. release mechanism turned from fickian to non-fickian. It is clear that the drug release from these formulations was controlled by liquid diffusion in to formulation and polymeric chain relaxation. The release from F9 and F10 followed erosion mechanism i.e. there was a possibility of a change in surface area or the diameter of the tablets with time during dissolution.

In vitro mucoadhesive strength

The values of the mucoadhesive strength of Metoprolol tartrate buccal tablets are given in table 4. The bioadhesive characters

were found to be affected by the nature and proportions of the bioadhesive polymers used in the formulations as seen from fig.6. In all the formulations, as the polymer mixture concentration increased, the mucoadhesion was increased.

The order of bioadhesion of polymers used in the preparation can be given as HPMC K4M < Sodium alginate < Carbopol 934 (Table 4). Buccal tablets formulated with a mixture of Carbopol 934 and HPMC K4M showed comparatively higher bioadhesion than that of sodium alginate and HPMC K4M. Very strong mucoadhesion could damage the epithelial lining of the buccal mucosa. Bioadhesive strength exhibited by the formulation F8 tablets can be considered satisfactory for maintaining them in the oral cavity for 12hrs.

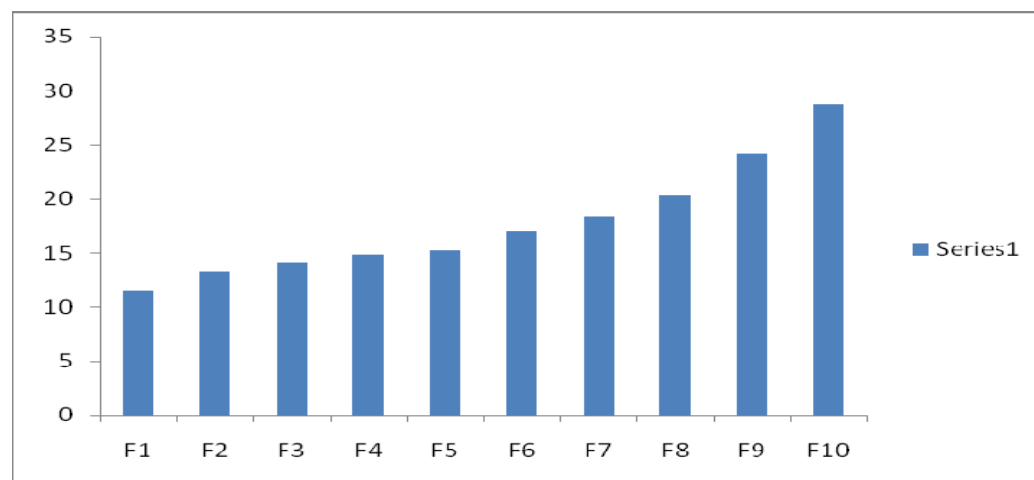


Fig. 6: In vitro mucoadhesive strength of different formulations

Ex-vivo residence time

The *Ex-vivo* residence time is one of the important physical parameter of buccal mucoadhesive tablets. The *Ex-vivo* residence time was determined by using specially designed dissolution

apparatus. Formulations F6 to F10 showed higher residence time when compared to the formulations F1 to F5. As the concentration of bioadhesive polymer increased, the residence time also increased. This examination reveals the mucoadhesive capacity of polymers used in formulations. The results showed that the mixture of

Carbopol 934 and HPMC K4M containing group formulations showed better bioadhesion than the mixture of sodium alginate and HPMC K4M formulations. Formulation F8 showed optimum residence time of above 8 hours.

Moisture absorption

Moisture absorption studies evaluate the integrity of the formulation upon exposure to moisture and the results were shown in Table 4. The hygroscopic nature of the polymers is one of the important property that affecting moisture absorption. Moisture absorption was increased from formulation F1 to F5 and F6 to F10.

The increasing moisture absorption of formulations may be due to the increased concentration of polymer mixture from formulation F1 to F5 and F6 to F10. The moisture absorption was more in formulations containing Carbopol 934 and HPMC K4M group when compared to formulation containing sodium alginate and HPMCK4M. The comparative moisture absorption for various formulation was in order of HPMC K4M < Sodium alginate < Carbopol 934 (Table 4 & figure 7). This may be due to the more hydrophilic nature of Carbopol. Among all the formulations the F8 formulation showed minimum matrix erosion and optimum moisture absorption (35.61 ± 0.18 %) at the end of 8 hrs.

Table 4: *In vitro* mucoadhesive strength, moisture absorption, *in vitro* residence time

| Formulation | Mucoadhesive strength (gm) ^a | % moisture absorbed ^a | <i>In vitro</i> retention time (hrs) ^a |
|-------------|---|----------------------------------|---|
| F1 | 11.47 ± 0.15 | 23.47 ± 1.22 | 3 hrs 30 min |
| F2 | 13.27 ± 0.12 | 27.44 ± 1.75 | 3 hrs 50 min |
| F3 | 14.10 ± 0.20 | 28.80 ± 1.28 | 4 hrs 15 min |
| F4 | 14.80 ± 0.10 | 32.08 ± 1.48 | 5 hrs 30 min |
| F5 | 15.20 ± 0.10 | 32.91 ± 1.36 | 6 hrs 15 min |
| F6 | 17.00 ± 0.10 | 30.31 ± 0.07 | 5 hrs 45 min |
| F7 | 18.37 ± 0.15 | 32.46 ± 0.22 | 6 hrs 30 min |
| F8 | 20.30 ± 0.10 | 35.61 ± 0.18 | Above 8 hrs |
| F9 | 24.20 ± 0.36 | 40.51 ± 0.22 | Above 8 hrs |
| F10 | 28.77 ± 1.19 | 43.89 ± 0.18 | Above 8 hrs |

Mean ± SD; ^a n = 6.

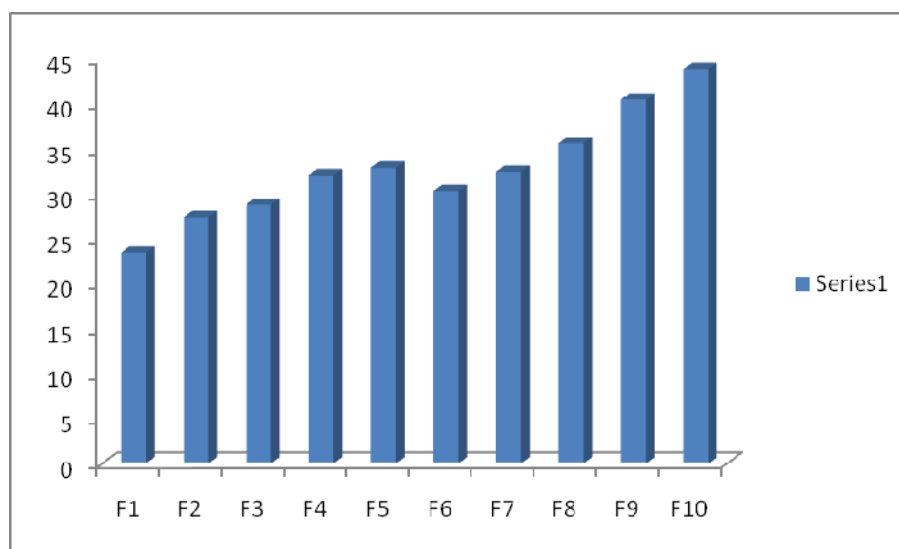


Fig. 7: Percentage moisture absorption of different formulations

Surface pH

Surface pH evaluation of oral mucosal dosage forms is an important characterization study. An acidic or alkaline pH may cause irritation to the oral mucosa. It was therefore necessary to determine if any extreme surface pH changes occurred with the tablets during the drug release period under investigation. The surface pH of the formulation depends on the nature of polymer. Attempts were made to keep the surface pH as close as to buccal / salivary pH as possible by proper selection of polymers for developing the buccal tablets. Surface pH of all the formulations is in an acceptable pH range of 6.5 to 7 (salivary pH). Hence they may not produce any local irritation or damage to the mucosa.

Stability study

The stability studies are generally performed in phosphate buffer, whose pH is similar to buccal cavity. But, the stability studies

performed in normal human saliva would be more accurate to mimic the stability of the Metoprolol tartrate buccal tablet in oral cavity *in vivo*. Hence the stability of buccal tablet was examined in natural human saliva. Based on the results of *ex vivo* mucoadhesion, *in-vitro* release studies, moisture absorption, *ex vivo* residence time the formulation F8 was selected as optimized formulation among the other formulations. Hence stability studies were conducted for tablets of optimized formulation (F8).

Stability studies in normal human saliva showed no change in the colour of buccal tablets, which would have happened if drug was unstable in human saliva. This reveals that the tablets are having sufficient stability in the human. The thickness and diameter of tablets increased due to swelling of the polymers in human saliva but tablets did not collapse till the end of studies indicating the stability of shape of the tablets. The results were shown in table.5.

Table 5: Stability data of buccal tablets in normal human saliva

| Time (hrs) | Color change | Thickness (mm) | Change in shape Diameter (mm) | Collapsing |
|------------|--------------|----------------|-------------------------------|------------|
| 0 | No | 3.96 | 8.01 | - |
| 1 | No | 4.09 | 8.12 | No |
| 2 | No | 4.23 | 8.29 | No |
| 3 | No | 4.48 | 8.41 | No |
| 6 | No | 4.71 | 8.63 | No |

In vitro drug permeation

It was concluded that formulation F8 containing Carbopol and HPMC k4M showed good moisture absorption, mucoadhesive strength, a convenient residence time as well as promising drug release pattern. On the basis of above result F8 formulation was selected for Ex vivo study. The buccal mucosa of pigs resembles that of humans more closely than any other animal in terms of structure and composition and therefore porcine buccal mucosa was selected for drug permeation studies.

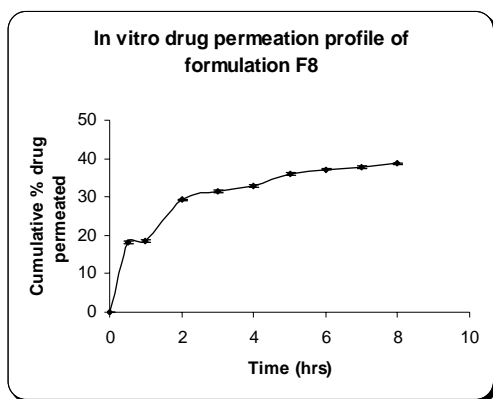


Fig. 3: *In vitro* permeation of Metoprolol tartrate from optimized formulation

The results of drug permeation from buccal tablets through the porcine buccal mucosa revealed that Metoprolol tartrate 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 3) and $38.76 \pm 0.21\%$ of Metoprolol tartrate could permeate through the buccal membrane in 8 hours with a flux of $0.14 \text{ mg h}^{-1}\text{cm}^{-2}$.

Characterization of drug in buccal tablets

In IR spectrum of pure Metoprolol tartrate, the presence of peaks at 2980.27 , 2934.03 , 2869.46 , 2826.78 cm^{-1} (OH stretching), 3328.70 cm^{-1} (NH stretching), 1596.38 cm^{-1} (C=O group) were characteristic to that of the pure drug and all of them remained unaltered in the IR spectrum of powder sample of tablets (Formulation F8). IR analysis (figure 5) revealed that there was no known chemical interaction of drug with polymers and other ingredients in prepared buccal tablets.

DSC studies were performed to investigate the physical state of the drug in the tablets and to know the interactions of drug with polymers in the formulation. Pure Metoprolol tartrate showed a single sharp

endothermic melting peak at 126.2°C (figure 4), which was unaltered in the thermogram of powdered sample of tablets (figure 4) evidencing the absence of interactions. It indicates that the drug is in crystalline form without undergoing any degradation and that polymer (carbopol 934 and HPMC K4M) could be considered compatible with Metoprolol tartrate.

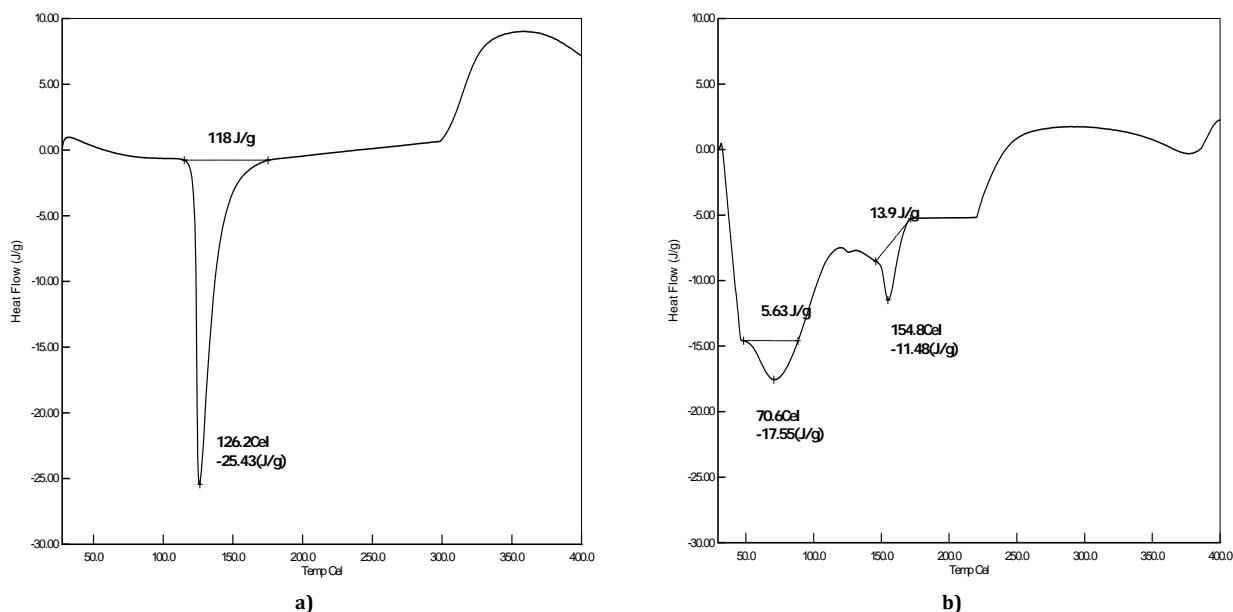


Fig. 4: Thermograms of a) Pure Metoprolol tartrate and b) Powdered sample of F8 formulation

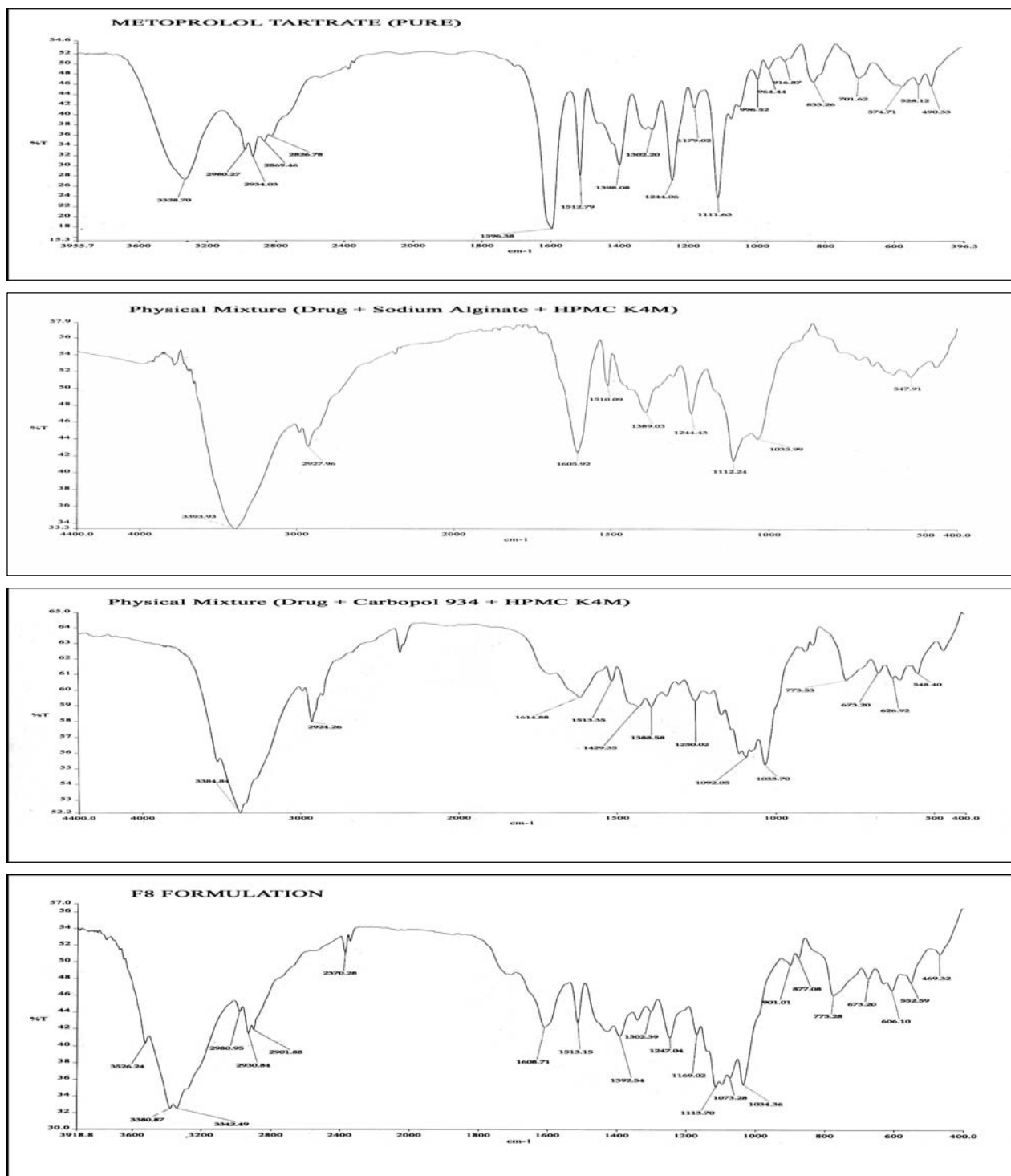


Fig. 5: IR spectrum of pure 1) Metoprolol tartrate, 2) Physical mixture containing drug + sodium alginate + HPMC K4M, 3) Physical mixture containing drug + Carbopol 934 + HPMC K4M and 4) F8 formulation

CONCLUSION

Mucoadhesive buccal tablets of Metoprolol tartrate were prepared by direct compression method. It was shown that with the developed formulations, the Metoprolol release and bioadhesion properties of buccal tablets can be controlled by changing the polymer type and concentration. The formulation F8 consist of

metoprolol (50mg), HPMC K4M (25mg), Carbopol (37.5mg), Mannitol (98.7mg), magnesium stearate (4.4mg) and talc (4.4mg) was selected as optimum formulation. Various physicochemical parameters tested for this formulation showed good results. Bioadhesion of the optimized formulation provided a longer period of residence time, reducing loss of drug by swallowing, which should result in higher bi-availability.

It was concluded that development of bioadhesive buccal drug delivery of Metoprolol tartrate tablets was one of the alternative routes of administration to avoid first-pass effect and to improve the bioavailability of Metoprolol through buccal mucosa and enhance the release of drug for extended period of time. In addition, these formulations reduce the need of frequent administration and enhance patient compliance. This finding suggested that the Metoprolol tartrate tablets have a strong potential for use as a buccal delivery system. However, more studies are necessary to evaluate the in vivo drug delivery and permeation of the final formulation.

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