





Formulation and evaluation of Metoprolol succinate buccal tablets in hypertension treatment

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Abstract



The research aims to formulate and evaluate the Metoprolol succinate buccal tablets in hypertension treatment. The Fourier transform infrared (FTIR) results depict no incompatibility between the drug and excipients. The study results of pre-compression parameters have excellent flow qualities and compressibility. The post-compression parameters show that the results are within the specified standard deviations. The swelling index reveals that the formulation F6 shows that the complete drug was released and the tablet integrity was maintained during the expected duration. Formulation F6 chitosan and Carbopol 934 were used in a ratio of 1:1, resulting in the release of the drug up to the 10th hour and completely. Therefore, formulation F6 was optimized and compared with the marketed product. Formulation F6 exhibited better drug release performance than the marketed product.

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Introduction

Pharmaceutical research is gradually shifting its focus from inventing novel chemical entities to developing novel drug delivery systems for already-existing drug molecules to enhance their efficacy in terms of therapeutic action, patient compliance, and minimized side effects. The

invention of a drug delivery system that targets different absorptive mucosa, such as ocular, nasal, pulmonary, buccal, vaginal, etc., by adhering to associated tissue or the tissue's surface coating has gained attention in recent years. This drug delivery system is known as the mucoadhesive drug delivery system¹. The rectal, vaginal, and ophthalmic all have benefits, but because of their low patient acceptance, systemic medication administration is not recommended for these locations; instead, local application is the only option [1].

The introduction of drugs to the systemic circulation through the buccal mucosa, or the lining of the cheek, is known as buccal drug delivery. Drug absorption through the oral cavity's mucous membranes was first observed by Sobrero in 1847. The buccal area of the oral cavity

is a desirable location to administer the medication of choice. The process of administering a desired medication through the mouth cavity's buccal mucosa is known as buccal drug delivery. The reticulated vein, which resides under the oral mucosa, allows medications to enter the systemic circulation through the facial, internal jugular, and brace-cephalic veins. This process of drug absorption occurs in the oral cavity. Therefore, the buccal and oral sublingual routes can be used to avoid the hepatic first-pass metabolism of medications. The polymeric adhesive composition of the bioadhesive drug delivery systems allows them to adhere to the oral mucosa when in contact with saliva. This allows the system to remain on the mucosa for 12 hours. During this time, the drug substances are released into the oral cavity for transmucosal absorption into the systemic circulation [2].

It is well established that mucoadhesion prolongs and improves the degree of contact between a mucosal surface and a drug-containing polymer. The device's mucoadhesive properties are thought to extend the time the medication remains in the body. Combining the reduction in excretion rate and the direct drug absorption improves the medicine's bioavailability. Lower API doses and fewer administration frequencies may be necessary to provide the intended therapeutic effect in the presence of increased residence duration and adhesion [3].

Metoprolol succinate is a selective antagonist of the β_1 receptor that is predominantly used to treat heart failure, angina, hypertension, and myocardial infarction. Metoprolol succinate's physicochemical characteristics, such as its 50% oral bioavailability, 12–16% plasma protein binding, and an appropriate elimination half-life ($t_{1/2}=3-7$ h), make it suitable for buccal administration [4].

Materials and methods

Chemicals

The study used analytical grade chemicals (Sigma Aldrich, Hi-media, and Merck India Ltd).

U.V. spectral analysis of metoprolol succinate

The calibration curve is the primary basis for estimating the drug release rate in *in vitro* drug dissolution studies. A UV-visible

spectrophotometer was used to perform a U.V. spectral analysis of metoprolol succinate between 200 and 400 nm to detect the selected candidates' maximum absorption wavelength [5].

Compatibility studies

FT-IR Spectroscopy studied the chemical compatibility between the metoprolol succinate and excipients [6]. About 2% of the test sample was combined with potassium bromide (KBR) to obtain fine powder by grinding using a small glass mortar and then crushed into KBR pellets by a hydraulic press at a pressure of 10000 psi and waited for 1 minute collecting the pellet. Each sample was screened for 32 single scans at 400-4000 cm^{-1} .

Preparation of metoprolol succinate buccal tablets

The direct compression method was used to prepare the metoprolol succinate buccal tablets. Drug, polymer, and other excipients were dispensed in the calculated quantity. Before their use in the formulation, the medication and polymers were passed through using a #30 sieve [7].

Table 1 Formula for the preparation of metoprolol succinate tablets

Ingredients	F1	F2	F3	F4	F5	F6
Metoprolol succinate	50	50	50	50	50	50
Carbopol 934	-	-	100	-	20	50
Chitosan	100	-	-	50	80	50
Sodium Alginate	-	100	-	50	-	-
Talc	15	15	15	15	15	15
Magnesium stearate	7.5	7.5	7.5	7.5	7.5	7.5

Pre compression parameters [8][9]

Bulk density (D_b)

A bulk density apparatus was used to determine the bulk density of the powder mixture. It is the ratio of total powder mass to total powder volume. It was calculated by pouring the weighted powder into a measuring cylinder and recording the volume. It is presented in gm/ml and is represented as

$$D_b = M/V_b$$

Tapped density (D_t)

It is the ratio of total powder mass to tapped powder volume. Tapping the powder to constant volume yielded the tapped volume. It is measured in g/ml and is provided by.

$$D_t = M/V_t$$

Compressibility index (I) and Hausner's ratio

Carr's index and Hausner's ratio measure the powder mixture's compressibility and flow nature. It was calculated employing the following formula.

$$I = D_t - D_b / D_t \times 100$$

$$\text{Hauseners ratio} = D_t / D_b$$

Angle of repose

The angle of repose is frequently used to determine the frictional forces in a loose powder. This is the maximum angle formed between the powder pile surface and the plane. A weighed powder was delivered via a funnel from a specific height (2 cm) onto a level surface, forming a heap. The heap's height and radius were recorded. The formula used to determine the angle of repose.

$$\text{Angle of repose } \theta = \tan^{-1}(h/r)$$

Post-compression parameters Dimensions

The tablet's thickness and diameter were evaluated using digital vernier calipers or screw gauge. The permitted difference is $\pm 5\%$.

The percent difference in thickness and diameter can be calculated by using the formula:

$$\text{Percent difference} = \frac{\text{Average} - \text{Individual reading}}{\text{Average}} \times 100$$

Hardness [10]

It was performed with a hardness tester and stated in kg/cm².

Friability (F)

Friability was determined using the Roche friability and represented as a percentage. Randomly collect 20 tablets, weighed collectively, recorded as W_1 , and placed in the friability chamber, rotated at 25 rpm for 4 minutes. Then, collect the tablets and weigh the record as W_2 . The % friability is computed using the formula below.

$$\%F = \frac{W_1 - W_2}{W_1} \times 100$$

Weight variation test

Collect 20 tablets randomly, weighed individually. Determine the average weight for 20 tablets. Calculate the % weight variation for 20 tablets individually [11]. Not more than two individual weights of tablets should fall out of the limits, i.e., $\pm 5\%$.

$$\% \text{ Weight variation} = \frac{\text{Average weight} - \text{Individual tablet weight}}{\text{Average weight}} \times 100$$

Uniformity of drug content:

The amount of drug in the prepared metoprolol succinate tablets was examined. Three tablets of each formulation were finely ground into powder. A precise weight of 100 mg of powder was then used to extract the medication metoprolol succinate entirely using pH 6.8 phosphate buffers. The resulting solution was then filtered. Metoprolol succinate concentration was measured using a U.V. spectrophotometer set to 222 nm in 1 ml of the filtrate, which had been appropriately diluted [12].

Swelling Studies:

The buccal tablets were weighed (W_1) and placed in separate Petri plates containing 20 mL of distilled water. The dishes were kept at room temperature. The tablets were removed at one-hour intervals, and the water left on their surface was carefully removed using filter paper for up to 8 hours. The swelled tablets were reweighed (W_2), and the swelling index was computed using the method [13].

$$\text{Swelling index} = \frac{W_2 - W_1}{W_1}$$

Dissolution studies

The formulations' in vitro dissolution experiments were performed using a USP equipment type II. The dissolving media was 900 mL of pH 6.8 phosphate buffer for 10 hours. The temperature was kept at $37^\circ\text{C} \pm 0.5^\circ\text{C}$, and the stirring rate was 50 rpm. Samples were taken at regular intervals, and the same volume was replaced with new dissolving media and diluted with 5 ml. Metoprolol succinate concentrations were determined in the samples using a U.V. Spectrophotometer at 222 nm against a blank. The release examinations were carried out in triplicate, plotting the mean values against time [14].

Release kinetics

Data from the in vitro release studies were fitted to various kinetic equations such as zero order, first order, Higuchi model, and Korsmeyer-Peppas model [15].

Results and discussion

UV Spectral Analysis of metoprolol succinate

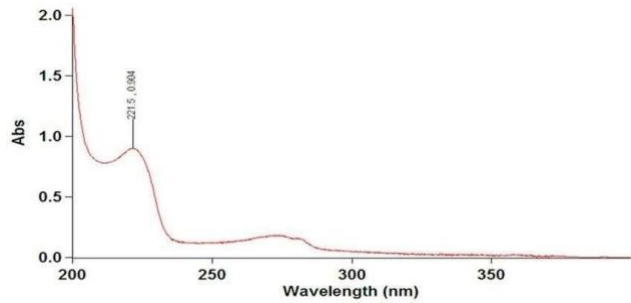


Figure 1 UV-Vis absorption spectra of metoprolol succinate

The metoprolol succinate solution was examined between 200 and 400 nm, as shown in Fig.1. The absorption maximum was 222 nm used for further studies, as shown in Figure 1.

FTIR study

FTIR of metoprolol succinate

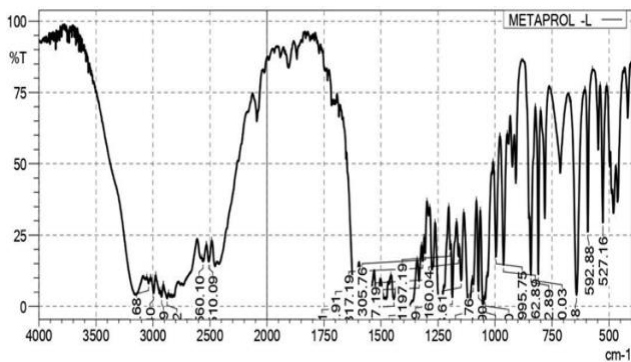


Figure 2 FTIR spectrum of metoprolol succinate

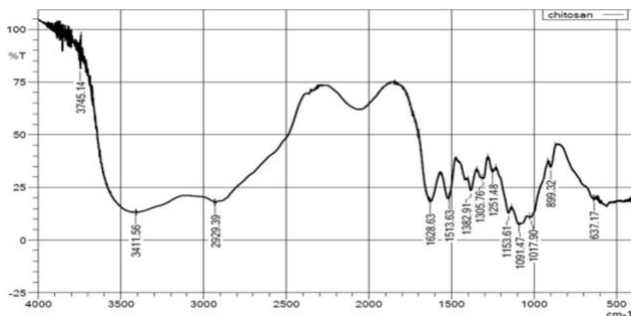


Figure 3 FTIR of Chitosan

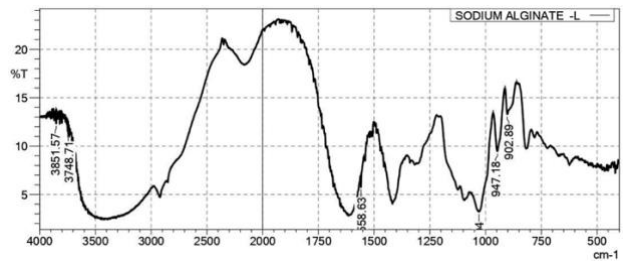


Figure 4 FT-IR spectrum of Sodium alginate

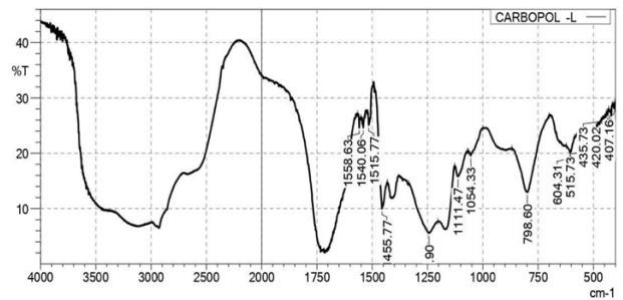


Figure 5 FT-IR spectrum of Carbopol 934

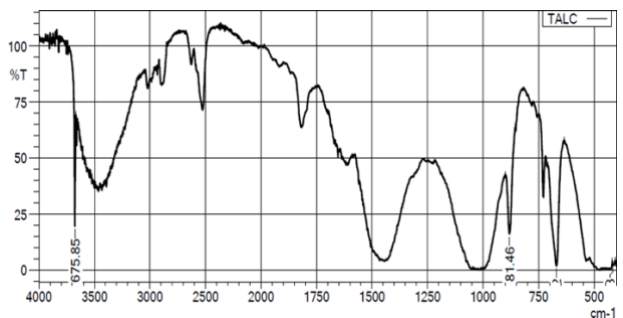


Figure 6 FT-IR of Talc

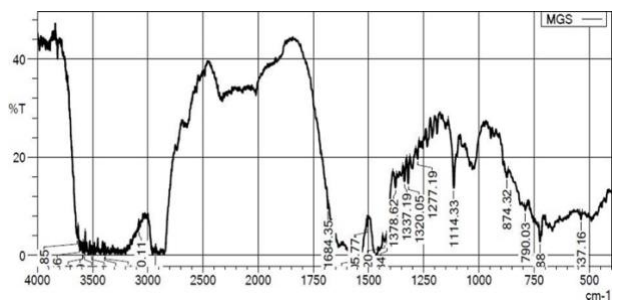


Figure 7 FT-IR of Magnesium stearate

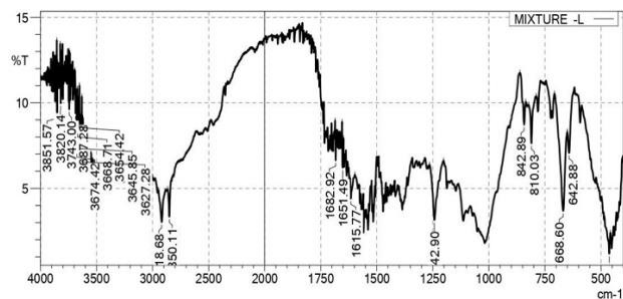


Figure 8 FT-IR of metoprolol succinate and excipients

Table 2 Precompression parameters of formulation F1-F6

S.No	Formulation	Angle of repose	Bulk density	Tapped density	Carr's index	Hausner's ratio
1.	F1	22.46	0.94	0.90	1.14	1.01
2.	F2	23.12	0.91	0.89	2.19	1.02
3.	F3	21.06	0.90	0.89	3.37	1.03
4.	F4	24.73	0.92	0.91	1.13	1.01
5.	F5	21.89	0.94	0.92	2.22	1.02
6.	F6	22.70	0.91	0.89	5.43	1.05

Table 3 Post compression parameters of formulation F1-F6 & MP

S.No	Formulation	Thickness & Diameter (Limit:<5%)	Hardness (Limit : 3-5 Kg/cm ²)	Friability (Limit:<1%)	% Weight variation	Drug content uniformity (Limit: 90-110%)
1.	F1	Within limits	5	0.72	Pass	Within limits
2.	F2	Within limits	5	0.68	Pass	Within limits
3.	F3	Within limits	4.5	0.83	Pass	Within limits
4.	F4	Within limits	4.5	0.73	Pass	Within limits
5.	F5	Within limits	5	0.45	Pass	Within limits
6.	F6	Within limits	4.5	0.71	Pass	Within limits

The FTIR studies reported compatibility of metoprolol succinate with excipients, and no significant interactions were observed.

Under the study, results of pre-compression parameters include angle of repose, cars index, and Hausner ratio, the powder mixture of all formulations (F1-F6) has excellent flow qualities and compressibility.

Post compression parameters

The observation of post-compression parameter results depicts that the compressed tablets' thickness and diameter are within limits (i.e., <5%) and states no variation in the tablet weight. Hardness and friability reveal the tablets of all formulations (F1-F6) have sufficient surface strength. The results of percentage weight variation and drug content uniformity of formulations F1-F6, including marketed products, reveal tablet weight variation within the prescribed limits.

Swelling Index

Formulation F1 containing 100mg of Chitosan undergoes disintegration by the end of first hour. At pH6.8 chitosan undergo fast disintegration. F2 formulation containing 100mg of sodium alginate has better control on drug release in comparison with chitosan. Out of three polymers employed

the F3 formulation containing 100mg of Carbopol 934 has good control on drug release and also maintains the tablet integrity. Formulation F4 & F5 depicts that complete drug release and the tablet integrity was affected before the expected time period. Formulation F6 shows that complete drug was released and the tablet integrity was maintained during the expected duration.

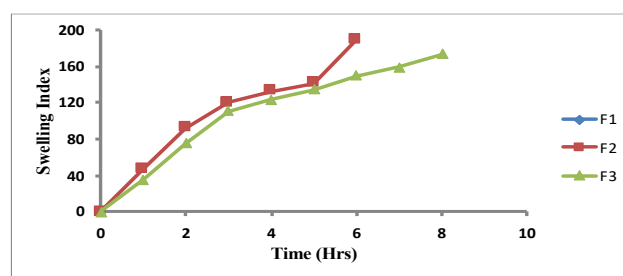
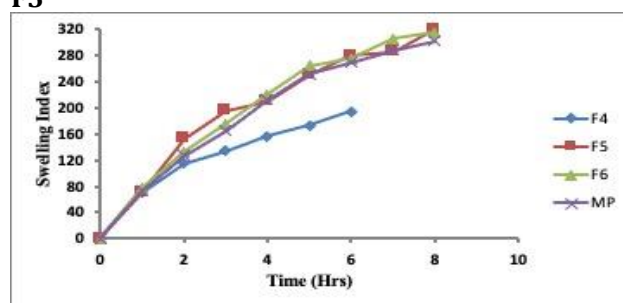
**Figure 9 Swelling index of Formulation F1 to F3****Figure 10 Swelling index of Formulation F4 to MP**

Table 4 Release kinetics of formulations F1 - F6 & MP

Formulation	Zero Order (r)	First Order (r)	Higuchi (r)	Hixson Crowell (r)	Korsmeyer Peppas	
					(r)	(n)
F1	0.9974	0.8785	0.9452	0.9154	0.9456	0.78
F2	0.9843	0.8683	0.9134	0.9472	0.9513	0.96
F3	0.9979	0.8753	0.9265	0.9516	0.9576	0.58
F4	0.9682	0.8469	0.8923	0.9248	0.9692	0.88
F5	0.9867	0.8961	0.9014	0.9187	0.9124	0.97
F6	0.9986	0.8521	0.9112	0.9107	0.9645	0.81
MP	0.9955	0.8521	0.9112	0.9057	0.9546	0.73

Dissolution studies

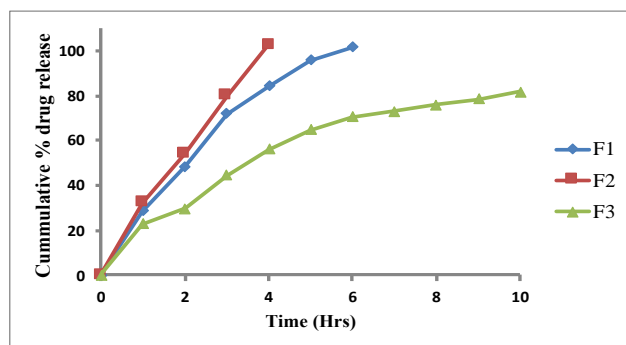


Figure 11 Dissolution studies of formulations F1-F3

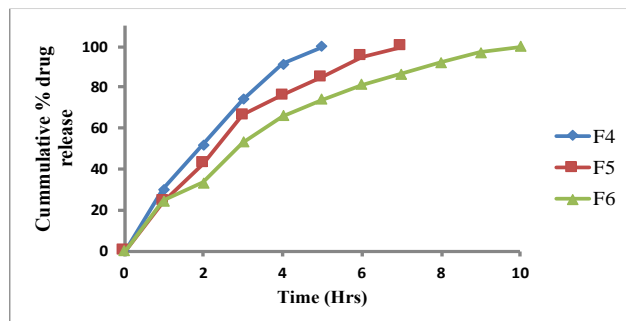


Figure 12 Dissolution studies of formulations F4-F6

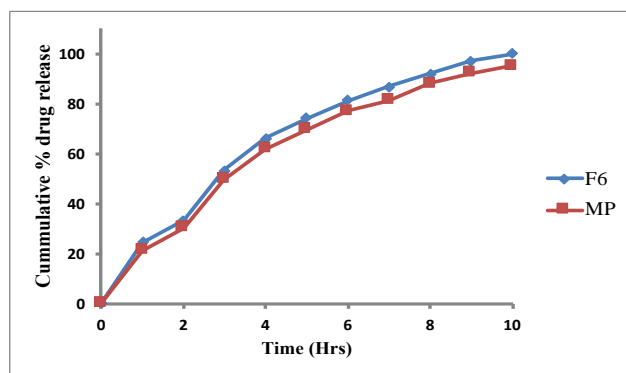


Figure 13 Dissolution studies of formulations F6 and Marketed Product

Carbopol 934 in formulation F3 has good drug retarding properties in comparison with chitosan and sodium alginate in formulations F1 & F2, respectively. A combination of chitosan and sodium alginate polymers in the ratio of 1:1 reveals that the drug releases entirely by the end of 5th hour, which was not the expected release rate. To retard the rate of drug release, Chitosan and Carbopol 934 were employed in the ratio of 4:1 in formulation F5. The drug release rate was extended, but the expected duration was the complete drug releases by the end of 7th hour of study. In formulation, Chitosan and Carbopol 934 were used in a ratio of 1:1, resulting in the full release of the drug up to the 10th hour. Therefore, formulation F6 was optimized and compared with the marketed product. It was observed that formulation F6 exhibited better drug release performance than the marketed product.

Mathematical Model Fitting of Obtained Drug Release Data

The obtained drug release profile data from all six runs of Metoprolol succinate buccal tablets and marketed formulations at different time intervals was fitted to various drug release kinetic models such as zero order first order, Higuchi, Korsmeyer peppas, and hixsoncrowell model. As mentioned in the table, the correlation coefficient value (r) was found to be the maximum for the zero-order model. The maximum r value for the zero-order model confirmed that the diffusion of the drug into the dissolution medium is dose-independent.

Conclusion

Drug-excipient compatibility studies and API (Active Pharmaceutical Ingredient) characterization were conducted as part of the formulation investigation. It proved that the swelling index and drug release rate from buccal

tablets could be adjusted by adjusting the polymer type and concentration in the developed formulations. In comparison to the marketed product, the formulation F6, which contains 50 mg of Metoprolol Succinate, 50 mg of Chitosan, 50 mg of Carbopol 934, 15 mg of talc, and 7.5 mg of magnesium stearate, was shown to be the most effective in terms of the swelling index and drug release rate. The development of mucoadhesive buccal drug delivery for Metoprolol Succinate buccal tablets proved to be one of the alternative routes of administration to prevent the first-pass effect, increase the drug's bioavailability through the buccal mucosa, and improve its sustained release. These formulations also improve patient compliance and minimize the need for frequent dosing.

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