International Journal for Pharmaceutical Research Scholars (IJPRS)

V-3, I-1, 2014 ISSN No: 2277 - 7873

RESEARCH ARTICLE

Development and Characterization of Mucoadhesive Buccal Tablet of Metaprolol Succinate

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Manuscript No: IJPRS/V3/I1/00134, Received On: 17/03/2014, Accepted On: 23/03/2014

ABSTRACT

The present investigation is concerned with development and characterization of mucoadhesive buccal tablets containing antihypertensive drug, Metoprolol Succinate to circumvent the first pass effect and to improve its bioavailability with reduction in dosing frequency and dose related side effects. The tablets were prepared by direct compression method. Twelve formulations were developed with varying concentrations of polymers like HPMC K-15M, Carbopol 934 P, Sodium CMC and PVP K-30. The tablets were tested for weight variation, hardness, surface pH, drug Content uniformity, swelling index, and bioadhesive strength and *in-vitro* drug dissolution study. FTIR studies showed no evidence on interactions between drug, polymers, and excipients. The *in vitro* release of Metoprolol Succinate was performed under sink conditions (Phosphate buffer pH 6.8, 37±0.5ºC, rpm 50) using USP-XXIV dissolution apparatus type II. The *in vitro* release kinetics studies reveal that all formulations fits well with zero order kinetics followed by Korsmeyer-Peppas, first order and then Higuchi's model and the mechanism of drug release is non-Fickian diffusion. From the all evaluation test carried for the each buccal tablet formulation of Metoprolol Succinate, it is conclude that, the formulation F 10, in the view of mucoadhesion study, *in vitro* residence time, drug content uniformity and percentage drug released over 1hr to 20 hr, F 10 was found to be optimized batch.

KEYWORDS

Metoprolol Succinate, Mucoadhesive, Carbopol 934, HPMC K15M

INTRODUCTION

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, the buccal drug delivery system reveals that this drug delivery system gives promising results for the low dose, high lipophilicity and high first pass metabolism agents. Metoprolol Succinate which is a beta-blocker having anti-anxiety and anti-hypertensive activity but having high first pass metabolism, lipid solubility and low dose, these properties makes the Metoprolol Succinate for the incorporating it into the buccal drug delivery system .The objective of present study is to investigate the properties of different polymers as carriers for Mucoadhesive Buccal dosage forms. The physicochemical and mechanical properties and the mechanisms of drug release of the dosage forms formulated by different technique shall be studied. Advantages associated with buccal drug delivery have rendered this route of administration useful for a variety of drugs.

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MATERIALS AND METHOD

Metoprolol succinate, HPMC K15M was a gift sample from Liben Lab Pvt. ltd., Akola.

Carbopol 934p, sodium CMC, polyvinyl pyrrolidone K-30, Mannitol, magnesium stearate, talc was gift sample from Ozone International Mumbai. All other reagents used were of analytical grade.

Formulation & Preparation of Mucoadhesive Buccal Tablets of Metoprolol Succinate

The mucoadhesive buccal tablets were prepared by a direct compression method. The drug/ mucoadhesive polymer mixture was prepared by homogeneously mixing the HPMC K-15M, Carbopol 934 P, Sodium CMC and PVP K-30 polymer they show good bioadhesion property[1].

All the ingredients of the mucoadhesive buccal tablet of Metoprolol succinate was weighed, sifted and mixed in mortar with the help of pastel, then in the last magnesium stearate and talc was added as lubricating agent. The 120 mg mixture was then compressed using a 6 mm punch in a single stroke on single punch tablet machine. Each tablet weighed 120 mg.

Pre-Formulation Studies

The drug-excipient compatibility studies were carried out using Fourier Transform Infrared Spectrophotometer. Infrared spectra of pure drug and mixture of drug and excipients were recorded

Post-Formulation Studies

Weight variation, Tablet Friability, Hardness, thickness Uniformity, Content uniformity, Swelling Index, Mucoadhesion studies, Residence Time, Surface pH Determination were performed for prepared tablets[5].

Hardness

Hardness is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation.

The degree of hardness varies with the different manufactures and with the different types of tablets. Hardness was measured using Pfizer hardness tester. For each batch three tablets were tested.

Friability

Twenty tablets were weighed and placed in the Roche friabilator. The apparatus was rotated at 25 rpm for 4 minutes and tablets were allowed to fall from height of 6 inches. After revolutions the tablets were de-dusted and weighed again. The percentage friability was measured using the formula,

% loss= {1-(initial weight of tablet / weight of tablets after revolution)}×100

Weight Variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 10 tablets was calculate

Thickness Uniformity

Three tablets were selected randomly from each batch and thicknesses were measured by using Vernier calipers (mutotoya, Japan).

Content Uniformity

Ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 10 mg of metoprolol was extracted into distilled water and liquid was filtered through 0.22 µm membrane filter disc (Millipore Corporation). The metoprolol content was determined by measuring the absorbance at 223 nm (using UV-VIS spectrophotometer, Shimadzu 1700) after appropriate dilution with distilled water. The drug content was determined using standard calibration curve.

In Vitro Mucoadhesion Study

Porcine buccal mucosa was used as the model membrane and phosphate buffer 6.8-pH solution was used as a moistening fluid. Porcine buccal mucosa was obtained from slaughterhouse was kept in Kreb's buffer at 37^0C for 2 hours. The underlying mucus membrane was separated and washes thoroughly with phosphate buffer 6.8-pH solution. It was then tied over the protrusion in the Teflon block using a thread. The block was then kept in petri dish.

Two side of the balance were made equal, before the study keeping a 5 g weight was

placed on the right pan. Petri dish with Teflon block was kept below the left hand set up of the balance. The tablet was stuck on to the lower side of the hanging Teflon cylinder. Five-gram weight from the right pan was then removed. This lowered the Teflon cylinder along the tablet over the membrane with a weight of 5 g. this was kept undisturbed for five minutes. Then the weight on the right hand side was slowly added in an increment of 0.5 g until the tablet just separated from the membrane surface. The excess weight on the right pan i.e. total weight minus 5 g was taken as a measure of the mucoadhesive strength. From the mucoadhesive strength following parameter was calculated.

Determination of 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. The disintegration medium was composed of 800 ml phosphate buffer pH 6.8 maintained at 37 ± 0.5 °C. A porcine buccal mucosa, 3 cm length, was glued to the surface of a glass slab, vertically attached to the apparatus. The mucoadhesive patch was hydrated from one surface using 15µl phosphate buffer pH 6.8 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 of each formulation from the mucosal surface was recorded.

Swelling Study

Six tablets of every batch were weighed and then kept on the agar gel plate surface in petri-dishes, which were placed in an incubator at $37^0C \pm 0.1^0C$. Then, these all swollen tablets were weighed at different intervals; the excess water on the surface of tablet was removed by using filter paper. The average weight was calculated and the swelling index was calculated by the formula, Swelling Index (S.I.) = {(Wt-Wo)/Wo} ×100

Where, S.I. = swelling index, Wt = average weight of tablet at time t, Wo = average weight of dry tablet before placing on the agar Plate.

Surface pH Determination of Mucoadhesive Tablets

The surface pH of the tablets was determined in order to investigate the possibility of any side effects, on the oral cavity. As acidic or alkaline pH was found to cause irritation to the buccal mucosa, hence attempt was made to maintain surface pH close to the neutral pH.

Mucoadhesive buccal tablets were swells for two hours in 1ml of distilled water. The surface pH was measured by pH meter placed on the core surface of the swollen tablet.

In Vitro Release Study

During the course of study whole assembly was maintained at 37^0C. Five ml of the sample was withdrawn at time intervals of 1, 4, 8, 20 hrs and replaced with the same amount of the fresh medium. The amount of Metoprolol succinate released was determined spectroscopically at 223 nm. The observations for different batches are shown in succeeding tables the cumulative percentage of Metoprolol Succinate released with respect to time for each batch are graphically shown

Drug Release Kinetic Studies

To describe the kinetics of the drug release from the sustain release matrix base buccal tablets of optimized batch F10, mathematical models such as zero-order, first order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas models were use.

Stability Studies

Stability studies were carried out on the formulation. Tablets of batch were first wrapped in aluminium foil then placed in an amber colored bottle. These were stored at room temperature for 1 month. Tablet was evaluated the optimized batch (F10) was subjected to Cumulative (%) Drug Release, Mucoadhesion Strength (g), Drug Content (%). Results obtained were compared with data obtained for zero time at ambient temperature.

RESULTS DISCUSSION

Evaluation Parameters

Table 1: Evaluation parameters of formulation batches

Formulation Batches	Evaluation Parameters					
	Weight Uniformity (gm) ± SD	Thickness (mm)	Hardness (Kg/cm2)	Friability (%)	Content Uniformity (%)	Surface pH ± SD
F1	120.3±0.35	2.7±0.07	3.9±0.14	0.51	98.21	6.41±0.12
F2	118±0.20	2.9±0.03	4.3±0.17	0.41	96.0	6.29±0.39
F3	121.9±0.10	2.7±0.02	4.5±0.24	0.33	97.53	6.36±0.45
F4	119.8±0.40	2.7±0.04	5.2±0.23	0.45	95.0	6.13±0.23
F5	122.1±0.30	2.5±0.01	6.5±0.12	0.40	99.83	6.20±0.35
F6	117.4±0.10	2.6±0.03	5.5±0.15	0.36	93.23	6.52±0.41
F7	121.4±0.30	2.7±0.02	4.9±0.25	0.47	98.32	5.79±0.58
F8	118.6±0.42	2.8±0.02	5.3±0.54	0.49	99.0	5.65±0.24
F9	115.9±0.57	2.6±0.02	5.1±0.45	0.55	96.85	5.70±0.69
F10	120.2±0.07	2.4±0.21	6.7±0.11	0.26	99.78	6.24±0.28
F11	122.7±0.23	2.5±0.01	6.4±0.21	0.31	99.4	6.17±0.17
F12	122.3±0.21	2.6±0.02	5.9±0.27	0.29	92.3	5.96±0.31

* SD = Standard Deviation

The prepared formulation were evaluated for weight uniformity, hardness and friability, Drug content, and thickness for all batches (F1 to F12) .The results of all these were in compliance with specification of I.P are indicated in table no.1

Weight Uniformity

The pharmacopoeial limits for deviation for tablets of more than 100mg are ± 10%.the average percentage deviation for all tablets formulation was found to be within the specified limits and hence all formulation complied with the test for uniformity of weight.

Hardness and Friability

The formulation showed hardness value in the range of to 3.9 to 6.7 kg/cm^2. Another measure of tablets strength is friability. In present study, the friability value for all tablet formulation were found to be less than 1% indicate that the friability within the prescribed limits.

Drug Content

Good uniformity of drug content was found within and among the different types of tablet formulation. The value ranged from 92.3% to 99.83%.

Thickness

Thickness of all tablet formulations ranged from 2.3mm to 2.9 mm.

Surface pH Determination of Mucoadhesive Buccal Tablets

Tablets of all the batches had shown a surface pH in the range of 5.65-6.52 that indicates no risk of mucosal damage or irritation.

***In Vitro* Mucoadhesion Study and *In Vitro* Retention Time**

The mucoadhesive properties of prepared formulation F1 to F12 were determined. Results of mucoadhesive study indicate that all batches were of good mucoadhesive properties. The highest mucoadhesive force was possessed by batch F10 (0.178) i.e. formulation containing HPMC K 15 M and Carbopol 934 P. The results were shown in Table No. 1 and Figure No. 1.[7]

In vitro residence time of the tablets of batch (F10) showed better results. The formulas which contain HPMC K 15 M and Carbopol 934 P were having higher in vitro residence time. The result were recorded in the table no. 2.

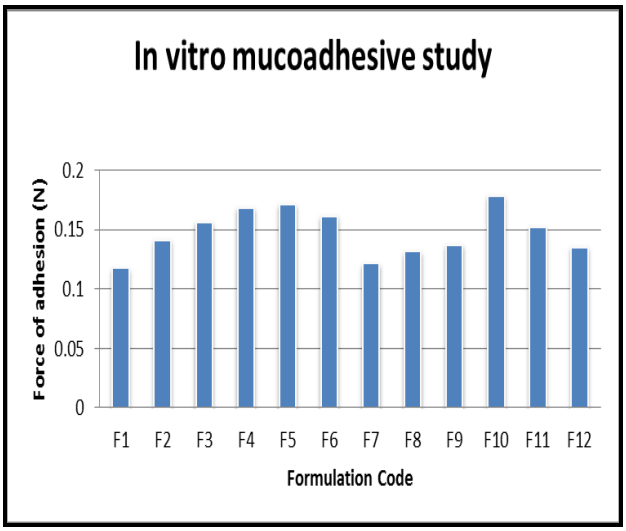

Figure 1: *In vitro* mucoadhesive study

The swelling properties of prepared formulation F1 to F12 were determined appropriate swelling is an essential property for uniform and prolonged release of drug release. The formulation F10 containing HPMC K 15 M and Carbopol 934 P showed maximum swelling index. In vitro swelling index of formulation are plot of swelling index versus time (hrs) was shown in Figure No.2.

Table 2: *In vitro* mucoadhesive strength study and *In Vitro* Retention Time of Metoprolol Succinate buccal tablets

Formulation Batches	Mucoadhesive Strength (gm)	Mucoadhesive Force (N)	*In vitro* retention Time
F1	12.0±0.10	0.117	8 hrs 15 min
F2	14.4±0.12	0.141	8 hrs 50 min
F3	16.0±0.08	0.156	9 hrs 17 min
F4	17.2±0.31	0.168	8 hrs 52 min
F5	17.5±0.50	0.171	9 hrs 20 min
F6	17.9±0.61	0.175	9 hrs 37 min
F7	12.4±0.06	0.121	8 hrs 50 min
F8	13.4±0.18	0.131	9 hrs 10 min
F9	14.0±0.22	0.137	9 hrs 25 min
F10	18.2±0.32	0.178	9 hrs 45 min
F11	15.5±0.15	0.152	9 hrs 41 min
F12	13.8±0.17	0.135	9 hrs 16 min

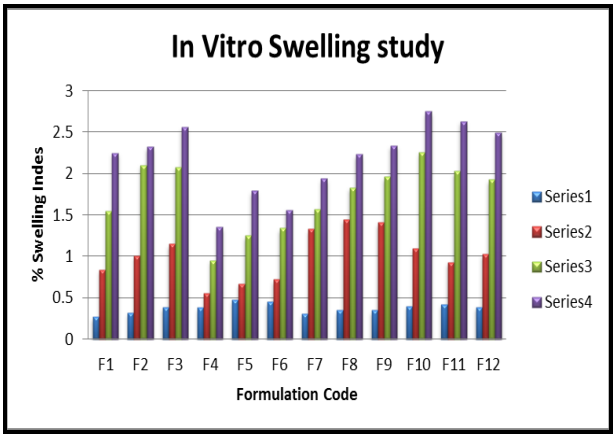

Figure 2: *In vitro* Swelling Study

Stability Study

Due to the lack of the time period and stability chamber, the optimized batch (F 10) was subjected to the accelerated stability of one month at the room temperature. The optimized batch was wrapped in to aluminums foil and kept at the room temperature for a period of one month. After one month the optimized batch was subjected to main evaluation parameter such as in-vitro dissolution study, drug content, disintegration, hardness, weight variation. The result obtained from this evaluation test at room temperature is as follows.

In Vitro Drug Release Study

Table 3: *In Vitro* Release Kinetic Data of Metoprolol Succinate from Mucoadhesive Buccal Tablet

Formulation code	Zero order	First order	Higuchi	Korsmeyer-Peppas		Best Fit Model
	R	R	R	R	Release exponent (n)	
F1	0.940	0.984	0.994	0.998	0.557	Pepppas
F2	0.923	0.997	0.997	0.998	0.545	Pepppas
F3	0.912	0.996	0.998	0.997	0.515	Matrix
F4	0.921	0.988	0.998	0.999	0.544	Pepppas
F5	0.936	0.984	0.995	0.998	0.564	Pepppas
F6	0.928	0.992	0.996	0.998	0.551	Pepppas
F7	0.921	0.987	0.997	0.996	0.525	Matrix
F8	0.919	0.993	0.997	0.995	0.518	Matrix
F9	0.900	0.996	0.998	0.997	0.512	Matrix
F10	0.937	0.980	0.995	0.998	0.564	Pepppas
F11	0.942	0.972	0.993	0.998	0.570	Pepppas
F12	0.922	0.987	0.996	0.996	0.526	Matrix

The all formulation batches F1 to F10 were subjected to various release models, by using PCP-Disso-v3 software made by faculty from Poona College of Pharmacy. The most of the formulations showed Korsmeyer-Peppas model equation (Diffusion/Relaxation Model) as best fit model, describes the drug release from the formulation.[4]

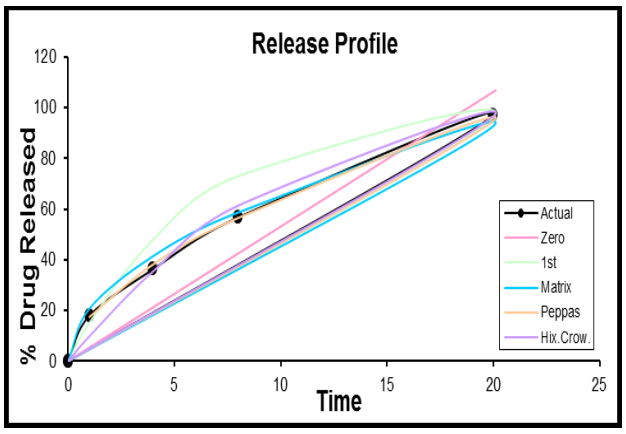

Figure 3: Drug release profile for Optimized Batch F 10 with model fitting

CONCLUSION

The *ex-vivo* mucoadhesive strength (bioadhesive strength) of buccal tablets which was found to be in the increasing order as the concentration of polymer increases. The mucoadhesive strength was increased linearly, with increasing concentration of Carbopol 934P and no significant change with increase in the concentration of sodium CMC. While optimized formulation F10 showed greatest mucoadhesive strength due to the combine effect of HPMC K 15 M and Carbopol 934 P.

Finally based on bioadhesive strength, in vitro residence time, swelling study and in vitro drug release study it was found that F10 was best formulation and selected as optimized formulation for stability study.

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