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Research Article

"FORMULATION AND EVALUATION OF METOPROLOL SUCCINATE BUCCAL TABLET CONTAINING TAMARIND SEED POLYSACCHARIDES"

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ABSTRACT

The emergence of mucoadhesive drug delivery as an effective way to enhance patient compliance and extend the life cycle of a drug has led to the need for novel ways to controlling the drug release profile. Buccal tablet of Metoprolol Succinate were prepared for avoid first pass metabolism, to increase bioavailability, the tablets were prepared using carbopol-934, sodium CMC, cross linked TSP and TSP as a mucoadhesive polymer, Nine formulations were developed with varying concentration of polymer. Carbopol-934 is used as a primary polymer because of its excellent mucoadhesive property and secondary polymer like sodium CMC, cross linked TSP and TSP were used. The comparison of secondary polymers on bioadhesive property, swelling index and drug release was studied. The formulation F8 showed maximum drug release at the end of 8 hrs also showed maximum swelling index and maximum retention. Formulation F6 showed maximum bioadhesive strength. The results indicate that suitable buccal tablet of Metoprolol succinate using natural polysaccharides TSP with desired properties was prepared.

Keywords*:* Metoprolol succinate, Buccal tablet, Bioadhesive and swelling index, Cross- linked TSP

INTRODUCTION

In recent years the oral cavity is being increasingly used for the administration of many drugs. The buccoadhesive drug delivery is promisingly option for those drugs having high first pass hepatic metabolism, gastric degradation in the harsh gastrointestinal environment. Moreover buccal drug delivery offers, safer methods of drug utilization since toxicity produced drug absorption can be promptly terminated by removing dosage form from the buccal cavity. The advantages of buccal drug delivery are localization effect, excellent route for the systemic drug delivery, significance reduction in dose, increased the bioavailabity[2].

Metoprolol succinate is a cardio selective beta1 adrenergic antagonist and widely used in treatment of diver's diseases of the cardiovascular system, such as hypertension, angina pectoris, arrhythmias. Metoprolol succinate is freely soluble in water and administered at a dose of 100-450 mg daily. The half life of Metoprolol succinate is about 3-4 hrs, Metoprolol undergoes extensive first pass metabolism resulting in only 50% oral bioavailability[10].

Hence the aim was to prepare buccoadhesive tablet of Metoprolol tartrate to ensure satisfactory bioadhesive strength and release behavior of drug from tamarind seed polysaccharides and cross linked Tamarind Seed Polysaccharides[20].

MATERIALS

Metoprolol succinate was obtained as a gift sample from Sun Pharma ltd, Ahmednagar, Carbopol- 934, sodium carboxymethyl cellulose; ethyl cellulose was obtained from Watson Pharma, Ambernath, Thane.

METHODS

Preparation of Metoprolol Buccal tablets

Mucoadhesive buccal tablets were prepared by direct compression techniques using carbopol 934, sodium CMC, TSP, and crossed linked TSP with different ratio as shown in table-1: All the ingredients were mixed properly and then compressed using 8 mm flat faced punch on a multi rotary punch machine. The upper punch was removed and ethyl cellulose as a backing layer were added on it and finally compressed that gave 8-10 kg/cm2 hardness.

Isolation of Tamarind seed polysaccharides [13, 18]

Tamarind seed polysaccharides was prepared following methods by Rao et al., Tamarind Kernel Powder is obtained from the seeds of the plant Tamarindus Indica. Tamarind seeds are broken. The hull is removed through heating, grinding and sieving. The endosperm is separated from the germ through grinding and sieving and is then pulverized to get a fine powder called Tamarind Kernel Powder. To 20g of tamarind kernel powder, 200ml of cold distilled water was added and slurry was prepared. The slurry was poured into 800ml of boiling distilled water. The solution was boiled for 20 minutes under stirring condition in a water bath. The resulting thin clear solution was kept overnight so that most of the proteins and fibbers settled out. The solution was then centrifuged at 5000 rpm for 20 minutes. The supernatant was separated and poured into twice the volume of absolute alcohol by continuous stirring. The product was pressed between felt. The precipitate was washed with absolute ethanol, diethyl ether and petroleum ether and then dried at 50-60° C under vacuum. The dried material was ground and sieved to obtain granules of different particle size range. The particle size range of 150-75 microns was used for preparation of tablets.

Cross-linking of Tamarind seed polysaccharides [19]

The cross-linking of TSP prepared following methods by Lenaerts et al,

TSP was partially cross linked with epichlorohydrin (16). TSP 10g (soaked in water) and sodium hydroxide (50ml, 1 N, 54° C) was mixed with a glass rod. After homogenization (15 min), 0.5ml epichlorohydrin (6g/100g of TSP) was slowly added with continuous homogenization (15min). The gel was then neutralized with acetic acid and washed 3 times through a sintered glass filter with a solution of water/acetone (60:40 v/v). In the final step, the resulting solid gel was washed with pure acetone over a filter. The polymer was air dried at room temperature for 72 hours and stored in airtight container. After granulation, granular fractions between 75 and 250 microns were used for preparation of tablets. Cross-linked polysaccharide was prepared in three batches.

Evaluation of Buccal Tablet

Determination of Physicochemical Parameters [11]

Twenty tablets were weighed individually and the average weight was determined. Percentage deviation was calculated and checked for weight variation. Thickness was measured using Vernier callipers. Five tablets of each formulation were taken and amount of drug present in each tablet was determined. The surface pH of the tablets was determined in phosphate buffer pH 6.2 in order to investigate the possibility of any irritation in the oral cavity. The

tablets were kept in contact with phosphate buffer pH 6.2 for 2 h and pH was noted by using universal pH paper.

Bioadhesive strengt: [16]

Bioadhesive strength of tablets was measured on modified physical balance. Porcine Buccal mucosa was used as model membrane and phosphate buffer pH 6.8 was used as moistening fluid. Bioadhesive studies were performed in three batches.

Swelling Studies [16]

The swelling properties and the erosion characteristics of tablets were evaluated by determination of % of Hydration. Each tablet was weighed (W1) and immersed in a phosphate buffer at pH 6.2 for predetermined times (1 to 8 hr). After immersion, tablets were wiped off by the excess of surface water by the use of filter paper and weighed (W2). This experiment was performed in triplicate. The % hydration was calculated by formula using % hydration =W2 - W1/W1×100 and swelling of different formulations shown after 8 hours.

In-Vitro Release Studies[11, 17]

The drug release rate from buccal tablets was studied using the USP (II) dissolution test apparatus (Lab India dissolution test apparatus Disso 2000). The assembly is kept in a jacketed vessel of water maintained at 37±1^{0}C. Buccal tablet was made to stick on bottom of the flask (so as to allow one sided release from the tablet). The beaker is filled with 250ml of mixed phosphate buffer pH 6.8. The vessel maintained at 50rpm under stirring conditions by means of paddle fabricated for purpose in dissolution apparatus. At various intervals of time, samples were withdrawn and filtered through Whatman filter paper no.42. It is replaced immediately with equal amount of fresh buffer. The samples are then analyzed U.V. spectrophotometrically at 237 nm up to 8hours.

In-Vitro Retention Time of Buccal Mucoadhesive Tablets [20]

The in-vitro retention time is one of the important physical parameter of buccal tablet. The adhesive tablet was pressed over excised Porcine 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 phosphate buffer, pH 6.2, at 370c. 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.

Composition of Buccal Mucoadhesive Tablet

Table 1: Formulation of Metoprolol succinate buccal tablet

Formulation code	Metoprolol succinate	CP-934	Sodium CMC	TSP	Cross linked TSP	Pearlitol SD-200	Ethyl Cellulose	Magnesium Stearate	Total weight
F1	50	75	80	-	-	63	30	2	300
F2	50	50	100	-	-	68	30	2	300
F3	50	25	120	-	-	73	30	2	300
F4	50	75	-	80	-	63	30	2	300
F5	50	50	-	100	-	68	30	2	300
F6	50	25	-	120	-	73	30	2	300
F7	50	75	-	-	80	63	30	2	300
F8	50	50	-	-	100	68	30	2	300
F9	50	25	-	-	120	73	30	2	300

All quantity in milligrams

CP –carbopol, sodium CMC- sodium carboxymethyl cellulose, TSP- Tamarind seed polysaccharides

RESULT AND DISCUSSION

Physicochemical properties

The average weight of the tablet was found to be 297mg to 302mg with the maximum % deviation of ±0.56 for all nine formulations. The tablets showed thickness in the range of 4.36 to 4.64 mm with the maximum % deviation of ±o.171. The percentage drug content of all the formulation was found to be 97.36-99.36 (±0.19). Thus the all formulations meet the standard specification. All the results shown in table: 2

Table 2: **Thickness, Hardness, Weight variation and Drug content of Metoprolol succinate buccal tablet**

Formulation code	Thickness* (mm)	Percent Friability	Hardness* (Kg/cm^2)	Weight variation* (mg)	Drug content uniformity
F1	4.33±0.021	0.454	5.2±0.198	297±0.23	98.55
F2	4.42±0.031	0.982	5.6±0.156	298±0.32	97.61
F3	4.64±0.171	0.345	5.6±0.214	299±0.11	97.11
F4	4.52±0.031	0.677	5.7±0.123	302±0.56	98.35
F5	4.53±0.213	0.238	5.7±0.125	301±0.23	97.15
F6	4.35±0.0450	0.899	5.4±0.135	299±0.21	98.36
F7	4.26±0.034	0.226	5.4±0.312	299±0.43	98.36
F8	4.23±0.098	0.215	5.2±0.198	300±0.21	99.36
F9	4.36±0.064	0.437	5.6±0.156	302±0.33	97.36

*The values represent mean ± SD, n = 3.

Bioadhesion study

The highest bioadhesion strength was possessed by the formulation F6 containing CP-934 and Tamarind seed polysaccharides in the 1:5 ratio. Increase in the concentration of TSP and crossed-linked TSP increases bioadhesion strength, hence it was confirmed that TSP has a good bioadhesion property.the results shown in table: 3

In-vitro swelling study

The swelling index of mucoadhesive tablets for a period 8 hrs studied.the swellingindex increases with increases concentration of the TSP and cross linked TSP. The polymer absorbed large volumes of water rapidly and swells to its maximum hydrated size without dissolving in aqueous media. The formulation F8 possessing highest

swelling index containing CP-934 and cross linked TSP.

In-vitro retention time study

The in-vitro retention time study was conducted using goat mucosa. The formulation F8 possessing highest retention time , the F8 formulation containing CP-934 and cross linked TSP in the 1:2 ratio, hence it was confirmed that the cross linked TSP has good retention property.

Results shown in table-3.

Table 3: Bioadhesive strength, swelling index and In-vitro retention time of Metoprolol succinate buccal tablet

Formulation code	Bioadhesive strength* (gm)	In vitro retention time	Swelling index*
F1	15.68±0.45	2 hours 21 minute	9.91±3.08
F2	15.98±0.12	3 hours 52 minute	8.95±3.09
F3	16.21±0.34	3 hours 15 minute	8.85±4.67
F4	18.86±0.25	5 hours 25 minute	9.82±1.34
F5	18.02±1.23	6 hours42 minute	9.93±2.43
F6	19.98±2.35	5 hours10 minute	8.99±5.65
F7	17.22±1.27	5hours 15 minute	11.12±7.68
F8	18.15±2.47	7 hours 21 minute	12.55±9.45
F9	18.19±1.34	6hours 22 minute	11.95±6.87

*The values represent mean ± SD, n = 3.

In-vitro drug release study

In-vitro release studies of Metoprolol succinate buccal tablets were determined using USP type II apparatus. The drug release was found to vary according to the ratio of bioadhesive polymers. The formulation F8 shows the optimum drug release 78.66 % at the end of 8 hrs containing CP-934 and cross linked TSP. Other formulation also shows good drug release at the end of 8 hrs, containing TSP and cross linked TSP with different ratios. Hence, from results it was concluded that cross linked TSP has good drug release property. The graphically representation shown in Fig-1, 2, 3.

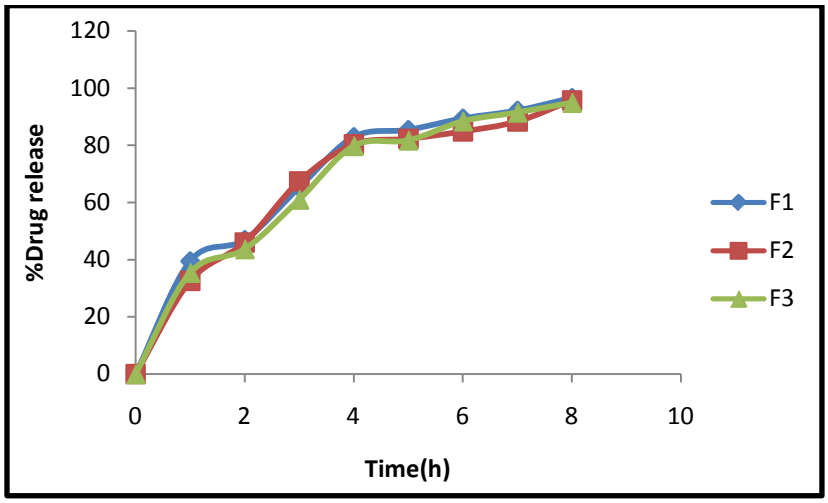

Fig. 1: Release profile of the formulation F1, F2 and F

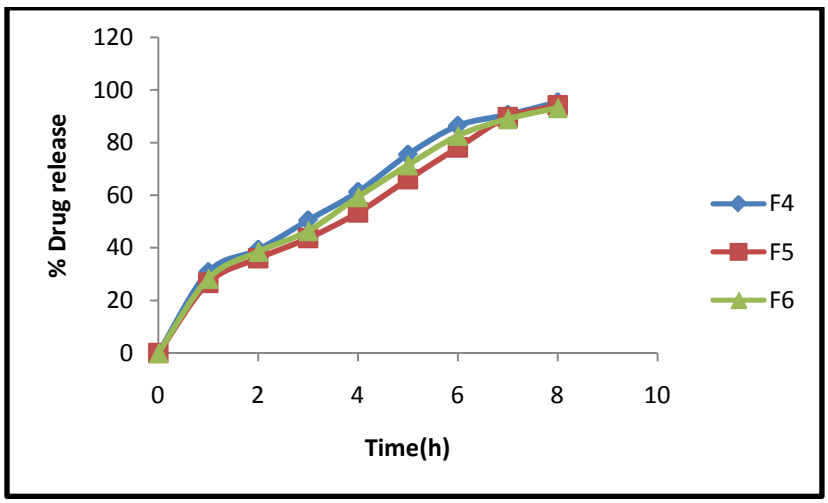

Fig. 2: Release profile of the formulation F4, F5 and F6

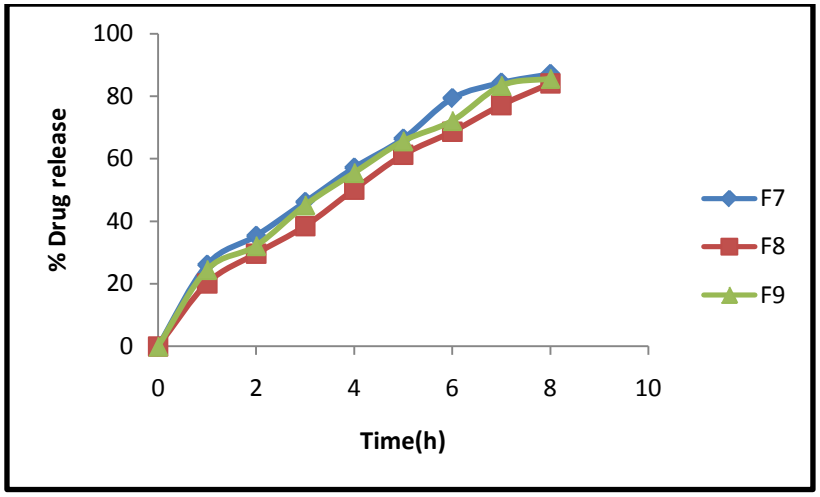

Fig 3: Release profile of the formulation F7, F8 and F9

CONCLUSION

The present work was aimed to develop the buccoadhesive drug delivery system for Metoprolol succinate with prolonged effect and to avoid first pass metabolism. From the study, it is observed that formulation F8 was best in terms of drug release, bioadhesive Performance, swelling index and physicochemical properties. Therefore it can be concluded that stable formulation could be developed by incorporating carbopol 934 and cross linked Tamarind seed polysaccharides in the ratio of 1:2 for the sustained release of Metoprolol from mucoadhesive tablet with adequate bioadhesiveness and swelling properties without the risk of mucosal damage. The release amount of drug can be controlled by partially cross linking the matrix, the extent of release can be varied by controlling degree of cross linking.

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