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Formulation and Evaluation of Mucoadhesive Microspheres of Metoprolol Tartarate

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***Abstract*:-** The purpose of this research was to prepare and evaluate mucoadhesive microspheres of Metaprolol tartarate an antihypertensive drug for prolonged residence time and sustained drug release. Microspheres were prepared by Ionotropic gelation technique using sodium alginate, HPMC K4M as polymers in varying ratios. The microspheres were evaluated for its percentage yield, drug entrapment efficiency, particle size and shape, in vitro mucoadhesion study and in vitro drug release studies. The mucoadhesive microspheres showed particle size, drug entrapment efficiency and yield in the ranges of 280.14 – 596.16 µm, 55.47 – 88.36 % and 78.16 – 87.06 % respectively. In vitro drug release and mucoadhesion study confirms formulation F13 was the best formulation as it releases 97.96 % at the end of 12 hr. in controlled manner and percentage mucoadhesion of 76.13 % after 10 hr. This confirms the developed Metaprolol tartarate mucoadhesive microspheres are promising drug delivery system for oral sustained administration of Metaprolol tartarate.

Keywords :- *Drug entrapment efficiency, In vitro mucoadhesion study, Metaprolol tartarate, Mucoadhesive microspheres, Residence time.*

I. INTRODUCTION

Oral controlled drug delivery system is the most versatile, convenient and commonly employed route of drug delivery for drugs having less plasma half life and residence time in GIT. Many concepts have been proposed in recent years to provide a dosage form with a longer transit time and therefore a more efficient absorption. The concept of bioadhesion or more specifically mucoadhesion is one of them to increase gastric retention of drugs. Among the various approaches for mucoadhesion, microencapsulation process have gained good acceptance as a process to achieve controlled release and drug targeting. Several studies reported mucoadhesive drug delivery systems in the form of tablets, films, patches and gels for oral, buccal, nasal, ocular and topical routes; however, very few reports on mucoadhesive microspheres for oral administration are available. The side effects of conventional drug delivery systems have been attenuated by designing the drug in the form of mucoadhesive microspheres which provides advantages like, maximized absorption rate due to intimate contact with the absorbing membrane, improved drug protection by polymer encapsulation, longer gut transit time resulting in extended periods for absorption. Metoprolol tartarate is a β1-selective adrenergic blocking agent and is prescribed widely in cardiovascular diseases like hypertension. Administration of conventional tablets of Metoprolol tartarate has been reported to exhibit fluctuations in plasma drug levels resulting either in manifestation of side effects or reduction in drug concentrations at the receptor sites. Based on these observations mucoadhesive microspheres of antihypertensive drug was formulated to achieve efficient absorption, enhanced bioavailability, increasing patient compliance, prolonged residence time at the site of absorption, release of the drug for extended period of time and facilitate an intimate contact with the absorption surface to get better therapeutic performance of drug. All above advantages can be achieved by combining the advantage of particulate system (microsphere) and mucoadhesive drug delivery system by using sodium alginate and other mucoadhesive polymers like HPMC K4M. [1, 2, 3]

II. MATERIALS AND METHODS

2.1. Materials

Metoprolol tartarate was received as a kind gift from Emcure pharmaceuticals Pvt. Ltd, Pune. Sodium Alginate and Sodium hydroxide and Potassium dihydrogen phosphate were procured from Loba Chemie, Mumbai. HPMC K4M procured from Meditab Pharmaceuticals Pvt. Ltd, Satara. Calcium chloride procured from Research lab fine chem industries, Mumbai.

2.2. Method of preparation of mucoadhesive microspheres of Metoprolol tartarate

Ionotropic gelation method

Microspheres containing Metoprolol tartarate were prepared by ionic gelation technique by adding sodium alginate alone and in combination with HPMC K4M in varied quantities, were dissolved in purified

water. Metoprolol tartarate was added to the above polymer solution and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added manually drop wise into Calcium chloride solution through a syringe with a needle of size no.26. The added droplets were retained in the Calcium chloride (cross linking agent) solution for the defined period of time to complete the curing reaction and to produce spherical rigid microcapsules. The microcapsules were collected by decantation, and the product thus separated was washed repeatedly with water and dried at 40°C for 12 hours. The compositions of the microspheres formulations are listed in Table 1. [4, 5, 6]

Table 1 Composition of Mucoadhesive microspheres of Metoprolol tartarate

Ingredients	Formulation Code												
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Metoprolol tartarate (mg)	100	100	100	100	100	100	100	100	100	100	100	100	100
Sodium alginate (mg)	100	200	300	100	150	200	250	300	100	150	200	250	300
HPMC K4M (mg)	--	--	--	50	50	50	50	50	100	100	100	100	100
Calcium chloride (%)	5	5	5	5	5	5	5	5	5	5	5	5	5

III. EVALUATION OF MUCOADHESIVE MICROSPHERES

3.1. Percentage Yield (% yield)

The dried microspheres were weighed and percentage yield of the prepared microspheres was calculated by using the following formula. [7]

$$\text{Precentage yield} = \frac{\text{The weight of microspheres}}{\text{The weight of polymer + drug}} \times 100 \ldots\ldots\ldots \text{"equation 1"}$$

3.2. Particle Size Determination

The particle size of the microspheres was determined using optical microscope fitted with an ocular micrometer and a stage micrometer. The particle diameters of 50 microspheres were measured randomly by optical microscope. The average particle size was determined by using Edmondson's equation. [8,9]

$$\text{D Mean} = \frac{\text{Summesion nd}}{\text{Summesion n}} \ldots\ldots\ldots \text{equation 2}$$

Where, n = Number of microspheres observed and d = Mean size range.

3.3. Surface Morphology (SEM Analysis)

Shape and surface morphology of microcapsules were studied using scanning electron microscopy (SEM).The microcapsules were mounted on metal stubs using double sided adhesive tape and the stub was then vacuum coated with gold film using sputter coater attached to the instrument. The photographs were taken using a scanning electron microscope (Jeol 5400, Japan).[10,11]

3.4. Estimation of drug entrapment efficiency

For determination of the drug content, microspheres equivalent to 100 mg of Metoprolol tartarate were crushed in a glass mortar and pestle and the powdered microspheres were suspended in 100 ml of phosphate buffer pH 7.4. After 24 h, the solution was filtered, 1 ml of the filtrate was pipetted out and diluted to 10 ml and analyzed for the drug content using Dynamica HaLoDB-20 UV Visible spectrophotometer at 276 nm. The drug entrapment efficiency was calculated using the following formula.[12,13]

$$\%\ \text{Drug entrapment efficiency} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100 \ldots\ldots\ldots \text{"equation 3"}$$

3.5. Swelling Index

Accurately weighed (50 mg) Metoprolol tartarate loaded microspheres (W_O) were placed separately in beaker containing 25 ml of phosphate buffer pH 7.4. After specified time the microspheres were filtered, blotted with

filter paper to remove excess water from surface, and weighed immediately on electronic weighing balance. The percent swelling index was calculated by reweighing (Wt) the microspheres at the end of 1 h, and at hourly intervals up to 10 hr, using the following formula.[14,15]

$$\% \text{ Swelling index} = \frac{\text{Wt} - \text{Wo}}{\text{Wo}} \times 100 \ldots\ldots\ldots \text{"equation 4"}$$

3.6. *In-vitro* wash-off test

The mucoadhesive property of the microspheres was evaluated by an in vitro adhesion testing method known as the wash-off method. In this method freshly excised pieces of intestinal mucosa (3 × 2 cm) of sheep were taken and mounted on paddle of USP dissolution test apparatus with thread. About 50 no. of microspheres were spread onto each wet rinsed tissue specimen, and immediately thereafter the support was hung onto the arm of USP dissolution apparatus. The USP dissolution test apparatus was operated at 25 rpm of paddle in phosphate buffer pH 7.4 at 37.5 ± 0.50C. At the end of 1 h, and at hourly intervals up to 10 h, the machine was stopped and the numbers of microspheres still adhering to the tissues were counted. Percent mucoadhesion was calculated by the using following formula.[16, 17]

$$\% \text{ Mucoadhesion} = \frac{\text{No. of microspheres remains on mucosa}}{\text{No. of applied microspheres}} \times 100 \ldots\ldots\ldots \text{"equation 5"}$$

3.7. *In-vitro* drug release study

The drug release study was performed using U.S.P. dissolution testing apparatus I (Basket type) at 37 ± 0.5°C and at 100 rpm using 900 ml of phosphate buffer pH 7.4, as dissolution medium for 12 h. Microspheres equivalent to 100 mg of Metoprolol tartarate were used for the test. 5 ml of sample solution was withdrawn at predetermined time intervals, filtered, diluted suitably, and analyzed spectrophotometrically at 276 nm. An equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample to maintain sink condition.[18]

IV. RESULTS AND DISCUSSION

4.1. Percentage yield (% yield)

The percentage yield of microspheres prepared by ionic gelation technique was found to be in between 78.65±1.21 to 88.18 ±1.21. It was observed that as the polymer ratio in the formulation was increased, the percentage yield was also increased. The low percentage yield in some formulations may be due to blocking of needle and wastage of the drug- polymer solution, and microcapsules lost during the filtration, washing process which ultimately decreased the percentage yields of microspheres. The percentage yield of the prepared microspheres is shown in Table 2.

Table 2 Percentage Yield

Formulation Code	% Yield*	Formulation Code	% Yield*
F1	78.65±1.21	F8	84.04±1.97
F2	81.27±0.75	F9	83.2±1.74
F3	85.38±1.47	F10	87.08±0.82
F4	78.16±1.34	F11	86.12±1.48
F5	82.23±1.29	F12	81.00±0.96
F6	80.08±1.24		
F7	83.12±1.37	F13	88.18±1.21

*****mean ± S.D., n=3

4.2. Particle size determination

Particle Size of the various batches of microspheres was found to be in the range of 280.14±1.97 µm to 596.16±4.02 µm. It was observed that particle size of the microspheres significantly increased with increasing polymer concentration. Increase in polymer concentration was attributed to increase in viscosity, which resulted in formation of large droplets, thus increasing the size of microspheres. The particle size of the prepared microspheres is displayed in Table 3.

Table 3 Particle size of F1 to F13 batch

Formulation Code	Particle size in µm*	Formulation Code	Particle size in µm*
F1	280.14±6.5	F8	498.06±4.03
F2	351.33±3.82	F9	364.26±4.11
F3	384.83±4.11	F10	437.83±2.78
F4	310.42±4.07	F11	455.5±4.20

F5	394.56±3.5	F12	576.41±3.15
F6	415.54±3.42	F13	596.16±4.02
F7	438.5±4.97		

*****mean ± S.D., n=3

4.3. Surface morphology (SEM analysis)

The morphological analysis of the mucoadhesive microspheres studied by Scanning Electron Microscopy (SEM). SEM photomicrographs of F13 formulation is reported in following fig. no.1 showed that the microspheres were almost spherical in shape with a rough outer surface and having particle size 500 µm.

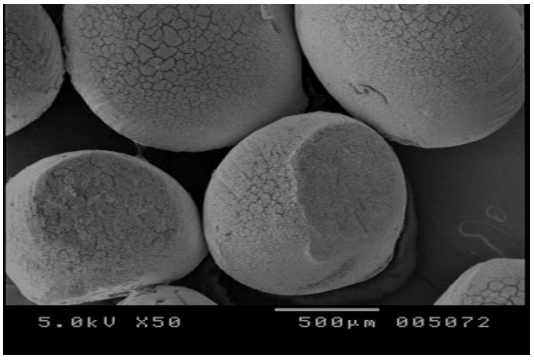

Figure 1 SEM photograph of mucoadhesive microspheres of F13 formulation

4.4. Estimation of drug entrapment efficiency

Entrapment efficiency of the various batches of microspheres was found to be in the range of 55.47±0.75% to 65.57±0.86. It was observed that entrapment efficiency of the microspheres was dependent on the concentration of polymer. It was observed that by increasing the concentration of sodium alginate and mucoadhesive polymer the entrapment efficiency of the microspheres also increases. The % drug entrapment efficiency of the prepared microspheres is displayed in Table 4.

Table 4 Drug Entrapment Efficiency

Formulation Code	%Drug entrapment efficiency	Formulation Code	%Drug entrapment efficiency
F1	55.47±0.75	F8	62.64±0.74
F2	57.52±0.82	F9	59.79±0.89
F3	58.14±0.83	F10	60.82±0.82
F4	56.35±0.86	F11	62.88±0.76
F5	58.67±0.91	F12	62.88±0.76
F6	59.11±0.79	F13	
F7	60.20±0.63		65.57±0.86

4.5. Swelling index

From the swelling study, the percent swelling of alginate microsphere (F1 to F3) was found within the range of 72.54±3.05% to 81.16±2.3. Whereas in case of Algino -HPMC K4M microsphere (F4 to F13), it was found within the range of 74.22±2 to 85.12±0.91. It was found that by increasing the polymer concentration, swelling of all the formulations were increases. The swelling index of the prepared microspheres after 10 hr is displayed in Table 5.

Table 5 Swelling index

Formulation Code	% Swelling	Formulation Code	% Swelling
F1	72.54±3.05	F8	82.28±3.89
F2	76.9±3.05	F9	77.14±3.20
F3	81.16±2.3	F10	79.26±3.09
F4	74.22±2	F11	80.22±2.30

F5	76.26±3.6	F12	83.14±0.82
F6	78.24±1.5	F13	85.12±0.91
F7	79.12±3.2		

4.6. *In-vitro* mucoadhesion study

Prepared microspheres were found good mucoadhesion strength. Percent mucoadhesion of the all batches of microspheres were found to be in the range of 48±3.05% to 76±1.35. It was observed that mucoadhesion of the microspheres significantly increased with increasing polymer concentration. Increase in polymer concentration was attributed to increase in viscosity; produce stronger mucus gel network which helps to increase mucoadhesion. The percentage mucoadhesion of microspheres adhering to tissue after 10 hrs. is displayed in Table 6. The F13 batch showed highest % mucoadhesion which was attributed to increase in concentration of polymers. The fig. 2 and fig. 3 showed mucoadhesive microspheres of F13 batch at initial time and after 10 hrs. respectively.

Table 6 *In-vitro* mucoadhesion Study

Formulation Code	% mucoadhesion	Formulation Code	% mucoadhesion
F1	48±3.05	F8	64±1.95
F2	50±2.45	F9	62±2.39
F3	62±1.68	F10	64±1.98
F4	52±1.82	F11	66±1.82
F5	58±1.59	F12	70±1.62
F6	60±1.62	F13	76±1.35
F7	64±1.38		

Figure 2 Mucoadhesive microspheres of F13 batch at initial time

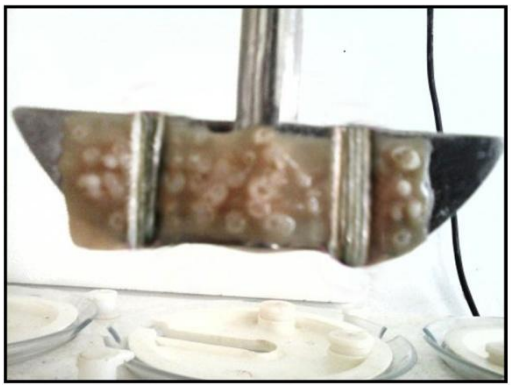

Figure 3 Mucoadhesive microspheres of F13 batch after 10 hrs.

4.7. *In-vitro* drug release study

The In vitro release profiles of Metoprolol tartarate from microspheres in phosphate buffer of pH 7.4 are shown in Table 7. It was observed that as concentration of polymer increases in the formulation, the release of the Metoprolol tartarate from the polymer matrix was retarded and could be attributed to increase in the density of the polymer matrix and also increase in the diffusional path length which the drug molecules have to traverse. Formulation F13 shows sustain drug release up to 95.40 % after 12 hrs. which was due to above reason. Fig. 4 and fig.5 showed in vitro release profile of Formulation F1 to F13

Table 7 *In-vitro* drug release study

Table 7 *In-vitro* drug release study

Time (Hours)	% Cumulative drug release												
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	25.88	23.29	21.54	24.03	22.76	22.39	20.11	19.58	22.12	21.60	21.28	19.58	17.57
2	42.98	37.16	29.17	39.28	33.08	31.02	29.48	27.31	34.57	33.35	28.69	24.72	22.97
3	56.17	49.54	40.55	52.51	42.98	40.60	38.75	56.52	42.98	41.98	36.63	31.02	28.58
4	70.41	60.14	50.82	63.47	53.78	51.67	47.70	43.72	51.67	53.25	43.83	37.37	37.11
5	83.27	71.47	56.32	72.95	61.39	60.93	56.32	51.98	60.45	61.14	50.71	44.57	43.72
6	92.96	82.48	64.72	84.28	72.47	69.35	63.58	58.02	69.35	68.13	57.01	53.84	51.98
7		93.22	72.95	93.33	81.42	78.40	70.57	65.96	78.24	76.81	63.42	61.09	58.50
8			81.58		92.01	84.24	78.40	71.74	86.61	82.69	71.36	68.13	67.12
9			94.87			94.65	86.61	78.14	93.54	89.41	79.72	75.38	74.51
10							93.07	82.48		95.71	87.45	81.84	79.62
11								90.37			94.55	88.20	86.92
12								96.45				96.19	95.40

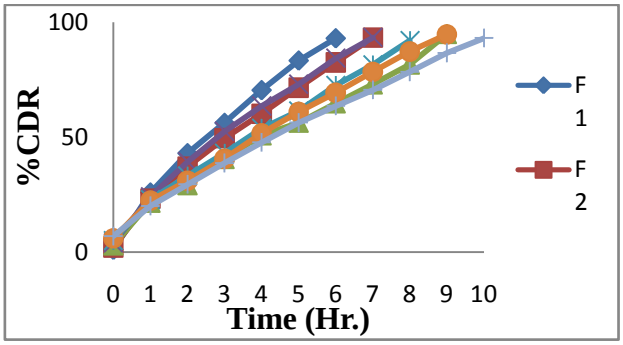

Figure 4 *In-vitro* drug release of F1 - F7 batch

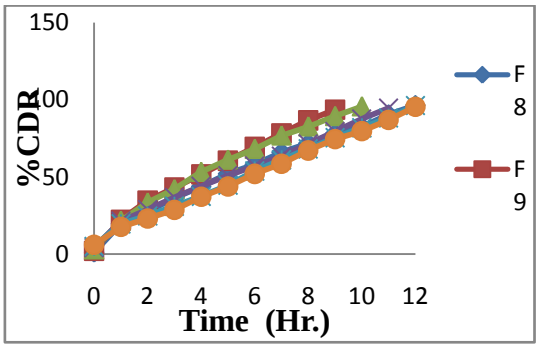

Figure 5 *In-vitro* drug release of F8 - F13 batch

V. CONCLUSION

In the present study, a satisfactory attempt has been made to formulate mucoadhesive microspheres of Metoprolol tartarate. From the experimental study result, it was concluded that optimized batch F13 showed 95.40% in vitro drug release and 76% in vitro Mucoadhesion. In vitro release of mucoadhesive microspheres of Metoprolol tartarate was found to be in sustained manner and is dependent on the concentration of polymer used. As the concentration of polymer increases in the formulation, the release of the Metoprolol tartarate from the polymer matrix was retarded. Hence, finally it was concluded that the prepared mucoadhesive microspheres of Metoprolol tartarate prove to be potential system for safe and effective sustained release over an extended period of time for treatment of hypertension.

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