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Research Article

DESIGN AND CHARACTERIZATION OF MUCOADHESIVE MICROCAPSULES OF METOPROLOL SUCCINATE

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ABSTRACT

Mucoadhesive microcapsules of metoprolol succinate ,a β_1-adrenergic blocker and antihypertensive agent , have been prepared from sodium alginate ,hydroxyl propyl methyl cellulose-K4M&E5LV,carbopol 934P,sodium CMC using 10% w/v calcium chloride solution by ionic gelation method. Drug : polymer ratio was 1:1 in all formulations and polymer mixtures employed were 1:1,2:1,3:1,4:1 of sodium alginate: polymer(hydroxy propyl methyl cellulose-K4M&E5LV,carbopol 934P,sodium CMC).Calcium chloride was used for ionic gelatin and cross linking of sodium alginate molecules. Microcapsules were spherical in shape and of sizes between 585 microns to 845 microns . carbopol 934P was found most effective in controlling drug release from microcapsules followed by hydroxyl propyl methyl cellulose K4M. Drug release from the best formulation from carbopol 934P follows Higuchi model while that from hydroxyl propyl methyl cellulose K4M follows anomalous transport.

Keywords: Mucoadhesive, Microcapsule, Metoprolol, Hydroxy-propylmethylcellulose, Carbopol, Ionic gelation.

INTRODUCTION

Microencapsulation by various polymers and its applications are described in standard text books and journals.[1,2] Microencapsulation is a suitable technique to achieve controlled release and drug targeting. The main aim of an oral controlled drug delivery should primarily aimed at achieving more predictable and increased bioavailability of a drug. The major absorption Zone(upper part of the intestine) ,can not provide complete drug release followed by absorption ,from the drug delivery system due to rapid transit of the delivery system throughout the zone leading to less bioavailability from the drug delivery system .

An attempt has been made for mucoadhesion of the drug delivery system in the upper part of the intestine to make intimate contact and increase duration of contact between the drug delivery system and mucus layer, resulting in prolongation of drug release, increased absorption and enhancement of bioavailability of the drugs.[3-6] These consideration has led to the development of oral controlled release microcapsules with mucoadhesive properties.

Alginate is easily gelled by the addition of calcium chloride solution to an aqueous solution of sodium alginate, since insoluble calcium alginate will be formed by cationic exchange between Na^+ and Ca^{2+}. The gelatin and cross linking are due to stacking of the glucoronic acid (G) blocks of alginate chains with the formation of egg-box –like junction.

Alginate microcapsules are non toxic, have a protective effect on mucous membrane of upper GIT and have property of re-swelling so they can act as controlled release systems.

Metoprolol is a β_1 adreno-receptor antagonist generally used in angina-pectoris and hypertension. It has an oral bioavailability of 50%, because of its poor absorption in lower GI tract. It undergoes hepatic metabolism and its elimination half life is 3-7hours[7].Therefore it is suitable candidate for the design of mucoadhesive microcapsules.

MATERIALS AND METHODS

Materials

Metoprolol succinate (I.P) was a gift sample from Matrix laboratory(Hyderabad,India). HPMC (E5LV, K4M) were procured from Glenmark pharmaceutical Ltd (navi Mumbai,India). Sodium alginate and Magnesium stearate were obtained from SPARC India Ltd. (Vadodara, India). Others were of analytical reagent grade.

Preparation of microcapsules –orifice ionic gelation method[4]

Coating materials (sodium alginate) and mucoadhesive polymers (HPMC K4M, HPMC E5LV ,Carbopol 934P,Sodium CMC) were dissolved in distilled water (40 ml) to form a homogeneous mixture. The core material metoprolol succinate (1000mg) was added to the polymer solution with the help of magnetic stirrer to form a viscous dispersion. The resulting dispersion was added dropwise with the help of a needle size (20 gauze) into the 50 ml calcium chloride solution (10%w/v) . The added droplets are retained in the solution for 60 minutes for curing to produce microspheres. Then the microspheres were filtered and washed with distilled water to remove the extra calcium chloride retained and dried at 50°C for 12 hours. The prepared microcapsules were kept in the desiccator for further use. The composition of the formulations are given in Table-1

Composition of the formulations

Table 1: A) Formulations of the metoprolol succinate microcapsules (1-8)

Formulation no. (F)	Metoprolol succinate (mg)	Sodium alginate (By part)	HPMC (E5LV) (By part)	HPMC (K4M) (By part)	Distilled water(ml)	Calcium Chloride solution (10%w/v)
1	1000	4	0	1	Upto 40ml	50 ml
2	1000	3	0	1	Upto 40ml	50 ml
3	1000	2	0	1	Upto 40ml	50 ml
4	1000	1	0	1	Upto 40ml	50 ml
5	1000	1	1	0	Upto 40ml	50 ml
6	1000	2	1	0	Upto 40ml	50 ml
7	1000	3	1	0	Upto 40ml	50 ml
8	1000	4	1	0	Upto 40ml	50ml

B) Formulations of metoprolol succinate microcapsules (9-14)

Formulation no. (F)	Metoprolol succinate (mg)	Sodium alginate (By part)	Carbopol 934p (By part)	Sodium *CMC (By part)	Distilled water(ml)	Calcium chloride solution (10%w/v)
9	1000	1	1	0	Upto 40ml	50 ml
10	1000	2	1	0	Upto 40ml	50 ml
11	1000	3	1	0	Upto 40ml	50 ml
12	1000	4	1	0	Upto 40ml	50 ml
13	1000	3	0	1	Upto 40ml	50 ml
14	1000	4	0	1	Upto 40ml	50 ml

*CMC-Carboxy Methyl Cellulose

Analytical method[11]

Estimations of metoprolol succinate at pH 1.2,6.8,7.4 were done at absorption maxima at 276 nm using UV spectro-photometer(SHIMADZU) in the concentration range25 to200 ppm with the help of standard curve.

Evaluations and characterization

Particle size analysis of the prepared microcapsules[8]-

The mean diameter of 10 dried microcapsules was determined by optical microscopy(metzer, India). The optical microscope was fitted with a stage micrometer by which the size of the microcapsules were determined. From the Formulations the highest size was observed in formulation **F1** (0.845±0.45) and lowest size was observed in formulation **F12** (0.585±0.66) which is given in Table-2.

Determination of flow properties of microcapsules

Angle of repose, bulk and tapped density, Carr's index, Hausner's ratio have been measured which are given in Table-3.

Angle of Repose[9]: Angle of repose has been used as indirect method for quantifying microcapsules' flowability,because of their relationship between interparticular cohesion. It is measured according to fixed funnel standing method.

$\Theta = \tan^{-1} h/r$,Where Θ is the angle of repose , r is the radius , and h is the height .

Bulk density and tapped density[10]: Bulk and tapped densities were measured by using 10 ml of graduated cylinder. The sample poured in the cylinder was tapped mechanically for 100 times, then tapped volume was noted down and tapped densities were calculated, each experiment of this was triplicated.

Carr's index[10] : Compressibility value or carr's index value of microparticles were computed according to the following equation;

$$\text{Carr}(\%) = \frac{(\text{tapped density} - \text{bulk density}) \times 100}{\text{Tapped density}}$$

Hausner's ratio[10]: Hausner's ratio was found to be related to interparticular friction, and such can be used to predict the flow properties of the microcapsules. It is measured by comparing the tapped density to the bulk density using following equation.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Kawakita constants evaluations

Kawakita equation;

$(Vo - Vp)/ Vo = abp/(1_{+bp})$ equation-1

Or

$N/C = (1/ab) + (1/a)N$ equation-2

C: Degree of volume reduction (Vo - Vp / Vo = C)

Vo: Initial apparent volume of the microcapsules Vp: microcapsules volume under applied pressure (P)

a,b: Constants, characteristic of the microcapsules

N = number of tapping

In the Kawakita equation (a) is a numeric parameter indicating the initial porosity of the compressed microcapsules and (b) is the compression coefficient.

Table 2: Kawakita equation values of different formulations and sizes of microcapsules

Formulations (F)	Size (diameter in mm.)	Compressibility(C)	N/C	a	b
1	0.845±0.045	0.038±0.002	2631.57±6.0	0.042	0.119
2	0.815±0.067	0.076±0.007	1315.78±8.5	0.084	0.039
3	0.817±0.012	0.047±0.005	2127.65±9.2	0.053	0.094
4	0.810±0.013	0.022±0.008	4545.45±9.8	0.023	0.217
5	0.780±0.014	0.029±0.005	3448.27±7.2	0.014	0.357
6	0.790±0.190	0.029±0.005	3448.27±7.2	0.033	0.071
7	0.780±0.178	0.029±0.005	3448.27±7.2	0.032	0.103
8	0.750±0.230	0.030±0.006	3333.33±6.8	0.038	0.038
9	0.595±0.450	0.025±0.007	4000.00±8.2	0.025	0.038
10	0.590±0.570	0.071±0.005	1408.45±5.3	0.074	0.063
11	0.587±0.620	0.022±0.002	4545.45±4.2	0.023	0.217
12	0.585±0.660	0.044±0.003	2252.25±5.8	0.023	0.217
13	0.680±0.190	0.064±0.006	1562.50±5.2	0.067	0.129
14	0.685±0.140	0.045±0.002	2222.20±6.8	0.021	0.212

* Figures are expressed as ± standard deviation, where n=3

The prepared microparticles have angle of repose varying from (16.13±0.689) to (24.08±0.145) , carr's index ranging from (14.04±1.716) to (17.34±1.25), similarly hausner's ratio ranging from (1.14±0.026) to (1.28±0.02)which are given in Table-3.

The above data show that these are close approximates to the data which correspond to free- flowing nature of the microparticles.

From Kawakita equation values in table 2 it is found that Formulation F4 is having less compressibility(0.022±0.008) and less porosity(0.023) but more compressibility index(0.217) which might be due to more internal crosslinking. Similarly Formulation F12 is having less compressibility(0.044±0.007) and less porosity(0.023) but more compressibility index(0.217) also due to well organized cross linking.

Table 3: Flow properties of the prepared microcapsules of metoprolol

F	Angle of repose (θ)		Bulk density (g/ml)		Tapped density (g/ml)		Carr's index (%)		Hausner's ratio	
	Mean	S.D(±)	Mean	S.D(±)	Mean	S.D(±)	Mean	S.D(±)	Mean	S.D(±)
1	16.79	0.689	0.555	0.007	0.649	0.009	14.46	1.385	1.16	0.02
2	16.16	0.621	0.429	0.009	0.499	0.004	14.04	1.225	1.162	0.05
3	16.16	0.164	0.429	0.005	0.517	0.004	17.34	0.576	1.2	0.011
4	18.65	0.202	0.426	0.008	0.497	0.009	14.04	1.716	1.14	0.026
5	16.66	0.622	0.424	0.007	0.496	0.008	14.51	1.245	1.164	0.019
6	19.22	0.689	0.427	0.007	0.498	0.005	14.25	1.144	1.166	0.25
7	20.25	0.017	0.426	0.008	0.496	0.001	14.04	1.716	1.145	0.08
8	16.86	0.517	0.419	0.005	0.494	0.012	15.18	1.236	1.178	0.22
9	17.52	0.621	0.516	0.009	0.614	0.007	15.89	0.697	1.18	0.01
10	17.12	0.524	0.511	0.012	0.61	0.011	16.22	0.854	1.193	0.32
11	16.98	0.711	0.517	0.033	0.598	0.052	13.54	0.429	1.156	0.23
12	16.13	0.621	0.507	0.013	0.606	0.008	16.16	1.965	1.19	0.035
13	20.78	0.586	0.494	0.005	0.673	0.014	26.58	0.829	1.35	0.015
14	24.08	0.59	0.562	0.012	0.735	0.02	22.47	1.248	1.28	0.02

s*S.D=standard deviation, where n=3

Scanning electron microscopy of the formulation[12]

The microcapsules were coated with gold- palladium by using sputter coater (POLARON SC 76430). After fixing the sample in individual stabs, Samples were examined for the surface and internal structure of the microcapsules by using scanning electron microscope which is given in fig.1.

Fig. 1: SEM images showing surface view of the formulation Containing sodium alginate and HPMC(K4M)

Percent drug loading and encapsulation efficiency

Formulation F5 showed lowest percentage of drug loading (32.265%) and lowest percentage of encapsulation efficiency (64.53%), similarly formulation F12 showed highest percentage of drug loading (35.675%) and highest encapsulation efficiency (71.29%).

In vitro wash-off test for mucoadhesion[4]

The mucoadhesive property of the microcapsules was evaluated by an *in vitro* adhesion testing method known as the wash-off method. Freshly excised pieces of intestinal mucosa (4x5cm) from sheep were mounted onto glass slides (3x1 inch) with cyanoacrylate glue. Two glass slides were connected with a suitable support. About 50 microcapsules were spread onto each wet rinsed tissue specimen, and immediately thereafter the support was hung onto the arm of a USP tablet disintegrating test machine. When the disintegrating test machine was operated, the tissue specimen was given a slow, regular up-and-down movement in the test fluid (400 ml) at 37 ºC contained in a 1000 ml vessel of the machine.

At the end of 1 hr, and at hourly intervals up to 10 hr, the machine was stopped and the number of microcapsules still adhering to the tissue was counted. The test was performed both in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.4 phosphate buffer). The data of test are shown in Table-4

Table 4: In vitro wash-off test for mucoadhesion

Formulation(F)	pH used	% of microcapsules adhering to the tissue at various time interval* in hours				
		1	2	4	6	8
1	7.4	97.3±1.2	62.96±2.12	44.56±2.0	22.22±1.8	5.66±1.7
2	7.4	88.22±2.3	52.33±1.8	28.12±1.5	11.23±2.5	-
3	7.4	82.56±1.8	53.65±2.2	27.62±1.9	10.99±2.1	-
4	7.4	79.78±1.9	59.13±1.5	32.16±1.9	19.28±1.5	5.11±1.8
5	7.4	78.22±1.7	51.22±1.2	28.11±1.8	9.33±1.7	-
6	7.4	81.23±1.8	53.5±1.5	27.8±1.9	11.23±1.5	-
7	7.4	80.1±2.2	58.22±1.5	28.2±2.5	14.7±1.8	-
8	7.4	81.22±1.8	57.56±2.5	29.1±2.8	15.22±2.1	
9	7.4	72.9±2.2	53.85±1.2	24.9±2.5	14.77±1.2	-
10	7.4	76.8±1.2	54.45±1.8	26.22±2.2	14.33±2.1	-
11	7.4	79.22±2.1	56.23±2.3	25.63±2.3	18.5±2.2	-
12	7.4	84.28±1.1	62.98±1.2	28.11±2.1	21.56±2.3	4.78±1.8
13	7.4	61.23±2.2	43.22±1.7	15.19±1.2	-	-
14	7.4	62.33±1.7	36.99±2.3	16.22±1.8	-	-

Mean ± S.D. , n=3

In vitro drug release study[13]

In vitro dissolution studies were carried out in Microcapsules at 37°C at 50 rpm with USP dissolution apparatus II ; 200mg metoprolol microcapsules were placed into the dissolution apparatus. The in vitro studies were performed at two different pH values; (i) 1.2(simulated gastric fluid), (ii) 7.4(simulated intestinal fluid). An accurately weighed sample responded in dissolution media consisting 900 ml of 0.1 N (pH 1.2) HCl and the dissolution was done for two hours. At the end of two hours, 28.062 gm of disodium hydrogen phosphate and 10.305 gm of potassium dihydrogen phosphate with 0.171 gm of sodium chloride were added to change the pH upto 7.4 and after that the study was performed for 12 hrs. The sample (5ml) was withdrawn at each hour interval and replaced with same volume of medium and the withdrawn samples were diluted if required and then estimated for metoprolol concentration at 274nm spectrophotometrically (by using UV/VISIBLE double beam spectrophotometer Shimadzu). Finally the drug content in all fluids were determined from the calibration curve of metprolol succinate. Drug release in cumulative percentage from different formulations versus time were compared which are given in fig.2-5.

Kinetics parameters were also obtained by mathematical processing of drug release data. Evaluation of the formulation variables in release rate constant K values, obtained from different groups of microcapsules which are given in table 5.

Permeability[14]:

It is useful parameter to study the micoparticulate which forms a gel layer. since the drug is dispersed in the hydrogel , the slopes of plot of Mt versus square root of time will yield d , the drug diffusion coefficient , where Mt is the amount released in time 't' . The results are reported in table-5

Drug release mechanism and release [15,16,17]

To describe kinetics of drug release from the controlled release microcapsules of, mathematical models, such as zero order, first order and Higuchi square root of time model , Korsmeyer model and peppas equation were used,when the release mechanism is not well known or when more than one type of release phenomena could be involved.

The criteria for selecting most appropriate model was based on goodness of fit test. Korsmeyer and peppas equation : $Mt/M\alpha = Kt^n$, where $Mt/M\alpha$ is the fraction of drug released at time t.K=constant incorporating of structural and geometric characteristic of controlled release device.n=diffusional release exponent indicative of release mechanisms.The best fit model was determined statistically employing comparision of correlation coefficients. The drug release rate from the formulations and the respective half lives were calculated. The preparation of graphs and statistical calculations were carried out with the help of computer.

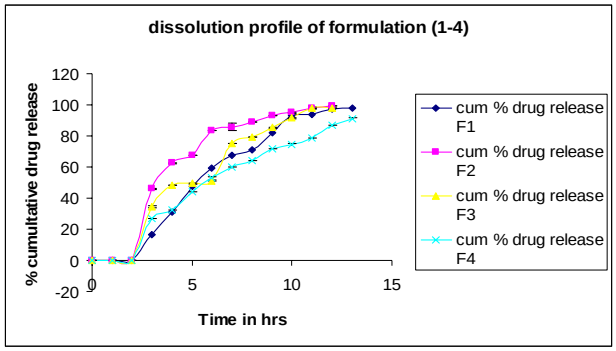
Table 5: Drug release mechanism and release constants from prepared microparticles

Formulation(F)	Drug diffusion coefficient	First order rate Constant (K)	'n' value in peppas plot
1	33.386	0.1688	0.7411
2	30.415	0.1891	0.3328
3	31.838	0.1751	0.4833
4	27.508	0.0853	0.5344
5	36.818	0.1762	0.8982
6	36.754	0.2128	0.6431
7	34.637	0.1791	0.6293
8	32.949	0.1645	0.7021
9	26.318	0.0972	0.3264
10	27.126	0.0839	0.4023
11	27.208	0.099	0.5157
12	26.502	0.097	0.4177
13	34.876	0.0934	0.9303
14	32.058	0.1759	0.873

Drug diffusion coefficient increased when concentration of sodium alginate increased in case of formulation containingHPMC,but in case of formulation containing carbopol 934P it was decreased with increase in sodium alginate concentration.F4&F12 showed slow and longest release (8hrs) making the two formulations most effective. Highiest percentage of swelling was observed in F1(179.56±5.8) and highest percentage of erosion was found in F14(9.2±1.8). Similarly Lowest percentage of swelling was observed in F 9(132.22±2.6) and lowest percentage of erosion was found in F4 (2.1±1}.pH 1.2 media.

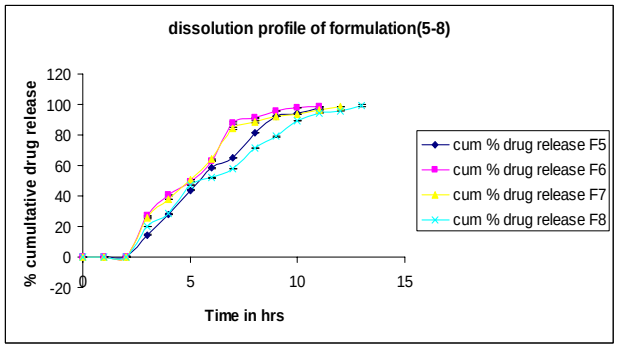
Infrared spectrum was taken in the Perkin Elmer (spectrum RX -1) by scanning the sample in potassium bromide (KBr) discs . before taking the spectrum of the sample , a blank spectrum of air back ground was taken . The sample of pure drug , pure polymer and the formulations containing both the drug and polymer were scanned and plotted with the help of bruker software.No interaction between the drug and polymer was found as evident from analysis of characteristics peaks.

Fig. 2: Dissolution profile comparison of formulations (1-4)



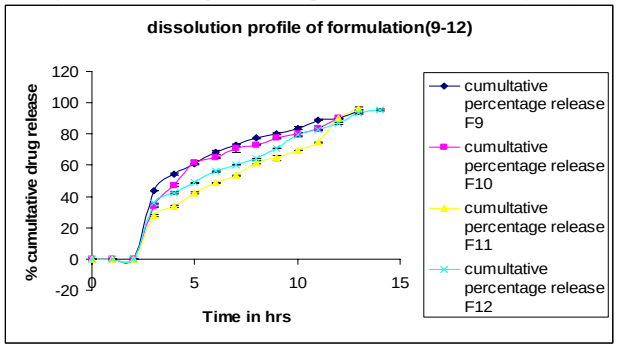
* Where dissolution is done first two hours in pH 1.2 then in pH 7.4 for rest of the time

Fig. 3: Dissolution profile comparison of formulation(5-8)



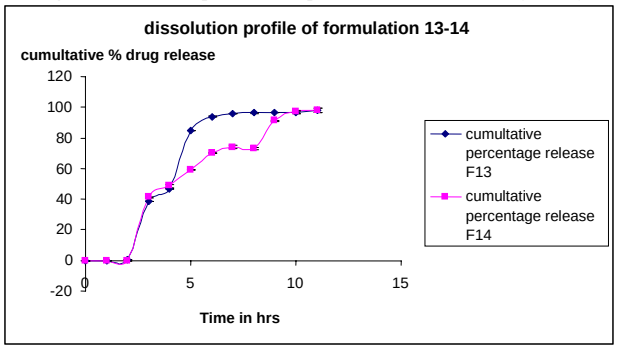
* Where dissolution is done first two hours in pH 1.2 then in pH 7.4 for rest of the time

Fig. 4: Dissolution profile comparison of formulation(9-12)



* Where dissolution is done first two hours in pH 1.2 then in pH 7.4 for rest of the time

Fig.5: Dissolution profile comparison of formulation(13-14)



*Where dissolution is done first two hours in pH 1.2 then in pH 7.4 for rest of the time9. Infrared Spectroscopy (I.R)

Statistical analysis

Anova was applied to F1,F2,F3,F4,F8,F12,F14 to see whether significant differences are there in release characteristics at $p \leq 0.05$ level due to variation in polymer concentrations and variation in polymer.Results showed all formulations were significantly different in release characteristics

Stability study

Microcapsules of formulations F4,F12 were put on short term stability study at 30^0c and 40^0c/75 RH for a period of three months. Microcapsules showed no significant changes in drug content and dissolution profile at 30^0c but significant changes were observed at 40^0c.So microcapsules needs storing in a dry place at a temperature not exceeding30^0C.

CONCLUSION

Microcapsules were spherical in shape and of good flow properties with mucoadhesion upto 8 hours.carbopol was most effective to control the release of the drug. Drug release mostly followed Higuchi equation and anamolous transport.There was no interaction between drug and excipients. Microcapsules were stable at 30^0C in dry atmosphere.

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