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PREPARATION AND EVALUATION OF MUCOADHESIVE MICROCAPSULES OF METOPROLOL TARTRATE

R. Sunitha*[1], M. Lakshmi Surekha[1], R. Padma[1] and M. Murali Krishna[1]

A. M. Reddy Memorial College of Pharmacy, *Narasaraopet, Guntur (Dt),* Andhra Pradesh, India.

Corresponding Author: R. Sunitha

A. M. Reddy Memorial College of Pharmacy, *Narasaraopet, Guntur (Dt),* Andhra Pradesh, India.

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ABSTRACT

The present research work was aimed at development and optimization of metaprolol tartrate mucoadhesive microcapsules to avoid first pass metabolism and to improve the therapeutic efficacy in the treatment of hypertension and angina pectoris. Metoprolol tartrate microcapsules with a coat consisting of alginate and mucoadhesive polymers such as sodium carboxy methyl cellulose, poly vinyl alcohol, carbopol 934, and HPMC were prepared by an ionotropic gelation technique. The microcapsules were prepared and found to be discrete, free flowing, spherical to near spherical and without aggregation. The microencapsulation efficiency was found to be in between 72.03 to 89.02%. The percent yield, drug entrapment and drug content in all formulations were good. The average particle size was found to be in the range of 817 to 920µm. A percentage of moisture loss was calculated for all the prepared metaprolol tartrate microcapsules and was found to be within limit. The shape and surface characteristics were determined by scanning electron microscopy (SEM) which depicted the spherical nature and nearly smooth surfaces of the microcapsules. *In vitro* release studies in pH 7.2 phosphate buffer indicated non-Fickian or anomalous type of transport for the release of metaprolol tartrate from the microcapsules. Among all formulations metoprolol microcapsules containing sodium alginate and carbopol 934 showed higher encapsulation efficiencies, good flow property and maximum prolongation of drug release and goo mucoadhesion properties.

KEYWORDS: Metaprolol tartrate, ionotropic gelation, *in-vitro* wash off test, microcapsulation efficiency.

INTRODUCTION

The novel design of an oral controlled drug delivery system should be intended to achieving an expected and increased bioavailability of drug and it also important for either to achieving the desired level of therapeutic activity required for a new drug entity or to extend life cycle of an existing drug through improved performance. From the last few decades much research works has been done on mucoadhesive microcapsules for various routes of drug administration[1] Microencapsulation and the resulting microcapsules (by various polymers) have been accepted as a process to achieve controlled release and drug targeting.[2] Mucoadhesion is used in the design of drug delivery systems to prolong the residence time of the dosage form at the site of application and to facilitate intimate contact of the dosage form with the original absorption surface to enhance the bioavailability of the drug.[1]

In general oral route is not suitable for drugs which are susceptible to gut and/or hepatic metabolism and also for drugs which cause GI side effects. So, mucoadhesive dosage forms are being developed which avoid the disadvantages of oral route.[3] The bioavailability and duration of action of drugs administered by these routes are increased by use of the principle of mucoadhsion.[4] The objective of this study was to develop, characterize, and evaluate mucoadhesive microcapsules of metoprolol tartrate using various mucoadhesive polymers. Thus the microcapsules were prepared by using ionotropic gelation technique. This study describes the development and evaluation of Mucoadhesive microcapsule of drug for oral controlled release.[5]

MATERIALS AND METHODS

Metoprolol tartrate was a gift sample from M/S Mecloids industries, Mumbai. Hydroxy propyl methyl cellulose E-50 (rolex), carbopol 934 (S.D.Fine chem.). All other reagents (hydrochloric acid, potassium dihydrogen phosphate, sodium hydroxide) used in the study of analytical grade.

Instrumentation

Double beam U.V. visible spectrophotometer (Cyber lab), electronic weighing machine (Schimadzu, Ax-200), Hot air oven (Thermolabs), sieves (jayant scientific industries), Glass ware (Borosil), Tablet disintegration test machine I.P,U.S.P,B.P, Standard (Cambell),

mechanical stirrer universal motors (Remi), Dissolution test apparatus (Lab india).

Methods

Preparation of Microcapsules

Ionic gelation process[7]

The ionic gelation process was used to prepare microcapsules. Sodium alginate (1.0 g) and Mucoadhesive polymer viz..., carbopol (1.0 g), sodium CMC (1.0 g), HPMC (1.0 g), Polyvinyl alcohol(1.0 g), were dissolved in purified water (32 ml) to form a homogenous polymer solution. The core material, metoprolol tartrate (100 mg) was added to the polymer solution and mixed thoroughly to form a smooth viscous dispersion. The resulting dispersion was then added manually dropped into 10% w/v of 40 ml calcium chloride solution through a syringe rigid microcapsules. The microcapsules were collected by decantation and the product thus separated was washed repeatedly with water and dried at 45^0C for 12 hours.

Table 1: Composition of microcapsules.

S.NO	Metoprolol tartarate (mg)	Formulation code	Core : Coat ratio	Coat composition
1	100	F1	1:1	Na-alginate :Carbopol934
2	100	F2	2:1	Na-alginate :Carbopol934
3	100	F3	3:1	Na-alginate :Carbopol934
4	100	F4	1:1	Na-alginate: Sod CMC
5	100	F5	2:1	Na-alginate: Sod CMC
6	100	F6	3:1	Na-alginate: Sod CMC
7	100	F7	1:1	Na-alginate: HPMC
8	100	F8	2:1	Na-alginate: HPMC
9	100	F9	3:1	Na-alginate: HPMC
10	100	F10	1:1	Na-alginate: PVA
11	100	F11	2:1	Na-alginate: PVA
12	100	F12	3:1	Na-alginate: PVA

Evaluation of Microcapsules

Size distribution and Size analysis[7]

For size distribution analysis, different sizes in batch were separated by sieving, using a range of standard sieves. The amount retained on different sieves was weighed. The mean particle size of the sample was calculated by the formula.

Davg =**Σ**dn/**Σ**n

Where **n** is the frequency weight and **d** is the mean diameter size.

Determination of Flow Properties[8]

Angle of repose, Carr's index, Bulk density and Hausner's ratio were determined to assess the flow ability of the prepared microcapsules.

Determination of moisture Content[12]

The formulations were subjected to moisture content study by placing the microcapsules in desiccators for 24hrs then the moisture content was determined.

Surface Accumulation Study[7]

The study was conducted to estimate the amount of drug present on the surface of the formulation which may show immediate release in the dissolution media. 100mg of formulation were suspended in 100ml of phosphate buffer (p^H 7.2). The samples were shaken vigorously for 30 minutes by hand shaking. The amount of the drug leached out from the surface was analyzed spectrophotometrically at 275nm. Percentage of drug released with respect to entrapped drug in the sample was recorded.

Drug content Evaluation[12]

About 100mg of metoprolol was accurately weighed and transferred to 100ml volumetric flask. It was dissolved in distilled water and the solution was made upto the volume with distilled water. Each ml of this stock solution contained 1000mcg of metoprolol. 10ml of stock solution was taken and make up with 100ml distilled water (100mcg/ml). From this solution 10ml was taken and make up with 100ml of water (10mcg/ml). From that 2, 4, 6, 8,10mcg/ml solution are prepared. Further dilutions were made using pH 7.2 phosphate buffers. The absorbances of the above solutions were measured at 275nm using U.V.Visible spectrophotometer (pH 7.2 phosphate buffer was prepared as per I.P). The method was validated for linearity, accuracy and precision. The method obeyed Beer's law in the concentration range.

Encapsulation efficiency[12]

Estimated percent drug content was determined from the analysis of 100 mg microcapsules and the theoretical percent drug content was calculated from the employed coat : core ratio in the formulation of microcapsules.

Microencapsulation efficiency was calculated by using formula:

Microencapsulation efficiency = Estimated percent drug content / Theoretical percent drug/Content × 100

Percentage yield of the prepared microcapsules was calculated by using the formula

% Yield = amount of microcapsules obtained / theoretical amount

In Vitro release Studies[7,10]

Microcapsules containing equivalent to 50 mg of metoprolol tartarate were packed in '5' size hard gelatin capsule and subjected to in vitro drug release studies. Release of metoprolol tartrate from the capsule was studied in phosphate buffer p^H 7.2 (900 ml) using a united states pharmacopoeia (USP) XXIV 8-station dissolution rate test apparatus (Lab India) with a rotating paddle stirrer at 100 rpm and 37±0.5 ^{0}C samples of dissolution fluid were withdrawn at different time intervals and were analyzed at 275 nm. Metoprolol tartrate content determined using a cyberlabs UV-1700 double beam spectrophotometer (Cyberlab Corporation, Japan). The dissolution studies of the following marketed ER formulation of metoprolol tartrate were also conducted to compare with formulated microcapsules.

Brand name : MET XL
B.NO : 06688
Mfd. Date : 07/20008
Exp. Date : 06/2010
Mfd. By : Ajanta pharma Ltd.

Release kinetics[12,17]

Data obtained from the dissolution studies was fitted to various kinetic equations. Where kinetic model used were a zero order equation ($Q = Q_0 - K_0 t$), first order equation ($\text{Ln } Q = \text{Ln } Q_0 - K_0 t$) and Higuchi equation ($Q = K_h t^{½})^{½}$), Korsemeyer – peppas equation log Q_t vs log t, where Q_t is the cumulative amount of drug released at time t and Q_0 is the intial amount of the drug present in the microcapsules. K_0 is the zero order release rate constant , K_1 is the first order release rate constant and K_h is the diffusion rate constant.

In-vitro Wash – off Test[8,10,11]

The mucoadhesive property of the microcapsules was evaluated by invitro adhesion testing method known as in vitro wash off test method. Freshly excised pieces of intestinal pieces of mucosa (2×2cm) from sheep were mounted onto glass slides (3×1 inch) with cyanoacrylate glue. Two glass slides were connected with a suitable support. A bout 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 at 37 ^{0} C contained in a 1 L vessel of the machine. At the end of 30 minutes, at the end of 1 hr and at hourly intervals upto 8hrs, the machine was stopped and the number of microcapsules still adhering to the tissue was counted. The test was performed at both gastric p^H (0.1N HCl, p^H 1.2) and intestinal p^H (phosphate buffer, p^H 7.2).

STABILITY STUDIES[12]

An ideal controlled release dosage form apart from other requirements should provide consistency in drug release throughout its shelf life. The stability of drug release from mucoadhesive microcapsules developed in this investigation was studied under varying storage conditions. The formulation was filled into hard gelatin capsules (size '0'). The capsules was later packed in screw capped bottles and stored at

(1) 4 ^{0}C
(2) Room temperature
(3) 45 ± 2 ^{0}C

All the products are stored for 1 month after the stotage period the release of metoprolol from the stored product was studied.

IR Studies

The metoprolol tartrate, sodium alginate and optimized formulations are subjected to IR studies to determine the Drug and polymer incompatibilities.

RESULTS AND DISCUSSIONS

Microcapsules of metoprolol tartrate with a coat consisting of alginate and a mucoadhesive polymer – carbapol 934, sodium CMC, HPMC, and PVA in 1:1, 2:1, 3:1 ratio were prepared by orifice ionic gelation method. By this method, microcapsules were prepared in environment free organic solvents, by dropping a mixture of colloidal polymer dispersion, the drug metoprolol tartrate and mucilage of sodium alginate in calcium chloride solution which acted as a counter ion. The droplets instantaneously formed into gelled spherical beads due to cross linking of calcium ion with the sodium ion sufficiently hardened and then filtered and dried. The microcapsules thus formed using four different polymers showed significant results on evaluation. The size of the microcapsules ranged between 817 to 920 µm. The average particle size was on the highest side with carbapol polymer followed by PVA, sodium CMC and HPMC.

Rheology determination of microcapsules

The rheological parameters like angle of repose, carr's index and Hausner's ratio confirms very good flow and packing properties. Thus, the microcapsules if tableted or encapsulated requires less amount of lubricants and ensures low production cost leading to its feasibility for large scale production.

Table 2: Evaluation of microcapsules.

Formulation	Hausner's Ratio	Carr's index	Angle of repose (^{0})	% moisture content	Particle size (µm)
F1	1.17	14.7	13.7	0.03	920
F2	1.12	13.6	14	0.04	916
F3	1.13	12.24	14.3	0.04	9.7
F4	1.23	19.1	16.4	0.03	852
F5	1.08	14.13	16.9	0.03	846
F6	1.06	16.32	17.2	0.04	836
F7	1.19	16.6	18.4	0.03	834
F8	1.14	12.3	20.7	0.05	830
F9	1.15	13.2	21.4	0.04	817
F10	1.18	15.58	14.9	0.03	901
F11	1.02	16.4	15.7	0.04	888
F12	1.29	14.47	15	0.04	890

Percent Yield, Drug Content and Encapsulation Efficiency of Metoprolol Tartrate Loaded Microcapsules

The percent yield, drug entrapment and drug content in all formulations were determined. The results are summarized in table 3. The microencapsulation efficiency of all the formulations was in the range of 72.03% to 89.02%. And the production yield was in the range of 92.66 to 98.86%. Comparatively high entrapment efficiency of the drug with carbapol 934 formulation over other polymers confirms it being more rigid among the four.

Table 3: Percent Yield, Drug Content and Encapsulation Efficiency of metoprolol tartrate Loaded Microcapsules.

Formulation	Surface accumulation with respect to entrapped drug (%)	Microencapsulation efficiency (%)	Production yield (%)
F1	1.565	84.31	98.86
F2	1.728	86.52	94.66
F3	1.963	89.02	93.24
F4	2.875	73.01	97.76
F5	2.725	74.04	93.72
F6	3.001	78.63	92.86
F7	3.25	72.03	95.86
F8	3.33	73.46	93.83
F9	3.425	76.5	92.64
F10	2.005	80.32	95.68
F11	2.3	81.92	94.72
F12	2.015	84.94	92.66

In vitro wash-off test of microcapsules

The mucoadhesion of the selected microcapsules were studied by *in vitro* wash off test. The microcapsules with a coat consist of alginate and mucoadhesive polymer exhibited good mucoadhesive properties in the *in vitro* drug release profile. The wash off was faster at intestinal p^H (7.2) of the medium was critical for the degree of hydration, solubility and mucoadhesion of the polymers. The rapid wash off was observed at this p^H is due to ionization of carbonyl and other functional groups in the polymers at this p^H(7.2), which increases their solubility and reduces adhesive strength. The results of wash off test indicated that the microcapsules had very good mucoadhesive properties.

Table 4: Invitro Wash-Off Test.

Formulation	No. of microcapsules adhering to tissue after (hours)									
	0.1N HCl, p^H 1.2					Phosphate buffer, p^H 7.2				
	1	2	4	6	8	1	2	4	6	8
F1	50	50	50	50	50	50	50	49	49	40
F2	50	50	49	49	49	50	50	49	48	39
F3	50	50	48	48	48	50	49	48	48	38
F4	50	48	46	45	45	49	46	45	43	36
F5	49	48	46	44	43	45	44	41	40	29
F6	49	47	46	45	42	46	43	40	39	25
F7	48	46	45	44	42	42	39	36	35	25
F8	47	46	45	43	41	40	37	35	34	24
F9	48	46	42	40	39	44	40	30	32	20
F10	50	50	49	49	48	46	44	43	42	35
F11	50	48	48	47	47	45	43	42	40	3
F12	50	49	48	48	46	46	44	42	41	30

In-vitro release studies

Metoprolol tartrate release from the microcapsules was studied in phosphate buffer of p^H 7.2 for a period of 12 hours. Metoprolol tartrate release from all the microcapsules was slow and release over extended period of time. Release depends on composition of the coat i.e., the mucoadhesive polymer present in the coat and size of the microcapsules. Microcapsules of alginate – HPMC gave relatively fast release when compared to others. The order of increasing release rate observed with various microcapsules was

Alginate- HPMC > Alginate-sodium CMC > Alginate-PVA > Alginate-carbapol.

In case of alginate- carbapol formulations, F1 formulation containing alginate- carbopol (1:1), showed 97.8% of drug release over a prolonged period of 12 hours. F10 formulation containing alginate-PVA (1:1) showed 98.6% of drug release over a period of 12 hours. Whereas remaining formulations released approximately 98% of drug within below 10hours. When marketed formulation is subjected to invitro studies it released 98.89% of metoprolol tartrate in 8hours.from these results, we conclude that F1 formulation containing alginate-carbopol 934(1:1) is better formulation because it showed prolonged of drug release upto 12hours released almost total amount in 12hours.

The in-vitro release data were treated with zero order, first order, higuchi and korsmeyer-peppas equation as shown in table 6. as R^2 values of zero order kinetics shown greater values than R^2 values of first order kinetics, it is evident that drug release from the metoprolol tartrate mucoadhesive microcapsules followed zero order release.

Table 5: Dissolution Profiles Of Mucoadhesive Microcapsules Of Metoprolol Tartrate.

% CUMULATIVE DRUG RELEASE												
Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	22.41	22.31	22.42	21.13	24.26	23.32	24.41	24.5	25.6	23.7	26.23	25.62
2	28.64	31.56	32.72	32.46	33.72	34.62	36.89	35.7	36.52	26.72	28.62	29.42
3	32.54	36.42	38.62	39.64	36.7	39	40.61	44.72	46.89	38.43	39.49	39.36
4	36.42	39.3	42.4	44.71	48.68	50.42	51.61	53.76	57.43	40.02	42.34	44.45
5	42.51	44.64	46.81	48.73	59.92	67.89	68.76	69.92	70.62	45.76	46.84	53.78
6	50.62	57.43	58.93	56.82	67.42	78.62	76.43	78.64	86.74	52.89	58.62	68.34
7	54.86	67.92	69.28	68.34	79.65	88.2	86.24	88.74	96.41	64.32	66.42	72.49
8	62.51	68.43	78.66	76.43	84.38	96.32	92.31	97.16		69.71	76.82	86.73
9	73.9	79.4	89.4	88.8	97.8		97.6			78.62	89.45	97.3
10	84.5	85.2	96.2	98.6						84.39	97.5	
11	92.34	96.44								98.6		
12	97.8											

In-vitro drug release kinetic studies of microcapsules

The release data was analyzed according to different kinetic equation. All formulations followed first order kinetics. And formulations seems to be fit in Higuchi square root kinetic model and formulations have diffusion controlled release pattern which is dependent on concentration of release retarding polymer with process variables epitomized in table 6**.**

Table 6: Release Kinetics Of Mucoadhesive Microcapsules Of Metoprolol.

FORMULATION	CORRELATION COEFFICIENT VALUES (R^2)				No.
	Zero order	First order	Higuchi	Korse meyer peppas	Korse meyer peppas
F1	0.976	0.769	0.925	0.9218	0.6059
F2	0.975	0.807	0.9493	0.9547	0.6086
F3	0.977	0.827	0.9399	0.9546	0.629
F4	0.977	0.710	0.9416	0.969	0.6425
F5	0.981	0.776	0.9548	0.964	0.6448
F6	0.984	0.871	0.9458	0.9681	0.7058
F7	0.972	0.892	0.9674	0.9772	0.6598
F8	0.982	0.858	0.9647	0.9864	0.6791
F9	0.985	0.843	0.9529	0.9805	0.6896
F10	0.976	0.684	0.9414	0.9437	0.6091
F11	0.972	0.765	0.9297	0.9194	0.5962
F12	0.979	0.775	0.9377	0.9389	0.6332

To examine the release mechanism of metoprolol from the microcapsules the result were analyzed according to the Korse meyer-Peppas equation.

$$M_t / M\infty = K . t^n$$

Where $M_t / M\infty$ is the fractional drug release at time t, k is a kinetic constant incorporating structural and geometric characteristic of the drug / polymer system [device], n is the diffusional exponent that characterizes the mechanism of drug release. In this formulation the value of n which is greater than 0.5, in this formulation the release is non Fickian that is not depend upon the concentration gradient. If value of n is less than 0.5, so this release is the Fickian.

Stability Studies

Drug stability is a key quality attributed to be considered during the product development process. Forced degradation studies, chemical stability of the drug molecule under various stress conditions, and well designed degradation model systems can serve as a predictive tool to probe the long–term drug stability in actual formulations. The general practices for conducting forced degradation studies include stressing the bulk drug under accelerated temperature / humidity conditions alone and in the presence of excipients, as well as exposing the drug solution to acid / base, heat, light, hydrogen peroxide and radical indications to probe the intrinsic sensitivity of the drug molecule to hydrolytic, thermal, photolytic and oxidative degradative reactions.

Accelerated stability studies were conducted on metoprolol tartrate formulations containing alginate–carbapol 934 (1:1) and on metoprolol tartrate formulations containing alginate PVA(1:1). As described in table 7 there was no significant change in drug content of both formulations stored at 4^0c, room temperature and 45^0c after 4 weeks of study. The cumulative percentage drug release of metoprolol tartrate from microcapsules stored at different storage conditions during 0 to 4 weeks showed no significant effect of temperature of storage on the drug release.

Table 7: Stability studies of f1, f10 of metoprolol mucoadhesive microcapsules.

Formulation	Time (weeks)	%drug content		
		4^0c	Room Temperature	45^0c
F1	0	99.21	99.14	99.16
F1	1	98.66	98.52	98.41
F1	2	98.44	97.49	97.82
F1	3	97.89	97.32	97.44
F1	4	97.26	97.24	97.16
F10	0	99.18	99.12	99.19
F10	1	98.48	98.68	98.26
F10	2	98.36	98.55	97.79
F10	3	97.76	97.41	97.56
F10	4	97.12	97.22	96.92

IR STUDIES

From the infrared spectra, it is clearly evident that there were no interactions of the drug. IR spectrum of the pure drug shows that the characteristic peaks at 3341.78cm^{-1} and 1112cm^{-1} due to O-H stetching and C-O-C stetching of hydroxyl and ether linkage groups respectively exhibited peaks at 3438.89cm^{-1} and 1029 cm^{-1} due to hydroxyl and either linkage stretching at 2925.45cm^{-1} due to aromatic C-H group this confirms the undisturbed structure of the drug with the polymers used in the formulations. Hence, the formula for preparation of metoprolol tartrate mucoadhesive microcapsules can be

reproduced in the industrial scale without any apprehension of possible drug – polymer interactions.

CONCLUSION

Large, spherical and free flowing metoprolol tartrate microcapsule with a coat consisting of alginate and a mucoadhesive polymer (carbopol 934, sodium CMC, HPMC, PVA) were prepared successfully by orifice-ionic gelation process. The yield and entrapment efficiency were high for all the formulations. The prepared microcapsules exhibited good mucoadhesive properties as observed in wash-off test. Metoprolol release from these mucoadhesive microcapsules was slow extended over long period of time and depended on the mucoadhesive polymer contained in the coat (drug release was diffusion controlled followed kinetics). Among all formulations metoprolol microcapsules containing **sodium alginate and carbopol 934** showed higher encapsulation efficiencies, good flow property and maximum prolongation of drug release and good mucoadhesion properties.

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