

Formulation and Evaluation of Oral Mucoadhesive Multiparticulate System Containing Metoprolol Tartarate: An *In Vitro* – *Ex Vivo* Characterization

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Abstract: The aim of the present study was to prepare mucoadhesive multiparticulate system for oral drug delivery using ionic gelation technique. Microspheres composed of various mucoadhesive polymers including HPMC of various grades like K4M, K15M, K100M, E50LV, Carbopol of grades 971P, 974P and polycarbophil were prepared. In this technique cross linking of sodium alginate with calcium chloride was done which retarded the release of drug from the mucoadhesive polymer. In the present work Metoprolol tararate was used as a model drug. Interaction studies performed using FTIR spectroscopy revealed that there was no drug to polymer interactions. The preliminary mucoadhesive strength studies performed for various polymers using rotating cylindrical method showed that HPMC had greater mucoadhesive properties than carbopol and polycarbophil. Microspheres so prepared were discrete, bulky, free flowing and showed an average encapsulation efficiency ranging from 50-60%. Particle size of the microspheres, as determined by the optical microscopy was found to be between 400-650 μ m. The prepared formulations also exhibited a good mucoadhesive strength which was determined in *in vitro* conditions through falling film technique and was compared with *ex vivo* studies. The microspheres so prepared also exhibited a good swelling index which confirmed the strong mucoadhesive property of the formulation. Metoprolol release from the multiparticulate system was regulated and extended until 12 hours and exhibited a non fickian drug release kinetics approaching to zero order, as evident from the release rate exponent values which varied between 0.57 to 0.73. The stability studies performed on the optimized batches at 40°C / 75% RH for 90 days indicated no significant change in the physicochemical properties.

Keywords: Gastrointestinal delivery, mucoadhesion, ionic gelation, multiparticulate system.

INTRODUCTION

Oral controlled release systems continue to be the most popular ones among all the drug delivery systems. It offers several advantages over the conventional systems like better plasma level profile, lower dosing and toxicity and many more to list. The problem frequently encountered with controlled release dosage forms is its inability to increase the residence time of the dosage form in the stomach and proximal portion of the small intestine [1]. This may be due to the rapid gastrointestinal transit phenomenon of the stomach, which may consequently diminish the extent of absorption of many drugs since almost most of the drug entities are mostly absorbed from the upper part of the intestine [1]. Therefore it would be beneficial to develop a sustained release formulation which remain at the absorption site for an extended period of time. Several approaches have been immersed to prolong the gastric residence time of the dosage forms at the absorption site and one of these is the development of oral controlled release bioadhesive system [2].

Metoprolol tartarate is a β -selective adrenergic blocking agent and is prescribed widely in diverse cardiovascular diseases like hypertension, angina pectoris, arrhythmias and myocardial infarctions. Administration of conventional tab-

lets 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 [3]. The maintenance of a constant plasma concentration of a cardiovascular drug is important in ensuring the desired therapeutic response. Since the half life of metoprolol tartarate is 3-4 hours so multiple doses of the drug are needed to maintain a constant plasma concentration for a good therapeutic response and improve patient compliance [3]. It has been reported that metoprolol tartarate absorption in the duodenum and jejunum is directly proportional to dose availability [3-5]. Hence the objective of the study was made to develop and optimize gastrointestinal mucoadhesive multiparticulate system of metoprolol tartarate using various mucoadhesive polymers like HPMC, carbopol and polycarbophil of various grades. This will in turn increase the residence time of the drug at the absorption site, increasing the bioavailability of the drug and thus decreasing the dosing frequency of the drug.

In the present study multiparticulate system was preferred as a formulation over conventional tablet or capsule formulations as it has several advantages like, it increases the surface area of the formulation exposed to the absorption site thus increasing the absorption of drug and decreasing the dosing frequency of the drug.

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MATERIALS AND METHOD

Materials

Metoprolol tartarate was a gift sample from Ipca laboratories Ltd. (Ratlam, India), HPMC K4M, K15M, K100M, E50LV were gifted by Colorcon Asia Pvt. Ltd. (Goa), carbopol 971P, 974P, polycarophil were gifted by Noveon Pharmaceuticals Pvt. Ltd.(Cleveland, USA) and all the other reagents used were of analytical grade.

Method

Preparation of Microspheres by Ionic Gelation Technique [6]

In this technique cross linking of sodium alginate is done with calcium chloride solution to release the drug in a con-

trolled manner. Chemically, alginates are anionic block copolymer consisting monomers of d-mannuonc acid joined together by 1-4 glycosydic linkages. Bivalent alkaline earth metals like Ca²⁺ undergoes ionic interaction with COOH moiety of sodium alginate and results in cross linking of sodium alginate. Microspheres were prepared by using the technique in which sodium alginate in varied quantities as mentioned in Tables 1 and 2 was dissolved in 25ml of purified water. Secondly mucoadhesive polymer was slowly added to the above solution with continuous stirring to form a homogenous solution. High viscosity polymers were dissolved in aqueous sodium alginate solution by sonicating the mixture for 20 minutes. The drug substance metoprolol tartarate was then added to the above polymer-alginate mixture and stirred thoroughly to form the clear solution. The drug-polymer mixture was then added dropwise into the 5% cal-

Table 1. Formulation Composition, Production Yield and Encapsulation Efficiency of Microspheres

Quantities in (mg)	Batches											
	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12
Metoprolol tartarate	100	100	100	100	100	100	100	100	100	100	100	100
Sodium alginate	100	500	900	100	500	900	100	500	900	100	500	900
HPMC E50LV	300	300	300	-	-	-	-	-	-	-	-	-
HPMC K4M	-	-	-	300	300	300	-	-	-	-	-	-
HPMC K15M	-	-	-	-	-	-	300	300	300	-	-	-
HPMC K100M	-	-	-	-	-	-	-	-	-	300	300	300
Production yield (%)	91.07	82.45	83.78	79.41	74.54	74.67	70.54	69.64	69.78	67.51	65.01	65.14
Actual Drug content (%)	65.22	63.45	62.24	63.87	60.29	62.31	67.12	66.11	60.12	61.29	65.24	62.34
Encapsulation efficiency (%)	55.14	60.51	61.21	63.24	63.85	64.51	64.32	65.21	65.64	65.64	66.07	66.61

Table 2. Formulation Composition, Production Yield and Encapsulation Efficiency of Microspheres

Quantities in (mg)	Batches									
	A13	A14	A15	A16	A17	A18	A19	A20	A21	
Metoprolol tartarate	100	100	100	100	100	100	100	100	100	
Sodium alginate	100	500	900	100	500	900	100	500	900	
Carbopol 974P	300	300	300	-	-	-	-	-	-	
Carbopol 971P	-	-	-	300	300	300	-	-	-	
Polycarophil	-	-	-	-	-	-	300	300	300	
Production yield (%)	87.20	86.14	87.45	84.45	83.79	84.0	75.14	75.59	76.85	
Actual Drug content (%)	60.12	63.45	66.29	61.09	59.16	63.33	62.21	60.24	62.23	
Encapsulation efficiency (%)	55.14	60.51	61.21	63.24	63.85	64.51	64.32	65.21	65.64	

cium chloride solution using an insulin syringe. The added droplets were then retained in the calcium chloride solution for 25 minutes to complete the curing reaction and to produce spherical and rigid microspheres. The microspheres so prepared were collected by decantation technique, washed repeatedly with deionized water and dried at 45°C for 12 hours. Various formulations prepared using varied alginate to mucoadhesive polymer ratios in order to sustain the release of the drug for 12 hours are listed in Tables 1 and 2.

Preliminary Mucoadhesive Strength Determination of Various Polymers

Rotating Cylinder Method [7]

In this method 50 mg of the mucoadhesive polymer was compressed in to 5.0 mm diameter disc keeping the compression pressure same for every polymer. The discs so prepared were adhered to the freshly excised gastric mucosa of male Albino rats by just hydrating the discs with little amount of water and then placing them on the mucosal tissue. This whole system was then adhered on the stainless steel cylinder of USP XXVI apparatus (type 4) with the aid of the cyanoacrylate glue and the cylinder was immersed in the dissolution jar filled with phosphate buffer pH 7.2 at 37°C and was rotated at 125 rpm as shown in Fig. (1). The time required for the detachment, disintegration or erosion of the test discs was monitored and reported in Table 3.

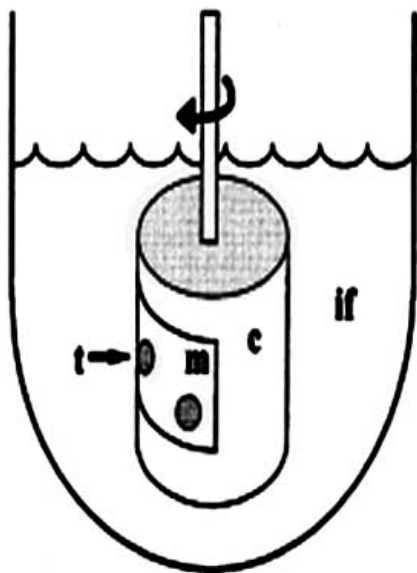


Fig. (1). Schematic presentation of the test system used to evaluate the mucoadhesive properties of tablets based on various polymers. c, cylinder; if, intestinal fluid; m, rat mucosa; t, tablet.

Interaction Studies

FT-IR Spectroscopy

The interaction studies between the drug and various mucoadhesive polymers was done by using the FTIR spectroscopy. Infrared spectra of metoprolol tartarate and various mucoadhesive polymers were taken individually first and then compared with the spectra of the formulations in which the drug was matrixed with various mucoadhesive polymers.

Characterization of Microspheres [8]

Yields of Production

The production yields of microspheres of various batches were calculated using the weight of finally dried microspheres with respect to the initial total quantity of the drug and polymer used for preparation. Percent production yields were calculated as per the formula mentioned below, and reported in Tables 1 and 2.

$$\text{Production yield} = \frac{\text{Practical mass (microspheres)} \times 100}{\text{Theoretical mass (polymer + drug)}}$$

Actual Drug Content and Encapsulation Efficiency

Actual drug content and encapsulation efficiency of the microsphere formulations were determined by following indirect method. In this method the calcium chloride solution in which microspheres were prepared was estimated for its drug content through UV spectroscopy by taking absorbance of the solution at 274 nm. The amount of drug in calcium chloride solution which is ultimately the amount of unloaded drug was thus determined. Amount so found was deducted from the total amount of drug added initially to obtain the actual quantity of drug which is encapsulated in the microsphere formulation. The quantity so obtained was subjected to the formula given below to find the encapsulation efficiencies of various formulations which were then reported in Tables 1 and 2.

$$\text{Percent encapsulation efficiency} = \frac{\text{Actual drug content (mg)} \times 100}{\text{Total mass of microspheres}}$$

Shape and Size of Microspheres

The shape and size of microspheres of the optimized batches of HPMC K4M and Carbopol 971P was determined through optical microscopy as shown in Fig. (2) and were reported in Table 4.

Swelling Determination of Microspheres

Amount of swelling incurred by the microspheres was determined by adopting the method wherein the microsphere was allowed to settle on the glass slide and the diameter (initial diameter) of the same was determined using the optical microscopy. Then the sphere was wetted by adding a little amount of water over the glass slide, allowing it to immerse in the water and the diameter of this immersed microsphere was redetermined (final diameter) after 20 and 60 minutes respectively. The percent swelling was then calculated using the formula mentioned below and the results were reported in Table 5.

$$\% \text{ Swelling} = \frac{\text{Final diameter} - \text{initial diameter}}{\text{Initial diameter}} \times 100.$$

In Vitro Mucoadhesive Strength Determination

Falling Liquid Film Technique [9]

In this technique male Albino rats (200-250g) were sacrificed and their intestine rejoin was isolated. Then from the intestine rejoin, jejunum part was separated and cut longitudinally. This separated portion was placed on the semi cylindrical Plexiglas support as shown in Fig. (3) and was washed

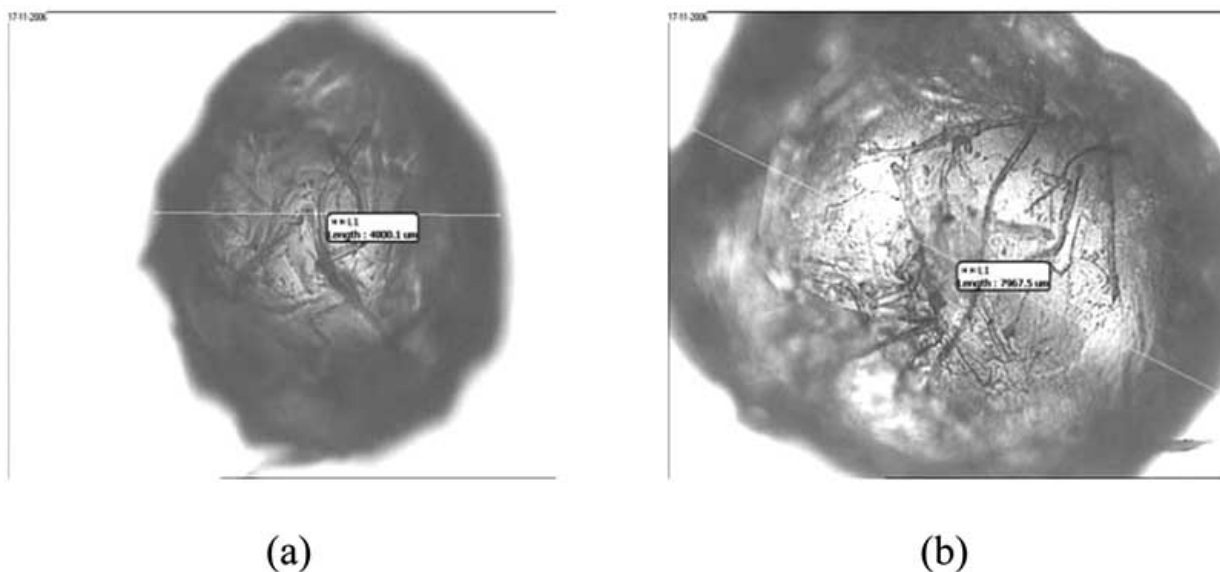


Fig. (2). Microscopic view of microspheres prepared by ionic gelation technique. (a) HPMC k4M microspheres, (b) Carbopol 971P microspheres

Table 3. Time of Mucoadhesion of Various Polymers on Rat Stomach Mucosa Determined Via Rotating Cylinder Technique

Polymer	Time in hours \pm S.D.
HPMC E50LV	7.20 \pm 0.15
HPMC K4M	18.30 \pm 0.10
HPMC K15M	24.48 \pm 0.17
HPMC K100M	25.50 \pm 0.14
Carbopol 971P	15.10 \pm 0.15
Carbopol 974P	19.45 \pm 0.20
Polycarbophil	17.14 \pm 0.12

Table 4. Size and Shape of Microspheres as Determined by Optical Microscopy

Batch	Size	Shape
A6	734.01 μ m	almost spherical
A18	480.00 μ m	almost spherical

Table 5. Percent Swelling of Microspheres After 20 Minutes and 60 Minutes Interval

Batch	Percent swelling	
	At 20 minutes	At 60 minutes
A6	48.56	85.32
A18	32.45	78.42

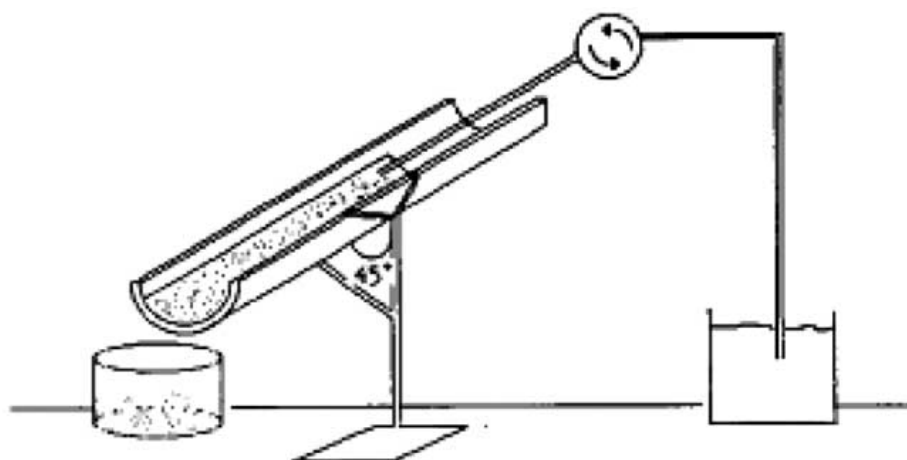


Fig. (3). Falling liquid film technique to measure microparticles mucoadhesion on rat jejunum.

with saline solution for 30 minutes at the rate of 30ml /minute. Then 25 number (N_0) of counted microspheres were hydrated with little amount of water and were dispersed on the mucosal tissue and left on it for 20 minutes for interaction with mucosal surface. During this period, whole system was placed in a constant humidity chamber which was adjusted to 90% relative humidity. At the end the system was washed with phosphate buffer pH 7.2 for 20 minutes at the rate of 22ml / minute and the number of microspheres remaining on the mucosal surface (N_s) were counted. The adhesive strength was determined using the formula given below and the results were reported in Table 6.

$$\% \text{ adhesive strength} = \frac{N_s}{N_0} \times 100 .$$

Ex Vivo Mucoadhesive Strength Determination [10]

In this technique four number of Albino rats were fasted overnight and then 25 number of microspheres (N_0) were ingested to these rats through an oral feeding needle. These rats were then sacrificed at an interval of 0, 4, 8, 12 hours respectively to isolate their stomach and intestine region. The

stomach and intestine regions were then cut opened longitudinally to note the number of microspheres adhering to these regions (N_s). This ultimately gave the adhesive strength of the formulation which was calculated using the formula given below. Results were reported in Table 7.

$$\% \text{ adhesive strength} = \frac{N_s}{N_0} \times 100$$

In Vitro Drug Release Studies [11,12]

Microspheres equivalent to 50 mg of metoprolol tartarate were taken and the release rate of drug from these microspheres was determined using U.S.P XXVI paddle apparatus. The microspheres were enclosed in the muslin cloth and the cloth was tied with the paddle. The paddle was then immersed in the phosphate buffer of pH 7.2 maintained at $37^\circ\text{C} \pm 0.5^\circ\text{C}$ and was rotated at the speed of 100 rpm. Sample aliquots of 5ml were withdrawn at every hour upto 12 hours and the withdrawn sample was estimated for its drug content using UV spectroscopy at 274 nm. The results of the release studies were reported in Figs. (4 and 5).

Table 6. Results of In Vitro Wash Off Test to Assess Mucoadhesive Properties of the Microspheres Prepared

Batch	Number of microspheres adhered to the mucosa initially (N_0)	Number of microspheres adhered to mucosa after 20 minutes (N_s)			Percent bioadhesion
		Test 1	Test 2	Average	
A6	25	23	24	24	96%
A18	25	25	25	25	100%

Table 7. Results of Ex Vivo Test to Assess Mucoadhesive Properties of the Microspheres Prepared

Batch	Microspheres adhered to stomach				Microspheres adhered to intestine				Total no. adhered to G.I.T	Percent bioadhesion
	0 hour	4 hour	8 hour	12 hour	0 hour	4 hour	8 hour	12 hour		
A6	14	06	05	05	08	16	16	16	21	84%
A18	17	09	09	09	07	15	14	14	22	88%

(Table 9) contd...

Batch	Percent release of metoprolol tartarate											
	1 hour	2 hour	3 hour	4 hour	5 hour	6 hour	7 hour	8 hour	9 hour	10 hour	11 hour	12 hour
A17	38.45	45.21	58.87	69.12	75.41	81.45	89.14	94.28	-	-	-	-
A18	22.32	31.56	49.66	54.00	57.11	63.26	70.35	74.93	82.54	86.40	92.21	95.97
A19	45.51	68.21	80.45	93.37	-	-	-	-	-	-	-	-
A20	23.54	32.56	47.45	54.76	62.12	70.15	79.87	87.18	95.45	-	-	-
A21	18.54	24.67	32.18	46.78	55.23	62.12	68.34	73.35	78.08	83.14	88.43	92.14

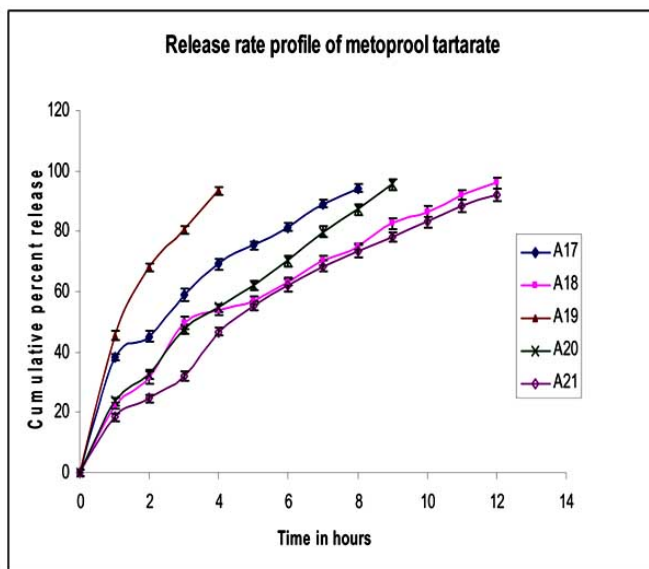
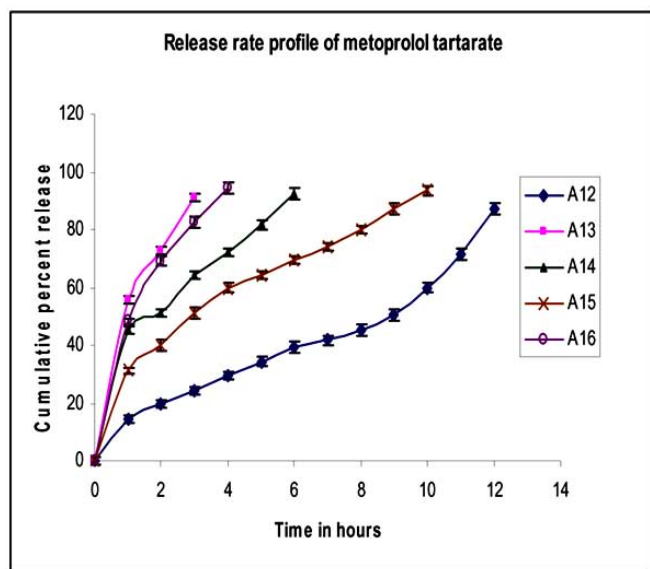


Fig. (5). Cumulative release rate profiles of metoprolol tartarate microspheres.

Stability Studies and Storage Conditions

Stability studies were carried out for optimized formulations as per ICH guidelines. Microspheres of optimized batches were placed in sealed vials which were then stored at 40°C / 75% RH for 90 days in stability chamber. The physical properties as well as drug release rate of the optimized batches were determined after stability studies. The dissolution profile of the optimized batches after stability studies is shown in Fig. (6).

RESULTS AND DISCUSSION

In Vitro Mucoadhesive Strength Determination of Various Polymers

Rotating Cylinder Method

From the time based technique which was used for mucoadhesive strength determination it was found that HPMC had greater mucoadhesive strength than that of Carbopol or polycarbophil. Similar observations were drawn in earlier research studies which explains that this may be due to the greater swelling rate of HPMC which results in larger surface of polymer that is exposed to the mucosal layer. This results in the increase in number of hydrogen bonding between the polymer and mucosal layer and thus increases in the mucoadhesive strength of the polymer [7].

Dissolution profile of metoprolol tartarate from optimized batches after stability studies.

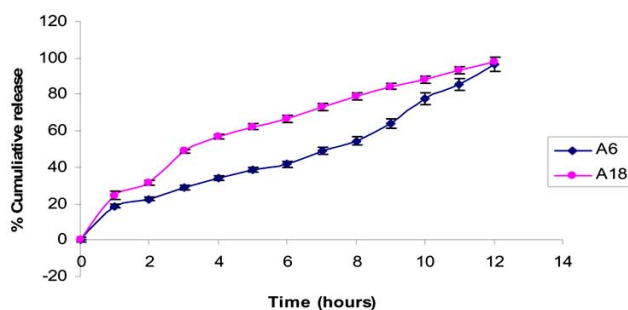


Fig. (6). Dissolution profile of drug from optimized formulation after stability studies.

Interaction Studies

FT-IR Spectroscopy

It is revealed from the FT-IR spectral results that there was no interaction between the drug and various mucoadhesive polymers. IR spectra of the plain drug showed the major peaks at wavenumbers 1049, 1110, 118, 124, 1512 and 3319, which was compared with the IR spectra of the microsphere formulations containing drug matrixed in various mucoadhe-

sive polymers. It was observed from the spectra's of the plain drug and formulations that there was no remarkable shift in the wave number of the peaks nor in the intensity of peaks of drug between two graphs which proved that there was no interaction between drug and polymer.

Yields of Production

The production yields of microspheres prepared by ionic gelation technique were found to be between 65% to 90%. It was found that production yields of polymer HPMC was greater than carbopol and polycarbophil. The probable reason behind this may be the high viscosity of the carbopol solution which decreased its syringeability resulting in blocking of needle and wastage of the drug- polymer solution which ultimately decreased the production yields of microspheres.

Actual Drug Content and Encapsulation Efficiency

The actual drug content and encapsulation efficiency of the various batches of microspheres were found to be in the range of 55% to 67%. It was observed that encapsulation efficiency of the microspheres was dependent on two parameters mainly the concentration of sodium alginate, concentration and molecular weight of the mucoadhesive polymer used. It was observed that by increasing the concentration of sodium alginate and mucoadhesive polymer the encapsulation efficiency of the microspheres also increases. Again increase in the molecular weight of the mucoadhesive polymer also increases the encapsulation efficiency of the microspheres due to formation of more intact matrix network by the sodium alginate. This slows down the diffusion of highly water soluble metoprolol tartarate in the aqueous calcium chloride solution in which the microspheres are prepared. Thus the amount of drug leached during formulation is decreased and encapsulation efficiency is increased.

Mucoadhesive Strength Determination Studies

From the mucoadhesive strength determination studies of the optimized batches it was found that mucoadhesive property of optimized formulations was observed to be greater in *in vitro* studies than *ex vivo* studies. This may be due to the reason that in *ex vivo* studies microspheres were ingested to rats and thus the peristaltic movement of the stomach forces the microspheres in the lower G.I.T. This reduces the time of contact between the microsphere and mucin layer and thus reduces the mucoadhesive strength of microspheres. While such peristaltic movements are absent in *in vitro* tests so the formulations showed a greater mucoadhesive property during this test.

Swelling Determination of Microspheres

From the swelling studies of the optimized batches performed at an interval of 20 minutes and 60 minutes respectively it was found that HPMC K4M has greater swelling properties than Carbopol 971P. As reported in the earlier research studies these may be due to higher cross linking in Carbopol 971P polymer which allows a lesser penetration of water inside the polymer matrix and thus results in lesser swelling of the polymer [13].

In Vitro Drug Release Studies

The *in vitro* release profiles of metoprolol tartarate from microparticles in phosphate buffer of pH 7.2 are shown in Figs. (4 and 5). It was observed from these profiles that as the concentration of sodium alginate increases in the formulation, the release of the metoprolol tartarate from the polymer matrix was retarded. The formulation with nine parts of sodium alginate and three parts of mucoadhesive polymers HPMC K4M (formulation A6) and carbopol 971P (formulation A18) extended the release of the drug for 12 hours. This is due to the reason that increases in the amount of alginate increases the no of COOH groups which are crosslinked by Ca^{2+} ions resulting in a formation of more intact matrix which makes the drug release more difficult. Increasing the concentration of calcium chloride solution also increases the crosslinking of the COOH groups of alginate molecule and thus retards the release of the drug from the alginate matrix. It was reported in earlier studies that increasing the concentration of calcium chloride decreases the mucoadhesive property of the formulation due to crosslinking of COOH groups which are responsible for mucoadhesion. So as reported in earlier studies 5% concentration of calcium chloride solution which maintains the mucoadhesive property of the formulation along with its release rate retarding property was selected [14,15]. The drug release data of these optimized batches was then explored for the type of release mechanism that they followed. The data were treated with zero order, first order, Higuchi and Korsmeyer-peppas equations as shown in Table 10. Through the correlation coefficient and n values obtained from these equations it was evident that metoprolol followed a non fickian drug release kinetics approaching to zero order.

Stability Studies

From the stability studies of the optimized batches it was concluded that the microspheres remained stable even after exposing to high temperature and moisture conditions, except for a little color change in the bulk drug after 90 days. The dissolution rates of metoprolol tartarate from the micro-

Table 10. Curve Fitting Data of Release Rate Profiles of Metoprolol Tartarate

Polymers	Regression coefficient values (r^2)			
	Zero order	First order	Higuchi release	Korsmeyer-peppas equation (n value)
HPMC K4M	0.9788	0.889	0.9818	0.653
Carbopol 971P	0.9798	0.9705	0.9939	0.58

spheres of optimized batches showed no significant change even after 90 days.

CONCLUSION

Thus large spherical microspheres consisting of alginate and mucoadhesive polymer in different ratios were prepared using ionic gelation technique. The microspheres so prepared exhibited good mucoadhesive properties in *in vitro* and *ex vivo* tests. Metoprolol release from the mucoadhesive microspheres was found to be slow, controlled and extended over a period of 12 hours. The drug release was found to be diffusion controlled which followed zero order kinetics. Thus the results of the present study clearly indicated a promising potential of mucoadhesive drug delivery system in the delivery of drugs with lower half lives and less bioavailability.

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