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Formulation and evaluation of colon specific tablet containing microsponges of metoprolol succinate

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Abstract

The aim of the present study was to design colon specific tablet containing microsponges of metoprolol succinate. Microsponges are porous microspheres which allow sustained flow out of the spheres. Emulsion solvent evaporation method was utilized to prepare the microsponges using ethyl cellulose as a polymer. Afterwards the effect of drug:polymer ratio on the physical characteristics and on drug release was investigated. The surface morphology and particle size were examined and microsponges were evaluated for encapsulation efficiency and drug content. Metoprolol succinate was selected as a model drug as it has short half life of 3-4 hours and after oral administration it undergoes first pass metabolism so the colon specific tablet was prepared owing to the plastic deformation of sponge like structure of microsponges. The tablets were prepared by compression coating of pectin:HPMC around core tablet prepared of microsponges. The tablets were evaluated and in-vitro release study was done.

Key-Words: Microsponges; Metoprolol succinate; Ethyl cellulose; Emulsion solvent evaporation; Colon specific

Introduction

Colon specific drug delivery system is mainly indicated in the treatment of local disorders of the colon such as inflammatory bowel diseases and carcinoma of the colon. The colon can also be used as an absorption site for delivering the drugs to the systemic circulation. Colon is associated with number of advantages including neutral pH, longer transit time, reduced digestive enzymatic activity and greater response to absorption enhancers. When drug is absorbed from the proximal colon, they are delivered directly into the systemic circulation, avoiding first pass effect. Conventional oral dosage forms are ineffective in delivering drug to the colon due to absorption or degradation of drug in upper gastrointestinal tract [1, 2]. There are various approaches which are utilized for achieving colon specific drug delivery namely, prodrug based approach, pH dependent systems, time dependent systems and microflora activated systems.

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Every approach has advantages and disadvantages. In prodrug based approach, pharmacologically inactive derivative of a parent compound which requires transformation within the body to release active drug but it is considered as new chemical identity from regulatory perspective. In pH dependent system, the drug release is prevented in stomach using enteric coated polymers but there is similarity in pH between small intestine and colon. In time dependent system, delayed release dosage forms are prepared but due to variable gastric emptying time and gastrointestinal movements, this system cannot be considered ideal [3-5]. But microflora activated system was found to be promising as it utilizes non starch polysaccharides which remain undigested in the stomach and small intestine and can only be degraded by the vast anaerobic microflora of the colon to simple saccharides. Here pectin is used as a polysaccharide. Pectin is an anionic polysaccharide extracted from plant primary cell wall for developing a colonic drug delivery system. The high methoxy pectin when applied as a compression coat protected the core tablet from disintegration and dissolution in the upper part of the gastrointestinal tract. The coat was susceptible to enzymatic attack in the colon thereby releasing the drug [6].

Microsponges are polymeric delivery system consisting of porous sphere. They have tiny sponge like spherical structure. As the surface is typically porous, it

allows sustained flow out of the sphere. They are mostly used for topical purpose but recently used for oral administration[7, 8]. Microsponges posses a unique compression property due to their sponge like structure. This property has been used to prepare the tablet by direct compression method and can be utilized for oral administration [9].

Microsponges were prepared by non aqueous emulsion solvent evaporation method which is simple and highly reproducible method. In this method a solution of drug and the polymer in the organic solvent was prepared and then added to the external phase which is a non solvent for the drug and immiscible with the organic solvent. An emulsifying agent has been added to the external phase. Emulsion formation takes place by constant stirring followed by evaporation of organic solvent. In the present study ethyl cellulose was used as a polymer, dichloromethane as internal organic phase, liquid paraffin oil as external phase and span 80 as an emulsifying agent [10, 11].

Metoprolol, a selective β1-adrenergic receptor antagonist, is widely used for the treatment of hypertension, angina pectoris, myocardial infarction, and arrhythmia. After oral administration, metoprolol is completely absorbed in, but undergoes extensive and saturable first-pass metabolism, such that its extent of absolute oral bioavailability (*F*) is 4–60% in rats and 38–60% in humans. Peak plasma concentration occurs about 1.5 hours after single oral dose. The half life of metoprolol is about 3-4 hours [12].

The purpose of this work was to avoid the absorption of metoprolol succinate from the upper gastrointestinal tract where it undergoes first pass metabolism and thus it is targeted in the proximal colon by formulating its colon specific tablet utilizing the microflora activated system as well as through microsponges the sustained release is also achieved as it has short half life of 3-4 hours.

Material and Methods

Materials

Metoprolol succinate was supplied by Cipla Ltd. (Mumbai, India). Ethyl cellulose was obtained from S.D. fine chemicals limited, Mumbai. Dichloromethane and Liquid paraffin were obtained from Merck chemicals limited, Mumbai. Span 80, Magnesium stearate, Hydroxy propyl methyl cellulose (HPMC) and Sodium carboxy methyl cellulose (Na CMC) were obtained from Loba chemie Pvt ltd, Mumbai. All other chemicals and reagents used were of analytical grade.

Preparation of metoprolol succinate microsponges by emulsion solvent evaporation method

In this method, organic internal phase containing metoprolol succinate and ethyl cellulose in 10 ml dichloromethane was gradually added into liquid paraffin oil, an external phase which contains 0.5% of span 80 as an emulsifying agent to form the emulsion. The mixture was stirred for 3 hours at room temperature at a stirring speed of 500 rpm for the evaporation of solvent. Microsponges obtained were filtered and washed with petroleum ether and then air dried over night.

For the evaluation of the effect of drug:polymer ratio on physical characteristics and on drug release from microsponges, different ratios of drug to ethyl cellulose (1:1, 3:1, 5:1, 7:1, 9:1, 11:1) were employed. In each formulation amount of drug, dichloromethane, liquid paraffin and span 80 were kept constant.(Table 1).

Table 1: Microsponge formulations prepared by emulsion solvent evaporation method.

Constituents	Microsponge formulation ratios		
	1:1	3:1	5:1
Inner Phase			
Metoprolol Succinate (g)	0.5	0.5	0.5
Ethyl Cellulose (g)	0.5	0.166	0.1
Dichloromethane (ml)	10	10	10
Outer phase			
Liquid paraffin (ml)	60	60	60
Span 80 %	0.5	0.5	0.5

Characterization and evaluation of microsponge formulations

Fourier transform infrared (FTIR) analysis

The FT-IR spectra of the metoprolol succinate and microsponge formulation consisting of drug and ethyl cellulose were obtained after making potassium bromide discs with the sample to detect drug excipient interaction.

Morphology and particle size

The optical microscopy method was used to study particle size. The particle size of each formulation was determined by spreading a thin layer of microsponges on a glass slide and viewing under an optical microscope fitted with an eye piece containing a micrometer. For each individual formulation, the mean particle size was determined as an average of 300 particles [13].

The surface morphology of the microsponge formulation was done by scanning electron microscopy (SEM).

Calculation of production yield

Production yield of the microsponges was determined by calculating accurately the initial weight of raw

materials and the final weight of the microsponges obtained.

Production yield (PY) % =

$$\frac{\text{Practical mass of microsponges}}{\text{Theoretical mass (polymer+drug)}} \times 100 \quad (1)$$

Determination of drug content and encapsulation efficiency

50 mg sample of drug loaded microsponges were dissolved in 50 ml of phosphate buffer pH 7.4 under ultrasonication. Then samples were filtered and after appropriate dilutions absorbance of samples were read at 272 nm against blank using UV Spectrophotometer (Shimadzu, 1800). The drug content and encapsulation efficiency were calculated using the given equation.

$$\text{Drug content \%} = \frac{\text{Mact}}{\text{Mms}} \times 100 \quad (2)$$

$$\text{Encapsulation efficiency \%} = \frac{\text{Mact}}{\text{Mthe}} \times 100 \quad (3)$$

Where, Mact is the actual drug content in weighed quantity of microsponges, Mms is the weighed quantity of powder of microsponges, Mthe is the theoretical amount of drug in microsponges calculated from the quantity added in the process.

***In vitro* dissolution studies**

Dissolution studies of all the microsponge formulations were carried out using USP dissolution rate test apparatus I (rotating basket) with a stirring rate of 50 rpm at 37.0±0.5℃. initial drug release studies were done in 0.1 N HCl for 2 hours. Drug release studies were further carried with phosphate buffer pH 7.4 for 8 hours. Samples were withdrawn after regular intervals of time and replaced with an equal volume of media. The collected samples were filtered through whatmann filter paper and then analysed spectrophotometrically at 272 nm.

Precompression evaluation of microsponge formulation

For the evaluation of precompression properties of the microsponge formulation, various characteristic parameters were evaluated. The angle of repose was determined using fixed funnel method. The bulk density and tapped density were determined by the cylinder method and carr's index was calculated using the following equation [14].

$$\text{Carr's index\%} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad (4)$$

Preparation of colon specific tablet

The core tablets were prepared by direct compression method. The core tablet consists of microsponges loaded with 50 mg drug, Na CMC as super disintegrant and magnesium stearate as a lubricant. All the constituents were weighed and mixed thoroughly. Final powder mixture was compressed using the 7mm concave punch to prepare the core tablets. Then pectin:HPMC (80:20) mixture was used for compression coating. The total coat weight was 200 mg. fifty percent of coat weight was placed in the die cavity of 11mm diameter then core tablet was placed and then remaining fifty percent of coat weight was placed and again compression was done on the same tabletting machine [2, 15] (Karnavati Engineering Ltd. Mehsana, Gujrat).

Evaluation of tablets [16]

Tablets were tested for their weight variation, hardness and friability. For weight variation,twenty tablets were randomly selected and individually weighed. The average weight and standard deviation of 20 tablets was calculated.Monsanto tablet hardness tester was used to measure the hardness.Friability of the tablets was determined using Roche friabilator. Preweighed sample of tablets was placed in the friabilator and subjected to the 100 revolutions at 25 rpm. Tablets were reweighed and % friability was calculated using the given equation.

Friability%=

$$\frac{\text{Initial weight of tablets} - \text{Final weight of tablets}}{\text{Initial weight of tablets}} \times 100 \quad (5)$$

***In vitro* dissolution study of colon specific tablets**

The drug release from the tablet was assessed by dissolution testing using the USP Dissolution rate test apparatus II (Paddle type) at a rotation speed of 50 rpm at 37.0±0.5˚C. Initial drug release was studied in 0.1 N HCl for 2 hours and then in phosphate buffer pH 7.4 till the end of 24 hours. Additionally, pectinase enzyme was added to the dissolution medium at 8th hour to stimulate the enzymatic action of the colonic bacteria. Samples were withdrawn at hourly intervals and were replaced with the equal volume of media. Samples were filtered through whatman filter paper and analysed spectrophotometrically at 272 nm.

Results and Discussion

The effect of drug:polymer ratio on the produced microsponges

It was found that emulsion solvent evaporation method seems to be promising for the preparation of microsponges as it is easy, reproducible and rapid method. The effect of drug polymer ratio (1:1, 3:1, 5:1,

7:1, 9:1, 11:1) on the formation of microsponges was investigated. The results of effect of drug:polymer ration on production yield, particle size, drug content and drug content are shown in Table 2.

While formulating the microsponges in drug:polymer ratio 1:1, fibrous aggregates were obtained while the drug:polymer ratios 3:1 and 5:1 gave spherical microsponges. When drug:polymer ratios 7:1, 9:1 and 11:1 were observed under optical microscope, very fine particles and free crystals of drug were observed as the amount of the polymer is very less to encapsulate the drug in the ratios 7:1, 9:1 and 11:1 compared to the ratios 1:1, 3:1 and 5:1.

Although the fibrous aggregates were obtained in the formulation drug:polymer ratio 1:1, the production yield was found to be higher that is 93.9% and increase in production yield was observed till the ratio 5:1. In ratios 7:1 to 11:1 the production yield decreases and found below 70 % in ratio 11:1. The highest production yield was obtained when drug:polymer ratio was 5:1.

As can be seen from the Table 2, the mean particle size can be greatly affected by the drug:polymer ratio. As the drug:polymer ratio increases the mean particle size decreases as the amount of polymer decreases. When the ratio of drug:polymer increased from 1:1 to 11:1 the mean diameter of microsponges decreased from 86.2 µm to 31.6 µm.

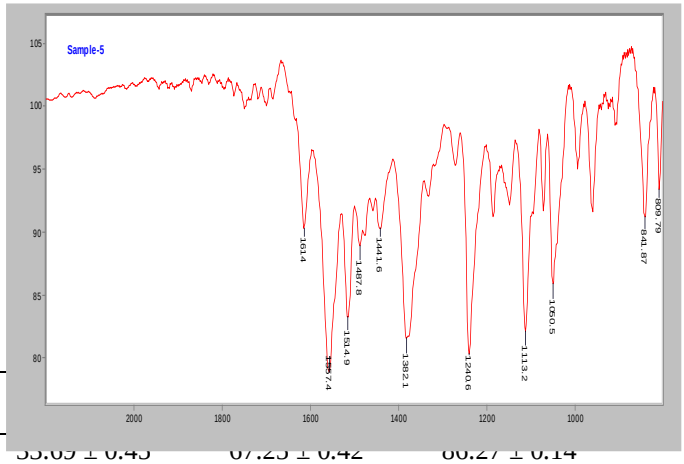
Table 2: Effect of drug:polymer ratio on production yield, drug content , encapsulation efficiency and mean particle size

Formulation code	Drug:polymer ratio	Production yield (%)
F1	1:1	93.90 ± 1.45
F2	3:1	94.89 ± 1.23
F3	5:1	95.83 ± 1.35
F4	7:1	74.31 ± 1.11
F5	9:1	70.20 ± 1.45
F6	11:1	62.31 ± 0.95

The drug content and encapsulation efficiency were found to increase up to ratio 5:1 after that there is no such increment but a decrease was observed. The drug content and encapsulation efficiency was found to be lowest in the ratio 1:1, this may be attributed to the fact that the sponges may remain empty as amount of polymer is higher in the ratio 1:1. In the ratio 3:1 drug content was found above 70% and encapsulation efficiency was found above 95% so this ratio was selected for tablet formulation.

Fourier transform infrared analysis (FTIR)

The microsponge formulation of drug:polymer ratio 3:1 was subjected to FTIR spectroscopic analysis to get the evidence of possible chemical interaction of drug with the polymer during the preparation of the microsponges. Figure 1a shows the IR spectra of the formulation and Figure 1b shows the IR spectra of the drug. Both the spectrum were compared. The spectrum is characterized by the absorption of –COOH group at 1614 cm^{-1}, -CH deformation of gem dimethyl group at 1382 cm^{-1}, peak at 1240 cm^{-1} is indicative of C-O stretching in a secondary alcohol. In the IR spectra of microsponge formulation, these bands shows same absorption patterns as that of pure drug which is the indicative of no chemical interaction between the drug and the polymer used in the preparation of microsponges [17, 18].



71.66 ± 0.78 95.61 ± 0.46 68.56 ± 0.23
75.81 ± 0.65 91.15 ± 0.26 52.33 ± 0.19

Figure 1. (a) shows FTIR spectra of microsponge formulation F2

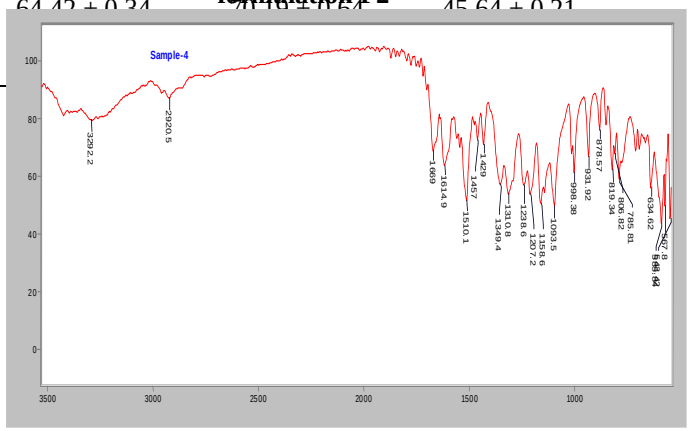


Figure 1. (b) shows FTIR spectra of pure drug

***In vitro* release study of microsponges**

Figure 2 shows a plot of % drug release against time. It was observed that in the first 2 h from the microsponge formulation of ratios 7:1, 9:1, 11:1 all the drug get released in 0.1 N HCl (pH 1.2) and thusno sustained release was observed. This may be attributed to the low encapsulation efficiency and lesser amount of polymer in these ratios and hence no further investigations were done on the ratios 7:1, 9:1. 11:1. But in the formulation of ratios 1:1, 3:1 and 5:1 sustained release of the drug was observed. Between 3-9 % of drug release was observed in first 2 h in 0.1 N HCl. When medium was changed from 0.1 N HCl to phosphate buffer pH 7.4, burst effect was observed (35.5 % for ratio 1:1, 37.5 % for ratio 3:1 and 39.1 % for ratio 5:1) within 2 h. the burst effect may be due to presence of drug on the surface of microsponges. At the end of 12thh 83.5 %, 97.81 % and 98.6 % drug was released from the formulation F1, F2 and F3 respectively. The microsponges having higher amount of polymer showed slower release than the microsponges having lesser amount of polymer.

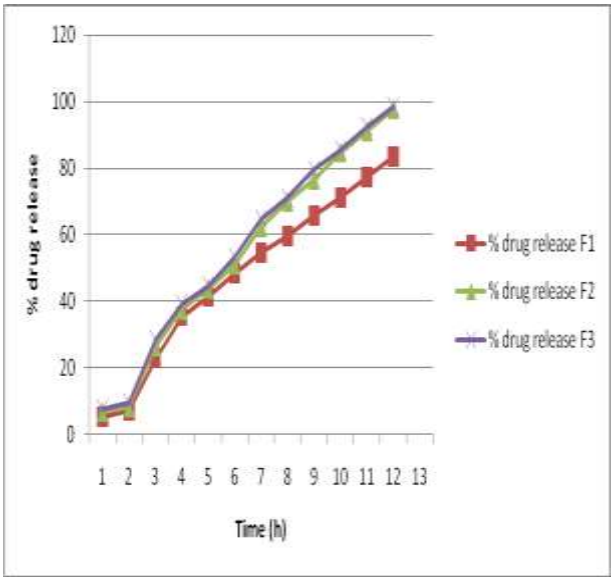


Figure 2: *In vitro* drug release profile of metoprolol succinate from microsponge formulations

Precompression evaluation of microsponges

Good flow of microsponges is essential for tabletting and thus carr's index and angle of repose of the microsponge formulation of ratio 3:1 was determined. The dried microsponges were found to possess good flow property as it has angle of repose of 28.72˚ and carr's index of 16.35 %.

***In vitro* release study of colon specific tablet**

Figure 3 shows the plot of % drug released against time. Drug release was not observed from the tablets in the first 2h in 0.1 NHCl (pH 1.2). upon replacing o.1 N HCl with phosphate buffer pH 7.4, slight amount of drug get released at the 7th and 8th h (less than 2%) . after the lag time of 8h, due to addition of pectinase enzyme to the dissolution medium, the proper drug release started with the burst effect and 32.61 % drug release was observed. Till the 16th h 83.4 % drug get released and 98.1 % drug release was observed at 24 h.

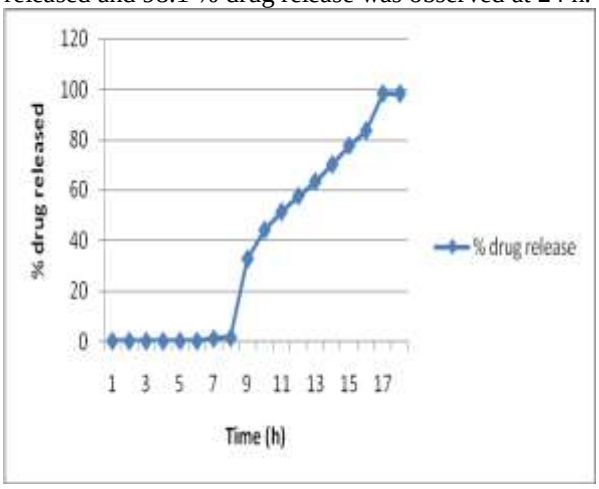


Figure 4: In vitro release profile of metoprolol succinate from compression coated tablet

This shows that pectin:HPMC (80:20) would protect the core tablets up to 8th h which is corresponding time to reach the colon and when it is exposed to the enzyme, the pectin degrades and delivers the drug to the proximal colon [2].

Conclusion

The mechanically strong tablets consisting of metoprolol succinate loaded microsponges can be successfully prepared owing to the plastic deformation property of sponge like structure of microsponges and sustained release is also achieved through microsponges. The absorption of drug can be avoided from the upper gastrointestinal tract and thus successfully targeted to the proximal colon by utilizing polysaccharides as a microflora activated system.

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