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FORMULATION AND *INVITRO* EVALUATION OF COLON TARGETING METOPROLOL TARTARATE MICROBEADS

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ABSTRACT

In Hypertension, Colon targeting drug delivery system plays a vital role in releasing the drug at early morning hours by delaying the release of drug from dosage form by applying novel approaches in it. This approach happens due to the chronological behavior of Hypertension confirms increased blood pressure at early morning hours, this need a preferable dosage form which will provide desired concentration of the drug at pre-determined time points especially early in the morning. The prepared dosage forms were optimized and evaluated. About eight formulations of Metoprolol tartarate microbeads were formulated with the help of different polymers, cross linking agent and coating polymer solution. From the *invitro* release studies datas it shows that MF2 was found to be an ideal formulation for colon targeting. It shows maximum amount of cumulative drug release from MF2 formulation, which was found to be 98.25±0.5 % at 16th hr in Colonic pH after lag time. From these studies it confirms that the delayed time and drug release profile of Metoprolol tartarate release from microbeads leads to sustainability and targetability of drug in colon.

Key Words:- Colon targeting, Metoprolol tartarate, Hypertension, Metoprolol tartarate.

INTRODUCTION

Colon specific drug delivery has gained increased importance not just for the delivery of drugs for the treatment of local diseases associated with the colon but also as potential site for the systemic delivery of therapeutic peptide and proteins (Watts P & Illum L, 1997; Chourasia MK & Jain SK, 2003). To achieve successful colon targeted drug delivery, a drug needs to be protected from degradation, release and/or absorption in the upper portion of the GI tract and then ensure abrupt or controlled release in the proximal colon. Drug modifications through covalent linkages with carrier or prodrug approach and formulation based approaches can be used for colonic delivery (Laila FAA & Sanjeev C, 2006; Gazzaniga et al., 1994; Ishibashi et al., 1998).

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The overall goal for optimum therapy is to match the needs of the patient while improving the efficiency and safety of the administered drugs. Various drug delivery approaches have always played a challenging and crucial role in ensuring and predicting the delivery of capable and successful drugs to the target site of delivery in the human body. Oral drug delivery is the chosen route of delivery, accounting for more than US$15 billion in annual global sales. Although oral delivery has become a widely accepted route of administration of therapeutic drugs, the gastrointestinal (GI) tract presents several formidable barriers to drug delivery. In the recent past, considerable interest has grown in targeting the delivery of drugs to the colon (Watts P & Illum L, 1997; Chourasia MK & Jain SK, 2003).

Rationale for Colonic Drug Delivery

Medical rationales for the development of orally administered colonic drug dosage forms include

1. The opportunity to reduce adverse effects in the treatment of colonic inflammation and colonic motility disorders by topical application of drugs active at the mucosal level.
2. Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon like ulcerative colitis, chron's disease, carcinomas and infections
3. The elucidation of the mode of action of some nonsteroidal anti-inflammatory drugs (NSAID) such as sulfide (metabolized in the colon to the active moiety, sulfide) that were found to interfere with the proliferation of colon polyps (first stage in colon carcinoma) possibly in local manner.
4. In some cases the colon is capable of absorbing drugs efficiently.
5. Drug absorption enhancement works better in the colon than in the small intestine.
6. Protein drugs can be absorbed better from the large bowel owing to hypothetic reduced proteolytic activity in this organ.
7. The unique metabolic activity of colon, which makes it an alternative organ for drug delivery system designer (Sarasija S & Hota A, 2000).

Advantages of Colonic Drug Delivery

1. Local action, in case of disorders like ulcerative colitis, chron's disease, irritable bowel syndrome, and carcinomas. Targeted drug delivery to the colon in these cases ensures direct treatment at the site with lower dosing and fewer systemic side effects.
1. In addition to local therapy colon can also be utilized as the portal entry of the drugs into systemic circulation for example molecules that are degraded/poorly absorbed in upper gut such as proteins and peptides may be better absorbed from the more benign environment of the colon.
2. The systemic absorption from colon can also be used as means of achieving chemotherapy for diseases that are sensitive to circadian rhythm such as asthma, angina and arthritis.
3. By colon targeting drug can be supplied to the biophase only when it is required and maintenance of the drug in its intact form as close as possible to the target site.

Disadvantages of Colonic Drug Delivery

1. The pH level in the small intestine and colon vary between and within individuals due to which drug may be released at undesired site due to pH variability. The pattern of drug release may differ from person to person which may cause ineffective therapy.
2. The pH level in the small intestine and cecum are similar which reduces site specificity of formulation.
3. Poor site specificity is the major disadvantage of colonic delivery of drug.
4. Diet and diseases can affect colonic microflora which can negatively affect drug targeting to colon. Nature of food present in GIT can affect drug pharmacokinetics. In diseased conditions pH level of GIT differs from pH level of healthy volunteers which alters the targeted release of formulations which release the drug according to pH of desired site.
5. Enzymatic degradation may be excessively slow which can delay the enzymatic degradation of polymer thus alters the release profile of drug (Laila FAA & Sanjeev C, 2006; Gazzaniga et al., 1994; Ishibashi et al., 1998; Sarasija S & Hota A, 2000).

MATERIALS AND METHODS

The materials used in the projects like Metoprolol tartarate are received as gift sample from Actavis ltd., Chennai, Sodium alginate and Eudragit L 100 from media lab, Chennai. And other solvents used are in analytical standards.

Formulation of Microbeads

The microbeads were prepared by the ionotropic gelation technique. The sodium alginate solution was prepared by dispersing the sodium alginate in de-ionized water under continuous stirring for 30 minutes. The weighed amount of the drug was thoroughly mixed with sodium alginate dispersion. By following the same procedure the alginate beads of different ratios of drug: polymer were prepared. The resulted homogeneous dispersion was extruded in to the 5% calcium chloride solution through hypodermic syringe with flat tip needle (20G) and stirred for 15 minutes at 100rpm using magnetic stirrer. The formed micro beads were allowed to cure for 30 minutes in the calcium chloride solution to complete the gelation reaction. The microbeads were then filtered and dried in hot air oven at 60˚C for 3 hr. After that it was coated with Eudragit polymer solution (Laila FAA & Sanjeev C, 2006; Manna et al., 1999; Bussemer et al., 2003).

EVALUATION PARAMETERS

Compatibility studies

Fourier transformed infrared (FTIR) spectroscopic analysis

Fourier transform infrared (FT-IR) spectra of the samples were obtained in the range of 400 to 4,000 cm−1. IR spectral analysis of pure drug and physical mixture of formulation were carried out. The peaks and patterns produced by the pure drug were compared with physical mixture.

Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) analysis was performed using Nietzsche DSC 200PC (Nietzsche, Selb, Germany). The instrument was calibrated with indium (calibration standard, > 99.999%) for melting point and heat of fusion. A heating rate of 100C/min was employed in the range of 25–2000ºC. Analysis was performed under nitrogen purge (20 mL/min). The samples were weighted into standard aluminium pans and an empty pan was used as reference.

Evaluation of Microbeads

Surface morphology /Scanning Electron Microscopy (SEM)

The external morphology of the microparticles was studied by scanning electron microscopy. The sample of the SEM analysis was prepared by sprinkling the microparticles onto one side of the double adhesive stub. The stubs were then coated with gold using polaran SC 500 sputter coater, to neutralize the electrons and to obtain a clear morphology of the microparticles. The SEM was performed on microparticles after and before dispersing it in 0.1N HCl (Manna et al., 1999; Bussemer et al., 2003; Lym-Ly and Wan-LS, 1997).

Drug entrapment efficiency or incorporation efficiency

To determine the drug entrapment efficiency or incorporation efficiency, the microparticles were crushed in glass mortar and powered, then suspended in 10 ml of methanol, after 24 h the solution was filtered and filtrate was analyzed for drug content spectrophotometrically at 274nm for Metoprolol tartarate. The drug incorporation efficiency was calculated by the following formula.

Incorporation efficiency = b/a X 100

b = calculated amount of drug present in the formulation,

a = theoretical amount of drug present in the formulation

Drug content

Four portions each containing 200 mg were randomly picked from the prepared samples and were crushed with help of mortar and pestle. Then it was stirred continuously for 3h with simulated gastric fluid (pH 1.2). After 3 h, the samples were filtered, suitably diluted and estimated spectrophotometrically at 274nm for Metoprolol tartarate. The estimation was done in 3 replicates to determine the uniformity of drug in microparticles.

Production yield

The production yield of the microparticles can be determined by calculating accurately the initial weight of the raw materials and the last weight of the microparticles obtained.

$$\text{Production Yield (Y)} = \frac{\text{Practical mass of Microparticles}}{\text{Theoretical Mass (Polymer+drug)}} \times 100$$

***Invitro* drug release of Metoprolol Tartarate Microbeads**

The second pulse release of metoprolol tartarate was investigated using the USP rotating basket type dissolution apparatus at 50 rpm and maintain the bath with 37+1ºC. The simulation of gastrointestinal transit conditions was achieved by altering the pH of the dissolution medium at various time intervals. The pH of the dissolution medium was kept at 1.2 for 2 h with 0.1 N HCl. Then, 1.7 g of KH_2PO_4 and 2.225 g of $Na_2HPO_4.2H_2O$ were added, adjusting the pH to 4.5 by adding 1.0 M NaOH. A release rate study was continued for another 2 h. After 4 h, the pH of the dissolution medium was adjusted to 7.0 and maintained for 24 h. The final volume in all cases was 500 ml. The samples were withdrawn from the dissolution medium at various time intervals using a pipette fitted with a micro filter, and the filtrate was subjected to UV analysis at 274nm. All dissolution studies were performed in triplicate (Lym-Ly and Wan-LS, 1997; Lin et al., 2004; Mohmad A & Dashevsky A, 2006; Sindhu A & Srinath MS, 2007).

***Invitro* drug release kinetics**

The release data obtained was fitted into various mathematical models using PCP disso-V2.08 software. The parameters 'n' and time component 'k', the release rate constant and 'R', the regression coefficient were determined by korsmeyer-Peppas equation to understand the release mechanism.To examine the release mechanism of drug from microparticles, the release data was fitted into the Peppa's equation.

$$M_t / M_\infty = Kt^n$$

Where, M_t / M_∞ is the fractional release of drug, 't' denotes the release time, 'K' represents a constant incorporating structural and geometrical characteristics of the device, 'n' is the diffusion exponent and characterize the type of release mechanism during the release process (Sindhu A, Srinath MS, 2007; Ghimire et al., 2007).

RESULTS AND DISCUSSION

Compatibility study using IR and DSC

In the IR spectrum of Metoprolol tartarate standard consists of characteristics band values at 2933 cm^{-1}(C-H-stretching) ,3344 cm^{-1} (N-H-stretching), 3340

cm^{-1} (OH- alcohol). These characteristic band values were observed in all the recorded IR spectra. i.e., for the Physical mixture band values are shown at 2989 cm^{-1}(C-H-stretching), 3400 cm^{-1} (N-H-stretching), 3300 cm^{-1} (OH- alcohol).DSC of Metoprolol tartarate showed a sharp endothermic peak at 146.39^0C (melting point). The physical mixture of Metoprolol tartarate and other excipients also showed the same thermal behavior as the individual component i.e., a blunt peak at 149.09^0C (melting point). Results are shown in Fig 1-4.

DSC results also revealed that the physical mixture of Metoprolol tartarate with excipients showed superimposition of the thermogram. There was no significant change observed in melting endotherm of physical mixture of Metoprolol tartarate and excipients. From the IR and DSC studies, it was found that there were no interaction took place between Metoprolol tartarate and the other ingredients used in the formulation of pulsincaps.

Particle size

The particle size and surface morphology was determined with the help of scanning electron microscopy (SEM). Spherical shaped Microbeads were observed. Among the five formulations of Microbeads MF2 possess small particle size 100.52 and also uniform particle size distribution because of increased concentration of polymer and optimum concentration of cross ling agent which leads to coat the drug effectively and uniformly through the surface .The particle size ranges of formulations were shown in Figure 6 and Table 3.

Drug Entrapment Efficient

On increasing the concentration the Sodium alginate and gelatin, the amount of drug entrapped with the polymers coat also increased, as it was observed maximum 85.31 ± 1.25 % in MF2 and less 73.89 ± 2.30 in MF6 .This shows that the best polymer for entrapping metoprolol tartarate in pulsincap microbeads was sodium alginate and optimum concentration of polymer is about 4% with 5% of cross linking agent calcium chloride. The results are shown in Table 3..

Product yield

The percentage yield of Microbeads was more than 70 % for all the formulation and among the prepared batches, batch MF2 show highest percentage yield of 89.34% due to increased concentration of the polymer and cross linking agent. The results of production yield for all the batches were shown in Table 3..

Drug content

The drug content in the micro beads was found to be in the range of 79.85 ± 2.25 to 98.59 ± 1.15 mg based on the polymer and cross linking agent ratio. Increase in concentration of the polymer and cross linking agent there will be increase in drug content of the formulation. The formulation MF2 shows maximum drug content and the values are given in Table 3.

***In-vitro* drug release studies**

These studies show the effect of environment of the body fluids on the drug release pattern from the prepared Microbeads. It was found that the release rate from the all formulations was found to be different for the polymer proportion and concentration of cross linking agent used in the all formulations. All the formulation shows a good initial lag time of around 4 hr in pH 1.2,4.5, that shows that the release pattern of drug is delayed and maximum amount of drug is released in colonic pH 7.0 at early morning hours in a cumulative sustainable manner. This lag time may due to the presence of Eudragit polymer coating in the microbeads. MF2 with Sodium alginate and Calcium chloride cross linking agent showed maximum Sustained release 98.25±0.5 in 16^{th} hr in a cumulative pattern. MF2 shows maximum drug release due to increase concentration of cross linking agent. The values are as shown in Figure 7.

Table 1. Formulation of Metoprolol tartarate Microbeads

Formulation code	Amount of Metoprolol tartarate (mg)	Amount of Gelatin in %	Amount of Sodium alginate	Amount of Calcium chloride	Coating Polymer Eudragit L 100 w/v
MF1	50	-	2%	5%	10%
MF2	50	-	4%	5%	10%
MF3	50	2%	-	5%	10%
MF4	50	4%	-	5%	10%
MF5	50	-	2%	10%	10%
MF6	50	-	4%	10%	10%
MF7	50	2%	-	10%	10%
MF8	50	4%	-	10%	10%

Table 2. Release Kinetics

Formulation code	Release kinetics			
	Zero order R^2	First order R^2	Peppa's R^2	'n' value for Peppa's
MF1	0.947	0.861	0.978	0.478
MF2	0.995	0.851	0.975	0.469

Table 3. Physical evaluation of Microbeads MF1-MF8

Formulation code	Particle size (nm)	Product yield in %	Drug content in %	% drug entrapment
MF1	105.15	77.59± 3.42	86.15 ± 1.12	79.16 ± 2.18
MF2	100.52	89.34± 3.80	98.59 ± 1.15	85.31 ± 1.25
MF3	107.89	74.32± 4.02	89.66 ± 1.96	78.23 ± 1.89
MF4	109.45	72.53± 3.44	79.85 ± 2.25	78.92 ± 1.45
MF5	110.52	71.52± 4.26	86.45± 1.85	81.58 ± 1.75
MF6	110.52	71.54± 3.80	84.25± 1.45	73.89 ± 2.30
MF7	120.42	74.58± 3.66	82.325± 2.42	76.58 ± 2.42
MF8	118.64	70.62± 4.04	83.40 ± 2.34	79.42 ± 2.64

***standard deviation (n = 3)**

Table 4. *In- vitro* release kinetics studies

Release Exponent 'n'	Drug Transport Mechanism	Rate as a function of time
0.5	Fickian Diffusion (Higuchi Matrix)	$t^{n-0.5}$
0.5<n<1.0	Non-Fickian Diffusion	t^{n-1}
1.0	Case – II Transport (Zero Order Release)	Zero Order Release
Higher Release (n>1)	Super Case – II Transport	t^{n-1}

Figure 1. DSC Spectrum of Metoprolol tartarate pure drug

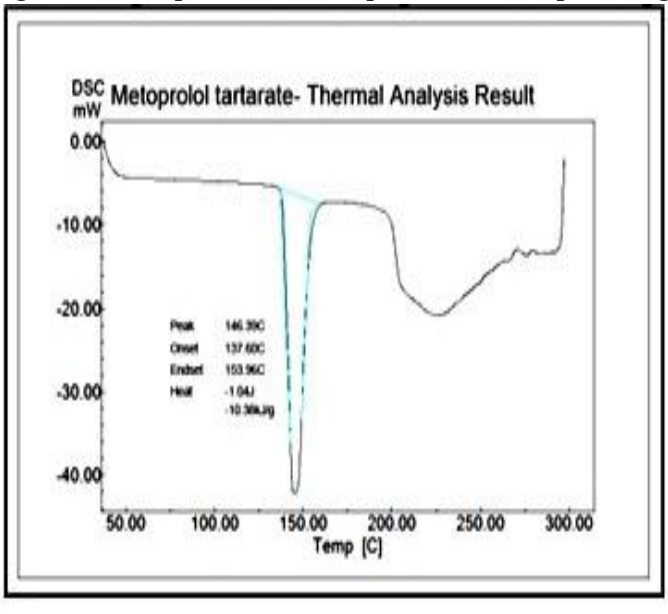


Figure 2. DSC Spectrum of Metoprolol tartarate and other excipients

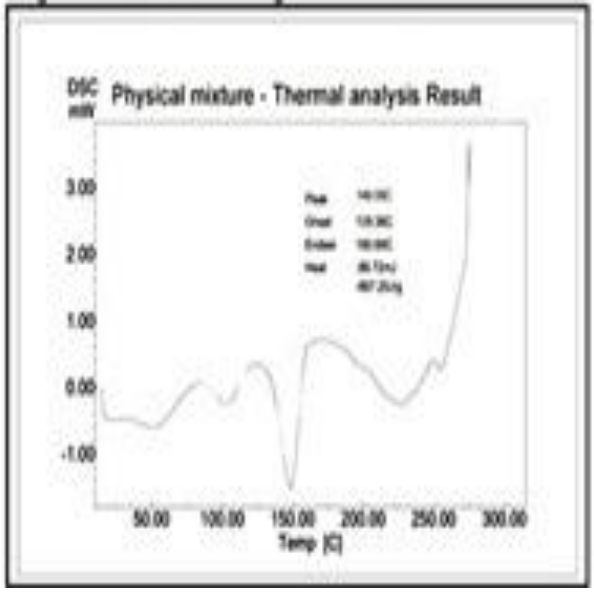


Figure 3. IR Spectrum of Metoprolol tartarate pure drug

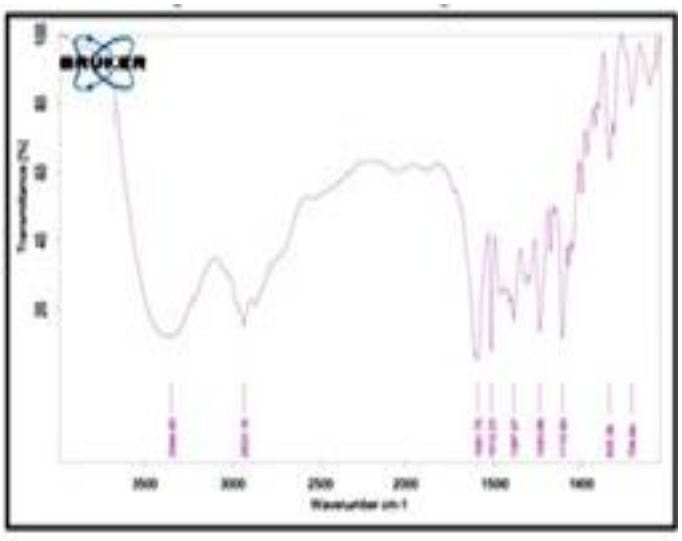


Figure 4. IR Spectrum of Metoprolol tartarate and other excipients

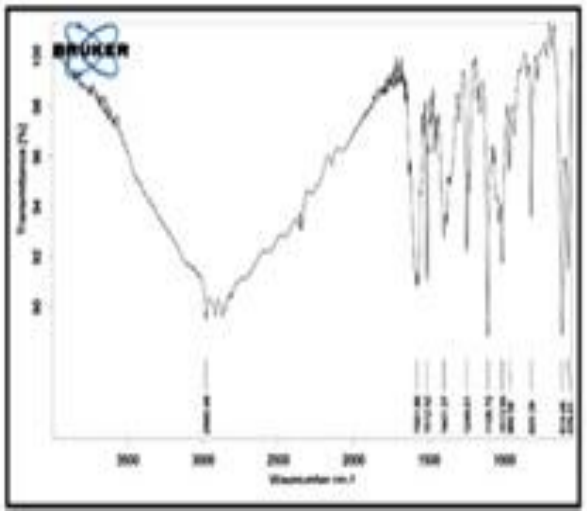


Figure 5. SEM Photography of Microbeads

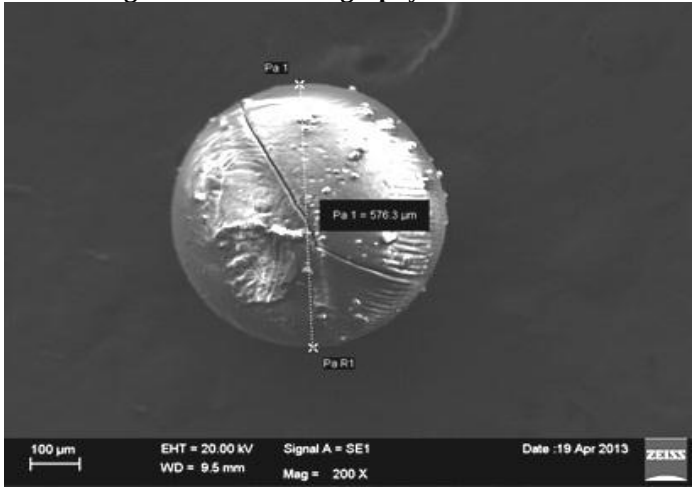
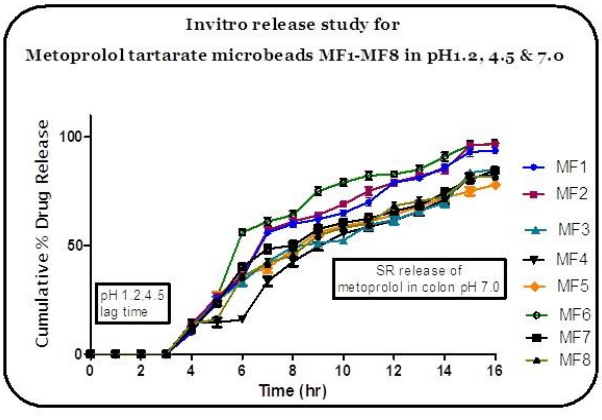


Figure 6. Cumulative % drug release profile for Metoprolol Tartrate Microbeads MF1 – MF8 in pH 1.2, 4.5 & 7.0



***In- vitro* release kinetics studies**

By applying the time vs. % CDR in release kinetics data, for best formulations MF1 & MF2 shows a R^2 value 0.995 and 0.947 in Zero order and applying time in hr vs. %log ARR shows a R^2 value 0.861 and 0.851 in First order represents an ideal release in order to prolonged pharmacological action. The results are shown in Table 4.And according to the peppas fitting both the formulation obeys nonfickian diffusion type of release mechanism.

CONCLUSION

The conditions required for the development of colon targeting drug delivery system for Metoprolol tartarate is to prevent the complications caused by early morning hour dose administration by controlling the early morning hypertension. Metoprolol tartarate colon targeting microbeads was formulated and evaluated. The *in vitro* dissolution studies was revealed that the formulated microbeads shows desired concentration of the drug release at pre-determined time points at colonic pH and it

shows the better desired results. Hence it may be concluded that the newly formulated Metoprolol tartarate colon targeting microbeads produce effective control of hypertension at early morning risk hours by allowing the drug to release after a lag time at colonic pH. Thus the objective of this work is to release the drug in delayed manner by timed release was achieved, with reduced dose and dosing frequency which leads to better patient compliance.

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