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FORMULATION AND EVALUATION OF METOPROLOL SUCCINATE PULSATILE DRUG DELIVERY SYSTEM FOR CHRONO BIOLOGICAL DISORDER: ANTI HYPERTENSION

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ABSTRACT

The objective of the present study was to develop and evaluate an oral pulsatile drug delivery system to mimic the circadian rhythm of the disease by releasing the drug with a distinct predetermined log time of 5 hrs (± 0.25 hrs). The basic design of the pulse in cap formulation of metoprolol provides time controlled release to treat the nocturnal symptoms of hypertension and angina pectoris. The pulsincap formulation of Metoprolol provides time controlled release to treat the nocturnal symptoms of hypertension and angina pectoris. If the formulation is administered in the night at 10.00 pm symptoms that are experienced in early morning hours could be avoided. In the present study, polymer such as Guargum selected for colon targeting of Metoprolol succinate. Metoprolol succinate granules were prepared using these polymers to prolong and target to the colon. Granules were prepared by wet granulation technique using a guar gum polymer in different ratios. These granules filled into the formaldehyde treated capsules and plugged with optimized HPMC plug, to maintain the 5hr lag time. Finally capsules are enteric coated with enteric coating polymers and conducted dissolution studies with different pH mediums.

INTRODUCTION [1]**:** In recent years considerable attention has been focused on the development of pulsatile drug delivery system. Pulsatile release pattern has gained most popular form of controlled drug delivery system because conventional systems with a continuous release are not ideal [1, 2]. Oral controlled drug delivery systems are generally used due to convenient dosage form & it also releases drug in constant or variable rates [2, 4].

Pulsatile release systems are formulated to undergo a lag-time of predetermined span of time of no release, followed by a rapid & complete release of loaded drugs.

The approach is based on the principle of delaying the time of drug release until the system transmits from mouth to colon [4, 3]. A lag-time of 5 hours is usually considered sufficient since small intestine transit is about 3-4 hours, which is relatively constant and hardly affected by the nature of formulation administered. Metoprololsuccinate is an antihypertensive agent, has biological halflife of 3-4hr [3, 5, 14].

Frequent administration of this agent is necessary due to it's short biological halflife. Prolonged release dosage forms are designed to complement the pharmacological activity of medicament in order to achieve the longer duration of the action. Treatment for hypertension is a long term therapy [5, 14]. [9, 15] Where

non compliance is high, hence prolonged release dosage forms are useful for quality health care.Most of the water soluble drug containing formulations release the drug at a faster rate and likely to produce toxic concentrations of the drug on oral administration. It produces gastro intestinal adverse effects like gastric irritation [9, 15]. [7] And 50% of the administer dose undergoes first pass metabolism. Absorption of the Metoprolol is more in the colon than compared to stomach and intestine.

Hence, designed "Pulsincap drug delivery system of Metoprolol succinate to the colon" to overcome all these disadvantages [7]. [6] The Pulsincap drug delivry system of Metoprolol succinate to the colon provides the following benefits Minimal toxic concentrations as this system directing the drug to absorb in colon. Avoidance of gastric irritation. Avoidance of first pass metabolism. Provides more absorption in colon. The pulsincap formulation of Metoprolol Succinate provides time controlled release to treat the nocturnal symptoms of hypertension and angina pectoris [6].

MATERIALS AND METHODS: Metoprolol Succinate was gift sample from NatcopharmaPvt.Ltd , Hyderabad, India. Guar gum andEudragit S from Reddy's labs,PVP, methanol, potassium dihydrogenortho phosphate, sodium hydroxide, talc, magnesium stearate were from commercially obtained from SD Chemical Ltd Mumbai , India.

Formulation of Pulsincap:

Step 1. Preparation of Formaldehyde-Exposed Hard Gelatin Capsules [10]: Hard gelatine capsule bodies (00 size) were placed on a wire mesh. Formaldehyde 15% was taken into a dessicator. The wire mesh containing bodies was then exposed to formaldehyde vapors. The reaction was carried out for 12 hr after which the bodies were removed and dried at 50ºc for 12 hr to ensure completion of reaction between gelatin and formaldehyde vapours. The bodies were then dried at room temperature to ensure removal of residual formaldehyde [10].

Step 2. Preparation of Metoprolol succinate granules: Metoprolol succinate granules were prepared by wet granulation method. The composition of different formulations used in the study is given in **Table 1, 2 & 3**.

In all the formulations, guar gum, Guar gum were sieved and pectin were sieved (<250 mm) separately and mixed with Metoprolol succinate (<150 mm) and PVP (<250 mm). The powders were blended and granulated with 5% of PVPK30. Isopropyl alcohol: water (1:1) was used as granulating agents. The wet mass was passed through a mesh and granules were dried at 50^{o}C for 1 hr.

TABLE 1: COMPOSITION OF METOPROLOL SUCCINATE GRANULES WITH GUAR GUM

INGREDIENTS	F-1 (mg)	F-2 (mg)	F-3 (mg)	F-4 (mg)	F-5 (mg)	F-6 (mg)
Metoprolol succinate	50	50	50	50	50	50
Guar gum	25	50	75	100	125	150
PVP	5	5	5	5	5	5
Talc	1.5	1.5	1.5	1.5	1.5	1.5

Step 3. Development of Modified Pulsincap Dosage Form: Granules equivalent to 50mg of Metoprolol succinate were accurately weighed and filled in to the formaldehyde exposed bodies by hand filling. Capsules containing the granules were then plugged with different grades of hydroxyl propyl methyl cellulose, with different concentrations (**Table 2**).

Plugs were punched by 7mm punch. It is called as tablet plug. The capsules were then completely coated withEudragit S 100 using different concentrations of 5%, 10% and 15% coating solutions were prepared using solvent acetone and mixed with 1% Dibutyl phthalate as plasticizer (**Table 3**). Coating was repeated until an 8-12% increase in weight was obtained. % weight gain of the capsules before and after coating was determined.

TABLE 2: FORMULATION OF HPMC HYDROGEL PLUG

Ingredients	FP1	FP2	FP3	FP4	FP5	FP6	FP7	FP8
HPMC 50Cps	50	100	150	200	-	-	-	-
HPMC 3000Cps	-	-	-	-	50	100	150	200

TABLE 3: EUDRAGIT COATING SOLUTION

Ingredients	5%	10%	15%
Eudragit S 100	500 mg	1000 mg	1500 mg
Methanol	10 ml	10 ml	10 ml
Dibutyl phthalate	1 ml	1 ml	1 ml

Evaluation Tests:

1. **Solubility study of formaldehyde exposed capsule body:** The Capsule bodies were exposed to 15% formaldehyde solution in varying time intervals. Then exposed capsule bodies were dried in an hot air oven. And the solubility of bodies were tested in 0.1N HCl and results were shown in **table 4**.

TABLE 4: SOLUBILITY STUDY OF 15% FORMALDRHYDE TREATED CAPSULES

Formaldehyde exposed time (hr)	Time to soluble in 0.1N HCl (hr)
2	3
4	8
6	14
8	20
10	26
12	32

2. **Angle of Repose:** The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$$\tan \theta = h/r \quad \ldots\ldots(1)$$

Where h and r are the height and radius of the powder cone.

3. **Bulk Density:** Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were caluculated using the following formulas.

LBD = weight of the powder/volume of the packing …….(2)

TBD = weight of the powder/ tapped volume of the packing…….. (3)

4. **Compressibility Index** compressibility index of the granules was determined by Carr's compressibility index:

Carr's Index (%) = [(TBD-LBD) × 100]/TBD …….(4)

5. **Total Porosity:** Total porosity was determined by measuring the volume occupied by a selected weight of a powder (V_{bulk}) and the true volume of granules (the space occupied by the powder exclusive of spaces greater than the intermolecular space, V).

$$\text{Porosity (\%)} = V_{bulk} - V/V_{bulk} \times 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots (5)$$

6. **Drug content evaluation:** 50 mg equivalent weight of granules were weighed and added 6.8 P^H phosphate buffer and made up to 100 ml with 6.8 P^H phosphate buffer. 1ml of this solution is made up to 100 ml with buffer. Metoprolol succinate content in the granules were estimated by an UV spectrophotometric method based on the measurement of absorbance at 275 nm and the results were shown in **table 5**.

TABLE 5: CHARACTERIZATION OF METAPROLOL SUCCINATE GRANULES FORMULATED WITH GUAR GUM

Formulation	Angle of repose	Bulk density (g/ml)	Tapped bulk density (g/ml)	Compressibility index (%)	Total porosity (%)	Drug content (%)
F-1	24.5º	0.285	0.331	13.5	36.5	97.5
F-2	25.5º	0.289	0.335	12.5	37.2	95.5
F-3	25.2º	0.283	0.332	12.2	36.2	96.5
F-4	24.5º	0.278	0.328	11.5	35.1	98.2
F-5	24.8º	0.269	0.321	13.2	36.5	98
F-6	25.2º	0.269	0.321	12.6	37.2	98.1

7. **Lagtime test for HPMC hydrogel plug:** The prepared HPMC plugs were plugged to the capsule bodies containing formulated granules. And the cap was closed. The lag time test was conducted using USP XXII dissolution testing apparatus using 7.4 P^H phosphate buffer as a medium. The drug release was observed after 3hr and the results were shown in **table 6**.

TABLE 6: INFLUENCE OF HPMC CONCENTRATION ON THE DRUG RELEASE OF METOPROLOL

HPMC plug concentration (mg)	Amount of drug released at the end of the 5 hr (%)
50	31
100	19
150	0
200	0

8. **Disintegration test for enteric coated empty capsules:** The disintegration test for the empty heard gelatin capsules that are coated with Eudragit and Cellulose acetate pthalate of different concentrations, conducted using disintegration test apparatus using 0.1N HCl as medium for 2 hr.

9. ***In vitro* dissolution studies:** Dissolution studies were carried out using USPXXII, Basket method (apparatus I). The agitation rate was 100 rpm. The ability of the Pulsincap dosage form to provide colon specific drug delivery was assessed by conducting *in vitro* drug release studies in simulated gastric fluid (SGF-pH 1.2) for 2 hr, simulated intestinal fluid (SIF-pH 7.4) for 3 hr and simulated colonic fluid (SCF-pH 6.8) for 19 hr. Sampling was done at predetermined time intervals and the samples were estimated for drug content after suitable dilution by UV method.

10. ***In-vitro* drug release testing in presence of rat caecal content medium:** *In-vitro* drug release studies were investigated in the presence of rat caecalcontet. The albino rats weighing between 150-200g were kept on normal diet and administered the 1 ml of 1% w/v solution of guar gum in water with the help of Teflon tubing directly into the stomach region via oral cavity. The treatment was continued for 6 days to induce enzyme responsible guar gum degradation animals were sacrificed before 30 min of commencing drug release studies and the caecum was exteriorized for content collection. The caecal content (anaerobic) were immediately transferred into buffer saline solution pH 6.8 to obtain an appropriate 2%w/v concentration solution which was previously bubbled with carbon dioxide-nitrogen gas to maintain anaerobic environment. Using USP dissolution rate testing apparatus basket type (100 rpm, 37±0.5^oC) in sealed anaerobic conditions with modifications the procedure was done.

A beaker (capacity 400 ml) containing 200 ml of rat caecal content medium was immersed in water maintained in the 1000 ml vessel, which, in turn, was kept in the water bath of the apparatus. The pulsincaps were placed in the baskets of the apparatus and immersed in the rat caecal content medium. As the caecum is naturally anaerobic, the experiment was carried out with continuous CO_2 supply into the beakers. At different time intervals, 2 ml of the samples was withdrawn without a pre-filter and replaced with 5 ml of fresh phosphate buffered saline (PBS) bubbled with CO_2 and the experiment was continued for 19 hr as the usual colonic transit time is 20-30 hr and the results were shown in **table 7**.

TABLE 7: DISSOLUTION DATA FOR METOPROLOL SUCCINATE WITH GUAR GUM

Dissolution medium	Time (hr)	% of Metoprolol succinate Released					
		F-1	F-2	F-3	F-4	F-5	F-6
Simulated Gastric Fluid	2	0	0	0	0	0	0
Simulated Intestinal Fluid	5	0	0	0	0	0	0
Simulated Colonic Fluid	6	51.714	32.47	20.30	14.46	6.16	4.5
	8	79.861	69.43	42.95	42.17	18.82	18.43
	10	96.87	82.66	60.36	58.40	27.17	27.30
	12		95.8	70.59	73.22	32.97	37.44
	14			96.93	85.83	45.45	45.33
	16				98.57	63.01	56.67
	18					70.30	70.04
	20					85.40	80.25
	22					99.30	90.26
	24						99.04

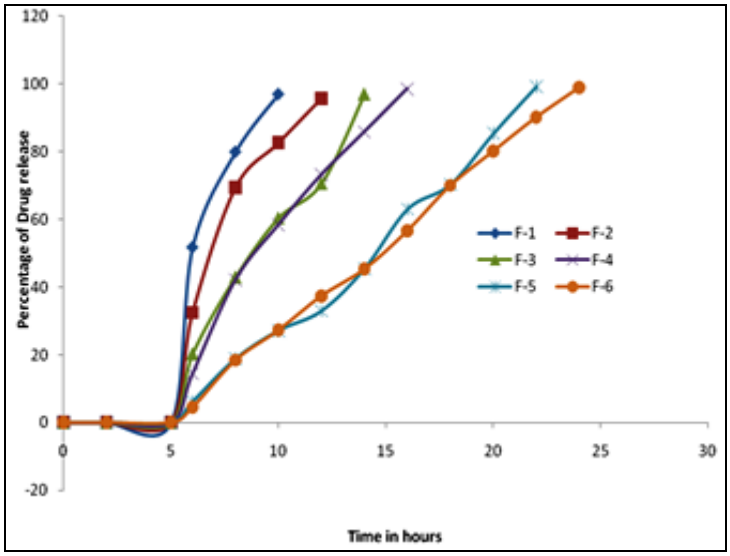

FIG. 1: COMPARATIVE RELEASE PROFILE OF THE FORMULATIONS PREPARED WITH GUAR GUM

RESULTS & DISCUSSIONS: The present study was carried out to develop colon target drug delivery for chronotherapy of Metoprolol succinate. The selection of this approach is Pulsincap drug delivery. The previous studies says that to sustain the drug release for 24hr, capsules treated with formaldehyde for 12hr. But my present work concludes 8hr formaldehyde treatment is sufficient to sustain the release for 24hr and found that the capsule has maintained the physical stability during the dissolution process. Metoprolol succinate granules prepared with Guar gum, in different ratios.

Among all the formulations formulated, F6 Guargum 1:3 sustained the release for 24hr and the ability of the used gums to sustain the release is following decreasing order F_6> F_5> F_4> F_3> F_2> F_1.Hydrogel plug is used in Pulsincap to maintain lag time and with an intention to direct the drug to colon. And found that the lag time maintained was directly proportional to the length of the plug employed. Tight fitting of the plug is advisable for better results. Enteric coating of capsule was done with Eudragits different concentrations. 10% of Eudragit S was found to be optimum from this study.

The study shows that the release of Metoprolol succinate in the physiological environment of colon is due to the microbial degradation of guar gum in the presence of rat caecal contents. The drug release was more in the presence of caecal content than with outcaecal content.

Metoprolol is one of the best drug for colon drug delivery system. Because the absorption is more in colon, can overcome first pass metabolism and no gastric irritation.

CONCLUSION: The present study was carried out to develop colon target drug delivery of Metoprolol Succinate. The selection of this approach is colon drug delivery. The main object was to target drug release for colon to maintain the chrono pharmacological Anti-Hypertensive activity. Metoprolol Succinate granules prepared with Guar gum, in different ratios. Among all the formulations formulated, F6 guar gum (1: 3) sustained the drug release for 24hrs and fulfilled the objective of this work. In future, if the pulsincap drug delivery overcomes this disadvantages it will be the best drug delivery for chronopharmacotherapy.

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