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FORMULATION AND EVALUATION OF FLOATING PULSATILE DRUG DELIVERY SYSTEM OF METOPROLOL TARTRATE

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Abstract:

Oral route is one of the most popular, preferable and convenient route for drug administration. It possesses certain advantages like ease of administration, self-medication, patient compliance and flexibility with a wide range of dosage form The present study was aimed to develop a floating pulsatile formulation comprising an active Beta blocker Metoprolol tartrate with pulsatile release. Floating behavior of tablet depends on added fillers in buoyant layer. Tablets containing lactose and 50% HPMCK100M floated earlier than tablets prepared with the lesser or higher concentrations of HPMCK100M. In addition, lactose has a higher water solubility, resultingin faster water uptake of medium into tablet. N2 formulation was used for further investigation. Only FPRT tablets of optimized batch (F3P9N2) were evaluated for in vitro drug release profile which was found to be 98.15% in 12hr. Stability studies on final formulation demonstrated its better stability profile at 4.0 ^{O}C and 25 ^{O}C however it was found a little unstable at higher temperature and humidity conditions.

Key words: *Metoprolol tartrate, Floating behavior, Formulation, Evaluation*

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INTRODUCTION:

Oral route is one of the most popular, preferable and convenient route for drug administration. It possesses certain advantages like ease of administration, self-medication, patient compliance and flexibility with a wide range of dosage form [1]. In the present era of drug delivery, tablet is the most successful and convenient oral dosage form and preferred by patient as well as physicians [2].

However with the advancement of the technologies in the pharmaceutical field, modified drug delivery systems have drawn an increasing interest. Nowadays, the emphasis of pharmaceutical research is aimed at development of more efficacious drug delivery systems according to the requirement of body and disease state and thus achieving optimal clinical outcome with constant drug plasma concentrations [3].

In case of certain diseases symptoms display circadian variations and hence drug release from the dosage form should also vary over time. Circadian cycles last about 24 hours, e.g. sleeping and waking patterns.T he coordination of medical treatment and drug delivery with such biological clocks and rhythms is termed Chronotherapy [4].If the peak of symptoms occur at daytime a conventional dosage forms can be administrated just before the symptoms are worsening. If symptoms of the disease became worse during the night or in the early morning the timing of drug administration and nature of the drug delivery system need careful consideration. In this case, modified-release dosage forms must be used [5].

The challenge of delivering drug at predetermined rate and time could be met by a wide range of newer techniques like osmotically driven pumps [6], matrices with controllable swelling [7], diffusion [8] or erosion rates [9], nonuniform drug loading profiles [10] and multi-layered matrices.

In cardiovascular diseases the focus is to optimally deliver the antihypertensive or antianginal drug in higher amounts in early morning and lower amount at night. Holter monitoring of the electrical properties of heart has revealed 24 hour variation in the occurrence of ventricular premature beats with the peak in events in diurnally active person, between 6 a.m. and noon. Drugs that are capable of reducing the morning increase in norepinephrine and angiotensin II, have more cardio protective effect and a better blood pressure lowering effect. The present study was aimed to develop a floating pulsatile formulation comprising an active Beta blocker Metoprolol tartrate with pulsatile release. Beta blocker is a type of drug that prevents the binding of norepinephrine and epinephrine to the beta receptors on nerves are known as beta blockers or beta adrenergic blockers. It is mainly used for the relief from several diseases including hypertension, myocardial ischemia, angina pectoris, acute myocardial infarction, and sudden cardiac death. Administration of metoprolol conventional tabletsin 50 mg/day doses may cause fluctuations in plasma concentrations resulting in side effects or a reduction in the drug concentration at receptor sites.

MATERIAL AND METHODS:

Preparation of Floating pulse release Tablets:

A pulsatile–floating drug delivery system consists of three different parts,a core tablet, containing the active ingredient, an erodible outer shell, and a top cover buoyant layer. Floating pulsatile release tablet of MPT was prepared by compression with different composition ratio of erodible coating (press-coated systems). Rapid release core tablet (RRCT) of MPT was first prepared and optimized. RRCT was then press coated with polymers in two steps to formulatePulsatile release tablet (PRT). Finally PRT were compressed with effervescent floating layer to prepare floating pulsatile released tablets (FPRT).

Preparation of the Rapid Release Tablet (RRCT):

Core tablets containing Metoprolol tartrate were prepared by using direct compression method.All the ingredients were passed through 60# mesh sieveseparately and collectively. Different preliminary batches of core tablets were prepared by mixing all ingredients with different superdisintegrants. Powder mixtures of MPT, Crospovidone, crosscarmellose sodium, Sodium Starch Glycollateand MCC were dry blended for 20min followed byaddition ofmagnesium stearate. The mixtures were then further blended for 10 min andresultant powder blend was compressed using rotary tablet machine (Cadmach Machinery, Ahmedabad, India) with a 6mm punch and die to obtain the core tablet containing 25mg of MPT.For the above batches disintegration study was conducted from which optimized batches were selected and only that batch was conducted for further study.

Preparation of Pulsatile Release tablet (PRT) [72]:

The optimized RRCT (F3) was taken as core for the preparation of PRT. For dry coating of F3 formulation 250mg coatings of HPMC K4M, Na CMC,HPMCE14and Magnesium stearate were used with two steps: In the first 125mgcoatings were filled into the die (11.8mm in diameter), followed by RRCT placed in the center of die, and slightly

pressed to fix the coatings around and under thecore, and then the rest of the coatings were filled and compressed (Table 6.5).

Preparation of Floating pulsatile release tablets (FPRT) [72]:

On the basis of drug release profile of PRTs best formula composition(F3P9) was selected for the preparation of FPRT (Table 6.6). Floating tabletswere prepared by placing 50% of pulsatile release layer in 11.8 mm die andoptimized RRCT was placed on it. Further remaining quantity of pulsatilerelease layer was added in cavity so as to cover the RRCT and finally precompressed it with lower compression pressure (hardness, 3-4 kg/cm2) by usingsingle punch tablet machine. The weighed amount (100 mg) of floating layerpowder composition was kept on pre-compressed tablet (PRT) in die, and thenfinally compressed it to give certain hardness (6-7Kg/cm2). The total weight ofeach FPRT tablet was adjusted to 500mg.

Table 1: Composition of Rapid release core tablet of MPT

Ingredients (mg)	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metoprolol Tartrate	25	25	**25**	25	25	25	25	25	25
Crospovidone	3.0	4.0	**5.0**	—	—	—	—	—	—
Cross Carmellose Sodium	—	—	—	3.0	4.0	5.0	—	—	—
Sodium starch glycolate	—	—	—	—	—	—	3.0	4.0	5.0
MCC	114	113	**112**	114	113	112	114	113	112
Magnesium stearate	4.0	4.0	**4.0**	4.0	4.0	4.0	4.0	4.0	4.0
Talc	4.0	4.0	**4.0**	4.0	4.0	4.0	4.0	4.0	4.0
Total Tablet weight	150	150	**150**	150	150	150	150	150	150

Table 2: Composition of Pulsatile release tablets

Ingredients (mg)	Formulation code								
	P1	P2	P3	P4	P5	P6	P7	P8	P9
HPMC K4M	140	160	180	-	-	-	-	-	-
Na CMC	-	-	-	140	160	180	-	-	-
HPMCE15	-	-	-	-	-	-	140	160	**180**
MCC	105	85	65	105	85	65	105	85	**65**
Magnesium stearate	5	5	5	5	5	5	5	5	**5**
Total Tablet weight	250	250	250	250	250	250	250	250	**250**

Table 3: Compositions of the Buoyant Layer

Ingredients (mg)	Formulation code		
	N1	N2	N3
HPMC K100M	40	**50**	60
Sodium Bicarbonate	20	**20**	20
Citric acid	10	**10**	10
Lactose	30	**20**	10
Total weight	100	**100**	100

Evaluation of floating pulsatile releasetablet:

Hardness:

Hardness (Kg/cm^3) of RRCT and FPRTs were determined by Monsanto hardness tester. Tablet hardness testing, is the test to determine the breaking point and structural integrity of a tablet "under conditions of storage, transportation, and handling before usage". The results of hardness of various formulations are shown in Table.

Friability (F):

RRCT and FPRT formulations (20) were weighed and placed in the Roche Friabillator that revolves at 25 rpm for 4 minutes dropping the from a distance of six inches with each revolution. After operation the tablets were de-dusted and reweighed. The % friability was then calculated by the following formula :

$$F = \frac{\text{Initial Weight - Finalweight}}{\text{Initialweight}} X100$$

Weight variation test:

FPRT formulationswere individually weighed, calculated the average weight, and compared the individual tablet weights to the average. The tablets met the USP tests that were not more than 2 tablets were outside the percentage limit and no tablets differed by more than 2 times the percentage limit. The maximum percentage difference allowed is 5% for average weight of tablets more than 324mg.

Disintegrationtime:

USP disintegration testapparatus was used to determine the disintegration time of RRCT formulation. To test the disintegration time oftablets, one tablet was placed in each tubeand the basket rack was positioned in a1 liter beaker containing 0.1N HCl at 37°C ± 1°C such that thetabletremains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

Drugcontent:

Total 10 tablets were weighed and powder equivalent to 25 mg of MPT wasweighed and dissolved in 0.1N HCl then filtered through Whatman filter paper.Solution was analysed for MPT content by UV Spectrophotometer at 222 nmusing 0.1N HCl as blank.

Floating LagTime:

The floating lag time is determined in order to assess the time taken by the dosage to float on the top of the dissolution medium, after placing the dosage form in themedium. Floating characteristics of the prepared formulations were determined using USP paddle apparatus at a speed of 50 rpm in 900ml of 0.1N HCl solution. The time required to float is noted.

Floating Time:

Floating time of the prepared formulations were determined using USP paddle apparatus at a speed of 50 rpm in 900ml of 0.1N HCl solutionat 37±0.2^{0}c for 24 hours. The time during which the dosage form remains buoyant (floating duration) was measured.

***In Vitro* Dissolution Studies of PRT & FPRT tablets:**

Dissolution studies on PRT & FPRT tablet of MPT was performed under gastric conditions. Test was performed using the USP dissolution apparatus type II at 50 rpm. A tablet containing 25mg of MPT was placed in the dissolution vessel containing 900mL of 0.1N HCl maintained at 37 ± 0.5^{0}C. At predecided time intervals, samples from the dissolution medium were withdrawn, filtered and concentration of MPT was determined spectrophotometrically at λ_{max} 222nm.

Stability Studies:

Stability studies were performed to determine the changes on the final formulation at different storage conditions. Initial drug content was considered as 100 percent and drug content at each time interval was determined. It was found that the percent drug content after a period of 3 months for MPT was 99.84±0.14% at 4±1^{0}C whereas it was 99.42±1.3% at 25±2^{0}C & 60±5%. On the other hand it was 99.29±1.6% at 40±2^{0}C & 75±5%.

RESULT ANDDISCUSSION:

It was observed that the disintegration time for formulation varied from 21 to 44 second. It was observed that when crosspovidon was used asdisintegrant, tabletwas disintegrate within short time due to easy and high swelling ability of crosspovidon as compared to CCS and SSG. It is observed that disintegration time of tablet decreasedwith increased in concentration of crosspovidon, CCS andSSG.

Core tablet (RRCT) of MPT was prepared and evaluated for various parameters. On the basis of different studies F3 formula for core tablet was selected for further studies. Pulsatile release tablets containing F3 RRCT was evaluated for hardness, friability, weight variation and in vitro drug release. Formulation P9 was found to be most suitable to include in final formulation of FPRT on the basis of 98.28% drug release in 12hr.It was observed that HPMC E15LV shows the lag time of 4 hr then follow the sigmoidal release pattern with 100% drug releaseat 10hr. As the concentration of the HPMC E15LV coating increases from 140 to 180mg the lag time extended to 4.5 hr and then follow the delayed release profilewith the 100 % drug release at the 12 hr.From above discussion it wascleared that NaCMC and HPMCK4 cannot be used to develop asuccessful pulsatile drug delivery system.

Floating behavior of tablet depends on added fillers in buoyant layer. Tabletscontaining lactose and 50% HPMCK100M floated earlier than tablets prepared with the lesser or higher concentrations of HPMCK100M. In addition, lactose has a higher water solubility, resultingin faster water uptake of medium into tablet. N2 formulation was used for further investigation.Only FPRT tablets of optimized batch (F3P9N2) were evaluated for in vitro drug release profile which was found to be 98.15% in 12hr. Stability studies on final formulation demonstrated its better stability profile at 4.0 ^{O}C and 25^{O}C however it was found a little unstable at higher temperature and humidity conditions.

Table 4 Evaluation of RRCT tablets

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hardness (Kg/cm^2)	3.8	3.7	**3.6**	3.4	3.6	3.6	3.2	3.6	3.9
Friability (%)	0.65	0.62	**0.60**	0.64	0.61	0.62	0.67	0.64	0.63
%Drug Content	98.32	98.40	**99.82**	98.60	99.22	98.68	99.12	98.88	99.10
Disintegration Time (Sec)	36	26	**21**	44	31	24	30	28	25

Table 5 Evaluation of PRT tablets

Parameter	P1	P2	P3	P4	P5	P6	P7	P8	P9
Hardness (Kg/cm^2)	3.4	3.4	3.2	3.5	3.8	4.4	3.2	3.6	**4.3**
Friability (%)	0.40	0.37	0.35	0.46	0.38	0.32	0.45	0.38	**0.31**
Uniformity of weight (mg)	394	398	398	402	398	398	399	404	**399**
Dissolution study (hr)	**% Drug Release**								
0.5	0	0	0	0	0	0	0	0	**0**
1	0	0	0	0	0	0	0	0	**0**
2	0	0	0	0	0	0	0	0	**0**
4	6.26	5.42	5.15	6.88	5.3	5.64	5.22	6.84	**2.56**
6	35.86	30.26	27.65	31.35	34.38	28.53	35.37	32.4	**28.58**
8	68.42	76.14	61.36	74.45	70.9	69.54	75.57	71.68	**68.80**
10	99.88	98.65	86.23	99.42	100.3	91.48	95.61	96.52	**90.36**
12			98.68			97.12			**99.85**

Table 6 Evaluation of FPRT tablets

Parameter	N1	N2	N3
Hardness (Kg/cm^2)	6.6	6.8	7.2
Friability (%)	0.72	0.54	0.6
Uniformity of weight (mg)	496	498	499
Floating Lag Time (sec)	54	26	45
Floating Time (hr)	10	12	17

Table 7*In vitro* release profile of optimized FPRT tablets (F3P9N2)

Time (hr)	Cumulative % drug release
0.5	0
1	0
2	0
4	2.56±0.68
6	30.58±1.82
8	71.86±3.44
10	88.36±4.65
12	97.85±5.28

Value represent mean±SD (n=3)

Table 8: Stability studies at different conditions

Storage Conditions	Observations on storage for Drug content (%)(F3P9N2)			
	Initial	1 months	2months	3 months
4±1^{o}C	100	99.94±1.2	99.88±4.1	99.84±0.14
25±2^{0}C and 60±5%	100	99.92±4.6	99.76±3.3	99.42±1.3
40±2^{o}C and 75±5%	100	99.82±3.7	99.63±3.1	99.29±1.6

Values are mean± SD

CONCLUSION:

The present work was based on the floating pulsatile drug delivery of Metoprolol Tartrate.The core containing crosspovidone disintegrate the tablet within shorttime due to easy and high waterpenetration ability of as compared toCCS and SSG. The PRT containing the buoyant material, such as HPMC K100M,NaHCO3,and citric acid achieved a satisfactory buoyant force in vitro, whereasthe floating onset time was less than 1 min. The pulsatile releasing mechanismof PRT is based on the exploitation of the peculiar interaction betweenhydrophilic polymeric coating and the aqueous gastrointestinal fluids.

The in vitro release profiles of MPT from PRT prepared using HPMC E15LV as retarding polymer are characterized by a predetermined lag time (4 hr), the duration of which depends on the kind and amount of the polymeric layer applied on the cores as well as type of superdisintegrant in core tablet. The developed system offers a simple andnovel technique for pulse release of drugs. From the results it is concluded that the PRT we prepared could achieve a rapid release after lag time of 4hr with the relatively low variability. The drug release

profile of optimized batch F3P9 followedsigmoidal release profile. So it is concluded that this formulation could be ideal to achieve pulsatile release profile of Metoprolol Tartrate and to reduce the chances of early morning heart attack.

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