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Design and Characterization of Pulsatile Drug Delivery System for Metoprolol Succinate

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ABSTRACT:

Aim: The present research work was aimed at developing a metoprolol succinate pulsatile drug delivery system using core-in cup tablet design. Metoprolol is a potential beta blocker effective against hypertension. It has very good solubility and the drug is released quickly after its oral administration, thus there is a need to control the release of the drug from the formulation and to reduce the dosing frequency.

Methods: Core in cup designing was done by using HPMC K 100M, Sodium Alginate and Polyox WSR 303 polymers for the preparation of core. Total of 9 formulations were developed and evaluated for various tablet properties. All the formulations complied with the specifications. The developed formulations were subjected to in-vitro drug release studies and found that a lag time of one hour was achieved.

Results: The formulation F9 containing Sodium Alginate and Polyox WSR 303 was found to be the best one with desired drug release characteristics.

Conclusion: The drug release from this formulation was by First order kinetics and the mechanism of drug release is by diffusion.

Keywords: Metoprolol succinate, Pulsatile drug delivery system, Core-in cup tablet design, Hypertension, Sodium Alginate, Polyox WSR 303.

INTRODUCTION

Controlled drug delivery systems have acquired very important role in pharmaceutical Research and Development (R&D) business. Such systems offer control over the release of drug and grant a new lease on life to a drug molecule in terms of patentability. These dosage forms offer many advantages over the conventional drug delivery systems; such advantages include nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance [1]. The oral controlled-release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time, thereby ensuring sustained therapeutic action.

However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release [2]. Recent studies have revealed that diseases have a predictable cyclic rhythm and that the timing of medication regimens can improve the outcome of a desired effect [2, 3]. This condition demands release of drug as a "pulse" after a time lag and such system has to be designed in a way that complete and rapid drug release should follow the lag time. Such systems are known as pulsatile drug delivery systems (PDDS), time-controlled systems, or sigmoidal release systems. PDDS have been developed in close connection with emerging chronotherapeutic views. In this respect, it is

well established that the symptoms of many pathologies, as well as the pharmacokinetic and pharmacodynamic profiles of most drugs, are subject to circadian variation patterns [4].

Several functions such as Blood pressure (BP), heart rate, stroke volume, cardiac output, blood flow of the cardiovascular system are subject to circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood [5, 6]. It was postulated that modification of these circadian triggers by pharmacologic agents may lead to the prevention of adverse cardiac events [7]. BP is at its lowest during the sleeping period and rises steeply during the early morning period. Most patients with essential hypertension have a similar circadian rhythm of BP as do normotensive persons, although hypertensive patients have an upward shift in the profile [8].

The core-in-cup design where the drug containing active core is surrounded by an impermeable cup made of hydrophobic material that acts as a barrier and allows drug release from a single exposed surface. An active core tablet containing the active ingredient is compression coated on the base as well as circumference to form a cup around the core. The application of this technology to the design of a metoprolol succinate tablet is being studied aiming to report the behavior of the system.

Metoprolol succinate, β_1 selective adrenergic receptor blocking agent used in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism and in the prophylactic treatment of migraine. The half-life of drug is relatively short approximately 4-6hrs and in normal course of therapy drug administration is required every 4-6hrs, thus warrants the use of sustained release/ control release formulation for prolong action and to improve patient compliance [9].

The present work is aimed to prepare a novel oral pulsatile release drug delivery system based on a core-in-cup dry coated tablet of metoprolol succinate, where the core tablet surrounded on the bottom and circumference wall with inactive material which helps in achieving a lag time along with controlled release of drug from the formulation.

MATERIALS AND METHODS:

Materials: Metoprolol Succinate was obtained as a gift sample from Dr. Reddy'S laboratories Hyderabad. HPMC K 100M was purchased from Loba chemicals,

Mumbai. Polyox WSR 301 and Sodium alginate were purchased from Apex pharmaceuticals, Chennai. Hydrogenated castor oil was purchased from KMC Enterprises. Microcrystalline cellulose and PVP K-90D were purchased from Colorcon, Ahmadabad. Aerosil and Magnesium Stearate were purchased from Vasa pharma chem. Pvt.Ltd, Ahmadabad.

Methods:

Drug-excipients compatibility analysis

The compatibility of drug and formulation components is important prerequisite for formulation development. It is therefore necessary to confirm that the drug does not interact with excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

The drug and individual excipient mixture of all excipient and drug were taken in the formulation ratio in a flint vial and stored at 40°C/ 75% RH, (Accelerated condition) and 60°C(stress condition). Samples were evaluated for any change in physical characteristics with reference to controlled sample stored at 40°C for 0, 10, 20 and 30 days. Taken out at 10 days interval and were subjected to physical testing and results were noted.

Preparation of core in cup tablets of metoprolol succinate [10, 11]

Steps involved in the preparation of core in cup tablets of Metoprolol Succinate are preparation of core tablet and then preparing a core in cup tablet. The core tablets were prepared by wet granulation method.

Wet granulation method

(i) Formulation of Core Tablets

The ingredients including drug, polymer and excipients were weighed accurately according to the batch formula mentioned in Table. 1 and then transferred to poly bag and mixed for 5 min.

Binder solution was prepared by dissolving PVPK-90D in hydro alcoholic granulating fluid of IPA: Water (9:1). This binder solution is added to the above blend to form granules. The granules were dried in a tray dryer at 60°C for sufficient time until the loss on drying was not more than 3%. The dried granules were passed through sieve no. 30 to form granules of uniform size. Finally colloidal silicon dioxide was added and dry mixed. After uniform mixing of granules, they are lubricated with magnesium stearate. Core tablets composed of the active ingredient were punched on a RIMEK 10 station compression machine using 5.5 mm round, flat punches to form disc shaped core tablets.

(ii) Formulation of Cup

Table. 1: Different formulations of core in cup metoprolol succinate tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
	CORE								
Metoprolol Succinate	100	100	100	100	100	100	100	100	100
HPMC K 100M	25	50	-	-			25	25	
Sodium Alginate	-	-	25	50			25		25
Polyox WSR 303					25	50		25	25
Avicel PH 101	117	92	117	92	117	92	92	92	92
PVP K-30	5	5	5	5	5	5	5	5	5
Yellow iron oxide	0.375	0.375	0.375	0.375	0.375	0.375	0.375	0.375	0.375
Aerosil	0.625	0.625	0.625	0.625	0.625	0.625	0.625	0.625	0.625
Mg.Stearate	2	2	2	2	2	2	2	2	2
Core tablet weight(mg)	250	250	250	250	250	250	250	250	250
	CUP								
HCO (hydrogenated castor oil)	130	130	130	130	130	130	130	130	130
Avicel PH 102	65	65	65	65	65	65	65	65	65
PVP K-90D	5	5	5	5	5	5	5	5	5
Total tablet weight(mg)	450	450	450	450	450	450	450	450	450

The same process used for the formulation of core is used to formulate cup, but without the addition of drug and the granular bend is not subjected to compression in the final step.

(iii) Compression Process

The size of the punches and dies selected for compression are given in Table. 2. The disc shaped tablets of the active core were manually placed in the centre of a larger round flat faced punch in the die cavity of the tablet press, before the addition of the cup material and the machine was run until the lower punch moved down slightly. Weighed quantity of the blend for the cup was manually poured into the die cavity using a spatula, and finally compressed. The second run of compression of the core tablets with the hydrophobic material resulted in a hydrophobic barrier on the circumference and the base of the core tablet to form the core-in-cup tablet of Metoprolol Succinate (8 mm round flat punch).

Evaluation methods:

Micromeritic properties [12]:

The prepared granules were evaluated for their micromeritic properties like bulk density, tapped density, hausner's ratio, compressibility index and angle of repose to determine the flow properties of granules.

Table. 2: Punches and die parameters during

Core		Cup	
Parameters	Standards	Parameters	Standards
Lower punch	5.5mm round	Lower punch	8mm round
Upper punch	5.5mm round	Upper punch	8mm round
Dies	5.5mm round	Dies	8mm round

Evaluation of tablets

i) Weight Variation Test

Twenty core and coated tablets with coat were selected at random and individually weighed in a single pan electronic balance and the average weight was calculated. The uniformity of weight was determined according to I.P. specifications (Table. 3).

Table. 3: I.P. Specification limits for weight

Average weight	% Difference
80mg	±10
More than 80 mg but less than 250mg	±7.5
250 mg or more	±5

ii) Thickness

The thickness of the tablets was determined using screw gauge. Five tablets were used for the above test from each batch. Thickness of the core tablets was noted prior to compression of the cup. Finally the thickness of core-in-cup tablets was determined [13].

iii) Hardness

The hardness of the tablet was measured using a Schleuniger tablet tester [13]. Five core tablets were taken and hardness was tested before compression of the cup and finally five core-in-cup tablets were taken and hardness was tested. Results are reported in kg/cm².

iv) Friability Test

This was measured using an electro lab friability apparatus where the tablets were subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets from a distance of 6 inches with each revolution. Prewighed samples of 20 tablets were placed in the friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Conventional compressed tablets that lose less than 0.5- 1.0% of their weight are generally considered acceptable [13].

v) Drug content determination (%Assay)

For determination of drug content three tablets from each formulation were weighed individually, crushed and diluted to 100ml with sufficient amount of purified water. Then aliquot of the filtrate was diluted suitably and analyzed spectrophotometrically at 274 nm against blank. The drug content of each formulation was

evaluated as per the standard protocol ranges between 99-101% w/v [14].

In-vitro dissolution studies

In vitro drug release studies of Metoprolol Succinate was studied using dissolution apparatus USP type II paddle method (Electro lab, India) with water as the dissolution media. Test was performed at a stirring speed of 50 rpm with the temperature maintained at 37 ± 0.5°C in 900ml of purified water for 24hrs. The dissolution samples of 10ml were withdrawn at sampling intervals 1, 2, 4, 8, 10, 12, 24 hours and were analysed spectrophotometrically at 274nm [15,16].

Drug release kinetics (dependent model method)

The mathematical models are used to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation coefficient (R^2) value in various models. The model that gives high ' R^2 ' value is considered as the best fit of the release data.

Mathematical models used are Zero order release model, First order release model, Hixson-Crowell release model, Higuchi release model, Korsmeyer – peppas release model [16].

Stability studies

Stability is defined as the ability of a particular drug or dosage form in a specific container to remain within its physical, chemical, therapeutic and toxicological specifications. Drug decomposition or degradation occurs during storage, because of chemical alteration of the active ingredients or due to product instability, lowering the concentration of the drug in the dosage form. The stability of pharmaceutical preparation should be evaluated by accelerated stability studies. The optimized formulation of Metoprolol Succinate tablets was selected for the stability studies. The accelerated stability studies were carried out according to ICH guidelines by storing the samples at 40 ± 2°C and 75 ± 5% RH for 3 months as given in Table. 4. The tablets were evaluated for hardness, drug content and dissolution study and compared with tablets which were evaluated immediately after manufacturing.

Table. 4: Storage Conditions in Stability Studies

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C/60%RH	3 months
Intermediate	30°C/75% RH	2 months
Accelerated	40°C/75% RH	1 month

RESULTS AND DISCUSSION:**Compatibility studies:**

The sample of drug and polymers were evaluated for physical compatibility and the results are mentioned in the Table. 5. From the results obtained, it is concluded that there are no changes in the physical nature of the samples. Thus the drug is compatible with polymers employed in the study.

Micromeritic properties:

Bulk density and tapped density for the formulations were in the range of 0.94 - 1.141gm/cc & 1.03 - 1.16 gm/cc. Compressibility index and Hausner's ratios were in the range of 5.45-11.4 % and 1.054-1.114 respectively. The results obtained confirm that all the batches which exhibit good flow properties. The results are given in the Table. 6.

Evaluation of tablets:

Thickness of tablets was found to be almost uniform in all the six formulations. They were found to be in the ranges of 2.18-2.54mm. All the tablets passed weight variation test as the % weight variation, which was within the Pharmacopoeial limits of $\pm 5\%$ of the weight. The average weight of all tablet formulations was within the ranges of 449-451mg. The weights of all the tablets were found to be almost uniform. The measured hardness of tablets of each batch of all formulations was ranged between 6.02-6.62Kg/cm², which is falling within the hardness specification as per I.P. The friability of tablets was found to be within the ranges between 0.001 to 0.118%, which are generally considered and acceptable as per I.P. The data indicates that the percentage friability was less than 1% in all the formulations ensuring no physical damage will take

Table. 5: Results of drug-excipient compatibility studies

API + Excipients	Ratios	Initial	40°C, 75% RH			
			10 days	20 days	30 days	Conclusion
API+HPMCK 100M	1:1	White	NCC	NCC	NCC	Compatible
API+ Sodium Alginate	1:1	White	NCC	NCC	NCC	Compatible
API+ Polyox wsr 303	1:1	White	NCC	NCC	NCC	Compatible
API+HCO	1:1	White	NCC	NCC	NCC	Compatible
API+Avicel PH 102	1:1	White	NCC	NCC	NCC	Compatible
API+PVP K 90 D	1:1	White	NCC	NCC	NCC	Compatible
API+Yellow iron oxide	1:0.1	Yellow	NCC	NCC	NCC	Compatible
API+Aerosil	1:1	White	NCC	NCC	NCC	Compatible
API+Magnesium stearate	1:0.1	White	NCC	NCC	NCC	Compatible

NCC- No Colour Change

Table. 6: Micromeritic properties of the formulations

Formulation code	Bulk Density (g/cc)	Tapped Density (g/cc)	Hausner's Ratio	Compressibility Index%	Angle of Repose(θ)
F1	1.041±0.3	1.16±0.1	1.114	11.4	25°43'±0.1
F2	1.02±0.4	1.12±0.2	1.09	9	26°46'±0.2
F3	1.01±0.2	1.11±0.1	1.09	9	23°31'±0.3
F4	1.02±0.28	1.11±0.21	1.08	8	26°89'±0.17
F5	0.96±0.24	1.03±0.27	1.07	7	29°14'±0.1
F6	0.95±0.24	1.03±0.27	1.095	9.5	28°14'±0.2
F7	0.94±0.2	1.03±0.2	1.095	9	29°12'±0.5
F8	0.96±0.2	1.04±0.2	1.08	8	24°21'±0.8
F9	1.1±0.5	1.16±0.4	1.054	5.45	19°81'±0.7

place during handling and shipping of tablets. The results indicate that the percentage of drug content was within the ranges of 99.08 to 99.94 % of Metoprolol Succinate which was within the acceptable limits as per the I.P. Trial (F9) is taken as optimized formulation batch, since all the parameters are found to be within limits when compared with all formulations. The results are given in Table. 7.

In-vitro dissolution study:

The results of in-vitro dissolution studies were mentioned in the Table. 8. The *in-vitro* dissolution studies were performed for the developed formulations and it was found that all the formulations have shown an initial lag time of 1 hour where there was no drug release for one hour, later the drug was released slowly

from the developed formulations. Of all the formulations developed formulation F9 was found to meet the requirements as a pulsatile drug delivery system, with zero order drug release.

Release kinetic models:

Drug release kinetics data obtained are represented in Table. 9 and figures 1-4, reveal that the optimized batch (F-9) follows first order kinetics and drug release mechanism is Higuchi model i.e., by diffusion.

Stability studies of optimized formulation

There was no significant change in physical and chemical properties of the tablets of formulation F-9 after 3 Months. Parameters quantified at various time intervals were shown in Table. 10.

Table. 7: Evaluations of post compression parameters

Batch no	Thickness(mm) $\pm$ S.D		Average Weight (mg) $\pm$ S.D	Hardness(Kg/cm ²) $\pm$ S.D		Friability (%) $\pm$ S.D	Assay (%)
	Core	Core-in-cup		Core	Core-in-cup		
F1	2.42 $\pm$ 0.012	4.32 $\pm$ 0.07	450 $\pm$ 1.922	6.23 $\pm$ 0.08	10.0 $\pm$ 2.02	0.033 $\pm$ 0.007	99.30
F2	2.39 $\pm$ 0.021	4.14 $\pm$ 0.12	449 $\pm$ 0.655	6.41 $\pm$ 0.05	10.9 $\pm$ 1.56	0.006 $\pm$ 0.023	99.08
F3	2.23 $\pm$ 0.014	4.01 $\pm$ 0.03	451 $\pm$ 1.01	6.23 $\pm$ 0.21	11.0 $\pm$ 0.98	0.083 $\pm$ 0.015	99.53
F4	2.32 $\pm$ 0.011	4.05 $\pm$ 0.09	450 $\pm$ 1.577	6.02 $\pm$ 0.01	11.1 $\pm$ 1.20	0.024 $\pm$ 0.025	99.56
F5	2.35 $\pm$ 0.017	4.11 $\pm$ 0.02	451 $\pm$ 1.09	6.62 $\pm$ 0.31	11.7 $\pm$ 2.30	0.118 $\pm$ 0.022	99.76
F6	2.18 $\pm$ 0.001	4.12 $\pm$ 0.01	450 $\pm$ 0.56	6.04 $\pm$ 0.42	10.5 $\pm$ 1.78	0.058 $\pm$ 0.029	99.02
F7	2.54 $\pm$ 0.012	4.01 $\pm$ 0.01	450 $\pm$ 1.01	6.20 $\pm$ 0.24	11.5 $\pm$ 1.94	0.001 $\pm$ 0.034	99.67
F8	2.24 $\pm$ 0.015	4.04 $\pm$ 0.03	450 $\pm$ 1.55	6.41 $\pm$ 0.15	10.1 $\pm$ 1.93	0.078 $\pm$ 0.044	99.75
F9	2.21 $\pm$ 0.015	4.02 $\pm$ 0.03	450 $\pm$ 1.08	6.34 $\pm$ 0.13	10.6 $\pm$ 1.51	0.045 $\pm$ 0.053	99.94

All the values are expressed as mean $\pm$ S.D; No. of trails (n) = 6

Table. 8: Dissolutions Profiles of Metoprolol Succinate formulations.

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	0
2	19.82	18.832	17.83	16.32	23.24	22.6	21.832	22.62	15.76
4	39.502	33.592	31.59	30.92	50.64	48.68	68.592	43.016	32.43
6	45.34	44.324	61.34	50.324	63.24	63.92	71.324	57.804	44.39
8	69.24	67.24	83.24	61.24	89.08	75.56	83.24	78.648	69.82
10	93.128	91.128	92.12	87.28	94.12	80.44	97.128	86.424	81.57
12	100	100	98.91	96.16	97.36	94.91	98.916	98.86	92.45
24	-	-	99.72	99.18	99.45	99.53	99.61	99.87	99.54

Table.9: Release kinetics for the optimized formulation

	ZERO	HIGUCHI	PEPPAS	FIRST
	Q Vs T	Q Vs $\sqrt{T}$	Log C Vs Log T	Log % Remain Vs T
Slope	4.646	29.92	1.9167	-0.0104
Intercept	13.85	-11.20	-0.0636	2.225
R 2	0.786	0.979	0.7222	0.9830

Table. 10: Results of stability studies of optimized batch.

Formulation Code	Parameters	Initial	1 Month	2 Month	3 Month	Limits as per Specifications
F-9	40°C/75% RH % Release	99.54	99.41	99.28	99.18	Not less than 85 %

Fig. 1: Zero order plot for the optimized formulation **Fig. 2:** First order plot for the optimized formulation **Fig. 3:** Higuchi plot for the optimized **Fig. 4:** Peppas plot for the optimized formulation

CONCLUSION:

In the present study, an attempt was made to design and characterize pulsatile drug delivery system for Metoprolol Succinate an anti Hypertensive drug by wet granulation technique. Ten formulations (F1-F9) of Metoprolol Succinate tablets were prepared by varying the ratio of the drug and polymer. Release of the drug from a matrix tablet containing hydrophilic polymers generally involves factors of diffusion. The core-in-cup formulation has a hydrophilic polymer HPMC K100M, Polyox WSR 303 and Sodium alginate (Natural polymer). The tablets equivalent to 450 mg of drug was formulated by core in cup method in which core tablet is 250 mg and the coating material with different polymers, at different concentrations. Tablets of each formulation were subjected to various evaluation parameters like thickness, hardness; friability, weight variation and drug content of the formulations were found to be satisfactory. Based on the results formulation F9 was found to produce a lag time of 1hr with subsequent first order release. Release of the drug from a matrix tablet containing hydrophilic polymers generally involves factors of diffusion. Diffusion is related to transport of drug from the dosage matrix into the in-vitro dissolution fluid. The core-in-cup technology is found to a potential technology, which can control the release of highly water soluble drugs for once-a-day administration with the use of a combination of hydrophilic and hydrophobic polymers. This core in cup technology along with pulsatile system of drug release helps in treating the diseases which follow circadian rhythms.

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