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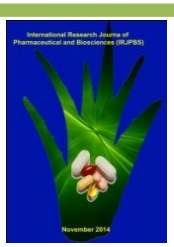

Development and Evaluation of Press Coated Core in Cup Tablets Containing Enalapril Maleate

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Abstract

The aim of the present work is to develop and evaluate press coated core in cup tablets containing model anti hypertensive agent enalapril for the treatment of hypertension. Pulsatile drug delivery system releases drug when and where required most. In the present studies three core tablet formulations viz., D1, D2, and D3 were fabricated using three novel super disintegrating agents viz., sodium starch glycolate, crospovidone, cross carmellose sodium and same was used to prepare different core-in-cup tablets using swellable and rupturable polymers with varying proportions. The powder blends of all the formulations for core tablet and core in cup tablets were evaluated for pre compression parameters viz., repose angle, bulk density, tapped density, Carr's index and Hauser's ratio. FT-IR studies were conducted to assess any interaction between the drug and the polymers. The powder blend of all the formulations for core tablets and core in cup tablets were subjected for direct compression into desired tablets using 10mm flat faced punches in 10 station rotary punching machine. These fabricated tablets were evaluated for post compression evaluation parameters viz., thickness, diameter, weight variation, drug content uniformity, hardness, friability, *in vitro* disintegration time and *in vitro* dissolution. *In vitro* dissolution data was statistically interpreted using PCP Disso V3 software. All the results were compliance with official specifications. *In vitro* dissolution studies showed three phases in all the graphs which were matching with sigmoid pattern for circadian rhythm.

Key words: Circadian rhythm, pulsatile tablets, super disintegrating, sigmoid pattern.

INTRODUCTION

Oral drug delivery systems are most popular, safe and convenient for the obvious merits of oral route of drug administration. In all the oral controlled dosage forms drug concentration is maintained in the therapeutic window so that it releases the drug for a prolonged period of time. But certain conditions that requires drug release after a lag time i.e., chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology [1]. several diseases show variation in circadian rhythm. Circadian i.e., 24 hrs time structure is the most common oscillation met in a number of diseases such as asthma and osteo arthritis where the severity of diseases and symptoms are mostly happening at night, in case of rheumatoid arthritis pain is very severe at the morning, in duodenal ulcer gastric acid secretion is high at night times [2]. Circadian changes are seen in all the cardiovascular diseases i.e., blood pressure, heart rate, stroke volume, which rises notably just before waking up is responsible for attacks. Capillary resistance and vascular reactivity are higher in the morning and decrease in the evening times [3,4]. For such chrono pathological conditions chronotherapeutic systems plays significant role, because these formulations release the drug whenever the symptoms are high. Such systems are designed to enable a pulsatile release of drug after a predetermined off release period i.e., lag time which controls the chronopathological conditions [5]. The present investigation is focused on development and evaluation of pulsatile tablets of enalpril an anti hypertensive agent. Pulsatile tablets releases certain amount of drug molecules with in a shorter duration spontaneously after predetermined lag period [5]. Enalapril is an anti hypertensive agent which is used to treat hypertension and it's an ACE (angiotensin converting enzyme) inhibitor. Enalapril lowers the hypertension/blood pressure by reducing peripheral vascular resistance without increasing heart rate, contractility and cardiac output. Many types of hypertension in patients suffering from diabetes and severe kidney failures can be easily treated with enalapril. It is best suitable drug for the treatment of heart failure. The bioavailability is 55% and its half life is 11 hrs; the absorption of enalapril will not be affected by taking food [6]. The concept of present investigation is aimed to develop and evaluate enalapril core in cup tablets by direct compression method which delivers the drug by chronotherapeutic approach.

MATERIALS AND METHODS

Materials

Enalapril active pharmaceutical ingredient was a gift sample from Cipla pharmaceutical company, Mumbai. PVP K90, talc, HPMC K4M, cross povidone, cross carmellose sodium, sodium starch glycolate, ethyl cellulose, MCC were procured from S.D. Fine chemicals. Mumbai. Magnesium stearate was obtained from Sigma Aldrich Company. Galen IQ 720 was used as directly compressible vehicle and it was obtained from Beneo palatinit industry, Germany. All other reagents used were of analytical grade throughout the study.

Methodology

In the present studies a model antihypertensive drug Enalapril is selected for the development of an alternative, simple, time lagged press coated core-in-cup tablets for pulsatile drug delivery to meet the needs to treat hypertension and some types of chronic heart failures. The press coated core-in-cup tablets were prepared by direct compression method using selected swellable polymers viz., MCC and rupturable polymers viz., ethyl cellulose and HPMC K4M. Three core formulations were tried with novel super disintegrating agents viz., sodium starch

glycolate, cross povidone and cross carmellose sodium. Six press coated core-in-cup tablets were designed with swellable and rupturable polymers.

Preparation of core tablet

Core tablet formulations viz., D-1, D-2 and D-3 were prepared using super disintegrating agent's viz., sodium starch glycolate, cross povidone and cross carmellose sodium in the ratio of 1: 0.5 for drug: polymer respectively by direct compression method. Calculated quantities of selected drug and polymers and directly compressible vehicle Galen IQ 72 were mixed in a polybag for 10min. to achieve uniform mixing. The mixture was subjected for direct compression using 8mm flat punch in Cadmach 10 station rotary punching machine. During compression weight variation, hardness was checked. The formulae of three core tablets are given in table 1.

Table 1: Formulae for Enalapril core tablets

Ingredients (in mg)	D-1	D-2	D-3
Enalapril maleate	20	20	20
PVP K90	20	20	20
Sodium starch glycolate	10	-	-
Cross povidone	-	10	-
Cross carmellose sodium	-	-	10
Talc	1	1	1
Mag stearate	1	1	1
Galen IQ 72	58	58	58
Total wt (mg)	110	110	110

Preparation of press coated core in cup tablets by direct compression method

Six batches viz., A-1 to A-6 were prepared by direct compression method. For each core tablet formulation two batches of core in cup tablets were prepared. Each core in cup tablets consisting of an impermeable layer of rupturable polymer ethyl cellulose was filled in the die cavity of 10 mm diameter then gently compact the powder bed with a flat surface spatula. The core tablet was carefully placed in the center of the powder bed then the die wall was filled with the mixture of swellable and rupturable polymers such as MCC (A1, A3, A5) and HPMC K4M (A2, A4, A6) so that the surrounding surfaces of the core tablet was fully covered. The powder bed was compressed directly by using 10 mm flat punch in Cadmach 10 station rotary punching machine. The different formulae of press coated core-in-cup are shown in table 2.

Table 2: Formulae of press coated core-in-cup tablets

BATCHES	A-1	A-2	A-3	A-4	A-5	A-6
Core tablets	**D-1**		**D-2**		**D-3**	
Core tablet wt in mg	110	110	110	110	110	110
Ethyl cellulose in mg	200	200	200	200	200	200
Micro crystalline cellulose	50	---	50	--	50	-----
HPMC K4M in mg	-----	50	----	50	--	50
Total weight in mg	360	360	360	360	360	360

Evaluation

Precompression and post compression evaluation [8,9]

The prepared powder blends during the preparation of core tablets were subjected for precompression characteristics viz., bulk density, tapped density, compressibility index, flow properties (angle of repose). Core tablets and core-in-cup tablets were evaluated for their thickness, diameter, weight variation, hardness, friability, disintegration time and dissolution rate profiles by adapting standard procedures. All studies were carried out in triplicate and mean values were shown in the tables.

In vitro release kinetic study [7]

In vitro drug dissolution studies were carried out for core tablets using 0.1N HCl as dissolution fluid, and for core in cup tablets initially the study was carried out in 900 ml of 0.1N HCl for first 2 hrs. and then 900 ml of phosphate buffer pH 7.4 from 3 to 12 hrs by using USP XXII dissolution apparatus type II (Campbell electronics, Mumbai). The drug release at different time intervals was measured at 207 nm using a double beam UV spectrophotometer. The study was conducted in triplicate and data were computed by using dissolution software PCP Disso V3.0. Results of *in vitro* release kinetic study and model fitting values are shown in tables 7-9.

RESULTS AND DISCUSSION

Precompression studies

The powder blend for core tablet and core-in-cup materials were prepared and subjected for precompression evaluation and the results are given in tables 3 and 4.

Table 3: Pre compression evaluation data for core tablet powder blend.

Batches	Bulk density*±SD	Tapped density*±SD	Carr's index ±SD *	Hausner's ratio*±SD	Angle of repose*±SD
D-1	0.364 ± 0.005	0.413 ± 0.006	11.03 ± 0.137	1.21 ± 0.074	21.59 ± 0.5
D-2	0.312 ± 0.002	0.385 ± 0.003	18.74 ± 0.006	1.23 ± 0.006	28.61 ± 0.7
D-3	0.355 ± 0.003	0.396 ± 0.002	10.23 ± 0.296	1.11 ± 0.004	21.08 ± 0.6

***Average of three determinations.**

Table 4: Pre compression evaluation data for core-in-cup materials.

Batches	Bulk density*±SD	Tapped density*±SD	Carr's index*±SD	Hausner's ratio*±SD	Angle of repose*±SD
A1	0.517 ± 0.003	0.578 ± 0.006	16.88	1.20	29.12 ± 0.769
A2	0.589 ± 0.004	0.597 ± 0.002	14.89	1.18	27.09 ± 0.739
A3	0.563 ± 0.006	0.588 ± 0.005	16.95	1.19	28.19 ± 0.634
A4	0.564 ± 0.004	0.658 ± 0.003	13.04	1.17	26.14 ± 0.698
A5	0.524 ± 0.003	0.626 ± 0.002	13.84	1.18	25.41 ± 0.784
A6	0.578 ± 0.004	0.646 ± 0.004	13.37	1.20	26.12 ± 0.804

***Average of three determinations.**

Post compression studies

The core tablet and core-in-cup tablets were prepared and subjected for post compression evaluation and the results are given in tables 5 & 6.

Table 5: Post compression evaluation data for core tablets

Parameters	D1	D2	D3
Weight variation*±SD	110.23±0.41	109.62±0.32	110.14±0.48
Thickness(mm) *±SD	3.61 ± 0. 14	3.24±0.41	3.29±0.74
Diameter(mm) *±SD	8.31 ± 0.217	8.17±0.15	8.36±0.12
Hardness(kg/cm^2) *±SD	3.5 ± 0. 57	3.3±0.32	3.6±0.41
Friability(%) *±SD	0.517±0. 25	0.4±0.39	0.6±0.63
Drug content(%) *±SD	99.56 ± 0.73	99.39±0.51	99.11±0.67
Disintegration time* ±SD (sec)	50.6 ± 0.46	121±0.32	110±0.53

***Average of three determinations.**

Fig 1: Digital photographs of core tablet formulations D1, D2, D3.

Table 6: Post compression evaluation data for core-in-cup tablets

Parameters	A1	A2	A3	A4	A5	A6
Weight variation*±SD	360.07 ± 0.02	360.01 ± 0.002	359.1 ± 0.015	359.95 ± 0.03	35.92 ± 0.021	350.05 ± 0.005
Thickness(mm) *±SD	5.91 ± 0.02	5.04 ± 0.04	5.05 ± 0.011	5.12 ± 0.02	5.12 ± 0.02	5.08 ± 0.015
Diameter(mm) *±SD	10.03 ± 0.057	10.13 ± 0.057	10.06 ± 0.115	10.14 ± 0.058	10.13 ± 0.057	10.10 ± 0.1
Hardness(kg/cm^2) *±SD	6.06 ± 0.057	6.93 ± 0.057	6.96 ± 0.115	6.07 ± 0.057	6.97 ± 0.058	6.0 ± 0.1
Friability(%) ±SD *	0.488 ± 0.025	0.42 ± 0.011	0.123 ± 0.012	0.43 ± 0.005	0.60 ± 0.006	0.673 ± 0.005

***Average of three determinations.**

Table 7: *In vitro* model fitting values for A-1 to A-6 core in cup tablets

Batch code	Zero order	1st order	Matrix	Hixon Crow	Peppas	n	k	Best fit model
A-1	0.9584	0.9576	0.8718	0.9653	0.9796	1.1282	6.6357	**Peppas**
A-2	0.9534	0.9620	0.8752	0.9685	0.9714	1.1332	6.7595	**Peppas**
A-3	0.9571	0.9496	0.8829	0.9731	0.9731	1.1617	6.6845	**Peppas**
A-4	0.9506	0.9563	0.8586	0.9595	0.9739	1.1419	6.0159	**Peppas**
A-5	0.9509	0.9629	0.8724	0.9659	0.9713	1.1483	6.5295	**Peppas**
A-6	0.9585	0.9659	0.9121	0.9802	0.9823	0.9951	10.2463	**Peppas**

DISCUSSION

In the present studies three core tablet formulations viz., D1, D2, and D3 were fabricated using three novel super disintegrating agents viz., sodium starch glycolate, crospovidone, cross carmellose sodium and same was tried to prepare different core-in-cup tablets using swellable and rupturable polymers with varying proportions. The powder blends of all the formulations for core tablet and core in cup tablets were evaluated for pre compression parameters viz., repose angle, bulk density, tapped density, Carr's index and Hauser's ratio. The powder blend of all the formulations for core tablet and core in cup tablets were subjected for direct compression into desired tablets using 10mm flat faced punches in 10 station rotary punching machine. These fabricated tablets were evaluated for post compression evaluation parameters viz., thickness, diameter, weight variation, drug content uniformity, hardness, friability, *in- vitro* disintegration time and *in- vitro* dissolution.

Pre compression evaluation of core formulation

The bulk density was found to be 0.312± 0.002 to 0.364 ± 0.005 g/cm^3; tapped density 0.385±0.003 to 0.413 ± 0.006 g/cm^3; compressibility index was found to be in the range of 10.23 ± 0.293 to 18.74 ± 0.006 and Hauser's value 1.11 to 1.23 for D1, D2, and D3 indicates a powder with good flow properties. All the formulations showed that the blend of powder in core formulation having good flowability. The angle of repose was found to be 21'08˚ ± 0.6 to 28.61 ± 0.7 for D1, D2, and D3 formulations indicates blend was free flowing and can be used for direct compression.

Pre compression evaluation of core in cup formulation

The bulk density was found to be in the range of 0.517±0.003 to 0.589±0.004g/cm^3; tapped density 0.578±0.006 to 0.658±0.003 g/cm^3; compressibility index value 13.04 to 16.95 and Hauser's value 1.17 to 1.20 for A1 to A6 respectively indicates a powder with good flow properties. A1 to A6 formulations showed that the blend of powder in all formulations having good flowability. The angle of repose was found to be in the range of 25'41˚ to 29'12˚ for A-1 to A-6 formulations showing that the blend of powder was free flowing and can be used for direct compression.

Post compression evaluation of core tablet

Thickness of the core tablet was found to be 3.24±0.41 to 3.61 ± 0.14 mm and the diameter was 8.17±0.15 to 8.36±0.12 mm for core tablet formulations. The results are within the limits and are in accordance with pharmacopoeial standards. The hardness of the tablets was about

3.3±0.32 to 3.6±0.41 kg/cm^2 and friability was found to be in the range of 0.4±0.39 to 0.6±0.63 which was below 1% indicating the sufficient mechanical integrity and strength of the prepared tablets. The hardness and friability data indicates good mechanical strength/resistance to the tablets. The weight variation results revealed that average percentage deviation for 20 tablets of core tablet formulation was less than ±10%, which provide good uniformity of the tablets and were found to be within acceptable limits as per the pharmacopoeial specifications where as the percentage drug content was found to be in the range of 99.11±0.67 to 99.56 ± 0.73 for D1, D2, D3 formulations. The low SD values indicate the drug content was uniform in all the formulated tablets. The disintegration test was performed and it was found to be 50.6 ± 0.46 sec, 121±0.32 sec and 110±0.53 sec for D1, D2 and D3 respectively for all three formulations indicating well within the standards.

Post compression evaluation of core in cup tablet

Post compression evaluation tests were done for core in cup tablets, the thickness of the core in cup tablets was found to be in the range of 5.04±0.04 to 5.91±0.02 mm and diameter was found to be in the range of 10.03 ± 0.057 to 10.14 ± 0.058 mm for A-1 to A-6 formulations. The results are within the limits and are in accordance with pharmacopoeial standards.

The hardness of the tablets was found to be in the range of 6.0 ± 0.1 to 6.96 ± 0.115 kg/cm^2 for A-1 to A-6 formulations. The friability was found to be in the range of 0.123±0.012 to 0.673 ± 0.005 % for A-1 to A-6 formulations which were below 1% indicating the sufficient mechanical integrity and strength of the prepared tablets. The hardness and friability data indicates good mechanical strength/resistance to the tablets. The weight variation results revealed that average percentage deviation for 20 tablets of core in cup tablet formulations was less than 5%, which provide good uniformity of the tablets and were found to be within acceptable limits as per the pharmacopoeial specifications. The low SD values indicate the drug content was uniform in all the formulated tablets. All parameters were found to be within specified limits as per IP/BP. The results were within the limits and are in accordance with pharmacopoeial standards. The press coated core-in-cup pulsatile system was developed consist of three components, the central core tablet made up pure drug enalapril and different concentrations of super disintegrating agents viz., sodium starch glycolate, cross povidone and cross carmellose sodium in the ratio of 1: 0.5 (drug: polymer) respectively by direct compression method. The impermeable surrounding (lateral) consist of ethyl cellulose and the top layer consist of swellable polymer MCC and HPMC K4M. Both the external layers are intended to regulate the function of the system and modify the release of drug. The polymer materials present in the core tablet regulate drug release in controlled manner. This type of tablet could be described as a hybrid system in which the top cover layer consists of a swellable polymer layer and the inner part of a conventional core tablet prepared with super disintegrating agents acting as a drug reservoir. The A-1, A-3, A-5 was designed with an active core using the ethyl cellulose: MCC and A2, A-4, A-6 with ethyl cellulose and HPMC K4M and hydrophobic cup with ethyl cellulose kept constant in all the six formulations.

In vitro drug dissolution studies were carried out for core tablets using 0.1N HCl as dissolution fluid, for core in cup tablets initially the tablets were subjected in dissolution in 900 ml of 0.1N HCl for first 2 hr and after that media was changed to 900 ml of phosphate buffer pH 7.4 from 3 to 12 hr by using USP XXII dissolution apparatus type II. The initial release was found to be of

6.78%, 6.19%, 6.15%, 6.34%, 6.04%, and 8.62% for A-1, A-2, A-3, A-4, A-5 and A-6 formulations respectively at the end of 1hr. The lag time for A-1, A-2, A-3, A-4, A-5 and A-6 formulations was found to be 4hr. The A-1 formulation prepared with MCC exhibited drug release 18.28% at the end of 4hr and release 64.30% at the end of 5 hr, 94.69% release at the end of 12hr. The A-2 formulation prepared with HPMC K4M exhibited drug release 17.23% at the end of 4hr and release 69.17% at the end of 5 hr, 96.04% release at the end of 12hr. The A-3 formulation prepared with MCC exhibited drug release 18.80% at the end of 4hr and release 69.18% at the end of 5 hr, 98.11% release at the end of 12hr. The A-4 formulation prepared with HPMC K4M exhibited drug release 18.47% at the end of 4hr and release 64.28% at the end of 5 hr, 92.01% release at the end of 12hr. The A-5 formulation prepared with MCC exhibited drug release 19.23% at the end of 4hr and release 69.17% at the end of 5 hr, 94.86% release at the end of 12hr. The A-6 formulation prepared with HPMC K4M exhibited drug release 17.82% at the end of 4hr and release 66.28% at the end of 5 hr, 97.87% release at the end of 12hr.

CONCLUSION

In all the six formulations the lag period was found to be 4hr. After lag period the drug release was rapid due to influence of combination of rupturable and swellable polymers and it was extended up to 6 hr. The cumulative amount of drug release after 6hrs was found to be 74.09%, 78.23%, 78.24% and 72.16%, 78.23% and 83.14% for A-1 to A-6 formulations respectively. Further, the drug was release was sustained for 12hr. The cumulative amount of drug release after 12hr was found to be 94.69%, 96.04%, 98.11%, 92.01%, 94.86% and 97.87% for A-1, A-2, A-3, A-4, A-5 and A-6 formulations respectively. The dissolution data was fitted with various kinetic models using dissolution software PCP DissoV.03. In all the six formulations the best fit model was found to be Korsemeyer peppas with exponential 'n' value ranging from 1.1282, 1.1332, 1.1617, 1.1419, 1.1483 and 0.9951 for A-1, A-2, A-3, A-4, A-5 and A-6 formulations respectively clearly indicates the release was bi exponential follows case II transport mechanism of drug release.

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