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DESIGN AND DEVELOPMENT OF MULTI-PARTICULATE TABLET FORMULATION OF ACE INHIBITOR FOR CHRONOTHERAPY

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ABSTRACT

The aim of the present study was to develop a chronotherapeutic drug delivery system containing enalapril maleate, an ACE inhibitor, enabling two pulse drug release for management of early morning high blood pressure. MUPS Tablet formulation has been prepared containing two different kind of pellets i.e. drug containing core pellets for immediate release and delayed release polymer coated pellets for providing pulse release after a predetermined lag time. Compression of pellets into MUPS tablets present certain challenges. The study design developed to obtained information on effect of different cushioning agents with its range on drug release profile from MUPS tablets. In addition of pellet size, comparison of pellets prepared with different techniques, effect of different % polymer coating , effect of pegylation above polymer coat on compression was also been evaluated. Silicified MCC with around 50 % w/w concentration of tablet weight along with PEGylated DR pellets identified for targeted pulsatile drug delivery system. And obtained chronotherapeutic formulation can be enable to treat nocturnal hypertension.

KEYWORDS: MUPS; Pulsatile drug delivery; Chronotherapeutic formulation; Pellet; ACE inhibitor.

INTRODUCTION

Conventional drug dosage forms have been widely used and first choice of the physicians for treatment of various conditions. These dosage forms typically provide an immediate or rapid medication release, and supply total amount of the drug to the systemic circulation without any rate control. To maintain the effective plasma drug concentration, frequent administration is required. Due to poor drug efficacy, the incidence of side effects, frequency of administration and patient noncompliance of these conventional drug preparations increases. These traditional drug dosage forms are undergoing replacement by second-generation, modified drug-release dosage forms, which can achieved continuous and constant-rate drug delivery, in which constant or sustained drug output minimize drug concentration "peak and valley" levels in the blood, so promoting drug efficacy and reducing adverse effects, by reduced dosing frequency compared to conventional release preparations.[1]

In upgradation of the conventional dosage form, numerous technical advancements in biodegradable polymers, formulations and comprehensive understanding of pharmacokinetics have resulted new techniques of drug delivery. These techniques are capable of not only sustaining the duration of drug release but controlling the rate of drug release and/or targeting delivery of a medicinal agent to a specific organ or tissue. It is for this reason controlled or targeted drug delivery systems have been, and continue to be, receiving more and more attention. However, recently one type of drug delivery system, where delivery system is capable of releasing drug after predetermined time-delay, known as pulsatile drug delivery system has drawn the attention of scientists.[2]

Optimum therapy is more likely to result when the right amount of drug is delivered to the correct target organ at the most appropriate time. Although many controlled-release preparations have been developed, the drug preparation according to the concept of chronotherapy should be preferably to deliver the drug in a pulsatile fashion, rather than a continuous delivery. This drug delivery aims to improve the therapeutic efficacy by varying drug release in accordance with patient need (i.e. the ideal drug delivery system should involve a non-delivery period rather than a continuous delivery period). For solid dosage forms, chronotherapy is achieved by the use of slowed-release coatings to delay the release of one or more drugs until an approximate predetermined time period.[3]

The onset and extent of disease symptoms in bronchial asthma, arthritis, duodenal ulcers, cancer, diabetes, neurological disorders and in hypertension varies in circadian rhythm and so required chronotherapeutic drug delivery system.[4]

Cardiovascular events occur more frequently in the morning, and ambulatory blood pressure (BP) exhibits a diurnal variation with increase in the morning (morning BP surge). The morning BP surge was reported to be associated with high risk of cardiac death, and ischemic and haemorrhagic stroke. Thus, antihypertensive medication more specific for morning BP in addition to 24-h BP would be useful for the prevention of cardiovascular events in hypertensive patients. An increase in incidences of early morning myocardial infarction, sudden cardiac death and stroke[2], lead towards a need for a time-programmed therapeutic scheme, whereby the drug is at the site of action at the right time in the required amount. This requires consideration of the time of drug release from the drug delivery system (Chrono-pharmaceutics) rather than maintaining constant plasma drug levels. A drug delivery system administered at bedtime, but releasing a higher concentration of drug well after the time of administration (during morning hours), followed by maintenance of plasma levels for the rest of the day, would be preferable in such cases.[4]

Clinical studies have consistently documented differences in BP-lowering efficacy, duration of action, and effects on the circadian BP pattern depending on the administration time of medications interacting with the renin-angiotensin-aldosterone system. Three Independent trials have demonstrated a different effect of several angiotensin-converting enzyme (ACE) inhibitors when dosed in the morning versus the evening.[5]

The objective of the recent research study was to develop a tablet formulation containing different multiparticulate with time-controlled / pulsatile release profile. Which can provide the initial loading dose of the active and suppress remaining amount of active to be release for predetermined lag time and then it released the drug rapidly; which can overcome problem described as above of chronobiology and chronotherapy.

Compression of the pellets is very challenging task, different process factors i.e. compression force, turret speed, dimension of compression tooling; and formulation's factors i.e. Nature of the cushioning agent, % of cushioning agent with respect to pellets, thickness of the polymer coat (% polymer coating gain), size of the pellets, % plasticizer used in polymer coating; affects pellets structure resulting in denature of the pellets , breakage of the polymer coat and leads to dose dumping or change in drug release profile.[6]

OBJECTIVE: Objective of the research work is skeletonised in figure 1 and figure 2.

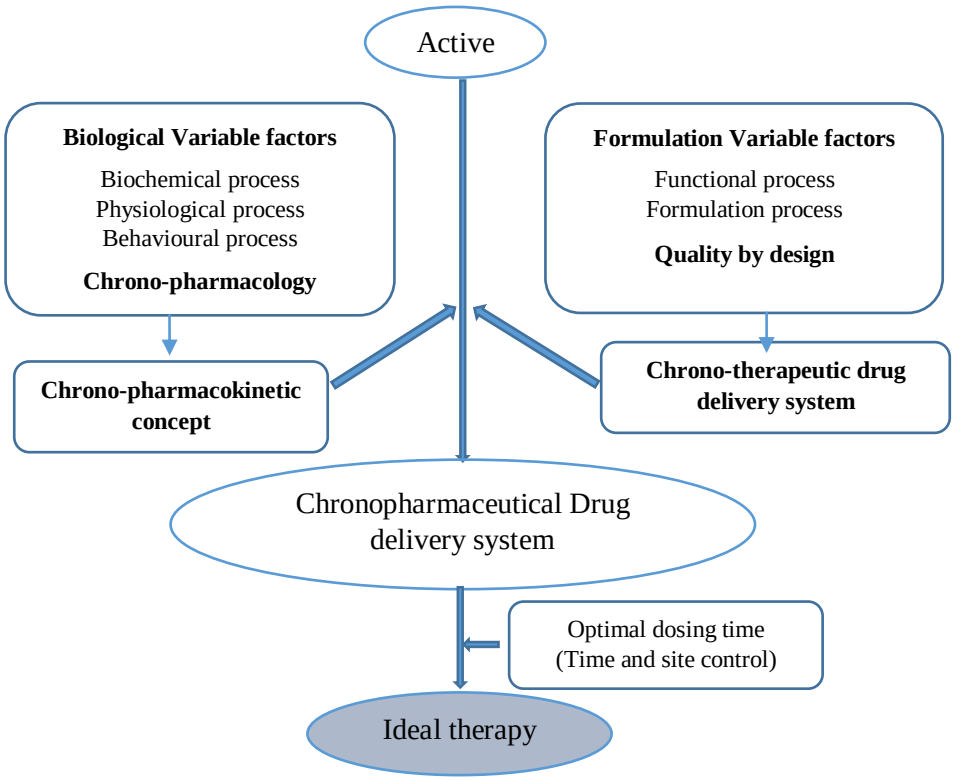

Fig 1: Design and development of chronotherapeutic DDS with respect to circadian rhythm.

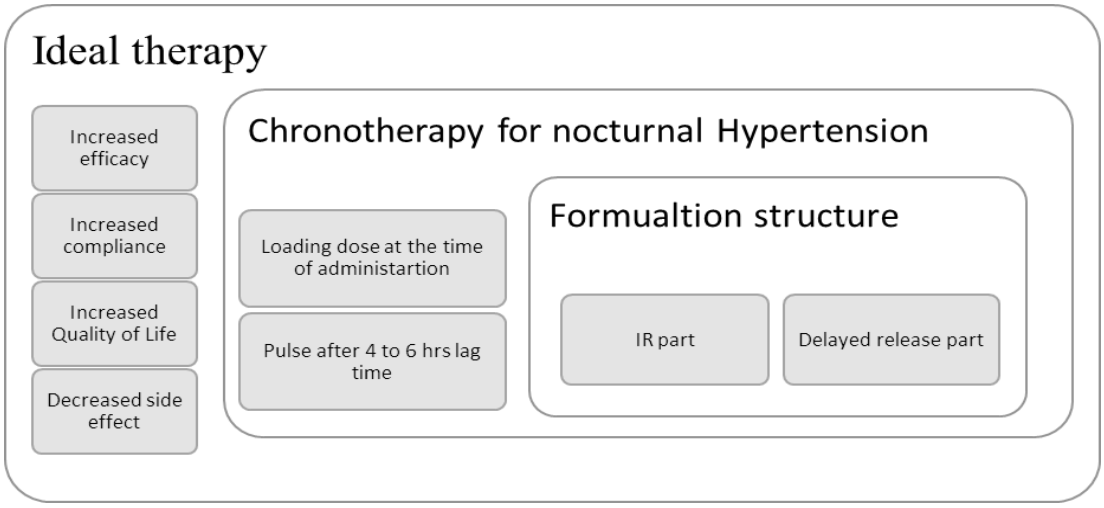

Fig 2: Conceptualisation of the proposed new drug delivery system.

With respect to objective of the formulation development, to design a tablet formulation with immediate release (IR) pellets along with delayed release (DR) pellets resulting 2 pulse of drug release i.e. one pulse at 1st hr of drug administration and 2nd pulse after 5 to 6 hrs lag time.

MATERIAL AND METHOD

MATERIAL

Enalapril maleate was a kind gift from Neuland laboratories Ltd (India). Microcrystalline cellulose, Lactose and Hydroxy propyl methyl cellulose (HPMC E 15) were supplied as free gift sample from Signet Chemical Corporation Pvt. Ltd. (India). Eud. RL and Eud. S® were obtained from Rohm Pharma (Gmbh, Germany). MCC NPS and Silicifed MCC obtained from JRS pharma, Lactose / MCC co process excipient obtained from Sheffield bio science. Other ingredients such as PEG 4000,Triethylcitrate (TEC), dichloromethane (DCM), Isopropyl alcohol (IPA), lubricants and glidants used to prepare the pellets were of standard Pharmacopoeial grade.

METHOD

A) Formulation of drug loaded pellets: Different techniques are available to prepare pellet formulations i.e. Agitation, Compaction, Layering and globulation. In this study Drug loaded pellets has been prepared with two different technology.[7]

1) Extrusion Spheronization: Microcrystalline cellulose (MCC) and lactose (4:1) based pellets containing HPMC (7.5 % w/w) as a binder has been prepared by Extrusion spheronization technique.[8]

Brief manufacturing process: MCC, lactose anhydrous and enalapril maleate were mixed sufficiently and was added a certain amount of aqueous solution of HPMC as a binder to make a wet mass which was subsequently extruded through a 0.5 mm screen by the extruder. The extruded material was spheronized with the use of spheroniser at 600 rpm speed to form pellets cores with appropriate dimeters. After spheronization, the obtained pellets cores were dried in a fluidized bed for 1 h. The inlet air temperature was 60 °C and the intake flow rate was 0.4 to 0.6 bar. Then the pellets were sieved and the moiety ranging in 30-35 mesh were collected to conduct further polymer coating process. The same experiment was repeated with 0.8 mm extrudes to get 20-25 mesh granules. Composition of the core pellets is shown in table 1.

Robustness of the pellets has been evaluated with respect to immediate drug release and friability of the pellets.

Table 1: Composition of core pellets prepared with extrusion Spheronization.

Excipients	% w/w composition
API	14.3
MCC	62.6
Lactose	15.7
HPMC	7.5

2) Drug layering on core pellets (Non-pareil seeds - NPS): MCC based NPS (35-40 mesh) was coated with aqueous dispersion of enalapril maleate with HPMC as binder in fluidised bed coater, the coating condition is shown in table 2. 70 mg of drug layered pellets provides a unit dose i/e/10 mg of enalapril maleate.

Table 2: Coating process parameters for drug layering on NPS.

Process Parameters	Specifications
Inlet temperature (°C)	50-55
Product temperature (°C)	35-40
Fluidisation (Bar)	0.5-0.7
Coating solution spray rate (g/min)	0.1 – 1.5
Automisation pressure (Bar)	0.5-0.7
Nossle used (mm)	1.0
Air drying after coating stage (min)	20 min

B) Rate controlling polymer Coating of pellets: All 3 variants of drug loaded pellets were subjected to polymer coating. The polymer selected for coating is a mixture of

different category of polymethacrylates i.e. Eudragit RL (pH nondependent polymer) and Eudragit s (pH dependent polymer – soluble above pH 7).[9, 10] Based on the detailed DOE study[8] on formulation variables, optimised formula has been selected for further processing i.e. 3:1 ratio of polymer with 6 % w/w and 12 % w/w coating on drug loaded core pellets. Polymer coating on pellets has been done in fluidised bed coater. Details of composition and coating process parameter is tabulated in table 3a and in table 3b respectively.

Table 3a: Detailed composition of polymer coated pellets.

% Coating (w/w)	*6%*	*12%*	*6%*	*12%*	*6%*	*12%*
Unit Composition in mg	A1	A2	A3	A4	A5	A6
Core pellets (0.5 mm extrudes)	70	70	--	--	--	--
Core pellets (0.8 mm extrudes)	--	--	70	70	--	--
Core pellets (prepared with drug layering)	--	--	--	--	70	70
Eud. S 100	1.05	2.1	1.05	2.1	1.05	2.1
Eud. RL 100	3.15	6.3	3.15	6.3	3.15	6.3
TEC	0.7	1.4	0.7	1.4	0.7	1.4
Total pellet weight	74.9	79.8	74.9	79.8	74.9	79.8
Total pellet weight with lubrication	76.4	81.4	76.4	81.4	76.4	81.4

Brief process for polymer coating of pellets: Six per cent (w/w) solutions of polymethacrylates (Eud. RL and Eud. S) were prepared in IPA:DCM (7:3) mixture. The solution was plasticized with Tri ethyl citrate (TEC) (≈16%, w/w, with respect to dry polymer), and then talc was added as a glidant. For each variant 200 grams of enalapril maleate pellets were coated in a fluidized bed coating apparatus (Pam-Glatt). Samples of coated pellets were removed from the apparatus when the coating load had reached 6 % and 12 % w/w.

Table 3b: Process parameters for polymer coating on drug loaded pellets.

Process Parameters	**Specifications**
Inlet temperature (°C)	45-50
Product temperature (°C)	35-40
Fluidisation (Bar)	0.4-0.6
Coating solution spray rate (g/min)	0.25 - 2
Automisation pressure (Bar)	0.4-0.6
Nossle used (mm)	0.8
Air drying after each % coating stage (min)	10 min

Drug release from polymer coated pellets: accurately weighed polymer-coated pellets equivalent to 10 mg of enalapril maleate were transferred to the dissolution medium. The test was carried out in a USP dissolution type I assembly , at a rotation speed of 100 rpm in 900 ml medium at 37°C $\pm$ 0.5 °C. The media selected for dissolution is pH 1.2 (HCl 0.1 N), followed by pH 4.5 followed by pH 6.8 (phosphate buffer) for 2 h, 2 h, and the remaining 8 h respectively. All the experiments were carried out in triplicates. 10 ml of samples were withdrawn at predetermined time points, filtered by 0.45 PVDF filter discarding first few ml of the filtrate for further processing of determination of content by HPLC. HPLC conditions were as follows: a Inertsil ODS 3V® C18 column (250mm_4.6 mm, 5µm) was used; The mobile phase was a mixture of acetonitryl and phosphate buffer (25/75, v/v); the flow rate was 2.0 ml /min and the column temperature was 50 °C. the detection wavelength is 215 nm.[8]

C) MUPS Tablet formulation: Compression of the pellets to prepare multiparticulate drug delivery system having pulse release profile.

All 3 kind of drug loaded core pellets showed similar dissolution profile and so to reduce the variability in formulation processing; as an immediate release granules part; drug layered core pellets has been selected for further tablet processing as a loading dose part.

MUPS Tablet formulation containing 10 mg enalapril maleate designed such a way that it contains 50 % of dose as immediate release part for loading dose and another 50 % of dose as DR part as a maintenance dose 9as a pulse release after a lag time period).

Tablets had been prepared with different formulation variables i.e. different natured cushioning agents, different concentration of cushioning agents, different hardness, different percent DR polymer coating on pellets and PEGylation on DR polymer coated pellets. Evaluation of the tablet has been done for drug release profile.

Drug release from MUPS tablet: MUPS tablet containing 10 mg of enalapril maleate were transferred to the dissolution medium. The test was carried out in a USP

dissolution type I assembly, at a rotation speed of 100 rpm in 900 ml medium at 37°C ± 0.5 °C. The media selected for dissolution is pH 1.2 (HCl 0.1 N), followed by pH 4.5 followed by pH 6.8 (phosphate buffer) for 2 h, 2 h, and the remaining 8 h respectively. All the experiments were carried out in triplicates. 10 ml of samples were withdrawn at predetermined time points, filtered by 0.45 PVDF filter discarding first few ml of the filtrate for further processing of determination of content by HPLC. HPLC conditions were as follows: a Inertsil ODS 3V® C18 column (250mm_4.6 mm, 5µm) was used; The mobile phase was a mixture of acetonitryl and phosphate buffer (25/75, v/v); the flow rate was 2.0 ml /min and the column temperature was 50 °C the detection wavelength is 215 nm.[8]

1) Effect of different cushioning agents

Avicel pH 102, co-processed Lactose/MCC, co-processed colloidal silicondioxide / MCC and spray dried lactose has been selected as a cushioning agents.

IR pellets and 5 mg equivalent DR pellets (formulation A5 and A6) has been mixed with equal amount of different cushioning agents in blender for 10 minutes. 3 % w/w cross povidone, 1 % w/w talc and 1% w/w magnesium stearate has been added in the pellet blend asa tableting aids. Detailed formulation is given in table 4.

Table 4: Basic formulation details for MUPS tablet.

Composition (mg)	Formulation X1	Formulation X2
IR pellets	35	35
DR pellets (6 % w/w polymer coated)	38.2	--
DR pellets (12 % w/w polymer coated)	--	40.7
Cushioning agent	70	72.5
Cross povidone	4	4
Talc	1.4	1.4
Magnesium stearate	1.4	1.4
Tablet weight	150	155

Compression has been done with standard concave punch tooling on rotary compression machine with keeping constant compression force.

Dissolution of the formulations has been done as per method described above, along with only pellet mix (IR pellets + DR pellets) as a target release profile as comparator.

2) Effect of concentration of cushioning agents

Avicel Ph 102 and silicified MCC has been selected for further study with 12 % w/w polymer coated pellets as DR part of composition, as other permutation combination showed drastic change / increase in drug release profile compared to target drug release profile.

Basic composition of the formulation with around 70 %, 60 % 50 % 40 % cushioning agent shown in table 5.

Table 5: Formulation details for MUPS tablet with varying conc. of cushioning agent.

Formulation composition (mg)	% w/w cushioning agent			
	70 %	60 %	50 %	40 %
IR pellets	35	35	35	35
DR pellets (12 % w/w polymer coated)	40.7	40.7	40.7	40.7
Cushioning agent	161.8	102.2	72.5	43.4
Cross povidone	7.5	5.5	4	3.5
Talc	2.5	1.8	1.4	1.2
Magnesium Stearate	2.5	1.8	1.4	1.2
Tablet weight	250	187	155	125

Dissolution of the formulations has been done as per method described above.

Based on the dissolution results 50 % and 60 % w/w silicified MCC has been selected as cushioning agent for further experiments.

3) Effect of compression force / hardness on pellet compression:

Formulation with silicified MCC 50 % w/w and 60 % w/w has been prepared with three different hardness, optimum, lower and high hardness and all six formulations were subjected to dissolution as per method described above.

4) Effect of PEG coating on DR pellets: 10 %w/w PEG 4000 has been coated on the DR pellets with 12 % polymer coat. PEG coated pellets has been compressed with silicified MCC 50 % w/w only with different hardness as similar as above. And all three formulations were subjected to dissolution as per method described above. Formulation detail is shown in table 6.

Table 6: Formulation details for MUPS tablet with PEGylated DR pellets.

Formulation composition (mg)	50 % cushioning agent
IR pellets	35
DR pellets (12 % w/w polymer coated + 10 % PEG 4000 coated)	44.8
Cushioning agent	72.2
Cross povidone	4.8
Talc	1.6
Magnesium Stearate	1.6
Tablet weight	160

RESULT AND DISCUSSION

A) Formulation of drug loaded pellets: The obtained granules drug load is around 14 % i.e. 70 mg pellets contains 10 mg enalapril maleate.

Physical parameters and robustness of all three different core pellets prepared with different techniques are shown in table 7 and comparative drug release profile is shown in figure 3.

Table 7: Comparative physical properties of different drug loaded core pellets.

Parameters	Core pellets (0.5 mm extrudes)	Core pellets (0.8 mm extrudes)	Core pellets (by drug layering)
% Friability	0.1	0.13	0.05
% moisture content	1.5	1.2	0.8
% agglomerates	≈ 10	< 5	< 5
% drug release in 15 min	72	69	80
Size of the pellets	b/w 400 - 500 µ	b/w 700 - 800 µ	b/w 350 - 450 µ

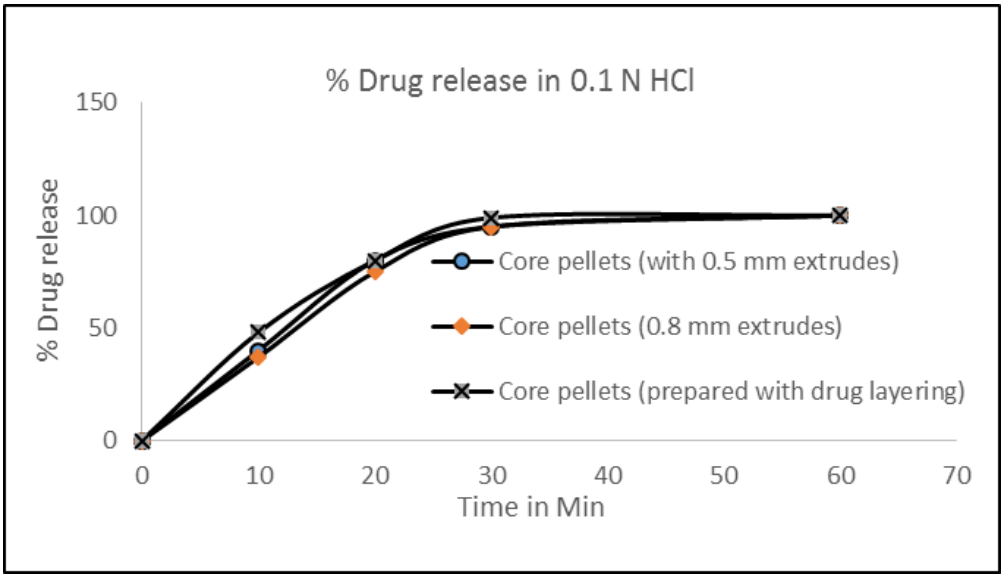

Fig 3: Comparative drug release profile of different drug loaded core pellets.

B) Rate controlling polymer Coating of pellets: Desirability plot obtained from detailed DOE study on formulation variables i.e Ratio of Eud. S to Eud. RL (1:0, 1:2 and 1:4) and % w/w polymer coating level (6, 12 and 18 % w/w) is shown in figure 4.

To get lag time around 4-5 hrs the desirable formulation is with 1:3 ratio of polymer and coating should be around 6 % and more.

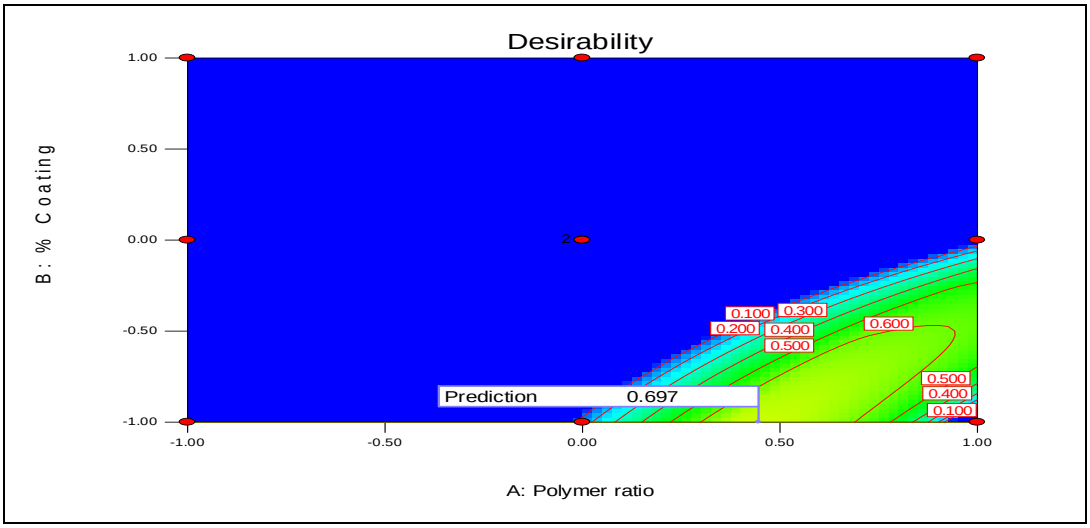

Fig 4: Desirability graph for polymer coating to achieve required lag time.

Comparative dissolution profile of the polymer coated pellets formulation A1 to A6 has been shown in figure 5.

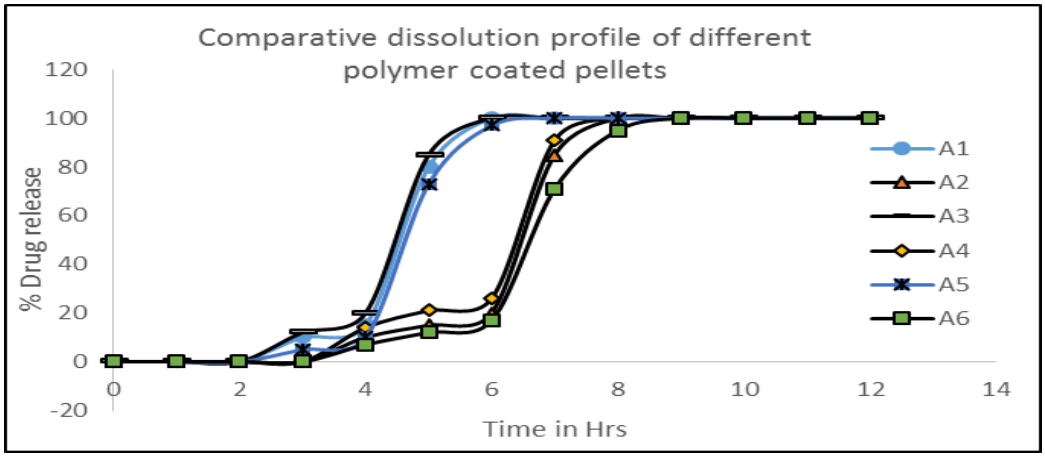

Fig 5: Comparative drug release profile of different DR pellet formulation.

All the pellet formulations are showing similar average release profile 6% w/w polymer coated pellets shows around 4 hr lag time and 12 % w/w polymer coated pellets shows around 6 hrs lag time before pulse release.

Comparative dissolution profile and % RSD for 6 % w/w polymer coated pellets is shown in table 8a and for 12 % w/w polymer coated pellets is shown in table 8b.

Table 8a: Dissolution profile with % RSD for 6 % w/w polymer coated pellets.

Time (Hr)	A1		A3		A5	
	% Release	% RSD	% Release	% RSD	% Release	% RSD
4	15	25.8	20	35.0	10	14.1
5	80	14.4	85	13.0	73	2.8
6	100	1.4	100	2.4	97	1.8
7	100	1.5	100	0.8	100	2.3
8	100	1.4	100	0.4	100	1.0

Table 8b: Dissolution profile with % RSD for 12 % w/w polymer coated pellets

Time (Hr)	A2		A4		A6	
	% Release	% RSD	% Release	% RSD	% Release	% RSD
4	10	41.9	14	39.8	7	14.0
5	15	25.8	21	23.0	12	11.8
6	20	30.6	26	15.5	17	8.2
7	85	15.1	91	7.7	71	2.0
8	100	1.4	100	1.4	95	0.5

Compared to extruded pellets, pellets prepared with drug layering shows less variability (% RSD) and so drug layered pellets has been taken further for compression trials.

This difference in variation in drug release profile is might be due to surface of the pellets, in general pellets prepared with extrusion spheronization is showing rough and less sphere surface compared to NPS, and so drug layering will be homogenous and more uniform providing smooth surface yielding uniform coating of DR polymer in this case.

C) Compression of pellets

1) Effect of cushioning agents: comparative dissolution profile of tablets prepared with different cushning agents has been shown in figure 6a for IR + 6 % w/w polymer coated pellets containing tablets, and in figure 6b for IR + 12 % w/w polymer coated pellets containing tablets.

Dissolution of pellets mix (without compression) has been also done as control to compare effect of compression variables.

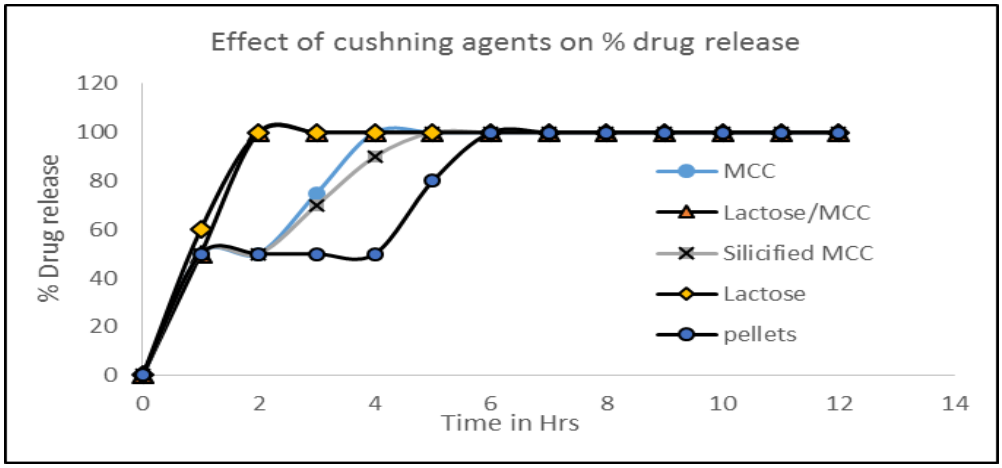

Fig 6a: Comparative drug release profile 6 % w/w polymer coat with different fillers.

6% w/w polymer coated pellets has not be able to sustained its physical properties and showing very fast drug release compared to pellets without compression in all the cushioning agent variants. MCC 102 and Silicified MCC showed some cushioning effect but that is also not as per desired target drug release profile.

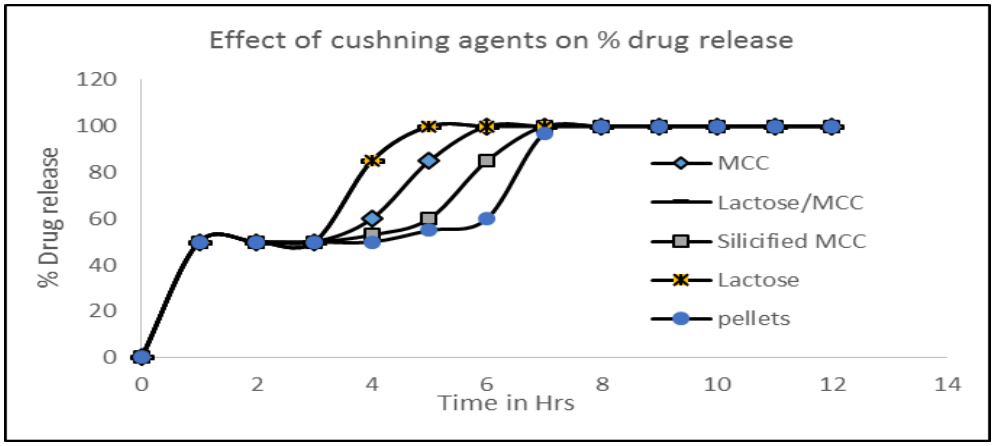

Fig 6b: Comparative drug release profile 12 % w/w polymer coat with different fillers.

12% w/w polymer coated pellets has shown some ability to sustain its physical properties and showing quite comparative drug release compared to pellets without compression in all the cushioning agent variants. Lactose and lactose/MCC is showing reduced lag time i.e. of 3 hrs against 6 hrs for pellet without compression. MCC 102 and Silicified MCC showed better cushioning effect compared to other two by giving 4 to 5 hrs lag time respectively.

2) Effect of % cushioning agents in composition: 12% w/w polymer coated pellets has been selected for this experiment. Comparative dissolution profile of tablets prepared with different amount of cushioning agents has been shown in figure 7a for MCC, and in figure 7b for silicified MCC as cushioning agent.

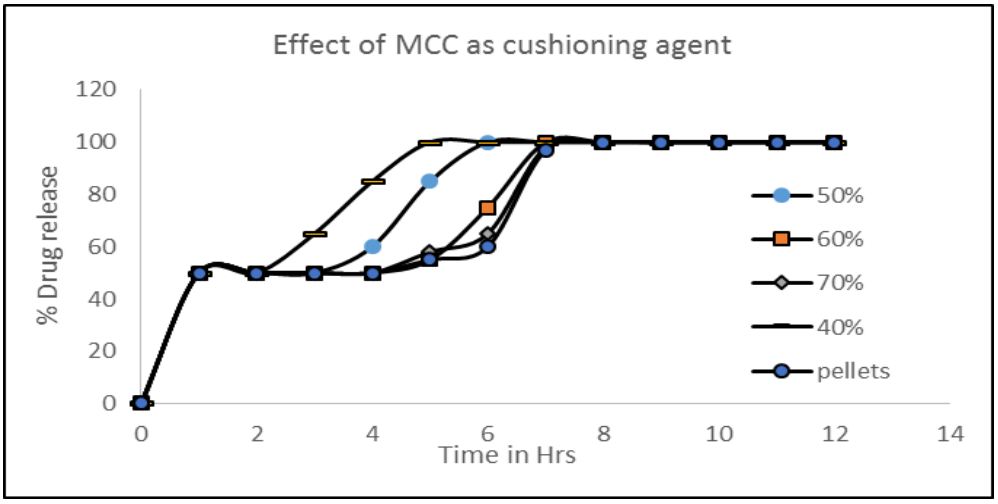

Fig 7a: Comparative drug release profile with different % of MCC.

Less amount of MCC is showing drastic increase in drug release with less lag time compared to high amount. More than 50 % w/w amount of MCC is showing desirable results which is comparable to target drug release profile. 60 % w/w and 70 % w/w are showing similar release profile with similar lag time compared to target drug release profile.

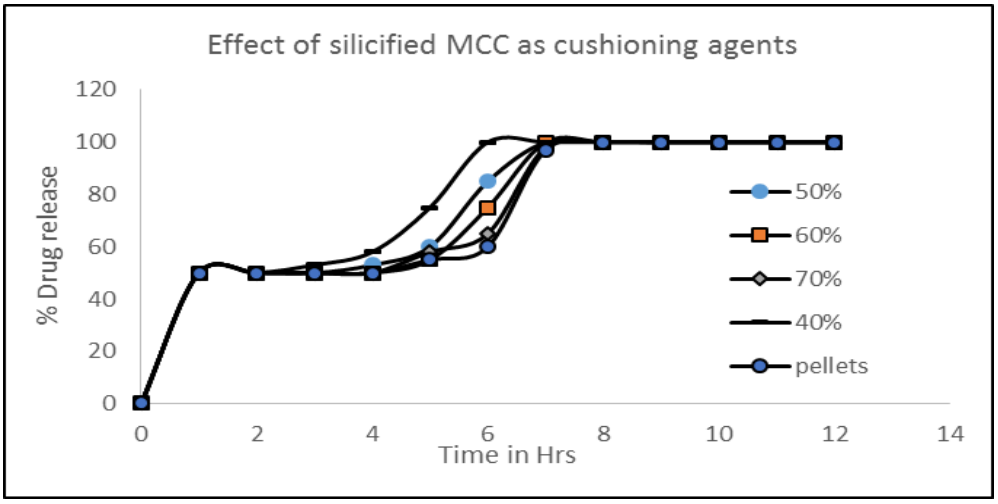

Fig 7b: Comparative drug release profile with different % of silicified MCC.

Silicified MCC is showing better result than alone MCC as a cushioning agent. More than 40 % w/w amount of MCC is showing desirable results which is comparable to target drug release profile. 50 % w/w to 70 % w/w are showing very similar release profile with similar lag time compared to target release profile.

3) Effect of hardness: Comparative dissolution profile of tablets prepared with different hardness has been shown in figure 8a for 50 % w/w silicified MCC, and in figure 8b for 60 % w/w silicified MCC as cushioning agent.

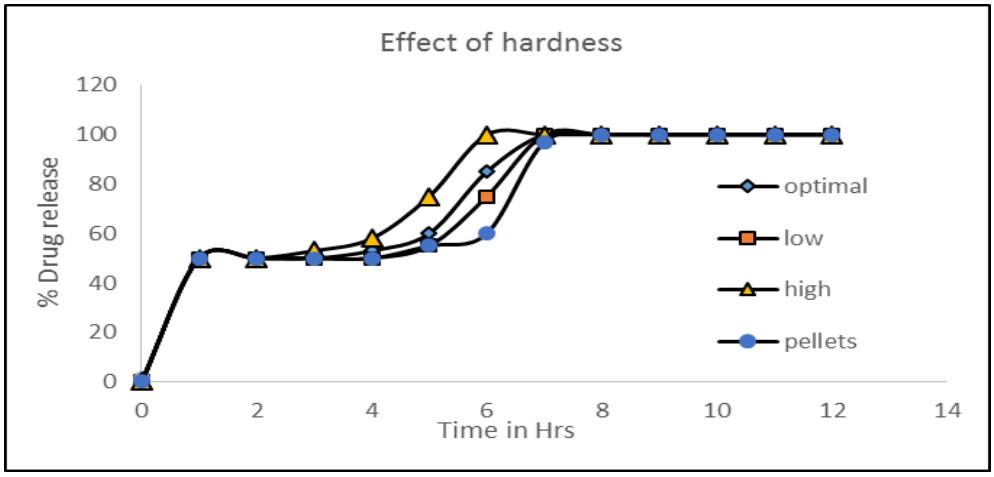

Fig 8a: Comparative drug release profile of different hardness tablet with 50 % w/w silicified MCC as filler.

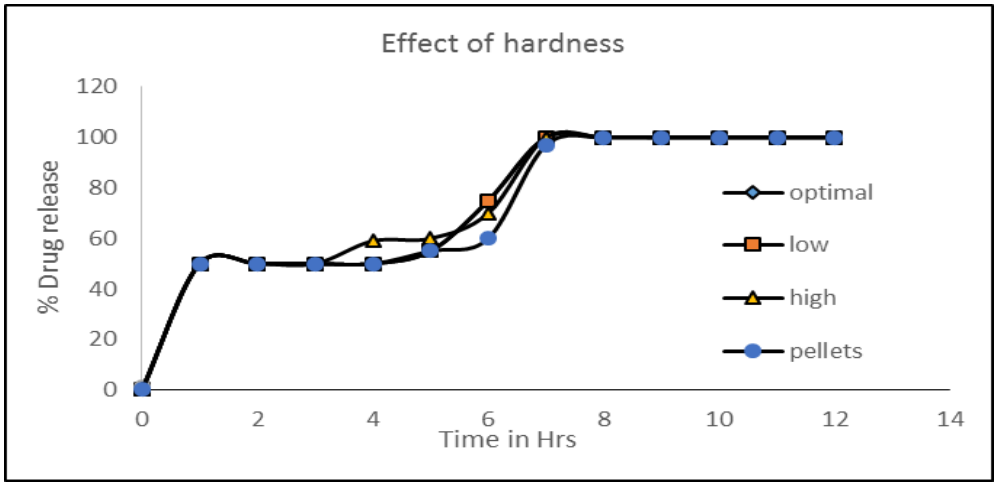

Fig 8b: Comparative drug release profile of different hardness tablet with 60 % w/w silicified MCC as filler.

With 50 % w/w silicified MCC level pellets showed some deformation and fast release of drug compared to low and optimum hardness, but similar to targeted lag time of 4 to 6 hrs.

With 60 % w/w silicified MCC level pellets showed very minimum difference in drug release compared to target drug release pattern. And not showing any impact of compression force.

4) Effect of PEG coating on DR pellets: Comparative dissolution profile of tablets prepared containing PEGylated DR pellets with different hardness has been shown in figure 9.

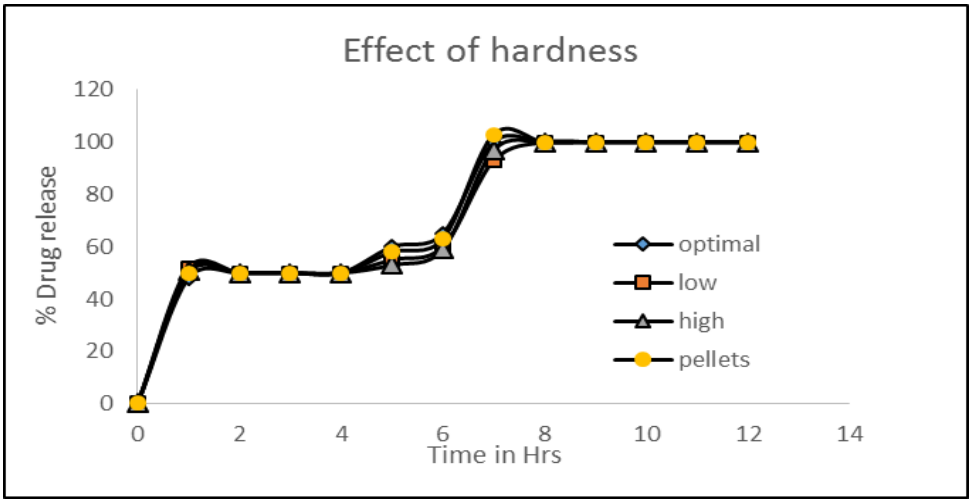

Fig 9: Comparative drug release profile of different hardness tablet for PEGylated DR pellets.

As expected PEG coating on polymer coat provided very effective cushioning effect, pellets showed very minimum difference in drug release compared to target drug release pattern. And not showing any impact of compression force.

CONCLUSION

The present study concludes that the both variables i.e. formulation variable and process variables of tablet compression affect DR pellets drug release performance, showing drastic structural change in pellets coating after compression. Optimal selection of cushioning agent in optimal amount with optimum % DR polymer coating on pellets is very much required to sustained pellets performance after compression. NPS showed less variability in drug release profile compared to pellets prepared with extrusion spheronization where spherical structure is not uniform providing non uniform DR polymer layer. Coating of elastic material on DR pellets provides better strength to pellets and showing less variability and less impact of variables on drug release profile after compression. MUPS Tablet formulation of enalapril maleate consist of IR pellets and DR polymer-coated pellets could be successfully provide targeted drug delivery system providing immediate drug release as a loading dose and a 5-6 hrs lag time before providing second pulse release. Thus, the designed formulation can be considered as one of the promising formulation for pulsatile drug delivery system for chronopharmaceutical management of hypertension, by dosing such formulation at night time to the patients it provides sufficient drug concentration in early morning hours where it requires most and fight with nocturnal hypertension issue.

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