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DESIGN AND EVALUATION OF MINI-TABLETS - PULSATILE DRUG DELIVERY SYSTEM OF RAMIPRIL

V. Rajesh Babu[1], V. Mallikarjun[2], Abdul Sayeed[1], P. Rajasridhar Rao[2]

[1]MESCO College of Pharmacy, Hyderabad, T.S.

[2]Chaitanya College of Pharmacy Education & Research, Hanamkonda, T.S.

Abstract:

The aim of present study was to design and evaluate mini-tablets: pulsatile delivery of Ramipril based on chronophamaceutical approach for the treatment of hypertension. In the present study the immediate release core mini tablets were prepared by direct compression by using different superdisintegrantslike sodium starch glycollate, croscaramellose sodium and crospovidone. The optimized core tablets were then coated with P^H sensitive polymers like Eudragit -S100 and Eudragit- L100. To get the desired dissolution profile various parameters like coating time and coat thickness studied. The formulated coated tablets were evaluated for hardness, thickness, friability, weight variation, drug content, and disintegration time and in-vitro drug release. In-vitro drug release was found to be 98.2% from coated tablets after 6hrs lag time. FT-IR spectra revealed that no chemical incompatibility between the drug and other excipients. The results concluded that the programmable pulsatile release has been achieved from coated tablets after a lag time of 6 hrs, which is consistent with the demands of the chronotherapeutic drug delivery and increasing bioavailability.

Key words: *pulsatile drug delivery, chronopharmaceutics, Ramipril, superdisintegrants, P^H sensitive polymers*

Corresponding Author:

V. Rajesh Babu,

Sr. Asst Professor

MESCO College of Pharmacy

Hyderabad,

Telangana State.

E-Mail: rajeshbabuvemula@gmail.com

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INTRODUCTION:

Pulsatile drug delivery:

Pulsatile drug delivery aims to release drugs on a programmed pattern i.e. at appropriate time and/or at appropriate site of action. Currently, it is gaining increasing attention as it offers a more sophisticated approach to the traditional sustained drug delivery i.e. a constant amount of drug released per unit time or constant blood levels [1-6].

Pulsatile drug delivery systems (PDDS) are characterized by at least two distinctive drug release phases following a predetermined lag time. Drug's release may be controlled by time, by site or a combination of the two parameters. A delayed release delivery system (where time controls the release) would meet the needs of chronopathologies with symptoms mostly recurring at night time or in the early morning whereas site-specific delivery in to the colon might enable an improvement in the treatment of inflammatory bowel disease and, hopefully in the oral bioavailability of peptide drugs. In time controlled delivery systems, the release profile is determined by formulation parameters while in site specific controlled delivery systems the release profile is determined by parameters related to gastrointestinal environment. Time controlled systems are divided into those using barrier technologies around the active agent designed to degrade or dissolve after a certain time, and in those that the degradation of the polymer itself induces the release of the active agent [7-9].

Coated mini tablets:

Mini-tabs are small tablets with a diameter typically equal to or less than 4 mm that are typically filled into a capsule, or occasionally, further compressed into larger tablets. It is possible to incorporate many different mini-tablets, each one formulated individually and programmed to release drug at different sites within the gastrointestinal track, into one capsule. These combinations may include immediate release, delayed release, and/or controlled release mini-tabs. It is also possible to incorporate mini-tabs of different drugs to treat concurrent diseases or combinations of drugs to improve overall therapeutic outcome, while delivering distinct release rates of each according to disease requirements. Mini-tabs could also offer a solution to the current issue in the pharmaceutical industry representing a lack of dosage forms which are suitable for paediatrics. Minitablets technology combines the advantages of multi particulate dosage forms with established manufacturing techniques used in tableting. Additional benefits of minitablets include excellent size uniformity, regular shape and a smooth surface thereby offering excellent substrate for coating with modified release polymeric systems [9-14].

The drug release profile in multiparticulates can be modified by coating them. Reasons for the application of coating onto multiparticulates are to obtain functional coats, provide chemical stability, improve physical characteristics and enhance patient acceptance.

Depending on the type of coating material used, functions such as sustained release (SR), targeted release, delayed release, and pulsatile release can be achieved. The most common method used for the application of coating onto multiparticulates is air suspension coating and pan coating. Other methods include compression coating, solvent evaporation, coacervation, and interfacial complexation. It is also possible to form coated multiparticulates by spray drying and spray congealing.

MATERIALS AND METHODS:

Ramipril was procured as a gift sample from glen mark pharmaceutical labs Pvt.ltd India. Sodium starch glycolate, Microcrystalline cellulose, Crosspovidone and croscarmelose sodium was acquired from sd fine chemicals, Mumbai. Other chemicals and reagent used in this study were of analytical grade.

Methodology

Formulation of compressed tablets of Ramipril:

Preparation of mini (core) tablets:

Mini tablets of Ramipril were formulated by incorporating super disintegrants like sodium starch glycollate, croscaramellose sodium and crospovidione, poly vinyl pyrrolidone-k 30 (binder), MCC (diluent), magnesium stearate and talc etc.

Table 01: Composition of various mini tablet formulations

Materials (mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Ramipril	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Sodium starch glycolate	1	2	3	-----	-----	-----	-----	-----	-----
Cross carmalose sodium	-----	-----	-----	1	2	3	-----	-----	-----
Cross povidone	-----	-----	-----	-----	-----	-----	1	2	3
PVP-K30	4	4	4	4	4	4	4	4	4
Magnesium sterate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Micro crystalline cellulose	31.75	30.75	29.75	31.75	30.75	29.75	31.75	30.75	29.75
Total weight	40	40	40	40	40	40	40	40	40

All the ingredients were accurately weighed as per formula and were dispensed in clean polythene cover, mixed well and sieved through 60mesh and subjected to compression. Direct compression of mini tablets was done in rotary compression tablet machine (Rimek mini press I) using 4mm concave punch.

Coating of tablets:

Compression coating:

For the optimized formulation (F_9) coating (press coat) was given by using different polymers. From the total weight of the powder half of the amount of powder was taken and poured into the die then the core tablet was placed upon it and the remaining powder from the total weight was added and compressed.

Table no.02 Composition of differntcompression coting formulations

Materials	F_1 (mg)	F_2 (mg)	F_3 (mg)
Ethyl Cellulose	75	37.5	-
Mg stearate	2	2	2
Talc	2	2	2
HPMC 15 CPS	-	37.5	75
Total weight	79	79	79

Dip coating:

Three different polymer coating solutions were prepared for dip coating. The tablet was dipped in 1st coating solution with the help of foreceps, removed and was dried for sometime. The same procedure were repeated by dipping the tablet in the 2nd and 3rd polymer solution .The polymer coated tablets were then dried in an oven at 45^0c.

Table 03: Composition of different dip coting formulations

Ingredients	FD_1	FD_2	FD_3
Eudragit L-100	2.5 g	3 g	3.5 g
Eudragit S-100	2.5 g	3 g	3.5 g
Titanium dioxide	0.5 g	0.5 g	0.5 g
Talc	0.5 g	0.5 g	0.5 g
Isopropyl alcohol	60 ml	60 ml	60 ml
Acetone	35 ml	35 ml	35 ml
Water	5 ml	5 ml	5 ml
Dibutylpthalate	1% w/v	1% w/v	1% w/v

Spray coating:

A coating pan containing tablets was taken and fitted to the coating equipment and the pan was rotating about it an own axis. For this rotating pan we have to spray the coating solution manually.

Table no. 04 Composition of spray coting formulation

Ingredient	Quantity
Eudragit L-100	2.5 g
Eudragit S-100	2.5 g
Titanium dioxide	0.5 g
Talc	0.5 g
Isopropyl alcohol	60 ml
Acetone	35 ml
Water	5 ml
Dibutyl phthalate	1% w/v

Pan coating:

Pan Coating is among the oldest industrial processes for forming small coated tablets. Active cores ~2mm and larger are cascaded through a spray region within a rotating perforated pan. Drying air is directed through or over the cascading bed of material as atomized coat solution or suspension spray is directed at the rapidly passing product. Spray rate, atomized spray pattern, pan speed, temperature, and airflow are adjusted for optimal coating efficiency .

The compressed tablets were subjected to coating with different coating solutions. Eudragit –L 100 and Eudragit-S 100 were used as coating polymers and isopropyl alcohol, acetone and water mixture used as solvent. Dibutyl phthalate used as plasticizer, titanium dioxide used as opacifier and talc used as antitacking agent. Solvent mixture was prepared with IPA, acetone and water mentioned quantity in table. Add the Eudragit powder slowly into 50 % of the diluent mixture and stir until the polymer is completely dissolved (approx. 30–60 minutes). Add talc and dibutyl phthalate in the remaining diluent mixture and stir for 10 minutes with a magnetic stirrer. Pour the excipient suspension slowly into the Eudragit solution while stirring with a conventional stirrer. Pass the spray suspension through a 0.5 mm sieve.

The mini tablets were coated with aqueous ethanolic solution of Eudragit-L 100 and Eudragit-S 100 using a pan coating system. Percentage weight gain calculated by the following equation

Percentage weight gain= $[(w_t-w_0)/w_0] \times 100$

Where, W_t= Weight of tablet after coating,

W_0= Initial weight of tablet

Table no.05 composition of pan coating solution

Ingredient	Composition
Eudragit-S100	2.5 g
Eudragit-L 100	2.5 g
Dibutyl phthalate	1% w/v
Titanium di oxide	0.5 g
Talc	0.5 g
Iso propyl alcohol	60 ml
Acetone	35 ml
Water	5 ml

Post Compression Parameters:

Evaluation of uncoated tablets:

Shape and colour:

The tablets were examined under a lens for the shape of the tablet and colour by keeping the tablets in light.

Uniformity of thickness:

Randomly 10 tablets were taken from formulation batch and their thickness (mm) was measured using a Verniercallipers.

Hardness test:

The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Six tablets were randomly picked from each formulation.

Friability test:

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche friabilator (Lab India, FT 1020). It is expressed in percentage (%). Ten tablets were initially weighed [$W_{(initial)}$] and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions.

The tablets were weighed again [$W_{(final)}$]. The percentage friability was then calculated by,

$$F = \frac{[W(initial) - W(final)]}{W(initial)} \times 100$$

Weight variation test:

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The % deviation in weight variation is shown in tableno.7.

Table 06: Limits of Weight variation

Average Weight Of Tablet(mg)	%deviation
130mg or less	10
> 130or <324	7.5
> 324	5

Drug Content estimation:
The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch.
Four minitablets were weighed and crushed in the mortar. The powder equivalent to 1.25 mg of the drug were weighed and dissolved in 100ml phosphate buffer P^H 6.8 to give a concentration of 12.5 µg/ml. 2ml of this solution was taken and diluted to 10ml to give a concentration of 2.5µg/ml. The absorbance of the prepared solution was measured at 218nm using UV Visible spectrophotometer (Lab India, UV-3200).

***In -vitro* disintegration time:**
The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using a modified disintegration test used only for fast disintegrating agents.The *in-vitro* disintegration time for immediate release core tablets were determined by using Disintegration test apparatus (Lab India, DT-1000) as per IP specifications. Place one tablet in each of the six tubes of the basket. Add a disc to each tube and run the apparatus containing pH 1.2 SGF (simulated gastric fluid) maintained at 37 ± 2^0C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute. The time in minutes with complete disintegration of minitablets without any palpable mass remaining in the apparatus was measured and recorded.

***In -vitro* dissolution studies:**
In-vitro release studies were carried out using a modified USP XXIII dissolution test apparatus (Lab India, DS-800). The dissolution fluid was 900ml of phosphate buffer P^H 6.8 at a speed of 50rpm at a temperature of 37^0c were used in each test. Samples of dissolution medium (5ml) were withdrawn at 5,15,30 and 45 mins and assayed for Ramipril by measuring absorbance at 218 nm. For all the tests 5ml of the test medium were collected at specified time intervals and replaced with same volume of phosphate buffer P^H 6.8.

Evaluation of coated mini tablets:
Characteristics of tablets of Ramipril such as thickness, hardness, disintegration, dissolution test were conducted. Thickness of coated tablets was determined by using digital verniercalipers.

6 tablets of each type of coated formulation were determined for thickness and average thickness of the formulation was determined. Similarly the thickness of the coating on the formulation was determined by deducting the thickness of core tablet from thickness of coated tablet. The hardness of the formulation was determined using Monsanto hardness tester taking 3 tablets individually. Averages of 3 tablets were noted down.The disintegration of coated mini tablets was determined by using disintegration test apparatus placing 6 tablets individually in the tubes. The disintegration time of the tablets was determined using P^H1.2.

Dissolution testing of pulsatile delivery systems with the conventional paddle method at 50 rpm and 37 ± 0.5^0c has usually been conducted in different buffers for different periods of time simulated GIT P^H and transit time that the pulsatile delivery system might encounter in-vivo. The samples were withdrawn at regular time intervals and the same volume of dissolution medium was replaced, the samples were analyzed for the release of drug by UV spectrophotometer (Lab India, UV-3200).

Table 07: Two different dissolution media were used during dissolution

Parameters	**Medium I**	**Medium II**
Type of medium	0.1N HCl	Phosphate buffer pH 6.8
Sampling time intervals	30,60,120min	30,60,120,180,240,300,360,420 and 480min
λ_{max}	218nm	218nm

RESULTS AND DISCUSSION:

Pre Formulation Studies:

Table 08: Evaluation of flow properties of powder blend

Formulation	Angle of repose (ɵ)	Bulk density (gm/cm^2)	Tapped density (gm/cm^2)	arr's index (%)	Hausner's ratio (HR)
F_1	25.82	0.71	0.81	12.34	1.14
F_2	27.35	0.69	0.81	14.81	1.17
F_3	25.28	0.70	0.80	12.5	1.14
F_4	29.05	0.67	0.78	14.10	1.16
F_5	26.76	0.69	0.79	12.65	1.14
F_6	25.12	0.69	0.80	13.75	1.15
F_7	25.29	0.71	0.81	12.34	1.14
F_8	29.51	0.70	0.82	14.63	1.17
F_9	25.11	0.71	0.83	14.45	1.16

Post compression parameters:

Evaluation of uncoated mini tablets:

Table 09: Evaluation of thickness, hardness and wt variation of uncoated mini tablets

Formulation	Thickness (mm) n=10	ardness (Kg/cm^2) n=6	Wt variation (mg) n=20
F_1	1.526±0.018	2.05±0.031	40.13±0.029
F_2	1.525±0.029	2.32±0.028	40.53±0.019
F_3	1.526±0.032	2.24±0.034	40.33±0.029
F_4	1.532±0.023	2.52±0.019	40.44±0.028
F_5	1.521±0.033	2.43±0.021	40.10±0.019
F_6	1.521±0.022	2.62±0.028	40.34±0.026
F_7	1.523±0.021	2.41±0.028	40.45±0.030
F_8	1.519±0.028	2.24±0.024	40.24±0.027
F_9	1.536±0.020	2.33±0.026	40.12±0.025

Table 10: Evaluation of friability, disintegration time and drug content of uncoated mini tablets

Formulation	Friability (%) n=10	ntegration time(min) n=6	Drug content (%) n=5
F_1	0.54	7.13±0.014	93.02
F_2	0.53	5.15±0.027	92.99
F_3	0.64	4.07±0.024	90.13
F_4	0.62	5.26±0.019	95.07
F_5	0.61	4.13±0.023	94.01
F_6	0.67	3.36±0.027	95.00
F_7	0.53	4.05±0.028	96.07
F_8	0.62	3.35±0.025	96.81
F_9	0.63	2.18±0.024	97.05

Table 11: Cumulative percentage drug release of core mini tablets with pH 6.8 Phosphate buffer

Time in (min)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
0	0	0	0	0	0	0	0	0	0
5	61.1	63.3	66.6	62.1	64.4	67.7	64.2	67.5	71.1
15	70.0	72.2	76.6	71.2	73.3	78.4	75.2	77.7	88.8
30	82.2	86.5	88.8	83.5	85.4	87.7	84.3	88.1	94.2
45	91.1	93.3	95.3	90.2	93.2	95.6	92.6	94.3	98.8

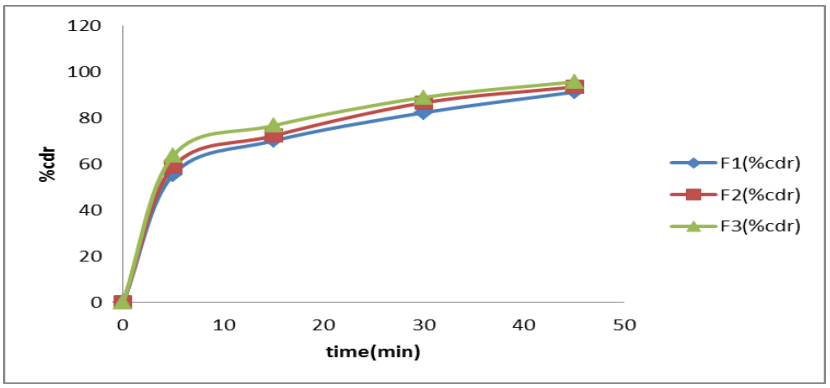

Fig.01: Cumulative percentage drug release of core tablets with superdisintegrant SSG

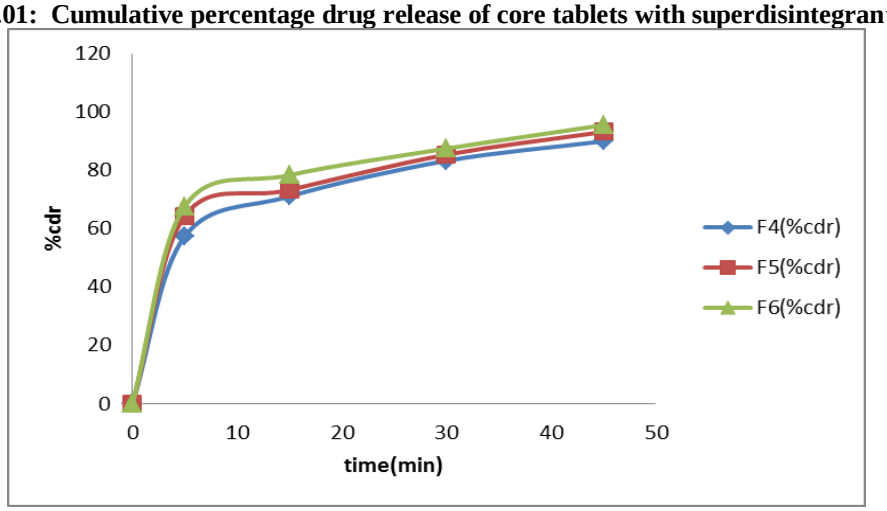

Fig.02: Cumulative percentage drug release of core tablets with superdisintegrant CCS

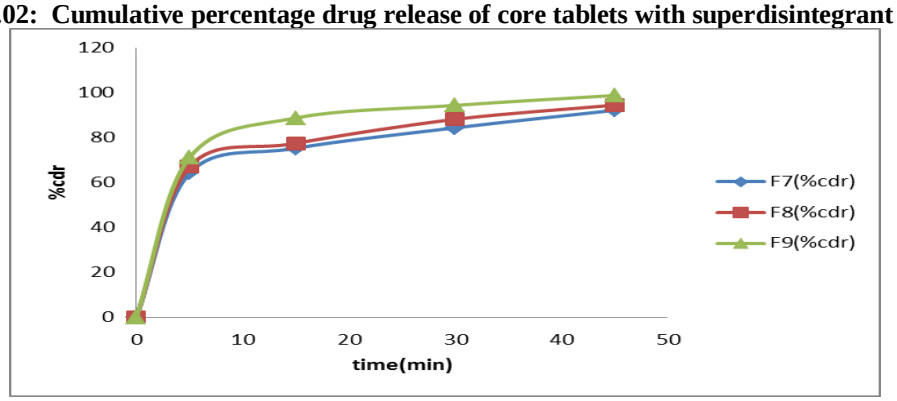

Fig. 03 Cumulative percentage drug release of core tablets with superdisintegrant CP

Table 12: Evaluation of thickness, hardness and wt variation of coated mini tablets

Formulation	Thickness (mm) n=10	Hardness (Kg/cm^2) n=6	Wt. variation (mg) n=20
F10	1.73±0.10	2.45±0.021	46.15±0.545
F11	2.07±0.13	2.53±0.028	52.05±0.43
F12	2.41± 0.16	2.75±0.019	58.19±0.39

Table 13: Evaluation of friability and drug content of coated mini tablets

Formulation	Friability (%) n=10	Drug content (%) n=5
F10	0.62	93.15
F11	0.67	95.64
F12	0.61	97.19

Table 14: Cumulative percentage drug release of coated mini tablets with 0.1N HCl and Phosphate buffer 6.8 P^H

Dissolution medium	Time in Hrs	F_{10} (15%) %DR	F_{11} (30%) %DR	F_{12} (45%) %DR
0.1 N HCl	0	0	0	0
	0.5	2.1	1.2	0
	1	6.4	2.9	0
	2	7.7	3.7	0
6.8 pH buffer	2.5	15.3	5.1	2.5
	3	78.7	7.3	4.3
	4	92.2	14.7	7.8
	5	97.9	76.2	10.5
	6	100.1	89.9	13.1
	7		94.7	60.7
	8		97.8	72.3
	9		99.2	84.3
	10		98.9	98.2

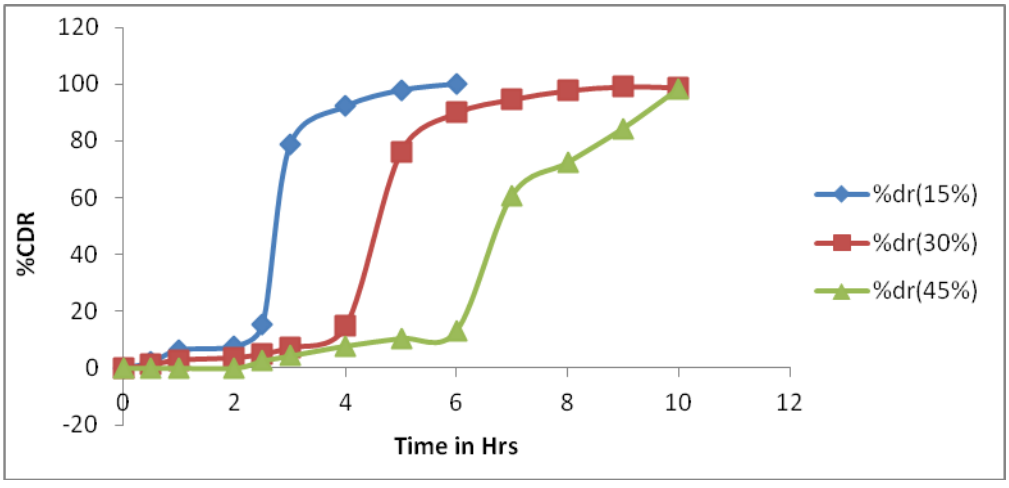

Fig. 04: Cumulative percentage drug release of coated mini tablets in 0.1N HCl and 6.8 PH phosphate buffer

DISCUSSION:

Pulsatile drug delivery system is a useful approach for the drugs for local as well as systemic action. The diseases which exhibit circadian rhythm can be treated by pulsatile drug delivery system which promises the predetermined lag time followed by the delayed release.

In the present study an attempt has made to formulate and evaluate pulsatile drug delivery system containing Ramipril as a prodrug for the better treatment of hyper tension. Pulsatile drug delivery of Ramipril releases the drug at early morning time and decreases the B.P in the morning time.

Pre Formulation Studies:

Melting point:

Melting point of Ramipril was determined by capillary method. Melting point of Ramipril was found to be in the range of 108-109^{0}C which compiles the standards thus indicating that purity of the drug sample.

Determination of lambda max :

In preformulation studies, it was found that the lambda max of Ramipril by spectroscopic method was 218nm with P^H 1.2 and P^H 6.8.

Construction of calibration curve:

In this study at 218nm in simulated gastric fluid (0.1N HCl) and phosphate buffer pH 6.8 had good reproducibility in the concentration between 10-60µg/ml. Correlation between concentration and absorbance was found to be closer to 1 indicating that the method obeyed Beer Lamberts law.

Drug –excipient Compatibility studies by FTIR:

FTIR techniques have been used to study the physical and chemical interaction between drug and excipients used. There was no significance difference between the absorption peaks of pure drug and optimized formulation. The results concluded that there was no interaction between pure drug and excipients.

Flow properties:

Loose bulk density:

Bulk density of the formulation blend plays an important role in the compression of the powder. Bulk density was carried out and results were reported in the table 5.4. The bulk density of the formulation was found to be in the range of 0.67 g/cm^3 to 0.71 g/cm^3.

Tapped density:

Tapped density also plays an important role in knowing the compressibility of the formulation blend. It was found to be in the range of 0.78g/cm^3 to 0.83 g/cm^3. It was noted that the tapped density of all the formulation were greater than their respective bulk density thus indicating that all the powder formulation had a good compressibility.

Angle of repose:

The angle of repose for the formulation blend was carried out and the results were shown in the table 5.4. It can be concluded that the angle of repose for all formulations blend was obtained in the range of 25.11^0- 29.51^0 thus falling in the range official limits 25-30(good flow). Hence all the formulation blends possess good flow property.

Carr's consolidation index:

Carr's consolidation index was carried out and the results were shown in the table 5.4. The CCI was calculated based on LBD and TD. It was found to be in the range of 12.34- 14.81 indicating that all the formulation blends possess good flow property for compression.

Hausner's ratio:

Hausner's ratio is the ratio between tapped bulk density and loose bulk density. Hausner's ratio was calculated for all formulation blends and reported in the table 5.4. All formulations having Hausner's ratio < 1.18.

Evaluation of post compression parameters of uncoated and coated mini tablets:

Shape and colour:

All the tablets were in concave oval shape and all the uncoated tablets were white in colour and coated tablets were red in colour. While giving coating with dip, spray and compression method the formulation showed capping, sticking, picking and mottling because of uneven distribution of heat or because of uneven distribution of coating solution.the compressed coated tablet showed capping but when coating were appied with pan coating, there was no such problem in coating.

Thickness:

Thickness of the all uncoated formulations was found to be 1.519±0.012 to 1.536±0.020mm with low standard deviation values.

The thickness of the coated formulations ranged between 1.73±0.10 to 2.41±0.16mm

Hardness:
The crushing strength of the uncoated tablets of each batch ranged between 2.05±0.031 to 2.62±0.028 kg/cm^2. This ensures good handling characteristics of all batches.
The hardness of the coated tablets ranged between 2.45±0.021 to 2.75±0.019 kg/cm^2.

Weight variation:
The % weight variation was calculated for all formulations. All the formulations (f1-f9) were passed the weight variation test as the % weight variation was with in the pharmacopoeia limits. The weights of the all formulations found to be uniform with low standard deviation values.
The coated tablets weight was increased up to 15 to 45%.

Friability:
The values of friability test were in the range from 0.53 to 0.67%. The per cent friability of all the formulation was less than 1% ensuring that the tablets were mechanically stable.

Disintegration time:
The values of disintegration time reported in the table no 5.5 the disintegration time found in the range of 2.18 min to 7.13min ensuring that all the core tablets were rapid disintegrating type.

Drug content uniformity:
The percentage of drug content for all formulations found to be in the range of 90.13-97.05%. It complies with official specifications.

***In-vitro* drug release studies:**
The *in-vitro* drug release study for uncoated tablets was carried out in P^H 6.8 as dissolution medium for about 45min.The drug release from the formulations increased as the concentration of super disintegrant increased. Based on the results obtained F9 formulation which was formulated by using 3% Cross povidone was found to be 98.80% with in 45min and selected for further coating process.
Coating was done with P^H sensitive polymers like Eudragit S100 and L100 (F10-F12). The dissolution was carried out by using 1.2 P^H & 6.8 P^H phosphate buffer.

In-vitro drug release studies were carried out for 10hrs and found to be good sustaining efficacy. The enteric coat of all the three formulations (F10(15%),F11(30%),F12(45%))was intact for 2hrs in 1.2 P^H but very slowly dissolved in intestinal P^H. Based on the thickness of the coating layer of F10 and F11 the drug was released after 2.5 hrs , 4hrs respectively and F12 the drug was released after 6hrs. F12 releases the drug 98.2% with in 4 hrs after a lag time of 6hrs. In all the three formulations (F10-F12) the F12 formulation which was coated with Eudragit S100 & L100 (45%) having better drug release after a lag time of 6hrs and followed by delayed release with in 4hrs.
On considering some important parameters like disintegration time, percentage drug content, hardness and *in-vitro* drug release study, F12 was selected as the best formulation.

CONCLUSION:

Formulation of mini tablets pulsatile release system using appropriate amounts of excipients for ramipril. Variables such as type and amount of super disintegrants and concentration of polymer affect the drug release. FTIR studies concluded that there is no interaction between drug and excipients. Based on disintegration time and dissolution time the formulation (F_9) which contains 3% cross povidone was optimised. The optimised formulation F_9 was coated with different coating techniques (compression, dip, spray and pan coating). In dip, spray and pan coating techniques different concentrations of pH sensitive polymers like Eudragit-L100 and Eudragit-S100 were used but in compression coating polymers like HPMC 15CPS and ethyl cellulose were used in different concentrations. Among other coatings Pan coating showed elegant appearance.Based on the thickness of the coating layer and solubility of the coating layer and the dissolution data the formulation (F_{12}) which was coated with 45% Eudragit-S100 and L100 was optimised and this formulation having lag time 6hrs and followed by delayed release of drug. Over the past two decades there has been a growing appreciation on the importance of circadian rhythms on GIT physiology and on disease states, together with the realization of the significance of time-of-day of drug administration on resultant pharmacodynamic and pharmacokinetic parameters. The significance of these day-night variations has not been overlooked from the drug-delivery perspective and pharmaceutical scientists have displayed considerable ingenuity in the development of time delayed drug delivery systems to address emerging chronotherapeutic formulations. The aim of the present study was to explore the feasibility of time dependent pulsatile drug delivery system of Ramipril for the treatment of Hypertension. A satisfactory attempt was made to develop and evaluate pulsatile system of Ramipril. Time-delayed formulations are the only way to ensure that the drugs are released into

the body at the correct time and this can be achieved by the proper selection of pH sensitive polymers.

REFERENCES:

1. Gothaskar AV, Joshi A M, Joshi NH. "Pulsatile drug delivery system-A review". *Drug Del Tech*. 2004;4(5):1-11.
2. Kalantzi Lida E. *et al*., "Recent advances in oral pulsatile drug delivery". *Recent patents on drug delivery & formulation*. 2009;3: 49-63.
3. Shivakumar HG, Pramod Kumar TM And Kashppa GD. "Pulsatile drug delivery system". *Indian J Pham Educ*. 2003;37(3).
4. Ganesh Rasve *et al*., "Pulsatile drug delivery system: current scenario", *International Journal of Pharma and Bio Sciences*. 2011;2(3):332-343.
5. Bae YH *et al*., "Pulsatile drug delivery-A review". *Makromol. Chem,1987;*. 8: 481-485.
6. Roy P, Shahiwala A. "Multiparticulate formulation approach to pulsatile drug delivery: current perspectives", *J. Control. Release*.2009; 80:134-74.
7. Ueda Y *et al*., "Development of a novel drug release system, time-controlled explosion system (TES). Part 1: concept and design". *J Drug Targeting1994;*. 2: 35- 44.
8. Dvane *et al*.,"Multiparticulate modified release composition". *US Patent* No.4863742.2009.
9. Pandey A, Rath B, Dwivedi A.K. "Pharmaceutical Preformulation Studies with Special Emphasis on Excipients Compatibility" *International Journal of Pharmaceutical technology.2011;* 3(2):1029-1048.
10. Yihong Diu, Yisheng Chen. Developing solid Oral dosage Forms-Pharmaceutical Theory and Practice.1st ed, ELSEVIER. P: 67.
11. Sinko PJ. Martin's Physical Pharmacy and Pharmaceutical Sciences. 5th ed. Philadelphia: Lippincott Williams & Wilkins. 2006. P. 558.
12. Aulton Me. Pharmaceutics the Science of Dosage Form Design. 2nd ed. Philadelphia: Churchill living stone. 2005. PP. 201-7.
13. C V S Subramanyam. Textbook of Physical Pharmacy.2nd ed, Vallabh prakashan, PP: 180-234.
14. www.eudragit.com/e-lab