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Chronomodulated Pulsatile Therapeutic System of Lisinopril for Blood Pressure on Early Morning Surge - Design and Quantification

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Abstract:

Pulsatile drug delivery system is the most prominent drug delivery system mainly helpful for diseases showing chronopharmacological behavior where night time dosing is required. The present study aimed to formulate and characterize the chronomodulated pulsatile therapeutic system of lisinopril for the treatment of hypertension. Lisinopril containing immediate release tablet (IMR) was formulated by direct compression using croscarmellose sodium as superdisintegrants with various concentrations (IMR1-IMR4). Pulsatile release mini tablets were coated by ethyl cellulose and sodium alginate as rate retardant with various concentrations to maintain the lag time during release. Developed formulations were quantified for its micromeritic properties. The drug-excipient study was carried out by using Fourier Transform Infrared Spectrophotometry (FT-IR). *In-vitro* drug disintegration and dissolution studies were performed using pH 6.8 phosphate buffer for 12 h. The observed pre and post compression result shows that the prepared formulations were having well in their flow properties and within the accepted limits with low standard deviation. It indicates all the prepared tablets were well in their physico-chemical properties. The *in-vitro* release profile suggested that the immediate release granules gives drug release within 40 sec at the time of evening attack while the programmed pulsatile release was achieved from coated mini-tablets after a lag time of 8hrs, which was consistent with the demand of drug during early morning hour attack.

Keywords: PDDS, Lisinopril, Mini Tablet, Chronopharmacology, Lag time, Hypertension

INTRODUCTION

Oral medication conveyance is the biggest section of the absolute medication conveyance market. It is the most favored course for drug organization. The oral controlled-discharge frameworks show an average example of medication discharge in which the medication focus is kept up in the restorative window for a delayed timeframe, accordingly guaranteeing supported remedial activity. There are sure conditions for which such a delivery design isn't reasonable that request arrival of a medication after a slack time. All in all, they require pulsatile drug conveyance framework (PDDS). Pulsatile drug conveyance frameworks are acquiring a ton of interest now days. These frameworks are planned by the circadian musicality of the body. These frameworks convey the medication at explicit time according to the pathophysiological need of the sickness, bringing about improved patient consistence and helpful adequacy. Which is implied as the freedom of medications following customized slack stages, has drawn expanding interest, particularly taking into account arising chronotherapeutic approaches. Pulsatile drug conveyance shows rhythms like rheumatoid joint inflammation, cardiovascular sicknesses, asthma, peptic ulcer, hypersensitive rhinitis [1].

The idea of chronotherapeutics starts from the finding of the significant sickness conditions like asthma, cardiovascular issues, unfavorably susceptible rhinitis, and joint inflammation following circadian illustration of indication upheaval. Chronotherapeutics conveyance frameworks have been created to give the best treatment regimens which rotate around the goal of guaranteeing greatest centralization of the medication at the hour of indication beginning. These days, idea of chronopharmaceutics has arisen, wherein, research is committed to the plan and assessment of medication conveyance frameworks that discharge a remedial specialist at a musicality that preferably coordinates the organic necessity of a given sickness treatment. Fate of medication conveyance should address the difficulty of future medicine [1].

Lisinopril is a prodrug having a place with the angiotensin changing over catalyst (ACE) inhibitor class of drugs. It is processed to Lisinoprilat in liver and, less significantly in kidneys. Lisinoprilat is an intense, serious inhibitor of ACE, the catalyst liable for the transformation of angiotensin I (ATI) to angiotensin II (ATII). ATII directs circulatory strain and is a critical part of the reninangiotensin-aldosterone framework (RAAS). Lisinopril might be utilized in the treatment of hypertension, congestive cardiovascular breakdown, nephropathy, and to diminish the pace of death, myocardial localized necrosis and stroke in people at high danger of cardiovascular events [2].

Lisinopril is ingested gradually and not entirely following oral organization and its retention changes somewhere in the range of 6 and 60% relying upon the individual, yet on normal is 25% of the portion [3]. To conquer the issues related with lisinopril, to improve its bioavailability and for the successful therapy of constant hypertension.

In the current examination meant to form lisinopril as PDDS to deliver the medication as prompt and furthermore at the site of activity at the opportune time in the perfect sum. Plan of such sort of measurements structure may improve patient's adherence to hostile to

hypertensive treatment. The fruitful result of this undertaking will give degree to new potential medication conveyance framework for the treatment of hypertension.

MATERIALS AND METHODS

Materials:

Lisinopril purchased from Yarrow Chem Products, Mumbai, India. Croscarmellose sodium purchased from S.D. Fine chem. Ltd., Mumbai, India. Magnesium Stearate, Polyvinyl pyrollidone K 30 and Talc purchased from Lobachemie Pvt Ltd, Mumbai, India. Ethylcellulose from Himed Labs Ltd, Mumbai, India. Sodium alginate and Avicel from Kemphasol, Mumbai, India. All the chemicals used were of analytical grade. All solutions were prepared using double distilled water.

Preformulation studies:

A preformulation study is the first step in the rational development of dosage forms of a drug substance. Thorough understandings of physicochemical properties may ultimately modification or merely confirm that there are no significant barriers to the compounds development.

Compatibility study

The drug and excipients chosen for the formulation were screened for compatibility by physical methods and Fourier Transform infrared spectrometric method (FTIR).

Fourier transforms infrared spectrometry (FT-IR)

Infrared spectroscopy can be used to identify a compound and also to investigate the composition of the mixture. Pure drug, polymers, excipients, drug excipient mixture and prepared formulations was subjected to FTIR studies using Shimadzu FT-IR spectrometer model to investigate the Drug-excipient interactions. The IR spectra of the test samples were obtained by pressed pellet technique using potassium bromide and the ratio of sample is 1:100[4].

Methods:

Formulation of immediate release granules in pulsatile device

Lisinopril immediate release granules (IMR) were made by wet granulation method. Lisinopril, croscarmellose sodium, Microcrystalline cellulose (MCC) were weighed accurately and blended homogeneously. Polyvinyl pyrollidone K 30 (PVPK30) was dissolved in isopropyl alcohol and mixed with the powder blend to get a coherent mass. The mass was passed through sieve no 22. In the end talc and magnesium stearate was added to enhance the flow property of granules. The powder blend was evaluated for flow properties such as angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio. The formula for immediate release granules was given in Table. 1.

Preparation of mini tablet of lisinopril

The mini tablets of lisinopril (LMT) were prepared by direct compression method.The dried granules were compressed as tablet by direct compression method directly using 6 mm flat punch[6]and the formula was given in Table 2.

Preparation of coated mini tablets

5% (w/w) coating solutions of ethyl cellulose 10 cps (hydrophobic polymer) combined with sodium alginate (hydrophobic polymer) were prepared in ethanol and dichloro methane (4:1). The coating solution was plasticized with polyethylene glycol (5%, w/w, with respect to dry polymer), and then talc was added as glidant (5%, w/w, related to dry polymer). The coating was made by the simple pan ladling method. In that, the coating solution was poured on the tablets in coating pan with ladle. Ateach stage the coated tablets were further air dried in the coating pan for 15min. The tablets were then placed in the oven at 40°C for 2h to remove the residual solvent[5].

Table. 1 Formula for immediate release granules

S.No.	Ingredients	IMR1 (mg)	IMR2 (mg)	IMR3 (mg)	IMR4 (mg)
a)	Lisinopril	20	20	20	20
b)	Croscarmellose sodium	-	50	100	150
c)	Microcrystalline cellulose	50	50	50	50
d)	Polyvinyl pyrollidone K 30	4	4	4	4
e)	Talc	1%	1%	1%	1%
f)	Magnesium Stearate	1%	1%	1%	1%

Table 2. Formula for mini tablet and coating solution

S.No.	Ingredients	MTF1 (mg)	MTF2 (mg)	MTF3 (mg)	MTF4 (mg)
a)	Lisinopril	20	20	20	20
b)	Microcrystalline cellulose	50	50	50	50
c)	Polyvinyl pyrollidone K 30	10	10	10	10
d)	Magnesium Stearate	1%	1%	1%	1%
Formula for time lagged coating solution					
e)	Ethyl cellulose (60%)	-	3.0	-	3.0
f)	Sodium alginate (40%)	-	-	2.0	2.0
g)	Ethanol: Dichloro methane (4:1)	-	Q.S to 100ml	Q.S to 100ml	Q.S to 100ml
h)	Talc (5%)	2	2	2	2

Preparation of tablet in capsule formulation

The first step in the formulation of tablet in capsule approach was to select the appropriate capsule size that can accommodate coated tablet and immediate release blend. For the purpose, size "1" capsule was selected according to specifications given by USP. According to USP, capsule size "1" can accommodate total weight of 500 mg. This capsule size can accommodate optimized batch of coated mini tablet and immediate release tablet weighing 340mg. Finally the filled capsules were sealed with the help of capsule hand filling machine [6,7].

Pre compression studies:

Measurement of bulk density

Bulk density is determined by pouring presieved powder into a graduated cylinder via a large funnel and estimate the volume and weight. The bulk density was calculated in g/cm^3 by the formula [8].

$$Bulk\ density\ (\rho 0) = M / V0$$

Where, M = mass of powder taken

V_0= apparent untapped volume

Measurement of tapped density

A known weight of the powder was transferred to a measuring cylinder, tapped manually 100 times, and the ratio of weight to volume of the powder gives the tapped density [6].

It is expressed in gm/ml and is specified by

$$\rho t = M / Vt$$

Where,

M= mass of powder

V_t=tapped volume of the powder.

Determination of carr's index (Compressibility)

This parameter was computed from tapped (DT) and bulk density (DB) data of the powder as in below formula [8].$Carr's\ index\ (\%) = poured\ density - tapped\ density/ poured\ densityX100[Carr's\ index = \{(DT - DB)/ DT\}100]$

Determination of hausner ratio

The Hausner ratio of the powder was determined from the ration of tapped density to bulk density [6].$Hausner's\ ratio = tapped\ density/ poured\ density$

Evaluation of angle of repose

The angle of repose of the powder, which measures the resistance to particle flow, was determined by the fixed funnel method. The height of the funnel was modifying in such a way that the tip of the funnel fair touches the heap of the blends. An accurately weighed sample of the powder was left to pass through the funnel freely on to a flat surface. The height (h) and radius (r) of the powder cone were measured and the angle of repose (θ) calculated using the following formula [9].

$$\theta = tan - 1(h/r)$$

Where,

h = height of pile in cm

r = radius of pile in cm.

The standard values for angle of repose, compressibility index and Hausner's ratio based on its flow properties were given in Table 3

Post compression studies:

The following post compression studies were performed on prepared tablets to confirm its quality with the standard limits.

Weight variation test:

The USP uniformity of weight test was done by weighing 20 tablets of each product using an electronic balance average weight was calculated. The tablets were then weighed individually, and the percentage deviation from the average weight was calculated [10].

$$\%\ Weight\ Variation = (Individual\ Weight/Average\ Weight) * 100$$

The tablets meet the USP test if not more than two tablets are outside the percentage limits, and no one tablet differs by more than 2 times the percentage limit according to USP were given Table 4.

Table 3. Standard values for angle of repose, compressibility index and Hausner's ratio

Flow property	Angle of repose(θ)	Compressibility index (%)	Hausner's ratio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very Very poor	>65	>38	>1.60

Table 4. Limit according to USP average

Weight of tablet	Limit
130 mg or less	±10%
130 mg to 324 mg	±7.5%
More than 324 mg	±5%

Friability test:

For tablets with a unit mass equal to or less than 650 mg, take a sample of whole tablets corresponding to 6.5 g. For tablets with a unit mass of more than 650 mg, take a sample of 10 whole tablets. The tablets should be carefully dedusted prior to testing. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablets. Remove any loose dust from the tablets as before, and accurately weigh [10].

$$Friability\ percent = (Initial\ weight - Final\ weight) / Initial\ weight \times 100$$

Hardness test:

Tablet hardness has been defined as "the force required breaking a tablet in a diametric Compression test." For each formulation, the hardness of three tablets was determined using Monsanto hardness tester. The tablet was placed in "Monsanto hardness tester'', the tablet was placed in Monsanto hardness tester vertically, and the force was applied with the help of screw the endpoint was detected by breaking the tablet [10].

Thickness:

The thickness of the tablet was determined using a Vernier Caliper. Six tablets from each batch of formulation were

used, and mean thickness value and SD were calculated for each formulation [10].

Determination of % Drug Content

The tablets were crushed and powder equivalent to 20 mg of lisinopril was weighed accurately and dissolved in distilled water. The solutions were filtered through a membrane filter (0.45 µm). The drug content was analyzed at 218 nm by a UV spectrophotometer [11]

In-vitro Disintegration test

The in-vitro disintegration time was determined for the immediate release layer using the USP disintegration apparatus, the basket rack assembly containing six open ended tubes and 10- mesh screen on the bottom was used, and the six tubes are filled with pH 6.8 phosphate buffer. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds [12].

***In-vitro*% drug release:**

The release profile of an entrapped drug has seen to review that how a delivery system might function and show valuable insight into its *in vivo* behavior. *In-vitro* release profile for prepared coated tablet exist performed using USP XXII type 2 dissolution apparatus (Veego, Electro lab, Mumbai, India) A 900 ml of phosphate buffer pH 6.8 was used as the dissolution medium maintained at 37 ± 0.5 °C at a rotation speed of 50 rpm. Aliquot of 5ml was withdrawn at time intervals of 0, 5, 15, 30, 60 min, 2, 4, 6, 12, 18 and 24 hrs. The withdrawn volume was restoring with the same volume of dissolution medium in order to retain the total volume constant and filtered through 0.45 µm cellulose nitrate filters in 30 seconds. Each study was performed in triplicate and the mean values were recorded accordingly. The absorbance of the samples was measure using spectrophotometrically at λ_{max} 218 nm after fitting dilution if necessary, using appropriate blank. (Cumulative percent drug released was found out at each time interval and graph was plotted between cumulative % drug released and time in h)[13].

RESULTS AND DISCUSSION

In the ebb and flow situation of drug research a lot of consideration has been centered around patients' wellbeing as far as helpful adequacy and security so remembering this thing, the target of the investigation is to cause an endeavor to control the custom of recommending the dosages of prescription all through a time of 12 hours as various explores to have given the possibility of organization of meds with day-night design and natural rhythms to lessen the portion recurrence.

Circadian rhythm regulates many body functions in humans, such as metabolism, behavior, sleep patterns, and hormone production. Blood pressure also shows circadian rhythm variation and exhibits 2 times peaks of 7 pm in the evening, and 4 am in the morning The conventional drug delivery systems releases drug immediately and requires to be taken during the peak hours of disease attack and hence it is not feasible to use such systems targeting diseases with the symptoms prevailing during early morning hours. In such cases release of drug is preferred in pulses and these systems are termed as chronomodulated pulsatile drug delivery system (PDDS) [14].

PDDS is time and site-explicit medication conveyance, subsequently giving spatial and worldly conveyance and expanding patient consistence. In this framework we can accomplish the fast and transient arrival of certain measure of atoms inside a brief timeframe period following a foreordained off-delivered period, i.e., slack (lag) time, or these frameworks have a particular component of conveying the medication quickly and totally after a slack time. Slack or lag time is characterized as the time between when a dose structure is put into a watery climate and the time at which the dynamic fixing starts to get delivered from the measurement structure [15].

This framework has more fascination due to their numerous advantages over customary measurement structures. These frameworks are planned by the circadian musicality of the body, and the medication is delivered quickly and totally as a heartbeat after a slack time. The aftereffects of the investigation could be gainful for drugs with chronopharmacological conduct, where nighttime dosing is required, and for drugs that show the principal pass impact [15].

Hypertension is a disease which shows circadian rhythm in the pattern of two peaks, one in the evening at about 7pm and other in the early morning between 4 am to 8 am. Generally in hypertension, the risk of getting heart attacks is just before the waking hours of the patient i.e. early in the morning and therefore the need of antihypertensive is typically felt during morning hours. For such cases, conventional formulations cannot be administered before the symptoms get worsened because at that time patients are asleep [14].

Lisinopril is a drug of the angiotensin-converting enzyme (ACE) inhibitor class that is primarily used in the treatment of hypertension, congestive heart failure, and heart attacks. It is also used in preventing the renal and retinal complications of diabetes. The drug has a half-life of 12 hrs. This drug belongs to BCS Class III, having good water solubility. Lisinopril is slowly and incompletely absorbed after oral administration with a bioavailability of 25–30% [11].

The objective of the present study was to improve gastric retention, so consequently, the bioavailability of the drug. The release is expected as a burst, i.e at once pulsatile drug Delivery of Lisinopril after a lag time. The rationale for the development of an appropriate formulation is to provide the drug at the right time, i.e. early morning. The formulation has a rapid release core tablet of lisinopril with different concentration of superdisintegrants and mini tablet coated by the layer of polymers like ethyl cellulose and sodium alginate as hydrophobic polymer to impart pulsatile release. Mini tablets are one such multiparticulate system which are filled in capsule and thus shows the benefit of tableting within capsule. These mini tablets can be scheduled to deliver the drug at different sites of the gastrointestinal tract. Mini tablets are available in different sizes that solve the problem of drug loading and generally ranges from 1.5 to 4 mm in diameter. Additional layering

can be done on the mini tablets for controlling the release at different rates.

Developed formulations were quantified for its micromeritic properties (bulk density, tapped density, Angle of repose and carr's index), hardness, thickness, weight variation, friability, drug content uniformity and invitro drug release study. The drug-excipient study was carried out by using FTIR. *In-vitro* drug release studies were carried out using pH 6.8 phosphate buffer for 12 h.

Compatibility studies

The results of compatibility studies shown in fig.1, 2. It revealed that both drug and polymers were compatible with each other and there is no interaction between the drug and the polymer.

Fourier transforms infrared spectrometry (FT-IR)

Infrared spectroscopy can be used to identify a compound and also to investigate the composition of the mixture. The results identify the compound as the pure drug while subjected to FTIR studies using Shimadzu FT-IR spectrometer model. The IR spectra of the test samples were obtained by pressed pellet technique using potassium bromide and the ratio of sample is 1:100[16].

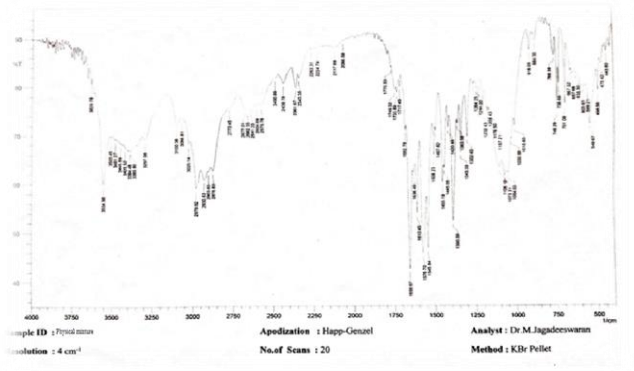

Fig.1: FTIR spectrum of Physical mixture

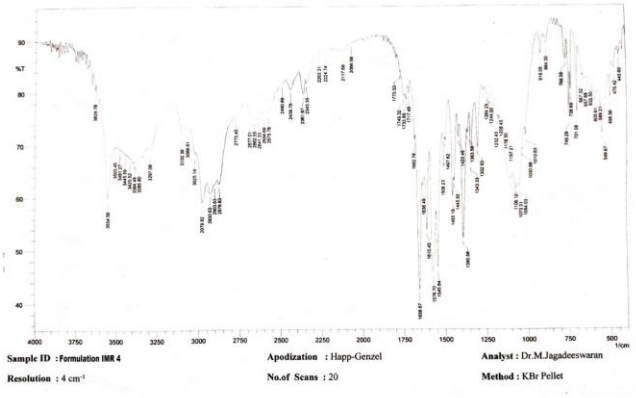

Fig. 2 : FTIR Spectrum of formulation of mini tablet formulation 4 (MTF 4)

Pre compression evaluation in tablet is most important. Evaluation of these properties will results the characteristics of powder ingredients before punch as a tablet. The observed result from pre compression evaluations shows that the prepared powders were having well in their flow properties and within the accepted limits with low standard deviation and the results given in Table 5, 7.

In general, post compression properties of tablets reflect their withstanding capacity during transportation, content uniformity and drug release. The result of post compression evaluation such as content uniformity, hardness, friability and weight variation shows within the Pharmacopoeial limits. It indicates all the prepared tablets were well in their physico-chemical properties and the results given in Table 6, 8.

Table 5. Preformulation studies of granules of lisinopril tablets (n=3, Mean ±SD)

Formula Code	Angle of repose(θ)	Bulk density(gm/ml)	Tapped density (gm/ml)	Carr'sindex(%)	Hausner's ratio
IMR1	33.18±0.577	0.4431±0.001	0.317±0.0035	13.33±0.9024	1.154±0.01
IMR2	34.67±0.499	0.3567±0.124	0.481±0.017	16.08±0.9841	1.137±0.01
IMR3	35.14±0.081	0.4145±0.012	0.529±0.021	16.67±0.0235	1.134±0.02
IMR4	33.32±0.015	0.2845±0.06	0.565±0.032	11.63±0.008	1.241±0.03

Table 6. Physico-chemical evaluation of prepared core tablets (n=3, Mean ±SD)

Formula Code	Weight variation (mg)	Thickness (mm)	Friability (%)	%Drug content	Disintegration time
IMR1	281±0.02	3.79±0.015	0.66±0.47	97.46±0.37	40.33±0.577
IMR2	285±0.02	3.72±0.016	0.71±0.48	96.96±0.01	38.66±0.576
IMR3	290±0.01	3.81±0.012	0.52±0.008	98.98±0.52	41.66±0.57
IMR4	295±1.24	3.79±0.015	0.64±0.021	99.27±0.27	41.00±0.01

Table 7.Pre compression studies for mini tablets of Lisinopril (n=3, Mean ±SD)

Formula Code	Angle of repose(θ)	Bulk density(gm/ml)	Tapped density (gm/ml)	Carr'sindex(%)	Hausner's ratio
MTF1	33.18±0.57	0.3431±0.0	0.552±0.07	15.31±0.02	1.186±0.03
MTF2	34.67±0.49	0.3567±0.1	0.581±0.01	15.00±0.01	1.174±0.021
MTF3	35.14±0.08	0.4145±0.	0.529±0.02	16.67±0.02	1.177±0.025
MTF4	33.32±0.015	0.3845±0.06	0.565±0.03	18.63±0.01	1.241±0.03

Table 8.Physico-chemical evaluation of prepared core tablets (n=3, Mean ±SD)

Formula Code	Weight variation (mg)	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	% Drug content
MTF1	290±0.816	6.5±0.43	4.79±0.015	0.76±0.48	98.94±0.014
MTF2	295±0.816	6.06±0.5	4.72±0.016	0.71±0.48	96.96±0.016
MTF3	290±0.816	5.66±0.76	4.81±0.012	0.72±0.008	98.36±0.012
MTF4	285±1.247	5.52±0.25	4.79±0.015	0.64±0.021	97.65±0.015

The results of *in-vitro* disintegration and dissolution study on lisinopril immediate release tablet and mini tablet were performed at 6.8 phosphate buffer for 12 hrs. The *in-vitro* disintegration from immediate release tablet varied according to the concentration of superdisintegrants used. The concentration of superdisintegrants increased the release also increased. Thus the Formulation IMR4 was considered as best due to its fast release compared to other formulations. The results were given in Fig.3

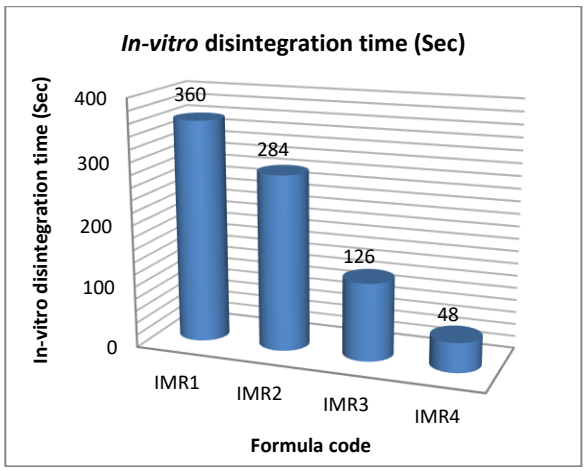

Fig. 3. % *in–vitro* Disintegration time of immediate release tablets

The result of determination of *in-vitro* % drug release profile from lisinopril mini tablet gives a programmable period of time and to deliver the drug in the early morning hours. The more appropriate drug release can be achieved in the formula MTF4 when compared to other formulations. This is due to the presence of both hydrophobic polymers such as ethyl cellulose and sodium alginate as coating layer in mini tablet. The cumulative % *in -vitro* drug release data were given in Fig.4.

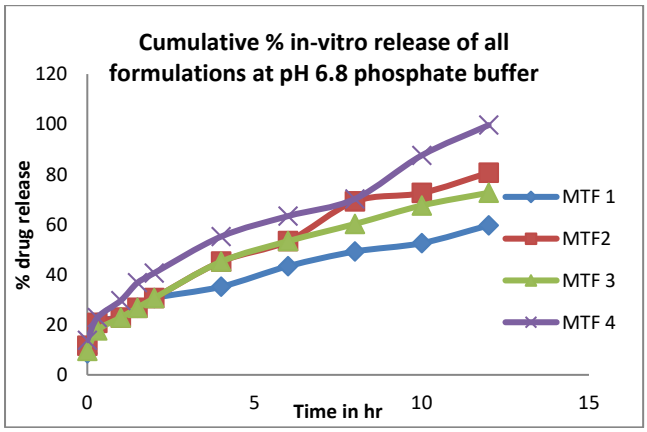

Fig. 4: Cumulative % *in- vitro* drug release from all formulations at pH 6.8 phosphate buffer.

As granules show immediate release so they can be preferred for release during the evening hours when there is mild attack of hypertension while the pulse dose will be released after predetermined lag time from mini-tablets during early morning hours when the attack of hypertension is at its peak.

The *in-vitro* release profile suggested that immediate release granules gives drug release within 40 sec at the time of evening attack while the programmed pulsatile release was achieved from coated mini-tablets after a lag time of 9hrs, which was consistent with the demand of drug during early morning hour attack.

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Conflict of Interests

The authors declared no conflict of interest.

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