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Development and Evaluation of Pulsatile Drug Delivery System for Management of Hypertension

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KEYWORDS
Solid dispersion, Immediate release granules, Sustained release microparticles

ABSTRACT:
The objective of this work was to develop the pulsatile drug delivery system of Ramipril i.e antihypertensive drug to enhance the patient compliance. The pulsincap system gives the desired lag time to release and carry the two different types of dosage form i.e immediate release granules and sustained release microparticles. An immediate release granules provides the immediate release of drug in 30 minutes after the lag time to achieve therapeutic concentration in the body, while sustained release microparticles provide sustain release of drug to maintain the therapeutic concentration of the drug for prolonged time. In this study physicochemical property of ramipril was improved by using solid dispersion technique. Solid dispersion of ramipril was prepared with PEG 6000 polymer at three drug: polymer ratios (1:1), (1:2) and (1:3). The solid dispersion (1:3) showed maximum solubility. Immediate release granules were prepared using wet granulation method. Cross carmellose sodium was used as super disintegrating agent. Sustained release microparticles were prepared by solvent evaporation technique. Ethyl cellulose was used as the polymer in different ratios with drug. The specific 6 hours lag time was achieved by treating gelatin capsules with formalin vapours. . So, it can be concluded that pulsincap system of Ramipril control the risk of high blood pressure and heart attack, by giving immediate release within 30 minutes and maintain the drug level for 12 hours.

INTRODUCTION:

A highly prevalent condition, especially after middle age, is hypertension. Although not an illness in and of itself, it is a significant risk factor for cardiovascular death. [1, 2] Cerebral and renal problems are also more likely to occur in hypertension patients. The quality of life during hypertension treatment is a critical health concern since many patients would stop taking their medication because of adverse effects. Therefore, therapy compliance issues will result in worse outcomes. Most cases of hypertension are essential (primary) hypertension. [3, 5] The primary cause of hypertension remains unknown. Elevated blood pressure in the arteries is a persistent medical disease known as high blood pressure. [6]

TYPES OF HYPERTENSION:

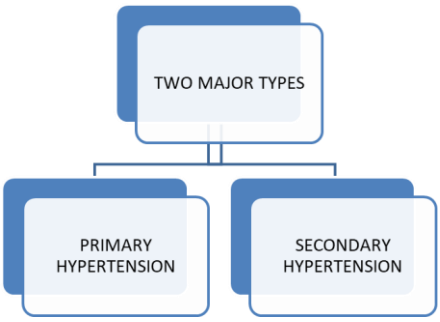

Fig. 1: Types of hypertension

PRIMARY HYPERTENSION: It affects 95% of persons with hypertension and is often referred to as essential or idiopathic hypertension. This kind of hypertension is identified after a clinician observes elevated blood pressure, but the cause is unknown. People with primary hypertension may not exhibit any symptoms, but they may frequently suffer from headaches, fatigue, dizziness, and nosebleeds. Alcohol,

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nutrition, genetics, smoking, obesity, and heredity all have a significant impact on primary hypertension.

MECHANISMS IN PRIMARY HYPERTENSION: Many patho -physiological mechanisms contribute their role to the development of primary hypertension. It includes: 1) Genetics 2) High salt intake 3) Low physical activity 4) Obesity 5) Insulin resistance 6) Renin – angiotensin system 7) Sympathetic nervous system. [7]

SECONDARY HYPERTENSION: The reason for secondary hypertension is understood, and it affects only 2-3% of people. A major contributing factor to secondary hypertension is an anomaly in the arteries that feed the kidneys with blood. Secondary hypertension can arise from a number of reasons. [8]

1) Endocrine causes: It includes Cushing's syndrome, Acromegaly, Hyperparathyroidism, Conn's syndrome etc.
2) Renal causes: It includes Diabetic nephropathy, Polycystic kidney disease, Glomerulonephritis, Renal artery stenosis.
3) Additional causes include: blockage of the airways; hormone abnormalities; tumors in the adrenal glands; thyroid disorders; excessive consumption of salt and alcohol; and acute stress. Secondary hypertension can also be brought on by certain over-the-counter medications, such as pseudoephedrine and ibuprofen.

PATHOPHYSIOLOGY OF HYPERTENSION:

- **Heredity**: Hypertension mostly caused by the interaction of environmental factors, demographic factors and genetic factors. [9]

- **Water and Sodium Retention**: Retention of water occurs when we consume higher concentrations of sodium. Some people are sensitive to sodium (Na), and certain demographics—such as those who are obese, becoming older, have diabetes, have renal illness, or are African American—are linked to this sensitivity.

- **Stress and increased sympathetic nervous system (SNS) activity**: It cause vasoconstriction leads to increase heart rate.

- **Renin – Angiotensin – Aldosterone mechanism**: Renin is an enzyme that the kidney secretes to keep the body's blood pressure, fluid volume, and sodium-potassium balance in check. The juxta glomerular (JG) cells release renin when blood pressure drops. Angiotensin I is produced when renin interacts with plasma protein, an angiotensin substrate. Angiotensin is changed into Angiotensin II with the aid of the angiotensin converting enzyme (ACE). Angiotensin II promotes the vasoconstriction activity by acting on the walls of blood vessels. Due to the vasoconstriction, TPR (Total peripheral resistance) will also increase and leads to increase blood pressure. It is the first mechanism.

Angiotensin II also activates the adrenal cortex in the second method. This will result in an increase in the hormone aldosterone secretion. Aldosterone stimulates the kidneys' ability to reabsorb sodium (Na) and water. Blood pressure (BP) rises as a result of this increased blood volume. [10-14]

MATERIALS AND METHODS:

Ramipril was obtained as a gift sample from Ind-Swift Laboratories Ltd. All other material like PEG 6000, Croscarmellose Sodium (super-disintegrant), Microcrystalline Cellulose, lactose, Magnesium Stearate, talc, Gelatin capsule, Ethyl cellulose were also of analytical grade.

PREPARATION OF SOLID DISPERSION BY USING FUSION (MELTING) METHOD:

PEG 6000 was melted on a water bath at 70^0C, then mixed with the drug and triturated till cold. The prepared solid dispersions were passed through sieve no. 80 and stored in desiccator until used. [15-17]

Table No. 1: Formulation of solid dispersions

Formulation codes	Drug (Ramipril)	Polymer (PEG 6000)	Ratio (D/P)
SD1	500 mg	500 mg	1:1

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SD2	500 mg	1000mg	1:2
SD3	500mg	1500mg	1:3

Solubility studies of Ramipril solid dispersion:

In distilled water, solubility tests for the solid dispersion of Ramipril were conducted. For 24 hours at room temperature, a solid dispersion corresponding to 10 mg of Ramipril was agitated with 10 ml distilled water using a magnetic stirrer. Following that, Whatman filter paper was used to filter the solutions. Distilled water was used to appropriately dilute the filtered solution. After that, Whatman filter paper was used to filter the diluted suspension that was left behind. Finally, the sample were analysed by UV spectrophotometer (SHIMADZU) at 208.5 nm.

Dissolution studies of solid dispersion:

USP Type II (Paddle type) dissolving device was used to dissolve the solid dispersion in vitro. The dissolving medium, 900 ml of phosphate buffer pH 6.8 solution, was kept at 37±0.50C. At 75 rpm, the medium was swirled. For forty minutes, 10 milliliter samples were obtained every five minutes and replaced with new dissolving medium. Following filtering at 205.5 nm, the samples were examined using a UV spectrophotometer in comparison to a blank. The percentage of drug release was computed once the drug release studies were completed.

PREPARATION OF IMMEDIATE RELEASE GRANULES:

The wet granulation process was used to prepare the granules. According to the geometric dilution method, solid dispersion (1:3), croscarmellose sodium (CCS), microcrystalline cellulose (MCC), and lactose monohydrate were precisely weighed and homogeneously blended for 15 minutes. To create a cohesive mass, polyvinyl pyrollidone (PVP) was dissolved in isopropyl alcohol and combined with a powder blend. After passing through sieve number 22, the coherent material was dried for 20 minutes at 500C. [18-20]

Table No. 2: Composition of Immediate Release Granules

Ingredients (mg)	A1	A2	A3	A4
Solid dispersion equivalent to 10 mg of the drug	40	40	40	40
Croscarmellose sodium (CCS)	2	3	4	5
Microcrystalline cellulose (MCC)	63	62	61	60
Lactose monohydrate	35	35	35	35
Magnesium stearate	5	5	5	5
Talc	5	5	5	5

EVALUATION OF BLENDS [21-26]

Bulk density: Bulk density was determined by pouring weighed quantity of blend into graduated cylinder and measuring the height. Bulk density is the ratio of mass of tablet blend to bulk volume. The bulk density was calculated by using the formula.

$$\textbf{Bulk density} = \frac{m}{Vb} \quad \textbf{.....eq (1)}$$

Here, m= weight of powder (gm)

Vb= Bulk volume (cm^3)

Tapped density: Accurately weighed amount of blend poured in graduated cylinder and height was measured. Then cylinder was allowed to 100 tap under its own weight onto a hard surface. The tapping was continued until no further change in height was noted. Here Vt was the tapped volume.

$$\textbf{Tapped density} = \frac{m}{Vt} \quad \textbf{.....eq (2)}$$

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Carr's index (compressibility index): Compressibility is the ability of powder to decrease in volume under pressure using bulk density and tapped density the percentage compressibility of powder were determined, which is given as compressibility index. It is indirectly related to the relative flow rate. Compressibility index was determined by the given formula.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \ldots\ldots \text{eq (3)}$$

Table No. 3: Compressibility index of powder flow properties

Carr's index (%)	Type of flow
5-12	Excellent
12-18	Good
18-21	Fair
23-35	Poor
33-38	Very poor
>40	Extremely poor

Hausner's ratio: Hausner's ratio indicates the flow properties of powder and measured by the ratio of tapped density to bulk density. Hausner's ratio was determined by the given formula;

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \ldots\ldots\ldots\ldots\ldots\ldots \text{eq (4)}$$

Table No. 4: Hausner's ratio of powder flow properties

Hausner's ratio	Type of flow
1-1.1	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.35-1.45	Poor
1.46-1.59	Very poor

Angle of repose (θ): The funnel method was used to calculate the blend's angle of repose. The precisely weighed mixture was poured into the funnel. The funnel's height was modified so that the tip of the funnel barely brushed the blend's apex. The mixture was let to freely pass through the funnel onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following formula;

$$\text{Angle of repose } (\tan \theta) = \frac{h}{r} \ldots\ldots\ldots\ldots\ldots\ldots \text{eq (5)}$$

Here, h was the height and r was the radius of powder cone.

EVALUATION OF IMMEDIATE RELEASE GRANULES

Percentage yield:

The prepared granules were collected and weighed. The yield was calculated by dividing the measured weight by the total weight of components. [27] The percentage yield of granules was calculated as follows;

$$\%\ \text{yield} = \frac{\text{Weight of granules}}{\text{Total weight of all components}} \times 100 \ldots\ldots\ldots\ldots\ldots\ldots \text{eq (6)}$$

Drug content:

Accurately weighted granules were dissolved in a small quantity of methanol and then volume was made up to 100 ml with methanol. The solution was filtered through whatman filter paper and the absorbance was measured at 208nm. [28]

***In- vitro* dissolution study for immediate release granules**

Under sink conditions, the USP Type II (Paddle type) dissolving apparatus was used to perform the in vitro dissolution. The dissolving medium, 900 ml of phosphate buffer pH 6.8 solution, was kept at 37±0.50C. At 75 rpm, the medium was swirled. For thirty minutes, 10 milliliters of sample were removed every five minutes and replaced with new dissolving media. Following filtering at 205.5 nm, the samples were examined using a UV spectrophotometer in comparison to a blank. The studies on drug release were conducted, and the percentage of drug release was determined. [29]

PREPARATION OF MICROPARTICLES (SOLVENT EVAPORATION TECHNIQUE):

15 ml of methanol were used to co-dispose ramipril and ethyl cellulose. Next, the polymer drug solution was used to disperse magnesium stearate. Next, the dispersion was slowly added to 50 ml of light liquid paraffin in a 250 ml

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beaker while stirring at a slow 500 rpm using a 10-milliliter plastic syringe. Following the full addition, the speed at which the methanol was stirring was raised and kept constant (between 500 and 1000 rpm) for two hours. The microparticles were filtered out and then dried for 24 hours at 400 degrees Celsius in an oven then kept until needed in a desiccator. The composition of microparticles was given in table no. 5 [30-31]

Table No. 5: Composition of microparticles

Formulation codes	Ratio D/P	Drug (mg)	Ethyl cellulose(mg)
M1	1:1	100	100
M2	1:3	100	300
M3	1:5	100	500
M4	1:7	100	700
M5	1:9	100	900

EVALUATION OF MICROPARTICLES:

- Determination of percentage yield
- Determination of average size of microparticles
- Determination of surface characteristics
- Determination of drug content
- In – vitro dissolution studies of microparticles
- Drug release kinetics

+RESULT & DISCUSSION

SOLID DISPERSION BY USING MELTING METHOD

Solubility profile of pure drug and solid dispersions is shown in Table No. 6. It was found that the solubility of drug increased with the increase in concentration of the polymer SD3 (1:3) showed maximum solubility.

SOLUBILITY DATA OF SOLID DISPERSION

Table No. 6: SOLUBILITY DATA OF SOLID DISPERSION PREPARED BY MELTING METHOD

Formulation code	Solubility (mg/ml)
Pure drug	**0.039±0.0131**
SD1	**0.111±0.0108**
SD2	**0.253±0.0132**
SD3	**0.431±0.0152**

Data are expressed as mean ± S.D (n=3)

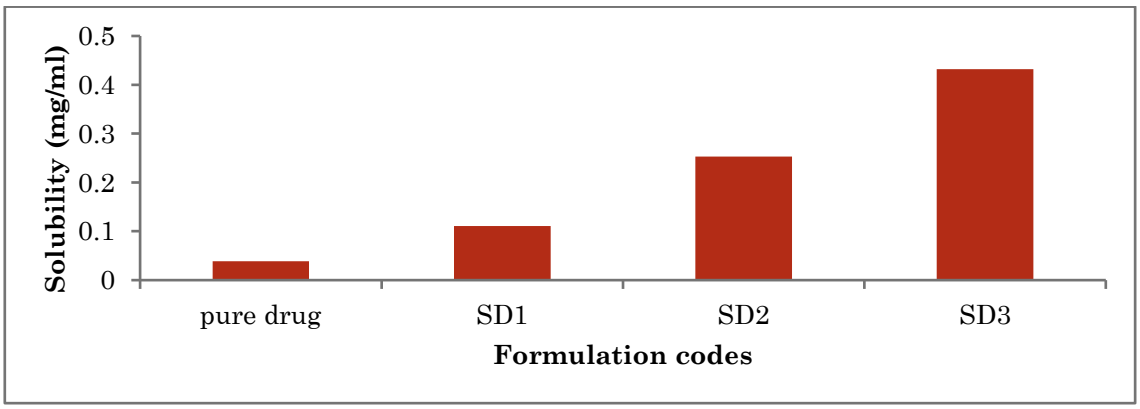

Fig 2: Solubility values of solid dispersion of different batches

DISSOLUTION STUDY OF SOLID DISPERSION

Table No. 7: Percentage drug release from solid dispersion

Time (minutes)	Pure drug	SD1 (1:1)	SD2 (1:2)	SD3 (1:3)
5	**8.54 ± 0.18**	**15.71± 0.46**	**22.28± 0.67**	**26.65± 0.35**

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10	13.54± 0.39	24.09± 0.67	34.25± 0.75	37.42± 0.24
15	17.72± 0.49	32.04± 0.33	41.22± 0.54	49.16± 0.57
20	22.50± 0.54	41.21± 0.76	53.35± 0.62	61.70± 0.54
25	29.47± 0.37	48.59± 0.38	61.20± 0.37	69.90± 0.33
30	34.25± 0.49	56.54± 0.65	70.87± 0.29	77.45± 0.48
35	38.43± 0.57	62.51± 0.55	77.44± 0.46	86.40± 0.26
40	41.33± 0.27	68.87± 0.45	84.21± 0.44	96.77± 0.59

Data are expressed as mean ± S.D (n=3)

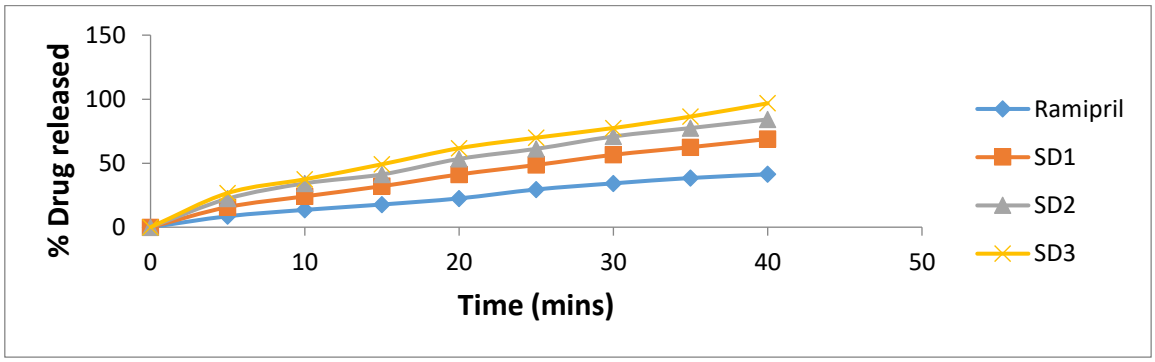

Fig. 2: Percentage drug release from solid dispersion

EVALUATION OF IMMEDIATE RELEASE GRANULES

Evaluation of Powders

Table No. 8: EVALUATION PARAMETERS OF POWDER BLEND

Formulation codes	Angle of repose (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio
A1	30.23±0.025	0.412±0.22	0.554±0.192	25.63±0.026	1.344±0.0243
A2	27.48±0.030	0.443±0.17	0.583±0.025	24.01±.030	1.316±.0233
A3	32.12±0.030	0.429±0.29	0.525±0.022	18.28±0.036	1.223±0.0152
A4	31.62±0.020	0.432±0.14	0.532±0.015	18.79±0.034	1.231±0.0123

Data are expressed as mean ± S.D (n=3)

EVALUATION OF IMMEDIATE RELEASE GRANULES

The percentage yield and percentage drug content was determined for all the formulations. The percentage yield for all the formulation was found to be from 81.20% to 93.21% as shown in Table No 9.

Table No. 9: PERCENTAGE YIELD

Formulation codes	% yield
A1	81.20±0.9
A2	89.80±0.8
A3	86.6±0.8
A4	93.21±0.5

Data are expressed as mean ± S.D (n=3)

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The drug content for all the formulation was found to be from 86.58% to 96.86% as shown in Table No. 10.

Table No. 10: % DRUG CONTENT

Formulation codes	% drug content
A1	**75.58±0.6**
A2	**82.32±0.2**
A3	**90.62±0.9**
A4	**96.86±0.4**

Data are expressed as mean ± S.D (n=3)

. DISSOLUTION STUDY OF IMMEDIATE RELEASE GRANULES

Table No.11: % Cumulative drug released from immediate granules

Time (min)	A1	A2	A3	A4
5	**29.65±0.151**	**34.64±0.194**	**38.22±0.254**	**46.59±0.143**
10	**40.18±0.253**	**46.77±0.136**	**51.78±0.135**	**57.65±0.207**
15	**48.21±0.121**	**56.25±0.294**	**64.50±0.176**	**68.04±0.426**
20	**55.72±0.163**	**62.82±0.183**	**75.55±0.294**	**81.73±0.370**
25	**62.94±0.142**	**70.30±0.314**	**81.77±0.564**	**90.78±0.335**
30	**71.68±0.211**	**77.25±0.111**	**86.67±0.295**	**95.92±0.264**

Data are expressed as mean ± S.D (n=3)

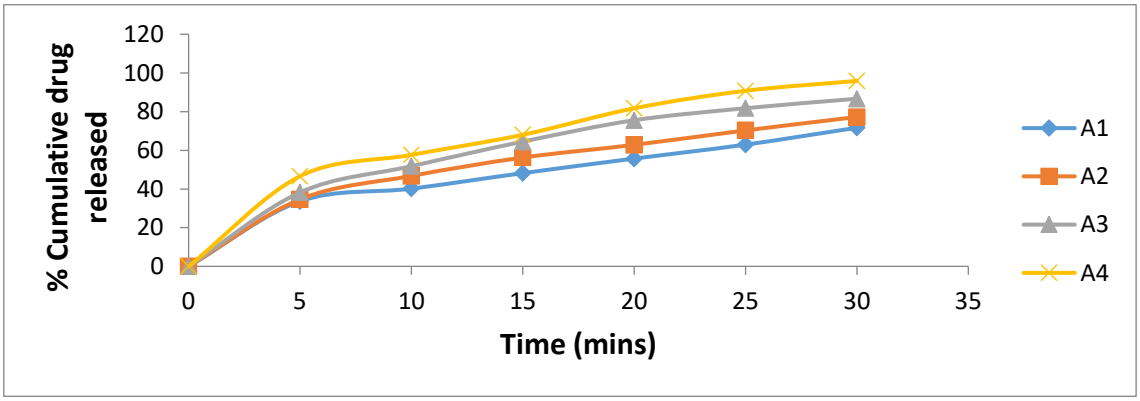

Fig 3*: In- vitro* drug release of Ramipril (A1-A4)

The formulation code A4 showed maximum drug release (95.92%) corresponding to 30 minutes. There was an enhancement in the drug release as the concentration of superdisintegrant increased. Hence A4 formulation was the best formulation.

EVALUATION OF SUSTAINED RELEASE MICROPARTICLES

The percentage yield and percentage drug content was determined for all the formulations. The percentage yield for all the formulation was found to be from 69.80% to 86.60% as shown in Table No. 12.

Table No. 12: PERCENTAGE YIELD

Formulation codes	% yield
M1	**69.80±0.4**

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M2	**73.53±0.8**
M3	**80.20±0.2**
M4	**77.21±0.4**
M5	**86.60±0.5**

Data are expressed as mean ± S.D (n=3)

The drug content for all the formulation was found to be from 75.58% to 93.25% as shown in Table No. 13.

Table No. 13: % DRUG CONTENT

Formulation codes	% drug content
M1	**75.58±0.6**
M2	**77.74±0.2**
M3	**84.31±0.9**
M4	**89.25±0.3**
M5	**93.25±0.5**

Data are expressed as mean ± S.D (n=3)

SHAPE AND SURFACE MORPHOLOGY

Microparticles formulations were visualized under optical microscope to check the shape and surface smoothness of the microparticles. The shape, size and surface morphology showed in Table no. 14.

Table No. 14: Shape, size and surface morphology of microparticles

Formulation	Particle size (µm)	Surface	Shape
M1	**27.78±0.53**	**Rough**	**Discrete**
M2	**55.63±0.25**	**Smooth, Rough**	**Aggregation**
M3	**44.36±0.88**	**Smooth**	**Spherical**
M4	**61.28±1.21**	**Smooth**	**Spherical**
M5	**38.73±0.77**	**Perfectly smooth**	**Spherical**

Data are expressed as mean ± SD (n=3)

Fig. 4: Optical microscopic image of M5 microparticles

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Microsphere XRD

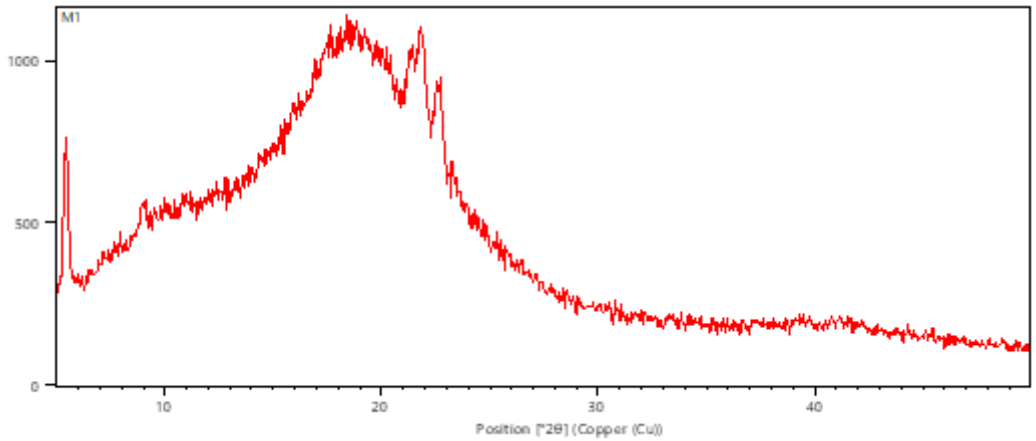

Fig. 5: XRD

Peak List: Table No. 15

Pos. [°2θ]	FWHM Total [°2θ]	d-spacing [Å]	Rel. Int. [%]	Area [cps*°2θ]
5.4431	0.2419	16.22281	100.00	9.55
9.0161	0.3359	9.80030	16.71	2.55
21.3306	0.2905	4.16216	31.81	3.02
21.8119	0.4530	4.07140	63.46	11.20
22.6289	0.3589	3.92622	52.43	7.03

SCANNING ELECTRON MICROSCOPY

The surface characteristics of microparticles were studied by scanning electron microscope. The results showed in fig. 6

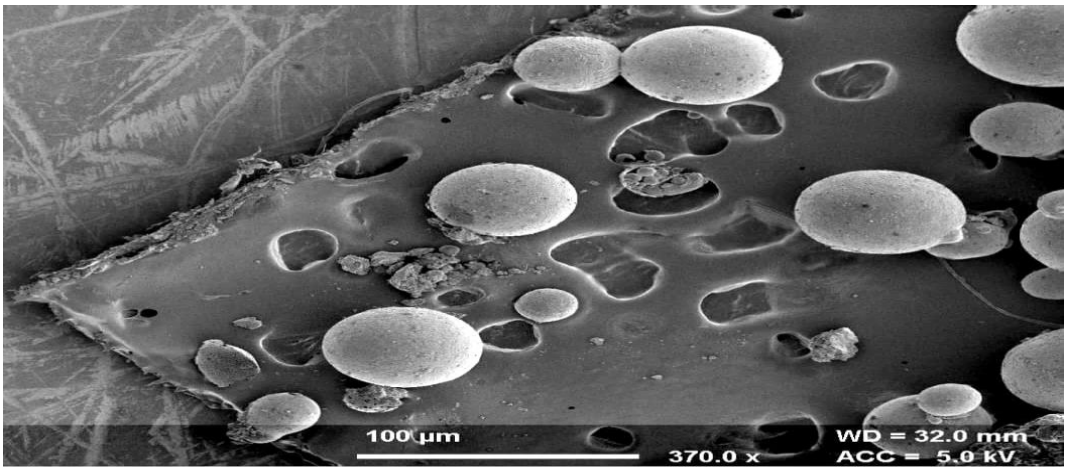

Fig. 6: Scanning Electron Microscopy of Ramipril microparticles

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Zeta Potential:

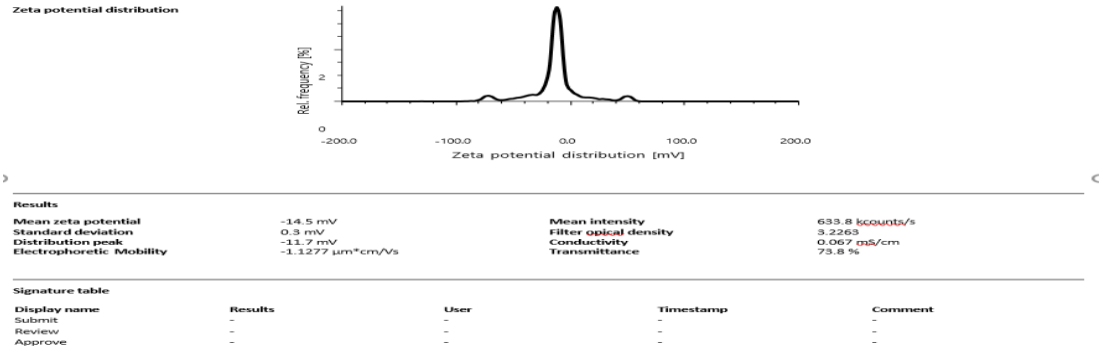

Fig. 7: Zeta Potential study

DISSOLUTION STUDY OF SUSTAINED RELEASE MICROPARTICLES

Table No. 16: % Cumulative drug released from microparticles

Time (hrs.)	M1	M2	M3	M4	M5
0	0	0	0	0	0
1	11.54±0.04	10.54±0.01	6.36±0.03	6.16±0.26	4.77±0.06
2	17.84±0.01	15.44±0.01	11.01±0.06	9.82±1.52	7.21±0.04
3	29.79±0.07	25.37±0.05	18.50±0.15	13.71±1.33	13.27±0.04
4	42.06±0.11	38.98±0.01	29.66±1.23	21.02±0.01	19.79±0.02
5	55.26±0.04	50.97±0.07	41.33±0.03	30.81±0.64	27.17±0.01
6	69.41±0.17	61.89±0.02	49.35±1.05	43.89±0.09	39.81±0.07
7	82.30±0.04	73.49±0.02	61.03±0.32	55.52±0.04	47.21±0.05
8	89.76±0.06	83.24±0.13	69.65±1.20	66.28±0.03	59.67±0.02
9	95.50±0.01	91.11±1.21	81.96±0.07	74.56±1.20	71.85±0.09
10	99.36±0.17	96.32±0.09	92.46±0.53	87.51±0.04	80.80±0.12
11		99.58±0.06	98.38±0.21	92.24±1.34	87.16±0.07
12				99.12±1.10	92.63±0.04
13					96.85±0.04
14					99.72±0.01

Data are expressed as mean ±S.D (n=3)

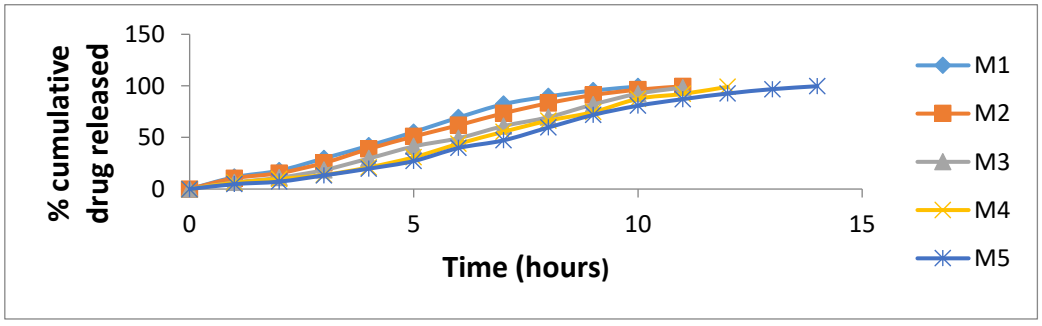

Fig. 8: In-vitro drug release of Ramipril (M1-M5)

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EVALUATION OF CROSS LINKED EMPTY CAPSULES

Identification:

Table No. 17: Physical identification

Capsules	Formaldehyde treated capsules
• "1" size capsules with red colour cap and body, lockable type and odourless. • Sticky when touched with wet fingers.	• No significant changes in the capsules. The colour, odor and type remain the same. • Non- sticky when touched with wet fingers.

DETERMINATION OF EFFECT ON CAPSULE WEIGHT

Total weight of all the formaldehyde treated capsules was determined by weighing individually on digital balance (Shimadzu, AX200, Japan). The results are summarized in table no.18.

Table No. 18: Weight of capsule

Normal capsules (mg)	C1 (mg)	C2(mg)	C3(mg)	C4(mg)
90	90	90	100	90
80	90	90	100	100
90	90	90	90	90
90	90	80	90	90
100	90	90	90	110
90	100	90	90	90
90	90	100	80	100
100	90	90	100	90
80	100	90	90	90
110	90	90	90	100

There is no major change in the weight of capsules when treated with formaldehyde as compared with the normal capsules.

DISINTEGRATION TIME STUDY

Table No. 19: Disintegration time

Treatment Time(hrs)	Disintegration time (hrs)
3 hours (C1)	2:17±1.21
6 hours (C2)	5:25±0.96
9 hours(C3)	6:40±1.15
24 hours(C4)	Above 8 hours

Data are expressed as mean ± SD (n=3)

From the above data, it is clear that the specific 6 to 7 hours lag time was achieved by treating hard gelatine capsules 9 hours with formalin vapours. Hence, (C3) formulation was the best formulation.

DISSOLUTION STUDIES OF BEST FORMULATION C3 (A4+M5)

Table No 20: In-vitro release study of best formulation C3 (A4+M5)

Time (hrs)	C3(A4+M5)
0	0
1	0
2	0

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3	0
4	0
5	0
6	0
7	53.24±0.32
8	57.85±0.16
9	61.87±0.65
10	65.13±0.76
11	68.82±0.16
12	72.15±1.24
13	75.85±0.71
14	77.08±0.52
15	80.17±0.11
16	83.84±0.95
17	88.05±0.33
18	94.64±1.49
19	96.52±0.66
20	98.17±0.53

Data are expressed as mean ±SD (n=3)

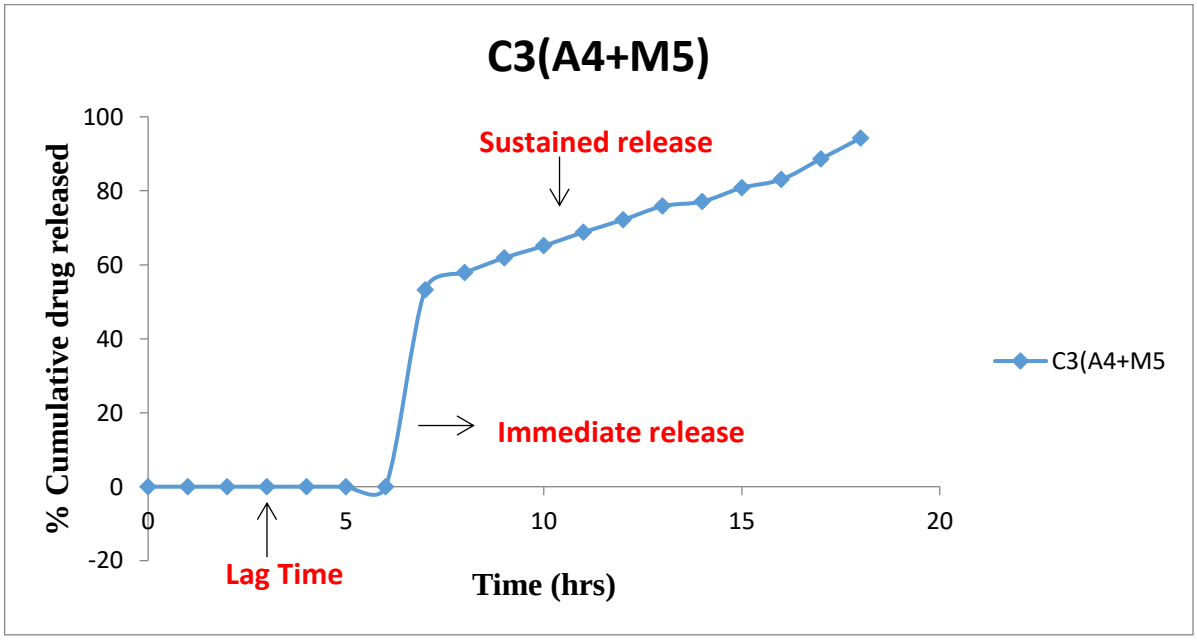

Fig. 9: In vitro drug release of Ramipril C3 (A4+M5)

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Conclusion

The goal of this research effort was to improve patient compliance by creating a pulsatile drug delivery system for the hypertension medication ramipril. The two distinct dosage form types immediate release granules and sustained release microparticles—are carried via the pulsincap system, which also provides the appropriate lag time for release. While sustained release microparticles provide sustained release of the drug to maintain the therapeutic concentration of the drug for an extended period of time, instant release granules provide immediate release of the drug in 30 minutes after the lag time to obtain therapeutic concentration in the body. [32-34]

The hypertension medication ramipril is categorized as an angiotensin converting enzyme inhibitor (ACE). Angiotensin converting enzyme (ACE) activity is inhibited by ramipril, which lowers angiotensin II synthesis and bradykinin breakdown. As blood is pushed through enlarged arteries, the reduction in angiotensin II causes the smooth muscle in the arterioles to relax, lowering overall peripheral resistance and blood pressure. [35-37]

For a number of reasons, including its primary usage in treating hypertension, congestive heart failure, nephropathy, and myocardial infraction, ramipril is the medication of choice. The half-life of ramipril is shorter (2-4 hours). Ramipril is a medication that has a first-pass metabolism and is poorly soluble in water. Ramipril's absolute bioavailability is very low, at 28–35%.

By preparing a solid dispersion, Ramipril's solubility was increased (by employing melting process). PEG 6000 was employed with the medication in various ratios, including 1:1, 1:2, and 1:3. Wet granulation was used to create instant release granules. The super disintegrating agent was cross-carmellose sodium. Using a solvent evaporation approach, sustained release microparticles were produced. Various ratios of ethyl cellulose were employed as the polymer with the medication. Formalin vapour treatment of the gelatin capsules produced the precise 6-hour lag period. The blend was evaluated for their flow properties and mass volume relationships. The results of bulk density, tapped density, hausner's ratio, compressibility index and angle of repose indicated good compressibility and acceptable flow properties of the formulated mixed blends. The immediate release granules were also evaluated and examined for various parameters like percentage yield, drug content and *in vitro* release response.

The sustained release microparticles were also evaluated for various parameters like average size of microparticles, determination of surface characteristics (SEM), percentage yield, drug content, entrapment efficiency and dissolution study. The formalin vapours treated capsules were observed physically. The treated capsules were non-sticky when touched with wet fingers. Disintegration time of capsules was determined by using distilled water as disintegration medium at 37 ± 2^0C. *In vitro* dissolution studies were performed using USP II dissolution apparatus (paddle type) at 50 rpm using 900 ml 0.1N HCI and phosphate buffer pH 6.8 as dissolution medium at 37 ± 0.5^0C throughout the studies of all formulations. The results of evaluation were found within official limits. So, it can be concluded that pulsincap system of Ramipril control the risk of high blood pressure and heart attack, by giving immediate release within 30 minutes and maintain the drug level for 12 hours. [38-42]

REFERENCES

1. Jagdale, S.C., Suryawanshi, V.M., Pandya, S.V., Kuchekar, B.S. & Chabukswar, A.R. (2014) Development of press-coated, floating-pulsatile drug delivery of lisinopril. *Sci Pharm.* 82(2): 423-440. Available from: DOI: 10.3797/scipharm.1301-27
2. Jain, D., Raturi, R. & Jain, V. (2011) Recent technologies in pulsatile drug delivery systems. *Biomatter* 1(1): 57-65. Available from: DOI: 10.4161/biom.1.1.17717
3. Khalifa, A.Z., Zyad, H., Mohammed, H., Ihsan, K., Alrawi, L., Abdullah, M & Akram, O. (2022) Recent advances in remotely controlled pulsatile drug delivery systems. *J Adv. Pharm Technol Res.* 13(2): 77-82. Available from: Doi: 10.4103/japtr.japtr_330_21
4. Kriplani, P., Pathak, K. & Philip, A. (2021), Preparation and evaluation of 3 Cap Pulsatile drug delivery system of Ramipril. *Cardiovasc Hematol Agents Med Chem*.19 (1): 50-61. Available from: DOI: 10.2174/1871525718666200528140527

5. Krishna, N.S., Jayanthi, B. & Madhukar, A. (2018) "Review of Pulsatile drug delivery system, *Indo Am. J. P. Sci*, 05(06), 5488-5494. Available from: DOI:10.5281/zenodo.1296981
6. Maestre, J., Pallares, J., Cuesta, I. & Scott, M.A. (2019), Dynamics of a capsule flowing in a tube under pulsatile flow. *J Mech Behav Biomed Mater*. 90: 441-450. Available from: DOI: 10.1016/j.jmbbm.2018.10.025
7. Mandal, A.S., Biswas, N., Karim, K.M., Guha, A., Chatterjee, S., Behera, M. & Kuotsu, K. (2010) Drug delivery system based on chronobiology- A Review. *J Control Release*. 147(3): 314-325. Available from: DOI: 10.1016/j.jconrel.2010.07.122
8. Maroni, A., Zema, L., Cerea, M. & Sangalli, M.E. (2005) Oral Pulsatile drug delivery systems. *Expert Opin Drug Deliv*. 2(5): 855-871. Available from: DOI: 10.1517/17425247.2.5.855
9. Maroni, A., Zema, M.L., Curto, M.D., Loreti, G. & Gazzaniga, A. (2010) Oral pulsatile delivery: Rationale and chronopharmaceutical formulations. *Int J Pharm.* 398(1-2): 1-8. Available from: DOI: 10.1016/j.ijpharm.2010.07.026
10. Nayana, D., Bari, M.M. & Barhate, S.D. (2013) A review on novel approach pulsatile drug delivery system. *Int.J.Pharm.Sci.Rev.Res*. 21(1), Jul-Aug; 36, 209-222. Available from: https://globalresearchonline.net/journalcontents/v21-1/36.pdf
11. Pandey, R., Thakur, G. & Selvamurthy, W. (2020), Design and in vitro characterization of novel pulsatile delivery system of biguanide antidiabetic drug. *J Pharm Bioallied Sci*. 12(3): 356-368. Available from: DOI: 10.4103/jpbs.JPBS_203_19
12. Patil, S.S. & Shahiwala, A. (2014) Patented pulsatile drug delivery technologies for chronotherapy. *Expert Opin Ther Pat.* 24(8): 845-856. Available from: DOI: 10.1517/13543776.2014.916281
13. Latha K, Uhumwangho MU, Sunil SA, Srikanth MV, Murthy KR. Development of an optimised losartan potassium press-coated tablets for chronotherapeutic drug delivery. Trop J Pharm Res. 2011; 10(5):551 Available from Doi: 10.4314/tjpr.v10i5.3.
14. Jain D, Raturi R, Jain V, Bansal P, Singh R. Recent technologies in pulsatile drug delivery systems. Biomatter. 2011; 1(1):57-65. Available from Doi: 10.4161/biom.1.1.17717, PMID 23507727.
15. Rashid, R., Zaman, M., Ahmad, M., Khan, M.A., Butt, M.H., Salawi, A., Almoshari, Y. & Sarfraz, R.M. (2022) Press-coated Aceclofenac tablets for pulsatile drug delivery: Formulation and In vitro evaluations. *Pharmaceuticals (Basel)*. 15(3): 326. Available from: DOI: 10.3390/ph15030326
16. Shah, N., Sharma, O.P., Mehta, T. & Amin, A. (2016), Design of experiment approach for formulating multi-unit colon targeted drug delivery system: in vitro and in vivo studies. *Drug Dev Ind Pharm*. 42(5): 825-835. Available from: DOI: 10.3109/03639045.2015.1082581
17. Sharma, R., Singh, A., Kumar, S. & Jamil, F. (2012) Pulsatile drug delivery system. *International Research Journal of Pharmacy*; 3(7): 103-107. Available from: https://www.scribd.com/document/190204711/1219-pdf
18. Taneja, R., Sharma, R. & Gupta, G.D. (2017), Development and characterization pulsatile microspheres of Nifedipine for hypertension. *Recent Pat Drug Deliv Formul*. 11(1): 67-76. Available from: DOI: 10.2174/1872211311666170213104321
19. Taranalli, S.S., Dandagi, P.M. & Mastiholimath, V.S. (2015), Development of hollow/porous floating beads of metoprolol for pulsatile drug delivery. *Eur J Drug Metab Pharmacokinet*. 40(2): 225-233. Available from: DOI: 10.1007/s13318-014-0194-9
20. Tzeng, S.Y., Guarecuco, R., McHugh, K.J., Rose, S., Rosenberg, E.M., Zeng, Y., Langer, R. & Jaklenec, A. (2016), Thermostabilization of inactivated polio vaccine in PLGA-based microspheres for pulsatile release. *J Control Release*. 233: 101-113. Available from: DOI: 10.1016/j.jconrel.2016.05.012
21. Prasanth V, Mitesh P, Modi, Sam T, Pulsatile: a tool for circardian rhythm- A review, Journal of

Drug delivery and Therapeutics, 2(1), 2012, 58-65.

22. Wani, S.U., Thakur, G. & Gautam, S.P. (2021) A Review on recent advancement in pulsatile drug delivery systems, *Int J Curr Pharm Res*; 13(02): 6-10. Available from: DOI:10.22159/ijcpr.2021v13i2.41543
23. Yadav, D., Survase, S. & Kumar, N. (2011) Dual coating of swellable and rupturable polymers on glipizide loaded MCC pellets for pulsatile delivery: formulation design and in vitro evaluation. *Int J Pharm*. 419(1-2): 121-130. Available from: DOI: 10.1016/j.ijpharm.2011.07.026
24. Bussemer T, Dashevsky A, Bodmeier R. A pulsatile drug delivery system based on rupturable coated hard gelatin capsules. J Control Release. 2003 Dec 12; 93(3):331-9. Available from Doi: 10.1016/j.jconrel.2003.08.012, PMID 14644583.
25. Kalantzi LE, Karavas E, Koutris EX, Bikiaris DN. Recent advances in oral pulsatile drug delivery. Recent Pat Drug Deliv Formul. 2009 Jan 1; 3(1):49-63. Available from Doi: 10.2174/187221109787158337, PMID 19149729.
26. Sershen S, West J. Implantable, polymeric systems for modulated drug delivery. Adv Drug Deliv Rev. 2002 Nov 5; 54(9):1225-35. Available from Doi: 10.1016/s0169-409x (02)00090-x, PMID 12393303.
27. Gandhi BR, Mundada AS, Gandhi PP. Chronopharmaceutics: as a clinically relevant drug delivery system. Drug Deliv. 2011 Jan 1; 18(1):1-18. Available from Doi: 10.3109/10717544.2010.509358, PMID 21138394.
28. Smolensky MH, Lemmer B, Reinberg AE. Chronobiology and chronotherapy of allergic rhinitis and bronchial asthma. Adv Drug Deliv Rev. 2007 Aug 31; 59(9-10):852-82. Available from Doi: 10.1016/j.addr.2007.08.016, PMID 17900748.
29. Yadav D, Survase S, Kumar N. Dual coating of swellable and rupturable polymers on glipizide loaded MCC pellets for pulsatile delivery: formulation design and in vitro evaluation. Int J Pharm. 2011 Oct 31; 419(1-2):121-30. Available from Doi: 10.1016/j.ijpharm.2011.07.026, PMID 21807081.
30. Portaluppi F, Lemmer B. Chronobiology and chronotherapy of ischemic heart disease. Adv Drug Deliv Rev. 2007 Aug 31; 59(9-10):952-65. Available from Doi: 10.1016/j.addr.2006.07.029, PMID 17675179.
31. Smolensky MH, Portaluppi F. Chronopharmacology and chronotherapy of cardiovascular medications: relevance to prevention and treatment of coronary heart disease. Am Heart J. 1999 Apr 1; 137(4 Pt 2):S14-24. Available from Doi: 10.1016/s0002-8703(99)70392-3, PMID 10097242.
32. Kowanko IC, Pownall R, Knapp MS, Swannell AJ, Mahoney PG. Circadian variations in the signs and symptoms of rheumatoid arthritis and in the therapeutic effectiveness of flurbiprofen at different times of day. Br J Clin Pharmacol. 1981 May; 11(5):477-84. Available from Doi: 10.1111/j.1365-2125.1981.tb01153.x, PMID 7272159.
33. Shanmugan P. Chronotherapeutic drug delivery systems. J Drug Metab Toxicol 2015;6(5). Available from Doi: 10.4172/2157-7609.1000194.
34. Kraft M, Martin RJ. Chronobiology and chronotherapy in medicine. Disease-A-Month. 1995 Aug 1; 41(8):506-75. Available from Doi: 10.1016/s0011-5029(95)90036-5, PMID 7628291.
35. Alekya, T., Narendar, D., Mahipal, D., Narala, A. & Banala, N. (2018), Design and evaluation of chronomodulated drug delivery of tramadol hydrochloride. *Drug Res (Stuttg)*. 68(3): 174-180. Available from: DOI: 10.1055/s-0043-119072
36. Arora, S. (2006) Pulsatile drug delivery systems: An Approach for controlled drug delivery. *Indian J. Pharm. Sci*. 68(3): 295-300. Available from: DOI:10.4103/0250-474X.26655
37. Battu, S., Yalavarthi, P.R., Reddy, S., Radhakrishnan, S., Thummaluru, R.M. & Konde, A. (2018) Biopharmaceutical process of Diclofenac multiparticulate systems for chronotherapy of Rheumatoid Arthritis. *Turk J Pharm Sci*. 15(3): 256-262. Available from: DOI: 10.4274/tjps.92400

38. Bhutkar, M., Khochage, S., Raut, I., Mali, S., Patil, S. & Navale, P. (2013) A review on pulsatile drug delivery system. *American Journal of Pharmtech Research*; 3(5), 18-35. Available from: http://ajptr.com/archive/volume-3/october-2013-issue-5
39. Bodmeier, R. & Krogel, I. (1999) Floating or pulsatile drug delivery systems based on coated effervescent cores. *Int J Pharm*. 187(2): 175-184. Available from: DOI: 10.1016/s0378-5173(99)00189-1
40. Chaudhari, M.P., Kuchekar, B.S. & Chaudhari, D.P. (2012) Formulation and evaluation of multiparticulate system for chronotherapeutic delivery of salbutamol sulphate. *J Pharm Bioallied Sci*. 4(1): 71-75. Available from: DOI: 10.4103/0975-7406.94144
41. Chaudhary, S.S., Patel, H.K., Parejiya, P.B. & Shelat, P.K. (2015), Chronomodulated drug delivery system of urapidil for the treatment of hypertension. *Int J Pharm Investing*. 5(2): 107-113. Available from: DOI: 10.4103/2230-973X.153389
42. Gandhi, B.R., Mundada, A.S. & Gandhi, P.P. (2011) Chronopharmaceutics: As a clinically relevant drug delivery system. *Drug Deliv*. 18(1):1-18. Available from: DOI: 10.3109/10717544.2010.509358