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Formulation and Evaluation of Pulsatile Drug Delivery System of Lisinopril

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ABSTRACT

The aim of the present investigation is to develop a Lisinopril pulsatile drug delivery system. Pulsin cap is based on an insoluble capsule body filled with Lisinopril Egg albumin microspheres and cap filled with uncoated granules, separated by HPMC K4M plug. Lisinopril microspheres were prepared by emulsion polymerization method with egg Albumin by varying drug to polymer ratio (1:1, 1:2, 1:3and 1:4). Granules were prepared by wet granulation method by varying concentration of superdisintegrant. Optimized microspheres were evaluated for the interaction study by FT-IR, percentage yield, angle of repose, drug content, SEM and particle size analysis. Optimized granules were evaluated for various parameters like angle of repose, carr's index and drug content. The formaldehyde treated capsule bodies were tested for physical appearance, visual defects, solubility studies and qualitative chemical test for free formaldehyde. The optimized Lisinopril loaded pulsincap were evaluated for *in vitro* drug release and kinetic study. The drug release from optimized Lisinopril pulsincap followed Zero order kinetics and mechanism of drug release was governed by peppas – korsmeyer model. Lisinopril microspheres with small particle size, good loading capacity are produced by M4 formulation. G4 showed better release profile. Thus optimized formulation were formulated as pulsincap and showed *in vitro* release up to 24hours.

Keywords: Pulsatile drug delivery, Formaldehyde treated capsules, Microspheres, Egg Albumin.

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INTRODUCTION

Background

Pulsatile drug delivery
system is defined as the rapid and transient release of certai n amount of molecules within a short time period immediately after predetermined off-release periods i.e. lag time[1]. Lisinopril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor class of medications. It is metabolized to Lisinoprilat in liver and, to a lesser extent in kidneys. Lisinoprilat is a potent, competitive inhibitor of ACE, the enzyme responsible for the conversion of angiotensin I (ATI) to angiotensin II (ATII). ATII regulates blood pressure and is a key component of the renin-angiotensin-aldosterone system (RAAS).

Lisinopril may be used in the treatment of hypertension, congestive heart failure, nephropathy, and to reduce the rate of death, myocardial infarction and stroke in individuals at high risk of cardiovascular events[2].

In present study Lisinopril granules and Lisinopril albumin microspheres were formulated as pulsincap for better patient compliance, to reduce dose frequency, reduced first pass metabolism for sustained release, for better absorption, and release of drug over predetermined period.

METHODS AND MATERIALS

Lisinopril was obtained as gift sample from Vee laboratories, kailer, Dist. Solan (H.P). Egg albumin was procured from Fisher Scientific. Size 1 capsules were procured from Gowtham distributors; HPMCK$_4$M was obtained as gift sample from MMC Healthcare Chennai. All other chemicals used were of analytical grade.

Formulation of Pulsatile Device of Lisinopril[2-10]

Preparation of Immediate release granules[2,3,13]:

Granules of Lisinopril were made by wet granulation method. Lisinopril, Sodium starch glycolate, Microcrystalline cellulose were weighed accurately and blended homogeneously. Polyvinyl pyrollidonewas dissolved in isopropyl alcohol and mixed with the powder blend to get a coherent mass. The mass was passed through sieve no 22. The formulation of immediate release granules in Table 1.

Table: 1 Formulation of Immediate Release Granules

S. No	Ingredient	G1 (mg)	G2 (mg)	G3 (mg)	G4 (mg)
1	Lisinopril	500	500	500	500
2	Sod. starch glycolate	86	178	272	386
3	MCC	180	180	180	180
4	PVP K30	3.6	3.6	3.6	3.6

Preparation of Lisinopril Albumin Microspheres[4]

Lisinopril albumin microspheres were prepared by single emulsion polymerization technique. 100ml of liquid paraffin was mixed with 0.4% w/v span 60, Stirred and heated to 70ºC. Drug and polymer were dissolved in methanol and phosphate buffer respectively and mixed together. This mixture was then added drop wise to liquid paraffin using hypodermic syringe with continuous stirring at 600 rpm. 0.25ml of glutaraldehyde was added and stirred for 3 hours. Microspheres were separated by decantation, washed 6 times with petroleum ether and dried at room temperature. The microspheres were stored in a dessicator. The formulation of microspheres is given in Table 2.

Table: 2 Formulations of Microspheres

S. No.	Drug (mg)	Polymer (mg)
F1	500	500
F2	500	1000
F3	500	1250
F4	500	1500
F5	500	2000

Preparation of Cross- Linked Gelatin Capsules[5, 6]

The "1" sized hard gelatin capsules about 100 in number were taken. The body of the capsules was placed on a wire mesh. 25ml of 15%v/v formaldehyde was taken into a desiccator and potassium permanganate was added to it to generate formalin vapours. The wire mesh along with the body was kept in the dessicator. The reaction was carried out for 12 hours, after which the body were removed and dried at 50ºC for 30 minutes to ensure completion of reaction between gelatin and formaldehyde vapour. They were dried at room temperature to facilitate removal of residual formaldehyde.

Preparation of Hydrogel Plug[6]

Plug for sealing the capsule body was prepared by compressing HPMCK$_4$M granules using 9mm punches on rotary tablet press.

Designing of Pulsincap[6]

The pulsincap is similar in appearance to a hard gelatin capsules, but the body is water insoluble. Microspheres equivalent to 2.5mg of Lisinopril were accurately weighed and filled into the formaldehyde treated body. The capsule body containing the microspheres was plugged with hydrogel plug and the capsule cap was filled with Lisinopril granules equivalent to 2.5mg and sealed over the body.

Evaluation of Lisinopril Immediate Release Granules

Angle of repose [9, 10]

Angle of repose was determined using funnel method. The frictional forces can be measured by Angle of repose. $\theta = \tan^{-1}(h / r)$ where, θ is the angle of repose, h is the height in cm and r is the radius in cm.

Compressibility index

It is an important measure that can be obtained from the bulk and tapped densities. The percentage compressibility of the bulk drug was determined using the following formula.

$$I = DT - Db / DT \times 100$$

Where, I is the Compressibility index, DT is the tapped density of the powder and DB is the bulk density of the powder.

Hausner's ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density. H = DT / Db Where, H is the Hausner's ratio DT is the tapped density of the powder and Db is the bulk density of the powder.

Drug content[2]

Granules were dissolved in a small quantity of methanol and the volume was made up to 100ml with phosphate buffer pH 7.4. It was stirred for 12hrs. After stirring the solution was filtered through whatman filter paper, the absorbance was measured spectrophotometrically at 210nm after suitable dilution and the drug content was calculated.

Evaluation of Microspheres[5,6,10]

Particle Size Analysis

The size was measured using an optical microscope and the mean particle size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer.

Angle of repose

Angle of repose was determined using funnel method. The frictional forces can be measured by Angle of repose. $\theta = \tan^{-1}(h / r)$ where, θ is the angle of repose, h is the height in cm and r is the radius in cm.

Percentage yield

The prepared microspheres were collected and weighed. The yield was calculated by dividing the measured weight by the total weight of all non-volatile components. The percentage yield of microspheres was calculated as follows.

$$\% \text{ Yield } = \frac{\text{Weight of microsphere}}{\text{Theoretical weight of drug and polymer}} \times 100$$

Drug content[2]

Drug loaded microspheres were dissolved in a small quantity of methanol and the volume was made up to 100ml with phosphate buffer pH 7.4. It was stirred for 12hrs. After stirring the solution was filtered through whatman filter paper and the absorbance was measured spectrophotometrically at 210nm after suitable dilution and the drug content was calculated.

Drug Loading capacity[7,8]

Drug loading capacity was calculated by formula

Drug loading (%) = M actual / weighed quantity of powder microspheres × 100

Where M actual is the actual drug content in weighed quantity of powder of microspheres

Physicochemical Characterization Of Hydrogel Plug[5]

Hydrogel Plugs were studied for hardness, friability, weight variation, lag time and Swelling Index table 6.

Determination of Swelling Index of Hydrogel Plug

Hydrogel plugs were kept immersed in three different pH conditions. Plugs were taken out carefully at 2,4,6,8,10,12 hours and their weights were determined accurately table 7.

$$\% \text{ Swelling} = \frac{\text{Wet weight} - \text{dry weight}}{\text{Wet weight}} \times 100$$

Evaluation of Cross Linked Empty Capsules[5]

Various physical and chemical tests were carried out for formaldehyde treated and untreated capsules.

Physical tests

Identification, Solubility test for formaldehyde treated capsules, dimension measurement was performed.

Chemical Test

Qualitative Chemical Test for Free Formaldehyde

Formaldehyde solution (0.0002%w/v) was used as a standard solution. A sample solution was prepared by cutting 25 formaldehyde treated body of the capsules into small pieces and placed in distilled water. This was stirred for 1hr with a magnetic stirrer, to solubilize the free formaldehyde. The solution was then filtered into a 50ml volumetric flask, washed with distilled water and the volume made up to 50 ml with the washings. To 1ml of sample solution, 9ml of water was added. 1ml of the resulting solution was mixed with 4ml of water and 5ml of acetone. The solution was warmed in a water bath at 40ºC and allowed to stand for 4 minutes.

***In-vitro* Dissolution Studies[2,5,6,13]**

For Lisinopril Immediate release granules

The *in vitro* dissolution was carried out using USP Type I (Basket) dissolution apparatus under sink condition. The dissolution medium was 900 ml of a 0.1N HCl solution (pH=1.2), at 37^{0}C±0.2^{0}C and the stirring speed was 50 rpm. The *in vitro* release studies were carried out for 2 hours.10ml samples were taken at 10 minutes intervals for 2 hours and were replaced with fresh dissolution medium. The absorbance of the solution was recorded at 210 nm using UV spectrophotometer.

For Lisinopril Microspheres

The *in vitro* dissolution was carried out using USP Type I (Basket) dissolution apparatus under sink condition. The dissolution medium was 900 ml of a phosphate buffer pH 6.8 at 37^{0}C±0.2^{0}C and the rotating speed was 50 rpm. 10ml samples were taken at 1hour intervals and were replaced with fresh dissolution medium. The absorbance of the solution was recorded at 210 nm using UV spectrophotometer.

***In Vitro* Release of Pulsatile Capsule**

Dissolution studies were carried out using USP XXIII dissolution test apparatus (paddle method). A Capsule was tied to paddle with a cotton thread so that the capsule was immersed completely in dissolution media but not float. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used, (sequential pH change method). The pH 1.2 was first used for 2 hrs then removed and the fresh phosphate buffer pH 7.4was added. After 3 hrs the medium was removed and colonic fluid phosphate buffer pH 6.8 was added for subsequent study. Nine hundred milliliters of the dissolution medium was used at each time. Rotation speed was 100 rpm and temperature was maintained at 37±0.5ºC. 10ml samples were withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 210 nm, by UV absorption spectroscopy and the cumulative percentage release was calculated.

Kinetic Analysis of Lisinopril *In Vitro* Release Data[10]

To analyze the mechanism for the drug release and release kinetics, the data obtained from the *in vitro* drug release studies was fitted to various kinetics models shown in figure 6.

RESULT AND DISCUSSION

Physical Compatibility Study:

The drug and excipients mixtures were kept at room temperature at 40 ± 2^{o}C / 75 ± 5% RH. The mixtures did not show any physical changes. They were compatible.

Chemical Compatibility Study (FTIR)

FTIR spectroscopy was carried out to study the compatibility of pure drug Lisinopril with the polymer albumin, and other excipients like microcrystalline cellulose, sodium starch glycolate, polyvinylpyrrolidone, hydroxyl propyl methyl cellulose. There is no appearance or disappearance of any characteristic peaks. This shows that there is no chemical interaction between the drug and excipients showed in figure 1.

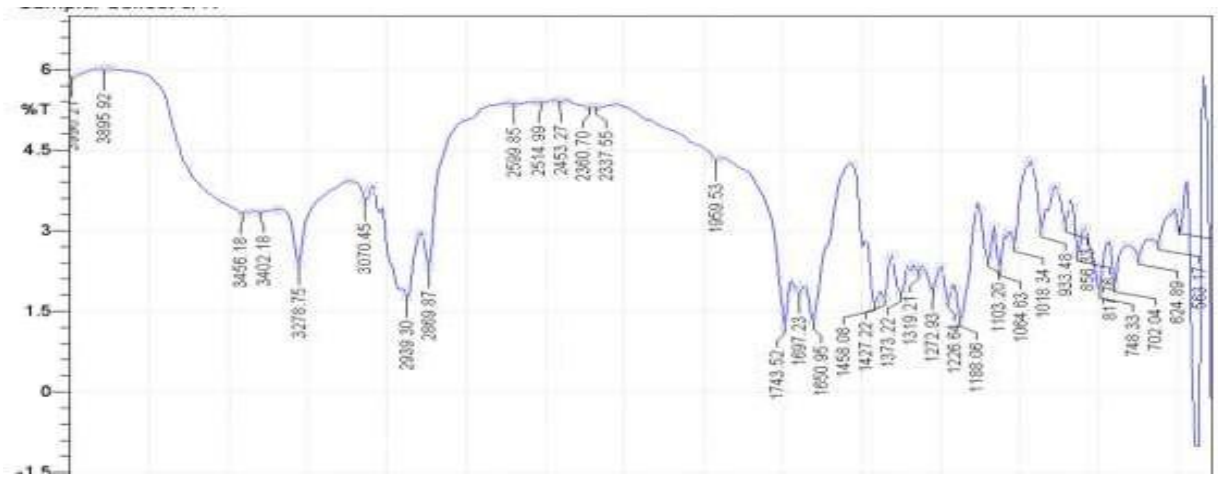

Figure 1: FTIR spectrum of Lisinopril with excipients

Table 3: Precompression Parameters For granules*

Properties	Drug	G1	G2	G3	G4
Angle of repose (θ)	42.15±0.267	34.48±0.0023	33.0±0.0012	34.62±0.0045	33.88±0.0056
Bulk density (g/ml)	1.20±0.0967	0.443±0.0124	0.485±0.0108	0.443±0.01699	0.456±0.01699
Tapped density (g/ml)	1.57±0.0989	0.552±0.0740	0.582±0.01766	0.521±0.0201	0.539±0.0335
Carr's index (%)	23.56±0.9969	18.63±0.008	16.67±0.0235	15.00±0.0162	15.31±0.0202
Hausner's ratio	1.30±0.0998	1.239±0.0128	1.2±0.03536	1.174±0.02166	1.177±0.02577

*Mean ±SD (n=6)

The angle of repose was 42º15' for the pure drug. It has very poor flow. The angle of repose was 33º to 34º48' for G1 to G4. The granules have passable flow. The pure drug have Carr's index of 23.56%. It has passable flow. The granules have Carr's index of 15 to 18.63%. They have good and fair flow. The Hausner's ratio of pure drug was 1.30. It has passable flow. The granules have Hausner's ratio of 1.174 to 1.2. It has good and fair flow. The formulation of granules improved the flow property.

Table 4: Precompression Parameters of Microspheres*

Properties	Drug	M1	M2	M3	M4	M5
Angle of repose (θ)	42.15±0.267	33.37±0.2011	33.3±0.7028	33.88±0.4929	34.34±0.3546	33.0±0.3750
Bulk density (g/ml)	1.20±0.0967	0.666±0.0070	0.6±0.005657	0.625±0.0075	0.666±0.0070	0.7±0.009428
Tapped density (g/ml)	1.57±0.0989	0.75±0.08957	0.666±0.0070	0.714±0.0098	0.75±0.00948	0.8±0.01084
Carr's index (%)	23.56±0.9969	11.2±0.988	9.90±0.9076	12.46±0.5666	11.2±0.8485	12.5±0.2854
Hausner's ratio	1.30±0.0998	1.136±0.0105	1.11±0.00282	1.142±0.0151	1.126±0.0224	1.142±0.0224

*Mean ±SD (n=6)

The angle of repose was 42º15' for the pure drug. It has very poor flow. The angle of repose was 33º to 34º88' for M1 to M5. The Microspheres have passable flow. The pure drug have Carr's index of 23.56%. It has passable flow. The Microspheres have Carr's index of 9.90 to 12.5%. They have excellent and good flow. The Hausner's ratio of pure drug was 1.30. It has passable flow. The Microspheres have Hausner's ratio of 1.11 to 1.142. It has excellent and good flow. The formulation of Microspheres improved the flow property.

Table 5: Drug content of immediate release granules*

Formulation code	Percentage yield (%)	Drug content (%) w/w	Drug Loading (%)
M1	87±0.0034	84.4± 0.0011	11.5± 0.0015
M2	90±0.0012	81.2±0.0032	18.6± 0.0042
M3	95.6±0.0019	83.2±0.0014	23.77±0.0012
M4	99.15±0.0021	86.3±0.0011	35.04±0.0021
M5	98.07±0.0032	76.04±0.031	25.09±0.0017

Table 6: Drug Content and Drug loading of microspheres*

Formulation	% Drug content
G1	94±0.0023
G2	96±0.0034
G3	92±0.0014
G4	98±0.0011

*Mean ±SD (n=3)

Evaluation Of Cross Linked Empty Capsules

Physical Tests

Identification

The '1' size capsules used were with purple cap and colourless body. They were lockable type, odorless, softy and sticky when treated with wet fingers. After formaldehyde treatment, there were no significant changes in the capsules. They were non-tacky when touched with wet fingers. The formaldehyde treatment converted the capsule body to be hydrophobic in nature.

Chemical Test

Qualitative chemical test for free formaldehyde

The solution was not more intensely coloured then a reference solution prepared at the same time and in the same manner using 1 ml of standard solution. The colour of the test and standard solutions were comparable.

Evaluation Parameters for Hydrogel Plug

Table 7: Evaluation of Hydrogel Plug*

Hydrogel plug code	Weight (mg)	Thickness (mm)	Hardness
P1	100	3.20 ±0.0023	2.4 ±0.0056

*Mean ±SD (n=3)

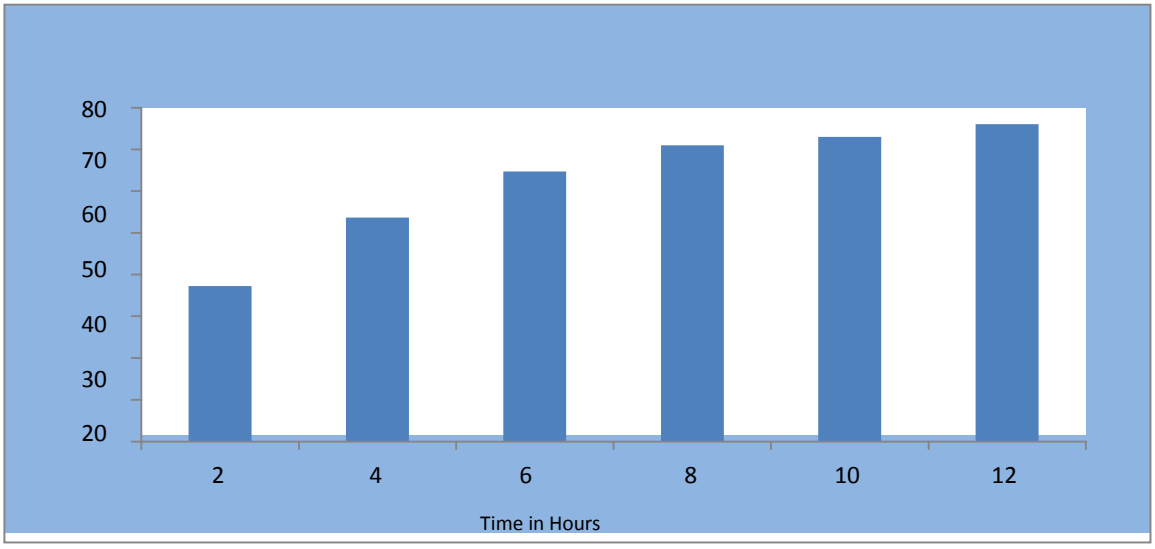

Figure 2: Swelling index

The swelling index of hydrogel plug increased with increase in time in pH 1.2, 7.4, 6.8. The swelling index of HPMCK$_4$M hydrogel plug showed plug integrity for 12 hours.

Table 9: *In vitro* dissolution of Lisinopril immediate release granules*

Time in minutes	Cumulative % drug release			
	G-1	G-2	G-3	G-4
10	30.6±0.236	34.88±0.442	38.87±0.447	38.52±0.132
20	36.68±0.583	73.15±0.246	79.18±0.242	72.84±0.612
30	61.6±0.134	87.64±0.463	94.56±0.293	**101.59±0.413**
40	75.88±.123	92.2±0.674	**101.67±0.473**	
50	90.07±.314	**102.68±0.349**		
60	**101.78±0.213**			

*Mean ±SD (n=3)

Table 10: *In Vitro* Dissolution of Lisinopril Microspheres*

Time in Hours	Cumulative % drug release				
	M-1	M-2	M-3	M-4	M-5
1	11.2±0.098	9.76±0.586	8.26±0.098	4.56±0.067	10.62±0.023
2	16.68±0.167	15.08±0.235	11.72±0.076	10.11±0.0789	15.2±0.197
3	36.28±0.056	31.72±0.067	29.69±0.309	14.86±0.543	25.59±0.942
4	44.6±0.087	41.12±0.054	36.12±0.209	23.91±0.0721	37.39±0.621
6	58.02±0.065	48.52±0.452	42.12±0.120	34.9±0.129	44.62±0.185
8	69.2±0.128	56.32±0.234	51.47±0.521	45.16±0.284	54.32±0.049
10	74.12±0.112	67.72±0.601	60.27±0.045	52.16±0.492	67.21±0.183
12	89.76±0.078	79.6±0.067	72.71±0.098	61.01±0.719	79.14±0.061
14	**99.21±0.478**	86.12±0.087	81.92±0.067	74.21±0.497	87.56±0.674
16		**99.92±0.012**	91.99±0.390	88.41±0.045	97.26±0.184
18			**101.77±0.865**	92.76±0.729	**101.08±0.295**
19				**101.02±0.571**	

*Mean ±SD(n=3)

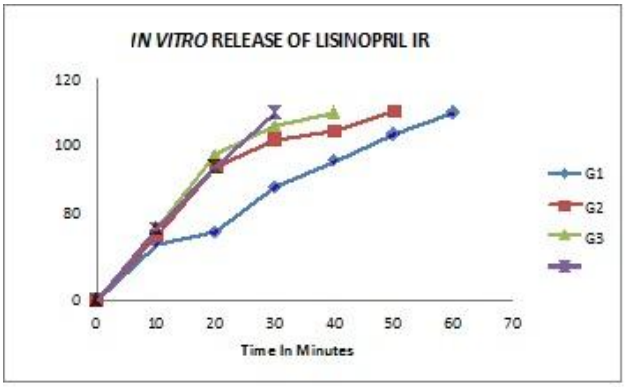

Figure 3: *In vitro* dissolution of Lisinopril immediate release granules

G1 released 101.78% of drug in 1hour.G4 released 101.51% of drug in 30 minutes. Increased in concentration of sodium starch glycolate result in quicker release of drug from the granules. The *in vitro*dissolution of Lisinopril IR showed that G4 was found to be optimum for immediate release.

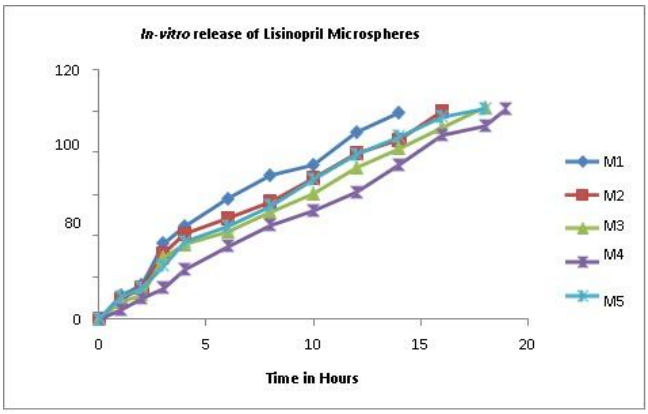

Figure 4: *In vitro* dissolution of Lisinopril microspheres

Increase in the albumin concentration delayed the drug release up to the ratio 1:3. Further increase in concentration did not delay the drug release. M4 has more sustained release than all the formulations therefore M4 was optimized.

Scanning Electron Microscopy

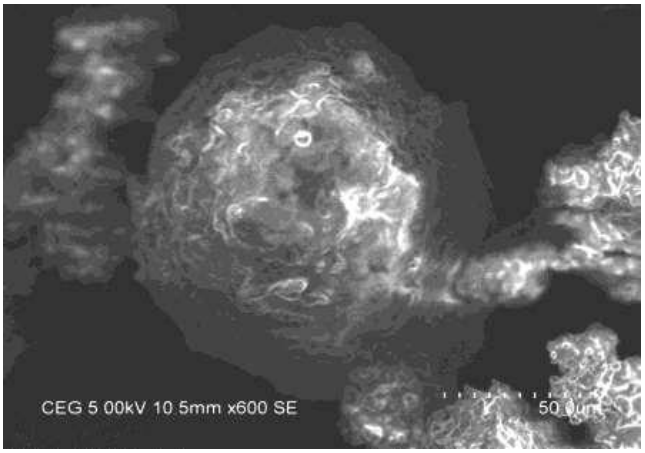

Figure 5: Scanning Electron Microscopy of M4

The average particle size of microspheres was 50µm. The particles were spherical in shape

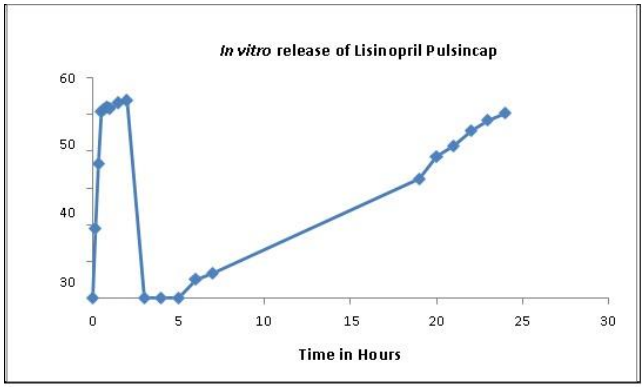

Figure 6: *In-vitro* release of Lisinopril Pulsincap

Table 11: *In vitro* release of Lisinopril Pulsincap*

Dissolution Medium	Time (Min)	% Cumulative Drug Release
0.1N HCl pH 1.2 Buffer	10	18.84±0.169
	20	36.47±0.278
	30	50.67±0.061
	40	51.26±0.037
	50	51.82±0.028
	60	51.51±0.069
	90	53.03±0.119
	120	53.67±0.043
pH 7.4 Buffer	3	0
	4	0
	5	0
pH 6.8 Buffer	6	4.95±0.042
	7	6.74±0.016
	19	32.50±0.075
	20	38.61±0.113
	21	41.45±0.0478
	22	45.46±0.171
	23	48.41±0.004
	24	**50.30±0.063**

*Mean ±SD (n=3)

The optimum formulation of granules and microspheres, G4 and M4 were formulated as pulsincap.

Release Kinetics of Lisinopril Pulsincap

The release was found to be zero order in which R^2 value was close to 1.The formulation followed zero order kinetics.

The mechanism of drug release was found to be diffusion and dissolution.

Stability Studies[9]

The optimized formulation was selected and the stability study was carried out at accelerated condition of 40°C / 75% RH condition for a period of 3 months. No significant changes were observed in the physical appearance, colour, drug content and drug release of Lisinopril pulsincap of the optimized batch at 40^{0}C /75% RH. The Lisinopril pulsincap was stable.

CONCLUSION

The present study was carried out to develop Lisinopril pulsatile drug delivery system. Lisinopril granules prepared

with SSG, in different ratios. Among all the formulations, G4 showed faster release of drug. Lisinopril microspheres with different ratios were prepared. Among all the formulations M4 containing drug, albumin ratio of 1:4 has more sustained release. These formulations G4 and M4 were used in the pulsincap. The pulsincap released the drug up to 24 hours. Although sustained and controlled drug delivery gained lot of success and application in field of medication these systems fail to deliver drug according to circardian behavior of disease for which pulsatile systems are beneficial.

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