Exploring the Potential of Natural Polymers in Chrono-Modulated Drug Delivery for Hypertension Management

Gomathi Swaminathan[2], C. Kannan*[1], R. Sambathkumar[1], S. Radhakrishnan[1], M. Sudha[1], N. Venkateswaramurthy[3], Kannan Raman[2]

1. The Erode College of Pharmacy, Perundurai Main Road, Veppampalayam, Vallipurathampalayam(Po),Erode - 638112,Tamil Nadu, India.

2. Department of Pharmaceutical Chemistry, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, Nilgiris, Tamilnadu, India.

3. J.K.K.Nattraja College of Pharmacy, Kumarapalayam, Namakkal Dt- 638183, Tamilnadu, India.

ABSTRACT:

Myocardial infarction and congestive heart failure symptoms seem to occur more commonly at night or in the early morning. These episodes are typically brought on by high blood pressure, especially immediately after waking up. There are many standard dose forms available to treat hypertension. The antihypertensive medications are currently administered in instant release dose forms. Because they don't provide the best doses at the critical moments, conventional medication delivery systems are ineffective for the effective control of hypertension. The term "chronotherapy" refers to the synchronization of biological rhythms with medical treatment. There are various methods for creating pulsatile drug delivery systems that are chrono regulated, and these methods have been evolved to closely resemble new chronotherapeutic concepts. These issues with conventional dose forms and controlled release dosage forms are resolved by the chorono modulated captopril drug delivery system. In order to effectively manage hypertension, a chorono regulated captopril drug delivery system that releases the medication at the site of absorption at a predetermined period has been developed and evaluated in this study.

Keywords: Congestive heart failure, Myocardial infarction, Hypertension, Biological rhythm, Chronotherapy, Pulsatile drug delivery, Chorono modulated.

INTRODUCTION

Elevated blood pressure is on the increase throughout the world, with India bearing a disproportionate share of the load. [1-5] The Global Burden of Disease Study (DALYs) found that of all the risk factors studied, hyper tension was the most significant, responsible for 10.2 million deaths and 208 million DALYs globally. [5] Around 10% of all deaths in India may be attributed to hypertension. [6-10]

Myocardial infarction, heart failure, stroke, chronic renal disease, and cognitive decline are all more likely to occur in those with poorly controlled hypertension. [7–13].

Recent epidemiological studies show that the prevalence of several cardiovascular diseases, such as myocardial infarction and stroke, varies predictably over the course of a day (the circadian period).[5–6] Myocardial infarction and congestive heart failure tend to manifest more frequently at night or in the early morning. [7] These attacks are typically brought on by high blood pressure, especially when one first wakes up.[5] Morning elevations of several hormones, such as plasma norepinephrine and plasma renin, can cause pronounced coronary vasoconstriction, which raises peripheral resistance in the morning and decreases at night [5-9]

There are many standard dose forms available to treat hypertension. The antihypertensive medications are currently administered in instant release dose forms. Because they don't provide the best doses at the critical moments, conventional medication delivery systems are ineffective for the effective control of hypertension. Traditional drug delivery methods release the medication instantly since the patients are asleep in the early morning hours and it is impossible to administer the medication just before the symptoms get worse. [7-13]. To overcome the limitations of current dosage forms, a novel drug delivery system is necessary to achieve synchronized peak and trough concentrations of antihypertensive medication with systolic and diastolic blood pressure, respectively. [9-12]

The term "chronotherapy" refers to the synchronization of biological rhythms with medical treatment.[13] There are various methods for creating pulsatile drug delivery systems that are chrono regulated, and these methods have been evolved to closely resemble new chronotherapeutic concepts. In order to mimic the chrono pathological symptoms, the chronotherapeutic pulsatile devices release the drug in a pulsatile way at a predetermined off-release interval (lag time) in a particular place.

Captopril (CP; 1-[(2s)-3-mercapto-2-methyl propionyl]-L-proline), an orally active angiotensin-converting enzyme (ACE) inhibitor, is often the medicine of choice in many countries for the management of hypertension as well as the treatment of congestive heart failure. Absorption of medicine is facilitated at the most distal portion of the small intestine..

As captopril is a structural derivative of the amino acid proline, it is thought to be partially absorbed from the small intestine. To enhance patient compliance, a once-daily captopril oral formulation would be highly advantageous. However, if the drug is solely absorbed from the proximal small intestine, any controlled release system would likely have suboptimal absorption characteristics over prolonged periods when the system has progressed into the distal (colonic) regions.[6] Captopril is not a good option for a controlled release device due to its site-specific absorption characteristics. These issues with conventional dose forms and controlled release dosage forms are resolved by the chorono modulated captopril drug delivery system.

In order to effectively manage hypertension, a chorono regulated captopril drug delivery system that releases the medication at the site of absorption at a predetermined period has been developed and evaluated in this study.

Materials Required

Magnesium stearate and lactose were procured from S.D. Fine-Chem. Ltd., while Guar Gum and Xanthan Gum were purchased from Loba Chemie Pvt. Ltd. and Yarrow Chem Products in Mumbai, respectively. Captopril was acquired from Yarrow Chem Products in Mumbai.

Preformulation Studies

Delineation

Material's appearance was evaluated by comparing it with specified monographs or standard materials.

Identification

Characterization is a crucial component of material qualitative analysis. Chemical and FT-IR methods were used to identify the ma

Solubility Analysis

During Preformulation research, solubility is a crucial variable because: 1. It impacts 1. 1. How well a medicine dissolves.

2. When a medicine is administered orally, its dissolution and absorption have a direct impact on its bioavailability.

3. Particle size, shape, and surface area should be assessed during Preformulation because these may alter the way a medicine dissolves.

Loss on drying (%)

The medicine was weighed to within 1g, and then dried for three hours at 60°C under decreased pressure (not exceeding 0.6 kPa or roughly 5 mm of mercury). The sample was

dispersed by moderate side-to-side shaking at the specified temperature for constant weight and should not lose more than 10 mg/g, as per The International Pharmacopoeia - Sixth Edition, 2016.

The drug specimen was kept in a desiccator until it reached room temperature, at which point it was weighed. There should not be more than a 0.5mg discrepancy in weight between readings. The following formula is used to calculate the loss due to drying.

$$\% \text{ LOD} = \frac{W3 - W2}{W2 - W1} \times 100$$

Wherein, W1 – Weight of empty weighing bottle

W2 – Weight of weighing bottle + sample

W3 – Weight of weighing bottle + dried sample

When dried at 60°C under reduced pressure (not exceeding 0.6 kPa or approximately 5 mm of mercury) for three hours, it experiences a maximum weight loss of 10mg/g.

Identification of the melting point

We measured the melting point of captopril using a capillary technique and compared the results to industry norms. Captopril was introduced to the machine in a predetermined amount.

Angle of repose

Since frictional forces between powder particles may lead to poor flow, the angle of repose is a measure of a substance's flow qualities. The angle between the surface of a powder file and a horizontal plane at its greatest extent. As a result, these frictional forces are measured in terms of the angle of repose.

$$Ø = \text{Tan}^{-1} h/r$$

Wherein, h = height of file

R = radius of the base of the pile

Ø = angle of repose

DETERMINATION OF DENSITIES:

Bulk density: The powder's bulk density may be determined by dividing the powder's mass by its bulk volume. Bulk density is greatly affected by particle shape, rising with more spherical particles and decreasing with larger granules..

Method: For the purpose of determining the bulk density, a powder sample weighing 5 grammes was first weighed, then transferred to a measuring cylinder, and the volume of the measuring cylinder was measured to determine the starting volume. For the calculation of bulk density, the following formula was utilized:

Bulk Density = Bulk Mass / Bulk Volume

Tapped density:

A measuring cylinder that contained a powder sample was mechanically tapped in order to get information on the tapped density. A rotating device was used to tap the cylinder at intervals of two seconds for predefined amounts of time at a height of 2.5 centimetres. This was done in order to limit any possible mass separation that might occur during the tapping process. Readings of the volume were taken until there was very little evidence of further change in the volume. After measuring the final volume of the sample, the tapped density was determined by using the following formula:

$$\textbf{Tapped Density} = \frac{m}{Vf}$$

Although Vf = material's tapped volume, m = material's starting weight in grammes. Several measurements should be performed to get an accurate reading of this quality.

Measurement of Powder Compressibility:

This formula, which takes into consideration both the apparent bulk density and the tapped density, was used to compute the percentage of the bulk's compressibility, which was expressed as a percentage.

$$\textbf{Compressibility index:} = 100\frac{(V_0 - Vf)}{V_0}$$

Where, Vf = final tapped volume, Vo = initial untapped volume

ASSAY

In order to make the captopril solution, 10 milligrams of captopril were carefully measured out, placed in a volumetric flask of 100 milliliters, and then diluted with phosphate buffer with a 6.8 pH until the volume reached the 100 milliliter threshold. After that, a total volume of 100 ml was obtained by diluting an additional 10 ml of the solution with phosphate buffer with a pH of 6.8. The absorbance of the solution that was produced was evaluated at 205 nanometers.

Research on the physical compatibility of drugs and their excipients

After combining the excipients and active ingredients, 2 ml glass vials were filled and sealed. The vials were kept for about a month at room temperature and 40 degrees Celsius with 75% relative humidity. The hue of the samples was analyzed after they had been removed for 10 days.

Excipient and Drug Compatibility Studies:

The selection of suitable excipients is an essential step in the process of producing a stable and efficient dosage form. This kind of dosage form facilitates the medication's simple administration, assures its consistent release and bioavailability, and safeguards it against deterioration. Studies of compatibility with the active pharmaceutical ingredients are carried out before the excipients are chosen.

Procedure:

The Fourier Transform Infrared Spectroscopy was used to investigate the interactions between the medication and the excipient (FT-IR). SHIMADZU (Shimadzu Corporation) FT-

IR spectra were collected to look for chemical bonds between the pure drug and the excipients in the solid form. The solid powder sample was mixed in a mortar with 100 times as much potassium bromide to make pellets. The powder was coarsely crushed before being put in a stainless-steel die and squeezed between polished steel anvils at a pressure of around 8 t/in2. Spectra were gathered from 4000 to 500 cm-1.

Preparation of Standard Curve Using 0.1N HCl:

Preparation of 0.1 M Hydrochloric acid:

Carefully measure 8.5 ml of hydrogen chloride and add it to a volumetric flask to make a 0.1 M hydrochloric acid solution. Then, fill the flask with water until the total volume reads 1000 ml.

Preparation of stock solution:

Place the captopril in a volumetric flask after weighing out exactly 100 milligrams. Finally, fill the container with 0.1 M HCl until it measures 100 ml.

Preparation of standard solution:

In order to produce the standard solutions, pipette 10 ml from the solution that was just described into a volumetric flask that has a capacity of 100 ml, and then add 0.1 M HCl to the volume until it reaches 100 ml. Next, transfer 5, 10, 15, 20, and 25 ml of the resultant stock solution to five distinct volumetric flasks of 100 ml each, and thereafter dilution each flask to a final volume of 100 ml with 0.1 M HCl to achieve concentrations of 5, 10, 15, 20, and 25 mg/ml.

CALIBRATION CURVE OF CAPTOPRIL USING 0.1 N HCl:

At a wavelength of 212 nanometers, the absorbance of the produced stock solutions was evaluated using an ultraviolet spectrophotometer. The next step is to create a graph that has the concentration measured in g/ml on the X-axis and the absorbance measured in nm on the Y-axis.

Preparationof Standard Curve Using 6.8 pH Phosphate Buffer:

Preparation of 0.2 M potassium dihydrogen phosphate:

With water, dissolve 27.218 grammes of potassium dihydrogen phosphate, and then add enough water to bring the total amount up to 1000 millilitres.

Preparation of 0.2 M sodium hydroxide:

Dissolve sodium hydroxide in water to make a solution with a w/v concentration of 40-60%, and then let it stand. To make a solution with a concentration of 8.0 g of sodium hydroxide per 1000 ml, syphon out the clear supernatant liquid and dilute it with carbon

dioxide-free water. Be sure to dilute with the right quantity of water. The 0.2 M sodium hydroxide solution has a shelf life of one month and should not be used beyond that time.

Preparation of 6.8 pH Phosphate Buffer:

Begin by mixing together 50.0 ml of 0.2 M potassium dihydrogen phosphate and 22.4 ml of 0.2 M sodium hydroxide in a graduated cylinder. The next step is to put the weighed and measured ingredients into a volumetric flask with a capacity of 200 ml. The flask can hold up to 200 ml of water, so fill it to that level. To ensure a complete blend, shake the flask vigorously.

Preparation of stock solution:

After carefully weighing out 100 milligrams of captopril, the drug should then be transferred to a volumetric flask for further analysis. Phosphate buffer with a 6.8 pH should be used to bring the total volume of the solution to 100 milliliters

Preparation of standard solution:

To begin making a set of standard solutions for captopril, first transfer 10 milliliters of the stock solution into a volumetric flask that has a capacity of 100 milliliters. After that, bring the volume of the solution up to 100 ml by diluting it with phosphate buffer with a pH of 6.8. After this, five individual 100 ml volumetric flasks should each have 5, 10, 15, 20, and 25 ml of the standard stock solution transferred into them. In the last step, pour enough phosphate buffer with a 6.8 pH into each flask such that the final volume is 100 ml. This will result in concentrations of 5, 10, 15, 20, or 25 g/ml.

Calibration Curve of Captopril Using 6.8 pH Phosphate Buffer:

Using an ultraviolet spectrophotometer, the absorbance of the stock solutions that were created was determined to be 205 nm. In a graph, the concentration should be written in g/ml, and the absorbance should be written in nm. The X-axis should be horizontal.

Formulation:

Its fast-acting tablet's core is made using the direct compression technique and a variety of super disintegrants. After this, the core tablet formulations' dissolving profiles will be examined, with the goal of selecting the most effective ones. Next, the enhanced core tablet will have a press coating process done to it utilizing both natural and synthetic polymers. [14-15]

TableNo.1.Rapid Release Core Tablets (RRCT)

S.No	Ingredients	C1*	C2*	C3*	C4*	C5*	C6*	C7*	C8*	C9*
1	**Captopril**	27	24	26	24	24	24	26	24	24
2	**Sodium Starch Glycolate**	6	11	14	-	-	-	-	-	-
3	**Croscarmellose Sodium**	-	-	-	6	10	14			-
4	**Crospovidone XL 10**	-	-	-	-	-	-	6	12	14
5	**Micro Crystalline Cellulose**	26	24	19	29	29	21	17	23	21
6	**Magnesium Stearate**	1	1	1	1	1	1	1	1	1
	Total*	60	60	60	60	60	60	60	60	60

TableNo.2.Formulation of Pulsatile Coated tablets: (Natural Polymer) [17-25]

S.No	Formulation	Compression Force (in Ton)	Ingredients in mg (Milli grams)					
			Core Tablets	Guar Gum	Xanthan Gum	Lactose	Mg. Stearate	Total
1	**F1**	1 Ton	60	70	-	168	2	300
2	**F2**		60	140	-	98	2	300
3	**F3**		60	210	-	28	2	300
4	**F4**		60	-	70	168	2	300
5	**F5**		60	-	140	98	2	300
6	**F6**		60	-	210	28	2	300
7	**F7**	2 Ton	60	70	-	168	2	300
8	**F8**		60	140	-	98	2	300
9	**F9**		60	210	-	28	2	300
10	**F10**		60	-	70	168	2	300
11	**F11**		60	-	140	98	2	300
12	**F12**		60	-	210	28	2	300
13	**F13**	3 Ton	60	70	-	168	2	300
14	**F14**		60	140	-	98	2	300
15	**F15**		60	210	-	28	2	300
16	**F16**		60	-	70	168	2	300
17	**F17**		60	-	140	98	2	300
18	**F18**		60	-	210	28	2	300

Evaluation of Pulsatile press coated Tablets of Captopril:

The Pulsatile Press Coated Captopril Tablets underwent the same evaluation test as core tablets in order to be evaluated.

1. Weight Variation Test
2. Thickness Test
3. Hardness test
4. Drug Content
5. Dissolution study
6. Friability test

Pre-compression parameters for core & press coated blends:

The precompression parameters were studied using both core and coated Captopril tablets.

1. Angle of repose
2. Bulk density and Tapped density
3. Compressibility index and Hausner ratio

Evaluation of Core Tablets of Captopril

All of the Core tablets, from C1 to C9, were evaluated based on the official and unofficial criteria that are listed below.

Weight Variation

Twenty pills were chosen at random from each batch, and all of them were subjected to the tests specified in the specifications.

$$\% \text{ deviation} = \frac{\text{tablet weight-average weight}}{\text{Tablet weight}} \times 100$$

Dimensions

Digital Vernier calipers were used to provide an accurate reading of the thickness of each tablet.

Hardness

The Pfizer hardness tester was used to determine the tablet's hardness, which is expressed as the amount of force needed to crack the tablet in kilograms per square centimeter. We tested six pills from each batch in order to compare them.

Friability

For this experiment, twenty tablets were measured and put into the Roche Friabilator, which was then spun at 25 revolutions per minute for four minutes. The percentage of friability was determined using the following formula,

$$\%F = \{1-(W_t/W)\} \times 100$$

Wherein, %F=friability in percentage

W=initial weight of tablets after revolution

Drug Content:

Crush twenty pills until the aggregate weight of the tablets is equivalent to twenty milligrams of captopril. Dissolve the crushed pills in a volume of 6.8 phosphate buffer that is 100 milliliters in volume. The next step is to generate a total volume of 100 ml by diluting 10

ml of the solution that was produced with 90 ml of phosphate buffer with a 6.8 pH. With an ultraviolet spectrophotometer, take a reading of the absorbance of the solution at 217 nanometers. The amount of captopril present in the dry component should range between 98.0 and 102.0 percent.

Disintegration test

The process by which tablets are broken up into smaller grains or particles is referred to as disintegration, and the amount of time it takes for this process to take place in an environment that is conducive to it is referred to as the disintegration time (DT).

Wetting time and water absorption ratio:

` There is a correlation between wetting time for dosage forms and contact angle. If the pill is allowed to get moist for a shorter period of time, there is a chance that it may dissolve more rapidly.

Wetting time:

Place five 10-centimeter-diameter tissue sheets in a 10-centimeter-diameter Petri dish and time how long it takes for them to get damp. The water-soluble pigment eosin should be added to 10 ml of water and placed in a separate Petri plate. At last, set the tablet on top of the tissue paper carefully.

Water absorption ratio:

Fold a piece of tissue paper and place it in the 6 ml of water in a small Petri dish. The time it takes for a tablet placed on top of the tissue paper to absorb all of the water is recorded. After the tablet has absorbed all of the water, you may measure its mass. Using the following equation, we can get the water absorption ratio:

$$R = 100\ (Wa-Wb) / Wb$$

Wherein,

Wb; The weight of the tablet before keeping in the petridish.

Wa; The wetted tablet from the petridish is taken and reweighed.

Dissolution study:

Requirements:

Medium: 6.8 Phosphate Buffer

Volume: 900 ml

Apparatus: USP II (paddle)

RPM: 50

Time: 2 h

Temperature: 37^0 c $\pm$ 0.5^0c

λmax :205 nm

In order to carry out the test, put one tablet into each of the six dissolving vessels. Each vessel should contain 900 ml of 6.8 pH phosphate buffer, and the temperature should be 37.0 degrees Celsius plus 0.5 degrees Celsius. To keep the sink conditions constant, remove the needed quantity of the sample at regular intervals and replace it with the same amount of 6.8 pH phosphate buffer. Find out what proportion of the substance was released by measuring the absorbance of the solution.

$$\% \text{ purity} = \frac{\text{absorbance} * 900 * \text{dilution}}{\text{Slope} * 1000 * \text{label claim}} * 100$$

Dissolution test for Pulsatile press coated Tablets of Captopril:

The drug release from coated tablets was evaluated in vitro using a USP paddle device at 50 rpm and 37.5°C. Both 0.1N HCl and phosphate buffer were included in the dissolving media (pH 6.8). After 2 hours of dissolving in 0.1N HCl, the tablets were transferred to phosphate buffer (pH 6.8). The drug's presence was determined by repeatedly taking samples in 0.1N HCl (at 212 nm) and 6.8 pH phosphate buffer (at 205 nm) (n = 3).

Stability Studies

Method:

The chosen formulation was subjected to stability studies since it was shown to be the most promising at simulating in vitro the drug release profile of the extended-release tablets. Standard real-time and accelerated research settings, including storage at 40°C and 75% RH for three months, were used to evaluate the formulation's stability. Appearance, assay, weight consistency, and in vitro drug release were all used to assess the formulation's stability.

Results:

TableNo.3.FTIR interpretation of pure drug captopril vs Optimized Formulations (Natural Polymer)

S. No	Type of bond	Actual frequency (cm^{-1})	Observed frequency (Captopril) (cm^{-1})	Observed frequency (cm^{-1}) F12	Observed frequency (cm^{-1}) F14
1	N-H Str Amide	3400-3500	3500.56 3476.45	3382.91 3355.91	3382.91 3354.94

2	C-H Str Alkane	2850-2960	2949.92	2917.13	2917.13
3	S-H Str	2550-2600	2566.11	2566.11	2566.11
4	C=O Str Ketone	1730-1760	1748.35	1748.35	1748.35
5	N-H Ben Amino Salt	1575-1600	1589.23	1586.34	1587.31
6	C-H Def Alkane	1440-1485	1473.51	1465.80	1471.59
7	C-O Str Alcohol	1260-1350	1347.19	1338.51	1338.51
8	C-N Str Aliphatic Amine	1020-1220	1228.57 1202.53 1190.96	1227.6 1190.96 1165.89	1202.53 1190.96 1165.89

FTIR Spectrum:

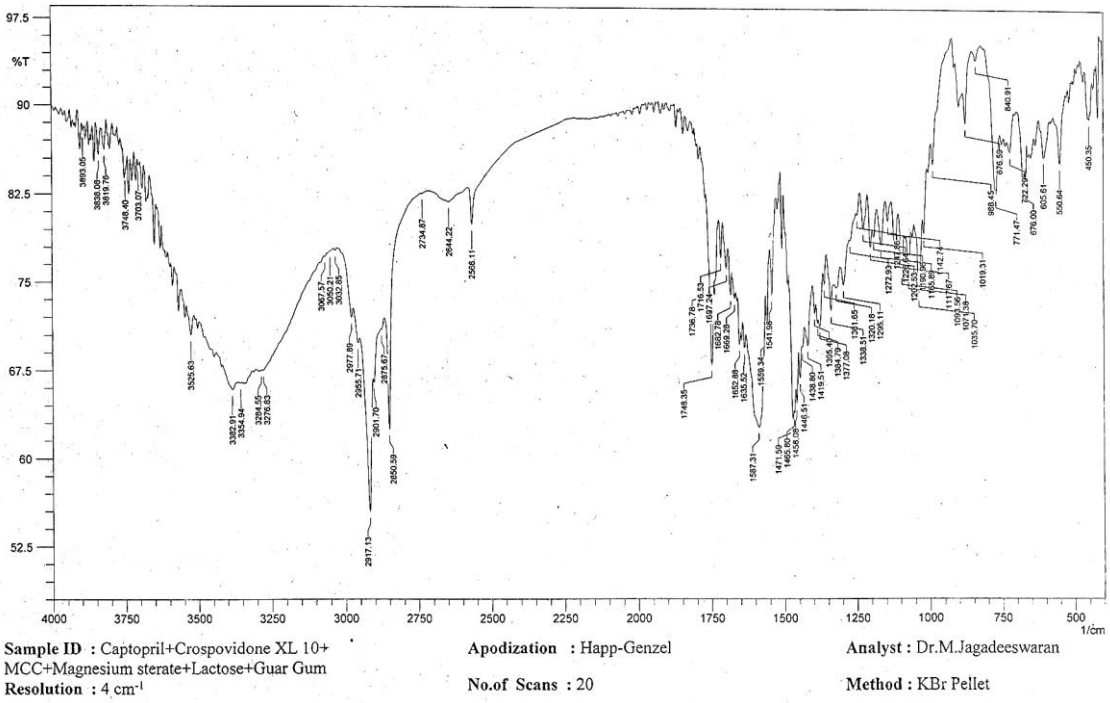

Table No. 1. FTIR interpretation of captopril with Natural Polymer Guar Gum

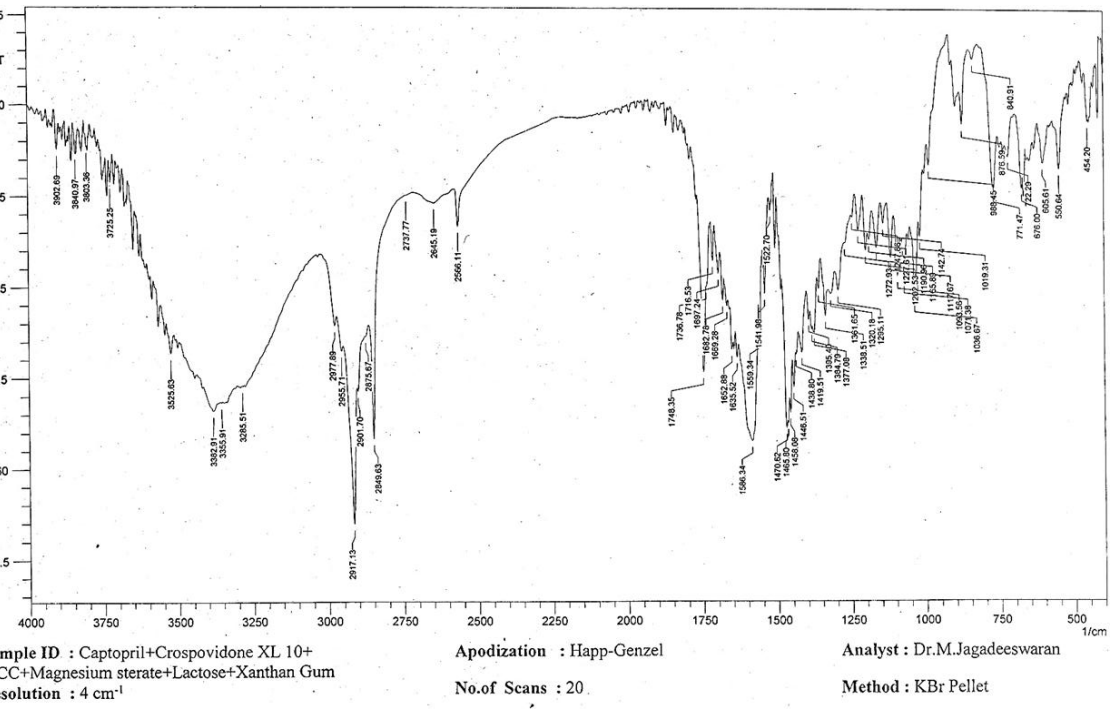

Table No.2.FTIR interpretation of captopril with Natural Polymer Xanthan Gum

Evaluation of Core Tablets:

Pre-Compression Parameters

Table No.4. Evaluation parameters of powder blend C1-C9

Batch. No.	Angle of Repose(^{0})	Bulk Density (g/ml)	Tapped bulk density (g/ml)	Carr's index (%)	Hausner's Ratio
C1	21°41'	0.538	0.612	13.33	1.14
C2	22°23'	0.569	0.629	14.28	1.23
C3	23°55'	0.556	0.631	13.99	1.25
C4	23°76'	0.541	0.636	14.26	1.21
C5	23°.55'	0.559	0.641	14.25	1.24
C6	22°.17'	0.536	0.629	13.29	1.26
C7	22°.85'	0.546	0.632	13.29	1.25
C8	22°.36'	0.596	0.628	13.46	1.27
C9	24°.46'	0.513	0.627	12.23	1.21

Post Compression Parameters:

Weight variation, Thickness, Friability, hardness, Wetting time, disintegration time & Drug Content

Table No. 5. Physical Parameters of Captopril Core Tablets

Batch. No	Weight Variation (%)	Friability (%)	Thickness (mm)	Hardness (Kg/cm^2)	Wetting Time (Sec)	Disintegration Time (seconds)
C1	60.2±1.26	0.51	1.9	3.08	99	121
C2	61.3±1.46	0.40	1.9	3.09	88	118
C3	60.3±1.24	0.56	1.9	3.12	82	101
C4	61.8±1.33	0.54	1.9	3.04	75	85
C5	60.8±1.36	0.46	1.9	3.06	68	79
C6	60.9±1.14	0.58	1.9	3.18	45	69
C7	61.6±1.25	0.47	1.9	3.11	52	78
C8	60.8±1.36	0.59	1.9	3.13	31	46
C9	61.2±1.34	0.51	1.9	3.05	18	39

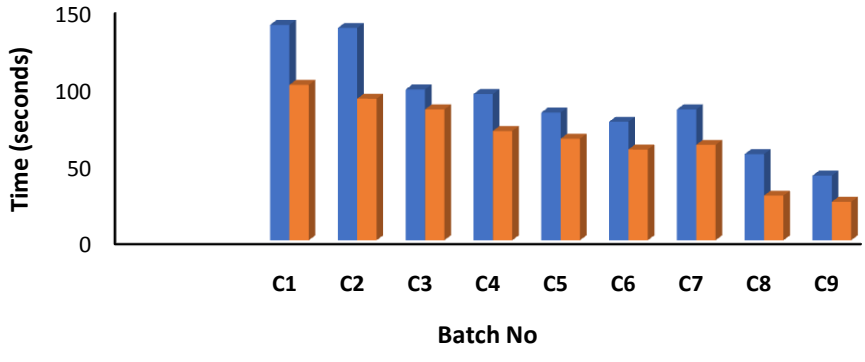

Figure No. 3. Wetting Time vs Disintegration Time of Core Tablets C1- C9

INVITRO DRUG RELEASE PROFILE OF CORE TABLETS:

Table No.6. *In vitro* Dissolution profile Captopril Core tablets

Time in Minutes	C1	C2	C3	C4	C5	C6	C7	C8	C9
0	0	0	0	0	0	0	0	0	0
1	10.43	16.63	18.32	15.34	17.43	24.23	16.79	18.41	29.13
2	20.48	22.22	27.56	26.36	28.82	33.79	27.21	31.85	37.16
3	29.40	33.35	36.88	34.37	36.54	41.46	35.45	44.73	49.25
4	37.53	44.69	46.76	48.97	49.48	54.13	48.36	56.45	60.22
5	45.45	51.47	59.32	60.42	63.72	68.45	61.08	65.13	74.99
6	51.45	59.33	70.46	71.33	74.25	79.09	73.56	76.45	85.57
7	59.63	66.69	80.23	78.55	81.79	89.26	80.55	88.90	99.47
8	64.56	70.86	85.45	84.49	90.10	98.45	91.14	99.03	
9	73.32	78.32	90.55	91.36	99.45		98.19		
10	84.85	89.36	99.31	98.46					
11	92.10	98.34							
12	99.34								

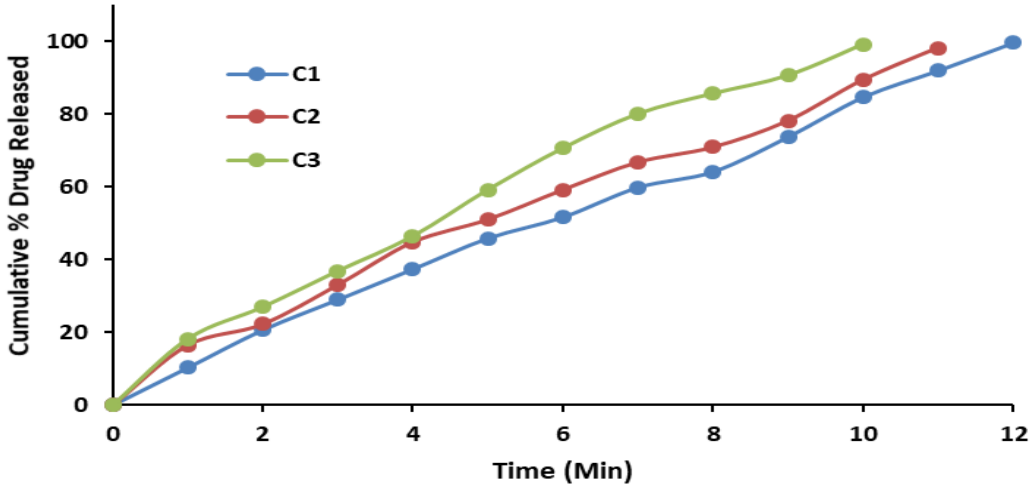

Figure No. 4.*In vitro* Drug Release for Captopril Core tablets of C1-C3 Formulation

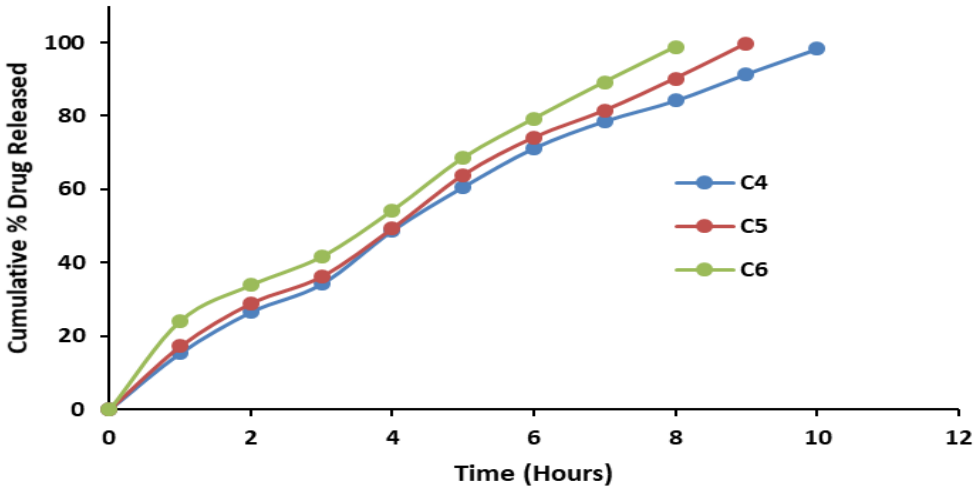

Figure No.5.*In vitro* Drug Release for Captopril Core tablets of C4-C6 Formulation

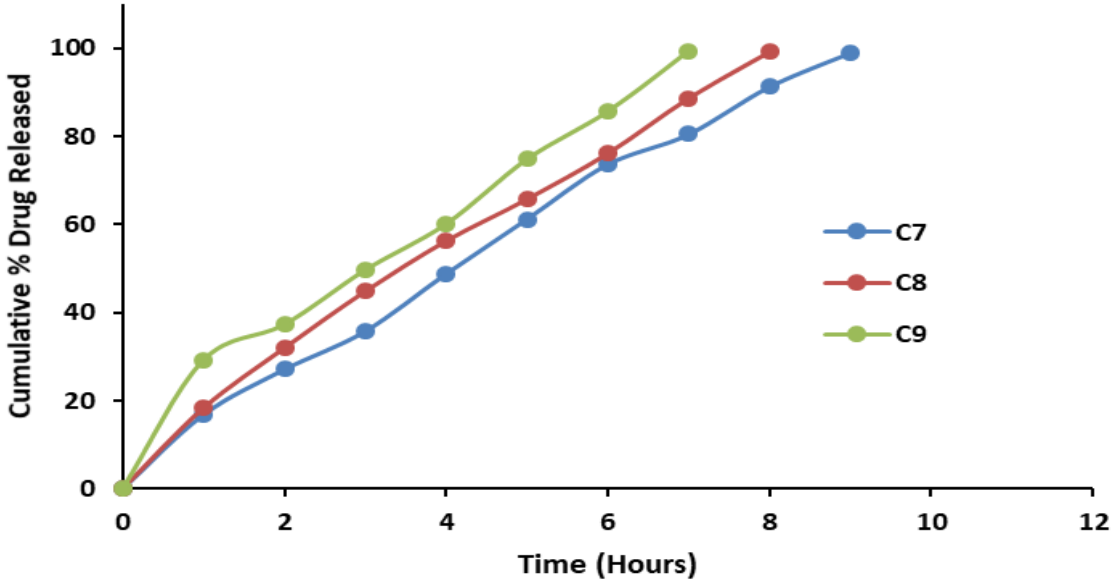

Figure No.6.*In vitro* Drug Release for Captopril Core tablets of C7-C9 Formulation

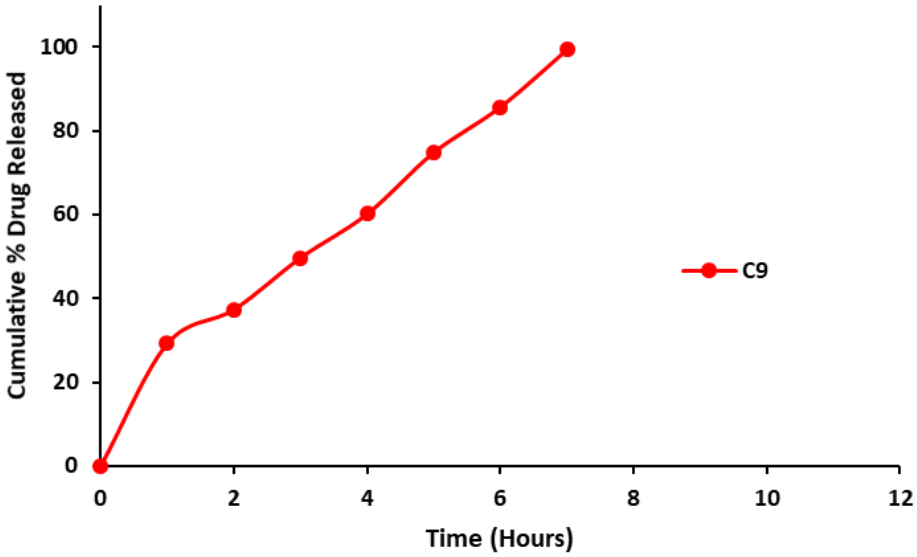

Figure. No.7.*In vitro* Drug Release for Captopril Core tablets of C9

Batch. N0.	Angle of Repose(^{0})	Bulk Density(g/ml)	Tapped bulk density(g/ml)	Carr's index (%)	Hausner's Ratio
F1	23°94'	0.55	0.66	10.8	1.11
F2	24°37'	0.56	0.67	10.9	1.12
F3	23°92'	0.56	0.66	10.7	1.11
F4	25°23'	0.54	0.65	11.9	1.13
F5	25°25'	0.55	0.64	11.9	1.13
F6	23°34'	0.56	0.67	12.5	1.14
F7	24°95'	0.57	0.68	10.8	1.12
F8	24°47'	0.57	0.65	10.9	1.11
F9	23°08'	0.58	0.67	11.2	1.11
F10	27°23'	0.60	0.69	12.3	1.13
F11	28°34'	0.59	0.69	12.5	1.14
F12	27°51'	0.58	0.68	12.1	1.13
F13	25°18'	0.59	0.67	11.1	1.12
F14	26°42'	0.59	0.69	10.9	1.11
F15	26°23'	0.58	0.68	10.8	1.12
F16	27°61'	0.59	0.69	12.3	1.14
F17	26°24'	0.59	0.67	12.3	1.13
F18	26°92'	0.58	0.69	12.5	1.13

TableNo. 7. Evaluation parameters of powder blend

Post Compression Parameters:

TableNo8 .Physical Parameters of Captopril Pulsatile Tablets

Batch. N0.	Weight Variation (%)	Friability (%)	Thickness (mm)	Hardness (Kg/cm^2)
F1	312±1.8	0.19	3.9	6.9
F2	304±1.3	0.14	4.0	6.8
F3	310±1.2	0.21	3.9	6.7
F4	310±1.6	0.19	3.8	6.8
F5	311±1.4	0.22	4.2	6.9
F6	309±1.2	0.25	4.2	6.9
F7	311±1.3	0.22	3.9	7.4
F8	309±1.2	0.19	3.8	7.5
F9	309±1.4	0.21	3.9	7.6
F10	310±1.7	0.18	3.9	7.4
F11	309±1.2	0.20	4.1	7.5
F12	309±1.5	0.20	4.0	7.5
F13	310±1.2	0.22	3.8	9.2
F14	309±1.3	0.19	3.8	9.1
F15	308±1.2	0.19	4.0	8.

F16	309±1.2	0.18	4.1	8.9
F17	310±1.5	0.21	3.8	8.8
F18	311±1.4	0.22	3.9	8.8

INVITRO DRUG RELEASE OF PULSATILE COATED TABLETS:

Table No.9 .*Invitro* Drug Release Profile for Captopril Pulsatile tablets ofF1-F6 Formulation

Time (hours)	0	1	2	3	4	5	6	7	8	9
F1	0	0	4.23	93.47	99.13	99.27	99.52			
F2	0	0	0	7.91	98.32	99.51	99.53			
F3	0	0	0	4.28	73.97	99.34	99.49			
F4	0	0	0	7.64	78.27	99.12	99.34	99.47		
F5	0	0	0	0	6.13	98.71	99.09	99.48		
F6	0	0	0	0	4.29	76.33	99.05	99.24		

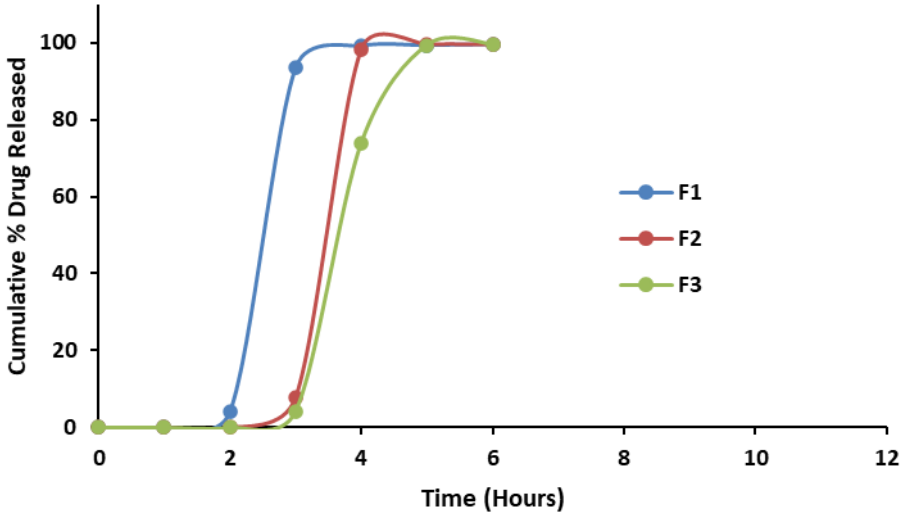

Figure No.8. *Invitro* Drug Release for Captopril Pulsatile tablets of F1-F3Formulation

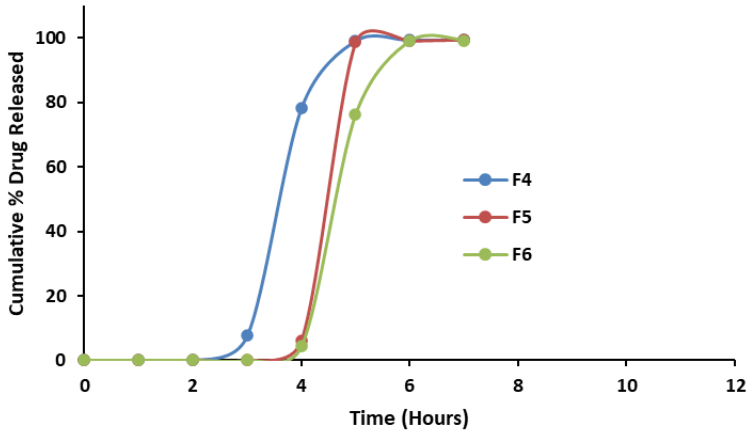

Figure No.9. *Invitro* Drug Release for Captopril Pulsatile tablets of F4-F6 Formulation

Table No. 10.*Invitro* Drug Release Profile for Captopril Pulsatile tablets of F7-F12 Formulation

Time (hours)	0	1	2	3	4	5	6	7	8	9	10	11
F7	0	0	0	0	7.39	99.24	99.77	99.69	99.73			
F8	0	0	0	0	4.21	49.36	99.08	99.63	99.72			
F9	0	0	0	0	0	6.04	94.27	99.34	99.62			
F10	0	0	0	0	0	7.02	99.39	99.45	99.36	99.52		
F11	0	0	0	0	0	6.75	81.92	99.08	99.13	99.37		
F12	0	0	0	0	0	0	5.83	91.49	99.34	99.47		

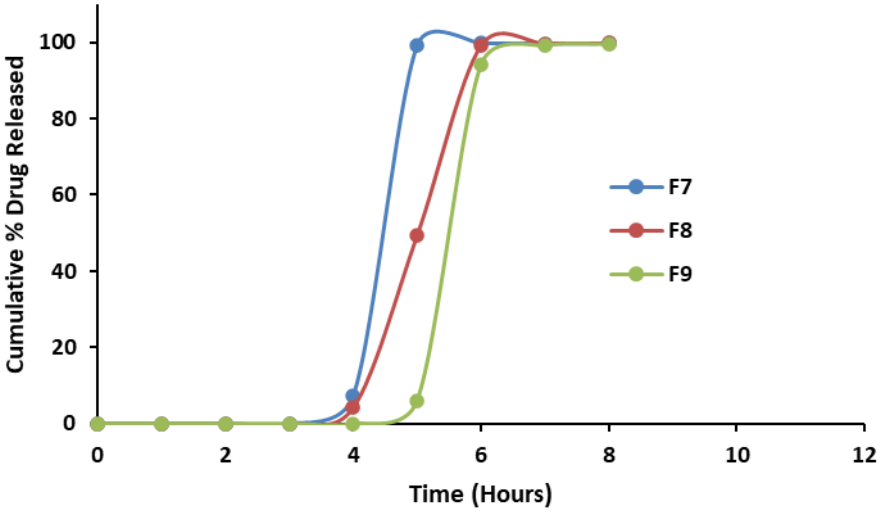

Figure No.10.*Invitro* Drug Release for Captopril Pulsatile tablets of F7-F9 Formulation

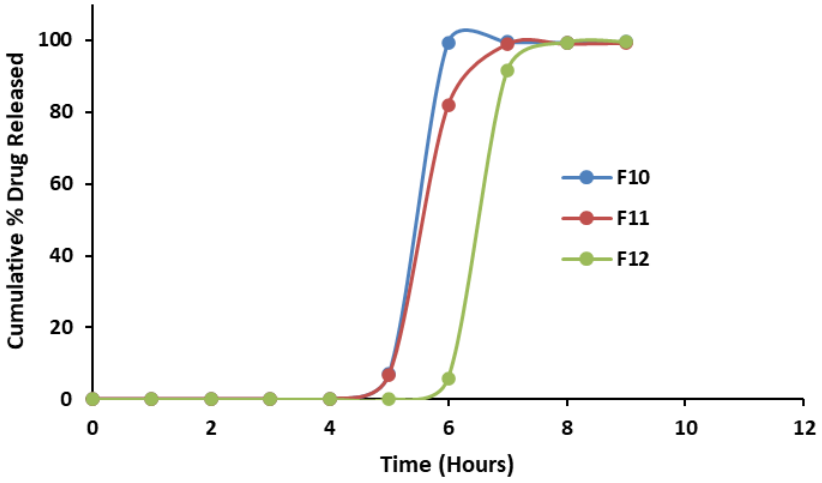

Figure No. 11.*Invitro* Drug Release for Captopril Pulsatile tablets of F10-F12

Formulation

Table No.11.*Invitro* Drug Release Profile for Captopril Pulsatile tablets of F13-F18 Formulation

Time (hours)	0	1	2	3	4	5	6	7	8	9	10	11	12
F13	0	0	0	0	0	4.48	98.61	99.14	99.36	99.47			
F14	0	0	0	0	0	0	7.34	97.43	99.51	95.65			
F15	0	0	0	0	0	0	4.28	69.39	97.13	96.57			
F16	0	0	0	0	0	0	0	3.98	94.17	98.31	99.53		
F17	0	0	0	0	0	0	0	0	7.26	93.27	99.34		
F18	0	0	0	0	0	0	0	0	5.81	78.38	99.13		

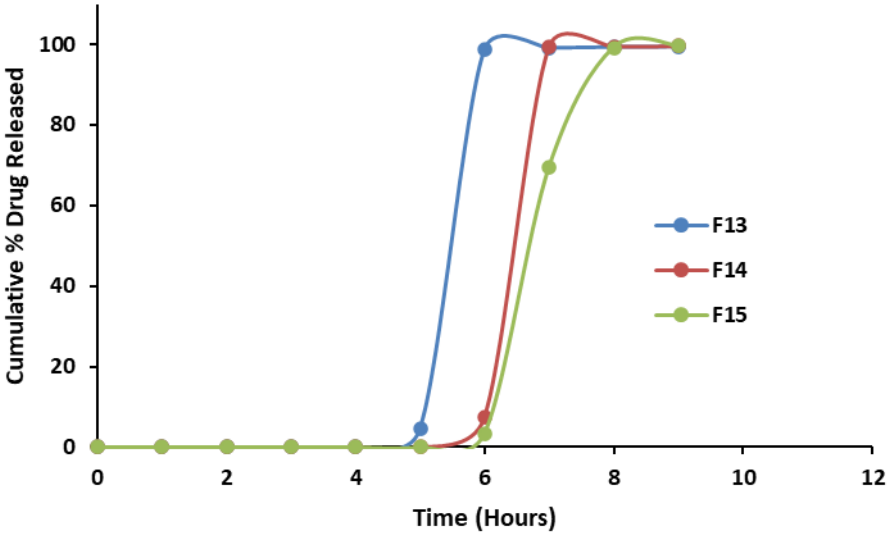

Figure No.12.*Invitro* Drug Release for Captopril Pulsatile tablets of F13-F15 Formulation

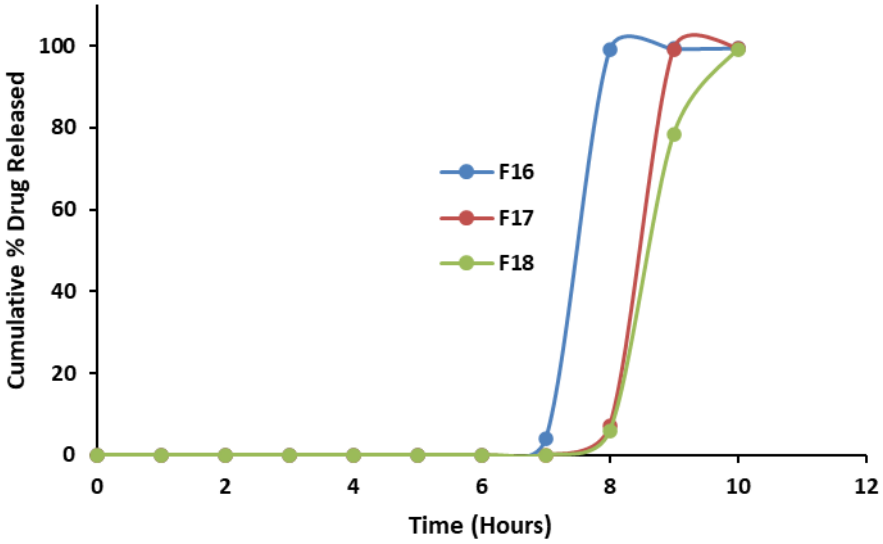

Figure No.13.*Invitro* Drug Release for Captopril Pulsatile tablets of F16-F18 Formulation

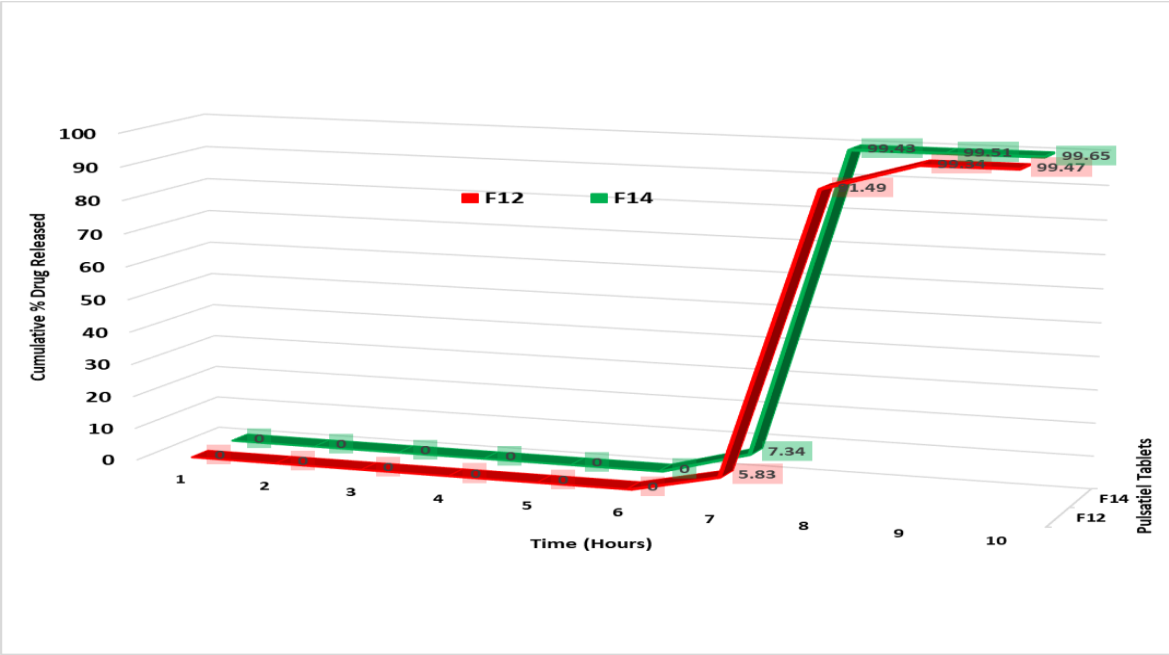

Figure No. 14..*Invitro* Drug Release for Captopril Pulsatile tablets of F12, F14

SUMMARY

As part of this research, many different formulations were created, and the direct compression technique was employed to create the most effective base tablet. Guar gum and xanthan gum, two natural polymers, were included in the formulation. Formulation optimization was predicated on the drug's rate of release. We evaluated the solution's bulk

density, tapped density, angle of repose, compressibility index, Hausner's ratio, melting point, and compliancy with solution parameters before formulating.

Using IR and UV spectroscopy, we were able to learn about the drug's properties; our analysis revealed that there was no interaction between the drug and its excipient. The best core tablet, C9, and natural polymers were then used to make press coated tablets. Each press coated tablet was tested for hardness, friability, weight uniformity, drug content uniformity, drug-polymer interaction, drug release, and stability in vitro.

Friability, weight variation, and chemical consistency were all well within acceptable ranges across all formulations. The pulsatile coated tablets were subjected to dissolving experiments in 0.1 N HCl and 6.8 pH Phosphate Buffer, with formulations F12 and F14 emerging as the most effective.

There were no significant changes in drug content, hardness, friability, or dissolution over the course of 90 days with a 30-day interval in stability experiments for formulations F12 and F14, showing that the formulations were stable per ICH guidelines.

CONCLUSION:

The goal of this research was to create a Captopril capsule having a pulsatile release profile (delayed followed by fast medication release) that might be used in chrono treatment. Captopril chronotherapeutic formulations were produced by pressing the drug along with natural polymers like guar gum and xanthan gum at varying concentrations and compression pressures. The delay in drug release was examined as a function of the presence of natural polymers, namely guar gum and xanthan gum..

It was shown that natural polymers, and particularly guar gum and xanthan gum, may significantly cut down on the waiting time. Our results show that a drug delivery system with a release profile customized to fit the needs of chrono treatment for captopril may be achievable via the substitution of factors such as guar gum and xanthan gum. Captopril tablets formulated with xanthan gum have shown promise in in vitro experiments for the treatment of hypertension. Patients who experience morning surge may benefit from this strategy since it offers a feasible mechanism for delivering pulsatile/programmable release of captopril with a single pulse. For further information on the safety and efficacy of this method, we need to do more studies with human volunteers.

REFERENCES:

1. Sundaran S, Rajanandh MG, Sankar S & Arun KP. Chronopharmacology - There is a Clock for Treatment. Global Journal of Pharmacology. 2015;9(1):102-106.
2. https://www.chronobiology.com/about-chronobiology accessed on 15/12/2018.
3. Martha U. Gillette, Introduction to Biological Timing in Health and Disease. 2013; 119:1-356.
4. GBD 2016. Risk Factors Collaborators, Global, regional, and national comparative risk assessment of 84 behavioral, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: A systematic analysis for the global burden of disease study 2016. The Lancet. 2017;390, 1345–1422.
5. Gupta R and Yusuf S. Towards better hypertension management in India. The Indian Journal of Medical Research. 2014;139(139):657–660.
6. Udupa N, Gupta PD. Concepts in Chronopharmacology. 1st ed. Jaipur: Shyam; Prakashan Publishers; 2009;pp.92–108.
7. Fox KM, Mulcahy DA. Circadian rhythms in cardiovascular diseases. Postgraduate Medical Journal, 1991;67:S33–6.
8. Millar-Craig MW, Bishop CN, Raftery EB. Circadian variation of blood pressure. Lancet. 1978;1:795–7.
9. Portaluppi F, Tiseo R, Smolensky MH, Hermida RC, Ayala DE, Fabbian F. Circadian rhythms and cardiovascular health. Sleep Medicine Reviews, 2012 Apr;16(2):151-66. doi: 10.1016/j.smrv.2011.04.003.
10. Smith H, Neutel JM and Weber MA, Circadian Rhythms and Clinical Medicine with applications to Hypertension, American Journal of Hypertension, 2001;14:14-19.
11. Takeda N and Maemura K,Circadian clock and cardiovascular disease. Journal of Cardiology, 2011;57:249–256.
12. Worland PJ, Drummer OH and Jarrott B. Gastric and intestinal absorption of captopril in acutely and chronically treated rats: Comparison with salicylic acid. Journal of Pharmaceutical Sciences, 1984;73:1755-1758.
13. Walter A. Brzezinski. Blood Pressure. Walker HK, Hall WD, Hurst JW, editors. Boston: Butterworths; Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition.1990.
14. Nimmi K Thampi, Boby Johns George, Jeny Samuel, Daisy PA and Betty Carla. Floating pulsatile beads: an oral multiparticulate Pulsatile drug delivery system - a review. International Journal of Pharmaceutical, Chemical and Biological Sciences, 2016;6(4):379-384.

15. Vinupama S, Shweta S, Kamath K, Keerthi TS. Pulsatile Drug Delivery System: A Review. International bulletin of Drug Research. 2007;1(1):19-31.
16. Vidhi R Patel and Vipulbhai P Patel. Pulsatile Drug Delivery System - A Review, International Journal of Pharmaceutical Sciences and Research 2015;6(9):3676-3688.
17. Krishnaiah Y S R, Satyanarayana V, Dinesh Kumar B, Karthikeyan R S, *In vitro* drug release studies on guar gum-based colon targeted oral drug delivery systems of 5-fluorouracil, European Journal of Pharmaceutical Sciences, 2002; 16, 185–192.
18. Khidir A M H, Kinetics of drug release of a guar gum matrix formulation targeting colon, using ibuprofen as a model drug, International Journal of Pharmaceutical Science and Technology, 2012; Vol-8, Issue - 2, 27-35.
19. Sougata Jana, Sabyasachi Maiti, Subrata Jana, Kalyan Kumar Sen, Amit Kumar Nayak,Guar gum in drug delivery applications, Chapter 17, Natural Polysaccharides in Drug Delivery and Biomedical Applications, 2019; 187-202.
20. Saleh M. Al-Saidan, Yellela S.R. Krishnaiah, Srinivas S. Patro and Vemulapalli Satyanaryana, In Vitro and In Vivo Evaluation of Guar Gum Matrix Tablets for Oral Controlled Release of Water-soluble Diltiazem Hydrochloride, AAPS Pharm Sci Tech, 2005; 6 (1) Article 5, E14 – E21.
21. Mallikarjuna N Nadagouda, Shrinivas D Joshi & Uttam A More Tejraj M Aminabhavi, Guar gum as platform for the oral controlled release of therapeutics, Expert Opinion on Drug Delivery, (2014) 11(5):753-766.
22. Pranati srivastava, rishabhamalviya, sumedhagupta, Pramod kumarsharma, Evaluation of Various Natural Gums as Release Modifiers in Tablet Formulations, 2010; Pharmacognosy Journal, Vol 2, Issue 13, 525–529.
23. Srinivas Mutalik Usha Yogendra Nayak, Gopal Venktesh Shavi, Yogendra Nayak, Ranjith Kumar Averinen, Sreenivasa Meka Reddy, Purshottam Das Gupta, Nayanabhirama Udupa, Chronotherapeutic drug delivery for early morning surge in blood pressure: A programmable delivery system, Journal of Controlled Release 136 (2009) 125–131.
24. Thiruganesh Ramasamy, Uma Devi SubbaihKandhasami, HimabindhuRuttala, Suresh Shanmugam, Formulation and evaluation of xanthan gum based aceclofenac tablets for colon targeted drug delivery, Brazilian Journal of Pharmaceutical Sciences, 2011; vol. 47(2), 299-311.
25. Wassel GM, Omar SM, Ammar NM. Application of guar flour and prepared guaran in tablet manufacture, Drug Research. 1989;18:1-8.