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Design and Evaluation of Controlled Released Tablets of Captopril in the Management of Hypertension by Using Karaya Gum as a Binder

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KEYWORDS
Captopril, Karaya Gum, HPMC, Direct Compressionand Controlled releasetablets.

ABSTRACT:
The present work aim to develop controlled-release tablets of Captopril by selecting different Types ofpolymers KarayaGum,Starch, and HPMC.A direct compression technique was adopted for the preparation of all these formulations. Theblend of allthe formulations showed good flow properties such as angle of repose, bulk density, and tappeddensity.Thepreparedtabletsshowedgoodpost-compressionparametersandtheypassedall the quality control evaluation parameters as per I.P limits. Hardness, Friability, Weight Variation, in vitro dissolution study. Among all the developed batches F2 showed the highest drug release 98.30% at the end of 12 h. as compared to other formulations for the development of a controlled drug delivery system.

1. Introduction

Controlled-release dosage forms are suppressing the usage of conventional dosage forms in the present era. The sustained-release tablet provides uniform release of the drug over a long period. Controlled-release dosage form covers a wide range of prolonged action formulations which provides continuous release of their active ingredient at a predetermined rate and time. A sustained or controlled drug delivery system reduces the frequency of dosing or increases the effectiveness of the drug by localization at the site of action, reducing the dose required, providing continuous drug delivery, reducing the incidence of adverse effects, and maintaining drug concentration in the system [1].

Thegoal in designing Controlled or Controlled delivery systems is to reduce the frequencyof the dosing or to increase the effectiveness of the drug by localization at the site of action,reducing the dose required, or providing uniform drug delivery. So, a Controlled release dosage form is a dosage form that releases some or more drugs continuously in predetermined pattern for a fixed period, either systemically or to a specified target organ.

Controlled-release dosage forms provide better control of plasma drug levels, less dosagefrequency,fewersideeffects,increasedefficacy,and constantdelivery.Therearecertainconsiderationsfor thepreparationofextended-releaseformulations:

- ✓ If the active compound has a long half-life, it is Controlled on its own,
- ✓ Ifthepharmacologicalactivityoftheactiveisnotdirectly relatedtoitsbloodlevels,
- ✓ Iftheabsorptionofthedruginvolvesanactivetransporta nd
- ✓ If the active compound has a very short half-life then it would require a large amount of drug to maintain a prolonged effective dose [2,3].

The use of natural excipients in pharmaceutical formulations has captured the interest of the whole pharmaceutical industry in recent times. The growing interest in natural-origin excipients may be attributed to their wide range of pharmaceutical uses, such as bases in suppositories, thickening agents in suspensions, and

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disintegrants, diluents, and binders in tablets [4]. Natural excipients are less expensive, eco-friendly, biocompatible, and harmful than synthetic ones. One of the most crucial excipients in the formulation of dosage forms is gum. Natural gums are inexpensive, nontoxic, and widely available, making them valuable medicinal excipients [5,6].

Gums are pathological products, produced when the plant is injured or growing in an atmosphere that is not favourable [7]. In other words, they are abnormal products of plant metabolism. Gums are amorphous substances produced by plants[8]. They are insoluble in most organic solvents but soluble in water. As stated earlier, one of the important applications of natural gums in pharmaceutical production is its use as a binder in tablet formulation [9]. Binders are a class of excipients employed to impact the cohesiveness of granules. Binders impact plasticity and also increase inter-particulate bonding strength in tablets. Binders increase the extent of consolidation or compaction while reducing brittle fracture in tablets. Binders are capable of forming a matrix and as such control drug release from tablets [10,11].

The benefits of captopril in hypertension and heart failure result primarily from suppressing the renin-angiotensin-aldosterone system (RAAS). An angiotensin-converting enzyme (ACE) inhibitor inhibits ACE, converting angiotensin I to angiotensin II. Angiotensin II binds to AT1 receptors on smooth muscles to produce vasoconstriction of precapillary arterioles and postcapillary venules, inhibits the reuptake of norepinephrine, and releases of catecholamines from the adrenal medulla, which all increases blood pressure. Angiotensin II also stimulates the adrenal cortex to secrete aldosterone. Aldosterone causes the distal tubules and collecting ducts of the kidneys to reabsorb water and sodium in exchange for potassium, which results in an expansion in extracellular volume and an increase in blood pressure[12].

ACE inhibition leads to decreased plasma angiotensin II, leading to vasodilation and decreased aldosterone secretion. Small increases in serum potassium and sodium and fluid loss may occur due to decreased aldosterone secretion. Administration of captopril results in a reduction of peripheral arterial resistance in hypertensive patients. Regarding the cardiovascular system, ACE inhibitors reduce preload by causing vasodilation and natriuresis, and reduce afterload by inhibiting the formation of angiotensin II[13]. The overall effect is the improvement of cardiac output and reduced blood pressure. ACE also metabolizes bradykinin, a peptide that causes vasodilation. ACE inhibitors impede the breakdown of bradykinin, resulting in vasodilation and a bradykinin-evoked cough. The only two ACE inhibitors that do not have to be activated in the body to be effective are lisinopril and captopril while others need to be activated to be effective [14].

Materials and Methods:

Captopril as gift sample from (Salvavidas Pharmaceutical Pvt. Ltd. Surat Gujrat),Karaya Gum (Neelkanth finechem Pvt. Ltd Jodhpur Rajasthan), Microcrystalline cellulose (Loba chemei. Pvt. Ltd. Mumbai, Maharashtra), HPMC (Loba chemei. Pvt. Ltd. Mumbai, Maharashtra), Starch (Loba chemei. Pvt. Ltd. Mumbai, Maharashtra), Magnesium stearate (Loba chemei. Pvt. Ltd. Mumbai, Maharashtra), Aerosil (Loba chemei. Pvt. Ltd. Mumbai, Maharashtra). other reagents and chemicals used were of analytical grade.

Preparation of Calibration Curve in 0.1N HCl

Standard curve was prepared to obey Beer's Law in the concentration range of 4-20 µg/ml. Estimation of captopril was carried out by UV spectrophotometer at λ max 212 nm in 0.1N HCl respectively. The linear co-efficient was found to be respectively 0.9986 in 0.1N HCl which is closer to 1 at concentration range between 4-20µg/ml.0.1 N HCl solution was selected as a suitable solvent for proposed method. Captopril raw material was 10 mg accurately weighed and transferred into the 100 ml volumetric flask and Volume makeup to 100 ml with 0.1N HCl solution, resulting in (100 µg/ml) of drug concentration. From the 100 µg/ml taking 0.4, 0.8, 1.2, 1.4, 1.6, 1.8, 2 ml and made up to 10 ml to obtain the concentration of 4, 8, 12, 14, 16, 18, 20 µg/ml respectively. The absorbance was measured at 212nm against the respective blank solution using UV visible spectrophotometer 1800[15].

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Formulation Composition for Tablets

Table 1: Formulation Composition for Tablets

Ingredients (mg)	Formulation Code					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Captopril	**25**	**25**	**25**	**25**	**25**	**25**
Karaya Gum	**10**	**15**	**-**	**-**	**-**	**-**
Starch	**-**	**-**	**10**	**15**	**-**	**-**
HPMC	**-**	**-**	**-**	**-**	**10**	**15**
Microcrystalline Cellulose	**90**	**85**	**90**	**85**	**90**	**85**
Lactose	**65**	**65**	**65**	**65**	**65**	**65**
Meg. Stearate	**5**	**5**	**5**	**5**	**5**	**5**
Aerosil	**5**	**5**	**5**	**5**	**5**	**5**
Total weight of each tablet (mg)	**200**	**200**	**200**	**200**	**200**	**200**

Preparation of Controlled Released Tablets of Captopril :

Controlled release tablets of Captopril using varying concentrations of Natural Karaya Gum, starch, and synthetic (HPMC) polymers were prepared by direct compression method. Other ingredients like Microcrystalline cellulose were used as the diluent, magnesium stearate as a lubricant, and Aerosil as a glidant. All the excipients along with API weighed as shown in Table 1 and passed through sieve no.20. Then, all ingredients were mixed following geometric mixing excluding glidant and lubricant for 15 minutes. The powder blend was thoroughly mixed with talc and magnesium stearate and compressed into tablets on a station rotary punch tablet machine (Karnavati, Rimek Mini Press- 2).

Precompression Parameters:

- ✓ Bulk density = *Mass of Powder/ Bulk volume of Powder*
- ✓ Tapped density = *Mass of Powder/ Tapped volume of Powder*
- ✓ Compressibility index (CI)= *100×Tapped density-Bilk density/Tapped density*
- ✓ Hausner's ratio =*Tapped density/ Bulk Density*
- ✓ Angle of repose=$Ø=tan^{-1}(h/r)$

Preparation and evaluation of Captopril controlled release tablet formulation:

- ✓ Weight Variation
- ✓ Hardness
- ✓ Thickness and diameter
- ✓ Friability
- ✓ Drug Contant
- ✓ In-vitro release Profile

Weight variation: A total of 20 tablets were individually weighed and then their average weight was calculated. The average weight was compared with the individual tablet weights, and the weight variation was calculated.

Hardness: The hardness of the prepared tablets was determined using Monsanto tablet hardness tester.

Thickness and diameter: Twenty (20) tablets were chosen at random from each batch of tablets. Their thicknesses and diameters were determined using a digital tablet hardness apparatus (Veego instruments Mumbai, India. model VDIGITABHI), and the mean values were recorded.

Friability test: Ten (10) tablets were selected at random from each batch and they were weighed and placed in the Erweka friability (Heusentamm, Germany). The apparatus was rotated at 25rpm for 4 min. After the set time the tablets were removed, dedusted, and reweighed and percentage friability was determined using

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JCHR (2024) 14(3), 579-587 | ISSN:2251-6727

Equation = 100×IW-FW\IW

Drug content

Take the powder of 20 tablets. Weighed a quantity of powder containing 0.1gm of Captopril with 150ml of phosphate buffer pH6.8 for 10 minutes, added sufficient phosphate buffer pH6.8 to produce 200ml and filter. Dilute 10 ml of filtrate to 100 ml with water and measure the absorbance at 212 nm.

In Vitro Drug release profile :

In vitro drug release studies of matrix tablets were done in USP type II dissolution test apparatus(Electro lab TDT-08, India) at 37°C (± 0.5°C) and 50 rpm speed in 900 mL of dissolution medium. The dissolution medium consisted of 0.1N hydrochloric acid for the first 2 hours and phosphate buffer pH 6.8 from 3 to 8 hours. Five milliliter (5ml) samples were taken by filtration at predetermined time intervals and after each sampling, the volume of dissolution medium was replaced with 5ml of phosphate buffer (pH 6.8). The amount of drug released is determined spectrophotometrically.

Fourier transform infra-red spectroscopy studies:

The infrared spectrophotometer is a useful analytical techniqueutilized to check the chemical interaction between the drugand the other excipients used in the formulation. The sample1mgwaspowderedandmixedwiththe10mgofdrypowdered potassium bromide. The powdered mixture wastakeninasamplerandthespectrumwasrecordedbyscanning in the wavelength region of 4000-400 cm^{-1}using an FTIRspectrophotometer. Fourier transform infrared spectroscopy studies revealedthat pure Captopril showed typical bands at 1734.06 cm–1due to C=Ostretching of the carboxylic groupand a band at1690cm–1duetoC=Osstretchingof the amidegroup, C-Hstretching at a 2970 cm -1and C-C stretching atcm–1 . Nosignificant shifts ofreduction in the intensity ofthe FTIR bandsofCaptoprilwere observed as shown in Figure 4.

Results and Discussion:

AnalyticalMethod: Captopril

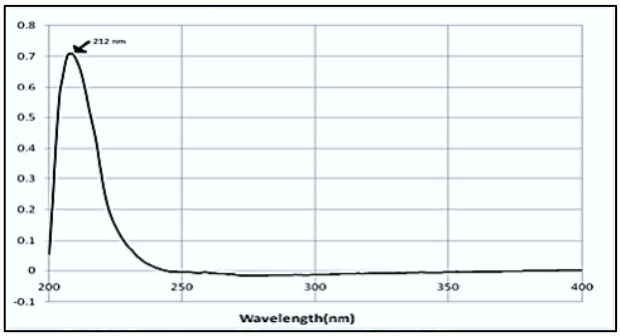

Fig.1 : UV Spectrum of Captopril

Table 2: Calibiration Curve of Captopril

Concentration (µg/mL)	Absorbance
0	0.00
4	0.196
8	0.336
12	0.513
16	0.686

Journal of Chemical Health Risks
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20	**0.798**

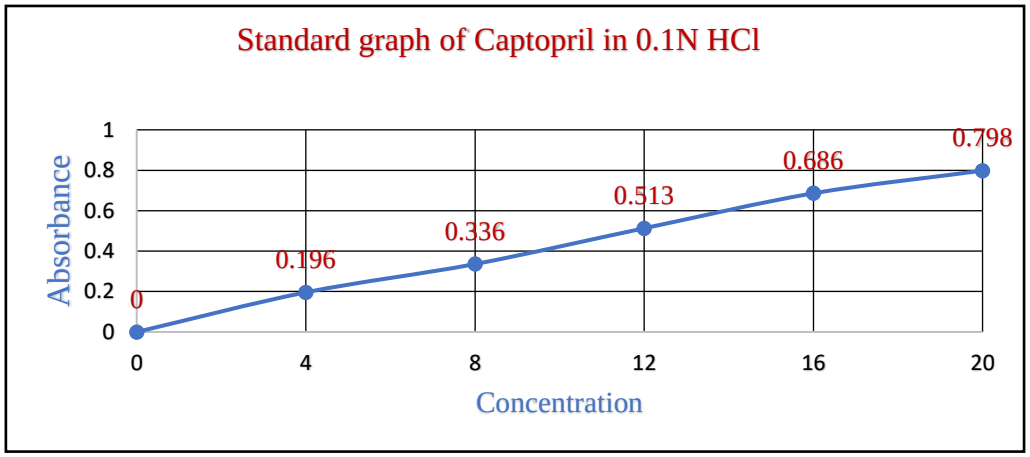

Fig. 2 : Calibiration curve of Captopril in 0.1N HCl

Table 3: Pre-compression parameter of CR formulations

Formulation Code	Angle of Repose	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	**24.87±0.05**	**0.48±0.04**	**0.51±0.04**	**14.21±0.06**	**1.08±0.06**
F2	**25.46±0.09**	**0.42±0.09**	**0.52±0.04**	**16.87±0.05**	**1.23±0.05**
F3	**23.51±0.06**	**0.52±0.03**	**0.55±0.05**	**17.13±0.01**	**1.14±0.03**
F4	**25.41±0.04**	**0.53±0.06**	**0.58±0.07**	**17.34±0.08**	**1.16±0.04**
F5	**24.34±0.05**	**0.50±0.03**	**0.54±0.03**	**16.82±0.04**	**1.21±0.08**
F6	**25.22±0.04**	**0.52±0.04**	**0.52±0.06**	**17.32±0.09**	**1.06±0.09**

Table 4: Post compression parameter of CR Formulations

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(3), 579-587 | ISSN:2251-6727

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	199.4	4.4	0.48	3.6	99.5
F2	200.6	4.5	0.50	3.8	99.8
F3	199.6	4.5	0.51	3.7	99.7
F4	200.4	4.6	0.54	3.7	99.6
F5	198.7	4.4	0.52	3.6	99.5
F6	199.1	4.5	0.45	3.7	99.8

Table 5: Cumulative % drug release

Time (hr)	Cumulative Percent Drug Release (%)					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.5	25.6	8.5	13.2	9.6	10.36	8.76
1	36.7	14.5	15.8	12.3	14.3	12.3
2	48.5	18.4	17.2	14.8	17.8	18.8
3	52.3	23.4	22.8	18.9	20.9	25.9
4	69.4	28.2	33.3	22.3	26.3	32.6
5	78.4	32.1	39.2	33.9	32.9	45.9
6	87.3	44.6	47.8	38.7	39.7	55.6
7	92.5	53.6	56.4	44.8	46.8	63.6
8	95.2	68.5	59.9	53.6	57.6	72.8
9	98.3	74.5	62.2	66.6	69.6	79.4
10	-	83.2	72.8	72.8	76.8	84.3
11	-	89.3	83.8	79.5	81.26	88.4
12	-	98.3	89.2	88.2	86.96	96.6

Journal of Chemical Health Risks
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JCHR (2024) 14(3), 579-587 | ISSN:2251-6727

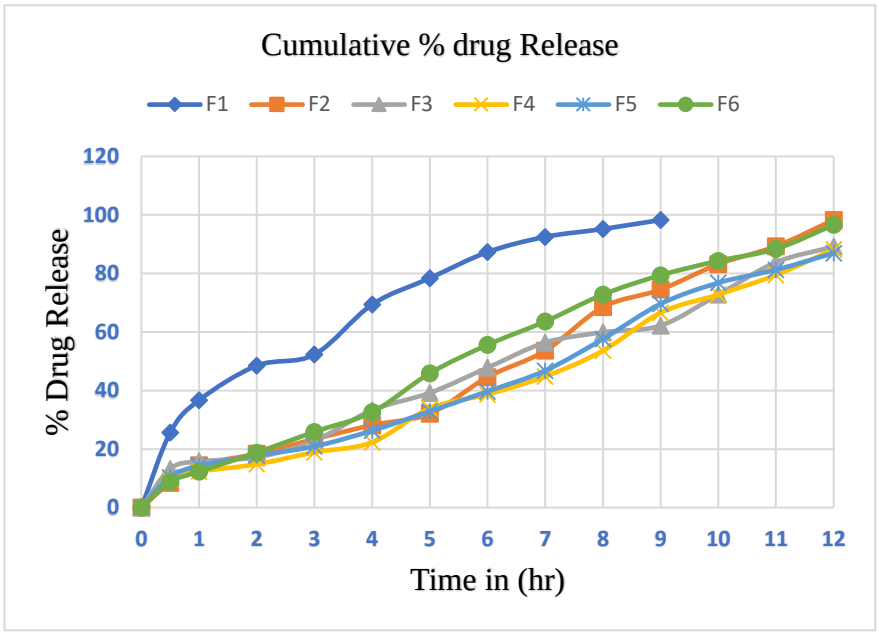

Fig. 3 : Cumulative % drug Release

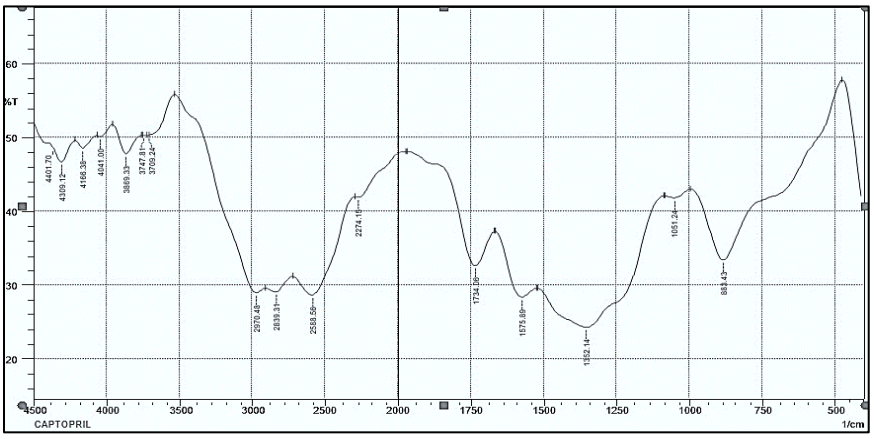

Fig.4 : FTIR spectra of pureCaptopril

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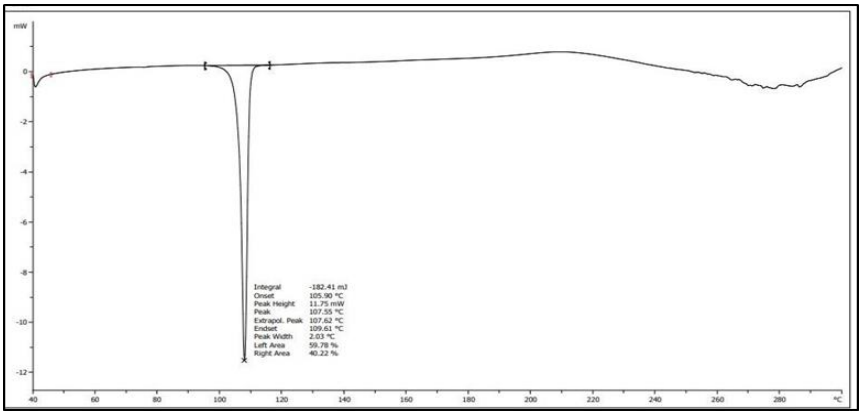

Fig. 5: DSC Thermogram of Captopril

Conclusion

In this study, Captopril CR tablets were prepared via direct compression method using a well established synthetic polymer (Karaya Gum) and HPMC as synthetic polymer. Pre-compression and post-compression studies of formulated tablets. At high concentration of Karaya gum 7.5% (15mg) drug release was sufficiently retarded. Thus, Karaya gum can be substituted for Starch and HPMC in controlled release tablets formulation. The drug release of Captopril was best in F2 showing 98.30% at the end of 12 h. Thus, it can be concluded that the formulation F2 can be more efficient and potential in comparison to other formulations for the development of controlled drug delivery system.

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