FORMULATION AND EVALUATION OF FLOATING MATRIX TABLET OF CAPTOPRIL AND LOSARTAN POTASSIUM IN TREATMENT AND MANAGEMENT OF HYPERTENSION

Tamboli Saifali[1], Prof. Deshmukh Rehan[2], Dr. Khan G. J. [3], Shaikh Mujeeb[4], Patel Raihan[5], Ansari Mohd.Hammad[6], Mohd. Shoeb Nawaz[7], Maaz Aaquil[8].

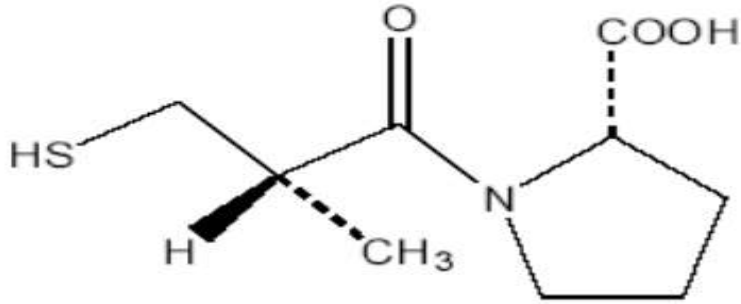
TAMBOLI SAIFALI, DEPARTMENT OF PHARMACEUTICS, ALI-ALLANA COLLEGE OF PHARMACY, AKKALKUWA, DIST. NANDURBAR, 425415.

Abstract: *The purpose of this investigation was to prepare a gastro-retentive drug delivery system of captopril and losartan potassium for treatment and management of hypertension. Matrix Floating tablets of captopril and losartan potassium were prepared using different grades of HPMC K-100 and HPMC K-4M by effervescent technique. Sodium bicarbonate and citric acid was incorporated as a gas-generating agent or effervescent agent. The matrix floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, in vitro buoyancy and dissolution studies. The effect of citric acid on drug release profile and floating properties was investigated. The prepared matrix floating tablets exhibited satisfactory physico-chemical characteristics. All the prepared batches showed good in vitro buoyancy. The tablet swelled radially and axia lly during in vitro buoyancy studies. It was observed that the tablet remained buoyant for more than 24 hours. A combination of sodium bicarbonate (27mg) and citric acid (13.5mg) was found to achieve optimum in vitro buoyancy. The formulation having HPMC K100 (60mg), HPMC K-4M (25mg) were found to float for longer duration as compared to other formulations and shows good drug release properties.*

KEY WORDS: Captopril, Losartan potassium, HPMC K-4M, HPMC K-100,

1.INTRODUCTION:

Captopril 1-(3-mercapto-2-D-methyl-1-oxoproppyl) -l-proline (S,S), is used as therapeutically in treatment of hypertension. It acts as a potent and specific inhibitor of angiotensin-converting enzyme (ACE Inhibitor). It is used in the Prevention and management of hypertension, in heart failure or cardiac failure, following myocardial infraction and in diabetic nephropathy. It is representative of the ACE-inhibitor class of antihypertensive, captopril, was studied for several reasons: firstly, it seems to be one of the most widely used drug of the group and, secondly, because it contains several donor groups, namely COOH, C=O, SH and proline nitrogen.

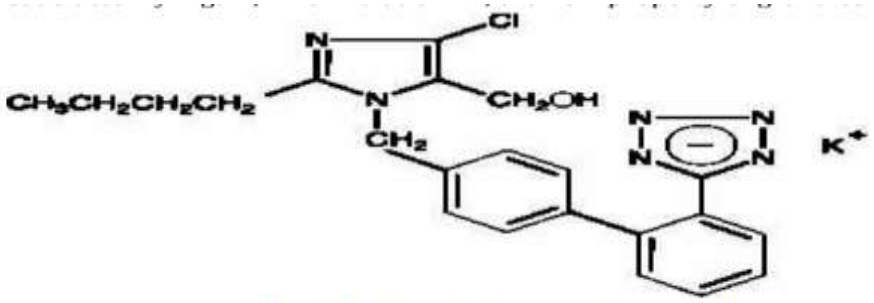


Structure of captopril

The Mechanism of action of Captopril is to block the conversion of angiotensin I to angiotensin II and prevents he degradation of vasodilatory prostaglandins, and inhibiting vasoconstriction and promoting systemic vasodilation, which contribute in decrease in Blood pressure The Pharmacokinetic parameters are well

different .Unlike the majority of ACE inhibitors, captopril is not administered as a prodrug (the only other being lisinopril). About 70% of orally administered captopril is absorbed through oral mucosa. Bioavailability is reduced if food is present in stomach. It is partly metabolised and partly excreted unchanged in urine. Captopril also has a relatively poor pharmacokinetic profile. The short half-life required dosing two or three times per day, which decrease patient compliance. Captopril has a short half-life of 2–3 hours and a duration of action of 12–24 hours.

Losartan potassium is an angiotensin receptor blocker (ARB) used as anti-hypertensive drug Its empirical formula is C22H22ClKN6O and its structural formula is presented in Figure.



Structural formula of losartan potassium

Losartan potassium, an orally active non-peptide molecules used for treatment of hypertension which is chemically described as 2-butyl-4-chloro-1-[p-(o-1H - tetrazol-ylphenyl) benzyl]imidazole – 5-methanol monopotassium salt.

The molecular weight of losartan potassium is 461.01. It is freely soluble in water and soluble in alcohols.

Losartan potassium is an angiotensin II receptor antagonist generally known as angiotensin receptor blocker (ARB Blocker) It suppresses the effects of angiotensin II at its receptors, thereby blocking the rennin-angiotensin system. Losartan potassium has more pharmacological action because of its enhanced specificity, selectivity, and tolerability.

Absorption of losartan potassium is not affected by food. Time to achieve the peak concentration are 1 h our for losartan, and 3.5 hours for the active metabolite The pharmacokinetics of both losartan and its active metabolite are linear, and not affected by repetitive dosing. Although clearance is both by hepatic and renal mechanisms, only hepatic impairment appears to affect plasma half-life.

In the present study, we made an attempt to develop a stable formulation of floating matrix tablet of captopril and losartan potassium in attempt to treat hypertension with optimum parameters and properties.

To achieve this goal, various formulation of captopril and losartan potassium matrix tablet were prepared by effervescent approach using two different grades of HPMC (k-4M & k-100M)and evaluate with respect to the various quality parameters both in process parameters for granules (loss on drying, bulk density, tapped density, compressibility index, Hausner's ratio) and parameters for finished products (average weight, weight variation, tablet thickness, friability, hardness, disintegration time, drug content, dissolution studies) with an aim to study effect of polymer on floating properties and release characteristic of drug.

2.MATERIALS AND METHODS

Materials

Captopril was received as a gift sample from WOCKHARDT LIMITED, Aurangabad , India and losartan potassium was received as gift sample from J.B. CHEMICALS LIMITED, Ankleshewar, India. HPMC K100M and HPMC K4M were purchased from Research Lab Fine Chem. Ltd. Mumbai. Magnesium stearate, hydrochloric acid, sodium bicarbonate and citric acid anhydrous (hereafter referred to as citric acid) were purchased from Research Lab Fine Chem. Ltd. Mumbai. Polyvinyl pyrrolidone K-30 (PVP K-30) was procured from Research Lab Fine Chem. Ltd. Mumbai. Lactose and purified talc were purchased from E. Merck (India) Ltd., Mumbai. All other ingredients were of laboratory grade.

Methods:

The composition of different formulation of matrix tablet of captopril and losartan potassium floating tablet is shown in table 1. Captopril and losartan potassium were geometrically mixed with the required quantities of microcrystalline cellulose, HPMC K-4M, HPMC K-100M, Sodium bicarbonate, citric acid, and poly-vinyl-pyrrolidone in a mortar and triturate them in mortar and mix them properly. Magnesium stearate and talc first pass through sieve no #80 and then add to above blend with continue mixing for 2-3 minutes. This mixture or blend of drug and excipients was compressed using single punch tablet machine having diameter of 9mm and weighing 270mg. compression force of the machine was adjusted to obtain hardness in the range of 4 kg/cm^2.

Ingredients	Formulation batch code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Captopril	25	25	25	25	25	25	25	25	25
Losartan potassium	50	50	50	50	50	50	50	50	50
HPMC K-4 M	15	15	15	25	25	25	35	35	35
HPMC K-100 M	60	75	90	60	75	90	60	75	90
Sodium bicarbonate	27	27	27	27	27	27	27	27	27
Citric acid	13.5	13.5	13.5	13.5	13.5	13.5	13.5	13.5	13.5
MCC PH-102	57.9	42.9	27.9	47.9	32.9	17.9	37.9	22.9	7.9
PVP K-30	13.5	13.5	13.5	13.5	13.5	13.5	13.5	13.5	13.5
Magnesium stearate	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4
Talc	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7
Total	270	270	270	270	270	270	270	270	270

Table No: 01

PRE-COMPRESSION PARAMETERS OF FORMULATED TABLETS

The Pre-compression parameter of tablet were characterized in terms of angle of repose, Carr index and Hausner ratio, bulk density and tap density. For determination of angle of repose (θ), the powder were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0cm above hard surface. The powder was poured till the time when upper tip of the pile surface touched the lower tip of the funnel and calculate the angle of repose using formula.

EVALUATION OF PREPARED MATRIX FLOATING TABLET

The prepared floating tablets were evaluated for uniformity of weight using 20 tablets, for hardness using Monsanto tester, for friability using 10 tablets and using Roche type friabilator, for drug content, in vitro buoyancy study and in vitro dissolution studies using usp type 2 apparatus the results are expressed as mean ± S.D. (n=3).

The in-vitro buoyancy was determined by floating lag time and total floating time as described. Tablets were placed in 100 ml beaker containing 0.1N HCl. Floating lag time is the time required by tablet to float on surface of liquid is considered to be floating lag time while the duration of floating is referred as total floating time both floating lag time & total floating time is shown in tabulated form.

Drug is identified and its compatibility with polymers and other excipients were carried out using FT-IR spectra and differential scanning calorimetry (DSC). As matrix tablet is composed of swellable polymers like HPMC K-4M and HPMC K-100M and AVICEL PH-102, swelling index of this polymer must be determined using formula for % swelling Index.

The release rate of matrix floating tablet of captopril and losartan potassium was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 2 : Electro lab – TDT – 08L (USP). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid as gastric fluid at 37 ± 0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus periodically and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and dilute it to suitable concentration with 0.1N hydrochloric acid. Absorbance of these solutions was measured at 207nm & 218nm using a Shimadzu UV/Vis double-beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

3.RESULT AND DISCUSSION

3.**1 FT-IR SPECTROSCOPY** OF PURE DRUG**:** Fourier transform-Infrared Absorption Spectroscopy, was carried out to determine purity of the Captopril, purity Losartan Potassium & compatibility of captopril & losartan with other excipients. Figure no 1-3 shown graphical data of FT-IR studies.

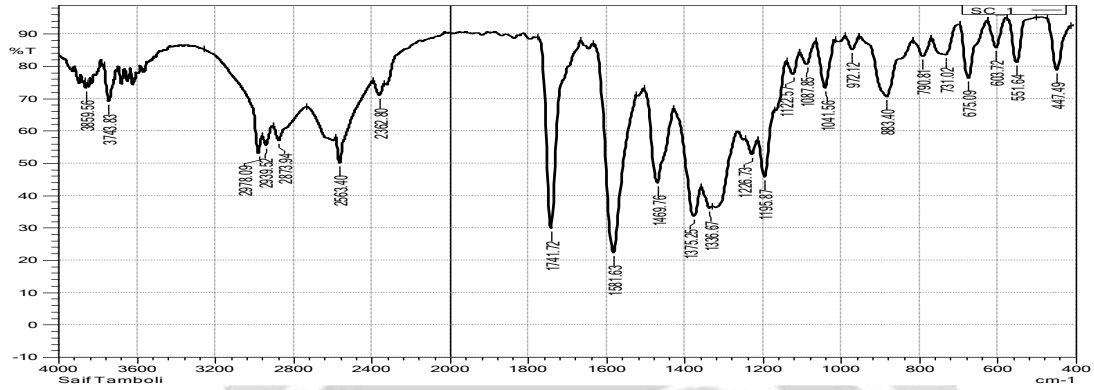


Figure 1: FT-IR spectra of Captopril.

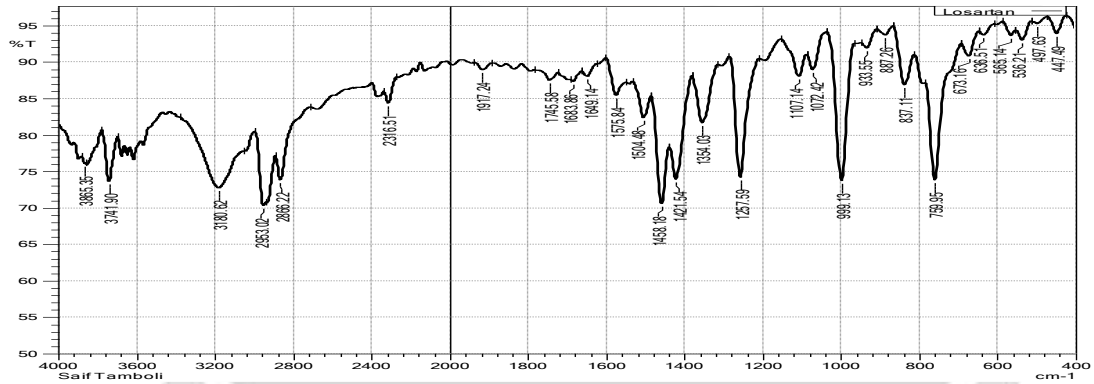


Figure 2: FT-IR spectra of Losartan Potassium

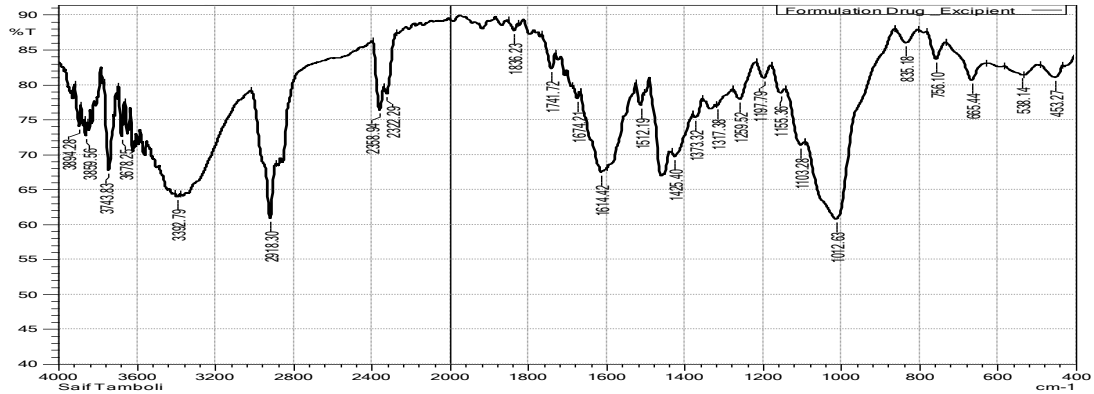


Figure 3: FT-IR spectra of Drug + Excipients

3.2 Differential Scanning Calorimetry: DSC studies was carried out to determine purity of the Captopril, purity Losartan Potassium & compatibility of captopril & losartan with other excipients. Figure no 4-6 shown graphical data of DSC studies of drug and excipients.

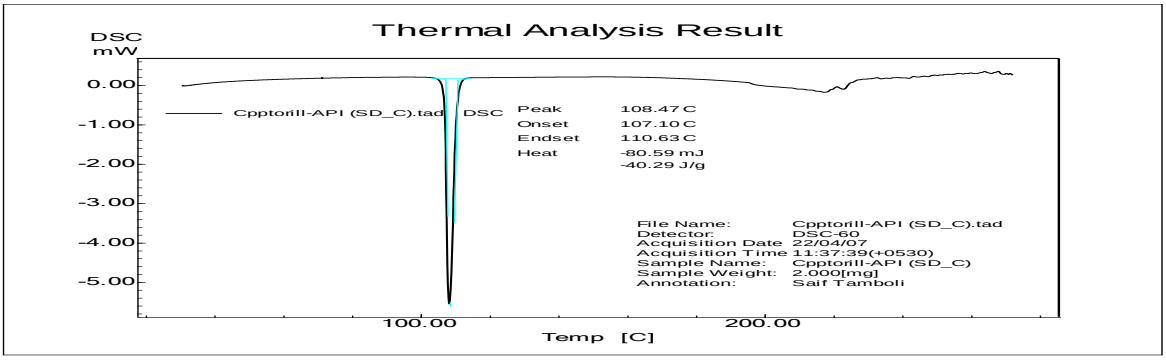


Figure 4: Differential Scanning Calorimetry of Captopril

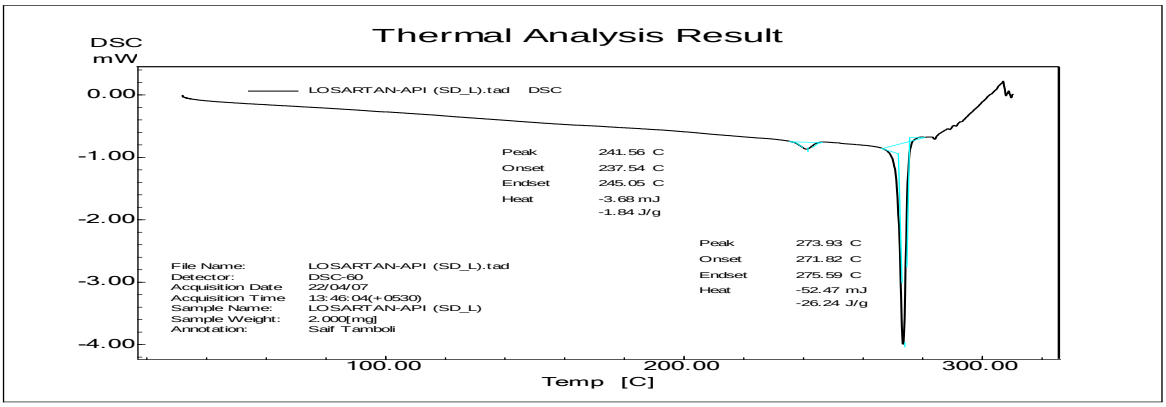


Figure 5: Differential Scanning Calorimetry of Losartan Potassium

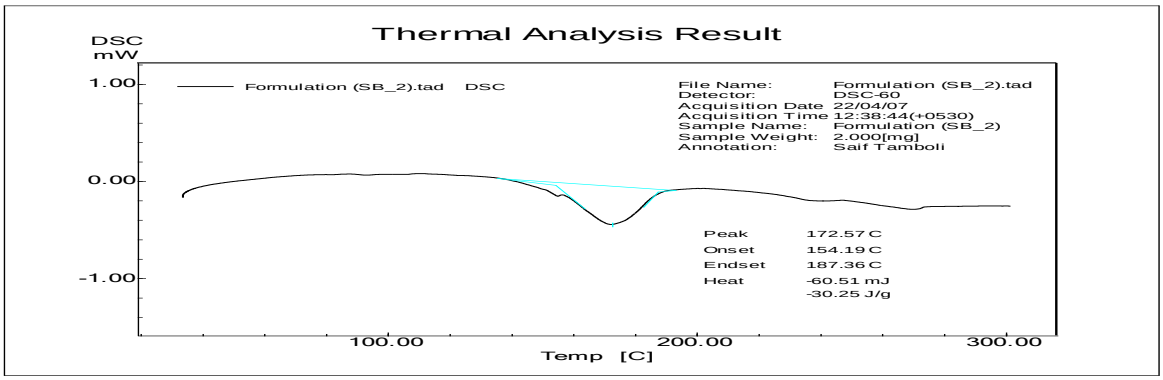


Figure 6: Differential Scanning Calorimetry of Drug with Excipients

3.3 Pre-compression parameter

The preformulation study can be described as phase of research and development process were scientist characterizes the physical ,chemical, and mechanical properties of drug substances along with an excipients in order to make or develop stable, safe, and effective dosage form It describes the stability and flow-ability of blend in order to make effective dosage form there is necessities to determine its angle of repose, tap density, bulk density, hausner's ratio, car's index. the all precompression or preformulation parameters of formulations F1-F9 are enlisted in table 2

Batch No.	Angle 0f Repose (θ)	Bulk Density (gm./ml)	Tapped Density (gm./ml)	Hausner's Ratio	Carr's Index(%)
F1	31.7	0.474	0.540	1.13	12.22
F2	28.5	0.432	0.480	1.11	10.14
F3	27.1	0.432	0.500	1.15	13.06
F4	25.5	0.450	0.519	1.12	11.20
F5	30.6	0.446	0.524	1.17	14.88
F6	32.4	0.432	0.492	1.13	12.90
F7	29.3	0.450	0.505	1.12	10.89
F8	31.2	0.529	0.600	1.13	11.83
F9	26.9	0.519	0.602	1.15	13.78

Table no 02: Pre-Compression Parameters

The value showed that powder has compressibility index vary from 10.89-13.78 and hausner's ratio varies from 1.11-1.15 this shows good compressibility index, except F1,F4,F8, all formulations shows good flowing properties of powder.

3.4 Post Compression Parameter

Formulated matrix floating tablet of captopril and losartan potassium were evaluated for Various parameters such as hardness, weight variation, thickness, and friability. Result obtained from this study are shown in table no;3

Formulations	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)
F1	269.7	3.62	4.82	0.81
F2	269.4	3.58	4.83	0.51
F3	268.8	3.69	4.82	0.67
F4	269.0	3.74	4.82	0.73
F5	269.8	3.72	4.85	0.59
F6	268.5	3.65	4.77	0.38
F7	268.7	3.79	4.80	0.65
F8	269.1	3.62	4.83	0.58
F9	270.1	3.85	4.85	0.42

Table no:03 post compression parameter

The above result showed that tablet passed the weight variation and friability test, hardness and drug content within specified limit.

3.5 *In-vitro* buoyancy study

The formulated matrix floating tablet of captopril and losartan potassium were evaluated for buoyancy studies as per procedure specified in pharmacopeia All the formulations shows good buoyancy study profile enlisted in table no: 4

Formulation batch code	Floating lag time (Sec)	Total floating Time (Hrs)
F1	52	16
F2	90	20
F3	95	24
F4	55	24
F5	60	24
F6	112	22
F7	95	24
F8	135	24
F9	155	24

Table no 04: in-vitro buoyancy study of formulations

3.6 Swelling index study

Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. The extent of swelling can be measured in terms of % weight gain by the tablet. For each formulation batch, one tablet was weighed and placed in a beaker containing 200 ml of buffer media. After each interval the tablet was removed from beaker and weighed again up to 12 (hrs) and calculate % swelling index using formula. Graphical representation of swelling index is shown in figure no 07. The data shows that all formulations shows good swelling index.

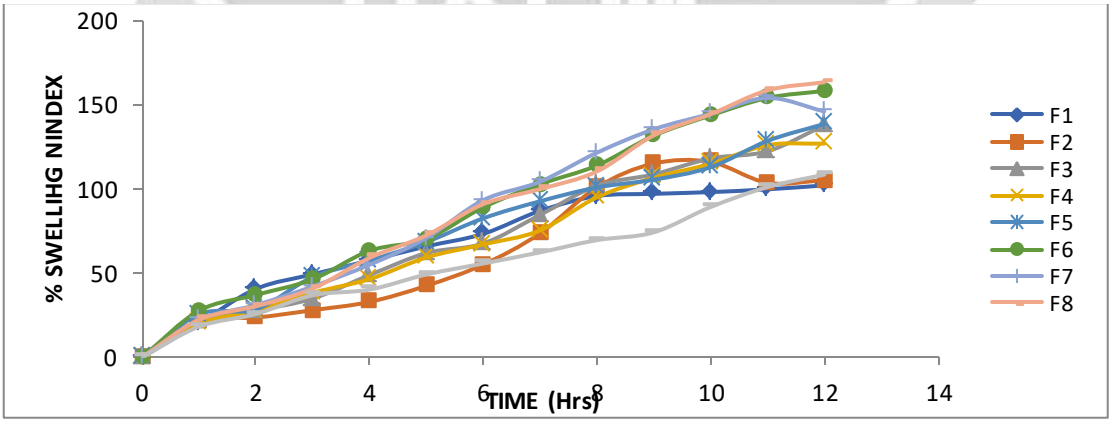


Figure 7: % Swelling Index

3.7 In Vitro Dissolution Studies

The in-vitro dissolution studies of formulated matrix floating tablet of captopril and losartan potassium were performed using dissolution type -2 paddle type apparatus using pH 1.2 as buffer and the data is represented in figure no 8 & 9.

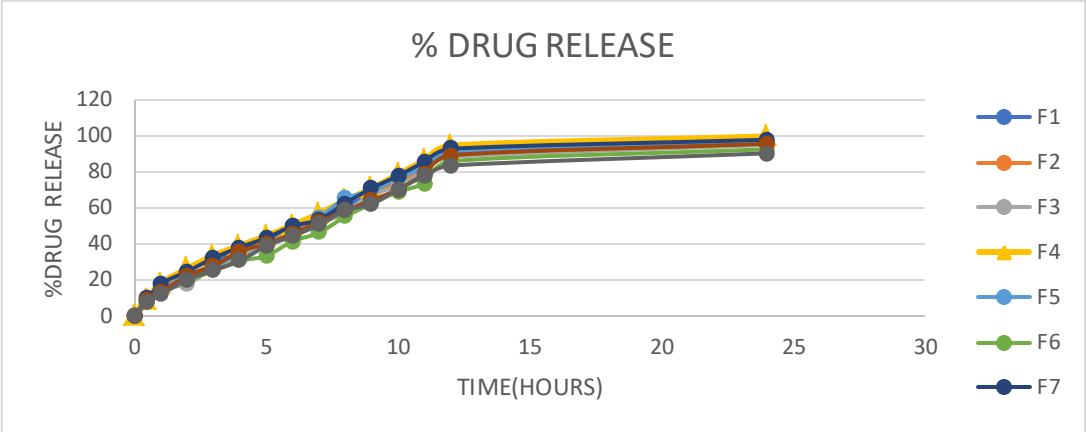


Figure 8:% Drug Release of captopril (F1-F9)

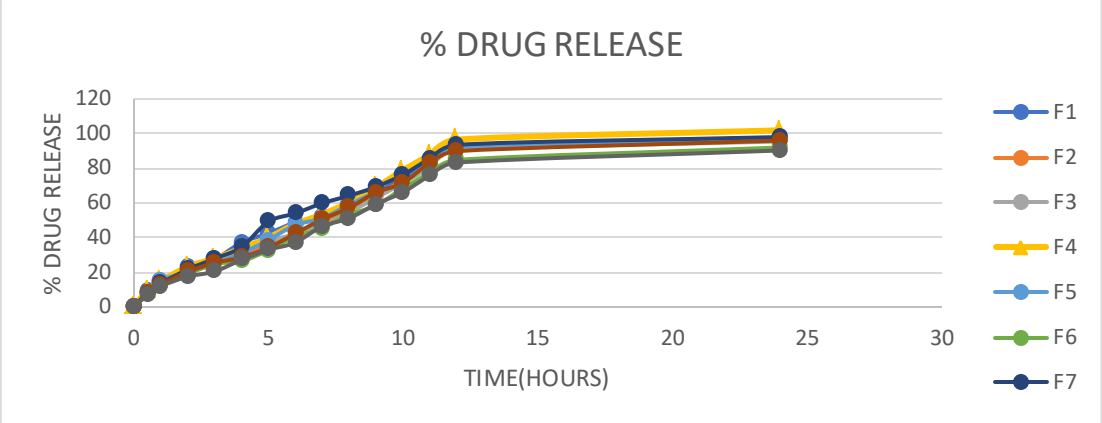


Figure 9% Drug Release of losartan potassium (F1-F9)

CONCLUSION

1/3rd of populations is suffering from hypertension and to overcome this many formulation are available in market as well as researches is going on, the approach that can use in management and treatment of hypertension is matrix floating tablet of captopril and losartan potassium as both drugs have synergistic property. It was concluded that effervescent floating tablet containing HPMC K 100M, HPMC K 4M, citric acid and sodium bicarbonate can float on 0.1N HCL. The data obtained thus suggests that gastroprotective drug delivery system can be successfully designed to give controlled drug delivery, improve bioavailability and other desirable characteristics. The present study shows that captopril and losartan potassium can be made into floating Dosage form and in effervescent form by direct compression technique. Matrix Floating tablet of captopril and losartan potassium shows good pharmacokinetic and pharmacodynamic property. captopril and losartan potassium floating tablet were prepared by direct compression technique and found to be good with chipping, capping, and sticking.IR spectroscopy study indicates no drug-excipient interaction in the formulation. Trial and optimized tablet of captopril and losartan potassium were formulated well in terms of hardness, thickness, weight variation, content uniformity. The in-vitro dissolution profile of optimized floating tablet formulated of captopril and losartan potassium were found sustained drug release up to 24 hours and release can be extended for longer period more than 24 hours by increasing the concentration of polymers. 3^2 full factional design and optimization technique successfully used in the development of floating tablet. Comparing the all formulations, formulation F4 was considered as optimized formulation which exhibited 99.70% & 98.88% of drug release in 24 hours, and floating lag time of 55 sec, total floating time over 24 hours.

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