FORMULATION AND IN -VITRO EVALUATION OF LOSARTAN POTASSIUM SUSTAINED RELEASE FLOATING TABLETS

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***ABSTRACT :** The sustained release drug delivery is the drug delivery system that achieves the release of the drug in the proper amount at regular time intervals over an extended period and is time-independent. The present work aimed to formulate and evaluate sustained release floating tablets of Losartan using synthetic polymers to reduce the various side effects associated with Losartan as well as to overcome the manufacturing difficulties. For formulating a sustained release floating drug delivery system, synthetic hydrophilic polymers are used. These binders prolong the dissolution rate of some slightly soluble drugs and can be chosen as a good candidate for sustained release. Tablets were prepared by direct compression method using different drug-polymer concentration. FT-IR study revealed that there was no chemical interaction between the drug and polymers used. Pre-compression and post-compression parameters complied with the Pharmacopeial limit for the tablets. The in vitro release study was performed and the results indicated that the formulation F4 has better percentage drug release profile with maximum (96.82 %) at the end of 10th hr sustained action. The F4 formulation was fabricated with HPMC polymer ratio and show a very good release profile at the end of 10th hr. The optimized batch tablets, stability studies are carried out for three months, as per ICH guidelines (40±20C/RH75±5). Tablets were evaluated for assay and in-vitro dissolution, but found no significant change during the study period .*

***Keywords:** Losartan, FTIR studies, Synthetic polymers, Direct compression technique, In vitro drug release studies.*

I.INTRODUCTION

Despite tremendous advancement in drug delivery, oral route of administration has received the more attention and success because the gastrointestinal physiology offers more flexibility in dosage form design than other routes. Hence, research continuously keeps on searching for ways to deliver drugs over an extended period of time, with a well-controlled release profile. Gastric emptying of dosage form is extremely variable process and ability to prolong and control the emptying time. Gastric transit time is valuable asset for dosage forms, which reside in the stomach for a long period of time than conventional dosage form[1]. Conventional oral dosage forms such as tablets, capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. Many attempts have been made to develop sustained release preparations with extended clinical effects and reduced dosing frequency[2,3]. A problem frequently encountered with conventional sustained release dosage forms is the inability to increase their residence time in stomach and no control over drug delivery, leading to fluctuations in plasma drug level.Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms[4]. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter-digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours[5] .Losartan Potassium is an angiotensin-receptor blocker (ARB) that may be used alone or with other agents to treat hypertension. The aim of study is to formulate and evaluate of sustained release floating tablet of losartan potassium[6]. To study the effect of polymers on the release of Losartan potassium, different polymers are used to attain floating sustained drug release and give maximum therapeutic effect for prolonged period of time when taken orally, to design a formulation of solid dosage of Losartan potassium tablets

with better stability of high product quality.[7]

II. MATERIALS AND METHOD

2.1 Materials

Losartan potassium was collected as a gift sample from Hetero labs, Hyd, polymers and other excipients were purchased from AR Chemicals,Hyd.

2.2 Methododology

Compatibility studies:

The drug-polymer compatibility was ascertained by subjecting the drug and homogenates of drug and polymer to Infrared spectrophotometric study.

Fourier Transform Infrared Spectroscopy (FTIR)[8,9]

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the preformulation stage during the development of a dosage form. The use of FTIR technique allows pointing out the implication of the different functional groups of drug and excipients by analysing the significant changes in the shape and position of the absorbance bands. In this method individual samples as well as the mixture of drug and excipients were ground mixed thoroughly with potassium bromide (1:100) for 3-5 mins in a mortar and compressed into disc by applying pressure of 5 tons for 5 mins in hydraulic press. The pellet was kept in the sample holder and scanned from 4000 to 400 cm-1 in FTIR spectrophotometer. Then the characteristics peaks were obtained of all sample as well as mixtures.

Formulation development

Table-:1Composition of Losartan potassium floating tablets

Ingredients	Formulations			
	F1	F2	F3	F4
Losartan potassium	200	200	200	200
Sodium alginate	25	50	-	
HpmcK5M	-	-	25	50
Lactose	15	15	15	15
Sodium bi carbonate (mg)	20	20	20	20
MCC	35	35	35	35
Magnesium stearate (mg)	3	3	3	3
Talc (mg)	2	2	2	2
Total wt (mg)	300	300	300	300

Procedure for Formulation

Preparation of Formulation:

1. Drug and polymers pass through 40 # mesh separately and then transfer it to poly bag and mix it for 3 minutes.
2. Add diluents and other excipients to the above mixture. Finally add the Glidant (Magnesium Stearate) and Lubricant (Talc) to the above blend mix it for 2min.
3. Compressed the above lubricated blend by using 10mm round punches[10].

Evaluation of tablets

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, Friability, Buoyancy test and in vitro-dissolution characters.

Physical Appearance[11]

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the

measurement of size, shape, colour, presence or absence of odour, taste etc.

Size & Shape[12]

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

Weight variation test[13]

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Content Uniformity[14]

Randomly select 30 tablets. 10 of these assayed individually. The Tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labelled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labelled content. If these conditions are not met, remaining 20 tablets assayed individually and none may fall outside of the 85 to 115% range.

Friability[15]

A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

$$\% \text{ friability} = (W_1 - W_2) / W_1 \times 100$$

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

Floating lag time[16]

The time between the introduction of the tablet into the medium and its rise to upper one thirdof the dissolution ve sselis termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotatio n time. These tests are usually performed in simulated gastric fluid or 0.1NHCl maintained at 37 ^{0}C, by using USP dissolution apparatus containing 900 ml of 0.1N HCl as the dissolution medium.

Drug release [17]

The drug release from the Losartan potassium tablets was investigated in a USP-II (paddle) apparatus, 900 ml of 0.1N HCl (50 rpm, 37°C). At predetermined time intervals, 5-ml samples were withdrawn and take 1ml sample and diluted to 10 ml and then analysed with UV spectrophotometry at λmax 282 nm.

Stability studies[18]

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile. The prepared Losartan potassium floating tablets were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2^{o}c and refrigerator 2-8^{o}c for a period of 30 days.

III.RESULTS AND DISCUSION

Compatibility Study

Compatibility studies were performed using an IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. The characteristic absorption peaks of Losartan were obtained at 3500 cm^{-1}, 1084 cm^{-1}, 3095cm^{-1}, 1745cm^{-1}.

The peaks obtained in the spectra of each formulation correlate with the peaks of the drug spectrum. This indicates that the drug was compatible with the formulation components.

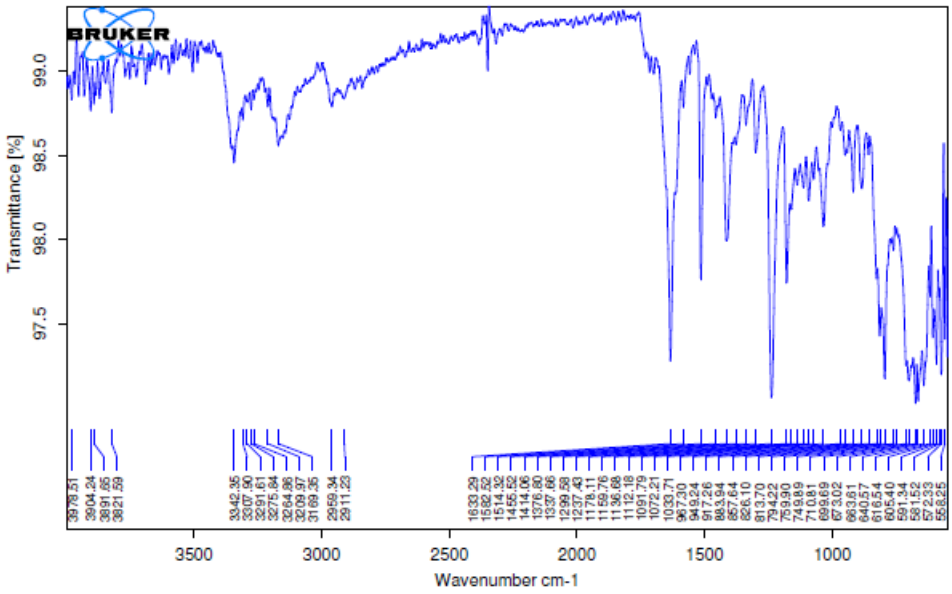

Fig no: 1 FTIR Spectra of Losartan

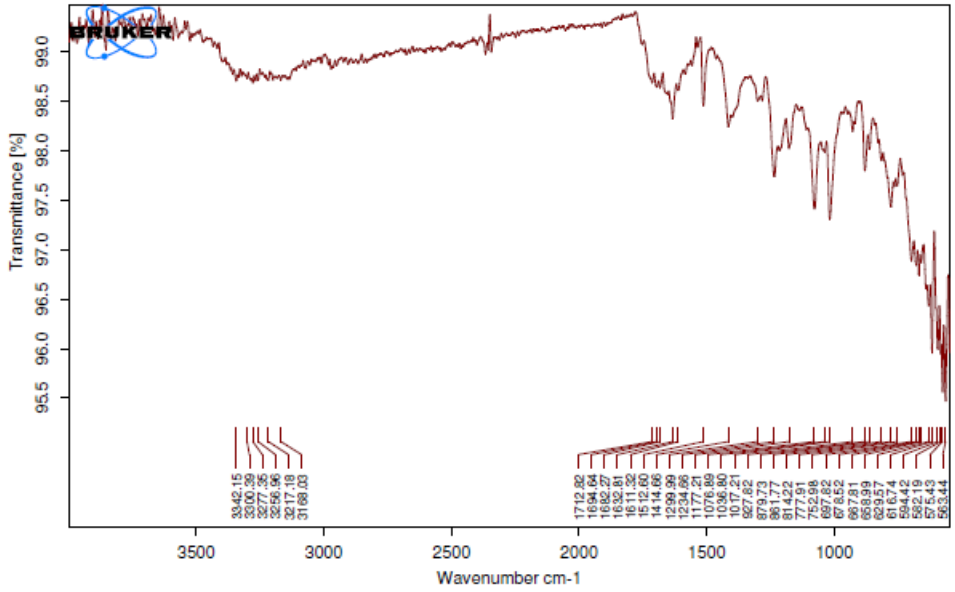

Fig no: 2 FTIR Spectra of Optimized formulation

Compatibility studies were performed using an IR spectrophotometer. The IR spectrum of Pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks was obtained as above and as they were in official limits (±100 cm-1) the drug is compatible with excipients.

Evaluation of Preformulation parameters

The properties like compressibility index, angle of repose and hausner ratio were calculated.

Table-: 2 Evaluation parameters of Losartan potassium

S. no	**Bulk density**	**Tapped density**	**Compressibility index**	**Hausner ratio**	**Angle of repose(0)**
F1	0.396	0.481	17.67	1.21	27^0
F2	0.412	0.496	16.93	1.20	30^0
F3	0.399	0.486	17.90	1.21	29^0
F4	0.400	0.502	20.3	1.25	30^0

Evaluation of the Prepared Tablets for Physical Parameters

All formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and

found to be within the Pharmacopoeial limits. The results of the tests were tabulated. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

Table-: 3Evaluation parameters of Losartan potassium floating tablets

Parameter	F1	F2	F3	F4
Weight variation	300	299	298	300
Thickness (mm)	3.2	3.5	3.4	3.5
Hardness (kg/cm^2)	4.2	4.1	3.9	4.0
Friability	0.42	0.46	0.49	0.5
Content uniformity	96.35	94.59	97.59	98.36
Floating lag time (Sec)	45	52	55	80

Floating lag time

The floating tablets of Losartan potassium were prepared by using direct compression technique. four different formulations were prepared using different ratios of polymers. The prepared formulations were evaluated for floating lag time and buoyancy time. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N HCl). It was observed that the gas generated is trapped and protected within the matrix, formed by polymers, thus density of the tablet decreased and it becomes buoyant. The floating lag time of the optimized formulation F4 was 80 sec.

In vitro Dissolution studies

The dissolution conditions used for studying the drug release from tablet of Losartan potassium are ,The samples were withdrawn at predetermined time points, and were analyzed spectrophotometrically at 282 nm.

Table-:4 In vitro drug release of Losartan potassium floating tablets

%Drug Release				
Time	**F1**	**F2**	**F3**	**F4**
0	0	0	0	0
30	13.25	18.36	19.65	20.65
60	28.94	29.92	31.85	33.68
120	44.64	47.93	51.25	57.91
240	54.95	64.72	63.92	79.97
360	66.55	75.92	79.90	82.20
600	88.92	87.83	90.15	96.82

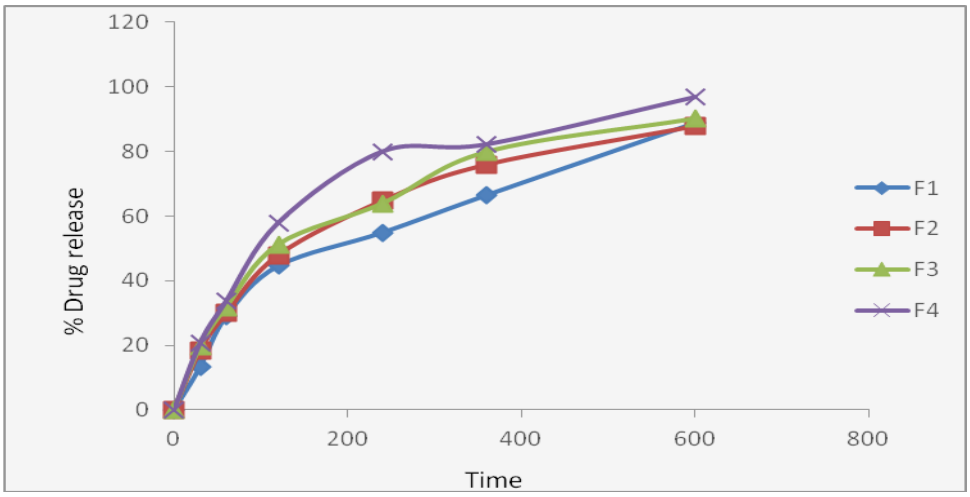

Fig-:3 In vitro drug release for all the formulations

Stability Study

There was no significant change in physical and chemical properties of the tablets of formulation F-4 after 30 days. Parameters quantified at various time intervals were shown.

Table-: 5 Stability study for optimized formulation

Formulation Code	Parameters	Initial	1st Month	Limits as per Specifications
F-4	25^0C/60%RH % Release	96.82	96.90	Not less than 85 %
F-4	30^0C/75% RH % Release	96.82	96.91	Not less than 85 %
F-4	40^0C/75% RH % Release	96.82	96.90	Not less than 85 %

IV. CONCLUSION

Losartan potassium tablets used for the treatment of hypertension. Losartan potassium tablets were successfully formulated by using different concentration of polymers (Sodium alginate, HPMC K5 M, MCC , MG.STERATE and ,Sodium bicarbonate and TALC) to sustain the drug for a prolonged period of time FTIR study performed for identification and compatability study of drug and excipients , found no characteristic change in drug-excipient powder mixture. Hence the excipients were selected for the formulation development. Powder blends were evaluated for tests, such as bulk density, tapped density, compressibility index and Hausners ratio before being punched as tablets. The *In-vitro* dissolution profiles of F1 to F4 were found to have different percentage of drug release. The percentage of drug release is low (88.92) for F1 tablets when compared to other formulations. F4 has better percentage drug release profile with maximum (96.82 %) at the end of 10th hr sustained action. The F4 formulation was fabricated with a very less polymer ratio and show a very good release profile at the end of 1Oth hr. The optimized batch tablets, stability studies are carried out for three months, as per ICH guidelines (40±20C/RH75±5). Tablets were evaluated for assay and in-vitro dissolution, but found no significant change during the study period ,It can be concluded that sustained release tablets of Losartan potassium can be performed by direct compression method .All the formulas show a very good drug release profiles and shown better sustained action till the end of last hour 10th hrs .And hence will improve patient compliance and increase in bioavailability.

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