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Formulation and in-vitro evaluation of sustained release matrix tablets of a selective angiotensin receptor-ii antagonist

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ABSTRACT

The present work was to formulate and evaluate sustain release matrix tablets of Losartan, an angiotensin II Receptor type 1 antagonist. Sustain release formulation are those which delivers the drug locally or systemically at a predetermined rate for a fixed period of time. The matrix tablet was prepared by direct compression method using by various concentration of chitosan and sodium alginate with combination of various release retardant polymer. The powder mixtures were subjected to various pre-compression parameters such as angle of repose, bulk density, tapped density and Carr's index shows satisfactory result and the compressed tablets are evaluated for post-compression parameters such as weight variation, thickness, hardness, friability, drug content, *in-vitro* dissolution and stability studies. In this study carbopol was chosen as polymer and it was combined with chitosan and sodium alginate to explore their sustain release capability. The *in-vitro* release data for chitosan-carbopol and sodium alginate-carbopol based Losartan sustain released matrix tablets are represented in table 17 and illustrated in figure 2. The *in-vitro* release of Losartan, from prepared matrix tablets formulations was mainly affected by dissolution medium, concentration of chitosan, concentration of sodium alginate and concentration of polymers. *The in-vitro* release of Losartan form prepared matrix tablets also depends on swelling behaviour of the tablets, higher the tablet swells comparative the lesser amount of drug release. The *in-vitro* release study was performed in 0.1 N HCl for initial first 2 hrs, and then the medium was replaced by phosphate buffer pH 6.8) and study was continued for 24 hour. The *in-vitro* release of Losartan was higher in first 6-7 hours in all formulations. After 1 hour, approximately 11.39%-19.54% of Losartan from chitosan-carbapol tablets, 17.10%- 22.11% from sodium alginate-carbapol, 26.22% from tablets containing only release retardant polymer has been released. Initially amount of drug release was higher but after 6-7 hrs drug release was retarded. The stability studies were carried out for 3 months and result indicates that the selected formulations (F_4 and F_7) were stable.

Keywords: Carbopol 934P, Chitosan, sodium alginate, sustain release matrix tablet, Losartan.

INTRODUCTION

Oral delivery of drugs is the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc. Many of the drug delivery systems available in the market are oral drug delivery type systems.[1] Approximately 50% of the drug delivery systems available in the market are oral drug delivery systems and historically too, oral drug administration has been the predominant route for drug delivery. It does not pose the sterility problem and minimal risk of damage at the site of administration.[2] Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption.

In order to overcome the drawbacks of conventional

drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.[3]

Design and formulation of oral sustained release drug delivery system[4,5]

The oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance. But here one has to take into consideration, the various pH that the dosage form would encounter during its transit, the gastrointestinal motility, the enzyme system and its influence on the drug and the dosage form. The majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal tract. Theoretically and desirably a sustained release delivery device, should release the drug by a zero-order process which would result in a blood-level time profile similar to that after intravenous constant rate infusion. Plasma drug concentration-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero order sustained release formulation.

Sustained release constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both. Sustained release system generally do not attain zero order type release and usually try to mimic zero order release by providing drug in a slow first order. Repeat action tablet are an alternative method of sustained release in which multiple doses of drug are an alternative method of sustained release, in which, multiple doses are contained within a dosage form and each dose is released at a periodic interval.

Delayed release system, in contrast, may not be sustaining, since often the function of these dosage forms is to maintain the drug in the dosage for some time before release, for example. Enteric coated tablet. A sustained release dosage form will provide a therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval with a reduction in a peak concentration ratio.

Factors Affecting the Oral Sustain Release Dosage Form Design[6-7]

Pharmacokinetics and pharmacodynamics factor

Biological half-life

Drug with biological half-life of 2-8 hours are considered suitable candidate for sustain release dosage form, since this can reduce dosing frequency. However this is limited in that drugs with very short biological half lives may require excessive large amounts of drug in each dosage unit to maintain sustained effects, forcing the dosage form itself to become limitingly large.

Absorption

Rate of absorption of a sustained formulating depends upon release rate constant of the drug from the dosage form, and for the drugs that are absorbed by active transport the absorption is limited to intestine.

Distribution

The distribution of drugs into tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending n the time course of drug disposition. Thus for design of sustain release products, one must have information of disposition of drug.

Metabolism

The metabolic conversion to a drug is to be considered before converting into another form. Since as long as the location, rate, and extent of metabolism are known a successful sustain release product can be developed.

Drug properties relevant to sustain release formulation

Dose size

A dose size of 500-1000mg is considered maximal for a conventional dosage form. This also holds true for sustain release dosage forms. Since dose size consideration serves to be a parameter for the safety involved in administration of large amounts with narrow therapeutic range.

Ionization, pKa and aqueous solubility

Most drugs are weak acids or bases and in order for a drug to get absorbed, it must dissolve in the aqueous phase surrounding the site of administration and then partition into the absorbing membrane.

Partition coefficient

Bioavailability of a drug is largely influenced by the partition coefficient, as the biological membrane is lipophilic in nature transport of drug across the membrane largely depends upon the partition coefficient of the drug. Drugs having low partition coefficient are considered as poor candidate for the sustain release formulation as it will be localized in the aqueous phase eg: Barbituric acid and vice a versa.

Drug stability

When drugs are orally administered, they come across acid-base hydrolysis and enzymatic degradation.

In this case, if the drug is unstable in stomach, drug release system which provides medication over extended period of time is preferred, whereas in contrast the drug unstable in intestine will face problem of less bioavailability.[8]

Matrix Tablets

Matrix tablets are the type of controlled drug delivery systems, which release the drug in continuous manner by dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials. One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug release, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the release retardant. Alternatively drug and release retardant blend may be granulated prior to compression.[9]

MATERIALS AND METHODS

Materials

Losartan, Carbapol 934P, Chitosan, Sodium alginate, Polyvinyl pyrrolidone K30, Magnesium stearate, Talc, Micro crystalline cellulose.

Pre-Formulation Studies

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of pre-formulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms which can be mass produced.

POST-COMPRESSION EVALUATION PARAMETERS[10-11]

Evaluation of Losartan sustain release matrix tablets

Tablets were subjected to various evaluation parameters including drug content uniformity, weight variation, tablet hardness, friability, and thickness, and *in-vitro* drug release with different media.

In-vitro dissolution studies[12-13]

The *in-vitro* dissolution studies were performed using the USP-II (Paddle) dissolution apparatus at 50 rpm. Dissolution media was 0.1 N HCl for first 2 hrs and phosphate buffer pH 6.8 for remaining hrs and temperature was maintained at 37±0.5^{0}C. A 5ml was withdrawn at specific time intervals and same volume of fresh medium was replaced. The withdrawn samples were diluted with pH 6.8, filtered and analyzed on UV spectrophotometer at 249 nm using pH 6.8 as a blank. Percentage cumulative drug release was calculated.

Stability studies [14]

Stability of a drug has been defined as the ability of a particular formulation in a specific condition, to remain within its physical, chemical, therapeutical and toxicological specifications". The reason of stability testing is to provide evidence on how the quality of drug formulation varies with time under the influence of various environmental conditions such as temperature, humidity, light. From this study we know about recommended storage condition, re-test periods and shelf-life of the drug can be established. This is an assurance given by the manufacturer that the patient would receive a uniform dose throughout the shelf life. The drug control administration insists on manufacturers on conducting the stability studies, identity, strength, purity and quality of the drug for an extended period of time in the conditions of normal storage. Stability testing prevents the possibility of marketing an unstable product. Both physical and chemical degradation of drug can result in unstable product.[15]

Purpose of stability studies

Stability studies are done to understand how to design a product and its packaging, such that product has appropriate physical, chemical and microbiological properties during a defined shelf life when stored and used.

Storage conditions

The selected formulations were subjected for three month stability study as per ICH guidelines**.** The selected formulations were placed in a wide mouth glass bottles, mouth of the bottle was tightly closed and packed in aluminum foils. In the present study, stability studies were carried out at 25ºC/60% and 40ºC/75% RH for a specific period of 3 months for the selected formulations.

RESULTS AND DISCUSSION

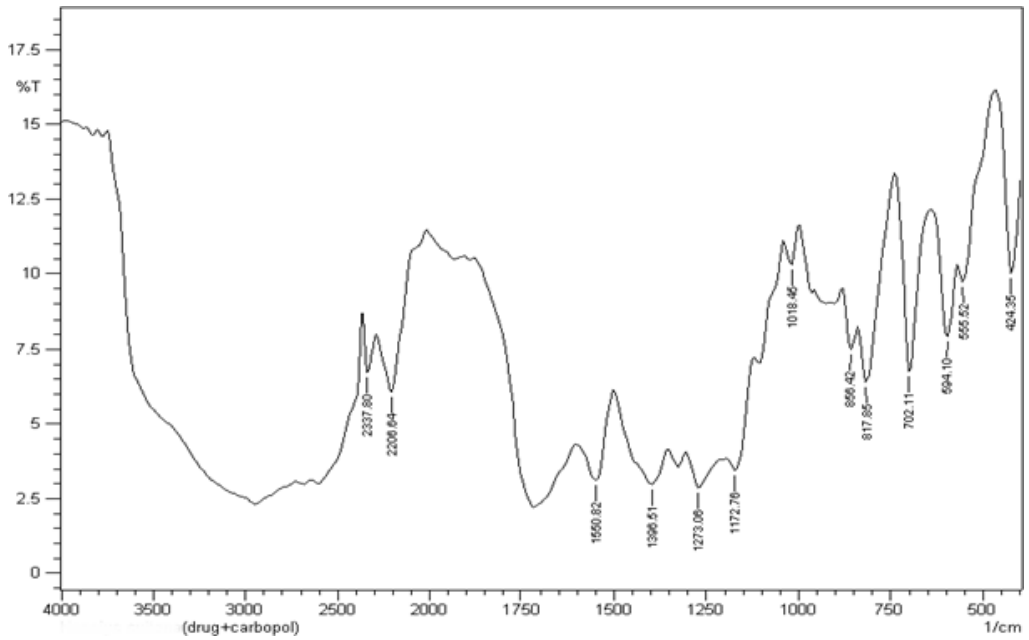

Fig 1: IR Spectrum of Pure Drug Losartan

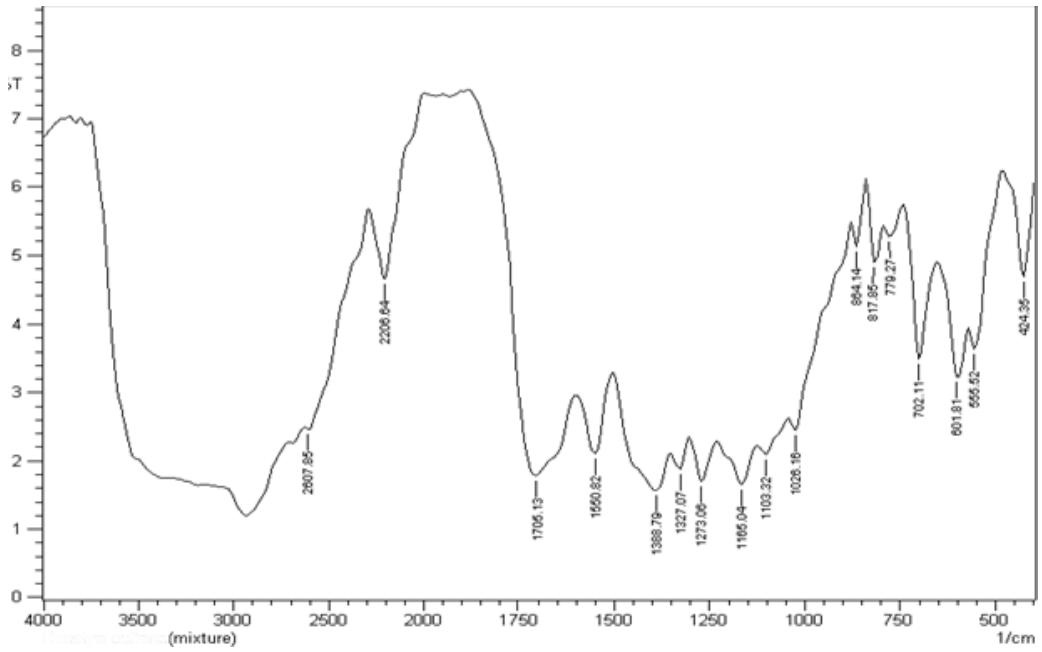

Fig 2: IR Spectrum of carbopol

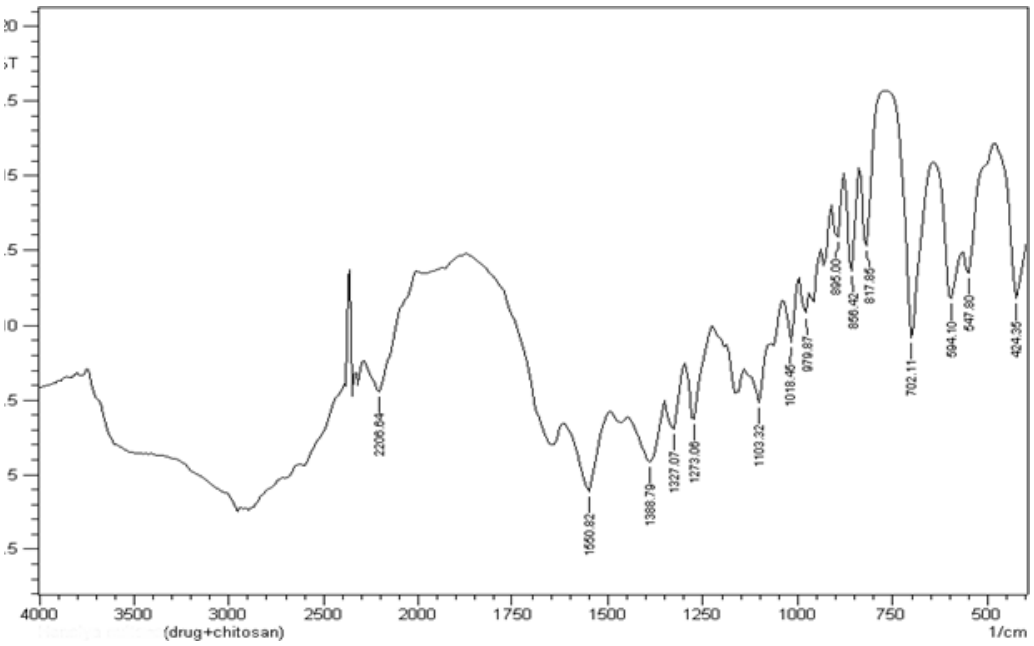

Fig 3: IR Spectrum of Chitosan

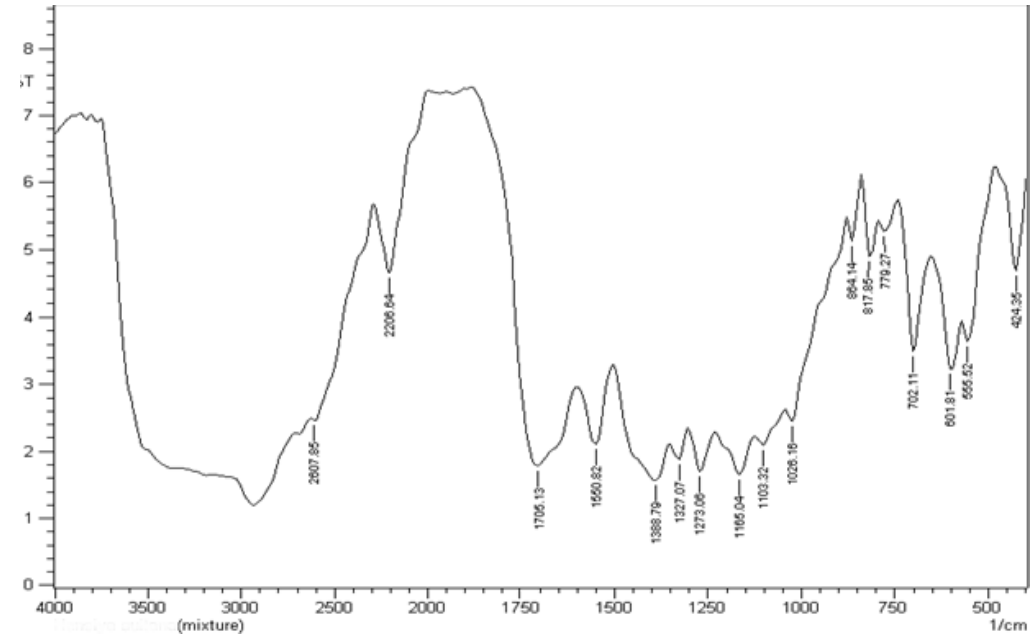

Fig 4: IR Spectrum of Drug + Physical mixtures

Formulation Design

The main aim of present study was to formulate sustain release matrix tablets of Losartan using chitosan in order to improve its therapeutic efficacy and decrease the adverse effects by minimizing the dosing frequency. In this case nine formulations of sustain released matrix tablets were prepared by using different polymers such as Chitosan, Sodium alginate, Carbapol, MCC and PVP K_{30} in different ratios. The powder mixture was subjected to pre-compression and post-compression evaluation before and after compression.

Evaluation Parameters

Evaluation of powder blended characteristics of matrix tablet formulation of Losartan

For each type of formulation, blends of Losartan and other excipients were prepared and evaluated for various parameters such as bulk density, tapped density, Carr‟s compressibility index, Hausner‟s ratio and angle of repose. Bulk density was found in the range of 0.356-0.3851 g/cm^3 and the tapped density between 0.4102-0.4881g/cm^3 indicating both parameters were found to be within the limits. Using the above two density data, Carr‟s compressibility index were calculated. The

compressibility index and Hausner"s ratio was found in the range of 7.28-18.42 % and 1.056-1.23 respectively indicating that all powder blends showed excellent to acceptable flow properties. The flow property of all powder blends was better explained from angle of repose. The angle of repose was found in the range of 25.34-31.35°. The results of angle of repose showed all powder blends exhibited good to acceptable flow property. The results of pre-compression parameters are shown in table 1.

Table 1: Evaluation parameters of pre-formulation characteristics of powder blend

Formulations Number	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (θ)
F1	0.3726±0.0012	0.4102±0.0015	7.28±0.168	1.179±0.0086	29.72 0.40
F2	0.3811±0.0006	0.4119±0.0016	7.60±0.235	1.056± 0.0070	25.34 0.61
F3	0.3851±0.0016	0.4121±0.002	7.44±0.896	1.058±0.0098	28.45 0.34
F4	0.374±0.0021	0.4269±0.0024	13.881.386	1.074±0.0083	27.49 0.55
F5	0.356±0.0018	0.4611±0.0034	17.29±0.794	1.223±0.015	31.35 0.16
F6	0.3811±0.0047	0.4881±0.0076	18.50±0.120	1.23±0.0026	28.27 0.48
F7	0.3851±0.0084	0.4383±0.143	10.90±0.080	1.124±0.0031	27.28±0.47

Table 2: Post-compression parameters results

Formulation	Diameter (mm)± SD	Thickness (mm)± SD	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	7.81±0.013	3.7±0.098	251.88±0.13	7.2±0.05	0.62±0.008	98.35±0.045
F2	7.90±0.005	4.1±0.03	252.87±0.61	7.9±0.04	0.51±0.006	100.41±0.027
F3	7.83±0.008	4.2±0.02	252.13±0.53	8.1±0.06	0.59±0.035	98.64±0.08
F4	7.82±0.021	3.9±0.08	250.82±0.14	6.6±0.05	0.71±0.017	99.65±0.079
F5	8.1±0.014	4.1±0.05	251.81±0.33	6.7±0.09	0.655±0.08	99.38±0.061
F6	7.93±0.011	3.8±0.07	249.93±0.45	7.2±0.04	0.709±0.07	98.98±0.069
F7	7.96±0.015	4.1±0.06	251.62±0.61	6.1±0.06	0.451±0.01	102.21±0.07

In-vitro drug release study

In this study carbopol was chosen as polymer and it was combined with chitosan and sodium alginate to explore their sustain release capability. The *in-vitro* release data for chitosan-carbopol and sodium alginate-carbopol based Losartan sustain released matrix tablets are represented in table 17 and illustrated in figure 5. The *in-vitro* release of Losartan, from prepared matrix tablets formulations was mainly affected by dissolution medium, concentration of chitosan, concentration of sodium alginate and concentration of polymers. *The in-vitro* release of Losartan form prepared matrix tablets also depends on swelling behaviour of the tablets, higher the tablet swells comparative the lesser amount of drug release. The *in-vitro* release study was performed in 0.1 N HCl for initial first 2 hrs, and then the medium was replaced by phosphate buffer pH 6.8) and study was continued for 24 hour. The *in-vitro* release of Losartan was higher in first 6-7 hours in all formulations. After 1 hour, approximately 11.39%- 19.54% of Losartan from chitosan-carbapol tablets, 17.10%- 22.11% from sodium alginate-carbapol, 26.22% from tablets containing only release retardant polymer has been released. Initially amount of drug release was higher but after 6-7 hrs drug release was retarded. Formulation F_1 do not contains any crosslinking agent, so almost all drugs was released at the end of 12 hrs. Formulation F_2, F_3, F_5, and F_7 containing lower concentration of chitosan and sodium alginate showed almost all drug release within 16 hrs, 20 hrs, 16 hrs and 18 hrs respectively. Thus these formulations were not considered as good formulation as the maximum amount of drug was released before desire period of time i.e. 24 hrs. The ionic interaction between crosslinking agents and negatively charged polymers was greatly reduced at this pH 6.8 and forms a loose network with increase porous surface which allows great part of dissolution media. Formulation F_4 and F_7 containing highest concentration of chitosan and sodium alginate respectively along with carbopol gum respectively prolong the release of Losartan to 24 hrs which might be due to the fact that the self-assembled poly electrolyte complexes film was formed on the surface of cross linking agent-polymer based system. Swelling study also showed that formulation which contains higher concentration of cross linking agent showed higher swelling capacity and prolonged the drug release to 24 hrs.

Table 3: *In-vitro* drug release profile of Losartan sustain release matrix tablets

Time (Hrs)	Cumulative Percentage Drug Release						
	F_1	F_2	F_3	F_4	F_5	F_6	F_7
0	0	0	0	0	0	0	0
1	26.22±0.09	19.54±0.43	14.356±0.33	11.39±0.55	22.11±0.54	17.95±0.32	17.10±0.85
2	41.12±0.12	28.94±0.31	27.105±0.45	25.14±0.62	29.82±0.43	29.85±0.22	25.80.128
4	59.12±0.14	36.15±0.33	30.965±0.21	30.98±0.53	39.40±0.54	35.10±0.64	34.11±0.61
6	71.91±0.14	49.01±0.2	47.017±0.13	42.14±0.45	52.04±0.11	49.02±0.13	42.05±0.24
8	81.01±0.21	60.09±0.14	51.196±0.99	47.99±0.89	64.03±0.15	60.98±0.15	53.98±0.24
10	90.61±0.14	67.96±0.95	64.17±0.02	60.68±0.11	73.06±0.12	70.02±0.18	60.97±0.43
12	99.08±0.52	78.01±0.66	72.03±0.74	62.88±0.98	80.93±0.82	78.03±0.15	76.04±0.33
14	--	86.16±0.36	75.90±0.15	74.91±0.93	88.97±0.91	87.24±0.12	83.17±0.12
16	--	91.95±0.63	87.06±0.62	84.09±0.26	96.09±0.12	91.58±0.77	89.05±0.14
18	--	99.91±0.92	91.08±0.19	86.31±0.71	98.97±0.99	96.02±0.73	93.03±0.18
20	--	--	98.44±0.53	93.48±0.25	--	99.78±0.78	94.90±0.18
24	--	--	--	99.83±0.21	--	--	97.24±0.38

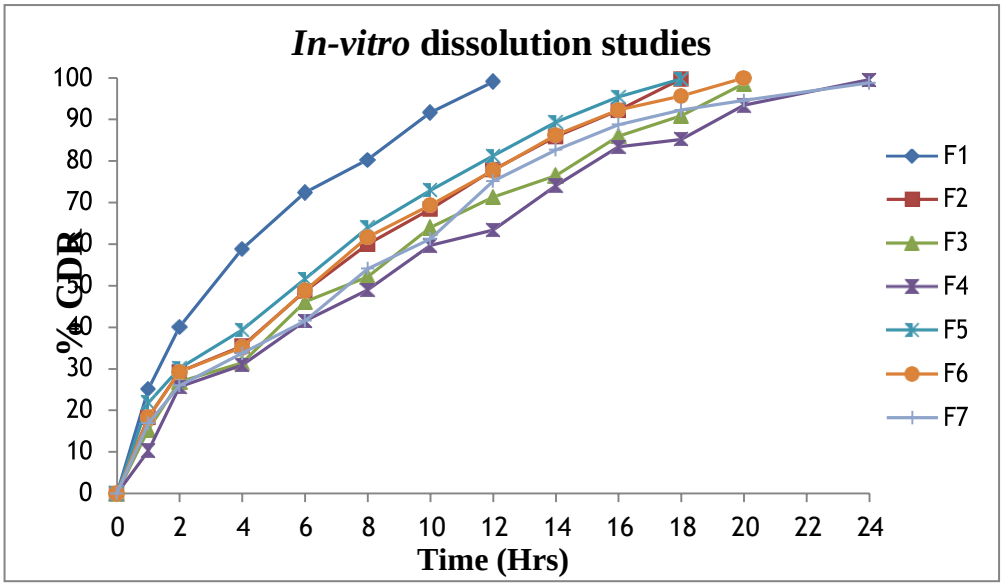

Fig 5: Comparative dissolution profile of the formulations F_1 to F_7

Stability studies

Based on the results of *in-vitro* drug release two best formulations F_4 and F_7 were selected for three month stability studies at 25ºC/60% RH and at 40ºC/75% RH. The stability studies were conducted according to the method described in section four. The selected formulations were evaluated for physical appearance, hardness, friability, and drug content and *in-vitro* drug release. The results showed that there was no significant change in physical appearance, hardness, friability, drug content and drug release profile throughout the study period. Three months of stability studies revealed that; there was no any significant degradation of the drug. Thus prepared formulations were physically and chemically stable. The result of stability studies were tabulated in table 4,5.

Table 4: Results of stability studies for formulation F_4 stored at 25ºC/60% and 45ºC/75% RH

Storage period	Stored at 25ºC/60% RH				Stored at 40ºC/75% RH			
	Formulation F_4				Formulation F_4			
	Hardness Kg/cm^2	% friability	% Drug content	% CDR	Hardness Kg/cm^2	% friability	% Drug content	% CDR
Initial	8.1±0.08	0.57±0.2	99.57±0.4	99.6±0.4	8.1±0.07	0.59±0.3	99.7±0.4	99.6±0.3
After 1 month	7.8±0.13	0.61±0.4	98.74±0.2	99.3±0.4	7.7±0.089	0.62±0.2	98.6±0.3	99.1±0.4
After 2 month	7.9±0.45	0.66±0.1	97.87±0.3	98.5±0.4	7.6±0.08	0.65±0.4	97.5±0.2	98.4±0.3
After 3 month	7.7±0.14	0.63±0.2	97.96±0.5	98.1±0.4	7.5±0.06	0.67±0.2	97.2±0.4	97.7±0.1

Table 5: Results of stability studies for formulation F_7 stored at 25ºC/60% and 45ºC/75% RH

Storage period	Stored at 25ºC/60% RH				Stored at 40ºC/75% RH			
	Formulation F_7				Formulation F_7			
	Hardness Kg/cm^2	% friability	% Drug content	% CDR	Hardness Kg/cm^2	% friability	Drug content	% CDR
Initial	6.7±0.07	0.55±0.3	101.8±0.4	98.7±0.5	6.5±0.08	0.56±0.4	96.7±0.3	98.4±0.6
After 1 month	6.6±0.16	0.58±0.4	99.7±0.2	98.6±0.5	6.5±0.12	0.56±0.2	96.6±0.3	98.6±0.4
After 2 month	6.4±0.23	0.61±0.5	99.6±0.3	98.3±0.5	6.3±0.23	0.58±0.3	96.3±0.3	97.7±0.3
After 3 month	6.1±0.14	0.63±0.4	98.5±0.7	97.8±0.5	6.1±0.24	0.62±0.4	96.1±0.3	97.6±0.2

CONCLUSION

Losartan is a potent, orally active non peptide tetrazole derivative and selectively inhibits Angiotensin II Receptor type 1 which causes reduction in blood pressure and is used in treatment of hypertension. The objective of the present study was to investigate the possibility of sustaining the Losartan release from matrix tablet prepared by using different concentration of cross linking agents and polymers.

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