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Formulation and evaluation of floating *in situ* gelling system of losartan potassium

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ABSTRACT

The present investigation deals with the formulation and evaluation of sodium alginate and pectin based In situ gel of Losartan Potassium. Sodium alginate and guar gum were used as a polymer and $CaCO_3$ was used as a cross-linking agent. The formulation of gel depends upon factors like temperature modulation, pH changes, presence of ions and ultra-violet irradiation, from which drug gets released in sustained and controlled manner. The objective of this study was to develop a novel in- situ gel. The system utilizes polymers that exhibit sol-to-gel phase transition due to change in specific Physico-chemical parameters. In-situ gel was formed at a biological pH. In vitro release studies were conducted in simulated gastric fluid and cumulative amount of drug release was analyzed by spectrophotometry. From designed set of experiments, it was evident that formulation containing 2% of sodium alginate and 1.5% of Guar gum control the release of drug for longer duration. The in-situ gel exhibited the expected, viscosity, drug content, pH, in vitro gelling capacity, in vitro floating ability and sustained drug release. The drug release from the in situ gels follows the Fickian diffusion type of release.

Keywords: Losartan potassium, floating drug delivery, natural biodegradable polymers.

INTRODUCTION

Gastroretentive Drug Delivery Systems [1]

Controlled and sustained drug delivery has become the standard in modern Pharmaceutical design and an intensive research have been undertaken in achieving much better drug product effectiveness, reliability and safety. The high level of patient compliance in taking oral dosage forms is due to the ease of administration and handling of these forms. In the development of oral controlled drug delivery system, one of the main challenges is to modify the GI transit time. Gastric emptying of pharmaceuticals is highly variable and is dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence times usually range between 5 minutes and 2 hours. In The transit of dosage forms is characterized by four phases: (A. A. Deshpande et al.,).

Phase I: Period of no contraction (40-60 minutes),
Phase II: Period of intermittent contractions (20-40 minutes),
Phase III: Period of regular contractions at the maximal frequency that travel distally. (10-20 minutes) and
Phase IV: Period of transition between phase III and phase I (0-5 minutes).

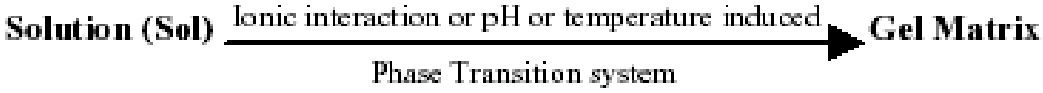
Drugs having a short half-life are eliminated quickly from the blood circulation. Furthermore, improved bioavailability is expected for drugs that are absorbed readily upon release in the GI tract. These drugs can be delivered ideally by slow release from the stomach. Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making

traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine.

Different Techniques of Gasroretention [2, 3, 4]
Various techniques were used to encourage gastric retention of an oral dosage form:
• Hydro dynamically balanced systems (HBS).
• Effervescent system.
• Low-density systems.
• Raft systems incorporate alginate gels.
• Bioadhesive or mucoadhesive systems.

Floating Drug Delivery Systems [5]
Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. This delivery systems is desirable for drugs with an absorption window in the stomach or in the upper small intestine[6]. This have a bulk density less then gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly as a desired rate from the system. After release of drug, the residual system is emptied from the stomach.

Oral Floating Insitu Gels[6-10]
In situ gel, or in vivo gel, environment sensitive gel is a new dosage form, which has been used in stomach-specific drug delivery recently. Oral administration of in situ gels as low viscosity solution and upon contact with the simulated gastric fluid, the polymer changes conformation producing a gel, so it cannot only prolong the contact time between the drug and the absorptive sites at the stomach, but also release drug slowly and continuously.(Shi-lei C et al.,)



Different Approaches of *In situ* Gelling [11]
There are different mechanisms used for triggering the in situ gel formation

In situ formation based on physical mechanism
➢ **Swelling and Diffusion[12]**
Swelling of polymer by absorption of water causes formation of gel. Certain biodegradable lipid substance forms in situ gel under such phenomenon.

Ex: Myverol 18-99 (glycerol mono-oleate)
Solution of polymer such as N – methyl pyrrolidone (NMP) involves diffusion of solvent from Polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. (Motto F et al.,)

In situ gelling based on chemical stimuli
➢ **Ionic cross-linking[13]**
Certain ion sensitive polysaccharides undergo phase transition In presence of various ions such as k+ , Ca+, Mg+, Na+**.**
Eg: carrageenan, Gellan gum (Gelrite®), Pectin, Sodium Alginate
Alginic acid undergoes gelation in presence of divalent/polyvalent cations e.g. Ca2+ due to the interaction with guluronic acid block in alginate chains.

➢ **Enzymatic cross-linking[14]**
Cert ain natural enzymes which operate efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators provides a convenient mechanism for controlling the rate of gel formation, which allows the mixtures to be injected before gel formation in situ.

➢ **Photo-polymerization[15]**
A solution of monomers such as acrylate or other polymerizable functional groups and initiator such as 2,2 dimethoxy-2-phenyl acetophenone, camphorquinone and ethyl eosin can be injected into a tissues site and the application of electromagnetic radiation used to form gel designed readily to be degraded by chemical or enzymatic processes or can be designed for long term persistence in vivo. Typically long wavelength ultraviolet and visible wavelengths are used.

- **In situ gel formation based on physiological stimuli**

- Temperature dependant in situ gelling[**16]**

These are liquid aqueous solutions before administration, but gel at body temperature. These hydrogels are liquid at room temperature (20ºC -25ºC) and undergo gelation when in contact with body fluids (35ºC -37ºC), due to an increase in temperature This approach exploits temperature-induced phase transition. At the LCST, hydrogen bonding between the polymer and water becomes un favorable, compared to polymer–polymer and water–water interactions, and an abrupt transition occurs as the solvated macromolecule quickly dehydrates and changes to a more hydrophobic structure. Alternatively, some amphiphilic polymers, that self-assembles in solution, show micelle packing and gel formation because of polymer–polymer interactions when temperature is increased. Temperature-

pH dependant gelling

Another formation of in situ gel is based on change in pH. Certain polymers such as PAA (Carbopol®, Carbomers) or its derivatives, polyvinylacetal diethylaminoacetate (AEA), Mixtures of poly (meth acrylic acid) (PMA) and poly (ethylene glycol) (PEG) shows change from sol to gel with change of pH. The polymers with a large number of ionizable groups are known as polyelectrolytes. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups.

The aim of this study is to develop a oral floating insitu gels containing Losartan Potassium To achieve the aim the drug is dispersed in polymer solution, which undergoes gelation in gastric pH. Calcium carbonate added to the formulation provides calcium ions and carbon dioxide. Calcium ions, due to ion interactions with the polymer, help in gelation. Carbon dioxide entraps in the gel and facilitates buoyancy of the gel.

MATERIALS AND METHODS

List of chemicals used

Table No:-1

SI.NO	Materials	Property	Supplier
1.	Losartan potassium	Anti hypertensive	Kwality pharmaceuticals pvt.ltd
2.	Guar gum	Gum	SD fine chem. India
3.	Sodium alginate	Gum	SD fine chem. India
4.	Calcium carbonate	Complexing agent	Brass scientificals
5.	Methyl paraben	Anti-fungal agent	GlaxoSmithKline pharmaceuticals ltd
6.	Propyl paraben	Anti-microbial agent	GlaxoSmithKline pharmaceuticals ltd

List of instruments

Table No:-2

S.NO	Instruments	Model	Manufacturer
1	Electronic Weighing balance	ELB300	Shimadzu
2	Magnetic stirrer	7 MLH	Remi equipments pvt ltd
3	pH Meter	L1/613	Elico
4	UV-Visible spectrophotometer	UV-L700	Shimadzu
5	Dissolution apparatus	TDL-08L	Electrolab
6	FT-IR	FTIR-8400 S	Shimadzu, Japan

METHODOLOGY [18-40]

PREFORMULATION STUDIES

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as 'investigation of physical and chemical properties of the drug substance alone and when combined with excipients. These studies should focus on those physicochemical properties of the new compound that could affect drug performance and development of an efficacious dosage form. (Sharma Y R et al.,)

Raw Material Analysis

Solubility analysis [41]

Solubility is an important parameter for Preformulation studies because:

- It affects the dissolution of drug.
- Bioavailability of drug is directly affected by dissolution and absorption of drug by oral administration.

- Particle size, shape, surface area may affects the dissolution characteristics of drug hence it should be determined during Preformulation.(Thilek Kumar M et al.,)

Method: Appropriate quantity of drug was weighed and added to the suitable volume of solvent and carried out as per the procedure.

Melting point [42]
The melting point of Active ingredient was determined by capillary method, using definite quantity of active taken and placed in apparatus and determined the melting point and matched with the standards. (Lachman L et al.,)

7.2. MICROMERITIC PROPERTIES OF PURE DRUG LOSARTAN POTASSIUM [43]

- **Bulk density (D_b)**

The bulk density of the formulated granules was evaluated using a bulk density apparatus. It is the ratio of to total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a graduated measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

$$D_b=M/V_b$$

Where, M - Mass of the powder
V_b – Bulk volume of the powder.

- **Tapped density (D_t)**

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gram/ml and is

$$D_t =M/V_t$$

Where, M - Mass of the powder
V_t – Tapped volume of the powder.

- **Compressibility index (I) and Hausner's ratio**

Carr's index and Hausner's ratio measure the propensity of granule to be compressed and the flow ability of granule. Carr's index and Hausner's ratio were calculated using following formula.

$$C.I = (D_t – D_b)\ 100/D_t$$

Where, D_t – Tapped density of the powder
D_b – Bulk density of the powder

- **Hausner's ratio**

$$\text{Hausner's ratio} = D_t/D_b = V_b/V_t$$

Where, D_t – Tapped density of the powder
D_b – Bulk density of the powder

- **Angle of repose**

The frictional forces in a loose powder can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Sufficient quantities of Losartan potassium granules were passed through a funnel from a particular height (2 cm) onto a flat surface until it formed a heap, which touched the tip of the funnel. The height and radius of the heap were measured. The angle of repose was calculated using the formula. (Sharma Y R et al.,)

$$\text{Angle of repose } ø = \tan^{-1} (h/r)$$

Where, h – Height of the pile
r – Radius of the pile

Drug- Excipient Compatibility Study
The compatibility of drug and formulation components is important prerequisite for formulation development. It is therefore necessary to confirm that the drug does not interact with excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

Goal of excipient compatibility studies are:

- To identify excipients that are compatible with the active ingredient which do not have any impact on the stability of active ingredient.
- To assign relative risk level to each excipient within a functional class.
- To expect a stabilizer to interpose at these points of contact on a random basis is rather simplistic. Because solid state reactions are generally heterogeneous reactions which occur only at points of contact between drug and excipients.

METHOD

Compatibility studies conducted to investigate and predict physico chemical interaction between drug substance and excipients and therefore to select suitability of chemically compatible excipients. Compatibility studies were performed by preparing compatibility blends at different ratios of different excipients with drug based on tentative average weight. These blends were stored at accelerated conditions at 40^0c, 75%RH for one month. The control samples were stored at 4^0c the ratio of drug and excipient varies from 11 to 110 depending on the purpose of use and samples were kept in double lined poly bags .the samples were evaluated for any change in physical characteristics. Samples were evaluated for any change in physical characteristics with reference to controlled sample stored at 4^oc for 30 days. Taken out at two weeks interval and were subjected to physical and chemical testing and results were noted. Chemical compatibility is tested by FTIR spectrometry, which is most powerful technique to identify functional groups of the drug.

Drug Excipient Ratio for Compatibility Studies

Table no:-3

S.NO	API and Excipients	API: Excipients	Initial Observation	Final observation 40°C,75%RH	
				2nd week	4th week
1	API + sodium alginate	1 :5	White or almost white crystalline powder	White or almost white crystalline powder	White or almost white crystalline powder
2	API+ Guar gum	1 : 5	White colour	White colour	White colour
3	API +$CaCO_3$	1 : 5	White colour	White colour	White colour
4	API+ Methyl paraben	1 : 5	White colour	White colour	White colour
5	API + Propyl paraben	1 : 0.1	Yellow colour	Yellow colour	Yellow colour

Preparation of oral floating gels of losartan potassium[44]

Losartan potassium was passed through sieve no #60 in order to break lumps, if any present, other polymers like sodium alginate, guar gum, and calcium carbonate were passed through sieve no # 40, to form free flowing powder. In order to protect solutions from microbial contamination and degradation, distilled water was boiled for sufficient period. At methyl paraben and propyl paraben (9:1 ratio) were added and allowed to cool to room temperature. Both solutions were prepared separately over mechanical stirrer and mixed to form final solution.

Accurately weighed quantity of drug was added to this polymer solution and stirred thoroughly for 10-15mins. Pre-weighed quantity of calcium carbonate was added with continuous stirring. And mixing was continued for 15-20 min. The solution so formed was sonicated for 10 min. In order to find the most suitable combination of guar gum, sodium alginate polymers, initial trials were done on individual polymers followed by combination of polymers. These amounts were increased till thick. Viscous solution was obtained. This solution was finally stored in amber coloured bottles until further use. This set of experiments was used to find most suitable viscosity of formulation for handling the formulation.

Composition of optimization formulation FG-1 TO FG-9

Table No:-4

	FG-1	FG-2	FG-3	FG-4	FG-5	FG-6	FG-7	FG-8	FG-9
Losartan potassium	50	50	50	50	50	50	50	50	50
Guar gum	500	500	1500	1000	1500	500	1000	1000	1500
Sodium alginate	1500	2500	2500	2500	2000	2000	2000	1500	1500
Calcium carbonate	2000	2000	2000	2000	2000	2000	2000	2000	2000
Methyl paraben	180	180	180	180	180	180	180	180	180
Propyl paraben	20	20	20	20	20	20	20	20	20
Purified water	100ml	100ml	100ml	100ml	100ml	100ml	100ml	100ml	100ml

Evaluation Parameters [45]

Gel strength

Gel strength is calculated using the gel strength apparatus. It contains two tubes; upper tube is attached with pan through thread in which weights are added. Two surfaces are tightly covered with egg membrane. 1 gm of gel was kept between the two surfaces. The weights are added into pan. The weight at which the two surfaces detach is noted and the gel strength is calculated by using formula:

$$\text{Gel strength} = Mg/a$$

M: Weight at which the two surfaces detaches
g: gravitational force
a: Area of surfaces

In-vitro buoyancy

The in-vitro buoyancy study was performed using the USP dissolution apparatus II, model USP TDL-08L with 500 ml of simulated gastric fluid (pH = 1.2). The medium temperature was kept at 37^{o}C. A 10 ml sample of the prepared solution (in-situ gelling formulation) was drawn up with the help of a disposable syringe and placed into a Petri dish. Then, the Petri dish was placed in the dissolution vessel containing the medium without much turbulence. The time for the gel to come to surface (floating lag time) and the time the gel remained floated on the medium surface (floating time) were recorded.

In-vitro gelling capacity

To evaluate the formulations for their in-vitro gelling capacity by visual method, coloured solutions of in situ gel forming drug delivery system were prepared. The in-vitro gelling capacity of prepared formulations was measured by placing five ml of the gelation solution (0.1N HCl, pH 1.2) in a 15 ml borosilicate glass test tube and maintained at 37±1^{o}C temperature. One ml of coloured formulation solution was added with the help of pipette. The formulation was transferred in such a way that places the pipette at surface of fluid in test tube and formulation was slowly released from the pipette. As the solution comes in contact with gelation solution, it was immediately converted into stiff gel like structure. The gelling capacity of solution was evaluated on the basis of stiffness of formed gel and time period for which they formed gel remains as such. Colour was added to give visualized appearance to formed gel. The in-vitro gelling capacity was graded in three categories on the basis of gelation time and time period for which they formed gel remains.

(+) Gels after few minutes, dispersed rapidly
(++) Gelation immediate remains for 12 hours
(+++) Gelation immediate remains for more than 12 hours

In-vitro drug release study

The study of the Losartan potassium release from the in-situ gelling preparation was carried out with some modification using USP dissolution test apparatus II with paddle stirrer; model USP TDL-08L at a rate of 50 rpm. The slow speed prevented breaking of the gelled formulation and ensured a low level of agitation. The dissolution medium used was 500 mL of a 0.1 N solution of HCl (pH = 1.2), and the temperature was kept at 37^{o}C. A 10 mL sample was withdrawn using a disposable syringe; the needle was then wiped clean and the excess sample removed from the needle end. The sample was then gently transferred into a petridish which was then immersed into the dissolution medium without much turbulence. At 1 hr intervals, an accurately measured sample of the dissolution medium was removed for analysis and replaced with the same amount of the pre-warmed (37^{o}C) fresh medium. The absorbance of the sample was measured at 294 nm using a UV spectrophotometer for analysis of Losartan potassium. Each experiment was performed for a period of 8 hr in triplicate.

Evaluation of invitro release kinectics

To study kinetices data obtained from invitro relesase were plotted in various kinetic models.

- **Zero-order equation**

$$\%R = Kt$$

This model represents an ideal release profile in order to achieve the pharmacological prolonged action. This is applicable to dosage forms like transdermal systems, coated forms, osmotic systems, as well as matrix tablets with low soluble drugs.

➢ **First order equation**

$$\text{Log\% unreleased} = Kt / 2.303$$

This model is applicable to study hydrolysis kinetics and to study the release profiles of pharmaceutical dosage forms such as those containing water soluble drugs in porous matrices.

➢ **Higuchi equation**

$$\%R=Kt^{0.5}$$

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drug.

➢ **Hixson and Crowell equation**

$$(\%\text{unreleased})^{1/3} = Kt$$

This expression applies to pharmaceutical dosage forms such as tablets, where the dissolution occurs in planes that are parallel to drug surface if the tablet dimensions diminish proportionality in such a manner that the initial geometrical form keeps constant all the time. When this model is used, it is assumed that release rate is limited by drug particles dissolution rate and not by diffusion that might occur through the polymeric matrix.

➢ **Korsmeyer-Peppas equation :**

$$\%R=Kt^{n}$$

This model is widely used, when the release phenomenon could be involved. The end value could be used to characterize different release mechanisms as

Table No:-5

N	Mechanism
0.5	Fickian diffusion(Higuchi matrix)
0.5<n<1	Anomalous transport
1	Case- II transport(zero order release)
n>1	Super case- II transport

RESULTS

Preformulation Studies
Solubility Analysis
The Losartan potassium was found to be freely soluble in water. The data demonstrate that from pH 0.6 to 6.8, the solubility of Losartan potassium is essentially constant (approximately 100 mg/mL). Losartan potassium is considered soluble to freely soluble in this pH range, as defined by USP nomenclature.

PHYSICAL PARAMETERS OF LOSARTAN POTASSIUM

Table No: 6

S.NO	Parameters	Results
1	Angle of repose	28^0
2	Bulk density	0.297gm / ml
3	Tapped density	0.53gm / ml
4	Compressibility index	36.9%
5	Hausner's ratio	1.4

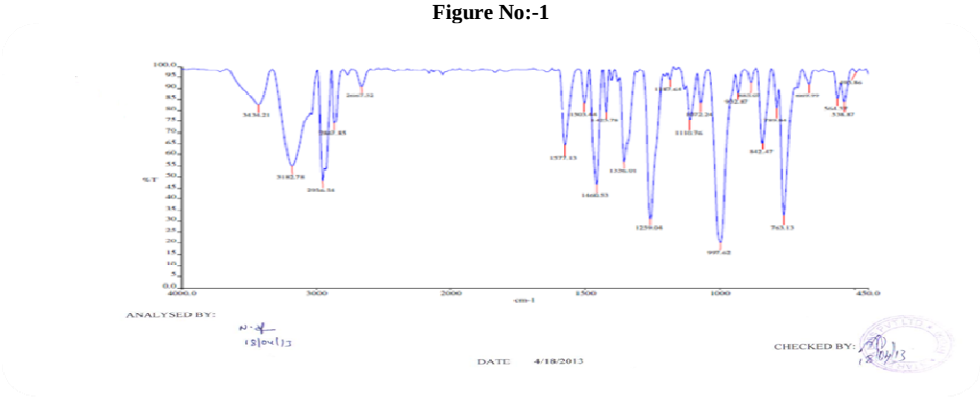
DRUG- EXCIPIENT COMPATIBILITY STUDIES

Table No:-7

S. No	API and Excipients	API: Excipients	Initial Observation	Final observation 40°C,75%RH		Conclusion
				2nd week	4th week	
1	API+ sodium alginate	1 :5	No change in appearance	No change in appearance	No change in appearance	Compatible
2	API+ Guar gum	1 : 5	No change in appearance	No change in appearance	No change in appearance	Compatible
3	API +$CaCO_3$	1 : 5	No change in appearance	No change in appearance	No change in appearance	Compatible
4	API+ Methyl paraben	1 : 5	No change in appearance	No change in appearance	No change in appearance	Compatible
5	API + Propyl paraben	1 : 0.1	No change in appearance	No change in appearance	No change in appearance	Compatible

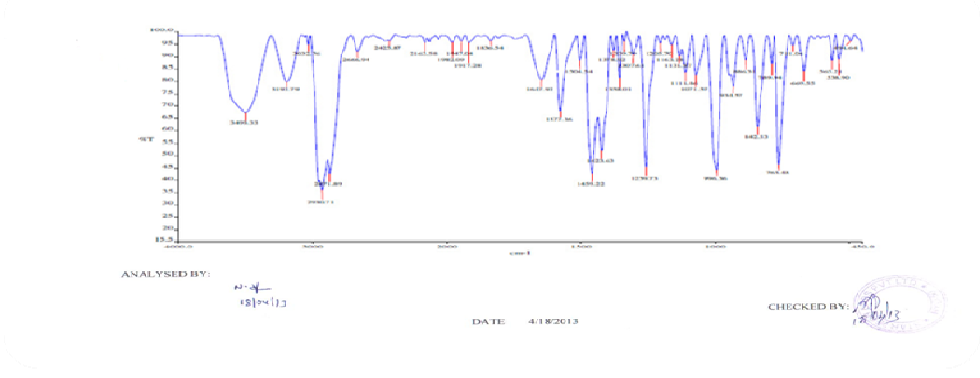
IR PURE DRUG (LOSARTAN POTASSIUM)

Figure No:-1



IR PURE DRUG (LOSARTAN POTASSIUM) WITH EXCIPIENTS

Figure No:-2



EVALUATION OF PARAMETERS
BUOYANCY STUDIES

Table No:-8

Formulation	Gel strength (N / m2)	Lag time (min)	Floating time (hr)
F-1	2029.58	<1	>24
F-2	2398.5	<1	>24
F-3	2767.5	<1	>24
F-4	2216.1	<1	>24
F-5	2031.4	<1	>24
F-6	2216.1	<1	>24
F-7	2195.2	<1	>24
F-8	2034.1	<1	>24
F-9	2033.7	<1	>24

Figure No:-3

INFERENCE:
Sol to gel transformation of polymers occurs in the presence of either monovalent or divalent cations in contact with the gastric fluids. The floating ability of the formulations was due to the presence of calcium carbonate. The calcium carbonate effervesced, releasing carbon dioxide and calcium ions. The released carbon dioxide is entrapped in the gel network producing buoyant formulation and then calcium ion reacted with gellan produced a cross linked three-dimensional gel network that might restrict the further diffusion of carbon dioxide and drug molecules and has resulted in extended period of floating and drug release, respectively. The prepared formulations floated more than 24hr[75].

***In-vitro* gelling capacity**
(+) Gels after few minutes, dispersed rapidly
(++) Gelation immediate remains for 12 hours
(+++) Gelation immediate remains for more than 12 hours

Gelling Capacity

Table No:-9

Formulation code	Gelling capacity
F1	+
F2	++
F3	+++
F4	+++
F5	+++
F6	+++
F7	+++
F8	+++

INFERENCE:- For F1 formulation there is no sufficient concentration of sodium alginate was present to form a gel. Hence it was dispersed when added to 0.1N HCL. For all other formulations sufficient concentration of sodium alginate was present to form a gel.

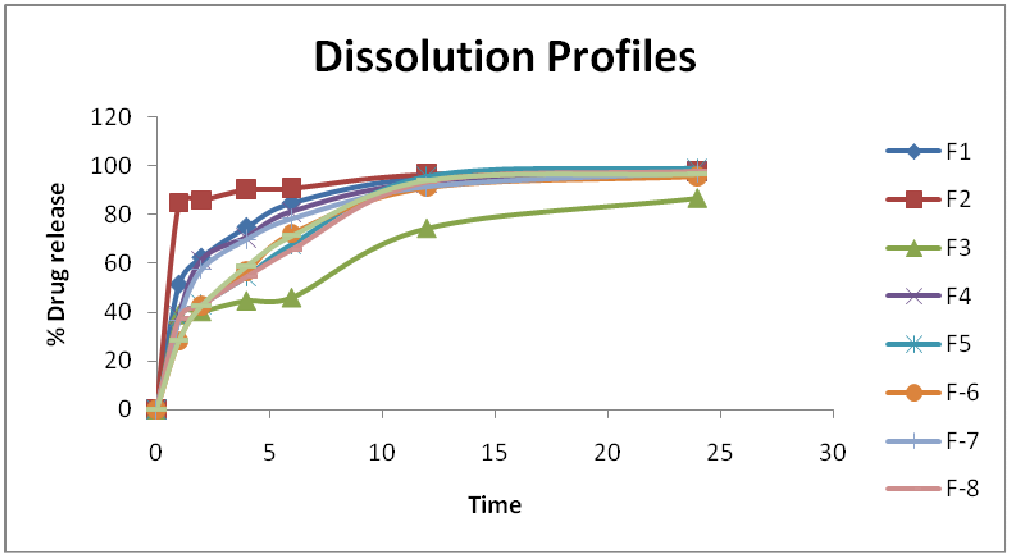
INVITRO DRUG RELEASE PROFILES
INVITRO DRUG RELEASE STUDIES OF DIFFERENT BATCHES

Table No:-10

S.NO	TIME (hr)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
1	0	0	0	0	0	0	0	0	0	0
2	1	51.3	84.8	39.1	38.7	37.6	28.3	36.7	37.6	28.3
3	2	62.4	85.9	40.4	61.47	43.2	42.6	57.47	43.2	42.6
4	4	74.9	90.3	44.8	70.76	54.6	56.96	69.76	54.6	58.96
5	6	84.77	90.8	46.1	81.24	67.7	72.3	78.24	65.7	71.3
6	12	95.22	96.5	74.6	93.36	95.6	91.2	91.36	93.6	94.2
7	24	97.2	97.8	87	98.1	99	95.8	97.1	98	96.8

***In vitro* drug release of different formulations**

Figure No:-4



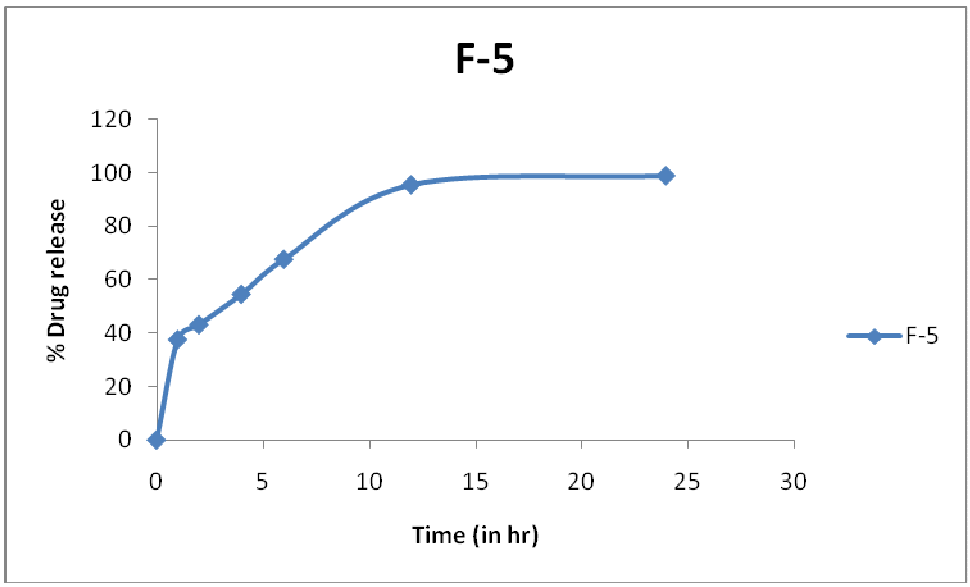
DISSOLUTION PROFILE OF OPTIMISED BATCH (F-5)

Table.No:-11

TIME (hr)	F-5
0	0
1	37.6
2	43.2
4	54.6
6	67.7
12	95.6
24	99

***In vitro* drug release of F5 formulations**

Figure No:-5



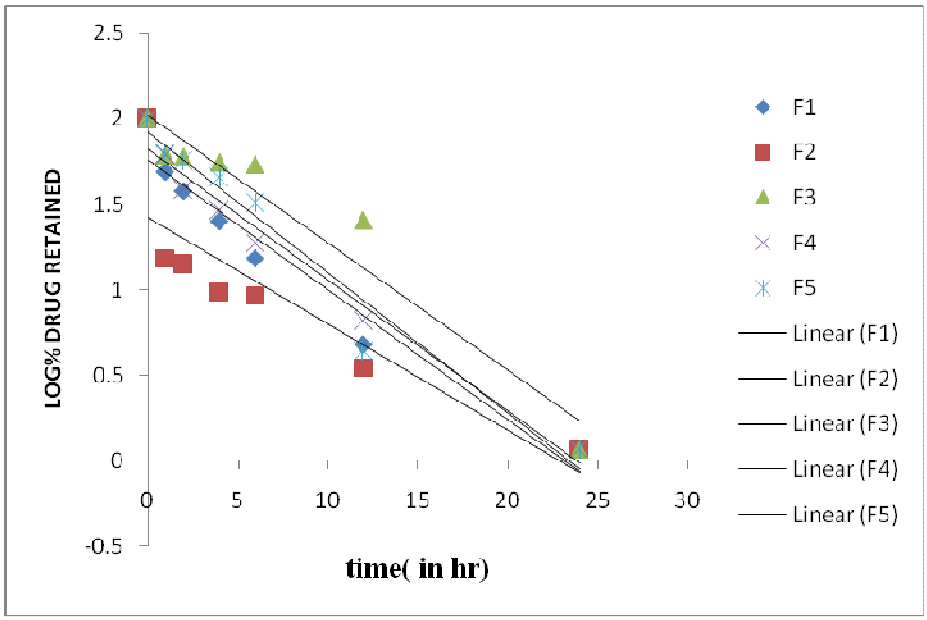
INFERENCE

F1 and F2 intial burst effect was 51.3 and 84.3% and drug release was upto 97.2 and 97.8% respectively at the end of 8h. F3 formulation with high concentration of gellen gum polymer, were intial brust effect was 39.1% and drug release was upto 87% at end of 8h. F4 with equal concentration of sodium alginate and gellan gum, intial brust effect was 38.7% and drug release was 98.1% at end of 8h. F5 and F6 the release was upto 99% and 95.8%. F7 ,F8 and F9 the release was initial burst and effect was 36.7%, 37.6% and 28.3% drug release was up to 97.1%, 98%, and 96.8%. A decrease in the rate and extent of drug release was observed with the increase in polymer concentration in in situ gels and is attributed to increase in the density of the polymer matrix and also an increase in the diffusional path length which the drug molecules have to traverse . Formulation with high concentration of gellan gum has shown decreased rate and extent of drug release with sustained effect. The intial high release and moderate release second, this bi-phasic pattern of release is a characteristic of the matrix diffusion kinetics[73]

INVITRO DRUG RELEASE KINETICS:

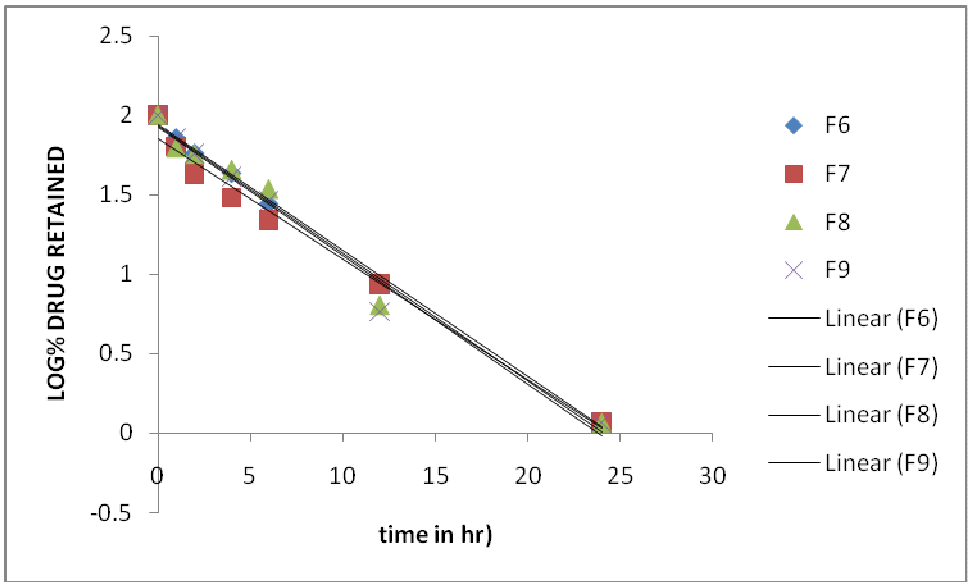
FIRST ORDER PLOT OF F1-F5

Figure No:-6



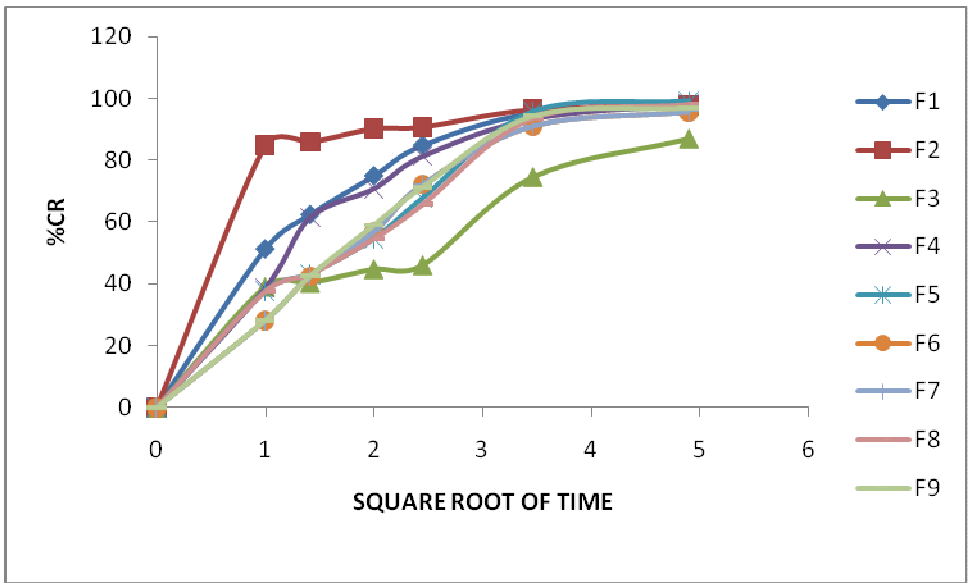
FIRST ORDER PLOT OF F6-F9

Figure No:-7



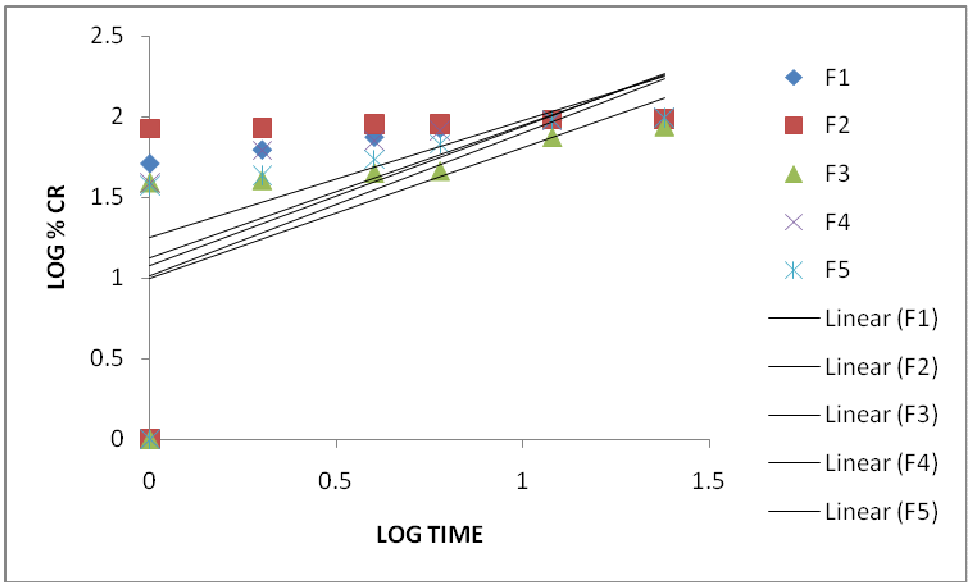
HIGUCHI PLOT OF F1-F9

Figure No:-8



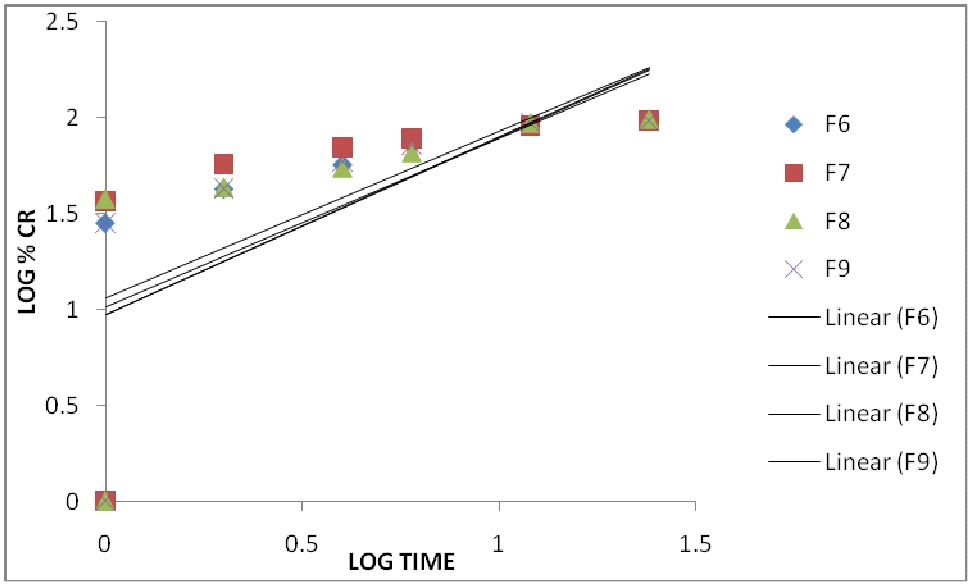
KORSEMEYER PEPPAS F1-F5

Figure No:-9



KORSEMEYER PEPPAS OF F6-F9

Figure No:-10



Release Kinetics Losartan Potassium (F1-F9)

Table No:-12

Model	Paramete	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Zero order	R^2	0.4843	0.4853	0.7506	0.5491	0.7095	0.6838	0.5735	0.7134	0.6826
First order	R^2	0.953	0.7812	0.9358	0.9751	0.9612	0.9972	0.9853	0.9832	0.9829
Higuchi	R^2	0.7732	0.4794	0.9642	0.8251	0.9241	0.9145	0.8442	0.9269	0.9129
Korsmeye Peppas	R^2	0.3671	0.2699	0.4176	0.4108	0.4566	0.494	0.422	0.4534	0.4966
Hixson-crowell	R^2	0.8208	0.5348	0.918	0.8621	0.9028	0.9386	0.8908	0.9284	0.9126

INFERENCE

The order of drug release was found to be first order cube root for all except F-2, in which regression value was close to 1. It was assumed that release rate is limited by drug particles dissolution rate and not by diffusion that might occur through the polymeric matrix. Where F-3 follows Higuchi.

Summary

The objective of this study was to develop and evaluate an oral floating insitu gelling system of Losartan potassium by using guar gum and sodium alginate, for delivery of drug to sustained period of time.

FTIR studies revealed that there was no interaction between Losartan potassium and guar gum and sodium alginate used in the formulation of oral floating insitu gels.

The analytical method used in the present study was found to be suitable for the estimation of Losartan potassium, which was indicated by the high regression values obtained in the standard plots.

The in-vitro drug release study was carried out for prepared oral floating insitu gels. The release profile constituted two different phases.

1. The first phase characterized by a high drug release (burst effect)
2. Followed by second phase that is conversely characterized by a slower release rate.

The order of drug release was found to be First order for all except F3 it follows Higuchi, in which regression value was close to 1.

The microbial studies of prepared oral floating insitu gels are effective compared standard drug.

CONCLUSION

This study showed the feasibility of invitro gel forming from aqueous solutions of sodium alginate and guar gum containing Ca++ ions in a complexed form. The in situ formed gel preserved its integrity without dissolving or eroding for prolonged period to facilitate sustained release of drugs locally. The developed formulations met all prerequisites to become an in situ gelling floating system, gelled, and floated instantaneously in the pH conditions of the stomach. It was observed that the resulting gel remained buoyant for 24 h and slowly released Losartan potassium during the 8 h period. It is concluded that Losartan potassium could be targeted to stomach and be released slowly over a period of time.

Future scope

The long term stability studies required to establish the stability data for these oral floating insitu gels.

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