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FORMULATION AND INVITRO EVALUATION OF GASTRO RETENTIVE INSITU FLOATING GELS OF LOSARTAN POTASSIUM CUBOSOMES

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Abstract:

Losartan Potassium is a BCS class III antihypertensive drug having a very short half-life (almost 2 hours).The aim of the present work is to formulate and evaluate a sustained release formulation of Losartan Potassium cubosomes and gastro retentive in-situ floating gels of cubosomes. The dug, excipients and formulations are characterized by FTIR. Cubosomes are prepared by Top down approach employing Glycerol monooleate (GMO) as lipid phase vehicle, pluronic F127 as stabilizer and water as aqueous phase, Losartan Potassium as active pharmaceutical ingredient. The resultant cubosomal dispersion is evaluated for drug release by diffusion studies, subjected to zeta sizing. Floating gels are prepared in a similar manner to cubosomal dispersions employing gelling agents like sodium alginate, xanthan gum, guar gum, carbopol 940B.P.The resultant gel formulations are evaluated for gelation property, pH, viscosity and %cumulative drug release by diffusion studies. The compatibility studies by IR spectroscopy showed no interaction between the drug and excipients. Different formulations by varying ratios of GMO LPF1(10%), LPF2(20%), LPF3(30%), LPF4(40%), LPF5(50%) were prepared. Cubosome formulation LPF3 containing 30%GMO showed a maximum drug release of 93.3% within 5hours. The concentration of GMO from the above cubosomal formulation (30%) is used in formulation of floating gels and sustained release up to 6 hours was observed in gels formulated with carbopol940, sodium alginate, guar gum, xanthan gum(LPFCNGX). In-vitro release kinetics exhibited sustained release and followed zero order kinetics by the selected formulations and satisfactory pH, viscosity values are obtained. cubosomes formulated with GMO serves as potential gastro retentive sustained drug delivery vehicle. Further sustained release will be achieved when they are formulated as floating gels.

Key-words: *Cubosome, Gastro retentive, in-situ gel, Losartan Potassium, oral drug delivery, GMO.*

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INTRODUCTION:

Cubosomes are discrete, submicron, nanostructured particles of discontinuous cubic crystalline phase. Cubosomes are a type of Lyotropic Liquid Crystals [3]. Lyotropic liquid crystals (LLC) are formed when amphiphilic lipids are added to polar solvents like water. Cubosomes are produced by top down approach. Glycerol monooleate (GMO) is a food drug additive, is a mixture of glycerides of oleic acid and other fatty acids, and has the ability to form lyotropic liquids in the presence of water. Losartan Potassium is a BCS class III antihypertensive drug having a very short half-life (almost 2 hours). In the present study attempt are made to formulate gastro retentive in-situ floating gels of losartan potassium cubosomes. GMO is used as a lipid phase that forms cubosomes when dispersed in water in the presence of pluronic F127. To produce sustained release of an oral liquid formulation could be successfully augmented substantially through a strategy of liquid in-situ floating gel systems [13, 14]. The formed gel is lighter than gastric fluids, floats over the stomach contents and produces gastric retention of dosage forms and increase gastric residence time resulting in prolonged drug delivery in GIT.

MATERIALS AND METHODS:

Materials:

Glycerol monooleate (GMO) was purchased from Premier trading co. Pluronic F127 was a gift sample from NATCO. Losartan Potassium was a gift sample from Aurobindo Laboratories. Dialysis membrane 110 was purchased from HIMEDIA laboratories. Sodium alginates, Guar gum, Xanthan gum, Carbopol 940B.P were obtained from UV Scientifics. Water used was distilled water and media used was 0.1 N HCl.

Methods:

Preparation of cubosomal dispersion:

The cubosomal dispersions were prepared by taking various concentrations of GMO(10-50%) and pluronic F127. The mixture was heated on an electrical water bath (40-45^{0}C) until pluronic F127 dissolves in GMO. After complete dissolution of pluronic F127, the drug Losartan Potassium was added and mixed well. Then the above solution was added drop by drop to distilled water and subjected to bath sonication for 15-45min to disperse and breakdown of aggregates**.** The end result will be a white opaque dispersion without presence of any aggregates. Formulations were prepared in such a manner such that each 10ml contains 5mg of drug. For placebo formulations, addition of Losartan Potassium is skipped. The prepared dispersions were stored in closed glass vials at room temperature for 72 hours in a dark place and later subjected to evaluation parameters.

Table 1: Various formulation codes of cubosomes:

Formulation code	Glycerol monooleate (% w/v)	Distilled water(%w/v)
LPF1	10	90
LPF2	20	80
LPF3	30	70
LPF4	40	60
LPF5	50	50

Preparation of floating gels:

The floating gels were prepared in a similar manner to cubosomal dispersions using the selected concentration of GMO (depending on the diffusion studies) along with pluronic F127. The mixture of GMO and pluronic F127 acts as lipid phase & aqueous solution of gelling agents (combination of sodium alginate, xanthan gum, guar gum, carbopol 940B.P) acts as aqueous phase.

Table 2: Formulation table of floating gels.

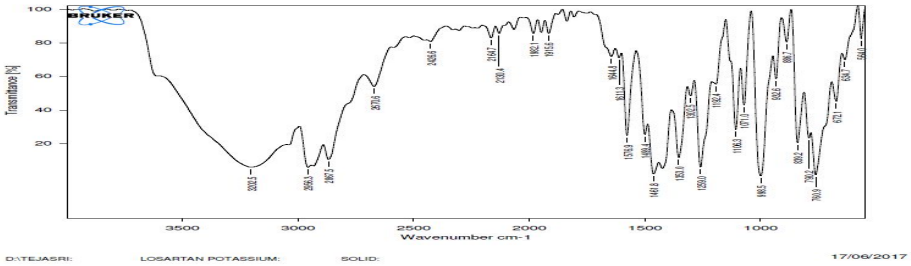
Formulation code	GMO (30%)	Aqueous solution of gelling agent (70%)				Total polymer conc.(%w/v)
		Sodium Alginate	Xanthan Gum	Guar gum	Carbopol 940 B.P	
LPFN1	,,	0.4				0.4
LPFN2	,,	0.8				0.8
LPFX1	,,		0.1			0.1
LPFX2	,,		0.2			0.2
LPFG1	,,			0.4		0.4
LPFG2	,,			0.8		0.8
LPFNG1	,,	0.2		0.4		0.6
LPFNG2	,,	0.4		0.2		0.6
LPFNGX	,,	0.2	0.2	0.4		0.6
LPFNX1	,,	0.2	0.1			0.3
LPFNX2	,,	0.4	0.2			0.6
LPFCN1	,,	0.2			0.1	0.3
LPFCN2	,,	0.1			0.2	0.3
LPFCNG1	,,	0.2		0.2	0.1	0.5
LPFCNX1	,,	0.2	0.1		0.2	0.5
LPFCNGX1	,,	0.1	0.1	0.2	0.2	0.6

Evaluation of Cubosomal Dispersions:

Light microscope: A light microscope (Edison Optics) was used to observe the cubosomal dispersion.

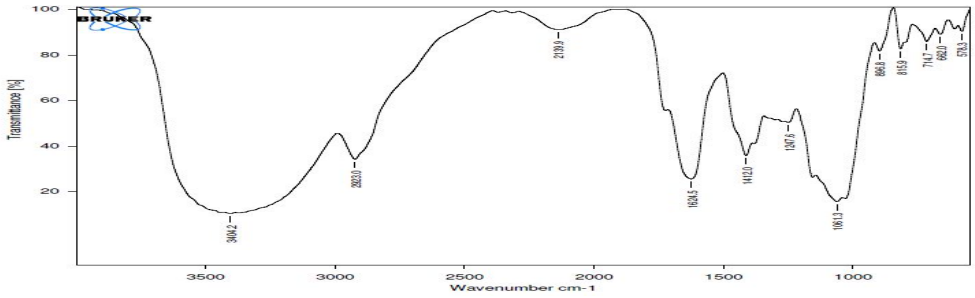
Fig 1: Cubosomal dispersion (Mag: 450X)

FTIR Studies: The interaction study of selected formulation was evaluated using IR spectrophotometer. The characteristic peaks of Losartan Potassium are given below.



Frequency(cm-1)	Bond	Functional group
3202.5 cm-1	O-H Stretch	Alcohol / Phenol
2164.7 cm-1	C=C Stretch	Aromatic
2956.3 cm-1	C-H Stretch	Alkane
1611.3 cm-1	N-H Stretch	Amide
1259 cm-1	C-O Stretch	Aromatic ester

Fig 2(a): FTIR Spectrum of Losartan Potassium



Frequency(cm^{-1})	Bond	Functional group
3404.2 cm^{-1}	O-H Stretch	Alcohol /Phenol
2139.9 cm-1	C=C Stretch	Aromatic
2923.0 cm^{-1}	C-H Stretch	Alkane
1624.5 cm^{-1}	N-H Stretch	Amide
1247.6 cm^{-1}	C-O Stretch	Aromatic ester

Fig 2(b): FTIR Spectrum of Cubosomal dispersion (LPF-3)

Diffusion Studies: Diffusion studies were characterized for formulations containing various concentrations of GMO (10-50%) and water (90-50%) in 0.1 N HCl. Sustained release was observed up to5 hours. The formulation codes &% cumulative drug release values are given below.

Table 3: % Cumulative Drug Release of cubosomal dispersions:

%cumulative drug release ± standard deviation(n=3)

Time (Hrs)	% cumulative drug release				
	LPF1	LPF2	LPF3	LPF4	LPF5
0	0	0	0	0	0
1	16.6±0.23	14.2±0.49	24.5±0.29	12.7±0.57	20.3±0.32
2	32.4±0.42	38.9±0.23	42.6±0.36	30.5±0.43	29.3±0.54
3	50.5±0.68	59.8±0.51	63.7±0.41	54.3±0.82	57.2±0.54
4	74.2±0.39	70.6±0.86	80.4±0.63	72.1±0.76	76.9±0.39
5	88.3±0.72	89.8±0.91	93.34±0.59	85.4±0.39	88.3±0.43

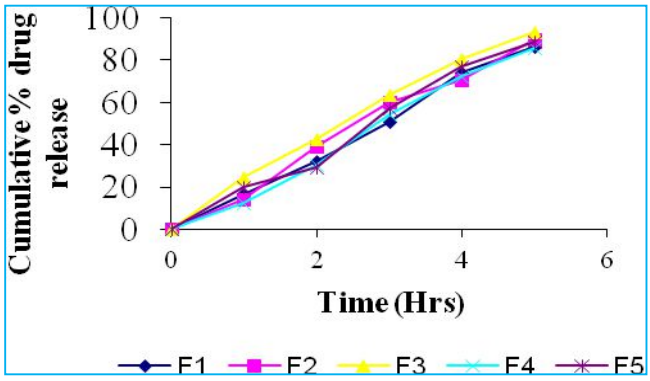


Fig 3: cumulative % Drug Release

Kinetic modeling: The selected cubosomal dispersion (LPF3) was subjected to kinetic modeling process, so that we know the pattern of drug release whether it follows zero order/first order/Higuchi/korsmeyer peppas model. Correlations of coefficient (r2) values were calculated from linear graphs.

Table 4: Release kinetics of cubosomal dispersion (LPF3)

Model	r^2 value	n value
Zero order	0.991	18.72
First order	0.943	42.29
Higuchi	0.950	0.146
Korsmeyer peppas	0.997	0.860

Based on the above results, it was concluded that cubosomal dispersion (LPF3) follows zero order kinetics and korsmeyer peppas model i.e. drug release is by diffusion process and shows zero order drug release.

Evaluation of Floating Gels:

Gelation Property: The prepared floating gel formulations were tested for gel formation by adding to 0.1N HCl. Depending on the gel formation, best combinations of gelling agents are selected &the results were given below.

Table 5: Gelatin property of different combinations of gelling agents used in the formulations.

Formulation code	Components	Results
LPFN	Sodium Alginate	++
LPFX	Xanthan gum	-
LPFG	Guar Gum	++
LPFC	Carbopol 940	-
LPFNX	Sodium Alginte+Xanthan Gum	+
LPFNG	Sodium Alginate +Guar Gum	++
LPFNGX	Sodium Alginate+ Xanthan Gum +Guar Gum	+
LPFGX	Guar Gum+ Xanthan Gum	-
LPFCN	Carbopol 940+Sodium Alginate	+
LPFCG	Carbopol 940+Guar Gum	-
LPFCX	Carbopol 940+Xanthan Gum	-
LPFCNG	Carbopol 940+Sodium Alginate + Guar Gum	++
LPFCNX	Carbopol 940+Sodium Alginate +Xanthan Gum	+
LPFCNGX	Carbopol 940+Sodium Alginate +Guar Gum +Xanthan Gum	+

++ → Excellent (Stiff White gel that stays floating for prolonged period of time).
+ → Good (White gel with film like appearance that floats on surface of 0.1N HCl).
- → Poor (Gel formed but breaks easily even on mild agitation).

From the above results the concentration of gelling agents was found to be 0.2% to 0.8% w/v. Depending on the gel consistency & floating period of gel on the surface of 0.1 N HCl, the best combinations of gelling agents were selected.

pH: pH of formulations was determined by a digital pH meter by immersing the electrode in gel formulation and checking the pH.

Table 6: The pH of the selected gel formulations

S.NO	Formulation code	PH
1	LPF3	6.94
2	LPFN1	6.89
3	LPFX2	6.85
4	LPFG1	6.72
5	LPFNG1	6.86
6	LPFNGX	6.84
7	LPFNX2	6.62
8	LPFCN2	6.54
9	LPFCNG1	6.42
10	LPFCNX1	6.39
11	LPFCNGX	6.56

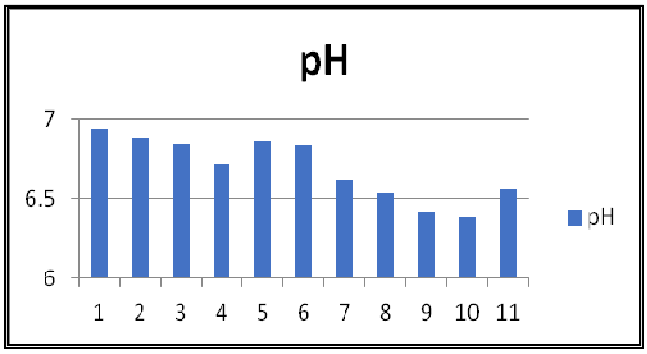


Fig 4: pH of the selected gel formulation

Light microscope: A light microscope (Edison Optics) was used to observe microscopically the difference between cubosomal dispersion and floating gels at a magnification of 450X.

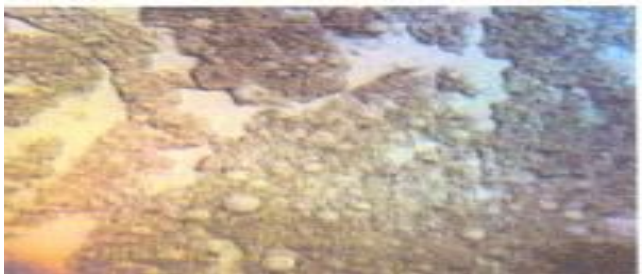
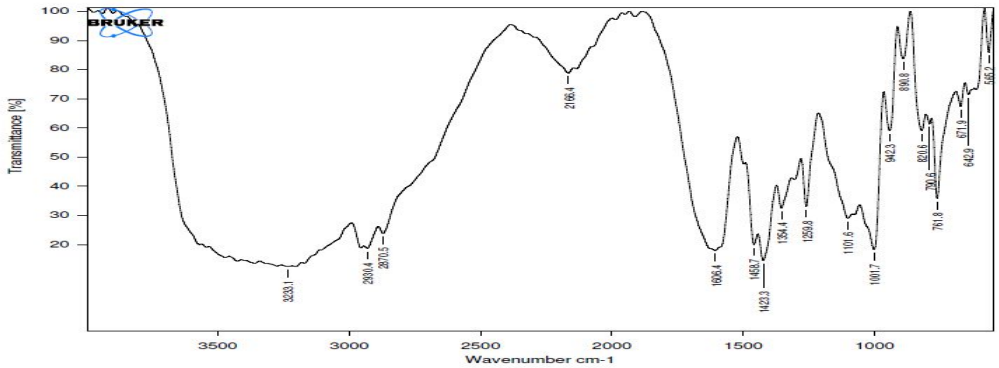


Fig 5: Floating Gel (Mag: 450)

FTIR: The interaction between the drug and excipients of optimized gel formulation was evaluated using IR Spectrophotometer.



Frequency(cm-1)	Bond	Functional group
3223.1 cm-1	O-H Stretch	Alcohol /phenol
2164.7 cm-1	C=C Stretch	Aromatic
2956.0 cm-1	C-H Stretch	Alkane
1613.9 cm-1	N-H Stretch	Amide
1259.1 cm-1	C-O Stretch	Aromatic ester

Fig 6: IR Spectrum of optimized gel formulation (LPFCNGX)

Diffusion studies:

Diffusion studies were characterized for the above combinations. From that combinations best one's are selected depending on the % cumulative drug release and then subjected to evaluation tests. The various formulation codes & % cumulative drug release values of selected formulations were given below.

Table 7: % Cumulative drug release of gel formulations LPFN1 to LPFX2
%cumulative drug release ± standard deviation(n=3)

Time (Hrs)	% Cumulative drug release			
	LPFN1	LPFN2	LPFX1	LPFX2
0	0	0	0	0
1	18.4±0.27	20.8±0.31	14.2±0.43	16.7±0.21
2	32.8±0.43	34.5±0.29	35.6±0.38	26.7±0.34
3	53.4±0.31	48.6±0.45	42.1±0.56	50.1±0.62
4	68.6±0.65	59.3±0.61	60.2±0.89	64.7±0.82
5	81.4±0.54	75.2±0.72	72.9±0.45	79.1±0.49
6	87.2±0.78	86.2±0.31	88.1±0.76	89.4±0.39

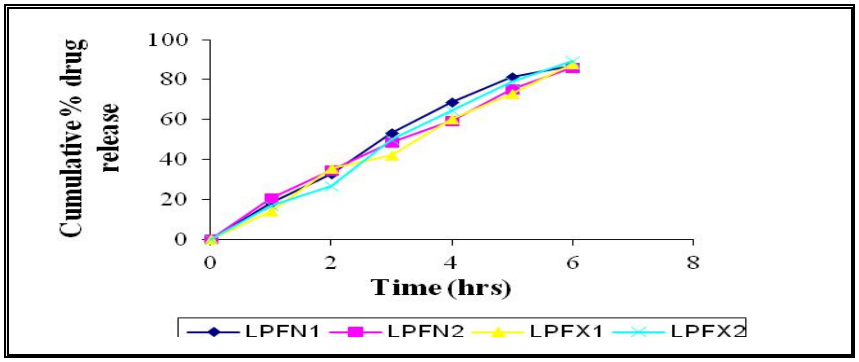


Fig 7: % cumulative drug release of gel formulations

Table 8: % Cumulative drug release of selected gel formulations LPFG1 TO LPFNG2
%cumulative drug release ± standard deviation (n=3)

Time (Hrs)	% Cumulative drug release			
	LPFG1	LPFG2	LPFNG1	LPFNG2
0	0	0	0	0
1	20.1±0.29	16.4±0.19	19.2±0.46	18.7±0.84
2	31.4±0.43	26.1±0.87	34.7±0.67	28.2±0.75
3	46.5±0.65	42.3±0.56	51.6±0.65	43.7±0.82
4	64.2±0.72	59.2±0.42	66.3±0.59	59.8±0.69
5	79.4±0.49	73.9±0.36	81.4±0.84	74.6±0.71
6	90.6±0.38	86.7±0.64	89.8±0.92	87.2± 0.94

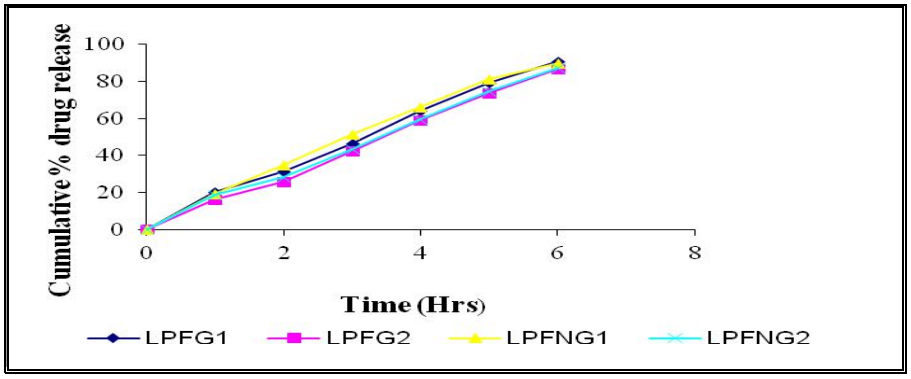


Fig 8: % cumulative drug release of gel formulations

Table 9: % Cumulative drug release of gel formulations LPFNGX to LPFCN2
%cumulative drug release ± standard deviation(n=3)

Time (Hrs)	% Cumulative drug release				
	LPFNGX	LPFNX1	LPFNX2	LPFCN1	LPFCN2
0	0	0	0	0	0
1	20.4±0.56	14.9±0.42	19.6±0.39	17.2±0.94	19.8±0.73
2	32.6±0.43	26.4±0.71	29.2±0.28	25.1±0.45	30.6±0.51
3	46.1±0.67	42.3±0.78	48.7±0.76	44.9±0.72	52.5±0.49
4	68.2±0.52	59.5±0.54	65.4±0.38	62.3±0.91	67.2±0.53
5	76.8±0.89	73.4±0.92	78.3±0.45	72.9±0.46	79.1±0.29
6	-	86.4±0.45	87.9±0.82	87.2±0.29	90.1±0.81

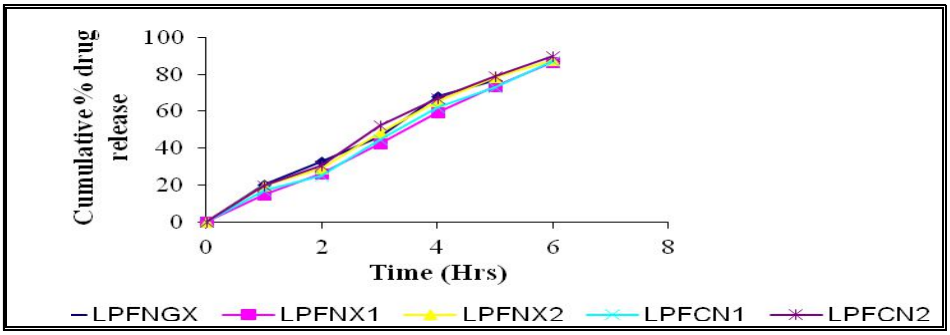


Fig 9: % cumulative drug release of gel formulations

Table 10: % Cumulative drug release of gel formulations LPFCNG1 to LPFCNGX
%cumulative drug release ± standard deviation (n=3)

Time (Hrs)	% Cumulative drug release			
	LPFCNG1	LPFCNG2	LPFCNX1	LPFCNGX
0	0	0	0	0
1	19.6±0.62	17.3±0.54	18.4±0.31	20.1±0.82
2	28.7±0.54	25.2±0.45	27.6±0.56	32.9±0.34
3	44.9±0.32	41.6±0.89	47.8±0.41	50.3±0.92
4	61.4±0.31	59.4±0.71	63.2±0.82	65.7±0.45
5	79.5±0.59	73.8±0.57	77.1±0.67	81.5±0.31
6	88.3±0.72	86.9±0.41	-	94.2±0.54

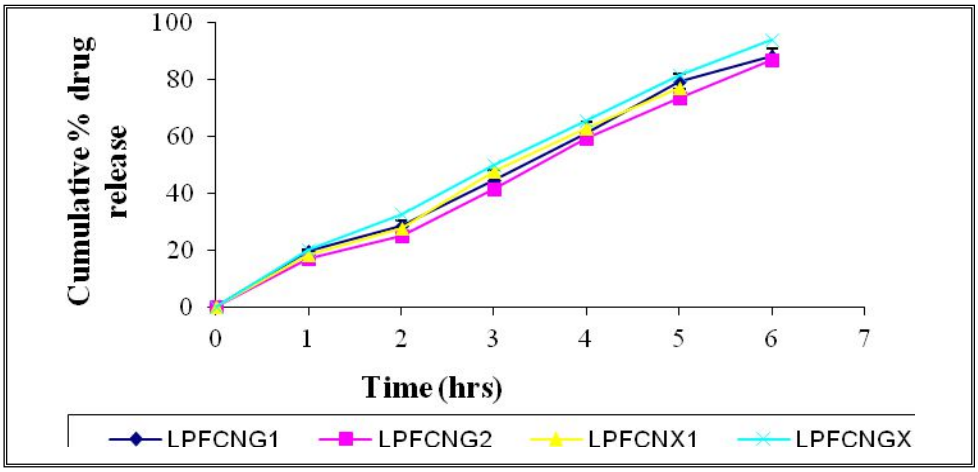


Fig 10: % cumulative drug release of gel formulations

Table 11: cumulative % drug release of selected gel formulations:

Formulation code	Cumulative % drug release	Sustained release (in hours)
LPFN1	87.2	6
LPFX2	89.4	6
LPFG1	90.6	6
LPFNG1	89.8	6
LPFNGX	76.8	5
LPFNX2	87.9	6
LPFCN2	90.1	6
LPFCNG1	88.3	6
LPFCNX	77.1	5
LPFCNGX	94.2	6

Table 12: % drug release of pure drug suspension:

Time(mins)	% Drug Release
5	13± 0.32
10	28± 0.58
15	50± 0.42
30	68± 0.83
45	76± 0.92

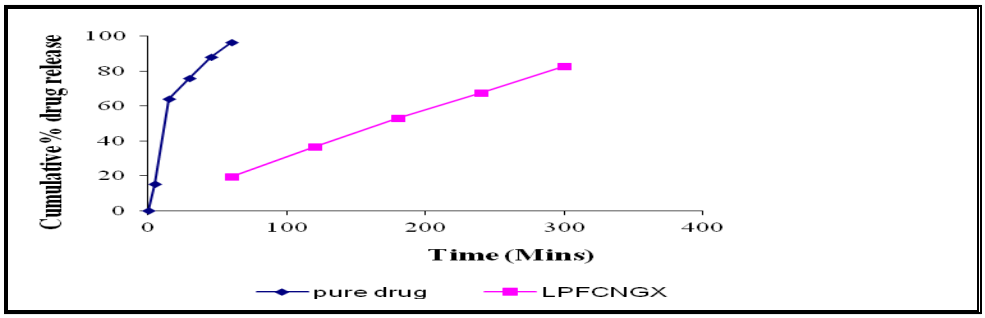


Fig 11`: Comparison of selected gel formulation with pure drug suspen

Table 13: Release kinetics of gel formulation (LPFCNGX)

Model	r^2 value	n value
Zero order	0.995	15.71
First order	0.913	0.216
Higuchi	0.943	39.32
Korsmeyer-peppas	0.999	0.888

Kinetic modeling: The selected gel formulation (LPFCNGX) was subjected to kinetic modeling process, so that we know the pattern of drug release whether it follows zero order/first order/Higuchi/korsmeyer peppas model. Correlations of coefficient (r2) values were calculated from linear graphs.

Based on the above results it is concluded that the gel formulation (LPFCNGX) follows zero order kinetics and korsmeyer peppas model i.e. drug release is by diffusion process and shows zero order drug release.

Stability Studies: As per ICH guidelines pH and % cumulative drug release values of selected gel formulations (LPFCNGX) were analyzed periodically through accelerated stability studies.

pH:

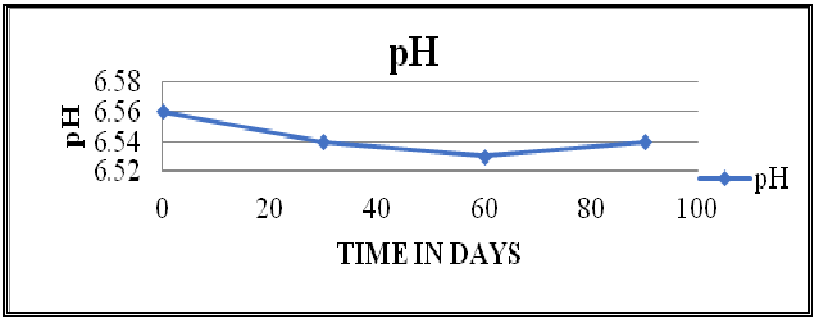


Fig 12: Stability studies of optimized formulation LPFCNGX.

% cumulative drug release:

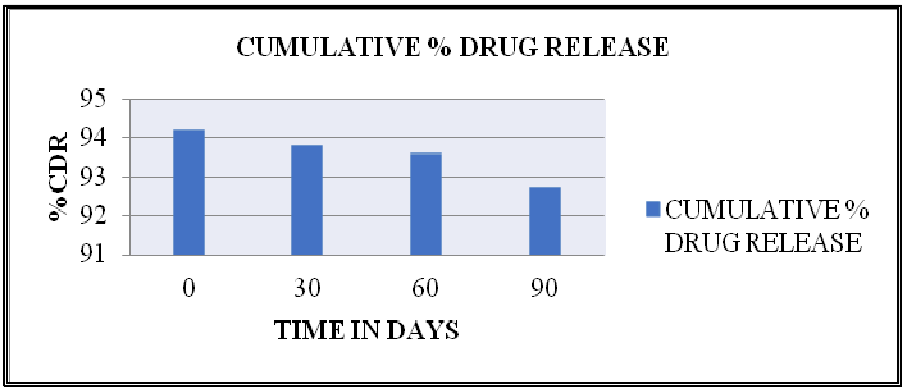


Fig 13: Stability studies of optimized formulation LPFCNGX.

DISCUSSION:

Gastro retention: The main principle behind the study is Gastro retention. Many Gastro retentive formulations are developed till now. This formulation procures attention because of its simple method of preparation and unique liquid crystalline structure. The main advantage of this method is to accommodate various drugs like hydrophilic & hydrophobic nature. Cubosomes are the dosage forms which are produced by adding mixture of GMO & pluronic F127 to the water. The GMO & pluronic F127 acts as lipid phase. When the lipid phase is added to water it tends to separated. Pluronic F127 is acts as stabilizer which prevents aggregation. The drug Losartan potassium is a BCS class- III angiotensin 2 receptor antagonist with antihypertensive activity & absorbed from the GIT. The prepared cubosomal formulation LPF3 showed maximum sustained release of 93.34% after 6 hours following zero order kinetics.The purpose of evaluating cubosomes are to know the concentration of GMO that showing maximum drug release.

According to literature even though GMO-based mesophase formulation must possess the inherent property of sustained release which is a, major pre-condition and the property of bio-adhesive can extend the formulations retention time in the GIT providing more time for drug absorption.GMO is an ester and GI fluids is rich in enzyme gastric lipase that acts on GMO break down into its constituents glycerol and acid leading to break down of cubosome structure, due to this the drug release decreases even before expected time.

The advanced strategy is to formulate the cubosomes in the form of floating gels by maintaining the cubosome structure prolonged drug release will be observed. Gelling agents like sodium alginate, xanthan gum, guar gum and carbopol 940B.P are used in the formulation to persuade gelation. The gelling agent solutions are used as aqueous phase. The gel formulations are similar in the appearance to cubosomal dispersions externally and they form gels when added to 0.1NHCl.

The main aspect of gel formulations is gelation property. Gelling agents acts as floating medium in GI fluids. Among the agents used, sodium alginate forms excellent gel followed by guar gum, xanthan gum and carbopol940B.P.When carbopol940B.P is used alone it doesn't form a gel but when used with the combination of sodium alginate guar gum and xanthan gum forms

excellent stiff gel. The various combinations of gelling agents are used and best ones are selected depending on the percentage cumulative drug release.

The concentration of GMO is kept constant and concentrations of gelling agents are selected by conducting diffusion studies. Among all formulations LPFCNGX showed maximum sustained release of 94.2% after 6 hours following zero order kinetics.

Fig 14: Gel formed on the surface of 0.1N HCL

The formulations possess a lag time in fraction of seconds & when added to 0.1 N HCl immediately they form gel on the surface of 0.1 N HCl (fig 14). The formulations which containing carbopol 940 showed high range of viscosity due to its thickening & swelling capability.

CONCLUSION:

Cubosomes can be formed by simple combination of biologically compatible lipids like GMO & water. Hence, they are well suited for pharmaceutical and body tissue. The ability to form cubosomes during manufacture offers enhanced flexibility for product development efforts. The above research specifies cubosomal utility as controlled release drug carrier. When they are formulated as gels Prolonged Gastro retention is achieved. Although they possess advantageous characteristics, there is a still long way to go before their clinical application. In near future we hope that a way will be opened for such formulations to be used as novel drug delivery systems to prevent the drawbacks of conventional dosage forms.

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