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Formulation and Evaluation of Gastro Retentive In-Situ Floating Gels Of Irbesartan Cubosomes

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Abstract
Objective: Irbesartan is a BCS class-II antihypertensive drug used in the treatment of hypertension having absorption window in the upper GIT and half-life of 11-15hours. The aim of the present work is to formulate and evaluate a sustained release formulation of Irbesartan in the form of cubosomes and gastroretentive In-situ floating gels of cubosomes. **Methods**: Cubosomes are prepared by top-down approach employing glyceryl monooleate (GMO) as lipid phase vehicle, Pluronic F127 as a stabilizer and distilled water as aqueous phase and Irbesartan as an API. The formulation is evaluated for drug release by diffusion studies subjected to Zeta sizing and visualized by transmission electron microscopy. Floating gels are prepared in a manner similar to cubosomes dispersion employing gelling agents like sodium alginate, Guar Gum, Xanthan Gum, Carbopol 940 B.P. **Results**: Cubosomes formulation IRBF 11 containing 55% GMO showed a maximum drug release of 93.22 % within 6 hours, having average particle size of 14.95 d. nm and Zeta potential -3.88mV. The cube-like structure with round vesicles was observed by TEM. Sustained release up to 8 hours was observed in gels formulated by using gelling agents. In vitro release kinetics exhibited sustained release and followed nonfickian diffusion and zero order kinetics by the optimized formulations. Satisfactory pH, viscosity and gelling capacity were obtained. **Conclusion**: cubosomes formulated with GMO serves as potential gastroretentive sustained Drug Delivery vehicles. Further sustained release will be attained when they are formulated as floating gels.
Keywords: cubosomes, floating gels, gastroretentive, Lyotropic Liquid Crystals, oral drug delivery.

Index Terms: Introduction[1], Materials and Methods[2] "Materials and Equipment's", **Preparations of Cubosome Dispersions[3], Preparations of Floating Gels[4], Evaluation of Cubosome Dispersions[5]** "FTIR Studies, Diffusion Studies, Zeta Sizer, Transmission Electron Microscope", **Evaluation of Floating Gels[7]** "FTIR Studies, Gelation Property, Viscosity, Diffusion Studies, pH, Light Microscope, Kinetic models, Accelerated Stability Studies, **Results[7]**, "FTIR Studies, Cubosome Dispersion-Diffusion Studies, Zeta Size and Zeta Potential, Transmission Electron Microscope, Gastroretentive Insitu floating gels- Diffusion studies, Viscosity, pH, Drug Release Kinetics, Accelerated Stability Studies", **Discussion[8], and References[9].**

1. INTRODUCTION

Cubosomes are a type of lyotropic liquid crystal. Lyotropic liquid crystal (LLC) systems are formed when amphiphilic lipids are added to polar solvents like water or glycerin. In recent years LLC systems have received considerable attention because of their excellent potential as a drug vehicle. Among these systems cubic phases, cubic phases are the most important and have been extensively investigated for their ability to sustain the release of a wide range of bio actives from low molecular weight to drug to proteins, peptide and nucleic acid.

Cubosomes are discrete, submicron, nanostructured particles of bicontinuous cubic crystalline phase. At present cubic phases are prepared by unsaturated monoglycerides (GMO) or Phytantriol (PT) are most frequently investigated liquid crystal structures for drug delivery. The compartmentalization in cubic mesophases can be used to introduce guest drugs of hydrophilic, lipophilic or amphiphilic nature. Cubosomes are produced typically by high energy dispersion of bulk cubic phase followed by colloidal stabilization using polymeric surfactants (Top-Down Approach).

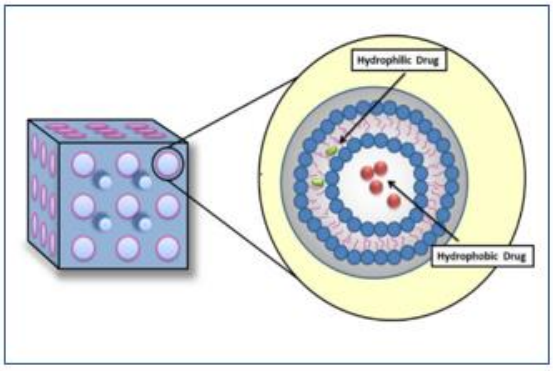


Figure 1: structure of cubosomes

Cubosomes possess advantages such as large surface area, low viscosity and exist at almost any dilution

level capable of carrying both hydrophilic and lipophilic molecules and potential for controlled drug release.

Glyceryl monooleate (monoolein or GMO), a Food and Drug administration approved food additive is a mixture of the glycerides of oleic acid and other fatty acids consisting mainly of the Monooleate and has the ability to form different types of lyotropic liquid crystals in the presence of water. The use of liquid crystalline phases of GMO as a drug delivery system has been widely investigated by many co-workers. The unique properties of cubic liquid crystalline phases formed from GMO systems have been utilized for the preparation of controlled release system.

The model drug investigated in this research is Irbesartan an antihypertensive drug which are used in the treatment of hypertension. In the present work an attempt has been made to prepare a sustained release gastroretentive formulation of Irbesartan as cubosomes and floating gel since it has absorption window in the upper GIT. GMO is used as a lipid phase that form cubosomes when dispersed in water with aid of high energy sonication in presence of a triblock polymer poloxamer 407 (known as plutonic F127, used to prevent cubosome aggregation). GMO is also investigated as gastroretentive lipid in some literature citing its bio adhesive property. The oral delivery of drugs with a narrow absorption window in the gastrointestinal tract is often limited by poor bioavailability with conventional dosage forms due to incomplete drug release and short residence time at site of absorption. To overcome this drawback and to maximize the oral absorption of these drugs Novel Drug Delivery systems has been developed, they provide controlled delivery of drugs. Among all oral dosage forms liquid orals are more prone to low bioavailability as far as stomach specific Drug Deliveries are concerned since they subjected to faster transit from stomach/duodenum. To produce sustained release formulation of an oral liquid formulation could be successfully augmented substantially through a strategy of liquid Insitu floating gel system.

The gel formed from Insitu gelling system, being lighter than gastric fluid floats over the stomach contents and produce gastric retention of dosage form and increase gastric residence time resulting in prolong drug delivery in gastrointestinal tract.

The Insitu floating gel system possess advantages such as ease of administration, reduced frequency of administration and improved patient compliance

Hence an attempt has been made in this research to develop formulation by combining cubosomes and Insitu floating gels.

2. MATERIALS AND METHODS

2.1 Material: Glyceryl monooleate (GMO) was purchased from Finar Chemicals (LR), Pluronic's F127 was gifted from Natco Pharma, Irbesartan gifted from Hetero, dialysis membrane 110 was purchased from HIMEDIA laboratories, Hyderabad, sodium alginate, gum Tragacanth, Carbopol 940 B.P was brought from Finar chemicals (LR), Water used is Millipore water and media used 0.1N HCl with pH 1.2.

2.2Equipment's: Bruker FTIR spectrometer shimadzu UV spectrophotometer, electronic water bath Bio technics; Mumbai, zetasizer Malvern zeta sizer ZS90, transmission electron microscope (JEOL, Japan) diffusion cell (Locally Fabricated), ultrasonic bath sonicator (REMI); magnetic stirrer (REMI), pH meter Systronics 361, light microscope (Edition instruments).

3. PREPARATION OF CUBOSOME DISPERSION

Varying concentration of Glyceryl monooleate (5-75%) is heated along with Pluronic F127(5% weight corresponding to GMO) on an electric water bath at temperature of 42-45^{o}C until Pluronic F127 completely dissolves in GMO. To the above solution Irbesartan is added and mixed well. This clear lipid solution obtained is added drop by drop to distilled water and subjected to bath sonication for period of 15 to 45 minutes with intermittent shaking and stirring to disperse and breakdown lipid aggregates. The end result will be white opaque dispersion without presence of any aggregates. Formulations are prepared in such a manner that each 5ml contains 72mg (on drug entrapment efficiency basis) of drug. For placebo formulations addition of Irbesartan is skipped. The prepared dispersions are stored in closed glass vials at room temperature for 72 hours in a dark place and later subjected to evaluation parameters.

4. PREPARATION OF FLOATING GELS: The floating gels are prepared in a similar manner to cubosomes dispersions using the optimized concentration of GMO (along with Pluronic F127) from the above study as lipid phase and aqueous solution of gelling agent (combinations of sodium alginate, Guar Gum, xanthan Gum Carbopol 940 B.P as aqueous phase.

5. EVALUATION OF CUBOSOME DISPERSIONS

5.1 FTIR spectroscopy: Bruker FTIR spectrometer is used to scan and characterize the IR spectra of various combinations of drug, excipients and optimized formulations in the present study and check the compatibility between drug and various excipients. KBr pellet method is employed for making pellets with aid of pressure of 8-10 tones in a KBr press and later scanning the pellets in the instrument with the aid of OPUS software that works in the sync with the instrument. Spectrum was scanned from 4000 to 400cm^{-1}

5.2 Diffusion studies: Optimization is done by observing drug release profile by conducting diffusion studies of prepared formulations with aid of locally fabricated diffusion cell. The diffusion cell (with capacity of 14 ml) consists of two chambers donor compartment and receptor compartment with sampling port. A dialysis membrane of grade 110 with molecular weight cut off of 12000 Daltons and sample volume capacity of 3.63 ml/$cm^3$is used for the study. 1cm^2 piece of membrane are cut and soaked overnight in buffer of pH 1.2 and are used in next day. The receptor compartment is filled with buffer and membrane is fastened onto it surface such that it covers the opening of compartment and touches the buffer solution. Then donor compartment is placed above and clamped followed by sample addition, the entire assembly is placed on a magnetic stirrer, temperature is then set to 37^oC with the speed of 30 rpm. Periodically 1ml samples are withdrawn and replaced with equal volume of buffer for every hour. Withdrawn samples are diluted and then analyzed spectrometrically in U.V spectrophotometer wavelength of 258nm and calculated for cumulative drug release.

5.3 Zeta sizing: The optimized formulation obtained from the above study is diluted 1:100 with Millipore water and subjected to Zeta sizing using Malvern zeta sizer ZS90 for determining the average particle size and Zeta potential employing laser scattering with an angle of 180^o.

5.4 Transmission electron microscope: High power 200 KV transmission electron microscope is used to visualize the cubosome dispersions. Both placebo and optimized formulations were observed. The dispersions are hydrated in alcohol or acetone. After that they are embedded in plastic that polymerize into solid hard plastic block. The blocks are cut into thin sections by a diamond knife in an instrument called ultra-microtome. Each section is only 50-100nm thick. The thin section of the sample is placed on a copper grid and stained with heavy metals. The specimen is then studied under the electron beam.

6. EVALUATION OF FLOATING GELS

6.1 FTIR studies: used in a manner similar to method mentioned above. Spectra of drug along with gelling agents, optimized gel formulation is taken and analyzed for presence of any incompatibility.

6.2 Gelation property: The prepared formulations are tested for gel formulation by adding to pH 1.2 buffer.

6.3 Viscosity: A Brooke field DV pro II viscometer with small sample adaptor and spindle no. 63 is used to determine viscosity for above formulations optimized by diffusion studies. Speed is increased from 10rpm to 50rpm and viscosity is noted in cps.

6.4 Diffusion studies: conducted in a manner similar to method used for cubosome dispersions.

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

6.6 Light microscope: A light microscope is used to observe microscopically the difference between cubosome dispersions and floating gels at a magnification of 450X.

6.7 Kinetic modelling/Data fitting: The optimized formulation is observed whether the pattern of the drug release follows zero order/first order/Higuchi/Kors-Meyer Peppas model or Hixson Crowell model. Coefficient of correlation (r^2) values are calculated for those linear curves obtained by regression analysis of the plots.

6.8 Accelerated stability studies: conducted as per ICD guidelines at 40^oC±2^oC/75%±5% RH for optimized gel formulation at sampling intervals of 0,30,60,90 days respectively. The drug content, viscosity, pH is determined periodically.

7. RESULTS

The main objective of the study is to develop gastro retentive dosage forms of Irbesartan in form of cubosomes and Gastro retentive floating gels using various concentrations of GMO, distilled water and gelling agents (Sodium alginate, Gum Tragacanth, Guar Gum, Carbopol 940 B.P) employing Pluronic F127 as a stabilizer using Top Down Approach. Advantages of the method is simple technique and easy availability of raw materials.

7.1 FTIR Studies: The interaction study between the drug and excipients as well as optimized formulation was evaluated using IR Spectrophotometer. Irbesartan has a characteristic absorption peak at 1173.2cm^{-1},2959.8cm^{-1},2430.5cm^{-1},1616.8cm^{-1} respectively. Similar peaks were observed in spectra of different combinations of excipients and in optimized formulations (cubosomes and floating gels), along with absence of interfering peaks indicating there is no unwanted reaction between Irbesartan and other excipients used in the study.

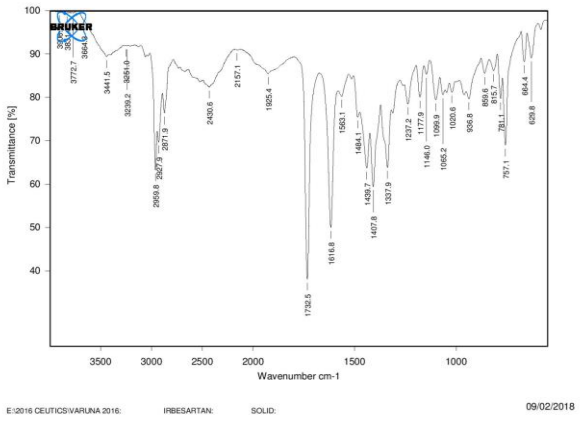


Figure 2: FT-IR spectrum of Irbesartan

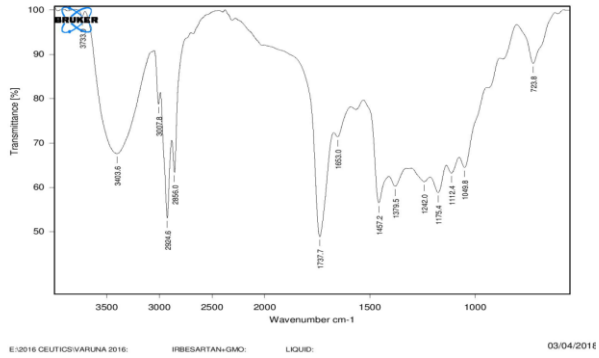


Figure 3: FT-IR of Irbesartan& GMO

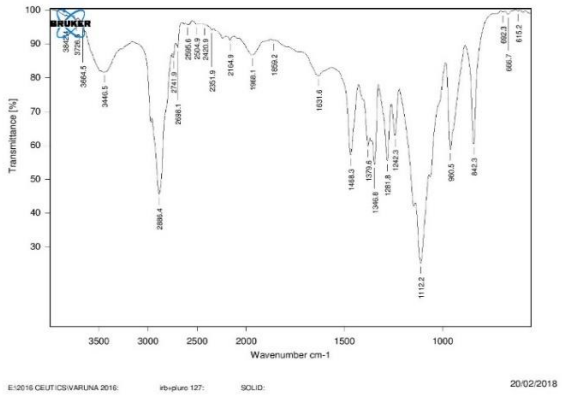


Figure 4: FT-IR of Irbesartan & Pluronic F127

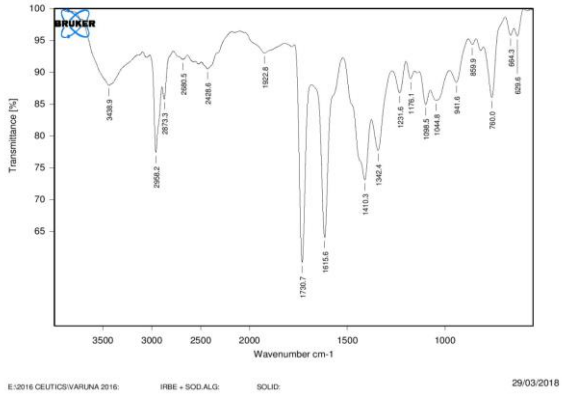


Figure 5: FT-IR of Irbesartan & Sodium Alginate

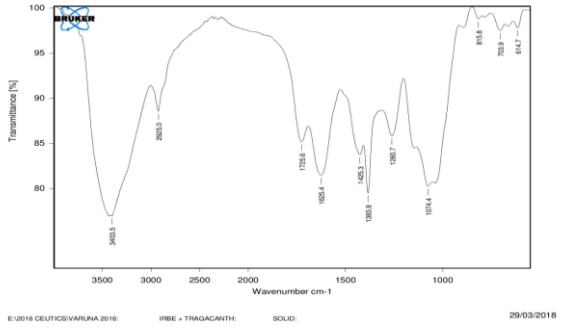


Figure 6: FT-IR of Irbesartan and Gum Tragacanth

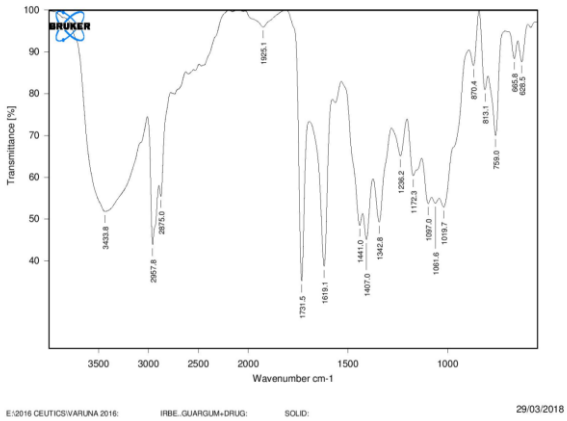


Figure 7: FT-IR of Irbesartan and Guar gum

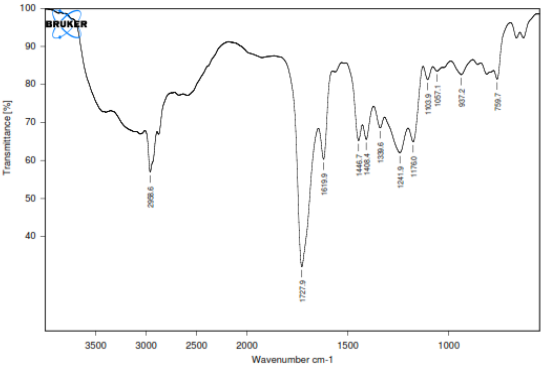


Figure8: FT-IR of Irbesartan and Carbopol 940

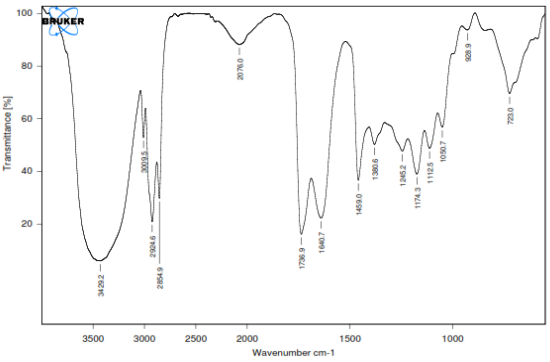


Figure 9: FT-IR of optimized cubosomes dispersion (IRBF11)

FORMULATION CODE	GLYCEROL MONOOLEATE		DISTILLED WATER		STABILIZER (in mg) (PLEURONIC F127)
	(%w/v)	(in ml)	(%w/v)	(in ml)	
IRBF1	5	0.25	95	4.75	7.5
IRBF2	10	0.5	90	4.50	15
IRBF3	15	0.75	85	4.25	22.5
IRBF4	20	1.00	80	4.00	30
IRBF5	25	1.25	75	3.75	37.5
IRBF6	30	1.50	70	3.50	45
IRBF7	35	1.75	65	3.25	52.5
IRBF8	40	2.00	60	3.00	60
IRBF9	45	2.25	55	2.75	67.5
IRBF10	50	2.50	50	2.50	75
IRBF11	55	2.75	45	2.25	82.5
IRBF12	60	3.00	40	2.00	90
IRBF13	65	3.25	35	1.75	97.5
IRBF14	70	3.50	30	1.50	105
IRBF15	75	3.75	25	1.25	112.5

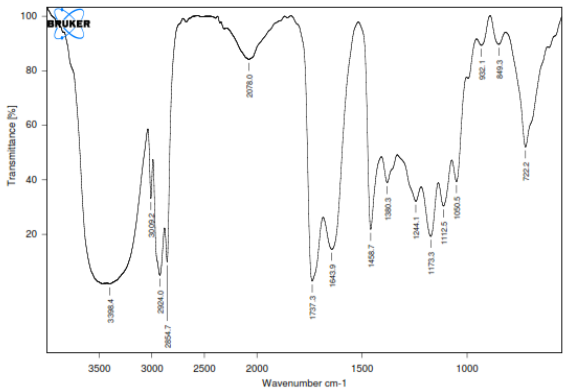


Figure 10: FT-IR of optimized gel formulation (IRBFSTGC)

7.2 Cubosomes dispersion

7.2.1 Diffusion studies: Diffusion studies are directed for different formulations containing different concentrations of GMO (5 to 75%) and water (95%25%) in 0.1N HCl (buffer of pH1.2). Sustained release action was seen up to 6 hours if there should arise an occurrence of cubosomes dispersions. The various formulation batches along with cumulative drug release values are given table.

Table 1: Various Formulation codes of cubosomes

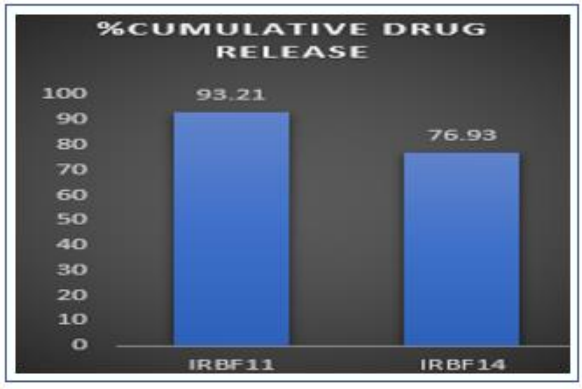
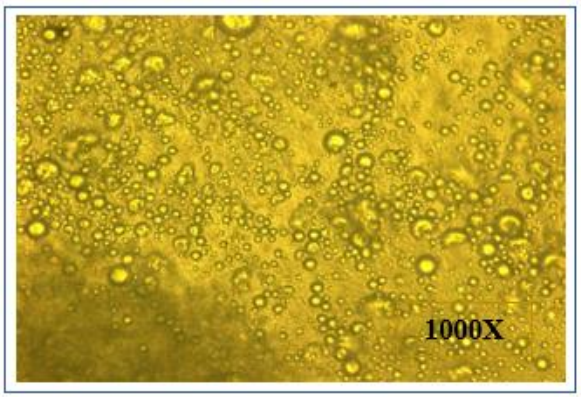


Figure 11: % Cumulative drug release

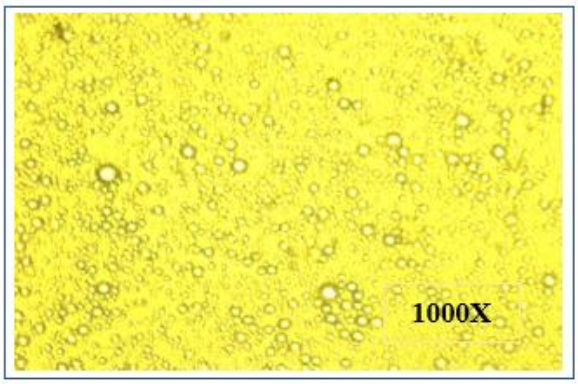
Formulation IRBF11 containing 70% GMO showed 93.21% cumulative drug release after 6 hours among other formulations. This formulation is subjected to other evaluation parameters.

7.2.2 Zeta size & Zeta potential: The average particle size of the selected formulation IRBF11 is found to be 14.95 d. nm, PDI value was found to be 0.246 and Zeta potential was found to be -3.88mV, showing that the formulation is stable.

7.2.3 Transmission Electron Microscopy: At an amplification of up to 1000X cubosomes are clearly noticeable. Both placebo treatment and improved optimized formulation were watched. Cube like structures and along with spherical vesicles are observed in the placebo and selected optimized formulation. Not very little distinction was seen in placebo and optimized formulation.



A) Placebo formulation



B) Optimized formulation IRBF-11
Figure 12: Transmission Electron Microscopy (TEM)-IRBF11

FORMULATION CODE	GMO (55%)	AQUEOUS SOLUTION OF GELLING AGENT (45%)				TOTAL POLYMER CONC.(%W/V)
		SODIUM ALGINATE	TRAGACANTH	GUAR GUM	CARBOPOL 940 B.P	
IRBFS1	”	0.4	-	-	-	0.4
IRBFS2	”	0.8	-	-	-	0.8
IRBFT1	”	-	0.4	-	-	0.4
IRBFT2	”	-	0.8	-	-	0.8
IRBFG1	”	-	-	0.4	-	0.4
IRBFG2	”	-	-	0.8	-	0.8
IRBFC1	”	-	-		0.4	0.4
IRBFC2	”	-	-	-	0.8	0.8
IRBFSTG	”	0.4	0.2	0.2	-	0.8
IRBFSTGC	”	0.2	0.2	0.2	0.2	0.8

Table 2: Formulation of floating gels

7.3 Gastro retentive in-situ floating gels: Using different concentrations of GMO (along with Pluronic F127) from the above investigation floating gels are prepared in a manner similar to preparation of cubosomes dispersion by varying concentrations of gelling agents keeping the concentrations of GMO and Pluronic F127 constant. The optimum range of gelling agent is found to be 0.4-0.8%as observed through gelation property. The formulation table is given below.

7.3.1 Diffusion studies: Diffusion studies are performed for above combinations and best among those are selected based on cumulative drug release values and subjected to other evaluation parameters. The various drug releases profiles of formulations and cumulative drug release values of gel formulations are given below.

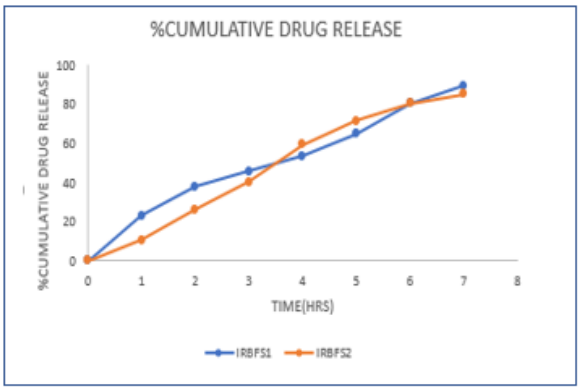


Figure 13: Drug release profiles of IRBFS1 AND IRBFS2

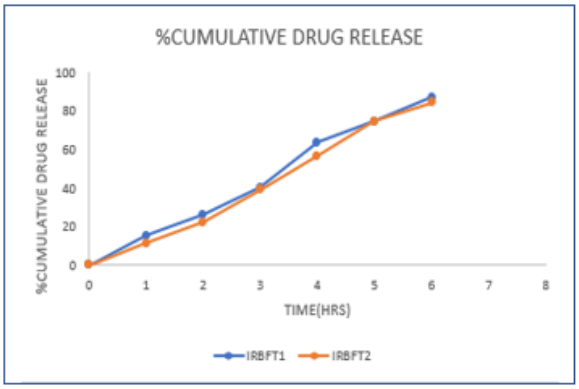


Figure 14: Drug release profiles of IRBFT1 AND IRBFT2

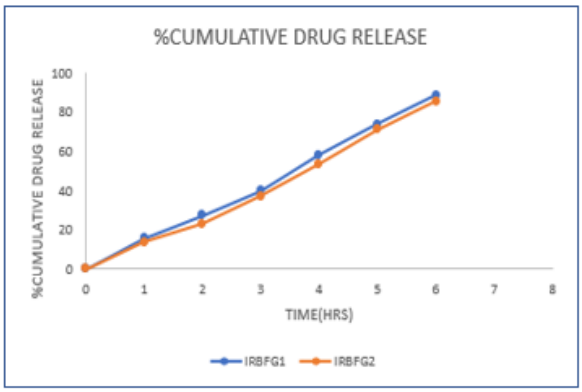


Figure 15: Drug release profiles of IRBFG1 AND IRBFG2

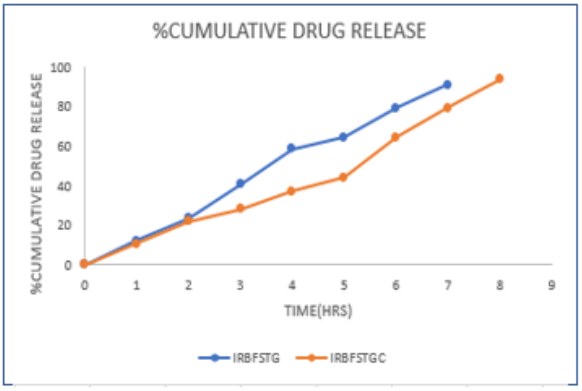


Figure 16: Drug release profiles of IRBFSTG AND IRBFSTGC

FORMULATION	**%CUMULATIVE DRUG RELEASE**	**SUSTAINED RELEASE DURATION**
IRBFS1	89.42	7
IRBFS2	85.09	7
IRBFG1	86.92	6
IRBFG2	84.16	6
IRBFT1	88.80	6
IRBFT2	85.33	6
IRBFSTG	91.15	7
IRBFSTGC	93.59	8

Table 3: Time and cumulative drug release % of all evaluated formulations

The above selected formulations are subjected to pH determination. In contrast to marketed formulation which shows the drug release within 1hour other gel formulations exhibited sustained drug release ranging from 5 to 8 hours respectively. Among all formulations IRBFSTGC showed sustained release of 93.21 up to 8hrs.

7.3.2 Viscosity: The viscosity of the selected formulation was found to be 359(at 10rpm), 312(at 20rpm), 243(at 30rpm). 222(at 50rpm).

7.3.3 pH: pH values of selected formulations are given below

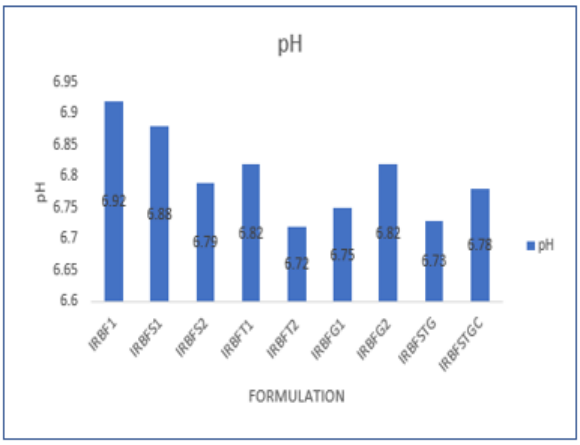


Figure 16: pH of selected gel formulations.

All samples possess nearly same values nearer to neutral pH favoring suitability for oral administration.

7.3.4 Release kinetics: Based on drug release values of cubosomes dispersions and gel formulations (IRBFSTGC) are studied for release kinetics inference is drawn from below values. With the above results it is inferred that cubosomes dispersion IRBFSTGC follows zero order kinetics with nonfickian diffusion (swellable and cylindrical matrix).

Table 4: Release kinetics of selected optimized

7.3.5 Stability Studies: pH and drug release values are analyzed periodically as per ICH guidelines

KINETIC MODELS	**r^2 values**
Zero order kinetics	0.9764
First order kinetics	0.7937
Higuchi	0.8494
Korsmaeyer-Peppas kinetics	0.7856
Hickson Crowell kinetics	0.8776

through accelerated stability studies for selected gel formulation (IRBFSTGC)

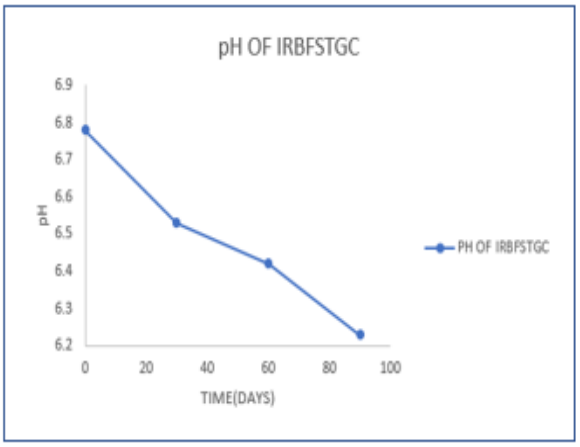


Figure 17: pH of the optimized formulation

%DRUG RELEASE	**TIME IN DAYS**			
	1	30	60	90
IRBFSTGC	93.59±0.63	93.26±0.49	93.1±0.29	92.7±0.40

Table 5: Stability studies of optimized formulation of IRBFSTGC

8. DISCUSSION

Gastro retention: The primary method of reasoning behind this examination is Gastro retention. Despite the fact that numerous gastro-retentive definitions are produced to date this formulation deserves attention because of its interesting liquid crystalline structure and simplicity of preparation. Favorable circumstances, for example, high level of biocompatibility controlled by GMO, the ability of obliging different medications regardless of hydrophilic or hydrophobic nature, sustained release action prompt an investigation in the detailing of liquid crystalline drug delivery vehicle through different courses of administration. Cubosomes are one such dose forms shaped by GMO when added to water. Since, it is a lipid and tends to separate in aqueous Pluronic F127 phase is utilized as a stabilizer to prevent conglomeration. The model medication irbesartan is a BCS class 2 antihypertensive medications that has absorption window in upper GIT and has short Half-Life. Cubosomes formulation IRBF11 indicates attractive medication release patterns in 0.1N HCl up to 6 hours following first order kinetics. The reason for assessment of cubosomes is to upgrade the centralization of GMO demonstrating most extreme drug release.

The Cubosomes formulation should have three imperative parameters. Firstly, the formulation must

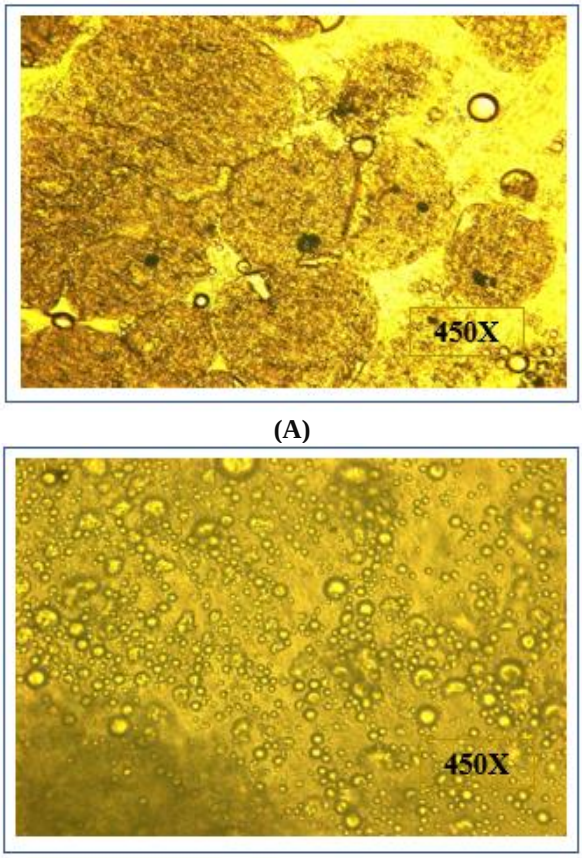
have the characteristic property of sustained release which is a noteworthy precondition. Second, they ought to steadily exist in the gastrointestinal fluids to give a persistent matrix from which medications can be discharged gradually. This requires the formulation to resist the digestive process to certain extent. Third the property of bio adhesive can broaden the formulation retention time in the GIT tract terms of more drug absorption.

As indicated by literature, GMO based mesophase formulation display the first and third highlights portrayed above it can't give a sustained release attributable to its affectability to the digestive process. GMO is an ester and GI fluids is wealthy in enzyme gastric lipase that effectively follows up on GMO breakdown to its constituent acid and glycerol prompting the breakdown of cubosomes structure, thus, drug release wanes of even before the normal time.

An option is to restart the enzyme attack keeping up the Cubosomes structure and dragging out drug release. The inventive methodology is to formulate Cubosomes in type of floating gels. Agents like Sodium alginate, Guar gum, Tragacanth and Carbopol 940 B.P are utilized as a part to prompt gelation. Solutions of this gelling agents are utilized as an aqueous phase. This gel formulations are comparative to cubosomes dispersions but they form gels when they are included to 0.1N HCl.

Figure 18: picture of floating gels formed on surface of pH 1.2 buffer

The other critical part of gel formulation is gelation property. Gelling agents are utilized as floating medium in GIT fluids. Agents like sodium alginate is superb gel forming agent trailed by Tragacanth, Guar Gum and Carbopol 940. Carbopol 940 did not frame a gel when utilized alone but rather superb firm gel formulation is seen when utilized with a blend of sodium alginate, Tragacanth, guar gum. Different mix of these gelling agents is utilized and best ones are chosen for pH determination and %cumulative drug release.



(A)

(B)

Figure 19: (A)-floating gels, and (B)-cubosome dispersion (magnification at 450X)

From the above figure it is evident that ordinary cubosomes dispersion (without gelling agents) contains individual entities whereas in case of gel formulations the gelling agents used forms matrix like structure around cubosome units that acts as a medium of gastro retention by forming floating gels and prolonging drug release.

The concentration of GMO is kept consistent and the concentration of gelling agents are varied and optimized by conducting diffusion studies on these formulations. Among all formulations, IRBFSTGC demonstrated sustained drug release to about 93.5% after 8 hours following zero order kinetics.

Conclusion: Cubosomes can be framed by the simple mixing of naturally compatible lipids (GMO) and water and are in this manner appropriate for pharmaceutical and body issues. The capacity to shape cubosomes during manufacture offers improved adaptability for product advancement efforts. The above research indicates Cubosomal utility as controlled release drug transporter. Prolonged Gastro

retention is accomplished when they are detailed as floating gels keeping up the Cubosomes structure. Although they possess beneficial 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 circumvent the drawbacks of conventional dosage forms.

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