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Formulation and Evaluation of Glimepiride Oral Capsules

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ABSTRACT: *Glimepiride (GMP) is poorly water soluble drug, so solubility is the main constraint for its oral bioavailability. The aim of this study was to investigate the potential of cubosomes as lipid nanocarrier to improve the solubility and sustained action of Glimepiride. Glimepiride is one of the third generation sulfonylureas used for treatment of type 2 diabetes. The rationale of this study was to improve the solubility, dissolution rate and sustained release of the drug. Glimepiride cubosomes were prepared by Top down approach[3] employing GMO as lipid phase vehicle, Poloxamer 407 as stabilizer and distilled water as aqueous phase. The resultant cubosome dispersion were characterized by encapsulation efficiency, in-vitro drug release, particle size, zeta potential, FTIR and SEM. Optimized formulation (F5) showed a maximum drug release of 71 % in 6 hours, particle size of 88.7nm and zeta potential of 43.6 mV. Glimepiride cubosomal Capsules were prepared with the optimized cubosomal dispersion, by using a new technique starch and aerosil were used as granulating agents to obtain a wet mass. Then the wet mass was passed through sieve no. 16 to form granules. Then the granules were dried in hot air oven. The dried granules were filled into capsules. The granules were evaluated for SEM, zeta potential, flow properties and in vitro drug release. Optimized capsule formulation (C2) contains starch showed a maximum drug release of 49 % in 6 hours, particle size of 213nm and zeta potential of -159 mV. In vitro release kinetics exhibited sustained release up to 6 hours and followed non-Fickian diffusion. Results suggest that GMO cubosomes, as lipid nanovectors, could significantly enhance oral efficacy when compared to Glimepiride powder.*

KEY-WORDS*: Cubosomes, Glimepiride, Lyotropic liquid crystal, Glyceryl monooleate, Top-down approach, capsules, Oral drug delivery.*

I. INTRODUCTION

Glimepiride is an oral hypoglycemic agent, which is commonly prescribed for the treatment of patients with type II diabetes mellitus. It belongs to sulfonylureas drug class. Glimepiride is a weak acid with PKa of 6.2. Glimepiride is practically insoluble in water and acidic environment but highly permeable (class II) according to (BCS). The oral absorption is uniform, rapid and complete with nearly 100% bioavailability. Therapy with Glimepiride is usually initiated with 1 to 2 mg. The pharmacokinetics and dosage schedule supports once daily sustained release formulations for Glimepiride for better control of blood glucose levels to prevent hypoglycaemia, enhance clinical efficacy and patient compliance. "Cubosomes" are discrete, sub micron nano structured particles of bicontinuous cubic liquid crystalline phases whose size ranges from 10-500 nm in diameter, they appear like dots square shaped, slightly spherical, each dot corresponds to the presence of pore size 5-10 nm, where "bicontinuous" refers to two distinct (continuous, but non-intersecting) hydrophilic regions separated by the bilayer. Cubosomes have great potential in drug nano formulations for oral delivery owing to their best advantages, like high drug payloads due to high internal surface area and cubic crystal structures, the encapsulating ability of hydrophobic, hydrophilic and amphiphilic molecules, controlled release and targeting of proteins like bioactive agents and drugs.

The purpose of the present study was to develop Glimepiride Cubosomal oral capsules to increase the solubility and to sustain the drug release.

II. MATERIALS AND METHODS:

Materials: Glyceryl monooleate (GMO) was gifted by Mohini organics Pvt. Limited, Mumbai, India. Poloxamer407 was a gift sample from Daewoong Pharmaceuticals, Hyderabad. Glimepiride was a gift sample from Vasudha pharma Pvt. Limited, Hyderabad, A.P, India. Starch and Aerosil were of commercial grade. All other reagents used were of analytical grade.

PREPARATION OF GLIMEPIRIDE LOADED CUBOSOMES.

Preparation of Glimepiride Cubosomes : Varying concentrations of Glyceryl monooleate (5 to 50%) were taken in test tube and heated along with Poloxamer407 (1 % weight corresponding to GMO conc.) on an electric water bath at a temperature of 40 to 45^{o}C until Pluronic F127 completely dissolves in GMO. To the above solution Glimepiride (2mg) was added and mixed well. The clear lipid solution obtained was added drop by drop to distilled water and subjected to bath sonication for period of 15 to 45 minutes with intermittent shaking and stirring. A white opaque dispersion was formed without presence of any aggregates. Various formulations were prepared using different concentrations of GMO. The prepared dispersions were stored in closed glass vials at room temperature for 72 hours in a dark place and later evaluation parameters were carried out.

Preparation of Glimepiride oral capsules: Optimized cubosomal formulation (15%GMO&1%poloxamer407) was selected for preparation of capsules. To the Glimipiride cubosomal dispersion, starch (C1-C7) and avicel (C8-C14) was added separately to obtain a wet mass. Then the wet mass was passed through sieve no. 16 to form granules. The granules were dried in hot air oven at a temp of 45^{0}c. The dried granules were filled into '000' sized capsules.

METHODS FOR OPTIMIZATION OF CUBOSOMES

[1] Optimization of formulation variables

[2] The effect of Poloxamer 407 concentration (P1-P5), GMO concentration(F1-F14) and sonication time on the formation of cubosomes were characterized by using optical electron microscopy.

[3] CHARACTERIZATION OF CUBOSOMES

Vesicle shape and size analysis of cubosomes: Size and shape of the cubosomes were determined using optical microscopy and SEM (Hitachi S 3700N).

Particle size measurement: The average diameter of sonicated cubosomes were determined by laser diffraction technique using Horiba particle size analyzer.

Zeta potential:

[4] Zeta potential was determined using Zetasizer (Malvern Instruments). Measurements were performed on the same samples prepared for size analysis. Zeta potential indicates the degree of repulsion between adjacent, similarly charged particles in dispersion system.

[5] 4. Entrapment Efficiency (EE):-

[6] Entrapment efficiency is defined as the percentage amount of drug which is entrapped by the cubosomes. For the determination of entrapment efficiency, the un-entrapped drug was first separated by centrifugation at 15000 rpm for 30 minutes. The resulting solution was then separated and supernatant liquid was collected. The collected supernatant was then diluted appropriately and estimated using UV visible spectrophotometer at 228 nm.

[7] The percent of encapsulation efficiency (EE %) was determined by the following equation:

$$\mathbf{EE\%} = \frac{\text{[Total drug]} - \text{[free drug]}}{\text{Total drug}} \times 100$$

[8] 5. In vitro drug release

[9] Studies were performed for all the formulations. In vitro release studies were carried out using bichambered donor receiver compartment model (Franz diffusion cell) and this was placed on magnetic stirrer and temperature was adjusted to 37 ± 0.5^{0} C. One end of the chamber was covered with Himedia dialysis membrane (cut-off molecular weight: 12000-14000), which was previously soaked in phosphate buffer pH 6.8. Phosphate buffer pH 6.8 was placed in the receptor cell. Accurately measured 2.5 ml of the formulation placed on a dialysis membrane, which was in contact with receptor medium Samples were withdrawn at specified time intervals and the medium was compensated with phosphate buffer pH 6.8. The samples were analyzed for drug using a UV-Vis spectrophotometer at 228 nm.

III. METHODS FOR EVALUATION OF CAPSULES:

A. FTIR: Spectra of drug along with granulating agents, optimized granules were taken and analyzed for presence of any incompatibility.

B. Morphology, Particle size measurement and Zeta potential of cubosomal granules: Conducted in a manner similar to method used for cubosome dispersions.

C. Flow Properties: The flow properties were studied by measuring the quality parameters like Bulk density, Tapped density, Compressibility Index, Hausner's ratio, weight variation and friability.

D. Drug content: 100 mg granules were accurately transferred into a 100 ml volumetric flask and add 10 ml of methanol to dissolve Glimepiride. The solution was made up to volume with pH 6.8 phosphate buffer. The resulted solution was filtered and suitably diluted and the drug content was estimated spectrophotometrically by measuring the absorbance at 228 nm.

E. In-Vitro Dissolution Study: Dissolution testing was performed in compliance with USP using apparatus II. A dissolution medium of 6.8 pH phosphate buffer was chosen. A paddle speed of 50 rpm was selected with media volume of 900 ml. The medium was maintained at 37 ± 0.5 ^{0}C. The dissolution vessels were covered to minimize evaporation. 5 ml of aliquots were collected at regular time intervals, and the same amount of fresh dissolution medium was replaced into dissolution vessel to maintain the sink condition throughout the experiment. The collected aliquots were filtered using Whatman filter No. 1, and further diluted suitably to analyze using UV method at 228 nm.

F. Data fitting/Kinetic Modelling: The optimized formulation was observed whether the pattern of drug release follows zero order/first order/Higuchi/Korse-Meyer peppas model. Coefficient of correlation (r2) values were calculated for the linear curves obtained by regression analysis of the plots.

G. Accelerated Stability Studies: Conducted as per ICH guidelines at 40^{o}C±2^{o}C/75%±5% RH for optimized gel formulation at sampling intervals of 0, 30,60 and 90 days respectively. The drug content, viscosity and pH are determined periodically.

IV. RESULTS AND DISCUSSIONS

A. FTIR Studies: The interaction study between the drug and excipients as well as optimized formulation was evaluated using IR spectrophotometer. Glimepiride has characteristic absorption peaks were shown in Table 5 and 6. Similar peaks were observed in spectra of different combinations of excipients and in optimized formulation (Cubosomes and granules), along with absence of interfering peaks indicating there is no unwanted reaction between Glimepiride and other excipients used in the study.

From the above Figures1, 2 and Tables 5, 6 it can be inferred that there was no appearance or disappearance of any characteristic peaks. This shows that there was no interaction between the drug and excipients used in preparation cubosomal granules.

B. Optimization of formulation variables:

a. Effect of poloxamer 407 concentration on formation of cubosomes : The effect of varying the Poloxomer407 concentration was studied on the cubosome formation. From the Figure 3, it is clear that as poloxomer407 concentration increased there will be change in the shape of cubosomes from the cubic shape to rod like shape was observed. A decrease in entrapment efficiency and drug release from cubosomes was also observed. It was found that 1% poloxomer407 concentration was the optimum concentration for cubosome formation and it showed the highest drug entrapment about 91.3%, and highest drug release about 71.12%.

b. Effect of Glycerol Mono Oleate concentration on formation of cubosomes : As seen in Figure 4, it was observed that Cubosomes were obtained by using GMO in the concentration range of 5% to 50%. Below 5% and above 50% GMO spherical shaped cubosomes were obtained rather than cubic structures.

c. Effect of sonication time on the formation of cubosomes. : As seen in, Figure 5 it can be concluded that optimum sonication time for cubosome formation was 25-45 minutes. Below this optimum sonication time large sized cubic structures were formed and above this time range the size of cubic structure were very small.

CHARACTERIZATION OF GLIMEPIRIDE LOADED CUBOSOMES:

[1] **Surface morphology of cubosomes**

[2] The surface morphology of the formulated cubosomes were determined using scanning electron microscopy. It was observed that that the obtained cubosome have a smooth surface and cubic in shape.

[3] **Particle size of cubosomes:**

[4] Particle size of cubosome dispersion was analysed by Horiba particle analyser.

[5] The diameter (nm) of cubosomes was found to be in the range of 10 to 500 nm and the average particle size was found to be 88.7 nm as seen in Figure 6.

[6] Zeta potential of cubosomes:

[7] The zeta potential of the cubosomes was determined using Zetasizer and the value of the cubosomes was found to be +43.6 mV which indicates that cubosomes were stable as shown in Figure 7.

[8] Entrapment Efficiency:

[9] Entrapment efficiency of cubosomes formulations were showed in Figure 8.

[10] From the above Figure 8 the entrapment efficiency was found to increase by increasing GMO concentration from 5 to 50 % (w/w). So Formulation F5 was optimized based on high entrapment and stability. The remaining formulations (F6-F14) were showing phase separation.

[11] Diffusion studies:

[12] Diffusion studies were performed for all formulations and formulation F5 was optimized. The drug release profiles of various formulations are given in Figure no 9 and 10.

[13] From the above Figure 9 and10, the drug release was found to increase by increasing GMO concentration from 5 to 50 % (w/w), the lipid concentration was increased, drug release was increased but phase separation was observed as seen in the remaining formulations. So Formulation F5 was optimized and it was formulated into granules.

[14] From the above Figure 11 it was showed that at the end of 6 hours the optimized Glimepiride loaded cubosome formulation F5 was sustained over a period of 6 hours in 6.8pH phosphate buffer compared with Glimepiride crude powder. It was found that crude Glimepiride powder releases 13.21% only in 6 hours because of Glimepiride is insoluble in 6.8 pH phosphate buffer. The optimized cubosome formulation releases 71.38% in 6 hours and it was observed that Glimepiride highly soluble in GMO.

[15] The formulation F5 was optimized based on cubic structure, high entrapment efficiency and it was stable compared to other formulations.

EVALUATION OF GLIMEPIRIDE LOADED CUBOSOMAL GRANULES:

A. Surface morphology of Glimepiride cubosomal granules:

SEM images microscopic evaluation showed that most of the granules were cubic in shape as shown in Figure12.

B. Particle size of Glimepiride cubosomal granules:

Particle size of Glimepiride cubosomal granules were analysed by Horiba particle analyser.

It was found that the diameter (nm) of Glimepiride cubosomal granules was found to be in the range of 10 to 500 nm and the average particle size was found to be 213.3 nm.

C. Zeta potential cubosomal granules:

The zeta potential of the cubosomes was determined using Zetasizer and the value of the cubosomes was found to be -159.6 mV which indicates that granules were stable.

D. Flow properties of Glimepiride cubosomal granules: Flow properties of optimized Glimepiride cubosomal granules formulation C2 were showed in below table 5.

From the results that are listed in the table 5, the flow properties of optimized granule formulation, bulk density 0.32gm/ml, tapped density 0.38gm/ml, Carr's index 13.3, hausner's ratio 1.14 and the values showed low intra particle friction between the granules. The angle of repose was 26.3 indicating good flow properties of the granules. The granules were found to be free flowing and showed suitability to be filled into capsules.

E. Drug content: Drug content was found to be 97.26 for optimized C2 formulation.

F. In vitro drug release studies

Drug release profiles of Glimepiride cubosomal capsules were using USP type II dissolution apparatus, at a rate of 50 rpm with pH 6.8 phosphate buffer as dissolution medium. The temperature was maintained at 37 ± 0.5^{o}C. Samples were withdrawn at regular intervals of time and the same volume was replaced with fresh dissolution medium. Required dilutions were made and samples were analysed at 228 nm using UV-visible spectrophotometer.

The results of in vitro drug release studies of Glimepiride oral capsules formulated using increasing concentrations of starch from 0.8gm to 2gm are represented in Figure 13. High drug release, at the end of 6 hour was obtained with C2 (49.64%0.

The results of in vitro drug release studies of Glimepiride oral capsules formulated using increasing concentrations of aerosil from 0.1gm to 0.7gm are represented in Figure 14. High drug release, at the end of 6 hour was obtained with C8 (45.87%).

F. Kinetic modelling: The optimized cubosomal capsule C2 was studied for release kinetics and it was shown in Table no 6 and it follows Non-fickian kinetics.

From above Table 6, it was observed that the optimized formulation C2 follows Non-fickian kinetics.

G. Stability studies: Drug content and drug release values are analyzed periodically as per ICH guidelines through accelerated stability studies for optimized capsule formulation C2.

SUMMARY: The cubosomal oral Capsules New technique deserves attention due to its unique liquid crystalline structure and ease of preparation. Advantages such as high degree of biocompatibility possessed by GMO, capability of accommodating various drugs irrespective of hydrophilic or hydrophobic nature, sustained release action lead to investigation in formulation of liquid crystalline drug delivery vehicles through various routes of administration. Cubosomes are one such dosage forms formed by GMO when added to water. Since it is a lipid and tends to separate in aqueous phase Poloxamer 407 is used as a stabilizer to prevent aggregation. Glimepiride was formulated into cubosomal capsules to increase its solubility and sustain the drug release. Cubosomal formulation prepared by GMO (15%), poloxamer407 (1%) shows good cubic structure, satisfactory entrapment efficiency (91.24) and drug release (71.38%). As GMO concentration increases entrapment efficiency and drug release are increased but the prepared formulations are not stable, the phase separation will occurred. To sustain the drug release the optimized cubosome formulation F5 was formulated into capsules by adding starch and aerosil were added separately as granulating agents to the optimized Glimepiride cubosomal formulation. Dealing with other aspects, Preparation (C2) containing starch show good cubic structure higher drug release (49.64%) at end of 6 hours in pH 6.4 buffer and stable than other formulations. The nature of cubosomal dispersion and granules formulation are observed microscopically. The difference is shown in below Figure16.

IV. CONCLUSION:

Cubosomes can be formed by simple combination of biologically compatible lipids (GMO) and water and are thus 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. Prolonged released is achieved when they are formulated as granules maintaining the cubosome structure. Although they possess advantageous characteristics, there is a still long way to go before their clinical application.

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Table 1: Formulation of cubosomes for optimization of poloxamer 407

Formulation code	Monooleine(%W/V)	Poloxomer407 (%W/W)	Glimepiride(mg)	Water (ml upto100%)
P1	15	1	2	100
P2	15	2	2	100
P3	15	3	2	100
P4	15	4	2	100
P5	15	5	2	100

Table 2: Formulations of cubosomes using GMO:

Formulation code	Monooleine(%W/V)	Poloxomer407 (%W/W)	Glimepiride(mg)	Water (%w/v upto100%)
F1	1	1	2	100
F2	2.5	1	2	100
F3	5	1	2	100
F4	10	1	2	100
F5	15	1	2	100
F6	20	1	2	100
F7	25	1	2	100
F8	30	1	2	100
F9	35	1	2	100
F10	40	1	2	100
F11	45	1	2	100
F12	50	1	2	100
F13	55	1	2	100
F14	60	1	2	100

Table 3: Formulations of Cubosomes using Starch powder:

Formulation code	Monooleine(%W/V)	Poloxomer407 (%W/W)	Glimepiride(mg)	Starch powder(gm)	Water (upto100%)
C1	15	1	2	0.8	100
C2	15	1	2	1.0	100
C3	15	1	2	1.2	100
C4	15	1	2	1.4	100
C5	15	1	2	1.6	100
C6	15	1	2	1.8	100
C7	15	1	2	2.0	100

Table 4: Formulations of Cubosomes using Aerosil:

Formulation code	Monooleine(%W/V)	Poloxomer407 (%W/W)	Glimepiride(mg)	Aerosil(gm)	Water (upto100%)
C8	15	1	2	0.1	100
C9	15	1	2	0.2	100
C10	15	1	2	0.3	100
C11	15	1	2	0.4	100
C12	15	1	2	0.5	100
C13	15	1	2	0.6	100
C14	15	1	2	0.7	100

Table 5: Characteristic IR peaks of Glimepiride pure drug

Functional Group	**Reported Value (cm^{-1})**	**Observed value (cm^{-1})**
N-H	3500-3300	3464.27
C-H	3000-2850	2970.48
O-H	2500-3300	2717.79
N=O	1550-1350	1477.52
C-O	1300-1000	1184.33

Table 6: Characteristic IR peaks of Glimepiride loaded cubosomal granules:

Functional Group	**Reported Value (cm^{-1})**	**Observed value (cm^{-1})**
N-H	3500-3300	3423.76
C-H	3000-2850	2926.11
O-H	2500-3300	27156.86
N=O	1550-1350	1477.52
C-O	1300-1000	1159.26

Table 6: Release kinetics of optimized gel G2 formulation

Model	**G2 r2 value**	**(Korse-Meyer peppas) peppas**
Zero order	0.962	0.995
First order	0.991	
Higuchi	0.984	

Table 7: Stability studies of optimized gel C2 formulation

Time in days	**Drug content**	**% Drug release**
0	97.26	49.64
30	96.78	48.26
60	95.13	47.56
90	94.54	46.27

Figure 1: Characteristics IR peaks of Glimepiride pure drug

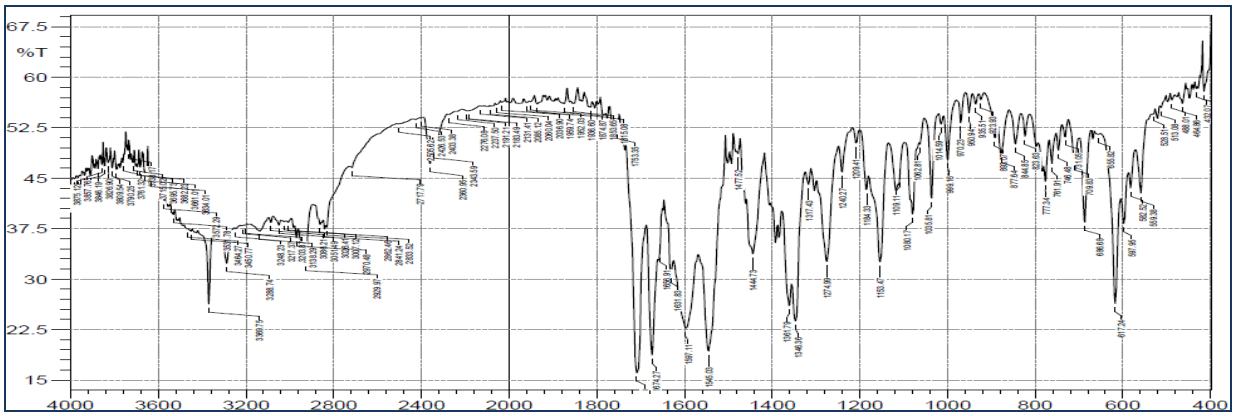
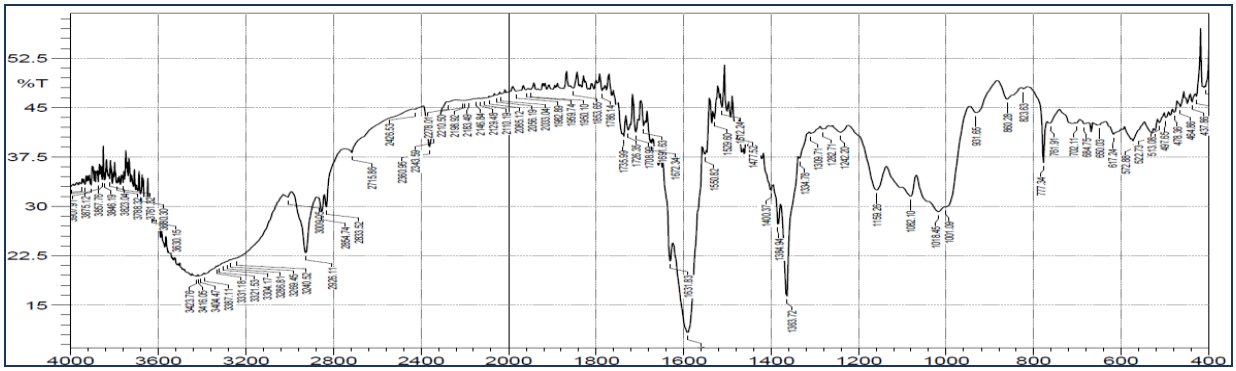


Figure 2: Glimepiride loaded cubosomal granules:



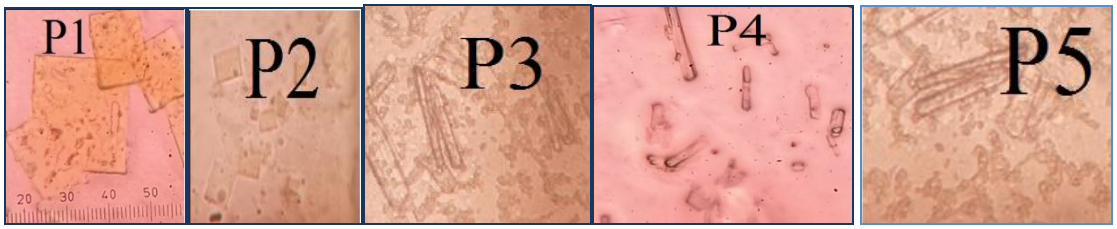
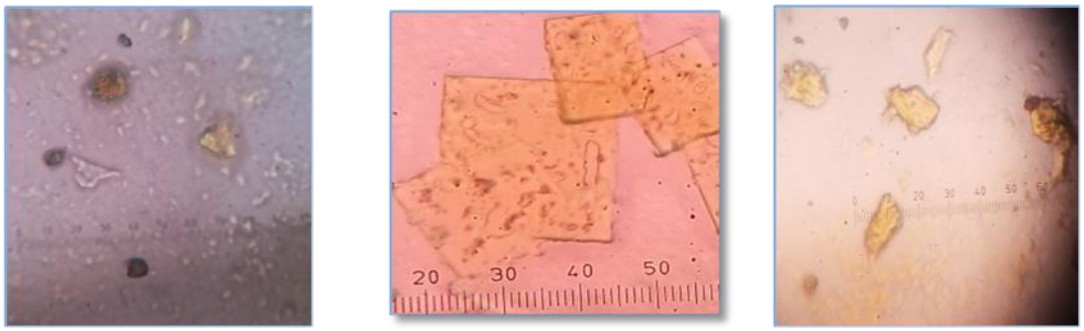
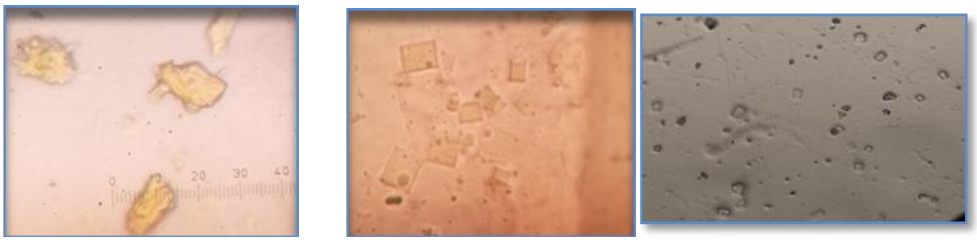


Figure 3: Different types of cubosomes formed using poloxomer407



(a) **(b)** **(c)**

Figure 4: Structure of cubosomes (a) below 5% GMO concentration, (b) 5-50% GMO concentration, (c) above 50% GMO concentration



(a) **(b)** **(c)**

Figure 5: Structure of cubosomes (a) 5-20 minutes sonication time, (b) 25-45 minutes sonication time, (c) above 50 minutes sonication time

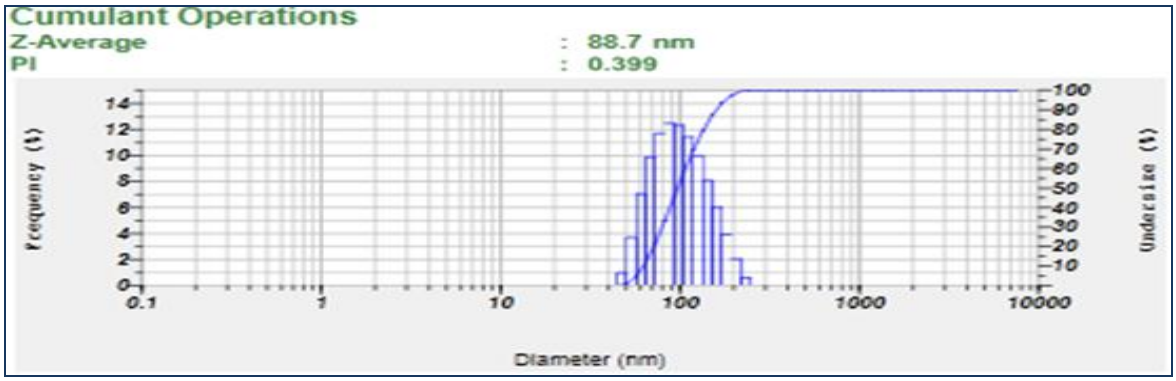
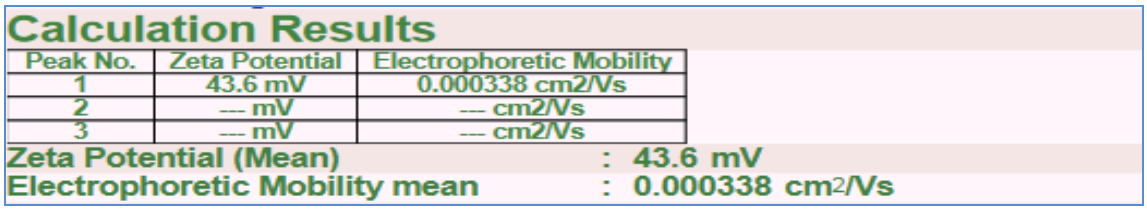


Figure 6: Particle size of cubosome formulation F5

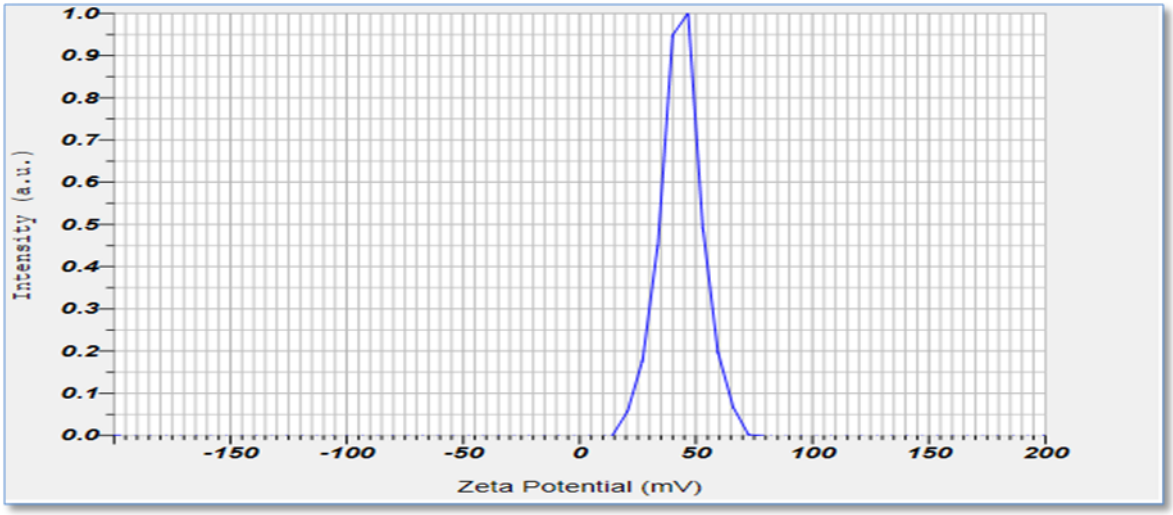


Calculation Results

Peak No.	Zeta Potential	Electrophoretic Mobility
1	43.6 mV	0.000338 cm2/Vs
2	--- mV	--- cm2/Vs
3	--- mV	--- cm2/Vs

Zeta Potential (Mean) : 43.6 mV
Electrophoretic Mobility mean : 0.000338 cm²/Vs

Figure 8: Zeta potential of



cu bosome formulation F5

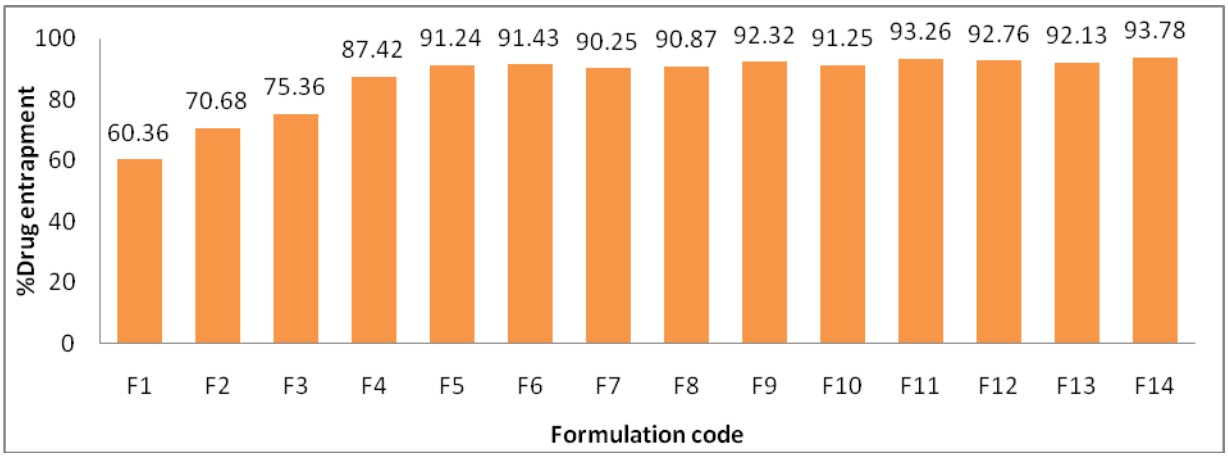


Figure 8: Entrapment efficiency of cubosomes

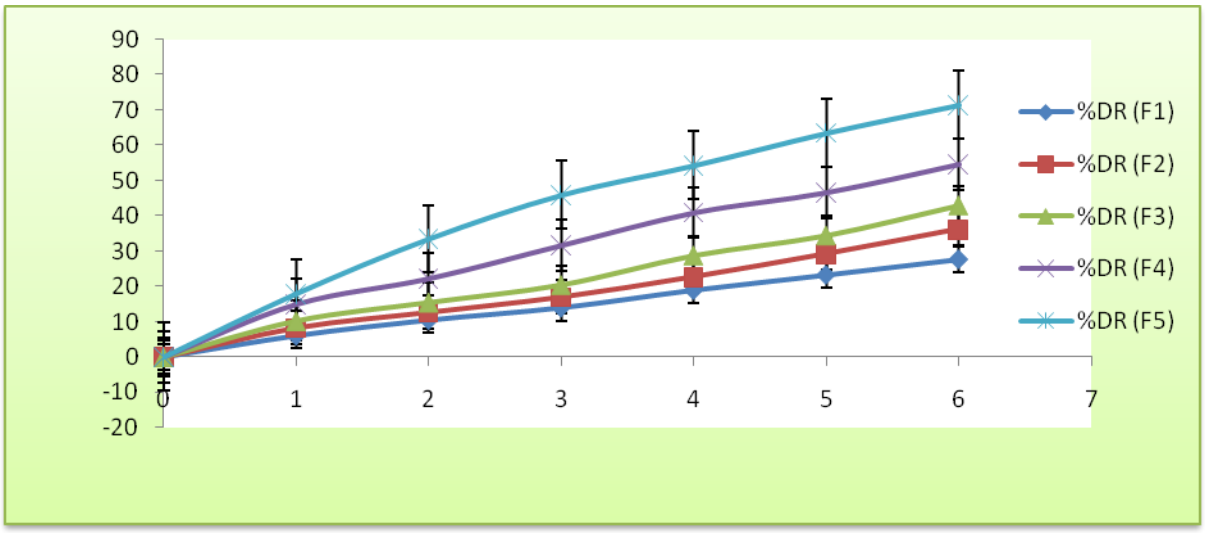


Figure 9: In vitro diffusion profile of Glimepiride cubosomesF1-F5 in 6.8pH phosphate buffer

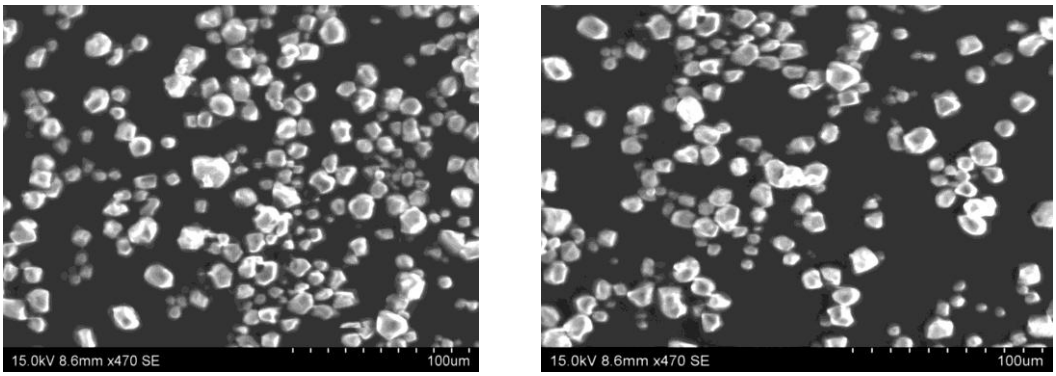


Figure 10: In vitro diffusion profile of Glimepiride cubosomesF6-F14 in 6.8pH phosphate buffer

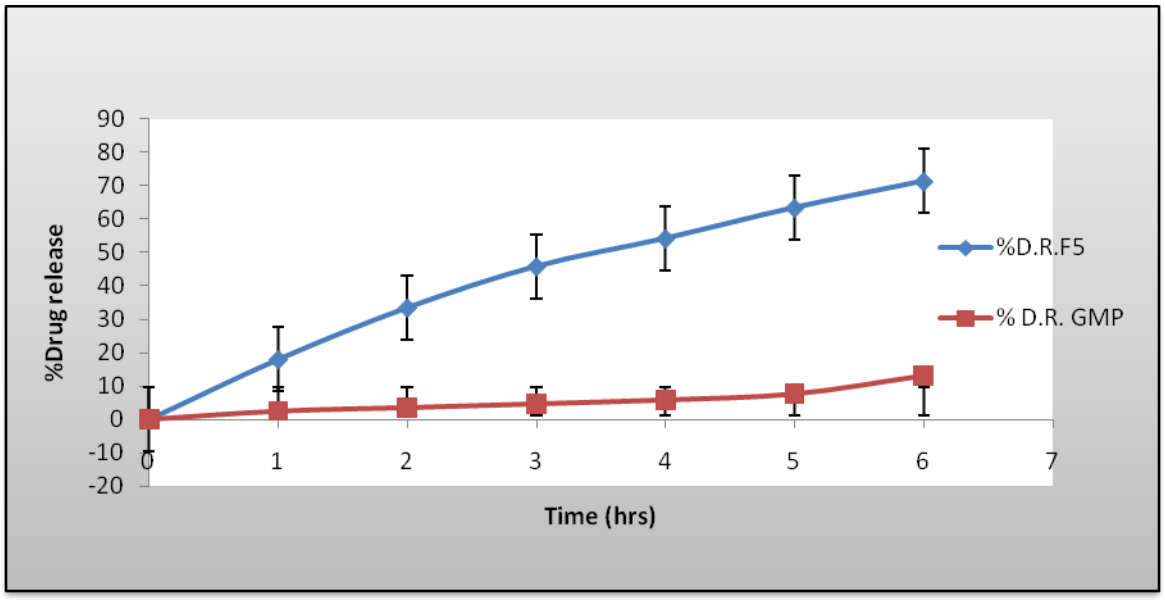


Figure 11: In vitro diffusion profile of Glimepiride crude drug and optimized Glimepiride cubosome formulation in 6.8pH phosphate buffer

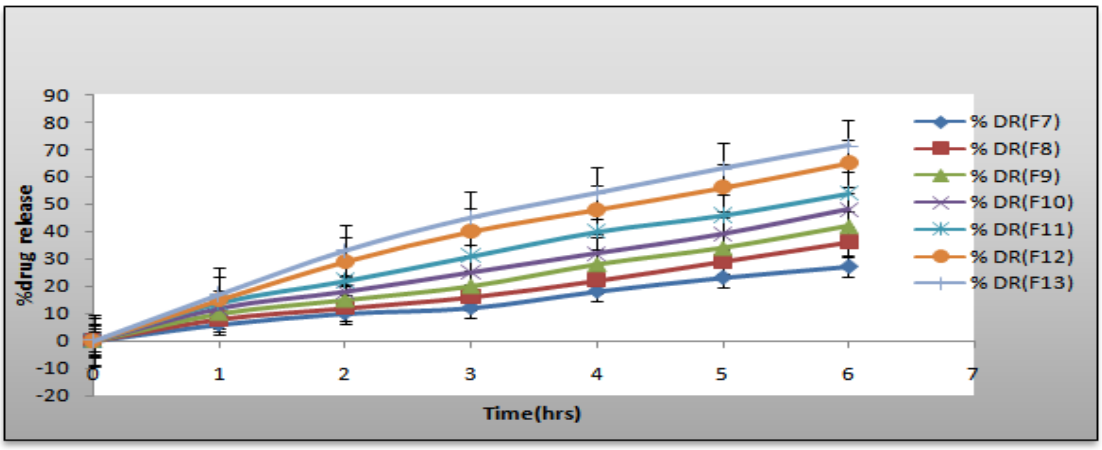


Figure 12: SEM images of Glimepiride cubosomal granules formulation C2

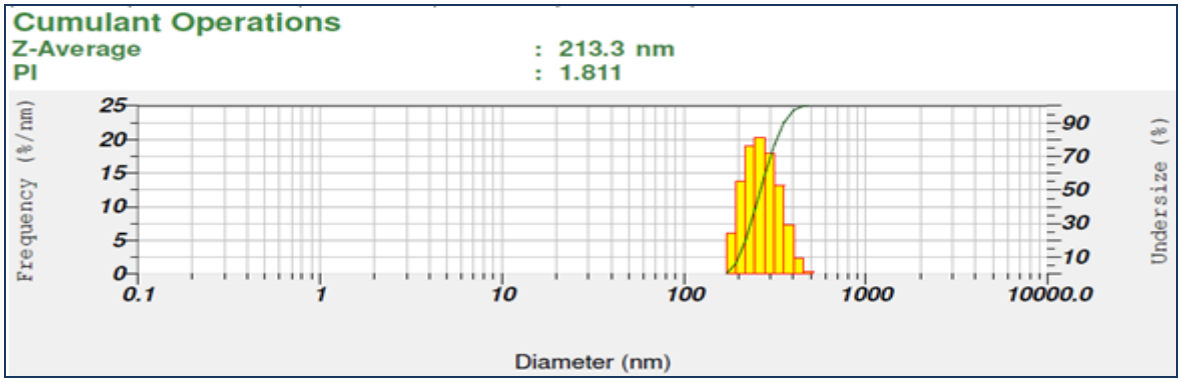


Figure 12: Particle size of Glimepiride cubosomal granules formulation C2

Peak No.	Zeta Potential	Electrophoretic Mobility
1	-159.6 mV	-0.001241 cm2/Vs
2	--- mV	--- cm2/Vs
3	--- mV	--- cm2/Vs

Zeta Potential (Mean) : -159.6 mV

Electrophoretic Mobility mean : -0.001241 cm^2/Vs

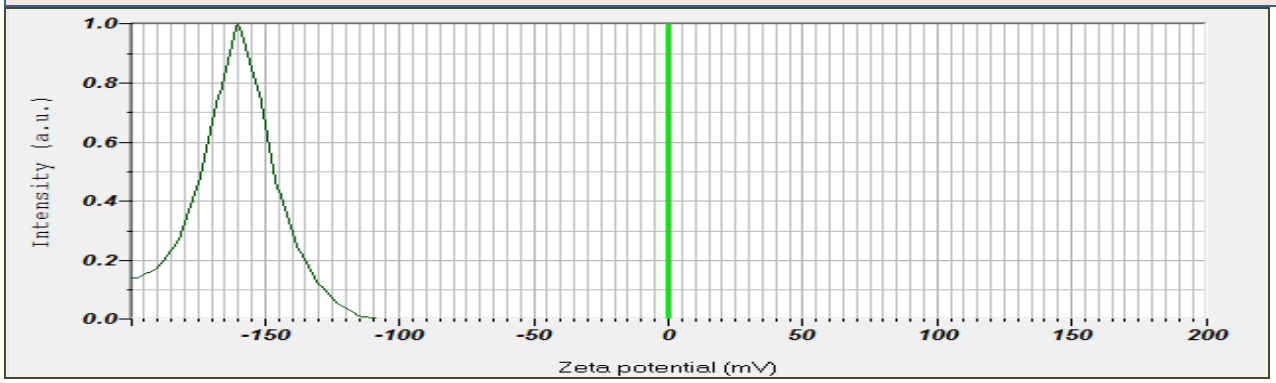


Figure 13: Zeta potential of Glimepiride cubosomal granules formulation C2

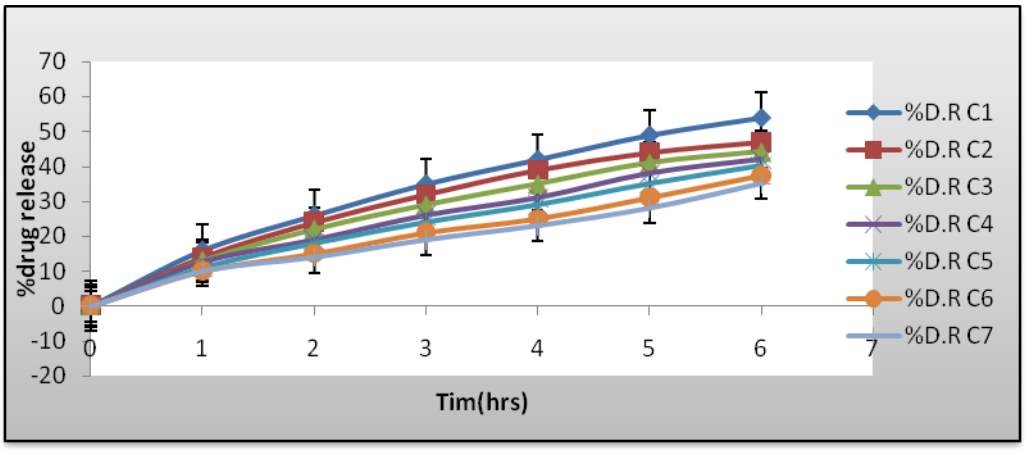


Figure 14: In Vitro dissolution profile of Glimepiride Cubosomal oral capsule using starch C1 to F7 in 6.8 pH phosphate buffer

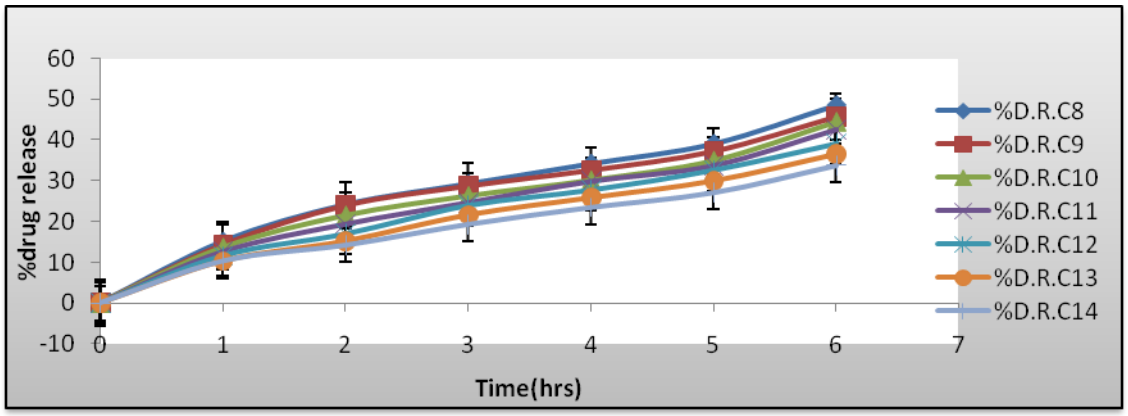
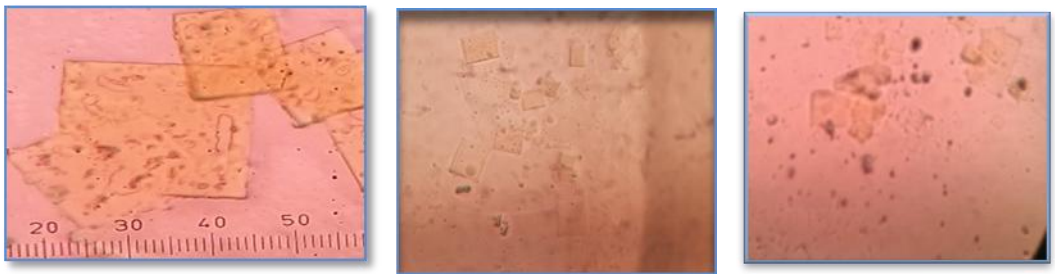


Figure 15: In Vitro dissolution profile of Glimepiride Cubosomal oral capsule using Aerosil C8 to C14 in 6.8 pH phosphate buffer



(a) **(b)** **(c)**

Figure 16: Optical microscopy of (a) Glimepiride cubosomal dispersion (b) starch loaded Glimepiride cubosomal granules, (c) aerosil loaded Glimepiride cubosomal granules