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REPAGLINIDE LOADED CUBOSOMES AS AN ORAL NANODELIVERY SYSTEM

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ABSTRACT

Cubosomes are nanoparticle, more accurately nanosrtructure particles of a liquid crystalline phase with cubic crystallographic symmetry formed by the self assembly of amphiphilic or surfactants like molecule. This study is to investigate the potential of cubosomes as lipid nanocarrier to improve the controlled release of Repaglinide. Repaglinde is used for treatment of type 2 diabetes. Repaglinide cubosomes were prepared by Top down approach employing GMO as lipid phase vehicle, Poloxamer 407 as stabilizer and distilled water as aqueous phase. The resultant cubosomes dispersion were characterized by encapsulation efficiency, *in-vitro* drug release, particle size, zeta potential, FTIR and SEM. Best formulation (F3) showed a maximum drug release of 95.99 % in 12 hours, particle size of 91.26nm and zeta potential of -19.1mV. Repaglinide cubosomal Capsules were prepared by lyophilization of the cubosomal dispersion, and starch was used as diluent. The capsules were evaluated for drug content, weight variation and *in-vitro* drug release. Optimized capsule formulation (F3) contains starch showed a maximum drug release of 95.55% in 12 hrs. The 'R^2' values of zero order plots were in range of 0.9853 to 0.9162 indicating drug release from most of the formulations was found to follows zero order kinetics.

KEYWORDS

Cubosomes, Repaglinide, Amphiphilic, Top-down approach, Lyophilisation and *In-vitro* drug release.

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INTRODUCTION

The oral route of drug administration is the most frequently used and acceptable among the various drug administration routes due to its simplicity and convenience, which improve patient compliance.

When amphiphilic lipid systems are placed in aqueous environment that will formed self assembled nanostructured dispersed particles which are expressed as "cubosomes" whose size ranges

from 10-500nm[1]. Cubosomes are nanoparticle, more accurately nanosrtructure particles of a liquid crystalline phase with cubic crystallographic symmetry formed by the self assembly of amphiphilic or surfactants like molecule[2].

Cubosomes can be loaded with poorly water soluble drugs in their three dimensional cubic phases, leading to pronounced increase in the solubility, stability and bioavailabilty of these drugs[3]. The large surface area, fluidity (low viscosity) and small size are offer control release. These can be used for carrier potential of hydrophilic, lipophilic and amphiphilic drugs to the particular site of action, thus allow drug targeting and sustained or controlled release of conventional medicines[4]. It offers well controlled delivery to variety of drug candidates like anti-inflammatory compounds, local anaesthetics, antidiabetic, antibiotics and anticancer drugs. In case of hydrophilic glucose and insulin moieties, the permeability through the biomembrane is limited; this can be successfully overcome by incorporating them in cubosomes[5].

Throughout recent years, scientists have been particularly interested in exploring the pharmaceutical application of cubosome and cubosome based systems. With recent developments in nano-pharmaceutical engineering, experience and expertise, cubosome-based systems are actively being explored as potential alternatives to now-common systems such as liposomes and niosomes. Cubosomes consist of a binary system of monoolein and water in which the monoolein acts as a precursor to lipid bilayer dividing the hydrophilic regions of cubic phases. This binary system can assemble itself into bi-continuous, cubic, liquid-crystalline phases, which are thermodynamically stable[6]. The critical characteristics of cubic liquid phases were their interface area (~400m^2), bilayer thickness (3.5mm) and pore diameter (5mm)[7]. Cubosomal cubic phase structure can be described by analogy with soap films by the concept of differential geometry and periodic minimal surfaces. Cubic phases were observed to have three structures: Diamond (Pn3m, Q224) or D surface, primitive surface (Im3m, Q299) or P surface and Gyroid surface (Ia3d, Q230) G surface (Figure No.4). The D-surfaces formed at high water levels in the monoolein water system, the G-surface is formed at lower levels and the P-surface is formed by adding caseins or amphiphilic block copolymer[8].

Repaglinide (REP) is an oral antidiabetic drug, which was developed to specifically control meal related glucose fluctuation in patients with type II diabetes mellitus by stimulating insulin secretion from the pancreas. The dose of drug is 0.5mg-2mg in 3-4 times daily. REP is a meglitinide derivatives belongs to BCS class II drug with short half life(1hr), having less than 60% bioavailability and low solubility[9].

MATERIAL AND METHODS

Repaglinide, glyceryl monooleate, poloxamer 407 and starch were procured from Yarrow Chem, Mumbai, India. All chemicals/ reagents used were of analytical grade.

METHODOLOGY

Compactibility study by FTIR[10]

FTIR spectra matching approach was used for detection of any possible chemical interaction between the drug and excipients. The mixture of drug and excipients was scanned in FTIR spectrophotometer (Jasco FTIR 4100, Japan) in the range of 4000 to 400Cm^{-1}. The FTIR spectrum of the mixture is compared with those of pure Repaglinide and peak matching is done to detect any appearance or disappearance of peaks.

PREPARATION OF CUBOSOMES[11]

Preparation of cubosomal dispersion was based on the emulsification of monoglycerides/ surfactant mixture in water. The composition of various formulation is presented in Table No.1. The poloxamer 407 and glyceryl monooleate (GMO) of varying concentration (1:3, 1:6, 1:9, 1:12) were melted at 70^oC using water bath. Poloxamer was completely dissolved in GMO, repaglinide was added to the molten mixture and stirrer to mix properly. The obtained molten solution was added drop wise to the 10ml aqueous solution at 70^oC

under magnetic stirrer (REMI Electroteknic) at 1000rpm to achieve homogenous state for 2hrs. Mixture was allowed to cool at room temperature for 24 hrs. The mixture was dispersed with water up to 20ml. The crude dispersion was subjected to probe sonication (AELTA FS-600) at 500w for 10 min. The final dispersion of cubic nanoparticles is stored at room temperature for later studies.

EVALUATION TEST FOR CUBOSOME CONTAINING REPAGLINIDE

Entrapment efficiency[12]

For the determination of entrapment efficiency, 3ml of diluted sample was placed in centrifuge tubes. The un-entrapped drug was first separated by centrifugation at 12000rpm for 15 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 λmax. The percent of encapsulation efficiency (EE %) was determined by the following equation:

EE%= total drug - free drug ÷ Total drug ×100

Average particle size[13]

Average particle size (in nanometer) and of the cubosomes was measured using a Malvern nano zeta sizer instrument.

Zetapotential[14]

Measurement of zetapotential of the cubosomes was done by using Malvern nano zeta sizer instrument. Measurements were performed on the samples prepared for size analysis. Zetapoetntial indicates the degree of repulsion between adjacent, similarly charged particles in dispersion system.

Scanning electron microscopy (SEM)[15]

The morphology of cubosomes is determined using scanning electron microscopy (SEM – Hitachi S 3700N). SEM gives a three dimensional image of the globules. The samples were examined at suitable accelerating voltage 20 kV, at different magnification.

***In-vitro* drug release from cubosomes**[16]

The *in vitro* release of Repaglinide from different cubosomes was performed by using the dialysis method. The semipermeable membrane was previously soaked in phosphate buffer of pH 6.8 and dried, and was stretched over the open end of the glass tube. 2.5ml of repaglinide loaded cubosomes dispersion is placed in the glass tube. The tubes were then immersed upside - down in a 250ml beaker containing 100ml phosphate buffer of pH 6.8. The tubes height was adjusted so that the membrane was just below the surface of the release medium. The whole assembly was shaken at 50rpm during the entire time of diffusion. For each sample, 3ml was withdrawn at 0.25, 0.5, 1, 2, 3, 4, 5, 6 and 12 hours time intervals and replaced by equal volume of fresh release medium maintained at the same room temperature. Samples were measured spectrophotometrically at λmax 244nm.

FORMULATION OF CAPSULE CONTAINING CUBOSOMES

The cubosomal dispersion was dried by using lyophilizer (freeze drier). To the cubosomal formulation starch was added separately to obtain a wet mass. Then the wet mass was passed through sieve no.16 to form granules. The granules were air dried at room temperature and were filled into '000' sized capsules.

EVALUATION TEST FOR FORMULATED CAPSULES CONTAINING CUBOSOMES

Morphology of cubosomal granules

The morphology of cubosomes was determined by using scanning electron microscopy (SEM-Hitachi S 3700N). The samples were examined at suitable accelerating voltage 20kv, at different magnification.

Flow properties[17]

The flow properties were studied by measuring the quality parameters like angle of repose, bulk density, tapped density, Hausner's ratio and carr's compressibility index.

Angle of repose (θ)

A funnel was filled to the brim and the test sample was allowed to flow smoothly through the orifice under gravity. From the cone formed on a graph sheet was taken to measure the area of pile (r),

thereby evaluating the flow ability of the granules. Height of the pile (h) also measured.

Tan θ = h/r

$\theta = \tan^{-1} h/r$

Bulk density and Tapped density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of accurately weighed powder (bulk) from each formula, previously shaken to break any agglomerates form was introduced into a 25ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5cm at 2 sec interval. The taping was continued until no further change in volume was noted. LBD and TBD were calculated using following formula,

LBD = Weight of the powder/volume of the packing.

TBL = Weight of the powder/tapped volume of packing.

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula,

Hausner's Ratio = TD / BD

Carr's compressibility index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it is packed down. The formula for (%) Carr's Index is as below:

Carr's Index (%) = [(TBD-LBD) x100]/TBD

Drug content[18]

Five capsules were weighed and their contents were removed. An accurately weighed samples of equivalent to 4 mg of Repaglinide were transferred into a 100ml volumetric flask, and add 10ml of methanol to dissolve Repaglinide. The solution was made up to volume with phosphate buffer pH 6.8. The resulted solution was filtered and suitably diluted and the drug content was estimated spectrophotometrically by measuring the absorbance at λmax.

Weight variation[19]

Twenty capsules were selected randomly and weighed individually to check for weight variation. The average net weight was then determined by sum up all the individual net wts. The percentage deviation of capsules weight was determined. The deviation of individual net weight should not exceed the limits given below.

***In-vitro* dissolution study**[20]

Dissolution testing was performed in compliance with USP using apparatus I. A dissolution medium of 6.8 pH phosphate buffer was chosen. A basket speed of 50rpm was selected with media volume of 900ml. The medium was maintained at 37 ± 0.5ºC. The dissolution vessels were covered to minimize evaporation. 5ml 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 λmax.

Kinetic modelling

The cubosomal oral capsule was studied for release kinetics. Coefficient of correlation values were calculated for the linear curves obtained by regression analysis of the plots.

Stability studies

Selected formulation was subjected to stability studies for 2 months at an accelerated condition at 30±2ºC/65±5% RH and 40±2ºC/75±5% RH due to lack of time to carry out for 6 months as per new ICH guidelines. Cubosome capsules were evaluated for drug content and *in-vitro* drug dissolution studies.

RESULTS AND DISCUSSION

Compactibility study by FTIR

The FTIR spectra of the Repaglinide was compared with the standard spectrum of formulation (F3) and the characteristic peaks associated with specific functional groups and bonds of the molecule and their presence/ absence were noted and the overlay of pure drug and formulation (F3) was shown in Figure No.4 and Figure No.5.

The prominent peaks associated with N-H stretch (3300-3500), C-H stretch (3000-2840), C=O (1590-1750), C-H deformation (1550-1640), C-O-C stretch (1300-1000) were analysed. The range of peak values were found to be the same indicating that there were no interaction of Repaglinide with polymer conforming the stability of drug in the formulation.

EVALUATION TEST FOR CUBOSOME CONTAINING REPAGLINIDE

Entrapment efficiency (EE)

The EE of all the formulation F1, F2, F3 and F4 is in the range of 31±0.55-77±0.76 as shown in Table No.3. The highest entrapment efficiency was found in the batch F3, consisted of GMO and poloxamer 407 in the ration of 1:9.

Average particle size and size distribution

Particle size analysis of cubosomes was determined using Malvern zeta sizer instrument. The results showed that as the GMO and poloxamer content increases, the particle size decreases. The particle size of formulation F1-F4 that is 175.1nm, 153.3nm, 91.26nm and 152nm, from which F3 (9:1) was lesser than other formulations (Figure No.6). It was found that the average particle size of F3 was approximately 91.26nm.

Zeta potential

Zeta potential of the Repaglinide cubosomes (F1-F4) was determined by Malvern nano zeta sizer instrument. It was found that zeta potential of all formulation was negative i.e -14.5Mv, to -20.6Mv. Negative potential indicates that the particles have no charge as a whole system is stable.

Surface morphology

The shape and surface morphology of the prepared cubosomes were observed by scanning electron microscopy. SEM photograph of the formulations F3 (Figure No.7) revealed that the coexistence of the particles and vesicles and well separated from each other with smooth surface.

The SEM studies of Repaglinide cubosomes showed that formulation (F3) is in the nano size, which confirms the results of particle size measurement.

In-vitro drug release from cubosomes

In-vitro drug dissolution profile or of the prepared cubosomes were observed by Dialysis method. The results obtained for all formulations (F1-F4) were shown in Figure No.8. The cumulative percent drug release after 12 hours were found to be 82±0.93, 83.11±0.49, 95.99±0.71, 89.01±0.78 respectively. Formulation F2 showed least percentage cumulative drug release value 82% at 12 hrs and formulation F3 showed highest percentage of drug release value 95.99% at 12 hrs. As expected all formulations (F1 -F4) were shows controlled drug release for 12 hours.

The drug dissolution is directly proportional to the concentration of GMO and inversely proportional to the concentration of poloxamer 407. Here F3 formulation exhibited the lowest particle size, highest entrapment efficiency, adequate zeta potential, high drug content and controlled drug release. Therefore cubosomal capsule formulation F3 with GMO: poloxamer 407 ratio of 1:9 was selected as the best formulation for stability studies

EVALUATION TEST FOR CAPSULE CONTAINING CUBOSOMES

Surface morphology (SEM) of Repaglinide cubosomal granules

The shape and surface morphology of the prepared cubosomes were observed by scanning electron microscopy. SEM photograph of the formulations F3 (Figure No.9) revealed that the coexistence of the particles and vesicles and well separated from each other with smooth surface.

From the results that are listed in the Table No.4, the angle of repose was found to be 22.1±0.14 to 27.3±0.32 indicating good flow properties of granules. The bulk density was found to be 0.41±0.02 to 0.67±0.01gm/cc. the tapped density was ranges from 0.49±0.02 to 0.76±0.01gm/cc. The carr's index was ranges from 11.2±0.27 to 14.13±0.12%. Hausner's ratio of all formulation was found to be 1.13±0.08 to 1.16±0.15. The values showed low intra particle friction between the granules. The granules were found to be free flowing.

Drug content

Table No.5 showed the percentage drug content in each formulation. Formulation F3 showed highest drug content value 94.25±0.08%, F4 showed lowest drug content value 84.10±0.15. Percentage drug content of Repaglinide in all the formulated capsules were found within the range of 84.10±0.15 to 94.25±0.08 indicates uniform mixing.

Weight variation test

The weight variations for all the formulations were shown in Table No.5. Formulations F1 showed least %weight deviation of 98±0.31% where F2 showed highest %weight deviation 100±0.61%. Weight variation value of all formulations ranges from 98±0.31% to 100±0.61%. All the capsules were passed weight variation test as the average weight variation was within the IP limit ±10%. The weight of all the capsules was found to be uniform with low standard deviation value.

% deviation of the individual weight from the average weight

$$= \frac{\text{the weight of individual capsule – the average weight}}{\text{The average weight}} \times 100$$

***In-vitro* drug dissolution**

In-vitro drug dissolution profiles obtained for all formulations (F1-F4) were shown in Figure No.10. The cumulative percent drug release after 12 hours were found to be 80±0.61, 82.11±0.11, 95.55± 0.85, 88.01±0.40 for formulation F1, F2, F3 and F4 respectively. Results revealed formulation F3 shows higher drug release i.e 95.55 at 12 hours. As expected all formulations (F1-F4) were showed controlled drug release for 12 hours. The drug dissolution is directly proportional to the concentration of GMO and inversely proportional to the concentration of poloxamer 407.

Here F3 formulation exhibited the lowest particle size, highest entrapment efficiency, adequate zeta potential, high drug content and controlled drug release. Therefore cubosomal capsule formulation F3 with GMO: poloxamer 407 ratio of 1:9 was selected as the best formulation for stability studies.

Release kinetics

The *In vitro* drug release data was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic models in order to determine the mechanism of drug release. When the regression coefficient values of zero order and first order plots were compared, it was observed that 'R^2' values of first order plots were in range of 0.7734 to 0.8242 and zero order plots were in range of 0.9853 to 0.9162 indicating drug release from most of the formulations was found to follows zero order kinetics. Table No.6 shows R^2 values of all formulations were shows the zero order and first order plots.

Stability studies

The results of the stability studies indicated that the cubosomes did not show any changes in the drug content during the stability study period. The percentage cumulative drug dissolution after 60 days at 30±2ºC and 65±5% RH and 40±2ºC and 75±5% RH showed 94.89±0.75 and 93.11±0.51 after 12 hours indicating no significant changes. The results obtained were depicted in Table No.7 and Figure No.11.

Table No.1: Formulation chart of cubosomes

S.No	Formulation code	Ratio	Poloxamer 407(gm)	GMO (gm)	Repaglinide (mg)	Water up to (ml)
1	F1	1:3	0.625	1.875	25	20
2	F2	1:6	0.357	2.143	25	20
3	F3	1:9	0.25	2.25	25	20
4	F4	1: 12	0.157	2.343	25	20

Table No.2: Formulation chart for cubosomal capsules

S.No	Ingredients	Quantity (mg)
1	Cubosomes	80mg
2	Starch	20mg

Table No.3: Percentage entrapment efficiency (%EE) of cubosomes (F1- F4)

S.No	Formula	% EE *
1	F1	31± 0.55
2	F2	42± 0.76
3	F3	77± 1.23
4	F4	64± 0.54

*data expressed as a mean ±SD, n=3

Flow properties

Table No.4: Flow properties of Repaglinide cubosomal granules

S.No	Formulation code	Angle of repose*	Bulk density (gm/cc)*	Tapped density (gm/cc)*	Hausner's ratio*	Carr's index*
1	F1	22˚.1'±0.14	0.57±0.17	0.63±0.17	1.11±0.02	13.5±0.10
2	F2	22˚.2'±0.24	0.52±0.25	0.56±0.25	1.16±0.15	12±0.14
3	F3	25˚.7'±0.19	0.41±0.02	0.49±0.02	1.13±0.08	11.2±0.27
4	F4	27˚.3'±0.32	0.67±0.01	0.76±0.01	1.12±0.11	14.13±0.12

*data expressed as a mean ±SD, n=3

Table No.5: Weight variation of capsules and drug content

S.No	Formulation code	% wt. deviation *mg ± SD	*Drug content
1	F1	98±0.31	87.93±0.29
2	F2	100±0.61	86.78±0.25
3	F3	99±0.23	94.25±0.08
4	F4	98±0.47	84.10±0.15

*data expressed as mean ±SD, n=3

Table No.6: Release kinetics of Repaglinide capsules

S.No	Formulation code	First order	Zero order
1	F1	0.8242	0.9356
2	F2	0.7989	0.9146
3	F3	0.7889	0.9853
4	F4	0.7734	0.9162

Table No.7: Evaluation of F3 during stability study

S.No	Evaluation parameter	Time (days) (accelerated condition at 30±2°C and 65±5%RH (*), 40±2°C and 75±5% RH (**)					
		0 Day		30th Day		60th Day	
1	Drug content	*94.25±0.08	**94.17±0.05	*94.30±0.29	**94.11±0.61	*94.28±0.73	**93.78±0.85

Figure No.1: Cubosomal dispersion

Figure No.2: Lyophilization of cubosomal dispersion

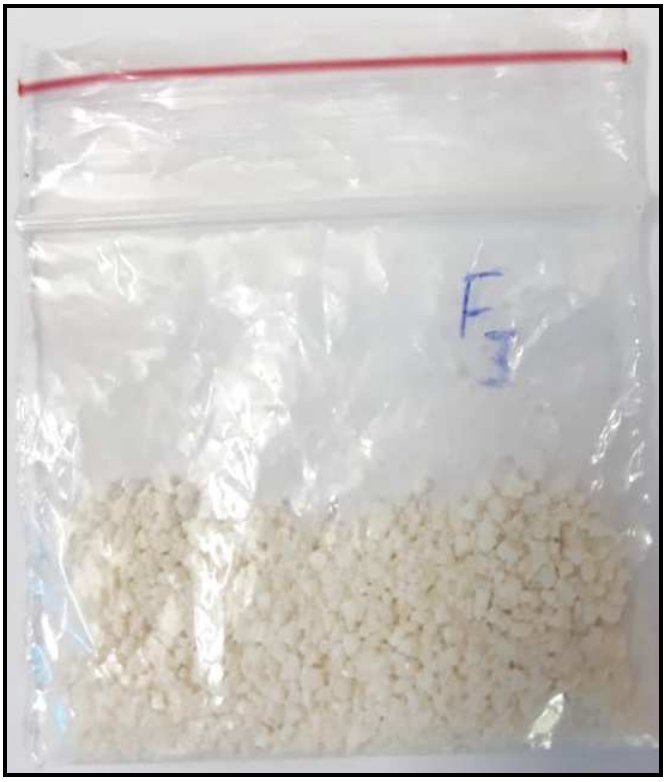

Figure No.3: Granules of Repaglinide

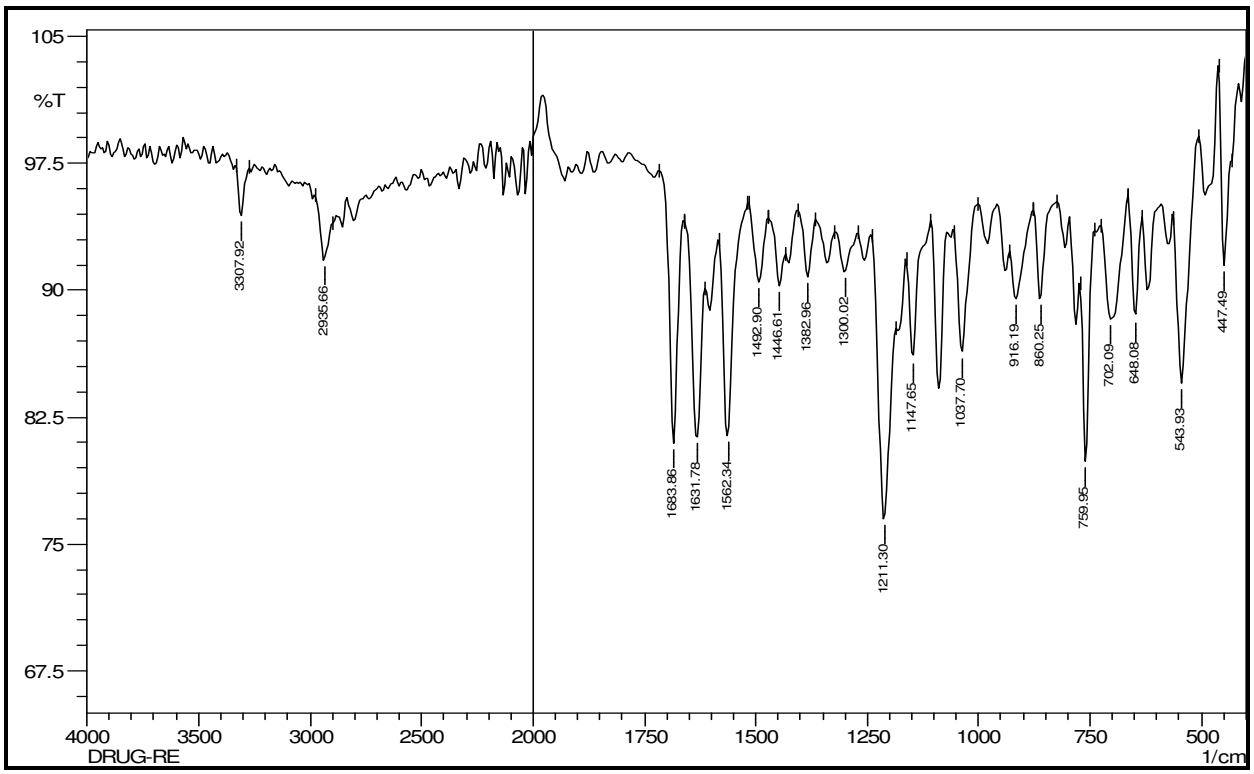

Figure No.4: IR-spectrum of pure drug Repaglinide

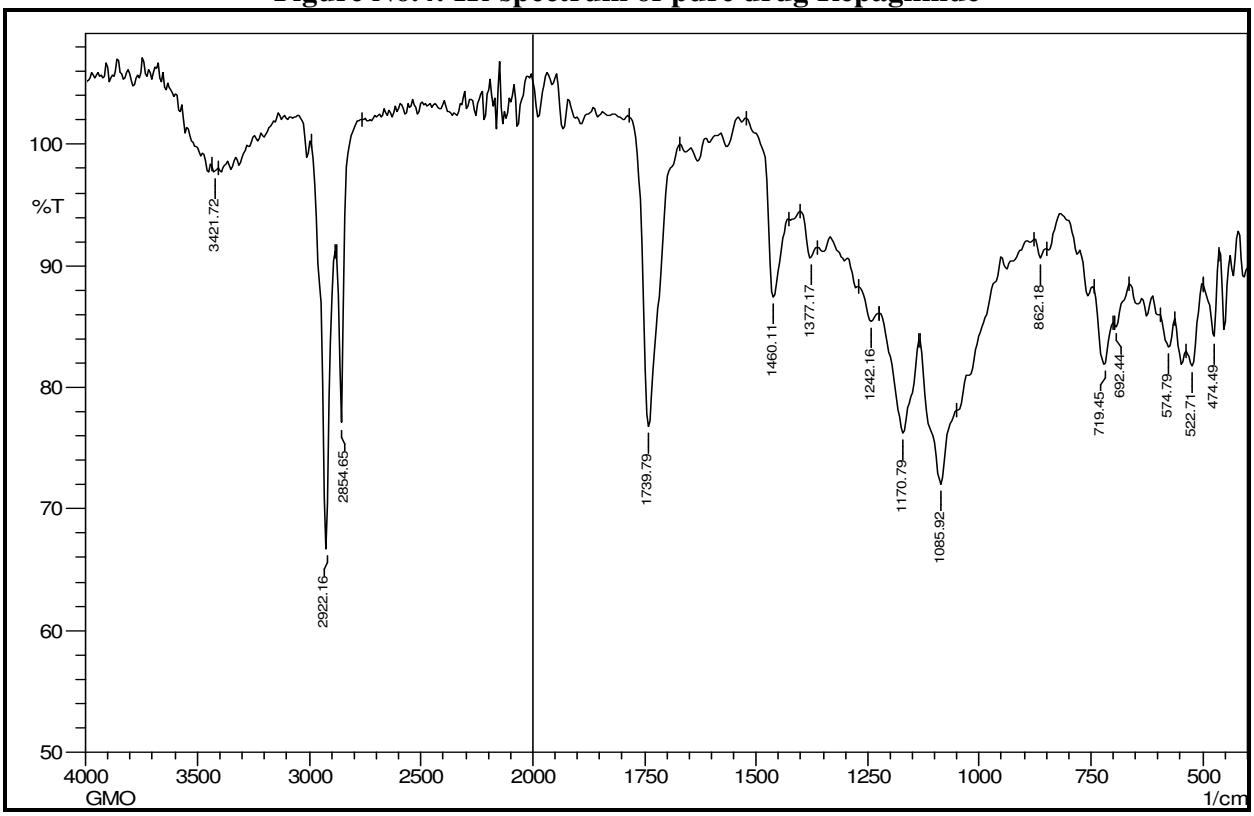

Figure No.5: Spectrum of formulation

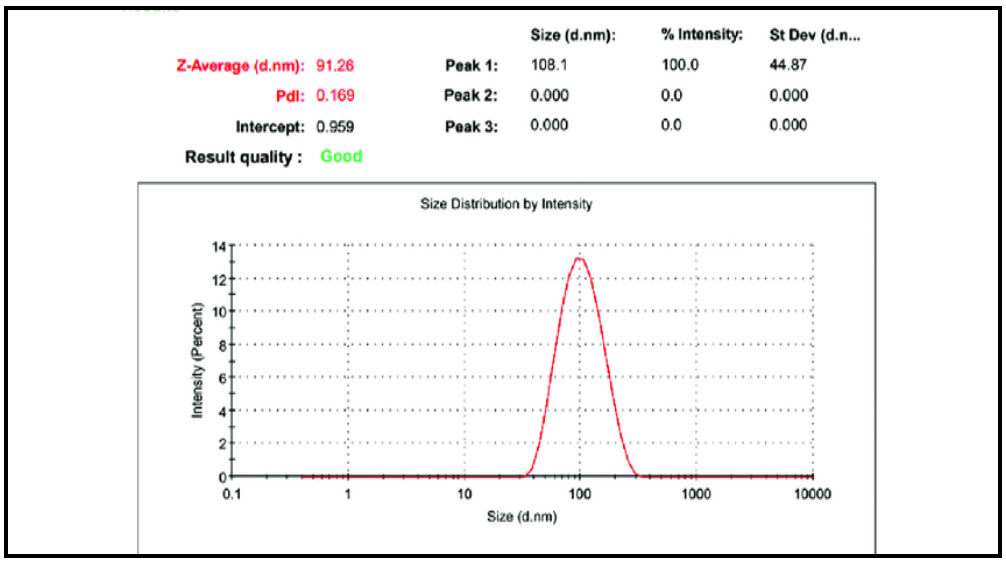

Figure No.6: Particle size of F3 by Malvern zeta sizer

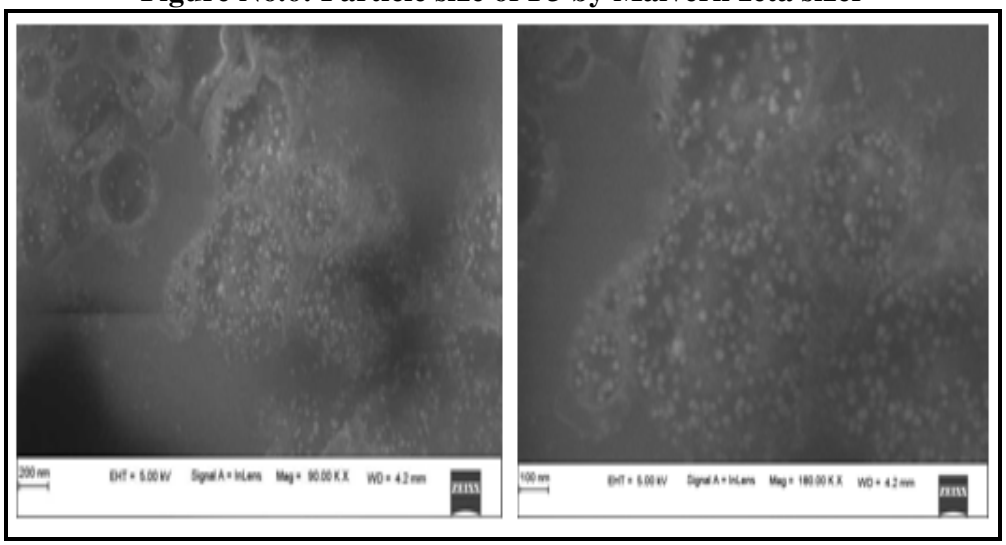

Figure No.7: SEM image of F3 formulation of cubosomes

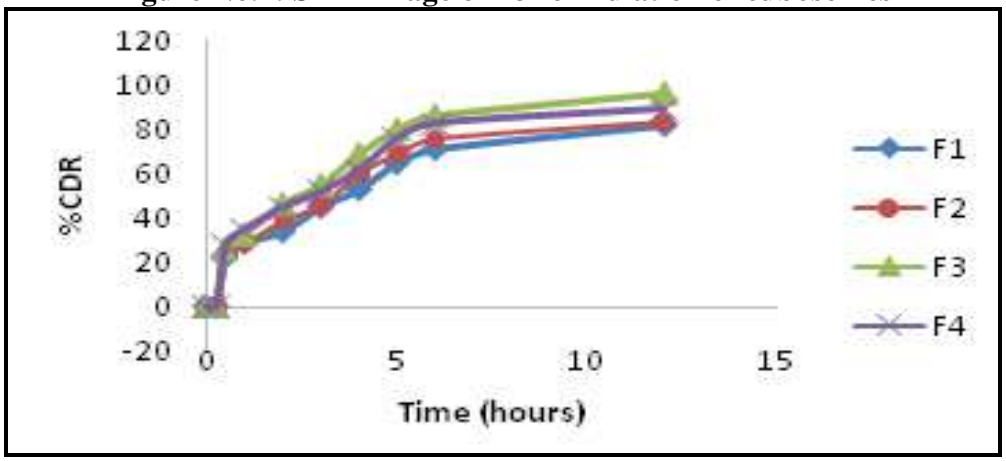

Figure No.8: *In-vitro* drug release profile of cubosomes (F1-F4)

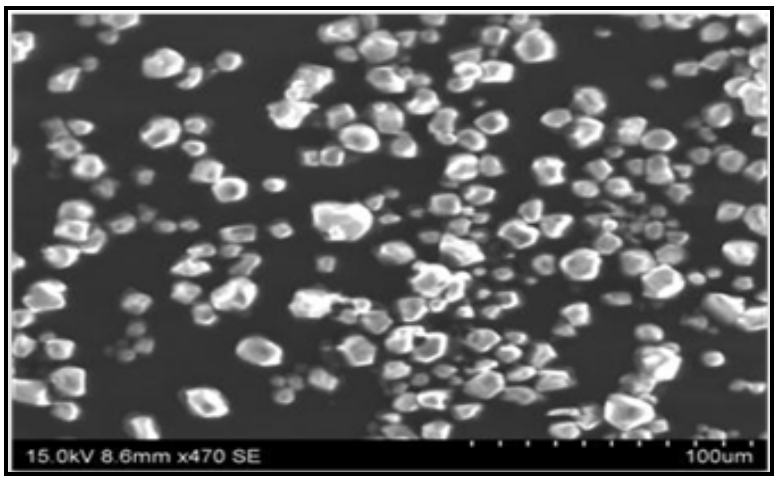

Figure No.9: SEM image of Repaglinide cubosomal granules of formulation F3

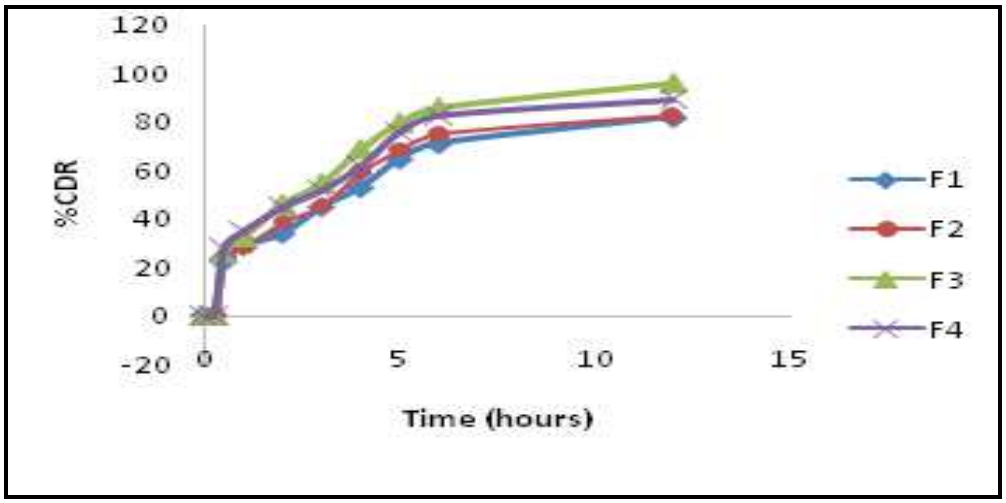

Figure No.10: *In-vitro* drug dissolution profile of formulations (F1- F4)

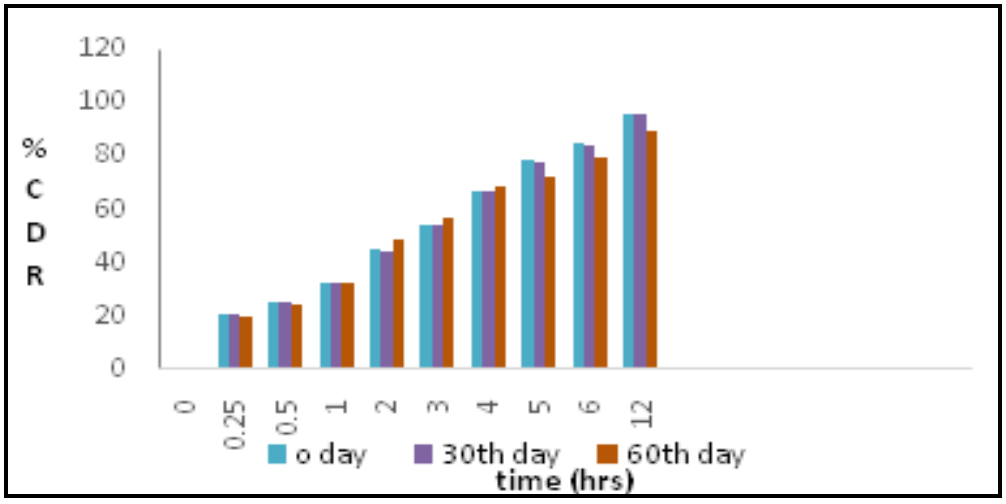

Figure No.11: *In-vitro* drug dissolution profile of F3 during stability study

CONCLUSION

The present study has been a satisfactory attempt to formulate cubosomal nano carriers for the controlled delivery of Repaglinide using lipid system glyceryl monooleate and surfactant poloxamer 407. From the reproducible results of the executed experiments, it can be concluded that: The Repaglinide cubosome were prepared by top-down approach based on the emulsification of glyceryl monoleate (lipid system) and poloxamer 407 (surfactant) mixtures in water. The entrapment efficiency of the prepared cubosome increased as the concentration of GMO increased. Formulation F3 was showed 77±0.76%.

The particle size determination of formulated cubosomes shows that the particles in all formulations were in nano range. From result F3 showed the smallest particle size that is 91.26nm.

In-vitro drug release study showed that the amount of GMO increases the extent of drug dissolution also increases. Result of dissolution study contended the ability of cubosome nano carriers to control release rate of the drug Repaglinide. The cumulative drug release from formulation F3 with poloxamer 407: GMO ratio of 1:9 showed the desired release rate, compared to other formulations. Showed desired drug release of about 99.55% after 12 hours.

Stability studies were carried out for the best formulation F3. The results of drug content and *in-vitro* drug release studies showed no significant changes indicating the formulation is stable.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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