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Dissolution enhancement of glimepiride dispersion using glyceryl monostearate and β-cyclodextrin as carrier

Md. Abu Shuaib Rafshanjani[1], *Md. Mofizur Rahman[1], Shumaia Parvin[2], and Md. Abdul Kader[2]

[1]Department of Pharmacy, Bangladesh University, 15/1, Iqbal Road, Mohammadpur, Dhaka-1207, Bangladesh
[2]Department of Pharmacy, University of Rajshahi, Rajshahi 6205, Bangladesh

ABSTRACT

Glimepiride is an antidiabetic drug of sulfonylurea group and indicated for the treatment of type 2 diabetes mellitus. The present study was conducted to enhance the dissolution rate of glimepiride solid lipid nano particle dispersions using hot homogenization method and glimepiride solid dispersion by precipitation method. Solid lipid nanoparticles have been used as suitable carriers for delivery of drug with poor solubility. In this investigation glyceryl monostearate and stearic acid were used as solid lipid, Lutrol F-68 as surfactant, Tween 80 as stabilizer and the used polymer were urea crystal and β-cyclodextrin. Three formulations were prepared in different ratios for two methods and were designated as GMLN1 to GMLN3 in case of hot homogenization method and GMP1 to GMP3 for precipitation method. The evaluation of all the dispersions were done by *in vitro* dissolution studies using US Pharmacopeia type II apparatus (paddle method) in 900ml distilled water at 50 rpm to a temperature of 37°C ± 0.5°C for 45 minutes. In situ and externally sink method revealed the release pattern of drug was found to follow zero order, first order and Korsmeyer-Peppas equations. Improved dissolution profile was observed in all the solid lipid nano particle dispersions as compared to pure drug as well as market preparation. Thus, glyceryl monostearate and β-cyclodextrin can be successfully used as carrier for improvement of dissolution and bioavailability of glimepiride.

Key Words: Glimepiride, solid lipid nano particles, dissolution rate, hot homogenization method, precipitation method.

INTRODUCTION

The aqueous solubility of a drug is a key determinant of its oral bioavailability. There are some drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Drug absorption, sufficient and reproducible bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependent on aqueous solubility of that compound (Jatwani *et al*., 2012; Wagh and Wagh, 2015). More than 40% of new drugs have poor aqueous solubility, resulting in unsatisfactory oral drug delivery. Thus, increased solubility, dissolution rate and bioavailability of drug have a very crucial role in the process of drug development (Yogesh *et al*., 2011). Besides this, BCS II drugs are very much prone to dissolution-rate limited gastrointestinal absorption (Shohin *et al*., 2011; Reddy *et al*., 2011). Hence, by improving drug dissolution in aqueous medium, various formulation techniques can accelerate a parallel improvement in bioavailability (Wei and Lobenber, 2006; Kawabata *et al*., 2011; Kawakami, 2012).

Drug dissolution enhancement has been extensively studied over the past decade through different techniques (Ahuja *et al*., 2007; Blagden *et al*., 2007; Cilurzo *et al*., 2008; Makar *et al*., 2013). Among these, the SD technique is the most successful in improving the dissolution and bioavailability of poorly soluble active pharmaceutical ingredients because it is very simple and economic (Leuner and Dressman, 2000; Chiou and Rigelman, 1971; Serajuddin, 1999). Solid lipid nanoparticles (SLN) are aqueous colloidal dispersions, is made up of solid biodegradable lipids having a lot of the advantages with a limited drawbacks

(Swathi *et al*., 2010; Sarathchandiran, 2012).

Glimepiride (GMP) is 3-ethyl-4-methyl-N-{2-[4-({[(4methylcyclohexyl) carbamoyl] amino} sulfonyl) phenyl] ethyl, is an antidiabetic drug originated from the second generation sulphonyl urea group and stimulates the release of insulin. It is also classified as class II drug according to biopharmaceutical classification system and used for treatment of non-insulin-dependent diabetes mellitus (Frick *et al*., 1998; Massimo, 2003). In acidic and neutral aqueous media, glimepiride shows very poor solubility at 37°C (<0.004 mg/ml). Solubility of drug is slightly increased by 0.02 mg/ml in media having pH>7. Poor dissolution and unsatisfied bioavailability of this drug are the results of this poor aqueous solubility (Frick *et al*., 1998). Previous reports on this drug revealed that dissolution rate is increased through formation of inclusion complex with cyclodextrin (Ammar *et al*., 2006) or preparation of solid dispersions using either water soluble carriers (Boregowda *et al*., 2011; Rajpurohit *et al*., 2011), insoluble carriers (Kiran *et al*., 2009; Reven *et al*., 2010; Vidyadhara *et al*., 2011) or preparation of spray congealed microparticles (Ilić *et al*., 2009). However, for improving its bioavailability only a few attempts have been made. Hence, the present investigation was done to improve the dissolution rate as well as bioavaibility of glimepiride by the preparation of solid lipid nano particle dispersion using glyceryl monostearate and stearic acid as solid lipid and by formation of inclusion complex with β-cyclodextrin and urea crystal.

MATERIALS AND METHODS

Materials

Glimepiride was a gift sample from Beximco Pharmaceuticals, Dhaka, Bangladesh. Glyceryl monostearate and stearic acid were procured from Balami Fine Chemicals, India. Tween 80 and lutrol F-68 (poloxamer) were received from Merk chemicals, Mumbai, India. Betacy-

Corresponding Author:
Md. Mofizur Rahman, Assistant Professor
Department of Pharmacy, Bangladesh University
15/1, Iqbal Road, Mohammadpur
Dhaka-1207, Bangladesh
E-mail: *rmfi02@yahoo.com*
Contact No.: +88-01911605139

clodextrin, urea crystals were obtained from BASF, Germany. All other reagents and solvent used were of analytical grade.

Preparation of solid lipid nanoparticle dispersions by hot homogenization method

Solid lipid nanoparticle dispersions were prepared by hot homogenization technique (Mehnert and Mader, 2001). Lipid was melted at temperature ten degrees above its melting point then glimepiride was added to the melted lipid. The dispersion was kept at the same temperature until it is appeared as optically clear. Tween 80 as stabilizer was dissolved in distilled water and heated at the same temperature of lipid mixture. Hot surfactant solution was then added to the melted lipid-drug mixture and emulsified by a homogenizer at 12000 rpm for 2 hours. The formulation was then removed from water bath and the dispersion of SLN was mixed gently at room temperature (table 1).

Preparation of solid dispersions by precipitation method

For the preparation of solid dispersion glimepiride (GMP) was dissolved in ethanol and β –cyclodextrin (β –CD) was dissolved in distilled water at room temperature (Sapkal *et al.*, 2007). Different ratios of drug, β–CD and urea crystal were taken (table 2). The mixture was stirred at room temperature for one hour and then slowly evaporated on a boiling water bath. The precipitates as a crystalline powder was pulverized followed by screening through sieve No. 100 and stored in a desiccator till free from any traces of the organic solvent.

In vitro dissolution studies

In vitro dissolution studies of the pure drug, solid dispersions and market preparations were carried out to estimate the cumulative percentage of drug release with respect to time (Khan and Rhodes, 1975). Distilled water (900ml) was placed in each vessel of the USP type II rotating paddle dissolution apparatus (Veego Vda 6DR, Germany). Two capsules or SDs granules (equivalent to 2mg of drug) were placed in each vessel and the medium was allowed to equilibrate at 50 rpm to a temperature of 37±0.5°C for 45 minutes. 10ml of the sample was withdrawn at definite time interval (5, 10, 20, 30, and 45 minutes) consecutively and replaced by fresh media to maintain the sink condition. The absorbances of sample were measured at λ_{max} 236nm on a UV-Visible spectrophotometer (UVmini-1240, Shimadzu, Kyoto, Japan).

Release kinetic modeling

The release pattern of drug from the dosage forms has been described by a number of kinetic models. As we know that the drug release, *in vivo* performance may be altered by qualitative and quantitative changes in a formulation thus *in vitro* drug dissolution data can be used in the rational development of controlled release formulations (Dash *et al.*, 2010).

Zero-order model

In zero order kinetics the drug release rate is independent of the initial concentration (Hadjioannou *et al.*, 1993) *i.e.*, whatever the amount of drug at absorption site release rate remains the same.

$$C_t = C_0 + K_0 t$$

Where, C_t is the amount of drug dissolved in time t, C_0 is the initial amount of drug in the solution (most times, C_0 = 0), K_0 is the zero-order release rate constant expressed in

concentration / time and t is the time in hours. The data obtained from *in vitro* drug release studies were plotted as cumulative amount of drug released *versus* time.

First-order model

The rate of appearance of drug at the absorption site can be measured by an exponential process (Bourne, 2002) in which the rate of release is only dependent on the remaining drug concentration.

$$\text{Log } C = \text{Log } C_0 - \frac{kt}{2.303}$$

Where, C is the concentration of drug at time t, C_0 is the initial concentration, K is the first order release rate constant expressed in time^{-1}. The data are plotted as log cumulative percentage of drug remaining *versus* time which would obtain a straight line with a slope of – K/2.303

Korsmeyer-Peppas Model

To describe the drug release phenomenon from polymeric systems, the Korsmeyer- Peppas equation (Korsmeyer *et al.*, 1983) is used usually.

$$\text{Log}\left(\frac{M_t}{M_f}\right) = \text{Log } k + n \text{ Log } t$$

Where M_t is the amount of drug release at time t; M_f is the amount of drug release after infinite time; k is a release rate constant; n is the diffusional exponent indicating the mechanism of drug release. The log of percentage drug dissolved is plotted against log time for each formulation. A value of n = 0.45 indicates Fickian diffusion (case-I) release; 0.45 < n < 0.89 for non-Fickian diffusion (anomalous) release; n = 0.89 case-II transport and n > 0.89 indicates super case II release.

Mean Dissolution Time (MDT)

Mean Dissolution Time (MDT) value is a model independed approach and can be calculated from dissolution data using Mockel and Lippold equation (Mockel and Lippold, 1993). This value can be used to characterize the drug release rate from the dosage form and the retarding efficiency of the polymer.

$$\text{MDT} = \left(\frac{n}{n+1}\right) k^{-1/n}$$

Where, n is release exponent and k is release rate constant.

Successive fractional dissolution time

To characterize the drug release rate in different experimental condition, $T_{25\%}$ (time required for 25% drug release), $T_{50\%}$, $T_{80\%}$ and MDT were calculated from dissolution data according to the equations: $T_{25\%}$ = $(0.25/k)^{1/n}$, $T_{50\%}$ = $(0.5/k)^{1/n}$, $T_{80\%}$ = $(0.8/k)^{1/n}$ and MDT = $(n/n+1)$ $k^{-1/n}$ where n is a release exponent and k is the release rate constant for Korsmeyer- Peppas equation.

Statistical analysis

A one way of analysis of variance (ANOVA) was used to analyze the dissolution data obtained for each batch of formulation to compare the drug release rate comparison of successive dissolution time ($T_{25\%}$, $T_{50\%}$, $T_{80\%}$, MDT). A confidence limit of P<0.05 was fixed and theoretical calculated values of F (Fcrit and Fcal) were compared for the interpretation of results.
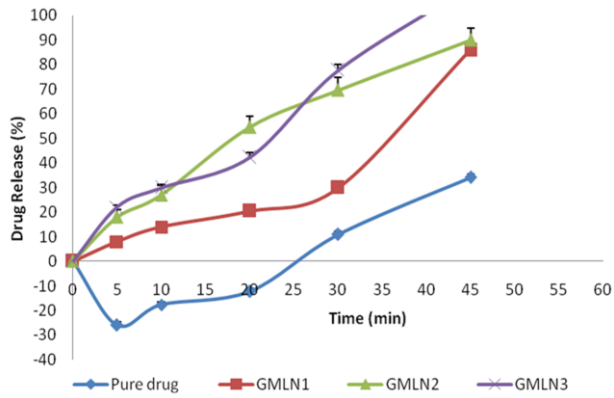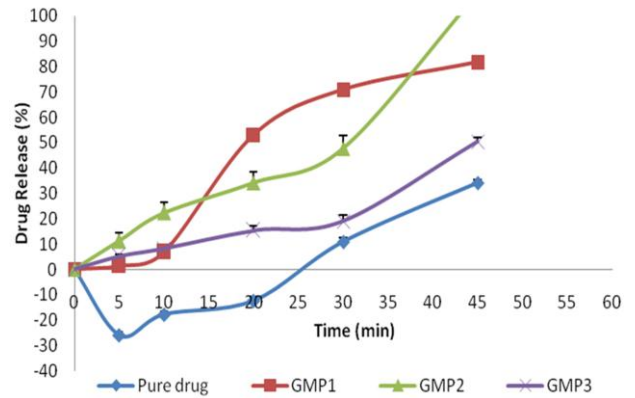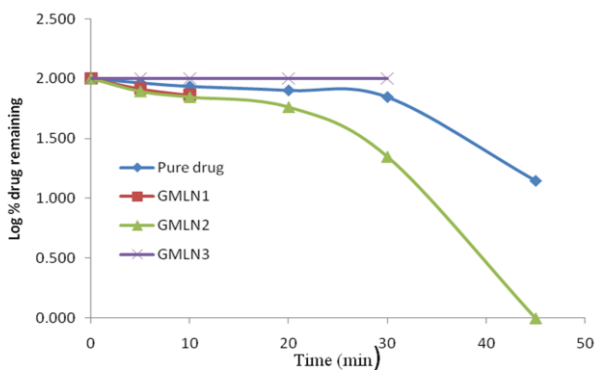
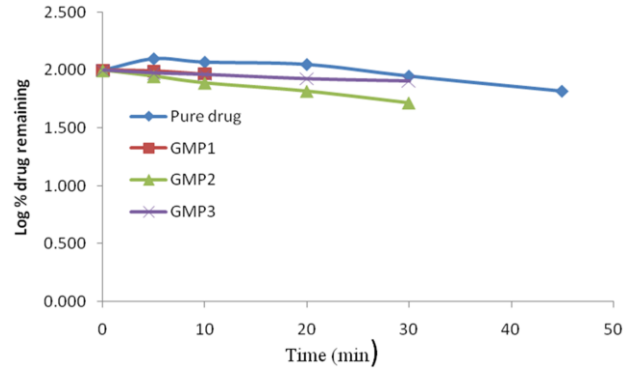(a) Glyceryl monosterate and stearic acid containing formulations   (b) β-cyclodextrin and urea crystal containing formulations

Figure 1: Zero orders plots of glimepiride SLNP formulations with different ratio of lipid and polymer in distilled water.
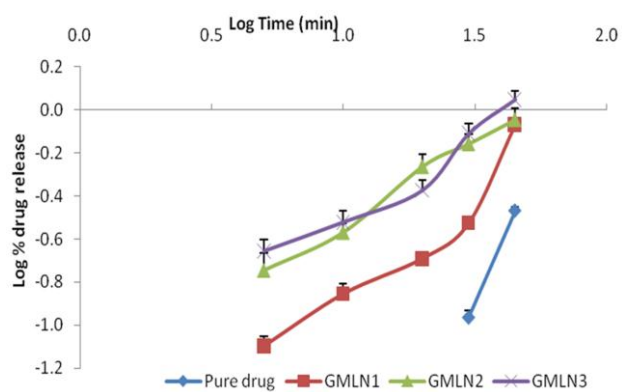

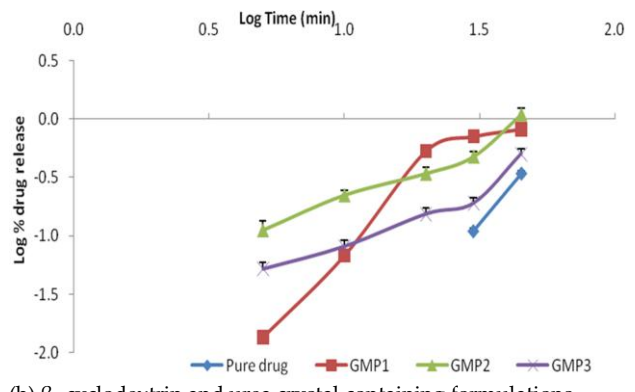(a) Glyceryl monosterate and stearic acid containing formulations   (b) β-cyclodextrin and urea crystal containing formulations

Figure 2: First orders plots of glimepiride SLNP formulations with different ratio of lipid and polymer in distilled water.

(a) Glyceryl monosterate and stearic acid containing formulations   (b) β- cyclodextrin and urea crystal containing formulations

Figure 3: Korsmeyer kinetic plots of glimepiride SLNP formulations with different ratio of lipid and polymer in distilled water.

Table 1: Formulation of glimepiride solid lipid nanoparticle dispersions through hot homogenization method.

Formulation Code	Solid lipid (200mg)	Surfactant, Lutrol F-68 (mg)	Stabilizer, Tween 80 (ml)	Water (ml)
GMLN1	Stearic acid	400	1	15
GMLN2	Stearic acid	400	1.5	15
GMLN3	Glyceryl monostearate	400	1	15

**Table 2: Formulation of glimepiride solid dispersions through precipitation method.**

Formulation Code	Drug-Polymer composition	Drug-polymer ratio
GMP1	GMP- βCD	1:1
GMP2	GMP- βCD	1:3
GMP3	GMP-urea crystal	1:1

Table 3: Regression coefficient (r^2) of different kinetic model and diffusion exponent (n) of Korsmeyer-Peppas model of glimepiride release from different SLNP formulations.

Formulations	Zero Order (r^2)	First Order (r^2)	Korsmeyer (r^2)	Korsmeyer (n)
GMLN1	0.877	0.789	0.901	0.965
GMLN2	0.972	0.837	0.990	0.762
GMLN3	0.826	0.909	0.942	0.741
GMP1	0.915	0.880	0.938	0.986
GMP2	0.936	0.994	0.954	0.946
GMP3	0.907	0.761	0.931	0.955

Table 4: Percent release of glimepiride from SLNP formulations with different carrier.

Time (min)	Percent of drug released						
	Pure Drug	GMLN1	GMLN2	GMLN3	GMP1	GMP2	GMP3
0	0	0	0	0	0	0	0
5	-25.90	8.00	18.00	22.00	1.36	11.20	5.21
10	-17.73	14.00	27.00	30.00	6.82	22.31	8.13
20	-12.27	20.45	54.55	42.27	53.18	34.09	15.40
30	10.90	30.00	69.55	77.73	70.91	47.73	19.09
45	34.09	85.90	90.00	111.82	81.82	109.09	50.45
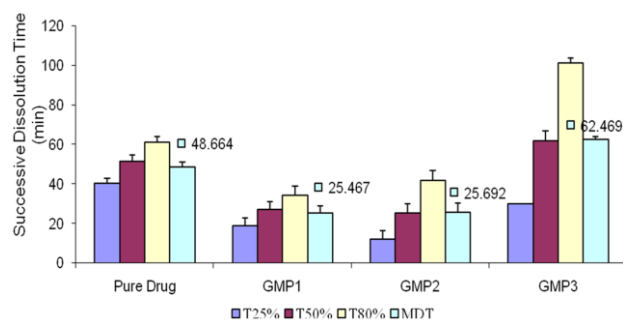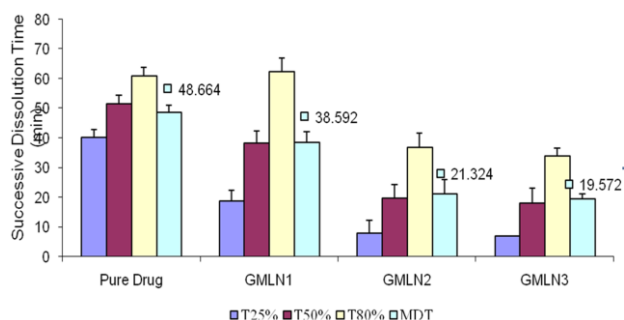
(a) Glyceryl monosterate and stearic acid containing formulations   (b) β-cyclodextrin and urea crystal containing formulations

Figure 4: Successive fractional dissolution time and MDT values of glimepiride SLNP formulations with different ratio of lipid and polymer in distilled water.
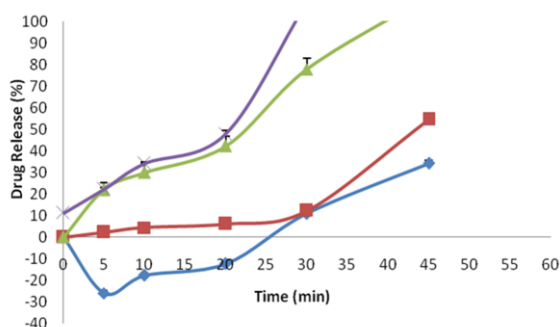

Figure 5: Optimization of release profile of glimepiride (pure drug, market preparation, GMLN3 and GMP2).

RESULTS

Different combination of lipid and polymer were used to provide glimepiride solid lipid nano particle dispersions. The dissolution profile of all the formulations were fitted to zero order, first order and Korsmeyer-Peppas model to ascertain the kinetic modeling of drug release (figure 1, 2 and 3, respectively). Table 3 showed data analysis of release profiles according to different kinetic models. It was found that the *in vitro* drug release was best explained by Korsmeyer-Peppas equation as the plots showed good linearity ($r^2 = 0.901$) followed by zero order ($r^2 = 0.972$) and first order ($r^2 = 0.909$). The values of n (release exponent) for all formulations studied here were between 0.741 to 0.986 indicating an anomalous behavior corresponding to diffusion, erosion and swelling mechanisms of drug release. Solid dispersions formulated with different carriers exhibited significant improvement in the dissolution (table 4) of glimepiride as compared to pure drug. GMLN3 and GMP2 showed highest dissolution rate that is 111.82% and 109.09% respectively whereas the release percentage of pure drug was 34.09%. Successful fractional dissolution time and MDT values calculated for all the SLNPs were illustrated in figure 4. This finding was also corroborated with the drug release process indicating that GMLN3 and GMP2 had least MDT values 19.572 min and 25.692 min respectively compared to other formulations. In order to evaluate the drug dissolution profile with optimized formulation and market preparation of glimepiride as well as pure drug, it was interesting to compare the results of the dissolution tests (figure 5). The results revealed that optimized formulation (GMLN3, GMP2) showed highest drug release rate than market preparation.

DISCUSSION

The kinetic modeling of drug release shows that these models have been established to describe the relationship between drug dissolution and drug release patterns mathematically. The corresponding plot (log cumulative percent drug release versus time) for the Korsmeyer Peppas equations indicated a good linearity ($r^2 = 0.901$). Value of the release exponent 'n' was in between 0.741 and 0.986, indicating anomalous diffusion, *i.e.*, drug release was controlled by more than one process. Reddy *et al* (2003) observed similar results with a matrix tablet of nicorandil with an n value of 0.71. From the proposed formulation, it is evident that when excipient glyceryl monostearate is used in hot homogenization method, the drug release increases significantly from solid lipid nano particles due to wetting ability and converting crystalline to amorphous form which enhance the solubility. This lipid also increases the entrapment efficiency of glimepiride by increasing the viscosity of medium which prevents rapid diffusion of glimepiride into bulk of medium (Yang, 2000). When this polymer is used the release percentage has been increased from 34.09% (pure drug) to 111.82%. This results are clear indication that glyceryl monostearate has lower drug retarding ability which is confirmed by smaller MDT value (19.572 min). Lutrol F-68 and glyceryl monostearate or stearic acid can act as gelling agent at high concentration and it affect the drug dissolution from solid lipid nano particles. When stearic acid is used instead of glyceryl monostearate drug release was almost near (90.00%) to that of glyceryl monostearate.

In case of precipitation method, when β-cyclodextrin and glimepiride is formulated as 1:1 ratio, the drug release rate is 81.82%, but in case of 1:3 ratio, the release rate is increased to 109.09%. On the other hand, when urea crystal is used instead of β-cyclodextrin, then the drug release rate is 50.45% which is not as high as betacyclodextrin containing formulation. So, it is clear that the polymer β-cyclodextrin in higher amount used in precipitation method can give very much better dissolution rate. It was verified that the presence of β-cyclodextrin into polymeric drug delivery systems can also influence the drug release mechanism by Bibby *et al* (Bibby *et al.*, 2000). In the present study, the results evidenced that release profiles of these formulations were only slightly slower than those containing glyceryl monosterate. This is probably due to an inclusion process of the glimepiride molecule in β-cyclodextrin, which may be considered energetically favoured when compared to inclusion of drugs, namely ibuprofen (Bragga *et al.*, 2003). So, the present study confirms that solid lipid nanoparticles of glimepiride with lipid, surfactant and stabilizer and precipitated formulation from large amount of β-cyclodextrin can be formulated as tablet with better dissolution characteristics.

CONCLUSION

The results of the present study provide useful information on the type of lipid and polymer that should be employed on the formulation of glimepiride solid lipid nano particle dispersion. The release mechanism of glimepiride from each formulation tested was evaluated in the light of zero order, first order and Korsmeyer-Peppas kinetic models. The Korsmeyer-Peppas model fits with the *in vitro* dissolution data and gives an insight into the possible drug release mechanism by Non-Fickian diffusion. *In-vitro* drug release through the USP type-Π apparatus from the prepared SLNPs containing glyceryl monostearate is much higher (111.82%) than the pure drug (34.09%) by hot homogenization method. Again in case of precipitation method the formulation containing β-cyclodextrin provide higher drug release (109.09%). Hence glimepiride SLNPs formulated with glyceryl monostearate and β-cyclodextrin enhance the dissolution rate as well as it will enhance the bioavailability of the drug and will increase the patient compliance.

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