International Journal of Chemistry and Pharmaceutical Sciences

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R E S E A E C H A R T I C L E

Formulation and In-vitro Evaluation of Glimepride Nanoemulsion and the Same Nano Emusion on the Suitable Carrier

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A B S T R A C T

Glimepiride, sold under the trade name Amaryl among others, is a medication used to treat diabetes mellitus type 2. Glimepiride takes up to three hours for maximum effect and lasts for about a day. In the present investigation, S-SNEDDS of glimepiride were projected for enhancing its bioavailability by enhancing its *in vitro* dissolution release profile. Liquid nanoemulsion was altered into solid nanoemulsion by adsorbing on to silicon dioxide and both formulations are very much investigated for *in vitro* studies. Scanning Electron Microscope (SEM) studies demonstrated that integration of drug into the pores of the silicon dioxide particles. Solid state characterization experiments like DSC and XRD investigation reports strongly confirmed the alteration of drug molecular components in to amorphous solid state. *In vitro* dissolution study reveals that drug release profile of liquid and solid emulsion formulations are greater than marketed formulations. Stability under accelerated conditions in present study revealed that there was no considerable difference in particle size, release profile and assay before and after storage. Thus, it can be concluded that the physico-chemically stable solid SNEDDS of glimepiride have prospective to progress the *in vitro* release profile of glimepiride. Aerosil® 200 formulated a solid self-nanoemulsifying molecular drug delivery system with superior emulsification property, enhanced dissolution profile and a standard route of oral therapeutic worth value of glimepiride. Solid state characterization confirmed conversion of drug into amorphous solid state; hence the physic-chemically stable S-SNEDDS with improved *in vitro* release and enhanced oral delivery of glimepiride with significant therapeutic efficacy over pure glimepiride.

Keywords: SNEDDS, solid Nano emulsion, glimepiride.

A R T I C L E I N F O

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PAPER-QRCODE

A R T I C L E H I S T O R Y: Received 21 Jan 2019, **Accepted** 10 June 2019, **Available Online** 27 Dec 2019

Citation: K. Anil Kumar, *et al. Formulation and In-vitro Evaluation of Glimepride Nanoemulsion and the Same Nano Emusion on the Suitable Carrier*. *Int. J. Chem, Pharm, Sci.*, 2019, 7(12): 336-345.

C O N T E N T S

1. Introduction

Glimepiride, 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxami-do) ethyl] phenyl] sulphonyl]-3-(trans-4-methyl-cyclohexyl) urea is the first third-generation sulphonylurea.Itisaverypotentsulphonylureaemployedforco ncomitantusewith insulin for the treatment of non-insulin-dependent (type II) diabetes mellitus. It produces hypoglycemia by stimulating release of insulin from pancreatic b cells and by increasing the sensitivity of peripheral tissue to insulin. It also supports the movement of sugar from the blood into the cells that need it. Glimepiride shows low, pH-dependent solubility. It exhibits very poor solubility at 37^0C (50.004mg/ml) in acidic and neutral aqueous media and it belongs to ‘‘BCS Class II’’drugs (Lobenberg & Amidon, 2000). It is likely to show low and irregular bioavailability following oral administration due to the low water solubility (Amidon et al., 1995; Grunenberget al., 1995). Hence administering glimepiride by oral appears as a tough challenge due to its poor absorption pattern and rapid and unpredictable hepatic first pass metabolism. The present study deals with formulation of an Aerosol200 based SNEDDS of a poorly water soluble drug (glimepride). The main objective of this study was to investigate solid self-nanoemulsifying drug delivery system, as a potential drug delivery system for glimepiride. S-SNEDDS (consisting of Tween80/PEG and 400/Mygliol812) was characterized with regard to morphological analysis, solid state characterization as well as its in vitro drug release.

2. Materials and Methods

Glimepiride, Tween® 20, Tween® 80, Span® 60, CremophoreRH40, Oleic acid, Soy bean oil, Ethyl alcohol, Cotton seed oil, Aerosil® 200, PEG 400, Span® 80, Propylene glycol, Potassium dihydrogen phosphate, Miglyol® 812all the chemicals were laboratory grade.

Preparation of L-SNEDDS of glimepiride

2 mg of glimepiride is dissolved in 1g of the mixture of oil and Smix respectively shown in table 1.The prepared mixture was vortexed using vertex mixer (Remi India) to obtain a clear homogeneous formulation (56 & 62). Various regions in phase systems (table 4.6 and 4.7) at lower, medium and higher concentration of oil and Smix were selected to load the drugs in to plain nano emulsions then the final drug content of the L-SNEDDS was 1 % and 0.2 % w/w for glimepiride. 12 formulations mentioned in table 1were prepared base on SNEDDS regions of phase diagrams shown in figure 1 glimepiride respectively. The final formulations of L-SNEDDS were examined for signs of turbidity and thermodynamic stability or phase separation after 72 hours prior to self-emulsification and droplet size determination studies.

Screening of the L-SNEDDS formulations for physical & thermodynamic stability

All the 12 formulations of glimepiride were employed to heating & cooling, centrifugation and freeze thaw analysis to observe thermodynamic stability.

Optimization of glimepiride L-SNEDDS using droplet size and polydispersity index

The diameter of nanoemulsions globules and polydispersity index of the L-SNEDDS selected in table 1 was determined by dynamic light scattering particle size analyzer (Nano ZS, Malvern, UK) at 635 nm wavelength of 90^0 scattering angle at 25^0C. 0.1 mL L-SNEDDS was added to 200 mL beaker containing 100mL of distilled water and shaken gently using magnetic stirrer to form fine and transparent nanoemulsions and kept at 25^0 C for 12 hours (47,61, 62 and 56).The z-average diameter were recorded. The z-average diameter also as the harmonic intensity weighed average hydrodynamic diameter of droplets. The z-average diameter of droplets obtained from cumulated examination by the auto measured software tool (Malvern Instruments, UK). The final and optimized formulations were shown in table 2 based on particle size and PDI.

Evaluation of post compression parameters for prepared Tablets:

Transmission electron microscopy, Determination of viscosity of L-SNEDDS, Determination of Refractive index of L-SNEDDS, *In-vitro* release studies of L-SNEDDS.

Preparation of the s-snedds from optimized L-SNEDDS

The L-SNEDDS of glimepiride formulated in methodology were adsorbed onto Aerosil® 200 (1:1 ratio) by physical mixing in a small motor and pestle for 5 minutes to form a free flowing and dry homogenous mass (47 & 48). The free flowing powder was passed through a sieve number 30 and the S-SNEDDS powder placed into the 0 size hard gelatin capsule shells and sealed manually. The resulting S-SNEDDS was a free flowing powder that was subsequently subjected to solid state characterization and dissolution studies. The formulations of the optimized S-SNEDDS of glimepiride were shown in table 3

Characterization of S-SNEDDS of glimepiride

Estimation of drug content in S-SNEDDS, Reconstitution properties of S-SNEDDS, Droplet size determination of reconstituted S-SNEDDS, Differential scanning calorimetry (DSC), Scanning electron microscopy (SEM), X-ray powder diffraction (XRPD) study, Stability of S-SNEDDS in simulated gastric fluid (SGF), *In-vitro* drug release studies of S-SNEDDS

3. Results and Discussions

RP-HPLC method development for estimation of glimepiride

Method Development: Acetonitrile and 0.2M phosphate buffer pH=7.4 in different proportions shown in Table 6.1 were used to develop RP-HPLC method and finally Acetonitril: 0.2M phosphate buffer pH=7.4 (40:60) was selected as an suitable mobile phase which gave high

quality resolution and acceptable system suitability parameters. The chromatogram of glimepiride working standard solutions was shown in figure 1.

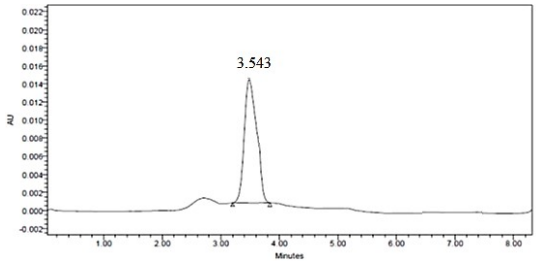


Figure 1: Typical chromatogram of glimepiride Standard

Mobile phase:

The mobile phase prepared was passed through a 0.45 micron membrane filter (PALL, USA) and the contents were transferred to solvent reservoir of the LC 20D pump and purged the solvent line with 30 mL of fresh mobile phase. The method development conditions for optimizing the mobile phase were depicted in Table 1.

Method Validation

Linearity

The test solutions of glimepiride were prepared in the concentration range of 0.8- 2 µg/mL. The drug stock solutions were injected in triplicate into HPLC system using 20 µL injection port. Acetonitril- 0.2 M phosphate buffer pH 7.4 in the ratio 40: 60 and is used as the mobile phase for glimepiride. Calibration curve was obtained by plotting peak area versus concentration of drug represented data in table 5 and the calibration curve was shown in figure 2.Regression equation was adopted to calculate correlation coefficient and slope values and the values were 37551 and 0.999, respectively.

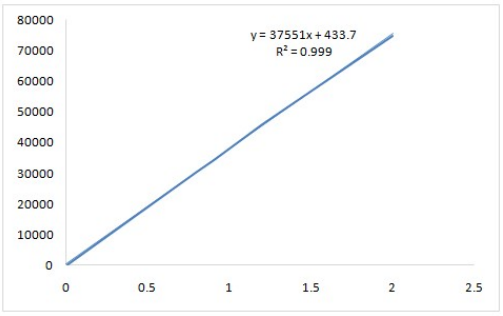


Figure: 2 Standard graph of glimepiride in mobile phas

Precision

The precision of the analytical method was verified by six injections of three different concentrations (1.2, 1.4 and 2 µg/mL for glimepiride) were analyzed on the same day and another day. The percent relative standers deviation (%RSD) were calculated to determine inter and intraday precision and the results tabulated in table 6.The RSD values in both the cases were <1.2 and <1.92%.The results conforming the method adopted was sufficiently precise. Intermediate precision values obtained by another analyst and HPLC system, which shown similar results.

Accuracy

The method accuracy was determined by the recovery experiments. The known amount of working slandered was added to the fixed concentration of the pre analyzed nanoemulsions. Percentage recovery was calculated by area of peak before and after the addition of working standard. The recovery studies were preformed three times. The standard addition method was performed at 50, 100 and 100 % level and the percentage recovery was calculated. Percent recovery was within the range of 99.2% to 100.8% for glimepiride which indicate that the method was accurate.

The limit of detection (LOD) and limit of quantification (LOQ): Standard stock solutions of glimepiride (0.8, 0.9, 1.2, 1.4, 2 ug /mL) were prepared by diluting standard stock solution with mobile phase (Acetonitrile-0.2 M pH 7.4 phosphate buffer in 40:60).The LOD and LOQ values for glimepiride estimated at signal to noise ratio (S/N) of 3:1 and 10:1 equally, by introducing a sequence of stock solutions with known concentrations. The LOD value for glimepiride was found to be 0.038 ng/ ml. The LOQ for glimepiride was found to be 0.117 ng/ml.

Robustness

The strength of method was checked by making slight changes in conditions of chromatography like pH of buffer, flow rate of mobile phase and mobile phase ratio. There was no significant changes in the chromatograms, which was demonstrated by RP-HPLC is robust and is given in Table 7.

Solubility studies of glimepiride in oils, surfactants and co surfactants: The SNEDDS are prepared by one or more surfactants and drug dissolved in oil. At room temperature the mixture should be an opaque, monophasic liquid and supposed to have fine solvent characters to permit solubilisation of drug in solution. The glimepiride solubility in different surfactants and oils are given in Table 8. During solubility experiments Miglyol® 812 showed the highest solubility for glimepiride compared to other oils like isopropymyristate, soy bean oil, sunflower oil and oleic acid. In the vicinity of triglyceride chains of Miglyol® 812 supports absolute solubilization of glimepiride. PEG 400 as cosurfactants , Myglyol® 812 as lipid and Tween® 80 as surfactant (47) were selected for the construction of ternary phase diagrams to identify the nanoemulsion domains such that at particular concentration of oil and surfactant co - surfactant ratios a stable nanoemulsion formulation is formed. The lipophilic surfactant promote emulsification of oil but it produce crude emulsion with large globule size as the lipophilic surfactants have HLB value less than 10.Hydrophilic surfactants HLB > 10 are superior at giving fine and uniform emulsion droplets which are more likely to empty quickly from the stomach (80). Large surface area helps in faster and complete absorption. In most cases it is the right blend of low and high HLB surfactants leads to the formation of stable nanoemulsion upon exposure to water (37). Based on the efficiency of self-emulsification, Tween® 80 with HLB value of 15 was selected for the formulation of glimepiridee SNEDDS. PEG 400 selected as cosurfactant correspondingly and Miglyol® 812 was selected as an oil phase.

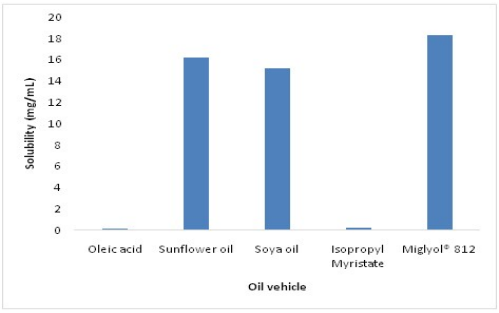


Figure 3: Solubility data of glimepiride in vehicles

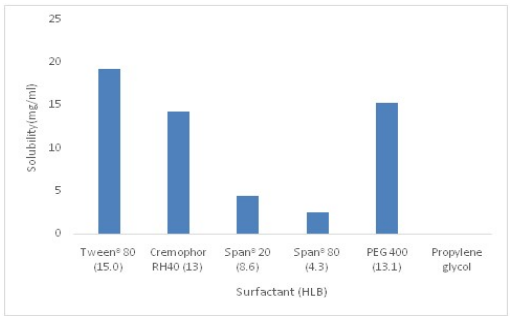


Figure 4: Solubility data of glimepiride in vehicles

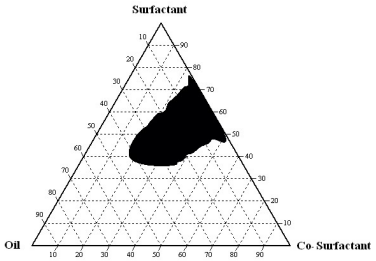


Figure 5: Ternary phase diagram of Miglyol® 812, Tween 80 and PEG 400 dispersed in water at 25^0 C

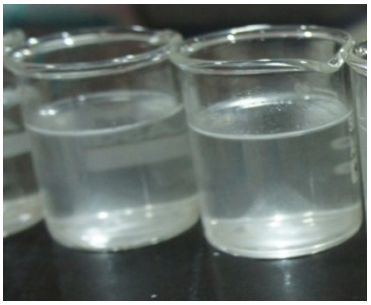


Figure 6: Nanoemulsion with in shaded area of phase diagram after spontaneous emulsification of SNEDDS

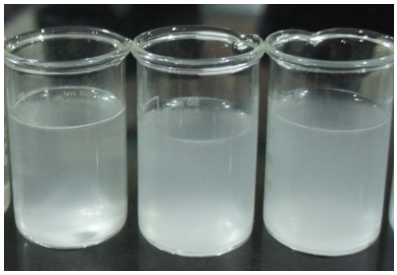


Figure: 7: Macro emulsions out of shaded area of phase diagram after spontaneous emulsification of SNEDDS

Preparation of L-snedds

Glimepiride showed highest solubility in Tween® 80 and PEG 400 among surfactants and cosurfactants respectively. There are more chances of drug precipitation when the drug concentration is more than its solubility. Only 2 mg/g i.e 0.2% w/w drug is loaded into the plain SNEDDS formulations shown in table 9. Upon aqueous dilution, the drug should not precipitate and is confirmed by spontaneous emulsification method discussed in methodology. After loading the drug all the formulation (FM1 to FM12) presented in table 9 do not show any drug precipitation after aqueous dilution.

Figure: 8 Droplet size and PDI of L-SNEDDS of Glimepiride (FM9)

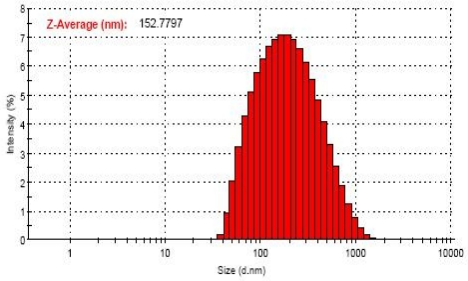


Figure: 9: Zeta potential of L-SNEDDS of Glimepiride (FM9)

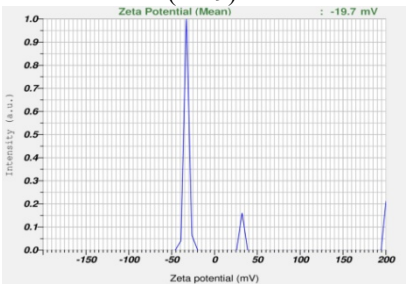


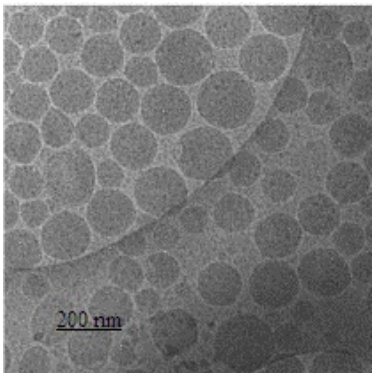
Figure 10: The optimized SNEDDS formulation (FM 9)

Characterization of optimized glimepiride L-SNEDDS

Transmission electron microscopy (TEM)

The microphotograph of the optimized L-SNEDDS (FM9) observed as dark globules with bright surrounding (figure 6.10). The TEM image demonstrates that nanoemulsion come into viewed as spherical oil droplets after dilution with aqueous phase, attributable to nanosize of Miglyol® 812 droplets loaded with glimepiride.

Figure 11: TEM image of liquid glimepiride L-SNEDDS.



Viscosity determination

Formulation FM9 L-SNEDDS of glimepiride was yielded a viscosity of 168±0.1cps. The viscosity evaluation confirming that the liquid formulation FM 9 behaves as Newtonian fluid (85).

Refractive index Determination

Formulation FM 9 L-SNEDDS of glimepiride was yielded a Refractive index of 1.38±0.005.The refractive index value was nearly closer to water value at 25^0 C. Furthermore the result of RI represents transparent homogenous nature of L-SNEDDS.

Preparation of the s-snedds from optimized L-SNEDDS

The formulation FM 9 was converted into dry S-SNEDDS using Aerosil® 200 as solid carrier to adsorb the liquid formulation FM 9. The S-SNEDDS formulation formed a free flowing homogeneous mass after transforming into S-SNEDDS (47).Aerosil® 200 had excellent oil adsorption capacity and the amount of Aerosil® 200required adsorbing L-SNEDDS were depicted in Table 11. Totally 1 gram of Aerosil® 200 is required to transform 1 gram of L-SNEDDS into S-SNEDDS. The S-SNEDDS formulation was shown in figure 12

Figure 12: The S-SNEDDS formulation

Characterization of S-SNEDDS of glimepiride

Estimation of drug content in S-SNEDDS

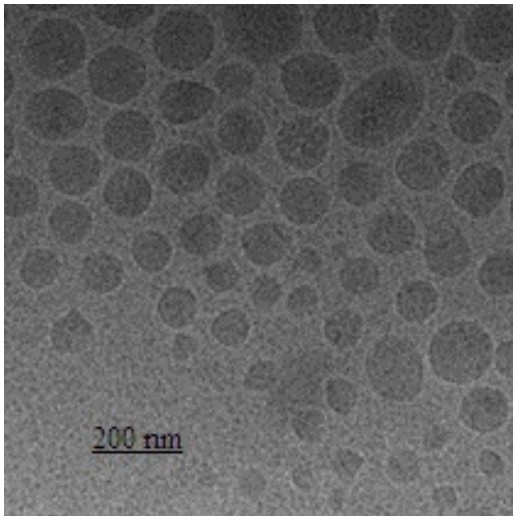
The L-SNEDDS and S-SNEDDS containing 2 mg equivalent amount of glimepiride were dispersed in corresponding mobile phase in 100 mL volumetric flask by adding 20 ml of mobile phase and sonicated using bath sonicator (Citizen, India) for 10 minutes andmade up to the volume with corresponding mobile phase to extract glimepiride, and centrifuged at 3000 rpm for 20 minutes separate un dissolved excipients (47).The supernatant was taken and was passed through a 0.45 micron membrane filter (PALL, USA). The samples were analyzed using RP-HPLC attached with PDA at a max of 228 nm (73).The experiments were performed in triplicate (n=3) and glimepiride content present in S-SNEDDS shown in table 12.

Reconstitution properties of S-SNEDDS

The time required for self-emulsification of L-SNEDDS or S-SNEDDS of glimepiride was determined using USP type II dissolution rate apparatus.100 mg of S-SNEDDS was taken in to 500 mL of distilled water in a dissolution vessel at 37◦ C under gentle agitation at 50 rpm. The emulsification time of S-SNEDDS assessed visually. All the studies performed triplicate to obtain accurate results. S-SNEDDS formulation should disperse quickly and completely in aqueous environment. The rate of emulsification of S-SNEDDS formulations is measured by visual observation as reported earlier (62). The form S-SNEDDS revealed that the emulsification time was25 ± 5 seconds. The emulsification efficiency of S-SNEDDS containing Tween® 80, PEG 400 is related to their HLB values. The Surfactant Tween® 80 and c0surfactant PEG 400 selected in present formulation have HLB in between 12-15 which results in good emulsification efficiency.

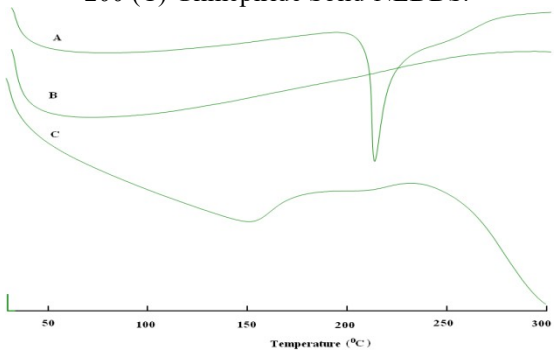
Droplet size determination of reconstituted S-SNEDDS

Figure 13: TEM image of liquid Glimepiride S-SNEDDS after reconstitution



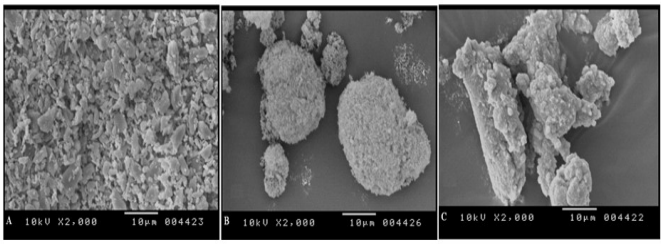
Differential scanning calorimetry (DSC)

Figure: 14: DSC thermograms (A) Pure drug, (B) Aerosil® 200 (C) Glimepiride Solid-NEDDS.

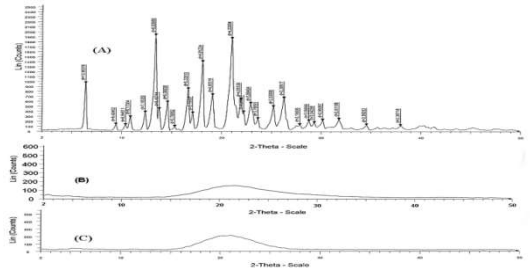


Scanning electron microscopy (SEM)

Figure 15: SEM images of A) Pure glimepiride B) Aerosil® 200 C) S-SNEDDS



X-Ray powder diffraction (XRPD) study
Figure 16: XRPD of
A) Pure glimepiride
B) Aerosil® 200 C) S-SNEDDS



Stability of S-SNEDDS in simulated gastric fluid (SGF)
The emulsions formed should be stable in simulated gastric fluid upto 3 hours as the lipids readily degraded by the gastric acid. The nanoemulsions should be stable for delivering drug effectively. The TEM images of droplets observed for the coalescence and break down of emulsion globules. The TEM analysis revealed that the globules formed are stable without any coalescence and breakdown as the globules are stable in SGF. The TEM image of nanoemulsions in SGF at 3rd hour was shown in figure 17.

Figure 17: TEM image of Glimepiride S-SNEDDS after 3 hours in SGF

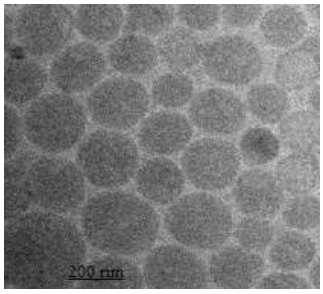
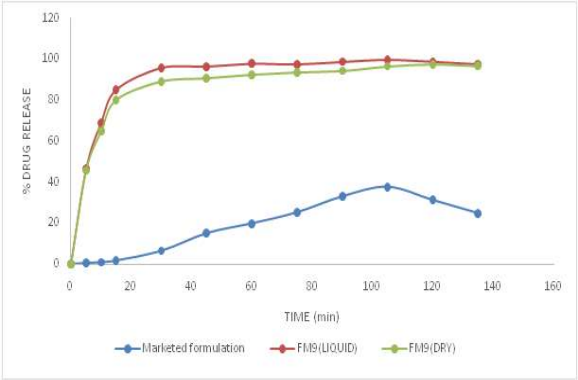


Figure 18: Comparative *invitro* drug release of glimepiride plain, marketed tablet (Amaryl® 1 mg), L-SNEDDS (FM 9) and S-SNEDDS



4. Conclusion

In the present investigation, S-SNEDDS of glimepiride were projected for enhancing its bioavailability by enhancing its *in vitro* dissolution release profile. Liquid nanoemulsion was altered into solid nanoemulsion by adsorbing on to silicon dioxide and both formulations are very much investigated for *in vitro* studies. Scanning Electron Microscope (SEM) studies demonstrated that integration of drug into the pores of the silicon dioxide particles. Solid state characterization experiments like DSC and XRD investigation reports strongly confirmed the alteration of drug molecular components in to amorphous solid state. *In vitro* dissolution study reveals that drug release profile of liquid and solid emulsion formulations are greater than marketed formulations. Stability under accelerated conditions in present study revealed that there was no considerable difference in particle size, release profile and assay before and after storage. Thus, it can be concluded that the physico-chemically stable solid SNEDDS of glimepiride have prospective to progress the *in vitro* release profile of glimepiride. Aerosil® 200 formulated a solid self-nanoemulsifying molecular drug delivery system with superior emulsification property, enhanced dissolution profile and a standard route of oral therapeutic worth value of glimepiride. Solid state characterization confirmed conversion of drug into amorphous solid state; hence the physicochemically stable S-SNEDDS with improved *in vitro* release and enhanced oral delivery of glimepiride with significant therapeutic efficacy over pure glimepiride.

Table 1: Formulations of glimepiride selected from the SNEDDS Region of phase diagram

S.No	Oil :Smix	Surfactant: Co-surfactant	Miglyol® 812 (%)	Tween®80 (%)	PEG 400 (%)
FM1	1:19	1:1	5	47.5	47.5
FM2	1:8	1:1	10	45	45
FM3	1:3	1:1	20	40	40
FM4	1:1.33	1:1	30	35	35
FM5	1:18	2:1	5	65	30
FM6	1:8	2:1	10	60	30
FM7	1:3	2:1	20	55	25

FM8	1:1.33	2:1	30	45	25
FM9	1:18	3:1	5	71.25	23.75
FM10	1:8	3:1	10	67.5	22.5
FM11	1:3	3:1	20	60	20
FM12	1:1.33	3:1	30	52.5	17.5

Table 2: Optimized SNEDDS of glimepiride

CODE	DRUG	%OIL	%SURFACTANT	%COSURFACTANT
FM 9	Glimepiride	5	71.25	23.75

Table 3: Composition of an optimized S-SNEDDS

Formula	Components in S-SNEDDS	Proportions in mg	% Drug in S-SNEDDS
FM 9	Glimepiride	2	0.1% w/w
	Miglyol® 812	50	
	Tween® 8080	712.5	
	PEG 400	237.5	
	Aerosil® 200	1000	

Table: 4 Method development conditions for optimizing the mobile phase.

S. No	Mobile phase B	Mobile Phase A	Mobile phase pH	Ratio of A/B
1	0.2 M Phosphate buffer	Acetonitrile	7.4	70/30
2	0.2 M Phosphate buffer	Acetonitrile	7.4	60/40
3	0.2 M phosphate buffer	Acetonitrile	7.4	50/50
4	0.2 M phosphate buffer	Acetonitrile	7.4	30/70

Table 5: Regression equation was calculated

Conc (µg/ml)	*Area*
0	0
0.8	30567.25
0.9	34346
1.2	46118
1.4	53223
2	74921

Table 6: Precision data for analytical method

First day					Second day			
Con ug/ml	Area	Con ug/ml	Area	Con ug/ml	Area	Con ug/ml	Area	Con ug/ml
1.2	95580				96025			
1.2	95491	95187	605	0.63	96290	96391	426.	0.44
1.2	94490				96859			
1.4	113557				115953			
1.4	113382	112849	1077	0.95	116809	115782	1121	0.96
1.4	111610				114586			
2	166589				169235			
2	166619	165844	1317	0.79	168742	169267	541	0.31973
2	164323				169823			

Table 7: Robustness

Condition	% RSD
pH of the buffer	1.371
Mobile phase ratio	1.362

Table 8: Solubility data of glimepiride in vehicles

Oil vehicle	Solubility (mg/mL)
Oleic acid	0.16±0.01
Sunflower oil	16.2±0.36
Soya oil	15.23±0.40

Isopropyl Myristate	0.28±0.02
Miglyol® 812	18.3±0.26
Surfactant (HLB)	**Solubility(mg/ml)**
Tween® 80 (15.0)	19.23±0.30
Cremophor RH40 (13)	14.3±0.4
Span® 20 (8.6)	4.41±0.17
Span® 80 (4.3)	2.50±0.15
PEG 400 (13.1)	15.34±0.21
Propylene glycol	0.06±0.005

Table 9: Thermodynamic Stability of L-SNEDDS formulations

S. No	Oil: Smix	Surfactant: Co-surfactant	Miglyol® 812 (%)	Tween 80(%)	PEG 400 (%)	Thermo dynamic Stability
FM1	1:19	1:1	5	47.5	47.5	Stable
FM2	1:9	1:1	10	45	45	Stable
FM3	1:4	1:1	20	40	40	Stable
FM4	1:2.33	1:1	30	35	35	Stable
FM5	1:19	2:1	5	65	30	Stable
FM6	1:9	2:1	10	60	30	Stable
FM7	1:4	2:1	20	55	25	Stable
FM8	1:2.33	2:1	30	45	25	Stable
FM9	1:19	3:1	5	71.25	23.75	Stable
FM10	1:9	3:1	10	67.5	22.5	Stable
FM11	1:4	3:1	20	60	20	Stable
FM12	1:2.33	3:1	30	52.5	17.5	Stable

Optimization of glimepiride L-SNEDDS using droplet size and polydispersity index

Table 10: Droplet size and PDI of L-SNEDDS of Glimepiride

Sno	Oil : Smix	Miglyol® 812 (%)	Tween 80 (%)	PEG 400 (%)	Z-Avg size (d nm)	PDI
FM1	1:19	5	47.5	47.5	11	0.636
FM2	1:9	10	45	45	250	0.565
FM3	1:4	20	40	40	890	0.645
FM4	1:2.33	30	35	35	1406	0.919
FM5	1:19	5	65	30	270	0.820
FM6	1:9	10	60	30	432	0.991
FM7	1:4	20	55	25	630	0.830
FM8	1:2.33	30	45	25	1270	0.999
FM9	**1:19**	**5**	**71.25**	**23.75**	**152**	**0.211**
FM10	1:9	10	67.5	22.5	355	0.368
FM11	1:4	20	60	20	917	0.113
FM12	1:2.33	30	52.5	17.5	1126	0.688

Table 11: Composition of S-SNEDDS

Formula	Components in S-SNEDDS	Proportions in mg
FM 9	Glimepiride	2
	Miglyol® 812	50
	Tween® 80	712.5
	PEG 400	237.5
	Aerosil® 200	1000

Table 12: Drug content of Glimepiride SNEDDS & S-SNEDDS

Formulation	Assay
L-SNEDDS (FM9)	99.743± 0.52
S-SNEDDS (FM9)	99.753± 0.67

Table 13: Z-average and PDI of glimepiride L-SNEDDS & S-SNEDDS

Formulation-FC 9	Z-Average (nm)	PDI
L-SNEDDS	153	0.212
S-SNEDDS	159	0.233

Table 14: *In-vitro* drug release studies

TIME (in min)	Marketed formulation	FM9 (LIQUID)	FM9 (DRY)
0	0	0	0
5	0.533	46.26	45.57
10	0.908	68.95	64.8
15	1.76	85	80.04
30	6.51	95.68	89.02
45	15.06	96.3	90.6
60	19.87	97.7	92.3
75	25.26	97.4	93.44
90	33.01	98.6	94.1
105	37.69	99.6	96.3
120	31.26	98.7	97.3
135	24.87	97.48	96.48

Table 15: Assay after stability studies after accelerated conditions

Formulation	Assay
L-SNEDDS FM9	98.66±0.23
S-SNEDDS of FM9	99.693±1.43

5. References

[1] Panchagnula R. Transdermal delivery of drugs. Indian J Pharmacol. 1997; 29:140–56.

[2] Rao PR, Diwan PV. Formulation and in vitro evaluation of polymeric films of diltiazem hydrochloride and indomethacin for transdermal administration. Drug Dev Indian Pharm. 1998; 24: 327–36.

[3] Rao PR, Diwan PV. Permeability studies of cellulose acetate free films for transdermal use: Influence of plasticizers. Pharm ActaHelv. 1997; 72:47–51.

[4] Thacharodi D, Rap KP. Development and in vitro evaluation of chitosan-based trandermal drug delivery system for the controlled delivery of propranolol hydrochloride. Biomaterials. 1995; 16: 145–8.

[5] Krishna R, Pandit JK. Carboxymethylcellulose-sodium based transdermal drug delivery system for propranolol. J Pharm Pharmacol. 1996;48:367–70.

[6] Bhat M, Shenoy DS, Udupa N, Srinivas CR. Optimization of delivery of betamethasone - dipropionate from skin preparation. Indian Drugs. 1995; 32:211–4.

[7] Misra A, Pal R, Majumdar SS, Talwar GP, Singh O. Biphasic testosterone delivery profile observed with two different transdermal formulations. Pharm Res. 1997;14:1264–8.

[8] Thacharodi D, Rao KP. Rate-controlling biopolymer membranes as transdermal delivery systems for nifedipine: Development and in vitro evaluations. Biomaterials. 1996;17:1307–11.

[9] Nanda A, Khar RK. Permeability characteristics of free films were studied using the drugs such as diltiazem hydrochloride and indomethacin. Drug Dev Indian Pharm. 1994; 20:3033–44.

[10] Mukhopadhyay A, Mukhopadhyay B, Basu K. Circumvention of multidrug resistance in neoplastic cells through scavenger receptor mediated drug delivery. FEBS Lett. 1995, 276: 95–8.