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Development and evaluation of Solid-self-Microemulsifying Drug Delivery system of Gliclazide

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Abstract

The objective of Gliclazide's self-microemulsifying drug delivery system (SMEDDS) was to address the issues of low solubility and bioavailability. The formulation strategy involved screening surfactants and co-surfactants for emulsification ability and choosing the oil phase based on saturated solubility experiments. Using a dilution approach, ternary phase diagrams were created to determine the self-emulsifying zone. Selected formulations were evaluated by Particle size, DSC, XRD, Transmission Electron microscopy, freeze thawing method, self-emulsification, precipitation and in-vitro release study. Silicon dioxide, magnesium alminometa silicate, microporous calcium silicate, and microcrystalline cellulose were used in the adsorption process to create SMEDDS, which were then tested for dissolution and disintegration. It was determined that the formulation with 40 mg of Gliclazide, 200 mg of Olive Oil, 550 mg of Tween 20, and 550 mg of Polyethylene Glycol was optimal. Up to 120 minutes, the improved SMEDDS showed 100% in vitro drug release, which was substantially higher than that of the pure drug. The SMDDS formulations that passed the thermodynamic stability testing were determined to be stable.

Key words : Bioavailability, phase diagram, solid-self-microemulsifying drug delivery system. Gliclazide.

Reduced insulin levels and insulin resistance, which raise blood sugar levels, are hallmarks of diabetes mellitus type 2, a dangerous metabolic disease. Numerous health issues that lead to increased rates of morbidity and mortality are caused by diabetes mellitus. Over 62 million instances of diabetes are now documented in India, indicating the potential healthcare burden that diabetes may impose in the future[1]. A second-generation antihyperglycemic medication called Gliclazide (GZ) is used to treat diabetes mellitus that is not insulin-

dependent. It increases peripheral glucose consumption and basal insulin secretion. It is an insulin secretagogues that is a member of the sulfonylurea class. Additionally, GZ decreases hepatic gluconeogenesis and increases insulin receptor sensitivity.[10] The main disadvantage of GZ's therapeutic use and effectiveness as an oral dosage form is its extremely low aqueous solubility (log P of 2.69), which results in uneven drug absorption and dissolution in the gastrointestinal tract and, ultimately, uneven drug bioavailability. The majority of GZ formulations on the market are oral. Although GZ is quickly and effectively absorbed, its bioavailability varies greatly across and within individuals, according to reports. Therefore, it is necessary to create a GZ formulation that would increase its oral bioavailability by decreasing intra- and inter-individual variability in absorption.[4-5]

Previous researchers have made attempts to improve the aqueous solubility of Gliclazide by preparing solid dispersion. The preparation of solid dispersion is easy, but its limitations include stability of the drug and the difficulty of incorporating into solid dispersion in suitable dosage forms. Moreover, the carriers used are usually expensive and the freeze-drying or spray-drying method requires particular facilities and processes, leading to a high production cost. Even if a conventional solvent approach can be used in its place, handling highly viscous co-precipitates is challenging.[13]

Formulations for self-microemulsifying drug delivery systems are isotropic blends comprising a drug, an oil, a surfactant, and a co-surfactant. The fundamental idea behind this technology is its capacity to create fine oil in water (o/w) microemulsions after being diluted by aqueous phases while being gently stirred. In other words, the agitation needed for self-emulsification in vivo in the gut lumen is provided by the digestive motility of the stomach and intestine.[11] The medication is presented in a solubilized state by this spontaneous emulsion formation in the gastrointestinal tract, and the small size of the resulting droplet offers a wide interfacial surface area for drug absorption. In addition to solubilization, the inclusion of lipids in the formulation influences medication absorption, which enhances bioavailability.

Materials :

A gift sample of glicazode was acquired from IPCA Laboratories Pvt Ltd in India. The Himalaya Agro Company in Ludhiana, India, was the supplier of the olive oil. We bought Tween 20 from Gattefosse in Mumbai, India. Analytical-grade compounds were also utilized.

Construction of Pseudoternary Phase Diagram :

Using a water titration procedure as previously described, pseudoternary phase diagrams were created in order to get a concentration range of components for the current microemulsion boundary. Surfactant to cosurfactant weight ratios of 1:3, 1:1, and 3:1 were used to create three phase diagrams. After that, the surfactant mixture and the oil phase were combined. After thoroughly mixing the oil and surfactant combination, the liquid was diluted dropwise with purified water while being stirred magnetically at 300 rpm at room temperature until a translucent ME was

achieved. To finish the pseudoternary phase diagram, the component concentrations were noted. The right material concentrations were chosen for the PG-based ME preparation based on these diagrams.[14]

Preparation of microemulsion :

The region of existence of the microemulsion was determined by constructing a pseudo-ternary phase diagram. The phase diagram obtained by mixing the components, should be weighed in advance in a glass vial and titrated with distilled water and stirred at room temperature. The formation of a single-phase/two-phase system is confirmed by visual inspection. If turbidity occurs after phase separation, the samples should be considered as biphasic. In the case of single-phase systems, a transparent and transparent mixture is visualized after agitation;[11-2] Samples should be labelled as microemulsion formulations.

Table-1. Formulation batches of Microemulsion

Sr. no	Mg	F1	F2	F3	F4
1	40	Gliclazide	Gliclazide	Gliclazide	Gliclazide
2	200	Olive oil	Capmul	Olive oil	Capmul
3	550	Tween 80	Tween 20	Tween 20	Tween 80
4	550	PropyleneGlycol	PEG 400	Propylene Glycol	PropyleneGlycol

Preparation of Microemulsion & self-microemulsifying drug delivery system :

Microemulsion formulation of Gliclazide was prepared by Spontaneous Emulsification Method. Gliclazide was solubilized in Capmul for vortexing mixing for 10 minutes and sonication for 15 minutes. Then Tween 20 and Polyethylene Glycol were added slowly in oil phase. Then mixture was sonication for 25 minutes. Then this microemulsion was visually observed for phase clarity and flowability.

The adsorption of the microemulsion was evaluated. Various types of adsorbents were used to accomplish this. Many adsorbents, including silicon dioxide, magnesium alminometa silicate, microporous calcium silicate, and microcrystalline cellulose were absorbed into the microemulsion created by employing Gliclazide. Different weights of these adsorbents were applied. After that, a glass rod was used to continually stir the contents for fifteen minutes.

Consequently, a firm gelatin capsule was filled with the combination.[12] Microemulsion physicochemical characterization.

Evaluation of drug loaded microemulsions:

The prepared microemulsions were evaluated to test their stability, which depicts there in vitro performance. Some of important parameter related to evaluation of microemulsions is discussed below :

Stability testing of drug loaded microemulsions :

To check whether microemulsions are stable, the drug-loaded microemulsions were subjected to stability testing, which comprises

of heating cooling cycle, freeze thaw cycle and centrifugation tests. Physical stability was continuously monitored over the period of time. Various aspects like phase separation and turbidity were observed at room temperature.

Centrifugation study :

The selected were centrifuged in the REMI centrifugation unit at the 5000-rpm for 30 minutes and the phase separation, creaming or cracking were checked and the selected formulations were screened out. The selected formulation were subjected to heating-cooling cycle, freeze-thaw cycles.

Heating cooling cycles :

It is used to see the stressed effect of heating and cooling on the microemulsions. In this study the formulation were placed at 45ºC and at refrigeration temperature for not less than 48 h for each temperature cycle.

Freeze-thaw cycles (Accelerated ageing):

It is done to monitor accelerated stability testing of microemulsions formulation. In this study we place the formulation at two different temperatures *i.e.* -21ºC and 21ºC. For the better estimation of accelerated stability studies three such cycles should be run for each batch of formulation.[9]

Determination of the particle size :

Particle size distribution, average particle size were determined by photon correlations spectroscopy using Zeta particle size, Nano ZS model. The separated microemulsion was measured and then diluted with distilled water. Particle size and PDI measurements were performed at a scattering angle of 90° and a temperature of 25°C. All experiments were performed in triplicate.[7]

FTIR spectroscopy :

It was determined using a Fourier transform infrared spectrometer (FTIR, Simadzu Corporation). The sample was scanned over the wavelength region from 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1} by dispersing the sample in KBr and compressing the sample into a plate by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellets are placed in the path of the light and the resulting spectrum.[6]

Self-Emulsification and Precipitation Assessment :

Visual assessment was used to evaluate the self-emulsifying qualities of SMEDDS formulations. The speed of emulsification, clarity, and apparent stability of the final emulsion were used to classify the various mixtures. The preconcentrate (SMEDDS) was added dropwise to 250 milliliters of distilled water for visual evaluation. This was carried out at room temperature in a glass beaker with the contents gently agitated magnetically at about 100 rpm. After a day, the precipitation was assessed visually by looking at the resulting emulsion. The formulations were then divided into four categories: nonclear (turbid), stable (no precipitation at the end of 24 hours), unstable (showing precipitation within 24 hours), and clear (transparent or transparent with bluish tint).[3]

TEM :

TEM was used to characterize of microstructure of gliclazide loaded microemulsion. Gliclazide was placed on a carbon coated copper grids and then a drop of 1% phosphotungstic acid covered on microemulsion. The superfluous phosphotungstic acid on ME was wiped off by filter paper. The Tem image were obtained using a Tecnai G2 20 TEM (Holland).[8]

Disintegration Test :

Place one dosage unit in each of the 6 tubes of the basket, then add disc. Operate the apparatus using the specific medium, maintained at 37±2° C, as the immersion fluid. At the end of specified time, lift the basket from the fluid and observe the dosage unit. The entire dosage units have disintegrated completely.

In vitro release studies :

The USP Type II apparatus (Paddle method) was used to conduct the dissolution research at 50 rpm and 37°C ± 0.5°C. PBS 7.4 with methanol in a 9:1 ratio used as the dissolving medium. In 900 milliliters of dissolving media, prepared SMEDDS containing 40 milligrams of the medication were added. At regular intervals of 5, 10, 15, 30, 60, and 120 minutes, a sample of 5 ml was taken out and filtered through a 0.45 ¼m filter. To keep sink conditions constant, an equivalent volume of the appropriate dissolution media was introduced. A UV spectrophotometer set to 253 nm was used to analyze the drug content of the sample.[13]

Stability Studies :

Stability studies were performed on the optimized formulation at 30 ± 2°C in a stabilization chamber (Thermolab) for 6 months. The optimal formula is stored in a sealed glass bottle. After 6 months, studies on drug content, particle size and sedimentation were performed.

Preparation of microemulsion :

Microemulsions are prepared by dissolving gliclazide in olive oil. At this optimum ratio of surfactant-tween 80 and co-surfactant-PEG-400 are mixed, then gently mixed with distilled water.

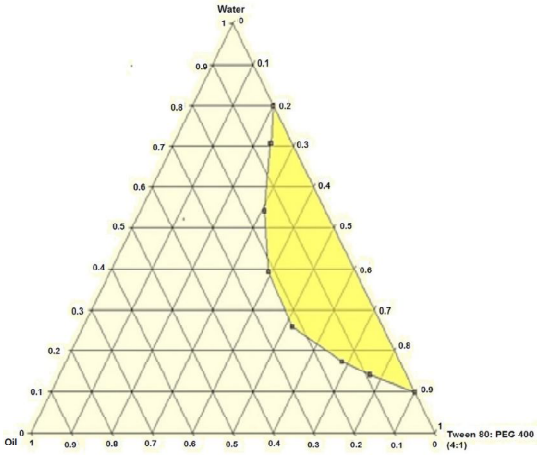

Figure 1. Ternary Phase Diagram with region of Microemulsification

Stability testing of drug loaded microemulsions :

The formulations were then observed for phase separation. Only formulations that were stable to phase separation were selected for further studies.

Table-2. Stability tests of selected microemulsion formulation

Sr. no	Formulation Code	Centrifu-gation Study	Heating-cooling cycle	Freeze Thaw Cycle	Inference
1	F1	X	√	√	Failed
2	F2	√	√	√	Passed
3	F3	√	X	X	Failed
4	F4	√	X	√	Failed
5	F5	√	√	X	Failed

Determination of particle size :

The size of the particle plays a significant role in the design of an oral drug delivery system when considering irritation and comfort. Figure 2 displays the average particle size of the prepared nanosuspension formulation. The range of particle sizes is 247.7–409.1 nm. The effect of various formulation factors, particularly the polymer concentration, had a big impact on particle size. The particle sizes obtained with lower polymer concentration were noticeably smaller than those obtained with higher polymer concentration, as shown in Fig. 2.

FTIR :

The obtained sample's IR spectrum was performed and compared to the IR spectrum of the Gliclazide reference standard. Similar characteristic peaks can be seen in the sample drug's IR spectra and optimized SMDDS formulation (F2).

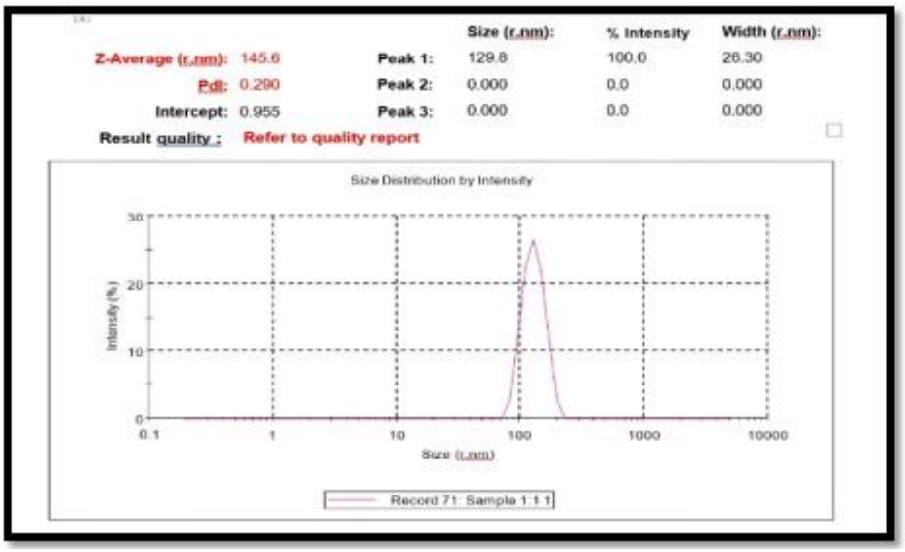

Figure 2. Particle Size of Microemulsion Formulations (F2)

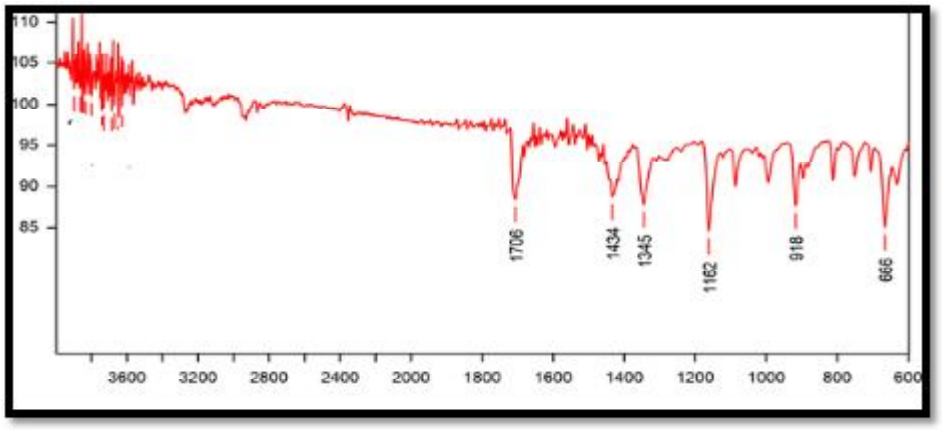

Figure 3. FT-IR Spectrum of Gliclazide

Self-emulsification and precipitation assessment :

Precipitation was evaluated by visual inspection of the resultant emulsion after 24 hours. The formulations were then categorized as clear (transparent or transparent with bluish tinge), nonclear (turbid), stable (no precipitation at the end of 24 hours), or unstable (showing precipitation within 24 hours).

TEM :

The Tem images revealed that particle size was nanometer in ranges and particles had nearly spherical in shapes.

Table-3. Evaluation of various formulations

Formu-lation	Dispersion time (sec)	Clarity	Precipi-tation
F1	78±5	Clear	Unstable
F2	59±3	Clear	Stable
F3	64±4	Clear	Unstable
F4	51±5	Non Clear	–

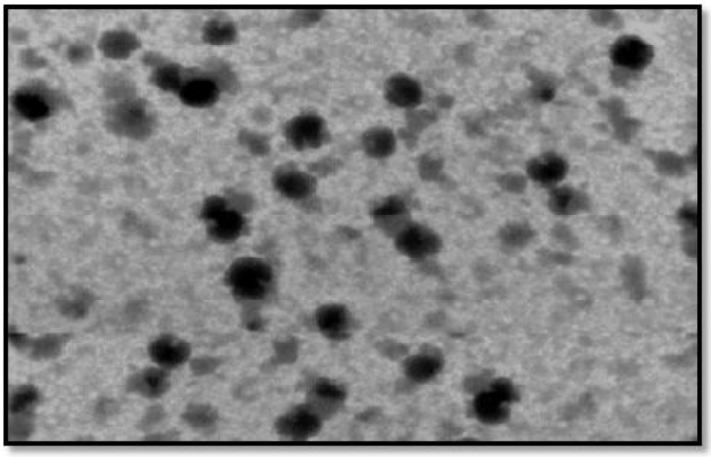

Figure 4. TEM image of Microemulsion loaded Gliclazide (F2)

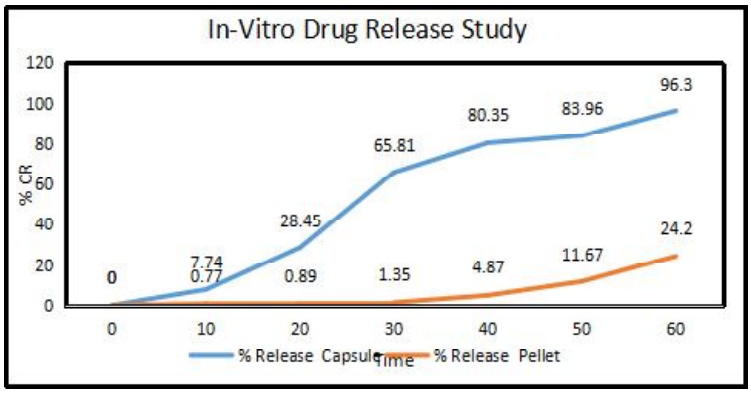

Fig. 5. Comparative results of drug release from plain Gliclazide and SMDDS formulation in water

Disintegration Test :

Disintegration test of SMDDS formulation (F2) was found to be 8.48 second.

In Vitro release :

From figure 5, it can be observed that the release profiles were comparable in water. The release profile of capsule containing Gliclazide was higher than plain Gliclazide. Where release profile obtained after 60 minutes in capsule was 96.3, it was found to be 24.20 in plain Gliclazide.

Table-4. Percent release have SMDDS formulation (capsule) and the plain Gliclazide in water

Time	% Release Capsule	% Release Pellet
0	0	0
10	7.74	0.77
20	28.45	0.89
30	65.81	1.35
40	80.35	4.87
50	83.96	11.67
60	96.3	24.20

Stability studies :

According to stability study results, the SMEDDS formulation maintained its clarity at 25°C ± 2°C and 40°C ± 0.1°C for three months. Phase separation did not exist in either system at any point in time. During the stability analysis, it was discovered that all of the F2 formulations were consistent in terms of their phase separation, and transparency.

A key strategy for resolving formulation issues and enhancing the oral bioavailability of hydrophobic/lipophilic medications is the self-microemulsifying drug delivery system. This study successfully prepared SMEDDS formulations for oral administration of gliclazide, a poorly water-soluble medication, using the microemulsion and adsorbent techniques, respectively. Additionally, their in vitro performances were evaluated. Among the different formulations, F2 in SMEDDS demonstrated encouraging outcomes in terms of in vitro drug release, particle size, stability studies and self-emulsification time. To sum up, SMEDDS made from castor oil, tween 20, and propylene glycol as an oil, surfactant, and co-surfactant

is a potential method to increase glicliazide's solubility, rate of dissolution, and therefore, bioavailability.

When compared to pure medication, the enhanced formulations demonstrated noticeably better drug release. The study's findings demonstrated the value of SMEDDS in improving the solubility and bioavailability of sparingly soluble chemicals, such as gliclazide, which may assist lower dosage and associated adverse effects. The potential use of SMEDDS for the administration of poorly water-soluble chemicals is effectively demonstrated by the current exploratory work.

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