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CANAGLIFLOZIN SILICA LIPID HYBRID PARTICLES FOR IMPROVED SOLUBILITY AND DISSOLUTION

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Keywords:

Canagliflozin, Silica Lipid Hybrid particles, Solubility, Lipid-based formulations

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ABSTRACT: Silica lipid-hybrid formulations have gained an increased interest in recent times as a means to enhance the solubility as well as dissolution of poorly water-soluble lipophilic drugs. The objective of the present investigation was to design and optimize silica lipid hybrid particles of Canagliflozin to improve its solubility. Canagliflozin is an antidiabetic drug used to improve glycaemic control in people with type 2 diabetes. In this study, we have fabricated a Solid-State Lipid-Based Oral Drug Delivery System as CNZ SLH with liquid lipids like Miglyol 812, Labrasol and Acrysol el 135. Sylloid 244 FP grade highly porous silica was used as adsorbent. The interaction of CNZ-SLH particles was studied using X-ray powder diffraction (PXRD), Differential Scanning Calorimetry (DSC) and FTIR spectroscopy. CNZ-SLH particles prepared with Miglyol and Labrasol enhanced the solubility of CNZ by 19.67 fold. Optimized SLH particles formulated as a tablet shows faster drug release than the marketed formulation of CNZ Invokana. Silica lipid hybrid particles can be a cost-effective method to formulate drugs with poor solubility.

INTRODUCTION: Solubility is a critical problem in the pharmaceutical industry for most of the drugs under the pipeline. It is reported that about 70% of drugs and active chemical entities are poorly water-soluble compounds and belongs to either BCS Class II/IV. Such drugs are difficult to scale up into pharmaceutical formulations as they usually exhibit poor solubility and variable bioavailability [1]. The expanding application of combinatorial chemistry and high-throughput screening in drug discovery contributes to the selection of poorly water-soluble new drugs, frequently making oral drug product development very critical [2].

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From various studies, it has been found that lipid-based formulations can improve the bioavailability of poorly water-soluble drugs. Lipid-based solid dispersion can become a better choice to enhance solubility. Lipid-based drug delivery strategies can increase lymphatic transport of lipophilic drugs thereby enhances bioavailability many folds [3, 4]. Miscellaneous lipid-based formulations range from simple solutions of drugs in lipids such as triglycerides (oil) to the use of a mixture of two or more triglycerides, partial glycerides, Emulsifying agent, hydrophilic and lipophilic surfactants, surfactants and co-solvent to solubilize drugs.

Lipid-based drug delivery can be formulated as SMEDDS, SEDDS, SNEDDS, and various nano-sized delivery. Lipid-based formulations allow drugs in the dissolved state during its transit through the gastrointestinal tract. As drugs get solubilize in colloidal dispersion of lipids, the more drug will be available for absorption [5, 6].

Lipid-based solid dispersions or solid formulation is a better alternative as it is in the solid-state. The drug can be available in the molecularly dispersed form it helps to release drugs as either solutions or finely divided and rapidly dissolving particles, thus leads to improved bioavailability [7].

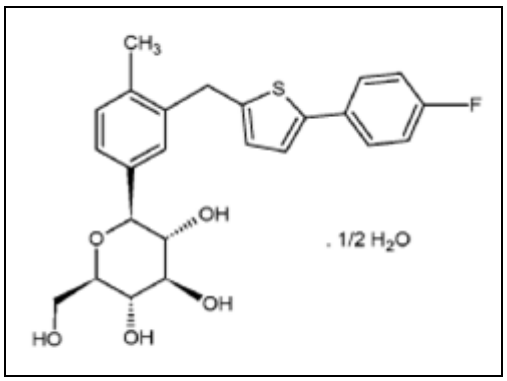
Tri-Hung Nguyen *et al*., has developed Silica–lipid hybrid (SLH) formulations of celecoxib and enhanced dissolution as well as bioavailability of the drug. The study proved that SLH microparticle systems as novel dry powder delivery vehicles for poorly water-soluble drugs [8].

Different grades of highly porous silica like Neusilin, Aerosil, Syloid available commercially, come up with high-surface-area. These are water-insoluble solid carriers. Liquid lipid-based systems can be adsorbed on highly porous silica and converted into dry powder forms, which can boost the stability and performance of the drug [9].

Canagliflozin (Invokana) this drug belongs to the Gliflozin class. Canagliflozin is a recently discovered class of oral hypoglycaemic drugs used to treat type II diabetes mellitus.CNZ is a selective oral Sodium-Glucose co-transporter 2 (SGLT 2) inhibitor. Canagliflozin is a poorly soluble drug showing incomplete bioavailability. Poor drug solubility, however, leads to slow and incomplete dissolution, which ultimately reduces drug bio-availability. CNZ has relative oral bioavailability 65%, belongs to BCS class IV drug with low solubility and low permeability. Canagliflozin is SGLT 2 inhibitor, SGLT 2 is responsible for 90% of the renal glucose reabsorption (SGLT1 is responsible for the remaining glucose reabsorption). CNZ Blocks SGLT 2 which causes the elimination of blood glucose through the urine and results in lowering of blood glucose [10, 11, 12].

Preparing a lipid-based nano-sized dosage form is a time-consuming and costly method to improve drug solubility performance. In our present investigation, we have tried to formulate solid lipid drugs with highly porous silica. We have selected and used Syloid 244FP silica as it is highly porous and has a large internal surface area that enables them to absorb up to 3x their weight in liquid. Syloid 244FP grade of silica improves the dissolution profile of the drug and facilitates gastric wetting. It helps in disintegration for orally disintegrating tablets. This grade of silica is an outstanding carrier for converting lipid or oil-soluble drugs into free-flowing powders. They can be used as adsorbents in the fabrication of solid dispersion, semi-solids, and lipid-based technologies, for instance, self-emulsifying drug delivery systems (SEDDS) [13, 14].

For our study, we have selected different lipids. Labrasol is chemically capryl o capryl macrogol-8 glyceride, non-ionic surfactant used as a solubilizer for o/w emulsions, penetration, and bioavailability enhancer. Labrasol improves solubility and wettability of Active Pharmaceutical Ingredient. Acrysol-EL-135 is PEG-35 hydrogenated castor oil, can also be called as Cremophor EL or Kolliphor EL. It can be used as a formulation vehicle for various poorly water-soluble drugs. Miglyol 812 is a medium-chain triglyceride, chemically it is an ester of saturated coconut oil used in various lipid-based formulations as a solubilizer. Transcutol HP is a highly purified diethylene glycol monoethyl ether. It can be used as a solvent and solubilizer for solubility and bioavailability enhancement for oral and alternative routes. It is suitable for adsorption on a neutral carrier like silica [15, 16].



CANAGLIFLOZIN HEMIHYDRATE

In the present work, we have fabricated silica lipid hybrid particles of Canagliflozin for improved solubility and dissolution. Silica lipid hybrid particles can be the best alternative to an oral lipid-based drug delivery system.

MATERIALS AND METHODS: Canagliflozin was obtained as generous a gift sample from Macleod's Ltd. (Mumbai). Acrysol EL-135 (Cremophor EL) was obtained as gift samples from

Corel Pharma Chem (Ahmedabad, Gujarat). Miglyol 812, Transcutol-P, and Tween 80 were purchased from Sigma Aldrich (India). Labrasol was obtained as a gift sample from Gattefosse (Mumbai, India). SYLOID® 244 FP Silica was purchased from Grace Ltd. (Pune). All remaining chemicals were purchased from Himedia Laboratories (Mumbai, India). Marketed tablets were purchased from the local drug store of Mumbai, India.

Method:

Determination of Saturation Solubility of the Drug: Drug saturation solubility was determined in dissolution media *i.e.* 0.75% SLS. For this in 10 ml vial, 5 ml media was taken to this excess drug was added. The mixture was kept shaking on a magnetic stirrer for 24 h. The supernatant was then filtered through a 0.45-micron filter paper. The aliquots were diluted appropriately and assayed spectrophotometrically at 292 nm using a UV-Vis spectrophotometer (UV-1700 Pharm spec, Shimadzu, Kyoto, Japan). The calibration curve in different media was previously prepared for CNZ at 292 nm.

Screening of Lipids: Dilpreet Singh *et al*., formulated Canagliflozin SMEDDS, determined CNZ solubility in various lipids. The solubility data is given in the following table. Based on this data, we have selected lipids for our study.

TABLE 1: THE SOLUBILITY OF CANAGLIFLOZIN IN VARIOUS LIPID EXCIPIENTS (MEAN ± SD, n = 3)

Lipid excipients	Solubility (mg/g)
PEG 400	76.645 ± 7.434
Labrasol	95.999 ± 6.432
Tween 80	135.93 ± 9.210
Cremophor EL	171.03 ± 6.902
Transcutol P	234.79 ± 5.438

For our study, we have selected the lipids in which there is good solubility of CNZ [17].

Fabrication of Silica Lipid Hybrid Particles: Accurately weighed amount of CNZ, liquid lipid and surfactant were added into glass vials. The vials were then sonicated for 30 min using ultra-probe sonication Model-frontline Sonicator FS-250 (Ahmedabad, India) to prepare homogenous Mixture. A clear solution was formed after the complete dissolving of a drug in lipid. Once the CNZ was dissolved, porous silica was added directly into the vials containing a solution of drug and lipid. Highly porous silica Syloid244FP silica physically mixed with drug lipid solution. The mixture was adsorbed on Syloid244FP silica and dry white powder was obtained. Powdered SLH were prepared with 100 mg drug [18].

TABLE 2: FORMULATION OF CANAGLIFLOZIN SILICA LIPID HYBRID PARTICLES

Ingredients	Formulation code			
	F1	F2	F3	F4
Canagliflozin	100 mg	100 mg	100 mg	100 mg
Miglyol 812	100 mg	-	100 mg	-
Labrasol	100 mg	-	-	-
Acrysol El 135	-	100 mg	-	-
Transcutol P	-	100 mg	100 mg	-
PEG 400				100 mg
Tween 80				100 mg
Sylloid 244 FP	100 mg	100 mg	100 mg	100 mg

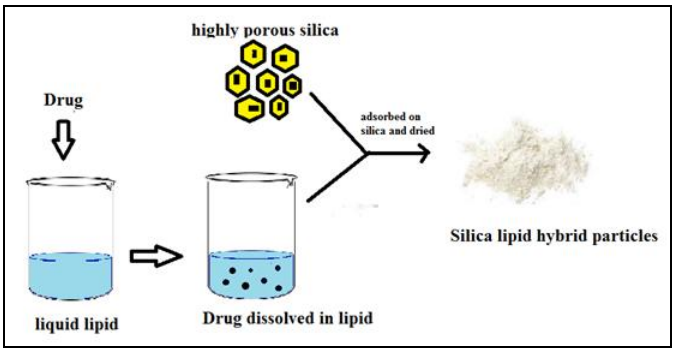


FIG. 1: GRAPHICAL ABSTRACT OF FABRICATION OF SILICA LIPID HYBRID PARTICLES

Formulation of Tablets: The silica lipid hybrid powders showing the best solubility were selected and formulated as a tablet. For the formulation of tablets karnavati tablet punching machine was used. The prepared tablet was then compared with the Marketed formulation of CNZ. All formulations studied for dissolution in different dissolution media.

TABLE 3: FORMULATION OF CNZ-SLH TABLETS

Ingredients	C1	C2	Marketed tablet
Canagliflozin	100 mg	100 mg	
Miglyol 812	100 mg	-	
Labrasol	100 mg	-	
Acrysol El 135	-	100 mg	
Transcutol P	-	100 mg	Invokana tablet
Sylloid 244 FP	100 mg	100 mg	(100 mg)
Avicel	60 mg	60 mg	
Magnesium Stearate	3 mg	3 mg	
Talc	3 mg	3 mg	
Total Weight	466 mg	466 mg	

Physicochemical Characterization of CNZ and CNZ Silica Lipid Hybrid Particles:

Determination of Saturation Solubility of the Silica Lipid Hybrid Particles: CNZ-SLH saturation solubility was determined in reported dissolution media of CNZ *i.e.* 0.75% SLS. A solubility study was conducted to determine the apparent solubility of CNF and Prepared Silica lipid hybrid particle dispersion. An excess quantity of CNZ-SLH has added to 5 ml of 0.75% SLS in a screw-capped sealed Vials of capacity 10 ml, maintained under continuous stirring (100 rpm) with REMI magnetic stirrer at room temperature, for 24 h to achieve an equilibrium. Samples were centrifuged, filtered using 0.45 µ size Millipore filter paper. Absorbance was measured spectrophotometrically at 292 nm.

DSC Study: DSC was performed to study the thermal behavior of CNZ and the SLH Particles. The device used was Mettlor Toledo, Japan DSC. A sample of about 5 mg of Pure dug CNZ and CNZ-SLH was packed inside a sealed aluminum pan and heated at a scanning rate of 10 °C/min on a temperature range from 40 °C to 400 °C. The software used was STAR- SW10.

FTIR Spectroscopy: FTIR studies for CNZ pure drug, prepared SLH particles were performed using IR Affinity-1 Spectrophotometer (Shimadzu, Japan) with KBr as a reference Standard. FTIR study was conducted to study any alteration of the structure of CNZ after the formation of SLH. FTIR helps to determine drug-polymer compatibility. A sample of about 5 mg of the drug was grounded, then mixed with potassium bromide and compressed through a manual press to form a thin disc and analyzed using FTIR spectroscopy in a range from 4000 to 500 cm^{-1}.

Powder X-ray diffraction (PXRD): Diffraction model of CNZ pure drug and the selected silica lipid hybrid particles were studied for X-ray Diffraction to determine the degree of crystallinity using MiniFlex II X-ray diffractometer (Rikagu, USA) by utilizing Cu K α radiation with a nickel filter, a voltage of 40 kV, and a current of 25 mA. The samples were analyzed in a range from 5 °C to 50 °C.

Micrometric of SLH Particles:

Flow Properties of CNZ Silica Lipid Hybrid Particles: Angle of repose, Cars compressibility index and Hausner ratio were studied. Flowability and compressibility of CNF-SLH were Determined. Micrometric is an essential powder property that is required for powder compression into tablets.

***In-vitro* Dissolution Studies of CNZ-SLH:** The dissolution study of SLH dispersion and the formulated tablet was performed using USP type II paddle dissolution test apparatus-Electrolab. The dissolution study was performed under sink conditions in 600 mL of 0.75% SLS (reported dissolution media) at 50 RPM. Dispersions, containing 100 mg of CNF, were placed into the dissolution media retained at 37 ± 0.5 °C. 5 mL aliquots were withdrawn and replaced with fresh media at predetermined time intervals (5, 10, 15, 20 and 30 min). The aliquots were filtered using 0.45 µm filters and analyzed with a UV spectro-photometer at 292 nm. The dissolution study of formulated tablets and the marketed formulation was conducted in the same manner.

RESULTS AND DISCUSSION:

Saturation Solubility of Pure Drug CNZ and CNZ-SLH: Saturation solubility of CNZ and formulation were performed in reported dissolution media 0.75% SLS. Saturation solubility CNZ was found to be 11.05 mg/ml. Among all SLH, F1 was found to have the highest solubility in dissolution media. There were 19.63 fold enhancements in solubility with F1 and 16.58 fold with F2 Silica lipid hybrid particles. From F3 and F4 formulations, there was 14.85 to 12.63 fold enhancement in solubility respectively. F1 formulation contains Miglyol 812 and Labrasol, a combination of these two lipids enhanced solubility of CNZ significantly.

TABLE 4: SATURATION SOLUBILITY OF PURE DRUG CNZ AND CNZ-SLH

Formulation	Saturation solubility (mg/ml)	Fold enhancement
CNZ- pure drug	11.05 ± 0.567	-
F1	216.99 ± 2.89	19.63
F2	183.27 ± 1.56	16.58
F3	164.18 ± 1.04	14.85
F4	139.63 ±1.35	12.63

DSC: DSC analysis of this silica lipid hybrid particles indicated that there was no chemical reaction between the drug and excipients and that a CNF-SLH. The characteristic peak was observed in the DSC thermogram of Canagliflozin at 70 °C to

80 °C, indicate its indicate melting point. Thus, CNF exhibited in crystalline form. The characteristic peak of the drug was disappeared at the thermogram of silica lipid hybrid particles. This indicates a molecular dispersion of CNF in SLH particles. The total disappearance of the drug melting peak indicates the occurrence of the amorphous nature of CNF in SLH.

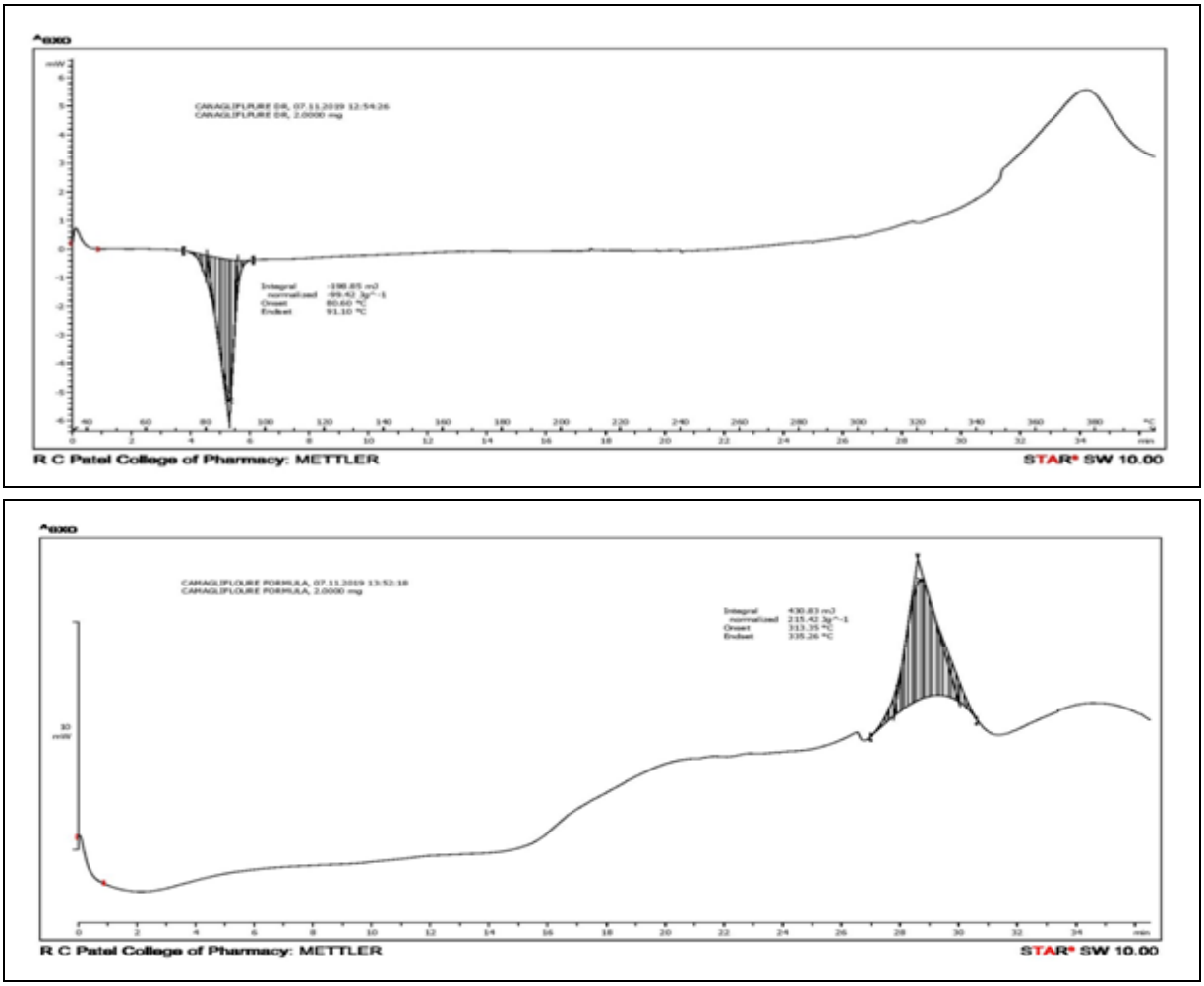


FIG. 2: COMPARATIVE DSC OF CNZ AND C1 FORMULATION

Fourier Transforms Infrared Spectroscopy (FTIR): FT-IR is an important technique to predict a possible interaction of a drug with polymers in solid-state. FT-IR spectra of CNZ and prepared Silica lipid hybrid particles were performed. FT-IR spectra of CNZ showed characteristic absorption bands. The main peak was observed at 3321 cm (aromatic N-H Stretching), 2927 cm (-CH aliphatic stretching), 1651 cm^{-1} due to C = C stretching, 1506 cm^{-1} due to $-NO_2$, 1415 is due to $-CH_2$ bending, 1076 cm^{-1} is due to ethereal linkage stretching, 1002 is due to – CO stretching.

The FTIR spectrum of SLH particles of CNZ showing the best solubility and dissolution, F1 shows broadening of the peak at 3500 cm shows the formation of a hydrogen bond. A sharp peak was observed at 1058 indicate significant intermolecular interaction between CNZ and lipid molecules.

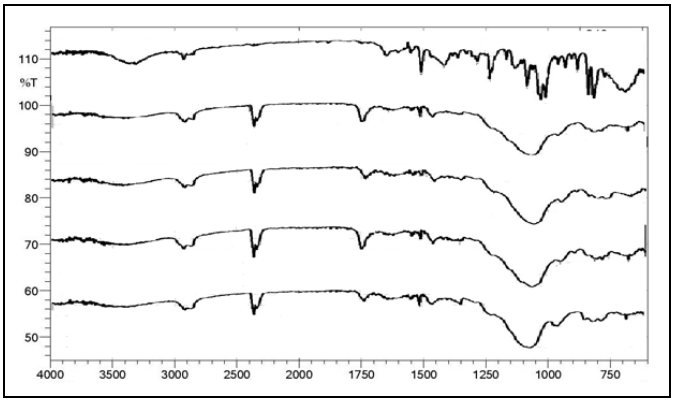


FIG. 3: OVERLAY OF FTIR OF PURE DRUG CNZ AND SLH –F1, F2, F3 AND F4

Powder X-ray Diffraction (PXRD): XRPD measurements were performed using a Miniflex II diffractometer (Regaku, USA) Powder X-ray diffractometry (PXRD) was performed to confirm the solid-state characteristics and determine the crystallinity of CNZ and the Silica lipid hybrid particles of CNZ. The XRPD patterns for crystalline CNZ showed sharp characteristic diffraction peaks confirming the crystalline nature of the pure drug used for the preparation of SLH particles. CNZX-ray diffraction (XRPD) pattern comprising sharp diffraction peak at two-theta values 5.22, 8.53 14.45, 16.44, 19.10 and 20.76. The XRPD pattern is shown in **Fig. 4**. In silica lipid hybrid particles of F1 formulation, no characteristic peaks were observed. Broad hallows were observed indicating the amorphous nature of CNF in SLH. The PXRD pattern of Dispersion did not exhibit crystallinity, where no thermal events were recorded corresponding to the melting of CNZ. Conversion of a crystalline form of the drug to amorphous form in prepared SLH indicates confirm solubilization of CNF in liquid lipid (Miglyol 812 and Labrasol) that was further adsorbed on (Syloid FP 244) carrier material.

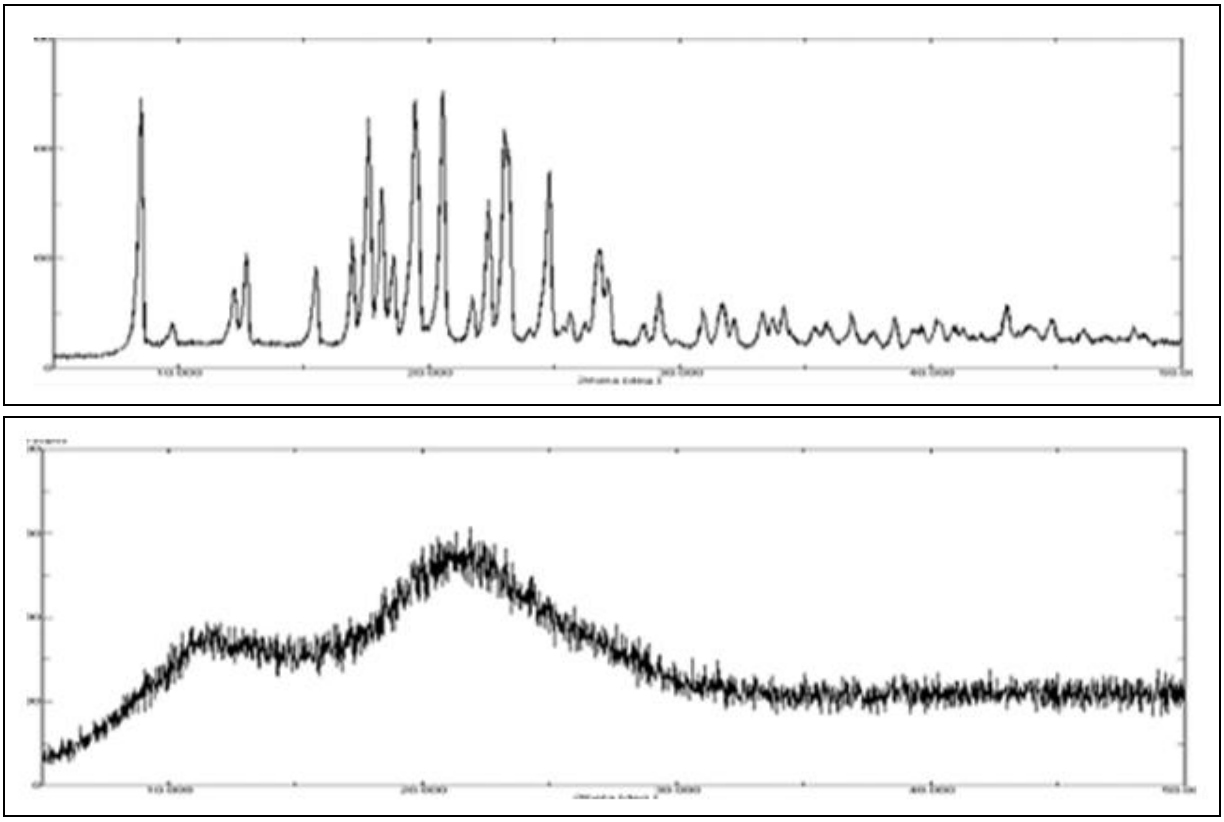


FIG. 4: PXRD OF CNZ, SILICA LIPID HYBRID PARTICLES OF CNZ

Flowability of SLH particles Dispersion (Micromeritics): Powder flow property is an important requirement for the formulation of the tablet. Mixing of ingredients and compression are influenced by flowability. As we have dissolved drug in lipids and adsorbed on Sylloid 244FP, flowability depends on the lipids present in the formulation. Sylloid 244FP having large surface area and high adsorption, the flowability of the formulation was very good. To study flowability parameters like angle of repose, Carr's compressibility index and Hausner ratio were determined as shown in the following **Table 5**.

TABLE 5: FLOW PROPERTIES OF SLH PARTICLES

Formulation code	Angle of repose (°)	Carr's Compressibility index (%)	Hausner Ratio
F1	32.18±1.01	11.04±0.2	1.12±0.24
F2	31.43±1.6	12.45±0.3	1.18±0.27
F3	32.61±1.4	11.67±0.2	1.24±0.32
F4	31.04±1.8	11.56±0.2	1.19±0.20

Percentage Drug Release through Powdered Silica Lipid Hybrid Particles: Powdered silica lipid particles shown 100% drug release within 10 minutes of dissolution. There was complete drug release through all the formulated silica lipid hybrid particles. All the formulations were having

excellent dissolution property. The dissolution media used was 0.75% SLS in water. Percentage drug release through SLH powder dispersion is given in the following table.

TABLE 6: PERCENTAGE DRUG RELEASE THROUGH CNZ-SLH

Formulation	Percentage drug release (%)
F1	104.067
F2	102.12
F3	103.04
F4	100.89

Percentage of Drug Release through Tablets: Drug release through prepared tablets and the marketed formulation was compared. It was found that drug release through C1 formulation was faster than the marketed tablet of CNZ- Invokana. From the prepared formulation, it was found that there is a complete drug release from C1 within 10 min of dissolution. 100 % drug was released within 10 min of dissolution. Through C2 formulation complete drug released after 15 min prepared formulation C1 was found superior to marketed formulation.

TABLE 7: PERCENTAGE DRUG RELEASE THROUGH CNZ-SLH TABLET FORMULATIONS

	Percentage Drug Release (%)		
Time (min)	C1	C2	Marketed tablet
0	0	0	0
5	89.98	67.56	76.48
10	100.23	92.04	99.23
15	103.45	100.74	101.36
20	104.56	103.89	103.46
30	104.56	105.37	104.23

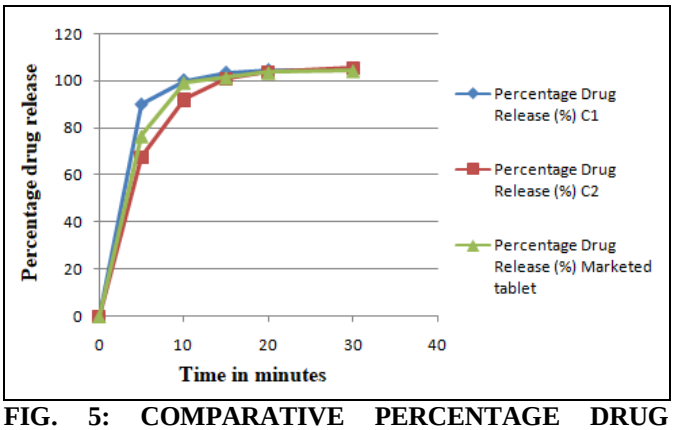


FIG. 5: COMPARATIVE PERCENTAGE DRUG RELEASE THROUGH TABLETS

DISCUSSION: With highly porous silica we can formulate liquid lipid-based drug delivery into a solid-state, with improved drug performance, solubility, and dissolution. SLH is a promising approach to formulate drugs with critical solubility [19, 20].

We have formulated silica lipid hybrid particles, with a combination of two different liquid lipids. Labrasol is a non-ionic surfactant as well as a solubilizer and Miglyol is medium-chain triglycerides act as a solubilizing agent. Combined lipids exerted a synergistic effect to enhance the solubility and dissolution behavior of CNZ. The drug was completely dissolved in liquid lipid which was later adsorbed on Sylloid 244 FP.

From the results of preformulation studies, we have chosen a combination of lipids that are compatible with the drug. From FTIR study, it has been confirmed that there is no chemical interaction between drugs and polymers. DSC and PXRD of pure drug and F1 formulation were compared. Pure drug shows crystalline nature, while in SLH, CNZ exists in amorphous form.

The various lipid excipients have been used, out of which Labrasol, Acrysol EL 135 and tween 80 acts as surfactants, Transcutol P act as co-surfactant and cosolvent, Miglyol 812 is oil, PEG 400 acts as cosolvent. Based on the results of the solubility of pure CNZ in various lipids, these lipids were chosen. In the F1 formulation combination of Miglyol 812 and Labrasol was used, which showed 19.63 fold enhancement in solubility, which is very significant. Sylloid 244 FP is a highly porous silica act as adsorbent, in addition to this, it is solubilizer. Sylloid 244 FP increases the wettability of drug and enhances solubility. In the F2 combination of Acrysol El 135 and Transcutol P were used as liquid lipids, with these, the solubility of CNZ was enhanced by 16.58 fold. This method was found a very significant, cost-effective and easy method to enhance the solubility of the drug-like Canagliflozin. Solubility and dissolution of drug CNZ were faster in F1 as compared to marketed formulation. Hence, with SLH particles, we can improve the overall biopharmaceutical performance of the drug. All the fabricated SLH particles demonstrated a great potential to enhance solubility.

CONCLUSION: Novel silica lipid hybrid particles of Canagliflozin were fabricated. Solubility and dissolution of Canagliflozin increased significantly with SLH of CNZ. With F1 and F2 formulation, there were 19.63, 16.58 fold enhancements in solubility of CNZ respectively. Drug release

through tablet C1 was found faster than a marketed tablet of Canagliflozin (Invokana). With Miglyol 812 and Labrasol there was a dramatic enhancement in solubility. As the drug release through the formulated tablet is faster than a marketed tablet it may improve the bioavailability of CNZ. Formulating SLH particles of CNZ can be a promising strategy to enhance the solubility and dissolution of CNZ. Thus, SLH particles can be a unique and novel approach to enhance the solubility and dissolution of poorly soluble drugs. SLH has the potential to improve its bioavailability, therapeutic efficacy, and cost-effectiveness. With this method, liquid lipid-based drug delivery can be converted into a solid-state.

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CONFLICTS OF INTEREST: The authors declare no conflicts of interest.

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