



Original Article

Formulation, optimization, and characterization of solid lipid dispersion

Lovepreet Kaur, Vineet Kumar Rai, Raj Kumar Narang, Tanmay S. Markandeywar*

Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India

Correspondence:

Mr. Tanmay S. Markandeywar, Department of Pharmaceutics, ISF College of Pharmacy, Moga - 142 001, Punjab, India. Phone: +91- 9878530306. E-mail: tmarkandeywar@gmail.com

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ABSTRACT

Aim: Present work was permeation enhancement of metformin hydrochloride using solid lipid dispersion (SLD) technique. **Method:** The SLD was prepared by coprecipitation method. SLD was prepared at ratio of drug: lipid carrier 1:14 (% w/w) by coevaporation method. **Result:** Prepared SLD was optimized and characterized by various parameters such as particle size, zeta potential, transmission electron microscopy, Fourier transform infrared, and percent entrapment efficiency. SLD had an optimum particle size and showed good stability. Differential scanning calorimetry showed that drug might exist in amorphous form. The maximum amount of drug was entrapped in SLD. In vitro release study revealed that minimum amount of drug was released in the first 2 h in simulated gastric fluid (pH 1.2) and maximum amount of drug was released up to 24 h in simulated intestinal fluid (pH 6.8). Ex vivo studies of plain drug and SLD showed that SLD had better intestinal permeability. **Conclusion:** SLD shows enhancement of intestinal permeability in turns to increase oral bioavailability.

Keywords: Permeation enhancement, coprecipitation, metformin, solid lipid dispersion

INTRODUCTION

The drugs belong to Class III (high solubility – low permeability) of biopharmaceutics classification system (BCS) classification system have very low oral bioavailability due to their limited permeability across the biological membrane. Colloidal drug delivery systems such as lipid drug conjugate nanoparticle, solid lipid nanoparticle, nanostructured lipid carrier, and solid lipid dispersion (SLD) are very good examples of lipid-based delivery systems which have successfully been incorporated into many drugs and which are proved helpful in increasing their permeability across the biological membrane. Among this, SLD is the most accepted carrier system for the delivery of hydrophilic BCS Class III drugs as the other three possess the drawback of aggregation. The lipidic delivery system after oral administration, due to their reduced size, can spread out throughout the length of the small intestine where they allow the drug to achieve a controlled and reproducible release with improved absorption and reduction of

potential side effects. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces a higher dissolution rate and bioavailability drugs.^[1] With SLD, hydrophilic drug which is present in crystalline form is converted to amorphous form upon a contact with lipid and the drug is molecularly distributed in the lipidic matrix where the surface hydrophobicity increases.^[2] The particle size also decreases and the amorphous form of drug will easily pass through the intestine. Particles in solid dispersions have been found to have a higher degree of porosity. The increased porosity of solid dispersion particles accelerates the drug release profile.^[3] Phospholipid (PL) -based drug delivery system, for instance, is among the most promising approaches for enhancing oral bioavailability. Being biocompatible, biodegradable, and having an amphiphilic character that allows PLs organized themselves as lipid bilayers when placed in water with the hydrophobic tails lines up against one another and the hydrophilic head-group facing the water on both sides.^[4] Phosphatidylcholine (PC) is used for the formulation of SLD due to its permeation enhancement property and their amphiphilic nature.^[5] It has been widely reported that drugs incorporated into lipid show high permeability of the intestine and also act as surfactant because lipids act as a good permeation enhancer of drugs from the gastrointestinal tract

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by solubilization of the drug in the intestinal milieu and reduce the first-pass metabolism of the drug by the transport of the drug through a lymphatic route to the systemic circulation.^[6] The SLD is becoming one of the most acceptable drug delivery systems for both lipophilic as well as hydrophilic drugs because of ease of production, easy scalability and most advantageously, the use of lipid excipients with generally regarded as safe status, avoiding the use of organic solvents.^[7] Anti-diabetic drug metformin hydrochloride was chosen because it is used as a first-line drug for the treatment of Type II diabetes and the only problem with this drug is its low bioavailability due to its low permeability across the biological membrane. PC was used as PL for many favorable properties such as amphiphilic nature, enhancement or alteration of uptake or release of drugs, biodegradable nature, and its extensive use in formulating various other colloidal systems for enhancement of permeability of drugs. Coevaporation method is used for the preparation of SLD due to the ease of availability, large-scale method, removal of solvent, and less time consuming.

MATERIALS AND METHODS

Materials

Metformin hydrochloride was obtained as a gift sample from Biocon Limited, Baddi. Methanol, ethanol, diethyl ether, chloroform, hexane, and acetone were obtained from Central Drug House, New Delhi. Phosphatidylcholine, potassium dihydrogen phosphate, purified pepsin, was obtained from HiMedia Laboratories Pvt. Ltd, Mumbai. Dialysis membrane having molecular weight cutoff 12–14 KD from Sigma Chemical Co., USA. All the other chemicals used were of analytical grade.

Methods

Preparation of SLD

The SLD was prepared by coevaporation method.^[8] Solid dispersions were prepared at ratio of drug:lipid carrier 1:14 (%w/w) by coevaporation method. An accurately weighed amount of metformin hydrochloride was dissolved in methanol. This alcoholic solution was poured into a solution of the lipid substance in diethyl ether. The mixture was continuously stirred at room temperature till almost complete evaporation of solvents. The remaining solid residue was dried in the refrigerator. The samples were stored in closed screw-capped glass vials away from the light and humidity until use.

Optimization of SLD

Different process parameters were systematically investigated to determine their effects on the formulation. The process parameters included concentration of PC, drug, and methanol and diethyl ether. To optimize the amount of solvent for lipid, different types of solvents were used with different concentrations (chloroform; hexane; chloroform; and diethyl ether). Other parameters were fixed such as concentration of drug's solvent (10 mL), concentration of lipid (100 mg), and concentration of drug (10 mg) which was fixed constant. Formulations were evaluated on the basis of the precipitation. Then, the best concentration of lipid's solvent (diethyl ether 10 mL) was selected to further optimize the concentration of solvent for the drug using various types of solvents (methanol, acetone, and chloroform) for the fixed concentration of lipid

(100 mg) and concentration of drug (10 mg). Again, the one best concentration of drug's solvent (methanol 3 mL) was selected to further optimize the concentration of lipid and drug. Both the solvents were selected on the basis of the rate of evaporation. Then, the same procedure was followed for different concentrations of lipid, that is, 100 mg, 250 mg, 350 mg, and 400 mg. After selecting the appropriate concentration of lipid (350 mg), different concentration of drug (10 mg, 15 mg, 25 mg, and 35 mg) was optimized so that no precipitation occurs.

Characterization of optimized SLD

Optimized SLD was characterized for various parameters such as morphology, size, size distribution, and zeta potential.

Particle size and distribution

Size and size distribution of optimized formulation was determined by Laser Diffraction using Beckman Coulter Delsa™ Nano C Particle Analyzer, US. It works on the principle of photon correlation spectroscopy, which determines particle size by measuring the rate of fluctuations in laser light intensity scattered by particles as they diffuse through a fluid. For the measurement of size and polydispersity index (PDI), 2 mL of SLD (0.1% w/v) was placed into cuvettes and analyzed under Beckman Coulter and measurements were recorded.^[9]

Zeta potential

The zeta potential is an indicator of the stability of the particles. Zeta potential of formulation was measured by a dynamic light scattering technique using Zetasizer (Beckman Coulter Delsa™ Nano C Particle Analyzer, US).^[8] The stability behavior of the colloidal system was recorded according to Table 1.

Transmission electron microscopy (TEM)

The morphology of SLD was observed using a Jeol transmission electron microscope, USA. A drop of sample diluted with water was placed on a carbon-coated copper grid and the excess was drawn off with a filter paper. The grid was air-dried thoroughly. The image was magnified and focused on a layer of photographic film. Images were taken at different magnifications and observed.

Differential scanning calorimetry (DSC)

DSC was performed with a Mettler Toledo DSC, USA. DSC is a tool to investigate the melting and recrystallization behavior of crystalline materials like SLD. The breakdown or fusion of the crystal lattice by heating or cooling the sample yields information about the internal polymorphism, crystal ordering, or glass transition processes. It uses the fact that different lipid modifications possess different melting points and enthalpies. The thermal analysis of the pure drug and SLD was done to observe for any significant changes in the pattern of the

Table 1: Stability behavior of the colloid

Zeta potential (mV)	Stability behavior of the colloid
From 0 to ± 5	Rapid coagulation or flocculation
From ± 10 to ± 30	Incipient instability
From ± 30 to ± 40	Moderate stability
From ± 40 to ± 60	Good stability
More than ± 61	Excellent stability

peaks. Samples were placed in a conventional aluminum pan and heated from 10°C to 250°C at a scan speed of 10°C/min.^[10]

Fourier transform infrared (FTIR) spectroscopy

Drug and carrier interactions were studied by FTIR spectroscopy in pure drug and SLD (Thermo Nicolet-380, USA). The pellets were prepared by gently mixing of 1 mg sample with 200 mg potassium bromide at high compaction pressure. The scanning range was 400–4000 cm⁻¹. The pellets thus prepared were examined and the spectra of all the samples were compared.^[11]

Percent entrapment efficiency

The analysis of entrapment efficiency was done by the centrifugation method. The SLD entrapped drug was separated from the free drug by the centrifugation method. The dispersion was subjected to centrifugation at 7000 rpm for 30 min. The clear supernatant liquid was separated from SLD. The supernatant was filtered and analyzed using UV at 232.54 nm to calculate the amount of entrapped drug.^[12]

The percent entrapment efficiency of the SLD formulation was calculated from the following equation:

$$\% \text{ Entrapment efficiency} = \frac{(DL - DF)}{DL} \times 100$$

DL = Initial drug loaded (mg) and DF = Free drug (mg).

Percent yield

Percent yield was calculated to check the efficiency of the method. The percentage yield was determined by weighing the dried SLD and calculated with respect to the weight of the initial components according to the following formula;

$$\% \text{ Yield} = \left[\frac{(\text{Mass of solid dispersion})}{(\text{Mass of drug} + \text{Mass of lipid substances})} \right] \times 100$$

In vitro release study of SLD

In vitro drug release study of the prepared SLD was determined by the dialysis bag method using a shaking incubator at a rotation speed of 100 rpm for 24 h. Simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 6.8) were used as a dissolution medium. Dialysis

membrane (molecular weight cutoff 12–14 KD, Sigma Chemical Co., USA) was introduced with 2 mL SLD (0.1% w/v) and tied from both the sides to form a dialysis bag. Volume and temperature of the dissolution medium were 100 mL and 37°C ± 0.2°C, respectively. At predetermined time intervals, samples (1 mL) were withdrawn from the simulated gastric fluid (pH 1.2) for 2 h and then dialysis was placed in simulated intestinal fluid (pH 6.8). Again, the samples were withdrawn from simulated intestinal fluid for 24 h and replaced with the same volume of fresh media, filtered, and assayed for drug content at 232.54 nm against blank by UV-visible spectrophotometer. Hence, samples at each interval of time were collected and absorbance was observed at 232.54 nm λ_{max} and then substituted in the above obtained standard curve's equation to get the concentration of drug in the samples. Each concentration value was converted to the amount of the drugs by simply multiplying by the volume of the medium and dilution factor. Hence, the percentage cumulative release of drug in the medium at each interval of time was determined.^[11]

Ex vivo permeation study

The study was conducted using the intestinal tissue of a goat that allowed to be fasted overnight. The duodenal part of the small intestine was isolated, divided into segment sacs, and thoroughly flushed with cold Ringer's solution to remove lumen contents. The segment sacs were filled with the SLD samples (0.1% w/v) and with plain drug, that is, metformin hydrochloride and threads were placed at both ends. The transport medium was simulated intestinal fluid (pH 6.8). The tissues were placed in a beaker filled with 30 mL simulated intestinal fluid (pH 6.8) under continuous aeration and constant temp of 37°C.

At predetermined time intervals, sample aliquots were withdrawn and replaced by fresh medium. The samples were analyzed for the drug concentration against blank. The samples were appropriately diluted and their absorbance determined at a wavelength of 232.54 nm under UV spectrophotometer and permeation of both plain drug and SLD was compared.^[8]

RESULTS AND DISCUSSION

Optimization of SLD

SLD was prepared by the coevaporation method and further were optimized on the basis of the rate of the evaporation of both the solvents and the rate of precipitation of drug (metformin

Table 2: Optimization of metformin hydrochloride-loaded SLD

Formulation	Lipid (mg)	Lipid solvent (mL)	Drug (mg)	Drug solvent (mL)	Inference
F1	100	Chloroform/hexane 1:1 (20 mL)	10	Ethanol (10 mL)	Precipitation
F2	100	Chloroform (10 mL)	10	Ethanol (10 mL)	Precipitation
F3	100	Diethyl ether (10 mL)	10	Ethanol (10 mL)	Moderate precipitation
F4	100	Diethyl ether (20 mL)	10	Methanol (3 mL)	Very less precipitation
F5	100	Diethyl ether (20 mL)	10	Acetone (6 mL)	Precipitation
F6	100	Diethyl ether (20 mL)	10	Chloroform (10 mL)	Precipitation
F7	250	Diethyl ether (20 mL)	10	Methanol (3 mL)	Precipitation
F8	350	Diethyl ether (20 mL)	10	Methanol (3 mL)	Very less precipitation
F9	400	Diethyl ether (20 mL)	10	Methanol (3 mL)	Precipitation
F10	350	Diethyl ether (20 mL)	15	Methanol (3 mL)	Precipitation
F11	350	Diethyl ether (20 mL)	25	Methanol (3 mL)	Solid lipid dispersion
F12	350	Diethyl ether (20 mL)	30	Methanol (3 mL)	Precipitation

hydrochloride) and lipid (PC). Process parameters included different concentrations of different solvents for lipid, concentration of lipid (PC), different concentrations of different solvents for drug, and concentration of drug (MH) shown in Table 2.

From above, it was observed that the metformin hydrochloride-loaded SLD containing 350 mg of lipid, that is, PC, 20 mL of diethyl ether with 25 mg of drug (MH) and 3 mL of methanol in formulation F11 showed no precipitation and both the solvents were evaporated simultaneously. Therefore, F11 was selected as the final optimized formulation [Table 3]. F11 was visually observed and found to be waxy solid material.

Characterization of optimized SLD

Particle size and PDI

The PDI or heterogeneity index is a measure of the distribution of molecular mass in a given polymer sample. The PDI values are in the range from 0 to 1. Size and size distribution of optimized SLD was determined by photon correlation spectroscopy method using Zetasizer. Size and size distribution of optimized formulation for metformin hydrochloride-loaded SLD was shown in Figure 1. Particle size and PDI of SLD were found to be 157 ± 5.28 nm and 0.303 $\pm$ 0.012, respectively, which was in the standard range.

Table 3: Optimized parameters for final formulation

Optimized parameters	F11
Lipid (mg)	350
Diethyl ether (mL)	20
Drug (mg)	25
Methanol (mL)	3

Zeta potential

Zeta potential of the optimized formulation was found to be -52.28 ± 2.09 mV (F11) which is an indication of good stability of the formulation [Figure 2]. Zeta potential values from ± 0 to ± 15 mV usually represent the onset of agglomeration. The range between ± 30 and ± 40 mV shows moderate stability. Values from ± 40 to ± 60 mV generally represent sufficient mutual repulsion to result in good stability (i.e., no agglomeration).

TEM

Optimized metformin hydrochloride-loaded SLD was visualized under TEM for determining the morphology. SLD has a particle size in the range of 10–1000 nm. TEM shows the segregated SLD particles within the range, thus confirming to the size as observed by photon correlation spectroscopy. Images indicated that SLD was well distributed and spherical in shape. As the SLD was non-aggregated, we can state that formulation was physically stable. TEM images of optimized formulation were shown in Figure 3.

DSC

DSC thermogram of metformin hydrochloride showed a sharp endothermic peak at 223.51°C , corresponding to its melting point (224°C) reflecting the crystalline state of the drug in Figure 4. With this DSC thermogram of MH-loaded SLD showed a reduction in melting point with the shifting of peaks at 129.20°C and 198.23°C due to surfactant and amphiphilic property of PC which improves the solubility of drug by which drug might exist in an amorphous or metastable state and prevents the stable crystal form of drug. Phase transition temperature was also reduced, as shown in Figure 5.

FTIR spectroscopy

FTIR spectroscopy was used to investigate the interaction between drug and lipid. Retention of peak at 3351.12 cm^{-1} attributed N-H

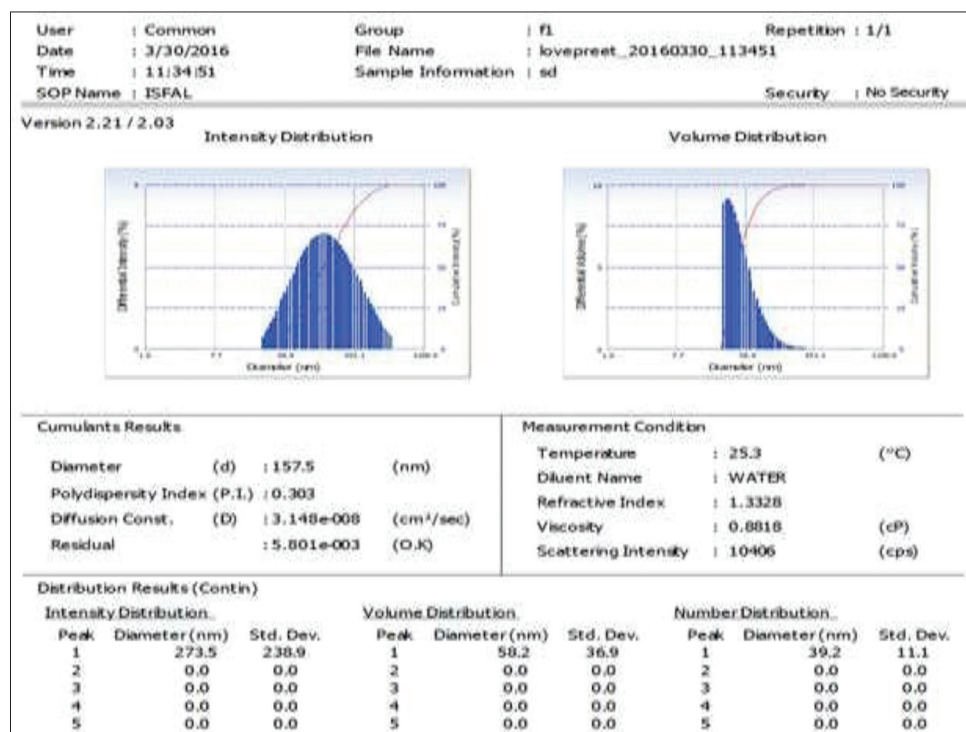


Figure 1: Particle size and polydispersity index of solid lipid dispersion

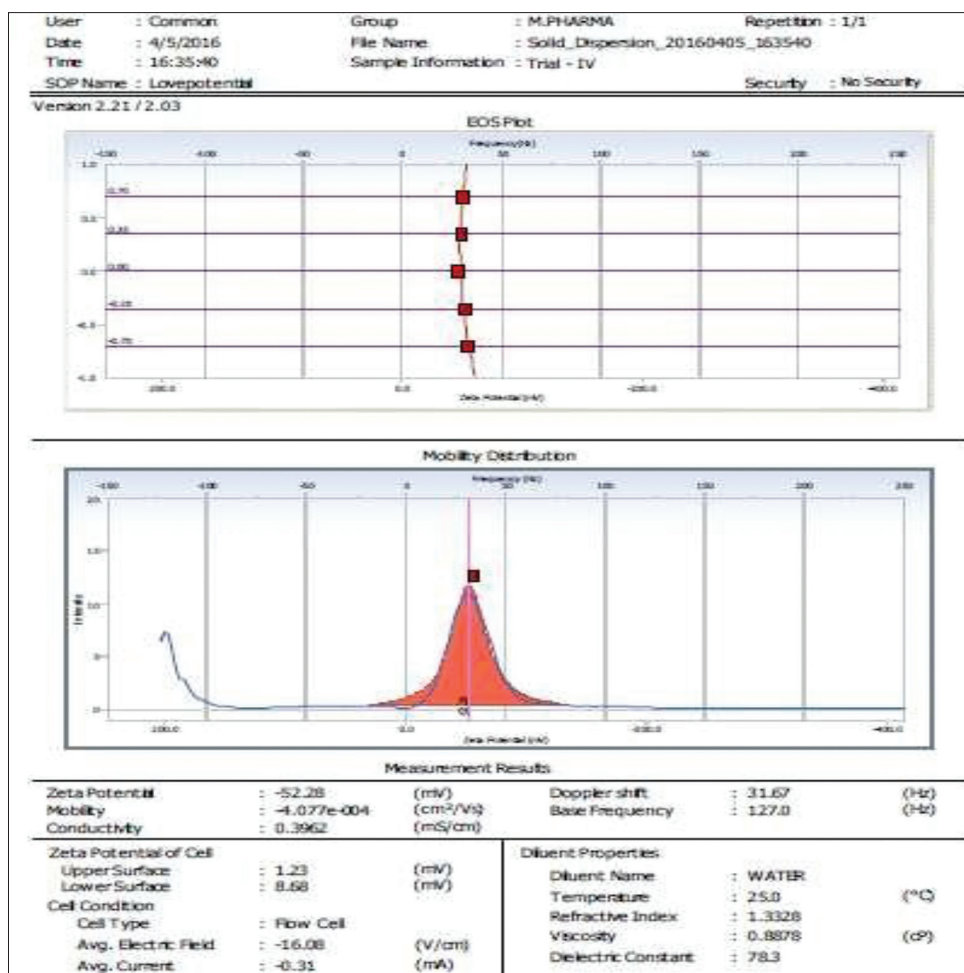


Figure 2: Zeta potential of MH-loaded solid lipid dispersion

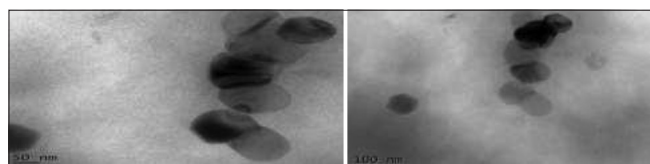


Figure 3: Transmission electron microscopy images of MH-loaded solid lipid dispersion

stretching of C=N-H and at 16.36 cm^{-1} showed C=Nzz stretching vibrations which indicates the presence of drug (MH). Retention of peak at 1064.77 cm^{-1} proved the formation of ester group which is present in the structure of lipid (PC). All the integral peaks were found to intact. No chemical interaction occurred between the MH and PC. Hence, the presence of these peaks revealed the formation of SLD in Figure 6.

Percent entrapment efficiency

Entrapment efficiency was expressed as a percentage of the total amount of drug initially used. Entrapment efficiency describes the efficiency of the preparation method to incorporate drug into the carrier system. Metformin hydrochloride-loaded SLD showed percentage entrapment efficiency $96 \pm 3.84\%$. The result of percent entrapment efficiency was clearly revealed that the maximum amount

of drug, that is, metformin hydrochloride, was entrapped in the prepared formulation.

Percent yield

Percent yield was calculated to determine the efficiency of the formulation. The percent yield of optimized formulation was in range $78 \pm 3.12\%$, indicating reproducibility and efficiency of the method of preparation.

In vitro release

In vitro release study of metformin, hydrochloride-loaded SLD was performed in simulated gastric fluid (pH 1.2) for the first 2 h and simulated intestinal fluid (pH 6.8) up to 24 h. The data obtained from *in vitro* release study of MH-loaded SLD is presented in Figure 7.

Within the first 2 h in SGF (pH 1.2), the drug showed a slight burst release initially and got sustained with maximum drug released around a period of 4–24 h in SIF (pH 6.8). *In vitro* release showed a sustained and controlled release profile of metformin hydrochloride from the SLD. The study indicated that the initial burst release was due to the surface drug release. A further release could be explained by the fact that the maximum amount of drug was encapsulated in the SLD and released only after the polymer

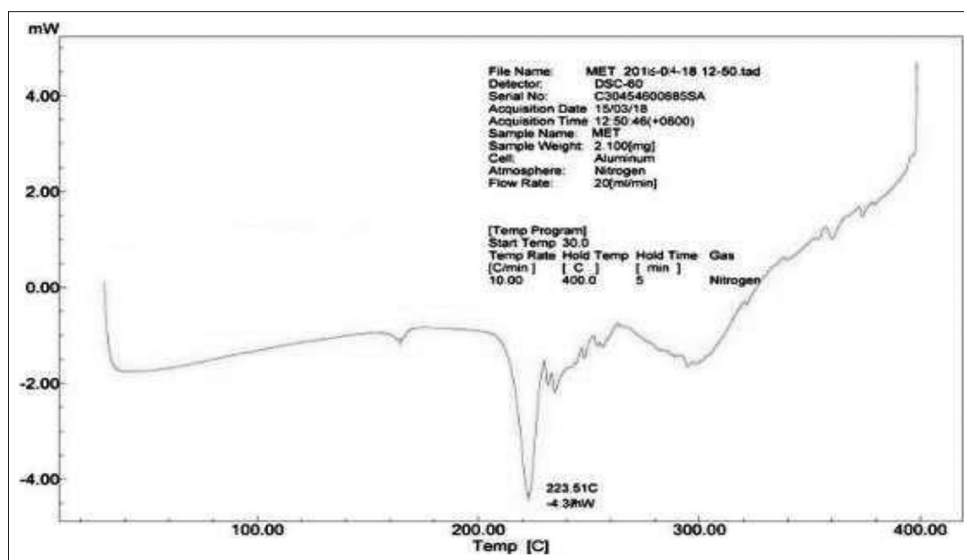


Figure 4: Differential scanning calorimetry thermogram of pure metformin hydrochloride

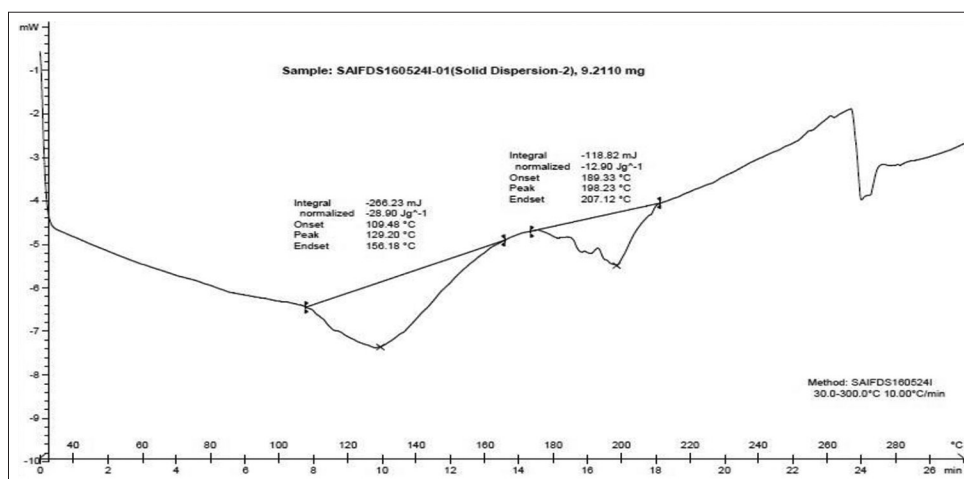


Figure 5: Differential scanning calorimetry thermogram of MH-loaded solid lipid dispersion

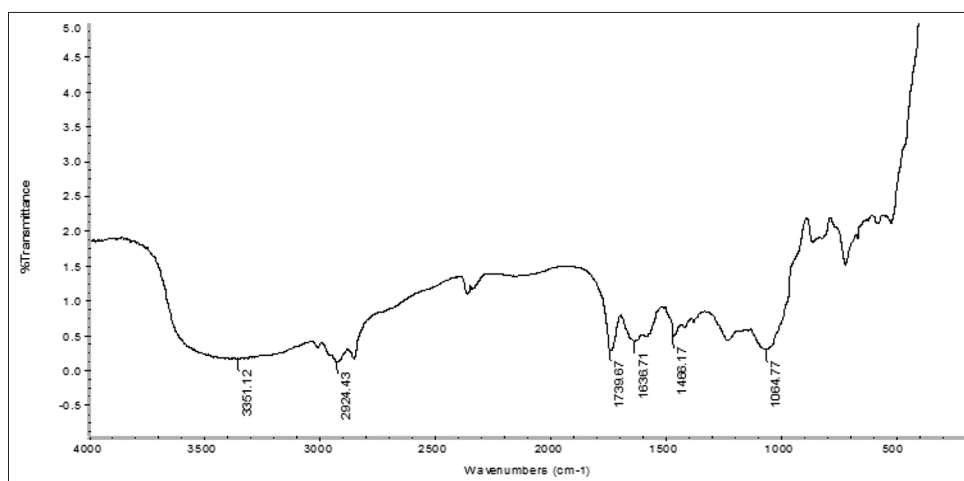


Figure 6: Fourier transform infrared spectroscopy of MH-loaded solid lipid dispersion

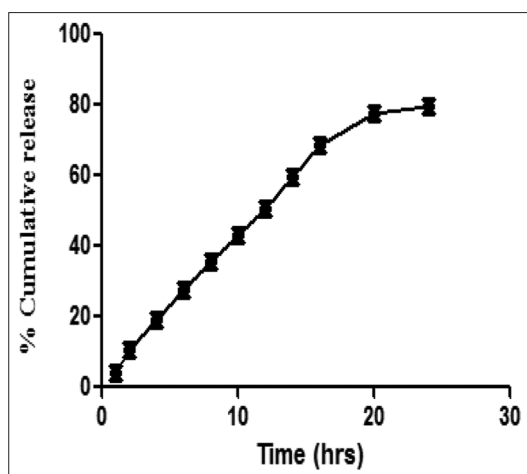


Figure 7: % Cumulative release from MH-loaded solid lipid dispersion

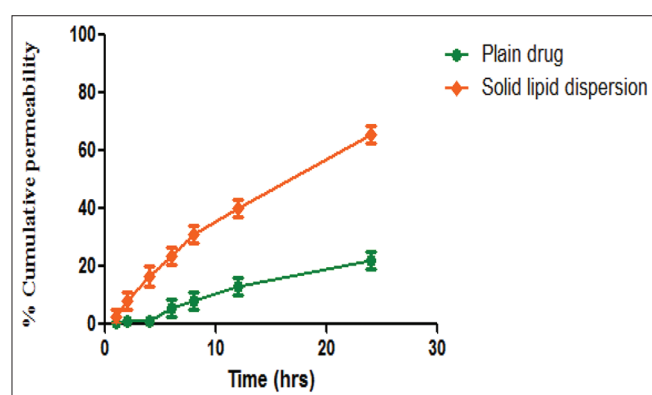


Figure 8: % Cumulative permeability of plain drug (MH) and solid lipid dispersion

degrade. Lipid tends to be more hydrolyzed in the alkaline medium, that is, simulated intestinal fluid (pH 6.8). Within the first 2 h release was based on the diffusion and then sustained release was due to the erosion of lipid.

Ex vivo permeability study

Permeability profile of optimized formulation was determined and compared with the plain drug (MH) in SIF (pH 6.8) using goat's intestinal mucosa to determine the intestinal permeability for 24 h presented in Figure 8.

Ex vivo permeation experiment was carried out for studying the effect of conjugating the hydrophilic drug (MH) to PC. The results demonstrated that PLs have a robust effect on improving the intestinal permeation of metformin hydrochloride-loaded SLD in comparison with the plain drug. These results showed the important role of PLs on improving the permeability of a hydrophilic drug

characterized by high aqueous solubility and low permeability through GIT membrane.

CONCLUSION

BCS Class III drugs are having high solubility and low permeability. Due to their low permeability, bioavailability is also poor as the drugs are unable to permeate the biological membrane. Metformin belongs to BCS III and is the first-line drug in the treatment of Type 2 diabetes. As the metformin belongs to BCS III, it has low bioavailability due to which dosing frequency is also high which is associated with many side effects such as blurred vision, chest discomfort, coma, and other side effects. At present, available marketed formulations also associated with the same problem, that is, low bioavailability and high dosing frequency. Hence, there is a need for the new formulation with new developments to increase the bioavailability and to decrease the dosing frequency to avoid the side effects. SLD has been proved to a better technique for the enhancement of intestinal permeability in turns to increase oral bioavailability.

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