ORIGINAL ARTICLE

Use of Bioactives from *Carica papaya* Seeds in Formulation and Evaluation of Solid Lipid Nanoparticles

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Abstract

Introduction: Papaya seeds are a rich source of proteins, fat, fibers, vitamins, minerals, monounsaturated fatty acids, polyphenols, and powerful antioxidants like flavonoids. *Carica papaya* is used for treating skin, fungal, viral, digestive, and dental disorders, as well as cancer, kidney, and nervous disorders. The bioavailability of a drug can be improved with the use of solid lipid nanoparticles (SLNs) if it is not very water-soluble. The targeted and controlled release of medications is another possible application. The objective of this research is to create and assess bioactive SLNs derived from *C. papaya* seeds. **Materials and Methods:** The ripe, shade-dried papaya seeds were first powdered and extracted using the Soxhlet method to obtain crude extract. Glycosides, alkaloids, tannins, saponins, phenols, and flavonoids were all assessed during the phytochemical examination. The SLNs of extract were formulated by a solvent evaporation method using Stearic acid as lipid and poloxamer 188 as surfactant. Several of characteristics were used to assess the prepared SLNs, including encapsulation efficiency, *in vitro* dissolution studies, zeta potential, particle size, and transmission electron microscopy (TEM). Chemical confirmation of the produced SLNs was achieved using Fourier transform infra-red (FT-IR) and powder X-ray diffractometry (XRD) analyses. The thermal stability of SLNs was studied with the help of differential scanning calorimetry (DSC). **Results and Discussion:** The improved formulation had a zeta potential of −28.4 mV and a polydispersity index of 0.021, and its particle size was determined to be 124.1 ± 22.3 nm. The effectiveness of drug encapsulation was determined to be 80.98 ± 1.59. Formation of SLN confirmed by TEM, FT-IR analysis, powder XRD, and DSC showed no unwanted peaks. The thermal stability of SLN was analyzed with the help of DSC. An *in vitro* drug release study showed 89.30 ± 0.55% release of the drug in 12 h. **Conclusion:** The evaluation results indicate an effective SLN formulation that might be used for antidiabetic effect.

Key words: *Carica papaya,* poloxamer 188, solid lipid nanoparticles, stearic acid

INTRODUCTION

Solid lipid nanoparticles (SLN) are nano-sized colloidal molecules made of physiological lipids and dispersed in water or aqueous surfactant solutions.[1] The size of SLN can vary between 10 and 1000 nm.[2] SLNs differ from other colloidal carriers in that they contain solid lipids instead of liquid.[3] Solid lipid is commonly used as a matrix material for oral drug delivery.[4] As this matrix is composed of physiological lipids, it reduces the risk of toxicity.[5] In SLN, the lipid concentration varies between 0.1 and 30%, and the concentration of surfactant can be between 0.5 and 5%.[6] SLN can encapsulate both hydrophilic and lipophilic drugs.[7] It also can bypass the reticuloendothelial system.[8]

SLN has various advantages over other colloidal formulations which include:[9]

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- Drug targeting and controlled drug release
- Improved stability of drug
- Improved bioavailability of bioactive substances
- No production of toxic metabolites
- Easy production on an industrial scale
- Cost-efficient and cheaper production.

Carica papaya commonly referred to as Papaya belongs to the family *Caricaceae*. Polysaccharides, enzymes, proteins, alkaloids, glycosides, lipids, oils, lectins, saponins, flavonoids, and steroids are some of the chemical components found in papaya.[10] The papaya plant's leaves, fruits, seeds, bark, stem, and root can all be used for dietary and medicinal product purposes.[11] Research suggests that papaya seeds have greater medicinal value than their fruits.[12] Papaya seeds can be used for a variety of diseases because of their pharmacological properties such as antifertility, contraceptive, anthelmintic, anti-inflammatory, analgesic, antimicrobial, carminative, emmenagogue, abortifacient, counterirritant, antihypertensive, antidiabetic, and antihyperlipidemic activity.[13] Several studies have reported that *C. papaya* seeds have hypoglycemic and hypolipidemic effects.[14,15] Papaya seed phytoconstituents, such as flavonoids, quercetin, steroids, phenols, quinones, and kaempferol, can significantly lower blood sugar levels by recovering pancreatic beta cells and increasing insulin secretion.[16] Because the important phytoconstituents of papaya seed, such as flavonoids and phenols, have low solubility, in the present study SLNs of papaya seed extract were formulated to improve the solubility, stability, and bioavailability of the crude extract.

MATERIALS AND METHODS

Materials

Petroleum ether, stearic acid, ethanol, and propylene glycol were procured from Modern Science Pvt. Ltd., Nashik. Poloxamer 188 was a gift sample from Merck Life Sciences Pvt. Ltd., Mumbai.

Methods

Collection of plant materials and extraction

C. papaya seeds were obtained from ripe Papaya fruits. The authentication of the plant was performed at the department of botany, Gokhale Education Society's HPT Arts and RYK Science College, Nashik, India. The collected seeds were washed and dried in a shed for 15 days. The seeds were ground to a coarse powder and extracted with petroleum ether to remove fat contents from them. After extraction with petroleum ether, the seed powder was extracted with ethanol as solvent by using Soxhlet extraction for 16 h. After extraction, the solvent was vaporized to obtain semisolid residue.

Phytochemical screening

The collected residue was tested for its phytochemical constituents. Standard procedures were used for the phytochemical evaluation of extracts.[17] The extract was tested for the presence of presence of proteins, saponins, carbohydrates, alkaloids, phenols, tannins, flavonoids, steroids, and glycosides.

Formulation of SLNs

The solid lipid particles were formulated by solvent evaporation method.[18,19] Trial batches containing varying concentrations of stearic acid and poloxamer 188 were prepared. An optimized batch was selected according to particle size, encapsulation efficiency, and % *in vitro* drug release.SLN was prepared by dissolving, poloxamer-188 (surfactant) in water, in this solution propylene glycol (co-solvent) was added. In ethanol, stearic acid (lipid) was added and solubilized. Papaya of seed extract was added to the lipid solution. Lipid solution and surfactant solution were mixed and stirred for 45 min with a magnetic stirrer. After stirring, the mixture was sonicated for 15 min followed by 15 min centrifugation at 11,500 g force at 25°C for a period of 15 min. The supernatant was discarded and SLN swerefreeze-dried at −40°C and stored for further evaluation.

Optimization of formulation

The formulation method was optimized by analyzing process-related variables like the concentration of lipids and surfactants.[18,19] Lipid and surfactant were independent variables (X1 and X2), resulting in a 3^2 factorial design with nine combinations that were possible. Particle size, encapsulation efficiency, and *in vitro* drug release (Y1, Y2, Y3) were the dependent variables. The design expert 13 program was employed to check the effect of independent variables on dependent variables. Table 1 represents a composition of SLNs and their formulation codes.

Table 1: Composition of SLN containing different concentrations of lipid and surfactant

S. No	Formulation code	Extract (mg)	Stearic acid (mg)	Poloxamer 188 (mg)
1	F1	100	100	20
2	F2	100	100	30
3	F3	100	100	40
4	F4	100	200	20
5	F5	100	200	30
6	F6	100	200	40
7	F7	100	300	20
8	F8	100	300	30
9	F9	100	300	40

SLN: Solid lipid nanoparticles

Evaluation of SLNs

Particle size, polydispersity index, and zeta potential

Nanoparticle stability is affected by several factors, including their size and zeta potential.[20] The SLN that was synthesized was tested for particle size, polydispersity index, and zeta potential using a particle size analyzer from Horiba Scientific (Kyoto, Japan) model SZ-100-Z2. It measures the size of particles and their distribution width by dynamic light scattering. 5 mg of sample was dispersed in 10 mL deionized water for particle size determination. Further dilutions were performed whenever required.

Encapsulation efficiency and drug content determination

Drug content determination and drug encapsulation efficiency can assist in knowing the exact amount of medicine in the formulation. The encapsulation efficiency of SLN was evaluated using a ultraviolet (UV) spectrophotometer. Weighed amounts of SLN (10 mg) were solubilized in 10 mL methanol. The mixture was then further diluted and the entrapped bioactive in SLN were measured at 273 nm. The encapsulation efficiency was determined using the given formula:[19]

$$\text{Encapsulation efficiency} = \frac{\text{Amount of entrapped drug}}{\text{Amount of initial drug}} \times 100$$

Drug content was determined using the following formula:

$$\text{Drug content} = \frac{\text{Amount of drug in complex}}{\text{Amount of complex}} \times 100$$

Transmission electron microscopy (TEM)

TEM provides direct information on the shape of the particle. The surface morphology of prepared SLN was studied using TEM (Model: ECNAI 12, Netherlands, Software: Tecnai imaging and Analysis; Source – Tungsten Filament). An electron beam is passed through the thin sample to form an image. In addition to the morphology and crystallography of a sample, this approach reveals its electrical structure, coordination number, chemical composition, and bonding strengths. TEM had an operating voltage range of 20–120 kV. It magnifies the image up to 700000 times.

Differential scanning calorimeter

Differential scanning calorimetry (DSC) is a widely used technique for analyzing the thermal properties of various materials. DSC can identify crystal structure in nanoparticles by measuring glass and melting point temperatures. The thermal stability of SLN was evaluated by DSC model no. DSC 4000 by Perkin Elmer. 9 mg of sample was sealed in an aluminum pan and a DSC thermogram was recorded at a heating rate of 10°C/min from a temperature range of 30°C–400°C.

Fourier transform infra-red (FT-IR) spectroscopy

FTIR is used to study drug excipient compatibility and structural elucidation of the formulation. FTIR spectrum of pure extract, stearic acid, poloxamer 188, drug- excipient mixture, and SLN were recorded using Bruker FT-IR alpha II FT-IR spectrophotometer. A small quantity of sample (5–10 mg) was directly placed on a diamond crystal of infrared (IR), the pressure arm was adjusted over the sample, and pressure was applied to the sample. The spectra were recorded using the software. The spectra were observed for any kind of interaction between drug and excipients in the physical mixture for drug-excipient compatibility study. The presence of any kind of physicochemical interaction in the formulation was observed.

Powder X-ray diffractometry (XRD)

The samples of pure extract, stearic acid, poloxamer 188, and SLN were analyzed to study their physical structure by obtaining their XRD scans. The scans were performed by using an XRD (Model no: Smartlab Cu 1.5 KV by Rigaku, Japan). This technique makes use of a 9 kW rotating anode X-ray source from PhotonMax along with a 2D multidimensional semiconductor detection system from HyPix-3000 that supports 0D, 1D, and 2D measurement modes, and has a high energy resolution.

In vitro dissolution study

In vitro dissolution study of crude extract and SLN was carried out using the dialysis bag method.[21] A dialysis bag was prepared using a dialysis membrane (Dialysis Membrane-70, Hi-media laboratories, Mumbai, India). 2 mL of suspension of crude extract (1 mg/mL) or SLN suspension (1 mg/mL) was placed in the dialysis bag. The bag was then kept in a beaker having 200 mL of phosphate buffer saline (pH 7.4). The beaker was kept on a magnetic stirrer rotating at 50 rpm. 5 mL samples were removed at intervals of 60 min each for 12 h and substituted with the same volume of fresh medium to keep the sink conditions stable. Withdrawn samples were filtered and evaluated at 273 nm by UV-spectroscopy to determine drug release from SLN.[22,23]

RESULTS

Phytochemical screening

Table 2 summarizes the presence of phytochemical constituents found in ethanolic *C. papaya* seed extract.

Formulation and optimization of SLN

The solvent evaporation method was used to obtain SLN. Stearic acid and poloxamer 188 were also components of the composition. Particle sizes of the synthesized SLN in this investigation varied from 2398 to 124.1 nm. The percentage of *in vitro* drug release ranged from 50.343 ± 0.42 to 89.30

± 0.55, while the range of encapsulation efficiency (%) was 40.02 ± 1.59–80.98 ± 1.59. The F4 batch was determined to be the most optimal based on the results provided by the design expert. Table 3 shows the results for dosage forms concerning particle size, encapsulation efficiency, and *in vitro* medication release. Independent variables have a significant impact on dependent variables, as seen by the contour graph and the 3D response graph. Figures 1-3 show the graphs for particle size, % entrapment efficiency (EE), and % *in vitro* drug release, respectively. Table 4 displays the results of the analysis of variance on the replies, whereas Table 5 displays the model summary statistics for the significant models that were chosen.

Evaluation of SLNs

Particle size, polydispersity index, and zeta potential

Nanoparticle size and zeta potential can predict their distribution and stability in a liquid medium.[21] The particle size of the optimized batch was determined to be124.1 ± 22.3 nm with a polydispersity index of 0.021. This low value of the polydispersity index indicates a narrow distribution size of particles. The zeta potential is responsible for stable colloidal suspension. The Zeta potential of the formulation was determined to be −28.4 mV which suggested good stability of SLN formulation. Figure 4 indicates the particle size and zeta potential of SLN.

Table 2: Phytochemical tests of ethanolic extract of *Carica papaya*

S. No	Test	Constituent	Result
1	Biuret test	Proteins	+
2	Molisch's test	Carbohydrates	+
3	Fehling's test	Carbohydrates	+
4	Wagner's test	Alkaloids	+
5	Mayer's test	Alkaloids	+
6	Ferric chloride test	Phenols	+
7	Gelatin test	Tannins	–
8	Braymer's test	Tannins	–
9	Alkaline reagent test	Flavonoids	+
10	Liberman burchard test	Steroids	–
11	Liberman's test	Glycosides	–
12	Keller Killiani test	Glycosides	–
13	Foam test	Saponins	+

Encapsulation efficiency and drug content determination

The encapsulation efficiency of the formulation was found to be 80.98 ± 1.59% and drug content was found to be 25.30 ± 0.49%.

TEM

TEM micrographs of the formulation are shown in Figure 5. The size of the particles was found below 500 nm. The surface morphology showed the round shape of the particles.

Differential scanning calorimeter

The endothermic peaks at 66.25°C and 88.75°C suggest the melting of poloxamer 188 and stearic acid. The melting point of poloxamer 188 is 52°C and stearic acid is 69.3°C which was not observed in the spectrum this indicates the complete incorporation of lipid and poloxamer 188 in the SLN matrix and the formation of chemical bonds between extract and excipients. The third peak suggests melting of formulation at 258.33°C. Figure 6 shows DSC thermograms of SLN formulation.

FT-IR spectroscopy

Crude extract of papaya seed shows characteristic peaks at 3326.54 (O-H stretch for alcohol), 2923.35, and 2853.20 (C-H stretch for alkane), 1620.60 (C=C stretch for cyclic alkene), 1394.91 (O-H bend for phenol), 1334.89 (O-H bend for phenol), 1046.02 (C-O stretch of primary alcohol), 932.96 and 896.69 (C=C bending for alkene) which are shifted to

Table 3: Formulation batches of SLN with their results of particle size, EE, and *in vitro* drug release

S. No	Formulation code	Particle size (nm)	Encapsulation efficiency (%)	*In vitro* drug release (%)
1	F1	2398	40.02±1.59	50.34±0.42
2	F2	2045.4	55.38±0.6	69.67±0.58
3	F3	2216.7	60.93±1.04	66.64±0.64
4	F4	124.1	80.98±1.59	89.30±0.55
5	F5	157.8	79.27±1.59	88.42±0.42
6	F6	155.4	77.99±1.59	88.81±0.53
7	F7	216.4	70.74±1.2	80.58±0.48
8	F8	223.1	66.048±1.28	75.22±0.45
9	F9	520.5	61.35±2.17	64.86±0.42

SLN: Solid lipid nanoparticles, EE: Entrapment efficiency

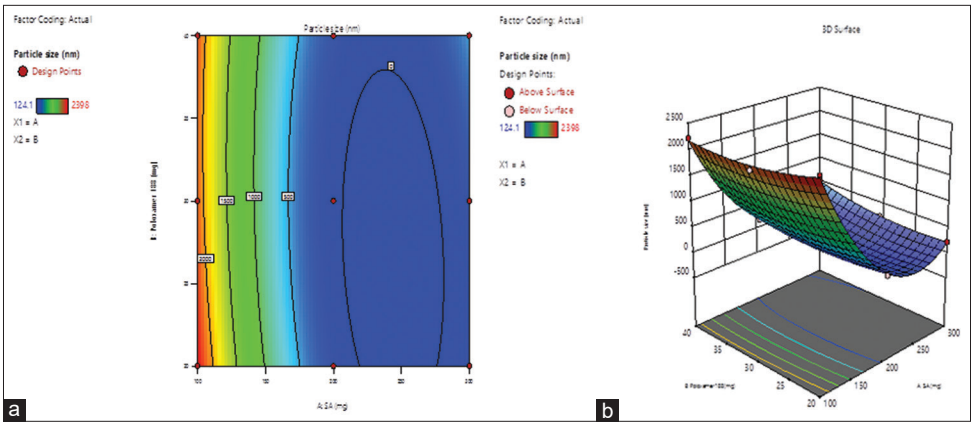

Figure 1: The contour plot (a) and 3D response graph (b) as a function of particle size

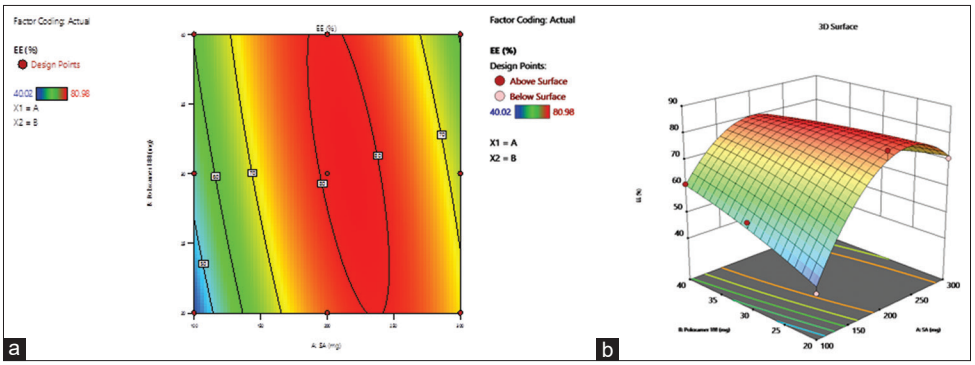

Figure 2: The contour plot (a) and 3D response graph (b) as a function of %EE

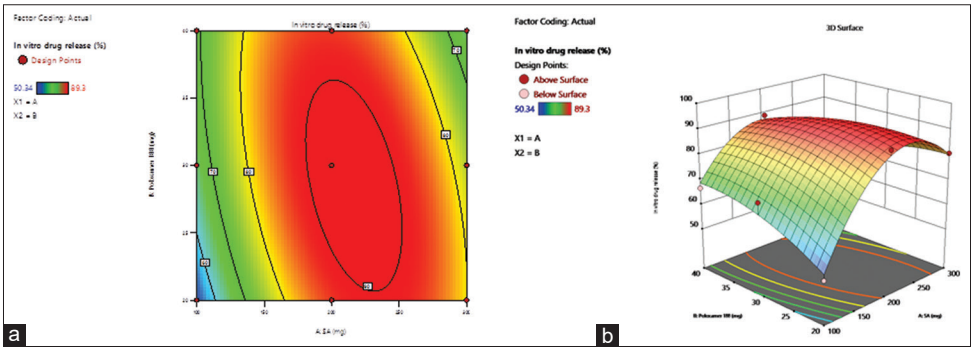

Figure 3: The contour plot (a) and 3D response graph (b) as a function of *in vitro* drug release

Table 4: ANOVA for response surface quadratic model for *Carica papaya*

Response factor	Model F-value	P-value	Lack of fit	
			F-value	*P*-value
Particle size	180.81	0.0006	144.02	0.0010
% EE	22.32	0.0140	34.01	0.0087
% *In vitro* drug release	16.34	0.0219	27.41	0.0118

ANOVA: Analysis of variance, EE: Entrapment efficiency

3376.38, 2914.49, 2849.14, 1618.06, 1400.51, 1333.57, 1040.58, 936.12, 894.82 in IR spectrum of SLN respectively. This indicates weak intermolecular interaction due to the formation of hydrogen bonds. The characteristic peaks of stearic acid (2913.55, 2844.39) and poloxamer 188 (1102.17, 953.82, and 839.40) were also found in the IR spectrum of formulation which indicates no major chemical interaction between the drug and excipients. The FT-IR spectra of the physical mixture of the extract, stearic acid, and poloxamer 188, as well as the crude extract, are displayed in Figure 7.

Table 5: Model summary statistics-influence of formulation variables on the response factors for *Carica papaya*

Response factor	Source	Standard deviation	R^2	Adjusted R^2	Predicted R^2	Adequacy precision
Particle size	Quadratic	94.30	0.9967	0.9912	0.9725	29.8670
% EE	Quadratic	3.50	0.9738	0.9302	0.6916	13.2604
% *In vitro* drug release	Quadratic	4.09	0.9646	0.9055	0.6515	11.6809

EE: Entrapment efficiency

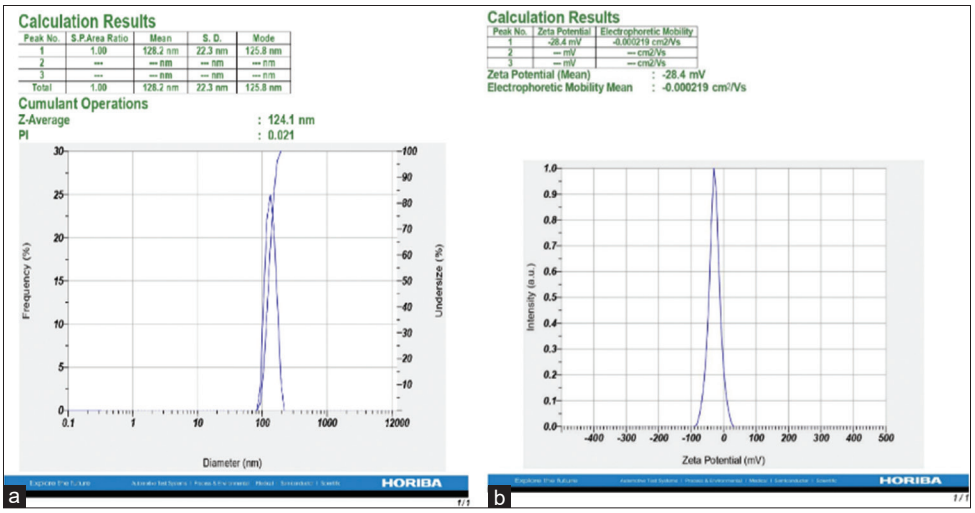

Figure 4: (a) Particle size of solid lipid nanoparticles, (b) Zeta potential of solid lipid nanoparticles

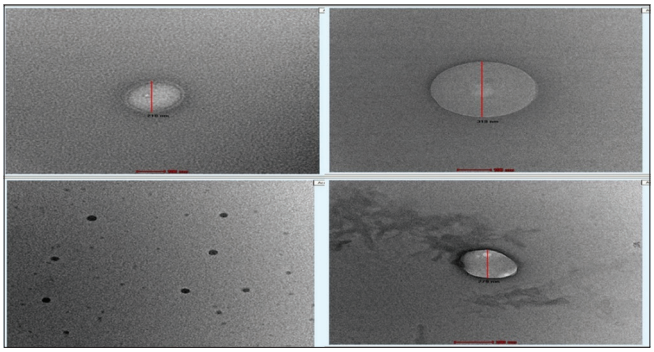

Figure 5: Transmission electron microscopy images of solid lipid nanoparticles

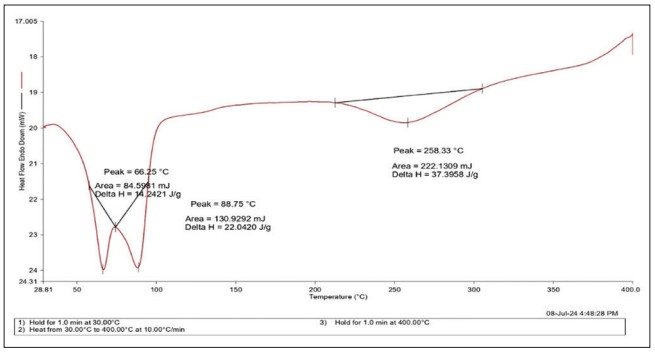

Figure 6: Differential scanning calorimetry thermogram of solid lipid nanoparticles

Powder XRD

Powder XRD spectrum of extract, stearic acid, poloxamer 188, and SLN formulation is shown in Figure 5. The XRD spectrum of the extract shows a single peak of height 201.09 indicating its amorphous nature. Stearic acid shows 13 sharp peaks of 495.6, 78.37, 336.08, 7488.94, 107.8, 1557.84, 56.92, 30.14, 71.29, 123.19, 50.51, 173.4, and 28.7 which indicates its crystalline nature. Poloxamer 188 shows seven sharp peaks with heights 57.41, 40.29, 1897.44, 122.18, 1980.58, and 160.17; this also suggests its crystalline nature. But, SLN shows five short and broad peaks at 141.9, 83.35, 84.55, 54.22, and 58.07 indicating the amorphous nature of SLN. Less intensity and broadness of these peaks indicate the amorphous nature of the formulation. Amorphous nature represents high solubility. XRD spectrum of extract, excipients, and formulation is shown in Figure 8.

In vitro dissolution study

The drug release mechanism of extract and SLN was different. *In vitro* dissolution studies of SLN showed that a fixed amount of drug was released at certain intervals. The extract showed 47.78 ± 0.59% CDR while the SLN showed 89.30 ± 0.55% CDR. This shows an increase in the dissolution of extract in SLN formulation. Figure 9 shows the dissolution profiles of SLN and crude extract.

DISCUSSION

Phenols and flavonoids are the compounds that are found in edible and non-edible parts of the plant which have numerous biochemical activities, including antioxidant, antidiabetic, anti-inflammatory, antimutagenic, and anticancer properties.

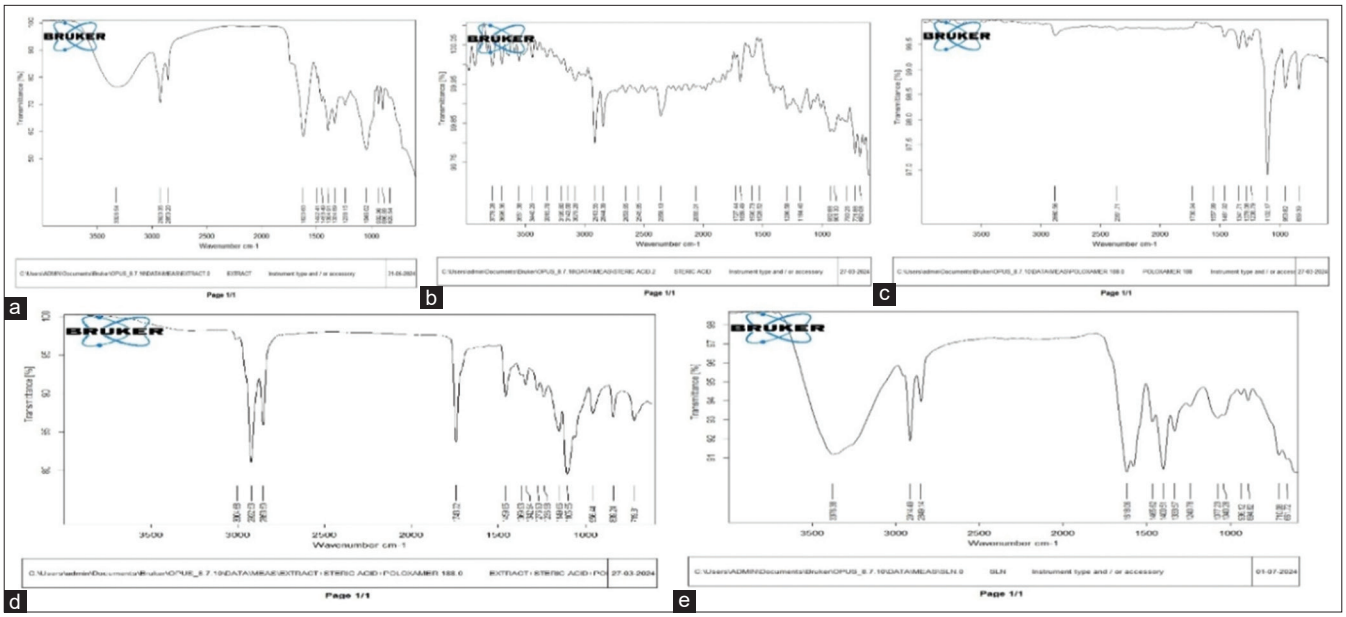

Figure 7: Infrared spectrum of (a) extract, (b) stearic acid, (c) poloxamer 188, (d) physical mixture of extract and excipients, and (e) solid lipid nanoparticles

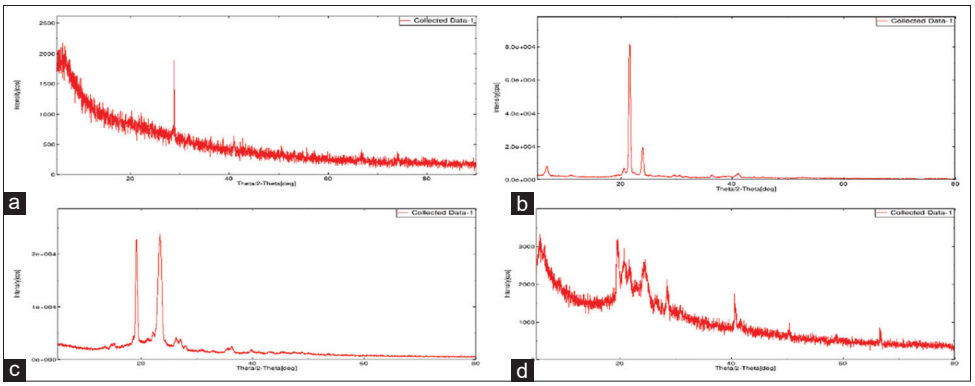

Figure 8: X-ray diffraction patterns of (a) extract, (b) stearic acid, (c) poloxamer 188, and (d) solid lipid nanoparticles

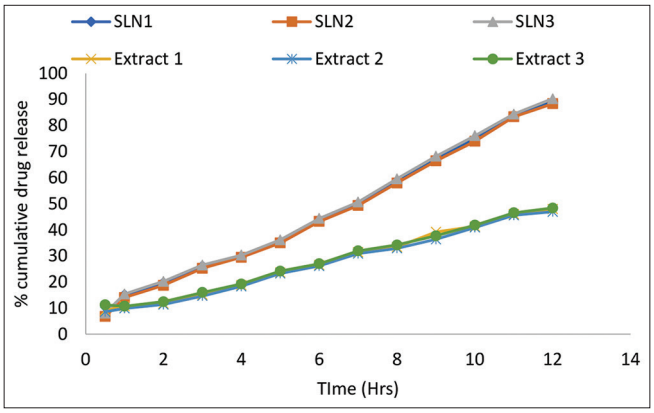

Figure 9: *In-vitro* dissolution profiles of solid lipid nanoparticle and extract

C. papaya L. (*Caricaceae*), also known as pawpaw, is a popular and cost-effective fruit tree with high nutritional value.[24] SLN are the dosage forms that can be used for controlled and enhanced release of the drug as well it can also give targeted drug release.[25] SLN of ethanolic extract of *C. papaya* seeds was formulated using the solvent evaporation method [Table 1]. In the formulation, stearic acid is used as a lipid which provides a solid matrix for the controlled release of the drug.[26,27] Poloxamer 188 is used as a surfactant which plays a role in the reduction of surface tension and particle size.[28] The formulated SLNs showed a mean particle size particles size 124.1 ± 22.3 nm with a polydispersity index of 0.021 and negative zeta potential of 28.4 mV 9 [Figure 4] which indicates excellent stability of particles. TEM study of SLN revealed a round shape and desired particle size <500 nm [Figure 5]. DSC study gives data regarding the thermal stability of the formulation [Figure 6]. FTIR study revealed the presence of functional groups of extract and excipients in the formulation which indicates no major chemical reaction between them [Figure 7]. XRD study shows the amorphous nature of SLN which indicates the high solubility of the formulation [Figure 8]. The *in vitro* dissolution study showed an improved dissolution rate of formulation as compared with pure extract [Figure 9].

CONCLUSION

Herbal medications have been used for decades and have been valued by patients and healthcare professionals for their superior therapeutic value and fewer side effects when compared to current medications. Poor solubility of herbal constituents limits their absorption and hence bioavailability. SLNs can be effectively used to improve the solubility, stability bioavailability, and targeted release of the drug. In this study, SLNs of *C. papaya* seed extract were prepared successfully for the 1st time to improve the solubility of its bioactive. The formulated SLN was evaluated for parameters such as particle size, zeta potential, %EE, *in vitro* drug release, TEM, FT-IR, and DSC. The results of the evaluation showed an effective and stable formulation of SLN from containing bioactive *C. papaya*. The formulation's solubility was found to be improved as compared with pure extract. *In vitro* dissolution study suggests prolonged release of bioactive from SLN. As a result, the SLN of extract may enhance bioavailability of extract and the SLN may be used for antidiabetic activity so further *in vivo* animal studies are suggested for antidiabetic activity of SLN.

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