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Original Article

SOLID LIPID NANOPARTICLES OF REBAMIPIDE: FORMULATION, CHARACTERIZATION AND *IN VIVO* PHARMACOKINETIC EVALUATION

NIHARIKA GIRISH MIRMEERA[1*], KANNAN K.[2]

[1,2]**Department of Pharmacy, Annamalai University, Tamilnadu**
[*]**Email: niharika.girish888@gmail.com**

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ABSTRACT

Objective: Rebamipide (REB) is a gastroprotective agent used to treat ulcers and gastritis throughout the stomach. Rebamipide is a BCS class IV drug with low oral bioavailability of less than 10%. The objective of this study was to develop an REB-SLNs formulation for oral administration to improve the bioavailability of rebamipide.

Methods: The hot homogenization and ultrasonication methods were used to prepare the REB-SLNs. Lipids are dynasan 114, dynasan 116, dynasan 114, imwitor 900 P. Non-ionic surfactants are poloxamer 188, polysorbate 80, and lipoid E 80 act as an amphoteric stabilizing agent used in the formulation. Developed SLNs were evaluated for particle size, PDI, zeta potential, entrapment efficiency, drug content, *in vitro* release, stability studies, and *in vivo* pharmacokinetic profile.

Results: The optimized REB SLNs (F9) formulation prepared with Dynassan 114 contains an average particle size of 234±3.5 nm, PDI of 0.228±0.05, ZP of-24.58±2.63mV, drug content of 99.89±0.04%, and entrapment efficiency of 96.15±0.32%. DSC studies revealed that no interactions occurred between drugs and excipients. SEM studies showed that SLNs were nearly spherical. *In vitro* drug release of the optimized formulation, F9 was 91.61% in 24 h as sustained drug release. The optimized formulation was stable under refrigeration and room temperature for three months. Invivo pharmacokinetic studies of optimized formulation (F9) exhibited higher Cmax and AUC values relative to the coarse suspension.

Conclusion: Compared to the reference standard coarse suspension, the relative bioavailability of the developed formulation of REB-SLNs of dynasan 114 and combination of poloxamer 188 and polysorbate 80 (F9) was increased by 3.87 times.

Keywords: Solid lipid nanoparticles, Rebamipide, Bioavailability, Pharmacokinetics, Homogenization, and ultrasonication

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INTRODUCTION

Among the lipid-based colloidal carrier drug delivery systems, SLNs are deemed most effective in improving the bioavailability of drugs with poor solubility and/or poor permeability [1]. They are a cardinally better alternative to other colloidal drug delivery systems such as polymeric nanoparticles and liposomes. SLNs are the first-generation lipid nanoparticle carrier systems with the solid matrix. Like nanoemulsions and liposomes, SLNs are constituted by physiologically biocompatible excipients, and like polymeric nanoparticles, their solid matrices protect the loaded drug material efficiently and provide stability to the APIs [2]. Due to the incorporation of biodegradable fatty acids, steroids, triglycerides, and partial triglycerides, and other materials generally recognized as safe (GRAS) in the process of preparation, SLNs are considered safe nanocarriers [3].

REB, chemically 2-(4-Chlorobenzoylamino)-3-[2(1H)-quinolinon-4-yl] propionic acid is a gastroprotective drug, clinically indicated for the protection of gastric mucosa against the numerous noxious factors that arise in acute and chronic gastritis conditions. Its gastroprotective effects are caused by the increased production of prostaglandins (by stimulating COX-II) in the gastric mucosa and inhibition of specific inflammatory mechanisms, especially activation of neutrophils in the blood capillaries scavenging oxygen free radicals [4].

Systemic absorption of oral drugs is essential for therapeutic efficacy. REB is a BCS class-IV drug that acquired low solubility and permeability. Thus, numerous research groups reported different formulations such as solid dispersions, nanoemulsions, and nanocrystals to improve the rebamipide bioavailability. SLNs as a potentially helpful technique are increasingly being used to enhance the oral absorption of poorly soluble drugs [5].

The cardinal aim of the current work is to develop REB-SLNs formulation to improve the oral bioavailability of rebamipide. The oral bioavailability of rebamipide is less than 10%. It is a water-insoluble drug with a lipophilic nature (logP 2.9) and a pKa of 3.3. It is appropriate to develop solid lipid nanoparticles of rebamipide based on the above drug characteristics [6].

MATERIALS AND METHODS

Materials

Rebamipide was acquired as a gift sample from Optimus Pharma Pvt Ltd, Hyderabad, and Telangana, India. Trimyristin was procured from Hi-Media Labs, Mumbai. Tristearin was obtained from Sigma Aldrich, Hyderabad. Lipoid E 80 was procured from Lipoid, Germany. Poloxamer 188 was gift samples from Aurobindo Labs, India. Polysorbate 80 was obtained from Rankem, Chennai. Methanol was of HPLC grade Merck, Mumbai, India. Double distilled water was obtained from a Milli-Q® apparatus (Millipore, USA).

Experimental methods

Preparation of rebamipide solid lipid nanoparticles (REB-SLNs)

The REB-SLNs were developed using a hot homogenization method followed by ultrasonication. Rebamipide (drug 100 mg), solid lipid (required quantity mg), and lipoid E80 (100 mg) were liquefied in 20 ml of chloroform and methanol (1:1) to get oil phase. The organic solvents were separated using a rota evaporator (Heidolph, Germany), and the drug-encapsulated lipid covering layer was molten using a heating system set at 5 °C above the melting point. Surfactants poloxamer 188 (Pluronic) and polysorbate 80 were used to develop the aqueous phase. These surfactants are dissolved in double distilled water and heated to a temperature similar to the oil phase. The hot aqueous phase was mixed with the oil phase and homogenized for 5 min (at 12,000 rpm) using a homogenizer. The resulting coarse oil in water (O/W) emulsion was sonicated for 20 min using a probe sonicator (Vibracell, Sonics, 12T-probe, USA). Allowing a heated nanoemulsion to cool to room temperature resulted in rebamipide-loaded solid lipid nanoparticles [7]. Table 1 shows the composition of various formulations prepared in the study.

Table 1: Formulation ingredients used in preparation of REB-SLNs

Formulation ingredients (mg)	Formulation codes											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Organic phase												
Rebamipide (API)	100	100	100	100	100	100	100	100	100	100	100	100
Dynasan 118	100	200	300	-	-	-	-	-	-	-	-	-
Dynasan 116	-	-	-	100	200	300	-	-	-	-	-	-
Dynasan 114	-	-	-	-	-	-	10	200	300	-	-	-
Imwitor 900P	-	-	-	-	-	-	-	-	-	100	200	300
Lipoid E 80	100	100	100	100	100	100	100	100	100	100	100	100
Chloroform: Methanol (1:1) (ml)	20	20	20	20	20	20	20	20	20	20	20	20
Aqueous phase												
Poloxamer 188 (Pluronic F 68)	100	100	100	100	100	100	100	100	100	100	100	100
Polysorbate 80	50	50	50	50	50	50	50	50	50	50	50	50
Double distilled water (ml)	10	10	10	10	10	10	10	10	10	10	10	10

Characterizations of REB-SLNs

Determination of particle size, PDI, and zeta potential of SLNs of rebamipide

The mean particle size and zeta potential (ZP) of REB-SLNs were determined by employing a Zetasizer Nano ZS90 (Malvern Instruments, UK). To achieve ideal kilo counts per second (KCPS) of 50-200 for measurements, the developed REB-SLNs 100 µl was diluted to 5 ml with double-distilled water. Before measurement, all samples were diluted to a sufficient concentration with double distilled water and analyzed in triplicate, with data presented as mean±SD [8].

Determination total of drug content

The REB-SLNs formulation of 0.1 ml was collected and dissolved in 0.9 ml of chloroform: methanol (1:1) mixture, further diluted with the mobile phase. HPLC was used to determine the amount of drug in diluted samples [9].

Determination of entrapment efficiency

Entrapment efficiency (EE) of developed formulations was assured by assessing the free drug concentration (unentrapped) in the aqueous phase. The aqueous phase was separated by ultrafiltration using centrisart tubes (Sartorius, Goettingen, Germany) composed of a filter membrane (M. Wt. cut off 20kDa) at the base of the test sample regeneration chamber. Approximately 2.5 ml of the formulation was placed on the sample and centrifuged for 30 min at 4000 rpm. The developed REB-SLNs aid in the encasing of the drug in the exterior chamber, while the aqueous phase is transferred into the sample recovery chamber via a filter membrane. HPLC was used to predict the appropriate amount of rebamipide in the aqueous solution phase [10].

***In vitro* release studies for REB-SLNs**

The dialysis technique was used to study *in vitro* release of REB-SLNs. For the release studies, a dialysis membrane (Himedia, India) with an adequate pore size of 2.4 nm and a molecular weight cutoff of 12,000-14,000 Da was used, and the membrane was immersed overnight in double-distilled water. The drug release studies of the developed formulations were carried out in 0.1N HCl for 2 h, then in pH 6.8 in phosphate buffer for 24 h by open tube approach. The required temperature was maintained at 37±0.5 °C, with dialysis membrane fixed to open tube (contained SLNs rebamipide dispersion) as donor compartment and buffer (100 ml) containing 200 ml beaker as receptor compartment. Approximately 2 ml of the sample was removed from the receiver compartment and replaced with fresh medium at intervals of 0.25, 0.5, 1, 2 h in 0.1N HCl medium, followed by 3, 4, 6, 8, 10, 12, and 24 h in pH 6.8 phosphate buffer medium. The drug release samples were collected, diluted, and analyzed by a UV-Visible spectrophotometer with a maximum wavelength of 240 nm [11].

Stability studies

REB-SLNs were stored for 3 mo at room and refrigerated temperatures. REB-SLNs were stored at room temperature and in the refrigerator, temperature conditions for three (3) months. The particle size, PDI, ZP, EE, and total drug content of REB-SLNs were determined regularly after the 1st day, 15 d, 1 mo, 2 mo and 3 mo. A t-test with a probability level of $p<0.05$ was used to determine the statistical significance of the collected data [12].

Solid-state characterization

Drug-excipient compatibility studies by DSC

Drug and excipient compatibility, as well as crystalline behavior, are determined using DSC studies. Perkin Elmer (DSC 4000, USA) instrument obtained DSC thermograms of pure drug, dynasan 114, dynasan 116, dynasan 118, and imwitor 90P, physical mixtures (1:1 ratio), and optimized REB-SLNs formulation in the range of 60-2000C with a heating rate of 100C/min. As a purging gas, nitrogen was used. Indium was used to calibrate the DSC instrument [13].

Surface morphology studies by SEM analysis

The surface appearance of developed REB-SLNs formulations was ascertained by SEM (Hitachi200, Japan). The formulated samples were fixed on a double adhesive carbon tape, which was stuck on aluminum stubs and then covered with gold under an argon atmosphere in the examination. Under a high vacuum of 40kv, samples of REB-SLNs were analyzed in a scanning electron microscope [14].

Pharmacokinetic study

Animals

Healthy male Wistar rats (weighing 200±30 gm)) were used in the pharmacokinetic study of the developed REB-SLNs formulation and a suspension. The animals had been starving for 24 h and had access to water. The animal studies were carried out with Institutional Animal Ethical Committee (Reg. No: 1692/PO/Ere/S/13/CPCSEA) prior approval.

Study protocol

Male Wistar rats with an oral dose of 10 mg/kg body weight were divided into two groups (n=6) and orally administered with a developed formulation (F9) of REB-SLNs and suspension (marketed tablet made into suspension form). At fixed predetermined time intervals (0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h), 0.5 ml blood samples were taken from the retro-orbital plexus into Eppendorf tubes, and serum was separated by centrifugation (Remi) for 10 min at 10,000rpm. Until the study, the serum was held at-20 °C. The rat oral feeding tube was used to administer all the formulations [15].

Group 1: Developed solid lipid nanoparticles of rebamipide (F9)

Group 2: Suspension (Marketed tablet: Rebagen, Manufactured by Macleods Pharmaceuticals)

HPLC analysis of rebamipide

At a flow rate of 1.0 ml/min, the HPLC column C18 (250 X 4.6 mm i.d., 0.5 µm) was equilibrated with an eluent mixture of methanol: water (60:40 v/v) (pH adjusted to 2.5 with acetic acid) as the mobile phase. The peaks were eluted without interference from serum at a wavelength of 240 nm.

Extraction studies of rat serum samples consisting of rebamipide

100 µl of internal standard (Ofloxacin 3µg/ml) and 100 µl of mobile phase were added to 100 µl of serum. After vortex stirring for 5 min at room temperature, the samples are centrifuged for 20 min at 500 rpm. The entire organic layer was separated after centrifugation and transferred to another microcentrifuge tube, where it was evaporated under reduced pressure in a vacuum oven. With 100 µl of mobile phase, the residue was reconstituted. Finally, a reconstituted sample volume of 20 µl was injected into the HPLC system for studies [16].

Pharmacokinetic parameters estimation and statistical significance

The calibration curve was used to determine the concentration of REB-SLNs in rat serum samples. Using the kinetic (2000) software, pharmacokinetic parameters such as peak serum concentration (C_{max}), time for peak serum concentration (T_{max}), area under the curve (AUC), biological half-life ($t_{1/2}$), and mean residence time (MRT) were calculated [17]. The data were presented as a mean±SD. The relative bioavailability of the developed formulations was calculated using the equation below.

$$\%\ Relative\ BA = \frac{(AUC_{SLN} \times DOSE_{Conrol})}{(AUC_{Control} \times DOSE_{SLN})} \times 100$$

RESULTS AND DISCUSSION

In this study, REB-SLNs formulations were developed using different lipids, each with varying lipid concentrations in the formulation, aided by a hot homogenization followed by the ultrasonication process. The homogenization and sonication times were optimized to four and twenty minutes, respectively, based on the physical parameters. We couldn't find any noticeable changes in particle size after this stage because the particle size couldn't change dramatically at higher stirring speeds. Furthermore, the obtained polydispersity indices are within acceptable limits, indicating that the particles produced are of uniform size.

Measurement of particle size, PDI, Zeta potential, drug content, and entrapment efficiency of REB-SLNs (n=3)

The effects of particle size distribution, ZP, PDI values, drug content, and (EE) on all the developed formulations are studied. The results of particle size, PDI value and zeta potential values of optimized formulation (F9) are shown in fig. 1 and 2. The REB-SLNs studies for their zeta potential, particle size distribution, drug content, and entrapment efficiency. The polydispersity indices were within the permissible range (<0.3) for developed formulations. REB-SLNs have been found to have an average particle size of 215-310 nm (table 2).

Table 2: REB-SLNs' size, PDI, ZP, drug content and EE

Formulation code	Size (nm)	PDI	ZP (mV)	Drug content (%) (mg)	EE (%)
F1	215.3±5.8	0.158±0.03	-28.42±2.46	99.79±0.15	92.75±0.52
F2	246.4±8.2	0.185±0.06	-29.52±2.24	99.91±0.09	91.74±0.46
F3	268.9±6.5	0.213±0.05	-30.37±2.46	98.74±0.06	94.17±0.38
F4	201.2±8.4	0.194±0.11	-25.91±2.75	101.15±1.23	92.91±0.65
F5	196.4±6.5	0.212±0.031	-27.28±2.28	98.52±0.05	95.71±0.71
F6	265.8±3.7	0.229±0.010	-23.47±2.67	98.92±0.09	91.42±0.39
F7	216.8±4.6	0.267±0.013	-31.79±2.75	99.56±0.17	93.10±0.27
F8	229.6±2.8	0.191±0.048	-29.95±2.89	97.42±0.08	94.65±0.68
F9	234.9±3.5	0.228±0.05	-24.58±2.63	99.89±0.04	96.15±0.32
F10	295.4±9.7	0.272±0.021	-29.21±3.57	99.82±0.07	92.13±0.46
F11	310.6±10.5	0.265±0.031	-30.73±2.89	99.18±0.04	93.75±0.28
F12	289.4±7.2	0.291±0.028	-31.15±2.31	99.65±0.07	91.49±0.63

Data expressed as mean±SD, N=3, The particle size of the SLNs formulation containing dynasan 114 was 216 to 234 nm, the PDI was 0.191 to 0.267, and the Zeta potential was-24.5 to-31.7 mV.

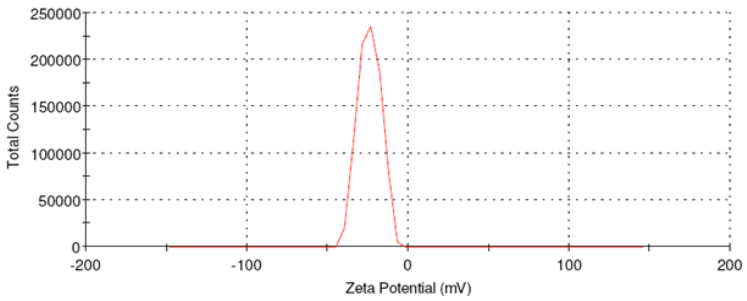


Fig. 1: Zeta potential of optimized REB-SLNs formulation (F9)

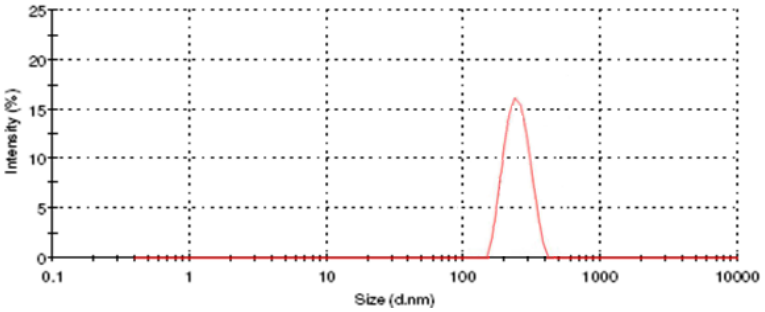


Fig. 2: Particle size distribution of optimized REB-SLNs formulation (F9)

The zeta potential of developed formulations containing REB-SLNs was in the extent of-31 mV to-23 mV. The particle size of the formulations containing dynasan 118 ranged from 215 to 268 nm, PDI was 0.158 to 0.213, and the zeta potential was-28.4 to-30.3 mV, respectively. In SLNs formulation containing dynasan 116, particle size ranging from 196 to 265 nm, PDI 0.194 to 0.229, and Zeta potential-23.4 to-27.2 mV were observed. The particle size of the SLNs formulation containing dynasan 114 was 216 to 234 nm, the PDI was 0.191 to 0.267, and the zeta potential was-24.5 to-31.7 mV. SLNs formulation containing imwitor 900 P showed particle size ranged from 289 to 310 nm, PDI 0.265 to 0.291, and Zeta potential-29.2 to-31.1 mV. The entrapment efficiency of all the developed formulations (F1-F12) was estimated be 91.42 to 96.15% and drug content was determined and there is no remarkable difference is observed between in drug content and entrapment efficiency was noticed.

The length of the alkyl chain determines the particle size of REB-SLNs in the lipids; the longer the alkyl chain, the larger the particle size. The external surface charge plays an essential role in colloidal dispersion stability. Solid lipid nanoparticles with smaller particle sizes have a higher level of stability [18]. The surfactant poloxamer 188, a non-ionic surfactant, was used in the formulation to reduce electrostatic repulsion among the particles after sterical stabilization of the nanoparticles by producing a coat over their surface to keep the SLNs stable. Compared to other formulations, the developed formulation (F9) containing dynasan 114 had a significantly higher PDI, ZP and particle size.

In vitro drug release studies of REB-SLNs

For the initial study, dynasan 118, dynasan 116, dynasan 114, and imwitor 900 P formulations showed drug release ranging from 64.28 to 78.15%, and 73.12 to 85.13%, 82.19 to 91.61% and 79.15 to 84.18%, respectively, in 0.1N HCl, followed by 6.8 pH phosphate buffer for up to 24 h (fig. 3). *In vitro* drug release of the developed formulation F9 was 91.61% in 24 h sustained drug release. The increased lipid content in formulations gradually; the release of drug was considerably prolonged in all the developed REB-SLNs formulations [19]. Further, all SLNs formulations gradually released to a certain extent compared to that of coarse suspension of rebamipide (Rebagen). All the developed formulations were carried out in triplicate (n=3).

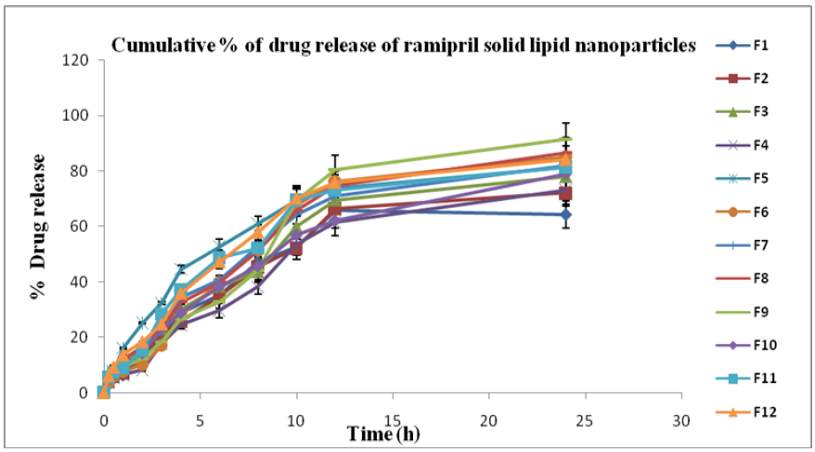


Fig. 3: *In vitro* drug release of REB-SLNs Error bars (mean±SD), n=3

In phosphate buffer, the *in vitro* release pattern of all developed REB-SLNs formulations showed a conventional biphasic arrangement with a primary expeditive phase followed by a slow phase release pattern. The primary rapid phase can occur because of the drug's burst release. A small diffusion path caused by drug adornment in the outer region of REB-SLNs on the one hand, and a tiny diffusion path caused by the adornment of the drug in the outer region of SLNs on the other hand, is a verifiable assertion [20].

Solid-state characterization

Drug and excipient compatibility studies

Determination of purity of the drug by DSC

Differential scanning calorimetry (DSC) studies were used to determine the presence of any drug-excipient interactions and any changes in the crystallinity of the drugs. Physical mixtures of lipids and rebamipide (1:1 mass/molar ratio) were prepared and filled with 5-10 mg in crucibles. Analysis was performed under a nitrogen purge. The heating rate was maintained at 10 °C/min, and the thermograms were analyzed to determine which type of interaction was occurring. The melting point of rebamipide has been stated to be between 300-310 °C. The DSC thermogram revealed a sharp endothermic peak for rebamipide (fig. 4) at 305.85 °C, corresponding to the drug's melting point, indicating crystalline nature. The DSC studies help assess the interaction of different components of the formulation.

DSC thermograms of physical mixtures of drug and different lipids

Endothermic peaks are observed at 112.53 °C and 288.86 °C, respectively, due to the physical blend of drug and dynasan 118. The drug and dynasan 116 physical blend produced intense sharp endothermic peaks at 176.89 °C and 288.98 °C, respectively. The drug and dynasan 114 physical blend produced endothermic peaks at 54.59 °C and 289.44 °C, respectively. At 180.41 °C and 306.13 °C, the physical blend of drug and imwitor 900 P exhibits endothermic peaks. Fig. 5 illustrates the DSC thermograms of a physical drug-lipid blend.

SEM analysis of REB-SLNs

The REB-SLNs external morphology revealed circular particles, with a constrained size allocation and flat uniform surfaces. The samples were examined in SEM at a vacuum of 20kV. The samples did not contain any drug crystals or agglomeration of solid lipid nanoparticles. This SEM photograph gives information about the shape of particle or aggregation of particles. The SEM photograph of optimized formulation ramipril loaded solid lipid a nanoparticle (F9) is shown in fig. 6.

Stability studies

The characteristic particle size, ZP, and PDI of REB-SLNs were studied at room and refrigerated temperatures after 90 d of storage. The REB-SLNs stability studies aided the formulation (F9), resulting in increased effective particle size, PDI, and ZP. The predicted number of samples predicted was in triplicate (n=3). The resultants data are summarized in table 3.

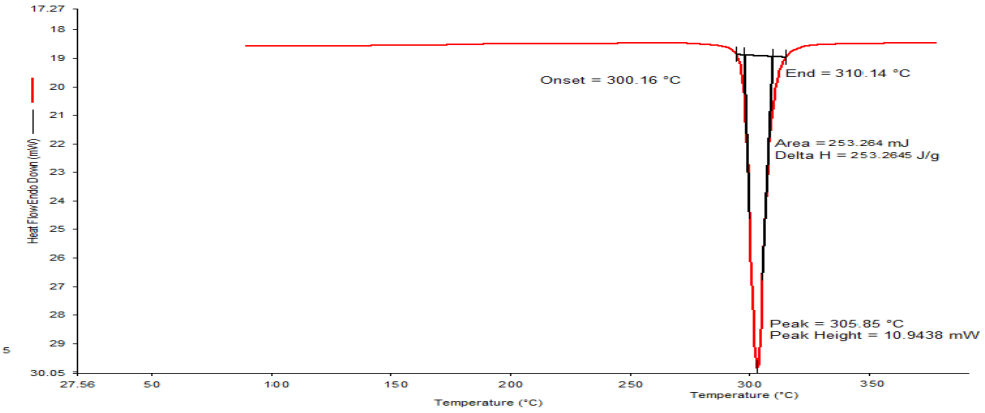
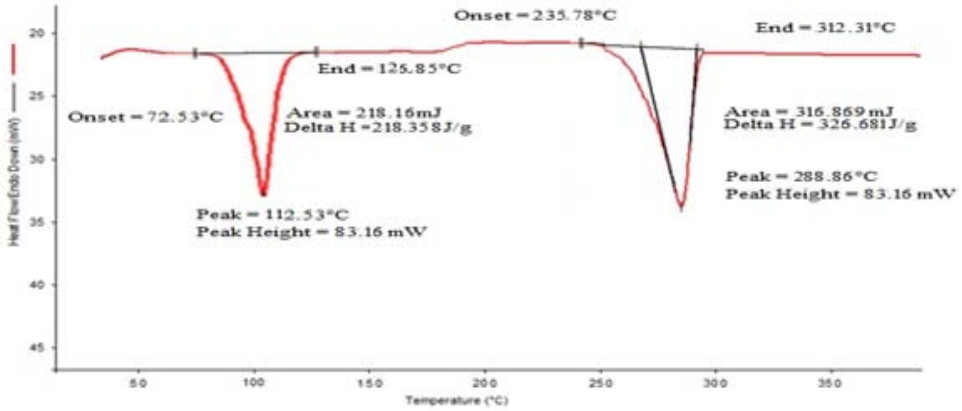
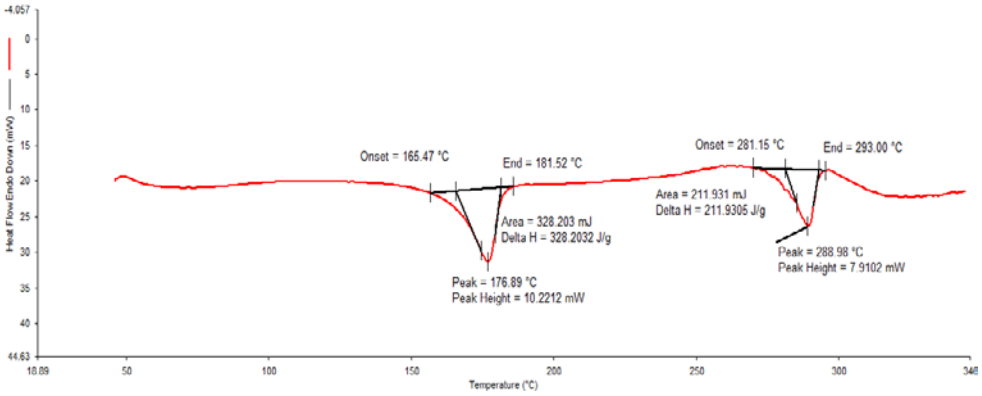


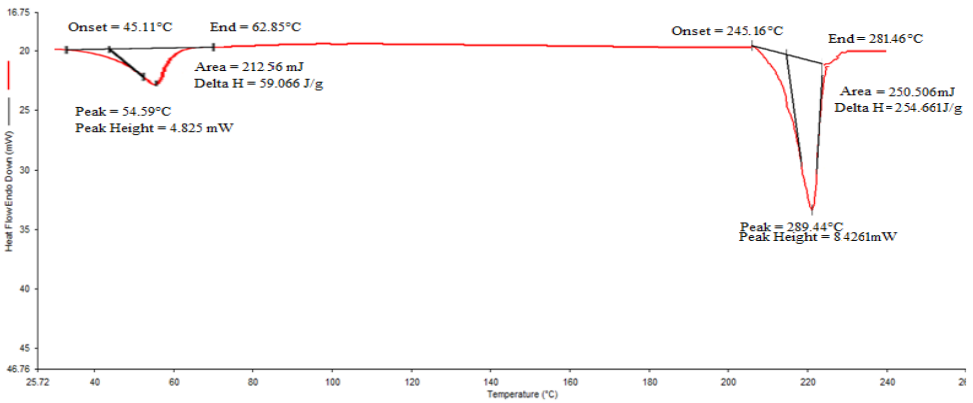
Fig. 4: DSC thermogram of pure form of rebamipide drug showing a single endothermic peak at 305.85 °C



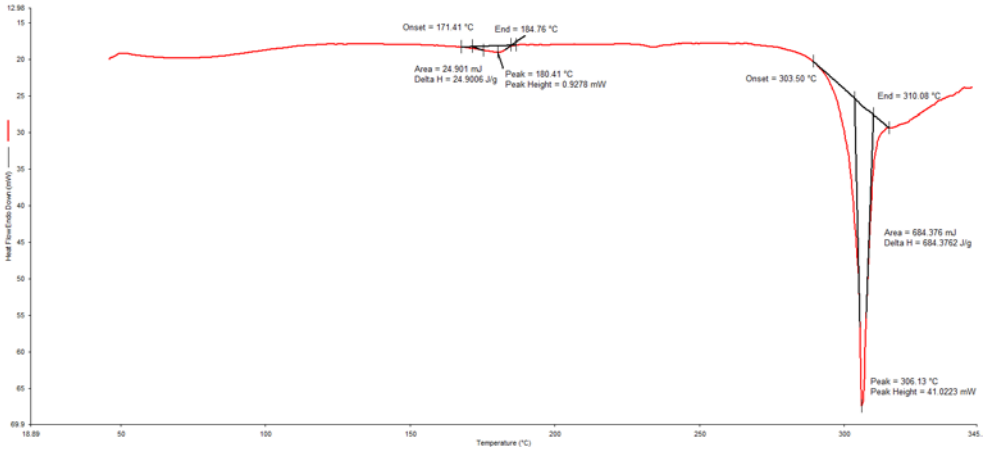
5a: Dynasan118 and rebamipide



5b: Dynasan116 and rebamipide



5c: Dynasan114 and rebamipide



5d: Imwitor 900P and rebamipide

Fig. 5: DSC thermograms of physical blend of drug and various lipids

Table 3: Effect of storage at refrigerated (4 °C) and room (25 °C) temperature conditions on size, PDI and ZP for a period 3 mo

Day	At room temperature (4 °C)			At refrigerated temperature (25 °C)		
	Size (nm)	PDI	Zeta potential (mV)	Size (nm)	PDI	Zeta potential (mV)
1	231.5±4.2	0.261±0.05	-24.51±1.9	230.9±2.8	0.265±0.08	-24.1±2.3
15	238.2±3.9	0.272±0.04	-25.91±2.3	241.6±3.4	0.285±0.05	-26.5±2.8
30	242.6±2.7	0.279±0.02	-26.32±2.4	245.5±4.6	0.288±0.03	-25.8±2.5
60	249.1±.3.1	0.287±0.06	-26.72±3.2	251.8±3.3	0.291±0.09	-23.9±2.2
90	252.4±2.8	0.292±0.03	-26.98±2.8	256.2±4.2	0.298±0.07	-22.8±1.4

Data expressed as (mean±SD, N=3)

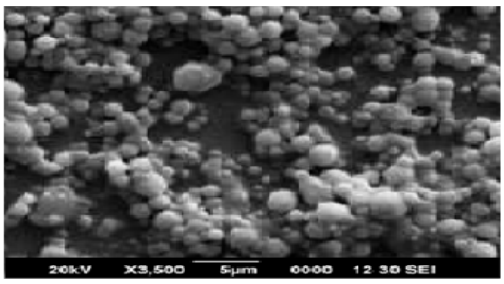


Fig. 6: SEM image of REB-SLNs (F9)

Pharmacokinetic study

The pharmacokinetic parameters of REB-SLNs in distinct rats were determined using non-compartmental conceptions and Kinetica 2000 software for two formulations (coarse suspension (Rebagen) and developed REB-SLNs formulation (F9). The AUC, Cmax, Tmax, MRT, and t ½ pharmacokinetic parameters were achieved for the developed REB-SLNs formulation and compared to the coarse suspension of rebagen marketed product. As a result, various pharmacokinetic parameters were determined and are listed below in table 4. Based on results, it was found that REB-SLNs (F9) exhibited high Cmax and AUC values relative to coarse suspension (Rebagen marketed tablet).

Compared to the coarse suspension, the bioavailability of formed REB-SLNs is higher. This higher bioavailability is due to either increasing the drug's aqueous solubility or increasing the drug's surface area available for release. When comparing the relative bioavailability of the REB-SLNs and the coarse suspension, the coarse suspension had a 3.87-fold increase in relative bioavailability. As a result of the development of REB-SLNs formulation, oral bioavailability could be improved shown in fig. 7.

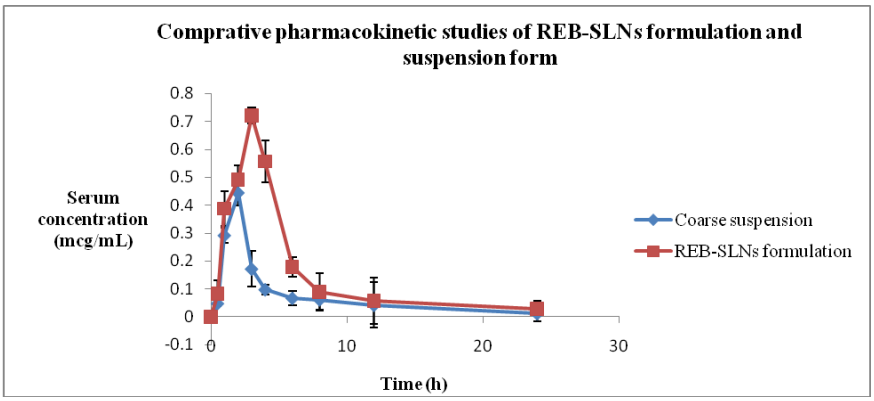


Fig. 7: Pharmacokinetic profile of developed REB-SLNs formulation (F9) and coarse suspension in rat serum and by oral administration

Statistical testing of pharmacokinetic data of developed REB-SLNs formulation (F9) and coarse suspension were performed. Graph pad prism software (version 8.0) was used to perform an unpaired t-test with a significance level of p-value<0.05. Statistical comparisons of pharmacokinetic parameters such as Cmax, Tmax, MRT and AUC of developed REB-SLNs and coarse suspension is shown below in table 4.

Table 4: Pharmacokinetic studies of optimized REB-SLNs and coarse suspension

Parameter	Optimized REB-SLNs (F9) mean±SD (n=6)	Coarse suspension mean±SD (n=6)
C_{max} (µg/ml)	2.652±0.25#	1.281±0.21
T_{max} (h)	3#	2
AUC(µg/ml). h	65.054±4.79#	16.810±1.84
$T_{1/2}$(h)	15.47±1.38#	4.971±1.21
MRT	23.68±1.85#	9.173±1.63

#-indicates significance at p<0.001 when compared to the control (coarse suspension)

CONCLUSION

The low solubility of rebamipide was improved by formulating into REB-SLNs using lipids. Particle size, ZP, PDI, drug content, EE, and *in vitro* studies were all examined in REB-SLNs made with dynasan 118, dynasan 116, dynasan 114, and imwitor 900 P. *In vitro* release studies were performed on REB-SLNs for 2 h in 0.1N HCl followed by 24 h in pH 6.8 phosphate buffer. The drug release pattern of REB-SLNs was prolonged. SLNs of dynasan 114 loaded with rebamipide were prepared with a surfactant (poloxamer 188 and polysorbate 80), forming a stabilizing layer over the solid lipid nanoparticles. The REB-SLNs formulation (F9) showed good zeta potential and particle size. In the current research, SLNs carriers can increase rebamipide bioavailability for the therapy of gastric ulcers and gastritis. In the pharmacokinetic studies in male Wistar rats, the fabricated formulation (F9) had 3.87 times higher relative bioavailability than the coarse suspension.

ETHICAL ISSUES

Animal studies approved by IAEC with Reg. No: 1692/PO/Ere/S/13/CPCSEA

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

The authors disclose no conflict of interest.

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