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Research article

Lipid based approach for bioavailability enhancement of boswellia serrata

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ABSTRACT

In past numerous studies reported the potential effect of *Boswellia serrata* in the treatment of various topical and systemic inflammatory diseases. Despite of potential pharmacological effects the oral delivery of BS is challenging due to poor bioavailability limiting its clinical applications. The objective of this study was to formulate and optimize lipid-based sustained release pellets of *Boswellia serrata* in order to improve solubility and oral bioavailability. Initially, solid dispersions were formulated by fusion method using hydrophilic grade lipids Gelucire 44/14 and 50/13 in different ratio (1: 0.25, 1: 0.5, 1:0.75, 1:1, and 1:2 w/w). Extrusion spheronization technique was used to further formulate solid dispersion of *Boswellia serrata* into sustained release pellets utilizing hydrophobic grade lipid carrier gelucire 43/01 and ethyl cellulose as a release retarding agent. Using a 3-level, 2-factor factorial design, the effect of the amount of gelucire 43/01 and ethyl cellulose was investigated and optimized. Compared to pure drug, solid dispersion of *Boswellia serrata* (batch-F9) demonstrated a 5-fold increase in aqueous solubility and dissolution behavior. The optimum system (batch-F16) achieved a maximum drug release of 95.69 % in 6 hours. In comparison to the marketed preparation, pharmacokinetic investigation in male Wistar rats revealed a 2.52-fold improvement in relative bioavailability of the optimized formulation. The obtained BS lipid-based pellets could be a promising choice for its efficient use in various clinical applications. The developed system could be effectively applied to deliver other phytochemicals having potential pharmacological effects but limited clinical use due to poor bioavailability.

Keywords: Boswellia serrata, Gelucire, Solid dispersion, Pellets, Spheronization, Bioavailability.

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INTRODUCTION

The most extensively used medications for treatment of pain, fever, and inflammatory illnesses are non-steroidal anti-inflammatory drugs (NSAIDs) [1,2]. However, prolonged use of NSAID leads to gastrointestinal (GI) complications including bleeding, abdominal discomfort further causing ulceration and GI wall perforations [3]. To overcome the GI complications extremely selective cyclo-oxygenase (COX)-2 class inhibitors were developed having superior gastric tolerability profile but suffers with drawback of severe adverse cardiovascular actions [4,5]. Considering the associated drawbacks of NSAIDs there is need of investigation and development of anti-inflammatory agents of natural origin having potential therapeutic benefits with well tolerated systemic profile.

In past numerous studies reported the potential effect of *Boswellia serrata* (Indian frankincense, Salai Guggal) in the treatment of various topical and systemic inflammatory diseases including rheumatoid arthritis, ulcerative colitis and osteoarthritis [6,7]. BS has also been traditionally used in ayurvedic system. BS contains an essential potent component responsible for the anti-inflammatory activities i.e. Boswellic acid (triterpenes) which noncompetitively inhibits 5-lipoxygenase, microsomal prostaglandin E synthase and serineprotease-cathepsin G [8,9]. Additionally, BS also exhibits potential immunomodulatory and anticancer activity [10,11]. Despite of potential pharmacological effects the oral delivery of BS is challenging due to poor bioavailability (< 10%) limiting its clinical applications [12,13]. The probable reasons reported behind its poor bioavailability are its poor solubility and permeability. In addition, BS having shorter biological half-life (3- 4 h) require frequent administration [14,15]. In order for BS to be used effectively, its solubility and bioavailability must be improved.

Lipid-based systems have recently attracted lot of consideration due to their intrinsic potential to enhance bioavailability of lipophilic agents having low water solubility. Self-micro emulsifying systems, solid lipid nanoparticles, and phytosomes are some of the lipid-based systems that have been developed to improve BS oral bioavailability [16,17]. The disclosed methods improved bioavailability significantly, however they had issues with either poor drug loading or long-term stability [18,19]. One of the techniques that has been widely utilized to increase solubility of

weakly water-soluble drugs is solid dispersion [20,21].

To overcome drawbacks linked with the developed lipid-based formulation of BS, in the present research work it was decided to develop the lipid based sustain release pellet of BS so as to improve its bioavailability and reduction in frequency of administration. To improve solubility and dissolution rate of BS, fusion approach was employed for preparation of solid dispersion using gelucire 44/14 and 50/13. Using gelucire 43/01 and ethyl cellulose as a release retardant, the resulting BS solid dispersion formulated into sustain release lipid-based pellets by extrusion-spheronization process. A three-level, two-factor factorial model was used to investigate and improve the combined influence of independent factors on response.

MATERIAL AND METHOD

Boswellia serrata was obtained as a gift sample from Mprex Health Care, Pune, India. Gelucire grade polymer as the gift sample from Gattefosse India Pvt. ltd., Mumbai India. Ethyl cellulose was obtained from HI media Laboratories, Mumbai, India. Other reagents used are of analytical grade.

Preparation of solid dispersion by fusion method

The fusion process was used to make BS solid dispersion with gelucire 44/14 and 50/13 in weight ratios (1:0.25, 1:0.5, 1:0.75, 1:1, and 1:2) [22,23] (Table 1).In a porcelain dish, a precisely weighed gelucire quantity heated to 10° Cover melting point, followed by BS addition with stirring. Prepared mass allowed to cool for 24 hours at ambient temperature. Solid dispersions were dried and ground in a mortar-pestle, then sieved through a 60-mesh sieve. After then, the samples were kept in desiccators for further experiments.

Table 1: Saturated Solubility studies in distilled water

Batch	BS: Gelucire 44/14 (mg)	BS: Gelucire 50/13 (mg)	Solubility mg/ml
Pure drug	-	-	0.46 ± 0.13
F1	1:0.25	-	0.80 ±0.04
F2	1:0.5	-	1.19 ± 0.15
F3	1:0.75	-	1.27 ± 0.11
F4	1:1	-	1.50 ± 0.07
F5	1:2	-	1.58 ± 0.15
F6	-	1:0.25	0.85 ± 0.08
F7	-	1:0.5	1.38 ± 0.16
F8	-	1:0.75	1.75 ± 0.23
F9	-	1:1	**2.27± 0.019**
F10	-	1:2	2.32± 0.02

Mean ± S.D.; n = 3.

Solubility screening studies

Saturated solubility tests were conducted to measure the solubility of BS solid dispersion produced with gelucire. In a conical flask holding 10 ml distilled water, an excess of BS solid dispersion was added. The flask shaken at room temperature for 48 h using a bath shaker (Neolab, Mumbai) [23,24]. The contents of the flask filtered and spectrophotometrically examined at 340 nm Shimadzu, 1700 [25].

Preparation of BS sustain release pellets

The solid dispersion prepared with BS: Gelucire 50/13 (1:1) was further selected for the formulation of sustain release pellets based on the findings of saturated solubility experiments. Melt pelletization method by extrusion spheronization technique were used to make the BS pellets. Microcrystalline cellulose used as spheronizing aid, hydrophobic grade lipid Gelucire43/01 and Ethyl cellulose used as release retardant. Gelucire 43/01 melted in porcelain with further addition of ethyl cellulose, BS solid dispersion (batch – F9) equivalent to 100 mg of BS and microcrystalline cellulose, mixed well and passed from sieve no.16 to obtain extrudates. To get the pellets, extrudates transferred to spheronizer (Shakti PharmTech, Ahmedabad, India) and spheronized at 625 rpm for around 02 minutes. The core pellets were dried at room temperature overnight.

Experimental design

The factorial design method was used to optimize the formulation. For the optimization technique, a 3-level, 2-factor design was used. The independent variable was concentration of gelucire 43/01 (X1), concentration of ethyl cellulose (X2) and dependent variables selected was drug release in 6 h (Y1) indicated in Table 2. The data of 09 trial runs analyzed by Design Expert software (Stat Ease, version 10, USA). The formulations shown in (Table 3).

Table 2: Experimental design parameters

Factors	Levels used (coded value)			Actual value (%)		
	Low	Medium	High	Low	Medium	High
Gelucire 43/01 – X1 (% w/w of BS solid dispersion)	-1	0	+1	10	20	30
Ethyl cellulose - X2 (% w/w of BS solid dispersion)	-1	0	+1	05	7.5	10

Table 3: Formulation compositions

Batch No.	Gelucire 43/01 (% w/w of solid dispersion)	Ethyl Cellulose (% w/w of solid dispersion)
F 11	10	10
F 12	10	7.5
F 13	10	05
F 14	20	10
F 15	20	7.5
F 16	20	05
F 17	30	10
F 18	30	7.5
F 19	30	05

Evaluation of BS sustain release pellets

Calibration curve of boswellia serrata in various media (viz. 0.1n HCL PH 1.2 and phosphate buffer ph. 6.8)

10 mg of BS taken in 100 ml media to obtain 100 µg/ml stock solution. The stock solution diluted further with medium to get solutions ranging from 1 to 70 g/ml. At 340 nm, absorbance was measured using a spectrophotometer (Shimadzu 1700, Japan).

Fourier transform infra-red (ftir) spectrum

FTIR scans of BS, gelucire (50/13 & 43/01) and physical mixture were obtained by FTIR (Shimadzu, 8400S, Japan). Between 400 to 4,000 cm^{-1} infrared spectrum was obtained and spectral analysis was performed [25].

Physical characterization and drug content

Micromeritic characteristics of pellets were assessed using Carr's index, Hausner's ratio, and angle of repose. A digital hardness tester was used to determine the hardness of the pellets (Veego, India). Using a friabilator, the friability of formulations measured (Veggo Friability Tester, India). The % weight loss after 200 spins was calculated using 10 g of pellets held in a friabilator [26, 27]. Each

formulation's drug content was evaluated by grinding pellets containing about 100 mg of BS and transferring into 0.1 N HCl. To ensure complete drug extraction in 0.1 N HCl, mixture sonicated 30 min. The solution was then filtered, diluted with 0.1 N HCl, spectrophotometrically measured at 340 nm (Shimadzu, 1700, Japan) (n = 3).

Particle size distribution analysis

The BS pellet size determined by sieve analysis using mechanical sieve shaker (Kumar Lab, Delhi, India). Ten gram (g) of pellets was sieved through series of sieves (16, 22, 25, 30 and 36) for 30 min. To establish the size distribution of pellets, the weight retained on each sieve was calculated.

Scanning electron microscopy (SEM)

Surface appearance of the core BS pellets, pellets of BS: Gelucire 50/13 (1:1) solid dispersion and pellets formulation batch (F 16) examined by scanning electron microscope (Jeol, Oxford Instrument, United Kingdom).

In-vitro drug release study

Using USP Type –II dissolution apparatus, the release of BS from the pellet formulations was measured in triplicates (Veego DA-8D, India). Pellets containing 100 mg BS accurately weighed and placed in 900 ml 0.1 N HCl for two hours and then into PBS 6.8 for another four hours at 37ºC ± 0.5º C; 50 rpm. 5 ml Aliquots were taken, filtered and examined at 340 nm. The collected data of optimized formulation evaluated using mathematical models such as the zero-order model, first order model, Korsmeyer–Peppas model, and Higuchi model to better drug release kinetics [28,29].

Statistical optimization

Design-expert® used to analyze the datas, i.e. percent drug release in 6 hours, for all formulations. Polynomial models were created for all of the responses. The proposed model was then subjected to an ANOVA analysis in order to identify relevant model terms [30,31]. P value, response regression and plots calculated. The numerical optimization function based on the desirability technique used to estimate the optimum level of variables.

Stability studies

The optimized BS sustain release formulation s subjected to accelerated stability in accordance with ICH criteria. For six months, sample kept at 40°C and 75% relative humidity and analyzed for drug content and drug release at preset time intervals [32].

In-vivo pharmacokinetics-study design

Pharmacokinetics investigations in male wistar rats approved by the Institutional Animal Ethical Committee (DYPIPSR/IAEC/19-20/P-07). The study's goal was to compare designed BS pellets to commercially available preparations. Twelve 180–200 g wistar rats were divided in two groups at random, fasted overnight. Orally, BS pellets a commercial formulation (20 mg/kg) were given to the respective groups [33,34]. 0.5 ml samples taken at preset time intervals (0.25, 0.5, 1, 2, 4, 8, 12, and 24 hours). Plasma separated with centrifugation (4000 rpm), stored at –20°C for further experimentation.

HPLC analysis of BS in plasma

The BS plasma concentrations estimated using the HPLC technique. The mobile phase was made up of acetonitrile and a pH 4.5 ammonium acetate buffer (60:40). The flow rate kept constant 1 ml/min to 340 nm [34]. A 0.1 ml sample was mixed with 0.9 ml acetonitrile, centrifuged for 15 min at 10000 rpm to determine the amount of BS in rat plasma. The resulting supernatant filtered by 0.2 µ filter and 20 µl volume injected. The analysis was performed using a RP- HPLC column (Kromasil, 4.6 x 250 mm, 5 µm, Shreetech Associates; Mumbai, India) on a Shimadzu HPLC LC20 AD (Shimadzu Corporation, Japan).

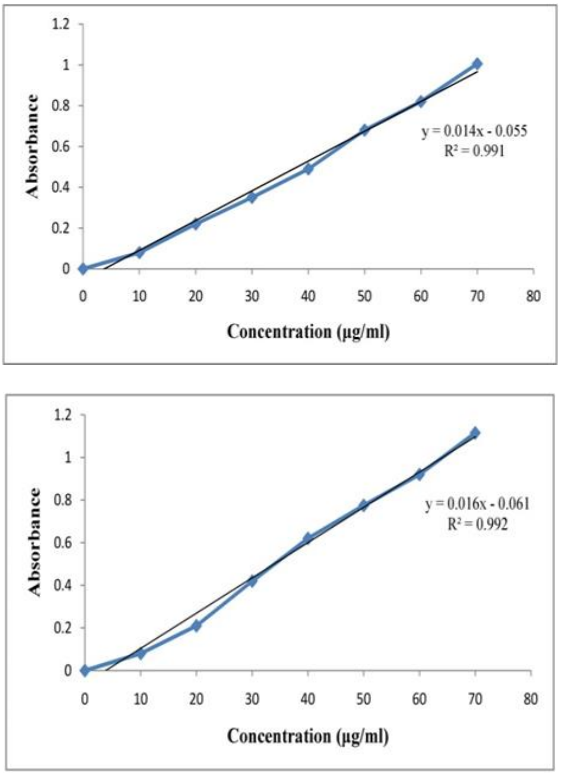
Pharmacokinetic analysis

PK solver (version 2.0) was used to calculate pharmacokinetic parameters such as duration and peak plasma amount (Tmax, Cmax), area under curve (AUC), mean residence time (MRT), and relative bioavailability. The parameters were assessed statistically by ANOVA, and any difference smaller with probability of 0.05 regarded statistically significant.

RESULTS AND DISCUSSION

Spectroscopic studies

Figure 1: Calibration curve of Boswellia Serrata in A 0.1N HCl and B PBS 6.8 at 340 nm



The BS λmax in 0.1 N HCl and PBS was obtained at 340 nm. In the examined range, BS calibration curve acquired in 0.1 N HCl and PBS 6.8 was found to be linear, and the regression analysis equation was also generated (Figure 1).

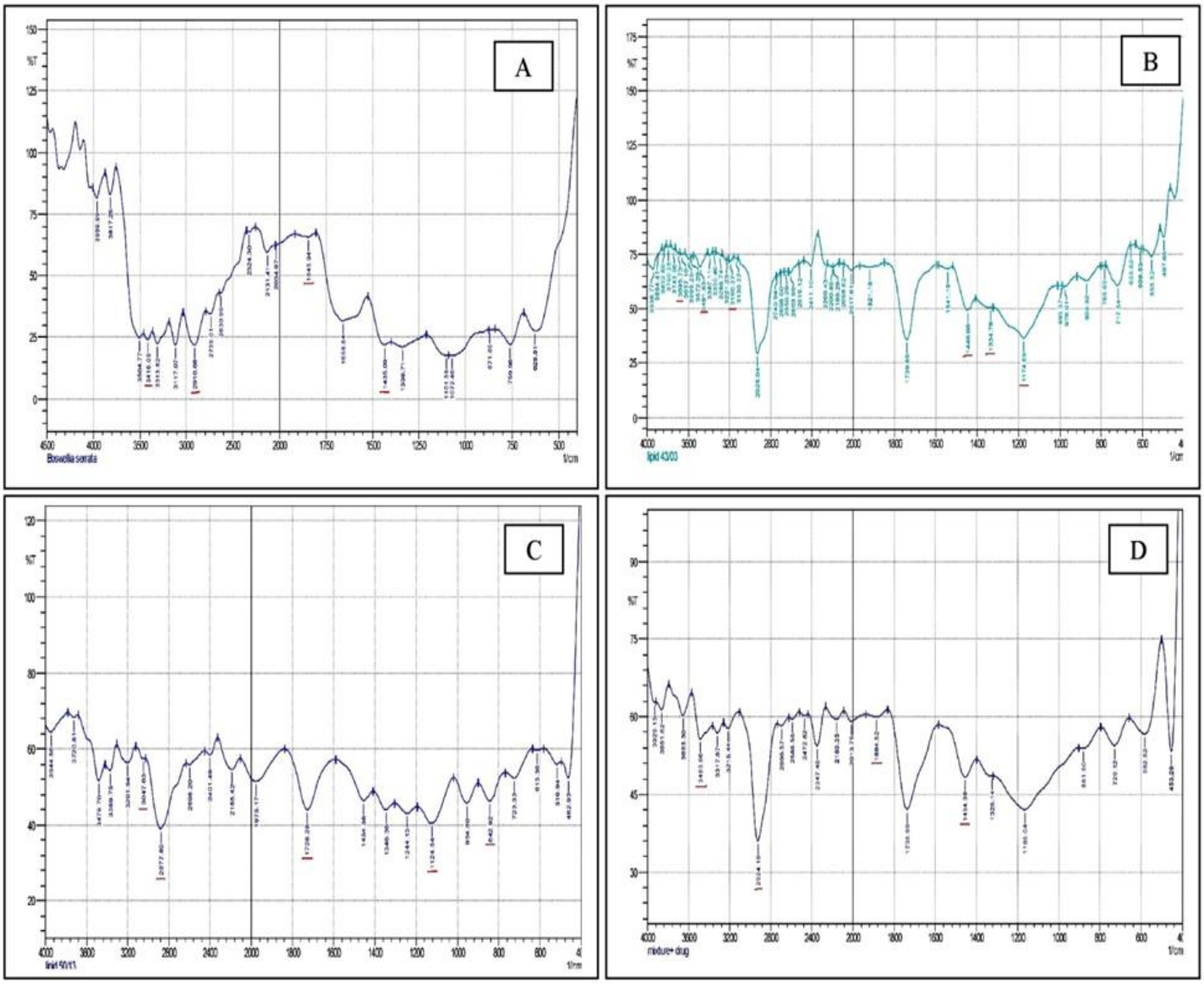
Fourier Transform Infra-Red (FTIR) spectrum

The FTIR spectra of BS showed peaks at 3416.05 cm^{-1} (O-H stretching), 2910.68 cm^{-1} (C-H stretching), 1845.94 cm^{-1} (C=O stretching in aromatic) and 1435.09cm^{-1} (C–H bonding of aromatic group) shown in (Figure 2). The major peaks found in the IR spectrum are identical to functional groups of BS. The typical peaks of Gelucire (50/13 and 43/01) are 3695.73 – 3190.37 cm^{-1} (OH stretching), 3047.63 and 2877.89 cm^{-1} (C-H stretching), 1728.99 cm^{-1} (C=C stretching), 1446.66 - 1174.32 cm^{-1} (C-H bending), 1334.78, 1124.27 cm^{-1} (C-O-C stretching), 1124.54, 1174.69 cm^{-1} (C-O stretching), 842.92 cm^{-1} (C-C stretching) and 727.97 cm^{-1} (C=C bending). The spectra of the mixture revealed drug and excipients distinctive peaks with insignificant wave number shifts, indicating that BS and gelucire are compatible.

Physical characterization and drug content

Carr's index and Hausner's ratio ranged between 3.8 ± 0.21% to 11.40 ± 0.39% and 1.03 ± 0.18 to 1.16 ± 0.27 respectively. Angle of repose values were found to be in the range of 21.60 ± 0.5 to 29.00 ± 0.5^0. Micromeritic analysis revealed that pellet formulations had good flow behavior. Hardness ranged from0.83 ± 0.3% to 1.40±0.42 kg/ cm^2. Friability found to be between0.19±0.05 to 0.53±0.03 %. Drug content in all prepared batches ranged from 96.40 ± 1.3 to 98.46 ± 1.7 % indicated good BS content homogeneity in the pallets.

Figure 2: FTIR scans of A. Boswellia serrata, B. Gelucire 43/01, C. Gelucire 50/13, D. Physical mixture (BS & Gelucire)



Particle size distribution analysis

The pellet size obtained with sieve analysis indicated narrow size distribution, majority of the pellet formulations were in range of 550 µm to 655 µm. The plot of pellet mean size vs. weight retained of pellet formulation was indicated in figure 3. The surface appearance of the core BS pellets, pellets of BS: Gelucire 50/13 (1:1) solid dispersion and pellets formulation batch (figure 16) are shown in (figure 4). The core BS pellets exhibited rough external appearance. Pellets containing BS-Gelucire 50/13 solid dispersion showed slight smooth surface. Pellets formulation batch (figure 16) showed spherical and smooth surfaces.

Figure 3: Plot of pellet mean size vs. weight retained of pellet formulation (figure 11 – figure 19) Mean ± S.D.; n = 3

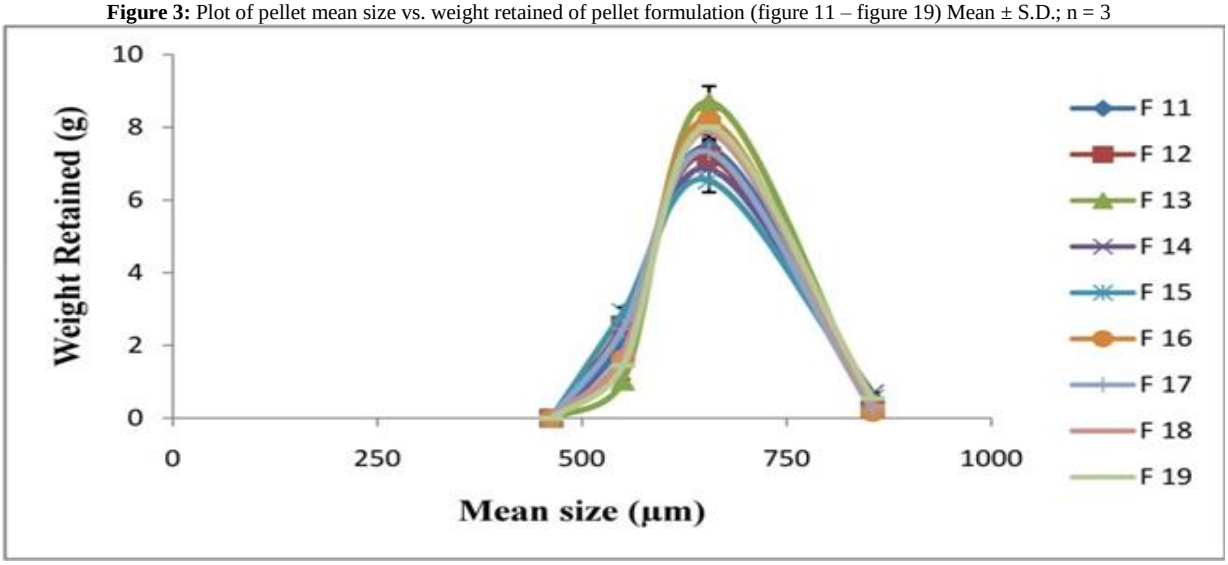
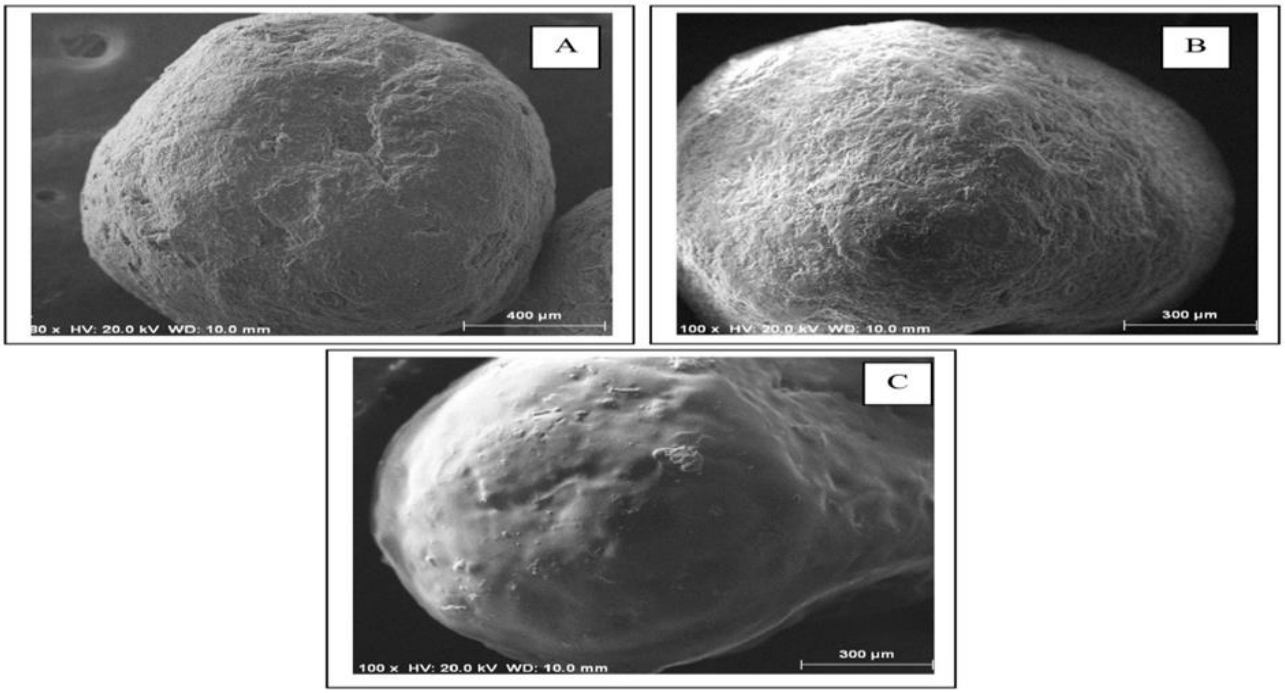


Figure 4: Scanning electron microphotographs of (A) Pellets containing core BS pellets, (B) Pellets of BS: Gelucire 50/13 (1:1) solid dispersion (C) Pellets formulation batch (F 16).



In-vitro drug release study

At room temperature, the determined aqueous solubility of BS was 0.46 mg/ml. Hydrophilic carriers' gelucire 50/13 and gelucire 44/14 were investigated to improve drug solubility. Solubility experiments for formulated solid dispersions utilizing various hydrophilic carriers revealed that gelucire 50/13 had a higher drug solubility than gelucire 44/14 (Table 1).The solubility increased proportionally as the amount of carrier increased, however after a 1:1 ratio (drug: carrier), increasing the carrier concentration did not result in a substantial increase in solubility. When compared to pure BS, the solubility of BS solid dispersion (batch— figure 9) increased about 5-fold. In addition, in 0.1 N HCl, in-vitro release profiles of drug and formulated BS solid dispersion (batch— figure 9) were investigated indicated in figure 5. In 2 hours, the pure drug and the BS solid dispersion released 16.45 percent and 88.57 percent of the drug, respectively. Due to low solubility, the pure drug had a slow dissolution rate. However, the developed solid dispersion (batch-figure 9) greatly improves drug solubility. The solubilization behavior of gelucire 50/13could be responsible for the increased dissolution rate [35,36]. For the development of sustain release formulation (batch— figure 11 to figure 19), the BS solid dispersion (batch – figure 9) was chosen. As a release-retarding polymer, Gelucire 43/01 (10, 20, 30% w/w of solid dispersion) and ethyl cellulose (05, 7.5, and 10% w/w solid dispersion) were utilised.

The in-vitro dissolution studies of prepared pellets were also performed shown in (Table 4 & figure 6). In preliminary studies alone gelucire 43/01 was used as release retardant, but even the higher level of gelucire 43/01 not able to sustain the release for more

than 4 h (data not shown). Hence, additionally ethyl cellulose was used as release retardant for sustain release. The results of dissolution studies indicated that as gelucire 43/01 and ethyl cellulose increases drug release retardate. This could be attributed that higher polymer layer thickness, medium penetration decreases causing sustain release. The batches (figure 11 to F19) prepared with varying levels of release retarding polymer showed drug release in the range of 70.47% to 95.69% in 6 hours.

Figure 5: *In-vitro* dissolution study of pure drug and solid dispersion batch (F 8), Mean ± S.D.; n = 3

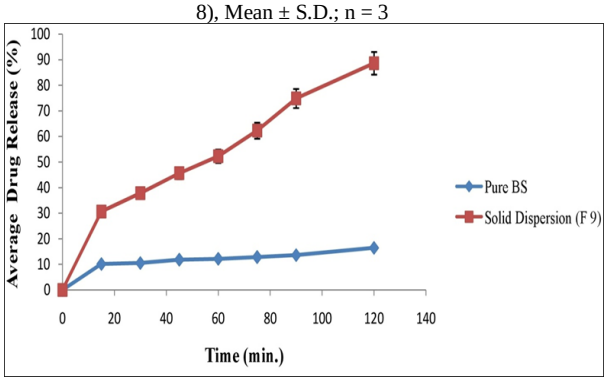
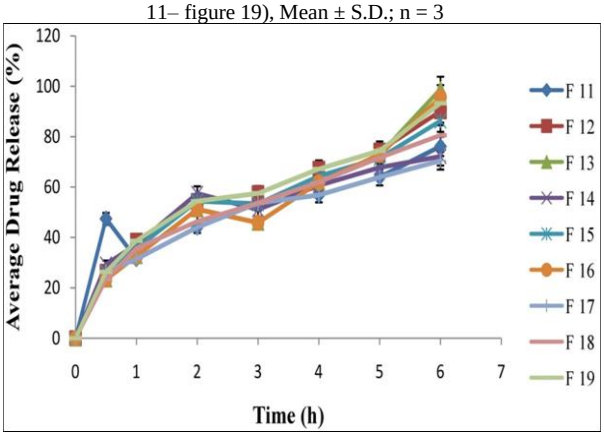


Table 4: Response data of batches figure 11– figure 19 Mean ± S.D.; n = 3.

Batch	Drug release in 6 h (%)
F11	76.14 ± 1.32
F12	90.07± 2.07
F13	98.84 ± 1.20
F14	72.84 ± 1.13
F15	86.24± 1.28
F16	95.69± 1.42
F17	70.47± 2.19
F18	80.54 ± 2.17
F19	93.24± 1.23

Figure 6: In-vitro dissolution study of sustain release pellets (batch figure 11– figure 19), Mean ± S.D.; n = 3



Drug release data of optimized formulation batch (figure 16) was analyzed with various models to determine release kinetics. The Higuchi model or zero order was found to be the greatest fit with the highest correlation shown in Table 5. Both dissolution and diffusion mechanism liable for initial release, as drug exhausted from outer zone diffusion of drug particle occur with lesser rate from polymer layers.

Table 5: Regression coefficients of dissolution models

Batch No.	Zero order	First order	Higuchi release	Korsmeyer Peppas (n)
F 16	0.991	0.961	0.997	0.69

Statistical optimization

Using design expert software, drug release in 6 hours for 09 batches (figure -11 to figure -19), were fixed in several models. For all of the responses, a linear model is recommended, and the ANOVA findings for the response model are shown in Table 6. The terms are significant, as evidenced by the P values (0.05). Figure 7A shows the obtained response surface plot for release in 6 hours. The amount of gelucire 43/01 and ethyl cellulose had a substantial effect on drug release in 6 hours, according to the response plot. With increasing levels of gelucire 43/01 and ethyl cellulose, drug release decreases. The obtained equations (A: gelucire 43/01; B: Ethyl cellulose) can be used to correlate the results. The regression equation (Y1) coefficients indicated more pronounced negative effect of A: gelucire 43/01; B: Ethyl cellulose on drug release. The generated diagnostic plot (predicted vs. actual) revealed that the predicted and experimental values were in reasonable agreement indicated lesser extent of error (Figure 7B).

Table 6: ANOVA data for response surface linear model

Source	Sum of Squares	Degrees of freedom	Mean Square	F Value	p-value Prob> F	Remark
Drug Release in 6 h						
Model	850.04	2	425.02	311.00	< 0.0001	Significant
Conc of gelucire	72.11	1	72.11	52.76	0.0003	
B- Conc of ethyl cellulose	777.94	1	777.94	569.25	< 0.0001	
Residual	8.20	6	1.37			

Regression equations - Drug release (%) (Y1) =+84.90-3.47A-11.42B

Figure 7: (A Surface response plot B) Actual and predicted values of % drug release in 6 h Figure (A)

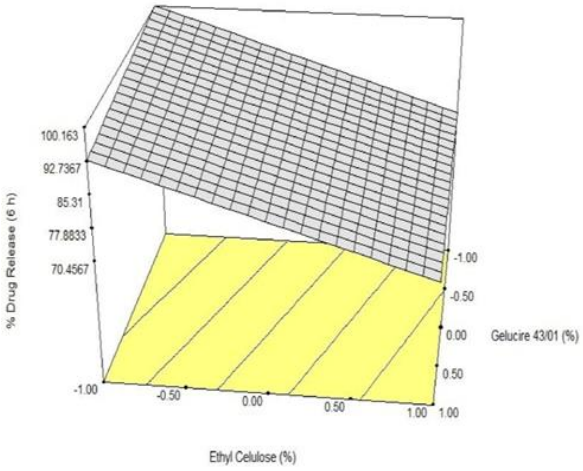
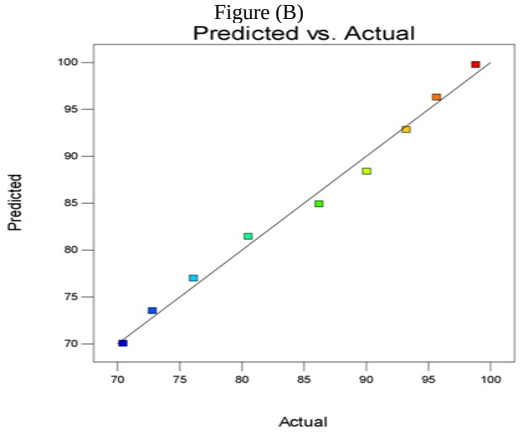


Figure (B)



The desirability approach employed to get the optimum formulation by applying constraints. Drug release in 6 hours was set to maximal, while t variables were set in range. The most desirable option suggested by the design expert software was chosen, as shown in Table 7. The response was assessed using an optimized formulation (batch figure 16) as shown in Table 3. The acquired experimental results for batch figure 16 were close to the theoretical drug release values.

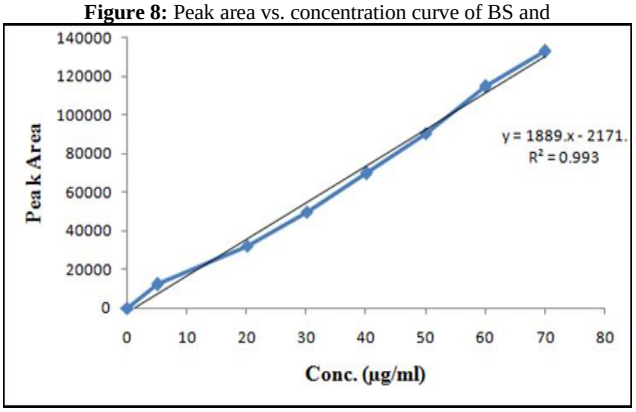
Table 7; Summary of numerical optimization Mean ± S.D.; n = 3

Parameters	Goal	Solution	Desirability	Remark
Independent Variables				
Gelucire 43/01	in range	0 (20%)	0.95	Selected
Ethyl Cellulose	in range	-1 (5%)		
Dependent Variables				
Percent drug release in 6 h	Maximum	96.18 %		

In-vivo pharmacokinetics-study

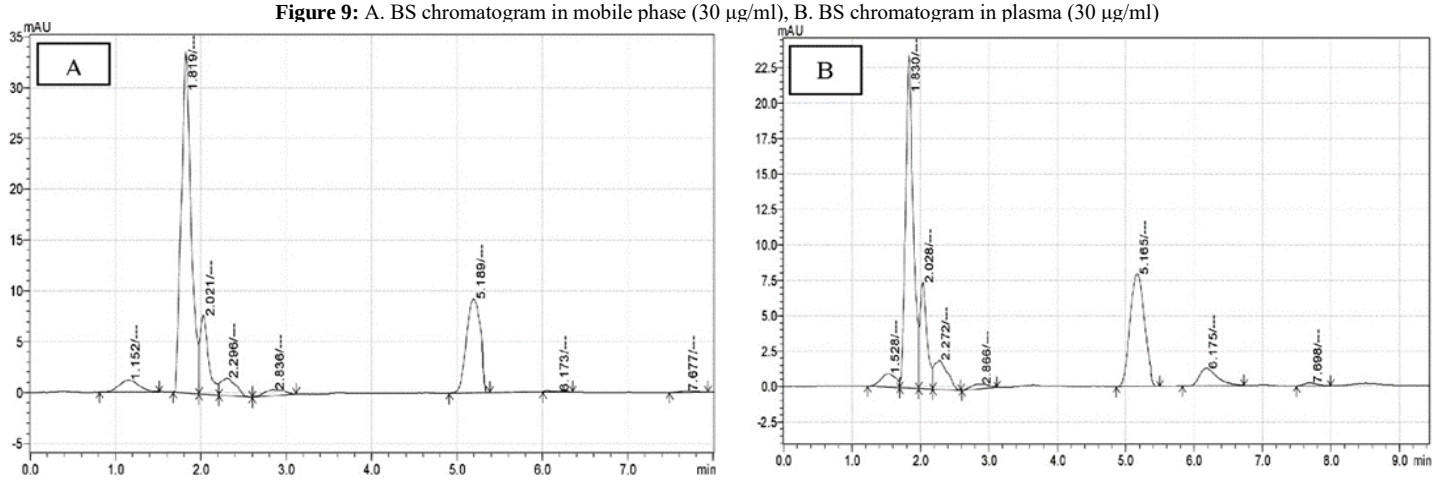
HPLC method was employed to determine plasma concentrations of BS. Stock solution of BS (100 µg/ml) was prepared using mobile phase and further diluted in concentration range of 5 to 70 µg/ml. The calibration curve of working standard solutions was obtained and used for estimation of BS in plasma. A linear relationship was observed between the BS concentration and the peak areas of BS with a high correlation coefficient (r^2 = 0.993) shown in figure 8.

Figure 8: Peak area vs. concentration curve of BS and



The mobile phase was made up of acetonitrile and a pH 4.5 ammonium acetate buffer (60:40). The flow rate kept constant 1 ml/min to 340 nm. A 0.1 ml sample was mixed with 0.9 ml acetonitrile, centrifuged for 15 min at 10000 rpm. The resulting supernatant filtered by 0.2 µ filter and 20 µl volume injected to determine the amount of BS in rat plasma. The HPLC method showed retention time of 5.1 min for BS as indicated in figure 9A & B. The intra-day and inter-day precision of less than 2.0% and 1.0% respectively with limit of quantification of 100 ng/mL were observed.

Figure 9: A. BS chromatogram in mobile phase (30 µg/ml), B. BS chromatogram in plasma (30 µg/ml)



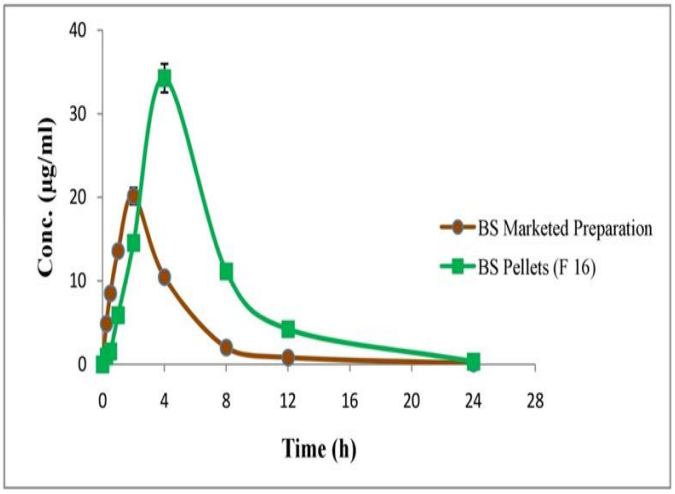
The pharmacokinetic parameters were determined and compared for BS pellets (batch figure 16) and marketed preparation shown in (Table 9 & figure 10). The change in Cmax and Tmax values revealed sustained release of BS pellets (batch figure 16). When comparing prepared BS pellets to commercial preparations, there was a 2.52-fold improvement in relative bioavailability. Longer resident period of BS pellets was indicated by higher MRT and lesser elimination rate constant values. The statistical analysis found that the studied pharmacokinetic parameters were all significantly different.

Table 9. Pharmacokinetics of BS pellets formulation & marketed brand

Parameters	BS Pellets (F16)	BS Marketed brand
C max (µg/ml)	34.26 ± 3.05*	20.15 ± 3.46
T max (h)	4.00 ± 0.25*	2.00 ± 0.44
$AUC_{0-\infty}$(µg-h/ml)	489.77 ± 6.43*	194.35 ± 8.11
MRT (h)	4.85 ± 0.17*	3.40 ± 0.11
K_{el} (h^{-1})	0.21 ± 0.14*	0.49 ± 0.09

*P<0.05 as compared to marketed preparation, Mean ± S.D.; n = 6

Figure10: Plasma concentration profiles of BS pellets (F 16) and BS marketed preparation, mean ± S.D.; n = 6



CONCLUSION

The present study demonstrated feasibility of BS-SD loaded lipid-based pellet formulation for enhancement in bioavailability. The obtained BS solid dispersion (batch F - 9) showed nearly 5-fold rise in solubility and dissolution behavior compared to BS. The BS solid dispersion further formulated into sustain release lipid-based pellets using extrusion spheronization technology. The optimization study indicated that sustain release pellets of BS (batch figure - 16) prepared with gelucire 43/01 (20%) and ethyl cellulose (5 %) was optimized showed maximum 95.69% drug release in 6 h. Increased Cmax, longer Tmax, and MRT with reduced elimination rate were found in a pharmacokinetic profile analysis in male Wistar rats, indicated sustained drug release behavior. The results of pharmacokinetic studies indicated improvement in relative bioavailability by 2.52-fold of optimized BS pellet formulation compared to BS marketed preparation. The designed system of BS lipid-based pellets with improved bioavailability could be effectively used for its potential pharmacological effects.

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CONFLICTS OF INTEREST

None.

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ETHICAL APPROVAL

The In-vivo pharmacokinetics studies were approved by the Institutional Animal Ethical Committee (DYPIPSR/IAEC/19-20/P-07). This review is an earnest attempt to inspire young researchers to pursue research in the said domain in order to develop new immunomodulating medications.

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