RESEARCH ARTICLE

Design, Development, and *Ex vivo* Characterization of *Boswellia serrata* Loaded Emulgel

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ABSTRACT

The objective of this study was to investigate the potential of emulgel as a topical delivery system to enhance the permeation of *Boswellia serrata* (BS). BS loaded emulgel was prepared using 3^2 factorial design and was characterized using scanning electron microscopy (SEM), % drug content, and spreadability determination. The design of the experiment was done to optimize the result, and then surface plots were generated to compare with the practical results. The prepared BS loaded emulgel showed an average spreadability of 29.840 to 75.6 g.cm/sec; the pH of all formulation was in the range of 6.3 to 7.09. Rheological behavior was studied using viscosity measurements, and a skin irritation test was performed to evaluate the biocompatibility of formulation. The skin permeation study was carried out with rat dorsal skin using a modified Franz diffusion cell. BS emulgel showed high drug deposition on excised rat skin; the test showed biocompatibility of formulated emulgel. These results show that BS loaded emulgel as a superior topical application vehicle for BS.

Keywords: *Boswellia serrata*, Emulgel, Factorial design, Skin irritation test, Spreadability.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that arises more frequently in females than males, is predominantly observed in the elderly. The prevalence rate reported in 2019 ranged from 0.5 to 15% of the population and had regional variation. RA primarily affects the lining of the synovial joints and can cause progressive disability, premature death, and socioeconomic burdens. The clinical manifestations of symmetrical joint involvement include arthralgia, swelling, redness, and even limiting the range of motion.[1]

The BS *(Salai/Salai guggul)* (family: Burseraceae; genus: *Boswellia*) is a moderate to large-sized branching tree that grows in dry mountainous regions of India, Northern Africa, and the Middle East.[2] The family of Burseraceae is represented in the plant kingdom with 17 genera and 600 species wide-spread in all tropical regions.[3]

The BS exhibits anti-inflammatory property in human peripheral blood mononuclear cells (PBMCs) and mouse macrophages through inhibition of tumor necrosis factor-alpha (TNF-alpha), interleukin-1beta (IL-1beta), NO, and mitogen-activated protein (MAP) kinases. Incensole acetate, a novel anti-inflammatory compound isolated from *Boswellia* resin, inhibits nuclear factor-kappa B activation.[4] Boswellic acids are direct 5-LO inhibitors that efficiently suppress 5-LO product synthesis in common *in vitro* test models. However, the pharmacological relevance of such interference *in vivo* seems questionable.[5] Acetyl-11-keto-β-boswellic acid inhibits prostate tumor growth by suppressing vascular endothelial growth factor receptor 2-mediated angiogenesis.[6] This makes BS a potent anti-rheumatoid agent.

Many widely used topical agents like ointment, creams, lotions are applied for the treatment of RA, but have many disadvantages. They are sticky in nature causing uneasiness to the patient, have lesser spreading coefficient so applied by rubbing, and they exhibit the problem of stability. Due to all these factors within the major group of semisolid preparation, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparation. In spite of many advantages of gels, a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation, an emulsion-based approach is being used so that even a hydrophobic therapeutic moiety can be successfully incorporated and delivered through emulgel.[7]

As the name suggests, they are a combination of emulsion and gel. In recent years, there has been great interest in the use of novel polymers with complex functions as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase. In fact, the presence of a gelling agent in the water phase converts a classical emulsion

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into an emulgel. Both oil-in-water and water-in-oil emulsions are used as vehicles to deliver various drugs to the skin.[8] Emulgels for dermatological use have several favorable properties, such as, being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, having a longer shelf life, bio-friendly, transparent, and having a pleasing appearance.[9]

In the development of emulgel dosage form, an important issue is to design an optimized formulation with an appropriate drug diffusion rate in a short period and minimize the number of trials. For this purpose, a computer-based optimized technique with a 3-level factorial 10 design utilizing a polynomial equation has been widely used.[10] Response surface methodology (RSM) is a wide practical approach in the development of optimization of the drug delivery system. Based on the principle of design of experiments (DoE), the methodology encompasses the use of various types of experimental design, generation of polynomial equations, and mapping of the response over the experimentation domain to determine the optimum formulation.

METHOD AND MATERIALS

Materials

The BS was purchased from Konark Herbal and Health Care, Daman. Triethanolamine, span 80, tween 20, methyl paraben, liquid paraffin, and propylene glycol 400 were purchased from Merck Specialities Pvt. Ltd., Mumbai. Carbopol 934 was purchased from Hi Media Laboratories Pvt. Ltd., Mumbai, and all reaming chemicals used were of analytical grade.

Method

Preparation of BS Loaded Emulgel

Emulgel of BS was prepared by using 3^2 factorial design. A total of nine batches were prepared with varying concentration of span 20 and tween 80 as shown in Table 1. The gel in formulations was prepared by dispersing carbopol 934 in purified water with constant stirring at a moderate speed; then, pH was adjusted to 6 to 6.5 using triethanolamine (TEA). The oil phase of the emulsion was prepared by dissolving span 80 in light liquid paraffin while the aqueous phase was prepared by dissolving tween 20 in purified water. Methylparaben was dissolved in propylene glycol, where drug BS was dissolved in water, and both solutions were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70 to 80ºC; then, the aqueous phase was added to the oil phase with continuous stirring until cooled to room temperature using a homogenizer. Then mixing of gel and emulsion in ratio 1:1 to obtain the emulgel.[11]

Experimental Design (3^2 Full Factorial Design)

To investigate the efficiency of the process on the formulation of emulgel, a three-level, 3^2 full factorial design was constructed with no center points. Two variables were chosen, namely, the concentration of tween 20 (X1), the concentration of span 80 (X2). Each independent variable had three levels which were coded as –1, 0, and +1, i.e., the concentration of tween 20 (0.5, 0.75, and 1 mL), for the concentration of span 80 (0.5, 0.75, and 1 mL). Nine runs were carried out to obtain a promising effect and Nine batches were formulated as shown in Table 2.

Statistical Analysis and Optimization of Formulation using Response Surface Methodology (RSM)

The design was used for the generation and evaluation of the statistical experimental design. Response surface modeling and evaluation of the quality of fit of the model for the current study were performed employing Design Expert® DX 10.0.7.0 license version software. Polynomial models, including linear, interaction, and quadratic terms, were generated for all the response variables using multiple linear regression analysis (MLRA). A second-order polynomial equation that describes the effect of independent factors on the response is expressed in the following forms:

$$\text{Quadratic model} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2$$

Where X is the dependent variable; β_0 is the arithmetic mean response of the nine runs and β_i (β_1, β_2, β_{12}, β_{11}, and β_{22}) is the estimated coefficient for the corresponding factor

Table 1: 3^2 full factorial design with dependent variable

Batch code	*Span 20 (mL)*		*Tween 80 (mL)*	
F1	-1	0.5	-1	0.5
F2	0	0.75	-1	0.5
F3	+1	1	-1	0.5
F4	-1	0.5	0	0.75
F5	0	0.75	0	0.75
F6	+1	1	0	0.75
F7	-1	0.5	+1	1
F8	0	0.75	+1	1
F9	+1	1	+1	1

Table 2: Composition of nine batches of BS loaded emulgel

Ingredients	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*
Carbopol 934 (g)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Span 80 (mL)	0.5	0.75	1	0.5	0.75	1	0.5	0.75	1
Liquid paraffin (mL)	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Tween 20 (mL)	0.5	0.5	0.5	0.75	0.75	0.75	1	1	1
Methyl paraben (g)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PEG 400 (mL)	5	5	5	5	5	5	5	5	5
Drug (g)	1	1	1	1	1	1	1	1	1

X_i (X_1, X_2, X_1X_2, X_1X_1, and X_2X_2). The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The equations enable the study of the effects of each factor and their interaction over the considered responses. The polynomial equations were used to draw conclusions after considering the magnitude of coefficients and the mathematical sign they carry, i.e., positive or negative.

Characterization of BS Loaded Emulgel

Physical appearance and pH determination: The BS loaded emulgel formulation was used solely to determine the optimum polymer type, viscosity, and release properties of the gel. The pH of the gel was measured using a digital pH meter (ELICO) at room temperature. The viscosity of the gel was determined by using Brookfield viscometer.

Drug Content Studies

Accurately weighed 1-gram of the gel was transferred into a 100 mL volumetric flask containing 20 mL of saline phosphate buffer (pH 6.8) and stirred for 30 minutes, followed by sonication. The volume was made up to 100 mL with saline phosphate buffer (pH 6.8). After suitable dilution, the absorbance was measured using a UV-visible spectrophotometer (Model: SPECTRO 2060 PLUS, Analytical Technologies Ltd., Gujarat, India).[12]

Spreadability

The spreadability of the formulation was determined by an apparatus suggested by Muttimer *et al*., which was suitably modified in the laboratory and used for the study. It consists of a wooden block, which was provided by a pulley at one end. A rectangular ground glass plate was fixed on this block. An excess of gel (about 1-gram) under the study was placed on this ground plate. The gel was then sandwiched between this plate and another glass plate, having the dimension of a fixed ground plate and provided with the hook. A 1 kg weight was placed on the top of two plates for 5 minutes to expel air and to provide a uniform film of the gel between the plates. The excess of the gel was scraped off from the edges. The top plate was then subjected to pull of 10 grams with the help of string attached to the hook, and the time (in seconds) required by the top plate to cover a distance of 5 cm was noted. Spreadability = ml/t, where, m = weight tied to the upper slide (10 gm), l = length of glass slide (7.5 cm), and t = time in seconds.[13]

Skin Irritation Test

The skin irritation study was conducted using white male rabbits (nn = 3) as test animals. The hair of rabbits on the dorsal side was shaved with electrical shaver and emulgel (about 4 gm) applied to each site (two sites per rabbit) by introduction under a double gauze layer on one square inch of the skin. After 24 hours of exposure, the formulation was removed. The test sites were wiped with tap water to remove any residual gel. The development of erythema/ edema was monitored for 3 days by visual observation.

Skin Deposition Study

Skin deposition study was performed using the same procedure as described above for skin permeation study. At the end of the permeation experiment, the surface of the skin was washed five times with 50% ethanol to remove the excess drug from the surface. The washing protocol was verified and found to remove >95% of the applied dose at zero time. The skin was then cut into small pieces. The tissues were further homogenized with 50% ethanol and left for 24 hours at room temperature. After shaking and centrifuging at 3,000 rpm, the drug in the supernatant was determined by UV analysis.[14]

SEM

Emulgel was visualized using SEM electron microscope with an accelerating voltage of 100 kV and magnification up to 20.00 kx. Samples were stained with a 1% aqueous solution of phosphotungstic acid (PTA) as a negative stain. Emulgel solution (10 mL) was dried on a microscopic carbon-coated grid for staining. The excess solution was removed by blotting. After drying, the stained samples were examined in the SEM electron microscope accelerated.

In vitro release of BS Loaded Emulgel

In vitro diffusion study was carried out in a modified Franz diffusion cell using a cellophane membrane, which is heated for 1-hour in boiling water. The membrane was tied to the donor compartment and mounted on the reservoir compartment of the Franz diffusion cell containing 21 mL of pH 6.8 phosphate buffer. A 1 gm of BS gel was placed over the cellophane membrane of the donor compartment. The whole set was placed on the magnetic stirrer. The study was carried out at 37 ± 0.5ºC and 100 rpm. Samples were withdrawn from the sampling port of reservoir compartment at regular intervals, and absorbance was measured UV-visible spectrophotometer (Model: SPECTRO 2060 PLUS, Analytical Technologies Ltd., Gujarat, India) at 210 to 215 nm.[15]

Ex vivo Diffusion Studies

Skin permeation study was carried out with rat dorsal skin using modified Franz diffusion cell by the same method as described above in the *in vitro* drug releases study of BS loaded emulgel. The skin was carefully checked through a magnifying glass to ensure that the sample was free from any surface irregularity such as tiny holes or crevices in the portion that was used for the permeation studies. The ability of polymer-lipid hybrid vesicle gel to help retain the drug within the skin (i.e., depot-effect) was investigated by determining the amount of drug retained in the skin sample employed in permeation studied. For this, skin from the donor compartment pipette out and dissolved in phosphate buffer. Absorbance was measured by a UV spectrophotometer to determine the amount of drug retained and remaining to diffuse.[16]

Kinetic Study of Release Profiles of BS Loaded Emulgel

After completing *in vitro* release profiles of all the investigated batches, the data were treated with different mathematical models, i.e., zero-order kinetics, first-order kinetics, and Higuchi model. The release rate constant (K) values and the correlation coefficient (R^2) was determined.

Stability Studies

Stability studies of drug product being as a part of drug discovery and ends with the commercial products, to assess the drug and formulation stability, stability study was carried out for most satisfactory formulation was sealed in a glass vial, and kept at 30 ± 2 and 40 ± 2ºC at 65 ± 5 and 75 ± 5 RH for 2 months. At the end of 1 and 2 months, the samples were analyzed for the drug content and *in vitro* diffusion study.

RESULTS AND DISCUSSION

Analysis of Data by Design Expert Software

A 3^2 full factorial design was selected, and the two factors were evaluated at three levels, respectively. The concentration of tween 20 (mL) (X1), concentration of span 80 (mL) (X2) were selected as independent variables, and the dependent variables were spreadability (gm.cm/sec) and percent drug content as represented in Table 3. The data were also subjected to 3D response surface methodology as shown in Figure 1 to study the interaction of concentration of tween 20 (mL) (X1), the concentration of span 80 (mL)(X2) on dependent variables, which gave the maximum and minimum value for the dependent variables in Table 4.

Optimization (Model Validation)

The process was optimized for the response spreadability and % drug content. The results clarified an optimum setting for BS loaded emulgel. To verify the reproducibility, the spreadability g.sec/cm^2 62.7507 and % drug content 100.52% was formulated as shown in Table 5. The formulations were evaluated for response study, and the results showed a good relationship between the experimental and predicted values, which confirms the practicability of the model. BS loaded emulgel formulation (F1) showed relevant results to the predicted results and was found to be an optimized batch.

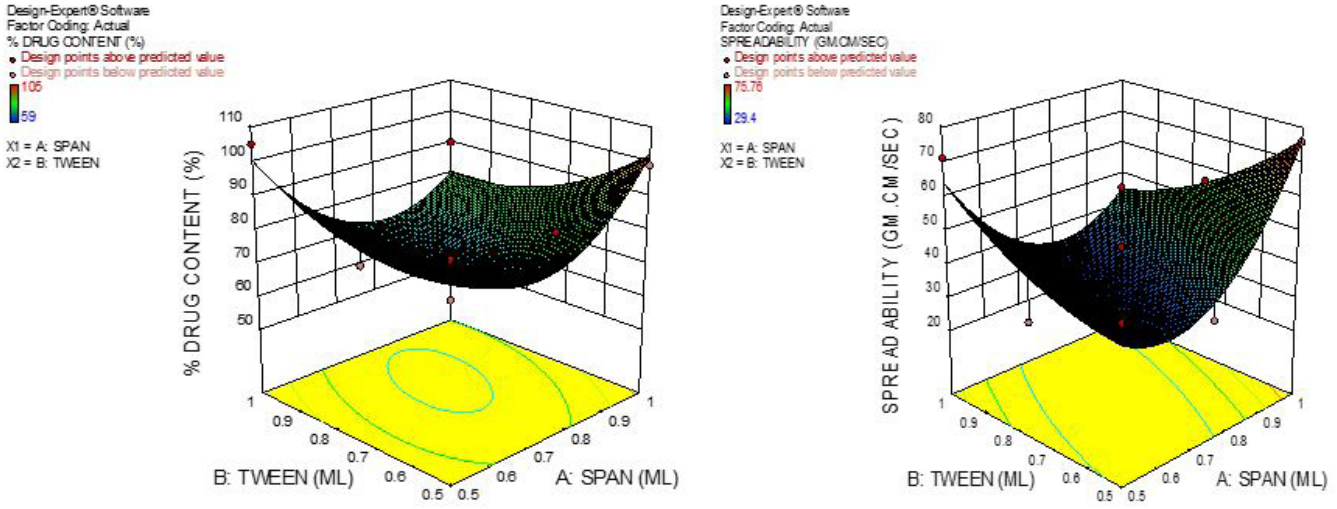

Figure 1: Response surface diagrams showing optimum concentration of independent variables (images obtained from Design Expert®DX 10.0.7.0 license version software)

Table 3: Design summary of BS loaded emulgel formulation

Factor	*Name*	*Units*	*Type*	*Subtype*	*Minimum*	*Maximum*
A	Spreadability	gm.cm/sec	Numeric	Continuous	2	6
B	Drug content	%	Numeric	Continuous	2	9

Table 4: Design summary of dependent BS loaded emulgel formulation

Response	*Name*	*Units*	*Observations*	*Analysis*	*Minimum*	*Maximum*	*Mean*
Y1	Spreadability	gm.cm/sec	9	Polynomial	29.4	75.76	48.5311
Y2	% drug content	Percent	9	Polynomial	59	105	84.7778

Table 5: Comparison of predicted and experimental values central surface model (CSM)

	CSM	
Responses	*Predicted*	*Experimental*
Spreadability g.sec/cm	62.7507	75.76 ± 1.4
% drug content	100.52	99 ± 2.1

Data Analysis by Design Expert Software

The 3^2 full factorial design was selected to study the effect of independent variables concentration of tween 20 (mL) (X1), the concentration of span 80 (mL) (X2) on dependent variables spreadability, and % drug content. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses.

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where, Y = dependent variable, b_0 = arithmetic mean response of the nine runs, and b_i (b_1, b_2, b_{12}, b_{11}, and b_{22}) = estimated coefficient for the corresponding factor X_i (X_1, X_2, X_{12}, X_{11}, and X_{22}), which represents the average results of changing one factor at a time from its low to high value. The interaction term (X_1X_2) depicts the changes in the response when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity.

The responses of the formulations prepared by 3^2 factorial design batches are indicated. The data clearly indicate that values are strongly dependent on the selected independent variables. The fitted regression equations relating the responses hardness and disintegration time are shown in the following equations, respectively.

Final equations in terms of actual factors:

Spreadability = +7.87425 - 1.46458 - 0.45116 + 0.0375 + 0.1675 + 0.023265

% drug content = +137.215419 - 70.238 - 20.04082 + 1.14286 + 1.54167 + 1.60544

Evaluation of BS Loaded Emulgel

Physical appearance and pH determination of BS emulgels demonstrated that formulated emulgel was creamish, viscous, creamy preparation with a smooth homogeneous appearance. The pH values of all prepared formulation ranged from 6.3 to 7.09, which are considered acceptable to avoid the risk of irritation upon application to the skin, as demonstrated in Table 6. One of the essential criteria for an emulgel is that it should possess good spreadability, a more viscous formulation would have poor spreadability. Spreadability is a term expressed to denote the extent of the area on which the gel readily spreads on application to the skin. The spreadability of the formulation was found in the range of 29.840 to 75.6 g.cm/sec. After studying the spreadability of the formulation, it was found that as the concentration of the gelling agent increases, spreadability decreases values of spreadability are shown in Table 6. The viscosity of the emulgel was found in the range of 11,220 to 19,680 cps. As the shear stress is increased, the normally disarranged molecules of the gelling material are caused to align their long axes in the direction of the row. Such orientation reduces the internal resistance of the material and hence decreases the viscosity of all formulations was found to be in a given range formulation (F9) show less viscosity it might be due to the higher concentration of the surfactants and less consistency as exemplified in Table 6. After determining the drug content in the prepared formulation of the emulgel, it was found that 75.76 to 105% of the drug was present in the formulation, as illustrated in Table 6.

Skin Irritation Test

Skin irritation studies were carried out to evaluate the tolerability of the emulgel components after application. It was observed that BS loaded emulgel was very well tolerated by the albino rats, and no signs of erythema and/or edema were seen even after 3 days.

Skin Deposition Study

The value of the total deposition amount was used to evaluate the efficacy of formulations. In comparison with the drug in solution form, the total deposition amount increased about 7.3-fold in the case of emulgel formulation. When emulgel was used as a drug carrier, the total deposition amounts (0.981 ± 0.1 mg/cm^3) further increased 1.2~1.9-fold compared with the drug in solution form, indicating that the emulgel has even more potential for BS skin transportation. Hence, the skin deposition of BS in emulgel was observed to have higher deposition when compared to the pure drug in the solvent.

SEM

The surface morphology of the optimized emulgel formulation examined by SEM was illustrated in Figure 2. The emulgel formulation appeared as amorphous particles. When at ×1,000 magnification, it could be seen that presence of almost

Table 6: Evaluation of BS loaded emulgel

				Viscosity 50 rpm 64 spindle	
F. Code	*pH*	*Spreadability (g.cm/sec)*	*% drug content*	*%*	*CPS*
F1	6.7	75.76	99	93.6	18,720
F2	7	56.2	78	98.4	19,680
F3	7.09	71.2	105	99.2	11,220
F4	7.1	45.3	81	93.5	11,900
F5	6.2	29.4	59	97.7	19,400
F6	6.8	34.4	89	95.8	19,680
F7	6.56	45.22	71	93.7	11,220
F8	6.3	34	91	91.2	13,670
F9	7.01	45.3	90	97.8	1,100

Table 7: Comparison of diffusion parameters of optimized formulation with BS gel

Formulation	*Flux (Jss) (μg/cm²/hr)*	*(Kp) (cm/hr) × 10³*	*Permeability enhancement at 12 hr (μg/cm²)*
Emulgel F5	312.28	29.17	2,313.1
1% BS gel	105.3	12.3	1,091.1

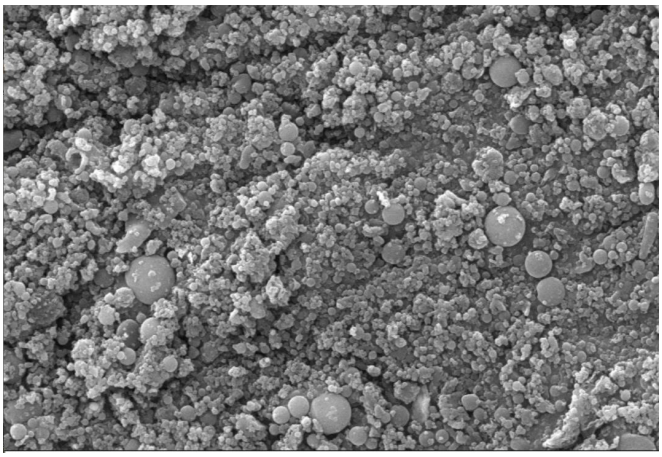

Figure 2: Morphological study of BS emulgel via SEM

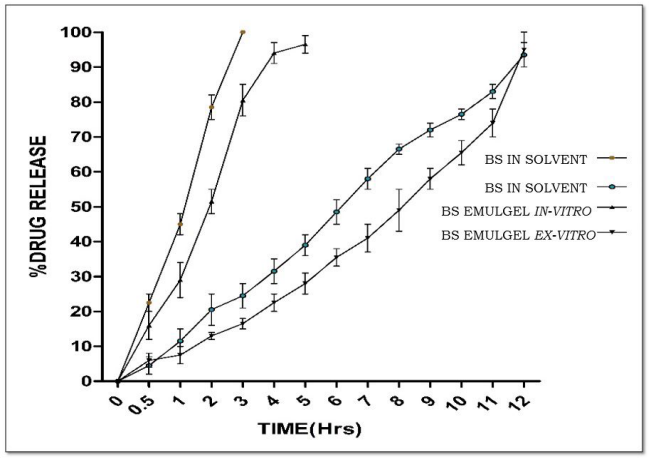

Figure 3: Percent drug release of BS loaded emulgel a comparison on *in vitro* and *ex vitro* release

spherical structures of emulgel, while in formulation surface morphology, was shown to be a fluffy and in an amorphous phase.

In vitro Drug Release

The *in vitro* diffusion profiles of BS from various emulgel formulations are represented in Figure 3. It was observed that all the formulation had become liquid at the end of experiments, indicating water diffusion through the membrane. The optimized batch F1 was opted for *in vitro* drug release evaluation. In general, it can be observed from the figures that emulgel showed better release as compared to a plain drug formulation in the solvent. The higher drug release was observed due to the presence of carbopol 934 at its low level and emulsifying agent at its high level. This led to an increase in the hydrophilicity of the emulgel, which in turn facilitated the penetration of the release medium into the emulgel.

Ex vivo Drug Release

The *ex vivo* release study of optimized emulgel compared with the 1% BS gel formulation. The optimized emulgel and BS gel showed 91 and 54% release at the end of 12 hours, respectively. The emulgel exhibited a higher flux and permeation coefficient, as compared to the BS gel formulation Figure 3. The results showed that the BS emulgel has the steady-state flux (Jss) 312.28 (μg/cm^2/hr) and apparent permeation coefficient (Kp) 29.17 (cm/hr) × 10^3 (Table 7). The permeability enhancement factor for emulgel when compared with 1% BS formulation was found to be 3.1.

Release Kinetics of BS Loaded Emulgel

The correlation coefficients (R2) values showed that the release of drugs from formulations best-fitted to Higuchi's kinetics, where it showed the highest (R2) values. The results point to sustained release characteristics with a dissolution pattern of drug release, the highest concentration of surfactant showed sustained dissolution, and the lowest concentration showed comparatively less sustained dissolution.[17]

Stability Studies

The emulgel was subjected to accelerated stability testing at 30 ± 2 and 40 ± 2ºC at 65 ± 5 and 75 ± 5 RH for formulation for 2 months. The results indicated that there were no significant changes in physical appearance, % viscosity, % spreadability, and drug content. The formulation of emulgel was found to be stable with respect to its physical appearance, % viscosity, % spreadability, and drug content.

CONCLUSION

In the present work, the attempt was made to formulate and evaluate BS loaded emulgel as an anti-rheumatoid agent. The results showed that the carbopol and other surfactant components had a significant effect on their physical, rheological, and *in vitro* drug release characteristics. Finally, the results of this work suggested that the BS loaded emulgel formulation can be considered as a promising formulation for the delivery of BS with the enhanced treatment of rheumatoid arthritis.

REFERENCES

1. Walsh JA, Pei S, Penmetsa GK, Sauer BC, Patil V, Walker JH, *et al*. Treatment patterns with disease-modifying antirheumatic drugs in U.S. Veterans with newly diagnosed rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis. J Manag Care Spec Pharm [Internet]. 2019 [cited 2020 Jul 15];25(11):1218–1226.
2. Brady LR. Textbook of Pharmacognosy. Fifth Edition. J Pharm Sci [Internet]. 1971 Jan 1 [cited 2020 Jul 15];60(1):165.
3. Houghton PJ. Book Reviews : Trease and Evans' Pharmacognosy 14th Edition William Charles Evans WB Saunders Company Ltd, 24-28 Oval Road, London NW1 7DX 1996, pp 612,

£40.00. Hum Exp Toxicol [Internet]. 1997 Mar 2 [cited 2020 Jul 15];16(3):182–183.
4. Roy NK, Parama D, Banik K, Bordoloi D, Devi AK, Thakur KK, *et al*. An update on pharmacological potential of boswellic acids against chronic diseases [Internet]. Vol. 20, International Journal of Molecular Sciences. MDPI AG; 2019 [cited 2020 Jul 15].
5. Siemoneit U, Pergola C, Jazzar B, Northoff H, Skarke C, Jauch J, *et al*. On the interference of boswellic acids with 5-lipoxygenase: Mechanistic studies in vitro and pharmacological relevance. Eur J Pharmacol [Internet]. 2009 Mar 15 [cited 2020 Jul 15];606(1–3):246–254.
6. Pang X, Yi Z, Zhang X, Sung B, Qu W, Lian X, *et al*. Acetyl-11-keto-β-boswellic acid inhibits prostate tumor growth by suppressing vascular endothelial growth factor receptor 2-mediated angiogenesis. Cancer Res [Internet]. 2009 Jul 15 [cited 2020 Jul 15];69(14):5893–5900.
7. Wiffen PJ, Xia J. Systematic review of topical diclofenac for the treatment of acute and chronic musculoskeletal pain [Internet]. Vol. 36, Current Medical Research and Opinion. Taylor and Francis Ltd; 2020 [cited 2020 Jul 15]. p. 637–650.
8. Full text of "The Theory And Practice Of Industrial Pharmacy By Lachman And Lieberman (3rd Editn)" [Internet]. [cited 2020 Jul 15].
9. Richards BL, Whittle SL, Buchbinder R. Neuromodulators for pain management in rheumatoid arthritis. Cochrane Database Syst Rev [Internet]. 2012 Jan 18 [cited 2020 Jul 15];1(1).
10. Sinha P, Srivastava S, Mishra N, Singh DK, Luqman S, Chanda D, *et al*. Development, optimization, and characterization of a novel tea tree oil nanogel using response surface methodology. Drug Dev Ind Pharm [Internet]. 2016 Sep 1 [cited 2020 Jul 15];42(9):1434–1445.
11. Ajazuddin, Alexander A, Khichariya A, Gupta S, Patel RJ, Giri TK, *et al*. Recent expansions in an emergent novel drug delivery technology: Emulgel [Internet]. Vol. 171, Journal of Controlled Release. Elsevier B.V.; 2013 [cited 2020 Jul 15]. p. 122–132.
12. Mohamed MI, Abdelbary AA, Kandil SM, Mahmoud TM. Preparation and evaluation of optimized zolmitriptan niosomal emulgel. Drug Dev Ind Pharm [Internet]. 2019 Jul 3 [cited 2020 Jul 15];45(7):1157–1167.
13. Perioli L, Pagano C, Mazzitelli S, Rossi C, Nastruzzi C. Rheological and functional characterization of new antiinflammatory delivery systems designed for buccal administration. Int J Pharm [Internet]. [cited 2020 Jul 15];356(1–2):19–28.
14. Kumbhar D, Wavikar P, Vavia P. Niosomal gel of lornoxicam for topical delivery: In vitro assessment and pharmacodynamic activity. AAPS PharmSciTech [Internet]. 2013 Sep [cited 2020 Jul 15];14(3):1072–1082.
15. Batheja P, Sheihet L, Kohn J, Singer AJ, Michniak-Kohn B. Topical drug delivery by a polymeric nanosphere gel: Formulation optimization and in vitro and in vivo skin distribution studies. J Control Release [Internet]. 2011 Jan 20 [cited 2020 Jul 15];149(2):159–167.
16. Aziz DE, Abdelbary AA, Elassasy AI. Investigating superiority of novel bilosomes over niosomes in the transdermal delivery of diacerein: in vitro characterization, ex vivo permeation and in vivo skin deposition study. J Liposome Res [Internet]. 2019 Jan 2 [cited 2020 Jul 15];29(1):73–85.
17. Wadher K, Patel D, Trivedi S, Umekar M. Design, Formulation and Evaluation of Topical Nimesulide Emulgel. Int J ChemTech Res. 2018;11(10):52–59.