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FABRICATION AND EVALUATION OF ELASTOSOMES OF *BOSWELLIA SERRATA* FOR TRANSDERMAL DRUG DELIVERY

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Boswellia serrata, Elastosomes, Span 80, Tween 80, Brij 30, Transdermal drug delivery

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ABSTRACT: The extracts of *Boswellia serrata* possess notable medicinal uses. *Boswellia serrata* is a highly lipophilic drug. It undergoes extensive hepatic first-pass metabolism. The $t_{1/2}$ is approximately 6 h. There are reported side effects with the administration of *Boswellia serrata*. This research work aims to fabricate Elastosomes which get hold of many desired features for transdermal drug delivery. The Elastosomes are prepared using thin-film hydration technique using edge activators like Span 80, Tween 80, and Brij 30. The prepared elastosomes are evaluated for entrapment efficiency percentage (EE %), particle size (PS), polydispersity index (PDI), zeta potential (ZP), deformability index (DI), drug release study, and permeation study. EF-10 was regarded as the optimized formulation with all the desired characteristics. The optimized formulation (EF-10) resulted in better prolong drug release and sustained therapeutic action as compared to the marketed product.

INTRODUCTION: *Boswellia serrata*, the gum resin possesses potent anti-inflammatory activity and also used in other diseases like, joint pain, hyperlipidemia, crohn's illness. The anti-inflammatory action of boswellic acids (Bas) is due to the inhibition of 5-lipoxygenase. It also plays a major part in targeting the microsomal prostaglandin (PG) E2 synthase-1 (mPGES-1) as well as cathepsin G (Cat G), thereby accompanying the inflammatory action of Boswellic acids [1]. *Boswellia serrata* is highly lipophilic drug. The systemic absorption of *Boswellia serrata* is very low as it undergoes extensive hepatic first-pass metabolism.

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The elimination half-life of *Boswellia serrata* is approximately 6 h. *Boswellia serrata* causes side effects like very mild gastrointestinal upset, urticaria, nausea, skin rashes, and contact dermatitis [2]. Thus, there is a need to overcome these issues to enjoy the beneficial effects of the drug. Transdermal applied Elastosomes stands as an eclectic option for all the issues regarding *Boswellia serrata*. Incorporation of *Boswellia serrata* into the elastosomes avoids direct contact to the skin, which can reduce skin rashes and contact dermatitis. The edge activators in the composition of elastosomes make the vesicles ultra deformable and aids in deeper penetration of *Boswellia serrata* through the skin layers. The elastosomes retard the drug release in a controlled manner. All these characteristics of elastosomes may increase the bioavailability of *B. serrata* [3].

The objectives of the present research work include: a selection of appropriate edge activators,

developing the novel elastosomal formulation, evaluate the prepared elastosomal formulations.

MATERIALS AND METHODS:

Materials: *Boswellia serrata* was obtained from West coast pharmaceutical works ltd. Cholesterol (CH) was purchased from Fisher scientific Pvt., Ltd. Span 60 (sorbitan monostearate), Sodium deoxycholate (SDC), Brij 30, Span 80, Tween 80 were purchased from Loba Chemie Pvt., Ltd. All other reagents were of analytical grade and were used as received.

Procedure for Fabrication of Elastosomes of *Boswellia serrata*: The method employed for fabrication of elastosomes of *Boswellia serrata* is thin-film hydration. Initially, bilosomes of *Boswellia serrata* were prepared using *Boswellia serrata* (1% w/w), 5% w/w of vesicle forming materials (Span 60 and CH) in ratio 5:1 and 5% w/w - 15% w/w of sodium deoxycholate.

Elastosomes: From the above-obtained bilosomes, the ones with better dissolution efficiency and entrapment efficiency were selected and added with edge activators (Brij 30, Tween 80, Span 80) in 1% w/w and 2% w/w to form elastosomes.

All the ingredients were accurately weighed into a round-bottom flask and dissolved in 10 mL of chloroform-methanol mixture (2:1). The obtained clear organic solution was reduced to thin lipid film by slow evaporation at 60 ºC under reduced pressure using a rotary evaporator for 30 min at 90 rpm. The dry film was then hydrated using 10 mL of double distilled water by rotating the flask in a water bath maintained at 60 ºC for 30 min at 150 rpm using the same apparatus under normal pressure to form milky dispersion of *Boswellia serrata* elastosomes. The obtained suspension was then sonicated for 15 min using a probe sonicator at room temperature for particle size reduction. The prepared formulae were left overnight at 4 ºC and then used for further characterization [3, 4, 5].

TABLE 1: FORMULA TABLE FOR EF1 TO EF5 FORMULATIONS

S. no.	Ingredients	Quantity (mg)				
		EF1	EF2	EF3	EF4	EF5
1	*Boswellia serrata* extract	100	100	100	100	100
2	Span 60	400	380	360	340	320
3	Cholesterol	100	95	90	85	80
4	Sodium deoxycholate		25	50	75	100
	Total			600		

TABLE 2: FORMULA TABLE FOR EF6 TO EF11 FORMULATIONS

S. no.	Ingredients	Quantity (mg)					
		EF6	EF7	EF8	EF9	EF10	EF11
1	*Boswellia serrata* extract	100	100	100	100	100	100
2	Span 60	340	340	340	340	340	340
3	Cholesterol	85	85	85	85	85	85
4	Sodium deoxycholate	75	75	75	75	75	75
5	Brij 30	5	10	-	-	-	-
6	Tween 80	-	-	5	10	-	-
7	Span 80	-	-	-	-	5	10
	Total				600		

FIG. 1: PREPARED ELASTOSOME FORMULATION

Characterization of *Boswellia serrata* Elastosomes:

Entrapment Efficiency (EE%): The free *Boswellia serrata* was separated from the prepared elastosomes by centrifugation of 5 mL of the vesicular suspension at 6000 rpm for 1 h at 4 ºC using a refrigerator centrifuge. The resultant supernatant was separated, properly diluted, and analyzed for free *Boswellia serrata* concentration spectrophotometrically at λ_{max} 249 nm [3].

Drug EE% was determined according to the following equation:

EE% = Entrapped amount of drug × 100 / Total amount of drug

Particle Size (PS), Polydispersity Index (PDI), and Zeta Potential (ZP): The average PS, PDI, and ZP of the prepared elastosomes were determined using Malvern-Zetasizer-nanosize-nano- instrument.

Measurement of Vesicular Elasticity in Terms of Deformability Index (DI): The vacuum extrusion method was used for assessment of the elasticity of the bilayer for the prepared elastosomes. The vesicular dispersions were diluted (10 folds) before extrusion through a 0.22-micron pore size MCE filter under the constant pressure of 300 mm Hg. DI was determined according to the following equation

$$DI = J (r_v / r_p)^2$$

Where J -the weight of dispersion extruded in 10 min, r_v -the size of vesicles after extrusion (nm), r_p- the pore size of the barrier (nm).

Transmission Electron Microscopy (TEM): The morphology of the optimal elastosomes was visualized using Hitachi-7500 model-Germany. A drop of the undiluted dispersion was stratified on a carbon-coated copper grid and then left to dry at room temperature. Finally, the air-dried sample was visualized at different magnifications at room temperature (25 ºC) [3].

***In-vitro* Release of *Boswellia serrata* Elastosomes:** A dialysis method was selected for determination of the release profiles of *Boswellia serrata* from the prepared elastosomes. Dialysis membrane of molecular weight of 12,000-14,000 Da was soaked in double-distilled water overnight before use for the experiment. An accurate amount of elastosomes vesicular dispersion, equivalent to 1.5 mg drug, was placed in the pre-soaked dialysis bag which was then clamped and placed in a beaker containing 50 mL of pH 7.4 phosphate buffer as a receptor compartment to simulate body physiological conditions.

The study is carried at room temperature, with continuous stirring at 100 rpm using a magnetic stirrer and at specified time intervals (initially for 30 min and later for each hour), aliquots of 5 ml were withdrawn from receptor compartment and replaced by an equal volume of fresh medium to preserve sink condition during the release study. The samples were properly diluted and analyzed for *Boswellia serrata* concentration spectrophotometrically at λ_{max} 249 nm [3].

***Ex-vivo* Permeation Studies:** The optimized formula was subjected to an *ex-vivo* permeation study. Rat's skin was carefully excised. Subcutaneous tissues and adhering fats were removed by rubbing with cotton. The excised full-thickness skin samples were equilibrated by soaking in PBS solution pH 7.4 at 4-8 ºC about 1 h before beginning the experiment. Skin samples were then sandwiched securely between the donor and receptor compartments of a vertical Franz diffusion cell (3.14 cm^2). SC was exposed to ambient condition (donor compartment) while the dermal side was batched with 50 mL of PBS pH 7.4 (receptor compartment) with temperature adjusted at 32 ºC. The donor compartment was charged with 1mL of one of the selected formulae, namely; the optimal elastosomes, under non-occlusive conditions. At predetermined time intervals (0.5, 1, 2, 4, 5, 6, 8, 12, and 24 h), samples from the receptor fluid (3 mL) were withdrawn and the cell was refilled by an equal volume of freshly prepared receptor fluid. The samples were properly diluted and analyzed for *Boswellia serrata* concentration spectrophotometrically by measuring the ultraviolet (UV) absorbance at λ_{max} 249 nm [3].

The flux J_{max} was calculated using the formula:

J_{max} = Amount of drug permeated / Time × area of membrane

ER = J_{max} of the nanovesicles / J_{max} of the drug suspension control

Where, J_{max} – Flux; ER - Enhancement ratio

RESULTS AND DISCUSSION:

Standard Curve for *Boswellia serrata* Extract:

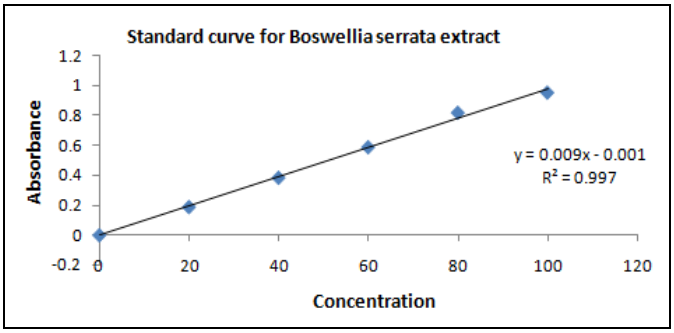

FIG. 2: CALIBRATION CURVE FOR *BOSWELLIA SERRATA* EXTRACT

Entrapment Efficiency (EE %) of Prepared Formulations: The entrapment efficiency of the first 5 formulations EF1 to EF5 ranged from 75% to 98%. The entrapment efficiency of plain niosomes (EF1) reveals the almost 98% drug is entrapped into the prepared vesicles. The EE% for EF2 to EF5 showed that the EE% reduced comparatively to the EF1. The EF4 showed the highest EE% among the prepared formulations.

The EF4 was selected for further proceedings because of its highest EE%. The EE% of EF6 to EF11 ranged from 57% to 87%. The EF6 containing Brij 30 as edge activator showed the highest EE%, which may be due to its (Brij 30) alkyl chain length. The EE% may be influenced by the edge activators' alkyl chain length and HLB. The amount of the edge activator also influenced the EE%. The formulations with edge activator added in 2%w/w showed less EE% than those with 1%w/w may be due to the amount of edge activator destabilized the bilayer of the vesicle leading to pore formation or may be due to solubilization of the drug and diffusion through the aqueous media [3].

TABLE 3: ENTRAPMENT EFFICIENCY (EE %) OF PREPARED FORMULATION

S. no.	Formulation code	EE%
1	EF1	98.6
2	EF2	75.44
3	EF3	95.6
4	EF4	95.8
5	EF5	75.84
6	EF6	80.56
7	EF7	69.3
8	EF8	73.8
9	EF9	57.42
10	EF10	87.72

Particle Size (PS), Polydispersity Index (PDI), and Zeta Potential (ZP): The lipophilic edge activators (Span 80) resulted in small size vesicles comparatively with the other edge activators (Brij 30 and Tween 80) employed for the work. The hydrophilic edge activator Tween 80 resulted in the larger vesicles because of the increasing water uptake by the vesicles.

The PDI of vesicles formed with Brij 30 is highly polydisperse in comparison to vesicles formed with Tween 80 and Span 80.

The zeta potential values of the prepared elastosomes indicate that these are stable vesicles [3, 6, 7].

TABLE 4: PARTICLE SIZE (PS), POLYDISPERSITY INDEX (PDI), AND ZETA POTENTIAL (ZP)

S. no.	Formulation code	Particle size (nm)	PDI	Zeta Potential (mV)
1	EF1	1010	0.515	-52.7
2	EF2	3409	0.217	-72.3
3	EF3	4623	0.409	-73.7
4	EF4	3948	0.310	-71.7
5	EF5	4314	0.070	-74
6	EF6	1037	0.415	-75.9
7	EF7	1563	0.399	-70.2
8	EF8	1285	0.400	-67.7
9	EF9	1682	0.356	-72.5
10	EF10	450	1.000	-71.5
11	EF11	380.8	0.474	-76.7

Deformability Index (DI): The elastosomes obtained are 300nm in size.

The DI of the elastosomes was calculated using the formula

$$DI = J (r_v / r_p)^2$$

Where, J = 10mg, r_v = 300 nmr_p= 200 nm

TABLE 5: DEFORMABILITY INDEX (DI) OF OPTIMIZED FORMULATION

S. no.	Formulation	DI	Inference
1	EF 10	22.5 mg	The elastosomes are deformed to some extent due to the presence of edge activator

TEM: The TEM image depicts that the prepared elastosomes are non-aggregating vesicles.

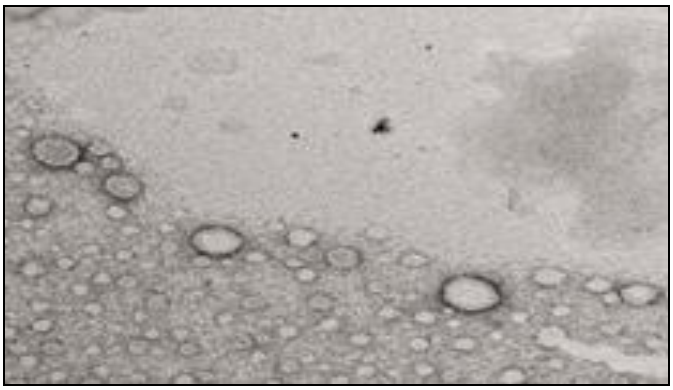

FIG. 3: TRANSMISSION ELECTRON MICROGRAPH OF EF 10

***In-vitro* Release of *Boswellia serrata* Elastosomes:** The prepared vesicles released the *Boswellia serrata* extract up to 12 h. The presence of cholesterol in equal amounts in all formulae prevents drug leakage from the vesicular. Therefore the elastosomes could retard the drug release [3].

TABLE 6: *IN-VITRO* RELEASE OF BOSWELLIA SERRATA ELASTOSOMES

S. no.	Time in hours	EF1	EF2	EF3	EF4	EF5
1	0	0	0	0	0	0
2	0.5	5.28	7.74	11.67	10.8	10.3
3	1	6.45	9.73	12.5	13.02	11.7
4	2	6.69	12.04	12.6	13.24	12.7
5	3	7.98	13.39	12.71	24.51	13.51
6	4	8.29	14.62	14.68	28.87	14
7	5	9.27	17.5	17.13	29.3	14.8
8	6	10.75	19.22	40.73	35.87	15.91
9	8	12.16	23.1	52.4	45.21	17.75
10	12	15.72	31.02	65.88	63.882	21.37

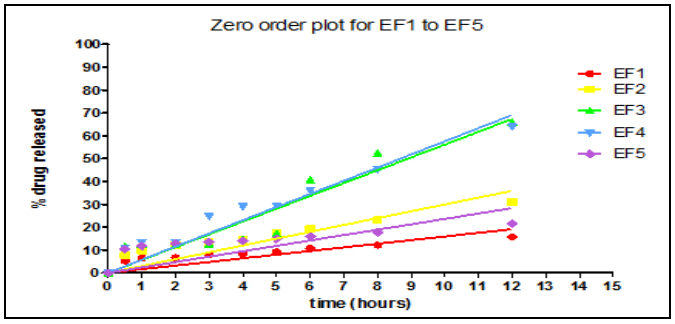

FIG. 4: ZERO ORDER PLOT FOR EF 1 TO EF 5

TABLE 7: *IN-VITRO* RELEASE OF *BOSWELLIA SERRATA* ELASTOSOMES

S. no.	Time in hours	EF6	EF7	EF8	EF9	EF10	EF11
1	0	0	0	0	0	0	0
2	0.5	13.3	18.24	15.38	18.34	12.34	14.28
3	1	17.78	22.02	20.73	27.46	17.13	18.87
4	2	18.89	36.21	27.64	38.24	19.99	27.18
5	3	29.02	39.34	36.67	43.86	25.43	31.14
6	4	42.38	47.45	45.33	48.19	29.02	43.71
7	5	45.43	52.8	47.91	55.38	35.47	47.27
8	6	52.89	61.09	57.4	62.75	42.75	55.38
9	8	68.19	76.85	72.61	78.6	51.41	70.49
10	12	98.1	107	102	108	72.06	100

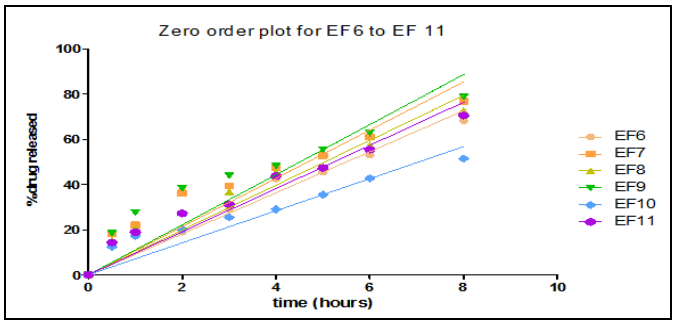

FIG. 5: ZERO ORDER PLOT FOR EF 6 TO EF 11

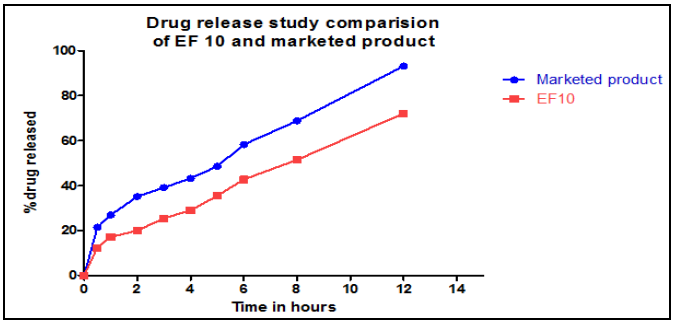

FIG. 6: DRUG RELEASE COMPARISON OF EF 10 AND MP

Ex-vivo Permeation Studies:

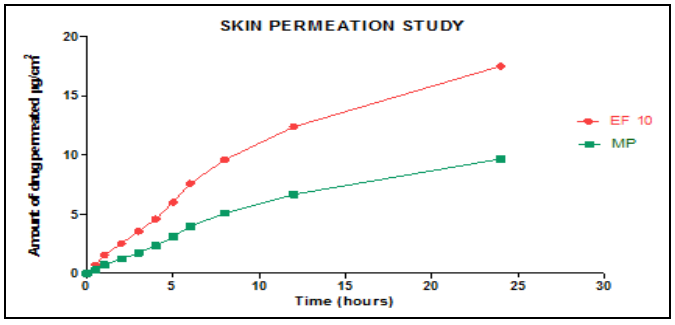

FIG. 7: SKIN PERMEATION STUDY

TABLE 8: CUMULATIVE AMOUNT OF DRUG PERMEATED

S. no.	Time in hours	Cumulative amount of drug permeated (mg)	
		EF-10	Marketed product
1	0	0	0
2	0.5	0.721	0.293
3	1	1.566	0.740
4	2	2.539	1.221
5	3	3.558	1.740
6	4	4.602	2.327
7	5	6.005	3.092
8	6	7.602	3.976
9	8	9.593	5.092
10	12	12.368	6.675
11	24	17.490	9.658

TABLE 9: FLUX AND PERMEABILITY COEFFICIENT VALUES OF EF 10 AND MARKETED PRODUCT

S. no.	Product	Parameter	Value
1	EF-10	Flux	0.232 mg cm^{-2} hr^{-1}
		Permeability coefficient	0.0232 cm^{-2} hr^{-1}
2	Marketed product	Flux	0.128 mg cm^{-2} hr^{-1}
		Permeability coefficient	0.0008 cm^{-2} hr^{-1}
3	Enhancement ratio	Permeability coefficient of EF10 / Permeability coefficient of MP	29

SUMMARY: The elastosomal formulations were successfully prepared by thin-film hydration method using span 60, cholesterol, sodium deoxycholate, and edge activators (Brij 30, Tween 80, Span 80). The calibration curve of Boswellia serrata in PBS (pH 7.4) was plotted, and it was observed that perfect linearity between the concentration of the drug and absorbance was obtained in the range of 20 -100 µg/ml. Among the elastosomal formulations, EF-10 was regarded as the optimized formulation with all the desired characteristics. The particle size of the formulation was 380.8 nm, PDI was 1.000, and zeta potential is -71.5. The entrapment efficiency in 91.52%. EF-10 showed controlled drug release (73.44%) up to 12 hours. Skin permeation study results show that the enhancement ratio (ER) of EF 10 formulation was 29 times more than that of the marketed product. The optimized formulation (EF-10) resulted with better prolong drug release and sustained therapeutic action as compared to the marketed product.

CONCLUSION: These results established the controlled and prolonged delivery of *Boswellia serrata* from elastosomal formulation through transdermal drug delivery.

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CONFLICTS OF INTEREST: Nil

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