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Original Article

Development and Optimization of Solid Lipid Nanoparticle Based Gel of Desoximetasone

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ABSTRACT

Background: The present study enlightens to enhance the residence time and prolonged release of the desoximetasone by incorporating it into solid lipid nanoparticles (SLN), prepared by hot melt homogenization process. The desoximetasone loaded SLN were incorporated into gel for topical application. **Materials and Methods:** The preliminary trial batches were carried out by varying the concentration of Poloxamer 188 and lipid concentration. The prepared solid lipid nanoparticles were evaluated for particle size and % entrapment efficiency. From preliminary batches, the levels of Poloxamer 188, Glyceryl Monostearate and Homogenization speed were selected. Desoximetasone loaded SLN were optimized by box-behnken design by Design Expert 10.0.1.0 software. **Results:** Optimization was done to study influence of X1-amount of lipid, X2-surfactant concentration and X3-speed of homogenization on particle size(Y1), polydispersity index(Y2) and % entrapment efficiency(Y3). From overlay plot, 3.330 g (X1), 0.542 g (X2) and 20930 rpm (X3) were selected. It was observed that there was influence of independent variables over dependent variables. Transmission Electron Microscopy was performed to physically check prepared SLNs. It was observed that majority of SLNs were in the range of 150-200nm. Various parameters like pH, Spreadability, Viscosity, % drug release in 24 hrs of optimized batch was found to be 7.1 ±0.04, 40.99 ± 0. 32g.cm/sec, 10255 ± 18.78 cps, 90.89 ± 0.52% respectively. Accelerated Stability study revealed that there were no significant changes observed upon accelerated stability conditions. **Conclusion:** Prolonged release of desoximetasone was achieved by preparing desoximetasone loaded SLN based gel for topical application.

Keywords: Box-behnken design, Psoriasis, SLN, Topical dosage form.

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INTRODUCTION

Desoximetasone (Pregna-1,4-diene-3,20-dione,9-fluoro-11,21-dihydroxy-16-methyl-, (11β,16α)-9-Fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione) is a Corticosteroid drug.[1] Corticosteroids stabilizes leukocyte lysosomal membranes and it inhibits macrophage accumulation in inflamed areas. Desoximetasone is very widely used in the treatment of psoriasis.[2] Topical corticosteroids can be absorbed from intact healthy skin. However, there are many hindrances to absorption of corticosteroids from the skin.[3] Psoriasis is a lifelong autoimmune ailment which is characterized by white to red color patches of abnormal skin with patches of itchy and scaly.[4,5] The term psoriasis derived from Greek word "Psora" which means "itch". Psoriasis is a chronic skin disease, which occurs to about 2% of the population.[6] Psoriasis is mostly inherited and is categorized by crusty, erythematous plaques that expand in a relatively equal distribution. Psoriasis majorly affects scalp, soles, knees, fingers, palms, elbows and underneath the breast and genitals.[7,8]

Solid lipid nanoparticles [SLNs] contain lipid phase dispersions which is stabilised by surfactant in water phase. The API is incorporated in the lipid phase. The main difference between a nano-emulsion and SLN dispersion is that in the former, lipids are in a liquid state, whereas in SLNs, as its name implies, lipids are in a solid state. SLNs are submicron-sized lipid particles in which, the liquid lipid is replaced by a solid lipid. Advantages of SLNs are large surface area, small size, high drug loading. SLNs are an attractive approach to enhance the action or activity of pharmaceuticals, nutraceuticals and other materials.[9] SLNs are being extensively studied for novel colloidal drug carrier.[10] Objective of the study is to reduce the dosing frequency of desoximetasone topical application. Dosing frequency of desoximetasone for psoriasis is twice a day.[2,3] SLN based formulations are used for extending the drug release.[11] The objective of the study is to formulate SLN

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based desoximetasone loaded gel is prepared to extend the drug release for 24 hr for single day application.

MATERIALS AND METHODS

Materials

Desoximetasone was procured from Gonane Pharma Private Limited, Ahmedabad. Methanol was procured from Thomas Baker, Mumbai. Glyceryl monostearate was procured from Chemdyes Corporation, Rajkot. Carbopol 934 was procured from Ozone International, Mumbai. Poloxamer 188 was procured from Analab fine chemical, Mumbai. Triethanolamine was procured from Astron chemicals, Ahmedabad. All chemicals and solvents were of analytical reagent grade.

Preliminary Trial Batches

Screening of type and concentration of surfactant, Concentration of lipid, Homogenization speed, Homogenization time

Tween 80 and Poloxamer 188 (0.2, 0.5, 1.0 %w/v) were added into the aqueous phase in different concentrations for the preparation of SLN. Screening of type and concentration of surfactant, concentration of lipid, homogenization speed and homogenization time were done from the observations of entrapment efficiency (%) and particle size (nm). The surfactant, lipid concentration of Glyceryl monostearate, homogenization speed and time that showed lowest particle size and high % entrapment efficiency were selected.

Optimization by using Box-Behnken experimental design

The solid Lipid Nanoparticle was optimized by Box-Behnken experimental design. Amount of lipid (%w/v) (X_1), Concentration of Surfactant (%w/v) (X_2), Homogenization Speed (rpm) (X_3) were selected as independent variables. Particle size (nm) (Y_1), Poly dispersity index (Y_2) and Entrapment efficiency (%) (Y_3) were selected as dependent variables.

Evaluations of desoximetasone loaded solid lipid nanoparticles

Particle Size and Poly Dispersity Index (PDI)

The particle size and poly dispersity index (PDI) of SLNs were measured by particle size analyzer (Nano ZS, Malvern Instruments Ltd., Malvern, UK). The sample was diluted until solution was free from large particles and the resulting solution was analyzed for particle size and PDI.[11]

Zeta Potential

Zeta Potential of SLNs was measured by Zeta analyzer (Malvern Instruments Ltd., Malvern, UK).[11]

Transmission Electron Microscopy

The morphological examination of desoximetasone Loaded SLN was performed with Transmission Electron Microscopy (Philips, Holland).[11]

Entrapment Efficiency (EE)

The entrapment efficiency (EE) of the SLNs was determined by indirect method wherein the amount of un-entrapped drug in the aqueous surfactant solution i.e., supernatant after centrifugation at 22,000 rpm for 45 min was determined, against the total amount of drug added to the formulation. The supernatant was diluted appropriately with methanol and analyzed by using Shimadzu UV Spectrophotometer (UV-1900i) at 239.40 nm. The below mentioned formula was used for the calculation of entrapment efficiency:

$$\% \text{ Entrapment Efficiency} = [(Wi - Wf) / Wi)] \times 100$$

Where, Wi = amount of drug initially used in the formulation

Wf = amount of drug in the supernatant (free drug)[11]

Formulation of desoximetasone loaded SLN-bearing gel

Desoximetasone - SLN was incorporated into gel system using distilled water and Carbopol 934 as gelling agent. 0.75% w/v Carbopol 934 was dissolved in SLN dispersion. It was stirred for 10 min at 1500 rpm and kept overnight at 4°C. After one day, this mixture was stirred at 1500 rpm. It was neutralized by drops of Triethanolamine. Prepared gel was allowed to stand overnight to remove entrapped air.[12]

Evaluations of desoximetasone loaded SLN-bearing gel

pH and Visual appearance

The pH of gel batch was determined using a pH meter. Visual appearance was done to check clarity of prepared desoximetasone - SLNs gel.[13]

Spreadability study

Spreadability was performed on the basis of "slip-drag" method. 2.5 gm of gel was placed on ground slide which was fixed on the wooden block. Another glass slide was placed on ground slide with a hook. 100g of weight was placed on the hook and the time (seconds) was noted till the top slide covers a distance of 7.5 cm. Test was carried out in triplicates.[14]

The spreadability (S) was calculated using the following formula:

$$S = M \times L / T$$

M is weight applied on the top of the glass slide,

L is the length of glass slide,

Table 1: Independent and dependent variables with actual units.

Translation of coded value in actual units			
Independent variables	**Variable level**		
	Low (-1)	**Medium (0)**	**High (+1)**
Amount of lipid (%w/v) (X_1)	2%	3%	4%
Concentration of Surfactant (%w/v) (X_2)	0.4%	0.6%	0.8%
Homogenization Speed(rpm)(X_3)	15,000	20,000	25,000
Dependent variable			
Particle size (nm) (Y_1)			
Poly dispersity index (Y_2)			
Entrapment efficiency (%) (Y_3)			

T is the time

Viscosity

The viscosity of gel was determined by using Brookfield DV-I Prime viscometer with spindle S92 at 20rpm. The procedure was repeated three times.

In vitro drug diffusion study

In vitro drug diffusion study was studied by Franz diffusion cell. Diffusion membrane (rat skin) was immersed in receptor compartment having phosphate buffer (pH 5.5) as diffusion medium. Temperature kept was 37 ± 2°C. Diffusion cell assembly was kept on magnetic stirrer. 1 g gel was placed on diffusion membrane in donor compartment. The content was stirred using magnetic stirrer at 50 rpm. Sampling was made at time intervals 15min, 30 min, 1, 2, 4, 6, 8, 12 and 24 hr. Withdrawn samples was replaced by equal volumes of same fresh medium. These samples were analysed using Shimadzu UV Spectrophotometer (UV-1900i) at 242.40 nm.[15]

Skin irritation study

Skin irritation study was carried out according to OECD 404 guideline and was approved by The Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA No. ROFEL/IAEC/2022/09).

It was performed on albino rats (*n*=3) (male). Rats were divided into three groups: (a) negative control, (b) test formulation and (c) positive control. 0.5 g of formulation was applied to the shaved area of rat for 24 hr. After 24 hr, visual inspection of the rats of was done. Rats were observed for the production of any irritant responses such as erythema, edema, and irritation after a single topical application.[13,16,17]

Accelerated Stability study

The accelerated stability study was carried out for the optimized formulation. The sample of gel was packed in the suitable container and placed in the stability chamber at 40±2°C/75±5% for a period of a one month. Sampling was taken at a predetermined time interval for determination of appearance, pH, viscosity, drug content and *in vitro* diffusion study.[11]

RESULTS

Preliminary Trial Batches

Screening of type and concentration of surfactant, Concentration of lipid, Homogenization speed, Homogenization time. Based on preliminary trial batch data, Poloxamer 188 showed better entrapment efficiency (63.23±0.46%) and low particle size (157.2±11.47 nm) as compared to tween 80. So poloxamer 188 was selected for further study. Glyceryl monostearate was selected 3% w/v as lipid concentration because it showed lowest particle size (157.2±11.47 nm) and high entrapment efficiency (63.23±0.46%). Homogenization speed and time was selected 20000 rpm and 15min because at that speed and time showed high entrapment efficiency (64.75±0.46%) and lowest particle size (136.4±21.68 nm). From the preliminary study, the levels selected were 2-4 % *w/v* and 0.4-0.6% *w/v* and 15000-25000 for amount of lipid, concentration of surfactant and homogenization speed respectively. The levels selected for further study are given in Table 1.

Optimization by using Box-Behnken experimental design

A three-factor, three levels box-Behnken statistical experimental design with twelve experimental runs with one centre point (13 batches) was done for optimization of the formulation. Actual values of formulation as per Design expert (10.0.1) software. For all experimental design batches of desoximetasone loaded SLN, responses like %Entrapment Efficiency, particle size and polydispersity index were evaluated and tabulated in Table 2.

Polynomial equations obtained for each responses are as below.

Polynomial full model equation of X_1, X_2 and X_3 on Particle Size (nm) (Y_1):

$$Y_1 = 133.10 + 60.65X_1 - 39.88\ X_2 - 160.60\ X_3 + 6.32X_1X_2 - 5.67X_1X_3 + 17.28\ X_2X_3 + 99.09\ X_1^2 + 40.84\ X_2^2 + 121.59X_3^2$$

Table 2: Experimental runs and observed responses in Box-Behnken experimental design.

Batch No.	Amount of lipid (%w/v) (X_1)	Conc. of surfactant (%w/v) (X_2)	Speed of homogenizer (rpm) (X_3)	% Entrapment Efficiency (%)	Particle size(nm)	PDI
SLN1	2	0.4	20000	64.72±0.42	269.6±30.46	0.312±0.032
SLN2	4	0.4	20000	70.02±0.70	364.3±25.37	0.363±0.027
SLN3	2	0.8	20000	57.12±0.95	169.1±17.33	0.278±0.013
SLN4	4	0.8	20000	65.12±0.19	289.1±18.69	0.320±0.017
SLN5	2	0.6	15000	64.71±0.52	439.8±22.94	0.384±0.023
SLN6	4	0.6	15000	72.97±0.65	586.4±27.53	0.411±0.031
SLN7	2	0.6	25000	57.95±0.76	132.5±11.36	0.229±0.014
SLN8	4	0.6	25000	62.11±0.90	256.4±16.38	0.295±0.017
SLN9	3	0.4	15000	72.75±0.40	510.5±14.29	0.402±0.022
SLN10	3	0.8	15000	63.29±0.29	404.3±17.44	0.362±0.024
SLN11	3	0.4	25000	61.16±0.48	152.2±19.74	0.254±0.026
SLN12	3	0.8	25000	56.7±0.84	115.1±26.46	0.216±0.021
SLN13	3	0.6	20000	64.08±0.46	133.1±12.73	0.241±0.018

All values are Mean ± SD (n=3)

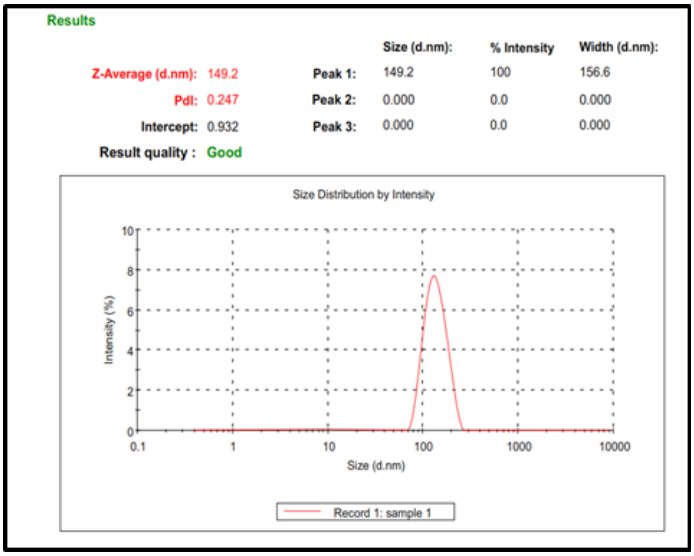

Figure 1: Particle size of optimized batch.

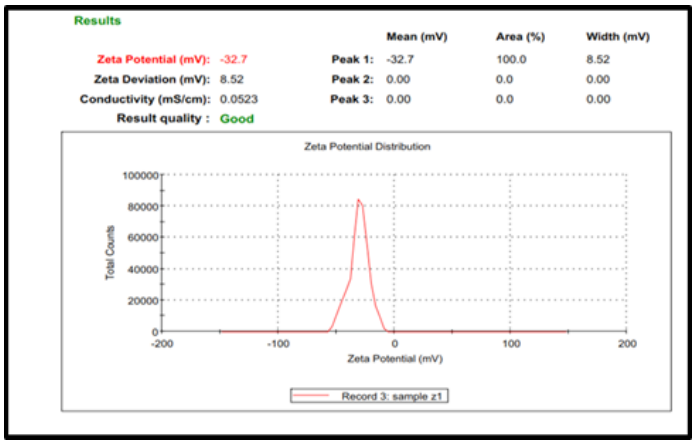

Figure 2: Zeta potential of optimized batch.

Polynomial full model equation of X_1, X_2 and X_3 on Polydispersity Index (Y_2):

$$Y_2 = 0.24 + 0.023X_1 - 0.019X_2 - 0.071X_3 - 2.250E{-}003\,X_1X_2 + 9.750*10^{-3}X_1X_3 + 5*10^{-4}X_2X_3 + 0.049X_1^2 + 0.028X_2^2 + 0.040X_3^2$$

Polynomial reduced model equation of X_1, X_2 and X_3 on %Entrapment Efficiency (Y_3):

$$Y_3 = 64.08 + 3.22X_1 - 3.30X_2 - 4.47X_3 + 0.68X_1X_2 - 1.03\,X_1X_3 + 1.25X_2X_3 + 0.56X_1^2 - 0.40X_2^2 - 0.21X_3^2$$

Evaluations of desoximetasone loaded solid lipid nanoparticles

The particle size and poly dispersity index (PDI) of SLNs were found to be 149.2±11.37 and 0.247±0.014 respectively and shown in Figure 1. Zeta Potential of SLNs was found to be -32.7mv shown in Figure 2. Transmission Electron Microscopy was performed to physically check prepared SLNs. It was observed that majority of SLNs were in the range of 150-200nm as shown in Figure 3. The % entrapment efficiency (%EE) of the SLNs was found to be 64.79±0.016.

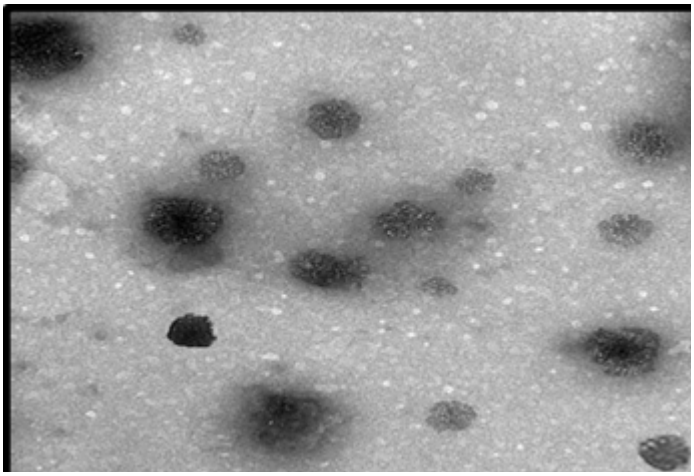

Figure 3: Transmission electron microscopy of optimized solid lipid nanoparticle of desoximetasone.

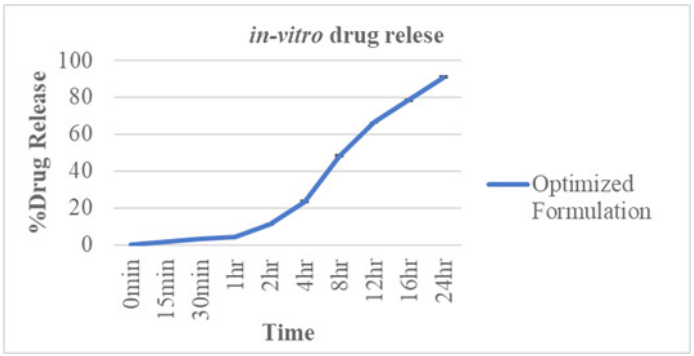

Figure 4: *In vitro* drug release study of optimized formulation.

Table 3: Various Evaluations of desoximetasone Loaded SLN Based Gel.

Sl. No	Evaluations	Result
1	Appearance	White colour
2	pH	7.1±0.04
3	Drug content (%)	98.12±0.44
4	Viscosity (cP)	10255± 18.78
5	Spreadability (g.cm/sec)	40.99 ± 0.32
6	*in vitro* drug release at 24 hr(%)	90.89 ± 0.524

All values are Mean ± SD (*n*=3)

Evaluations of desoximetasone loaded SLN-bearing gel

Appearance and pH

Appearance and pH of desoximetasone loaded SLN based gel are shown in Table 3.

Spreadability and Viscosity

Spreadability and viscosity of desoximetasone loaded SLN based gel are shown in Table 3.

In vitro drug release

In vitro drug release study of optimized formulation shown that the drug release was extended for 24 hr and it showed 90.89 ± 0.524 drug diffused at 24 hr as shown in Figure 4.

Skin irritation study

There was no apparent sign of erythema, oedema and redness on the rat skin which indicated the safety of the formulation. The formulation appeared to be safe for topical use.

Accelerated stability study

Accelerated stability study of optimized batch revealed that there was no significant change in physical parameters when stored at temperature and humidity condition of 40 ± 2°C/ 75 ± 5% RH respectively for 30 days. The Appearance, pH, Viscosity, Spreadability, Drug content and *in vitro* drug release study showed no significant difference from initial formulation. After completion of one-month stability study.

DISCUSSION

Desoximetasone is a corticosteroid drug which is used for the treatment of the Psoriasis disease. Recommended frequency for desoximetasone cream application is twice a day.[2,3,5] Present work focuses to develop prolonged release desoximetasone solid lipid nanoparticles based gel, which helps to provide higher drug loading and sustained delivery of drug. The preliminary studies were carried out by varying concentration of various surfactants, lipid, homogenization speed and time for preparation of solid lipid nanoparticles. On the basis of % entrapment efficiency and particle size data, independent variables were selected.

It was observed that Poloxamer 188 showed better entrapment efficiency and low particle size as compared to tween 80. High surfactant concentration showed low entrapment efficiency because, at high surfactant concentration, the drug diffuses into the vehicle liquid which is water. And very low surfactant concentration led to larger SLNs because at low concentration of surfactant, the emulsified globules relatively larger. And therefore, the optimized range was selected for surfactant, which was further optimized. Higher lipid concentration led to higher entrapment efficiency. But, if lipid concentration is further increased, it leads to larger particles. Same way, very high homogenization speed led to low entrapment efficiency and low homogenization speed resulted in larger particles. Therefore, the optimized range was selected for homogenization speed, which was optimized later. Optimization of formulation was done using Box-behken design with help of Design Expert 10.0.1.0 software. All prepared batches of SLN were evaluated for various parameters. The relationship

among variables revealed that up to certain limit, increase in lipid concentration decreases particle size and further increase of lipid concentration results into increase in particle size.[12,13] As surfactant concentration increases, particle size decreases but at higher concentration of surfactant, drug starts to get dissolved more in water media and it shows lower entrapment efficiency. As speed of homogenization increases, particle size decreases.[12,13] Therefore, optimization of the formulation was necessary to find optimum values of each factors, which finally gives lowest particle size and highest % entrapment efficiency. From overlay plot, batch at 3.330% w/v for X_1, 0.542% w/v for X_2 and 20930 rpm for X_3 was selected as optimized formulation. Transmission Electron Microscopy was performed to physically check prepared SLNs. It was observed that majority of SLNs were in the range of 150-200 nm. Optimized SLNs were incorporated into gel and its evaluations were performed. *In vitro* drug release studies revealed that prepared SLN based gel showed extended drug release. Skin irritation study revealed that there was no apparent signs of erythema, oedema and redness on the rat skin which indicated the safety of the formulation. So, the formulation was appeared to be safe for topical use.[16] Accelerated stability study of optimized batch revealed that there was no significant change in physical parameters when stored at temperature and humidity condition of 40 ± 2°C/ 75 ± 5% RH respectively for 30 days. The Appearance, pH, viscosity, spreadability, drug content and *in vitro* drug release study showed no significant difference from initial formulation.

CONCLUSION

Current research successfully developed desoximetasone loaded SLN based gel which shows extended drug release. The prepared gel was found to be stable under accelerated stability conditions and safe for topical application.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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