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Original Article

Enhancing Oral Bioavailability of Isotretinoin by Using Solid Lipid Nanoparticles (SLNs)

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ABSTRACT

Aim: Isotretinoin (ISTN) is a retinoid analogue and known as 13-cis retinoic acid. It is approved for the treatment of Acne vulgaris. Research work was done to improve bioavailability of Isotretinoin by preparing solid lipid nanoparticles and comparison of research formulation with commercially available formulation of Isotretinoin. Central Composite Design (CCD) from response surface methodology was used for test formulation optimisation. **Materials and Methods:** The test formulation was characterised for particle size, zeta potential, differential scanning calorimetry, drug entrapment efficiency and drug release from Solid Lipid Nanoparticles (SLN). Compritol 888 ATO was used as lipid for the formulation development. Lutrol F68 (poloxamer 188) was used as surfactant. Soy lecithin was also used to stabilize the formulation as it can increase the film forming properties of nanoparticles. Independent parameters, drug lipid ratio (X1) and homogenization speed (X2), were checked at three different levels by using CCD of response surface methodology. **Results:** *p*-values (0.003 and 0.000) in ANOVA tables showed the substantial impact of both independent parameters on dependent parameters. Output of central composite design recommended the level of X1 and X2 as 1 for maximum desirability. The optimized formulation was characterized for particle size, zeta potential, differential scanning calorimetry, drug entrapment efficiency and drug release from SLNs. **Conclusion:** Optimum percentage of the drug to oil phase ratio and higher homogenizer speed significantly impacted the particle size along with drug release.

Keywords: Isotretinoin, Solid Lipid Nanoparticles, Central Composite Design, Response Surface Methodology, *in vitro* drug release.

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INTRODUCTION

Isotretinoin (ISTN) is an analogue of retinoids as 13-cis retinoic acid. In addition to its success in curing acne, it has also shown promising results in other therapeutic areas.[1] Isotretinoin has chemical similarities to the two substances retinoic acid and vitamin A's retinol. The molecular weight of this yellow to orange crystalline powder is 300.44.[2] Solubility is highest in chloroform, lowest in alcohol/isopropyl alcohol and non-existent in water.[3] The only chemical that addresses the majority of acne's underlying causes is isotretinoin. The capacity to affect cellular-cycle progression, differentiation of cells, cell survival, and death is the primary driver of this behaviour. Isotretinoin's ability to decrease sebum production is due to its ability to do these things. There is a decrease in both surface and ductal acne as a result of this. The anti-inflammatory effects of isotretinoin are well-documented.[4] Isotretinoin oral suspension has a high absorption rate and a biphasic post-absorptive profile. In several trials, the metabolite 4-oxo-isotretinoin had a longer half-life of elimination than Isotretinoin. Unfortunately, 4-oxo-isotretinoin cannot be given to humans at this time. Isotretinoin has been approved for use in the treatment of severe acne, and it is often used for this purpose.[5] Isotretinoin is also used to treat hidradenitis suppurativa and rosacea by certain dermatologists.[6] Isotretinoin is only available by prescription in the United Kingdom when managed by a specialist dermatologist.[7] The immune system relies on retinoids, which are also powerful immunomodulators. In contrast to conventional immunosuppressants, their physiological effects are maintained even at high pharmacological doses, allowing them to suppressively govern a wide range of autoimmune disease states.[8] There is no regeneration of neural cells or other tissues without retinoids. The therapy of Alzheimer's disease and other neurodegenerative illnesses may benefit from the creation of retinoids that are highly selective for particular RARs. A recent study highlighted the important functions of retinoids in the treatment of neurodegenerative disorders such as amyotrophic lateral sclerosis, Alzheimer's disease, and schizophrenia.[9] After

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autologous stem cell transplantation, children with high-risk neuroblastoma who respond to first treatment had better event-free and overall survival when Isotretinoin medication was added.[10] Isotretinoin's physiochemical and biopharmaceutical characteristics were taken into account when formulating the solid lipid nanoparticles formulation. Drug delivery, clinical care, and other industries are quickly using SLNs technology. The capacity of SLNs to entrap medicines is useful for medications targeting the body's secondary and tertiary systems.[11,12]

MATERIALS AND METHODS

Materials

Isotretinoin, the drug, was provided as a free sample by Sun Pharmaceuticals. The products Compritol 888 ATO and Lutrol F68 (poloxamer 188) were acquired. Nikhil Chemical helped by supplying free samples of their soy lecithin. Thermo Fisher Scientific supplied both the HPLC-grade methanol and ethanol. Milli-Q RC equipment (Millipore Corporation, Bedford, MA, USA) was used to create deionized water.

Experimental Design

The best possible formulation was achieved by using a response surface technique. Using Minitab version 21, a central composite design was implemented for the experiments. Particle size (Y1) and drug release (Y2) were analyzed as a function of two independent variables: the drug to oil ratio (X1) and the homogenization speed (X2). Table 1 displays independent variables with three levels and dependent variables with their limits.[13-15]

Preparation of Isotretinoin SLNs

ISTN solubility was measured in various solid lipids. The solid lipid shown maximum Isotretinoin solubility was used for formulation development. Central composite design was selected from various techniques available for experimental design. The correlations among independent and dependent variables were analysed by Minitab version 21 software. Drug release (Y2) and particle size (Y1) were improved in ISTN formulations. Both the drug-to-oil ratio (X1) and the surfactant concentration (X2) were considered independent variables. The formulation was optimized by the creation of experiments using independent variables. We used a high shear homogenization procedure to get the SLN ready. To prepare the medication, the necessary amount was combined with the solid lipid in around 2 mL of ethanol and heated to 80°C. Using a magnetic stirrer; we mixed soy lecithin and surfactant into distilled water and heated the mixture to 80°C. After the ethanol was gone, the water phase was added to the lipid phase at 80°C, drop by drop. Sonication was applied for 10 min to the set-up mixer. Next, a high-pressure homogenizer was used to process the coarse emulsion in three separate cycles. Distilled water was used to modify the volume after being pushed through a 0.45-micron membrane placed directly over the dispersion.[16-19]

Characterization of test formulations

Optimized ISTN formulation was characterized for following parameters. Each test was performed five times to remove and testing error.

Particle size and zeta potential

Malvern Zetasizer Nanoseries nano-ZS was used to analyze particle size and distribution. The sample cell (quartz cuvette) was inserted in the sample holder unit, the test formulation was diluted, and a measurement was obtained. At 25°C and a scattering angle of 90°, the zeta potential was determined using dynamic light scattering. In order to evaluate the zetapotential and determine the particle size of the SLN dispersion, the solution was diluted 20 and 50s times, respectively.[20,21]

Differential scanning calorimetry

Differential Scanning Calorimetry (DSC) is used to evaluate the physical state of the nano-formulated substance. Using a Shimadzu DSC-60 Differential Scanning Calorimeter, thermograms of ISTN, surfactant, co-surfactant, and dried nanosuspension were recorded between 40 and 300°C at a heating rate of 10°C/min and a discharge of 40 mL/min of nitrogen gas.[22,23]

Drug Entrapment efficiency

Ultracentrifugation was used to evaluate SLNs for their ability to entrap drugs. Ultra filtration tubes were prepared by adding 0.5 mL of ISTN-SLNs and centrifuging them at 12,000 rpm for 15 min at 4°C. HPLC was used to determine the concentration of the medication in the supernatant. The free drug-bearing supernatant. The effectiveness of drug entrapment was evaluated using the formulas below:[24]

Table 1: Central composite experiment design.

Component		level	Responses	Constraints
Drug to Oil ratio (X1)	Homogenizer Speed (X2)			
0.1	14000	1	Particle size (Y1)	Minimum
0.2	10000	0		
0.3	6000	-1	Amount of drug Release (Y2)	Maximum

Table 2: Experimental formulations and observed responses according to design.

Sl. No.	Pt	X1	X2	Y1	Y2
1	−−	-1	-1	326.2	753.7
2	0A	0	1.414214	214.3	1787.4
3	−+	-1	1	273.5	1401.3
4	a0	-1.41421	0	302.1	994.9
5	0a	0	-1.41421	389.7	711.8
6	0	0	0	231.3	1398.6
7	++	1	1	172.6	1905.2
8	+−	1	-1	348.4	981.4
9	A0	1.414214	0	223.4	1489.1

Drug entrapment efficiency (%)=[(Amount of drug in the formulation − Amount of free drug)]/(Amount of drug used in formulation)]X100[25]

In vitro Drug Release from SLNs

Dialysis bag technique was used to determine the medication release from SLN in 0.1 M HCl, distilled water, pH 6.95, and phosphate buffer, pH 7.4. The dialysis bag serves as a reservoir for nanoparticles, from which the medicine may be released into the dissolving medium. Before usage, the bags were submerged in double-distilled water for 12 hr. Next, 2 mL of SLN dispersion was added, and the bag's ends were clamped together. The bags were putted in a conical flask and 50 mL dissolution solution was added. Following the removal of the medium from the conical flasks through filtration for analysis and the addition of new dissolving medium, the flasks were put in a static shaker at 37°C and a rate of 140 times per minute to maintain sink condition. The filtrate was analysed by the UV spectroscopy. The experiments were performed in the dark.[26,27]

RESULTS

Formulation Optimization

Based on solubility studies of compritol 888 ATO used as solid lipid. Lutrol F68 (poloxamer 188) was used as surfactant and soy lecithin was used as stabilizer. With the help of central composite design, effect of independent variables (X1 and X2) on dependent variables (Y1 and Y2) was analysed. During model development, one centre points was selected and suggested 09 randomized trials as shown in Table 2.

Response surface analysis

Response surface methodology has shown good results in the statistical optimization of various parameters to obtain the desired response. Two parameters i.e., drug and solid lipid ratio (X1) and homogenizer speed (X2) were selected as independent variables and investigated at three different levels. The observed responses of dependent variables (Y1 and Y2) against different levels of independent variables (X1 and X2) are available in Table 2. The 22 factorial designs shown in Table 2 have four axial points and a single center point. This equation for the necessary number of experiments (N) reads: 2k (22=4; star points)+2k (2x2=4; axial points)+1 (centre point). There were a total of nine tests performed, three for each of the two components over three levels and a central point, using the response surface approach with CCD. The responses of the two variables' coded values were modelled using polynomial regression, and the results were analyzed. Both particle size and drug release rate were shown to be influenced by the two variables examined in the regression equation represented by equations 1 and 2. Synergistic effects are indicated by a plus sign, whereas antagonistic effects are shown by a minus sign. By comparing the experimental data to the expected values and computing relative error (%), the chosen experimental design was verified. The relative error was determined using the following formula. Table 3 displays the relative error findings. The relative error was below 5%, demonstrating the accuracy of the design.

$$\text{Relative Error (\%)} = \frac{\text{Predicted Value} - \text{Experimental Value}}{\text{Predicted value}} \times 100$$

Particle size

Table 4 displays the results of an ANOVA performed on the CCD-obtained quadratic regression model for particle size. At the 95% confidence level, the model was shown to be significant for particle size with an F-value of 127.53 and a very small *p*-value of 0.001. The particle size interactions between X1 and X2 were statistically significant at the p =0.005 level. R2 and R2 (Adj) values for particle size were found to be 99.53 and 98.75 percent. It's a representation of how well the models match the data.

Equation 1

$$\text{Particle size (Y1)} = 231.30 + (-23.75)X1 + (-59.57)X2 + 15.71X1*X2 + 34.80X1*X1 - 30.78X2*X2$$

Response (Y1) was significantly affected antagonistically from both tested parameters. The above polynomial equation may

Table 3: Relative Error for experiments design precision.

Experiment No.	Particle size (Y1)			Amount of drug release (Y2)		
	Experimental Value	Predicted value	Relative Error (%)	Experimental Value	Predicted value	Relative Error (%)
1	326.2	333.819	2.28	753.7	756.8	0.41
2	214.3	216.6565	1.09	1787.4	1803.6	0.90
3	273.5	276.2307	0.99	1401.3	1391.8	-0.68
4	302.1	295.2373	-2.32	994.9	996.4	0.15
5	389.7	385.1435	-1.18	711.8	710.2	-0.22
6	231.3	231.3	0.00	1398.6	1398.6	0.00
7	172.6	167.181	-3.24	1905.2	1887.5	-0.94
8	348.4	347.8693	-0.15	981.4	976.3	-0.52
9	223.4	228.0627	2.04	1489.1	1502.2	0.87

Table 4: ANOVA regression model for particle size (PS) and percentage drug release (%DR).

Source	Degree of Freedom		Sum of squares		Mean square		F value		*p*-value	
	PS	% DR	PS	% DR	PS	% 0DR	PS	% DR	PS	% DR
Model	5		40449.3	1489206	8089.9	297841	127.53	1020.17	0.001	0.000
X1	1		4512.4	255793	4512.4	255793	71.14	876.15	0.003	0.000
X2	1		28387.9	1195466	28387.9	1195466	447.51	4094.75	0.000	0.000
X1*X2	1		3788.4	19072	3788.4	19072	59.72	65.32	0.005	0.004
X1*X1	1		669.9	16211	669.9	16211	10.56	55.53	0.048	0.005
X2*X2	1		3523.0	14603	3523.0	14603	55.54	50.02	0.005	0.006

be used to estimate the response from any certain value of independent variables. Homogenizer speed (X2) showed more negative impact on particle size as compared to drug to oil ratio. The increase in particle size is inversely proportional to both the independent variables which mean increasing the oil percentage and speed of homogenizer would result in decreased particle size. Contour and 3D-surface plots are depicted in Figure 1 to demonstrate the impact of independent variables on particle size. The optimization process was done to get the optimum level of X1 and X2 for particle size by using Minitab software. The anticipated goal for each parameter (drug to oil ratio (% w/w) and percentage of surfactant) was selected "within" the studied range. The ideal solutions for the input variables, along with optimization plots are shown in Figure 1. Using the Response surface optimizer, the maximum response at level 1 of X1 was 172.6 nm for particle size. To confirm the suggested values, the formulation was prepared with recommended levels of independent variables. The values of the X1 and X2 from the response optimizer suggestion were calculated and formulation was prepared by using them. The observed value of particle size was 174 nm.

Drug release

The results of the Analysis of Variance (ANOVA) for the quadratic regression model of particle size acquired from CCD are shown in Table 4. The model was statistically significant for the quantity of drug release at the 95% confidence level, with an F-value of 1020.17 and an extremely low *p*-value of 0.0001. The p-value for the interaction between X1 and X2 in terms of drug release was 0.004. R2 and R2 (Adj) values obtained for drug release were 99.94% and 99.84%, respectively. It is a measure of how well a given model fits the data.

Equation 2

$$\text{Percentage drug permeation}\ (Y2) = 1398.6 + 178.81X1 + 386.57X2 + 69.05\,X1*X2 + (-74.6)\,X1*X1 + (-70.8)\,X2*X2$$

Response (Y2) was significantly affected synergistically by both independent parameters. The above polynomial equation may be used to estimate the response from any certain value of X1 and X2. Homogenizer speed was the most relevant parameter as its coefficient (386.57) is bigger than the drug to oil ratio (178.81) coefficient. The drug release is directly proportional to the drug to (X1) oil ratio and (X2) percentage of surfactant in the optimized formulation.

Contour and response-surface plots are depicted in Figure 1 to demonstrate the impact of independent variables on drug release. Through the use of Minitab software, we were able to optimize X1 and X2 to achieve maximum medication permeability. Maximum responses at X1 and X2 levels 1 were 172.6 nm for particle size and

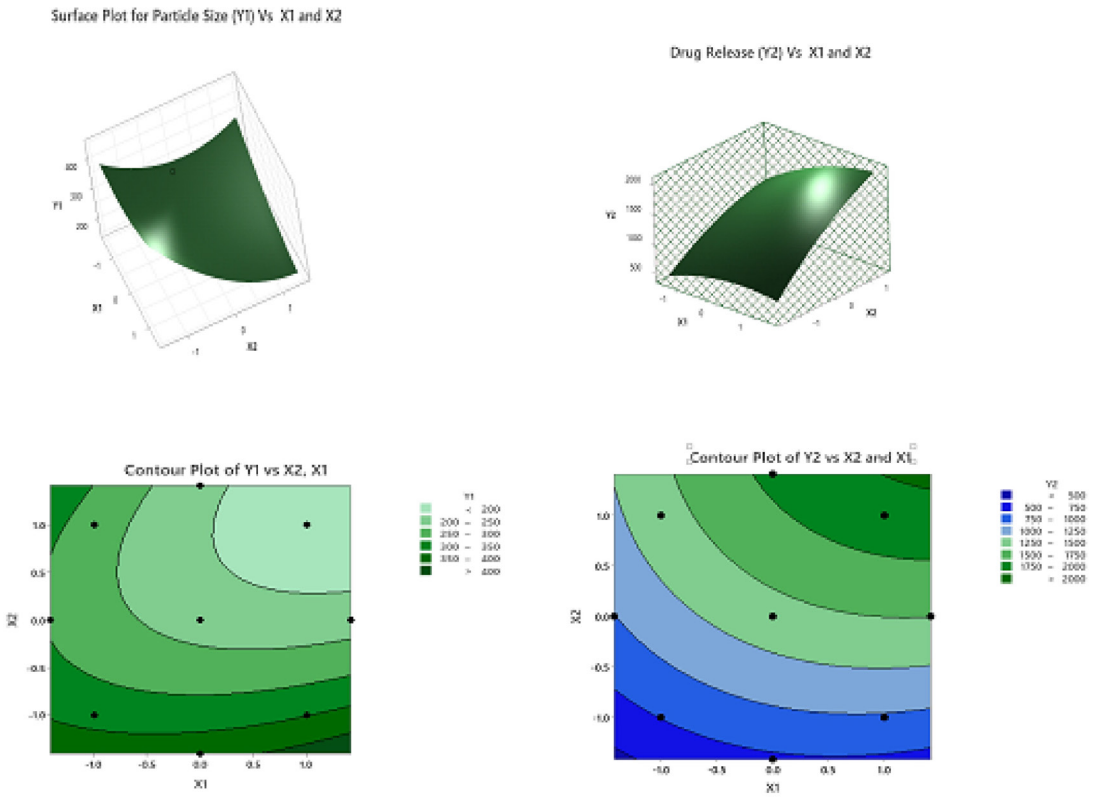

Figure 1: Surface and Contour Plots of Central Composite Design.

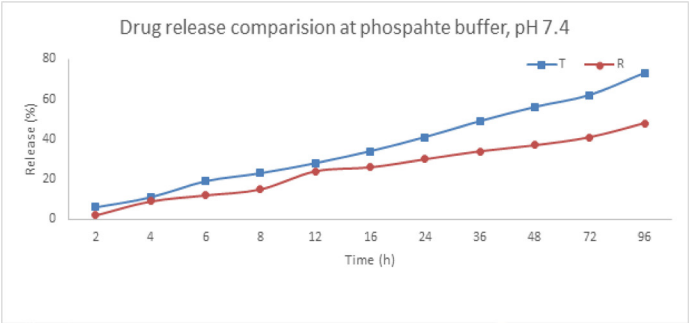

Figure 2: Drug release comparison between test and marketed formulation.

1905.2 ng/mL for drug release when using the Response surface optimizer. To confirm the suggested values, the formulation was prepared with recommended levels of X1 and X2. The values of the X1 and X2 from the response optimizer suggestion were calculated and formulation was prepared by using them. The experimental value of amount of drug release was obtained as 1905.2 ng/mL which is like the predicted value. Therefore, there is a strong correlation between predicted and experimental results under ideal circumstances.

Particle size and zeta potential

Using a Malvern Zetasizer Nanoseries Nano ZS (Malvern Instrument, UK), we determined that the average particle size was 174 7.18 nm, with a PDI of 0.27 0.67. Monodisperse and uniform SLNs have PDI values between 0 and 0.5. Generally, SLNs have PDI below 0.3 is acceptable. The particles size and distribution are satisfactory for nano size formulation.

Measurements were obtained after a nano suspension was diluted and applied to a sample cell (a quartz cuvette) in a sample holding device. Zeta potential was measured with same instrument. The observed zeta potential was 27.32±1.89 mV, which indicates the system is stabilized.

Differential scanning calorimetry

The Differential Scanning Calorimetry (DSC) thermograms of plain ISTN, oil phase, blank SLN and ISTN-SLN were obtained. Absorption peak of IST and compritol 888 ATO was at 179 and 88.1°C. Absorption peak of oil phase was not shifted which means SLNs had not impact on physical properties of oil phase. This removal of the endothermic peak of ISTN-SLNs suggests that the ISTN has been uniformly dispersed in an amorphous state, and that no ISTN crystals have formed as a result of the dispersion.

Drug Entrapment efficiency

The drug entrapment efficiency of ISTN was found as 90.66±1.66. During formulation development it was observed that entrap efficiency increased initially and reduce later. Surfactant did not show any impact on entrapment efficiency. A larger concentration of soy lecithin, which improves the nanoparticles' film-forming characteristics, resulted in a better entrapment efficiency. Soy

lecithin improves the safety as allergic reactions triggered by drugs in SLNs are reduced.

In vitro Drug Release from SLNs

Drug release from the SLN formulations and marketed product was compared and depicted in Figure 2. The rate of drug release is dependent on the pH of dissolution medium. The increased release rate was observed with increase of pH. Significant impact of drug to oil ratio and speed of homogenizer was observed ($p<0.05$).

DISCUSSION

A lot of techniques are available to improve oral absorption of drug having poor water solubility. However, incorporation of poorly soluble drug into SLNs is still need to explore. This research was conducted to determine whether or not orally administering poorly soluble medicines had a beneficial effect on absorption. The possible mechanism for improving oral absorption of ISTN by SLN is being discussed here. The formulation at micro level showed the improved peroral performance of poorly soluble drugs. The increased surface area and saturated solubility result from particles being shrunk to less than 400 nm in size. In addition, SLN shields the medicine from chemical and enzymatic breakdown, which slows its metabolism in the body. Multiple oxidized and conjugated metabolites quickly break down ISTN. By being a part of a solid lipid matrix, ISTN is protected from enzymatic breakdown after absorption. Response surface methodology's central composite design was applied to optimize the formulation. The impact of two independent parameters i.e., drug to oil phase ratio and homogenizer speed was evaluated on dependent parameters particle size and drug release. The dependent parameters were tested at three different levels. Homogenizer speed shown more impact on particle size and drug release which was evident with its higher coefficient when compared with drug to oil phase ratio. Both independent parameters significantly impacted the dependent parameters as observed *p*-values are less than 0.001. The observed R2 and R2 (Adj) for particle size and drug release was more than 99%. Both independent parameters had shown the maximum output at level 1. The final drug to oil phase ratio was 1:9 and surfactant percentage selected as 5. The developed formulation had particle size of 174.88 nm and approximately 78% drug release in 12 hr. The obtained particle size 174±7.18 nm and PDI of 0.27±0.67 are indicative of monodisperse and uniform SLNs. The SLN system was stabilised as obtained zeta potential was 27.32±1.89 mV. An amorphous distribution of ISTN was verified by the lack of an endothermic peak in ISTN-SLNs, indicating that no ISTN crystallized from the dispersion. The entrapment efficiency of SLN was observed as 90.66±1.66. The entrapment efficiency was improved with the higher concentration of soy lecithin which enhances the film-forming properties of nanoparticles. Soy lecithin provides the improved safety as allergic reactions causes by drugs in SLNs are reduced. The drug release rate and extend from developed formulation is much higher than the marketed formulation. As a result, SLNs provide a fresh angle on how to enhance the solubility of medications that have traditionally been difficult to work with. The insolubility of ISTN in water prevented the development of its parent formulation. However, some researches are ongoing for potential use of SLN for parental formulations.

CONCLUSION

In this research study isotretinoin solubility was enhanced by using solid lipid nanoparticles. SLN increases the surface area which helps to increase the solubility of a drug. Moreover, SLN is known for medicine degradation from chemical and enzymatic interaction. Response surface methodology was used to optimise the formulation. Independent parameters drug to oil ratio and homogenizer speed significantly impacted the particle size and drug release from formulation. p-value observed was less than 0.001 and both R2 was more than 99% for both dependent parameters. Oil to drug ratio was 1:9 and surfactant percentage selected as 5 % in final formulation. Dependent parameters i.e. particle size and drug released in 12 hrs were observed as 174.88 nm and 78 %, respectively. The entrapment efficiency was improved with the higher concentration of soy lecithin which enhances the film-forming properties of nanoparticles. Soy lecithin provides improved safety as allergic reactions caused by drugs in SLNs are reduced. The drug release rate and extent from developed formulation is much higher than the marketed formulation. As a result, SLNs provide a fresh angle on how to enhance the solubility of medications that have traditionally been difficult to work with.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AD: Alzheimer's disease; **ANOVA:** Analysis of variance; **CCD:** Central composite design; **CV:** Coefficient of variation; **DSC:** Dynamic scanning calorimetry; **DOE:** Design of experiment; **DSC:** Differential scanning calorimeter; **HPLC:** High Performance liquid chromatography; **ISTN:** Isotretinoin; **PDI:** Polydispersity Index; **RAR:** Retinoic acid receptors; **SLN:** Solid Lipid Nanoparticles; **UV:** Ultraviolet-visible spectroscopy.

SUMMARY

Isotretinoin (ISTN) is a retinoid analogue and known as 13-cis retinoic acid. It is approved for the treatment of Acne vulgaris and has potential in other therapeutic area as well. Isotretinoin is able to reduce sebum production significantly as it influences edogenesis, lowers surface and reduces ductal acnes. This study included the preparation of SLN to increase the drug's soluble form. Drugs are protected against chemical and enzymatic breakdown thanks to SLN as well. CCD was used for the formulation optimisation. Two independent parameters had shown the significant impact on the dependent parameters. The developed formulation was compared with the market formulation and test formulation released significantly higher drug.

REFERENCES

1. Abou Zommar GOH, Nofal A, Ibrahim ASM. Possible side effects of isotretinoin use in dermatology: Review Article. Egypt J Hosp Med. 2022; 89(1): 4562-5. doi: 10.21608/ejhm.2022.258686.
2. Layton A. The use of isotretinoin in acne. Dermato-Endocrinology. 2009; 1(3): 162-9. doi: 10.4161/derm.1.3.9364, PMID 20436884.
3. Patel MR, Patel RB, Parikh JR, Patel BG. HPTLC method for estimation of isotretinoin in topical formulations, equilibrium solubility screening, and *in vitro* permeation study. J Liq Chromatogr Relat Technol. 2011; 34(16): 1783-99. doi: 10.1080/10826076.2011.579218.
4. Kochhar DM, Christian MS. Tretinoin: a review of the nonclinical developmental toxicology experience. J Am Acad Dermatol. 1997; 36(3 Pt 2):S47-59. doi: 10.1016/s0190-9622(97)70060-4, PMID 9091508.
5. Khoo KC, Reik D, Colburn WA. Pharmacokinetics of isotretinoin following a single oral dose. J Clin Pharmacol. 1982; 22(8-9): 395-402. doi: 10.1002/j.1552-4604.1982.tb02692.x, PMID 6957421.
6. Nickle SB, Peterson N, Peterson M. Updated physician's guide to the off-label uses of oral isotretinoin. J Clin Aesthet Dermatol. 2014; 7(4): 22-34. PMID 24765227.
7. Goodfield MJD, Cox NH, Bowser A, McMillan JC, Millard LG, Simpson NB, *et al.* Advice on safe introduction and continued use of isotretinoin in acne in the UK 2010. Br J Dermatol. 2010; 162(6): 1172-9. doi: 10.1111/j.1365-2133.2010.09836.x, PMID 21250961.
8. Carratù MR, Marasco C, Mangialardi G, Vacca A. Retinoids: novel immunomodulators and tumour-suppressive agents? Br J Pharmacol. 2012; 167(3): 483-92. doi: 10.1111/j.1476-5381.2012.02031.x, PMID 22577845.
9. Shudo K, Fukasawa H, Nakagomi M, Yamagata N. Towards retinoid therapy for Alzheimer's disease. Curr Alzheimer Res. 2009; 6(3): 302-11. doi: 10.2174/156720509788486581, PMID 19519313.
10. Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, *et al.* Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J. 2010; 363(14): 1324-34. doi: 10.1056/NEJMoa0911123.
11. Mukherjee S, Ray S, Thakur RS. Solid lipid nanoparticles: a modern formulation approach for drug delivery system. Indian J Pharm Sci. 2009; 71(4): 349-58. doi: 10.4103/0250-474X.57282, PMID 20502539.
12. Tan ME, He CH, Jiang W, Zeng C, Yu N, Huang W, *et al.* Development of solid lipid nanoparticles containing total flavonoid extract of *Dracocephalum moldavica* L. and their therapeutic effect for *myocardial ischemia*–reperfusion injury in rats. Int J Nanomedicine. 2017; 12: 3253-65. doi: 10.2147/IJN.S131893, PMID 28458544.
13. Molpeceres J, Guzman M, Aberturas MR, Chacon M, Berges L. Application of central composite designs to the preparation of polycaprolactone nanoparticles by solvent displacement. J Pharm Sci. 1996; 85(2): 206-13. doi: 10.1021/js950164r, PMID 8683450.
14. Jain K, Sood S, Gowthamarajan K. Optimization of artemether-loaded NLC for intranasal delivery using central composite design. Drug Deliv. 2015; 22(7): 940-54. doi: 10.3109/10717544.2014.885999, PMID 24512368.
15. Mehrandish S, Mirzaeei S. Design of novel nanoemulsion formulations for topical ocular delivery of itraconazole: development, characterization and *in vitro* bioassay. Adv Pharm Bull. 2022; 12(1): 93-101. doi: 10.34172/apb.2022.009, PMID 35517876.
16. Silva AC, González-Mira E, García ML, Egea MA, Fonseca J, Silva R, *et al.* Preparation characterization and biocompatibility studies on risperidone-loaded solid lipid nanoparticles (SLN): high pressure homogenization against ultrasound. Colloids Surf B Biointerfaces. 2011; 86(1): 158-65. doi: 10.1016/j.colsurfb.2011.03.035, PMID 21530187.
17. Gupta S, Kesarla R, Chotai N, Misra A, Omri A. Systematic approach for formulation and optimization of solid lipid nanoparticle of efavirenz by high pressure homogenization using design of experiments for brain targeting and enhanced bioavailability. BioMed Res Int. 2017; 5984014. doi: 10.1155/2017/5984014, PMID 28243600.
18. Durán-Lobato M, Enguix-González A, *et al.* Statistical analysis of solid lipid nanoparticles produced by using high-pressure homogenization: a practical prediction approach. J Nanopart Res. 2013; 15: 1-4.
19. Li M, Zahi MR, Yuan Q, Tian F, Liang H. Preparation and stability of astaxanthin solid lipid nanoparticles which are based on stearic acid. Eur J Lipid Sci Technol. 2016; 118(4): 592-602. doi: 10.1002/ejlt.201400650.
20. Varenne F, Coty JB, Botton J, Legrand FX, Hillaireau H, Barratt G, *et al.* Evaluation of zeta potential of nanomaterials by electrophoretic light scattering: fast field reversal versus Slow field reversal modes. Talanta. 2019; 205: 120062. doi: 10.1016/j.talanta.2019.06.062, PMID 31450425.
21. Kovačević AB, Müller RH, Savić SD, Vuleta GM, Keck CM. Solid lipid nanoparticles (SLN) stabilized with the polyhydroxy surfactants: preparation, characterization and physical stability investigation. Colloids Surf A Physicochem Eng Aspects. 2014; 444: 15-25. doi: 10.1016/j.colsurfa.2013.12.023.
22. Knopp MM, Löbmann K, Elder DP, Rades T, Holm R. Recent advances and potential applications of modulated differential scanning calorimetry (mDSC) in drug development. Eur J Pharm Sci. 2016; 87: 164-73. doi: 10.1016/j.ejps.2015.12.024, PMID 26721421.
23. Lopes MS, Catelani TA, Nascimento ALCS, Garcia JS, Trevisan MG. Ketoconazole: compatibility with pharmaceutical excipients using DSC and TG techniques. J Therm Anal Calorim. 2020; 141(4): 1371-8. doi: 10.1007/s10973-019-09137-0.
24. Souto EB, Wissing SA, Barbosa CM, Müller RH. Development of controlled release formulation based on SLN and NLC for topical clotrimazole delivery. Int J Pharm. 2004; 278(1): 71-7. doi: 10.1016/j.ijpharm.2004.02.032, PMID 15158950.
25. Singh S, Dobhal AK, Jain A, Pandit JK, Chakraborty S. Formulation and evaluation of solid lipid nanoparticles of a water-soluble drug: zidovudine. Chem Pharm Bull (Tokyo). 2010; 58(5): 650-5. doi: 10.1248/cpb.58.650, PMID 20460791.
26. Weng J, Tong HHY, Chow SF. *In vitro* release study of polymeric drug nanoparticles: development and validation of a novel method. Pharmaceutics. 2020; 12(8): 732. doi: 10.3390/pharmaceutics12080732, PMID 32759786.
27. Kushwaha AK, Vuddanda PR, Karunanidhi P, Singh SK, Singh S. Development and evaluation of solid lipid nanoparticles of raloxifene hydrochloride for enhanced bioavailability. BioMed Res Int. 2013; 2013: 584549. doi: 10.1155/2013/584549, PMID 24228255.

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