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**INTRODUCTION** Acne vulgaris is a widespread skin disorder among adolescents, and it affects 90% of the individual at some point in their life<sup>1</sup>. Its chronic condition leads to an increase in sebum production, resulting in keratinization changes, inflammation under hair follicles by *Propionibacterium acnes*. Acne persists for a very long time with depressing consequences in adults<sup>2,3</sup>. Acne is commonly treated using benzoyl peroxide, topical antibiotics (erythromycin and clindamycin), and topical retinoid (tretinoin, isotretinoin, retinaldehyde, and retinoyl  $\beta$ -glucuronide)<sup>4</sup>.

Isotretinoin is a crystalline yellowish-orange powder with a faint odor<sup>5</sup>. The isotretinoin powder is soluble in chloroform and methylene chloride and sparingly soluble in water<sup>6</sup>. Isotretinoin incites apoptosis (cell death) in different parts of the body cells. Apoptosis may induce hippocampus cells, hypothalamic cells, meibomian gland, and vital in acne therapy in sebaceous gland cells<sup>3,7,8</sup>. Isotretinoin has modest interaction for retinoid X receptors (RXR) and retinoic acid receptors (RAR) but might transform intracellularly to metabolites that mimic an agonist RXR nuclear receptors and RAR<sup>9</sup>.

Isotretinoin is the exclusive acne drug available which influences all vital pathogenic action in acne; it differentiates from antibiotics treatments and considers its therapeutic efficacy in severe, nodulocystic cases. The repercussions of isotretinoin on sebum output can be short-term, or remission of the disease can be absolute and for an extended period<sup>10</sup>. Liposomes are small artificial vesicles of the spherical shape created from cholesterol and natural, nontoxic phospholipids<sup>11,12</sup>.

Due to their size and hydrophobic and hydrophilic character (besides biocompatibility), liposomes are promising systems for drug delivery. Liposomes are extensively used as carriers for numerous molecules in the cosmetic and pharmaceutical industries<sup>13,14</sup>. A liposomal drug delivery system was developed for isotretinoin using the spray drying technique<sup>15</sup>. Spray-drying using a two-fluid nozzle was tested to dry liposome preparations, i.e., liposomes composed of hydrogenated soy phosphatidylcholine (HSPC), distearoyl phosphatidylglycerol (DSPG), cholesterol, and isotretinoin. Isotretinoin other products are available in the market, such as isotretinoin suspension capsules which are expensive<sup>16</sup>.

Isotretinoin shows stability problems to overcome these problems and to prepare a cost-effective product to dry liposome of isotretinoin was prepared using spray drying technique<sup>17</sup>. Based on this background, this study aims to develop liposomal preparation of isotretinoin for acne by using the spray drying technique. **MATERIALS AND METHODS** Materials Isotretinoin was obtained from Sun Pharmaceuticals, Gurgaon, Haryana, India. All solvents (distilled water, methanol, and chloroform) were purchased from CDH (Central Drug House Pvt. Ltd, New Delhi, India).

Other ingredients include borate buffer, HSPC, DSPG, cholesterol, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), mannitol, propyl gallate, and phosphate buffer. The instruments used include the UV spectrophotometer (Shimadzu), mini spray dryer B-290 (Buchi), Eclipse E600POL microscope (Nikon), differential scanning calorimeter (DSC, Shimadzu), rotary evaporator, high-pressure homogenizer (HPH), and dissolution test apparatus type II (paddle). Methods Physical characterization of isotretinoin Solubility – The saturation solubility studies of class II model drug-like isotretinoin were conducted as per Biopharmaceutics Classification System (BCS) guidelines<sup>18</sup>.

An excess amount of isotretinoin was placed in pH borate buffer at room temperature and stirred until saturation point. After 24 hours, the sample was filtered, suitably diluted, and absorbance was taken at 346 nm against pH 8 borate buffer as blank on UV spectrophotometer. The excipient and drug solubility were observed in the solvent, i.e., water, methanol, and chloroform, to optimize the ratio of solvent combination, i.e., chloroform : methanol (1 : 1) and chloroform : methanol (2 : 1).

Quantitative estimation of isotretinoin – The UV spectrophotometric method was used to estimate the drug because the method was simple, economical, and gives reproducible results within acceptable limits. The double beam UV spectrophotometer was used for analysis<sup>19</sup>. Isotretinoin was dissolved in borate buffer pH 8.0 containing 0.5% cetrimide. The solution was scanned for maximum absorbance in a UV double beam spectrophotometer in the range from 200 to 400 nm, using the respective solution as a blank. Selection of lipids – Optimization batches were prepared to optimize the number of lipids.

Initially, the quantities were taken in 2 : 1 mmol of HSPC and cholesterol, respectively. The Amount of DSPG was kept constant at 0.16 mmol. Tests were carried out on three batches with variations in the number of HSPCs, as shown in Table I. Table I.

Batch	Ingredients	HSPC (mmol)	Cholesterol (mmol)	DSPG (mmol)
1	2	1	0.16	2
3	1	0.16	3	4
4	1	0.16	3	4

Excipients were dissolved in the solvent and then spray-dried by mini spray dryer B-290 with an inlet temperature of 70°C, the outlet temperature of 42°C, aspirator rate was kept at 70%, nitrogen pressure was at 2 kg/cm<sup>2</sup>, and pump rate kept at 5%.

The spray-dried powder was collected and dispersed in an appropriate amount of water and then observed under a microscope using a 50X lens. Drug loading – Pre-optimization studies of isotretinoin liposomal formulation were tried to formulate

along with the lipids, HSPC, DSPG, and cholesterol to optimize the drug loading for the isotretinoin liposome formulation. A review of the literature revealed that these were the lipids that can be used in formulation development.

Thus, for selection of the range, various pre-optimization trials were done with the exact quantities of lipids but with the increasing quantity of isotretinoin<sup>20</sup>, as shown in Table II. Table II. Pre-optimization trials of various batches

Batch	Ingredients	HSPC (MW 783.8 g/mol)	Cholesterol (MW 368.7 g/mol)	DSPG (MW 801 g/mol)	Isotretinoin (MW 300.4 g/mol)
1	4	1	0.16	0.25	2
2	4	1	0.16	0.5	3
3	4	1	0.16	1	4
4	4	1	0.16	1.4	5
5	4	1	0.16	2.2	6
6	4	1	0.16	3.1	

All ingredients were dissolved in chloroform : methanol (2 : 1) solvent and spray-dried at the same parameters used earlier in this study. Batches were manufactured with isotretinoin quantities of 0.25 mmol to 3.1 mmol to check the solubility of the drug in a given excipient. Resulted in dried drug lipid dry powder was dispersed in phosphate buffer pH 6.8 and observed for multivesicular vesicles and free drug crystals using a microscope with a 50X lens.

Differential scanning calorimetry – Differential scanning calorimetry experiments were performed with DSC. Sample of isotretinoin and spray dried liposomal formulation containing isotretinoin and lipids (HSPC, DSPG, and cholesterol) were submitted to DSC analysis. The analysis was performed on 5 mg samples sealed in standard aluminum pans. Thermograms were obtained at a scanning rate of 10°C/minutes. Each sample was scanned between 0°C to 200°C. The temperature of maximal heat capacity was defined as the phase transition temperature<sup>21</sup>.

Preparation of liposomal formulation of isotretinoin Isotretinoin liposomes were prepared by using a spray drying technique. The spray drying technique was employed through three different strategies, i.e., suspension spray drying (SSD), thin-film hydration and spray drying (TFHSD), and emulsion spray drying (ESD). Suspension spray drying The solution of suspension spray drying was prepared by dissolving HSPC, cholesterol, DSPG, and isotretinoin in the ratio of 4 : 1 : 0.16 : 3.1 mol, respectively.

These ingredients were dissolved in chloroform : methanol (2 : 1) solvent. The DSPG was dissolved in the solvent in the presence of heat 60°C to prevent aggregates formation. Ingredients other than DSPG are mixed with the swirling of the solution<sup>22</sup>. The suspension was spray-dried with a mini spray dryer B-290 combined with inert loop B-295 at the following parameter: inlet temperature 60-80°C; outlet temperature 38-45°C; aspirator rate at 50-70%; pump rate at 5-10%; and nitrogen pressure 2 kg/cm<sup>2</sup>. The dried powder so retained from the spray drier was characterized further. The batch was named SSD 1. Thin-film hydration and spray drying The TFHSD technique's objective was to overcome the hygroscopicity problem that was coming in the previous

SSD23.

The TFHSD was conducted in several steps. Preparation of solution – The solution for dispersion spray drying was prepared with the same composition and according to the optimized amount. This was done in the solution spray drying method. Antioxidants BHA and BHT was added within allowed daily intake limits. Thin-film formation using rotary evaporator – Thin-film of the solution containing formulation was the suitable organic solution formed using the rotary evaporator at the following parameters: bath temperature 450°C; RPM 30; vacuum 250-500 mm of Hg for 1 hour<sup>24</sup>. Hydration of thin-film with Buffer containing 5% mannitol – The hydration of the thin-film was prepared using phosphate buffers pH 6.8 and 5% mannitol in it. The hydration was carried out for 1-2 hours.

The appropriate amount of the buffer was put in the rotary evaporator vessel over the thin-film, so the formed process started again with temperature 50-55°C, and vacuum was applied. If a problem occurs in hydration, sonication was performed to recollect the total amount of material<sup>24</sup>. The above suspension was passed through the HPH to reduce the size of the particles in the suspension. Spray drying – The prepared suspension so obtained from HPH was then spray-dried using mini spray dryer B-290 with the following parameters: aspirator rate 70%; inlet temperature 80°C; outlet temperature 52°C; and pump rate 5%.

The spray drying was performed using air as well as nitrogen. The dried powder was collected and was analyzed. This technique was employed to overcome the hygroscopicity<sup>25</sup>. Only related substance characterization was done of TFHSD. The batch was named TFHSD 1. Emulsion spray drying Emulsion spray drying was the technique in which emulsion was prepared by emulsifying organic solvent containing drug and lipids with water containing mannitol using high-speed homogenization<sup>25</sup>. The ESD was performed in several steps. Preparation of the organic and aqueous phases – The organic phase and aqueous phase ratios were kept at 70% and 30%, respectively.

The organic solution was prepared with the optimized quantities of the Excipient and the drug. The composition used was HSPC : cholesterol : DSPG : isotretinoin (4 : 1 : 0.16 : 3.1 mol, respectively), BHA, BHT, and propyl gallate (within allowed daily intake limits). These all were mixed in the solvent of chloroform and methanol (2 : 1), making 5% w/w solution, and then processed further. Mannitol (2.5/5 times of drug quantity) was dissolved in a suitable amount of distilled water. High-speed homogenization – The aqueous solution was added drop-wise to an organic solution under high-speed homogenization for speed up to 18000 RPM, resulting in an emulsion<sup>26</sup>.

The homogenization was done for 5 minutes with breaks for 10 seconds after 2, 3, and 4 minutes in between to avoid overheating due to heat generation. Spray drying – The prepared emulsion was then spray dried using the following parameters: inlet temperature 70°C; outlet temperature 42°C; aspirator rate 70%; pump rate 5%; nitrogen pressure 2 kg/cm<sup>2</sup>; and humidity of room 55-60%. The spray-dried powder was collected and filled in the hard gelatin capsules, and analyzed further. The batch was named ESD 1.

Physical characterization of isotretinoin liposomal formulation Drug content – As much as 10 mg of spray-dried powder was dissolved in 100 mL of solvent, i.e., chloroform : methanol (2 : 1) in a 100 mL volumetric flask. As much as 2 mL was taken from this solution and diluted up to 10 mL with the solvent in a 10 mL volumetric flask. The absorbance of the resulting solution was measured at the maximum at 346 nm using a UV spectrophotometer<sup>27</sup>. The linearity equation obtained from the calibration curve was used to estimate isotretinoin in the liposomal formulations. Results were compared with the USP monograph limits.

In vitro release studies – The release rate of 40 mg capsule isotretinoin liposomal formulation was determined using type II dissolution test apparatus. The dissolution test was carried out using 900 mL of borate buffers pH 8 with pancreatin at 37±0.5°C and 100 RPM using a 40-mesh basket. Sample no. 108 (10 mL) was withdrawn from the dissolution apparatus and replaced with a fresh medium. Sample no. 109 was filtered through a 0.45 µm membrane and diluted to a suitable solvent. The absorbance of samples was measured at 346 nm using a UV spectrophotometer, and cumulative drug release was calculated<sup>28</sup>. Sample no. 110 drug release data were analyzed using PCP Disso software version 2.08.

The dissolution profile of all the batches was fitted to zero-order, first-order, Higuchi, Hixson-Crowell, as well as Korsmeyer and Peppas to ascertain the kinetic modeling of drug release, and the model with the highest correlation coefficient was considered to be the best mode. Results were compared with the USP monograph limits. Microscopy – Liposomal dispersion was prepared by dispersing spray-dried formulation in phosphate buffer pH 6.8 and was observed under 50X lens under Polarizing microscope. The microscopy revealed the particle size, shape of vesicles (regular or irregular), and free drug crystals<sup>29</sup>. The 50X resolution lens was used for the particle size analysis. In a microscope, 1 unit of the scale present on the lens was taken as 2µ.

The required amount of blend was reconstituted with the necessary amount of water, and then the slide was prepared and observed under a microscope. Related substances (detection of impurity) – This characterization was done to check impurities in the

prepared liposomal formulation of isotretinoin—5,6 epoxy-13-cis retinoic acid, tretinoin, and others unknown. Some impurities were observed with the related substance test of the liposomal formulation<sup>30</sup>. The results were compared with the USP monograph limits.

**RESULTS AND DISCUSSION** Physical characterization of isotretinoin Solubility studies – The isotretinoin was found to be yellowish-orange, crystalline powder with a faint odor that resembles vitamin A. The drug was insoluble in water, whereas it was soluble in the organic solvent, thereby suggesting it was lipophilic. Chloroform : methanol (2 : 1 respectively) was taken for the formulation as solvents. Isotretinoin exhibits solubility across the borate buffer pH 8. Therefore, it could be classified as a “less soluble” material. A review of the literature revealed that the drug exhibits high permeability.

According to BCS classification, if the highest dose of the drug was insoluble in aqueous media and exhibited high permeability, it was called a BCS class II drug<sup>18</sup>. Therefore, the isotretinoin falls under BCS class II. Selection of lipids – Excipient for isotretinoin liposomal formulation was selected based on maximum solubility, in which isotretinoin was found to be a lipophilic drug. Batches were prepared and observed under the microscope 50X lens for free drug crystals, and the shape and size of vesicles formed to determine the excipient ratios used. Batch no.

1 had shown the presence of free drug crystals while vesicles were irregular in shape. Batch no. 2 had also shown the presence of free drug crystals, and vesicles were also irregular in shape and size. Batch no. 3 had not shown any free drug crystals, but multivesicular structures were regular in round shapes. As observed, batch 3 excipient ratios were selected for the preparation of the liposomal formulation<sup>31</sup>. Clear vesicular structures with no free drug crystals found with HSPC : cholesterol 4 : 1. Therefore, the 4 : 1 ratio was found to be sufficient. Drug loading – Isotretinoin quantity of 3.1

mol resulted in powder blend, which contains 40 mg drug in 200 mg blend.

Hygroscopicity was observed, and for the collection of spray-dried powder, RH was maintained below 25%. The collected powder was filled in 00 sizes hard gelatin capsule with a suitable amount. Further increase in drug quantity leads to free drug crystals. The drug loading of various batches in different quantities was presented in Table III. Table III. Microscopic observation for drug loading Batch \_Isotretinoin quantity (mol)  
\_Observation \_ \_1 \_0.25 \_No free drug crystals were found. Multivesicular structures were observed but the powder was sticky because of relative humidity i.e. 60% \_ \_2 \_0.5

\_No free drug crystals, dry powder. Relative humidity maintained below 25%. Large multivesicular vesicles were found at 50X \_ \_3 \_1 \_ \_ \_4 \_1.4 \_ \_ \_5 \_2.2 \_ \_ \_6 \_3.1 \_ \_ \_



Differential scanning calorimetry – Differential scanning calorimetry study was carried out for isotretinoin and drug-loaded dry liposome's containing lipids (HSPC, DSPG, and cholesterol). The DSC thermograms of isotretinoin and drug-loaded dry liposomes were illustrated in Figures 1 and 2, respectively. The DSC thermogram of isotretinoin showed endothermic at 181.73°C. It proves that the isotretinoin was pure<sup>32</sup>.

The DSC thermogram of drug-loaded dry liposomes with lipids showed endothermic at 76.58°C. The DSC thermogram of isotretinoin-loaded liposomes composed of HSPC, DSPG, cholesterol, and isotretinoin in the ratio of 4 : 1 : 0.16 : 3.1, respectively, showed the disappearance of melting endothermic of isotretinoin and major endothermic was observed at 76.58°C. The absence of the melting endothermic of isotretinoin suggested significant interaction of isotretinoin with lipids leading to enhanced entrapment of the drug<sup>33</sup>. The isotretinoin was dissolved in lipids.

The incorporated isotretinoin was associated with lipids and interacted to a large extent with them. The DSC results of liposome's suggested enhanced entrapment efficiency of isotretinoin in a lipid bilayer. Microscopy – Microscopy of batches was done to observe particle size, shape, and free drug crystals. The particle size multivesicular vesicles of sizes 2 to 60µ were observed. Figures 3a and 3b of SSD 1 microscopy showed that multivesicular vesicles of drug solubilized lipids were found. Free drug crystals were not found. The drug was solubilized entirely in lipids.

In Figure 3c of TFHSD 1, microscopy-free drug crystals were found, and the size and shape of the vesicles were also irregular. Thus, the strategy was dropped, but beneficial points were taken into considerations from this strategy, such as this strategy was successfully able to remove hygroscopicity. In Figure 3d of ESD 1, microscopy large lipid vesicles in the aqueous medium were found. No free drug crystals were found.

In SSD 1, no free drug crystals were found, and the vesicles were also in regular shape and size, which states that the drug was utterly solubilized in lipids<sup>34</sup>. In ESD 1, large lipid vesicles were found, and no free drug crystals were found. Thus, both these strategies pass the microscopy test. In TFHSD 1, free drug crystals were found, and the vesicles were irregular in shape; this strategy fails the microscopy test.



/ Figure 1. Differential scanning calorimetry thermogram of isotretinoin / Figure 2.  
Differential scanning calorimetry thermogram of dry liposomes of isotretinoin and lipids

// a b // c d Figure 3.

The SEM images of SSD 1 (a and b), TFHSD 1 (c), and ESD 1 (d) taken at 20,000x magnification Physical characterization of isotretinoin liposomal formulation Drug content – The formulation should contain not less than 90.0% and not more than 110.0% of the labeled amount of drug according to the USP monograph [120]. The triplicate batches were prepared for every strategy, and the assay was also done in triplicate average best assay results<sup>35</sup>. Batch SSD 1 had shown drug content 96.6%, while batch ESD 1 had shown 91.1% of drug content. The assayed drug content in formulations ranges from 90.0 % to 110.0 %, which were under the USP limit.

**In vitro drug release** – The in vitro drug release studies were performed in borate buffer with pancreatin to determine the release of the drug. The dissolution profiles of all the formulations were determined and shown in Figure 4. The results were analyzed by plotting cumulative drug release/time. The dissolution was done in low intensity of light as the drug was light-sensitive. The dissolution was done in triplicates of each strategy. The average best results were shown in Figure 4—the dissolution profile of SSD 1 and ESD 1. According to the USP monograph, 70% of the drug should be released in 90 minutes.

Dissolution of SSD 1 batch slow-release, which did not fulfill the USP requirement as there was 61% release in 90 minutes. Dissolution of ESD 1 batch 95% release in 90 minutes fulfills USP requirement and shows immediate release action<sup>36</sup>. / Figure 4. **In vitro drug release profile** Related substances – The related substance analysis was done to detect impurity in the formulation, which was compared with the USP limits<sup>37</sup>. The analysis was done in triplicates of each batch, and the best results were given in Table IV. The analysis revealed that the impurities of batch SSD 1 and ESD 1 were according to the USP limits.

The impurities of batch THFSD 1 (using nitrogen; 1N and using air; 1A) were not found out of the limits of USP. Table IV. Related substance (impurity testing) data

Impurities	Limits (% w/w)	SSD 1	TFHSD 1	ESD 1	1N (nitrogen)	1A (air)
5,6-epoxy-13-cis retinoic acid (peak 1 and 2)	0.5	0.22 ± 0.1	0.11 ± 0.3	1.2 ± 0.5	0.05 ± 0.1	
Tretinoin	0.2	0.07 ± 0.2	0.38 ± 0.5	0.36 ± 0.3	0.14 ± 0.1	
Highest unknown	0.1	0.07 ± 0.1	0.07 ± 0.2	0.1 ± 0.1	0.05 ± 0.1	
Total unknown	0.5	0.24 ± 0.4	-	-	0.14 ± 0.3	
Total related substances	1.5	0.53 ± 0.2	-	-	0.33 ± 0.4	

**CONCLUSION** Dry liposomes of isotretinoin were successfully prepared using three different strategies of spray drying, i.e., SSD, TFHSD, and ESD. The formulation of each respective strategy was analyzed. Related substance (impurity study) revealed that the

impurities of SSD and ESD were under the USP limits, whereas the impurities of TFHSD were out of USP limits, so the formulation of two strategies SSD and ESD, were further analyzed. Therefore, a liposomal formulation of isotretinoin through ESD was found successful, time-effective, and cost-effective in comparison with the other two strategies.

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