



Research Article

FORMULATION AND EVALUATION OF BARICITINIB TRANSFERSOMES

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ABSTRACT

Transfersomes are specially optimized particles or vesicles, which can respond to an external stress by rapid and energetically inexpensive, shape transformations. The present study was carried out to use statistical techniques of quality by design to develop and optimize Methotrexate Transfersomes by conventional rotary evaporation sonication techniques. A32 full factorial design was used to understand the main effects and interaction of formulation variables. The relationship between the dependent and independent variables was further elucidated using contour plots. Then, experimental design combined with desirability functions to predict the desired quality.

A conventional rotary evaporation sonication technique was developed to prepare Baricitinib transfersomes using Phospholipon 90 G as a lipid (SPC) and SPAN 80 as an edge activator (EA). Preformulation studies proved the purity of drug and compatibility of drug and excipients was evaluated by DSC study. BCT loaded transfersomes was successfully formulated using 32 full factorial design and desirability function. The % entrapment efficiency, deformability index and particle size were highly dependent on the SPC: EA ratio, and BCT concentration for the preparation of BCT loaded Transfersomes. SPC: EA ratio and BCT concentration had a positive effect on % Entrapment efficiency and negative effect on deformability. But particle size was not much affected. Using contour plots, response surface plots and % Bias, formulation was optimized. Batch M5 (1:1PC: EA, 2%w/v BCT) is best batch among nine combinations. Surface morphology of transfersomes was evaluated by TEM study. A good interaction between drug and excipients were found with FTIR study of transfersomes. It was advisable to store BCT-TFS at refrigerated conditions (4±2 °C). Optimum drug: lipid ratio is 0.1-0.4. BCT-TFS was successfully optimized with experimental design and desirability function.

KEYWORDS: Baricitinib, transfersomes, BCT-TFS.

INTRODUCTION

Transfersome (TFS) is a term registered as a trade mark

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by the German company IDEAAAG, and used by it to refer to its proprietary drug delivery technology. The name means "carrying body", and is derived from the Latin word 'transferre', meaning to carry across, and the Greek word soma, for a „body“. A transfersome carrier is an artificial vesicle designed to be like a cell vesicle or a cell engaged in exocytosis, and thus suitable for controlled and, potentially targeted, drug delivery. Transfer some is a highly adaptable and stress-responsive, complex aggregate. Its preferred form is an ultra-deformable vesicle possessing an aqueous core surrounded by the complex lipid bilayer. Interdependency of local composition and shape of the bilayer

makes the vesicle both self-regulating and self-optimizing. This enables the transfersome to cross various transport barriers efficiently, and then act as a drug carrier for non-invasive targeted drug delivery and sustained release of therapeutic agents. The presence of surface-active agents in the transfersomes enhances the rheological properties and sensitivity to the driving force which results from water concentration gradient across the skin. This enhances the propensity of sufficiently large but deformable penetrant, transfersomes to move across the skin barrier. Such capability combined with the inclination to deform into elongated shapes while maintaining the vehicle integrity can explain the usually high efficiency of transfersomes across the skin.

Preparation of transfersomes has many variables which significantly affect the characteristics of it. Among all variable 3 variables were significant as described by results of placket burman design. The present study, therefore, deals with the optimization of formulation variables to design the best product under conditions of competitive objectives, because interactive effects via a trial-and-error approach are time-consuming and often unsuccessful. Mathematical optimization by means of an experimental design is most helpful in shortening the experimental time⁶.

MATERIALS AND METHODS

Materials

Baricitinib was received as gift sample from West Coast Pharmaceutical Pvt. Ltd. Ahmedabad, (India). Phospholipon 90 G (lipid) was obtained as a gift sample from Lipoid AG, Germany. Double distilled water was prepared in laboratory for study. All materials used for study conformed to USP 24 standards and purchased from ACS chemical Pvt. Ltd. Ahmedabad (India).

METHODS

Preparation of Baricitinib Transfersomes

Baricitinib Transfersomes were prepared by conventional rotary evaporation sonication method. Precisely, Phospholipon 90G (SPC) mixed with Edge activator Span80 were taken in a clean, dry, round bottom flask and the lipid mixture (100 mg/ml) was dissolved in Methanol: Chloroform (1:2). The organic solvent was removed by rotary evaporator above the lipid transition (400C). Final traces of solvent were removed under vacuum overnight. The deposited lipid film was hydrated with 15 ml PBS (pH 7.4) containing Drug Baricitinib to furnish the desired concentration in the final preparation by rotation at 50 rpm for 1 h at 50 0C. The resulting vesicles were swollen for 2hr at room temperature to get large multilamellar vesicles (LMLVs). The thick suspension thus obtained was broken by sonication for 30 min at 4 0C at a frequency of 53 kHz to achieve desired vesicle size (200-300 nm)

9. Composition of Baricitinib transfersomes were described in Table 1.

Table1: Composition of 32 factorial design of BCT-TFS

| Coded factors | Factors/Levels | -1 | 0 | 1 |
|---------------|----------------|-------|-------|-------|
| X1 | SPC: EA | 0.5:1 | 1:1 | 2:1 |
| X2 | BCT | 1%w/v | 2%w/v | 3%w/v |

Optimization of formulation parameters

Optimization of formulation was carried out using Experimental design and desirability function. A two-factor, three-level full factorial design was applied for the optimization procedure using DOE++ software (Version 1.0.7.2 ID -DS-1, ReliaSoft Corporation, USA). The ratio of SPC: EA and Baricitinib (BCT) concentration were used to prepare each of the 9 formulations are given in Table 6.2. These high, medium, and low levels were selected from the preliminary experimentation. After generating the polynomial equations, relating the dependent and independent variables, the process was optimized for the % Entrapment efficiency (Y1), Deformability Index (Y2), Particle size (Y3). After the fitting of the mathematical model, the desirability function was used for the optimization.

Table 2: Formulation of 32 factorial design batches of BCT-TFS

| Run | Coded Value | | | Actual Value | | | |
|-----|-------------|----|---------|--------------|----------|--------------|-----------|
| | X1 | X2 | SPC: EA | SPC in gm | EA in gm | BCT in % w/v | BCT in gm |
| M1 | X1 | X2 | SPC: EA | SPC in gm | EA in gm | BCT in % w/v | BCT in gm |
| M2 | -1 | -1 | 0.5:1 | 0.5 | 1.0 | 1 | 0.15 |
| M3 | -1 | 0 | 0.5:1 | 0.5 | 1.0 | 2 | 0.30 |
| M4 | -1 | 1 | 0.5:1 | 0.5 | 1.0 | 3 | 0.45 |
| M5 | 0 | -1 | 1:1 | 0.75 | 0.75 | 1 | 0.15 |
| M6 | 0 | 0 | 1:1 | 0.75 | 0.75 | 2 | 0.30 |
| M7 | 0 | 1 | 1:1 | 0.75 | 0.75 | 3 | 0.45 |
| M8 | 1 | -1 | 2:1 | 1.0 | 0.5 | 1 | 0.15 |
| M9 | 1 | 0 | 2:1 | 1.0 | 0.5 | 2 | 0.30 |

Characterization of Baricitinib transfersomes

Determination of percent drug content

% Entrapment Efficiency

Transfer some entrapped Baricitinib was estimated by centrifugation method. The prepared transfer some were placed in centrifugation tube and centrifuged at 14000 rpm for 30 minute. The supernatant (1ml) was with drawn and diluted with phosphate buffer (pH7.4). The entrapped Baricitinib was determined by UV spectrophotometer at 305.2 nm.

% Entrapment Efficiency = (Total Drug - Unentrapped drug) / Total Drug X 100

Deformability Index (Vesicle Elasticity Measurement)

The deformability study was done for the transfersomal formulation using a home-built device¹⁴. The elasticity of transfersomes vesicles were measured by extrusion method. The transfersomes formulation were extruded through filter membrane (pore size diameter 100 nm), using a stainless steel filter holder (50 mm diameter), by applying a pressure of 2.5 bar. The quantity of vesicles suspension extruded in 5 minutes was measured. The deformability index of prepared batches is depicted in Table 6.4.

$$E = J * (rv / rp)^2$$

Where, E =Elasticity of vesicles membrane,

J = Amount of suspension extruded in 5 minutes, rv = Vesicles size,

rp = pore diameter.

Particle Size and Surface Charge

The droplet size and zeta potential of the transfersomes was determined by a Malvern Particle sizer and Zeta Potential Analyzer (Malvern Instruments Ltd., UK) at roomtemperature¹⁵.1ml of the transfer some suspension was diluted with deionized water.

Transmission Electron Microscopy

Transmission Electron Microscopy (TEM) was used to visualize the transfersomal vesicles using TEM microscope (Model: Philips Tecnai 20 G2, Holland) at SICART, Vallabh Vidhynagar. The vesicles were dried on a copper grid and adsorbed with filterpaper¹⁵. After drying, the sample was viewed under the microscope at 10–100k magnification at an accelerating voltage of 100 kV. The TEM image of best batch is shown in Figure.

Fourier Transform Infrared Spectroscopy

Fourier transform infrared spectroscopy (FTIR) study was carried out to confirm structure of formulation. FTIR spectra of pure drug, lipid and formulated Transfersomes containing drug were recorded on FTIR Spectrophotometer (SHIMADZU, Japan) at Ratnamani Healthcare, Indrad. The scanning range was from 4000 to 600 cm⁻¹ and there solution was 1 cm⁻¹.

Physical stability

This study was carried out in stability chambers at Ratnamni health care. After measuring the initial percentage entrapment of the drug in the various formulations, the three batches of the same formulation were stored in sealed glass ampoules at different temperature⁹. According to ICH, physical stability was carried out at refrigeration temperature (4±20C) and room temperature (25±20C/65% RH±5%RH) for a period of 3 months

RESULTS AND DISCUSSION

Melting point determination

DSC thermo gram of Baricitinib explains that melting point of drug was 192.87°C (Figure 1). Reported range of melting point of BCT is 185-204°C¹⁷⁻¹⁸. So BCT has confirm edits physicochemical property.

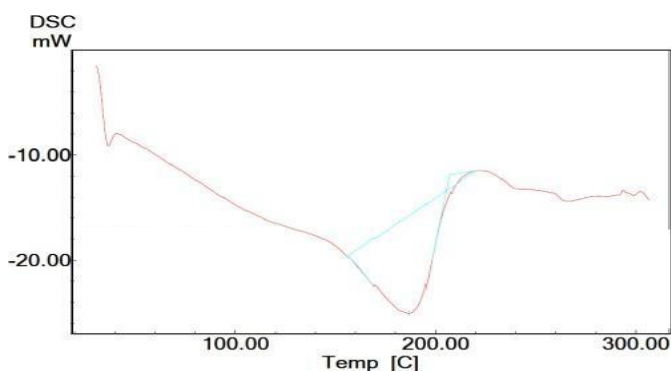


Fig 1: DSC thermo gram of Baricitinib

Drug-Excipients compatibility study

Compatibility of drug and lipid was confirmed from comparison of DSC thermo gram of Baricitinib and physical mixture of Baricitinib and lipid (Figure2).

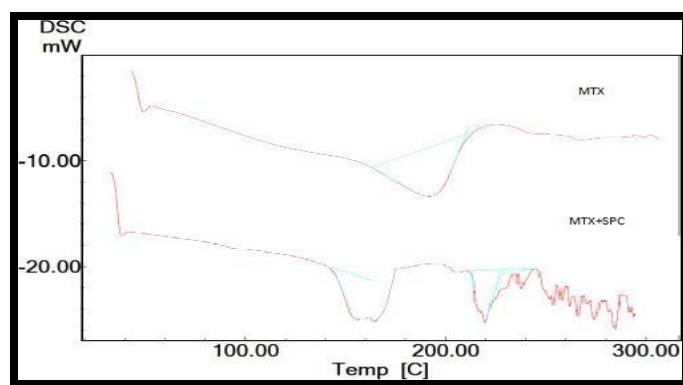


Fig 2: DSC spectra of mixture of Baricitinib and lipid

% Entrapment efficiency

The maximum entrapment efficiency 90.71 ± 3.4 was found in case of transfersomal formulation M4 (Table 3). Lipid composition of the batch M4 was higher in comparison to that of other batches and this may result in higher entrapment efficiency measured with transfersomes. Further, transfersomes contains a mixture of lipid and membrane softener, SPAN 80. The lipid is a stabilizing factor and SPAN 80 is a destabilizing factor. In the preparation method of transfersomes, the vesicles content is exchanged with the dispersion medium during breaking and resealing of phospholipid bilayer as they are sonicated using probe sonicator. During the successive cycles, the drug stayed inside the transfersomes suggesting that interaction between lipid membrane and drug did not allow free displacement of drug.

| Run | Dependent variables | | |
|-----|----------------------|------------------|-----------------|
| | Y1 | Y2 | Y3 |
| M1 | 89.02 ± 1.4 8 | 38.21 ± 1.23 | 265.8 ± 1.2 |
| M2 | 64.67 ± 0.4 6 | 32.87 ± 1.14 | 272.5 ± 1.8 |
| M3 | 45.92 ± 0.4 8 | 33.50 ± 2.09 | 325.4 ± 0.7 |
| M4 | 90.71 ± 0.6 6 | 21.77 ± 0.70 | 267.3 ± 2.4 |
| M5 | 84.77 ± 0.2 6 | 27.13 ± 1.13 | 314.2 ± 1.4 |
| M6 | 58.51 ± 0.3 5 | 26.41 ± 1.06 | 317.5 ± 1.5 |
| M7 | 90.45 ± 0.6 6 | 17.63 ± 1.99 | 281.8 ± 0.5 |
| M8 | 88.32 ± 0.4 0 | 10.65 ± 0.64 | 332.5 ± 2.2 |
| M9 | 73.21 ± 0.3 | 14.82 ± 1.7 | 342.4 ± 1 |

Table 3: Results of dependent variables of 32 factorial design batches of BCT-TFS

Particle size and surface charge

Droplet size was measured by Malvern particle analyzer. Average sizes of all transfersomes formulations were in the range of 250-350nm. This suggests that prepared transfersomes are good for penetration through skin as they have nano sizes. Differences in particle size within and among the batches were observed to be insignificant ($P < 0.05$). It was also noticed that size of BCT-entrapped transfersomes increased with the increasing SPC: EA

ratio. Increase in the concentration of surfactant was found to decrease in BCT-TFS size significantly ($P < 0.05$).

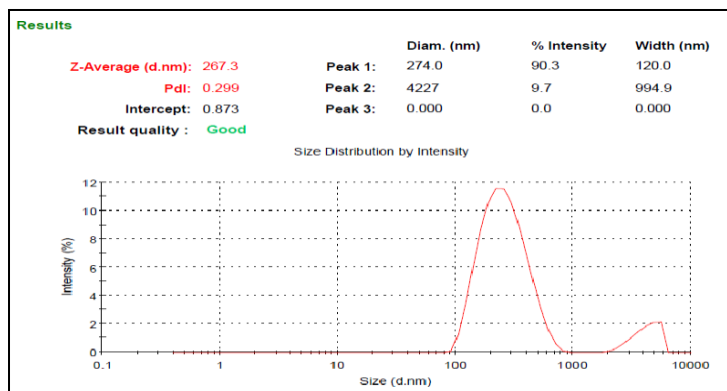


Fig 3: Particle size distribution of transfersomes batch M5

Transmission electron microscopy

TEM image for optimized Transfersomes is shown with SPC: EA ratio; 1:1 and BCT concentration: 2%w/v (Figure 6.14). Transmission electron microscopy was used to characterize transfersomes. These carriers invariably appeared as unilamellar vesicles. Bioactive molecules larger than 500 Da normally do not cross the skin. This prevents non-invasive delivery of high-molecular-weight bioactive. In order to cross the intact mammalian skin, transfersomes should be capable of passing through pores of diameter less than 50 nm under influence of suitable transdermal gradient.

FTIR Study

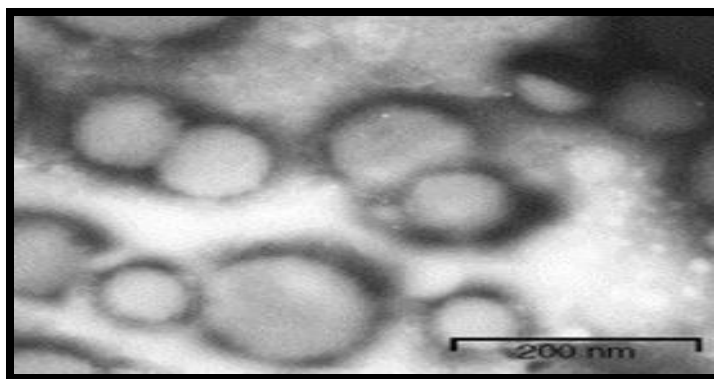


Fig 4: Transmission electron micrograph of optimized BCT-TFS batch M5

The Fourier transform infrared spectroscopy (FTIR) spectrum of the formulation (transfersomes) was compared with pure drug and lipid spectrums. This study reveals that all major lipid peaks were observed in spectra of Baricitinib transfersomes and

Baricitinib peaks were merged and shifted in the same. So it was concluded that drug was completely incorporated in transfersomes.

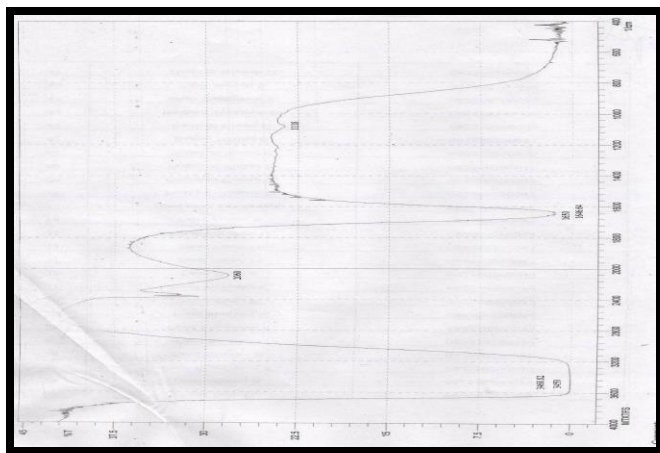


Figure 5: IR spectra of Baricitinib transfersomes

Physical stability of Baricitinib Transfersomes

Stability is an essential quality attribute for drug products. This evaluation checked by pharmaceutical scientist and regulators quantify drug product stability and shelf life. Drug stability concerns about drug product safety, efficacy, and quality, found it to appropriate³⁰. Physical stability represents the ability of a product to maintain its physical dimensions and properties when exposed to conditions normally encountered in its service environment³¹. Figure 6.18 explains that % drug loss from transfersomes was higher at room temperature ($25 \pm 20^\circ\text{C}/65\% \text{RH} \pm 5\% \text{RH}$) as compared to refrigeration temperature ($4 \pm 2^\circ\text{C}$).

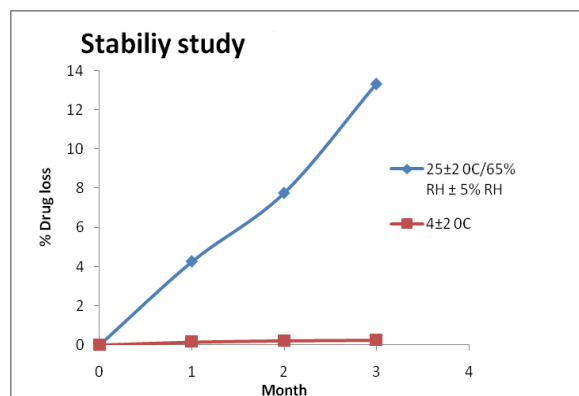


Fig 6: Physical stability of BCT-TFS Batch M5

Derivation of Optimum Drug: Lipid ratio

From the data of 32 factorial design, drug: lipid ratio can also take for desired drug loading. Drug: lipid ratio is derived and drug loading (%EE) is compared. Table 6.8 explains as drug: lipid ratio is increased from 0.1 to 0.9, drug loading capacity of transfersomes is decreased from 90% to 40%. It is recommended from the results that optimum drug: lipid ratio can be used is 0.1 - 0.4.

| Run | SPC | EA | BCT | BCT:SPC | %Drug loading |
|-----|------|------|------|---------|---------------|
| M7 | 1 | 0.5 | 0.15 | 0.15 | 90.45±0.66 |
| M4 | 0.75 | 0.75 | 0.15 | 0.2 | 90.71±0.66 |
| M1 | 0.5 | 1 | 0.15 | 0.3 | 89.02±1.48 |
| M8 | 1 | 0.5 | 0.3 | 0.3 | 88.32±0.40 |
| M5 | 0.75 | 0.75 | 0.3 | 0.4 | 84.77±0.26 |
| M9 | 1 | 0.5 | 0.45 | 0.45 | 73.21±0.35 |
| M2 | 0.5 | 1 | 0.3 | 0.6 | 64.67±0.46 |
| M6 | 0.75 | 0.75 | 0.45 | 0.6 | 58.51±0.35 |
| M3 | 0.5 | 1 | 0.45 | 0.9 | 45.92±0.48 |

Table 6.8: Optimization of Drug: Lipid ratio

CONCLUSION

Transfersomes are specially optimized particles or vesicles, which can respond to an external stress by rapid and energetically in expensive, shape transformations. A conventional rotary evaporation sonication technique was developed to prepare Baricitinib transfersomes using Phospholipon 90 G as a lipid (SPC) and SPAN 80 as an edge activator (EA). Preformulation studies proved the purity of drug and compatibility of drug and excipients was evaluated by DSC study. BCT loaded Transfersomes was successfully formulated using 32 full factorial design and desirability function. The % entrapment efficiency, deformability index and particle size were highly dependent on the SPC: EA ratio, and BCT concentration for the preparation of BCT loaded Transfersomes. SPC: EA ratio and BCT concentration had a positive effect on % entrapment efficiency and negative effect on deformability. But particle size was not much affected. Using contour plots, response surface plots and % Bias, formulation was optimized. Batch M5 (1:1PC: EA, 2%w/Vbct) is best batch among nine combinations. Surface morphology of transfersomes was evaluated by TEM study. A good interaction between drug and excipients were found with FTIR study of transfersomes. It was advisable to store BCT-TFS at refrigerated conditions ($4 \pm 2^\circ\text{C}$). Optimum drug: lipid ratio is 0.1-0.4. BCT-TFS was successfully optimized with experimental design and desirability function.

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