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Formulation, Development and Evaluation of Budesonide Loaded Transferosomes in a Transdermal Patch

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ABSTRACT

Transfersomes are quasi-metastable which makes the vesicle membrane ultra-flexible, and thus, the vesicles are highly deformable so can penetrate into the stratum corneum under non occlusive conditions and can even carry huge molecules across intact skin. The aim of this study is to develop budesonide (BUD)-loaded transfersomesin corporated into transdermal patch for the treatment of asthma. This drug is given conventionally by DPIs , metered Sprays etc. through pulmonary route but use of complex devices and various physiological and pharmaceutical factors result in losses affecting reproducibility of the dose. TDDS formulation can reduce the losses achieving high local concentration in the lung and improve the patient compliance. Budesonide undergoes significant first pass elimination about 80-90% and is rapidly biotransformed. Also the drug has a half-life of 2-3.6 hours making it a suitable candidate for transdermal delivery. Hence, an attempt was made to deliver budesonide through transdermal route. Transfersome were made using phospholipon-90G and Span-40. A 2^3 Factorial design was applied. Drugentrapment efficiency, vesicle morphology and size wasdetermined. Drug permeation study was carried out to observe drug releaseprofile.

KEYWORDS: Transfersome; Budesonide; Entrapment efficiency; Transdermal patch; Permeation study

I. INTRODUCTION

Oral route is most frequently used route of drug administration due to its simplicity and convenience. This route of drug administration is limited by poor absorption, first pass metabolism and limited drug solubility. Bioavailability of orally administered drugs varies greatly. Hence due to these drawbacks there is an obvious need for an alternative route of drug administration. Transdermal delivery is free from hepatic first pass effect, deactivation by intestinal enzymes or degradation by gastric acids. Transdermal route is beneficial for improving bioavailability, good permeability (mainly for lipophilic and low molecular weight drugs), ease of self-administration, ease of handling etc. Transdermal delivery is quite a fascinating alternative to oral drug administration as it offers the benefit of rapid drug delivery to systemic circulation. Skin of an average adult body covers a surface of approximately $2m^2$ and receives about one-third of the blood circulating through body. Thus , skin acts as a good medium from which absorption of drug takes place and enters the circulatory system within few minutes after administration.Transdermal drug delivery has evovled from basic transdermal gels and patches to vesicle loaded drug delivery systems i.e., liposomes, proliposomes, niosomes, transfersomes loaded transdermal systems. Transfersomes are a type of modified liposome includes ultra-deformable liposomes. Transfersomes are made up of phospholipids and edge activators. An edge activator is a surfactant which enhances the deformability of the vesicles. Sodium cholate, Sodium deoxycholate, Span 60, Span 80, Span 40, Tween 80 and Tween 60 are examples of some commonly used edge activators. Transfersomes have advantages over conventional liposomes . Because of their high deformability and self optimized properties, they overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of the stratum corneum and carry drug across the whole skin. The name means “carrying body”, and it is derived from the Latin word 'transferre', which means ‘to carry across’, and the Greek word ‘soma’, means for a ‘body’.

Budesonide is a glucocorticoid used in the management of asthma, lung cancer and COPD. It is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and

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weakmineralocorticoid activity. Inflammation is an important component in pathogenesis of asthma and hence corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types. Budesonide undergoes significant first pass elimination about 80-90% with its systemic bioavailibilty 39%. It is rapidly biotransformed by CYP3A4 to its major metabolites 6β-hydroxybudesonide and 16α–hydroxyprednisolone. Also the drug has a half-life of 2-3.6 hours making it a suitable candidatefor transdermal delivery. Oral bioavailability of Budesonide is less than 5% and 95 % of the drug is protein bound. As it falls into the category of preventors, transdermal drug delivery will help to sustain the release of drug and prolong its action.

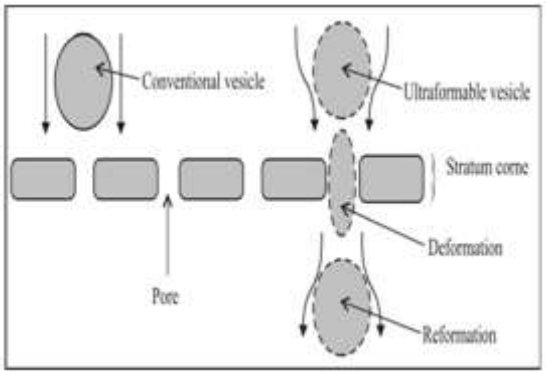

Fig 1. Diagram representing deformable nature of transfersomes

The objective of the study was to develop budesonide loaded transfersome which were further incorporated in a transdermal patch for treatment of asthma and chronic obstructive pulmonary disease. Hence, this study will increase the solubility as well as to enhance the permeability of BCS class 2 drug Budesonide via Transdermal route.

II. MATERIALS AND METHODS

Budesonide was a kind gift sample from Avik Pharmaceuticals (Gujrat, India). Phospholipon90G was obtained as a gift sample from Lipoid GmbH (Germany). Span 40 and Methanol was purchased from Molychem (Mumbai, India). Potassium dihydrogen orthophosphate and sodium hydroxide were obtained from S. D. Fine-Chem Ltd. Mumbai, India. Dialysis Membrane was purchased from Himedia (Mumbai, India).

Drug excipient interaction study was done by the following:-

Fourier Transform Infrared spectroscopy (FTIR):-

The crystal of FTIR – ATR was cleaned with isopropanol on cellulose tissue. The background was measured with ATR unit. The dry sample of budesonide was placed on the crystal ensuring good contact and then measured. The entire operation was conducted under controlled humidity. The sample was then scanned using optic GmbH, ALPH-T , Germany over range of 3600-600cm $^{-1}$

Differential Scanning Calorimetry(DSC):-

DSC of drug, drug-excipient mixture and formulation was carried out for determining drug–excipient compatibility. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10^{o}C/min over a temperature of 30°C to 300°C.

III. EXPERIMENTAL WORK

1.) Preparation of Transfersomes:-

Rotary evaporation method was used for preparation of transfersome. Weighed quantity of drug, edge activator (Span 40) and Lipid (Phospholipon 90G) were dissolved in methanol. The organic solvent was removed under vacuum using Rotary vacuum evaporator to deposit a thin dry film. The deposited film was hydrated with phosphate buffer pH 7.4 for one hour at room temperature. The transfersomal dispersion was then centrifuged using cooling centrifuge for 20 minutes at -4°C to obtain ultradeformable vesicles.

2.) Screening of factors for preparation of transfersomes:-

Trial batches for drug loaded transfersomes by using thin film hydration method were taken.

Screening of factors (lipid conc, edge activator conc, rpm, temperature, hydration volume and hydration time) affecting the method and response (% entrapment efficiency) was carried out using Placket Burman design. The values for coefficients were determined and significant factors affectingtransfersomes (lipid conc, edge activator conc and hydration time) were selected for further optimization.

3.) Optimization of transfersomes:-

Traditional methods of formulation by changing one variable at a time are very time consuming hence it becomes essential to use tools

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to minimize time and maximize utility. Hence Placket Burman design was used out of which 3factors were chosen with high coefficientvalues and 2 levels were set for developing 2^3 factorial layout. For more accuracy Software Design Expert (Version 11.0, Stat-Ease Inc, Minneapolis, MN) was used to optimize and evaluate main effects, interaction effects of the formulation.The Responses chosen were Percentage drug entrapment efficiency and Flux. Analysis of variance (ANOVA) and all statistical analyses were also performed using the same software.

Fabrication of transfersomal loaded Transdermal Patch

Different polymers with varied concentrations were tried but finally for preparation of transdermal patches PVPK30 and HPMCK4M were used as film forming agents. These selected polymers were kept constant throughout the study. Propylene glycol wasused as plasticizer and penetration enhancer. Methyl paraben as preservative. Transfersomes equivalent to 12 mg of budesonide was weighed and dispersed in 10 ml of water. After uniform dispersion of transfersomes in water, film forming agent i.e. PVPK30and HPMCK4M were added to form viscous solutions, then propylene glycol and methyl paraben were added to above viscous solution and uniformly mixed using a magnetic stirrer. A glass mould of area 30.6 cm^2 was used for casting the film .The film was dried for 24 hours then packed in aluminum foil and stored in a desiccator till further use.

Characterization Of Transfersomes:-

Determination of drug entrapment efficiency of transfersomes:-

Entrapment of drug was determined using centri- fugation method. Transfersomal dispersion were subjected to centrifugation at 12,000 rpm at -4 °C for 20 minutes using eltek centrifuge. Sediment was collected, air dried to remove any liquid and then weighed. The vesicles were broken using methanol and thenpellet was analyzed for the drug content after suitable dilution with buffer by measuring absorbance at 247 nm using UV Spectro-photometer. Encapsulation efficiency was calculated according to equation below.

$$\text{Percentage entrapment (EE \%)} = \frac{\text{Amount of Entrapped drug} * \text{Total drug added}}{100}$$

Determination of EE % was conducted for various transfersomal formulations and the effect of variables was studied.

Vesicle morphology:-

JEOL JSM 7600F Field Emission Scanning Microscope was used for studying the morphology of transfersomes.

Vesicle size and vesicle size distribution

Examination of the transfersome vesicle size after sonication was performed by using HORIBA SZ-100 Nanopartica Analyzer based on dynamic light scattering.

Permeation study

In vitro Diffusion Study

Franz diffusion cell was used to perform diffusion study. The receptor compartment was filled with phosphate buffer pH 7.4 and maintained at 37 ºC. Dialysis membrane was used for the study. Magnetic stirrerwasplacedinreceptor compartment and drivenat 150 rpm. At regular time intervals aliquots were removed from receptor. The samples were analysedspectro-photometrically for drug content. Percentage cumulative release was determined.

Ex vivo skin permeation study

Goat skin has similarity to human skin in lipid content and permeability hence it was used for ex vivo study. Goat skin was obtained from local slaughter house immediately after sacrificing the animal. Then the hair was removed from the upper portion of skin surface using an animal hair clipper and the fatty layer adhering to the dermis side was removed by surgical scalpel. Finally, the skin was rinsed with deionized water and packed in an aluminum foil. The skin samples were stored at –20 °C and used within a week. The skin was soaked in phosphate buffer overnight before the diffusion study. Skin was mounted between two half cells and diffusion study was performed.

EVALUATION OF PATCH

Thickness

The thickness of each patch was measured at the different sites using screw gauge and the average thickness was calculated. Percentage deviation from mean thickness was determined.

Film folding endurance

This was determined by repeatedly folding the patches until it shows any crack or break. The number of times the film could be folded without breaking/cracking gave the value of folding

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endurance.

Moisture content

The film was weighed and kept in a desiccator containing calcium chloride at 40 °C in a drier for at least 24 hrs or more until it showed a constant weight. The moisture content was the difference between the constant weight taken and the initial weight and was reported in terms of percentage (by weight) moisture content .

Percentage of moisture content =[Initial weight – Final weight / Final weight] × 100

Percentage moisture uptake

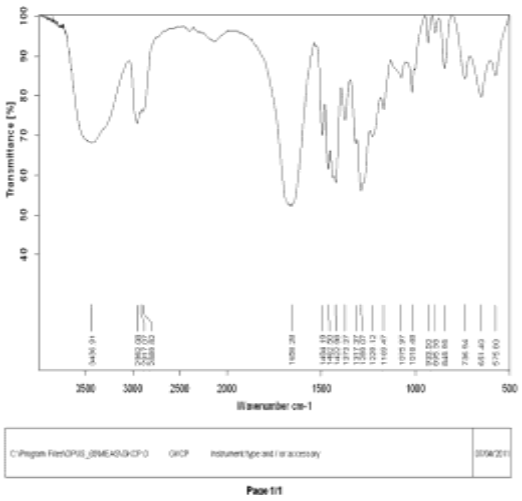
The weighed films were kept in a desiccator at room temperature for 24 hours and then exposed to 84% RH using a saturated solution of potassium chloride. The films were weighed repeatedly until they showed a constant weight. Values for the percentage of moisture uptake were calculated using the formula

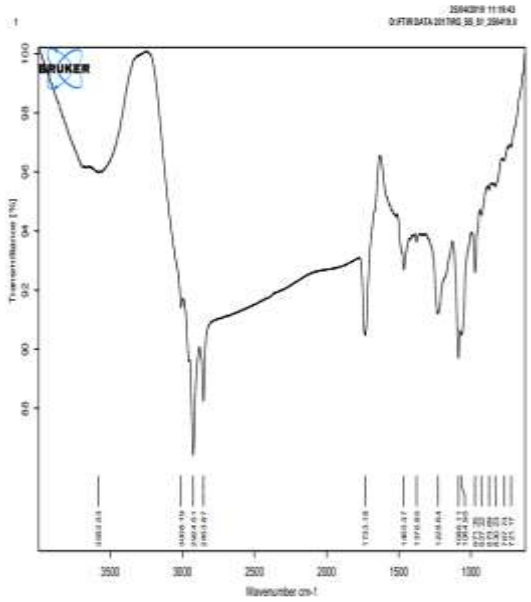
Percentage of moisture uptake =[Final weight – Initial weight / Initial weight] × 100

IV. RESULTS

Drug excipient interaction study by FTIR

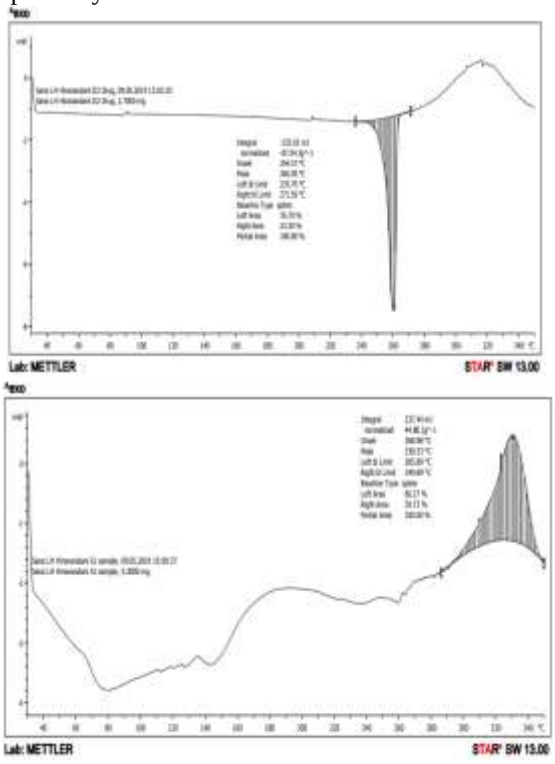
Drug shows peak at 3378 cm^{-1} which corresponds to OHstretching vibration and 883.43 cm^{-1} which depicts C-C aromatic vibrations. Peak at 3105 cm^{-1} denotes C-H stretching of aromatic group. On combining drug with excipients there was no disappearance of any peak. The final formulation containing drug along with all the excipients showed the major peaks. The IR study concluded that there was no incompatibility between famotidine and any of the excipients.





Drug excipient interaction study by DSC

The DSC of budesonide shows sharp peak at 260 °C. DSC of drug loaded transfersomal dispersion shows a broad peak at 330 °C representing that the lipid has interacted with the drug to a large extent indicating enhanced entrapment of budesonide. The DSC results show that there is enhanced entrapment of drug in the lipid bilayer.



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Experimental design

The 3^2 Factorial design was used and ANOVA was applied. The responses obtained are represented in Table 3. For percentage entrapment efficiency polynomial equation in terms of coded factors was obtained as

Entrapment efficiency = + 48.22 + 12.83 × A – 3.17 × B

TABLE 3
Responses for factorial design batches

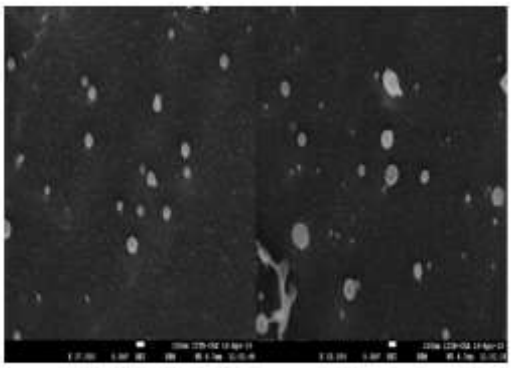
R^2 was found to be 0.9932 which implies that 99.32% of the variation in the responses was attributed to independent variables. The Model F-value of 435.46 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. The signal to noise ratio of 50.51 implies that the model can be used to navigate the designspace.In case of Flux the experimental data was fitted into a polynomial equation and equation in terms of coded factor for optimum flux was found tobe

Flux = + 21.76 + 1.30 × A + 0.63 × B – 0.15 × AB – 0.53 × A^2 – 0.033 × B^2.

The R^2 was 0.9934. Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 27.68 indicates an adequate signal hence this model can be used to navigate the designspace.

Vesicle morphology

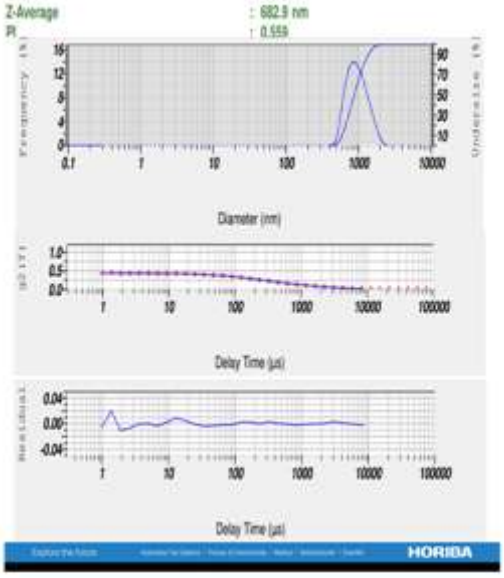
The Vesicles were found to be spherical in shape ranging 10-100nm.



(a.) X3700 magnification (b.) X3300 magnification

Vesicle size and vesicle size distribution

Vesicles size after sonication was measured using HORIBA SZ-100 Nanopartica Analyzer based on dynamic light scattering. The graph of percentage cumulative distribution VS Praticle size (nm) was plotted. Mean size of particles was found to be 682.9 nm and polydispersity index was found to be 0.559. Low polydispersity index indicated particle size uniformity whithin theformulation.



Evaluation of patch

Evaluation of patch are given in Table 4.

V. DISCUSSION

It was found using exhaustive grid search that formulation T3 was the optimized formulation having permeation flux of 22.4 µgm/cm^2 hour and drug entrapment efficiency of 61 %. Mean particle size for this formulation was 215 nm which was also beneficial as small particle size helps in penetration of drug whereas liposomes of larger sizes penetrate into the deeper layers of the skin with difficulty (Seyed et al., 2011). A polydisersity index of 0.3 indicated uniform size distribution of particles. The morphology of the Transfersome was determined by TEM and demonstrates the spherical shape and nano size range of vesicle. The patch formulated was also uniform and had good physical characteristics. In vitro and ex vivo diffusion study indicated sustained drug release over a period of 24hours.

Transdermal patches loaded with ultradeformable liposomes showed enhanced delivery as compared to the plain drug patch. Since in case of transfersome they are highly elastic vesicles and can squeeze through the stratumcorneum intact. Transfersomes are hence ideal candidates for delivery through transdermal route. The study suggests that incorporation of transfersome of Famotidine in patch is an excellent

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approach for delivery of the drug.

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