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Formulation and Evaluation of Fenofibrate Niosome-Loaded Capsules

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ABSTRACT

The present study was undertaken to formulate and evaluate niosome capsule containing Fenofibrate, where the bioavailability of the drug preferably increased. Fenofibrate is a drug that has low solubility thus the absorption of the drug is less and so is the bioavailability. To overcome these problems, Fenofibrate was incorporated into niosomes. The niosome vesicular drug delivery system was preferred due to its greater solubility, permeability, and bioavailability. It carries a significant quantity of the drug, thus enhancing the penetration of the drug. Non-ionic surfactant Tween 80 and modified surfactant Span 60 were used in different combinations at different ratios to prepare the niosomes. The ether injection method was used to prepare niosomes and evaluated for morphology, percentage yield, percentage entrapment efficiency, drug content and *In-vitro* drug release study. Formulation of F3 containing drug, surfactant and cholesterol was found to be optimized formulation based on the evaluation parameters. The optimized formulation was further evaluated by FTIR, DSC. The optimized formulation was formulated as niosomal capsule. Formulation F3 shows an *In-vitro* drug release study and the optimized niosomal capsule formulation shows *In-vitro* drug release at the end of 7th hrs We can conclude that it is possible to formulate niosomes of Fenofibrate using Tween 80 and Span 60 by Ether injection method for the treatment of Hyperlipidaemia. The prepared niosomes can be used to enhance the solubility of drug may lead to its increased bioavailbility and may reduce the dose and dose frequency.

INTRODUCTION

Niosomes, a unique non-ionic surfactant-based vesicular drug delivery system, assist in the efficient transport of drugs to their sites of action. They are bilayer vesicular structures comprised of cholesterol and a non-ionic surfactant.[1] Because of their amphiphilic nature, niosomes have improved biological membrane penetration and successfully cross it. Niosomes have a bilayer structure that is similar to a liposome, however, they have additional advantages than liposomes due to their increased stability and low cost. Niosomes are extremely small, with sizes ranging from 10 nm to 100nm.[2] They can entrap both hydrophilic and lipophilic drugs due to their amphiphilic character, which means they contain both hydrophilic and lipophilic portions. Drugs that have poor aqueous solubility and low bioavailability can be incorporated into these niosomes to enhance the permeability and obtain better bioavailability.[3] The cell membrane contains cholesterol, a waxy steroid by-product. By adding cholesterol to the bilayer structure of the niosome, membrane stabilizing activity and a reduction in membrane leakiness are achieved. When combined with a non-ionic surfactant, cholesterol gives niosomal preparations the right shape and conformation while also increasing rigidity.[4] Non-ionic surfactant-based niosomes are nanocarriers having broad role in targeted, sustained and controlled drug delivery system. Hydrophilic heads of non-ionic surfactant don`t contain any change group, hence the hydrophilic head stay opposite to aqueous solution and the hydrophobic tails present opposite to organic solutions, which result in formulation of the noisome structure. Due to this property, niosomes are formed by the self-assembly of non-ionic surfactant in aqueous dispersion.[5]

Objectives

The main objective of the study is to formulate and evaluate Fenofibrate niosome.

MATERIAL AND METHODS:

PRE-FORMULATION STUDIES

Solubility Analysis of Fenofibrate Drug in Water and Different pH:

Solubility analysis was carried out for the Fenofibrate sample by preparing a saturated solution in water and various buffers from pH 1.2 to 7.4 and keeping it overnight and then the absorbance was taken by using UV-spectrophotometer.[6]

Melting point determination of Fenofibrate:

The melting point of Fenofibrate was determined by using Thiele's tube method by taking a little amount of pH the drug in a capillary tube closed at one end and placed in Thiele's tube containing liquid petroleum and the temperature at which the drug melts was recorded. This was performed in triplicates and the average value was reported.[7]

Determination of λ max of the drug:

Fenofibrate solution was dissolved in 0.1N HCL, Phosphate buffer pH 6.8, and phosphate buffer pH 7.4. The UV spectrum of the solution was taken on UV Shimazdu 1800 UV/Vis double beam Spectrophotometer at 200-400nm. The value was compared with the standard value.[7]

Identification of drug by Infrared Spectral studies:

Approximately 1mg of Fenofibrate was mixed with 100 mg KBr (transparent in IR) in a ratio of 1:100 in a mortar. The mixture was pressed into a pellet die manually. Placed in FTIR Spectrophotometer (Shimadzu corporation 8400s, Japan). The spectrum of Fenofibrate was obtained and compared with standard values.[7]

Melting point determination by Differential Scanning Calorimetry (DSC)

The drug-excipient interaction was determined for the pure drug and physical mixture of drug and polymer. Thermogram was obtained and the endothermic peak of the pure drug was retained in the physical mixture of drug and excipients.[8]

PREPARATION OF FENOFIBRATE NIOSOMES BY ETHER INJECTION METHOD:

INGREDIANTS	F1	F2	F3	F4	F5
FENOFIBRATE (mg)	200	200	200	200	200
TWEEN 80 (mg)	50	100	200	300	400
SPAN 60 (mg)	400	300	200	100	50
CHOLESTEROL (mg)	200	200	200	200	200
DIETHYL ETHER (ml)	8	8	8	8	8
METHANOL (ml)	2	2	2	2	2
PHOSPHATE BUFFER (7.4pH)	15	15	15	15	15

Weigh the amount of non-ionic surfactant (span60, tween80) taken along with cholesterol and dissolved in 8ml of di-ethyl ether which was mixed with 2ml of methanol previously

containing weighed quantity of a drug. The resultant solution is injected using a micro syringe at the rate of 1ml/min into 15ml 7.4 pH phosphate buffer. Then the solution is stirred continuously with a magnetic stirrer and the temperature is maintained at 60-65°C. The difference in the temperature between the phases causes vaporization resulting in the formation niosome.[10]

EVALUATION OF NIOSOMES

Microscopic and morphological study:

The Niosomal preparation was spread on the glass slide using glass rod. The formulation of large uni-lamellar vesicles was confirmed by examining the niosomal suspension under the optical microscope with a magnification of 10X and 45X.[9]

Percentage practical yield:

Percentage practical yield is calculated to know about the percentage yield or efficiency of any method thus it helps in the selection of the appropriate method of production. The Practical yield was calculated as the weight of Fenofibrate niosomes recovered from each batch about the sum of starting material. The percentage yield of prepared Fenofibrate niosome was determined by using the formula.[11]

Determination of drug content and entrapment efficiency:

Niosomes equivalent to 5mg Fenofibrate were crushed using a mortar and pestle. Then they were suspended in 25mlof phosphate buffer pH 7.4 after 24 hours, the solution was filtered and 1 ml of the filtrate was diluted 10 times and analyzed for the drug content by UV-visible spectrophotometer at 286 nm.[12]

Determination of solubility:

Drug solubility was determined by adding excess amounts of pure Fenofibrate and niosomes in distilled water at 37 ± 0.5°C, respectively. The solution formed was equilibrated under continuous agitation for 24 hours and passed through a 0.8 µm membrane filter to obtain a clear solution. The absorbance of the samples was measured using the UV spectrophotometer method at 286 nm and the concentrations in µg/ml were determined.[13]

***In-Vitro* Release:**

The *In-vitro* dissolution study was performed by using the United States Pharmacopoeia (USP) Type 2 (Paddle) Apparatus at a rotational speed of 100 pm. Exactly 900ml of phosphate buffer pH 6.8 for 2 hours and pH 7.4 for rest was used as the dissolution medium and the temperature was maintained at 37 ± 0.5°C. A sample (1ml) of the solution was withdrawn from the dissolution apparatus at the specified time interval for 7hrs and the same volume was replaced with pre-warmed fresh dissolution media. The samples were filtered through Whatman filter paper and diluted to a suitable concentration with phosphate buffer pH 6.8 and pH 7.4. The absorbance of these was solutions measured at 286 nm using a UV spectrophotometer.[14]

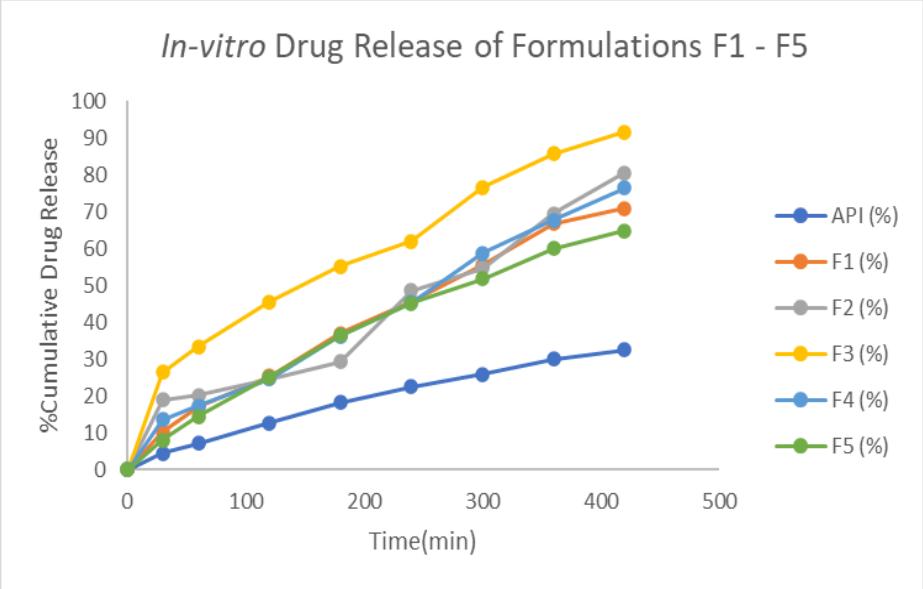
RESULTS AND DISCUSSION

The purpose of this study was to "Formulation and Evaluation Fenofibrate niosome loaded capsules". Fenofibrate, a class of drugs used to treat hyperlipidemia, belongs to BCS Class II drugs (low solubility and high permeability). The dose of Fenofibrate ranges from 160-200mg/day. The saturated solubility of Fenofibrate was found to be 0.67 µg/ml by preparing a saturated solution of Fenofibrate in water. The solubility of the drug was found to be insoluble in water, slightly soluble in pH 1.2, sparingly soluble in pH 6.8 and soluble in pH 7.4. The melting point of Fenofibrate was determined by Thiele's tube method and it was found to be 82° C. The value obtained is within the standard range of values of 79-84°C which implies the purity of the drug. DSC thermogram showed an endothermic peak at 83.91°C which corresponds to the melting point of the drug. This value is between the standard ranges of 79-84°C. Thus, the presence of Fenofibrate can be confirmed. The absorption spectrum of the pure drug (Fenofibrate) was scanned between 200-400nm with 2.5 µg/ml concentration in a pH 7.4 phosphate buffer solution using a UV Spectrophotometer. The maximum peak was obtained at 286 nm which was taken as λ max. The IR spectrum of Fenofibrate was recorded by FT- IR spectrophotometer. It observed that the functional group peak frequencies resemble the standard range values of Fenofibrate. Thus, the presence of Fenofibrate can be confirmed. The standard stock solution of Fenofibrate was prepared in phosphate buffer pH 7.4. It was carried out as per the method described in the methodology section and scanned by UV-visible spectrophotometer (Shimadzu-1800, Japan) between 200-400 nm. The UV absorption spectrum of Fenofibrate showed λ max at 286 nm and the same was used as an analytical wavelength for further analysis. The calibration curve of

Fenofibrate in phosphate buffer pH 7.4 was plotted and the values were recorded. The individual IR spectrum of Cholesterol, Tween 80, and span 60 was performed. Then the IR spectrum of Fenofibrate was determined in niosomes formulation to check for any interaction. It is confirmed that there is no interaction.

The percentage yield of prepared Fenofibrate niosomes was found in the range of 72.80% - 95.31%. The entrapment efficiency of Fenofibrate niosomes was found in the range of 70.78 – 87.35%. The Drug Content of Fenofibrate niosomes was found in the range of 46.32% - 77.33%. The weight variation of formulation F3 was found to be 0.4 %. Drug content of formulation (F3) was found to be 77.33 %. This Indicates a good vehicle for the release of the drug and no degradation of the drug was seen. The disintegration time of F3 was found to be 14.43 minutes. *In-vitro* release studies were carried out using a dialysis bag in pH 7.4 phosphate buffer. The results were estimated for up to 7 hours at 100 rpm. The Formulation F3 showed 91.56 % over 7 hours. The Formulation follows Zero order kinetic which implies that it follows a controlled release pattern. Higuchi showed linearity with its R^2 value greater than 0.9. It supported the release of encapsulated Fenofibrate from the niosomes followed by the diffusion process therefore, controlled release formulations such as diffusion, swelling, and erosion mechanisms were involved in drug release from the niosomes.

***In-vitro* Drug Release of Formulations (F1-F5)**



***In-vitro* Drug Release of Formulations (F1-F5)**

CONCLUSION

Fenofibrate was formulated as niosomes for controlled release and to improve its solubility with a reduction in dosing frequency, thereby achieving better patient compliance. In this study, Niosomes were prepared by Ether Injection Method using different concentrations of Tween 80 and Span 60. different parameters like percentage yield, entrapment efficiency, drug content, particle size, *In*-vitro release, and controlled-release capsule parameters such as weight variation, drug uniformity, and *in-vitro* release were evaluated. The pre-formulation studies involving description, solubility, melting point, ʎmax, DSC graph, IR spectrum graph of the drug was found to be compatible with the standard values. IR Spectrum of Fenofibrate niosomes formulation indicated that the drug is compatible with the polymers. The risk potential of the formulation and process-related parameters were identified and it was revealed that the formulation parameters of niosomes for optimization of drug entrapment efficiency and *in-vitro* drug release. The optimized niosomes exhibited a porous spherical structure wherein the Fenofibrate sustained its intact structure. The niosomes released Fenofibrate in a controlled release pattern in media for 7 hours which followed the Higuchi and Korsmeyer-Peppas release mechanism. Thus, from the above result, we can conclude that it is possible to formulate niosomes of Fenofibrate using Tween 80 and Span 60 by Ether Injection method for the treatment of hyperlipidaemia. The prepared niosomes can be used to enhance the solubility of the drug may lead to its increased bioavailability and may reduce the dose and dose frequency.

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