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Design, Development and Evaluation of Micro Emulsion by Using Simvastatin

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A B S T R A C T

Microemulsion containing simvastatin was formulated by using pseudo ternary phase diagrams, components & concentration ranges of oils, surfactant & co-surfactants for micro emulsion were screened. Simvastatin microemulsions were developed using olive oil like Tween 80, oil phase as surfactant & ethanol, Iso propyl alcohol & N-propanol like co-surfactant. Micro emulsion containing simvastatin was studied for drug release, viscosity, refractive index, stability, and pH. The developed system showed an increase in bioavailability, the prolonged release of the medication up to 8 hours could result in several profit, like a reduction of Overall Dose frequency of pill-related systemic & administration side effects with improved patient adherence. Considering in vitro release, all these ME showed sustained drug permeation through excised albino rat skin & followed non-Fickian, "anomalous" Korsmeyer-Peppas model for 8 hours. The highest among them (%) drug release was measured in the case of Simvastatin ME F4A. Apart from F2A formulation other formulations of F1A and F9A showed satisfactory results of pH, centrifugation and conductivity.

Keywords: Micro emulsion, TDDS, Simvastatin,

1. Introduction

Much work has been carried out over the last twenty years on the micro emulsion (ME) system to provide new solutions to solve a problem with low aqueous solubility of medicines with high lipophilic compounds and a provide reproducible bioavailability. Because it is a promising vehicle for the delivery of transdermal drugs (TD).

The main issues of conventional simvastatin therapy possess some drawbacks like lower bioavailability and major side-effects. But, a better alternative for conventional simvastatin drug therapy may be micro emulsion-based (TDDS).

1.1 Types of Microemulsion

There are five different types of microemulsion phases in equilibriums.

1. **O/W or Winsor I microemulsions**;- The lower (o / w) microemulsion stage is in line with the top excess oil with two stages.

2. **W/O or Winsor II microemulsions**:- The upper (w/o) microemulsion stage in equilibrium with excess water with two stages.

3. **Bi-continuous or Winsor III microemulsions**:- Three stages: the middle microemulsion stage, in balance with upper excess oil & lower excess aquatic water [o / w + w/o called bicontinuous]

4. **Winsor IV**:- Homogeneously mixed oil-water in a single-phase or(S).

5:- **Winsor V**:- Simultaneous existence of two phases of ME, one in liquid contact and one in oil contact.

1.2 Components of microemulsion formulations

Microemulsion are isotropically systems that are hard to formulate than ordinary emulsion as they have highly specific (F) development involving random connections between constituent molecules. Some oils, surfactants, and co-surfactants can be used as ME components but their toxicity, annoying ability, as well as an unknown mechanism of action, limit their use in the microemulsion(F). The materials used to MEF must be biocompatible, medically

acceptable, non-toxic & emulsifiers within the correct Range of concentration resulting in mild or non- aggressive ME. Surfactant, co-surfactant & oil phase

1.3 Oil Phase

The oil element has an effect on the twist by its ability to penetrate the surfactant monolayer region of the tail group and therefore swell it. Short-chain oils penetrate more widely than long-chain alkanes in the tail group region and thus swell more in this region, leading to improved negative curvature (reduced effective HLBs).

1.4 Surfactant

Surfactants are a wide range of surface-active substances with many (cleaning) uses. Most surfactants have the potential to degrade or clean. The surfactants ' function is to reduce interfacial tension during the synthesis of ME, which eventually stimulates the dispersion cycle during the ME preparation and provides the droplets with flexibility.

1.5 Co-surfactant

A co-surfactant is often added to the mixture to increase the solubility power of the surfactant system. Different substances can be used as co-surfactants, mainly alcohol, amines or ether-alcohols. For the following reasons, cosurfactants(CF) are mainly used in microemulsion (F)The presence of (CF)enables interface film to take on a wide range of curvatures required in order to form microemulsions.

Material and Methods

Apparatus and chemicals: Simvastatin by M/s Intas Pharmaceuticals Ltd., Oliv oil by Thomas Baker Chemical Ltd,Mumb, Isopropyl Alcohol by Ranchem Ltd.., India, Polyethylene glycol 400 SD Fine Chemical Ltd Mumbai

Methods: The Microemulsion Formulation (MEF)was prepared using the water titration method. Three different compositions of MEF s were prepared. They are:

2.1.Olive oil in Ethanol Formulation

Surfactant- tween 80 Co-surfactant- ethanol

Ratio of surfactant: cosurfactant- 1:1, 1:2, 2:1, 1:3, 3:1 Oil- olive oil

2.2.Olive oil in Isopropanol Formulation

Surfactant- tween 80

Co-sufactant- Isopropanol

Ratio of surfactant: cosurfactant- 1:1, 1:2, 2:1, 1:3, 3:1 Oil- olive oil

2.3.Olive oil in Propanol Formulations Surfactant-tween 80

Co-surfactant- n-propanol

Ratio of surfactant: cosurfactant- 1:1, 1:2, 2:1, 1:3, 3:1 Oil- olive oil

Firstly the stock solution of co-surfactant & surfactant in the ratio of 1:1, 1:2, 2:1 & 1:3 were prepared in sufficient quantity by mixing it with a magnetic bead on a magnetic stirrer. After that required quantity of the drug was dissolved in a mixture of co-surfactant & surfactant. Now the exact quantity of oil was mixed with the previous mixture of drug, cosurfactant & surfactant. This final mixture is titrated by distilled water or stirred continuously. with the help of the vortex mixture, the titration continuous until the cloudy or turbid endpoint was achieved. The above procedure was repeated for different compositions of Microemulsion Formulation (surfactant:co-surfactant) for each formulation of 1:1, 1:2, 2:1, 1:3 & 3:1.

Table 2.1 :-Formulation OE (1:1)

Compositions(gm)	F1 A	F1 B	F1 C	F1 D	F1 E	F1 F	F1 G	F1 H	F1 I
Olive Oil	0.2	0.4	0.6	0.8	1.0	1.2	1.4	1.6	1.8
Surfactant with co-surfactant	1.8	1.6	1.4	1.2	1.0	0.8	0.6	0.4	0.2
Water	6.51	2.90	2.40	1.31	0.61	0.41	0.32	0.21	0.08
Simvastatin	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005

Experimental Work

3.1 Preformulation Studies –

Preformulation is an exploratory process that begins early in the development of drugs. Preformulation studies are designed to determine the compatibility of initial excipients for a biopharmaceutical, a physicochemical substance with the active substance & analytical Research to support promising experimental (F).

3.2 Spectroscopic Studies

The infrared spectrum of the pure (S), ethanol, isopropanol & n-propanol sample was recorded or spectral analysis was done. The spectra were recorded over the wavenumber of 4000cm-1 to 650cm-1.

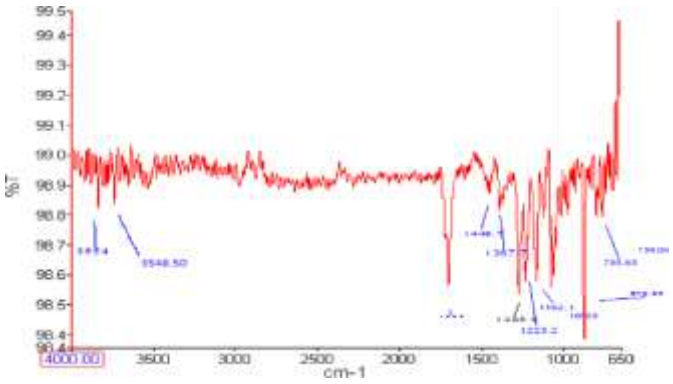

Figure 3.1 :-IR spectrum of Pure Simvastatin

Table 3.1 Characterization of peak in FT-IR spectrum of pure Simvastatin

Sr.No	**Functional group**	**Standard wave number (cm-1)**	**Peak observed in simvastatin API (cm-1)**
1	Free O-H stretch	3546	3548.50
2	Ester C=O stretch	1690-1760	1690.00
3	Methylene C-H symmetric bend; Methyl C-H asymmetric bend	1350-1480	1448.70
4	Lactone -C-O-C bend	1268	1265.50
5	Ester -C-O-C- bend	1164	1162.10
6	Secondary alcohol C-O stretch	1070-1150	1072.90

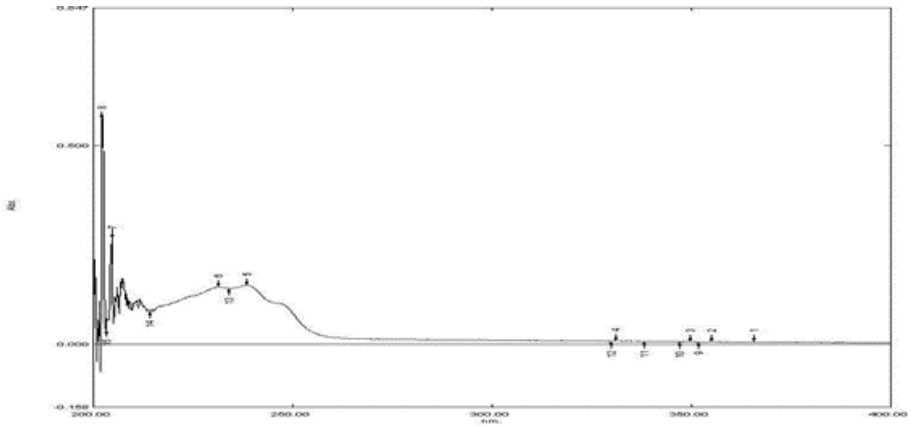

Figure 3.2 :-UV spectrum of Simvastatin at intraday

3.3 Evaluation Parameters

3.3.1 Model Dependent Methods

The Model-dependent approaches are focused on a variety of numerical features that describe the dissolution profile. Model-dependent approaches involved Higuchi, Korsmeyer Peppas & regression models, zero order & first order.

Hixson-Crowell,

Selection of microemulsion formulations for in vitro studies

The following formulations are based on pseudo ternary phase diagrams of ME region are selected for in vitro studies:-

F1A, F2A, F3A, F4A, F9A & F14A

3.3.2 Short term stability study –

Short-term stability of learning from ME carried at 25±20 & 75 percent HR for two months. pH & viscosity of ME at the end of stability study was checked and along with its centrifugation and in vitro release study was done.

4. Results and Discussion

4.1 Characterization of Microemulsion

The average droplet size & zeta potential of the Micro Emulsion System(MES) was described using Zetasizer Nano-ZS.

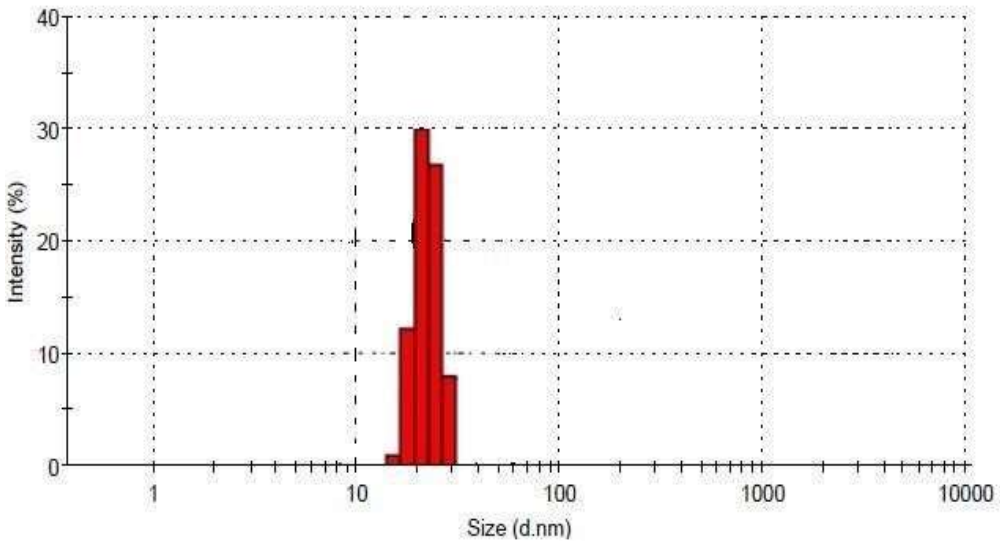

Figure4.1 -Droplet Size of F2A

Determination of pH

The pH of specified formulations is measured with a pH meter. A pH meter was first calibrated using regular pH 4 and pH 9 buffers.

Table4.1 :-Determination of pH

Formulations	pH
F1A	6.05
F2A	6.70
F3A	5.25
F4A	6.65
F9A	6.95
F14A	5.72

Viscosity measurement

A viscosity of ME was assessed use by a viscometer. of Ostwald. The measurement was performed at ambient temperature. These systems must have low viscosity for greater skin penetration. Viscosity of F1A, F2A, F3A, F4A, & F9A, F14A, were found to be.

Table4.2 :-Determination of Viscosity

Formulations	Viscosity Centipoise (cp)
F1A	38.33
F2A	14.70
F3A	42.02
F4A	10.02
F9A	08.05
F14A	06.94

Dye test

Taken a small quantity of (F) in a test tube. Added 1-2 drops of methylene blue reagent and allowed it to stand for a few minutes. The blue color of the sample indicates o/w type of ME.

4.2 Release kinetic studies of microemulsion

The results obtained from studies of in vitro release attempts have been made to fit the following into various mathematical models:

Zero-order model, First-order model, Hixson-Crowell model, Korsmeyer Peppas model, Higuchi model,

Table4.3 :- Model Fitting for the Release Profile of Formulations(OE) by Using 5 Different Models

		Zero Order	**First Order**	**Higuchi Matrix**	**Korsmeyer Peppas**	**Hixon-Crowell**	**Best Fit Model**	**Route of transport**
		R2	R2	R2	R2	R2		
OE Formulati	F1A	0.993	0.978	0.914	0.995	0.993	KorsmeyerPeppas	Non – fickian diffusion
	F2A	0.987	0.987	0.934	0.994	0.987	KorsmeyerPeppas	Non – fickian diffusion
	F3A	0.990	0.988	0.925	0.987	0.991	Hixon- Crowell	Non – fickian diffusion
	F4A	0.990	0.967	0.913	0.993	0.990	Korsmeyer- Peppas	Non – fickian diffusion

$$E.R. = \frac{(\%)\ \text{drug release from test formulation}}{(\%)\ \text{drug release from controlled formulation}}$$

Enhancement Ratio (E.R.)

Table 4.4 :-Enhancement Ratio of formulations used for in vitro study

Formulations	**Enhancement Ratio**
Controlled	1
F1A	2.27
F2A	2.33
F3A	1.62
F4A	2.58
F9A	1.95
F14A	1.66

4.3 Stability Studies

Centrifuge Stress Test

The identified formulations are found to be stable as there was no indication of phase division.

Freeze-Thaw Cycles (FTC) Test

The selected (SF) was established as Being stable because there was no sign of stage separation.

Refractive Index Measurements

Refractive indexes of all the (SF) were established to be in the range i.e. 1.364 to 1.391.

Conductivity Measurements

The conductivity of the (SF)was performed, into which F4A formulation shows the highest conductivity of 0.899mS/cm.

Comparison of (%) Drug Release of the formulations used for in vitro study

F4A formulation shows the highest 81.12 (%) drug release while controlled (F) shows the least 31.44 (%) drug release of all the other formulations. Discussion:-Permeation of the ME drug was significantly enhanced compared to the microemulsion formulation control.

Short Term Stability Study

Short-term stability study(SS)from (ME)-F1A, F2A, F4A & F9A was carried at 25±20 and 75% RH for three months. The pH & viscosity of (ME)at the end of SS was 6.05 for F1A, 6.70 for F2A, 6.65 for F4A & 6.95 for F9A and 38.33 cps for F1A, 14.70 cps for F2A, 10.02 for F4A & 08.05 for F9A respectively. The centrifuge test It has shown that ME has no phase separation and Good physical stability has been observed for 3 months. In vitro drug transport profile of ME of F1A, F2A, F4A & F9A before and at the last SS was similar. The number of medicines transported at the end of 24 hr from ME of batch F1A, F2A, F4A & F9A was 90%, 89%, 95% & 95% respectively.

Table 4.5 :-Determination of short term stability study

Formulations		**Storage condition**	**3 Months stability study**				
			pH	**Viscosity (cps)**	**Centrifugation**	**Drug transport profile**	**% drug content**
rmulation	F1A	25±2^{0}C/75% Relative Humidity	6.05	38.33	No phase separation	Similar	90
	F2A	25±2^{0}C/75% Relative Humidity	6.70	14.70	No phase separation	Similar	89
	F4A	25±2^{0}C/75% Relative Humidity	6.65	10.02	No phase separation	Similar	95
OI Formulation	F9A	25±2^{0}C/75% Relative Humidity	6.95	08.05	No phase separation	Similar	95

8. Results and Discussion

The main issues of conventional (S) therapy possess some drawbacks like lower bioavailability and major side-effects. But, a better alternative for conventional (S) drug therapy may be micro emulsion-based (TDDS). For (T) application, microemulsion containing (S) was formulated. Using pseudo ternary phase diagrams, components & concentration ranges of oils, surfactant & co-surfactants for MEF were screened. (S) microemulsions were developed using olive oil like Tween 80, oil phase as surfactant & ethanol, Iso propyl alcohol & N-propanol like co-surfactant. Results suggest that the system of ME studied possibly suitable vehicles by transdermal delivery of Simvastatin lipophilic hypolipidemic mediator. However significant work remains to be done to validate these results and to explore vehicle tolerance in healthy patients.

The future viewpoint toxicological & clinical elaborated preclinical, study for developing the commercially viable formulation.

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