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LIPID BASED NANOEMULSIONS AS DRUG DELIVERY SYSTEM FOR POORLY-WATER SOLUBLE DRUG

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ABSTRACT

To improve the bioavailability of the inadequately water-solvent medication Aceclofenac, a lipid-nanoemulsion involving ethanolic arrangement of phospholipids 90 G and tween 80 in 1:1 proportion (Smix), triacectin and a seed oil as oil stage and refined water as watery stage, in the proportion of 55:15:30 (% w/w) was produced by building pseudo-ternary stage charts and assessed for consistency, % transmittance, and surface morphology of nanoemusions. IN VITRO dispersion (discharge) of Aceclofenac from three distinct bases to a watery receptor stage through cellophane layer was checked spectrophotometrically at 273 nm. Contrasted and hydroalcoholic tranquilize arrangement, sleek arrangement, and regular emulsion and suspension. The lipid-nanoemulsion demonstrated increment in medication discharge contrasted with medication suspension. This might be ascribed to expanded dissolvability of the medication from nano estimated emulsion.

KEYWORDS: Aceclofenac, Lipid-Nanoemulsion, Viscosity, Transmittance: Viscosity.

INTRODUCTION

Various poorly water-soluble drug candidates present a rigorous challenge for their successful formulation, clinical efficacy, industrial applicability, and marketing. Despite the prevailing good pharmacological activity of such drugs, anticipated clinical effectiveness has not been documented. In most cases when these drugs are orally administered, because of their poor water solubility, the dissolution rate in the gastrointestinal (GI) tract is considered to be the rate-limiting step. This complication has hampered the permeation as well as the quantity of the drug absorbed, which further leads to low and unpredictable oral

bioavailability. To conquer this challenge many formulation design approaches are currently in use, including solid dispersion, complexation, and aggregates of compounds. However, these approaches cannot guarantee the physicochemical stability of the drug compounds.[1-3] The use of lipid- and surfactant-based formulations is among several approaches found to be capable of improving the bioavailability of poorly water-soluble drugs.

Nanoemulsifying drug delivery systems as lipid- and surfactant-based formulations encompass a practical achievement in improving the oral bioavailability of poorly water-soluble drug compounds by presenting and maintaining the drug in a dissolved state, at the molecular level, in small droplets of oil, throughout its transit through the GI tract.[4-7] Nanoemusions are mixtures of oil, surfactant, and cosurfactant, and they are capable of forming thermodynamically stable oil-in-water (o/w) nanoemusions upon moderate stirring provided by the stomach and the upper small intestine. The permeation and absorption of drugs from nanoemusions are subject to the rate of dispersion, extent of emulsification, droplet size, solubilization, and precipitation of drug from the formulation upon dispersion. The Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) possess anti-inflammatory, analgesic and antipyretic activities. Aceclofenac is a Diclofenac derivative (phenyl acetic acid group) of the Non– Steroidal Anti-Inflammatory Drug which is chemically, (2-[2-[2-(2, 6 dichlorophenyl) aminophenyl] -acetyl] oxyacetic acid). Aceclofenac exhibited potent Anti-Inflammatory Analgesic activity and is widely prescribe for the treatment of osteoarthritis, rheumatoid arthritis, acute lumbago, and dental pain condition. A unique feature of aceclofenac pharmacology is that it stimulates glycosaminoglycans (GAG) synthesis, which in turns enhances skin permeation of NSAIDs. Nanoemusions are isotropic, thermodynamically stable transparent (or translucent) systems of oil, water, surfactant and co-surfactant with a droplet size usually in the range of 20–200 nm. Their long-term stability and ease of preparation (spontaneous emulsification) make it promising tool for drug delivery. The purpose of this research work was to formulate aceclofenac-loaded nanoemusions as to augment the in vitro release by improving solubility and to enhance the ex vivo intestinal permeation of aceclofenac by delivering it at the molecular level in the form of nanocarriers. In addition, aceclofenac - loaded were compared with a hydroalcoholic solution, oily solution, and conventional emulsion and suspension of aceclofenac. In Initial studies nanoemusions are prepared by High pressure homogenizer the basic characterization studies are carried out.

MATERIAL AND METHODS

Aceclofenac drug obtained as gift sample from the IPCA Pharmaceuticals, Mumbai, Ethanol, propylene glycol, Span 20, and Span 80 were purchased from S.D. Fine Chemicals (Mumbai, India). Cell phone membrane was purchased from Hi Media Laboratories (Mumbai, India). All other chemicals used in the study were of analytical reagent grade and were used as received.

Preformulation Studies of Pure Aceclofenac Preformulation study is one of the important prerequisite in development of any drug delivery system. It gives the information needed to define the nature of the drug release is either dissolution or diffusion. Hence, Preformulation studies on the obtained sample of drug for identification including FTIR study of drug, solubility analysis, melting point determination.

Solubility Analysis: Preformulation solubility analysis was done, which include the selection of suitable solvent, to dissolve the respective drug. The solubility was done by adding the solute in small incremental amounts to the fixed volume of solvents, after each addition, the system was vigorously shaken and examined visually for the un dissolved solute particles. When some amount of the solute remains un dissolved, the total amount added up to the point served as a good and rapid estimate of solubility.[9]

Melting Point Determination: Melting point determination of the obtained sample was done as it is a good first indication of purity of the sample. The presence of relatively small amount of impurity can be detected by a lowering as well as widening in the melting point range. Melting point of drug sample was performed by using Thieles tube method. A fine powder of Aceclofenac was filled in a capillary tube, previously sealed at one end and the capillary tube was tied to the bottom of the thermometer. The thermometer and capillary tube were immersed in to the liquid paraffin taken in the tube. Bottom of the tube was heated gently by means of burner. When the sample starts to melt the reading was recorded.[8,9]

Determination of λmax

A stock solution of Aceclofenac was prepared by dissolving 10mg of drug in 25ml of methanol (0.1 N) to obtained stock solution of 400 µg/ml. From this stock solution working standard are prepared & then scanned in spectrum mode in the range of 400- 200 nm using UV-visible spectrophotometer to determine the lambda max (wavelength of maximum absorption) of the drugs.[10]

Equilibrium solubility studies of aceclofenac

Components for the development of were selected on the basis of equilibrium solubility studies so as to incorporate the desired dose of aceclofenac. Solubility of aceclofenac was determined in various oils (triacetin, an seed oil, Miglyol 812, castor oil, isopropyl myristate, soybean oil, and olive oil), surfactants (Span 20, Span 80, Labrafac PG, Plurol Oleique, and Lauroglycol 90), co-surfactants (ethanol, PEG 200, PEG 400, propylene glycol), and aqueous phase (distilled water) using the shake flask method.[11] An excess amount of aceclofenac was mixed with solvents (n = 3) and kept on a water bath shaker at room temperature (27° ± 2°C) for 72 hours. Samples were taken at predetermined time intervals and centrifuged at 5000 rpm for 10 minutes. The supernatant was filtered through 0.22 µ membrane filter and then diluted with methanol, and the amount of aceclofenac solubilized was analyzed spectrophotometrically at 273 nm.

Construction of pseudo-ternary phase diagrams

For the development of aceclofenac-loaded, pseudo-ternary phase diagrams were constructed to recognize the zone of nanoemulsion formation. For the construction of each phase diagram, oil and specific Smix ratio were mixed carefully in diverse weight ratios from 9:1 to 1:9 (% w/w). Additionally, each weight ratio of oil and Smix mixture was titrated slowly with distilled water with gentle stirring to allow equilibration.[11] The pseudo ternary phase diagram for selection of clear region for the formulation of the primary nanoemulsions as the shown in the Figure 1.

Preparation of nanoemulsion by HPM

The nanoemulsion of aceclofenac were prepared by using triacetin and anseed oil mixtures as oil phase and Smix in 1:1 ratio of the ethanolic solution of phospholipid 90 G and Tween 80. The best clear region for formulation is selected from the pseudo ternary phase diagram. The various formulation of aceclofenac were formulated from F1 to F5 using the High pressure homogenizer to get the secondary primary nanoemulsion of previously developed primary nanoemulsion using the high speed mixture at 10000 to 15000 rpm. The various formulations from F1-F5 with varying S_{MIX} and oil phase showed in the **table 1**. The secondary nanoemulsion of the aceclofenac passed through the HPM for 3-4 cycles to get the desired opalescent and transparent nanoemulsion. Further these nanoemulsion formulations are characterized by viscosity, % transmittance, optical microscopy.

RESULTS AND DISCUSSION

Solubility of aceclofenac is insoluble in water, freely soluble in acetone, soluble in ethanol. Melting Point of Aceclofenac was found to be 150 ^{0}C. The oil-in-water lipid nanoemulsions were prepared by screening the excipients from the nanoemulsion region of pseudo ternary phase diagram. The prepared nanoemulsions were subjected to different thermodynamic stability tests.

From the solubility of drug in various oils it show good solubility in triacectin and an seed oil as this combination is used as oil phase and ehanolic solution of Phospholipids' 90G and Tween 80 combination used. Aceclofenac is a pro drug less stable as previous studies reported on the plain nanoemulsion of the aceclofenac but in this work we tried to develop the complex of the aceclofenac with the ehanolic solution of the phosphoric 90 G.

The complex formation of aceclofenac in the lipid nanoemulsion of the aceclofenac using the blend of triacectin and an seed oil. The interaction of the aceclofenac with solid lipid steric acid also studied for the development of solid lipid nanoparticles can be developed from the lipid nanoemulsions. DSC thermogram of aceclofenac containing steric acid, pure aceclofenac and pure steric acid showed in the figure 2, 3 and 4 respectively. The prepared lipid nanoemulsion are characterized for Viscosity, % Transmittance showed in the table 2 and 3 respectively.

Nanoemulsion formulations were developed for aceclofenac with the aim to increase the effect, controlled permeation, increased drug solubilisation capacity and to minimize oral side effects of drug. Pharmaceutically acceptable, non-irritating, and non-sensitizing excipients were selected for this. From pseudo ternary phase diagram, the concentration of oil phase; Smix and distilled water were optimized and further processed for the formulation of aceclofenac lipid nanoemulsion. The same degree of release and permeation among was observed, which turned out to be a good o/w nanoemulsion in the GI tract, thereby enhancing the absorption and bioavailability of poorly water-soluble drugs. These results demonstrate the principal suitability of as a promising approach for aceclofenac delivery. Furthermore, it is possible to enclose aceclofenac -loaded in a capsule dosage form for further preclinical and clinical studies. Stability study: There was no evidence of phase separation, development of disagreeable odour, change in colour and consistency of the all three products during stability study for three months at both room temperature and at refrigerator temperature.

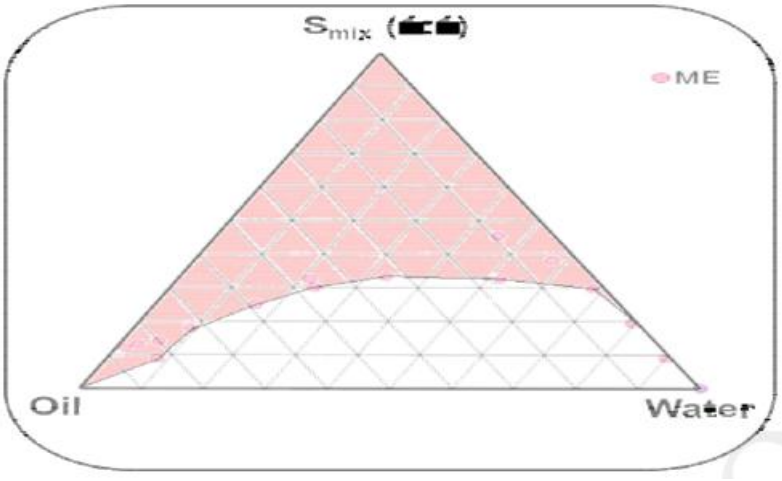

Figure. 1: Pseudo Ternary phase diagram of triacetin with Aceclofenac in 1:1 S_{MIX}.

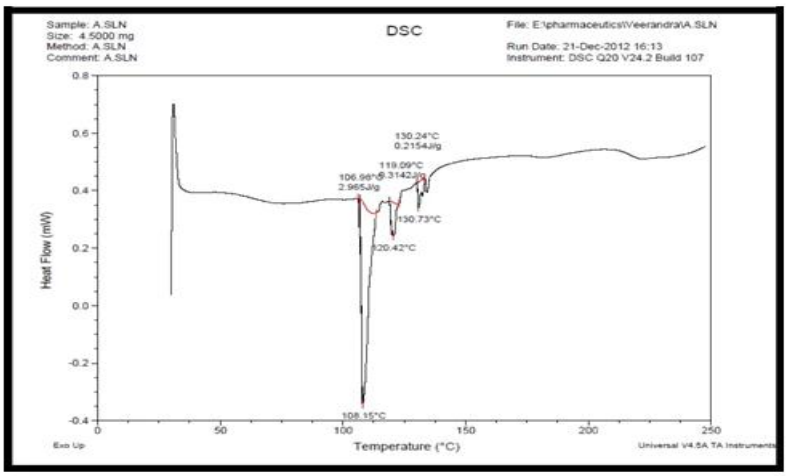

Fig. 2: DSC of aceclofenac containing stearic acid

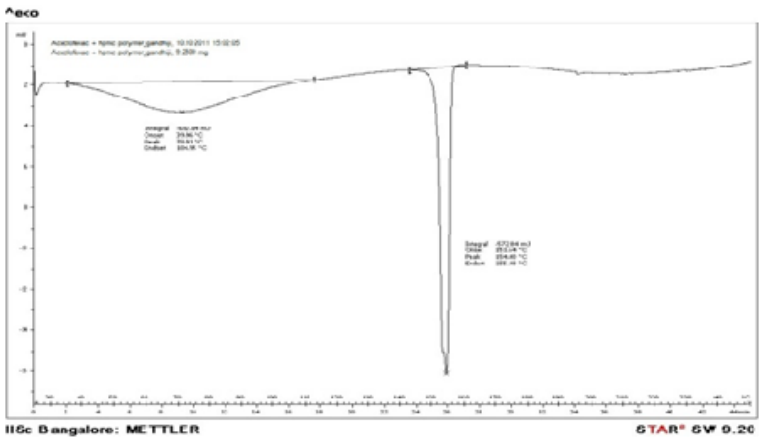

Fig. 3: DSC of pure Aceclofenac.

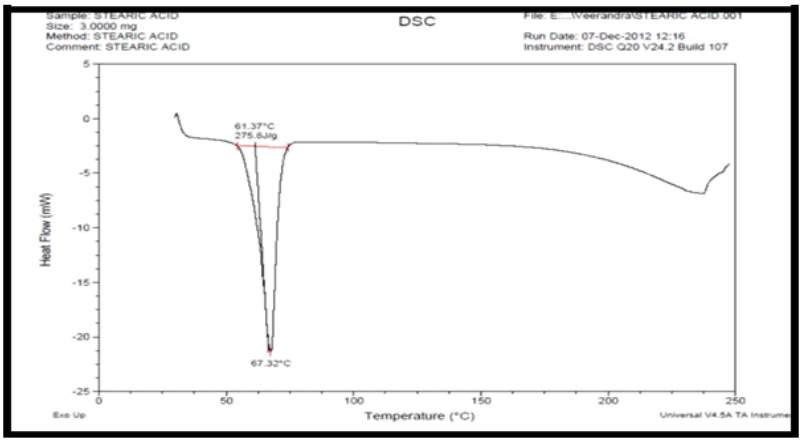

Fig. 4: DSC of pure Stearic acid.

Table. 1: The composition of Aceclofenac lipid- nanoemulsion for 100 gm % w/w.

Formulation/Components	F1	F2	F3	F4	F5
Aceclofenac	41	59	32	33	37
Triacetin & Anseed oil	10	11	13	15	21
S_{mix}	53	32	54	52	47
Water	1.5	1.5	1.5	1.5	1.5

Table. 2: The viscosity of the nanoemulsion formulations.

Formulation/rpm	F1 (centipoise)	F2 (centipoise)	F3 (centipoise)	F4 (centipoise)	F5 (centipoise)
20	0	0	1.5	0	0
50	1	1	2.0	1	1
100	1.5	1.5	1.5	1.5	1.5
50	1	1	0	0	0
20	0	0	0	0	0

Table. 3: The % Transmittance of the nanoemulsion Formulations.

Formulations	%Transmittance
F1	93.5
F2	94.3
F3	95.1
F4	92.2
F5	90.3

CONCLUSION

In conclusion, it was observed that the solubilization capacity and complexation of aceclofenac with phospholipid and stearic acid as suitable candidate for the novel lipid nanoemusions, a poorly water-soluble drug, strongly depends on the composition as well as concentration of Smix used. Based upon improving drug solubility in addition to nano size-range globules. A significant increase in drug processing and performance characteristics as

optimized formulation F3 composed of Smix, oil, and water in ratio of 55:15:35 (% w/w), respectively. Accordingly, this novel aceclofenac loaded lipid nanoemulsions is a versatile, useful formulation that enhances the release and permeation of drug across the intestine by raising the solubility. The permeation, in vivo bioavailability and stability studies are in progress. It can be concluded that the selection of surfactant and cosurfactant on the basis of their emulsification capabilities other than the solubilizing capacity of drug is an important criterion for the formulation of lipid nanoemulsion.

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