STUDIES ON NANOLIPID EMULGEL OF NIMESULIDE FOR TRANSDERMAL DELIVERY

ABSTRACT

The objective of the present study was to develop and evaluate a nanolipid transdermal emulgel of Nimesulide. The nanolipid particles of Nimesulide were developed using Compritol 888 ATO and Labrafil M1944 as lipids, Polysorbate 80 as surfactant with Poloxamer 188 and Polyethylene Glycol 400 as stabilizer and cosolvent respectively. The nanoparticles were developed by Hot Nanoemulsification Low Temperature Solidification method and showed drug entrapment efficiency of 67 ± 2.316 % with particle size of 500 – 600 nm. TEM studies indicated presence of spherical particles in the nanometric range. The nanolipidic dispersions were suitably gelled to form emulgel. The *in vitro* release of the developed emulgel showed sustained drug release for 8 hours with no evidence of toxicity during histopathological testing after *ex vivo* permeation studies. The nanolipid emulgel of Nimesulide can thus provide sustained release action due to enhanced skin deposition for effective treatment of chronic arthritic conditions, thereby improving patient compliance.

Keywords: Nimesulide, nanolipid particles, hot nano emulsification low temperature solidification method, emulgel

INTRODUCTION

In chronic conditions such as osteoarthritis and rheumatoid arthritis, there is a need for frequent dosing for prolonged periods which can alleviate pain and provide relief by improving the quality of life. Transdermal drug delivery is the most promising route for the delivery of drugs in the treatment of arthritis offering advantages of localized drug action, avoidance of peripheral side effects, suitability for drugs with short half-lives, termination of drug action when desired etc[1]. For successful transdermal drug delivery, nanometric size of particulate lipid carriers can provide greater permeability through the stratum corneum due to similarity with physiological lipids and their larger surface area making these carriers suitable for transdermal delivery of encapsulated drugs[1,2]. The particulate lipid carriers include solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). NLCs are a blend of biodegradable solid and liquid lipids that along with enhanced permeation through tissues prolong the drug release, thus being favorable for chronic conditions like arthritis. Their nanosize ensures close contact with the stratum corneum and can increase the amount of drug penetration into the skin, providing sustained release and reducing the frequent applications of drug. Thus, due to the mentioned advantages, NLCs are attractive as nanolipid carriers for transdermal applications[3,4]. Nimesulide, BCS Class II drug is a preferential COX- 2 inhibitor used in the treatment of rheumatoid and osteo arthritis[5,6]. Emulgels are either oil in water or water in oil emulsions that are gelled using gelling agents. The aim of the present investigation thus, was to develop and evaluate nanolipid emulgel of Nimesulide (1% w/w) for transdermal delivery. Such a delivery system is proposed to enhance drug penetration through the stratum corneum and provide sustained effect to improve patient compliance in arthritis[7-10].

MATERIALS AND METHODS

Materials

Nimesulide (NMS) was a kind gift sample from Aarti Drugs Pvt Ltd, Mumbai, India. Compritol 888 ATO, Labrafil M1944 CS were provided as generous gift samples from Gattefosse Pvt. Ltd, India, Poloxamer and Tween 80 were kind gift samples from BASF Ltd, India and Carbopol was received as gift sample from Lubrizol Ltd, India. PEG 400 and Methanol AR were as purchased from SD Fine Chemicals, India.

METHODS

Development of nanolipid carriers and nanolipid emulgel of Nimesulide

Saturation solubility of Nimesulide was studied by incorporating excess of drug in solid and liquid lipids, surfactants, stabilizers and cosolvents to optimize the excipients for development of nanolipid carriers of Nimesulide. The quantities of lipids, surfactants, cosolvents and stabilizers were optimized based on drug loading and stability of the formed nanolipid dispersions. The nanolipid dispersions were prepared by hot nano emulsification low temperature solidification method by the mentioned procedure. The lipids along with surfactants,

cosolvents, stabilizers and the drug were heated to 8-10° C above the melting point of the solid lipid. Aqueous phase was also heated to the same temperature and gradually added to the lipidic phase under stirring at 1500 rpm for 20 minutes. The crude emulsion was immediately cooled in ice bath for 15 minutes to yield nanolipid dispersion. The nanolipid dispersion of Nimesulide was then formulated into a gel using 0.5% w/w Carbopol Ultrez NF 10. The gelling agent was dispersed in the nanolipid dispersion under stirring at 800 rpm for 3 hours and then neutralized using Triethanolamine AR to pH 7.2-7.4. The developed formulations were evaluated for quality control parameters including particle size, polydispersity and zeta potential. The morphology of the nanolipid carriers was determined by Transmission Electron microscopy (TEM).

In vitro release and *ex vivo* permeation studies:

The *in vitro* drug release from Nimesulide nanolipid dispersion and emulgel was evaluated using presoaked dialysis bag (molecular weight cut off: 12 – 14 kDa) tied to the paddle in USP apparatus Type II at 25 rpm for 8 hours with 200 mL of phosphate buffer, pH 7.4 containing 2 % w/v Tween 80 as the release medium maintained at 32 °C ± 0.5°C. The *ex vivo* permeation of Nimesulide nanolipid emulgel was evaluated using Franz diffusion cells. The diffusion medium used was 20 ml of phosphate buffer, pH 7.4 containing 2 % w/V Tween 80. The study was carried for 8 hours at 32 °C ± 0.5 °C using Sprague Dawley female rat abdominal skin. Suitable aliquots during the studies were withdrawn at specific time intervals and the cumulative amount of Nimesulide released and permeated at various time intervals were analysed spectrophotometrically at λ_{max} 261 nm using Jasco-V-530, Japan. The *in vitro* release data was fitted to different mathematical models and the release kinetics was determined. The steady state flux [J_{ss}] and permeability coefficient [K_p] of the drug was calculated as follows:

Steady state flux [J_{ss}] = Q/AxT, where Q = quantity of compound transported through the membrane in time T, A = area of exposed membrane in cm^2, permeability coefficient K_p = [J_{ss}] X C_o, where, [J_{ss}] = steady state flux, C_o is the initial drug concentration in the donor compartment.

Histopathological studies:

After completion of *ex vivo* permeation studies, the excised rat abdominal skin was prepared for histopathology study by chemical fixation. Thin transverse sections of skin were examined for any microscopic alterations due to permeation of the developed formulation.

Table I: Evaluation of the developed formulations

Sr. No	Parameters	Nanolipid particles of Nimesulide	Nanolipid emulgel of Nimesulide
1	Appearance	Light yellow dispersion	Light yellow, smooth gel
2	Particle Size	428 ± 34 nm	663 ± 20 nm
	Polydispersity Index	0.3 ± 0.034	0.23 ± 0.049
3	Zeta Potential	-25 ± 4.78 mV	-28 ± 5.07 mV
4	pH	7.2 - 7.4	7.2 - 7.4
5	Drug Entrapment Efficiency	67 ± 2.67%	-
6	Drug content	-	98.95± 2.67%
7	*In vitro release* (at the end of 8 hours)	65% ± 5.98%	45% ± 6.78
8	*Ex vivo* permeation (at the end of 8 hours)	-	14 % ± 5.87 J_{ss}= 0.564µg/ cm^2/hour, Kp = 5.6x 10^{-4}
9	Histopathological studies	-	Absence of changes in anatomical outlines, epidermis, dermis and hypodermis were well preserved

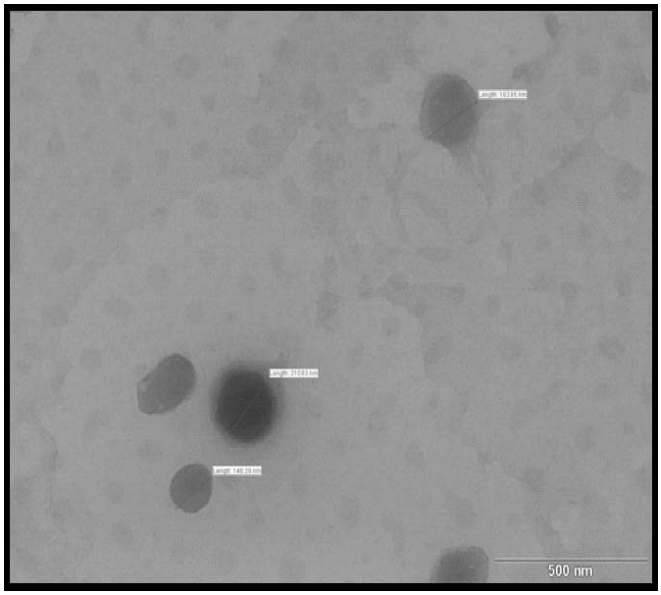

Fig. 1: Transmission electron photomicrograph of Nimesulide nanolipid dispersion

Differential Scanning Calorimetry

Thermal characterization of Nimesulide nanolipid particles was performed using DSC Q 20 V24.11. Build 124 and compared with pure drug, Nimesulide. The thermograms were recorded from 25 – 500°C at a heating rate of 10°C/minute and nitrogen flow rate of 20 mL/minute was used for each run.

Viscosity

Brookfield viscometer (LVT model) using spindle number 3 was used to determine the viscosity of the developed emulgel at shear rate of 30 rpm.

Stability studies

The developed emulgel was subjected to accelerated stability studies for a period of three months as per ICH guidelines.

RESULTS AND DISCUSSIONS

Compritol 888 ATO (5% w/w) as solid lipid, Labrafil M1944CS (5% w/w) as liquid lipid, Polysorbate 80 (8.4% w/w) as surfactant, Poloxamer 188 (3.6% w/w) as stabilizer were selected in combination with Polyethylene glycol 400 (6% w/w) as cosolvent and optimized for the development of stable nanolipid carriers of Nimesulide (1% w/w).The stabilizers and cosolvent were added to prevent drug precipitation. The results of the evaluation of the nanolipid particles and the nanolipid gel of Nimesulide are depicted in Table I. The transmission electron micrographs revealed spherical nature of the lipidic particles which were in the nanometric range (Fig. 1). The nanolipid Nimesulide emulgel showed slower drug release than the nanolipid drug dispersion in *in vitro* studies due to drug partitioning between the lipid matrix and the crosslinked three-dimensional viscous gel network, thus retarding the drug release. The Differential Scanning Calorimetry showed reduction in the peak intensity at 150.38°C (Nimesulide endotherm) indicating solubilisation of drug in the lipidic blend. The viscosity of the developed gel was found to be 15700 $\pm$ 0.86 cps and the formulation was found to remain stable at the end of 3 months at accelerated conditions in accordance with ICH guidelines.

CONCLUSIONS

Nimesulide nanolipid carriers were successfully prepared by hot nanoemulsification low temperature solidification which is a simple technique, obviates use of organic solvents and is reproducible. The nanolipid carriers were prepared using Compritol 888ATO and Labrafil M 1944CS as lipids, Polysorbate 80 and Poloxamer 188 as surfactant and stabilizer respectively with PEG 400 as the cosolvent to improve drug loading and prevent drug precipitation. The differential scanning calorimetric studies revealed successful drug entrapment in the lipid matrix while TEM confirmed the spherical and nanometric size of the lipid particles. The nanolipid emulgel was developed using Carbopol Ultrez 10 NF as gelling agent showing sustained drug release upto 8 hours in *in vitro* and *ex vivo* studies. The developed emulgel was found to be stable and non-irritant. This approach can be promising for pain management by improving the quality of patient's life by reducing the frequency of applications, prolonging the drug action and maintaining the functional integrity of joints by reducing inflammation and pain. Thus, the emulgel can provide consistent drug deliveries for extended periods of time with an improved bioavailability especially for chronic pain conditions like rheumatoid arthritis, ankylosing spondylitis, osteoarthritis etc.

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