Journal of Scientific Research in Pharmacy
Available online through
www.jsrponline.com

Research Article
ISSN: 2277-9469

Mepivacaine Hydrogel using Trimyristin

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Received on: 04-02-2014; Revised and Accepted on: 24-02-2014

ABSTRACT

The objective of the present investigation was to formulate solid lipid nanoparticles (SLN) for improving the dermal delivery of a local anesthetic agent mepivacaine.SLN were characterized for particle size distribution, polydispersity index, entrapment efficiency, X-ray powder diffraction pattern (XRD), thermal behavior by differential scanning colorimeter (DSC). Mepivacaine loaded SLN was formulated into hydrogels for topical application. Mepivacaine SLN showed a particle size of 87.9 nm with a polydispersity index of 0.14.The entrapment efficiency of mepivacaine was found to be 99% .The SLN formulation was stable with respect to particle size, polydispersity, and entrapment efficiency.

Key words: *Solid lipid nanoparticles, Mepivacaine, Hot homogenization.*

INTRODUCTION

The skin, the largest organ of the body is a natural protective barrier against penetration of toxic exogenous compounds, excessive loss of water and other essential compounds, or as a promising portal of entry of drugs for local and/or systemic action. Mepivacaine is an effective local anesthetic of rapid onset, intermediate action, and low systemic toxicity [1]. The available formulations are characterized by immediate release and short duration of action.

In any anesthetic topical application, the drug should penetrate the stratum corneum and desensitize the underlying pain receptors within the skin. New topical drug delivery systems such as particulate carriers help the drug to reach the site and exert the desired pharmacological action at a controlled rate. There are many particulate carriers available [2]. A number of carrier systems like microemulsion, liposomes, and nanoparticles have been investigated for dermal delivery of drugs. These systems may enhance drug permeation in skin, increase duration of local action, and prevent systemic absorption of drugs thereby reducing side effects associated with the drugs [3].

Local anesthetics incorporated into liposomes have shown greater effectiveness with fewer side effects [4, 5]. Combination of iontophoresis and microemulsion has also been reported for better permeation in the skin layers [6].

Solid lipid nanoparticles (SLN) have emerged as an alternative to liposomes due to various advantages such as improved physical stability, low cost compared to phospholipids, and ease of scale-up and manufacturing [7-9].

In this research mepivacaine solid lipid nanoparticles will be prepared and characterized for topical application.

MATERIALS AND METHODS

Materials:

Trimyristin (TM) was generously supplied by Sasol (Witten, Germany). Poloxamer 188 (Pluronic F 68) was purchased from HiMedia (Mumbai, India). All other chemicals and solvents were of analytical reagent grade and were used without further purification.

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Preparation of Mepivacaine SLN:

SLN were prepared by a hot homogenization followed by ultrasonication method[10] Mepivacaine (0.1% wt/vol), trimyristin (2% wt/vol), and phosphatidylcholine 95% (1.5% wt/vol) were dissolved in a 10-ml mixture of chloroform and methanol (1:1). Organic solvents were completely removed using a rotary evaporator. The drug-embedded lipid layer was melted by heating 5°C above the melting point of the lipid. An aqueous phase was prepared by dissolving poloxamer 188 (1% wt/vol) in double-distilled water and heating to the same temperature as the oil phase. The hot aqueous phase was added to the oil phase, and homogenization was performed (at 6000 rpm and 70°C) for 3 minutes. The coarse hot-oil-in-water emulsion so obtained was ultrasonicated using a sonicator for 30 minutes.. Mepivacaine SLN was obtained by allowing the hot nanoemulsion to cool to room temperature. Blank and Mepivacaine SLN prepared were named as BL-TM and Mep-TM respectively.

Measurement of Size, Zeta Potential, Entrapment Efficiency, and Assay:

Sizes of blank and Mepivacaine SLN of TM with different percentages of poloxamer 188 were measured using zetasizer. Zeta potential, entrapment efficiency and assay was measured and calculated as per standard procedure. The results are tabulated in **Table 1**.

Differential Scanning Colorimeter Studies:

SLN without mepivacaine and mepivacaine loaded SLN were freeze dried. The thermograms of individual components and of SLN were recorded on Chromatopac R6A (Shimadzu, Japan) thermal analyzer. An accurately weighed amount (5 mg) of individual components was transferred to aluminum pans and the samples were scanned from 30°C to 110°C at the heating rate of 5°C/min using an empty aluminum pan as reference.

X-ray Diffraction Pattern Studies:

X-ray diffraction patterns (XRD) were recorded to evaluate the physical nature of the formulations. SLN without drug and mepivacaine -loaded SLN were freeze dried so as to keep the formulation in powdered form.

Formulation of topical gel:

One ml of acetic acid 6% was dissolved in 100 ml of water. To this one gram of chitosan was added. This preparation was kept overnight and the viscosity determined. One gram of drug loaded SLN and SLN without drug, 1% glycerine, 2.5% propylene glycol was added and made up to 100g with purified water.

In vitro Studies:

In vitro permeation of mepivacaine from the lipid nanoparticulate-based gel and marketed formulation Xylocaine gel (AstraZeneca, India) was evaluated using cellophane paper. This was mounted on modified Franz diffusion cell with a surface area of 6 cm^2. The receptor compartment consisted of phosphate buffer pH 7.2. Five gram of gel formulations (Xylocaine and SLN) was used for the study. The temperature was maintained at 37 ± 0.5°C. One milliliter of receptor medium was withdrawn at time intervals of 0, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 15, 18, and 24 h and was replaced by the same volume of fresh buffer to maintain the sink condition. The amount of drug released in the receptor medium was calculated.

RESULTS AND DISCUSSION

Preparation of Mepivacaine SLN:

SLN prepared by a hot homogenization followed by ultrasonication method was found satisfactory and the colloidal dispersions were found satisfactory with respect to visual observation and did not sediment in 15 days.

Characterization of Mepivacaine SLN:

Sizes of blank and Mepivacaine SLN of TP with different percentages of poloxamer 188 were measured using zetasizer. As the poloxamer 188 concentration increased from 0.5% to 1.0%, the mean particle size decreased. In all the formulations, the optimum size (60.1-89.9 nm) was obtained at the 1% poloxamer concentration. The zeta potential of mepivacaine SLN was slightly lower than that of blank SLN (**Table 1**). The entrapment efficiency of mepivacaine SLN was more than 99%, and assay values was 0.95 mg/ml.

XRD Studies of LID SLN:

X-ray scans of SLN confirmed that the individual components lost their crystalline nature when incorporated into SLN.

***In vitro* Permeation Study:**

Fig. 1 gives the invtro permeation study. Marketed gel Xylocaine showed complete permeation at the end of 6-8 h. The mepivacaine SLN provided biphasic permeation pattern wherein about 50% of drug was permeated in 6-8 h followed by a sustained release till 24 h. During the initial 1-2 h of the study, burst of mepivacaine permeation from SLN was observed. Furthermore, the system was able to achieve a slow permeation for 6-8 h wherein about 50% of the entrapped drug was permeated.

Stability studies:

Mepivacaine SLN formulations did not show visual physical instability up to a period of 6 months. The SLN formulations were stable with respect to particle size, entrapment efficiency and showed some leakage.

Table No. 1: Size, Zeta Potential, Entrapment Efficiency, and Assay of SLN of (mean ± SD, n = 3)*

SLN	Size (nm)	Polydispersity Index	Zeta potential (mV)	Entrapment Efficiency (%)	Assay (mg/ml)
BL-TP	85.3±1.2	0.163±0.06	21.5±0.6	----	----
MEP-TP	87.9±0.6	0.136±0.02	20.2±1.4	99.5±0.34	0.97±0.06

*SLN indicates solid lipid nanoparticles; BL, Blank;MEP Mepivacaine.

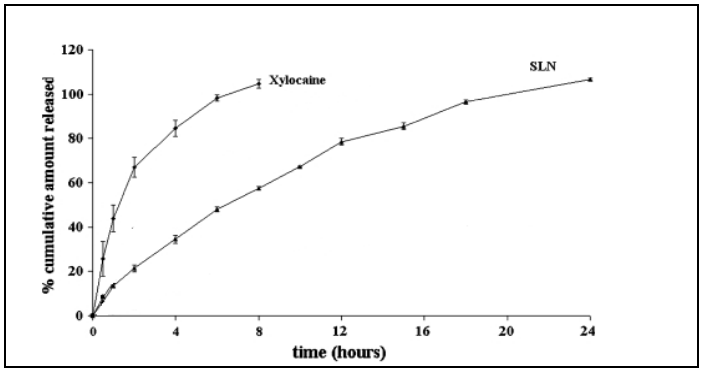

Fig. 1: In-Vitro Permeation study

CONCLUSION

Mepivacaine can be formulated as SLN and incorporated in to the gel which gives a slow permeation so that deep anesthesia effect can be seen.

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Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil