

Research Article

FORMULATION AND EVALUATION OF MELOXICAM LOADED NANOEMULGEL FOR TOPICAL DRUG DELIVERY

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ABSTRACT

Objective: To formulate and evaluate meloxicam loaded nanoemulgel for topical drug delivery. **Methods:** Nanoemulsion is prepared by spontaneous emulsification technique. Nanoemulgel is prepared by adding nanoemulsion into the gel matrix. Characterization of meloxicam loaded nanoemulgel were performed. **Results:** The nanoemulgel was evaluated for clarity, homogeneity, pH, viscosity, percentage drug entrapment and In vitro drug release study. The results of the formulation was found to be satisfactory. The drug content was within acceptable range. The drug release mechanism from the tablets was found to be non fickian transport kind of diffusion. **Conclusion:** Meloxicam nanoemulgel can be effectively used for topical drug delivery.

Keywords: Meloxicam, Nanoemulsion, Nanoemulgel, spontaneous emulsification.

INTRODUCTION

Nanoemulsions are formulated using high concentration of surfactant for the effective topical delivery system. Nanoemulsions containing active pharmaceutical ingredient with large surface area due to small droplet size and low surface tension. Nanoemulsions improve the efficacy and minimize the side effects by allowing rapid penetration of lipophilic actives and thus reducing the dose. They also provide greater absorption of solubilized lipophilic drugs. Nanoemulsions shows improved physical stability, nonirritant and non-toxic nature, they can be employed in topical drug delivery systems. The emulsion and nanoemulsion differ mainly in size and shape of the particle dispersed in the continuous phase [1,2].

Nanoemulgel is the formation of nanoemulsion-based hydrogel in the addition of nanoemulsion system into the hydrogel matrix. Nanoemulgel drug delivery system exhibit better adhesion on the surface of the skin and high solubilizing capacity which leads to high concentration gradient towards the skin, hence influences better skin penetration. Nanoemulgel is a gel based formulation and it has upgraded properties of thixotropic, longer shelf life, effortlessly spreadable, non-greasy, and can be easily removed [1,2].

MATERIALS AND METHODS

MATERIALS

The following materials were used (Grade-LR): Meloxicam -API (Apex Healthcare Limited Ankleshwar, Gujarat), Labrafac PG (Gattefosse India), Sodium Hydroxide, Potassium Dihydrogen Phosphate, Thioglycolic acid (Spectrum Reagents and Chemicals, Cochin), Span 80, Tween 80, Glycerin, Methanol, Ethanol (Nice chemicals, Cochin).

METHODS

PREFORMULATION STUDIES

Solubility

The solubility of drug was observed in different solvents such as water, acetone, dichloromethane, diethyl ether, dimethylsulphoxide, chloroform, ammonia and water [3].

Melting point Determination

Melting point of the drug was determined by melting point apparatus [3].

Compatibility Studies

IR spectral analysis of pure drug and polymer was carried out as physical mixtures. Observation was made whether changes in the chemical constitution of drug occurred after combining it with the polymer. The absorption maxima in spectrum were compared with the reference spectrum [3].

PREPARATION OF MELOXICAM LOADED NANOEMULSION

Nanoemulsion is prepared by spontaneous emulsification technique. A homogenous organic solution composed of Labrafac PG and Span 80 in ethanol and meloxicam is dispersed in the organic phase. The aqueous phase is formed by Tween 80 and water. The organic phase was injected to aqueous phase under magnetic stirring at 500 rpm. O/w emulsion was formed continuously by the diffusion of the organic solvent in the external aqueous phase leading to the formation of the nanodroplets. The magnetic stirring was maintained for 30 min to the system to reach equilibrium. The excess of ethanol was removed by evaporation [4].

EVALUATION OF NANOEMULSION

pH

The pH meter was calibrated using a standard buffer solution. About 0.5gm of the nanoemulsion was weighed and dissolved in 50ml of distilled water and the pH of the solution was measured [5,6].

Clarity and visual appearance

Appearance and clarity were determined by visual examination of the formulation under light against white and black backgrounds [5, 6].

Homogeneity

The formulations were tested for homogeneity by visual appearance and feel on the skin [5, 6].

Viscosity

Viscosity of the nanoemulsion was determined by viscometer VISCO Cat. Number 6800 [5,6].

Drug entrapment efficiency

Dissolved 1ml of NE in PBS pH 7.4 and made up to 5ml with the same and centrifuged for 1 hour at 2000 rpm. From this supernatant was separated and 1ml was made up to 10 ml. The absorbance was measured at 366 nm by UV Spectroscopy [5,6].

In vitro drug release study

The *in vitro* drug release studies were carried out in an open diffusion tube which was opened at both ends. The nanoemulsion (1ml) was spread uniformly on the surface of cellophane membrane (previously soaked in Phosphate Buffer pH 7.4 for overnight) and was fixed to the one end of the tube such that the preparation occupies inner circumference of the tube. The whole assembly was fixed in such a way that the lower end of tube containing nanoemulsion was just touched (1-2 mm deep) the surface of diffusion medium i.e., 50ml pH 7.4 phosphate buffer contained in 100 ml beaker which was placed in water bath and maintained at $37 \pm 2^\circ\text{C}$. The cellophane membrane acts as a barrier between the nanoemulsion and pH 7.4 phosphate buffer (sink condition). A quantity of 1 ml samples was withdrawn from receptor fluid at the time interval of 15min, 30min, 45min, 1, 2, 3, 4, 5 and 6 hrs. The released drug was estimated spectrophotometrically at 366 nm and 1 ml phosphate buffer pH 7.4 was replaced each time [5,6].

FORMULATION OF MELOXICAM LOADED NANOEMULGEL

Nanoemulgel is prepared by adding nanoemulsion in to the gel matrix. The optimized nanoemulsion was incorporated into overnight soaked 1% w/v gelling agent, carbopol34 with continuous stirring at 500 rpm. 1.5 % w/v thioglycolic acid was added as permeation enhancer. The final formulation also contained glycerine as humectant, methyl paraben as preservative [6].

EVALUATION OF NANOEMULGEL

pH

The pH meter was calibrated using standard buffer solution. About 0.5gm of the cream was weighed and dissolved in 50ml of distilled water and the pH of the solution was measured [6,7].

Clarity and visual appearance

Appearance and clarity were determined by visual examination of the formulation under light against white and black backgrounds [6,7].

Homogeneity

The formulations were tested for homogeneity by visual appearance and feel on the skin [6,7].

Viscosity

The viscosity of nanoemulgel was determined by using viscometer VISCO cat. number 6800 [6,7].

Spreadability

It was determined by wooden block and glass slide apparatus. For the determination of spreadability excess of sample was applied in between two glass slides and was compressed to uniform thickness

by placing 100 gm weight for 5 minutes. Weight (75gm) was added to pan. The time required to separate the two slides, i.e. the time in which the upper glass slide moves over the lower plates was taken as measure of spreadability (S). Spreadability was calculated by using the formula [6,7]:

$$\text{Spreadability, } S = \text{ML}/T$$

Where,

S = Spreadability

M = Weight tide to upper slide

L = Length moved on the glass slide

T = Time taken to separate the slide completely from each other

Drug Content

For estimation of drug content 1 g of nanoemulgel was diluted to 100 ml with pH 7.4. Again 1 ml sample was diluted to 10 ml with pH 7.4. The drug content was measured by using UV visible spectrophotometer at 366 nm [6,7].

In vitro drug release study

The *in vitro* drug release studies were carried out in an open diffusion tube which was opened at both ends. The nanoemulgel (1g) was spread uniformly on the surface of cellophane membrane (previously soaked in phosphate buffer pH 7.4 for overnight) and was fixed to the one end of the tube such that the preparation occupies inner circumference of the tube. The whole assembly was fixed in such a way that the lower end of tube containing nanoemulgel was just touched (1-2 mm deep) the surface of diffusion medium i.e., 50ml pH 7.4 phosphate buffer contained in 100 ml beaker which was placed in water bath and maintained at $37 \pm 2^\circ\text{C}$. The cellophane membrane acts as a barrier between the nanoemulgel and pH 7.4 phosphate buffer (sink condition). A quantity of 1 ml samples were withdrawn from receptor fluid at the time interval of 15min, 30min, 45min, 1, 2, 3, 4, 5 and 6 hrs. The released drug was estimated spectrophotometrically at 366 nm and 1 ml phosphate buffer pH 7.4 was replaced each time [6,7].

Kinetics of in-vitro drug release

To study the release kinetics of in-vitro drug release, data obtained from in-vitro release study were plotted in various kinetic models: Zero-order as % drug released Vs time, First order as log % drug retained Vs time, Higuchi as % drug released Vs $\sqrt{\text{time}}$, Korsmeyer-Peppas as log %drug released Vs log time [6,7].

Stability studies

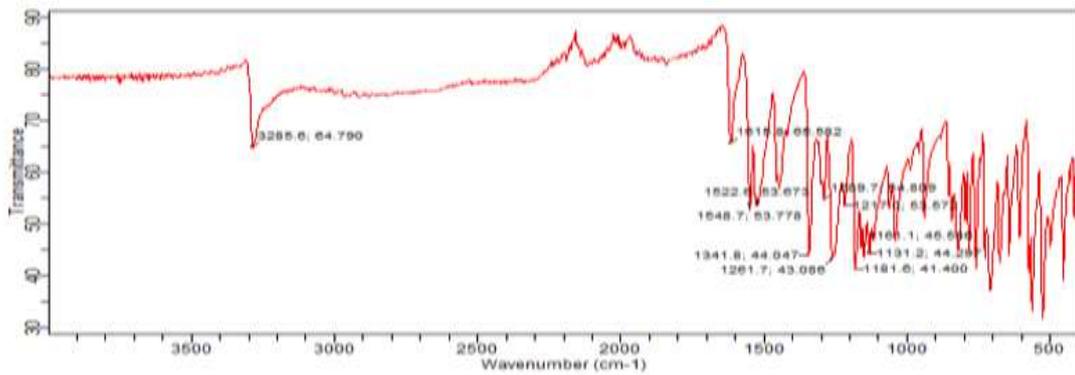
Stability studies were carried at room temperature for 60 days in the stability chamber. The sample was evaluated for drug content, *in vitro* drug release, pH and clarity [8].

RESULTS AND DISCUSSION

PREFORMULATION STUDIES

From the solubility study it was observed that Meloxicam was insoluble in water and diethyl ether, partially soluble in dichloromethane, acetone and chloroform, soluble in ammonia water and dimethylsulphoxide. The melting point of the drug was found to be 247°C . The major peaks observed in drug spectrum (Fig: 1) were also observed in spectrum of drug with polymer.

Fig. 1: IR spectra of Meloxicam.



PREPARATION OF MELOXICAM LOADED NANOEMULSION

Meloxicam nanoemulsion was prepared by spontaneous emulsification technique. Using Labrafac PG, Span 80, Tween 80, ethanol and distilled water (Fig: 2).

Fig. 2: Preparation of nanoemulsion using magnetic stirrer.



EVALUATION OF NANOEMULSION

pH

pH of the formulation at room temperature (25°C) was 7.17

Clarity and visual appearance

Prepared nanoemulsion was clear with a good homogenous appearance.

Homogeneity

The formulation showed good homogeneity with the absence of lumps.

Viscosity

Viscosity of the nanoemulsion was found to be 2198.2mpas (Fig: 3)

Fig. 3: Determination of viscosity using viscometer



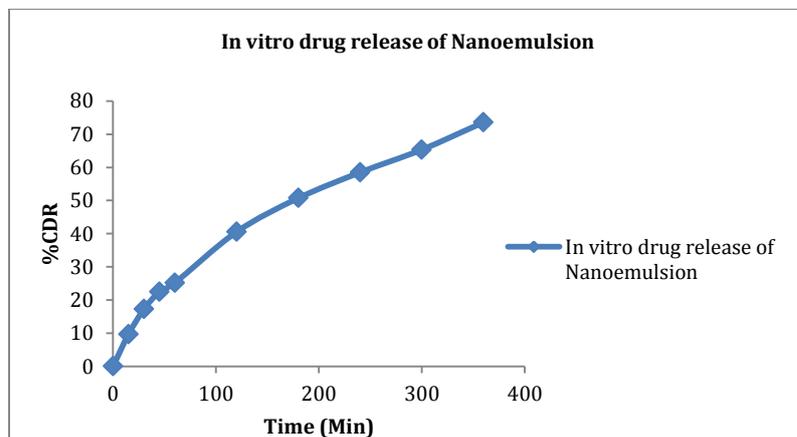
Drug entrapment efficiency

The percentage drug entrapment of the formulation was found to be 83.17%

In vitro drug release study

In vitro drug release study was carried out in open tube. The percentage of drug released as a function of time was determined. The percentage drug release of meloxicam from nanoemulsion at 6th hour was found to be 73.58%

Fig. 4: In vitro drug release of nanoemulsion.



FORMULATION OF MELOXICAM LOADED NANOEMULGEL

Meloxicam loaded nanoemulsion was incorporated into a hydrogel matrix to formulate nanoemulgel.

EVALUATION OF NANOEMULGEL

pH

pH of the formulation at room temperature (25°C) was 7.04

Clarity and visual appearance

Prepared nanoemulgel was clear with good homogenous appearance.

Homogeneity

The formulation showed good homogeneity with absence of lumps.

Viscosity

The viscosity of nanoemulgel was found to be 23510 mpas.

Spreadability

Spreadability was found to be 30.6 gcm/s.

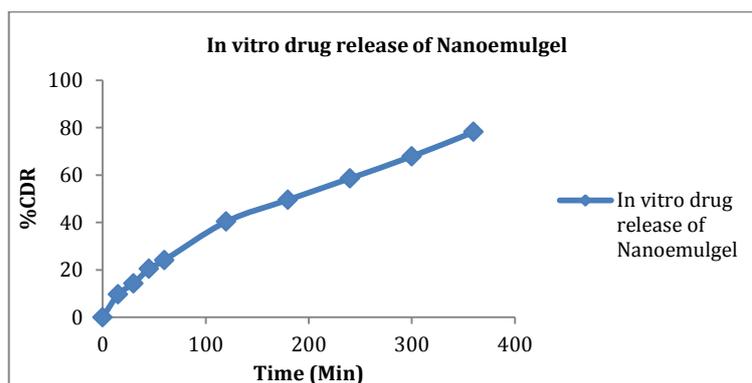
Drug Content

Drug content was found to be 88.76%.

In vitro drug release study

In vitro drug release study was carried out in open tube. The percentage of drug released as a function of time was determined. The percentage drug release of meloxicam from nanoemulgel at 6th hour was found to be 78.17%

Fig.5: In vitro drug release of Nanoemulgel.



Kinetics of in-vitro drug release

Based on highest regression value, the best fit model was observed as Higuchi matrix model. The n value obtained from Peppas model reveals that formulation follows non Fickian diffusion.

Stability studies

Percentage drug release, drug content, clarity and pH of formulation before and after 60 days of stability study are given below. It can be seen that there is no considerable change in these parameters. The nanoemulgel was found to be physically stable.

Table: 1 Stability studies.

Formulation	Before stability study	stability	After stability study	
	Drug content	% Drug release	Drug content	% Drug release
Meloxicam Nanoemulgel	88.76	78.17	88.39	78.04

CONCLUSION

Meloxicam loaded nanoemulsion was prepared by the spontaneous emulsification technique. FTIR spectrum revealed that drug compatibles with the excipients. The formulated nanoemulsion was evaluated for clarity, homogeneity, pH, viscosity, percentage drug entrapment and *In vitro* drug release study. The formulated nanoemulsion was chosen for the preparation of nanoemulgel. The nanoemulgel was evaluated for clarity, homogeneity, pH, viscosity, percentage drug entrapment and *In vitro* drug release study. The percentage drug entrapment study shows formulation having improved drug entrapment efficiency *In-vitro* drug release study of prepared nanoemulsion showed enhanced drug release. The stability studies carried out for 60 days in room temperature and the formulation was found to be stable. It can be concluded that

meloxicam nanoemulgel can be effectively used for the treatment of moderate to severe pain in rheumatoid arthritis.

REFERENCE

- Patrick S. Doyle, Ankur gupta, H. Barak Eral, T. Alan Hattona. Nanoemulsion: Formulation Properties and Application. Royal society of chemistry. 2016; 12: 2826-2841.
- Kalpna Basera, Ganesh Bhatt, Preeti Kothiyal and Pooja Gupta. Nanoemulgel: A Formulation Approach for Topical Delivery of Hydrophobic Drugs. World Journal of Pharmacy and Pharmaceutical Sciences. 2015; 4(10): 1871-1886.
- Arun Raj R, Nandkishore K. Formulation and Evaluation of Meloxicam Crystals Using Spherical Crystallization for Solubility Enhancement. Res Rev A J Drug Formul Dev Prod. 2016; 3(2):15-35.
- Navneet Sharma,Shardendu Mishra. Preparation and Optimization of Nanoemulsion for Targeting Drug Delivery. International Journal for Drug Development and research. 2013; 5(4): 37-48.
- S.Sampathy,S.K. Mankala, Nanoemulsion Based Hydrogels For Itraconazole For Transungual Drug Delivery. Journal for Scientific and Industrial Research. 2015; 74: 88-92.
- Asiya Mahtab, Mohammed Anwar, Neha Mallick, Zrien Naz, Gaurav K. Jain and Farhan J. Ahmad, Transungual Delivery of Ketoconazole Nanoemulgel for the Effective Management of Onychomycosis. AAPS PharmSciTech. 2016; 17(6): 1477-1490.
- Jilby Saju, Arun Raj R. Formulation and Evaluation of Lamotrigine Nanoparticles Incorporated In-Situ Gel for Epilepsy. Int J Pharm Pharm Res. 2018; 13(4):177-94.
- Arun Raj R. Formulation evaluation and in vitro permeation studies of transdermal nifedipine from matrix type patches. Int J Pharm Pharm Sci. 2014; 6(1):185-8.