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Formulation and *In vitro* characterization of Ketorolac loaded Nanosponges

R Gangadhara*

Department of Chemistry, Jawaharlal Nehru Technological University Anantapur, Andhra Pradesh, India.

***Corresponding author:** Gangadhara R, Department of Chemistry, Jawaharlal Nehru Technological University Anantapur, Andhra Pradesh, India; E-mail: gangadharaphd7@gmail.com

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Abstract

Topical gel preparations are intended for skin application or to certain mucosal surfaces for local action or transdermal penetration of medicament or for their emollient or protective action. The aim of the present study is to formulate ketorolac nanosponge loaded topical gel. For this purpose, ketorolac was entrapped in nanosponge and incorporated into gel and evaluated. By solvent evaporation method, using β cyclodextrin and ethyl cellulose Ketorolac Nanosponges was formulated. The particle size and entrapment efficiency was found below 620 nm and below 98.42 % respectively. Based on its particle size and entrapment efficiency, F6 formulation was optimed and further loaded into topical gels using guar gum, Xanthan gum & HPMC K4M and evaluation tests was performed which reveals satisfactory results. From the drug release studies, F6K6 formulation containing guar gum with higher proportions shows 96.07% of drug release at the end of 11hrs & follows zero order kinetics.

***Keywords:** Ketorolac; Xanthan; Gum cyclodextrin; Ethyl cellulose*

Introduction

In recent years, significant focus has been put on the development of novel drug delivery systems based on nanosponge in order to alter and monitor the release behavior of the drugs. It is possible to alter the therapeutic index and duration of drug activity by integrating it into a carrier system. Nanosponges are a new class of hyper-cross-linked colloidal polymer-based structures consisting of colloidal-sized rigid nanoparticles and nanosized cavities. They increase safety, decrease side effects, and enhance the release of drugs. Usually, the outer surface is porous, allowing for continuous drug release. They are also used for the distribution of topical drugs. In the epidermis and dermis, traditional formulations of topical drugs accumulate excessively. Nanosponge avoids the accumulation in the dermis and epidermis of the active ingredient.

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The nanosponge method decreases the discomfort of an important medicinal product without decreasing its effectiveness. They can be used to target drugs at particular sites, to avoid degradation of drugs and proteins. These tiny sponges will circulate across the body until they reach the particular target site and bind to the surface and have started to release the drug in a regulated and predictable way. Drug delivery through the skin is one of the most promising alternative drug delivery routes that greatly assists in passing first pass metabolism and other side effects on systemic drug administration. The biggest problem with the distribution of topical drugs is the barrier existence of the skin that prevents most drugs from entering. In order to maximize drug release and drug penetration through the skin and minimize drug toxicity and enhance patient compliance by extending dose intervals, nanosponges can be effectively integrated into a topical hydrogel drug delivery system.

Ketorolac is a Non-steroidal anti-inflammatory drug (NSAID). It is analgesic properties make it a useful pain management tool across many settings including postoperative pain, rheumatoid arthritis, osteoarthritis, menstrual disorders, headaches, spinal and soft tissue pain, and ankylosing spondylitis. The aim of the present investigation is to assess the applicability of nanosponge loaded topical gel in delivering ketorolac through skin. For this purpose, ketorolac was entrapped in nanosponge and incorporated into gel and evaluated the in vitro studies.

Materials and Methods

Ketorolac was obtained as gift sample from Vasudha pharma from India, β cyclodextrin, Ethyl Cellulose, Guar gum, Xanthan gum, HPMC K4M was procured from BMR Chemicals, Hyd. and other suppliers. All other chemicals used were of analytical grade.

Formulation of Ketorolac Nanosponges using solvent evaporation method

Disperse phase consisting of Ketorolac and requisite quantity of polymers dissolved in 20ml solvent (Methanol:Dichloromethane) was slowly added to a definite amount of PVA in 100ml of aqueous continuous phase, prepared by using magnetic stirrer. The reaction mixture was stirred at 1000 RPM on a magnetic stirrer for 2hours and kept on hot plate upto complete removal of organic solvent from the formulation. The nanosponges formed were collected by filtration through whatman filter paper and dried (Table 1).

TABLE 1. Formulation table of Ketorolac loaded nanosponges

Excipients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Ketorolac (g)	1	1	1	1	1	1
Ethyl Cellulose (g)	0.5	1	1.5	--	--	--
β-cyclodextrin (g)	--	--	--	0.5	1	1.5
PVA (mg)	500	500	500	500	500	500
DCM:methanol	20	20	20	20	20	20
Water (mL)	100	100	100	100	100	100

Formulation of Nanosponge loaded gel

The polymer was initially soaked in water for the gel for 2 hrs and dispersed by agitation at 600rpm by using magnetic stirrer to get smooth dispersion. Triethanolamine (2% v/v) was added to neutralise the pH. The previously prepared optimized nanosponge was thereby added and permeation enhancers (Propylene glycol) were added as methanolic solution to the aqueous dispersion. The composition of nanosponge gels is shown in (Table 2).

TABLE 2. Formulation of Ketorolac nanosponges loaded gels

Ingredients	**F6K1**	**F6K2**	**F6K3**	**F6K4**	**F6K5**	**F6K6**
Optimize Nanosponge (% w/w)	2%	2%	2%	2%	2%	2%
HPMC K4M (gm)	1	2	--	--	--	--
Xanthan gum (gm)	--	--	1	2	--	--
Guar gum (gm)	--	--	--	--	1	2
Propylene Glycol (ml)	1	1	1	1	1	1
Distilled Water (ml)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Triethanolamine (2%v/v) (ml)	1	1	1	1	1	1

Evaluation parameters

Entrapment efficiency

Ketorolac nanosponge was analyzed by dissolving the sample in 10ml of Methanol. After the drug was dissolved 10ml of clear layer of dissolved drug is taken. Thereafter the amount of drug in the water phase was detected by a UV-Spectrophotometric method at 295 nm (U.V Spectrophotometer). The concentration of the drug is determined with the help of calibration curve. The amount of drug inside the particles was calculated by subtracting the amount of drug in the aqueous phase from the total amount of the drug in the nanosponges.

Drug Content uniformity

Drug content uniformity of prepared gels was carried out using Spectrophotometric method. The assay of these formulations was carried out by pipetting 1 ml of all optimized formulations, and it was diluted up to 100 ml of pH 7.4. The formulations were shaken for 2-3 min, until it gives a clear gel solution. The solution was filtered through Millipore membrane filtrate (0.45 um) and the absorbance was measured at 295 nm using UV-Visible spectrophotometer.

Rheological Studies

It is the important factor to determine the residence time of drug in the eye by considering the viscosity of the instilled formulation. The prepared solutions were allowed to gel at physiological temperature and then the viscosity determination was carried out by using Brookfield viscometer (Brookfield DV+Pro, Brookfield Engineering Laboratories, Middleboro, MA, USA).

***In vitro* Drug Release studies of nanosponge gel formulations**

The diffusion studies of the prepared gels can be carrying out in Franz diffusion cell for studying the dissolution release of gels through a cellophane membrane. Gel sample (1 g) containing 2% w/w of ketorolac was taken in cellophane membrane and the diffusion studies were carried out at 37 ± 1° using 40 ml of phosphate buffer (pH 7.4) as the dissolution medium. One milliliters of each sample was withdrawn periodically at regular intervals of time and each sample was replaced with equal volume of fresh dissolution medium. The drug analysis was done using UV spectrophotometerically at 295 nm (Table 3).

Results and Discussion

Entrapment Efficiency

TABLE 3. Entrapment Efficiency of Ketorolac nanosponges (F1-F6)

Formulation code	% Entrapment
F1	95.02
F2	96.28
F3	98.42
F4	91.35
F5	95.02
F6	96.78

TABLE 4. Physicochemical evaluation of Nanosponges Loaded Gels

Formulation code	pH	Drug content (%)	Angular Velocity	
			10 (rpm)	100 (rpm)
F6K1	7.2	96.24	890	520
F6K2	7.5	95.42	920	640
F6K3	7.4	96.38	1050	740
F6K4	7.3	96.85	1300	820
F6K5	7.1	97.02	1120	680
F6K6	7.3	95.94	1260	790

Conclusion

From the *invitro* drug release studies, F6K6 shows maximum drug release at the end of 11th hour than remaining formulations. So formulation F6K6 containing Guar gum was considered as the optimized formulation. Using ethyl cellulose & β cyclodextrin ketorolac Nanosponges was formulated by solvent evaporation method. Based on its particles size and entrapment efficiency, F6 formulation was optimized further incorporated as topical gels using polymers like guar gum, Xanthan gum & HPMC K4M and evaluation tests were performed. From all the formulations, F6K6 showed drug release upto 11hrs & follows zero order with case II transport mechanisim.

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