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Assessment of NSAID Loaded Gel

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ABSTRACT

To overcome this problem and to enhance the permeation of drug into the skin and also to reduce the skin irritation the drug was formulated in the form of nanoparticles using chitosan as a polymer and these drugs loaded nanoparticles were incorporated in gel for more effective delivery of drug into the skin. The prepared drug loaded nanoparticulate gel was evaluated for physical appearance, homogeneity, pH, drug content, viscosity, spreadability, extrudability and in vitro diffusion studies. All the nanoparticulate gel formulations were clear without any aggregates, particles and fibres indicating excellent homogeneity of all the formulations. The pH of the formulations was closer to neutral indicating absence of skin irritation and damage. The viscosity was directly proportional where as extrudability and spreadability was inversely proportional to the concentration of Carbopol employed. Formulation NG4 showed sustained release for 24 h.

INTRODUCTION:

Topical drug delivery can be defined as the application of a medication to the skin or mucous membrane for local or systemic action. Delivery of drugs via skin is effective and avoids first-pass effect and metabolic degradation associated with oral administration [1]. Development of successful topical drug delivery system has been limited in scope due to the significant penetration barrier provided by the stratum corneum (SC), the topmost skin layer. To overcome this barrier, numerous active and passive penetration enhancement methods have been assessed [2-3]. Although active methods including iontophoresis, electroporation, and micro needles have shown some efficiency, more work is needed to establish for their safety band and cost effectiveness. Passive methods include the use of chemical penetration enhancers, supersaturated systems, prodrugs, liposomes, microemulsions, and colloidal polymeric suspensions. This approach provides design flexibility (with formulation optimization) and the possibility of application over a larger area of skin compared to active methods [4-5]. Chemical penetration enhancers have been intensively investigated over the years, but the concentrations required for improved penetration often lead to irritation or sensitization. The use of vesicular delivery systems such as liposomes, transfersomes, ethosomes and niosomes is still limited due to stability issues and insufficient understanding of the mechanism of penetration across intact skin. Additionally, lipid based colloidal carriers have shown improved drug penetration through skin, but their limited drug loading and the phase stability remain to be addressed, restricting their clinical applicability. Dispersion of polymer-based nanoparticles in hydrophilic gels can further improve drug delivery to the skin. The gel can aid in creating a uniform dispersion of the carriers in the matrix and increase the contact time and deposition of the carriers on the skin, resulting in enhanced skin penetration of the payload [6-7].

Ketoprofen, a potent NSAID is a preferential inhibitor of cyclooxygenase -2 and has analgesic and anti-inflammatory activity, widely used in the treatment of rheumatoid arthritis, osteoarthritis and other joint disease. The poor aqueous solubility and wettability of ketoprofen leads to difficulty in formulating oral and topical formulation. Ketoprofen is classified in the Biopharmaceutics Classification Scheme as a class II drug. Since dissolution is the rate-limiting step during drug absorption, the poor water solubility in oral forms of ketoprofen results in low bioavailability due to incomplete absorption. In addition to absorption difficulties, oral

formulations of ketoprofen can cause gastric mucosal damage, which may result in ulceration and bleeding. Therefore, a better oral or topical formulation can be developed by increasing the water solubility of drugs. Topical application of NSAID on the inflamed site can offer the advantage of delivering a drug directly to the disease site and producing its local effect. This occurs by avoiding gastric irritation and also reduced adverse systemic effect [8-10].

In the present work an attempt was made to enhance the absorption and provide sustained release of drug by incorporating the drug in nanoparticles and further in gel for effective delivery of drug into the skin.

MATERIALS:

Ketoconazole was a gift sample from Emcure Pharmaceuticals Ltd., Pune. Chitosan, Poloxamer 188 and Sodium tripolyphosphate were procured from Sigma Aldrich, USA. Acetic acid was purchased from SD fine chemicals, India. Deionized water was obtained from Millipore filtration system, USA.

METHODS:

Preparation of nanoparticles [11-13]:

Nanoparticles were prepared by using chitosan (CS) as polymer and sodium tripolyphosphate (STPP) as cross linking agent by ionic gelation method. Initially,0.4 % of chitosan solution in 1% acetic acid was prepared and pH was adjusted to 4. To the chitosan solution, drug solution was added slowly under constant stirring. 1.5 %w/v poloxamer 188 was added as stabilizer. After 15 mins, 0.25% w/v STPP solution was added drop by drop slowly under magnetic stirring (Remi, India) at constant speed of 1500 rpm for 2h and finally subjected to high speed homogenizer (SB1, Thomas Scientific, USA) at 25,000 rpm for 1 h. The suspension of nanoparticles was then centrifuged at 10,000 rpm at 4 °C for 20 min and the separated nanoparticles were resuspended in purified water and then freeze dried (Bioline Technologies, Thane, India) using 5% mannitol as cryo protectant.

Preparation of nanoparticulate gel [14]:

Nanoparticulate gel was prepared by dissolving required quantity of Carbopol 934 in 100 ml distilled water containing 0.3 ml methylparaben (0.5%w/v) and stirred until it forms a clear transparent gel. Triethanolamine was slowly added and the pH was adjusted to 7. It was then allowed to stand for 24 h at room temperature. Then finally drug loaded nanoparticles were incorporated in gel by slow stirring. The various formulations prepared are shown in table 1.

Table No. 1: Formulations of nanoparticulate Topical gels

Ingredients	**NG1**	**NG2**	**NG3**	**NG4**	**NG5**	**NG6**
Ketoprofen (%w/w)	1	1	1	1	1	1
Carbopol 934 (%w/w)	0.5	1.0	1.5	2.0	2.5	3.0
Methyl paraben (ml)	0.3	0.3	0.3	0.3	0.3	0.3
Triethanolamine (ml)	q.s	q.s	q.s	q.s	q.s	q.s
Water (ml) Upto	100	100	100	100	100	100

Physical appearance and homogeneity [15]

All the prepared nanoparticulate gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates, particles and fibers.

Determination of pH

The pH measurements were done using a digital pH meter (Thermo scientific) which was calibrated with buffer and the pH of the formulations was measured by dipping the glass electrode into the topical gel.

Determination of drug content

1.0 gm of nanoparticulate gel was transferred to 50 ml volumetric flask and was diluted with ethanol. 5 ml of this solution was further diluted to 25 ml with ethanol. The drug content was determined by measuring the absorbance at 254 nm using UV- Visible spectrophotometer.

Determination of viscosity [15]

The viscosity of the prepared formulations was determined at ambient temperature using Brookefield digital viscometer (DV-II + Pro) with spindle no. 6 at 5 rpm at room temperature and values were noted.

Determination of spreadability

A weighed quantity (500 mg) of topical gel or gels was placed within a circle of 1 cm diameter pre-marked on a glass plate (10 X 10 cm). Another glass plate (10 X 10 cm) was placed on the gel. A weight of 500 g was allowed to rest on the upper glass plate for 5 min. The increase in the diameter due to gel spreading was noted.

Determination of Extrudability

The quantity (g/cm^2) of topical gel extruded from lacquered aluminium collapsible tube on application of weight (in grams) required to extrude at least0.5 cm ribbon of topical gel in 10 seconds. The measurement of extrudability of each formulation was done in triplicates using the below equation and the average values are presented.

$$\text{Extrudability} = \text{Applied weight (in g)}/\text{Area (in cm}^2\text{)}$$

***In-vitro* diffusion studies through dialysis membrane**

The membrane utilized was dialysis membrane number 70, having average flat width 29.31 mm, average diameter of 17.5 mm and a capacity of 2.41 ml/cm (Molecular weight cut off 12000). The dialysis membrane was cut to size and boiled in distilled water for 1 hour. Then soaked in absolute alcohol for 1 hour and was finally soaked in pH 7.4 phosphate buffer saline for 24 hours. In vitro drug release studies was carried out by taking required quantity of nanoparticulate gel on the dialysis membrane, which was mounted on the Franz diffusion cell, the top of which

was clamped securely. The receptor compartment with pH 7.4 phosphate buffer saline was maintained at constant temperature of 37° C by circulating water bath. Samples were withdrawn from the receptor compartment at predetermined time intervals and replaced with an equal volume of fresh buffer solution. The samples were analyzed for drug content using UV spectrophotometer at 254 nm.

RESULTS AND DISCUSSION:

Preparation of nanoparticulate gel:

Drug loaded chitosan nanoparticles were prepared using ionotropic gelation method. In nanoparticle preparation, chitosan was the polymer and cross-linked with sodium tripolyphosphate, the cross-linker, by ionic linkage. In the preparation of gel, Carbopol was used as gelling agent. One of the main ingredients of the formulation is the gelling agent. The concentration of viscosity enhancer or gel former is of immense value as a less concentration will lead to simple solution or lotion with very low consistency, while high concentration may lead to formation of gels with high viscosity leading to non-uniform distribution of drug and problem with handling of gel.

Physical appearance and homogeneity

All the nanoparticulate gel formulations were clear without any aggregates, particles and fibres indicating excellent homogeneity of all the formulations. The results are indicated in Table 2. At low concentrations of Carbopol (NG1 to NG3) a very thin gel that liquefies within 24h of preparation was formed. Gel containing 2.0% of Carbopol 934 (NG4) formed uniform and smooth gel that does not liquefy upon keeping. At further higher concentrations of gelling agent (NG5 and NG6) the gel was very thick and stickier that could not be properly spread out.

Table No. 2: Results of Physical appearance and homogeneity for gels

Formulation code	Appearance	Homogeneity
NG1	Clear,white fluid	+++
NG2	Clear,white fluid	+++
NG3	Clear,white fluid	+++
NG4	Clear,white fluid	+++
NG5	Clear,thick white	+++
NG6	Clear,thick white	+++

Excellent+++, Good++, Satisfactory+

Determination of pH

The pH of all the formulations was in the range of 6.78±0.04- 7.25±0.06 (Table 3) enduring them most acceptable to avoid the risk of irritation up on application to the skin. This also indicated that the selected ingredients of the formulation did not alter the pH of the formulation.

Table No. 3: Results for determination of pH for gels

Formulation code	pH (mean±SD*)
NG1	6.72±0.04
NG2	6.78±0.03
NG3	6.82±0.08
NG4	6.95±0.05
NG5	7.25±0.06
NG6	7.15±0.04

*Standard deviation, n=3

Determination of drug content

The drug content for all the prepared nanoparticulate gel formulations was found between 95.5% to 97.0%. The drug content analysis showed that the drug loaded nanoparticles were uniformly and properly distributed in the gel formulations. The results obtained are shown in figure 1.

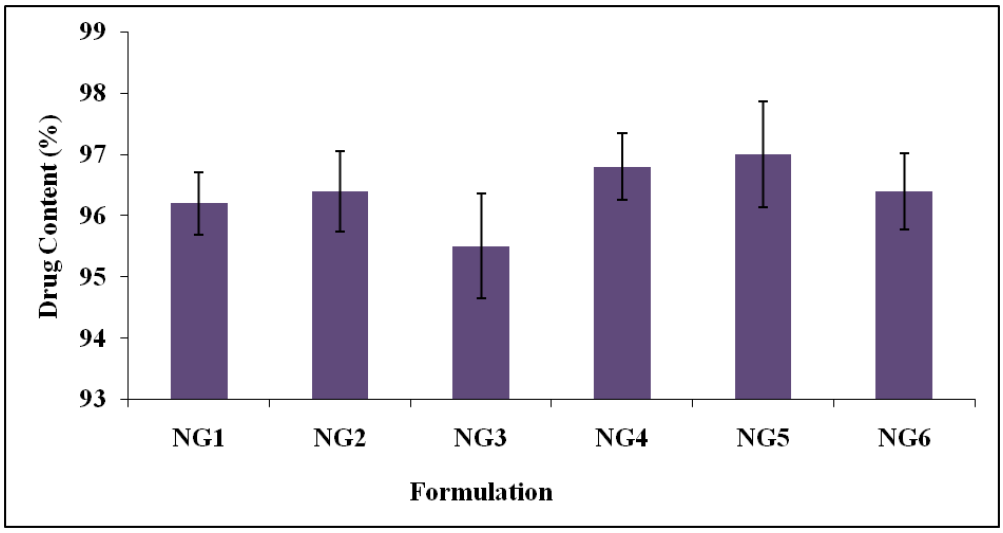

Fig. No. 1: Drug content for various formulation of gels (mean ± standard deviation, n=3)

Table No. 4: Results for determination of spreadability and extrudability for gels

Formulation code	**Spreadability (cm) (mean±SD*)**	**Extrudability (g/cm^2) (mean±SD*)**
NG1	15.4±0.75	22.30±1.02
NG2	11.56±0.63	21.52±0.85
NG3	10.75±0.54	19.23±0.75
NG4	9.26±0.23	15.42±0.62
NG5	8.46±0.42	8.62±0.45
NG6	6.23±0.16	6.45±0.32

*Standard deviation, n=3

Determination of Extrudability

It was found that extrudability of topical gel was a function of concentration of Carbopol. Extrudability was decreased with increase in the concentration of Carbopol (table 3).

***In-vitro* diffusion studies through dialysis membrane**

Diffusion studies were carried out using Franz type diffusion cell for NG1 to NG6 formulations in pH 7.4 Phosphate buffer saline solution (Figure 2). The drug release from NG5 and NG6 was less due to more concentration of Carbopol. As more concentration of Carbopol was employed the drug was not able to completely diffuse through the thick gel barrier. Drug release was in the following order, NG6>NG5>NG4>NG3>NG2>NG1. The drug release profile of NG4 was greater. Hence NG4 can be considered as the optimized formulation.

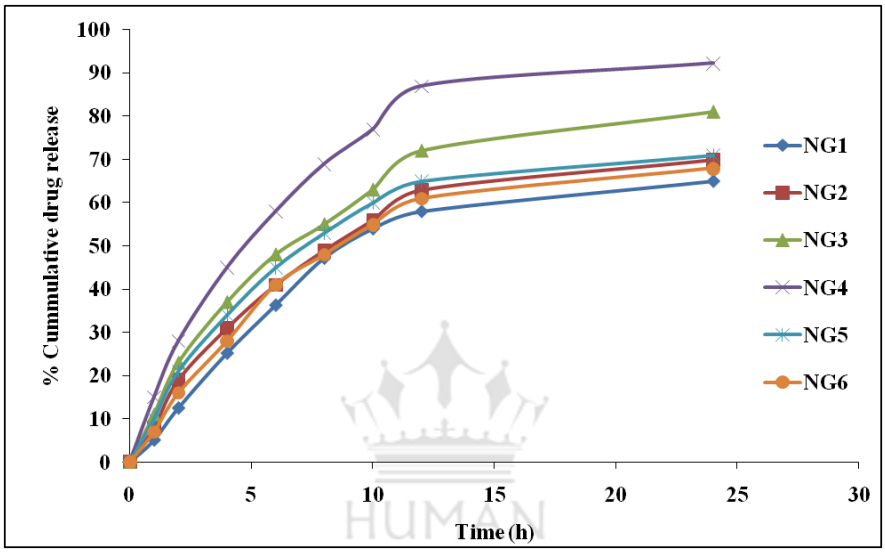

Fig. No. 2: *In vitro* release of ketoprofen from formulations NG1 - NG6 (mean ± standard deviation, n=3)

CONCLUSION:

The aim of the present work was to formulate, develop and evaluate a topical gel containing ketoprofen. Topical gels have emerged as a promising drug delivery system for the delivery of hydrophobic drugs. Formulations were prepared and evaluated for physical parameters, drug content, viscosity, spreadability, extrudability and diffusion studies. Carbopol, a gelling agent has a direct influence on appearance, viscosity, spreadability and extrudability. As the concentration of gelling agent increases the viscosity of the formulation increased and release was retarded. From the results of the experimental work carried out it can be concluded that the ketoprofen loaded nanoparticles incorporated in gels can be employed for effective sustained

topical delivery of lipophilic drugs, and drugs with high molecular weight which shows poor permeation into the skin.

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