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Formulation and Invitro characterization of Flurbiprofen loaded Nanosponges

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ABSTRACT

The aim of this analysis is to see how effective a Nanosponge-loaded topical gel is at distributing flurbiprofen through the skin. Flurbiprofen was entrapped in Nanosponge and formulated into a gel for this purpose. Flurbiprofen Nanosponges were developed by solvent evaporation using pluronic F68 and ethyl cellulose. The particle size and entrapment quality were discovered to be in the range of 200-410 nm and 90.94% to 98.68%, respectively. For gel formulation, Nanopsonges with high entrapment efficiency and the smallest particle size (F3) were chosen based on the characterization. Using Guar gum, Carbopol, and HPMC K4M, a total of 6 formulations were produced to determine the sustained drug release and were tested for physiochemical tests, producing positive results. According to the findings of the above in vitro drug release trials, formulations containing carbopol release more drug at the end of 11 hours than other formulations and follow a zero-order with case II transport mechanism.

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INTRODUCTION

In recent years, much focus has been put on the development of novel Nanosponge-based drug delivery mechanisms in order to regulate and monitor drug release actions. It is possible to adjust the therapeutic index and length of drug action by integrating it into a carrier system (Trotta *et al.*, 2009). Nanosponges are a new form of hypercrosslinked polymer-based colloidal structure that consists of colloidal-sized dense nanoparticles and nanosized cavities (Sharma *et al.*, 2011). They increase drug stability, decrease side effects, and change drug release. The outer surface is generally porous, allowing for long-term drug release. They're also used to handle topical drugs (Lala *et al.*, 2011; Ahmed *et al.*, 2013). Topical medications in their conventional forms concentrate excessively in the epidermis and dermis. Nanosponge stops the active ingredient from circulating in the dermis and epidermis. The nanosponge method decreases the irritation of working medications without compromising their effectiveness (David, 2010). They can be used to target medications to particular sites and to protect drugs and proteins from degrading. These tiny sponges will circulate across the body until they come across a certain target spot, where they bind to the surface and start releasing the substance in a coordinated and predictable fashion. The most

challenging aspect of topical drug distribution is the skin's membrane function, which prohibits most medications from penetrating (Nacht and Kantz, 1992; Maravajhala *et al.*, 2012). Nanosponges can be successfully integrated into a topical hydrogel drug delivery system to improve drug release and penetration through the skin, as well as to reduce drug exposure and enhance patient safety by extending dose intervals (Shishu and Aggarwal, 2006; Dick and Scott, 2011).

Flurbiprofen, a propionic acid analogue, is an antipyretic and analgesic nonsteroidal anti-inflammatory drug (NSAIA). The aim of this analysis is to see how effective a nanosponge-loaded topical gel is at distributing flurbiprofen through the skin. Flurbiprofen was entrapped in a nanosponge and incorporated into a gel for this purpose, and the in vitro permeation tests were analysed (Maravajhala *et al.*, 2012).

MATERIALS AND METHODS

Flurbiprofen was obtained as a gift sample from Sun Pharma from India. Pluronic F-68, Ethyl Cellulose, Guar gum, Carbopol, HPMC K4M was procured from BMR Chemicals, Hyd. and other suppliers. All of the other compounds were of analytical consistency.

Formulation of Flurbiprofen Nanosponges

Nanosponges using different proportions of Ethyl cellulose, Pluronic F-68 as rate restricting polymer and co-polymers like polyvinyl alcohol were prepared by a solvent evaporation method. Flurbiprofen and the required amount of polymers were dissolved in 20 mL solvent (Methanol: Dichloromethane) and slowly applied to a particular amount of PVA in 100 mL of continuous aqueous phase prepared with a magnetic stirrer.

The reaction mixture was stirring it up at 1000 RPM for 2 hours on a magnetic stirrer and kept on a hot plate until the organic solvent was completely extracted from the formulation. Filtration through Whatman filter paper and collect the dried Nanosponges produced (Maravajhala *et al.*, 2012; Sharma *et al.*, 2011; Ansari *et al.*, 2011) (Table 1).

Formulation of Nanosponge loaded gel

To ensure smooth dispersion, the polymer was first immersed in water for 2 hours before being stirred at 600rpm with a magnetic stirrer. To neutralise the pH, triethanolamine (2 percent v/v) was applied. Permeation enhancers (Propylene glycol) were applied to the aqueous dispersion as a methanolic solution (Sharma and Pathak, 2011; Swaminathan *et al.*, 2007; Bose *et al.*, 2016). (Table 2).

Evaluation parameters

Entrapment efficiency

By dissolving 100mg of Flurbiprofen weight equal Nanosponge in 10ml of Methanol, the sample was analysed. Once the substance has been dissolved, take 10ml of the dissolved drug. After that, a UV-Spectrophotometric process at 246 nm was used to detect the concentration of the drug in the water phase (U.V Spectrophotometer). The calibration curve is used to assess the drug's concentration. By subtracting the amount of drug in the aqueous phase from the overall amount of drug in the Nanosponges, the amount of drug within the particles was determined. (Bose *et al.*, 2016; Sharma and Pathak, 2011)

pH

A pH meter was used to calculate the pH of the prepared in-situ gelling method after completion of the process (Sharma and Pathak, 2011; Phatak and Chaudhari, 2012; Bose *et al.*, 2016)

Drug content uniformity

The Spectrophotometric approach was used to verify the drug content uniformity of the prepared gels. Pipetting 1 ml of optimised formulations and diluting it up to 100 ml of pH 7.4 was used to test these formulations. The formulas were shaken for 2-3 minutes before a transparent gel solution was obtained. The absorbance was measured at 246 nm using a UV-Visible spectrophotometer after the sample was purified into Millipore membrane filtrate (0.45um) (Swaminathan *et al.*, 2007; Srinivas and Sreeja, 2013).

Rheological Studies

The viscosity of the formulation is an important element in defining the drug's residence time in the eye. The viscosity was measured using a Brookfield viscometer (Brookfield DV+Pro, Brookfield Engineering Laboratories, Middleboro, MA, USA) after the formulated solutions had gelled at physiological temperature. (Srinivas and Sreeja, 2013; Bose *et al.*, 2016).

In-vitro Drug Release studies of Nanosponge gel formulations

For testing the dissolution release of gels via a cellophane membrane, diffusion tests of the prepared gels may be carried out in the Franz diffusion cell. The diffusion experiments were carried out at 37± 0.5°C using 40 ml of phosphate buffer (pH 7.4) as the dissolution medium and a gel sample (1g) in a cellophane membrane. At daily intervals, one millilitre of each sample was extracted, and each sample was supplemented with an equivalent amount of fresh dissolution medium. The substance

Table 1: Formulation table of Flurbiprofen loaded Nanosponges

Excipients	F1	F2	F3	F4	F5	F6
Flurbiprofen (g)	1	1	1	1	1	1
Pluronic F-68 (g)	0.5	1	1.5	–	–	–
Ethyl Cellulose (g)	–	–	–	0.5	1	1.5
PVA (mg)	500	500	500	500	500	500
DCM:Ethanol	20	20	20	20	20	20
Water (mL)	100	100	100	100	100	100

Table 2: Formulation of Flurbiprofen nanosponges loaded gels

Ingredients	F3G1	F3G2	F3G3	F3G4	F3G5	F3G6
Optimize Nanosponge (weight equivalent in %w/w)	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Guar gum (gm)	1	2	–	–	–	–
Carbopol (gm)	–	–	1	2	–	–
HPMC K4M (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

was tested using a UV spectrophotometer calibrated to 246nm (Swaminathan *et al.*, 2007; Srinivas and Sreeja, 2013; Gangadharappa *et al.*, 2017).

RESULTS AND DISCUSSION

Entrapment Efficiency

It is measured to assess the utility of any process, which aids in the selection of the most suitable production method. After preparing the formulations, the functional yield was determined by dividing the number of Nanosponges recovered from each preparation by the total amount of starting material. (Theoretical yield). (Table 3)

Morphology determination by scanning electron microscopy (SEM)

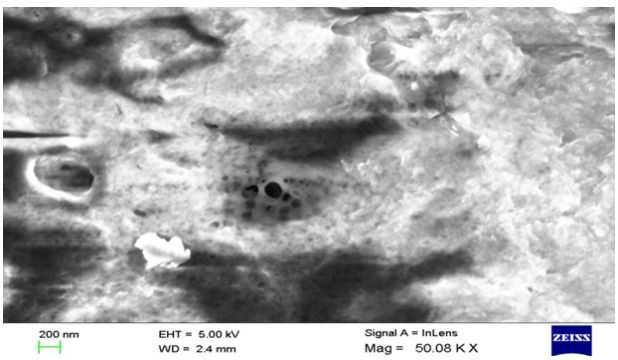

Figure 1: Nanosponges structure optimized formulation (F3)

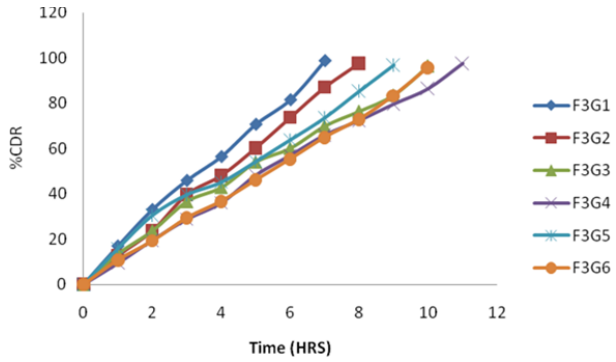

Figure 2: In-vitro drug release graphs of formulation (F3G1-F3G6)

Both formulated topical gels had tested their physicochemical properties. The physicochemical properties of gel formulations, such as viscosity, pH, and drug material, were calculated and tabulated in Table 4. Both of the formulations have a pH level of 7.1 to 7.6, which is ideal for topical use.

The formulated gels' drug quality was found to be adequate, varying from 95.02 to 98.65 percent. Many of the formulations had viscosities ranging from 320cps to 1260cps.

In-vitro drug release of Flurbiprofen nanosponges loaded gels

Using Guar gum, Carbopol, and HPMC K4M, a total of 6 formulations were produced to assess the sustained drug release.

Table 3: Entrapment Efficiency of Flurbiprofen Nanosponges (F1-F6)

Formulation code	% Entrapment Efficiency
F1	93.02
F2	96.42
F3	98.68
F4	90.94
F5	96.35
F6	97.04

Formulation F1-F6's entrapment efficiency was found to be between 90.94 and 98.68 %.

Table 4: Physicochemical evaluation of Nanosponges Loaded Gels

Formulation code	pH	Drug content (%)	Angular Velocity 10 (rpm)	100 (rpm)
F3G1	7.4	95.02	650	320
F3G2	7.3	96.43	830	590
F3G3	7.6	98.65	880	460
F3G4	7.5	97.02	1260	620
F3G5	7.2	98.42	620	340
F3G6	7.3	96.02	940	460

According to the findings of the above in vitro drug release trials, the formulation containing Carbopol has the largest drug release at the end of 11 hours than the other formulations.

As a result, the formulation F3G4 containing Carbopol was selected as the best. (Figure 1 and Figure 2)

Release Kinetics of Flurbiprofen Nanosponges loaded gels

The release was discovered to be in zero-order, with an R2 value similar to null. Zero-order kinetics is used in the formulation.

The drug release mechanism was discovered to be a case II transport mechanism.

CONCLUSION

The present study was aimed to develop Flurbiprofen Nanosponges loaded gels for targeting drug delivery systems. Flurbiprofen Nanosponges were formulated using ethyl cellulose, Pluronic F68 with different ratios. Developed Nanosponges were further evaluated for particle size morphology in which F3 formulation containing Pluronic F68 shows the spongy structure with minute pores of 200nm particle size shows good entrapment efficiency than remaining formulations. So further F3 formulation was incorporated as a topical gel by using 3 different rate retarding polymers in which F3G4 formulation containing carbopol revealed sustained drug release upto 11hrs and follows zero-order with case II transport mechanism.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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