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Original Article

Formulation and Evaluation of Nanoparticles as Sustained Release Topical Formulation Containing Non-Steroidal Anti - Inflammatory Drug

Abitha M H*, Flowerlet Mathew
Department of Pharmaceutics, Nirmala College of Pharmacy, Muvattupuzha, Ernakulam, Kerala, India
E-MAIL: abitha.mh@gmail.com

ABSTRACT

The objective of this work is to prepare flurbiprofen nanoparticles, and then incorporated into the freshly prepared gels for transdermal delivery, providing controlled release of the drug, reducing the oral side effects of the drug and for enhancing stability. Flurbiprofen is a non-steroidal anti-inflammatory drug used to treat gout, osteoarthritis, rheumatoid arthritis, and sunburn. In this study Flurbiprofen nanoparticles are prepared by nanoprecipitation method. A total of 8 batches are prepared by using polymers such as ethyl cellulose, Eudragit L100 and are evaluated for various parameters. Drug-excipients compatibility was performed by FTIR study. Optimized batch of nanoparticles F3 was further formulated as gel for topical delivery. A total of 4 batches of gel were prepared using different concentrations of carbopol 934. Prepared gel formulations are evaluated for physical parameters and in vitro drug permeation study. The in-vitro release rate of gel preparations was evaluated by diffusion cell method using cellophane membrane with phosphate buffer pH 7.4 as the receptor medium. F3-G1 showed highest in-vitro release rate and superior physicochemical properties. These formulations were evaluated for ex-vivo permeation study through chicken skin using Franz diffusion cell. The drug release data of optimized batch were fitted into different kinetic models which show that the drug release from gel formulations follow zero order release. The overall studies concluded that the F3-G1 Flurbiprofen nanoparticle gel can be effectively used for the treatment of chronic conditions of rheumatoid arthritis, osteoarthritis.

Keywords: Nanoparticle, Flurbiprofen, Gel, Ethyl cellulose.

INTRODUCTION

Drug delivery from colloidal systems such as nanoparticles dispersed in a gel appears to be unique when compared to the delivery from traditional topical and dermatological formulations. During the last decade, considerable attention has been paid to the development of new controlled delivery systems, in order to supply a long-term drug release and, therefore, increase patient's therapeutic compliance and acceptance. The transdermal drug delivery system can be used to deliver anti-inflammatory drugs across the skin for the treatment of acute and chronic pain and inflammation. Osteoarthritis, rheumatoid arthritis and ankylosing spondylitis are a group of related, but distinct, disorders of the cartilage of osteoarticular joints. Non-steroidal anti-inflammatory drugs are in use to reduce the pain and inflammation. Their main benefit derives from their anti-inflammatory and analgesic effect, but the use of these agents is not innocuous since their regular use may lead to chronic side-effects such as gastric irritation to severe bleeding and ulceration of gastric due to both inhibition of synthesis of prostaglandins and direct contact of the drug with mucosa. Since long-term NSAID treatment is indicated for such illnesses, the ideal agent should have good efficiency and a low propensity to cause adverse events. Therefore, recent focus of the researchers has been to deliver such potential NSAIDs in a controlled manner by using a dosage form that will minimize its release in stomach and thereby overcomes its chronic adverse effect.

Flurbiprofen is a chiral non-steroidal anti-inflammatory drug (NSAID) of the 2-arylpropionic acid class. Flurbiprofen, one of the most potent inhibitors of platelet aggregation currently available, is used to treat gout, osteoarthritis, rheumatoid arthritis, and sunburn. Flurbiprofen has also been found to cause a dose-dependent inhibition of collagen-induced platelet aggregation in platelet-rich plasma from human, rats and rabbits *in vitro*. Upon oral administration, the most frequently reported side effects of flurbiprofen are abdominal discomfort along with other gastrointestinal effects. Also, it has a short elimination half-life of 3.9 h and requires frequent dosing. Therefore long-term percutaneous absorption of flurbiprofen at a controlled rate is needed. Transdermal delivery would provide a means to avoid the gastrointestinal

damage associated with oral route. However intercellular lipid barrier in the stratum corneum has formidable barrier properties and most of the drugs cannot penetrate the skin readily.

MATERIAL AND METHODS

Materials

Flurbiprofen was obtained from Yarrow Chem Products (Mumbai). Ethylcellulose & Eudragit L100 was obtained from Yarrow Chem Products, Mumbai. Carbopol 934 were obtained from Himedia laboratories Pvt. Ltd, Mumbai. Dichloromethane and Ethanol was obtained from Spectrum reagents and chemicals Pvt. Ltd, Cochin**.** All other chemicals and reagent used in this study were of analytical grade.

Methods

Preparation of Flurbiprofen nanoparticles

Flurbiprofen nanoparticles were prepared by nanoprecipitation method. Drug and polymer were dissolved in ethanol: Dichloromethane mixture by using mechanical stirrer. This organic phase added drop by drop (2 ml/min) in external aqueous phase containing surfactant tween 80 in a fixed concentration. During this mixing, the aqueous phase was homogenized using homogenizer at 10,000 rpm for 30 minute followed by magnetic stirring for 3hrs and kept overnight. The formed nanoparticles suspension were filtered through whatman filter paper and washed nanoparticles were dried.

Table 1: It shows the formulation of Flurbiprofen nanoparticles F1-F8

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
Internal phase								
Flurbiprofen (mg)	200	200	200	200	200	200	200	200
Ethyl cellulose (mg)	400	600	800	1000				
Eudragit L100 (mg)					400	600	800	1000
Ethanol (ml)	10	10	10	10	10	10	10	10
Dichloro methane (ml)	10	10	10	10	10	10	10	10
External phase								
Tween 80 (%)	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.3
Water (ml)	150	150	150	150	150	150	150	150

Evaluation of Flurbiprofen Nanoparticle

Following parameters were used for the evaluation of Flurbiprofen nanoparticle:

Particle size

Particle size of nanoparticles formulation was performed by **Scanning Electron Microscopy (SEM).** Samples (7*2mm) were mounted on the SEM sample stab using a double sided sticking tape. The samples were coated with gold (200 A0) under reduced pressure (0.001 torr) for 2 min using an ion sputtering device (model JFC-1100 E, Jeol, Japan). The gold coated samples were observed under the SEM at room temperature and photomicrographs of suitable magnifications were obtained.

Shape and surface morphology

Particle size of nanoparticles formulation was performed by scanning electron microscopy

Percentage yield

The prepared nanoparticles of all batches were accurately weighed. The weighed nanoparticle was divided by the total amount of all the excipients and drug used in the preparation of the nanoparticles, which gives the total percentage yield of nanoparticles. It was calculated by using following equation,

$$\text{Percentage yield} = \frac{\text{Mass of nanoparticles recovered}}{\text{Mass of drug and formulation excipients}} \times 100$$

Entrapment efficiency

Nanoparticles equivalent to 10 mg of drug were dissolved in 10 ml phosphate buffer (pH 7.4) solution and were kept for centrifugation for 40 minutes. The supernatant was carefully decanted and analyzed by using Ultraviolet spectroscopy at 248 nm. The % entrapment efficiency were calculated using equation as given below

$$\text{Entrapment efficiency (EE \%)} = \frac{\text{Total drug content} - \text{Amount of free drug}}{\text{Total drug content}} \times 100$$

***In-vitro* Drug Release Study:**

In-vitro release was evaluated using a dialysis bag technique. The *in- vitro* release of nanoparticles was carried out in stirred dissolution cells by suspending nanoparticulate suspension into a beaker containing 100ml of release media: phosphate buffer saline pH 7.4. Then, the beaker was placed over a magnetic stirrer and the temperature of the assembly was maintained at 37 ± 0.5°C throughout the study. Samples (5 ml) were withdrawn at definite time intervals (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11and 12 hrs) and replaced with equal amounts of fresh buffer. The samples were analyzed for drug concentration by UV-Vis spectrophotometer at 248 nm

Preparation of Nanoparticle loaded carbopol gels

Gel forming polymer (Carbopol) was soaked in water for 24 hours and then dispersed by agitation to get a smooth dispersion. The dispersion was allowed to stand for 15 min to expel entrapped air. Simultaneously nanoparticles, propylene glycol, permeation enhancer was added to water and undergoes gentle stirring. This was added to carbopol mixture by stirring, triethanolamine is added to form gel.

Table 2: It shows the composition of Flurbiprofen Nanoparticle Gel F3G1-F3G4

INGREDIENTS	F3-G1	F3-G2	F3-G3	F3-G4
Flurbiprofen nanoparticles equivalent to 5 %w/w of Flurbiprofen (gm)	2.59	2.59	2.59	2.59
Carbopol-934 (gm)	0.3	0.5	0.7	0.9
Propylene glycol (ml)	1.5	1.5	1.5	1.5
DMSO (ml)	1	1	1	1
Propyl paraben (%)	0.01	0.01	0.01	0.01
Triethanolamine (ml)	0.2	0.2	0.2	0.2
Distilled water	q.s to 10	q.s to 10	q.s to 10	q.s to 10

Evaluation of Flurbiprofen nanoparticle gel:

pH

The pH of Flurbiprofen nanoparticle gel formulations was determined by using digital pH meter. One gram of gel was dissolved in 100 ml of distilled water and pH was measured. This was done in triplicate and average values were calculated.

Viscosity

The measurement of viscosity of the prepared gels was done with a Brookfield Viscometer. The gels were rotated at 10 rpm using spindle no. 64. At each speed, the corresponding dial reading was noted.

Spreadability

1 g of gel was sandwiched between 2 horizontal plates (20 X 20 cm^2) for 1 minute. The upper plate was then removed and the diameter of the gel adhering to it was measured. The standardized weight tied on the upper plate was 125 gm.

Spreadability was then calculated by using the formula:

$$S = d^2 \times \pi/4$$

Where,

S = Spreadability

d = diameter of gel

π = 3.14

***In-vitro* Drug Release Studies Using the Pre-hydrated Cellophane Membrane:**

Preparation of cellophane membrane for the diffusion studies:

The cellophane membrane was washed in the running water. It was then soaked in distilled water for24 hours, before used for diffusion studies to remove glycerin present on it and was mounted on the diffusion cell for further studies.

Procedure: The in vitro diffusion studies of prepared gel were carried out in hollow tube diffusion cell using prehydrated cellophane membrane. 100 ml of phosphate buffer of pH 7.4 was used as receptor compartment, and then 1g of gel containing Flurbiprofen nanoparticle was spread uniformly on the membrane facing the donor compartment. The donor compartment was kept in contact with a receptor compartment and the temperature was maintained at 37±10^{0}C. The buffer solution was kept on the receptor side. At pre determined time intervals, pipette out 5ml of solution from the receptor compartment and immediately replaced with the fresh 5ml phosphate buffer. The drug concentration on the receptor fluid was determined spectrophotometrically at 248 nm against appropriate blank.

Calculation of percentage drug release:

$$\% \text{ drug release} = \frac{\text{Concentration of drug (mg)}}{\text{Label claim}} \times 100$$

***Ex- vivo* diffusion study**

Ex –vivo release study was conducted using fresh chicken skin from slaughter house. The skin was then soaked in sodium bromide solution for 5-6 hours and washed with water so as to remove adhering fat tissue. The epidermis was thoroughly washed with water, dried at 25% RH, wrapped in aluminium foil and stored in freezer until further use.

For *ex vivo* permeation studies, skins were allowed to hydrate for 1 h before being mounted on the Franz diffusion cell with the stratum (SC) facing the donor compartment. The sample was applied on the skin and then fixed in between donor and receptor compartment of Franz diffusion cell. The receptor compartment containing phosphate buffer of pH 7.4.The temperature of the medium was thermostatically controlled at 37±10^{0}C by surrounding water. Aliquots of 5 ml were withdrawn at predetermined intervals and were spectrophotometrically estimated at 248 nm against their respective blank formulation treated in the same manner.

Stability studies of optimized formulation

Optimized formulation was selected and kept for stability studies. Formulations were packed in a glass bottles and studies were carried out for 30 days by keeping at 5^{0}C, 25^{0}C, 40^{0}C. Samples were withdrawn on 0th, 15th, 30th day and were analysed for physical appearance, pH, viscosity, spreadability and drug content.

RESULTS AND DISCUSSION

Evaluation of Flurbiprofen nanoparticles

Particle size, Shape and surface morphology using SEM

The SEM photographs of Nanoparticles are shown in figure

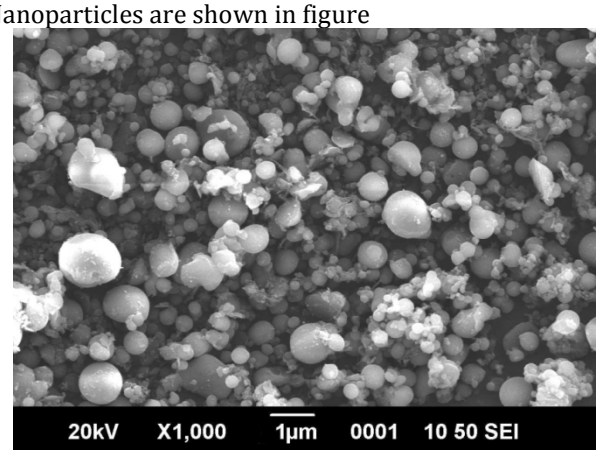

Figure 1: SEM Photographs of Flurbiprofen nanoparticle

SEM photographs of flurbiprofen nanoparticle shows that particles are spherical in shape.

Percentage yield and Percentage drug entrapment

Table 2: It shows the Percentage yield and Percentage drug entrapment of formulations F1-F8

FORMULATIONS	% YIELD	% DRUG ENTRAPMENT
F1	81.16	72.47±0.13
F2	86.87	82.91±0.74
F3	92.01	89.33±0.50
F4	94.25	91.50±0.54
F5	67.56	65.77±0.12
F6	72.32	70.51±0.35
F7	78.45	75.77±0.12
F8	83.78	78.63±0.36

***In-vitro* drug release studies**

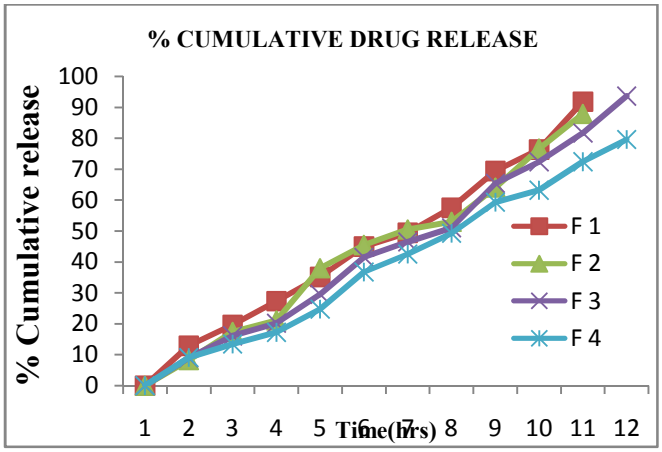

Figure 2: Comparison of in-vitro % cumulative release profiles F1-F4

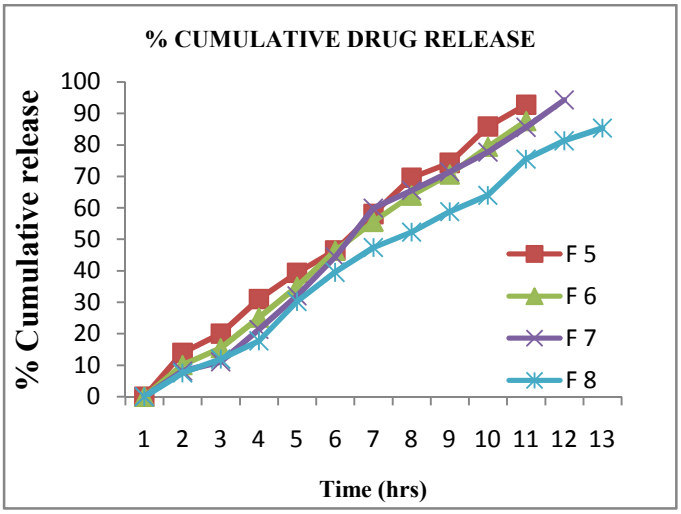

Figure 3: Comparison of in-vitro % cumulative release profiles F5-F8

- F7 of Eudragit gives maximum cumulative drug release at 11 hour
- Drug release from nanoparticles formulation can be ranked in the following descending order F7 > F3 > F5 > F1 > F2 > F8 > F6 > F4
- As polymer concentration increases, drug release decreases.

Best Formulation F3 was selected for the preparation of nanoparticle loaded gel based on the high % Drug release, % Drug entrapment and high yield.

Evaluation of Flurbiprofen nanoparticle gel

Physicochemical evaluation data

The physicochemical evaluation includes measurement of pH, Viscosity, Percentage Drug content and Spreadability.

Measurement of pH

The pH of the all formulations was in the range of 6.73 to 7.11, which lies in the normal pH range of the skin and would not produce any skin irritation. This may be due to the addition of base triethanolamine to the resultant gel during mixing so as to neutralize the acidic groups present in the polyacrylates chains of carbopol polymer. There was no significant change in pH values as a function of time for all formulations.

Measurement of viscosity

The viscosity of gels was found to increase with increase in the concentration of the polymer used.

Determination of spreadability:

The parallel-plate method is the most widely used method for determining and quantifying the spreadability of semisolid preparations. The spreadability of formulations was expressed in terms of spreading area instead of spreading coefficient which gives an accurate estimate of spreadability of the formulations. The spreading area was found to decrease with increase in viscosity since spreadability and viscosity are inversely proportional.

***In-vitro* drug diffusion study**

The release of Flurbiprofen from the gels was varied according to concentration of polymer. The release of the drugs from gel formulations ranked in the order F3-G1 > F3-G2 >F3-G3 > F3-G4, Where the amounts of the drug released after 12 hours were 88.12%, 85.35%, 79.05%, 72.34% respectively. The progressive increase in the amount of drug released from the formulations attributed to gradual decrease with increase in concentration of polymer. It has been concluded that, if we increase the concentration of polymer, the diffusion of drug through the membrane also decreases.

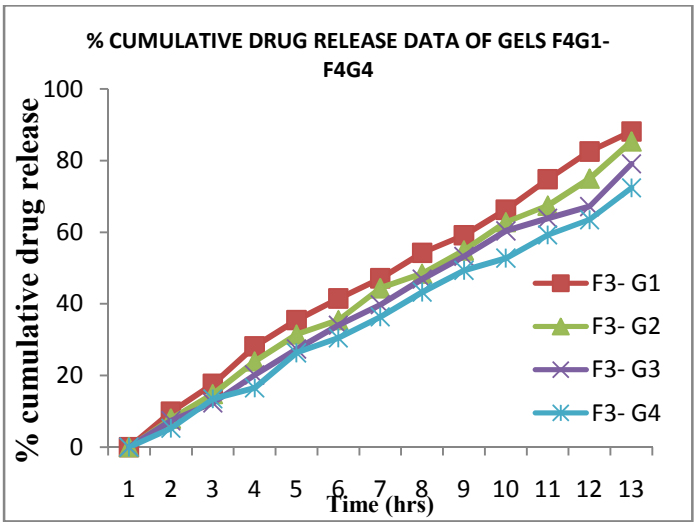

Figure 4: It shows the comparison of *in-vitro* % cumulative release profile of gels F3G1-F3G4

- **Best formulation F3-G1 was selected**

***Ex-vivo* release study**

The best formulations selected F3G1 were subjected to *ex-vivo* release study through chicken skin using Franz diffusion cell. The *ex-vivo* release would give a better estimate of drug permeation characteristics through animal skin. The amount of drug permeated through skin after 12 hours from F3G1 was 85.16%. The results are shown in table26 and the release pattern of F3-G1 were given in Fig45.

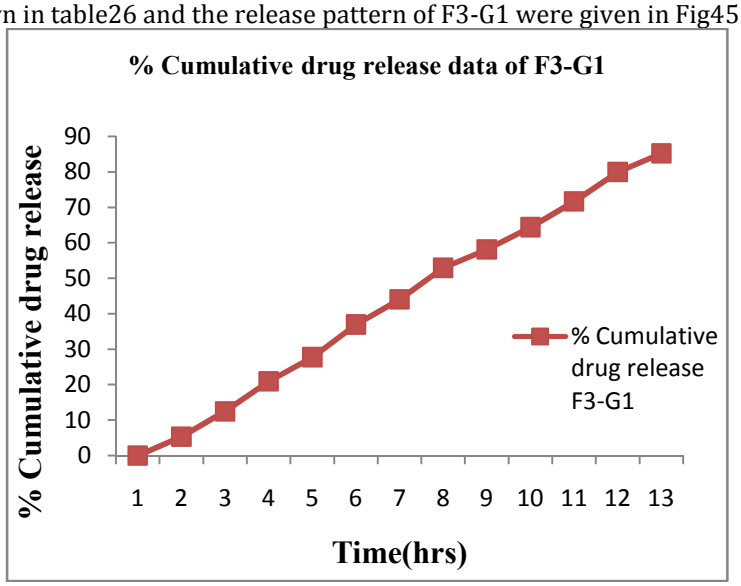

Figure 5: It shows the *Ex-vivo* % cumulative release profile of F3-G1

Stability study

Optimized formulation F3-G1 was subjected to stability studies by storing at 5^0C, 25^0C, 40^0C for 30 days. These Samples were analyzed and checked for changes in physical appearance, pH, viscosity, spread ability and drug content at 0, 15, 30 days. The obtained data is presented in Table 45-47. From the table, it is clear that the formulation did not undergo any chemical changes found more stable at 25^0C.

CONCLUSION

Nanoparticles are prepared by nanoprecipitation method. Firstly nanoparticles of 4 different concentrations of Ethyl cellulose and Eudragit L100 are prepared and evaluated for Particle size and shape, Percentage yield, Percentage drug entrapment and *In-vitro* drug release studies. From the results it was found out that the particle size is in the nanometer range and it is spherical in shape. Percentage yield and percentage drug entrapment efficiency slightly increases with polymer concentration. The percentage yield and entrapment efficiency is high in Ethyl cellulose compared to Eudragit L100.From the in-vitro drug release studies of Ethyl cellulose and Eudragit L100 nanoparticles, it was found that the drug release is decreased as polymer concentration increased. Eudragit L 100 show high release. But these formulations are avoided for preparing gel because of low yield and entrapment efficiency. Formulation of Ethyl cellulose nanoparticles "F3", selected as optimum formulation based on percentage yield, drug content & *in-vitro* drug release.

The optimized formulation of nanoparticles F3 were formulated in to gels using different concentration of carbopol 934 and subjected to physicochemical studies i.e. rheological studies, in-vitro release studies and ex-vivo release studies. The pH of all the formulations was in the range of 6.73 to 7.11, which lies in the normal pH range of the skin and would not produce any skin irritation. The spreading area was found to decrease with increase in viscosity since spreadability and viscosity are inversely proportional. From the in-vitro drug release results it was found that, F3-G1 shows highest drug release rate.

Ex-vivo release studies performed for F3-G1 which implies the best comparison of release rate since permeation through chicken skin gives precise results and difference in release mode. From the stability study, it is clear that the formulation did not undergo any chemical changes and found more stable at 25^0C.

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