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RESEARCH ARTICLE

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IONIC GELATION-BASED DEVELOPMENT AND OPTIMIZATION OF FLURBIPROFEN NANOGEL FOR IMPROVED DERMAL DELIVERY IN ARTHRITIS

Saurabh Gupta[*1], S. K. Gupta [2], Jitender Kumar Malik [2]

Research Scholar [1], Professor [2], Faculty of Pharmacy, P. K. University, Shivpuri - 473665, India.

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Correspondence should be addressed to
Saurabh Gupta,
Research Scholar,
Faculty of Pharmacy, P. K. University, Shivpuri - 473665, India.

Email- saurabh.gupta.gwalior@gmail.com

ABSTRACT: Arthritis is a persistent inflammatory disease that needs long term treatment, although traditional NSAIDs like flurbiprofen usually show side effects being systemic and low drug penetration at the inflamed location. As a way of overcoming these shortcomings, the current study was set out to design and optimize an ionically gelated flurbiprofen loaded nanogel. The nanoparticles were developed through different polymer concentration, cross-linker concentration, the speed of stirring, time of stirring, and time of sonication after which they were incorporated in a thermosensitive pluronic F127 gel. The optimized nanoparticles had a particle size of less than 200 nm, and a narrow PDI, positive zeta potential, and high entrapment. In vitro release experiments revealed a biphasic release which was characterized by an initial burst and sustained release over 24 hours. The end nanogel formulation was found to have appropriate pH, spreadability, and stability at refrigerated and accelerated conditions. In general, the flurbiprofen nanogel is optimized to be the most effective local drug delivery system in treating arthritis and it has good therapeutic efficacy, with little systemic adverse effects.

Keywords: Flurbiprofen; Nanogel; Ionic gelation; Chitosan nanoparticles; Topical drug delivery; Arthritis therapy; Sustained release; Pluronic F127

I. INTRODUCTION

Arthritis is an inflammatory disorder of the progressive and debilitating type, which affects millions of individuals all over the world and can be classified as one of the main causes of chronic pain and disability [1]. Arthritis is a severe and chronic inflammation of the joints, stiffness, swelling as well as progressive loss of movement that can profoundly deteriorate the quality of life and social and economic performance of the victims. The long-term management is problematic, even with easily accessible pharmacological treatment, such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs [2]. Traditional oral NSAIDs like flurbiprofen are commonly used in symptomatic treatment but when administered systemically, they are often accompanied by gastrointestinal discomfort, renal failure, cardiovascular side effects and other dose related toxicities. Also, the low absorption of NSAIDs into inflamed synovial tissues and rapid clearance in the body is usually leading to suboptimal therapeutic levels at the site of action, thus requiring re-administration and decreasing the level of patient adherence [3].

Drug delivery systems involving nanotechnology are an area where special interest has been given in recent years in order to overcome the drawbacks of conventional therapy. Nanogels, cross-linked, polymeric soft and nanoscale networks are among these systems which have shown great promise as a carrier of topical and localized delivery of anti-inflammatory drugs. Nanogels have a number of benefits such as the high capacity of drug-loading, improved permeation through skin layers, high biocompatibility, controlled and sustained drug release and minimized systemic exposure. Their capacity to hold water, swell and react with the biological tissues enables effective deposition of therapeutic agents to the inflamed joints with minimal off-target effects [4].

Flurbiprofen- a high-potency NSAID which belongs to the propionic acid group- is a good inhibitor of cyclooxygenase mediated synthesis of the prostaglandin, and is actively involved in the prevention of inflammation and pain related to arthritic conditions. Although the system has good therapeutic potential, the systemic adverse effects that are linked with oral administration and low effectiveness of traditional topical formulations indicate the necessity of a better delivery strategy [5]. By placing flurbiprofen in a nanogel matrix, the local bioavailability of the drug can be greatly stimulated, the permeation of the drug into the skin will be enhanced, the drug will be stabilized, the retention of the drug at the site of action will be increased, and finally, the therapeutic effect of the cell will be improved at fewer side effects [6]. The intention of the current study is to prepare and maximize a flurbiprofen-impregnated nanogel through the ionic gelation system, which is a gentle and solvent-free procedure incorporating chitosan and sodium tripolyphosphate. The formulation variables such as the polymer concentration, cross-linker concentration, stirring conditions and sonication time were systematically optimized to obtain nanoparticles with desired physico-chemical properties that could be incorporated into a thermosensitive Pluronic F127 gel.

The resulting nanogel was again tested in the areas of nanogel size, polydispersity, zeta potential, entrapment, pH, spreadability, in vitro drug release, and stability. In this way, the study aims at developing a more effective, safer and patient-friendly topical delivery system in the management of arthritis [7].

2. Materials and Methods

2.1 Materials

The active pharmaceutical ingredient (API) was flurbiprofen. A medium molecular weight of chitosan was used as the main polymer in the formation of nanoparticles and sodium tripolyphosphate (TPP) was used as ionic cross-linker. The nanogel was prepared by the use of pluronic F127 as a thermosensitive gel base. The rest of the reagents and chemicals employed in the study were of an analytical grade and the use of double distilled water throughout all the experiments [8].

2.2 Formulation of Flurbiprofen Nanoparticles (Ionic Gelation)

The nanoparticles of flurbiprofen were prepared by an ionic gelation method of chitosan and TPP on the basis of electrostatic interactions [9].

Preparation of polymer solution

The required amount of the polymer was dissolved in 1% v/v acetic acid under magnetic stirring to form a clear solution of chitosan solution (0.2-1.0% w/v). The solution of flurbiprofen was put in the chitosan solution and stirred [10].

Addition of TPP

TPP solution (0.2-1.0% w/v) was made under distilled water separately. A dropwise addition of the TPP solution to the drug-polymer solution started the ionic cross-linking and was performed at a controlled rate of about 2 mL/min [11].

Stirring process

Magnetic stirring was done on the mixture at different speeds (250-1250 rpm) and at different time periods (15 hours) to allow homogenous nanoparticle formation. Optimization studies that were performed included a modification of stirring parameters [12].

Sonication

To bring the nanoparticle dispersion to a smaller size and even density, the resulting was exposed to probe sonication (1-5 minutes, 35% amplitude). The resulting nanoparticles were harvested and kept at 4 ºC awaiting use [13].

2.3 Optimization Steps

To identify the most effective formulation, the variables were optimized using one-factor-at-a-time approach to systematically fit the following variables:

Polymer concentration variation

The concentration of chitosan used ranged between 0.2 and 1.0 percent w/v to determine the influence of the concentration on the size of particles, entrapment and stability [14].

Cross-linker concentration variation

The concentration of TPP was also changed between 0.2 and 1.0% w/v to test its effects on the density of cross-linking and nanoparticle properties [15].

Stirring speed variation

The impact of stirring rates (250-1250 rpm) on particle formation, homogenization and reducing their size was considered [16].

Stirring time variation

The time of the stirring (1-5 hours) was adjusted to obtain the optimal time of nanoparticles formation [17].

Sonication time variation

The time of sonication was kept at random between 1 and 5 minutes to achieve a minimum piece size and small size distribution of nanoparticles [18].

2.4 Preparation of Flurbiprofen Nanogel

The optimized nanoparticle preparation was entrusted into a Pluronic F127 gel base to make the final nanogel. Pluronic F127 was stirred by magnetic stirring at 1000 rpm with cold distilled water to a concentration of 22%w/v and left overnight at 4-8 ºC to allow sol–gel conversion. The nanoparticles of flurbiprofen previously made were safely suspended into the gel matrix by gentle stirring to generate a smooth homogeneous nanogel to be used in topical treatment [19].

2.5 Characterization

Particle size analysis (DLS)

The size distribution and mean particle size of the nanoparticles were determined using Dynamic Light Scattering (DLS) [20].

Polydispersity Index (PDI)

The values of PDI were calculated in order to measure the homogeneity and uniformity of the nanoparticle dispersion [21].

Zeta potential

Zeta potential analysis was done to check surface charge and colloidal stability [22].

pH measurement

A digital pH meter was used to determine the pH of the nanogel and it was adjusted to a pH of 7.5 to enable its use in the skin [23].

Spreadability

The spreadability was measured by putting the set amount of gel between two glass slides with standard weight and measuring the area covered [24].

Drug entrapment efficiency (EE%)

The level of entrapment was also calculated by measuring the quantity of flurbiprofen entrapped in the nanoparticles by means of UV-Visible spectroscopy following centrifugation [25].

Morphological evaluation

Scanning electron microscopy (SEM) or transmission electron microscopy (TEM) was used to measure the morphology of the nanoparticles in terms of shape and surface properties [26].

***In vitro* drug release**

The dialysis bag technique was used to release the drugs in phosphate-buffered saline (pH 7.4) at controlled temperature and agitation, where samples were sampled after predetermined times [27].

Stability studies

To analyze the variations in the particle size, pH, and drug content over time, stability was measured in conditions of accelerated (40 °C ± 2°C, 75% RH) and refrigerated (4 ºC) environments [28].

3. Results

Influence of Polymer Concentration

The concentration of polymer had a significant influence on nanogel properties. The increase in polymer content in Table 1 resulted in an increase in particle size, 165.73 nm up to 219.25 nm because of an increase in the viscosity, which constrained the breakup of droplets during ionic gelation. The entrapment efficiency also improved to 68.17% as compared to 61.49% as a result of better loading of drug with more polymer chains available. The values of the Zeta potential were steady, indicating that the degree of colloidal stability was good.

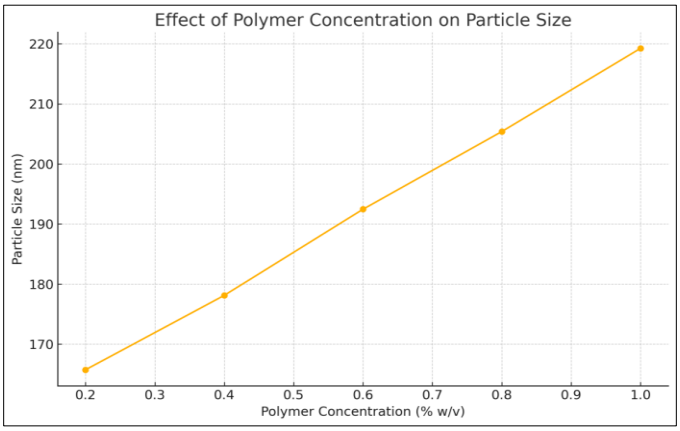

Figure 1: Effect of Polymer Concentration on Particle Size

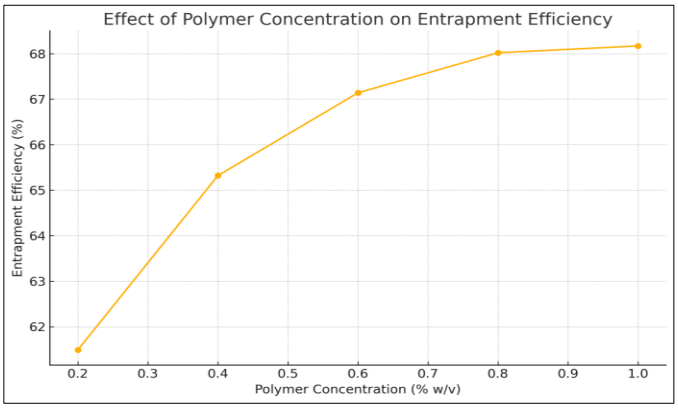

Figure 2: Effect of Polymer Concentration on Entrapment Efficiency

Table 1: Effect of Polymer Concentration on Nanoparticle Characteristics

Form.	*Polymer %*	*Particle Size (nm)*	*EE (%)*	*Zeta Potential (mV)*
F1	0.2	165.73±2.1	61.49±1.8	+28.6
F2	0.4	178.12±1.9	65.32±1.4	+29.4
F3	0.6	192.46±2.6	67.14±1.1	+30.1
F4	0.8	205.39±2.8	68.02±1.7	+30.7
F5	1.0	219.25±3.4	68.17±1.5	+31.2

Influence of Cross-Linker Concentration

When TPP concentration was raised to 0.2-1.0% the particle size steadily increased (Table 2), which was probably caused by the formation of a cross-linked network. The maximum efficiency of the trap was 0.8% TPP and reduced a little higher because of over-cross linking which limits the diffusion of the drug into the matrix.

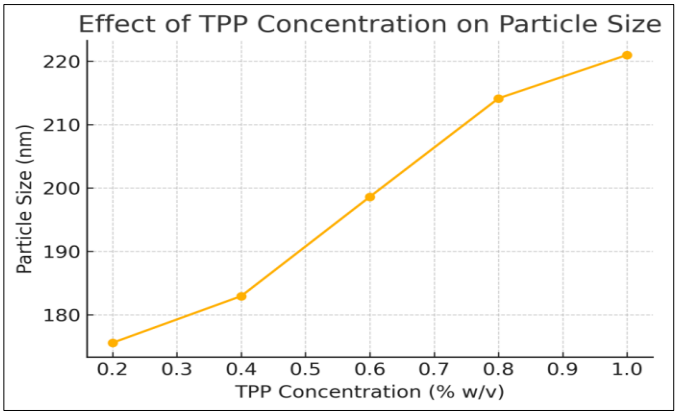

Figure 3: Effect of TPP Concentration on Particle Size

Table 2: Influence of Cross-Linker Concentration

TPP (%)	*Particle Size (nm)*	*EE (%)*
0.2	175.59 ± 2.3	64.12 ± 1.3
0.4	182.95 ± 2.2	67.25 ± 1.6
0.6	198.61 ± 2.7	71.86 ± 1.8
0.8	214.13 ± 3.1	73.52 ± 1.7
1.0	220.98 ± 3.4	72.94 ± 1.5

Influence of Stirring Speed

The speed of stirring had a significant influence on the formation of particles. Rising the speed by increasing 250 rpm to 1250 rpm resulted in a great decrease in particle size (Table 3) as the shear forces cause the formation of smaller droplets. Efficiency of entrapment declined marginally at a faster speed, and this may be attributed to the mechanical stress leading to loss of drugs in small amounts.

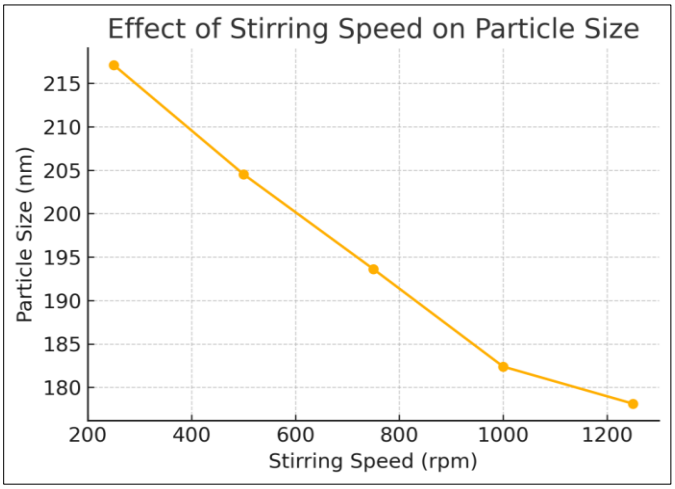

Figure 4: Effect of Stirring Speed on Particle Size

Table 3: Effect of Stirring Speed

Speed (rpm)	*Particle Size (nm)*	*PDI*	*EE (%)*
250	217.12 ± 3.1	0.41	74.26 ± 1.9
500	204.54 ± 2.8	0.36	73.84 ± 1.4
750	193.62 ± 2.4	0.29	72.56 ± 1.1
1000	182.39 ± 2.1	0.25	72.14 ± 1.3
1250	178.12 ± 1.9	0.23	71.62 ± 1.5

Influence of Stirring Time

Stirring time had an effect on maturation of nanoparticles. The size of the particles reduced to 177.02 nm (5 h) as compared to 197.02 nm (1 h) (Table 4). There was a minor decrease in the trap efficiency at longer mixing times which may be because of mild leakage of drugs.

Table 4: Effect of Stirring Duration

Time (h)	*Particle Size (nm)*	*EE (%)*
1	197.02 ± 2.6	73.86 ± 1.4
2	190.55 ± 2.4	73.22 ± 1.6
3	183.19 ± 2.3	72.41 ± 1.2
4	179.66 ± 2.1	71.82 ± 1.5
5	177.02 ± 1.9	71.07 ± 1.3

Influence of Sonication Time

The increase in duration of sonication resulted in a reduction in particle size as the duration of sonication was increased up to 5 minutes (189.43nm-174.16nm). PDI was reduced, and it signifies enhanced uniformity. Acoustic and thermal stress reduced the degree of trapment efficiency slightly.

Table 5: Influence of Sonication Duration

Time (min)	*Particle Size (nm)*	*PDI*	*EE (%)*
1	189.43 ± 2.0	0.31	72.98 ± 1.3
2	185.37 ± 1.9	0.27	72.64 ± 1.2
3	181.25 ± 1.8	0.25	72.23 ± 1.5
4	177.89 ± 1.6	0.22	71.81 ± 1.3
5	174.16 ± 1.5	0.21	71.45 ± 1.4

In Vitro Drug Release

The optimized formula had biphasic release where the first burst (surface-bound drug) was followed by persistent release to 24 h because of slow diffusion through the polymer matrix.

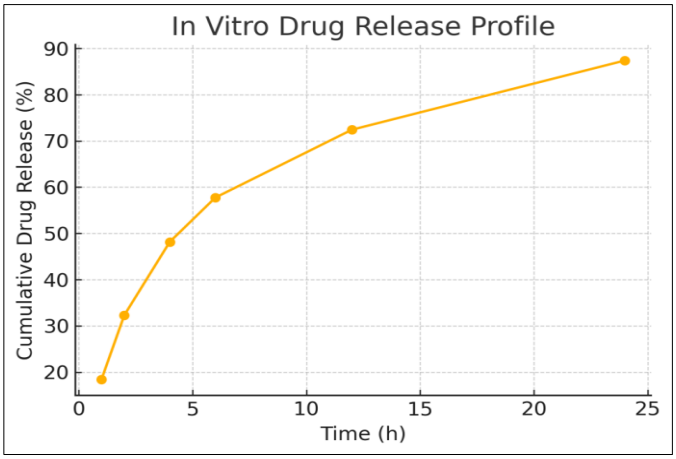

Figure 5: *In Vitro* Drug Release Profile

Table 6: In Vitro Drug Release Profile

Time (h)	*% Release*
1	18.42
2	32.28
4	48.16
6	57.73
12	72.41
24	87.39

Stability Studies

The stability results have verified that the nanogel was stable regarding particle size, pH as well as appearance in refrigerated, room temperature and accelerated conditions.

Table 7: Stability Summary

Condition	*Particle Size Change*	*pH*	*Appearance*
4°C	< 5 nm	Stable	Unchanged
25°C	< 10 nm	Stable	Unchanged
40°C/75% RH	~12 nm	Slight ↓	Acceptable

4. Discussion

The current work was able to design and optimize the flurbiprofen loaded nanogels via ionic gelation, proving that the variables of the formulation have a great impact on the behavior of nanoparticles. The concentration of polymer and

cross-linker had a direct impact on the particle size and entrapment efficiency, and an increase in the concentration of chitosan or TPP increased the particle size and rigidity but enhanced drug encapsulation to an optimum level. Process parameters were also important, more stirring speed and longer mixing time decreased the particle size through more droplet breakup and diffusion of the cross-linkers, but the redundant mixing increased entrapment a little because of mechanical stress. Additional enhancement of particle uniformity and reduction of size by cavitation was realized by sonication where 5 minutes was considered optimum without impairing drug loading.

The optimized nanoparticles had a particle size of less than 200 nm, small PDI, positive ZP, and high entrapment, which are desirable characteristics of nanoparticles in dermal delivery. The addition of a Pluronic F127 gel generated a thermosensitive, stable nanogel that could be used as topical. In vitro release experimentation revealed a burst release and a continuous release that is a favorable profile in maintaining extended therapeutic concentration in the arthritic joints. The stability experiments yielded good physical and chemical robustness at normal and accelerated conditions. Altogether, the results prove that ionic gelation is a promising method of creating flurbiprofen nanogels that can improve the localized delivery of the drug with minimized systemic side effects of NSAIDs.

CONCLUSION

The current research was able to design and optimize an nano gel loaded with flurbiprofen through the ionic gelation method and proved that the concentration of the polymer, the level of cross-linkers, the stirring rate, and sonication duration have a strong impact on the properties of the nanoparticles. The optimized nanoparticles had their desirable characteristics such as particle size of less than 200 nm, narrow PDI, positive Zeta potential, and high entrapment efficiency, which rendered them applicable in the topical drug delivery process. Adding to a Pluronic F127 gel led to a stable, thermosensitive nanogel with desirable pH and spreadability and in vitro release testing found an initial burst of release and followed by sustained release of the drug in the therapeutic nanogel. Analysis of stability also established the strength of the formulation. On the whole, the optimized nanogel has a high probability of being a dependable and effective localized delivery system of arthritis treatment, which is more effective with fewer side effects on the system.

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CONFLICT OF INTEREST: Nil

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