



DEVELOPMENT AND EVALUATION OF FLURBIPROFEN-LOADED GELATIN MICROSPHERES FOR TARGETED INTRA-ARTICULAR DRUG DELIVERY

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ABSTRACT

The paper is concerned with the design and testing of flurbiprofen-encased gelatin microspheres as a desirable system to deliver drugs straight to the joints with a goal of maximizing treatment efficacy and reducing the number of systemic side effects in the body. Four experiments (F1 4) were calculated through different polymer concentration, drug-to-polymer ratio, and crosslinking. The sphere size, entrapment efficiency and the in-vitro drug release of the microspheres was described. The yielded results showed that the size distribution was mostly mid-sized (5170 μm), and exhibited low aggregation, which indicates consistency and reproducibility. Efficiency of entrapment was between 56.2 and 84.5 and the optimized formula (F3) showed maximum level of drug loading. Classical in-vitro release No differences in the level of release were observed between the two solutions in real-time which is why the pattern displayed by in-vitro release was biphasic with the first release being burst release and the second release was sustained release till after 24 hours when F3 demonstrated the most controlled and sustained release. On the whole, the optimized gelatin microspheres provide promising system in sustained and targeted intra-articular delivery of flurbiprofen which could enhance the compliance and success of patients in the treatment of joint disorders.

Keywords: Flurbiprofen, Gelatin Microspheres, Intra-Articular Delivery, Drug Encapsulation, Controlled Release, Particle Size.

1. INTRODUCTION

Direct injection into the joint space has proven to be an interesting approach to the treatment of both inflammatory and degenerative joint diseases, including osteoarthritis and rheumatoid arthritis. Traditional

systemic delivery of anti-inflammatory medications usually leads to the low concentration of the drug at the site of action, a high frequency of administration, and unwanted systemic adverse effects. Intra-articular drug delivery systems have great benefits in this regard since the delivery system offers local therapy, an increase in the bioavailability of drugs, and a reduction in the systemic exposure. Microspheres being a particulate drug delivery system have been of much interest because of their capability to entrap active pharmaceutical substances, to protect them against degradation and to deliver controlled and prolonged release of drugs. Gelatin is a natural biocompatible, bio-degradable polymer that has been extensively used in microsphere formulations due to its ability to ease crosslinking, desirable drug entrapment, and low immunogenicity of gelatin, among others; making it one of the most appropriate polymers to be used in intra-articular administration.

Non-steroidal anti-inflammatory drug (NSAID) called Flurbiprofen is commonly administered as used to treat pain and inflammation related to joint diseases. Nevertheless, its more traditional modes of administration are restricted by quick clearing of the joint cavity and low half-life that necessitates a continuous repetition of dosage and heightens the risk of systemic side effects. In order to address these shortfalls, the current paper is devoted to the design and testing of microspheres of flurbiprofen that were to be loaded with gelatin and delivered sustained and directed release of drugs in the intra-articular cavity. The study will pursue a goal of achieving homogenous microsphere size, high drug entrapment efficacy and controlled drug release by setting formulation parameters like concentration of the polymer or drug to polymer ratio and conditions of crosslinking. The effective implementation of such a delivery system can lead to an enhancement of therapeutic outcome, a decrease in the frequency of doses, and compliance in such a system in patients managing chronic joint disorders.

1.1. Research Objectives

- To formulate and optimize flurbiprofen-loaded gelatin microspheres for intra-articular delivery.
- To evaluate entrapment efficiency and identify the best-performing formulation.
- To assess in-vitro drug release for sustained and controlled delivery.

2. LITERATURE REVIEW

Bulut (2020) examined the development and testing of chitosan-coated and uncoated microspheres made of sodium carboxymethyl cellulose and polyvinyl alcohol crosslinked with ferric ions, to deliver flurbiprofen.

The preparation of microspheres with different polymeric constitutions was the subject of study to determine their drug-loading capacity and in-vitro release property. It was found that the chitosan-coated microspheres had an improved entrapment efficiency of the drug and a smoother release profile of the drug than the uncoated formulations. This paper has proven that polymeric microspheres can be used to deliver drugs at sustained concentrations and enhance therapeutic activity and the study demonstrated that crosslinking and surface modification of microsphere are important in enhancing the performance of these hydrated spheres.

Dashnyam et al. (2018) investigated the use of biomaterials-based intra-articular skills of administering medication to treat the temporomandibular joint disorders. The review examined the possibility of using different biomaterials to deliver drugs locally into the joint cavity such as hydrogels, microspheres, and nanoparticles and their application. The improvement in drug retention, systemic exposure and delivery of lasting therapeutic outcomes was reported to be greatly enhanced through biomaterials assisted delivery systems. The study underscored the benefits of applying biodegradable and biocompatible carriers, which enhanced patient treatment through constant levels of drug in the joint and reduced the necessity to take a drug regularly. The study presented the importance of the intra-articular delivery system based on microsphere as a mode of targeting chronic joint disorders.

Farhangi, Dadashzadeh, and Bolourchian (2017) examined biodegradable microspheres of gelatin as a controlled-release drug delivery system, intra-articularly, by considering the effect of formulation factors on the microsphere properties. The study was able to establish that the changes in factor like polymer concentration and crosslinking degree and drug to Polymer ratio had a great impact on particle size, drug entrapment efficiency and release kinetics. The research indicated that optimized gelatin microspheres yielded slow drug release and small initial burst, which demonstrated that these microspheres can have a significant role in treating joint disorders intra-articularly.

Hathout and Omran (2016) studied particle drug delivery systems that use gelatin as the polymer to find out their physicochemical characteristics, biocompatibility and drug release characteristics. They had found that gelatin microspheres were capable of effectively entrapping therapeutic material and afford controlled release to enhance drug bioavailability and reduce systemic side effects. The study focused on highlighting that gelatin was peculiar carrier due to its biodegradability and biocompatibility that enabled its use in sensitive delivery sites which justifies its extensive usage in localized drug delivery systems such as intra-articular in delivery systems.

3. RESEARCH METHODOLOGY

3.1. Research Design

The current study is an experimental research design that will be carried out to develop and test flurbiprofen-loaded gelatin microspheres to deliver intra-articular drugs to a particular location. The experiment will entail the systematic preparation, characterization, and in-vitro analysis of various formulations of microsphere (F1-F4) to identify the best formulation, with respect to particle size, segregation efficiency of the drug and possible drug release profile. The design gives results reproducibility and reliability, as the procedures of formulation are standardized and the methods used are validated.

3.2. Sampling and Population

The population of this experiment means the ready batches of flurbiprofen-impregnated gelatin microspheres. The critical formulation parameters, e.g. polymer concentration, ratio of drugs to polymer, crosslinking conditions were varied to create four different formulations (F1, F2, F3, and F4). Every batch was represented as a sample used to assess the effect of the formulation variables on the microsphere properties. At least 100 microspheres a batch were examined to guarantee statistical dependability in the particle size disposition, entrapment efficiency and release of the drug subjects.

3.3. Data Collection

Information gathering was conducted in a regulated laboratory environment utilizing reliable methods of analysis:

- **Particle Size Distribution:** Microspheres were assessed by optical Microscopy and Image analysis software size. There were some size ranges (40 50 70 90) and these ranges were calculated in frequencies and percentages.
- **Entrapment Efficiency:** Quantification of drug loading was done by solvent extraction of flurbiprofen in microspheres and analysis by spectrophotometry. Each formulation (F1 through F4) was calculated with regard to the entrapment efficiency (in percent).
- **In-vitro Drug Release:** Cumulative drug release of microspheres was calculated within the 24 hours by the dissolution test in phosphate buffer (pH 7.4) using phosphate buffer. The release profile was determined using UV- visible spectroscopy to measure the concentration of drugs in predefined intervals (2, 6, 12 and 24 hours).

Measurements were also done in triplicate in order to provide precision and reliability.

3.4. Data Analysis and Techniques

Data collected were analyzed both through the descriptive and the graphical forms:

- **Particle Size Analysis:** Frequency distribution tables and histograms were prepared to identify the range of predominant particle size range and identify homogeneity in microsphere formation. The findings were put in percentages to be compared.
- **Entrapment Efficiency:** Drug entrapment Mean values of the formulations were determined to select the optimized batch. The charts used to demonstrate trends and present differences were bar charts and line charts.
- **Drug Release Kinetics:** Tabulation and plotting of Cumulative percentage drug release data in terms of time vs. release (%) curves were made to test the biphasic pattern of release and sustained release. The understanding of the drug release mechanism was conducted by releasing kinetics according to the conventional models (e.g., zero-order, first-order, and Higuchi models).

The statistical interpretation oriented on the trend analysis, comparative evaluation and the choice of maximally efficient formulation of F3 to continue intra-articular delivery researches.

4. DATA ANALYSIS AND INTERPRETATION

Table 1 displays the particle size distribution of the flurbiprofen- Loaded gelatin microspheres that have been prepared. The findings show that most of the microspheres lie in the 5170 mn range which constitutes 38 percent of the entire population. Particles within 7190 μ m range (28%), 4050 90-range (22) are followed and particles that exceed 90 00.3 m (12) are only 12 percent. Distribution pattern implies the presence of a mostly mid-sized formulation and little formation of very small or very large particles. This profile size is preferred in intra-articular drug delivery because microspheres between 50 and 90 μ m size increase retention in the joint cavity and decreases clearance or phagocytic rapidity. Good reproducibility and stability of the emulsification-crosslinking method applied is also seen in the uniform distribution.

Table 1: Particle Size Distribution

Size Range (μ m)	Frequency (n)	Percentage (%)
40–50	22	22%

51–70	38	38%
71–90	28	28%
>90	12	12%
Total	100	100%

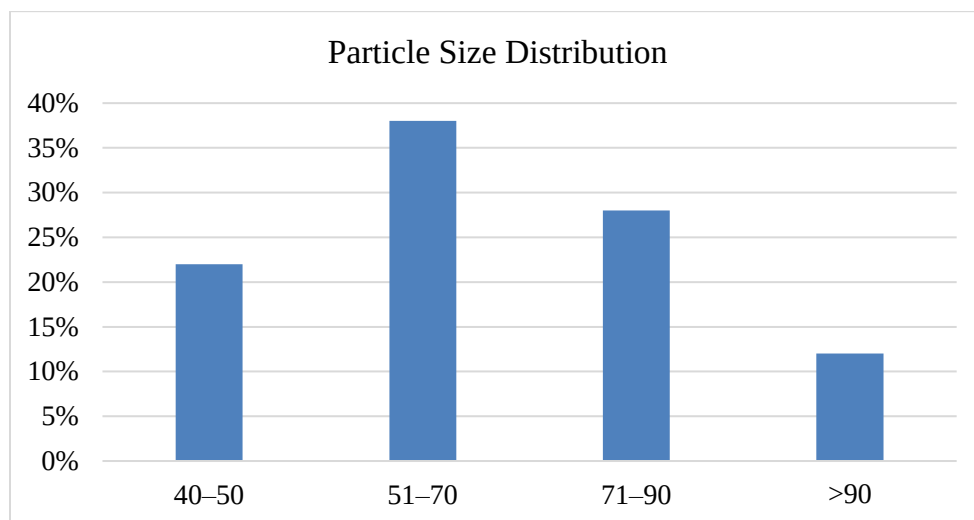


Figure 1: Particle Size Distribution

Figure 1 represents graphically the size distribution of the particle sizes of the microspheres that provides a visual representation of the number of particle sizes at the specified ranges. This is the most dominant size category as indicated by the plot that demonstrates a sharp peak at 51–70 μm range. The progressive slowing of the frequency of the particles towards the size range of larger dimension (>90 μm) implies that not much aggregation was achieved in the process of preparation. The plot trend reveals a homogeneous distribution in particle formation since it has a almost normal distribution. This size distribution uniformity is important to the achievement of predictable drug release kinetic and intra-particle therapeutic performance of the microspheres.

Table 2 presents the entrapment efficiency of four formulations (F1- F4) of flurbiprofen-loaded gelatin microspheres. The findings indicate the obvious enhancement of entrapment efficiency in the need to optimize the formulation parameters. Formulation F1 has the least entrapment efficiency of 56.2 which means that no drugs were encapsulated effectively and this might have been because of a low concentration of the polymer or the emulsification conditions were not optimum. F2 exhibits an intermediate increase with

68.7% with the optimized system F3 getting the highest entrapment efficiency of 84.5% showing better drug retention inside the microsphere matrix. F4 has a lower value of F3 but a high degree of efficiency of 79.3, which indicates that encapsulation is stable. Altogether, the results show that formulation modifications have a significant impact on entrapment efficiency with F3 being the most promising formulation in intra-articular delivery of drugs maintained at a certain level.

Table 2: Entrapment Efficiency (%) of Microspheres

Formulation Code	Entrapment Efficiency (%)
F1	56.2%
F2	68.7%
F3 (Optimized)	84.5%
F4	79.3%

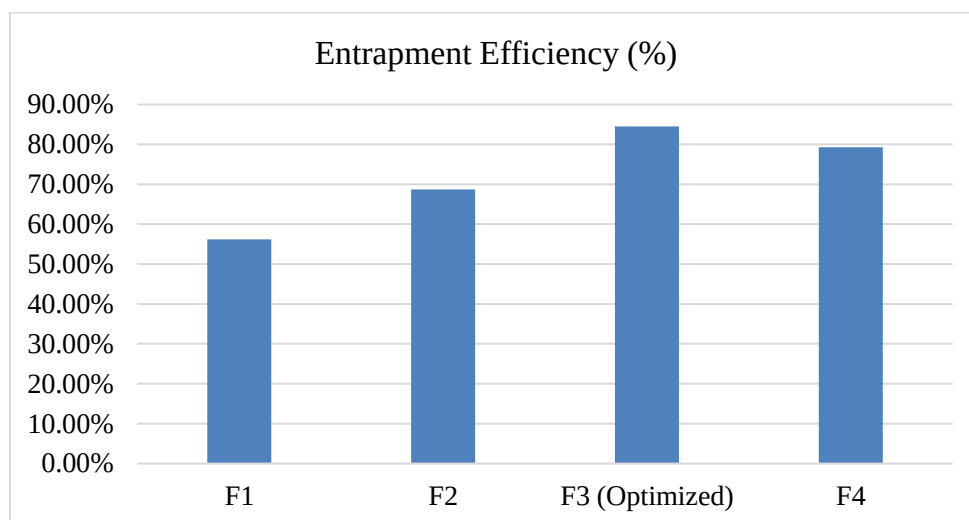


Figure 2: Entrapment Efficiency (%) of Microspheres

The difference between the values of entrapment efficiency of the four formulations is further indicated in figure 2 which is a graphic illustration of the entrapment efficiency values of the four formulations. The brood of graphics depicts gradual increasing tendencies between F1 and F3 leading to a clear peak at the optimized drug loading presenting the maximum drug loading capacity. This very small drop between F3 and F4 is an indication that the significant increase in the parameters of the formation might not bring any further advantage and rather (although the difference is very small) might decrease the efficiency of

encapsulations. The figure is effective to demonstrate how well the formulation optimization influences drug entrapment and helps to choose F3 as the most outstanding batch to be involved in the further assessments.

Table 3 shows the release profile of four formulations (F1-F4) of drugs in 24 hours, as a percentage. All formulations have displayed a biphasic release profile on initial bursts occurring in the initial 2 hours, followed by a modulated release occurring between 2-24 hours. F3 is the formula with maximum cumulative release with each time point, 31.6% at 2 hours, 61.1% at 6 hours, 85.6% at 12 hours and 92.4% at 24 hours. This shows that it has optimized polymer concentration and crosslinking conditions that make it easy to get flurbiprofen to diffuse through the gelatin matrix. F1 has the least release over time, which indicates a relatively denser or nonporous structure of the microsphere. All results indicate that composition of the formulations has a profound effect on the release kinetics, in which F3 offers the best sustained release characteristics that can be used in intra-articular drug delivery.

Table 3: In-Vitro Drug Release (%)

Time (Hours)	F1 (%)	F2 (%)	F3 (%)	F4 (%)
2	25.2	28.4	31.6	29.3
6	48.3	52.7	61.1	55.2
12	72.4	77.8	85.6	80.1
24	88.5	90.4	92.4	91.2

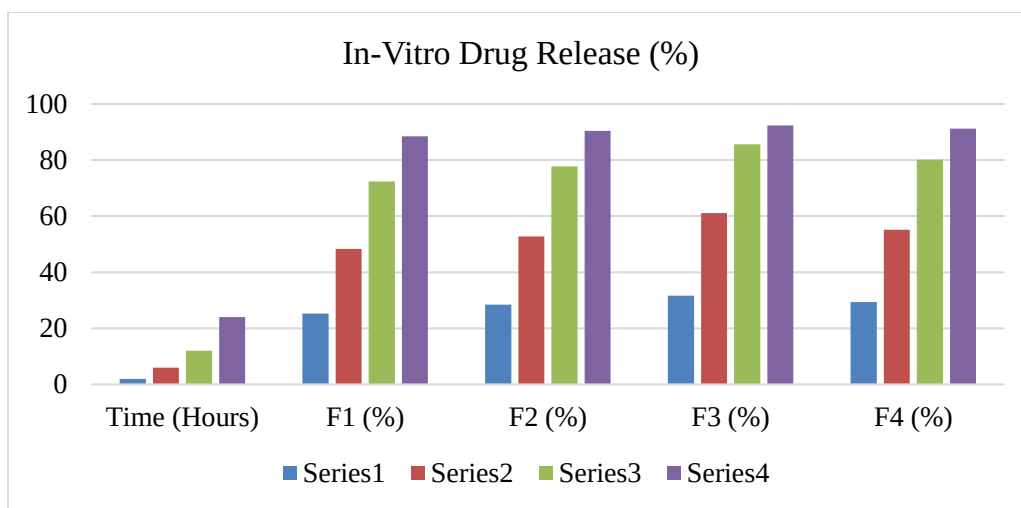


Figure 3: In-Vitro Drug Release (%)

The drug release behaviour of all four formulations at the 24-hour study time was graphically explained using figure 3. The curves reveal that the efficiencies of each formulation vary distinctly with release of F3 always having the highest release trajectory, then F4, F2 and F1. The sharp increase in the first stage can be attributed to the normal burst release that is characteristic of the surface adsorbed or weakly bound drug molecules. The following gradual slope is indicative of sustained release that is regulated by that of matrix erosion and diffusion. The curves are smooth and ascending, which comes as a reassuring confirmation of the stability of the microspheres and stability in drug release behaviour. The aesthetic tendency strongly substantiates the idea that F3 has the optimized and controlled release properties and will become the best one that will be used as a targeted intra-articular therapy with the necessities of the extended availability of drugs.

5. CONCLUSION

The current research was able to synthesize and evaluate the gelatin microspheres laden with flurbiprofen to be used as a target delivery system intra-articularly proving their abilities as a successful and prolonged drug delivery system. F3 out of the four formulations was found to be the optimized batch showing the highest entrapment efficiency (84.5%), most of the mid-sized size (5170 m), and had a good biphasic in-vitro drug release profile with prolonged and controlled release up to 24 hours. The findings suggest that the parameters used in formulation like ratio, concentration of polymer and crosslinking play a critical role in determining the microsphere properties, which include size homogeneity, drug loading and release mechanism. In general, the optimized gelatin microspheres provide a promising methodology to increase the localized therapeutic effects, decrease the dosage rate, hold down on the side effects of the systemic exposure, and work out compliance in patients in the treatment of long-term joint diseases.

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