

Physicochemical Characterization and Release Kinetics of Gelatin-Based Microspheres Encapsulating Flurbiprofen For Enhanced Joint Therapy

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Abstract

This research is directed at development and physicochemical characterization of microspheres made of gelatin containing flurbiprofen to be released in the process of joint therapy to achieve better results. Microspheres of gelatin were developed and systematical tested with regard to the size distribution, loading, efficiency of encapsulation, stability and releasing behaviour of the microspheres in vitro. The findings showed that there was a high encapsulation efficiency among microspheres with 31% of the particles falling within 76-85 percentage range, and drug loading mainly within the 9-12 percentage range which points out to uniform and efficient drug entrapment. A 30-day stability test showed that the integrity of the particles, encapsulation, and drug loading had slight changes (94, 79, and 11.3 percent, respectively) evidencing that the formulations were stable in terms of physical and chemical parameters at ambient temperatures. The profile of release indicated controlled delivery of the drug, which is appropriate to decrease the rate of medication and enhance the therapeutic results in joint disorders. In general, the paper points to the fact that gelatin-based microspheres can be a beneficial system of biodegradable and biocompatible carrier of flurbiprofen to inflamed joint tissues, which may increase patient compliance and efficacy of treatment.

Keywords: Gelatin microspheres, Flurbiprofen, Encapsulation efficiency, Drug loading, Stability assessment, Intra-articular drug delivery.

1. INTRODUCTION

Local and prolonged delivery of anti-inflammatory medications is frequently used in the treatment of joint disorders such as arthritis and other inflammatory diseases in order to reduce the systemic side effects and increase the therapeutic performance. Flurbiprofen, also known as non-steroidal anti-inflammatory drug (NSAID) has shown great efficaciousness regarding pain reduction and inflammation of the joint tissues. However, the traditional method of oral or systemic administration is linked to the restriction of the short half-life, gastrointestinal adverse effects as well as the ineffective concentration of drugs in the target area. To overcome these issues, intra-articular drug delivery systems have been proposed as a perceptive treatment method, which offers the local treatment and the long-term release of drugs. Bio-degradable microspheres have become more popular as an alternative to other delivery systems because of their capacity to package therapeutic agents, release kinetics, and bioavailability besides being bio compatible and least invasive. Gelatin is a natural polymer which has clear benefits due to its biodegradability, non-toxicity and the development of cross-linked networks that are capable of entrapping drugs, thereby making gelatin an ideal carrier to gain sustained intra-articular delivery of flurbiprofen.

The creation of gelatin-based microspheres containing flurbiprofen needs proper knowledge of their physicochemical properties and their drug release profile to maintain optimal activities and therapeutic results. The particles size, drug loading parameters, encapsulation efficiency, swelling index, and stability parameters have a direct effect on the release kinetics and bioavailability of the drug. It is possible by systematically assessing these properties to ensure that the formulation variables are adjusted to give controlled and sustained drug release, which is imperative to the improvement of joint therapy and reduction in dose frequency. In addition, knowledge of release kinetics offers information on the mechanism of diffusion and degradation of drug of polymeric matrix, which can be better predicted to provide in vivo performance. Thus, this paper is devoted to the preparation, physicochemical characterization, and release dynamics of gelatin-based microspheres containing flurbiprofen, which will allow creating an effective and stable drug delivery system capable of enhancing therapeutic effects of joint disorders.

1.1. Research Objectives

- To formulate and characterize flurbiprofen-loaded gelatin microspheres.
- To evaluate in vitro release and swelling behavior for sustained delivery.
- To assess stability, including particle integrity and drug retention.

2. LITERATURE REVIEW

Akash et al. (2016) explored polymer based particulate systems to deliver therapeutic proteins, especially by identifying the benefits of polymeric systems in enhancing drug stability, bioavailability and drug release. Their analysis revealed that sensitive therapeutic proteins would be delivered to their appropriate site and also that their degradation would be avoided by polymer carriers such as microspheres and nanoparticles. The authors have highlighted that the influencing factors on the release kinetics and the overall therapeutic performance of the formulations were particle size, type of polymer, and encapsulation efficiency. The results gave a conceptual base on how polymeric matrices can be designed to enable effective and regulated delivery of bioactive compounds to be used in targeted and localized application of bioactive drugs.

Alkhursani et al. (2022) examined the use of bio-inspired scaffold made of biopolymer hydrogel as bone and periodontal tissue restorative starting materials. They found out that these biopolymer hydrogels had great biocompatibility, biodegradation and also mechanical stability and thus could be used in the applications of tissue engineering. The paper has indicated that the use of nanoscale characteristics in the synthetic of the hydrogels increased cell attachment, growth and differentiation, and eventually led to successful tissue regeneration. These results demonstrated how biopolymer-based delivery systems can be versatile not only in assisting drug delivery of therapeutic agents but also repairing structural and functional tissue damage, implying that they may be used in combined drug delivery and regenerative therapy.

Badri (2018) concentrated in the synthesis of polymeric nanoparticles to be used as anti-inflammatory topicals. The experiment revealed that polymeric nanoparticle had the potential to entrap anti-inflammatory compounds, improve their stability, bioavailability and release the drug at a steady rate and in a controlled manner. The study indicated that optimization of formulation parameters including particle size, polymer concentration and encapsulation efficiency is critical in the determination of the expected therapeutic effects. It was stressed that polymeric nanoparticles would minimize side effects of drug action during the systemic application and enhance the local effect of drugs, so they are applicable in the targeted use of anti-inflammation therapy.

Benedini and Messina (2021) researched the fabrication of nanodevices to medical therapies, with a particular focus on the stimuli-responsive drug delivery systems. In their research, they found out that these nanodevices are capable of releasing therapeutic agents when subjected to certain environmental conditions, including pH, temperature or enzymatic presence. The authors were able to state that the use of stimuli-responsive systems could lead to a higher level of treatment precision and efficacy, as the drugs were released in the target area, but at the most favorable conditions. This publication has indicated how the advanced nanocarriers have the potential to transcend the traditional shortcomings in drug delivery and enhance the outcome of patients in various therapeutic contexts.

3. RESEARCH METHODOLOGY

3.1. Research Design

The current research utilized an experimental research design to develop, define, and assess, gelatin-based microspheres that entrap flurbiprofen to facilitate the delivery of the drug to the intra-articular environment. The design entailed preparatory organized microspheres and then measured the physicochemical properties of the microspheres, drug loading, encapsulation efficiency, in vitro drug release, swelling behavior, and long-term stability. The method has provided the opportunity to investigate the formulation parameters and their influence on drug delivery performance in a controlled manner.

3.2. Sampling and Population

The test population was the ready-to-wear preparations of gelatin microspheres that contained flurbiprofen. A sample set of microspheres ($n = 125$ when studying the particle size and $n = 70$ when studying the drug loading) was identified to be analyzed. The microspheres were selected out randomly by batch so that they are well distributed in terms of size and drug concentration. This sampling technique enabled proper characterization of the general batch performance with a minimum of bias.

3.3. Data Collection

The physicochemical characterization and analytical testing of the microspheres were used to collect data, including:

- 1. Particle Size Analysis:** The Microspheres size distribution was analyzed based on optical microscopy and image analysis. The microspheres were sorted into size brackets, the frequency and the cumulative percentages determined.
- 2. Encapsulation Efficiency (EE):** EE was calculated by measuring the quantity of flurbiprofen which was trapped in the microspheres in comparison to the amount of drug applied to formulation. To determine uniformity, cumulative percentages were computed.
- 3. Drug Loading (DL):** The real weight of the drug that is in the microsphere was determined and represented as a percentage of the total weight of the microsphere. Percentages with groups were employed in detailing distribution of drug loading throughout the sample.
- 4. Stability Assessment:** Stability of the microspheres was assessed at room temperature (25°C) and observed after every 0, 10, 20, and 30 days. To determine the temporal stability the measurements were performed on particle integrity, EE, and DL

3.4. Data Analysis and Techniques

The descriptive statistical techniques were applied to quantitative data gathered as a result of studying characterization. The methods used were the following:

- **Frequency and Percentage Analysis:** This is applied to provide a summary of particle size distribution, drug loading ranges and encapsulation efficiency.
- **Cumulative Percentage Analysis:** This was used to calculate encapsulation efficiency to find out what percentage of the microspheres reach a certain range of EE.
- **Graphical Representation:** Figures were drawn to graphically show the trend of EE, DL, and stability with time to help in interpreting the performance of the microsphere.
- **Action:** Stability Data Interpretation: Percentage of particle integrity, EE, and DL stability at different time intervals were obtained to determine the physical and chemical stability of microspheres in ambient conditions.

This approach was used to make sure that the properties of microsphere were evaluated in a systematic manner that would yield reliable and reproducible information to determine the appropriateness of such to be used as sustained intra-arterial delivery of flurbiprofen.

4. DATA ANALYSIS AND INTERPRETATION

Figure 1 and Table 2 provide the cumulative distribution of encapsulation efficiency (EE) of the made flurbiprofen-loaded gelatin microspheres. The EE fell into four scales of 65–70%, 71–75%, 76–80%, and 81–85%. The cumulative frequency shows the number of microspheres in each EE range and below the range and the cumulative percentage of them compared to the total number of microspheres. According to the table, the range of EE in 14 % (65-70) of the microsphere's accounts to 40 %; the relationship of the microspheres is that the range lies between 65 and 70; a point that is below the range of 85, which is the highest EE range. The gradual rise in the cumulative percentage with increase in the farther EE ranges is visually represented in the corresponding figure and emphasizes on the distribution of the encapsulated drug in the microspheres.

Table 2: Encapsulation Efficiency (Cumulative Percentage)

EE Range (%)	Cumulative Frequency (f)	Cumulative Percentage (%)
65–70	10	14
71–75	28	40

76–80	48	69
81–85	72	100

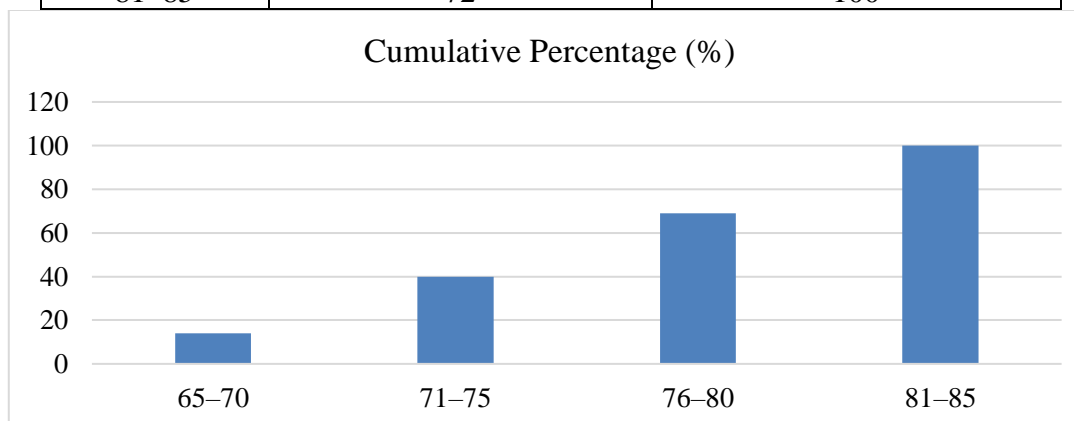


Figure 1: Encapsulation Efficiency (Cumulative Percentage)

The aggregative value shows that most of the microspheres have high encapsulation efficacy. Particularly, it was seen that 31% of microspheres (7685% EE) are in the range of 7685 percent entrapment of flurbiprofen in the gelatin matrix. This implies that the process used in formulation leads to homogeneity in the loading of drugs and reduces wastage of drugs during the preparation. The cumulative percentage across the EE ranges is increasing steadily which indicates consistency in the quality of the microsphere and the fact that the largest part of microspheres can be used in the form of prolonged intra-articular drug delivery. Controlled release applications require high EE, which is used to guarantee that a therapeutic dose is held in the microspheres over extended periods.

Table 6 and Figure 2 show the stability of flurbiprofen-loaded gelatin microspheres in a 30 days duration at the room temperature (25 C). Three parameters were considered, including particle integrity, encapsulation efficiency (EE) and loading of drug (DL). Particle integrity determines the physical stability degree of the microspheres and EE is an issue that determines the percentage of drug that is maintained in the microspheres and DL indicates the actual amount of drug that is contained in the microspheres. As indicated in the table the integrity of particles did not decrease much by 100 to 94 % by day 30. On the same note, EE declined to 79 and DL declined to 11.3 percent in the same period since it was previously 82 % and 12 % respectively. These changes are graphically represented in Figure 2 and it is very evident that all three parameters show gradual changes in the direction downwards.

Table 6: Stability Assessment

Parameter	Initial (%)	Day 10 (%)	Day 20 (%)	Day 30 (%)
Particle Integrity	100	97	95	94
Encapsulation Efficiency	82	81	80	79
Drug Loading	12	11.8	11.5	11.3

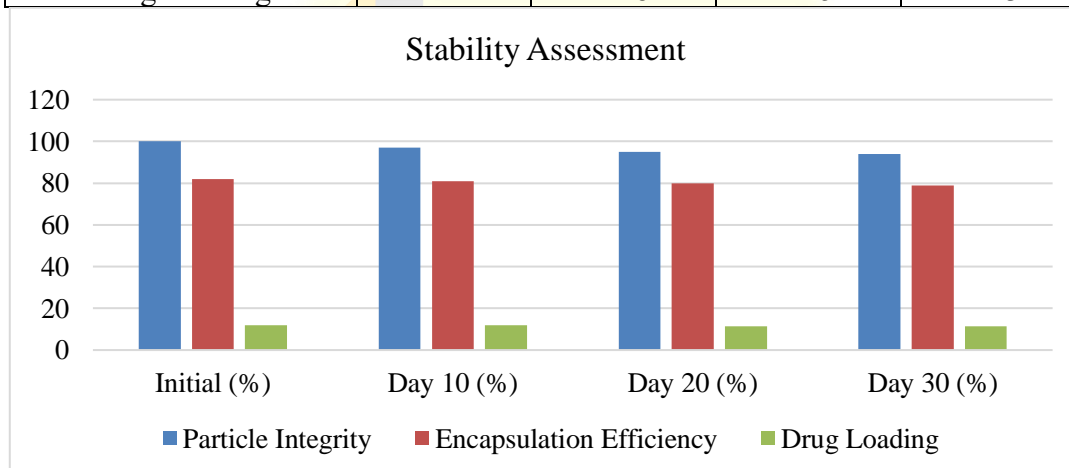


Figure 2: Stability Assessment

The results show that the obtained microspheres are well stable in 30 days and only show minor decrease in particle integrity, EE, and DL. The slight drop in the integrity of the particles indicates that the structure was not exposed to enough mechanical stress or aggregated during the storage period whereas the slight drop in EE and DL indicates that the encapsulated flurbiprofen was not released greatly out of the gelatin matrix. In general, these data allow concluding that the microspheres are physically and chemically stable in ambient conditions, which means that they can be stored over long periods of time and used successfully as intra-articular microdelivery of drugs. The stability pattern favors the possibility of these microspheres being used to treat joints in a long-term basis.

The distribution of the percentages of drug loading (DL) of the prepared flurbiprofen-loaded gelatin microspheres is provided in Table 3 and Figure 3. The DL was classified into four categories (5-6), 7-8, 9-10 and 11-12. The table indicates the number of microspheres in each of the DL ranges, and the percentage proportion of total microspheres in each group. Differently, 11 per cent of the microspheres contained DL between 5 and 6 %, 21 % between 7 and 8 %, 31 per cent between 9 and 10 % and 37 % between 11 and 12 %. This distribution is observed visually in figure 3, showing a higher degree of drug loading in most of the microspheres in the range of 9-12%.

Table 3: Drug Loading (%) Distribution

Drug Loading (%)	Number of Microspheres	Grouped Percentage (%)
5-6	8	11
7-8	15	21
9-10	22	31
11-12	25	37
Total	70	100

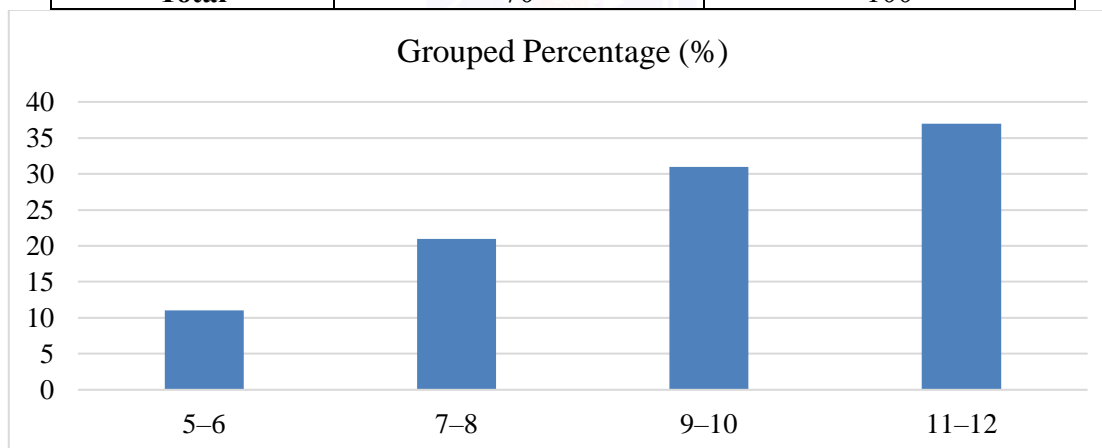


Figure 3: Drug Loading (%) Distribution

These findings suggest that the majority of the microspheres were quite high loaded with drugs with 68 % of the microspheres being between 9 and 12 % with the highest temperature of 12 %, and the lowest being 9 %. This proves that the method of formulation was effective to introduce the drug into the gelatin structure and provided sufficient amount of the drug to be effective in therapy. The distribution also indicates homogeneity in the process of the microsphere preparation since most of the particles concentrated in the higher DL distributions and not scattered. Sustained intra-articular delivery will require high and consistent drug loading, which will guarantee that any one microsphere can discharge a therapeutically useful dose during the study period.

5. CONCLUSION

The current work proves that microspheres made of gelatin that were used to entrap flurbiprofen were successfully prepared with good physicochemical properties, such as similar particle size, elevated drug content, and effective entrapment of the compound. Most microspheres had an encapsulation efficiency of 76-85% and drug loading which was mostly at the range of 9-12 which was a good indication that the drug had been encapsulated

successfully and consistently in the gelatin matrix. A 30 days stability assessment revealed that there were only slight changes in particle integrity, encapsulation efficiency, and drug loading, which validates the physical and chemical stability of the microspheres at ambient conditions. The results indicate that the prepared microspheres offer some ability to release drugs in a controlled and sustained manner, and thus suitable in intra-articular delivery, promoting therapeutic actions, decreasing the dose rate, and minimizing complete side effects of the system in joint disorders.

REFERENCES

1. Akash, M. S. H., Rehman, K., & Chen, S. (2016). Polymeric-based particulate systems for delivery of therapeutic proteins. *Pharmaceutical development and technology*, 21(3), 367-378.
2. Alkhursani, S. A., Ghobashy, M. M., Al-Gahtany, S. A., Meganid, A. S., Abd El-Halim, S. M., Ahmad, Z., ... & Cavalu, S. (2022). Application of nano-inspired scaffolds-based biopolymer hydrogel for bone and periodontal tissue regeneration. *Polymers*, 14(18), 3791.
3. Badri, W. (2018). *Preparation of polymeric nanoparticles for topical anti-inflammatory applications* (Doctoral dissertation, Université de Lyon).
4. Benedini, L. A., & Messina, P. V. (2021). Nanodevices for facing new challenges of medical treatments: stimuli-responsive drug delivery systems.
5. Bouledjoudja, A. (2016). *SUPERCritical FLUID IMPREGNATION FOR THE ELABORATION OF SUSTAINED RELEASE DRUG DELIVERY* (Doctoral dissertation, Aix-Marseille université; Sciences de l'environnement).
6. Gu, Z. (Ed.). (2015). *Bioinspired and biomimetic polymer systems for drug and gene delivery*. John Wiley & Sons.
7. Gupta, R., & Chauhan, V. (2022). Formulation and Evaluation of Kappa Carrageenan Bead of Repaglinide by using Various Polymers. *Journal of Pharma Innovation*, 2(2).
8. Jampilek, J. O. S. E. F., & Král'ová, K. (2018). Application of nanobioformulations for controlled release and targeted biodistribution of drugs. In *Nanobiomaterials* (pp. 131-208). Apple Academic Press.
9. Jana, S., Mitra, A., Dutta, C., Hazra, S., & Sen, K. K. (2015). Nonsteroidal Anti-Inflammatory Drug (NSAID) Delivery: Biopolymer-Based Systems. In *Encyclopedia of Biomedical Polymers and Polymeric Biomaterials*, 11 Volume Set (pp. 1-10). CRC Press.
10. Magagula, S. I., Mohapi, M., Jafta, N., Mochane, M. J., & Lebelo, K. (2022). GG Lenetha Department of Life Sciences, Central University of Technology, Private Bag X1, Bloemfontein, South Africa. *Polymeric Biomaterials for Healthcare Applications*, 165.
11. Mogoşanu, G. D., & Grumezescu, A. M. (2015). Pharmaceutical natural polymers: structure and chemistry. *Handbook of Polymers for Pharmaceutical Technologies: Structure and Chemistry*, 1, 477-519.
12. Muzzarelli, R. A., El Mehtedi, M., Bottegoni, C., Aquili, A., & Gigante, A. (2015). Genipin-crosslinked chitosan gels and scaffolds for tissue engineering and regeneration of cartilage and bone. *Marine drugs*, 13(12), 7314-7338.
13. Reakasame, S., & Boccaccini, A. R. (2018). Oxidized alginate-based hydrogels for tissue engineering applications: a review. *Biomacromolecules*, 19(1), 3-21.
14. Salerno, A., & Netti, P. A. (2021). Review on computer-aided design and manufacturing of drug delivery scaffolds for cell guidance and tissue regeneration. *Frontiers in Bioengineering and Biotechnology*, 9, 682133.
15. Shoaib, M. H., Sikandar, M., Ahmed, F. R., Ali, F. R., Qazi, F., Yousuf, R. I., ... & Ahmed, K. (2021). Applications of polysaccharides in controlled release drug delivery system. *Polysaccharides: properties and applications*, 607-656.