Research Article

Formulation, evaluation and optimization of microspheres of anti-inflammatory drug diacerein using polymer carbopol for the treatment of osteoarthritis

Shallu*, Ramandeep Singh, Satinder Kakar

[1]Ganpati Institute of Pharmacy - [GIP], Yamuna Nagar,Haryana,India

[2]Himachal Institute of Pharmacy Paonta Sahib, Himachal Pradesh, India

Received: 15-08-2024 / Revised: 11-02-2025/ Accepted: 01-03-2025

Abstract

The objectives of the present study were to select a formulation that has an ideal *in vitro* dissolution profile and to compare the sustaining/ controlling efficacy of the selected formulation with that of the commercial conventional tablet in order to establish a good degree of *in vitro–in vivo* correlation. The microspheres were subjected to characterization for particle size, encapsulation efficiency, loose crystal study, stability study, *in vitro* release rate profile, release kinetics and *in vivo* study in New Zealand white rabbit species. A single-dose oral bioavailability study revealed significant differences in C_{max}, T_{max}, T, K_a, K_e, MRT, MDT and AUC between the conventional tablet and optimized microsphere dosage forms. Furthermore, linear relationship obtained between the percentages dissolved and absorbed suggests a means to predict *in vivo* absorption by measuring *in vitro* dissolution. Thus F5 formulation showed the best *in vivo* performance exhibiting deliberate release.

Keywords : Dissolution rate, *in vivo* parameters, *ivivc*, release kinetics.

Introduction

Novel drug delivery systems (NDDS) have revolutionized the field of pharmaceutical research and development, offering improved therapeutic outcomes, enhanced patient compliance, and reduced side effects. This review aims to provide an overview of re- cent advancements in NDDS, highlighting their potential applications and advantages over traditional drug delivery methods. Various innovative NDDS, including nano- technology-based systems, targeted drug delivery systems, and implantable devices, are discussed. Additionally, the challenges and future prospects of NDDS are ex- plored to shed light on the direction of future research in this exciting field.

Nanotechnology-Based Drug Delivery Systems:This section focuses on the application of nanotechnology in drug delivery systems. It discusses the use of nanoparticles, liposomes, dendrimers, and carbon nanotubes as carriers for drug delivery. The advantages of nanotechnology-based systems, such as enhanced drug solubility, prolonged release, and targeted delivery, are highlighted.

Targeted Drug Delivery Systems:Targeted drug delivery systems aim to deliver drugs specifically to the site of action, reducing systemic side effects and improving therapeutic efficacy. This section dis- cusses various targeting strategies, including active targeting (ligand-receptor interac- tions), passive targeting (enhanced permeability and retention effect), and stimuli-responsive targeting (pH, temperature, or enzyme-sensitive systems)[1,2]

*Correspondence

Shallu

Ganpati Institute of Pharmacy - [GIP], Yamuna Nagar,Haryana,India

Materials and methods[3,4]

Microspheres containing the anti-inflammatory drug Diacerein were prepared by solvent evaporation method.In this technique drug and polymer carbopol in various proportions were dis- solved in 20ml acetone which was placed in a small beaker with magnetic bed on the magnetic stirrer at room temperature.The drug polymer mixture was poured into 30ml liquid paraffin containing Tween 80 maintained at a temperature of 30-40°C and subsequently stirred by the stirrer at ranging agitation speed that is 1200rpm for 60 minutes.Allow the volatile solvent to evaporate.The microspheres formed were filtered, washed with N-hexane and air dried for 24 hrs and stored in a desiccators.

CHARACTERIZATION OF MICROSPHERE[6,7,8]

Particle size determination

The size of the prepared microspheres was measured by the optical microscopy method using a pre-calibrated stage micrometer. Particle size was calculated by using equation

$Xg = 10 \times [(ni \times \log Xi) / N]$

Xg is geometric mean diameter, ni is number of particle in range, Xi is the midpoint of range and N is the total number of particles. All the experimental units were analyzed in triplicate (n=3).

Scanning electron microscopy[9-11]

Morphological characterization of the microsphere was done by taking scanning electron micrograph in (JEOL JSM Model 5200, Japan). Cross sectional view were obtained by cutting the microspheres with a razor blade[3]

Table 1. Composition of Diacerein Microspheres

Formulation code	F1	F2	F3	F4	F5
Diacerein	40mg	40mg	40mg	40mg	40mg
Carbopol	100mg	150mg	200mg	250mg	300mg
Acetone	20ml	20ml	20ml	20ml	20ml
Liquid Paraffin	30ml	30ml	30ml	30ml	30ml
N-hexane	q.s	q.s	q.s	q.s	q.s

Table 2: Angle of Repose, Compressibility Index and Hausner's Ratio

Flow property	Angle of Repose(θ)	CompressibilityIndex (%)	Hausner'sRatio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26- 1.34
Poor	46-55	26-31	1.35-1.45
Very Poor	56-65	32-37	1.46-1.59
Very very Poor	>65	>38	>1.60

Table 3: Diffusion exponent and solute release mechanism for cylindrical shape Diffusion

Diffusion coefficient	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anamolous (non-fickian diffusion)
0.89	Case II transport
n>0.89	Super Case II transport

RESULT AND DISCUSSION

FT-IR STUDY

Interaction between the drug and excipients used in the formulation was studied. The results are as follows :

Table 4: FT-IR Spectral interpretation of Diacerein

Wave number(cm^{-1})	Types of vibration
1766.67	C=O Stretching
2923.87	Ar-H Stretching
3440.76	O-H Stretching
1211.21	C-O Stretching

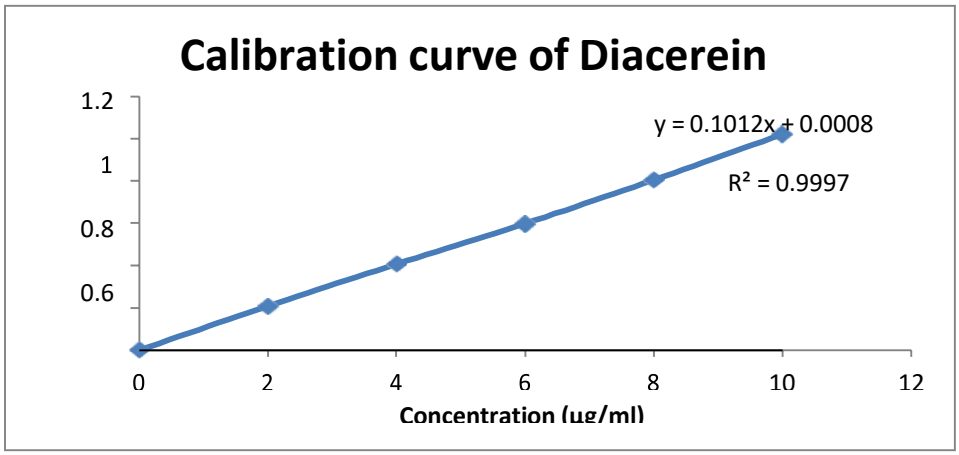
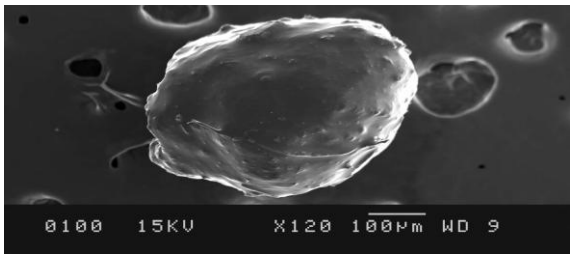


Fig 1: Standard graph of diacerein in phosphate buffer pH 6.8

It was found that the solutions show linearity (R2=0.999)in absorbance at a concentration of 2-10µg/ml and obeys Beer Lambert's law.

SCANNING ELECTRON MICROSCOPY



EVALUATION OF MICROSPHERES
PERCENTAGE YIELD

Table 5: Percentage yield of Diacerein microsphere

Formulation code	Theoretical yield (g)	Practical yield (g)	Percentage yield (%)
F1	0.6	0.393	65.60
F2	0.8	0.536	67.09
F3	1	0.781	78.10
F4	1.2	1.000	83.34
F5	1.4	1.176	84.02

Microspheres were prepared and their Percentage yield was calculated. They were found to be in the range of 56.38% to 85.64%. It shows increasing drug polymer ratio increased the percentage yield. The results correspond to earlier reports.

Conclusion

The present study reports a novel attempt to formulate microspheres of the drug Diacerein by using polymer carbopol for better treatment of osteoarthritis. Microspheres of Diacerein were prepared by solvent evaporation method. Various evaluation parameters were assessed with a view to obtain controlled release of Diacerein.Details regarding preparation and evaluation of formulation have been discussed in previous chapters. From the study following conclusion can be drawn:

- Physical compatibility study showed drug and excipients were physically compatible with each other.
- Chemical compatibility study (FT-IR) was carried out. It revealed no interac- tion between the drug and excipients.
- Standard graph was drawn for Diacerein and it was found that the solutions showed linearity (R2=0.999) and obeyed Beer Lambert's law.
- The effect of stirring rate was studied on optimized formulations for determin- ing production yield, drug content, mean particle diameter and drug release. The stirring rate increases production yield and drug content, while mean particle diameter decreased. No particular pattern was observed for drug release.
- The effect of internal phase concentration was studied on optimized formulations for determining production yield, drug content, mean particle diameter and drug release. The internal phase concentration increases production yield, drug content and decreases mean particle diameter. F5 showed a decrease in drug release with increase in solvent amount.
- The effect of external phase concentration was studied on optimized formula- tions for determining production yield, drug content, mean particle diameter. The external phase concentration increases production yield, mean particle di- ameter but decreases drug content. No particular pattern was followed for drug release.
- Even on increasing drug: polymer ratio, amount of solvent, concentration of emulsifying agent and rate of stirring on optimized microspheres (F5). F5 was optimised as the best formulation as it showed better results.
- Preformulation study was carried out for drug and F5 microspheres. It revealed that the flow property of pure drug was very poor, but the microsphere has good flow.
- The dissolution data of the optimized formulation were fitted to various kinet- ic models and the formulation F5 fitted best to Zero order kinetics.

Future scope

1. In-vivo study.
2. Pharmacokinetic and toxicity study.
3. Stability studies.

Reference

1. Singh MN, Hemant KS, Ram M, Shivakumar HG. Microencapsulation: A promising technique for controlled drug delivery. Res Pharm Sci. (2020);5(2):65-77.
2. Gurunathdhadde :A Review on Microspheres, Types, Method of Preparation, Characterization, and Application. Asian Journal of Pharmacy and Technology 2021;11(2):1-7
3. Kumar Sarvan K, Ramu S, Ishwarya M., Floating Microspheres: A Promising Drug Delivery, International Journal of Pharmacy and Pharmaceutical Re- search, 2021;11(1): 375-388
4. Farah Hamad Farah, Magnetic microsphere: A novel drug delivery system. Journal of Analytical and Pharmaceutical Research 2016;3(5):1-10.
5. M.F. Maitz, Applications of synthetic polymers in clinical medicine, Biosur- face and Biotribology 2018;11:61–176.
6. Chaturvedi G Saha RN, A Review in microsphere technology and its applica- tion Birla Inst Tec and sci, 2009: 56 -58.
7. Singh, B., Singh, R., &Bandyopadhyay. Microspheres as promising tool in the controlled drug delivery systems: a comprehensive review. International Jour- nal of Pharmaceutical Sciences and Research,2017; 8(7), 2697-2707.
8. Preeti K. Suresh et al.Development and In Vitro Characterization of Piroxicam Loaded Emulgel for Topical Delivery Ijppr.Human, 2021; Vol. 2 (3): 18-32.

9. BalasubramaniamJ, Rao VU, Vasudha M et al., Sodium alginate microspheres of metformin HCl: formulation and in vitro evaluation. Current Drug Delivery , 2007; 4(3):249-256
10. Icon, XuejingGu,Teng(2022): Formulation and in vitro Evaluation of Diacerein Loaded Transferosomal Topical Gel for the Effective Treatment of Osteoarthritis. Volume 34 [Issue 13A]
11. Mukesh Bansal, Dilip Kumar Gupta, Monika Sachdeva, Kamini: Formulation and Characterization of Expandable Tablet of Diacerein using Swellable Polymers. 202222(2):2
12. Tathagata Roy, Tapan Kumar Chatterjee (2022) : Formulation, Evaluation, and Optimization of Diacerein Loaded Transferosomal Gel for Arthritis.2022;9(2):1
13. Patel Krushika Sendhabhai and Sunita Chaudhary. Formulation and Evalua- tion Of Bioadhesive Buccal Tablet Of Diacerein. International Journal of Pharmaceutical Research and Bio Science. 2014; Volume 3(2): 860-879.
14. Randa Zakia, Adel Alia, Shahira F El Menshawea And Ahmed Abdel Baryb. Formulation and In -Vitro Evalution Of Diacerein Loaded Niosomes. Interna- tional Journal of Pharmacy and Pharmaceutical Sciences.2011; 3(2):515-521.
15. Randa Zakia, Adel Alia, Shahira F El Menshawea And Ahmed Abdel Baryb. Formulation and In -Vitro Evalution Of Diacerein Loaded Niosomes. Interna- tional Journal of Pharmacy and Pharmaceutical Sciences.2011; 3(2):515-521.