Original Article

FUTURE JOURNAL OF PHARMACEUTICALS AND HEALTH SCIENCES

Published by Pharma Springs Publication Journal Home Page: https://pharmasprings.com/fjphs

Formulation and evaluation of pioglitazone microspheres

Rajaguru Rajagopal*

Formulation Research and Development – Manager, Cure Afya Pharmaceutical Ltd, Plot 69, Malindi Road, Kimbiji, Kigamboni District, Dar Es Salaam, Tanzania, P.O Box 17101, East Africa

Article History:

Received on: 07 Feb 2024
Revised on: 28 Feb 2024
Accepted on: 03 Mar 2024

Keywords:

Nonprescription drugs,
OTC drugs,
OTC medications,
Over-the-counter medicines,
Self-care,
Self-medication

Abstract

The current study focuses on the formulation, development, and in vitro testing of pologlitazone microspheres containing guar gum and chitosan as naturally occurring polysaccharides that delay release. Nine formulations were created by altering the chitosan and guar gum ratios, using span-85 as an emulsifier as well as glutaraldehyde as a chemical cross linking agent. The microspheres were assessed in terms of particle size, encapsulation effectiveness, drug loading capacity, and in vitro drug release tests. The average particle size ranged from 30.2 mm (PP 1) to 36.5 mm (PP 2). There was a range of 0.45 to 0.78 in the swelling index. Microspheres smooth surfaces were found by SEM investigation. In order to verify that there are no chemical interactions between the medication and the polymer and to understand the structure of microspheres, differential scanning calorimetry as well as Fourier transform infrared spectroscopy were employed. At 10 hours, the optimised batch PP 1 released 97.45% using phosphate buffer pH7.4 as a dissolving media. In terms of release kinetics, the optimised formula's data were best fitted with the Higuchi model (r2= 0.671) and demonstrated zero order release (r2= 0.980) via a non-Fickian diffusion mechanism.

∗Corresponding Author
Name: Rajaguru Rajagopal
Phone: +255 685865339
Email: rajaguru94mrv@gmail.com

eISSN: 2583-116X
DOI: https://doi.org/10.26452/fjphs.v4i2.592

Production and hosted by
Pharmasprings.com

INTRODUCTION

Any drug therapy's effectiveness can be summed up as obtaining the target drug concentration in blood or tissue, which is both therapeutically beneficial and non-toxic for an extended length of time. Based on a well-designed dosing regimen, this objective can be accomplished. Drug delivery via microspheres may be possible in a regulated manner. While polglitazone is a useful medication for treating diabetes, it also produces neutropenia and is highly attached to plasma proteins, which can lead to gastrointestinal problems [1]. Delivering this medication in a prolonged release dose form may consequently be more preferable. The production of sustained release pioglitazone microspheres employing the emulsification solvent evaporation method was the main goal of the current investigation. Solid, roughly spherical particles with sizes ranging from 1 to 1000 µm are known as microspheres [2]. Examples include carbohydrates, gums, proteins, lipids, as well as waxes.

Creating novel delivery systems for regulated medication release is one of the most fascinating areas of pharmaceutical science study. Drugs, immunisations, antibiotics, and hormones can all be released under regulated conditions using microparticles. By utilising the properties of microspheres, for instance, one can benefit from their larger surface area, easier estimation of diffusion and mass transfer behaviour, precise kinetic modelling of the diffusion of encapsulated small molecules out of the barrier, and controlled release of drugs into bodily fluids [3]. Ethyl cellulose, a weak cationic polysaccharide, is one of the polymer systems used, and it has several benefits for creating microparticles for drug release applications. Shrimp and crab shells, among those of other crustacean species, are commonly used to extract chitin [4].

MATERIALS AND METHODS

Pioglitazone and chitosan (Indian Research Products, Chennai) were obtained as gift samples from Macleod's Pvt. Ltd., Mumbai, India. Glutaraldehyde (Chandamal, Paxmy) Every other reagent that was utilised was analytical grade.

METHODOLOGY

In order to maximise the concentration of the polymer, nine formulas were created using drug to polymer ratios of 1:1, 1:2, and 1:3. The drug and chitosan microspheres were made by combining 2% w/v guar gum with double distilled water and 2% w/v chitosan solution in aqueous acetic acid (1% v/v) [5]. In order to create a w/o emulsion, the medication was subsequently added, and this dispersed phase was stirred in while heavy liquid paraffin and liquid paraffin were added in a 1:1 ratio with 1% w/v span 85. The stirring was maintained at 4000 rpm with a propeller stirrer with three blades. Dropwise additions of a determined quantity of 2.5% v/v toluene-saturated glutaraldehyde (2.5 ml each) were made at 15, 30, 45, 60, 75, 90, 105, and 120 mnts. After one hour of stirring, the microspheres were obtained. They were then separated by vacuum-assisted filtering and cleaned twice once with petroleum ether and once with distilled water—to get rid of the glutaraldehyde and adherent liquid paraffin, respectively. Finally, the microspheres were dried in a desiccator. The finished product was a free-flowing powder made up of particles the size of spherical microns. Nine different formulas, PP 1 to PP 3, were made by combining 2%w/v chitosan with drug polymer ratios of 1:1, 1:2, and 1:3. PP 4 through PP 6 were made using 2%w/v guar gum, and PP 7 through PP 9 were made with a combination of 2%w/v guargum and 2%w/v chitosan. The emulsification solvent evaporation method was used to manufacture the medication, chitosan, and guargum microspheres [6].

Compatibility studies:

IR studies

Studies that address the drug-polymer interaction are therefore extremely important in appropriate polymers. Drug and polymer may interact during drug manufacture since they are in close touch with one another [7]. This could cause the instability of drug preformulation. The compatibility of pioglitazone with the cellulose polymer was ascertained by FT-IR Spectroscopy.

Differential scanning calorimetry

A plot of heat flux (rate) against temperature at a particular temperature rate is the result of a DSC. DSC offers details about the sample's physical characteristics, such as whether it is crystalline or amorphous, and also suggests potential interactions between the medicine and the polymers used in formulations [8].

Percentage yield

Each batch's weight of recovered microspheres was divided by the total weight of the medication and polymer used to create it, and the result was multiplied by 100 to determine the yield.

$$\text{Percentage yield} = \frac{\text{Weight of microspheres}}{\text{Weight of drug} + \text{weight of polymer}} \times 100$$

Drug content estimation

100 mg of drug-loaded microspheres were pulverised and suspended in 100 millilitres of methanol. The resulting dispersion was filtered through a 0.45 µm membrane filter after being left for 20 minutes to ensure thorough mixing under constant agitation. Spectrophotometric analysis at 228 nm was used to determine the drug content using a regression equation that was generated from the reference graph [9].

Drug Entrapment efficiency:

The following formula was used to determine the drug entrapment efficiency (DEE).

$$DEE = (Pc / Tc) \times 100$$

Particle size analysis [10]:

The microsphere size distribution was obtained using optical microscopy with a calibrated stage micrometre (μm) and computed using the equation below:

$$\text{Eye piece division} = \frac{Y}{X} \times \text{least count}$$

In-vitro drug release:

Using phosphate buffer pH7.4 as the dissolving medium, a USP paddle type dissolution test apparatus was used for the in vitro drug release examination. Over the course of the investigation, the bath temperature was kept constant at (37±1)°C, and the dissolving media volume was 900 ml. A 50 rpm paddle speed was set. After one hour, five ml of the sample was taken and replaced with five ml of new medium, and the Pioglitazone content was measured using a UV-Visible spectrophotometer at 228 nm [11].

Scanning electron microscopy (SEM)

The morphological properties of pioglitazone microspheres were investigated using scanning electron microscopy. Microspheres were between 30 and 35μm in size. Over eight hours were spent using the medication. For eight hours, the drug release was maintained by the robust gel matrix that glutaraldehyde's action created [12].

RESULT AND DISCUSSION

Compatability studies

IR studies

The IR spectra of the pure Pioglitazone sample obtained by an FTIR spectrometer is presented in Figures &. This was compared to the typical functional group frequencies of pioglitazone, as reported in **Table 1**.

Pioglitazone, the pure medication, was found to have the following characteristic peaks in the FTIR analysis: OH (3130.57), CH Stretching Aromatic (3003.27 cm-1), CH Stretching Aliphatic (2963.12 cm-1), C=O (1749 cm-1), Al-CH-bend (1454.3 cm-1), Ar-CH In plane Bending (10911.75), Ar-CH Out plane Bending (920.08 cm-1), and c-o-c Ether inkage (1193.98 cm-1). The same wave length was available for each peak that was obtained for the pure drug for SLN: Ar-CH In plane Bending (10911.75), Ar-CH Out plane Bending (920.08 cm-1), C=O (1749 cm-1), CH Stretching Aromatic (3003.27 cm-1), CH Stretching Aliphatic (2963.12 cm-1), OH (3130.57), and c-o-c Ether inkage (1193.98 cm-1). Additionally, the formulation's remaining peaks in the IR spectra displayed in **Figure 1** and **Figure 2** were either moved or swapped out.

EXAMINATION OF PIOGLITAZONE'S FT-IR SPECTRUM WITH FORMULAE

Table 1 IR Interpretations of Polymers and Pure Drugs

Functional groups	Pioglitazone	Pioglitazone+ chitosan
OH	3130.57	3140.12
CH Stretching (Aromatic)	3003.27	3020.34
CH Stretching (Aliphatic)	2963.12	2862.10
C=O	1749	1630
C=C	1600	1560
Al-CH-bend	1454.3	1334.2
Ar-CH (In plane Bending)	1091.75	1082
Ar-CH (Out plane Bending)	920.08	900.21
c-o-c (Ether inkage)	1193.98	1082.23

FTIR Spectroscopy

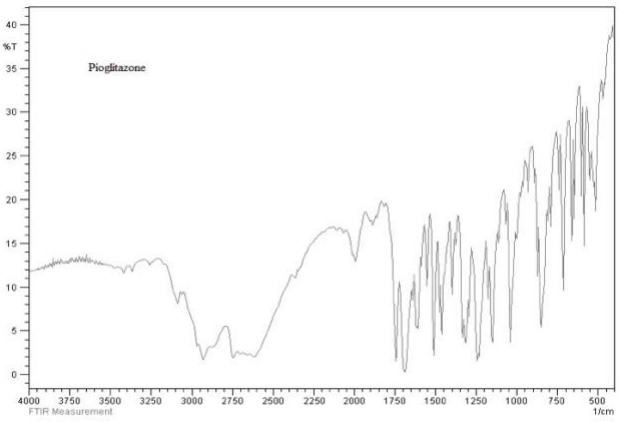

Figure 1 FT – IR of Pioglitazone

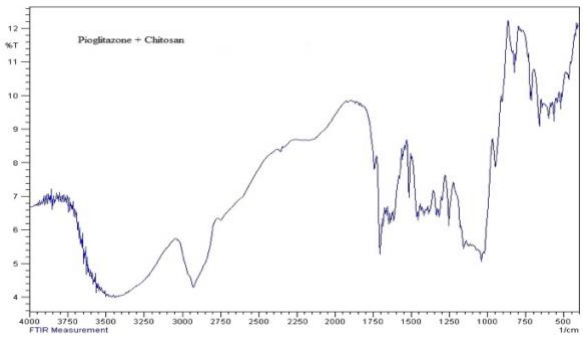

Figure 2 FT –IR of Pioglitazone + Chitosan

DSC studies

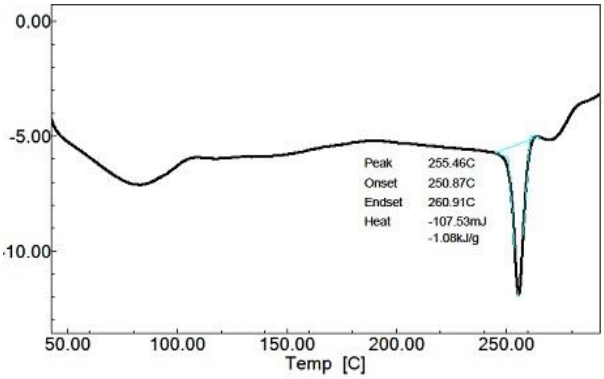

Figure 3 DSC of Pioglitazone

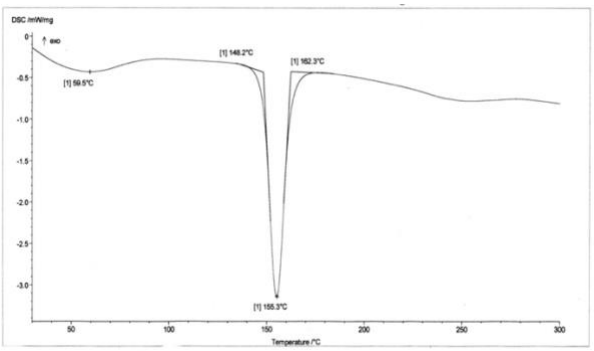

Figure 4 DSC of Pioglitazone + Chitosan

MORPHOLOGY OF PARTICLES

The size, distribution, as well as form of chitosan microspheres can be assessed using the following techniques.

SEM

By using a scanning electron microscope (SEM) (Hitachis-2600N, Japan) to identify the morphology and structure of the stealth microspheres, photomicrographs were taken at the proper magnifications. **Figure 5** depicts pictures of the optimised PP 6 formulation collected using scanning electron microscopy.

SHAPE AND SURFACE MORPHOLOGY

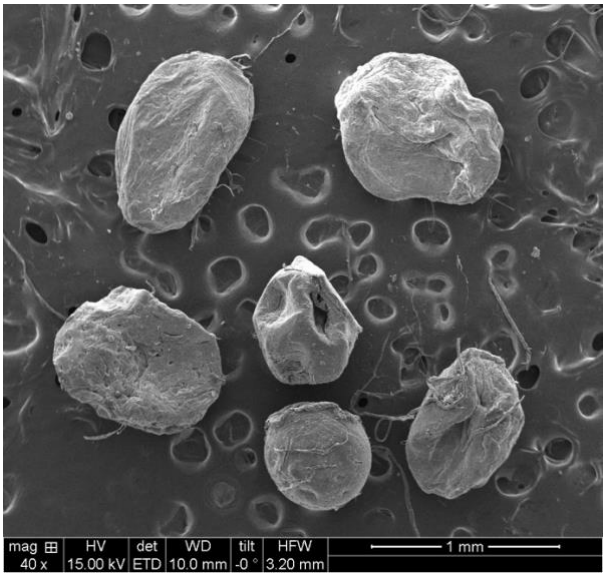

Figure 5 SEM Picture of Pioglitazone Microspheres

Evaluation of Pioglitazone Microspheres

Percentage Yield

The yield of chitosan-based pioglitazone microsphere manufacturing. The Table 2 displays the results for PP 1 (76%) through PP 9 (88.5%).

Encapsulation efficiency

Drug entrapment efficiency (%EE)

From PP 1 (43.5%) to PP 9 (39.73%), the percentage entrapment efficiency varied. High efficiency as well as well-formulated product, PP 1. Table 2 presents the findings.

Entrapment Loading (%EL)

PP 1 (79%) to PP 9 (42%) in terms of percentage entrapment loading. A well-formulated and highly efficient product is demonstrated in PP 1. Findings are displayed in **Table 2**.

Particle size

According to the microspheres particle size distribution, the particles were in the nanometric range. which is good for an overactive bladder. PP 1 (37.6%) to PP 9 (188.47%) Formula, as indicated in **Table 2**.

***In vitro* drug release kinetics**

To understand the mechanism of drug release rate kinetics from dose forms. The values are listed in **Table 3**. **Figure 6** depicts the percentage of drug

Table 2 Characterization of Pioglitazone microspheres

Formulation code	Percentage yield (%)	Percentage drug content	Drug entrapment efficiency (%)	Particle size (µm)	Cumulative percentage release (%/hrs)
PP1	76	43.5	79	37.6	99.14
PP2	86.7	95.4	86	33.7	98.45
PP3	75	91.13	83	34.3	99.8
PP4	82	72.24	51	203.03	58.85
PP5	78	68.20	59	233.16	52.49
PP6	81	56.15	66	257.05	44.32
PP7	83.4	44.18	31	157.72	75.48
PP8	87.5	41.20	35	173.86	69.46
PP9	88.5	39.73	42	188.47	56.71

Table 3 Cumulative % drug releases of Pioglitazone microspheres

Formulation Code	Mints	PP 1	PP 2	PP 3	PP 4	PP 5	PP 6	PP 7	PP 8	PP 9
Cum. % drug Release	5	10.2	12.4	14.8	3.2	6.5	3.2	5.8	9.8	10.8
	10	16.8	22.6	25.3	17.6	18.2	9.12	10.4	14.8	19.8
	15	22.4	26.5	28.4	19.4	26.4	13.2	15.6	17.8	29.7
	20	28.2	30.5	43.2	21.83	38.2	18.4	19.8	29.8	40.6
	25	36.5	48.5	54.4	38.4	47.5	25.5	25.8	37.6	48.8
	30	40.2	54.5	68.3	40.3	54.8	30.6	35.8	40.4	57.9
	35	44.2	63.4	79.4	43.2	68.4	38.2	45.6	48.7	60.3
	40	46.2	68.9	86.7	49.2	74.6	46.2	50.7	59.7	69.4
	45	54.2	72.6	92.4	51.3	80.4	50.1	60.9	68.9	70.6

release with data from multiple kinetic models for different microsphere formulations.

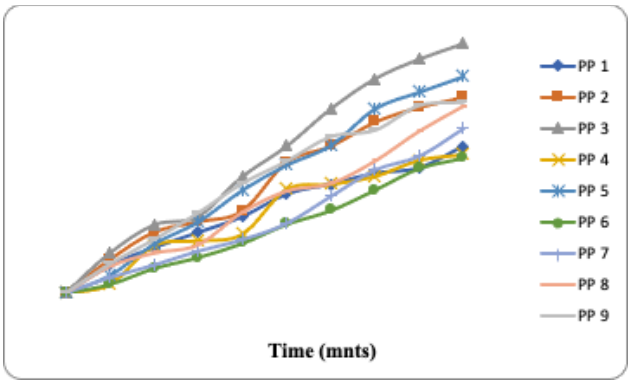

Figure 6 Cumulative % drug releases of Pioglitazone microspheres

CONCLUSION

The optimised batch PP 1 released 97.45% using phosphate buffer pH7.4 as a dissolving media. In terms of release kinetics, the optimised formula's data were best fitted with the Higuchi model (r2= 0.671) and demonstrated zero order release (r2= 0.980) via a non-Fickian diffusion mechanism. The results of this investigation clearly show that chitosan microspheres containing pioglitazone (1:2 drug to polymer ratio) have the ability to administer the medication over an extended period of time in anti-diabetic medications.

ACKNOWLEDGEMENT

I would like to thanks to HR manager for encouragement & support for doing Research Work.

Funding Support: The Author declares that there is no funding.

Conflict of Interest: The Author declares that there is no conflict of interest.

REFERENCES

[1] DV Gowda, and HG Shivakumar. Encapsulation of griseofulvin in wax / fat Microspheres: preparation, characterization and release kinetics of microspheres. Indian drugs, 42(7):453-460, 2005.

[2] Rani KN Shobha, AG Goundalkar, K Prakasam, and N Shobha K. Preparation and evaluation of microsphere of diclofenac sodium. Indian Journal of Pharmaceutical Sciences, 56(4):45-50, 1994.
[3] M.C. Gohel, R. K. Parik, A.F. Amin, and A.K. Surati. Preparation and formulation optimization of sugar cross linking gelatin microspheres of diclofenac sodium. Indian Journal of Pharmaceutical Sciences, 67(8) :575-581, 2005.
[4] D. M. Morkhade, S. V. Fulzele, P. M. Satturwar and S. B. Joshi. Gum copal and gum dammar: Novel matrix forming material for sustained drug delivery. Indian Journal of Pharmaceutical Sciences, 68(1):53-58, 2006.
[5] Nicolas Grattard, Marc Pernin, Bernard Marty, Gaëlle Roudaut, Dominique Champion, and Martine Le Meste. Study of release kinetics of small and high molecular weight substances dispersed into spray-dried Ethyl cellulose microsphere. Journal of Controlled Release, 84:125–135, 2002.
[6] A Dashevsky, and G Zessin. The effect of ethylcellulose molecular weight on the properties of theophylline microspheres. Journal of Microencapsulation, 14(3):273-280, 1997.
[7] AJ Shukla, and JC Price. Effect of drug loading and molecular weight of cellulose acetate propionate on the release characteristics of theophylline microspheres. Pharmaceutical Research, 8(11):1396-400, 1991.
[8] A Ghosh, U K Nayak and P Roy. Development, Evaluation and Method selection for the Preparation of lamivudine microspheres. The International. Pharma Times, 9:67-71, 2007.
[9] Prasant K Rout, Amitava Ghosh, Udaya K Nayak and Bhabani S Nayak. Studies on Effect of Variabilities by response Surface Methodology for Naproxen microspheres. Indian Drugs, 40(8):455-461, 2003.
[10] Anam Abrar, Shayasta Yousuf, and M. K. Dasan. Formulation and evaluation of microsphere of antiulcer drug using Acacia nilotica gum. International Journal of Health Sciences, 14(2): 10–17, 2020.
[11] Praveen Kumar Gaur, Shikha Mishra, and Meenakshi Bajpai. Formulation and evaluation of controlled-release of telmisartan microspheres: In vitro/in vivo study. Journal of Food and Drug Analysis, 22(4):542-548, 2014.
[12] Hema Jaiswal, Mohammad Tahir Ansari, Tarique Mahmood, Farogh Ahsan, Vaseem Ahamad Ansari, and Usama Ahmad. Aceclofenac loaded microspheres: Formulation and evaluation of novel preprogrammed drug delivery for the treatment of arthritis. Intelligent Pharmacy, 2(1): 69-82, 2024.