FORMULATION DEVELOPMENT & OPTIMIZATION OF PIOGLITAZONE HYDROCHLORIDE MICROSPHERES USING IONOTROPIC GELATION TECHNIQUE

Abhishek Pandey[1], **Vivek singh Bhadoria**[1]
Gurukul Institute of Pharmaceutical Science& Research, Gwalior-474010

Abstract

The objective of the present study is to prepare sustained-release Pioglitazone Hydrochloride microspheres in different ratios by calcium chloride cross-linking method using iontropic gelation method. The prepared microspheres were subjected to various physicochemical evaluation and in vitro release studies.

An attempt was made to prepare Microsphers of Pioglitazone by ionotropic gelation technique, with a view to deliver the drug at sustained or controlled manner in gastrointestinal tract and consequently into systemic circulation.

The prepared Microsphers were evaluated for Compatibility study, Drug Entrapment Efficiency, In-vitro Dissolution, Scanning Electron Microscopy, DSC method. Among the six formulations prepared and evaluated F5 are found to show satisfactory results. The Prepared Microsphers shows entrapment efficiency of 69.62% to 91.25% and % yield value from 72% to 90%. Infrared spectroscopy confirmed the absence of any Drug-Polymer interaction. In-vitro release of Optimize batch (F5) was carried out in 7.4 pH phosphate buffer solution shows 92 % release up to 12 hour.

Key Words: Microspheres, Piogiltazone Hydrochloride, calcium chloride cross-linking method, Ionotropic gealtion.

Introduction

Microspheres are the colloidal drug delivery system. Microspheres are characteristically free-flowing powders consisting of proteins/synthetic polymers that are biodegradable in nature and ideally having a particle size less than 200 μm. [1, 2]. Pioglitazone Hydrochloride an antidiabetic drug used in the treatment of type 2 diabetes (non-insulin dependent diabetes mellitus). Pioglitazone Hydrochloride is a water insoluble drug with a short biological half life of 3-6 hrs and is eliminated rapidly from the body. Repeated daily administrations are required to maintain effective plasma concentration.

It has been suggested that drugs with biological half-life in the range of 2-8 hrs are good candidate for sustained release formulations. The oral route of administration for sustained release products has by far received major attention with respect to research on physiological drug constrains as well as design and testing of products. The route has gained importance because of the technological advance which helps to achieve zero order release rates of the drug, low cost etc [3].

Material and Method

Pioglitazone hydrochloride was procured as gift sample from Ranbaxy Laborateis Ltd. Dewas, sodium alginate was purchased from Apex Chemicals, Mumbai. Ethanol (95%), HPMC K15M.Calcium

Address for Correspondence
Abhishek Pandey
Gurukul Institute of Pharmaceutical Science& Research, Near Sahara city homes, Lashkar, Gwalior-474010
Mail id: pandey_pharma@yahoo.co.in

chloride, Potassium Chloride, Acetone. was purchased from Loba-Chem Pvt. Ltd Pune. Potassium Dihydrogen Phosphate was purchased from Pure Chem. Lab. sodium Hydroxide was purchased from Research Lab, Pune.

Preparation of Pioglitazone Microspheres by Ionotropic gelation

In the present study, Microsphers of Pioglitazone were prepared by ionotropic gelation technique. In this method weighed quantity of Pioglitazone was added to 50 ml sodium alginate and HPMC solution and thoroughly mixed with a stirrer at 1000 rpm. 50 ml of this solution was extruded drop wise from a needle into 100 ml aqueous calcium chloride solution and stirred at 1000-1500 rpm. After stirring for 10 minutes the obtained

Formulation no.	Sodium alginate w/v	Cal.chloride w/v	Hpmc w/v	Drug in mg.
F1	1%	2%	0.5%	150 Mg
F2	2%	3%	1%	150 Mg
F3	2%	4%	1.5%	150Mg
F4	2%	4%	2 %	150 Mg
F5	2%	4%	2.5%	150 Mg

Table1 : Formulation Batches of Pioglitazone Hydrochloride Microspheres.

Evaluation of Microspheres

Particle Size and Shape Analysis

All the microspheres were evaluated with respect to their size and shape using optical microscope fitted with an ocular micrometer and a stage micrometer [4, 5]. The average particle size was determined by using the Edmondson's equation $D = \Sigma nd/\Sigma n$. Mean size of 300 particles was considered as size of the microspheres. Particle size distribution analysis was carried out results are given in table 2.

Drug Entrapment Efficiency [4,5,6]

To determine entrapment efficiency, 100mg accurately weighted microspheres were washed and crushed and dissolved in 100 ml with phosphate buffer pH 7.4 solution. The microspheres were kept to soak for overnight. After 12 hrs the solution was filtered through 0.45m membrane filter. The volume was made up to 100 ml with phosphate buffer pH 7.4 and analyzed for drug content spetrophotometrically at 269 nm. Corresponding drug concentrations in samples was calculated from calibration plot. results are given in table 2.

Percentage Yield Value

The percentage yield value is defined as the quantity of beads produced as a function of loaded drug and polymer. results are given in table 2.

$$\text{Entrapment efficiency} = \left[\frac{\text{Estimated \% drug content in microspheres}}{\text{Theoretical \% drug content in microspheres}} \times 100 \right]$$

$$\text{Percent yield} = \frac{\text{Weight of microspheres}}{\text{Total weigth of drug and polymer taken}} \times 100$$

In Vitro Drug Release Profile

A USP paddle apparatus has been used to study in vitro drug release from microspheres [6]. In vitro drug release studies were carried out for all batches in USP type II dissolution test apparatus at 100 rpm and the dissolution medium used is 900ml of phosphate buffer pH 7.4. Microspheres containing 500 mg of drug was used for dissolution study. Five ml of the aliquot was withdrawn at predetermined intervals .The required dilutions were made with 7.4 pH phosphate buffer and filter the solution and analyzed for the drug content spetrophotometrically (UV 1200, Shimadzu, Japan) at 269nm against suitable blank. Equal volume of the dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition.[7] (Fig.1)

Scanning Electron Microscopy

The shape and surface morphology of the microspheres were examined using scanning electron microscopy (JSM-6390, Japan). Microspheres were dusted onto double-sided carbon dust, which was placed onto a sample carrier in the shape of cylinder. After fixing the samples on the stubs, capture a photomicrograph [8] (Fig.2)

Differential Scanning Colorimetry

DSC was use to determine a shift of Sodium Alginate and HPMC endothermic peak or the appearance of exothermic peaks and consequently detect interaction between Pioglitazone Hydrochloride and Sodium Alginate and HPMC. DSC thermograms of empty microspheres, pure drug and microspheres with drug were determined. Absence of any new endothermic peak or disappearance of no shift of endothermic peak confirms that there is no any interaction and hence the polymer compatible with drug.[9]. (Fig. 3)

Results And Discussion

In the present study an attempt has been made to reduce the dosing frequency and side effects associated with Pioglitazone Hydrochloride. In this study we achieve the satisfactory sustained release of drug, microspheres system with hydroxy propyl methyl cellulose K15 M. Various formulation batches were prepared using the different ratios of the drug: hydroxy propyl methyl cellulose in order to achieve sustained release. The formulation batch F5 was found to show satisfactory percent yield, entrapment efficiency and drug release pattern along with uniform particle size. Microspheres of all batches were discrete and free flowing and were evaluated further.

Percent yield of microspheres was between 72 to 90.5 %, while the size of microspheres prepared in this study was in the range of 41-52 μm. It was observed that as the amount of polymer increased in the microspheres the particle size also increased proportionally The microspheres were analyzed for the encapsulation efficiency and was found to be encapsulated 69-91 % in which batch F5 shows highest

entrapment efficiency 91.25%.(Table-2). There is an increase in the concentration of the polymer, the encapsulation efficiency also increases. SEM analysis of microspheres revealed that all microspheres prepared were spherical in shape and is having porous outer skins (Figures 1). DSC studies were performed on pure drug, and drug-loaded microspheres have shown sharp endothermic peak. Pioglitazone Hydrochloride exhibit a sharp peak at 194^{0}C presented in Fig. 3.The sharp peak of the pure drug and drug loaded microspheres was found to be at temperature 194^{0} C. It was observed that absence of endothermic peak of the drug at 194^{0}C in the drug loaded microspheres indicate that the drug is uniformly distributed at molecular level in the microspheres. The drug release from all batches was sustained for 12 hrs F1: Shows the fast release of the drug. Percentage yield was found to be not good. Entrapment efficiency was found to be good.F2: Shows the slow release of drug. The percent yield was found to be improved.F3: The drug release is slower. and percent yield was increase matching F4: Shows the good release pattern than F3 but still need to improve.F5: The drug release was found to be very good and satisfactory also percent release is satisfactory. F6: As the conc.of polymer is increased the dissolution rate is decreased, and percent release was not satisfactory. Finally on the basis of results obtained in batches F1 to F6 formulation F5 find as optimized batch with maximum % release of Pioglitazone hydrochloride.

Sr. no.	Formulation HPMC K15M (gm)	Stirring speed (rpm)	% Yield	Entrapment efficiency (%)	Mean diameter (μm)
F1	0.5	900-1000	72	69.62	41-44
F2	1	1000-1200	78	74.81	42-43
F3	1.5	1000-1200	82	86.44.	45-46z
F4	2	1200-1400	86	.88.33	47-49
F5	2.5	1200-1500	90.25	91.25	48-52
F6	3	1200-1500	87	90.80	47-52

Table.2 Optimization of Pioglitazone microspheres

Time (hrs)	% Drug Release					
	F1	F2	F3	F4	F5	F6
1	19.5	18.2	16.1	17	15.8	16.1
2	38.9	33.4	29.9	29.6	26.9	25.5
3	58.4	49.8	44.2	41.2	36.4	34.1
4	73.2	64.1	56.4	50.8	45.1	42.9
6	93.8	88	78.3	68.9	61.5	56.4
8	---	---	95.2	81.1	74.8	68.2
10	---	---	---	96.4	85	78.5
12	---	---	---	---	93.2	87.1

Table No.3 In vitro percent drug release profile of batches F1 to F6.

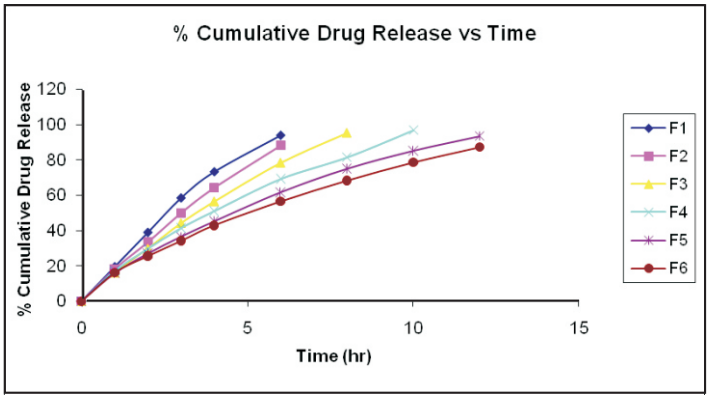

Fig.1 Comparison of Dissolution Profile of Different Batches of Pioglitazone Hydrochloride Microspheres

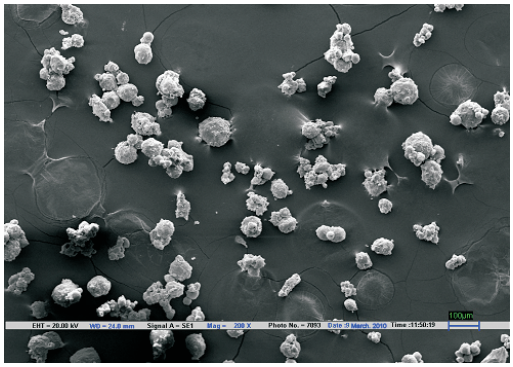

Fig. 2. SEM photograph of Pioglitazone Hydrochloride HCL microspheres F5.

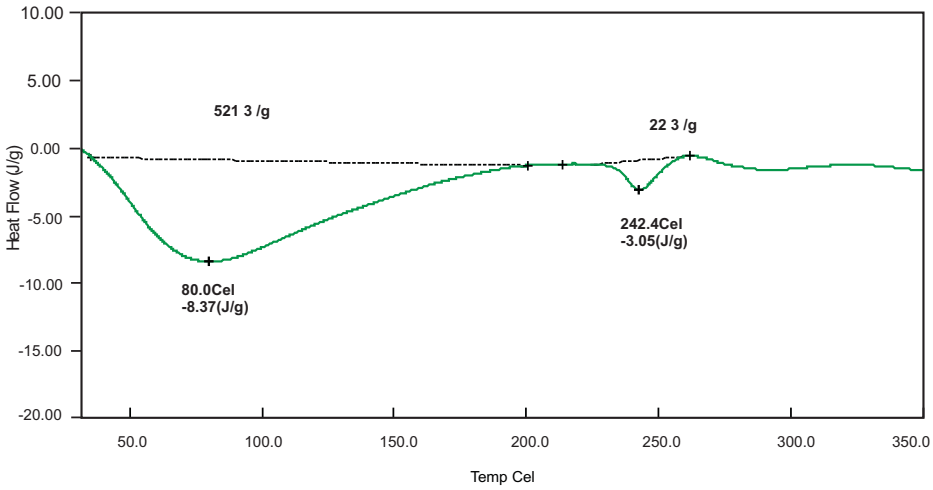

Fig. 3. DSC of Optimized Formulation F5.

Conclusion:

The microspheres of Pioglitazone hydrochloride were prepared with different concentration of polymer HPMC in different batches. Batch f1-f6. Prepared microspheres were evaluated for Particle size using scanning electron microscopy, percent yield, drug entrapment efficency, Differential scanning calorimetry and drug relase of all batches were found satisfactory among them batch F5 show excellent results with maximum drug release of 93.2%.

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