Journal of Comprehensive Pharmacy

Research Article

Available Online at: www.jcponline.in

ISSN NO: 2349-5669

FORMULATION AND EVALUATION OF METFORMIN HYDROCHLORIDE SUSTAINED RELEASED MICROSPHERES

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ARTICLE INFO

Article history:

Received 22 August 2014
Accepted 25 September 2014
Available online 27 October 2014

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ABSTRACT:

Aim: The aim of the present investigation was to development and characterization of sustained release microspheres using anti-diabetes drug Metformin hydrochloride.

Method: Metformin microspheres were prepared by ionic gelation method using sodium alginate polymer in different concentrations. The prepared microspheres were evaluated for size analysis, drug entrapment efficiency, SEM and in vitro drug release.

Results: FT-IR studies revealed that there was no interaction between the drug and polymers. *In vitro* release profile of all formulations showed slow sustained release upto 6hrs. Amongst the developed microspheres, F3 formulation (with drug, alginate 1:6 ratio) exhibited maximum prolonged drug release at gastrointestinal pH or at least 6 h.

Conclusion: This oral sustained Metformin formulation could potentially improve the bioavailability of the drug as well as patient compliance.

Keywords: Ionic gelation method, Metformin, Microspheres, Sustained release, Sodium alginate.

INTRODUCTION

Microspheres have gained wide acceptance as a means to achieve oral and Parenteral controlled drug delivery systems. They often require a polymer as carrier as well as core material [1]. Among the various methods developed for the formulation of microspheres, the solvent evaporation method, ionic gelation method has gained much attention due to its ease of fabrication without compromising the activity of the drug. Metformin is an oral anti diabetic drug in the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes, in particular, in overweight and obese people and those with normal kidney function. Its use in gestational diabetes has been limited by safety concerns. It is also used in the treatment of polycystic ovary syndrome, and has been investigated for other diseases where insulin resistance

may be an important factor. Metformin improves hyperglycaemias primarily by suppressing glucose production by the liver (hepatic gluconeogenesis). The "average" person with type 2 diabetes has three times. Alginic acid is an anionic polysaccharide distributed widely in the cell walls of brown algae, where through binding with water it forms a viscous gum. In extracted form it absorbs water quickly; it is capable of absorbing 200-300 times its own weight in water. Diabetes mellitus (DM) is the name given to a group of disorders characterized by chronic hyperglycemia, polyurea, polydipsia, polyphagia, emaciation and weakness due to disturbance in carbohydrate, fat and protein metabolism associated with absolute or relative deficiency in insulin secretion and/or insulin action. A drug of choice, either alone or

in combination with other hypoglycemic agents, particularly in Type II diabetes, metformin, is an effective antidiabetic drug, belonging to the biguanide class [2]. Metformin also has beneficial effect on several cardiovascular risk factors such as dyslipidemia, elevated plasma-plasminogen activator inhibitor, other fibrinolytic abnormalities and insulin resistance [3]. It has a short biological half-life of 1.5–1.6 h and the daily requirement of it is 1.5–3 g/day [4, 5]. Therefore, the marketed immediate release product needs to be administered 2- 3 times daily to maintain effective plasma concentration [6]. Henceforth, there being high incidence of gastrointestinal side effects and toxicity. These drawbacks can be overcome by designing suitable sustained release Metformin HCl formulations.

MATERIALS AND METHODS

Metformin (Med Rich pvt. limited, Hyderabad), Alginic acid (Sd-fine chem. Limited Hyderabad), calcium chloride (Merck specialties private limited, Hyderabad).

Preparation of microspheres of Metformin hydrochloride:

Ionic gelation method [7]

Alginate particulate system for Metformin HCl release was prepared using this technique. Metformin was added to 2% (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it was added drop wise to a solution containing Calcium chloride solution. Microspheres which were formed were kept in original solution for 24 hr for internal Jellification followed by filtration for separation. The complete release was obtained at pH 6.4-7.4 but the drug did not release in acidic pH. Formulation plan for the preparation of microspheres were shown in Table.1 & 2.

Table.1: Formulation Plan of Metformin hydrochloride microspheres.

S.no	Drug: polymer	Metformin hcl (mg)	Sodium Alginate (%)	Calcium Chloride (%)
1	1:2	100	2	4
2	1:4	100	4	4
3	1:6	100	6	4

Table. 2: Drug and Polymer ratios

S.no	Drug:Polymer	Polymer code
1	1:2	F1
2	1:4	F2
3	1:6	F3

Spectroscopic studies

Standard curve of Metformin hydrochloride:

Metformin hydrochloride is a white fine powder which is soluble in water. Though several methods are reported for its estimation, the UV spectrophotometric method is employed in the study. Metformin hydrochloride shows maximum absorbance at 233nm in 7.4 phosphate buffer. Based on this information, a standard graph was constructed. The results were shown in Table. 3 & Fig.1.

Table. 3: Standard curve of Metformin

S.no	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.134
3	4	0.264
4	6	0.403
5	8	0.524
6	10	0.707

Fig. 1: Standard Calibration curve of Metformin HCl

Preparation of calibration curve of Metformin hydrochloride:

50 mg of Metformin hydrochloride was accurately weighed and transferred in to 50ml standard flask and then volume was made up of 50ml with ml of phosphate buffer. Pipette out 0.2ml, 0.4ml, 0.6ml, 0.8ml and 1ml from above solution transferred in to the 10ml standard flask and diluted to 10ml with phosphate buffer of pH 7.4

Evaluation of Metformin hydrochloride microspheres: [8]

Percentage practical yield:

Percentage crystal yield was calculated to know about percent yield or efficiency of any method and thus its help in selection of appropriate method of formulation.

The final weights of the prepared microspheres were taken and percentage crystal yield was calculated with the following equation and the results are tabulated in Table. 4.

$$\% \text{ percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Table. 4: Percentage practical yield of Metformin microspheres

S.no	Formulation code	% Practical yield
1	F1	90.9%
2	F2	87.8%
3	F3	91.8%

Drug Entrapment efficiency:

100 mg microspheres were treated with 100ml of phosphate buffer (ph 7.4).the solution was kept for overnight and filtered. The filtered solution was analyzed photo metrically at 233 nm using UV visible spectrophotometer.

Drug entrapment (%) = (Actual drug concentration/Theoretical drug concentration) × 100
 Drug loading (%) = (Weight of drug / Weight of microspheres) × 100
 Yield (%) = (Weight of microspheres [9]. The results were shown in Table. 5.

Table. 5: percentage drug content of Metformin HCl microspheres

S.no	Formulation Code	% Drug Entrapment Efficiency
1	F1	85.08%
2	F2	83.37%
3	F3	80.37%

In vitro dissolution studies:

In vitro dissolution studies of Metformin hydrochloride microspheres were conducted with the USP type II apparatus (paddle type). The dissolution studies were performed using phosphate of pH 7.4 buffer as dissolution medium at 37±0.5°C with 75 rpm speed. Samples of each preparation equivalent to 100 mg of microspheres were added into the dissolution medium. The sample of 1ml aliquots were withdrawn periodically (1, 2, 3, 4, 5 and 6 hrs) and filtered through 0.45 µm membrane filter. The withdrawn sample was replaced every time with same quantity of fresh dissolution medium. The filtered solutions were diluted suitably. Samples were analyzed for their drug content by using UV spectrophotometer at wavelength of 233

nm. Percent of metformin hydrochloride dissolved at various time intervals was calculated and plotted against time. The release profiles were shown in Table.6 and Fig. 2.

Table. 6: Percentage Drug release for Metformin microspheres

S. no	Time (hrs)	Percentage drug released		
		F1	F2	F3
1	1	27.68	15.02	10.28
2	2	59.06	31.08	19.02
3	3	76.03	43.07	27.01
4	4	92.08	51.06	33.03
5	5	-	63.01	42.06
6	6	-	70.03	50.9

Fig. 2: % Drug release for Metformin HCl microspheres

Particle size determination (µm):

The eye piece micrometer was calibrated by using a standard stage micrometer at 45X. One drop of glycerine placed on stage piece micrometer in that glycerine the microspheres are placed it. Microspheres are poured in glycerine and the prepared suspension was mounted on a slide and placed on a mechanical stage. The size of particles was estimated with the help of eye piece micrometer. Around 10 particles were counted [10]. The results were shown in Table.7.

Table. 7: Average Particle size range

S.no	Formulation code	Average particle size(µm)
1	F1	480±9.8
2	F2	503±11
3	F3	576±3.6

Characterization of microspheres

Scanning Electron Microscopy (SEM):

Scanning electron micrographs of Metformin hydrochloride microspheres and pure drug powder were taken using a scanning electron microscope (Philips, Philips XL 30 ESEM, and Japan). Samples were fixed on an aluminum stub with conductive double-sided adhesive tape [11]. The results were shown in Fig. 3.

FT-IR Spectroscopy:

Fourier Transform Infrared (FT-IR) spectral measurements for Metformin hydrochloride, sodium alginate, calcium chloride and their microspheres were recorded using Thermo-IR 200 FTIR spectrophotometer. Potassium bromide pellet method was employed. The microspheres were finely ground with KBr to prepare the pellets under a hydraulic pressure of 600 psi and background spectrum was collected under identical conditions. Each spectrum was derived from 16 single average scans collected in the range of $4000\text{--}400\text{ cm}^{-1}$ at the spectral resolution of 2 cm^{-1} [12]. The results were shown in Fig. 4.

RESULT AND DISCUSSION

Percentage practical yield

Three formulations of microspheres of metformin were prepared and weighed accurately. Then the percentage practical yield was calculated by using the formula as follows:

$$\text{Percentage of practical yield} = \frac{\text{practical yield}}{\text{theoretical yield}} \times 100$$

Percentage yield of different formulation was determined by weighing the microspheres after drying. The percentage yield of different formulation was in range of F1 -90.9%, F2- 87.8%, and F3-91.8%

Drug entrapment efficiency:

The formulations containing drug: sodium alginate: calcium chloride in 1:2:4, 1:4:4, 1:6:4 ratios, the drug entrapment efficacies of different formulations were in range of F1 85.08%w/w, F2 83.37%w/w, and F3 80.37 % w/w. Drug entrapment efficacy in first formulation slightly increased compare than second formulation. F2 formulation drug entrapment slightly increased than F3 formulation. Drug entrapment ratios are decreased microspheres.

Scanning electron microscopy(SEM)

Pure drug

F1 Formulation

F2 Formulation

F3 Formulation

Fig. 3: SEM Studies

Fig. 4: FTIR Studies

In vitro release studies:

The in vitro release of metformin from sodium alginate microspheres was biphasic with the initial burst effect; this was varied from 20–70% depending on the polymer-to-drug ratio. The initial burst effect was due to the presence of drug particles on the surface of the microspheres, which was revealed by SEM studies. The initial burst effect may be attributed as a desired effect to ensure initial high plasma concentrations of drug to elicit pharmacological activity. The effect of retardation on the release rate depends on the polymer to-drug ratio. As the concentration of sodium alginate increased with respect to drug concentration, the release rate was decreased which may be attributed to the slower rate of diffusion of dissolution medium into the microspheres due to increased thickness of the polymer matrix. As sodium alginate concentration increased, the drug release was extended up to 6 hours.

Scanning electron microscopy (SEM):

The microspheres were spherical and porous. The surface of the microspheres was rough and revealed the presence of pores in the drug loaded microspheres. The study of drug loaded microspheres showed the

presence of drug particles on the surface, which was responsible for the initial burst release of the drug during dissolution. Surface study of the microspheres after dissolution showed bigger pores, suggesting that the drug was released through pores and the mechanism of drug release may be diffusion controlled. An incident electron beam is raster-scanned across the sample's surface, and the resulting electrons emitted from the sample are collected to form an image of the surface. Imaging is typically obtained using secondary electrons for the best resolution of fine surface topographical features. Alternatively, imaging with backscattered electrons gives contrast based on atomic number to resolve microscopic composition variations, as well as, topographical information. Qualitative and quantitative chemical analysis information is also obtained using an energy dispersive x-ray spectrometer with the SEM.

FTIR STUDIES

The FTIR spectrum of pure metformin hydrochloride and pure sodium alginate and metformin HCl+sodium alginate are shown. The spectra obtained from the drug-polymer combination presented band assignments

at the equivalent wavelength ranges depicting no interaction between the drug and polymer combinations.

CONCLUSION

This study reveals that the sustained release of Metformin HCl can be successfully achieved by inotropic gelation technique using sodium alginate as polymer. Prepared microspheres shown higher drug entrapment efficiency and prolonged release characteristics. Metformin HCl release from microspheres was influenced by different alginate concentrations. Among the different formulations of micro beads, F3 Formulation was estimated as best formulation because this formulation drug release was observed that drug was released in controlled manner.

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Cite this Article as: Yaddalapudi S, Palla G, Kaza R. FORMULATION AND EVALUATION OF METFORMIN HYDROCHLORIDE SUSTAINED RELEASED MICROSPHERES J Compr Phar 2014;1(4):136-141.