International Journal for Pharmaceutical Research Scholars (IJPRS)
ISSN No: 2277-7873
RESEARCH ARTICLE **V-2, I-1, 2013**

Formulation and Evaluation of Metformin Hydrochloride Microspheres by Solvent Evaporation Method

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Manuscript No: IJPRS/V2/I1/00033, Received On: 22/02/2013, Accepted On: 06/03/2013

ABSTRACT

The aim of the present study was to formulate and evaluate Metformin HCl microspheres to produce a drug delivery system with better pharmaceutical and therapeutic properties. Metformin HCl microspheres were prepared by using ethyl cellulose as a release retardant polymer by solvent evaporation method .Formulations F_1, F_2 and F_3 were prepared using ethyl cellulose in the drug polymer ratio of 1:1, 1:2 and 1:3. A plasticizer (N-dibutyl phthalate) was added in formulations F_4,F_5 and F_6 .The prepared microspheres were evaluated for the parameters like Percentage yield, Particle size analysis, Micromeritic properties like angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio, melting point determination, drug content estimation, microencapsulation efficiency and *in vitro* drug release studies. The *in vitro* release of Metformin HCl was slow and extended over longer period of time. As the concentration of polymer was increased, the drug release was decreased. The drug release was found to be slow in formulations F_4, F_5 and F_6 when compared to F_1, F_2 and F_3. Thus the study clearly indicated a promising potential of sustained release Metformin HCl microspheres containing ethyl cellulose as rate controlling polymer for effectively treating diabetes mellitus.

KEYWORDS

Diabetes mellitus, Ethyl cellulose, Metformin Hydrochloride, Plasticizer, Solvent evaporation, Sustained release

INTRODUCTION

Microencapsulation is a process whereby small discrete solid particles or small liquid droplets are surrounded and enclosed by an intact shell. Microencapsulation is a means of applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions[1]. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery.

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Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery[2, 3].

Metformin HCl is a odourless, bitter, white crystalline powder which is a anti hyperglycaemic agent[4, 5, 6]. Metformin HCl is an orally administered drug indicated for patient with non-insulin-dependent diabetes mellitus (NIDDM), particularly those with refractory obesity. The aim of the present study was to formulate Metformin HCl microspheres to overcome inherent drawbacks associated with conventional dosage form of Metformin HCl. The study was aimed to formulate Metformin HCl microspheres to prolong the action of drug for a period of over 12 hrs. The microspheres

were prepared by solvent evaporation method. Ethyl cellulose was used as release retardant polymer in all formulations. Plasticizer (N-dibutyl phthalate) was included in 3 formulations. The solvent used was acetone and liquid paraffin was used as a liquid manufacturing vehicle phase.

MATERIALS AND METHODS

Materials

Metformin HCl was obtained from Sun chemicals, Chennai. Ethyl Cellulose was procured from S.D Fine chem. Limited, Mumbai. Acetone was obtained from Molychem, Mumbai. Liquid Paraffin and Potassium Dihydrogen Phosphate were obtained from Merck Chemicals, Mumbai. N-dibutyl phthalate was procured from Loba Chemie Pvt. Ltd, Mumbai and Sodium Hydroxide was obtained from RFCL limited, New Delhi, India.

Method

Preparation of Metformin Hydrochloride Microspheres

Ethyl cellulose microspheres containing Metformin HCl were prepared by solvent evaporation method (F_1, F_2 & F_3). Ethyl cellulose was dissolved in acetone to form a homogeneous polymer solution. Metformin HCl was added to polymer solution and dispersed thoroughly. The resulting mixture was then added in a thin stream to the liquid paraffin in a 250ml beaker under stirring at 1000rpm to disperse the added mixture as fine droplets. System was stirred to evaporate the solvent at room temperature for 2hrs to form ethyl cellulose microspheres of Metformin HCl. Prepared microspheres were collected by filtration and washed with cyclohexane to remove adhering liquid paraffin[7]. Microspheres were dried over night at 40ºC and stored in a well closed container (Table 1).

Similarly, Plasticized Ethyl Cellulose Microspheres (F_4, F_5 & F_6) were prepared by using N-dibutyl phthalate as plasticizer by adding it to the homogeneous polymer solution by adopting the above method (Table 2).

Table 1: Formulation of Metformin Hydrochloride Microspheres

INGREDIENTS	FORMULATION CODE AND DRUG POLYMER RATIO		
	F_1	F_2	F_3
	1:1	1:2	1:3
Metformin Hydrochloride	500 mg	500 mg	500 mg
Ethyl cellulose	500 mg	1000 mg	1500mg
Acetone	30 ml	30 ml	30 ml

Table 2: Formulation of Plasticized Metformin Hydrochloride Microspheres

INGREDIENTS	FORMULATION CODE AND DRUG POLYMER RATIO		
	F_4	F_5	F_6
	1:1	1:2	1:3
Metformin Hydrochloride	500 mg	500 mg	500 mg
Ethyl cellulose	500 mg	1000 mg	1500mg
N-dibutyl phthalate	30 %w/w of polymer	30 %w/w of polymer	30 %w/w of polymer
Acetone	30 ml	30 ml	30 ml

Micromeritic Properties

The prepared microspheres were evaluated for micromeritic properties including angle of

repose, bulk density, tapped density, Carr's compressibility index and hausner's ratio. The angle of repose was determined by the fixed-base cone method[8]. Bulk and tapped density were determined using digital bulk density apparatus[9, 10]. The compressibility index and the Hausner's ratio were calculated by using the formula[11]:

Hausner's Ratio = Tapped density/ Bulk density.

Carr's index (%) = [(TD-BD) / TD] ×100.

TD = Tapped density, BD = bulk density.

FT-IR Studies[12]

To determine any interaction between drug and polymer, Fourier Transform Infra red (FT-IR) study was carried out. The drug and excipients must be compatible with one another to produce a stable, efficacious, easy to administer and safe product. FT-IR analysis of pure drug, individual polymer and combination of drug and polymer in higher concentration were taken for the study.

Samples were compressed with potassium chloride and transformed into disk. Disk was applied to the centre of the sample holding device and scanned between 4000-400 cm^{-1} in a SHIMADZU FT-IR (IR Affinity-1) spectrophotometer.

Evaluation of Microspheres

Percentage Yield (%)

The percentage yield of microspheres of various batches were calculated using the weight of final product after drying with respect to the initial total quantity of the drug and polymer used for preparation of microspheres[3]. Percentage yield were calculated as per the formula mentioned below.

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

Particle Size Analysis

Microspheres were separated into different size fractions by sieving for 20 minutes using mechanical sieve shaker containing standard sieves of different mesh numbers arranged in a nest with the coarsest at the top and finest at the bottom. The microspheres retained on each sieve were weighed and the average diameter of microspheres were determined[14].

Meting Point Determination[15]

The melting point test of the microspheres were carried out to find out if there is any change in the nature of the coated drug due to the process of preparation. Melting point determination was done by using melting point apparatus. Small amount of microspheres were taken and ground for the removal of coating material and it was placed in glass capillary tube whose one end was sealed by flame. The capillary tube containing samples was kept in the melting point apparatus and the melting point was noted.

Surface Morphology (SEM Analysis)

Shape and surface morphology of microspheres were studied using scanning electron microscopy (SEM). The microspheres were mounted on metal stubs using double sided adhesive tape and the stub was then vacuum coated with gold film using sputter coater attached to the instrument[16] .The photographs were taken using a Jeol scanning electron microscope (JEOL-JSM-6390LV, Japan).

Determination of Drug Content[17]

Weigh accurately about 100 mg of microspheres in a clean 100 ml volumetric flask. Add 70 ml of phosphate buffer pH 6.8 and shake for 15 minutes. Make up the volume to 100 ml with phosphate buffer pH 6.8 and filter. From the filtrate, pipette out 10 ml and dilute with phosphate buffer pH 6.8 to 100 ml and mix well. Further dilute 10 ml of this solution to 100 ml with phosphate buffer pH 6.8. Measure the absorbance of the resulting solution using double beam UV spectrophotometer at 233nm using phosphate buffer pH 6.8 as blank.

Microencapsulation Efficiency[18]

The encapsulation efficiency was performed to find out the amount of drug that gets encapsulated in the microspheres so that sufficient amount of drug is present in the

microspheres to ensure the drug remains in the therapeutic range once it enters the systemic circulation. The microencapsulation efficiency was determined by using the following formula.

$$\text{Encapsulation efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

In-Vitro Dissolution Study[19]

The *in vitro* release of Metformin HCl from formulated microspheres were carried out for 8 hours in USP dissolution apparatus I (Basket) at 37 ± 0.5° C. 900ml of phosphate buffer solution pH6.8 was used as dissolution medium. A quantity of microspheres equivalent to 50mg of Metformin HCl was filled in empty capsule shell and placed in the basket and the basket was rotated at 50rpm. Samples were taken at 1, 2, 3, 4,5,6,7 and 8 hours and diluted to suitable concentration and analyzed for Metformin HCl content at 233nm by using Double beam UV–visible spectrophotometer.

RESULTS AND DISCUSSION

In this study three formulations F_1, F_2 and F_3 of Metformin HCl microspheres were prepared by employing ethyl cellulose, as a release retardant polymer.

Formulations F_4, F_5 and F_6 were prepared by using ethyl cellulose as a polymer and N-dibutyl phthalate as plasticizer. A total of 6 formulations were prepared and studied for micromeritic parameters like bulk density, tapped density, angle of repose, compressibility index, and Hausner's Ratio. All the formulations showed good flowability as expressed in terms of micrometric parameters (Table 3).

The FT-IR studies of pure Metformin HCl, Ethyl cellulose and Metformin HCl +Ethyl cellulose were carried out to study the interaction between the drug and polymer. IR spectral analysis showed that the fundamental peaks and patterns of the spectra were similar both in pure drug and combination containing drug and higher proportion of polymer. This indicated that there was no chemical interaction between Metformin HCl and the polymer used.

The percentage yield of microspheres prepared by solvent evaporation method varies with drug polymer ratio. It was observed that percentage yield of formulations F_1, F_2, and F_3 were 82.12%, 98.6% and 83.46% respectively and formulations F_4, F_5 and F_6 were 98.14%, 98.61% and 84.69% respectively.

Table 3: Micromeritic Properties of Metformin Hydrochloride Microspheres

Formulation code	Angle of repose (θ)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index(%)	Hausner's ratio
F_1	27.25±0.61	0.276±0.005	0.313±0.03	11.8±0.03	1.13±0.007
F_2	28.52±0.35	0.296±0.002	0.345±0.02	14.2±0.18	1.16±0.004
F_3	30.53±0.20	0.320±0.006	0.345±0.02	7.25±0.02	1.08±0.002
F_4	30.52±0.27	0.257±0.003	0.296±0.06	13.17±0.11	1.15±0.013
F_5	29.94±0.24	0.274±0.011	0.308±0.01	11.03±0.09	1.12±0.005
F_6	29.39±0.31	0.270±0.007	0.289±0.06	6.57±0.13	1.07±0.011

*All the values are expressed as mean ±Standard deviation; n=3

The melting point of pure Metformin HCl and Metformin HCl microspheres were found to be 225° C and 226° C respectively. The melting point of pure drug and Metformin HCl microspheres are very similar, this shows that even after entrapment inside the formulation, the drug retain its behaviour and nature as its original free state. It reveals that the nature of drug was not affected due to the process of preparation.

Scanning electron micrographs of Ethyl cellulose microspheres and plasticized ethyl cellulose microspheres were shown in Figure: 1.The microspheres were found to be discrete, uniform and spherical in shape. Cracks and pores were found in ethyl cellulose microspheres whereas plasticized ethyl cellulose microspheres were devoid of cracks and pores.

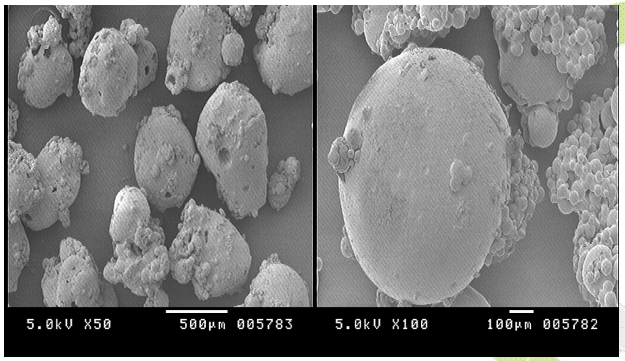

Figure 1: SEM of Ethyl cellulose Microspheres and Plasticized Ethyl cellulose Microspheres

The particle size analysis was carried out by standard sieve shaker and average particle size of microspheres was found to be in the range of 497.4±0.36µm to 642.7±0.07µm. The particle sizes of microspheres were found to be increased as the concentration of polymer was increased. Drug content in different formulations were estimated by UV spectrophotometric method. Three samples were tested from each batch and the drug content was determined. The standard deviations among the three values were found to be small. This indicates that the drug was distributed almost uniformly throughout in all batches of microspheres. The microencapsulation efficiency was found to be in the range of 56.52±0.08 to 97.0±0.11**.** The order of micro encapsulation efficiency of various formulations was found to be as follows: $F_4 > F_5 > F_6 > F_1 > F_2 > F_3$. The results of particle size, drug content and microencapsulation efficiency are given in Table 4.

Table 4: Evaluation of Metformin Hydrochloride Microspheres

Form code	Particle size(µm)	Drug content (mg)		Microencapsulation efficiency (%)
		Theoretical	Practical	
F_1	565.3 ±0.16	50	31.5± 0.03	63.0±0.03
F_2	593.4 ±0.07	33.3	19.29 ±0.13	57.65±0.13
F_3	642.7 ±0.07	25	14.13 ±0.08	56.52±0.08
F_4	497.4 ±0.36	50	48.5± 0.11	97.0±0.11
F_5	542.6 ±0.20	33.3	30.9± 0.04	92.79±0.04
F_6	570.34±0.12	25	22.25 ±0.07	89.0±0.07

*All the values are expressed as mean ±Standard deviation; n=3

Formulation F_1, F_2 and F_3 were prepared using ethyl cellulose as a release retardant polymer in drug polymer ratio 1:1, 1:2 and 1:3.The drug release was faster in the initial period of 2 hrs. Later a slow release of drug was observed in all formulations. The faster drug release may be due to the embedment of drug in the surface of the coating during microencapsulation. The faster drug release may serve as a initial loading dose. The drug release at the end of 8th hour

from F_1, F_2 and F_3 was 82%, 76% and 73% respectively. The release profiles were presented graphically in Figure: 2.

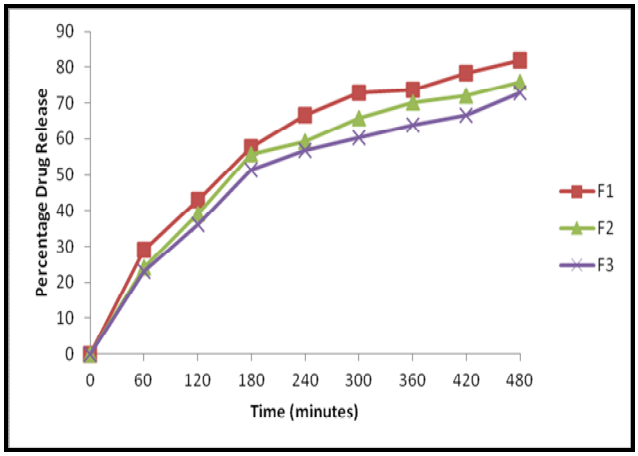

Figure 2: *In Vitro* Release Profile of Metformin HCl Microspheres (F_1, F_2, F_3)

Formulations F_4, F_5 and F_6 were prepared using ethyl cellulose in the drug polymer ratio of 1:1, 1:2 and 1:3. A plasticizer (N-dibutyl phthalate) was added in all the three formulations. The drug release was found to be slow in F_4, F_5 and F_6 when compared to F_1, F_2 and F_3. This may be due to that plasticizer will improve the flexibility, increase chemical resistance of coating, so that microspheres may be devoid of cracks, also N-dibutyl phthalate is a poorly water soluble plasticizer that prevents the permeation of water through the film, thereby it controls the diffusion of drug molecules out of core. The release profiles were presented graphically in Figure: 3.

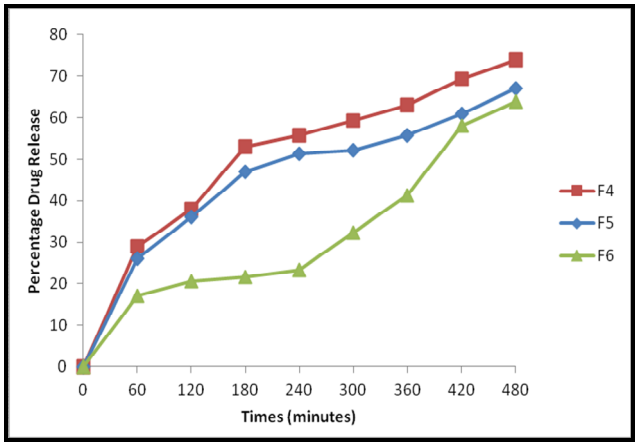

Figure 3: *In Vitro* Release Profile of Plasticized Metformin HCl Microspheres (F_4, F_5, F_6)

In all the formulations, as the concentration of polymer was increased, the drug release was decreased. This may be due to increased surface thickness of coating as the concentration of polymer is increased.

CONCLUSION

Thus the present investigation indicates that the microspheres with ethyl cellulose could be used to control the release of Metformin HCl in gastro intestinal tract and these microspheres as such could be used as sustained release dosage forms which release the drug slowly over extended period of time to maintain effective concentration for longer period. The frequency of dosing and side effects are avoided. The method followed was also economical. Thus the study clearly indicated a promising potential of sustained release Metformin HCl microspheres containing ethyl cellulose as rate controlling polymer for effectively treating diabetes mellitus.

ACKNOWLEDGEMENT

The authors are thankful to Mr. S. Sriram Ashok B.E, Correspondent, Sankaralingam Bhuvaneswari College of Pharmacy, Anaikuttam, Sivakasi, for providing necessary facilities to carry out the work.

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