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FORMULATION AND EVALUATION OF FLOATING MICROSPHERE CONTAINING ANTI-DIABETIC (METFORMIN HYDROCHLORIDE) DRUG

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Abstract: The present study involves preparation and evaluation of floating microspheres with Metformin Hydrochloride as model drug for prolongation of gastric residence time. The microspheres were prepared by the emulsification solvent diffusion technique using polymers Hydroxypropylmethyl cellulose K4M and Eudragit RS100. The shape and surface morphology of prepared microspheres were characterized by scanning electron microscopy, respectively. In vitro drug release studies were performed and drug release kinetics was evaluated using the linear regression method. Effects of the stirring rate during preparation, polymer concentration, solvent composition and dissolution medium on the size of microspheres and drug release were also observed. The prepared microspheres exhibited prolonged drug release (8 h). The mean particle size increased and the drug release rate decreased at higher polymer concentration. No significant effect of the stirring rate during preparation on drug release was observed. In most cases good in vitro floating behavior was observed and a broad variety of drug release pattern could be achieved by variation of the polymer and solvent ratio, which was optimized to match target release profile. The developed floating microspheres of metformin hydrochloride may be used in clinic for prolonged drug release in stomach for at least 8 hrs, thereby improving the bioavailability and patient compliance.

Keywords: Floating microsphere; Metformin Hydrochloride; Emulsion Solvent Diffusion technique; Methacrylic acid copolymer (Eudragit RS100); Bioavability; In-vitro release.

1. Introduction

Diabetes is one of the major causes of death and disability in the world. The latest, WHO estimate for the number of people with diabetes worldwide, in 2000, is 171 million, which is likely to be at least 366 million by 2030. The focus of medical community is on the prevention and treatment of the disease, as is evident from the rising number of research papers every year on the subject. A plethora of antidiabetic drugs are used in clinic, of which Metformin hydrochloride is a very widely accepted drug. Unlike other antidiabetics, metformin hydrochloride does not induce hypoglycemia at any reasonable dose, and hence? It is usually called an Antihyperglycemic(or Euglycemic) rather than a hypoglycemic drug[1]. In spite of its favorable clinical response and lack of significant drawbacks, chronic therapy with metformin hydrochloride suffers from certain specific problems of which, the most prominent being the high dose (1.5-2.0 g/day),low bioavailability (60%) and high incidence of GI side effects (30% cases). Therefore, there are continued efforts to improve the pharmaceutical formulation of Metformin hydrochloride in order to achieve an optimal therapy. These efforts mainly focus on controlled/slow release of the drug including the sophisticated gastro retentive systems. Formulation development has also accelerated with this drug after its patent expiry in

2001[2-7]. The situation is complicated further with decrease in absorption of the drug with food that delays t_{max} by up to 35 mins[8].The rationality, therefore, exists for formulation of Metformin hydrochloride as a CR/SR formulation of it has been reported[2].However, bioavailability of the drug has been found to be reduced further with CR dosage forms, probably due to the fact that passage of the CR single unit dosage forms from absorption region of the drug is faster than its release and most of the drug released at the colon where Metformin hydrochloride is poorly absorbed [9-10]. CR formulation suitable for metformin hydrochloride, therefore, should be a gastro retentive dosage form[2], which releases the drug slowly in the stomach for gradual absorption in the intestines. The slow but complete drug release in the stomach is expected to increase bioavailability of the drug as well its complete utilization which may results to, lower dose and GI side effects. Multi unit dosage forms are considered to release the drug at a controlled rate and remain in the stomach for a prolonged period with much less chance of dose dumping. Furthermore they are supposed to cause less gastric adverse reactions and are insensitive to concomitant food intake, thereby reducing inter and intra-patient variability and increasing the predictability of the dosage form[11-18]. There are several excellent reviews on the gastro-retentive systems including floating dosage forms to which the interested readers are referred[31,32, 33]. However, no floating microsphere of metformin has been reported. A non-floating multi-particulate metformin containing system has been reported in literature [34], though the intention of the work was to optimize the pellets for extrusionspheronization purpose rather than to extend the drug release. There have been contradictory reports on the utilization of metformin in gastro-retentive dosage forms[2,35]. However the investigated systems were single-unit type. Therefore, it seemed reasonable to improve the earlier studies by formulating metformin in a multiparticulate floating (gastro-retentive) system in order to optimize the pharmacokinetics and pharmacodynamics of the drug. Hence, to achieve the ultimate goal of formulating a clinically effective FDDS of metformin hydrochloride for effective control of Non Insulin Dependent Diabetes Mellitus (NIDDM), the present work was designed to address the following objectives preparation of micro-particles, evaluation of FDDS in vitro, predicting the release, and optimization of floatation and drug release pattern to match target release profile.

2 Materials and methods

2.1. Materials

Metformin hydrochloride was a gift sample from Ranbaxy Laboratories Ltd., Hyderabad, India. Hydroxypropylmethyl CelluloseK4M (18-22 cps) and Polyvinyl Alcohol Loba chem Pvt. Ltd, Mumbai; Ethanol from Sakthi Sugar Pvt, Ltd. Erode, Eudragit RS 100, Rohm Pharma, Germany. Dichloromethane was obtained from Nice Chem. Pvt. Ltd., Cochin, and India. All other Chemicals were of analytical grade.

2.2 Methods

2.2.1. Preparation of microsphere

Floating microsphere containing Metformin hydrochloride was prepared using emulsion solvent diffusion technique [19]. The drug to polymer ratio was used to prepare the different formulation. The polymer content was a mixture of Eudragit RS 100 Hydroxypropylmethylcellulose (HPMC K4M).The drug polymer mixture is dissolved in a mixture of ethanol (8 ml) and dichloromethane (8 ml) was dropped in to 0.75% polyvinyl alcohol solution (200 ml). The solution was stirred with a propeller-type agitator at 40° C temperature for 1 hour at 300 rpm. The formed floating microspheres were passed through sieve no:-12 and washed with water and dried at room temperature in desiccators. The various batches of floating microsphere were prepared as follows.

2.2.2. IR spectroscopy

The Fourier transform infra-red analysis was conducted for the analysis of drug polymer interaction and stability of drug during microencapsulation process. Fourier transform infra-red spectrum of pure metformin hydrochloride, Eudragit RS100, HPMC K4M, Physical mixture and floating microspheres (formulation) were recorded.

2.2.3. Particle size analysis [36]

Particle size analysis plays an important role in determining the release characteristics and floating property. The sizes of floating microspheres were measured by using an optical microscope, and the mean particle size was calculated by measuring nearly 200 particles with the help of a calculated ocular micrometer.

2.2.4 . Morphology

From the formulated batches Formulation which showed an appropriate balance between the buoyancy and the percentage release were examined for surface morphology and shape using scanning electron microscope JEOL, JSM-670F Japan(Sastra university , Tanjavur). Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 3.0 KV during scanning. Microphotographs were taken on different magnification and higher magnification (500X) was used for surface morphology.

2.2.5. Percentage Yield

The prepared microspheres with a size range of 609-874 μm were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

% Yield = (Actual weight of product / Total Weight of excipient and drug) × 100

2.2.6. DEE (Drug Entrapment Efficiency)

The various formulations of the floating microspheres were subjected for drug content. 50 mg of floating microspheres from all batches were accurately weighed and crushed. The powdered of microspheres were dissolved with 10ml ethanol in 100ml volumetric flask and makeup the volume with 0.1 N HCl. This resulting solution is than filtered through whatman filter paper No. 44. After filtration, from this solution 10 ml was taken out and diluted up to 100 ml with 0.1 N HCl. Again from this solution 2 ml was taken out and diluted up to 10 m1 with 0.1 N HCI and the absorbance was measured at 233 nm against 0.1 N HCI as a blank. The percentage drug entrapment was calculated as follows.

DEE = (Amount of drug actually present / Theoretical drug load expected) × 100

2.2.7. Floating behavior of Floating microsphere [12,37]

100 mg of the floating microsphere were placed in 0.1 N HCI (300 ml) containing 0.02% of tween 20. The mixture was stirred with paddle at 100rpm. The layer of buoyant microspheres was pipetted and separated by filtration at 1, 2, 4 and 6 hours. The collected microspheres were dried in desiccators over night. The percentage of microspheres was calculated by the following equation

%Floating microspheres= (weight of floating microspheres/ initial weight of floating microspheres) × 100

2.2.8. In-vitro Release Studies [30]

The drug release rate from floating microspheres was carried out using the USP type II (Electro Lab.) dissolution paddle assembly [38]. A weighed amount of floating microspheres equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCI (pH 1.2) maintained at 37 ± 0.5°C and stirred at 100 rpm. One ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. The collected samples were suitably diluted with 0.1 N HCI and analyzed spectrophotometrically at 233 nm to determine the concentration of drug present in the dissolution medium. The dissolution studies were repeated using phosphate buffer pH 6.8 as dissolution medium.

2.2.9. Stability Study

From the prepared floating microspheres which showed appropriate balance between the buoyancy and the percentage release was selected for stability studies. The prepared formulation (F_4) were placed in borosilicate screw capped glass containers and stored at different temperature (27 ± 2° C), oven temperature (40±2° C) and in refrigerator (5-8° C) for a period of 90 days. The samples were assayed for drug content at regular intervals of two week.

3. Result and discussion

3.1. IR spectroscopy

Several preformulation trials were undertaken for various proportions of drug and polymer by variation of the ethanol and dichloromethane volumes for qualitative and quantitative determination of microsphere characteristics. It was found that hydroxypropyl methylcelluloseK4M microspheres show desirable high drug content, yield, floatation and adequate release characteristics and hence was suitable for development of a CR system. FTIR spectra show C-N stretching-1039.67, C=N stretching-1564.72, CH2 Scissoring-1475.59 which indicate there is no drug polymer incompatibility was observed. To precisely understand and quantify the effect of drug-polymer ratio and the effect of process variables such as volume of solvent and manufacturing vehicles a Central Composite Design (CCD) was devised in which the polymer and solvent were used as the variables.

3.2. Morphology

The surface morphology and internal texture of microspheres were determined by scanning electron microscopy (SEM) as shown in Figure 1. The microspheres, however, did not change in shape or size after dissolution as is expected for a hydrophobic water insoluble polymer hydropropylmethylcelluloseK4M

3.3. Drug Entrapment and Percentage Yield

The formulation containing drug:HPMC K4M: Eudragit RS100 ratio, The drug entrapment efficacies of different formulations were in range of 41.14 - 74.19 % w/w. Drug entrapment efficacy slightly decrease with increase HPMC content and decreased Eudragit ratio in microballoons. Percentage yield of different formulation was determined by weighing the microballoons after drying. The percentage yield of different formulation was in range of 54.35 - 82.87% all is as shown in Table-1

3.4. Floating behavior of microsphere Hollow Microsphere were dispersed in 0.1 HCl containing Tween 20 (0.02% w/v) to simulate gastric fluid. Floating ability of different formulation was found to

be differed according to EudragitRS100 and HPMC K4M ratio. F_1-F_4 formulations showed best floating ability (91.47-72.97%) in 6 hours. F_5-F_8 formulation showed less floating ability (66.12-36.18%) as showed in Table-9. The floating ability of microsphere is decreased by increasing the HPMC K4M ratio Shown in Table-2

3.5. Stability Study

Stability study was carried out for the F4 formulation by exposing it to different temperature 5-8°C, 27°C and 40°C for 3 months. The sample was analyzed for drug content at the regular intervals. It was found that no remarkable change in the drug content of F_4 formulation. This indicates that F_4 was stable for following temperature.

3.6. In-vitro drug release study

In-vitro drug release study of microballoons was evaluated in 0.1 N HCl and phosphate buffer pH 6.8. Eudragit RS100 which is present in all formulation has low permeability in acid medium. Since Eudragit RS100 is less soluble in acidic pH, release of drug in 0.1 N HCl was generally low compared to phosphate buffer pH 6.8 Release rate of F_1, F_2, F_3 formulations (43.791%, 56.311%, and 78.809% respectively).It was found to be slow and incomplete in both dissolution medium. In order to increase the release rate of drug the ratio of Eudragit RS100 and HPMC K4M is decreased and increased respectively. F_5, F_6, F_7, F_8 (94.681%, 97.348%, 96.295%, 95.329% respectively) formulations showed high release rate with less floating property. F_4 formulation showed best appropriate balance between buoyancy and drug release rate.

4 Conclusion

The experimental design supported product development and optimization procedure yielded the desired microspheres with drug release equivalent to those of the marketed single unit dosage forms with the added advantage of floatability in gastric juice for prolonged slow release. The optimized multi-unit floating metformin HCl delivery system is expected to provide clinicians with a new choice of an economical, safe and more bioavailable formulation in the management of type II diabetes mellitus. Therefore, it may be concluded that drug loaded floating microspheres are a suitable delivery system for metformin hydrochloride, and may be used for effective management of NIDDM.

Table 1. Characteristics of the microspheres obtained following CCD.

Product Code	Drug:HPMCK4M: EudragitRS 100 (In gm)	Percentage Yield	Drug Entrapment Efficiency (%W/W)
F1	0.1 : 0.0 : 0.7	82.87	76.19
F2	0.1 : 0.1 : 0.6	78.53	70.59
F3	0.1 : 0.2 : 0.5	76.47	66.23
F4	0.1 : 0.3 : 0.4	71.56	64.76
F5	0.1 : 0.4 : 0.3	69.31	61.01
F6	0.1 : 0.5 : 0.2	66.03	57.38
F7	0.1 : 0.6 : 0.1	56.84	48.47
F8	0.1 : 0.7 : 0.0	54.35	41.32

Table 2. Floating Behavior of Metformin Hydrochloride microsphere

Formulation	1 hour	2 hours	4 hours	6 hours
F_1	98.41	97.08	93.23	91.47
F_2	98.11	95.58	92.17	87.34
F_3	98.54	95.64	85.34	78.45
F_4	99.54	92.49	80.57	72.97
F_5	98.72	91.95	73.49	66.12
F_6	98.45	86.62	65.14	57.76
F_7	88.34	75.41	56.04	45.09
F_8	81.51	67.23	52.20	36.18

Table-3 Stability Study Data for F4 Formulation

S. No	Days	% Drug Remaining 5-8°C	% Drug Remaining 27±2°C	% Drug Remaining 42±2°C
1.	0	100 ± 00	100 ± 00	100 ± 00
2.	30	99.6 ± 0.015	99.9 ± 0.003	99.4 ± 0.041
3.	45	99.5 ± 0.013	99.8 ± 0.027	99.2 ± 0.036
4.	90	99.4 ± 0.15	99.6 ± 0.012	99.1 ± 0.02

*** Values are mean ± S.D.**

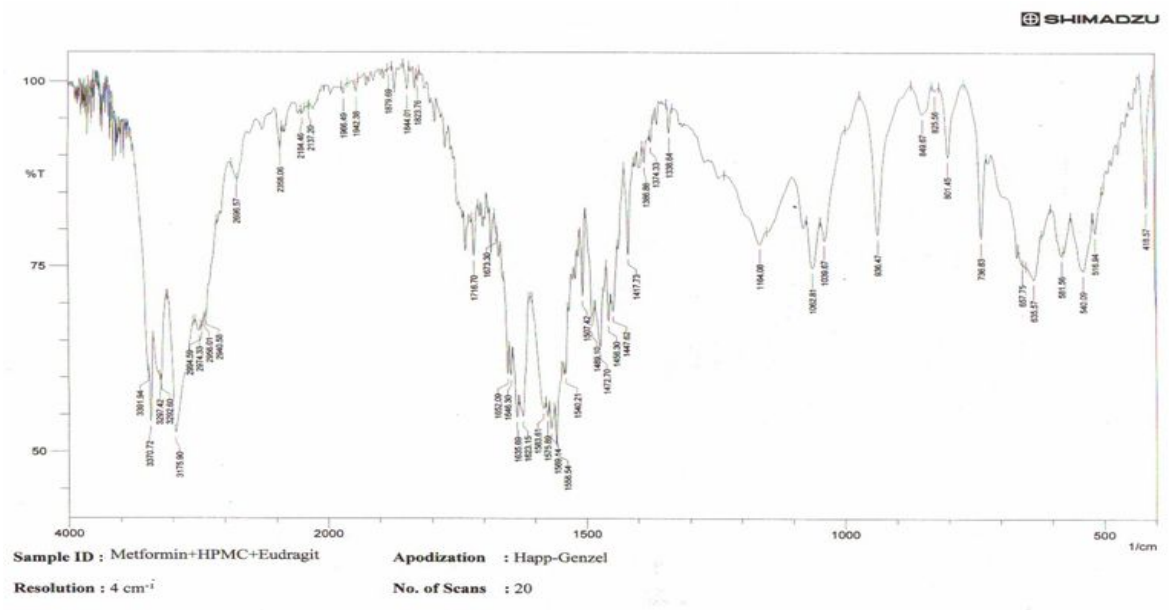

Fig 1. FT-IR spectroscopy of Physical Mixture.

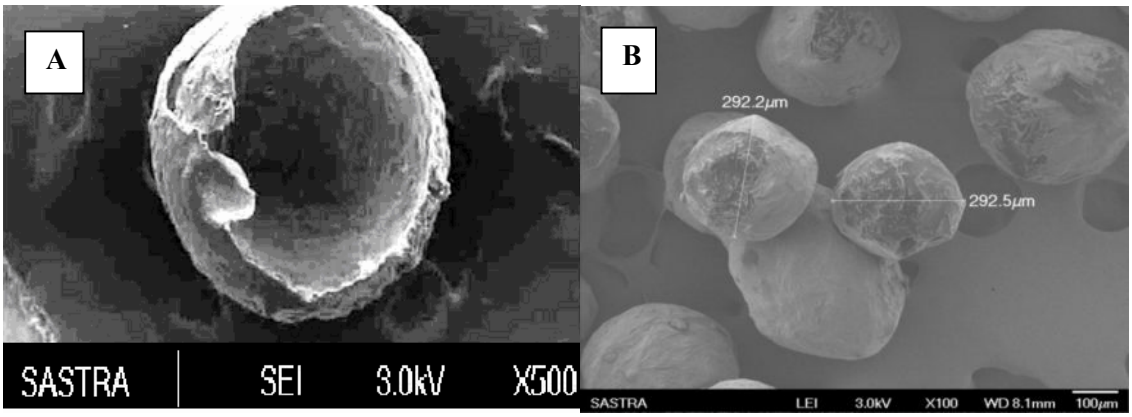

Fig 2. SEM of Metformin Hydrochloride floating microspheres A; Cross Section of microspheres, B; Surface morphology of original microsphere.

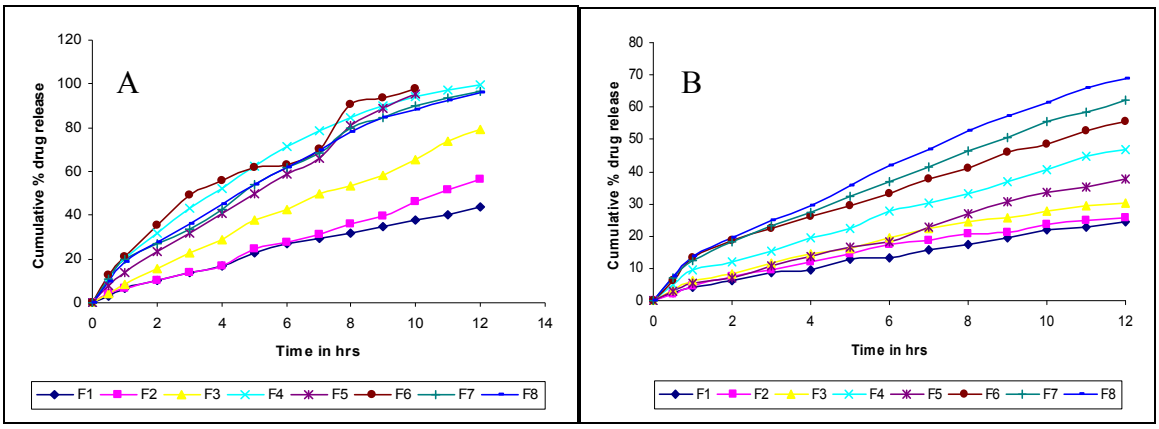

Fig 3. In-vitro release Studies of Metformin hydrochloride microsphere
A; Phosphate buffer pH 6.8 B; 0.1 N HCl

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