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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF METFORMIN HYDROCHLORIDE MICROPARTICLES BY EMULSION SOLVENT EVAPORATION TECHNIQUE

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ABSTRACT

Metformin HCl-loaded microparticles of ethyl cellulose were prepared by the emulsion solvent evaporation technique. The aim of this work was to investigate the influence of process variation in polymer type via viscosity grades of ethyl cellulose E1and E10 and drug to polymer ratio on the micromeritic properties. Microparticles evaluated for various characteristic properties such as encapsulation efficiency, particle size & size distribution, surface morphology and drug release pattern. The optimized formulation parameters were used to prepare porous, spherical micro particles (67 µm to 127 µm) with high encapsulation efficiency (93 to 97%). Drug release over a period of 12 hrs ranged from 85.7 % to 98.3 %. Microspheres were more spherical in shape in their manufacture with ethyl cellulose E10 and higher ratio of both polymers. Thus, in the case of ethyl cellulose, the viscosity and ratio of the polymer in dispersion medium were found to be the controlling factors of drug release.

Key words: Metformin, Ethyl cellulose, micro particles, sustained release, encapsulation efficiency.

INTRODUCTION

Advances over the last decade in site-specific and/or controlled drug delivery systems are contributing to new and/or improved drug therapies. Drug delivery is becoming an increasingly important aspect in new product research and development in the pharmaceutical industry [1]. Microencapsulation is one of the techniques used to prepare microparticles based sustained release formulation. The techniques of microencapsulation employing various polymers and their applications are described in standard text books. They are widely used techniques to achieve sustained, oral & parenteral controlled release products and for drug targeting [2-4] Microspheres are one of the multi particulate drug delivery systems and are prepared to obtain prolonged (or) controlled drug delivery, to improve bioavailability or stability and to target drug to specific sites. Microspheres can be defined as solid, approximately spherical particles ranging from 1 to 1000µm, containing dispersed drug in either solution (or) microcrystalline form [5,6]. Ethyl cellulose is non-biodegradable, bio-compatible, non-toxic natural polymer and widely used in oral and topical formulation [7]. The microspheres can be produced by several methods utilizing emulsion system (o/w, w/o, o/w/o and w/o/w). The common emulsion system used oil-in-water (o/w), with microspheres being produced by the emulsion solvent evaporation method. This relatively simple method enables the entrapment of a wide range of hydrophobic drugs [8]. The main object of present study was to investigate the possibility of obtaining sustained release aspirin microsphere by using different concentration of ethyl cellulose, different composition of solvent mixture, different concentration of emulsifying agent and different stirring rate. Aspirin used as a model drug for the present investigation.

Metformin HCl is a biguanide antihyperglycemic drug, which is orally used in the management of noninsulin-dependent diabetes mellitus (NIDDM or Type II diabetes mellitus) alone or in combination with other hypoglycemic [9, 10]. Its antihyperglycemic effect is due to the metabolic activities at several sites (biophase), including liver, intestinal muscle cells, and adipocytes [11]. Metformin also has beneficial effect on several cardiovascular risk factors such as dyslipidemia, elevated plasma-plasminogen activator inhibitor, other fibrinolytic abnormalities and insulin resistance [12]. 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 [13, 14]. Therefore, the marketed immediate release product needs to be administered 2- 3 times daily to maintain effective plasma concentration [15]. Henceforth, there being high incidence of gastrointestinal side effects and toxicity. These drawbacks can be overcome by designing suitable sustained release Metformin HCl formulations. Administration of a sustained Metformin HCl release dosage form could reduce the dosing frequency and improve the patient compliance. In this present study an attempt is made to prepare Metformin HCl ethyl cellulose micro particles by emulsion solvent evaporation technique using ethyl cellulose as a carrier to extend the period of drug release by retarding the release rate. The prepared microparticles were evaluated for drug entrapment efficiency, various micromeritic properties, surface morphology and in-vitro drug release pattern.

MATERIALS AND METHODS

Materials

Metformin HCl was a gift sample from Abhilasha Pharma Pvt Ltd, Ankleshwar, Gujarat, India. Ethyl cellulose,EC-1,(18–22 cps) Ethyl cellulose (40-42 cps), Sigma Aldrich Pvt. Ltd., USA), Span 80 (Himedia Chemicals Ltd., India), Dichloromethane (International Chemicals, India), (Merck Specialties Pvt. Ltd., India), potassium

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dihydrogen orthophosphate (Himedia Chemicals, India), were used. All other chemicals were of analytical grade and were used as procured.

Methods

Preparation of microparticles

Emulsion-solvent-evaporation technique with some modifications was used to prepare ethyl cellulose microparticles containing Metformin HCl Briefly Metformin HCl was dissolved in 5 ml distilled water ethyl cellulose was dissolved in Dichloromethane at various drug - polymer ratios (1:2, 1:4 and 1:6). Then these drug and polymer solutions were mixed and emulsified using a Remi Lab Magnetic stirrer (type-RQg-128A) at 2000 rpm for about 10 min to form stable w/o emulsion. This stable w/o emulsion was slowly added to 200 ml aqueous solution containing 1 % PVA and stirred at 800 rpm by a mechanical stirrer equipped with a three bladed propeller (Remi motors, India) at room temperature for 2 h to allow the solvent to evaporate completely. Microspheres were isolated by filtration and washed with distilled water several time to remove PVA. The produced microspheres were dried at ambient temperature (25^0C) for 24 h and dried in vacuum chamber at 25^0C for 2 h to remove any residual solvent. Ethyl cellulose microparticles containing Metformin HCl with their experimental formulation variables settings are presented in Table 1.

Table1: Formulation parameters of prepared Metformin HCl-loaded ethyl cellulose microparticles.

Formulation	Polymer	Drug to Polymer Ratio	Stirring rate (rpm)
F1	EC1	1:2	800
F2	EC1	1:4	800
F3	EC1	1:6	800
F4	EC10	1:2	800
F5	EC10	1:4	800
F6	EC10	1:6	800

Characterization of Microspheres

Percentage Drug Loading

Metformin content in the microspheres was estimated by UV Spectrophotometer based on the measurement of absorbance at 206 nm Microspheres equivalent to 100 mg were weighed and added in 100 ml of 0.1N HCl which was dissolved in a volumetric flask. The volume was made up to 100 ml with 0.1N of HCl. The sample was withdrawn, diluted suitably and measured spectrophotometrically at 206 nm for the drug content. It was performed in triplicates. The percentage of drug loading in microspheres was estimated using the formula below:

$$\%\ Drug\ loading = \left(\frac{Weight\ of\ drug\ in\ microspheres}{Weight\ of\ microspheres}\right)\times 100$$

Encapsulation Efficiency

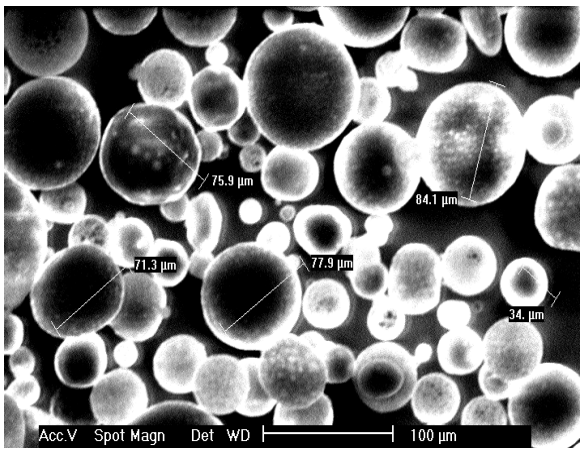
The entrapment efficiency of the prepared microspheres was calculated by the formula:

$$\%\ Encapsulation\ efficiency = \left(\frac{\%\ Drug\ loading}{\%\ Theoretical\ loading}\right)\times 100$$

Scanning electron microscopy (SEM)

Shape and surface characteristics of the Metformin HCl-loaded microspheres were investigated and photographed using scanning electron microscopy (SEM, JEOL JSM-840A). The samples were mounted on an aluminum stage using adhesive carbon type and placed in a low humidity chamber for 12 h prior to analysis. Samples were coated with gold-palladium for 60 sec under an argon atmosphere using sputter coater in a high vacuum evaporator equipped with an omnirotary stage tray. Images (figure1.A and B) were taken at an acceleration voltage of 20 kV and magnifies of 33- 150.

(A)



(B)

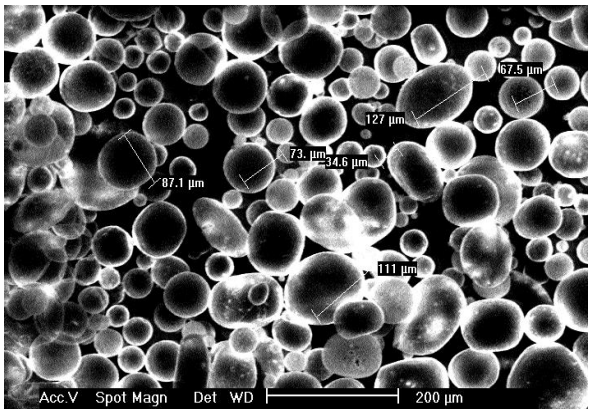


Figure 1: SEM photographs of drug loaded microparticles A. (EC1), B. (EC10).

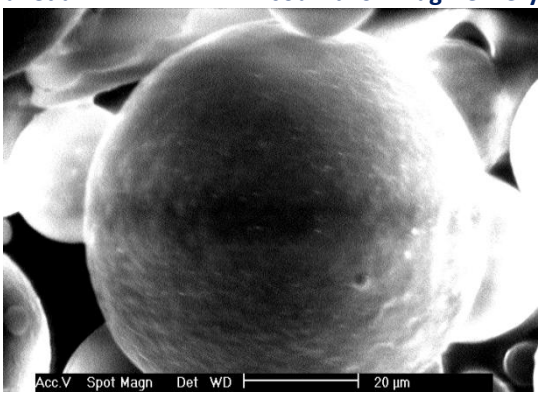


Figure 2: SEM photographs surface of drug loaded microparticles.

X-ray diffraction

The crystalline nature of drug and drug loaded microparticles was evaluated by powder XRD technique using Philips model "X" Pert, diffractometer attached to the digital graphical assembly and a computer with Cu target X ray tube-4 as Cu α-radiation source in the range of -3˚to 136˚ of 2θ. X-Ray powder Diffraction analysis is a powerful method by which X-Rays of a known wavelength are passed through a sample to be identified in order to identify the crystal structure. The wave nature of the X-Rays means that they are diffracted by the lattice of the crystal to give a unique pattern of peaks of 'reflections' at differing angles and of different intensity, just as light can be diffracted by a grating of suitably spaced lines. The diffracted beams from atoms in successive planes cancel unless they are in phase, and the condition for this is given by the BRAGG relationship.

$$nI = 2\,d\,\sin\theta$$

Where,

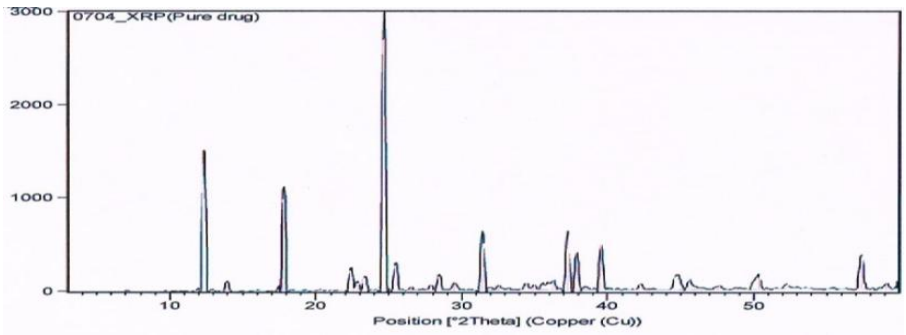
l is the wavelength of the X-Rays

d is the distance between different plane of atoms in the crystal lattice.

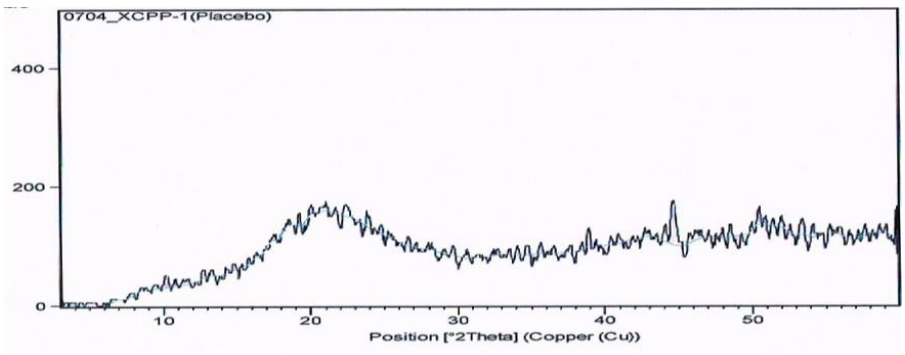
θ is the angle of diffraction.

The X-Ray detector moves around the sample and measures the intensity of these peaks and the position of these peaks [diffraction angle 2 θ]. The highest peak is defined as the 100% * peak and the intensity of all the other peaks are measured as a percentage of the 100% peak.

(A)



(B)



(C)

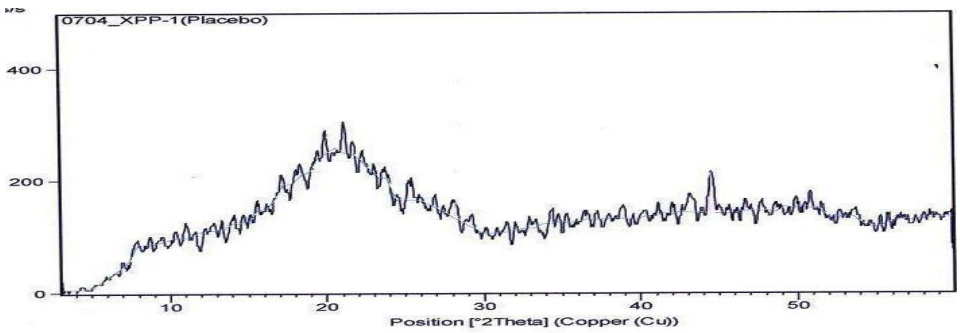


Figure 3: X- ray diffraction of (A) Metformin HCl (b) Ethyl cellulose (C) EC + Drug.

***In-vitro* Drug Release Studies**

The percentage of drug (Metformin HCl) released from ethyl cellulose microparticles were evaluated in 0.1N HCl, pH 1.2 and phosphate buffer, pH 6.8. The sustained release characteristic of these microparticles was more prominent in pH 6.8 than pH 1.2.The collected aliquots were filtered and suitably diluted to determine the absorbance using a UV-VIS spectrophotometer (Shimadzu, Japan) at 233nm for phosphate buffer, pH 6.8 and 206nm for 0.1NHCl, pH 1.2. The release of Metformin HCl from formulations is shown in figure. 4 and figure.5.

RESULT AND DISCUSSION

In this study, attempts have been made to develop and formulate Ethyl cellulose coated microspheres by solvent displacement technique at various drug - polymer ratios (1:2, 1:4 and 1:6) using two different grade of ethyl cellulose. Metformin HCl was used as a model drug to check the drug entrapment efficiency and drug release study. The prepared microparticles were evaluated to check the effect of key parameter affecting on the properties of microparticles. The formulations in Table 1 were prepared in which the increasing amounts of ethyl cellulose either E1 or E10 types were added to the fixed weight of Metformin HCl with constant stirring rate.. Optimization and proper control of all these variables were essential for the formation of discrete and spherical microspheres. The higher the viscosity and concentration of the selected polymer, the more spherical in shape microspheres can be obtained with lesser micropores on the surface. The SEM micrographs and typical surface morphology of the microspheres is shown in Figure 2. For this reason, F6 microspheres prepared with the highest amount of ethyl cellulose E10 have more regular particles. Microspheres presented a narrow distribution of particle size and generally fallen into the 67 µm to 127 µm range. Type of ethyl cellulose and its added amount in formulations had a major effect on the viscosity, influencing the particle size distributions. The viscosity of the organic phase due to the concentration of polymer inside was effective on solvent diffusion and emulsification, while the shearing rate during stirring was kept constant. The geometric mean diameters of microspheres were found to be dependent on polymer concentration dispersed in the organic phase.

XRD study of samples (Figure 3A-3C) shows that the drug Metformin HCl has a crystalline nature Placebo of ethyl cellulose amorphous nature (fig.2B). And the drug loaded particles shows the intermediate nature of crystalline drug and amorphous polymer which clearly indicates dispersion of drugs at molecular level in the formulation and also intensity of XRD was dependent on particle size and its distribution. XRD studies are most important tool for defining nature of any particles.

There is no any interaction between Metformin HCl and ethyl cellulose during the evaporation process and microsphere formation as indicated in Table 2. The drug loading was affected by neither polymer content nor stirring rate variables, but was consistently and slightly lower than the theoretical loading, with high encapsulation efficiencies close to 100 % in all cases. Also the recovered amount of total microspheres demonstrated the adequacy of process variables during solvent evaporation.

Table 2: Drug loading capacity (Metformin HCl content), encapsulation efficiency and percent yield of prepared Metformin HCl-loaded microspheres.

Formulation	Theoretical Metformin HCl Content a (%)	Measured Metformin HCl Content b(%)±S.D.1	Encapsulation efficiency (b/a x100)	Yield (%) ±S.D.1
F1	33.20	31.54±1.20	95.00	80.13±0.33
F2	33.20	31.05±0.96	93.52	88.34±0.15
F3	27.00	25.49±0.14	94.40	86.78±0.74
F4	27.00	25.86±0.32	95.77	86.41±0.86
F5	22.00	21.19±0.66	96.31	92.16±0.67
F6	22.00	21.41±0.29	97.31	80.79±0.11

The ultimate aim of this present work was to develop sustained release drug delivery system of Metformin HCl. It is observed from the dissolution study that concentration of ethyl cellulose offers sustained effect of the drug up to12hrs. With increasing polymer amount and viscosity, the initial burst effect was significantly decreased in addition to the decrease in second drug release phase. The subsequent decreasing related to drug release rates can be attributed to the resulting decreased drug concentration gradients. In vitro drug release strongly depended on the type of polymer. This might be explained by the higher viscosity of the organic phase in the case of ethyl cellulose. It has been reported that the release of the drug depends on viscosity grade of the ethyl cellulose. With an increasing viscosity grade, the rate of release decreases. It has also been described that, in addition, the release rate depends on the overall viscosity of the system. The present study was able to confirm these findings; for F6 microsphere formations (1:6 drug to polymer ethyl cellulose E10), which had the highest overall viscosity, the slowest release was observed.

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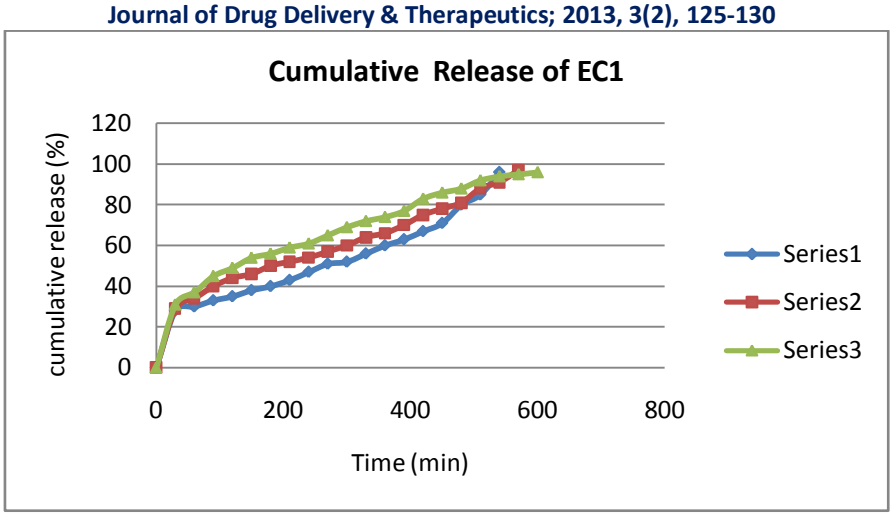

Figure 4: Effect of different drug-polymer ratio (1: 2, 1: 4, and 1: 6) on the drug release of (EC1). Series1 (1:2 – EC1), series 2 (1:4 –EC1) and series 3 (1:6 –EC1)

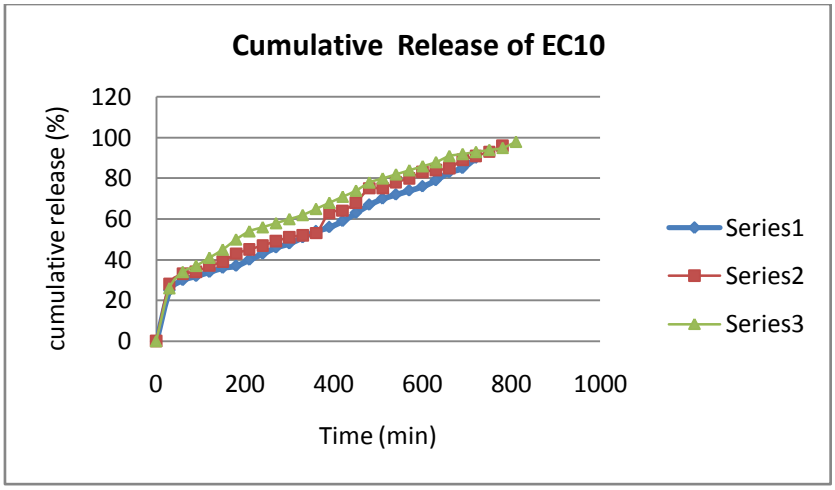

Figure 5: Effect of different drug-polymer ratio (1: 2, 1: 4, and 1: 6) on the drug release of (EC10). Series1 (1:2 – EC10), series 2 (1:4 –EC10) and series 3 (1:6 –EC10)

CONCLUSION

The Metformin HCl microparticles were prepared successfully by solvent evaporation technique. This study showed that during manufacture of the microspheres by solvent evaporation method, the viscosity and ratio of polymer in dispersion medium were the controlling factors of microsphere micromeritic parameters [16] and drug release. Microparticles prepared using ethyl cellulose was found to be spherical, discrete and free-flowing. High encapsulation efficiency can be attributed to the probability for the drug to be entrapped within the microparticles when increasing the amount of ethyl cellulose.

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