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EFFECT OF MANUFACTURING VEHICLES ON GLIBENCLAMIDE LOADED ETHYL CELLULOSE MICROSPHERES

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ABSTRACT

Glibenclamide loaded ethyl cellulose microspheres were prepared by solvent evaporation technique using in different manufacturing vehicles like F1 (liquid paraffin light), F2 (liquid paraffin heavy), F3 (palm oil) and F4 (mixture of light and heavy liquid paraffin) to find out the suitable choice of manufacturing vehicle. The microspheres were characterized for particle size, SEM, FT-IR study, percentage yield, drug entrapment efficiency, in-vitro release kinetics and stability study. The shape of microspheres was found to be spherical by SEM study in all manufacturing vehicle. The size of microspheres was found to be ranging 59.3±6.3µm to 86.22±4.23µm. Among the four formulations, F3 showed maximum percentage yield of 83.34±2.46 due to high density of manufacturing vehicle. F2 showed highest drug entrapment of 76.92±3.24%. From the FT-IR study, it was found that there was no interaction between drug, polymer and manufacturing vehicle. In the in-vitro release study, F3 formulation showed 90.34% drug release at 15hrs and found to be sustained followed by Higuchi kinetics indicating diffusion control drug release. No appreciable difference was observed in the extent of degradation of product during stability studies of various microspheres, which was stored at various temperatures.

KEY WORDS: MICROSPHERES, GLIBENCLAMIDE, SOLVENT EVAPORATION, MANUFACTURING VEHICLE

INTRODUCTION

Glibenclamide is an oral antidiabetic agent which is widely used in the management of non-insulin dependent diabetes mellitus (type II). It is a second generation sulphonyl urea which is more potent than the first generation drugs in this class [1, 2]. Its biological half-life is 4- 6hrs. Due to its low biological half-life (5 hrs), it requires frequent administration to maintain plasma concentration. This causes inconvenience to the patient and also leads fluctuations in plasma drug concentration that may cause inferior therapeutic effects or toxic effects [3, 4]. It is Needless to say that one of the most difficult problems of the new millennium is the management of vast majority of our population afflicted with diabetes specially the Type-2, which are not dependent on insulin production. It is feared that within few years India would have 50 million cases of diabetes especially among the younger generation among men and women including children will suffer from this destructive disease [5, 6]. Extensive work is being taken up not only to develop newer more specific molecules for Type-2 diabetes but also develop proper delivery system to maintain the activity of the drug over a prolong period of time so the proper compliance of taking the drugs regularly [7,8]. Therefore, development of controlled release dosage forms would clearly be beneficial in terms of decreased dosage requirements, thus increase patient compliance [9, 10]. Lots of attempt was made to prepare glibenclamide loaded ethyl cellulose microspheres of by an industrially feasible emulsion solvent evaporation technique and the microspheres were investigated [11, 12]. So it is required to find out the suitable vehicle for the preparation of microspheres in an economic manner. The present investigation aim is to prepare the glibenclamide loaded ethyl cellulose microspheres in an economic vehicle.

MATERIALS

Glibenclamide was obtained as a gift sample from Nutra specialties private Ltd, A.P., Ethyl cellulose was obtained from Fulka Cemika, Sigma-Aldrich Chemie, Switzerland, Liquid paraffin light, , Liquid paraffin heavy and Palm oil was procured from Loba chemicals private Ltd. All other chemicals were used of analytical grade.

METHODS

Ethyl cellulose microspheres were prepared by Solvent evaporation technique. Drug (glibenclamide) and polymer (ethyl cellulose) ratio was kept constant (1:5) for different formulations in different manufacturing vehicle F1 (liquid paraffin light), F2 (liquid paraffin heavy), F3 (palm oil) and F4 (mixture of liquid and heavy liquid paraffin). Accurately weighed

quantities of drug and polymer were dissolved in 10 ml of Acetone [13, 14, and 15]. This solution was added in 200 ml of liquid manufacturing vehicle separately (light liquid paraffin, heavy liquid paraffin, palm oil and mixture of light and heavy liquid paraffin) containing 2% of Span-80 and stirred continuously for 5 hrs at 600 rpm, flow chart is shown in Figure 1. The microspheres were filtered and washed three times with 50 ml of n-Hexane and dried at room temperature for 12 hrs for further evaluation [9].

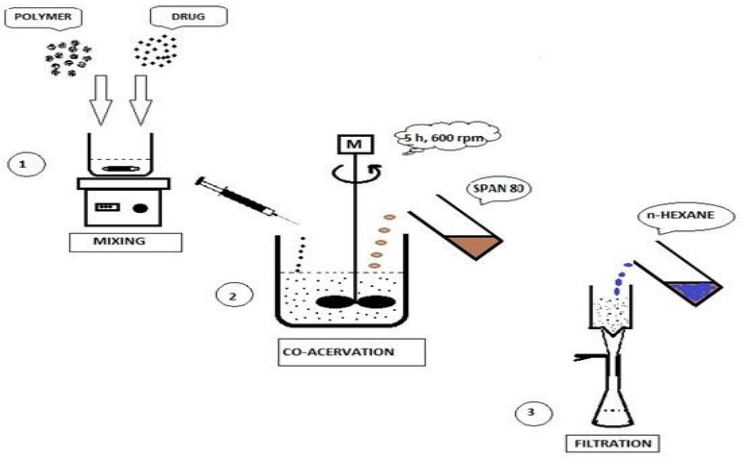

Figure 1. Flow chart for preparation of Microspheres

Table 1. Formulation code and evaluation parameters

Formulation code	Drug Polymer Ratio	Liquid Manufacturing Vehicle	Percentage yield	Entrapment efficacy (%w/w)	Average particle size (µm)
F1	1:5	Liquid paraffin Light	79.63±2.49	73.14±2.64	59.3±6.31
F2	1:5	Liquid paraffin Heavy	80.97±3.66	76.92±3.24	65.6±4.46
F3	1:5	Palm Oil	83.34±2.46	74.69±2.38	78.52±7.41
F4	1:5	Mixture of Liquid Paraffin Light and Heavy (1:1)	81.28±4.00	71.96±2.94	86.22±4.23

Evaluation of microspheres

The yield of microspheres preparation was calculated using the formula:

$$\text{Percentage Yield} = \frac{\text{Practical Amount of Microspheres obtained}}{\text{Theoritical Amount}} \text{X } 100$$

Microspheres of known weights were stopper tightly in a flask containing 50 ml of 7.4 pH phosphate buffer. The flasks were shaken using orbital shaker for 48 hours to break the beads completely. After 48 hours the solution was filtered using Whatman's filter paper and the filtrate was centrifuged using a tabletop centrifuge to remove the polymeric debris. Then the polymeric debris was washed twice with fresh solvent (water) to extract any adhered drug. The clear supernatant solution was then analyzed for glibenclamide content by a UV spectrophotometer (JASCO-V500, Japan) at the λ max value of 275 nm. The complete extraction of drug was confirmed by repeating the extraction process on the already extracted polymeric debris [16, 17]. The % entrapment efficiency of the matrix was then calculated as:

$$Percentage \text{ Entrapment efficiency } = \frac{Actual\ Drug\ Loading}{Theoritical\ Drug\ Loading} \text{X } 100$$

Particle size analysis

Particle size analysis was carried out using optical microscopy. About 200 microspheres were selected randomly and their size was determined using optical microscope fitted with a standard micrometer scale. The surface morphology and the internal textures of microsphers were observed under a scanning electron microscope (Jeol JSM–5610, Japan). FT-IR spectra of glibenclamide loaded ethyl cellulose microspheres from different manufacturing vehicles were taken to check drug polymer interaction and degradation of drug during microencapsulation [18, 19].

Stability studies

The microspheres were placed in screw capped glass container and stored at ambient humidity conditions, at room temperatures (27±2°C), oven temperature (40±2°C) and in refrigerator (5-8°C) for a period of 60 days, then the microspheres were analyzed for drug content [20].

***In vitro* release studies**

The in vitro release profile of glibenclamide from microspheres was examined in phosphate buffer pH 7.4 using the rotating paddle method (Electro Lab, Mumbai) under sink conditions.

Accurately weighed samples of microspheres were added to dissolution medium kept at 37±0.5°C. At preset time intervals aliquots were withdrawn and replaced by an equal volume of dissolution medium to maintain constant volume. After suitable dilution the samples were analyzed spectrophotometrically at 275 nm [21].

Kinetics of drug release

In order to understand the mechanism and kinetics of drug release, the result of the in vitro dissolution study of microspheres were fitted with various kinetic equations, like zero order (percentage release vs. time), first order (log percentage of drug remaining to be released vs. time) and Higuchi's model (Percentage drug release vs. square root of time). Correlation coefficient (r^2) values were calculated for the linear curves obtained by regression analysis of the above plots [22].

RESULTS AND DISCUSSION

Glibenclamide loaded ethyl cellulose microspheres were prepared by solvent evaporation technique. Ethyl cellulose was selected as a polymer for the preparation of microspheres due to its compatibility with Glibenclamide. Based on density different manufacturing vehicles were used to prepare the microspheres. The scanning electron microphotograph of microspheres is shown in Figure 2, which indicates that microspheres were spherical and discrete for all prepared formulations. The particle size was analyzed by optical microcopy. The particle size differed due to variation in the density of manufacturing vehicle in same starring speed (600 rpm). The particle size gradually increased with increasing when density increased. The mean particle size of the microspheres is shown in Table 1. The percentage yield and entrapment efficiency were high for all the formulations and were in the range of 79.63±2.49–83.34±2.46% and 71.96±2.94–76.92±3.24% w/w, respectively, as shown in Table 1.

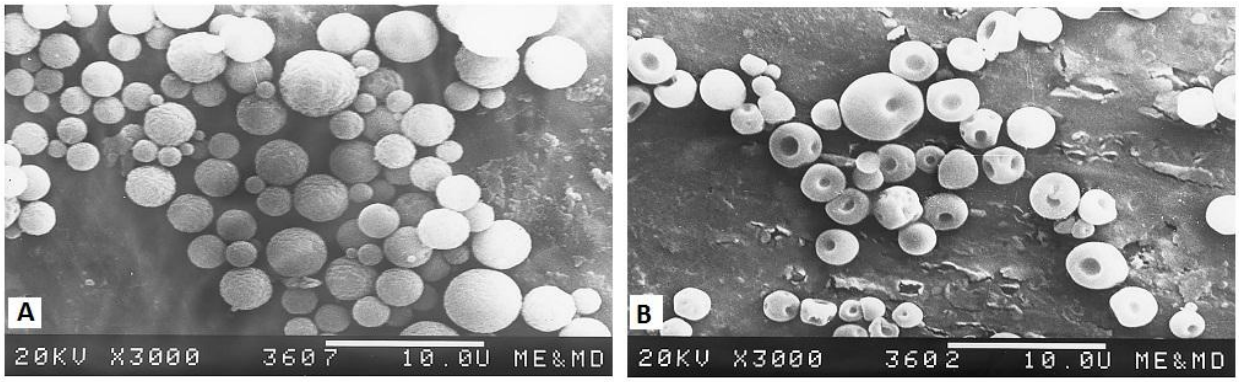

Figure 2. SEM of glibenclamide microspheres from palm oil

(A-Before Dissolution, B-After Dissolution)

Among the four formulations F3 showed maximum percentage yield of 83.34±2.46% and F2 showed highest drug entrapment efficacy of 76.92±3.24% w/w. The FT-IR spectra obtained for Glibenclamide and ethyl cellulose microspheres (Figure 3). The results indicated that the characteristic peaks due to pure glibenclamide have appeared in microspheres, without any change in their position after successful encapsulation, indicating no chemical interaction between glibenclamide and ethyl cellulose on the stability of drug during microencapsulation process. In the stability studies, no appreciable difference was observed in the extent of degradation of products during 60 days on the microspheres which were stored at various temperatures.

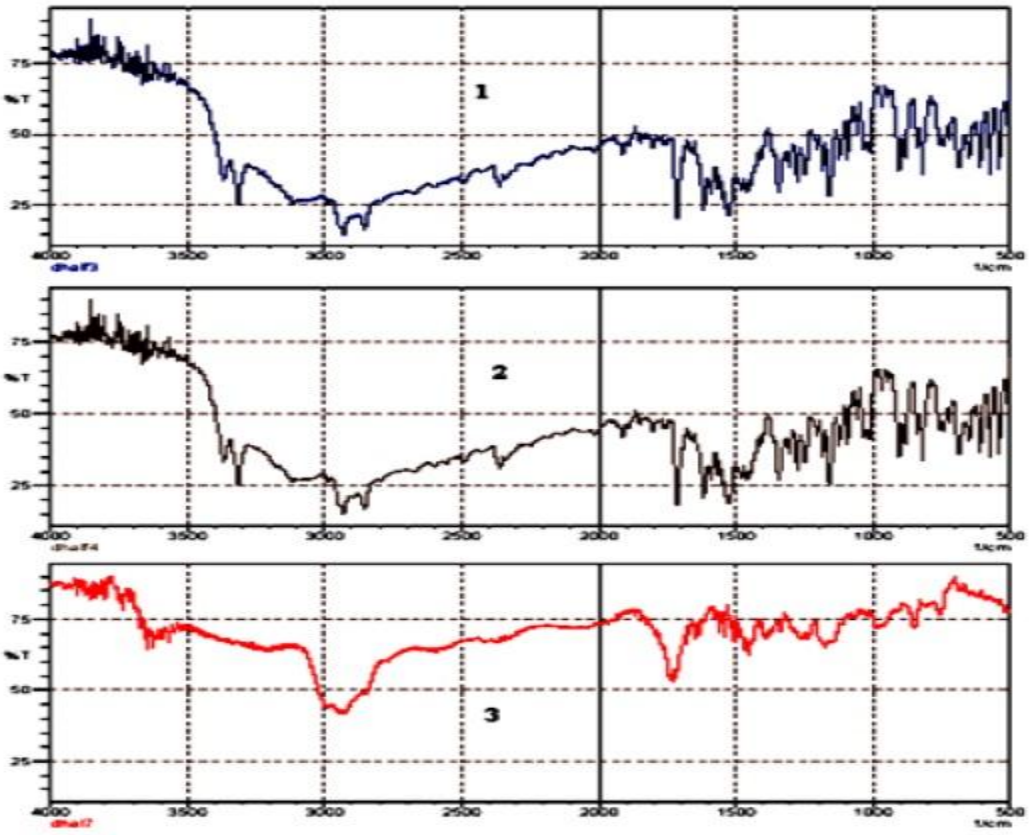

Figure 3. FT-IR for Pure Glibenclamide (1), Ethyl cellulose (2), Microspheres (3)

The cumulative percent release of glibenclamide from different formulations is shown in Figure 4A. Glibenclamide release from all the formulations was slow and sustained over 15 h. The drug release rate was decreasing on increasing the density of manufacturing vehicle where the microspheres were prepared.

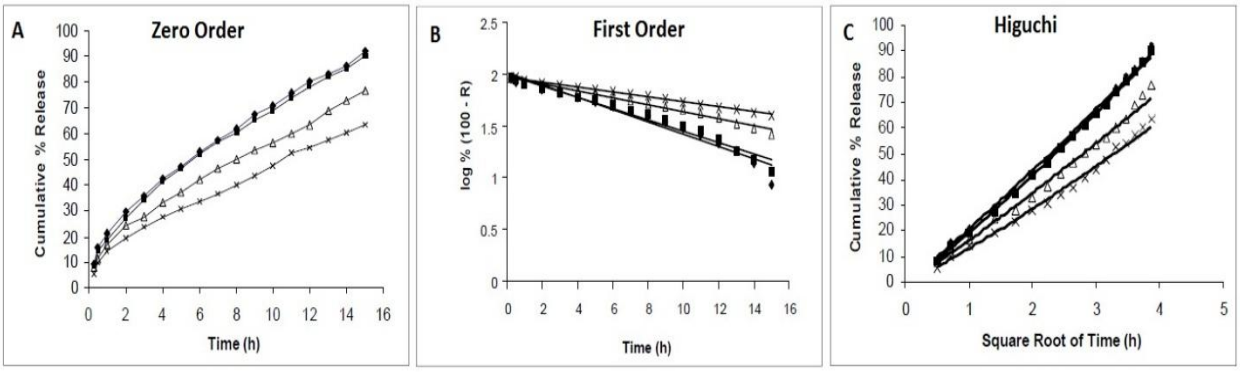

Figure 4. In-vitro dissolution profiles of glibenclamide from ethyl cellulose microspheres formulation F1 (-□-), F2 (-▪-), F3 (-□-) and F4 (-□-) were studied in pH 7.4 phosphate buffer over a period of 15 h.

Table 2. Release kinetics of various formulations

Release Model	F1	F2	F3	F4
Zero Order	0.853	0.865	0.883	0.877
First Order	0.994	0.965	0.983	0.954
Higuchi	0.987	0.978	0.985	0.979

By the end of 15h of dissolution from the formulations F1, F2, F3 and F4 the percentage of drug release were found 92.21%, 76.65%, 90.34% and 63.39 % respectively. Microspheres prepared in palm oil (F3) showed better drug entrapment and release pattern. It controlled the drug release over 15 h and was found to be the most suitable among other formulations. The in-vitro release data were applied to various kinetics models to predict the drug release mechanism and kinetics. The drug release mechanism from the microspheres was diffusion controlled release as a plot of the amount released versus square root of time (Figure 4C) was found to be linear. The correlation coefficient (r^2) was in the range of 0.978–0.987 for various formulations as shown in Table 2. When log percentage of drug remaining to be released vs. time was plotted in accordance with first order equation, straight lines were obtained (r^2 >0.95) indicated that drug release followed first order kinetics (Figure 4B).

CONCLUSION

In present study, an attempt was made to prepare glibenclamide microspheres using ethyl cellulose by solvent evaporation technique in different manufacturing vehicles to study the effect and suitability of manufacturing vehicle on microspheres. The method was found to be simple

and reproducible. The results obtained from the various evaluations and performance studies of microspheres that palm oil may be useful as a liquid manufacturing vehicle to prepare glibenclamide loaded ethyl cellulose microspheres for controlled drug release formulation and may help to reduce the cost efficacy.

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