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Formulation and evaluation of repaglinide microspheres

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Abstract

The present investigation involves formulation and evaluation of microspheres with Repaglinide as model drug for prolongation of drug release time. An attempt was made to prepare microspheres of Repaglinide by Quasi emulsion solvent diffusion technique, with a view to deliver the drug at sustained or controlled manner in gastrointestinal tract and consequently into systemic circulation. The microspheres were formulated by using various concentration of HPMCP, Ethyl cellulose and Eudragit RSPO as a retarding agent to control the release rate. The prepared microspheres were evaluated for Flow behavior, Compatibility study, Drug Entrapment Efficiency, In-vitro Dissolution, Scanning Electron Microscopy and Particle size analysis. Among the nine formulations prepared and evaluated F1 and F9 are found to show retarded release. In-vitro release studies indicated that, as the concentration of retarding agent (HPMCP, Eudragit and Ethyl cellulose) increases the formulation become more sustained.

Key-Words: Repaglinide, Microsphere, Quasi-emulsion, *In-vitro* release

Introduction

Repaglinide induces rapid onset short lasting insulin release. It is administered before each measure meal to control postprandial hyperglycemia: the dose may be omitted if a meal is missed. Because of short lasting action it may have a lower risk of serious hypoglycemia[1]. The quasi-emulsion solvent diffusion method of spherical crystallization technique has been accepted as a useful technique for particle size design for pharmaceuticals. It provides remarkable advantage over conventional microsphere preparation methods. In this process, drug and polymer are co precipitated to form functional drug devices according to the polymer properties. For example, acrylic resin (Eudragit RS,Eudragit RL) and Ethyl Cellulose (EC) could produce sustained release microspheres.However, further application of quasi-emulsion solvent diffusion method to produce solvent disposition system with poorly water soluble drug to improve the dissolution rate has seldom been reported until now.

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In this study,the principles of above two methods were combined to design the sustained-release microspheres having solid dispersion structure of poorly water-soluble drug[2].Release of core material from a non-erodible microparticle can occur in several ways. Non-erodible spherical microparticles release the encapsulated material by steady-state diffusion through a coating of uniform thickness. The rate of release remains constant as long as the internal and external concentration of core material and concentration gradient through the membrane are constant[3].

Material and methods

Preparation of microsphere

All the formulations were prepared according to the formulae given in Table 1. The microspheres were prepared using the quasi emulsion solvent diffusion method of spherical crystallization technique. In the first three formulation Repaglinide was dissolved with HPMC Phthalate, Ethyl Cellulose and Eudragit RSPO in mixed organic solution containing ethanol, acetone and dichloromethane then aerosil was suspended uniformly in drug polymer solution under vigorous agitation and Propylene Glycol was added as plasticizer; the resultant drug polymer aerosil suspension was poured in water phase containing (SLS) 0.08% that is poor solvent under moderate agitation 500-1000rpm at controlled temp 0-40˚c.The suspension, finely dispersed into quasi emulsion droplet, after10min agitation, 200ml of poor solvent was added to it and agitation was continued for 40min until translucent microspheres turned into opaque

microspheres. The solidified microspheres were recovered by filtration and washing with water and kept for drying for 6 hour at 50˚c.

Drug Entrapment Efficiency[4]

Drug entrapment efficiency was determined by measuring the concentration of free drug (unentrapped) in aqueous medium. The 50 mg of microspheres were centrifuged at 4000 rpm for 15 min and 1ml of supernatant liquid was taken, after suitable dilution, drug content in the filtrate was analyzed spectrophotometrically at 242 nm using Shimadzu 1201 UV-visible spectrophotometer and the entrapment efficiency was calculated by the equation:

E E(%) = Wt. of drug in the formulation – Wt. of drug in aqueous phase X 100/Wt. of drug used in the formulation

In-vitro Dissolution Studies[3, 5]

In-vitro release profile of the microspheres was evaluated using rotating basket dissolution apparatus. 900 ml of acid buffer (pH1.2), and phosphate buffer (pH7.4) maintained at 37±0.50C were used as dissolution media respectively, and the basket was rotated at a constant speed of 100 rpm. Accurately weighed amount of microspheres equivalent to 4 mg of drug were placed in the baskets. Aliquots of samples were withdrawn at the interval of 1 hour for pH1.2 for 2 hrs and for 7.4 pH 10 hrs. The samples withdrawn were filtered, diluted suitably and analyzed at 246 nm spectrophotometrically for drug release.

Particle size determination

The particle size analysis was carried out by CIS-50 (Computer inspection system) Ankersmid. Range of the particles used for scanning is 5-600 µm, lens used was lens-B. The particles were suspended in glycerin or distilled water to give a concentration of 10-9 particles with a SNF (Standard Normalizing Factor) value of 1, the sample prepared was placed into the cuvettes made up of polystyrene of 1 cm path length. The particles were analyzed for their size (length x breadth x volume) by using laser channel beam. The mechanism of working of CFS-50 is TOT (Time of Transition).

Scanning electron microscopy[2, 6-7]

Morphology details of the specimens were determined by using a scanning electron microscope (SEM), Model JSM 35CF, JEOL, Japan.

Angle of Repose[8-10]

The flow characteristics are measured by angle of repose. A glass funnel is held in place with a clamp on a ring support over a glass plate. The glass plate is placed on a stand. Approximately 100 mg of particles is transferred into funnel keeping the orifice of the funnel blocked by the lower thumb. As the thumb is removed, the particles are emptied from funnel, and the angle of repose is determined.

Results and discussion

The drug entrapment efficiency of all the formulations was in the range between 73.45% to 95.17%. Formulation containing Eudragit RSPO shows an increased entrapment compared to the formulation containing Ethyl cellulose and HPMCP. Overall all the drug entrapment was found to be good in the formulation with Eudragit RSPO, further the results indicated that quasi emulsion solvent diffusion method can be adopted for the preparation of microspheres. Dissolution test results shows that formulation containing Eudragit RSPO as retarding agent shows more sustained release when compared with formulations containing Ethyl cellulose and HPMCP. The reason might be due to the more cross linking property of Eudragit RSPO and increased viscosity. The values of co-efficient of correlation were found to be best fitted to zero order model. The mean size range for F1, F2 and F3 was 96.75µm, 113.65µm and 140.13µm respectively, for F4, F5 and F6 the mean size range was 174.34µm, 157.61µm and 135.80µm respectively and for F7, F8 and F9 it was 49.32µm, 189.93µm and 151.80µm respectively. Eudragit RSPO microspheres showed good particle size distribution than Ethyl cellulose microspheres and HPMCP microspheres. Morphology of the microparticles was investigated by Scanning electron microscopy. Microparticles of formulation F1and F4 were spherical and their surface was smooth, giving them a good appearance. The surface characteristics observed for formulation F7 shows slightly spherical structure with rough appearance. From the photographic observation it can be assumed that co-precipitation of drug and polymer occurred on surface of the quasi emulsion droplets and then the film like a shell was formed on the outer surface of droplets. It showed the retarding ability of HPMCP forF1, Ethyl cellulose for F4 and Eudragit RSPO for F7respectively. F1 and F4 shows smooth texture on the outer surface where asF7 shows tight matrix formation appears to be as sandy. Hence formulation containing Eudragit RSPO shows highly retarded drug release. The flow property of the prepared formulations was checked by the method, angle of repose. All the formulations showed an angle of repose within the range (25- 32). Formulations F1 to F7 showed an angle of repose in the good range, which indicates a good flow property and Formulations F8 to F9 are in passable range.

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Table 1: Formulation design of microspheres

S/No.	Ingredients /RPM	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Drug (mg)	50	50	50	50	50	50	50	50	50
2.	HP-55 (mg)	500	750	1000	---	---	---	---	---	---
3.	Ethyl Cellulose(mg)	---	---	---	500	750	1000	---	---	---
4.	Eudragit RSPO (mg)	---	---	---	---	---	---	500	750	1000
5.	Acetone (ml)	8	8	12	8	8	10	12	12	20
6.	DCM (ml)	8	8	12	8	8	10	12	12	20
7.	Ethanol (ml)	4	4	6	6	6	6	6	6	10
8.	SLS Solution 0.08% (ml)	300	300	300	300	300	300	300	300	300
9.	Aerosil (mg)	500	500	750	200	300	350	100	150	200
10.	RPM	500	600	700	600	700	700	700	800	900
11.	Propylene Glycol 5%(mg)	---	---	---	---	---	---	25	37.5	50

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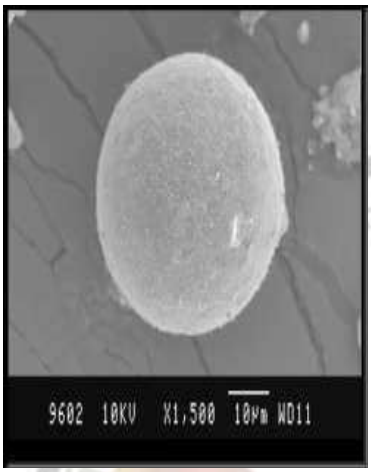

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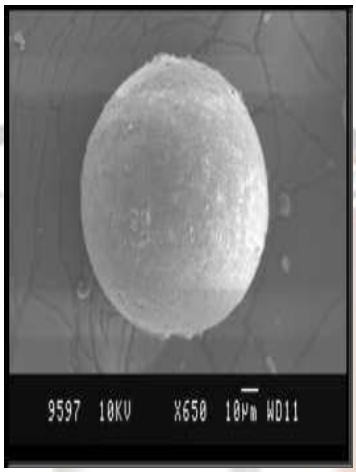

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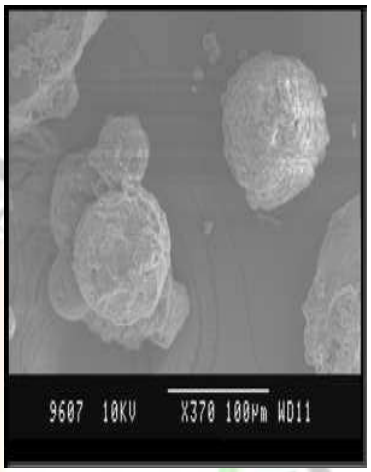
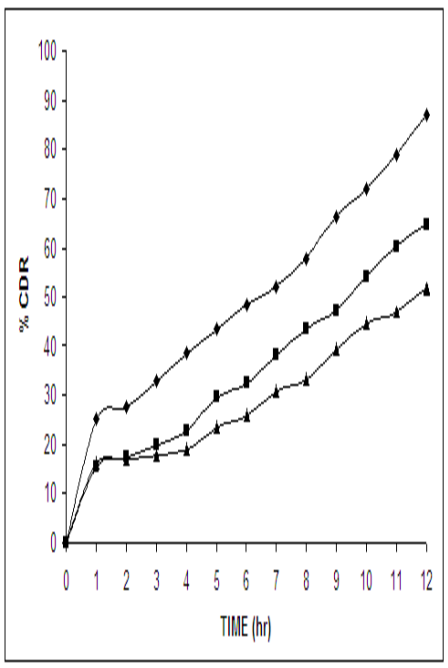


3

Fig. 1: Scanning Electron Microscopy of F1
Fig. 2: Scanning Electron Microscopy of F4
Fig. 3: Scanning Electron Microscopy of F7



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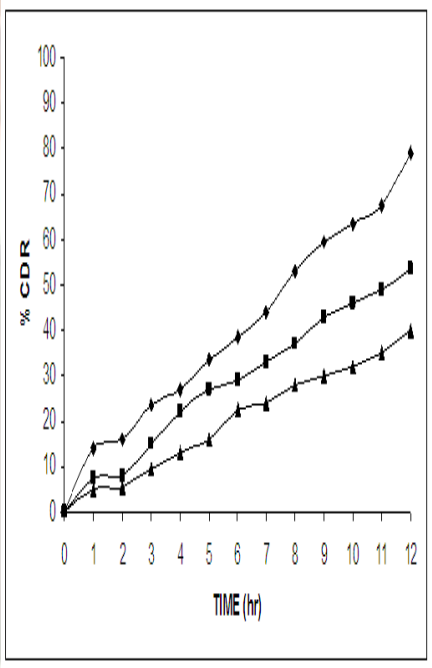

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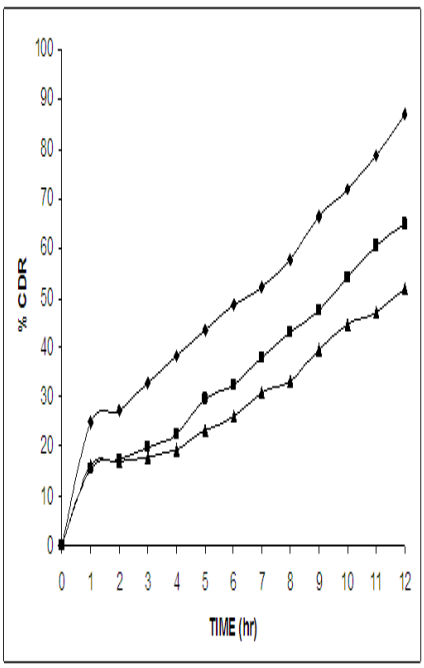

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Fig. 4: *In vitro* release profile of Repaglinide microsphere
Fig. 5: *In vitro* release profile of Repaglinide microsphere
Fig. 6: *In vitro* release profile of Repaglinide microsphere