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Research Article

Formulation and in vitro characterisation of repaglinide floating microspheres

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ABSTRACT

The present study Formulation and invitro Characterization of Floating microspheres of Repaglinide has been carried with an aim to improve the drug's bioavailability by delaying its gastric residence time. Repaglinide, an oral hypoglycemic agent used for the treating Type II diabetes has been chosen as a model drug for these studies. Microspheres were prepared by Solvent evaporation method employing different concentrations of polymers such as sodium alginate, HPMC K100, sodium carbonate and effect of these polymers on the formulation parameters of drug was studied. Obtained microspheres were studied for micromeritic properties such as Angle of Repose, Hausner's ratio, Carr's index, Bulk and Tapped density. In addition, in-vitro evaluation studies for microspheres were carried like % entrapment efficiency, drug-polymer compatibility, in-vitro buoyancy, SEM studies and in-vitro drug release studies. Results of FT-IR and SEM studies demonstrated that drug and polymer have not interacted and all the microspheres were spherical and smooth in nature. Data obtained from in-vitro release studies showed F5 formulation retarded drug release over a period of 8hrs and is considered an ideal formulation. Ideal formulation when observed for kinetic studies indicated that F5 followed Korsmeyer-peppas release kinetics.

Keywords: Microspheres**;** Repaglinide; Sodium alginate; HPMC K100; Sodium bicarbonate; Carr's index; Hausner's ratio.

INTRODUCTION

Oral route is considered an important and convenient route for the delivery drugs. Maximum number of drugs get absorbed through GIT and exhibit systemic effects (Banker GS, 2003). Upon comparision with other routes, oral route offers various advantages. Among them more patient compliance and sel f-medication are prominent. Gastric residence time play a vital role in the absorption of drugs. If gastric residence time of drug is more, absorption and biovailability of drug get increases. (Chein YW, 1992).

Novel Drug Delivery system, an approach that maintains continuous drug delivery to the target organ meanwhile maintaining its optimal concentration in blood. Controlled drug delivery has been developed with a view of maintaining constant drug levels at the target organ within the desired range (Welling PG, 1987). Whereas sustained drug delivery system extends the release of the drug from the formulations. Gastro Retentive Drug Delivery system, a site specific delivery that selectively delivers the drug to the stomach region. These systems maintain the dosage form in stomach for a longer period of time. Floating Drug Delivery System is one of the novel approaches that retain the dosage form in stomach and increase its residence time. Floating microspheres possess low density(<1gm/cm^2) than the gastic contents, thus they float in the gastric fluid (Yeole PG, 2005, 265-272).

Floating microspheres have been divided into effervescent and non-effervescent systems. Effervescent systems use effervescence as a driving mechanism for prolonging drug release. They use carbonates/bicarbonates, citric acid etc to produce effervescence. Reaction between carbonates/bicarbonates and citric acid/tartaric acid in presence of water produces carbon dioxide that causes microspheres to float on gastric fluid (Welling PG, 1987). Whereas non-effervescent systems employ volatile solvents that produce hollow structures inside microspheres that enable them to float on the gastric fluid. Examples of polymers that delay the drug release from the floating microsphere formulations are HPMC, ethyl cellulose, eudragit, sodium alginate (Sahoo SK, 2007, 65-8).

MATERIALS AND METHODS

Materials

Repaglinide was procured from Aurobindo pharma. Sodium alginate and HPMC K100 were obtained from Sd Fine Chemicals Pvt. Ltd, Mumbai. Dichloromethane, Ethanol, Hydrochloric acid, Sodium bicarbonate, Calcium chloride were purchased from Merck specialities Pvt Ltd, Mumbai.

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Preparation of Repaglinide Floating microspheres

Trial and error method for determining the floating property

Trial and error method was used to know the floating property of microspheres. Here, microspheres were prepared by employing different concentrations of sodium bicarbonate and their in-vitro buoyancy was compared. From the results, it was found that microspheres with sodium bicarbonate exhibited good buoyancy (Barhate SD, 2009, 1-8).

Preparation method

Technique used for the synthesis of Floating microspheres is Solvent evaporation. Appropriate quantities of drug, sodium alginate, HPMC K 100 and sodium bicarbonate were taken as mentioned in table no.1. Drug and excipients were dissolved in ethanol and dichloromethane in the ratio (1:1). Obtained drug –polymer solution poured to a beaker containing 100ml of 20% calcium chloride solution through a syringe. The resultant solution was stirred for about 1 hour at 300rpm. So formed microspheres were filtered using filter paper and dried them overnight at room temperatures (Deepa MK, 2009, 69-72).

EVALUATION OF FLOATING MICROSPHERES

Micromeritic properties

Microspheres were characterized for micromeritic properties like Angle of Repose, Bulk density and tapped density, Carr's index and Hausners ratio.

Bulk Density

Bulk density (ρ_b) of a powder blend can be determined by pouring the powder sample into a measuring cylinder. Resultant Bulk volume (V_b) and weight of powder (M) observed were used for calculating bulk density using formula

$$\rho_b = \frac{M}{V_b}$$

Tapped density

A graduated measuring cylinder is used for measuring Tapped density. In a measuring cylinder, known quantity of powder blend was taken and tapped for a particular duration of time (i.e., 100 tappings). Least volume (V_t) occupied by sample in measuring cylinder and weight of powder blend are used for measuring tapped density (ρ_t) using formula,

$$\rho_t = \frac{M}{V_t}$$

Carr's Index

Carr's or Compressibility index of a material is a sign of ease with which powder blend flows and it is the simplest way of measuring the extent of powder flow. It is represented by a formula,

$$Carr's\ Index = \frac{\rho b - \rho t}{\rho_b} \times 100$$

Where ρ_t = tapped density

ρ_b = bulk density

Hausners Ratio (H)

Hausner's ratio is an indirect indicator of ease of powder flow. It can be calculated using the formula:

$$Hausner's\ ratio\ (H) = \frac{\rho b}{\rho_b}$$

Where ρt = tapped density

ρ_b = bulk density

Angle of repose

Angle of repose can be determined by Funnel method. Powder blend was allowed to pass through a funnel which can be raised vertically to a maximum cone height (h). Radius of the obtained can be measured. Angle of repose can be calculated by the following formula:

$$\theta = tan^{-1}\frac{h}{r}$$

Evaluation studies

Percentage Yield

Synthesized microspheres were dried and weighed to obtain the percentage yield value of prepared microspheres. Then percentage yield was calculated using following formula:

$$\%\ Yield = \frac{Actual\ weight\ of\ dried\ microspheres}{Total\ weight\ of\ drug\ and\ excipients} \times 100$$

Particle size determination

Particle size of Repaglinide floating microspheres can be examined using optical microscopy. Little quantity of microspheres was dispersed in 10ml of purified water. Dispersion was kept under sonication for about 5 seconds. A small drop of resultant solution was placed on a clean glass slide and diameter of at least 200 particles was measured.

SEM (Scanning Electron Microscope) Studies

Surface morphology of drug loaded microspheres was inspected using SEM (JEOL Ltd., Japan). Little quantity of drug loaded microspheres was spread manually on a carbon tape (double adhesive carbon coated tape), which is attached to an aluminum stub. Stub was further coated with a thin layer of gold by employing POLARON – E 3000 sputter coater. Samples were analyzed by SEM with direct data capture of the images on to a computer screen.

Drug entrapment efficiency

Microspheres equivalent to 2mg of pure drug were crushed and transferred to a 100ml volumetric flask. Microspheres were dissolved in 10ml of ethanol and

final volume was made to 100ml with 0.1N HCl. Mi x-ture was then sonicated for about 1hr. Obtained solution was then filtered through whatmann filter paper and diluted appropriately. Resultant solution was analyzed spectrophotometrically to determine the amount of drug entrapped. The amount of drug entrapped in the microspheres was calculated by the following formula:

$$\%\ Drug\ entrapment\ efficacy = \frac{Experimental\ Drug\ content}{Theoratical\ Drug\ content} \times 100$$

Drug and Excipient Compatability studies

Compatibility between the drug and polymers was determined using FT-IR spectrophotometer (Bruker, Germany). Drug was placed on the yellow crystal made of ZnSe and the spectra were recorded over the wave number range of 400 to 4000cm^{-1}.

***In-vitro* Buoyancy**

Floating microspheres (equivalent to 2 mg of Repaglinide) were dispersed in 100ml of 0.1N hydrochloric acid at 37°C to imitate gastric fluid. The mixture was then stirred at 50 rpm with a paddle for a period of 12hrs. After 12 hrs, layer of buoyant microspheres (Wf) were pippetted out and separated by filtration. At the same time the sinked microspheres (Ws) were also separated. Both the microspheres were dried separately overnight at 40°C. After drying weight of microspheres were measured separately and buoyancy was determined on the basis of weight ratio of floating and sinked microspheres (Deepa MK, 2009, 69-72).

$$Buoyancy\% = \frac{W_f}{W_f + W_s} \times 100$$

Where W_f and Ws = the weights of the floating and settled microspheres, respectively. All the determinations were made in triplicate.

In vitro drug release study

Dissolution studies of floating microspheres were performed using USP type II dissolution testing apparatus over a period of 12hrs. Dissolution media used for the study was 900ml of 0.1N HCL maintained at a temperature of 37 °± 0.5°C, being agitated at 100rpm. 5 ml samples were drawn periodically at regular intervals and replaced with the fresh medium. Samples were diluted appropriately and analyzed spectrophotometrically using UV spectrophotometer at respective wavelength.

RESULTS AND DISCUSSION

Particle size determination

Mean particle size of microspheres increased with increasing polymer concentrations. This might be due to the significant increase in the viscosity of polymers which leads to an increased droplet size finally producing higher microsphere size. Microspheres with Sodium alginate as polymer had a size range of 385.15±1.08 µm to 493.24±2.43 µm, microspheres containing HPMC K 100 exhibited a size range between 381.55±2.54 to 477.5±2.15 µm.

Micromeritic properties

Results of micromeritic properties such as bulk density, tapped density, hausner's ratio, angle of repose and carr's index were within standard limits.

Values of tapped density, Carr's index, Hausner's ratio and Angle of repose were found in the range of 0.39±0.018 to 0.50±0.015gm/cm^3, 11.13±0.11 to 18.18±0.03, 1.13±0.02 to 1.22 and 26.02±1.80 to 30.88±2.78 respectively indicating good flow properties.

Percentage Yield

Percentage yield of floating microspheres was performed to determine the polymer effect (sodium alginate and HPMC K 100) on the formulations. Obtained results were found to be in the range of 84.05±0.39 to 97.48±0.57.

Entrapment efficiency

Percentage entrapment efficiency of Repaglinide loaded formulations was in the range of 81.62±1.72 to 95.62±2.07. F5 showed highest entrapment efficiency of 95.62±2.07**.** From the above results, it was clear that as polymer concentration increases, entrapment capability of formulations also increases.

SEM (Scanning Electron Microscope) Studies

Surface morphology of Repaglinide loaded microspheres was examined using SEM (JEOL Ltd.,Japan). Results of SEM reported that microspheres were spherical in structure and smooth in nature.

Drug and Excipient Compatability studies

FT-IR studies were performed using FT-IR spectrophotometer for drug and Repaglinide loaded formulation. Resultant spectra gave information regarding purity and compatibility of drug with polymers. IR spectrum of pure drug was showed that obtained drug was almost equal to that standard drug. In case of drug loaded formulation, characteristic peaks of drug and polymers were at their respective wavelengths, there was no interaction between drug and polymer confirming compatibility between drug and polymers. Thus there was no change in the chemical integrity of Repaglinide.

In-vitro Buoyancy

Purpose of synthesizing floating microspheres is to prolong the gastric residence time of a drug. Buoyancy test was carried to examine the floatability of synthesized microspheres. Prepared microspheres were spread over the surface of 0.1N HCl and the surface of 0.1 N HCL and the part of microspheres that buoyant and settled down as a function of time was determined. In vitro buoyancy of all formulations was in the range of 70.42±1.36 to 95.81±2.11. Amongst all for-

Table 1: Trial and Error formulations

Formulation Code	Sodium alginate (mg)	Sodium bicarbonate(mg)
T1	1000	-
T2	1000	100
T3	1000	200
T4	1000	300
T5	1000	400

Table 2: Formulation of floating Microspheres

Formulation code	Drug (mg)	Sodium alginate (mg)	HPMC K 100 (mg)	Sodium Bicarbonate (mg)	DCM (ml)	Ethanol (ml)
F1	2.0	2.0	-	0.4	0.01	0.01
F2	2.0	4.0	-	0.4	0.01	0.01
F3	2.0	6.0	-	0.4	0.01	0.01
F4	2.0	8.0	-	0.4	0.01	0.01
F5	2.0	2.0	1.0	0.4	0.01	0.01
F6	2.0	2.0	2.0	0.4	0.01	0.01
F7	2.0	2.0	3.0	0.4	0.01	0.01
F8	2.0	2.0	4.0	0.4	0.01	0.01
F9	2.0	2.0	5.0	0.4	0.01	0.01

Table 3: Micrometric properties of floating Microspheres

Formulation Code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hauseners Ratio	Carr's Index	Angle of Repose
F1	0.32±0.010	0.39±0.018	1.21±0.04	11.13±0.11	28.49±1.71
F2	0.35±0.012	0.40±0.015	1.14±0.05	12.5±0.64	27.72±1.89
F3	0.40±0.007	0.47±0.014	1.17±0.03	14.8±0.24	30.88±2.78
F4	0.36±0.014	0.44±0.014	1.22±0.01	18.18±0.33	27.00±1.93
F5	0.41±0.015	0.47±0.015	1.14±0.02	12.76±0.26	26.02±1.80
F6	0.40±0.012	0.48±0.021	1.2±0.01	16.66±0.33	26.56±1.43
F7	0.39±0.018	0.45±0.022	1.15±0.03	13.33±1.5	26.80±1.68
F8	0.41±0.015	0.48±0.027	1.17±0.01	14.5±0.86	27.11±1.59
F9	0.44±0.017	0.50±0.015	1.13±0.02	12±0.35	26.56±1.68

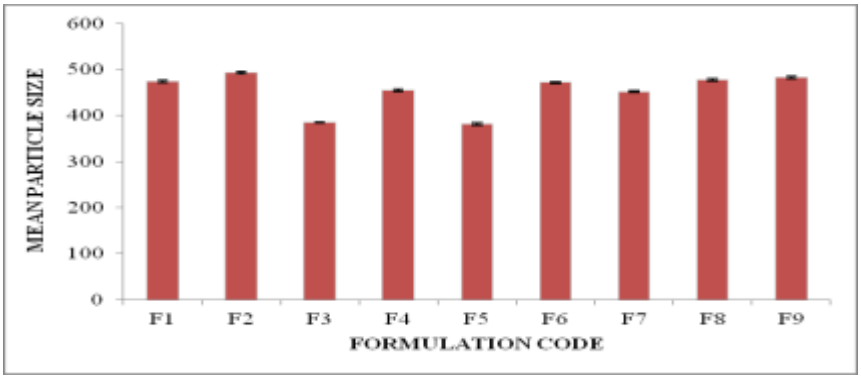

Figure 1: Mean particle size of Repaglinide floatimg microspheres

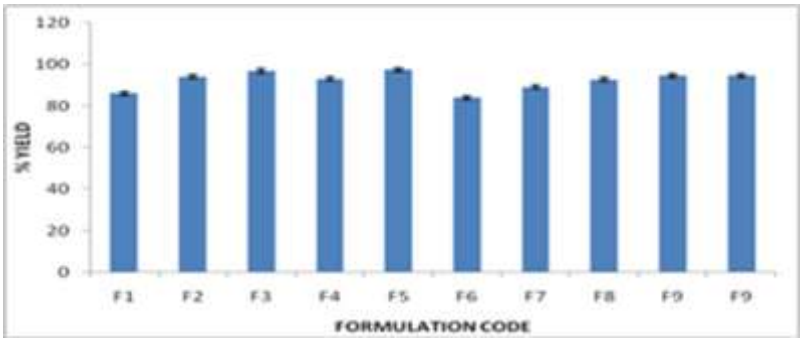

Figure 2: Percentage yield of Repaglinide floatimg microspheres

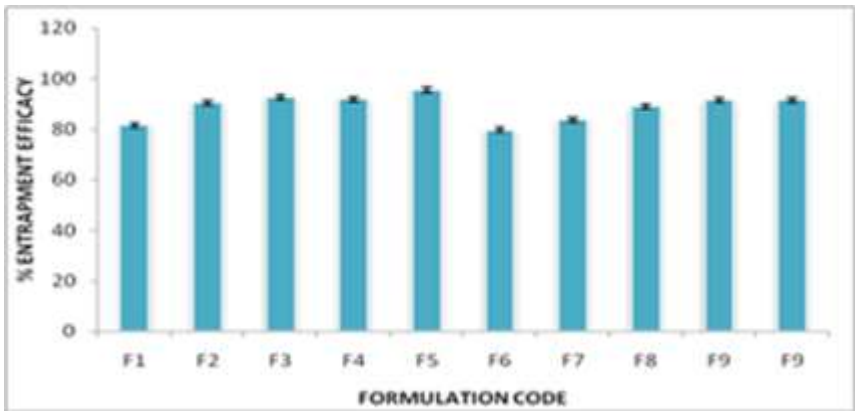

Figure 3: Comparison of drug entrapment efficiency of floating Microspheres of Repaglinide

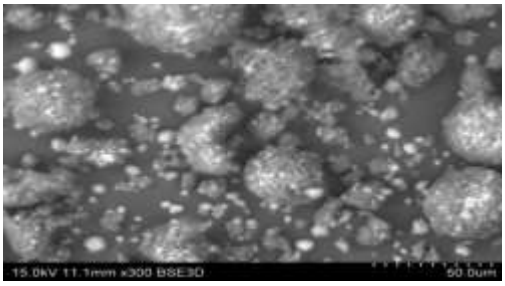

Figure 4: SEM of Repaglinide Floating microsphere

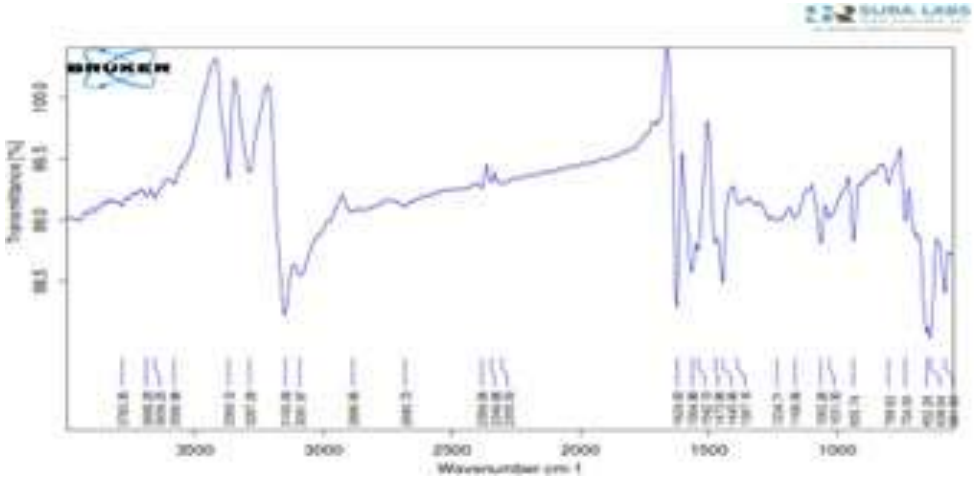

Figure 5: FTIR of Repaglinid

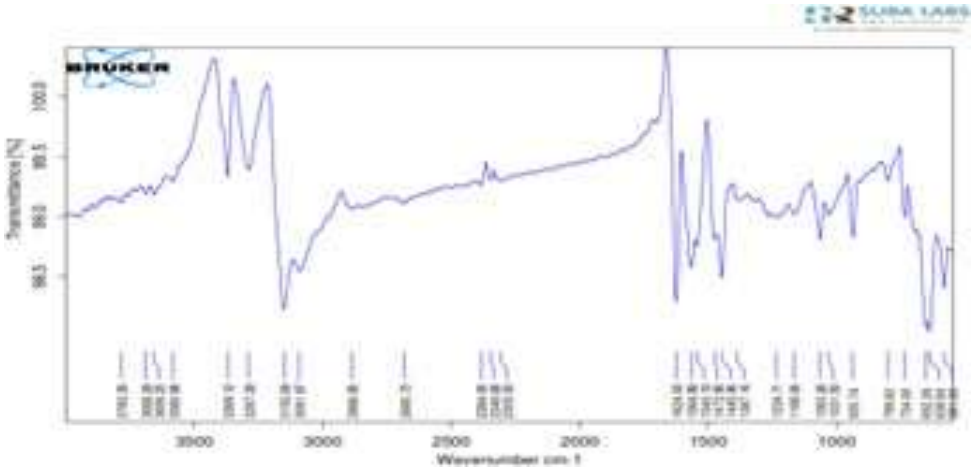

Figure 6: FTIR of Optimized formula

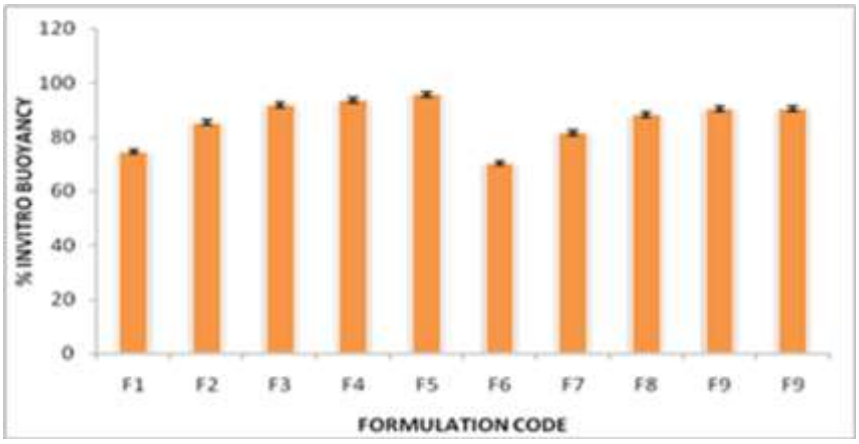

Figure 7: Comparison of in-vitro buoyancy of floating Microspheres of Repaglinide

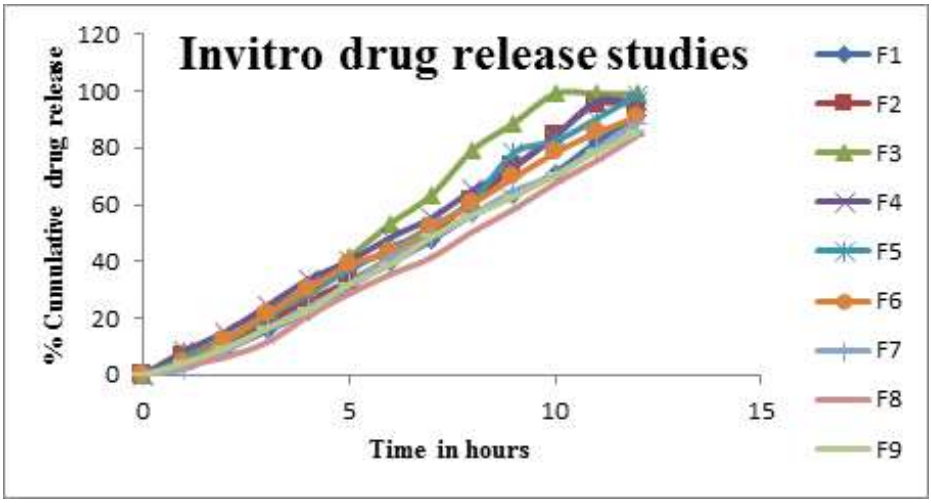

Figure 8: Invitro drug release studies of floating Microspheres of Repaglinide

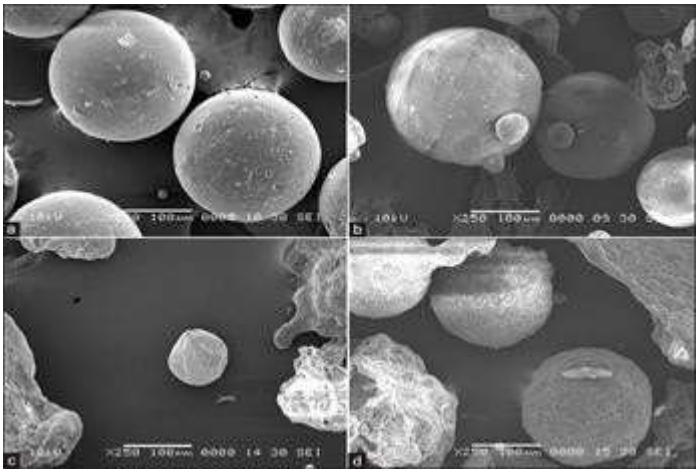

Figure 9: SEM of optimized formulation

mulations F5 exhibited maximum buoyancy. This is due to the fact larger the particle size, longer the floating time.

In vitro drug release study

In-vitro drug release of Repaglinide floating microspheres was performed using UV spectrophotometer. At the end of 12 hrs, drug release values were in the range of 84.32 to 99.19% with formulation F8 exhibiting the least and F3 the maximum drug release from the microspheres.

CONCLUSION

The aim of current study was to formulate and evaluate floating microspheres of Repaglinide by using different concentrations of polymers like HPMC K100 and sodium alginate. From the results of preformulation studies, it was concluded that there was no incompatibility between drug and polymers and microspheres

exhibited good flow properties. From different evaluation studies carried such as particle size analysis, % drug entrapment, floating behavior, in-vitro drug release, F5 was considered an ideal formulation. Drug release kinetics of ideal formulation showed that it followed Korsmeyer-peppas release. SEM studies performed on ideal formulation showed that microspheres were more spherical and smooth in nature. Thus the aim of the study to formulate floating microspheres of Repaglinide was achieved.

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