

Spray-dried gastroretentive floating microparticles: Preparation and *in vitro* evaluation

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Abstract: The full factorial design was employed to evaluate contribution of drug: polymer and Eudragit RS 100: Eudragit RL 100 on entrapment efficiency, time for maximum drug release, percentage of drug release. Floating microparticles were prepared using spray drying technique. Microparticles were evaluated for buoyancy and drug release study using paddle type dissolution apparatus using pH 1.2 buffer as dissolution medium. All the formulations showed good buoyancy with more than 90% microparticles floating for 12hrs. It was found that amount of polymer affected entrapment efficiency ($P < 0.05$). Eudragit RS 100: Eudragit RL100 affected time for maximum drug release ($P < 0.05$). The diffusion coefficient (n) value of the optimized formula was found to be 0.7042 which indicates mechanism of release is anomalous transport. Fourier Transform Infrared Spectroscopy and Differential Scanning Calorimetry studies showed that drug and excipients are compatible. Size of the microparticles ranged from 21-30 μm . Scanning electron microscopy showed that microparticles are spherical and non-aggregated. In this study it was found that spray drying can be used to produce floating microparticles successfully without use of solvents like dichloromethane, which is a class II solvent or aromatic solvents like ethyl acetate.

Keywords: Microparticles, Repaglinide, spray dried.

INTRODUCTION

Oral controlled release systems are developed to deliver drugs to the systemic circulation. Although such systems can control precisely and predictably the drug release rate for extended period of time, even over number of days, they do not always perform satisfactorily if they pass through the drug absorption site before the release of loaded drug is complete. Thus, attention must be given to prolonging the residence time of the system to achieve complete drug release in the gastrointestinal tract (stomach or small intestine) as well as to modulate the drug release rate as predicted by the system in order to obtain an ideal oral controlled release system (Kawashima *et al.*, 2005).

The gastrointestinal transit time is one of the several physiological limitations that must be controlled in the development of peroral sustained release dosage forms. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, and improves solubility for drugs that are less soluble in a high pH environment. It has application for local drug delivery to the stomach and proximal small intestines (El-Kamel *et al.*, 2001). The controlled gastric retention of solid dosage form may be achieved by the mechanisms of mucoadhesion (Arora *et al.*, 2005; Ponchel, 1998),

floatation (Lenaerts, 1990), sedimentation (Deshpande, 1997; Davis, 1986), expansion (Urguhart and Theeuwes, 1994; Kedzierewicz, 2005) modified shape systems (Chien, 1990 and Jain, 2002).

Floating devices administered in a single unit form are unreliable in prolonging the gastroretention time owing to their 'all or none' emptying process and, thus, may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of GIT. While the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation (Esposito *et al.*, 2002).

Repaglinide, a fast and short acting meglitinide analog was chosen as the drug candidate since it is indicated for the development of a dosage form with increased gastroretentive time. It has very short half life, low bioavailability (50%) and poor absorption in the upper intestinal tract (Jain, 2005).

The objective of this study was to formulate and evaluate floating microparticulate drug delivery system containing repaglinide as a model drug using spray drying technique with the application of factorial design by using Design Expert. The advantage of spray drying technique which produces hollow and porous microparticles which float

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well and this technique can be used in large scale production. This technique can be industrialized. The repaglinide microparticles were prepared by using biocompatible polymers -Eudragit RS100 and Eudragit RL 100 while acetone was used as a solvent. The effect of drug: polymer ratio and Eudragit RS100: Eudragit RL100 ratio on drug entrapment efficiency and time for maximum release was studied.

MATERIALS AND METHODS

Materials

Repaglinide was obtained as gift samples from M/s. Torrent pharmaceuticals, Ahmedabad, India. Eudragit RS 100 and Eudragit RL 100 were obtained as gift samples from Degussa Mumbai, India and Medreich limited Bangalore, India. All other chemicals used were of analytical grade.

Formulation

Floating microparticles of repaglinide using Eudragit RS 100 and Eudragit RL 100 polymers were prepared based on the full factorial design. Polymer: drug (factor A) and Eudragit RS 100: Eudragit RL 100 (factor B) was selected as two independent variables. Three levels of variable 'A' and four levels of variable 'B' were selected and 12 possible batches were prepared (table 1).

Preparation of floating microspheres

The floating microspheres were prepared using a Labultima LU-222 spray dryer. The experimental parameters of the process were set as follows: Inlet Temperature: 75°C, Feed pump speed: 120 ml/hr, aspirator setting: 30. A nozzle: 0.7µm was used throughout the experiments.

Repaglinide containing microparticles were prepared as follows: the organic solution of repaglinide, Eudragit RL100, Eudragit RS100, prepared in various drug: polymer and Eudragit RS100: Eudragit RL 100 ratio at a concentration of 25% was fed at the rate of 120 ml/hr (inlet temperature 75°C) by means of a peristaltic pump and sprayed, through a 0.7µm nozzle, in the drying chamber of the instrument by the means of a flow of heated air aspirated by a pump. The obtained particles were separated in a cyclone separator and settle down into a collector.

Characterization of floating microspheres

Micromeritic properties

The microspheres were characterized by their micromeritic properties, such as particle size, bulk density, tapped density, compressibility index and flow properties. The size was measured using optical microscope, and the mean particle size was calculated by measuring 200-300 particles with the help of calibrated ocular micrometer (Subrahmanyam, 2002). The tapping

method was used to determine the tapped density and percent compressibility index. Bulk density (ρ_b) was measured by tapping method (Martin, 1994).

$$\text{Compressibility index} = \left[\frac{\bar{n}\tau - \bar{n}\beta}{\bar{n}\tau} \right] \times 100$$

ρ_b , bulk density = mass of microsphere/ bulk volume of the microsphere

ρ_t , Tapped density = mass of microspheres/volume of microspheres after tapping

Angle of repose, θ of the microspheres, which measures the resistance to particle flow, was determined by a fixed funnel method.

Buoyancy

Floating microparticles (50 mg) were dispersed in a dissolution apparatus (paddle type) containing 500 ml pH 1.2 buffer. The mixture was stirred at 100 rpm. After 12 hrs, the layer of buoyant particles was separated by filtration and particles in the sinking were separated. Both particles types were dried in oven at 40°C until constant weight. The percentage of floating microparticles was calculated by the following equation:

$$\% \text{ floating microparticles} = \left(\frac{\text{weight of floating microparticles}}{\text{initial weight of floating microparticles}} \right) \times 100$$

Drug content

Floating microparticles equivalent to 5 mg of drug was taken into a 50 ml beaker and the particles were dissolved in 5 ml methanol. The samples were assayed for drug content by UV-Spectrophotometer (1601) at 244.5nm after suitable dilution. No interference was found due to other floating microparticle components at 244.5nm.

Drug entrapment efficiency

Floating microparticles equivalent to 5 mg of drug was taken into 200 ml capacity beaker containing 100 ml pH 1.2 buffer and placed on a magnetic stirrer. The mixture was stirred at 100 RPM. 10 ml of sample was withdrawn at 15 min and analyzed by UV-spectrometry at 244.5 nm this gives the amount of unentrapped. The microparticles were filtered; the filtered microparticles were dissolved in 5 ml of methanol, and assayed for drug content using UV-spectrophotometer at 244.5 nm after suitable dilution. The actual drug content was hence determined. The percentage drug entrapped was calculated as follows:

$$\% \text{ entrapment efficiency} = \left(\frac{\text{actual drug content in microspheres}}{\text{theoretical drug content in microspheres}} \right) \times 100$$

In vitro release studies

The drug release rate from floating microspheres was determined using USP XXII paddle type dissolution apparatus using pH 1.2 buffer as dissolution medium. Stirring was maintained at 100 rev/min and temperature at

Table 1: Formulation, dissolution characteristic and entrapment efficiency of batches in full factorial design

Std	Run	Factor 1 A:A	Factor 2 B:B	Response 1 Entrapment efficiency %	Response 2 Time of max. drug release hrs	Response 3 Max. % of drug release
1	1	9	2	79.619	12	90.765
11	2	6	0.001	60.4317	5	98.319
3	3	3	2	52.29	9	94.285
9	4	3	1.001	48.208	6	86.688
5	5	6	1	77.823	12	81.092
10	6	9	0.001	67.9087	5	96.994
7	7	9	1.001	74.387	9	91.008
12	8	3	0.001	55.0266	4	99.031
8	9	6	1.001	66.089	9	92.119
4	10	9	1	88.742	12	74.894
6	11	3	1	59.282	12	92.205
2	12	6	2	66.098	9	92.119

37°C $\pm$ 0.5°C. The samples were assayed by UV-spectrometry at the wavelength of maximum absorbance 244.5nm. All experiments were carried out in triplicate as mean $\pm$ standard deviation.

Differential scanning Calorimetry (DSC) studies

Individual coils that are heated and cooled at the same rate. Sample and reference containers are heated separately. Platinum resistance thermometers monitor the temperature of the sample and reference holders and electronically maintain the temperature of the two holders constant. Repaglinide alone and mixture of repaglinide with Eudragit polymers in 1:1 ratio were taken. Approximately 3-5 mg sample was weighed into aluminum pans and hermetically sealed. The samples were heated from 40°C to 350°C at a rate of 10°C per minute under nitrogen atmosphere with gas flow rate 100 ml /min. A covered, empty pan was used as a reference. The results obtained from the heating were recorded.

Scanning electron microscopy (SEM)

The surface morphology of the microspheres was examined by scanning electron microscope. The samples were fixed on a brass stub using double-sided tape and then gold coated in vacuum by a sputter coater. The pictures were taken at an excitation voltage of 20 Kvolts JSM-840A Scanning Microscope; Jeol-Japan with JFC-1100E Ion Sputtering Device was used.

Stability studies

Stability studies were carried out as per ICH Guidelines. The microspheres were stored at 40°C $\pm$ 2°C/75% RH $\pm$ 5% RH for 6 months. The formulations were analyzed for appearance, entrapment efficiency and drug content.

RESULTS

The floating microparticles were formulated by spray drying technique forming hollow spherical particles.

Drug-excipient compatibility studies

The drug-excipient interaction study carried out using IR i.e. by KBr pellet method and differential scanning calorimetry, showed no interaction between the drug and excipients.

FT-IR spectroscopy

In the drug-excipient interaction study, it was found that repaglinide was compatible with all the excipients used in the formulation. There were no extra peaks observed in the IR spectrum (table 2).

Differential scanning Calorimetry (DSC)

The DSC of the Eudragit RL polymer showed no peaks indicating it is amorphous in nature (fig. 1). The DSC of Eudragit RS 100 showed a peak at 64.8°C, indicating its glass transition temperature. The DSC of the pure drug shows two endothermic peaks. The peak at 134.2°C indicates its melting point and the other peak at 274.94°C may be the degradation peak.

Design of experiment, formulation and development

A multiparticulate floating drug delivery system was developed using Eudragit RS 100 and Eudragit RL100 as polymers, using full factorial design. Drug: polymer (A) and Eudragit RS Eudragit RL100 (B) was selected as two independent variables.

Kinetic mechanism (curve fitting)

Data were analyzed by Korsmeyer and Peppas equation. The diffusion coefficient (n) was found to be 0.7042 and K value 0.1740 for the optimized formulation.

Optical microscopy studies

The particle size was found to be in range of 20-30 μ m.

The response evaluated were % entrapment efficiency, time for maximum drug release, %drug release. Process parameters for producing the hollow microspheres were found to be as follows: inlet temperature at 85° C, outlet

temperature 50° C, flow rate 120 ml/hr and aspirator from initial trials.

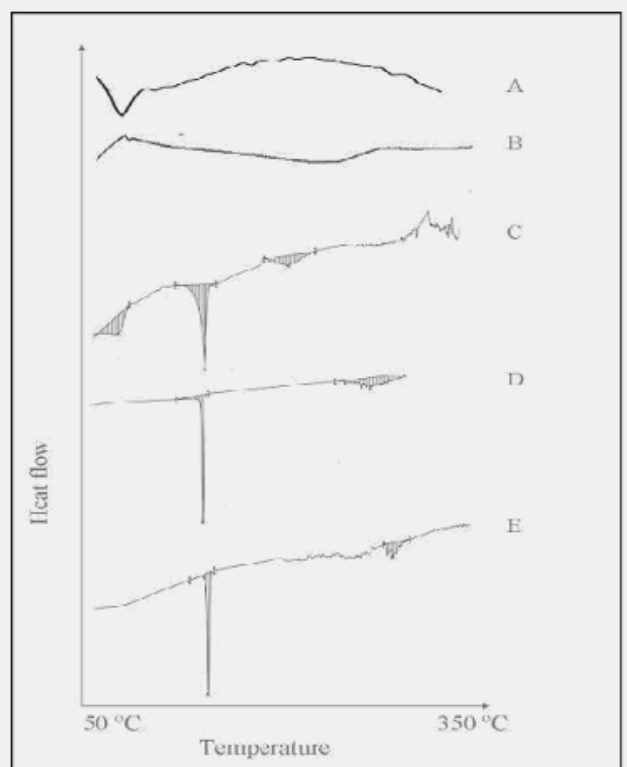


Fig. 1: DSC thermograms of Eudragit RS100 (A), Eudragit RL100 (B), Repaglinide and Eudragit RS100(C), Repaglinide and Eudragit RL100 (D), Repaglinide (E).

Scanning electron microscopy

The SEM studies reveal that microparticles were spherical in shape and were non aggregated (fig. 2).

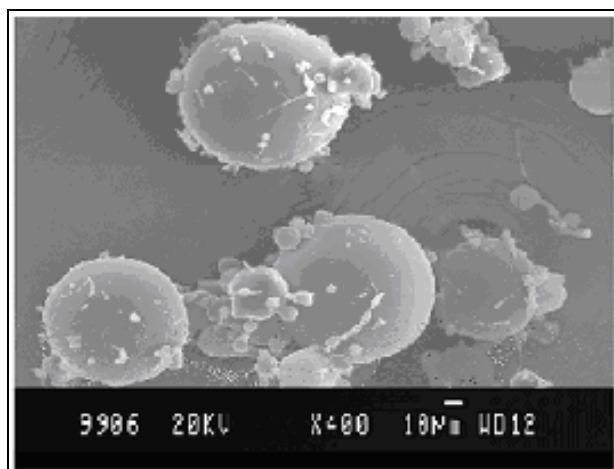
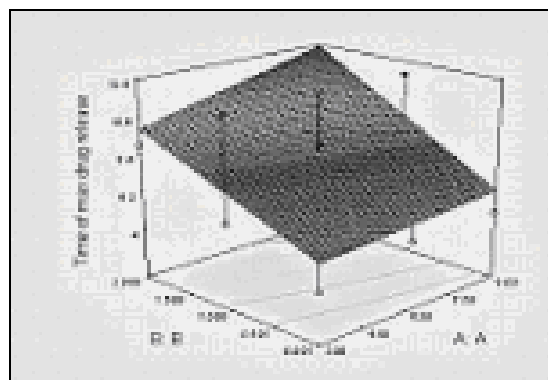


Fig. 2: SEM of microspheres containing the repaglinide.

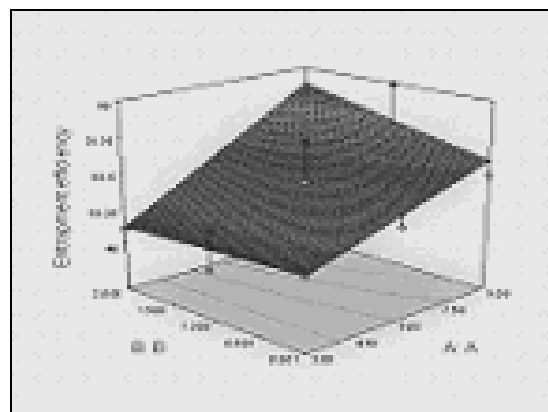
Flow property

The high Hausner ratio which measures the interparticulate friction indicates greater cohesion between particles. High Carr index and angle of repose

reveals that the spray-dried microparticles are likely to have poor flowability. This is mainly due to their small particle size and high interparticulate cohesiveness (table 3).



(A)



(B)

Fig. 3: Response surface plots showing the effect of polymers on response A) entrapment efficiency and B) time of max drug release.

Buoyancy

More than 90% of the microspheres remained buoyant for 12 hrs in all the formulations due to hollow nature of the microspheres (table 3).

Optimization

The factors selected were drug: polymer ratio (A) and RS: RL ratio (B). The responses taken were %drug entrapment efficiency, time for maximum drug release, % drug release. In the linear model equation, the positive sign of coefficient indicates a synergistic effect while a negative term indicates an antagonistic effect on the response. The largest coefficient means the factor has more potent influence on the response. The optimized formulation was prepared and the formulation was evaluated for the various responses. Optimized formula is drug 5 mg, Eudragit RS- 42. 5 mg and Eudragit RL- 2.5 mg.

Table 2: FTIR studies of repaglinide alone and with excipients

Interpretation	IR absorption band of pure repaglinide (cm ⁻¹)	IR absorption band of repaglinide with other excipients (cm ⁻¹)		
		Eudragit RL100	Eudragit RS100	Formulation
C=O stretch (2° amide)	1636.33	1636.39	1636.28	1636.36
C=O stretch(aromatic acid)	1687.43	1688.08	1687.88	1687.71
C-Ostretch(ethoxy)	1039.77	1039.53	1039.20	1039.67
C=C ring stretch	1491.25-1454	1491.22-1447.57	1490-1447.93	1491.49-1447.17
C-H stretch (alkyl gp)	2985-2866.70	2984.57-2866.96	2984.71-2867.06	2984-2867.21

Table 3: Micromeritic and buoyancy properties of the formulations of the floating microparticles

Micromeritic properties	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Angle of repose(°)	40.4	41.8	40.6	38.5	40.2	39.9	40.5	39.2	37.8	39.5	39.7	39.9
Bulk ensity(g/cm ³)												
Before tapping	0.42	0.47	0.42	0.45	0.40	0.41	0.40	0.41	0.45	0.44	0.45	0.42
After tapping	0.58	0.65	0.59	0.62	0.59	0.62	0.59	0.55	0.67	0.69	0.58	0.56
Compressibility (%)	27.58	27.69	28.81	27.41	27.11	33.87	32.20	25.45	32.85	36.23	22.41	25
Hausner ratio	1.38	1.38	1.40	1.37	1.37	1.51	1.47	1.34	1.48	1.56	1.28	1.33
Wf/Wit*100	94.37	91.73	89.53	90.87	93.50	91.68	88.98	92.86	91.58	90.64	90.46	89.64

Entrapment efficiency (EE)

The Model F-value of 8.67 implies the model is significant. Values of "Prob > F" less than 0.0500 indicate model terms are significant. The factorial equation for entrapment efficiency is given below:

Entrapment efficiency =

$$66.33+11.98*A+2.44*B+3.61*A*B$$

As the total amount of polymer increased the entrapment efficiency is increased as indicated by the response surface graph (fig. 3).

The entrapment efficiency of the microparticle ranged from 59% – 89%.

Time for maximum drug release

The factorial equation for time of maximum drug release is given below:

Time of maximum drug release =

$$5.25009+0.12471*A+1.66575*B+0.16688*A*B$$

The controlled release was achieved for 12 hours. (fig. 3)

Maximum percentage drug release

The factorial equation for maximum drug release is given below:

$$\text{Maximum \% of drug release} = 9.079-2.32*A -2.86*B-0.37*A*B$$

The drug release profiles of all the formulations are given in the fig. 4.

DISCUSSION

Generally, solution of materials which form tough tenacious outer skins on drying will form hollow spherical particles when spray dried. This happens because, after the surface of the particle has dried (due to high heat transfer rates), heat is transmitted to the droplet faster than the diffusion of the moisture from inside to the outside. This generates vapour in the centre of the drop. The material by now is too viscous and the vapour pressure blows the drop into a shell before the shell is finally ruptured and the internal pressure escapes. Sometimes, the particles get blown to form highly porous particles.

The DSC studies showed no shift in the endothermic peaks. Thus the chosen excipients for the formulations were found to be compatible with the active ingredients and having no chemical interaction with the active pharmaceutical ingredient.

Considering the entrapment efficiency, factor A i.e. polymer content was a significant model terms with P value 0.0012. Both the factors have a synergistic effect on entrapment efficiency. The higher entrapment efficiency can be attributed to the fact that the likelihood of a part of the drug being entrapped increases with higher polymer concentration. Entrapment efficiency was higher in case of microspheres prepared from Eudragit RS than those prepared from Eudragit RL. In case of RS/RL mixture, the Entrapment efficiency increased with an increase in the Eudragit RS content. Results indicate that

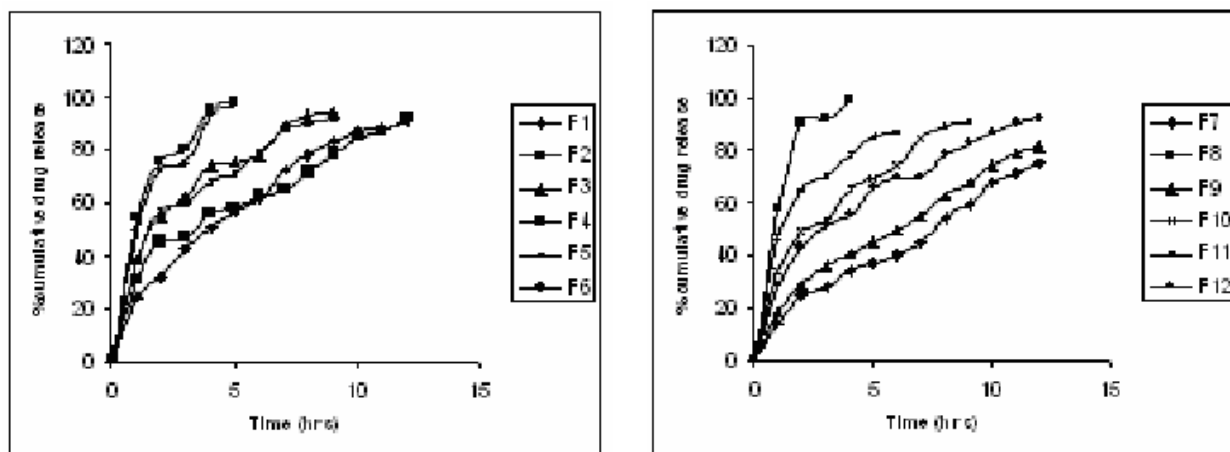


Fig. 4: Dissolution profiles of the formulations.

Eudragit RS is superior to Eudragit RL. When the level of factors 'A' (total polymer content) and 'B' (ERS:ERL) increases the time for maximum drug release also increases which is desirable for an extended release formulation. In this case A and B are significant model terms with P value 0.0322.

The curve fitting results of the release rate profile of the designed formulations gave an idea on the release rate and mechanism of drug release (Paulo Costa, 2001). The diffusion coefficient values indicate that the drug release follows non Fickian transport.

CONCLUSION

In this study it was found that spray drying can be used to produce floating microparticles successfully without the use of solvents like dichloromethane, which is a class II solvent or aromatic solvents like ethyl acetate which are generally used in the preparation of hollow microparticles by solvent diffusion technique.

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