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FORMULATION AND EVALUATION OF FLOATING MICROBALLONS OF REPAGLINIDE

G. Uma Rani*, R. Nagaraju and T. Lakshmi Rao

Department of Pharmaceutics, RBVRR Women's College of Pharmacy, Affiliated to Osmania University, Hyderabad, Telangana.

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***Corresponding Author**
G. Uma Rani
Department of Pharmaceutics, RBVRR Women's College of Pharmacy, Affiliated to Osmania University, Hyderabad, Telangana.
umagandi@gmail.com

ABSTRACT

Novel drug delivery system as a major advance to solving the problems related to the release of the drug at specific site. In recent years, in oral sustained or controlled release multiparticulate drug delivery system extensive research works have been occurs because of its advantages over monolithic dosage form. Now a day's floating concept of multiparticulate reservoir type delivery system more importance. These systems have several advantages over conventional multi dose therapy. There are various approaches in delivering a therapeutic substance to the target site in a sustained release fashion. One such approach is using Microballons as carriers for drugs. Microencapsulation is used to modify and delay drug release from pharmaceutical dosage forms. The present aim of study is to increase the solubility and permeability of drug to control of blood glucose values, Hence Repaglinide is formulated in the form of floating Microballons and inspite of having higher half life it is controlled mainly for inhibiting irregular release pattern of the drug. The model drug for Microballons was taken as repaglinide and the formulation were done with different ratios of polymers Eudragit RLPO and Eudragit RSPO taking Methanol and dichloromethane as solvent system, The best formulation was found to be F12 with eudragit RLPO which showed an entrapment efficiency of 65.87% and drug release of 96.57% for 24 hrs. The formulated Microballons were evaluated for Incorporation efficiency, Surface morphology of Microballons, Particle size analysis, Buoyancy Percentage and In vitro release.

KEYWORDS: Repaglinide, Floating Microballons, solvent evaporation technique, invitro drug release.

INTRODUCTION

Oral sustained release floating multiparticulate drug delivery system include low density floating micro pellets, floating micro beads (acrylic resin based), hollow Microballons (micro balloons) etc. The article published on the development of both effervescent and non-effervescent type of floating drug delivery. Much research has been focused and the scientists are still exploring the field of hollow Microballons.[1]

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus small intestinal transit time is an important parameter for drugs that are incompletely absorbed.

Gastroretensive 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, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

Conventional oral drug administration does not usually provide rate controlled release or target specificity.[1] This dosage form fails to maintain the drug plasma concentration over the extended period of time. This results in frequent administration of a drug with higher dose causing unwanted toxic effects and if they release the entire amount of drug so as to cause dose dumping. Various approaches are made to improve the concentration of drug in the plasma over the extended period of time.

Microballons constitute an important part of the particulate drug delivery systems by virtue of their small size and efficient carrier characteristics. The problem frequently encountered with controlled release dosage forms is the inability to increase the residence time of the dosage form in the stomach and proximal portion of the small intestine due to the rapid

gastrointestinal transit phenomenon of the stomach. Since almost most of the drug entities are mostly absorbed from the upper part of the intestine, therefore it would be beneficial to develop sustained release formulations which remain at the absorption site for an extended period of time.

Oral drug delivery is the most desirable and preferred method of administering therapeutic agent for their systematic effect such as patient acceptance, convenience in administration and cost effective manufacturing process. Thus wide variety of approaches of drug delivery system has been investigated for oral application.

Floating drug delivery system is noted orally applicable drug delivery system for prolongation of gastric emptying time. The bulk density of floating drug delivery system is lower than that of gastric fluid and thus it remains buoyant on stomach content for long time in the drug releasing process. Hence it is useful for obtaining sufficient bioavailability for long time and effective plasma level.[1]

Repaglinide has good absorption in stomach so for this reason it is formulated as gasto retentive drug.

The present aim of study is to increase the solubility and permeability of drug to control of blood glucose values, Hence Repaglinide is formulated in the form of floating Microballons and inspite of having higher half life it is controlled mainly for inhibiting irregular release pattern of the drug.

EXPERIMENTAL

1. MATERIALS

Repaglinide (Allied chemicals and Pharmaceuticals PVT Ltd), Dichlorometane (Hi pure chemicals) Methanol (Hi pure chemials) Ethyl cellulos (Paramount chemical cooperation, Mumbai), Tween 80 (Paramount chemical cooperation, Mumbai), Eudragit RSPo and RLPO grades (Evonik Pharma).

2. Methods

2.1. Formulation Table

Formulaiton code/Chemicals	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)	F7(mg)	F8(mg)	F9(mg)	F10(mg)	F11(mg)	F12 (mg)
Treated Repaglinide	20	20	20	20	20	20	20	20	20	20	20	20
Eudragit RSPO	5	7.5	10	12.5	15	17.5						
Eudragit RLPO							5	7.5	10	12.5	15	17.5
Sodium CMC	5	5	5	5	5	5	5	5	5	5	5	5

2.2. Procedure

Firstly the drug was dissolved in calcium silicate in organic solvent and then it is dried completely in a desiccator.

Floating Microballons of Repaglinide were prepared by solvent evaporation technique. The drug and the polymer in required ratio were dissolved in organic solvent of ethanol and dichloromethane at room temperature. The solution was introduced using microsyringe in 250 ml water containing 0.2% tween 80 as surfactant at 80 degrees. It was stirred at 1000 rpm using a 3 bladded propeller for 2 hrs.

The solvent was evaporated and the micsrospheres were filtered and dried in a desiccator.

2.3. Evaluation procedures

2.3.1. Construction of Calibration curve for Repaglinidesodium

Calibration curve of Repaglinide was constructed by preparing a stock solution of 100mg of drug in 100 ml of o.1N Hcl. From this 1 ml was diluted to 100 ml with 0.1N HCl. From the secondary stock samples of concentratons 2,4,6,8,10 were removed and were tested in a uv-Visible spectrophotometer at 291 nm.

2.3.2. Bulk density (D_b)

It is the ratio of total mass of Microballons to the bulk volume of Microballons. It was measured by pouring the weighed Microballons (passed through standard sieve # 20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It expressed in g/cc and is given by:

$$D_b = \frac{M}{V_0}$$

Where, M is the mass of Microballons, V_0 is the bulk volume of the Microballons.

2.3.3. Tapped density (D_t)

It is the ratio of total mass of Microballons to the tapped volume of Microballons. The volume was measured by tapping the Microballons for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2 %). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. It is expressed in g/cc and is given by:

$$D_t = \frac{M}{V_1}$$

Where, M is the mass of Microballons, V_t is the tapped volume of the Microballons.

2.3.4. Carr's index (%)

The bulk density is the measurement of weight to the volume of the sample. Tapped density is determined as the measurement of weight of the sample to the volume after tapping the measuring cylinder for 500 times from a height of 2 inches. The percentage compressibility (Carr's index) was calculated as 100 times the ratio of the difference between tapped density and bulk density to the tapped density.

$$\text{Carr's index} = 100 \times \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

2.3.5. Hausner's ratio

Hausner's ratio is the ratio of tapped density to bulk density. Lower the value of Hausner's ratio better is the flow property. The Microballons with Hausner's ratio less than 1.18, 1.19-1.25, 1.3-1.5 and greater than 1.5 indicates excellent, good, passable and very poor flow properties, respectively.

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

2.3.6. Angle of repose (θ)

It is defined as the maximum angle possible between the surface of a pile of Microballons and the horizontal plane.

$$\tan\theta = \tan^{-1} (h/r)$$

Where, θ is the angle of repose

h is the height in cms

r is the radius in cms

Method

The Microballons mixture was allowed to flow through the funnel with its tip fixed to stand at a definite height (h) from a graph paper placed on a horizontal surface. The angle of repose was then calculated by measuring the height and radius of the heap of Microballons formed. A value for angle of repose ≥ 40^o suggests a poorly flowing material.

2.3.7. In vitro evaluation of floating ability

Floating behavior of hollow Microballons was studied using a USP dissolution test apparatus II by spreading the Microballons (50 mg) on 900 ml of 0.1 N HCl containing 0.02% Tween 80 as surfactant. The medium was agitated with a paddle rotating at 100 rpm and maintained at 37°C.

After 10 hours, both the floating and the settled portions of Microballons were collected separately. The Microballons were dried and weighed. The percentage of floating Microballons was calculated using the following equation:

$$\% \text{ Floating Microballons} = \frac{\text{Weight of Floating Microballons}}{\text{Total weight of Microballons}} X\ 100$$

2.3.8. Percentage yield of Microballons

Percentage yield of Microballons was calculated using the following formula-

$$\text{Percent Yield} = \frac{\text{The amount of Microballons obtained}}{\text{The amount (g) of Non-volatile material taken.}} X\ 100$$

2.3.9. % Entrapment efficiency

Accurately weighed 10 mg of crushed Microballons were dissolved in 0.1N HCl and then transferred to 100 ml volumetric flask. The volume was made up to 100mL with 0.1N HCl.

The solution was filtered using Whatman filter paper no. 41. The samples were assayed for drug content using UV spectrophotometry at 270 nm.

Entrapment efficiency of Microballons were calculated using the following formula-

$$\text{Entrapment Efficiency} = \frac{\text{The amount of Drug Encapsulated.}}{\text{Theoretical amount of Drug.}} \times 100$$

2.3.10. In Vitro Drug Release Studies

In vitro drug release studies were carried out using the rotating basket method specified in USPXXIII dissolution apparatus (Apparatus I) with 100 rpm speed at 37 ± 0.50C). Dissolution wascarried out in 0.1 N HCl. The weighed amount of Microballons were wrapped in Filled in a capsuleand kept in baskets. The drug release studies were carried out in 900 ml of 0.1N HCl dissolution media. 5 ml Samples were withdrawn at predetermined time interval (1 h) from eachdissolution vessel, filtered using Whatman filter paper, samples were analyzed for drug at nm using a UV visible double beam spectrophotometer (Model-UV1701, Shimadzu, Japan) at 291 nm.

3. RESULTS AND DISCUSSIONS

3.1Calibration Curve For Repaglinide

Table 1: calibration plot for Repaglinide

S.no	Concentration(µg/ml)	Absorbance(nm)
1.	2	0.12
2.	4	0.24
3.	6	0.38
4.	8	0.51
5.	10	0.624

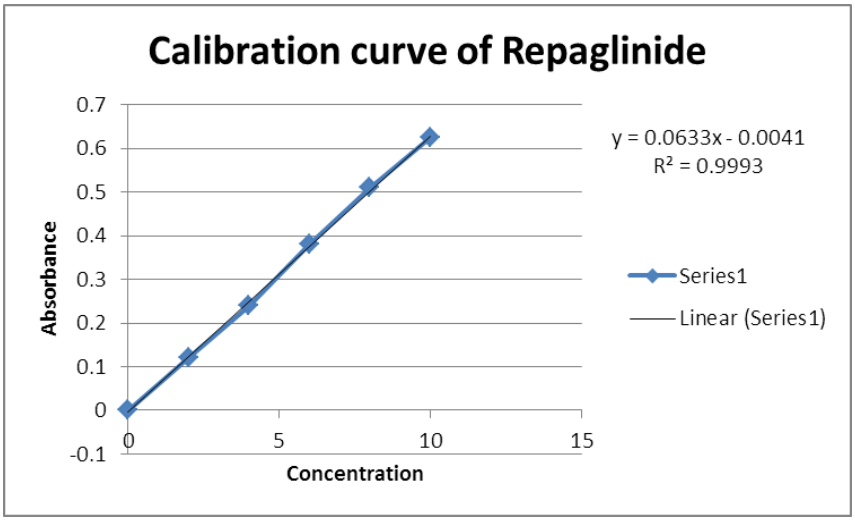

Fig 1: Calibration curve for Repaglinide

DISCUSSION

The λ max of Repaglinide in 0.1N Hcl buffer was scanned and found to have the maximum absorbance at 291 nm. Standard graph of Repaglinide in 0.1N Hcl buffer was plotted. The concentrations of 2,4,6,8,10 µg/ml were taken respectively and the absorbance was plotted. the calibration plot showed a regression value of 0.9993.

Table 2: Evaluation Tests for Repaglinide Microballons

Formulation code/ingredients	Bulk density	Tapped density	Angle of repose	Compressibility index	Carrs index	Particle size(µm)
F1	0.46	0.53	24.38	13.20	1.15	268.24
F2	0.43	0.49	23.72	12.24	1.14	245.28
F3	0.41	0.47	21.94	12.76	1.14	231.47
F4	0.39	0.44	20.48	11.36	1.12	263.54
F5	0.47	0.54	22.68	12.96	1.15	257.63
F6	0.46	0.53	21.82	13.20	1.15	278.96
F7	0.462	0.591	26.06	21.8	1.25	219.34
F8	0.469	0.561	25.42	21.39	1.19	268.25
F9	0.475	0.565	23.45	16.03	1.19	214.02
F10	0.469	0.561	27.4	16.39	1.19	263.78
F11	0.39	0.44	29.48	11.36	1.12	214.93
F12	0.46	0.55	26.62	16.36	1.19	218.62

Table 3: Percentage yield and buoyancy test of Repaglinide Microballons

Formulation code/ingredients	Theoritical drug loading	%yield	Actual drug yield	Buoyancy test
F1	600	67.52	405	79.26
F2	500	60.45	302	79.68
F3	650	80.76	525	83.54
F4	700	76.57	536	72.63
F5	600	70.83	425	76.97
F6	600	80.00	480	83.42
F7	700	68.57	480	86.71
F8	500	66.82	334	74.39
F9	650	67.38	438	88.49
F10	550	78.18	430	88.98
F11	700	75.71	530	8264
F12	800	66.87	535	88.17

Table 4: Entrapment efficiency of Repaglinide Microballons

Formulaiton code	Amount of drug present	Theoritically loaded drug	% entrapment effeciency
F1	23.65	40	59.12
F2	22.47	40	56.17
F3	21.63	40	54.07

F4	20.57	40	51.42
F5	24.69	40	61.72
F6	25.71	40	64.27
F7	21.24	40	53.10
F8	26.57	40	66.42
F9	23.54	40	58.85
F10	24.78	40	61.95
F11	25.26	40	63.15
F12	26.35	40	65.87

Table 5: Invitro drug release studies of Repaglinide Floating Microballons

Formulation code/Parameter	F1(%)	F2(%)	F3(%)	F4(%)	F5(%)	F6(%)	F7(%)	F8(%)	F9(%)	F10(%)	F11(%)	F12(%)
1 hr	83.24	52.26	48.64	45.34	37.18	30.52	52.63	47.64	48.26	31.24	28.26	16.24
2 hr	98.63	75.63	62.63	56.34	46.45	33.47	83.46	63.63	57.36	48.36	32.45	24.26
4 hr		92.54	83.64	73.54	53.67	41.53	98.25	79.64	76.24	57.75	39.64	35.98
6 hr			96.54	90.41	67.57	45.34		98.36	92.98	64.89	46.72	45.71
8 hr				98.63	78.71	56.44			97.24	68.62	51.69	53.98
10 hr					86.34	63.56				76.18	57.25	59.87
12 hr					97.78	72.24				82.34	67.64	66.34
14 hr						82.56				88.78	76.91	71.25
16 hr						92.47				91.63	84.24	76.28
18 hr						97.63				97.68	92.54	81.59
20 hr											98.69	87.29
22 hr												91.25
24 hr												96.57

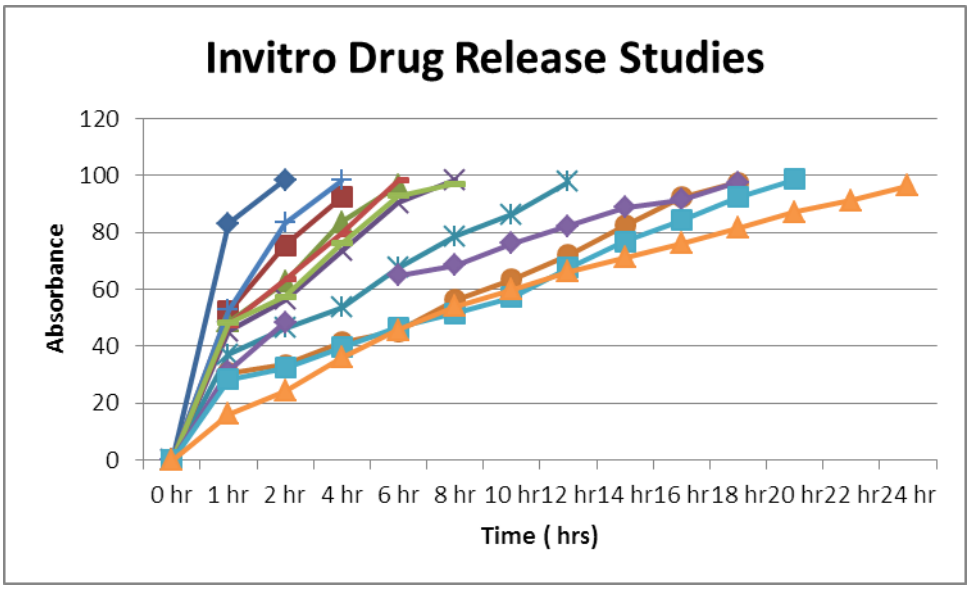

Fig 2: Invitro drug release kinetics of Repaglinide floating Microballons

DISCUSSION

The Bulk density and tapped density of the Microballons were found to be 0.41 to 0.69 and 0.44 to 0.56 respectively.

The angle of repose values obtained for the Microballons ranged from 20.48 to 29.48 This indicates good flow property of the Microballons.

The compressibility index values for the Microballons ranged from 11.36 to 21.39 This indicates the Microballons have good flow property.

The cars index values for the Microballons ranged from 1.12 to 1.19 This indicates the Microballons have good flow property. The particle size values of the Microballons were found to be in the range between 214.93 to 278.96 µm which were found to within the limits The % yield of the Microballons were found to be satisfactory of all the 12 formulations with values ranging from 66.87 to 80.76.

The % ent rapment efficiency of the Microballons were found to be 51.12 to 66.42% showing less wastage of the drug. The boyency test values for all the 10 formulations ranged from 72.63 to 88.98 showing satisfactory gastro retentive time.

In vitro drug release profiles for all Microballons were carried out by using 0.1N Hcl buffer as dissolution medium for about 24 hrs.

From the above results it was found that the release of drug from F12 formulation with Eudragit RLPO and sodium CMCin the concentration of 3:1 gave the better release than other Microballons. When the amount of Eudragit RLPO is increased the drug release decreased which was showed in Fig 2.

CONCLUSION

Repaglinide is a choice of drug for diabetes. **Repaglinide** is an antidiabetic drug in the class of medications known as meglitinides. Repaglinide is an oral medication used in addition to diet and exercise for blood sugar control in type 2 diabetes mellitus.[1] The mechanism of action of repaglinide involves promoting insulin release from β-islet cells of the pancreas; The concept of formulating and evaluating Floating microsphers that it offers a suitable and practical approach in serving desired objective of prolonged action for Diabetes activity exhibiting good absorption of the drug of the Different batches of formulations were prepared increasing the concentrations of polymers eudragit RLPO and Eudragit RSPO in combinaion with sodium CMC.

A controlled release Gastro retentive Microballons formulated were evaluated for Bulk density, Tapped density, Invitroboyencytest, Angle of repose, Compresibility index, carrs index % yield, Encapsulationeffeciency, % entrapment efficiency and invitro drug release studies.

Among the ten formulations of Repaglinide The formulation F12 with the highest concentration Eudragit RLPO and Sodium CMC showed the best results when compared to the others. The F12 with % entrapment efficiency of 65.87% and % floating of 88.17% and 96.17% drug release for 24 hrs was found to be the best formulation. As the viscocity of the polymers increased and the concentration of polymers increased there was a decrease in the drug release and control in the release pattern which IR-spectroscopic studies indicated that there are no drug–excipient interactions.

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