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Research Article

FORMULATION AND DEVELOPMENT OF NOVEL GASTRORETENTIVE MICROBALLOONS OF REPAGLINIDE

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ABSTRACT

The present study involves preparation and evaluation of Microballoons of Repaglinide which is having poor solubility in water and low oral bioavailability. Repaglinide, an oral hypoglycemic agent, is rapidly absorbed and eliminated from the body after oral administration. The peak plasma level occurs within an hour of oral administration with elimination half life of 1 hr. The objective of the present work is to prepare floating microballoons of Repaglinide for delivering the drug in controlled manner which will help to reduce dosing frequency and maintain the plasma concentration of drug for longer time without fluctuations. This will be helpful in having better control over clinical maintenance of the type 2 diabetic condition. The Microballoons were prepared by solvent evaporation emulsification technique using Sodium Alginate as coating agent and Calcium Chloride as cross-linking agent. The formation of spherical and hollow Microballoons was confirmed by SEM studies ranging from 220 to 310 µm. The percentage of drug entrapment was found to be 70-80%. The Micromeritic properties indicated better flowability of the spheres. The Buoyancy test showed good floatability for more than 12 hrs. Formulation B5, C5 and D3 showed higher buoyant percentage after 12 hours and percentage yield. Microballoons of Repaglinide were designed to increase the Solubility, Bioavliability and to improve the patient compliance. The microballoons with the smaller particle size enhanced the *in vitro* drug release of the Repaglinide. Thus, microballoons approach may be a promising carrier for Repaglinide and other BCS class II drugs.

Keywords: Floating Microballoons, Sodium alginate, Hydroxy Propyl Methyl Cellulose, Ethyl Cellulose, Repaglinide.

1. INTRODUCTION

Microballoons (Hollow microsphere) are drug delivery system that promises to be a potential approach for gastric retention. Microballoons are based on non-effervescent system containing empty particles of spherical shape without core. Microballoons drug delivery systems have shown to be of better significance in controlling release rate for drugs having site specific absorption. The floating microballoons showed gastro retentive controlled release delivery with efficient means of enhancing the bioavailability and promises to be a potential approach for gastric retention. Optimized hollow microballoons will find the central place in novel drug delivery, particularly in safe, targeted and effective *in-vivo* delivery promises to be a potential approach for gastric retention [1, 2].

Oral dosage forms face several restrictions like inability to retain the dose in GIT (Gastro Intestinal Track) due to fluctuation in gastric emptying which will lead to non-uniform absorption, inadequate medication & shorter residence time of dosage form in stomach these complications provoked to the development of control release dosage form with gastroretentive properties which lead to formulation of microballoons with low density, sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period of time. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma dug concentration [3]. Microballoons hold potential approach for gastric retention due to significant increase in gastric residence time, enhancement in bioavailability of BCS Class II Drugs e.g., Repaglinide, Glibenclamide, Glibornuride, Gliclazide, Glipizide, Gliquidone, Glisoxepide and Glyclopyramide, improve patient compliance by reducing

dosing frequency, enhance retention of medication which solubilize only in stomach, enhance solubility for drugs which are less soluble at higher pH [4].

Limitations of the Conventional Drug Delivery System such as Drugs with short half-life, require frequent administration, which increases chances of missing the dose of drug leading to poor patient compliance. The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication. The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overdosing occurs. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. In order to overcome the drawbacks of these conventional drug delivery systems, Microballoons is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste and improves the drug availability that are less soluble in a high pH environment as well as patient compliance and flexibility in formulation.

2. MATERIAL AND METHODS

Repaglinide was available as Gift Sample in College laboratory of Dr. Vithalrao Vikhe Patil Foundation's College of Pharmacy, Hydroxy propyl methyl cellulose K4M and Hydroxy propyl methyl cellulose K15M was purchased from Ranbaxy Fine chemicals, Mumbai. All other chemicals used were of analytical grade.

2.1. Preformulation Studies

2.1.1. Organoleptic properties [9]

Drug was characterized for its color; odor and taste. Results were reported utilizing descriptive terminology.

2.1.2. Melting Point Determination [10]

Melting point of Repaglinide was determined by taking a small amount of drug in a capillary tube closed at one end and was placed in melting point apparatus and temperature range at which the drug melts was noted and compared with reference value.

2.1.3. Fourier Transform Infra-Red (FTIR) analysis [11]

The FTIR study of pure drug sample was carried out using FTIR Spectrophotometer. The pure drug was mixed with IR grade KBr. This mixture was then scanned over a wave number range of 4000 to 400 cm^{-1}. The FTIR spectra of drug were compared with reference reported values.

2.1.4. Differential Scanning Calorimetry (DSC) [9]

DSC scans were recorded by using Differential scanning calorimeter. Samples weighing 5 mg were sealed in aluminum pans and heated to 200°C at rate 10°C/min. The equipment was calibrated using indium. Samples were heated from 40 to 200°C. If required, it was cooled to -10°C and then heating was continued to 200°C.

2.1.5. Determination of λ_{max}

Accurately weighed 10mg of Repaglinide was dissolved in 100ml of 0.1 N HCl and scanned on UV spectrophotometer between 200 to 400 nm to determine λ_{max}

2.1.5.1. Stock solution

An accurately weighed Repaglinide (10 mg) was dissolved in 0.1N HCl and then diluted to 100 mL, resulting in concentration 100 µg/mL. This was used to prepare working standards.

2.1.5.2. Working standards

From the stock solution (100µg/ml), different concentrations (2, 4, 6, 8, 10, 12, 16, 20µg/ml) were prepared by diluting appropriate volumes of stock solutions to 100ml with 0.1 N HCl. The absorbance was measured at 243 nm. A calibration curve was plotted for concentration against absorbance.

2.1.6. Solubility determination [9, 10]

The solubility of Repaglinide was determined in triplicate using saturation solubility method. Excess amount of drugs were added to 10ml of distilled water, phosphate buffer pH 6.8 and 0.1N HCl separately in glass vials. The content of vials was mixed vigorously for 30 minutes and further solutions were shaken mechanically to equilibrate. After 72 hours, content of each vial was centrifuged for 10 minutes at 2500 rpm. The supernatant of each vial was filtered through 0.45µ membrane filter and then filtrate was diluted suitably with solvent separately. The concentration of Repaglinide was analyzed by double beam UV visible spectrophotometer at 243 nm respectively against blank [16].

2.2. Drug Excipient Compatibility Study [10, 11]

2.2.1. Selection of method for the preparation of microballoons

Based on literature survey, primary research data available and primary trial batches prepared to check feasibility of method; solvent evaporation emulsification method was selected to prepare micro balloons of Repaglinide.

2.2.2. Selection of Polymers for the preparation of microballoons [12]

Based on literature survey, primary research data available on drug excipients compatibility and research objectives, following polymers are selected for preparation of batches of micro balloons.

- Sodium alginate (SA)
- Ethyl cellulose (EC)
- Methocel K15M
- Methocel K4M

Compatibility of drug with different polymers was studied by physical observation. Using a glass mortar, 10 mg of drug was mixed with different polymers and was triturated for 15 minutes separately. The mixture was packed in closed vials using butter paper and placed in accelerated environmental conditions (40°C/75% RH). Any physical change was observed visually after every week for 4 weeks.

2.3. FTIR Analysis [11]

FTIR spectrum of Repaglinide, Ethyl Cellulose, HPMC and physical mixture of drug with polymers were separately recorded using FTIR spectrophotometer to study any possible interaction between drug and polymer. Sample, about 5 mg, was mixed with 100 mg of Potassium bromide (KBr) and compressed to form pellets. The spectra of sample were scanned between wave number 400 to 4000 $cm^{-1}$and were analyzed for possible interaction.

2.4. Preparation of Microballoons [13, 14]

2.4.1. Optimization of Repaglinide: Sodium Alginate Ratio and stirring speed

Microballoons of Repaglinide were prepared by ionotropic gelation using sodium alginate as coating agent and calcium chloride as cross-linking agent. Sodium alginate and Repaglinide were dispersed in water (25 ml) at room temperature. Separately 100 mL of blend (50:50) of liquid paraffin (heavy and light) was placed in silicone treated round bottom flask. Sodium Alginate-Repaglinide dispersion was poured in liquid paraffin and stirred for 15 min, to it 50 mL of 4% calcium chloride solution was added slowly and stirring at 1000 rpm was continued for 20 min. Solidified Microballoons were filtered, washed for several times with petroleum ether to remove traces of oil and dried under vacuum. Microballoons thus obtained were dried further for 24 hrs. Then Sodium Alginate-Repaglinide ratio was altered from batch A1 to A5. Drug to polymer ratio was optimized to 1:6. Four batches (1-4) were prepared with constant concentration of cross linking agent (CLA) and cross linking time (CLT) with varying stirring speed 1000, 2000, 3000 and 4000. Stirring speed is optimized to 2000 rpm.

Table 1: Optimization of Sodium Alginate Ratio and stirring speed

Formulation Code	Drug (mg)	Sodium Alginate (mg)	Volume of CLA (4% w/v $CaCl_2$) ml	Batch	Stirring speed (RPM)
A1	100	200	100	1	1000
A2	100	400	100	2	2000
A3	100	600	100	3	3000
A4	100	800	100	4	4000
A5	100	1000	100		

**for all batches drug:polymer ratio kept constant - 1:6.*

2.5. Evaluation of Trial Batches of Micro-balloons Formulation [15, 16]

2.5.1. Drug loading and entrapment efficiency

Fifty mg of microballoons were weighed accurately and crushed in a glass mortar and pestle. Powdered microballoons were suspended in 10 mL of ethanol for 24 hrs. After 24hrs, the solution was filtered and volume was made to 50 mL with 0.1 N HCl. Filtrate was analyzed for drug content at 243 nm. Corresponding drug concentrations in samples were calculated from calibration plot generated by regression of data.

Drug loading and entrapment efficiency was calculated using following equations:

Drug loading = (Weight of repaglinide in microballoons /weight of micro particles) x 100

Entrapment efficiency = (Weight of repaglinide in microballoons/ Initial weight of Repaglinide) x 100

2.5.2. Preparation of Microballoons with copolymers-HPMC K4M, HPMC K15 M, ethyl cellulose and gas forming agent- $NaHCO_3$

Microballoons were prepared as per the procedure stated above with addition of copolymers as HPMC K4M (B1 to B9), HPMazC K15M (C1 to C9), Ethyl cellulose (D1 to D9) and gas forming agent- $NaHCO_3$. Nine formulations with each copolymer were prepared as per the formula given in Table 2.

2.6. Evaluation of Micromeritic properties of Microballoons [10]

2.6.1. Particle size analysis

The particle size of microballoons was determined by using optical microscopy method. The arithmetic mean diameter of total 300 Microballoons for each sample was calculated by using Edmundson's general equation.

$d_{mean} = \Sigma nd/\Sigma n$

Where "n" stands for the number of counted Microballoons, and "d" for the mean sizerange.

Table 2: Microballoons with HPMC K4M (B1 to B9), HPMC K 15M (C1 to C9), Ethyl cellulose (D1 to D9)

Formulation Code	Drug (mg)	Sodium Alginate (mg)	HPMC K4M (mg)	HPMC K15M (mg)	Ethyl Cellulose (mg)	$NaHCO_3$ (mg)
1	100	600	100 (B1)	100 (C1)	100 (D1)	50
2	100	600	100 (B2)	100 (C2)	100 (D2)	100
3	100	600	100 (B3)	100 (C3)	100 (D3)	150
4	100	600	200 (B4)	200 (C4)	200 (D4)	50
5	100	600	200 (B5)	200 (C5)	200 (D5)	100
6	100	600	200 (B6)	200 (C6)	200 (D6)	150
7	100	600	300 (B7)	300 (C7)	300 (D7)	50
8	100	600	300 (B8)	300(C8)	300 (D8)	100
9	100	600	300 (B9)	300 (C9)	300 (D9)	150

2.6.2. Bulk density

The mass of powder divided by bulk volume is termed as bulk density. Bulk volume is the true volume and it includes the void space among the Microballoons. Accurately weighed 25 g of samples were filled in a 50 graduated cylinder and reported for the unsettled level as bulk volume (Vb). Using the formula given below bulk density is calculated and its unit is g/cm^3.

Bulk Density=M/Vb

Where, M = mass of powder taken (g) and Vb= bulk Volume (cm^3)

2.6.3. Tapped density

The samples were weighed accurately to 25 g and filled in a 50 ml graduated cylinder and reported the tapped volume (Vt). Tapped density tester was used and 100 drops per minute mechanical tapping of the cylinder was done. Constant volume was observed and reported as tapped volume Vt (cm^3). Using the formula given below, tapped density was calculated in g/cm^3.

Tapped Density=M/V

Where, M = mass of powder taken (g) and Vt = tapped volume (cm^3)

2.6.4. Carr's Index or Compressibility index

Carr's index; also called as compressibility index, is an indication of compressibility of powder. The bulk density and tapped density of free-flowing powder is close in value, thus the value of Carr index will also be small. Whereas for poor-flowing powder, difference between two densities is greater due to greater inter-particle interactions thereby, the value of Carr index will also be larger.

Carr's Index= {(Tapped Density-bulk density)/Tapped Density} x 100

2.6.5. Hausner Ratio

Ratio of tapped density to bulk density is also a measure of flow properties and is termed as Hausner ratio.

Hausner Ratio= Tapped Density / Bulk Density

2.6.6. Angle of repose

The maximum angle formed between the surface and the horizontal plane is termed as angle of repose. Fixed funnel method was used to determine the resistance to

particle flow of prepared Microballoons. Funnel height was kept in such a manner that its tip just touches the heap of the blend. On a stand, a glass funnel was placed with the support of ring over a glass plate. With the help of lower thumb, the orifice of the funnel was blocked and an average 100 gm of Microballoons was placed into the funnel. Angle of repose was determined by formula mentioned below from the pile which is formed by flow of particles as the thumb is removed from the orifice.

Tan Θ =h/r

h= height of the pile and r= radius of powder cone

2.6.7. Percentage Yield

The prepared Microballoons of all the batches were accurately weighed. The percentage yield of floating formulations was calculated using following formula:

% Yield=(Actual weight of product/Total weight of drug and polymer) x 100

2.6.8. In-vitro buoyancy study

In-vitro buoyancy was determined by placing 50 mg of formulation in 100 ml of SGF (pH 1.2) containing Tween 20 (0.02 w/v %) stirred at 100 rpm using a magnetic stirrer. Layer of floating Microballoons were separated from the Microballoons which were settled down by filtration after 12 hours. Both the obtained particles were dried and separately weighed. Using the formula given below buoyancy of Microballoons was determined.

Buoyancy (%)= (Wf/W) x 100

Where Wf= weights of the floated Microballoons, W= total weight of Microballoons.

2.6.9. Determination of surface morphology

The microballoons were observed under scanning electron microscope. The Microballoons samples were observed at 20 kV by sprinkling sample on the aluminum stubs having double adhesive tape and subsequent evaporation of gold palladium alloy in the ion sputter unit.

Table 3: Interpretation of various Micromeritic properties

S. No	Carr's Index		Hausner ratio		Angle of repose	
	Carr's Index	% Flow	Hausner ratio	Properties	Angle of repose	Flow ability
1	5-15	Excellent	0-1.2	Free flowing	< 25	Excellent
2	12-16	Good	1.2-1.6	Cohesive powder	25-30	Good
3	18-21	Fair to passable			30-40	Passable
4	23-25	Poor			> 40	Very poor
5	33-38	Very poor				
6	>40	Very very poor				

3. RESULTS AND DISCUSSION

3.1. Drug Identification and Characterization

3.1.1. Organoleptic properties

The drug sample was found to be white to off white in color, crystalline and odorless powder. This observation matches with the specified description of Repaglinide.

3.1.2. Melting Point Determination

Melting point of drug was determined by capillary method and compared with reference value. Melting point was found to be in range as reference value, which confirmed the purity and identity of the drug.

Drug:-Repaglinide

Reference Melting Point [6]:-130-131°C

Observed melting point:-130°C

Fourier Transform Infra-Red (FTIR) analysis

The FTIR study of pure drug sample was carried out using FTIR Spectrophotometer.

3.1.3. DSC study of Repaglinide

The DSC thermogram of pure drug is shown in the Fig. 2. The curve showed melting of drug at 130.14°C and endothermic peak at 134.17°C. The values are corresponding to the melting point of pure drug and thus confirmed the identity and purity of the drug.

3.1.4. Determination of λ_{max}

The UV spectrophotometric scanning of Repaglinide in 0.1N HCl was done and λ_{max} was found to be 243 nm.

The calibration curve of Repaglinide in 0.1N HCl at 243 nm was developed. It was found to obey Beer's law in prepared concentration range.

3.1.5. Solubility determination

The solubility of Repaglinide was evaluated by equilibrium solubility method in orbital shaker. Solubility of Repaglinide was found to increase at higher

pH value. Repaglinide exhibits 2 pKa values of 4.19 and 5.78, 27 and being a weakly acidic compound, the drug is ionized at higher pH values, owing to its higher aqueous solubility at higher pH values.

Solubility in 0.1 N HCl (µg/ml):- 24.4
Solubility in Acidic Buffer pH4.5 (µg/ml):- 10.6
Solubility in Distilled water (µg/ml):- 23.5
Solubility in PBS pH 6.8 (µg/ml):- 19.4

Table 4: FTIR spectra of Repaglinide

Functional Groups	Reference Peak [18,19] (cm^{-1})	Observed Peak (cm^{-1})
N-H stretching vibration	3200-3400	3308.03
C-H stretching vibration	2800-3000	2947.33
C=O stretching	1600-1800	1685.84
N-H bending	1625-1650	1637.62
CH3 stretching vibration	1200-1250	1220.02

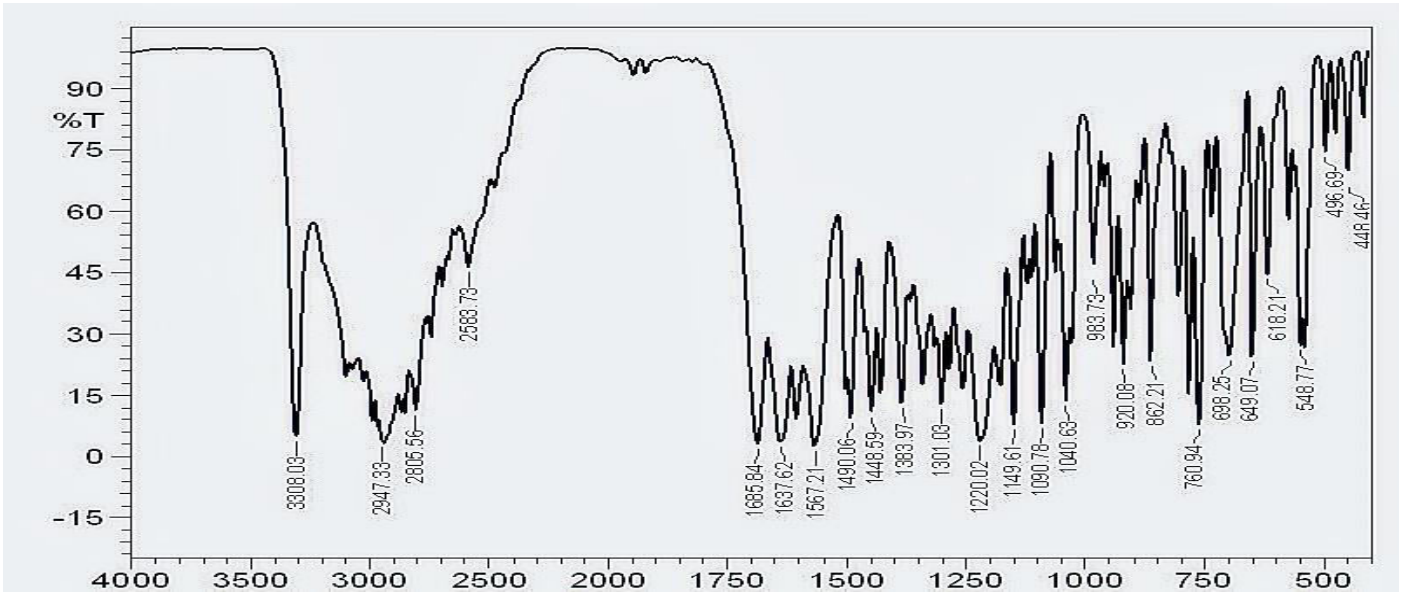

Fig. 1: FTIR spectra of Repaglinide sample

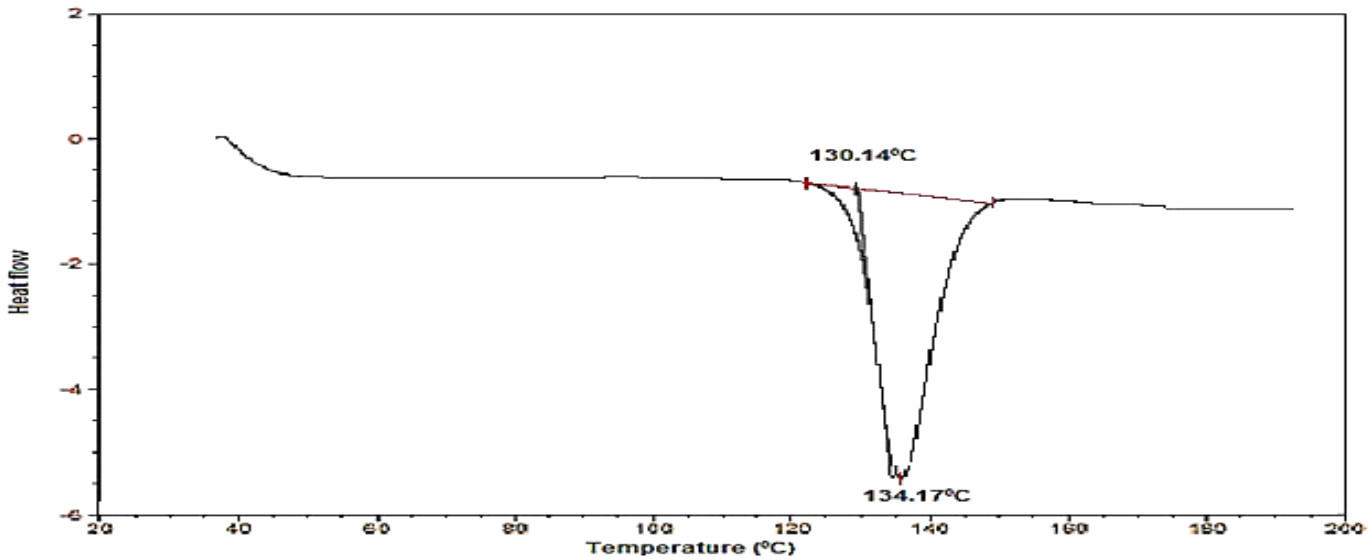

Fig. 2: DSC curve for Repaglinide

Concentration (µg/ml)	Absorbance (Mean ± SD) n=3
2	**0.045 ± 0.001**
4	**0.094 ± 0.0011**
6	**0.141 ± 0.0012**
8	**0.189 ± 0.0021**
10	**0.241 ± 0.0024**
12	**0.298 ± 0.0022**
16	**0.399 ± 0.0013**
20	**0.504 ± 0.0021**

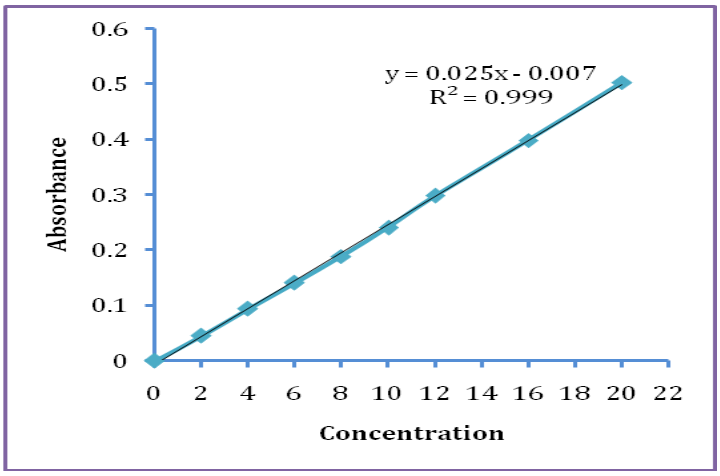

Fig. 3: Calibration curve of Repaglinide in 0.1N HCl

3.1.6. Drug Excipient Compatibility Study by Physical Observation

The physical mixtures were observed for any change in color, odor or formation of lumps or signs of liquefaction. There was no notable change observed in the mixture over the period of four weeks of storage.

3.1.7. FTIR Analysis

FTIR spectrum of Repaglinide, polymers and physical mixture of drug with polymers were separately recorded using FTIR spectrophotometer to study any possible interaction between drug and polymer. FTIR of pure repaglinide showed characteristic sharp peaks at 3308 cm^{-1} due to N-H stretching, 2947.33 cm^{-1} showing C-H stretching and 1685.84 cm^{-1} due to carbonyl group, 1220.22 cm^{-1} showing $C\text{-}H_3$ stretching vibration. These peaks were observed in FTIR spectrum of physical mixture of drug and polymer suggesting compatibility between drug and polymers to be used for formulation development.

3.2. Preparation and optimization of micro-balloons

Different batches (A1 to A5) were prepared with varying Repaglinide:Sodium alginate ratio. Micro-balloons with Repaglinide and sodium alginate in ratio 1:6 showed good entrapment efficiency with free flowing and spherical appearance. Effect of various formulation variables were studied and reported in Table 5. Batches 1-4 were prepared to study the effect of stirring speed on % EE, drug loading and particle size and stirring speed was optimized to 2000 rpm.

3.3. Evaluation of Microballoons

3.3.1. Evaluation of flow properties, Buoyancy and entrapment efficiency

The flow behavior, *in vitro* buoyancy behavior, drug entrapment of Microballoons was analyzed.

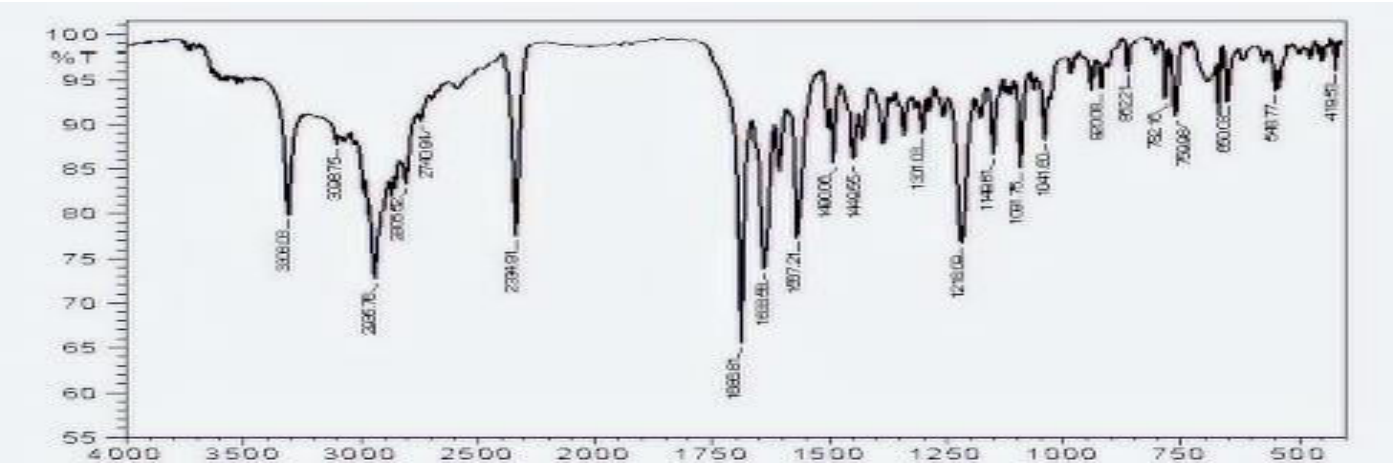

Fig. 4: FTIR spectra of physical mixture of Repaglinide and Ethyl Cellulose

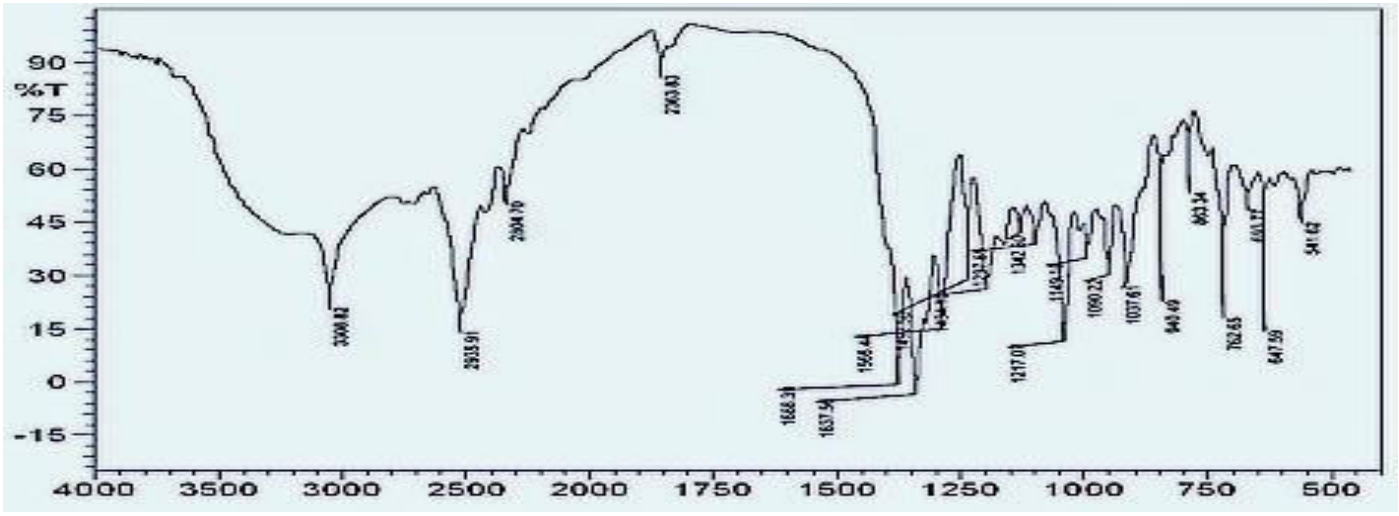

Fig. 5: FTIR spectra of physical mixture of Repaglinide and Sodium Alginate

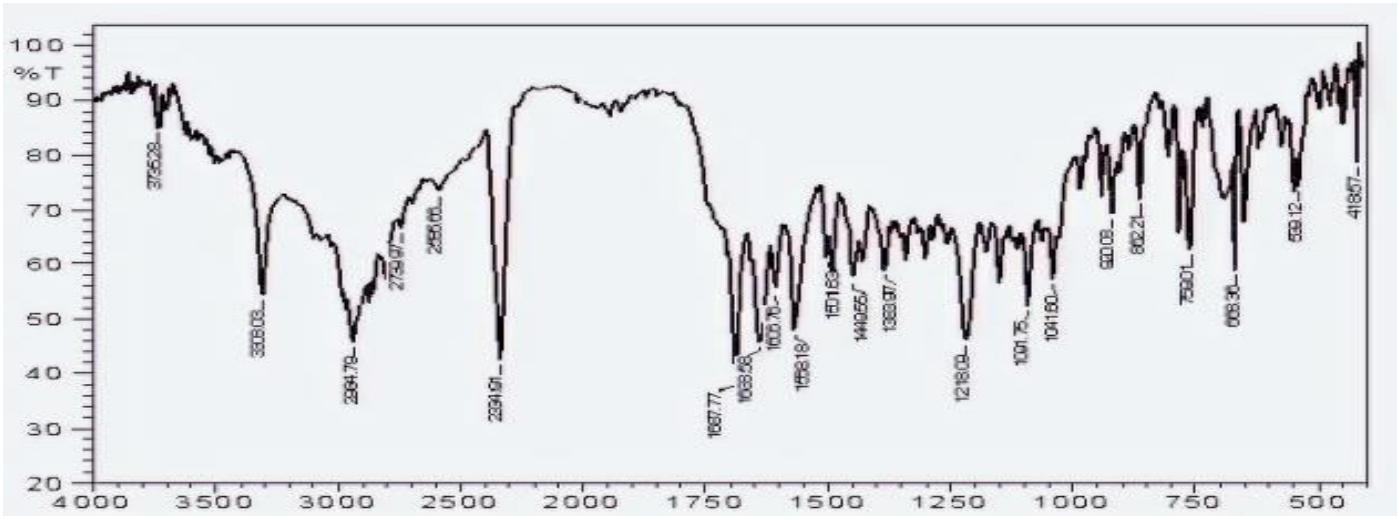

Fig. 6: FTIR spectra of physical mixture of Repaglinide and HPMCK4M

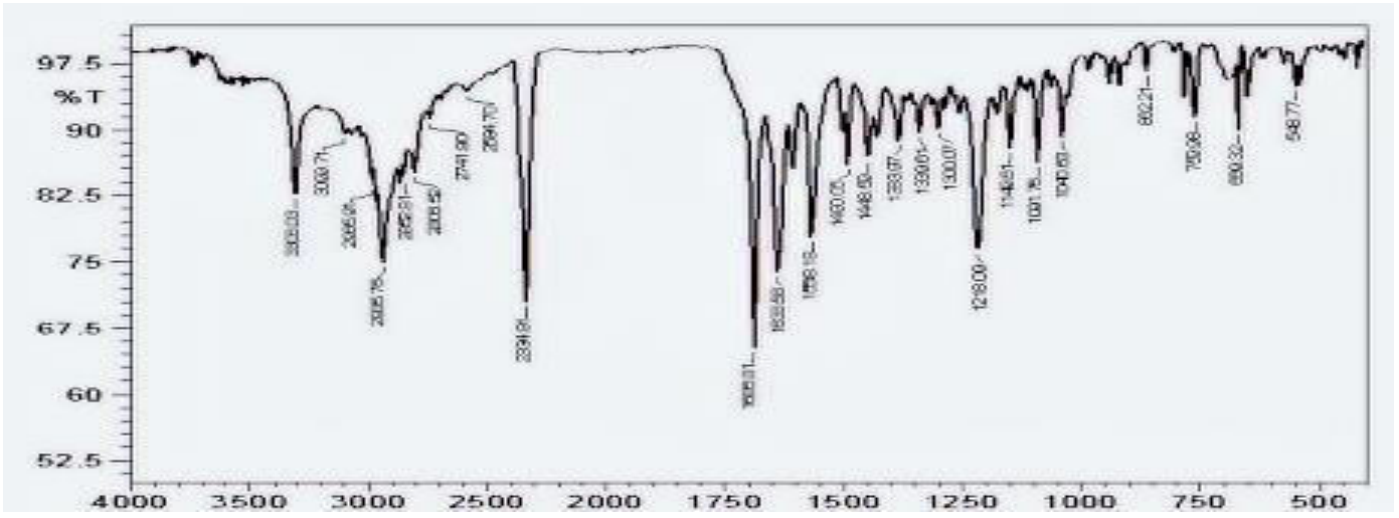

Fig. 7: FTIR spectra of physical mixture of Repaglinide and HPMC K15M

Table 5: Optimization of drug:polymer ratio

Formulation Code	Drug (mg)	Sodium Alginate (mg)	% Entrapment efficiency	% Drug loading	Avg. Particle size (µm)	Physical Appearance
A1	100	200	48.24 ±2.51	29.37±0.68	167.62	Irregular
A 2	100	400	59.63±1.87	23.41± 1.02	192.53	Spherical free flowing
A 3	100	600	78.88±3.05	18.32±1.34	214.76	Spherical free flowing
A 4	100	800	80.24±3.71	17.21±0.99	240.11	Spherical sticky
A 5	100	1000	76.47±3.25	14.23±0.59	273.82	Fibrous, Irregular

Data is expressed as mean ± SD, (n = 3)

Table 6: Optimization of stirring speed

Batch	Stirring speed (rpm)	Volume of CLA (4% w/v $CaCl_2$) mL	% Entrapment	% Drug loading	Arithmetic mean diameter (µm)
1	1000	100	73.54±2.25	17.12±0.64	258.78
2	2000	100	79.73±2.51	18.1±1.41	227.33
3	3000	100	74.24±1.44	16.62±1.53	195.68
4	4000	100	59.79±2.89	12.83±0.87	187.19

Data is expressed as mean ± SD(n = 3), for all batches drug:polymer ratio kept constant - 1:6

Table 7: Evaluation of Microballoons

Bulk density gm/cm^3			Tapped density gm/cm^3		
B	C	D	B	C	D
0.76±0.01	0.76 ±0.01	0.74 ±0.01	0.83 ±0.03	0.83 ±0.03	0.83 ±0.03
0.76±0.03	0.76±0.03	0.75±0.03	0.84±0.03	0.84±0.03	0.83±0.03
0.76±0.03	0.76±0.03	0.75±0.03	0.85±0.04	0.84±0.04	0.84±0.04
0.77±0.03	0.77±0.03	0.75± 0.03	0.86±0.05	0.86±0.05	0.84±0.05
0.75±0.02	0.76±0.02	0.76±0.02	0.84±0.03	0.84±0.03	0.84±0.03
0.77±0.02	0.77±0.02	0.76±0.02	0.85±0.02	0.85±0.02	0.85±0.02
0.77±0.02	0.76±0.02	0.76±0.02	0.85±0.05	0.85±0.05	0.84±0.05
0.77±0.02	0.77±0.02	0.77±0.02	0.85±0.03	0.85±0.03	0.85±0.03
0.76±0.03	0.76±0.03	0.76±0.03	0.86±0.04	0.86±0.04	0.86±0.04

Table 8: Evaluation of Microballoons

Angle of repose (θ)			Carr's Index		
B	C	D	B	C	D
28.9±1.2°	29.8±1.1°	30.7±0.9°	8.43	8.43	10.84
30.2±1.6°	29.9±1.1°	29.6±1.0°	9.52	8.43	8.53
31.8±1.4°	30.2 ±0.8°	29.8±0.9°	10.58	9.52	12.79
31.7±2.1°	30.7±1.0°	30.5±1.1°	10.46	10.46	10.71
29.2±1.7°	29.8 ±1.2°	30.3±1.0°	10.71	9.52	10.58
28.2±1.9°	29.2±1.5°	29.7±1.2°	9.41	9.41	9.41
27.4±1.1°	28.8±1.2°	29.8±1.1°	9.41	10.58	9.52
30.5±1.4°	30.2±1.2°	30.6±1.1°	9.41	9.41	9.41
30.2±1.7°	30.1±1.1°	30±1.4°	11.62	11.62	10.58

Table 9: Evaluation of Microballoons

Hausner Ratio			Particle size (µm)			Buoyancy (percentage)		
B	C	D	B	C	D	B	C	D
1.09	1.09	1.12	227.33	221.38	218.12	59.83±2.51	57.83±2.51	54.82±2.44
1.10	1.09	1.09	255.61	248.22	231.51	61.41 ±2.86	62.3±2.86	56.52±2.66
1.11	1.10	1.14	288.23	302.13	258.36	64.27±3.21	63.57±3.21	60.27±2.59
1.11	1.11	1.12	231.23	225.51	220.13	59.97±3.46	60.72±2.06	52.97±3.46
1.12	1.10	1.11	261.54	258.39	239.40	64.88±3.16	65.02±3.81	57.16±3.23
1.10	1.10	1.10	294.37	300.14	261.17	64.18±1.56	64.08±2.89	58.54±2.28
1.10	1.11	1.10	232.12	230.62	217.62	58.22±1.98	59.57±2.19	54.42±2.79
1.10	1.10	1.10	260.35	271.35	242.15	64.73±2.15	60.23±2.55	55.32±2.33
1.13	1.13	1.11	291.68	297.58	265.18	65.34±3.66	62.43±3.27	58.89±3.24

Table 10: Evaluation of Microballoons

Entrapment efficiency (percentage)			Percentage yield		
B	C	D	B	C	D
80.11±3.51	79.54±2.77	76.54±2.49	92.03±1.26	92.13±1.52	89.73±2.6
79.52±2.92	79.72±1.73	76.65±2.72	92.63±1.37	91.23±1.87	89.23±2.87
79.40±2.98	78.40±1.25	75.12±2.47	90.01± 1.28	90.66±1.88	88.35±3.28
78.21±2.87	78.38±1.69	73.24±2.73	92.01±1.33	91.56±1.93	89.57±3.54
78.12±2.58	79.47±3.08	74.24±3.34	92.36±1.92	91.21±2.35	87.62±2.94
78.23±4.01	77.23±3.71	73.19±3.11	90.34±1.22	90.34±1.22	85.64±2.37
74.25±3.54	72.50±2.64	71.53±3.04	89.81±2.33	88.21±1.98	86.21±2.46
74.89±3.62	73.88±2.67	72.55±2.44	90.94±2.16	87.32±2.60	86.4±3.26
73.26±2.94	72.66±1.98	71.56 ±2.64	88.94±2.16	85.94±2.58	85.84±2.83

Where B, C, D stands for codes of Formulation.

3.3.2. SEM Study of Microballoons

Formulation B5, C5 and D3 showed higher buoyant percentage after 12 hours' time respectively in three formulation batches (B, C and D). Among them, C5 Formulation showed highest buoyant percentage, Entrapment efficiency and percentage yield. The SEM photographs of C5 microballoons at low and moderate magnification indicated that the microparticles were discrete and spherical.

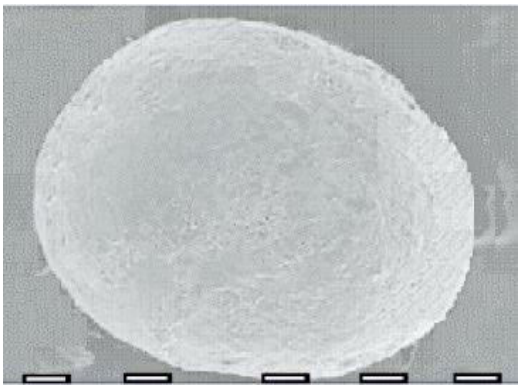

Fig. 6: SE Micrograph of microparticles (scale bars denotes 100 µm) Batch B5

Identification and characterization study of repaglinide confirmed purity of sample drug received. The melting point was found to be 130°C specified in the literature. DSC study showed endothermic peak at 130.14°C confirming purity of drug. FTIR spectra of drug was compared with reference FTIR spectra of Repaglinide and was found to be as per reported in the literature. Repaglinide in 0.1N HCl was scanned between 200 to 400 nm to determine the λ_{max} UV spectrophotometrically and was found to be 243 nm. The calibration curve of repaglinide in 0.1N HCl was developed. The calibration curve suggested linear relation between concentration and absorbance values with R^2 value of 0.999. Solubility of Repaglinide HCl was determined in 0.1N HCl, Buffer pH 4.5, Phosphate Buffer System pH 6.8 and distilled water and was found as 24.4, 10.6, 19.4 and 23.5µg/ml respectively. The drug excipient compatibility study using FTIR and DSC revealed no chemical interaction and thus no incompatibility between Repaglinide and excipients. The characteristic peaks of drug were similar to the peaks obtained in the mixture of drug with Sodium alginate, Ethyl cellulose and various viscosity grades of

HPMC (HPMC K4M and HPMC K15M). Formulations were evaluated for organoleptic properties, Micromeritic properties, SEM study, and buoyant properties. All batches of Floating Microballoons showed excellent flow properties and finer particle size ranging from 220 to 310 µm. Formulation B5, C5 and D3 showed higher buoyant percentage after 12 hours' time. SEM study of the same revealed that microballoons were discrete and spherical.

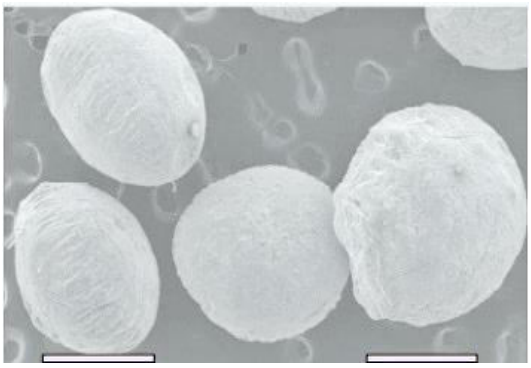

Fig. 7: SE Micrograph of microparticles (scale bars denotes 100 µm) Batch B5

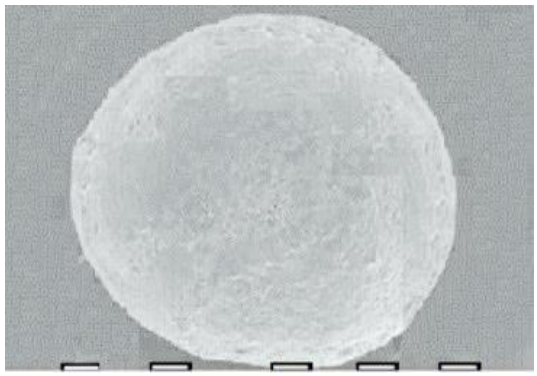

Fig. 8: SE Micrograph of microparticles (scale bars denotes 100 µm) Batch D3

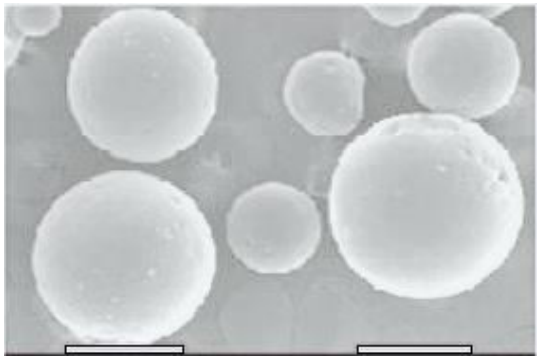

Fig. 9: SE Micrograph of microparticles (scale bars denotes 100 µm) Batch D3

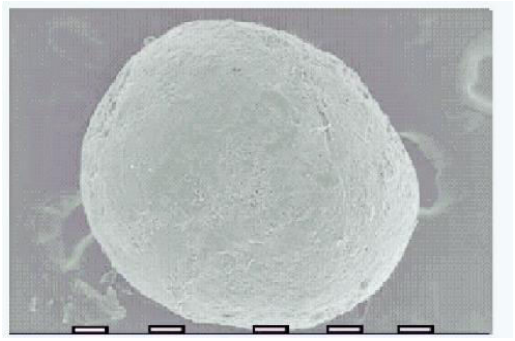

Fig. 10: SE Micrograph of microparticles (scale bars denotes 100 µm) Batch C5

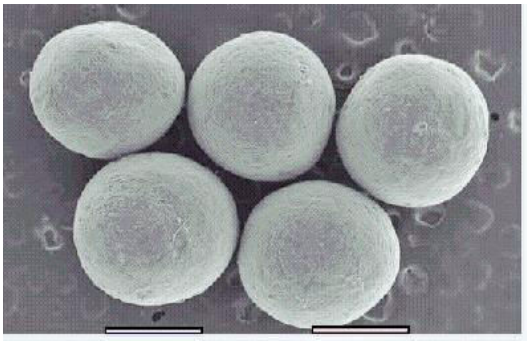

Fig. 11: SE Micrograph of microparticles (scale bars denotes 100 µm) Batch C5

4. CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable process. Hollow microballoons promises to be a potential approach for gastric retention by prolonging the dosage forms, and extending the time of drug absorption. Hence, the prepared floating microballoons of repaglinide prove to be a potential candidate for multiple-unit delivery devices adaptable for safe and effective sustained drug delivery.

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Conflict of study

None declared

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