SJIF Impact Factor: 7.001| ISI I.F.Value:1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 5 | Issue: 8 | August 2020 - Peer Reviewed Journal

DOMPERIDONE FLOATING BEADS: FORMULATION, *IN-VITRO* EVALUATION AND METHOD DEVELOPMENT BY UV-VIS SPECTROSCOPY

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ABSTRACT
The objective of present study was, to formulate and evaluate floating beads of domperidone. Floating beads were fabricated using Effervescent method, using HPMC E50 as a sustained release polymer. The parameters optimized for this preparation were polymer concentration, sodium bicarbonate and calcium chloride concentration. The floating system has density less than that of gastric content, which tends them to float on the surface of gastric fluid. Gastro-retentive floating drug delivery systems have emerged as an efficient means of enhancing the bioavailability, as domperidone has absorption window at upper part of GIT, so it is beneficial to localize the drug at its maximum absorption site. Domperidone is having less oral bioavaibility (13-17%), so in order to increase the bioavaibility of the drug gastric retention is the most efficient tool, as the sustained release of domperidone gives maximum therapeutic concentration of the drug for prolonged duration of time. The results obtained for drug entrapment efficiency, % yield , In-vitro drug release ,and % In- vitro buoyancy are 68.80%,67.21%,79.87%,87.30%,respectively.

KEYWORDS: *Domperidone, floating beads, sustained release, in-vitro release study*

INTRODUCTION

For the drugs having absorption at upper part of GIT , oral route of drug administration is the efficient mean of drug delivery as to maximize the effect of drug. The floating drug delivery system has tendency to remain buoyant in the gastric entity, as it having the density less than gastric fluid. The effervescent method utilizes polymers as hydroxypropylcellulose, hydroxypropyl methylcellulose the coating of polymer, is insoluble but permeable, and allows permeation of water. When beads comes in contact with gastric acid then carbon dioxide is released, causing beads to float on the surface gastric fluid gastro retentive drug delivery system has an efficiency to sustain the drug release for prolonged period of time.it is beneficial to improve plasma concentration of drug and giving maximum effect.it also helps to improve variation in bioavailability. Domperidone is a synthetic benzimidazole compound that acts as dopamine D2 receptor antagonist. Domperidone is also used as a prokinetic agent for treatment of upper gastrointestinal motility disorders. It can be a good alternative to metoclopramide because it has fewer side effects. After oral administration, domperidone is rapidly absorbed from the stomach and the upper

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part of the GIT with fewer side effects. It is a weak base with good solubility in acidic pH but significantly reduced solubility in alkaline medium.

Effervescent systems

Effervescent system involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating of polymer which is insoluble but permeable, it allows permeation of water. Thus, carbon dioxide is released, causing beads to float in the stomach Excipients used most commonly in these some of the polymers used are hydroxypropylcellulose, hydroxypropyl methylcellulose, cross povidone, sodium carboxy methyl cellulose, and ethyl cellulose. In this system floatability can be achieved by the generation of gas bubbles. They are formulated in such a way that when in contact with the acidic gastric contents, CO2 Therefore domperidone has been selected as a model drug so as to retain it in the stomach as well as to improve its bioavaibility, and dissolution rate is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to system.

Materials and methods: Domperidone, Propyl methyl cellulose E-50(HPMC) was provided by Sandip institute of pharmaceutical sciences, Nashik. All other chemicals/reagents used were of analytical grade.

Table No.1: Formulation of domepridone floating beads

Formulation Code	Drug (mg)	Pectin (mg)	Calcium carbonate (mg)	Calcium chloride (%)	HPMC (mg)	Sodium bicarbonate(mg)
F1	150	300	150	4	100	150
F2	150	300	150	3	120	125
F3	150	300	150	2	140	100
F4	150	300	150	1	160	90
F5	150	300	150	1	180	50

Preparation and optimization of Floating beads

- Dissolved accurately weighed quantity of pectin (3 gm) in 100 ml of deionized water, with continuous stirring.
- Add (1.5gm) of drug (Domperidone) in above pectin solution, this was followed by addition of sodium bicarbonate, calcium carbonate, and HPMC.
- Sonicate the resulting mixture for 30 min, in order to remove entrapped air bubbles.
- Prepare 2% w/v solution of calcium chloride in 10 % glacial acetic acid .
- Fill the syringe guaze with prepared solution and this homogenized mixture was extruded into 2% w/v calcium chloride solution with gentle agitation at room temperature.
- The formed beads were allowed to stand for 30 min in the solution for curing.(2% w/v calcium chloride solution)
- Filter solution and collect beads.
- Dry the beads in hot air oven below 40^0 c for 24 h.

EVALUATION OF PECTIN BEADS

Appearance:

The prepared beads were inspected visually for clarity, color, shape.

Percentage yield and drug entrapment efficiency (DEE):

The percent yield of the prepared beads were studied by the formula

Percentage yield =

$$\frac{\text{weight of beads recovered}}{(\text{weight of drug + polymer})} \times 100$$

To determine the incorporation efficiency, beads were taken, thoroughly triturated and suspended in a minimal amount of methanol. The suspension was suitably diluted with water and filtered to separate shell fragments. Drug content was analyzed spectrophotometrically at 285 nm. The amount of drug entrapped in the microspheres was calculated by the following formula

Entrapment efficiency= (Amount of drug actually present/theoretical drug load expected)× 100

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In- vitro release

Release studies were performed by using USP Apparatus type –II,(basket type) taking 10 mg of Drug loaded beads, introduced into the 900 ml of 0.1N hcl, The medium was maintained at 37±0.5ºc at 100 rpm. Aliquots (5ml) were withdrawn at regular intervals for 8 h and analyzed spectrophotometrically at 285 nm. The solution was filtered, appropriately diluted analysed spectrophotometrically at 285 nm. The same amount of fresh medium was replaced after every sample collection, to maintain the sink condition

Floating lag time

In a beaker 10 ml of 0.01 M HCl was taken and 1 mg of domperidone pectin beads were taken in the beaker and with the help of stopwatch the time taken by beads to reach at the top of the surface of fluid medium was noted as a floating lag time .

Percent (%) *In vitro* buoyancy study

Floating microspheres (equivalent to 100 mg) were dispersed in 900ml of 0.1 N Hydrochloric acid solution (pH1.2) containing tween 80 (0.02%W/ V) to simulate gastric fluid at 37°. The mixture was stirred with a paddle at 50 rpm and after 8 h, the layer of buoyant beads (Wf) was pipetted and separated by filtration simultaneously sinking beads (Ws) was also separated. Both beads type were dried at 40°C .Each weight was measured and % buoyancy was determined by the weight ratio of the floating beads to the sum of floating and sinking beads.

$$\% \text{ buoyancy} = \frac{Q_F \times 100}{(Q_f + Q_s)}$$

Q_f =weight of floating beads

Q_s =weight of settled beads

Swelling Index

The basket containing beads was put in a beaker containing 100 ml of 0.1 N HCl , maintained at 37^0 c. The beads were periodically removed at predetermined intervals and weighed. Then the swelling ratio was calculated as per the following formula.

% Swelling index = weight of wet beads/weight of dried beads X 100

Floating time of beads

The bead samples (10 mg) were placed in a beaker filled with 50 ml of 0.1 N HCl solution. Temperature was maintained at 37^0 C. The floating time of beads was observed for 24 hr. The preparation was considered to have buoyancy in the test solution only when all the beads floated in 0.1 N HCl solution.

RESULTS

Table no.1: Physical appearance of domperidone floating beads

Formulation code	Colour	Appearance
F1	White	Oval
F2	Creamy	Round
F3	White	Round
F4	White	Round
F5	Creamy	Round

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Table no.2:% yield ,floating time ,% in-vitro buoyancy and % swelling index

Formulation Code	Floating Lag Time	*% In-Vitro* Drug Release
F1	> 5 sec	79.87 %
F2	8 sec	74.20 %
F3	12 sec	66.40 %
F4	8 sec	59.05 %
F5	16 sec	56.01 %

Table no.3 : floating lag time , % In-vitro drug release

Formulation code	% yield	Floating time	% in-vitro buoyancy	% swelling index
F1	67.21 %	>24 h	87.30 %	85.90
F2	64.75%	< 18 h	81.57 %	77.4
F3	64.08%	12 h	80.76 %	79.3
F4	60.54 %	<9 h	78.16 %	74.1
F5	59.56 %	7h	73 %	72.9

Table no.4 : *In-Vitro* Drug Release For F1 BATCH

Time (min)	Absorbance	Conc ug/ml	Conc mg/ml	Con mg /10 ml	Correction factor	Conc Mg/900ml	Cumilitive Conc	% Release
30	0.595	85.42	0.085	0.85	0	76.88	76.88	51.25
60	0,656	94.14	0.094	0.94	0.854	84.72	85.58	57.05
120	0.692	99.28	0.099	0.99	1.795	89.35	91.15	60.76
180	0.747	107.1	0.107	1.07	2.788	96.42	99.21	66.14
240	0.782	112.1	0.112	1.12	3.86	100.92	104.7	69.85
300	0.824	118.1	0.118	1.18	4.981	106.32	111.3	74.20
360	0.845	121.1	0.121	1.21	6.162	109.02	115.1	76.79
420	0.858	123	0.123	1.23	7.374	110.7	118.0	78.71
480	0.862	123.5	0.123	1.23	8.604	111.21	119.8	79.87

DISCUSSION

Five formulations were prepared with the optimization of polymer (HPMC), calcium chloride and sodium bicarbonate. The variations of calcium chloride and HPMC were 1%,2% 3%, 4% with varying combinations. The drug loading was constant in each formulation.The buoyancy of each of the five formulations were find out and the maximum floating time was observed for formulation F-1. Formulations The percent yield was found to be maximum for f-1 as 67.21 % .All the formulations show presence of good drug content and low standard deviations of results. It indicates that the drug is uniformly dispersed in the formulations. Therefore, the method used in this study appears to be reproducible for the preparation of beads. Formulation F-1 prepared with 4% calcium chloride, which gives maximum drug release as 71.13 %which is may be due to less polymer concentration as less polymer concentration will help drug to diffuse well and was selected to observe further effect of calcium chloride concentrations on drug release.F1 having 4% calcium concentration gives spherical beads as having better cross linking. Formulation F-1 prepared with 100 mg of HPMC , 150 mg of sodium bicarbonate and syringing in 4% calcium chloride solution was selected. In vitro drug release profile of domperidone beads formulation F-1, is given in (Table 11).The physical appearance of domperidone floating beads was observed for colour and appearance for five formulations (F1 - F5). The results obtained were as follow,

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% yield

Formulation F1 shows higher yield ,i.e. 67.21 %.Overall the drug loading was decreased with increase in the polymer concentration due to its higher viscosity which affects the diffusion coefficient of drug. The reduction in yield was attributed to loss of material during preparation of beads and due to process parameters as well as during filtration of beads

METHOD DEVELOPMENT OF DOMPERIDONE FLOATING BEADS BY UV-SPECTROSCOPY

Preparation of standard (Bulk) solution of domperidone:

- Weigh 10 mg of domperidone powder. Dissolve it in sufficient amount of 0.1 N HCl. Make up the volume upto 100 ml with 0.1 N HCl.

Preparation of test solution:

- The beads were crushed with the help of mortar and pastel and weigh the powder equivalent to 10 mg of drug and transferred to 100 ml of volumetric flask.
- To this add diluent (0.1 N HCl) to adjust the volume and sonicate the solution for 30 minutes.
- After sonication final volume was made with 0.1 N HCl.

1. Linearity- Acceptance criteria for linearity is Correlation coefficient (r2) = 0.99.

Procedure:

Linearity solutions 2, 6, 8 , 10 , 12 ppm were prepared by diluting 0.2 ,0.4 , 0.6 , 0.8 , 1.0 and 1.2 ml of standard (bulk) solution with 0.1 N HCl upto 10 ml.

Six points calibration curve were obtained in a concentration range from 2-12 ppm for domperidone. The response of the drug was found to be linear in the investigated concentration range and the linear regression equation was y = 0.0942x + 0.1764 with correlation coefficient R^2 = 0.9915 (Table 2, Figure)

Regression Characteristics of Domperidone.

Parameters	Observation
Slope (b)	0.094
Intercept (a)	0.176
Correlation Coefficient (r^2)	0.991

Discussion:

The absorbance of these resultant solutions were measured at 285 nm against 0.1 N HCl as blank and a graph was plotted between absorbance obtained and the concentrations of the solutions. The Lambert-Beer's law was obeyed in the concentration range of 2 to 12 µg/ml at 285 nm

Limit of Quantitation and limit of detection.

- The Quantitation limit is the characteristic of Quantitative assay, for low levels of the compounds in sample matrices , such as impurities in bulk drug substances .
- It decides about the sensitivity of the method.
- LOD is the lowest detectable concentration of the analyte by the method, while the LOQ is the minimum quantifiable concentration.
- Linearity solutions were prepared of 2, 4, 6, 8, 10 and 12 ppm from standard stock solution for determination of LOD and LOQ

Observation table for LOD and LOQ

Validation Parameter	Observation	Test passes/ failed
LOD	0.596 ppm	Test Passed
LOQ	1.79 ppm	Test Passed

- **Discussion:** The results shows LOD and LOQ values within specified limits. It proves sensitivity of the method
- **Precision:**

Acceptance criteria:

1. Percent assay = It should be between 98-102 %
2. % RSD - < 2 %

Procedure for precision (10 ppm):

- Pipette out 1 ml from test solution and dilute it up to 10 ml with 0.1N HCl
- Repeat the same procedure for six times
- Take the UV absorbance of these six test sample and one standard sample of 10 ppm at 285 nm
- Calculate % assay , standard deviation , % relative standard deviation.

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Formula for calculation of % assay

$$\frac{\text{Absorbance of Test X}}{\text{Absorbance of Std}} \times \frac{\text{Weight of Std X Further dilution}}{\text{ml of solvent}}$$

$$\frac{\text{Ml of solvent}}{\text{wt of beads powder}} \times \text{Further dilution X average weight}$$

Further dilution X average Weight /Label claim X 100

Precision

Concentration	Absorbance	% assay	(X – x ‘)	(X – x ‘)²
10	0.6395	98.50 %	0.	0
10	0.6497	100.77 %	2.27	5.15
10	0.6583	101.00%	2.5	6.25
10	0.6539	100.72 %	2.22	4.92
10	0.6549	100.87 %	2.37	5.6169
10	0.6672	102.00 %	3.5	12.25

Observation table for Precision

Validation parameter	Acceptance criteria	Observation	Test passed / Test failed
Precision	% Assay=98-102 %	98.50 %	Test Passed
	% RSD =< 2	1.076 %	Test Passed

3. Accuracy

1. The accuracy of an analytical procedure is the closeness of test results obtained by that procedure to that true value.

2. Accuracy is calculated as percentage of recovery by assay of known added amount of analyte in the sample.

Acceptance criteria:

1. Percent recovery = 98 -102 %
2. % RSD - < 2 %
3. Accuracy of the method is ascertained by standard addition method at 3 levels. Standard quantity equivalent to 80%, 100% and 120% is to be added in sample. The result shown that best recoveries (95 -100%) of the spiked drug were obtained at each added concentration, indicating that the method was accurate (Table 7 .8).

PROCEDURE

- For Accuarcy, Prepare the solution of mixture of standard and test solution, i.e. 18, 20 and 22 ppm.
- Pipette out 0.8, 1, 1.2 ml from Stock standard solution with 1 ml of test solution of 100 ppm.
- The above mixture solution diluted upto 10 ml with 0.N 1 HCl.

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Accuracy

	Absorbance	Ppm	Ml of test	Ml of standard	Theoretical yield	Practical yield	% Recovery
80%	1.2011					18.50	102 %
	1.1890	18	1	0.8	18	18.31	101.74 %
	1.1855					18.26	101.44 %
100%	1.3195					20.32	101.62 %
	1.3090	20	1	1	20	20.16	100.61 %
	1.3085					20.15	100.77 %
120%	1.4020					21.59	98.16%
	1.4135	22	1.2	1	22	21.77	98.96 %
	1.4394					22.17	100.78 %

Absorbance of standard= 0.649

Observation table for Accuracy

Validation Parameter	Acceptance criteria	Observation	Test failed /passed
Accuracy	% Recovery=98-102 %	100.78 %	Test Passed

Robustness:

1. Robustness of an analytical procedure is a measure of its capacity to remain unaffected by small but deliberate variations in procedural parameters tested in the procedure documentation and provides and an indication of its suitability during normal uses.

Acceptance criteria:

% Relative standard Deviation = < 2

Procedure for Robustness (10 ppm):

- Pipette out 1 ml from test solution and dilute it upto 10 ml with 0.1N HCl
- Repeat the same procedure for six times
- Take the UV absorbance of these six test sample and one standard sample of 10 ppm at 285 nm
- Standard deviation , % relative standard deviation.

Table no. 7.10: Robustness

Concentration Ppm	Absorbance		
	284	285	286
10	0.968	0.966	0.963
10	0.9714	0.9711	0.9718
10	0.9894	0.9896	0.9893
10	0.9904	0.9907	0.9914
10	1.005	1.007	1.008
10	1.002	1.002	1.002
MEAN	0.9852	0.9841	0.9877
RSD	0.01535	0.01638	0.01741
% RSD	1.55	1.664	1.76

Observation Table for Robustness.

Sr .No	Parameter	Acceptance criteria	Observation	Test passed/failed
1	Robustness	% RSD = < 2	284 =1.55 285=1.66 286 =1.76	Test passed

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CONCLUSION

The results obtained after evaluation of domperidone floating beads shows that the prepared beads has good floating ability, buoyancy, and it gives better drug release. The polymer concentration was the determinant of release of the drug as concentration of the drug decreases it also decreases with the percentage yield of beads and shows better drug release with optimum polymer concentration, as drug can diffuse well. The polymer concentration as increases it gives enhancement in buoyancy of the beads, as decrease in porosity.

Acknowledgment-

Authors are thankful to Sandip University's School of Pharmaceutical Sciences, Nasik (Maharashtra) for providing all necessary facilities and all the staff for their time to time guidance and help.

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