AMERICAN JOURNAL OF PHARMTECH RESEARCH
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Formulation Optimization and Evaluations of Floating Tablet of Risperidone

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ABSTRACT

The objective of this research work was to formulate and evaluate the floating drug delivery system containing Risperidone drug, to improve oral bioavailability by increasing gastric residence time. Gastroretentive drug delivery system was developed by using Gum karaya & HPMC K 200M polymers. Formulations were prepared by using direct compression method. Optimization study was performed by using 3^2 full factorial design. The formulated floating tablets batches were evaluated for physicochemical parameters like hardness, thickness, weight variation, friability, drug content, floating lag time and swelling index. All prepared batches shown good in-vitro buoyancy studies and acceptable result of for various parameters. Comparing the all the formulations, formulation R6 was considered as optimized formulation which exhibited 99.41% of drug release in 12 hours, floating lag time of 2.14 ± 2.0 minutes total floating time of over 12 hours.

Keyword: Floating, hardness, floating lag time, drug release.

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Received 09 August 2017, Accepted 05 September 2017

Please cite this article as: Siraj SN *et al*., Formulation Optimization and Evaluations of Floating Tablet of Risperidone. American Journal of PharmTech Research 2017.

INTRODUCTION

Gastroretentive drug delivery system (GRDDS) can be defined as a system which retains in the stomach for a sufficient period of time and releasing active moiety in a controlled manner, and finally metabolized in the body. Over the last two decades, numbers of GRDDS have been designed to prolong GRT. The main aim of preparing GRDDS is to minimize the problem associated with existing oral sustained release dosage form and to develop patient benefited drug delivery.

Gastroretentive dosage forms are formulated to be retained in the gastric region for prolonged time and release incorporated drug candidates and thereby enable sustained and prolonged input of the drug to the upper part of the GIT thus leading its optimal bioavailability. Thus, they not only prolong the dosing intervals, but also increase the patient compliance beyond the level of existing controlled release dosage forms. This application is especially effective in delivery of sparingly soluble and insoluble drugs. Gastroretentive dosage forms greatly improved the pharmacotherapy of the GIT through local drug release, leading to high drug concentrations at the gastric mucosa.

MATERIALS AND METHOD

Risperidone drug was gift sample from Wockhardt Pharma Ltd. Aurangabad Gum karaya, Carbopol, Sodium Bicarbonate, Citric Acid, Magnesium stearate, HPMC K-200 M, Talc, Lactose were purchased from Research Lab Fine Chem. Ltd. Mumbai, Maharashtra, India .

Method

Drug-Excipient interaction study using Fourier Transform Infra-Red (FTIR) spectroscopy & DSC.

Infrared Spectrophotometry is a useful analytical technique utilized to check the chemical interaction between the drug & other excipients used in the formulation. 1 mg of the sample was powdered & intimately mixed with 10 mg of dry powdered potassium bromide. The powdered mixture was taken in a diffuse reflectance sampler & the spectrum was recorded by scanning in the wavelength region of 4000-400 cm-1 in an FTIR spectrophotometer. The IR spectrum of the drug compared with that of the physical mixture to check for any possible drug-excipient interaction

Preformulation study

Preformulation study is the first step in the justification of dosage forms of a drug. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful for the formulation and development of stable and bioavailable dosage forms,

which can be mass produced. Following Preformulation studies were performed. Preformulation study was performed as per previously reported method.

Preparation of Risperidone floating tablet

The tablets were prepared by direct compression method All the ingredients except Risperidone were passed through #85 mesh prior to mixing. The ingredients were weighed separately and mixed to get a uniform polymer mixture. The drug was then mixed with the polymer mixtures were lubricated with magnesium stearate and talc was compressed on tableting machine (Rimek Mini Press-II, Karnavati Engineering Ltd.) by using 9 mm flat punch to obtain tablets.

FORMULATION

Optimization by using 32 full factorial designs

In the present study, a 32 full factorial design was employed to study the effect of independent variables, i.e. amount of HPMC K200 M (X1) and GUM KARAYA (X2) on dependent variables i.e. Floating lag time, % Drug release and. A statistical model Incorporating interactive and polynomial terms was utilized to evaluate the responses.

Table 1: Translation of coded value in an actual unit

Coded value	HPMC K200 M (X1)	Gum Karaya (X2)
-1	10	15
0	20	30
+1	30	45

Table 2: Factor combinations as per the chosen experimental full factorial design

Batch No.	X1	X2
R1	-1	-1
R2	-1	0
R3	-1	+1
R4	0	-1
R5	0	0
R6	0	+1
R7	+1	-1
R8	+1	0
R9	+1	+1

Table 3: Optimization batches as per design

Ingredients	Formulation batch code								
	R1	R2	R3	R4	R5	R6	R7	R8	R9
Risperidone	6	6	6	6	6	6	6	6	6
Gum karaya	15	30	45	15	30	45	15	30	45
HPMC K200	10	10	10	20	20	20	30	30	30
Carbopol	30	30	30	30	30	30	30	30	30
Citric Acid	15	15	35	35	35	35	15	15	15
Sodium Bicarbonate	45	45	45	45	45	45	45	45	45

Magnesium Stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	119	104	69	89	74	59	99	84	69
Total	250	250	250	250	250	250	250	250	250

Evaluation of floating tablets batches

The floating tablets were evaluated for thickness, hardness, friability, weight variation test, drug content, in-vitro buoyancy study, Swelling Index, in-vitro bioadhesion time & in-vitro dissolution study. All prepared sustained release tablets were evaluated for the following official & unofficial parameters.

Thickness

Thickness was measured using a vernier caliper. Five tablets of the formulation were picked randomly and thickness was measured individually by vernier caliper

Hardness

Hardness was measured using Monsanto hardness tester. The hardness expressed in kg/cm2. For each batch three tablets were tested.

Friability

Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions, the tablets were dedusted and weighed again. The percentage friability was measured using formula,

$\% F = \{1-(Wt. /W)\} \times 100$

Where, % F = Friability in percentage

W = Initial weight of tablets

Wt. = Weight of tablets after revolution

Weight variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight.

Table 4: Weight variation limit as per I.P

Dosage form	Average weight	% deviation
Uncoated and film coated tablets	80 mg or less	10
	More than 80 mg but less than 250 mg	7.5
	250 and more	5

Drug Content Uniformity

Ten tablets for each batch was taken and triturated. Powder equivalent to 100 mg of drug was weighed and was transferred to breaker and 0.1N HCl was added and it was then shaken for 5 min and finally 0.1N HCl was added to make the volume up to 100 ml and solution was then sonicated for 15 min and filtered through Whatman filter paper. Finally, a solution was diluted suitably and the absorbance of the resultant solution was measured to determine the drug content spectrophotometrically at 238 nm using UV/Visible spectrophotometer Shimadzu 1800 against 0.1N HCl blank.

***In-vitro* Buoyancy Studies**

The in-vitro buoyancy was determined by floating lag time. The time required for the tablet to rise to the surface and float was determined as floating lag time. In this the tablets were placed in 100 ml beaker containing 0.1 N HCL.

Swelling index study

The extent of swelling can be measured in terms of % weight gain by the tablet. For each formulation batch, one tablet was weighed and placed in a beaker containing 200 ml of buffer media. After each interval the tablet was removed from beaker and weighed again up to 12 h. The swelling index was calculated using following formula.

Swelling index (S.I) = {(wt-wo) /WO} ×100

Where, S.I. = Swelling index

Wt. = Weight of tablet at time t

Wo = Weight of tablet before placing in the Beaker.

***In-Vitro* Dissolution Study of Risperidone**

The release rate of Risperidone from floating tablets was determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900 ml 0.1N HCl, at 37 ± 0.5°C and 50 rpm/min. A sample (1ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 h, and the samples were replaced with fresh dissolution medium. The samples were passed through Whatman filter paper and the absorbance of these solutions was measured at 238 nm.

Data Analysis:

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi matrix, Pappas and Hixson Crowell model using PCP-DISSO – v3 software. Based on the R-value, the best-fit model was selected.

Stability studies of optimized formulation

Stability of a pharmaceutical preparation can be defined as "the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life."

Accelerated testing: 40°C ± 2°C /75% RH ± 5% RH for 3 months.

RESULTS AND DISCUSSION

FT-IR Study of Drug & formulation

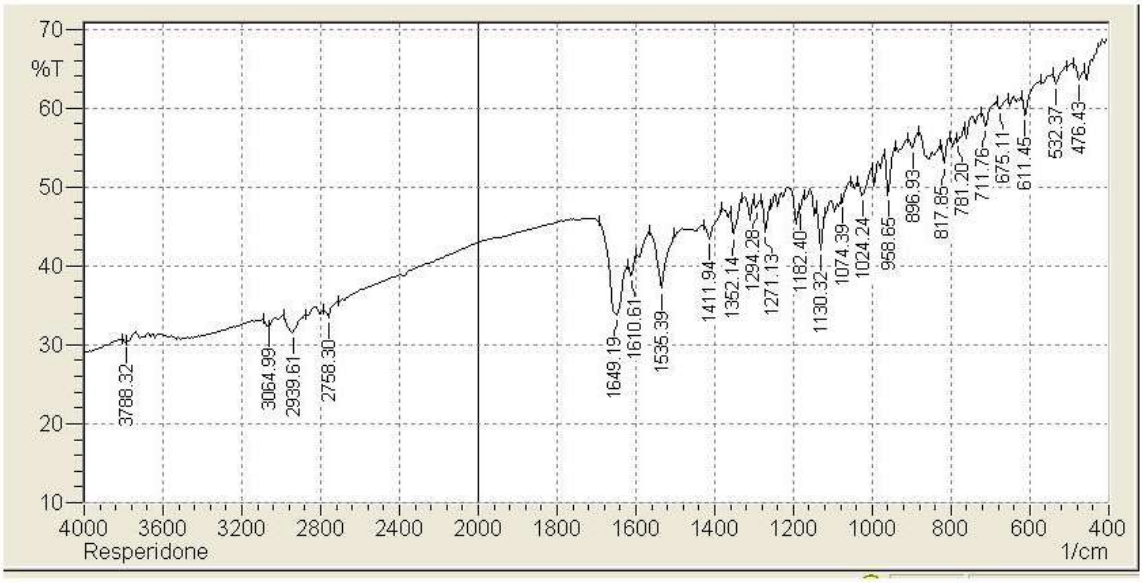

Figure 1: FT-IR spectra of Risperidone

Drug - Excipient Compatibility Studies

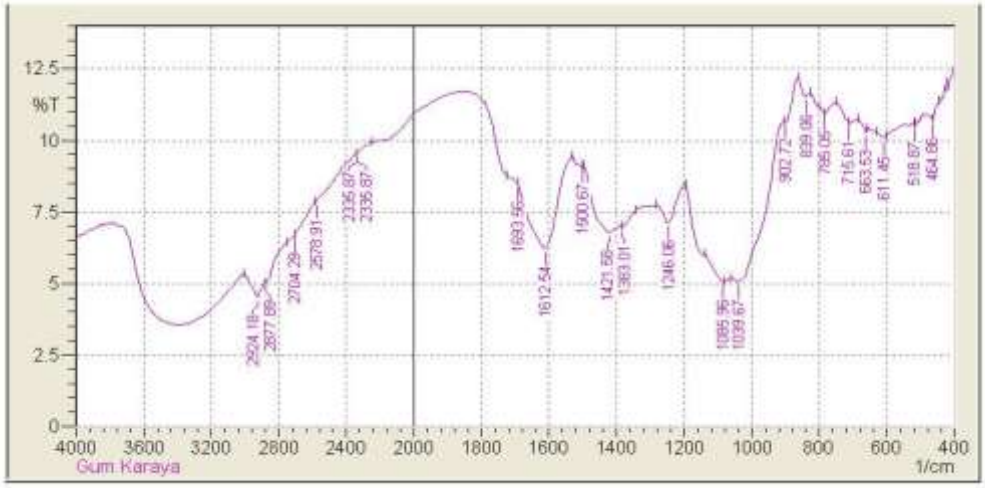

Figure 2: FT-IR spectra of Drug + gum karaya

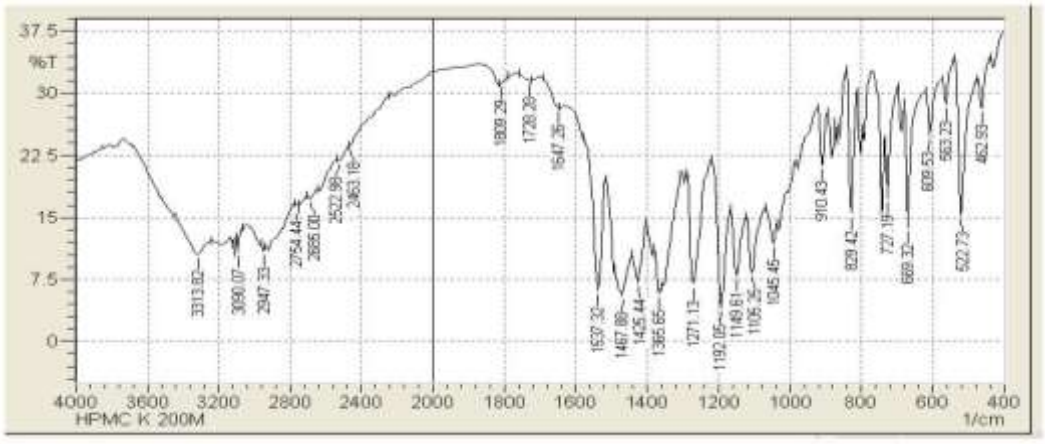

Figure 3: FT-IR spectra of Drug + HPMC K200M

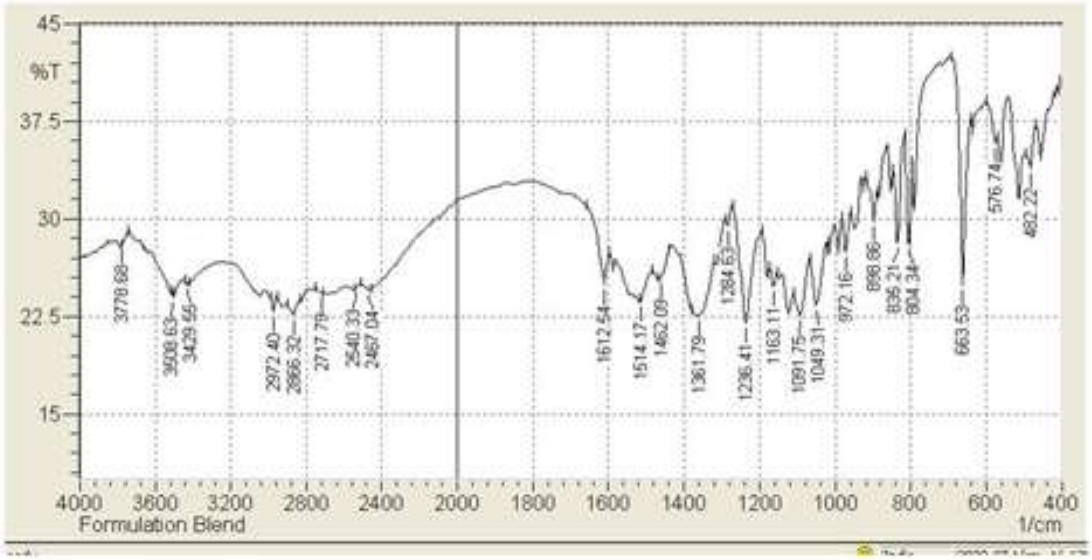

Figure 4 :Drug+polymers+excipient

Drug excipients interaction study demonstrates there is no drug interaction between drug and polymers in mixture.

DSC of Drug & formulation

Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. Accurately weighed samples were placed on the aluminum plate, sealed with aluminum lids and heated at a constant rate of 5 °C/min, over a temperature range of 0 to 250 °C.

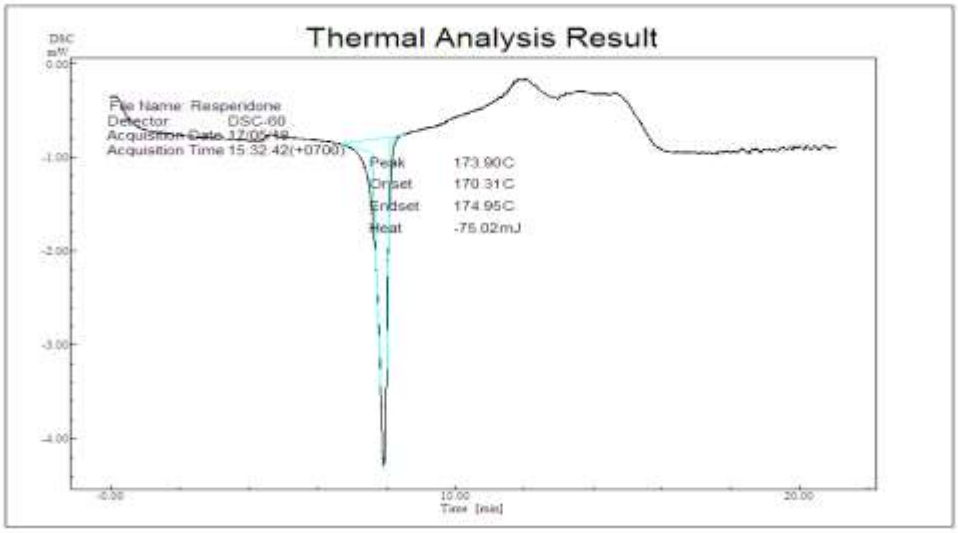

Figure 5: DSC of Risperidone

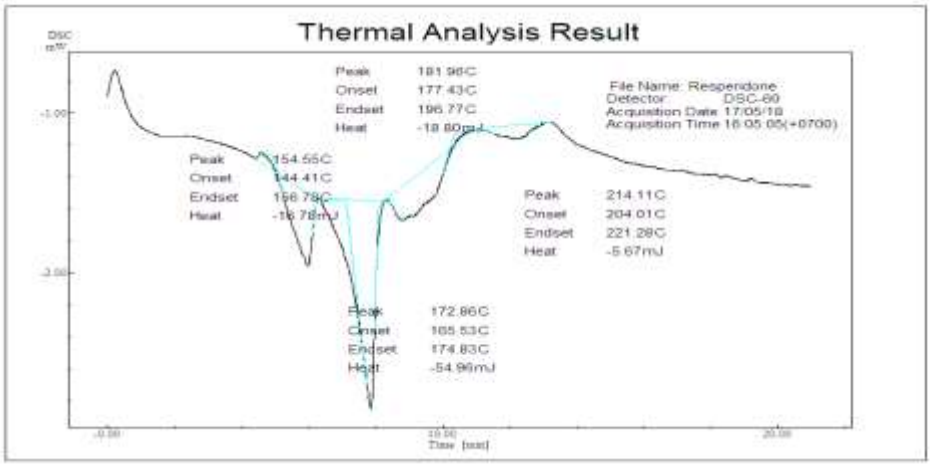

Figure 6: DSC of Risperidone+polymer+excipient

Drug excipients interaction study demonstrates there is no drug interaction between drug and polymers in mixture.

Table 5: Pre Compression Parameter optimized batches

Batch No.	Angle 0f Repose (θ)	Bulk Density (gm./ml)	Tapped Density (gm./ml)	Hausner's Ratio	Carr's Index (%)
R1	28.16±1.89	0.545 ±0.008	0.731±0.008	1.34	22.98
R2	29.00±1.00	0.636±0.031	0.762±0.011	1.19	16.53
R3	27.27±0.65	0.563±0.009	0.619±0.006	1.09	7.78
R4	27.73±1.41	0.552 ±0.007	0.721±0.066	1.30	23.43
R5	26.83±1.60	0.534±0.002	0.734±0.008	1.37	27.24
R6	29.00±1.00	0.670±0.007	0.743±0.010	1.10	9.82
R7	30.10±0.85	0.661±0.048	0.717±0.002	1.08	7.81
R8	26.80±1.70	0.623±0.006	0.871±0.006	1.39	28.47
R9	27.70±1.47	0.572±0.008	0.727±0.015	1.27	21.32

Data of Preformulation study

Table 6: Post-Compression Parameters of optimized batches:

Formulations	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug Content (%)
R1	247±2.21	5.6	4.5	0.53±0.01	99.23
R2	247±2.48	5.8	4.5	0.53±0.02	98.44
R3	247±2.58	5.9	4.5	0.54±0.01	97.36
R4	248±1.61	6.0	4.3	0.58±0.04	98.24
R5	248±1.89	5.2	4.2	0.59±0.02	98.15
R6	251±1.30	5.5	4.5	1.98±0.02	99.10
R7	251±1.08	6.3	4.5	2.17±0.01	92.48
R8	249±1.08	5.6	4.4	2.40±0.03	97.28
R9	249±0.94	6.0	4.5	2.65±0.53	96.54

Table 7: In-*vitro* buoyancy study of optimized batches R1-R9

Formulation Codes	Floating Lag Time (min)	Total FLT Hours
R1	2.30 ±1.24	>12
R2	2.43± 1.6	>12
R3	1.45± 1.8	>12
R4	2.24± 1.7	>12
R5	2 ± 1.4	>12
R6	2.14 ± 2.0	>12
R7	1.20± 1.5	>12
R8	1.20± 1.2	>12
R9	1.18 ± 2.0	>12

Table 8:% Swelling Index formulation R1-R9

Time in Hours	Formulation Codes								
	R1	R2	R3	R4	R5	R6	R7	R8	R9
1	23.10	29.52	28.32	36.80	13.10	37.54	58.20	65.45	71.39
2	41.34	37.70	44.29	47.26	40.15	54.65	74.40	82.20	86.45
3	48.22	45.33	65.85	58.16	50.87	70.43	90.40	96.68	105.45
4	64.48	57.62	87.25	66.53	58.26	85.61	105.60	150.32	120.13
5	68.75	65.20	98.34	80.20	81.49	91.42	132.20	194.52	135.85
6	71.15	73.66	115.40	93.58	93	93.28	165.45	223.65	146.97
7	79.85	98.07	142.26	107.56	122.54	130.50	189.62	245.82	120.80
8	105.42	105.43	165.76	138.67	136.18	156.28	202.14	260.87	135.21
9	98.65	125.52	172.57	165.58	151.06	169.56	220.54	289.68	310.24
10	87.27	129.80	191.40	153.24	174.72	186.40	236.21	310.42	335.85
11	83.96	104.15	175.54	142.23	160.39	205.26	246.6	335.19	354.30
12	74.20	90.45	162.06	130.45	140.55	190.42	240.6	320.42	346.76

Table 9: In-vitro Drug Release Study

Time in Hours	Formulation Codes								
	R1	R2	R3	R4	R5	R6	R7	R8	R9
0	0	0	0	0	0	0	0	0	0
1	16.70	17.19	14.76	16.22	15.00	15.73	19.33	18.65	16.70

2	22.55	20.61	15.75	17.21	16.33	16.72	20.13	20.61	18.18
3	31.82	27.44	16.74	17.71	16.74	17.71	26.47	25.50	21.60
4	40.60	37.68	17.73	21.62	18.21	18.94	43.51	29.41	26.49
5	47.45	44.53	18.72	32.34	32.82	27.38	54.74	43.06	32.35
6	65.98	60.13	19.71	41.13	37.23	35.48	71.33	45.54	35.30
7	75.29	80.13	69.81	55.27	42.13	46.50	75.30	48.50	42.64
8	91.42	87.03	84.96	70.89	58.22	61.14	81.71	57.31	51.43
9	99.30	98.79	94.29	85.07	69.47	76.77	85.69	69.04	57.32
10	99.41	99.01	97.31	90.51	84.62	83.66	87.24	76.90	65.65
11	99.52	99.01	97.42	98.39	98.32	92.99	89.28	81.84	71.07
12	99.63	99.12	97.52	98.50	96.43	99.41	92.30	84.85	74.55

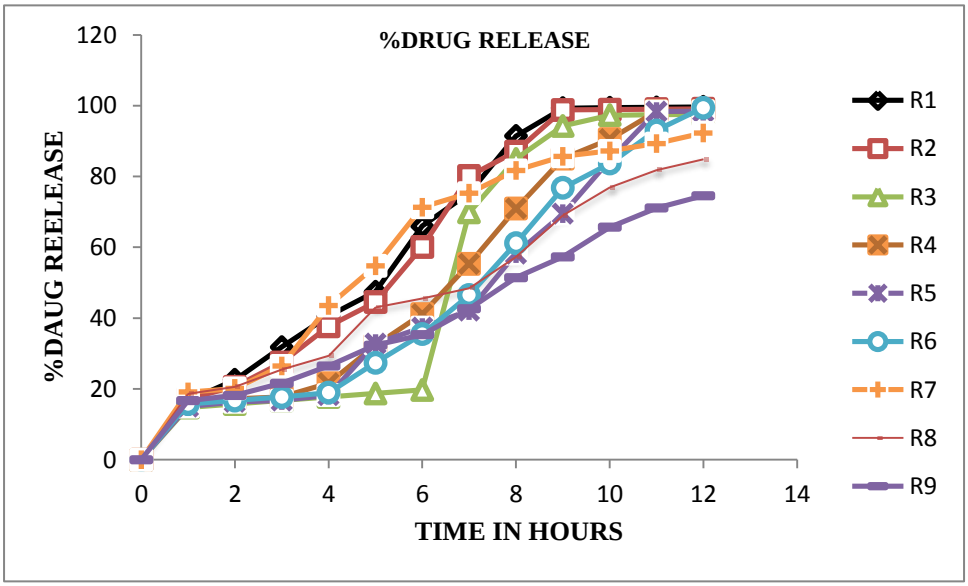

Figure 7: In-vitro Drug Release Study

Table 10: In vitro Drug release data Analysis

Batch	Zero order		First order		Higuchi		Korsmeyer-peppas		Hixson-Crowell	
R6	**R** 0.8462	**Slope** 8.7020	**R** 0.8237	**Slope** -0.3328	**R** 0.7208	**Slope** 23.6280	**R** 0.8294 **N** 4.990	**Slope** -0.0632	**R** 0.8328	**Slope** -0.0632

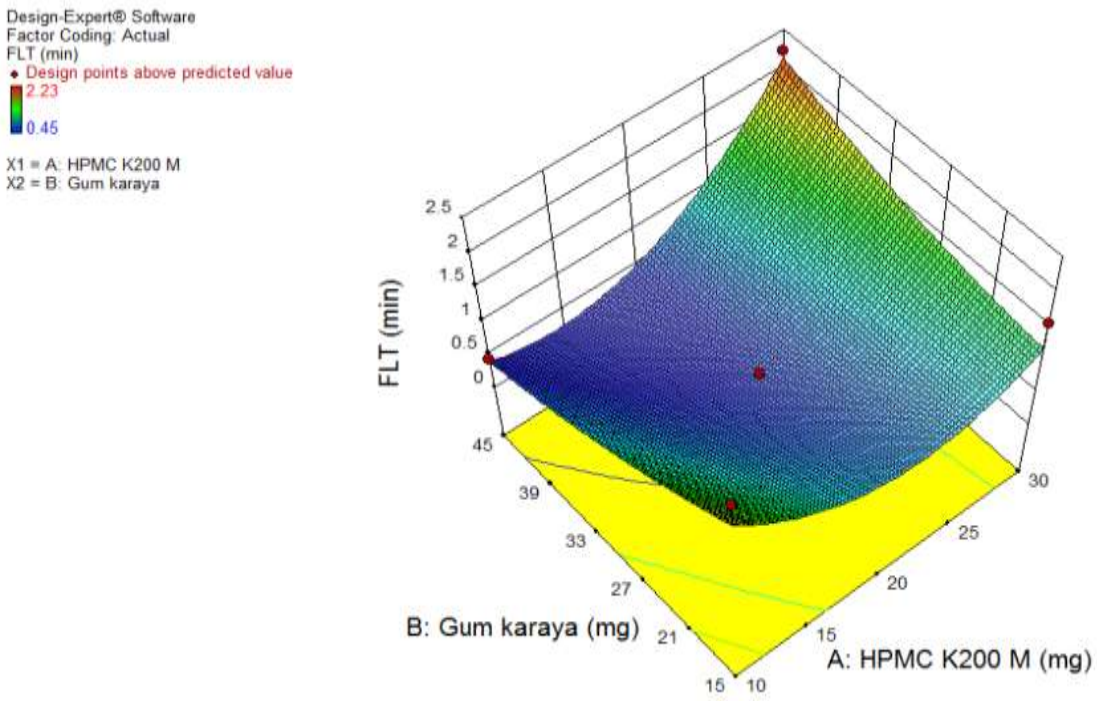

Figure 8:A response surface plot showing effect of concentration of independent variables on the floating Lag time.

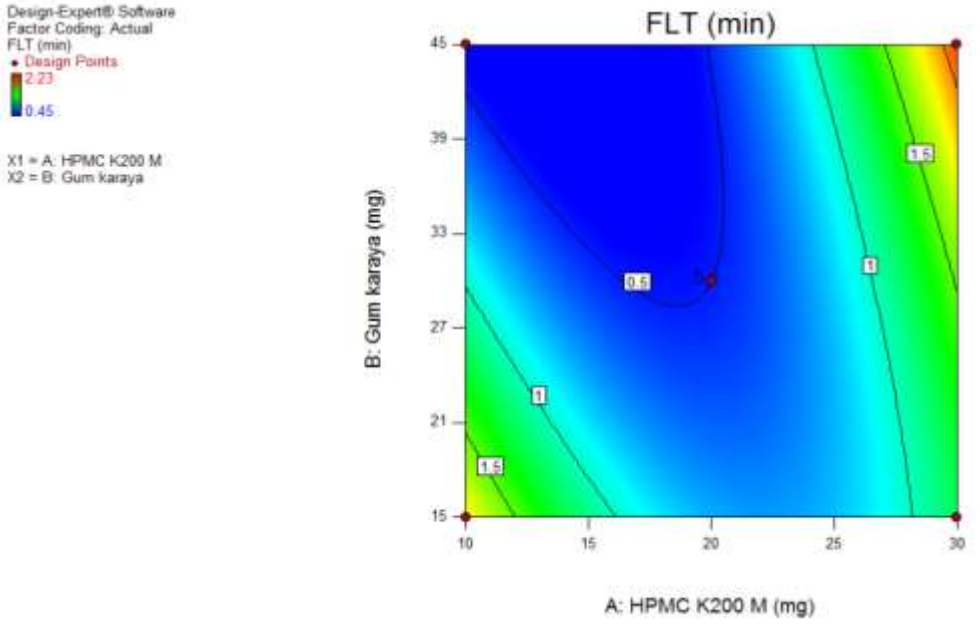

Figure 9: counter plot showing relationship between various levels of independent variables to gain fixed value of floating lag time.

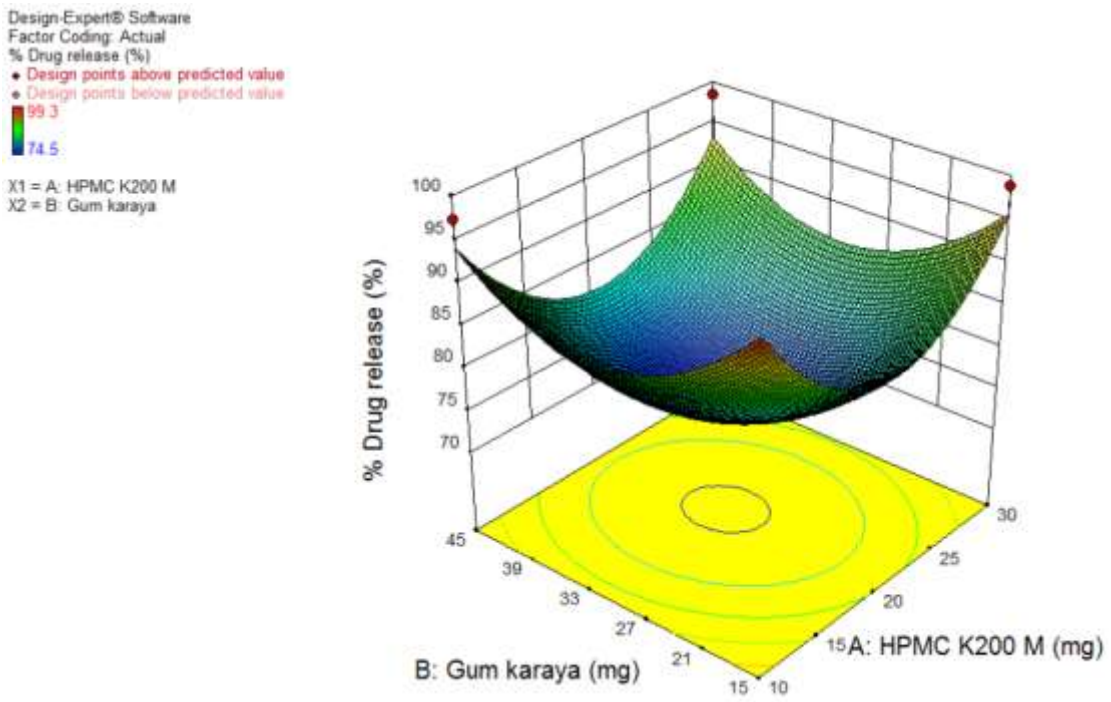

Figure 10: A response surface plot showing effect of concentration of independent variables on the % drug release

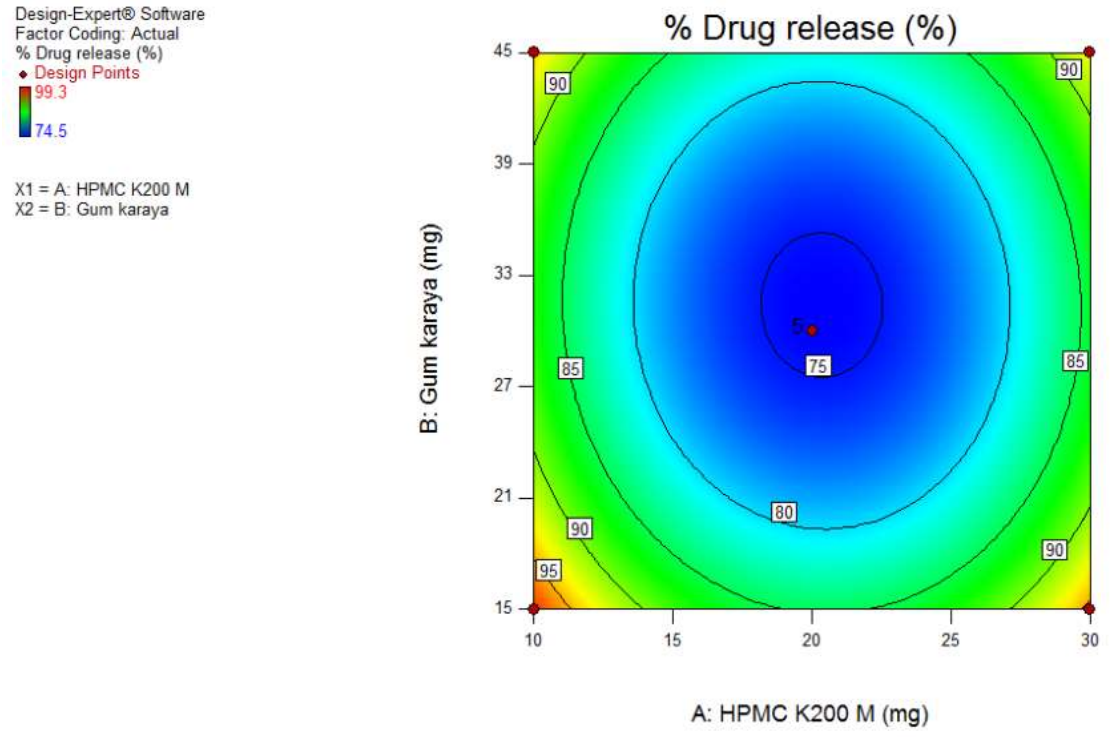

Figure 11: A counter plot of showing relationship between various levels of independent variables to gain fixed value of % drug release

Table 11: Result of ANOVA

Response model	Sum of square	Degree of freedom	Mean square	F value	P value	R square	Model significant /Not significant
% Drug release	1501.95	12	294.87	20.34	0.0005	0.9356	Significant
Floating lag time	6.54	12	1.281	17.01	17.01	0.0009	Significant

Stablity studies

Table 12: Stability study of optimized formula R6

Condition	Time (month)	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	Floating lag time (minute)	% Drug release
Accelerated temperature 40^{0}C and 75% RH	3	4.5	0.86	92.75	2.54	91.20

%Drug Release in Graphical Presentation

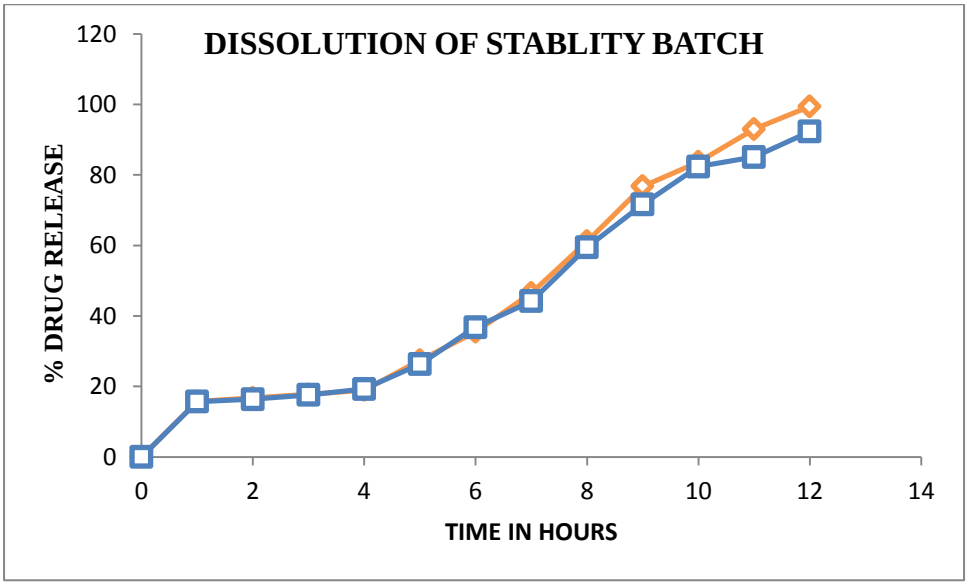

Figure 12 Stability Studies batch In Vitro %Drug Release

CONCLUSION

Formulations were prepared by using direct compression method. The prepared tablets exhibited satisfactory physicochemical characteristics. Floating tablets of Risperidone with shorter lag time prepared by direct compression method by using HPMC K200 M and Gum karaya and sodium bicarbonate as a gas generating agent. All prepared batches shown good in-vitro buoyancy studies and studies. The best result from optimized batches is of R6 which gives drug release 99.41% in 12hrs.

ACKNOWLEDGMENT

The authors are thankful to Hazrat Maulana G.M. Vastanvi sahab, President, Akbar Patel sir Coordinater of Jamia Islamia Ishaatul Uloom's Ali Allana College of Pharmacy Akkalkuwa Dist. Nandurbar Maharashtra for providing the necessary facilities to carry out this research work.

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