Formulation and Evaluation of Gastro-retentive Floating Tablets of an Anti Retroviral Drug-Ritonavir

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ABSTRACT

The aim of the present work is to design floating tablets of Ritonavir to prolong the gastric residence time and oral bioavailability of the drug. Tablets were prepared by wetand melt granulation techniques using alone or different combinations of hydrophilic and lipophilic polymers such as Gelucire 43/01, Gelucire 50/02, Geleol, HPMC polymers of K 15 and K 100 grades in various concentrations. Sodium bicarbonate is used as a gas generating agent along with Ethyl Cellulose, Talc and Magnesium Stearate and Micro Crystalline Cellulose. Prepared formulations were subjected to pre- and post-granulation parameters such as hardness, friability, swelling ability, floating behaviour, drug release and drug-polymer compatibility studies in accordance with ICH guidelines. Results shown that Ritonavir is soluble in 0.1N HClat pH 1.2, indicating good absorption in the stomach region and by observing the drug release studies RF13 formulation has shown controlled release of 98.67% for 12 hours with less floating lag time of 45 Seconds by using the combination of 1:1 ratio of Gelucire 43/01 and Gelucire 50/02: HPMC K15 polymer. So, it is concluded that RF13 was selected as anoptimized formulation as it follows zero order drug release with Higuchi diffusion mechanism.

Keywords: Ritonavir,Gastric residence time.

INTRODUCTION

Ritonaviran inhibitor of HIV protease, used asantiretroviral drug along with other medications in the treatment of HIV/AIDS. It is now rarely used for its own antiviral activity but remains widely used as a booster of other protease inhibitors.[1]Because of shortbiological half-life of ~3-5hrs, Ritonavir eliminates quickly from the body as it undergoes extensive first pass metabolism. Therefore, in order to improve drug bioavailability and to increase the drug residence time, controlled gastric retention system by various mechanismshas chosen.[2] Among those,floatingdrugdeliveryapproach have been most commonly used to formulate with different polymers such as Gelucire 43/01, Gelucire 50/02 and Geleolas carrier forming materials, Hydroxypropyl methylcellulose (HPMC) and Ethyl cellulose as controlled release agents, Sodium bicarbonate and Citric acid as gas generating agents and other polymers owing to their low density,hydrophilic lipophilic balance, floating and modified release properties.[3]AsRitonavir is soluble in acidic pH and predominantly get absorbed from the stomach, in the present work an attempt was made to use a combination of (various ratios) hydrophilic and lipophilic polymers to control the release and to increase the gastric residence time of the drug.

MATERIALS AND METHODS

Drugs and Excipients

The main drug Ritonavir was obtained as a gift sample from MSN Labs Limited, Hyderabad, India. Polymers such as Gelucire 43/01, Gelucire 50/02, Geleol were obtained from Gattefosse (St Priest, Cedex, France) as gift samplesand other polymers such as HPMC, Ethyl cellulose, Sodium bicarbonate, Magnesium Stearate,

Talc were purchased from S D Fine Chemicals Limited, Mumbai, India. And all the other reagents used were of analytical grade.

PRE-FORMULATION STUDIES[4]

Identification of the drug (Ritonavir) by organoleptic evaluation, determination of melting point and solubility profile were carried out as per Indian Pharmacopoeia, 2007 and literature survey. Standard calibration curve of Ritonavir was carried out in 0.1N HCl at 256nm by using UV-Visible spectrophotometer.

Drug Polymer Compatibility study by FTIR

Main purpose of FTIR study is to observe any prominent changes in the spectrum pattern of the drug due to polymers and thus to identify the drug polymer compatibility without any interactions. An IR spectrum of pure drug (Ritonavir) and optimized physical mixture of the Ritonavir with the polymers used was recorded at a range between 500-4000cm^{-1} with a resolution of 4cm^{-1} by using FTIR spectrophotometer.

Evaluation of Flow properties

Powder form of Ritonavir optimized mixture was evaluated for flow properties by measuring Bulk Density (Cylinder method), Tapped Density (Cylinder method), Angle of Repose (Fixed Funnel method), Compressibility by Carr's index and Hausner's ratio.

METHODS OF PREPARATION[5-7]

1)Wet Granulation Method

Required quantities of drug and polymers were weighed and blendedthoroughly. The so formed blend was then passed through 60# sieve. The powder mixture is granulated by adding binding agents and dried at ~55°C for about one hour to getgranules. The granules so obtained were sieved through 10 # sieve and finally compressed into tablets using compression machine after adding sufficient lubricant and glidant.

2) Melt Granulation Method

Mentioned quantities of drug and excipients were weighed according to the formulationchart. Respective lipoidal polymers were taken into a beaker and melted for a temperature above 2°C to their corresponding melting points. Previously prepared drug- excipient mixture was added to themolten mass with continuous agitation and allowed to solidify at4°C. The solidified mass was then passed through 60# sieve to attain uniform sizedgranules. The granules so obtained were sieved through 10 # sieve and finally compressed into tablets using compression machine after adding sufficient lubricant and glidant.

Each tablet contained 100mg of Ritonavir. Compositions of different formulations were given in the tables 1, 2 & 3 as shown below;

Table: 1 Composition of Ritonavir gastroretentive floating tablets from RF1- RF12[8-10]

Ingredients (mg)	RF1-RF12 (Drug: Polymer Ratio)											
	1:0.25			1:0.5			1:0.75			1:1		
	RF1	RF2	RF3	RF4	RF5	RF6	RF7	RF8	RF9	RF10	RF11	RF12
Ritonavir	100	100	100	100	100	100	100	100	100	100	100	100
Gelucire 43/01	25	---	---	50	---	---	75	---	---	100	---	---
Gelucire 50/02	---	25	---	---	50	---	---	75	---	---	100	---
Geleol pellets	---	---	25	---	---	50	---	---	75	---	---	100
HPMC K15	80	80	80	80	80	80	80	80	80	80	80	80
HPMC K100	---	---	---	---	---	---	---	---	---	---	---	---
Ethyl cellulose	30	30	30	30	30	30	30	30	30	30	30	30
Sodium bicarbonate	30	30	30	30	30	30	30	30	30	30	30	30
MCC	88	88	88	64	64	64	39	39	39	14	14	14
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3
Talc	4	4	4	4	4	4	4	4	4	4	4	4
Total Weight (mg)	360	360	360	360	360	360	360	360	360	360	360	360

Table: 2 Composition of Ritonavir gastroretentive floating tablets from RF13- RF18

Ingredients (mg)	RF13-RF18 Combination of different lipophilic Polymers: different ratios of HPMC					
	RF13	**RF14**	**RF15**	**RF16**	**RF17**	**RF18**
Ritonavir	100	100	100	100	100	100
Gelucire 43/01	50	---	50	50	50	50
Gelucire 50/02	50	50	---	50	50	50
Geleol pellets	---	50	50	---	---	---
HPMC K15	80	80	80	40	---	---
HPMC K100	---	---	---	---	80	40
Ethyl cellulose	30	30	30	30	30	30
Sodium bicarbonate	30	30	30	30	30	30
MCC	39	39	39	79	39	79
Magnesium Stearate	3	3	3	3	3	3
Talc	4	4	4	4	4	4
Total weight (mg)	360	360	360	360	360	360

EVALUATION OF TABLETS

Prepared tablets of Ritonavir were evaluated for hardness using a Monsanto tablet hardness tester. Friability was determined in a friability tester for 100 revolutions at 25 rpm for 4minutes. Weight variation test was done according to the official pharmacopeial procedure with the specification limit not more than two of the individual weight deviates by 10% of average weight and none should deviate twice that percentage.

Estimation of DrugContent[11]

The drug content in each formulation was determined in triplicates. For each batch of formulation, 20 tablets were taken, weighed and powdered finely using motor and pestle.100 mg equivalent of tablet powder was weighed and dissolved in 100 ml of pH 1.2 acetate buffer followed by stirring for 10 min and then filtered through 0.45µ membrane filter. The samples were analyzed after necessary dilutions using UV Visible Spectrophotometer.

In- vitro Swelling studies (SI)

To evaluate the water penetration characteristics, prepared floating tablet formulations were weighed individually(W1) and placed separately in a glass beaker containing 200 ml of 0.1 N HCl incubated at 37 ± 1°C. At regular 1 h time interval until 12 h, the tablets were removed from beaker and the excess surface liquid was wiped carefully using the paper. The swollen tablets were then reweighed (W2) and the swelling index (SI) was calculated by the following formula.

$\% SI = (W_2 - W_1)/W_1 * 100$

In-vitro BuoyancyStudies[12]

Buoyancy of a tablet is determined by its floatinglagtime.Preparedformulationswereplacedina 100 ml glass beaker containing 0.1 N HCl and the time required for each tablet to raise to the surface and float is determined and it is considered as floating lag time and also the total time duration by which a dosage form remain buoyant is determined, it is considered as total floating time.

In-vitro DissolutionStudies

In- vitro Drug Release Studies of prepared gastro-retentive formulations was carried out using USP type II Dissolution apparatus (paddle type).Conditionsappliedforthedissolutionstudieswere:900mlof0.1 N HCl (pH 1.2) as media for dissolution, temperature maintained at 37 ±0.5 °C with rotation speed of 50 rpm. 5 ml Aliquot of samples were withdrawn at specific different time intervals and filtered through Millipore 0.45 µ filter. The volume of dissolution fluid is adjusted to 900 ml by replacing 5 ml of dissolution medium after each sampling. Samples were diluted as per need, analyzed for absorbance and cumulative percentage of the drug release was calculated. The mean of cumulative % of the drug released from 6 tablets from different batch of formulations were used for analysis ofdata.

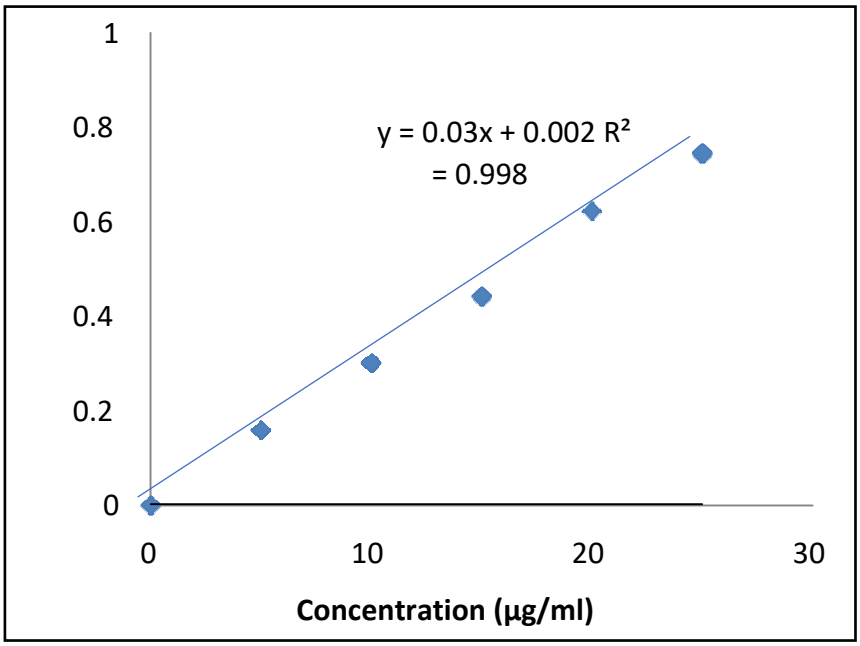
Kinetic modeling of Drug ReleaseProfiles[13]

To analyze and evaluate the drug release mechanism from the dosage form, the obtained dissolution data of optimized batches was fitted to various kinetic models like zero- order, first-order, Higuchi and Korsmeyer-Peppas equation to ascertain the kinetic modeling of drug release.

RESULTS AND DISCUSSION

Figure: 1Calibration Curve ofRitonavir

Ritonavir solution in 0.1NHCl was scanned at 200-400nm by using UV- Visible Spectrophotometer. It was found that maximum wavelength of Ritonavir is 256nm in 0.1NHCl.



A linear relationship was established between the Concentration on X-axis vs Absorbance on Y-axis with R^2 of 0.998.

Table: 3Absorbance of Ritonavir at Maximum wavelength

Concentration (µg/ml)	Absorbance (λmax) 256nm
0	0
5	0.159±0.02
10	0.301±0.05
15	0.442±0.04
20	0.623±0.01
25	0.745±0.09

FTIR study

There is no prominent difference was observed in the principal IR spectrum of Drug excipient mixture and optimized formulation (RF13) upon comparison with the peaks of drug and polymer alone, which is considered as drug and polymers were compatible enough without any interactions.

Figure: 2FTIR Spectrum of Ritonavir

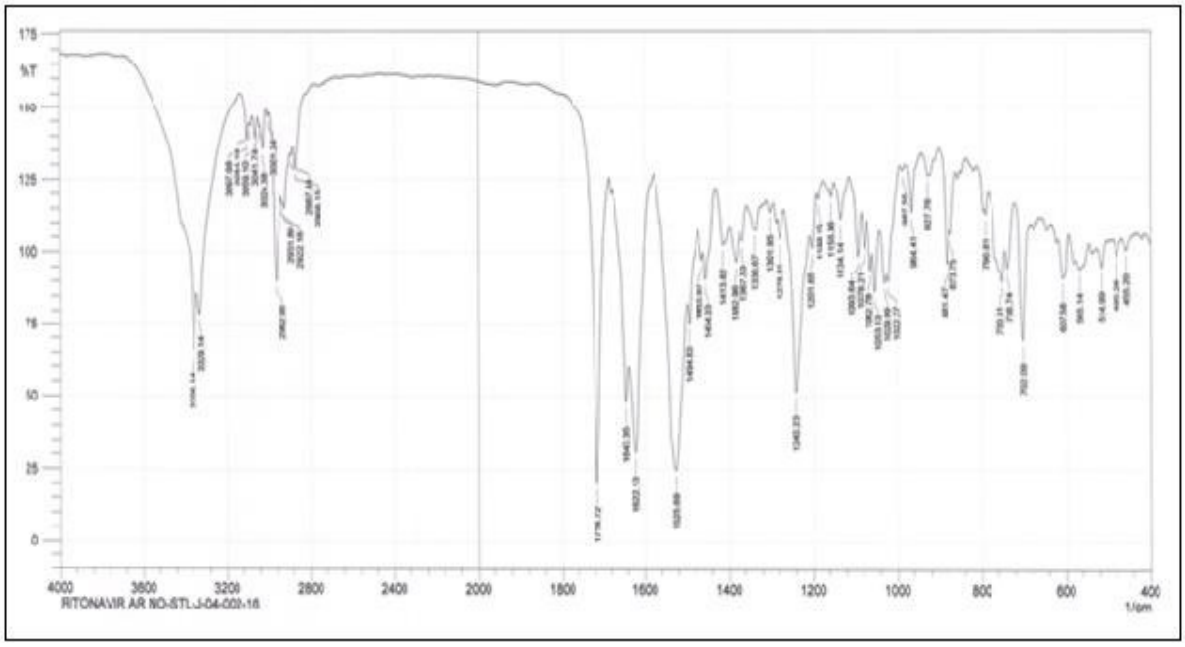


Table: 4FTIR Spectral data of Ritonavir

BOND	FREQUENCY RANGE	OBSERVATION
NH	3400-3500 cm^{-1} (Stretching) 1500-1650 cm^{-1} (Bending)	3356.14cm^{-1} 1525.69cm^{-1}
C=N	1630-1690 cm^{-1}	1645.35 cm^{-1}
C=O	1705-1725 cm^{-1}	1714.72 cm^{-1}
C=C	1680-1620 cm^{-1}	1622.13cm^{-1} 1643.35cm^{-1}

Figure: 3FTIR Spectrum of Ritonavir Optimized formulation

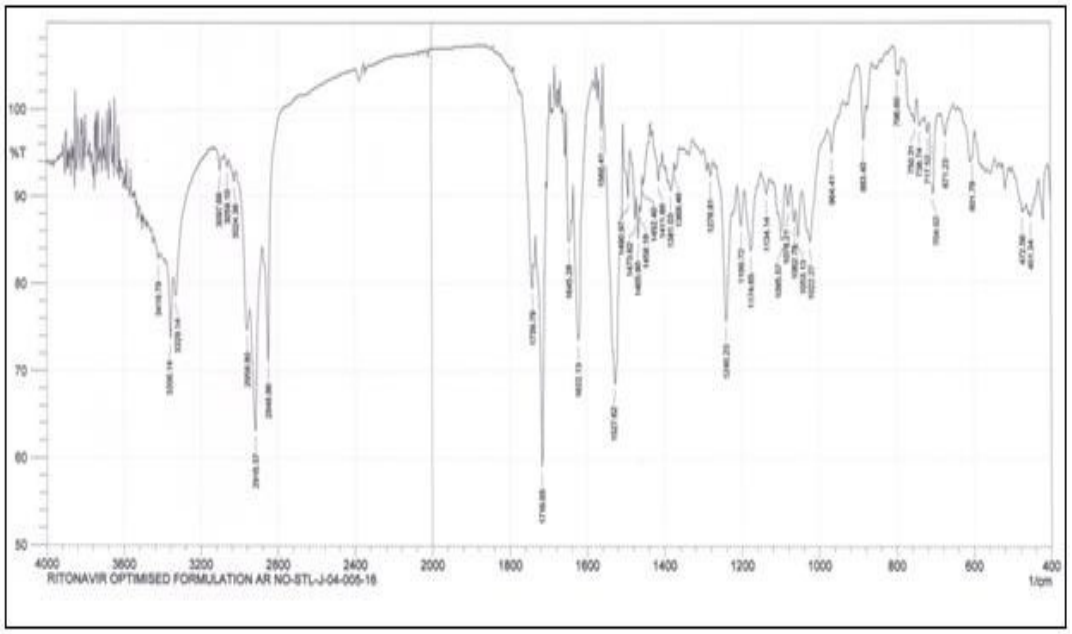


Table:5FTIR Spectral data of Ritonavir Optimized formulation

BOND	FREQUENCY RANGE	OBSERVATION
NH	3400-3500 cm^{-1} (Stretching) 1500-1650 cm^{-1} (Bending)	3419.79cm^{-1} 1527.62cm^{-1} 1622.13cm^{-1}
C=N	1630-1690 cm^{-1}	1645.28 cm^{-1}
C=O	1705-1725 cm^{-1}	1716.65 cm^{-1}
C=C	1680-1620 cm^{-1}	1622.13cm^{-1} 1645.28cm^{-1}

Evaluation of Flow Properties

Different flow properties of granules were calculated in the form of Bulk density, Tapped density, Carr's Index, Hausner's ratio and Angle of Repose.

Table: 6 Evaluation of Flow properties

Parameter	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (o)
RF1	0.521	0.632	17.56	1.21	31
RF2	0.513	0.614	16.44	1.20	34
RF3	0.488	0.623	21.66	1.27	39
RF4	0.503	0.618	18.60	1.22	37
RF5	0.523	0.617	15.23	1.17	34
RF6	0.534	0.621	14.00	1.16	33
RF7	0.527	0.623	15.40	1.18	31
RF8	0.513	0.632	18.82	1.23	30
RF9	0.524	0.631	16.95	1.20	33
RF10	0.499	0.617	19.12	1.24	32
RF11	0.517	0.622	16.88	1.20	31
RF12	0.523	0.633	17.37	1.21	34
RF13	0.555	0.642	13.55	1.15	32
RF14	0.553	0.654	15.44	1.18	33
RF15	0.542	0.651	16.74	1.20	34
RF16	0.522	0.632	17.40	1.21	36
RF17	0.533	0.643	17.10	1.20	37
RF18	0.540	0.647	16.53	1.19	29

Formulations RF1 to RF18 have shown varying bulk densities between 0.488 to 0.555 gm/ml, tapped density ranging from 0.614 to 0.654 gm/ml, angle of repose between 29 to 39, Carr'sindex between 14.00 to 21.66 and Hausner's ratio between 1.15 to 1.27. All these results indicate that, the powder mixture possess satisfactory flow properties and compressibility.

Evaluation of Formulated Tablets

Each formulated tablet was analyzed for hardness, weight variation, friability, drug content, floating characteristics and in vitro drug release.

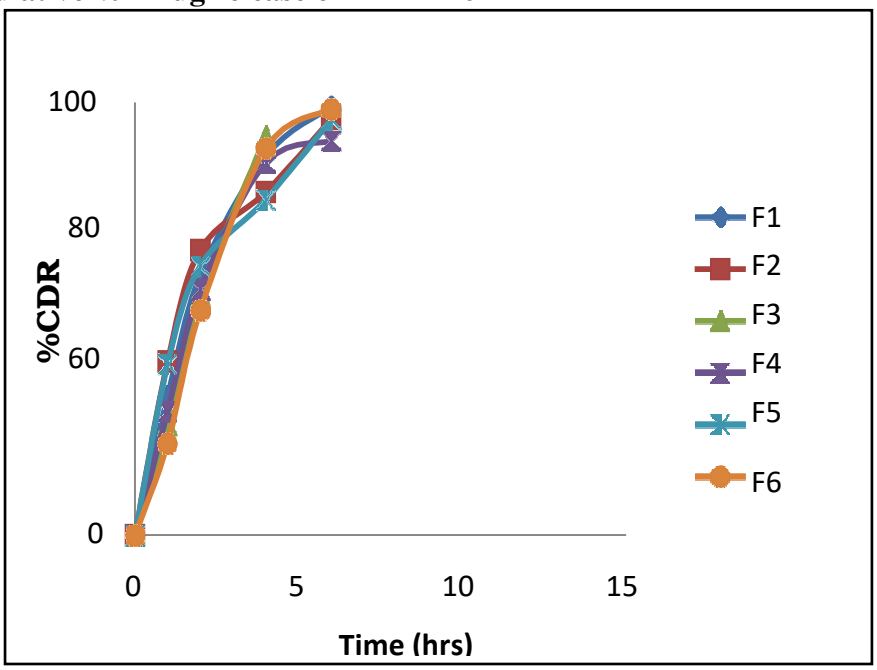
All the formulations passed the weight variation and friability tests, as all the tablets were within the range of limit. Weight loss in the friability test was less than 1% in all the cases. Hardness was in the range of 3.2±0.6 to 4.1±0.5 kg/cm^2, which was due to the presence of waxypolymers. Results were given the table as below

Table: 7 Evaluation of Formulated Tablets

Parameter	Average wt. (mg)(n=10)	Hardness (Kg/cm^2) (n=10)	Thickness (mm) (n=10)	Friability %	% Drug content
RF1	360±1.2	3.9±0.3	4.58±0.012	0.16	98.25
RF2	359±1.9	4.1±0.2	4.12±0.012	0.17	98.24
RF3	357±1.5	3.9±0.03	4.71±0.007	0.22	97.10
RF4	361±1.6	3.7±0.6	4.52±0.006	0.22	96.64
RF5	361±1.3	3.8±0.1	4.66±0.075	0.27	96.68
RF6	360±1.6	4.1±0.5	4.44±0.087	0.25	95.41
RF7	359±2.5	3.8±0.3	4.33±0.007	0.26	98.12
RF8	358±1.6	3.9±0.6	4.23±0.007	0.28	97.28
RF9	357±1.3	3.7±0.09	4.66±0.054	0.32	95.41
RF10	360±1.0	3.8±0.09	4.13±0.062	0.34	96.18
RF11	361±1.1	3.2±0.6	4.28±0.45	0.40	97.98
RF12	359±2.4	3.4±0.1	4.45±0.052	0.42	98.18
RF13	358±2.3	3.7±0.2	4.58±0.057	0.38	97.47
RF14	359±1.9	3.7±0.6	4.85±0.078	0.39	99.19
RF15	362±1.8	3.8±0.5	4.79±0.003	0.56	98.18
RF16	358±1.3	3.7±0.4	4.62±0.008	0.12	97.19
RF17	359±1.3	4.1±0.3	4.87±0.005	0.22	98.78
RF18	360±2.6	3.9±0.3	4.45±0.006	0.28	99.89

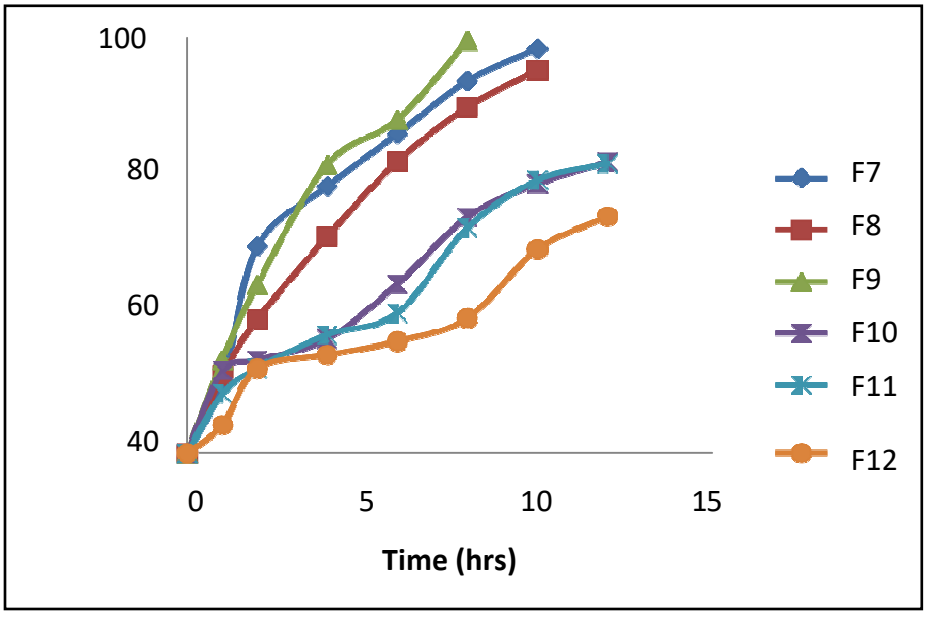
***In-Vitro* Drug Release Studies**

Figure: 4 Cumulative % Drug release of RF1-RF6



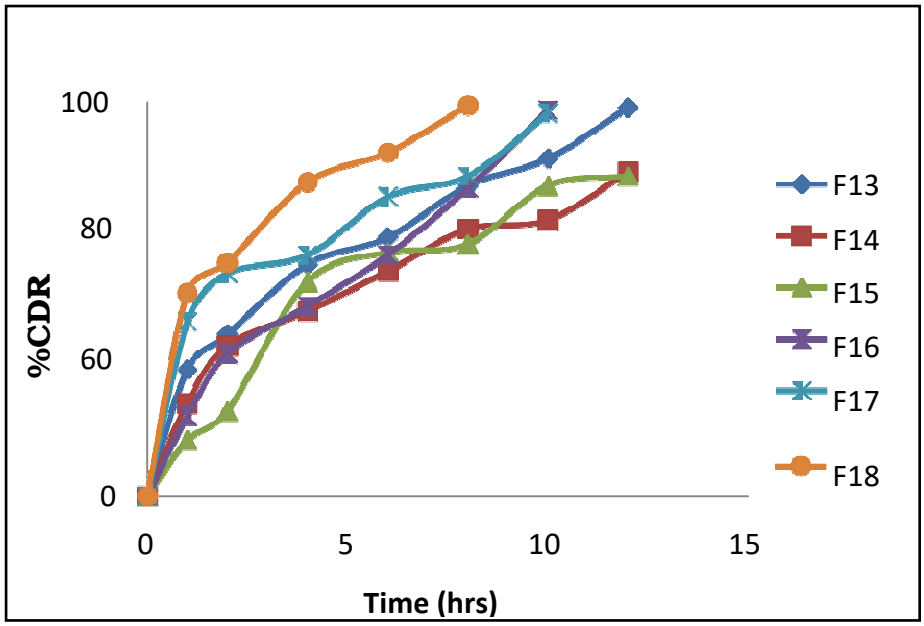
It was observed that RF1 and RF3 containing 1:0.25 concentration of the lipophilic polymers Gelucire 43/01, Gelucire 50/02 and Geleol have shown 99.22% for 6 hrs and 92.34% drug release in 4 hrs, respectively.RF4 and RF6containing 1:0.5 concentration of Gelucire 43/01, Gelucire 50/02 and Geleol have shown 91.21%,96.02% and 98.63% of drug release in 6 hrs, respectively. This indicates that 0.25 ratio concentration of any polymer is not sufficient to retard the drug release.

Figure: 5 Cumulative % Drug release of RF7-RF12



For formulations, RF7 to RF9 containing concentration ratios (1: 0.75) of Gelucire 43/01, Gelucire 50/02 and Geleol have shown 97.03% for 10 hrs, 92.28% drug release for 10 hrs and 99.32% for 8 hrs, respectively. Formulations RF10 to RF12 containing 1:1concentration of Gelucire 43/01, Gelucire 50/02 and Geleol has shown 70.10%, 69.72% and 57.06% for 12 hrs, respectively.

Figure: 6 Cumulative % Drug release of RF13-RF18



Formulations RF13-RF18 were prepared with combination of two lipoidal polymers with different ratios of HPMC K100 and HPMC K15. The formulation RF13 containing equal ratio of Gelucire 43/01 and Gelucire 50/02 have shown the drug release of 98.67% for 12 hrs. The retardation in drug release was found to be more in formulation RF13 which contained Gelucire 43/01 and Gelucire 50/02 in comparison to RF14 containing Gelucire 50/02 with Geleol and RF15 which contained Gelucire 43/01 andGeleol. The release was further retarded for formulations containing more concentrations of polymers. In case of RF16 RF17 and RF18, containing 1: 1 (drug to polymer ratio) it was found to be within 10 hrs. Among all the formulations RF13 was selected as optimized formulation because the drug release was retarded up to 12 hrs with a percentage of98.67%.

Kinetic modeling of Drug ReleaseProfiles

In order to establish the drug release mechanism, the *in-vitro* release data was fitted in to exponential forms like Zero order, First order, Higuchi Plot and Korsmeyer- Peppas Equations.

The regression coefficient obtained for zero order kinetics was found to be higher than first order kinetics for all the formulations, indicating that the drug release followed zero order kinetics. To evaluate the drug release mechanism, plots of cumulative percentage drug release vs square root of time as per Higuchi equation and also Korsmeyer-Peppas equation was constructed. These plots were found to be linear and among all the formulations RF13 containing 1:1 concentration ratio of Gelucire 43/01 and Gelucire 50/02 and HPMC K15 was optimized as the best formulation with R^2 of 0.907 and n value with 1.494, which indicates the mechanism of drug release was a non-fickian model.

Table: 8Release Kinetics data of Optimized formulation(RF13)

Parameter	R^2 Values				(n)Value
	Zero order	First order	Higuchi release	Korsmeyer-Peppas	Korsmeyer-Peppas
RF13	0.907	0.819	0.994	0.992	1.494

The optimized formulation (RF13) has high R^2value for Zero order kinetics and follows Higuchi diffusion mechanism of drug release.

Figure: 7Zero order plot of formulation RF13

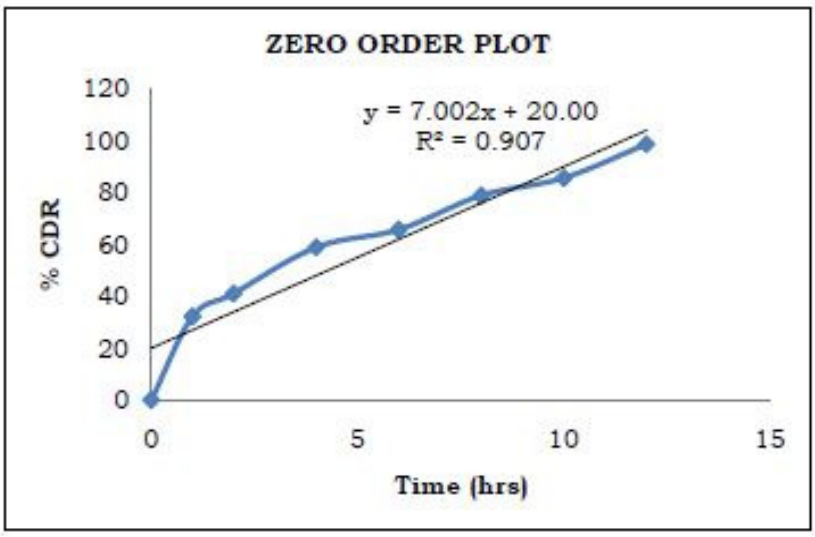


Figure: 8First order plot of formulation RF13

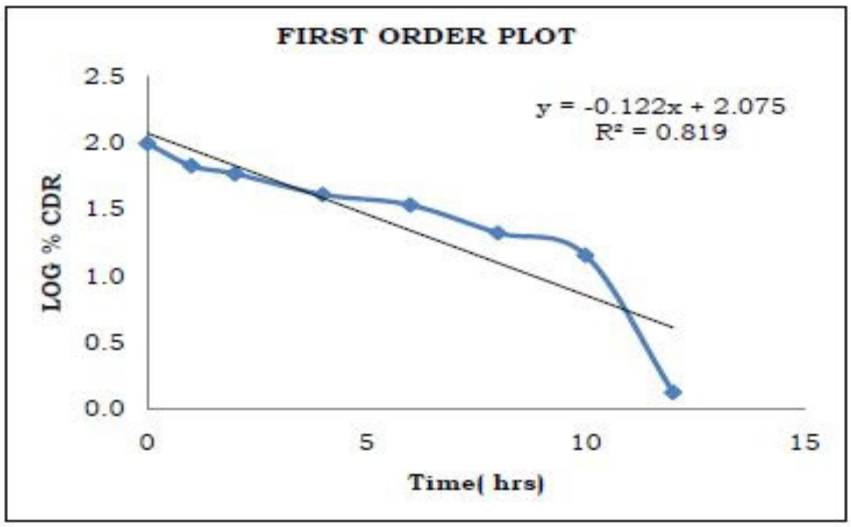


Figure: 9Higuchi plot of formulationRF13

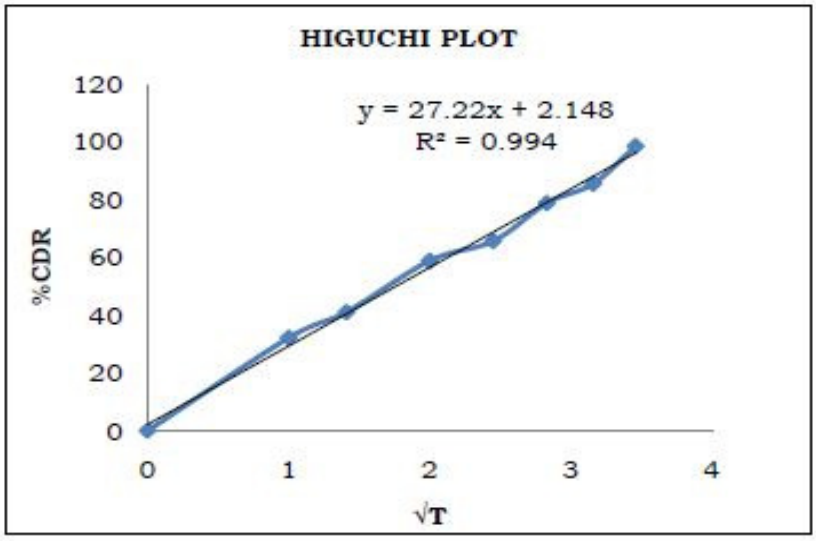
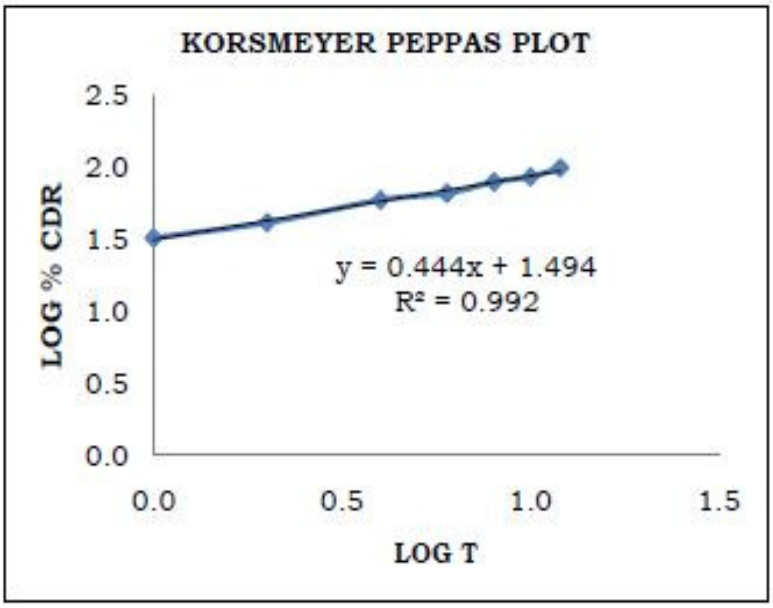


Figure: 10Korsmeyer-Peppas plot of formulation RF13



***In- vitro* Swelling Index studies (SI)**

All the formulations were evaluated for degree of swelling. The swelling index was found to increase with the increase in polymer concentration, for all type ofpolymers. Formulations which contain lipophilic polymers were found to possess fewer swelling properties in comparison to the hydrophilic polymers. As the concentration of lipophilic polymers increases from 1:0.25 to 1:1, the ability of the polymer to sell also increases but not predominantly. Among the hydrophilic polymers, formulations containing Geleol has showed less swelling when compared with formulations containing constant ratio of HPMC polymer. Formulations from F13-F18, containing combination of two lipoidal polymers has shown almost same swell ability with constant ratio of HPMC. Among those RF13(best optimized formulation), has shown more proportional increase in swelling, which contains combination of two lipophilic polymers in 1:1 ratio of Gelucire 43/01 and Gelucire 50/02 with constant ratio of HPMCK15.

Overall results suggest that there is a least but possible effect of swell ability on drug releaseprofile.

Table :9Swelling index (%)of Ritonavir Formulations RF1 to RF12

Time (hrs)	Gelucire 43/01				Gelucire 50/02			
	RF1	RF4	RF7	RF10	RF2	RF5	RF8	RF11
0	0	0	0	0	0	0	0	0
1	11.23±0.34	15.2±0.56	16.2±0.45	15.4±0.29	10.3±0.59	24.5±0.65	17.2±0.25	9.3±0.25
2	25.6±0.98	25.4±0.21	22.7±0.85	21.4±0.45	18.9±0.84	32.4±0.98	31.2±0.41	13.5±0.69
4	48.9±0.54	32.1±0.47	39.5±0.36	36.4±0.56	32.3±0.39	39.6±0.54	55.4±0.59	17.8±0.58
8	59.6±0.69	58.3±0.47	51.3±0.12	57.1±0.98	59.8±0.41	45.6±0.23	69.2±0.45	21.4±0.87
12	76.6±0.36	70.3±0.98	80.8±0.54	79.8±0.78	71.2±0.65	75.7±0.23	77.9±0.78	74.6±0.36

Table :10Swelling index (%)of Ritonavir Formulations

Time (hrs)	Geleol pellets			
	RF3	RF6	RF9	RF12
0	0	0	0	0
1	14.2±0.36	26.2±0.78	12.9±1.03	21.4±0.36
2	21.8±1.23	33.6±0.14	28.7±0.69	31.7±0.47
4	36.1±0.23	52.1±0.64	38.2±0.98	51.4±0.89
8	46.1±0.84	61.6±0.57	53.6±0.54	61.3±0.35
12	75.6±0.97	69.4±0.97	76.6±0.78	68.9±0.78

Table :11Swelling index (%)of Ritonavir Formulations RF13 to RF18

Time (hrs)	RF13	RF14	RF15	RF16	RF17	RF18
0	0	0	0	0	0	0
1	25.6±0.54	27.8±0.99	25.6±0.56	15.6±1.45	25.6±0.25	14.5±0.56
2	69.8±0.12	34.5±0.78	48.9±0.23	35.6±0.78	47.8±0.89	55.3±0.14
4	99.6±1.245	78.9±0.36	62.3±0.56	55.7±0.65	68.7±1.14	78.3±0.65
8	125.3±0.48	112.8±0.78	115.6±0.96	80.9±1.41	99.6±1.23	89.6±1.03
12	150.2±1.09	126.8±0.87	135.6±0.78	110.5±0.32	124.9±0.98	113.5±1.98

In-vitro Buoyancy Studies

The *in-vitro* buoyancy studies like floating lag time (FLT) and total floating duration time were performed to assess the gastric ability of Ritonavir gastroretentive tablets, according to the procedure. Results were represented in belowtable.

Table: 12*In-vitro* buoyancy studies of Ritonavir Formulations

Formulation	Buoyancy Lag time (Sec)	Floating Duration (Hrs)	Formulation	Buoyancy Lag time (Sec)	Floating Duration (Hrs)
RF1	5	2	RF10	1.5	12
RF2	2	4	RF11	2.2	10
RF3	4	4	RF12	1.2	10
RF4	20	4	RF13	0.75	11
RF5	22	5	RF14	1.5	12
RF6	20	3	RF15	2	10
RF7	0.92	12	RF16	0.7	10
RF8	5	10	RF17	0.87	10
RF9	0.66	8	RF18	1.5	8

Formulations RF1-RF6 with single lipophilic polymer and HPMC K15 were found to show negligible floating ability. Whereas formulations RF7–RF12 with increasing concentration of single lipoidal polymer and HPMC K15 were found to show increased buoyancy characteristics. Formulations RF13-RF18 containing combination of two lipophilic polymers and HPMC polymers were found to show even more increased buoyancy characteristics because of increased concentration of lipoidal polymers. Among all the formulations RF13 containing Gelucire 43/01 and Gelucire 50/02 in combination with HPMC K15, has shown floating lag time of 45 sec with 12 hrs floating duration. Therefore, RF13 is considered as the best optimized formulation as it is found to have the best buoyancycharacteristics.

CONCLUSION

In the present study floating drug delivery formulations of Ritonavir has been successfully designed using different combinations of hydrophilic and lipophilic polymers in various concentrations by wet and melt granulation methods with appropriate pre- and post-formulation studies. It is evident from the results that there is no drug-polymer interaction and RF13 is considered as the best optimized formulation with adequate floating property, non-fickian controlled drug release and followed zero order kinetics.

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