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DESIGN AND INVITRO EVALUATION OF FLOATING DRUG DELIVERY SYSTEM FOR ANTI RETROVIRAL DRUG: RITONAVIR

Pharma

Sunil Firangi* Ph.D Scholar, College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur. *Corresponding Author

Dr S. N. Hiremath Pravara Rural College of Pharmacy, Loni.

ABSTRACT

The drug Ritonavir belongs to class II under BCS, widely prescribed as antiviral drug in the treatment of HIV/AIDS, exhibit low and variable oral bioavailability because it is practically insoluble in water and aqueous fluids & as such it possesses challenging problems in its formulation.

This work was an attempt to increase therapeutic efficacy, reduce the frequency of drug administration, improve the bioavailability and patient compliance by developing Floating Ritonavir tablets for controlled release and to increase gastric retention time. The Floating tablets were prepared by wet granulation technique and were subjected to pre, post compressional parameters & ompatibility of the drug with excipients by FTIR studies. In all the formulations, hardness test indicated good mechanical resistance. Sodium bicarbonate was added as a gas generating agent, induced carbon dioxide generating in presence of dissolution medium (0.1N HCl). The combination of sodium bicarbonate & citric acid provided desired floating ability.

The research work concludes that the formulation RF8 consisting of HPMC K4M with Xanthan gum showed highest drug release in short duration of time.

KEYWORDS

Ritonavir, HPMC, Xanthan gum.

INTRODUCTION:

Oral controlled release dosage forms have been extensively used to improve therapy of many important medications. The bioavailability of drugs with an absorption window in the upper small intestine is generally limited with pharmaceutical dosage forms. The residence time of such systems and, thus, of their drug release into the stomach and upper intestine is often short[1]. Incorporation of the drug into a controlled release delivery system, which releases its payload in the stomach over a prolonged time period.

Oral route of administration has received more attention in the pharmaceutical field because of more flexibility in the designing of dosage form than the other routes of drug delivery[2]. The release of drug from the delivery system may be by diffusion, dissolution or by combination of both mechanisms in a desired and controlled manner. Floating Drug Delivery Systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time[14]. After release of drug, the residual system is emptied from the stomach. This result an increased gastric residence time and a better control of the fluctuations in plasma drug concentration. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release[2].

Limitations of FDDS[3-6,]

Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.

Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated.

High variability in gastric emptying time due to its non-emptying process.

Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size, so patients should not be dosed just before going to bed.

Drugs That Are Required To Be Formulated Into FDDS[7-9]

Drugs acting locally in the stomach.
Drugs that are primarily absorbed in the stomach.
Drugs those are poorly soluble at alkaline pH.
Drugs with a narrow window of absorption.
Drugs rapidly absorbed from the GIT
Drugs that degrade in the colon.

Method[10]:

Drug and polymers were mixed in a poly bag and the mixture was passed through a mesh No. 60. Granulation was done with a solution of PVP K30 in sufficient isopropyl alcohol. The wet mass was passed through mesh No. 12. The wet granules were dried at 60º for about 4 hours. The dried granules were sized by a mesh No. 18 and mixed with sodium bicarbonate, citric acid, magnesium stearate and talc. Granules thus obtained were compressed into tablets.

Table 1: Formulations Table (in mg)

Ingredients	RF1	RF2	RF3	RF4	RF5	RF6	RF7	RF8
Ritonavir	300	300	300	300	300	300	300	300
HPMC K4M	150	100	50				50	50
PVP K30	20	20	20	20	20	20	20	20
Mg Stearate	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10
Sod Bicarbonate	80	80	80	80	80	80	80	80
Citric acid	20	20	20	20	20	20	20	20
Lactose	60	110	160	135	185	235	120	70
Xanthan gum				150	100	50	50	100
Sodium Alginate				25	25	25	25	25
Cross carmellous Sodium				15	15	15	15	15

RESULTS AND DISCUSSION:

PRE-COMPRESSIONAL PARAMETERS:

Compatibility of drug-polymer studies was conducted using FTIR spectrophotometer by KBr pellet technique, suggesting that the drug and excipient are in the unreacted from. Spectra are in Figure 1.

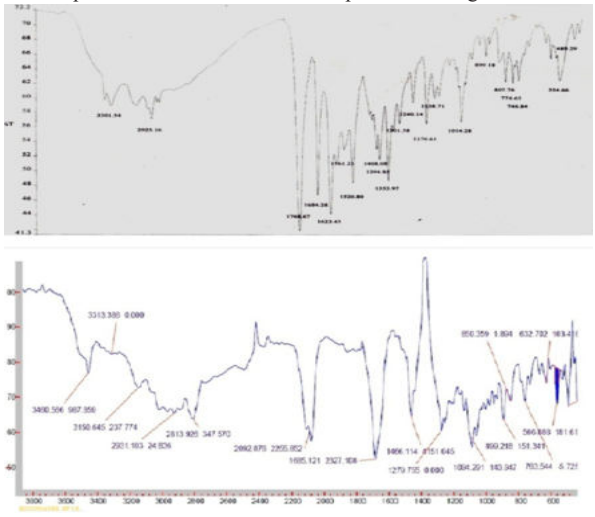

Fig 1: FTIR of Pure Ritonavir & Rf8

PRE COMPRESSIONAL PARAMETERS:

The bulk density found between 0.567±0.04 to 0.790±0.05gm/cm^3. Tapped density was 0.642±0.05 to 0.929±0.02gm/cm^3 indicating good packing capacity. Carr's index was found between 13.56±0.01 to 25.90±0.03. Hausner's ratio was found between 1.13±0.04 to 1.28±0.09 indicating good flowability. Angle of repose was in the range of 25.35±0.11 to 31.43±0.17 showed good flow properties. Data are in table 2.

Table 2: Pre-compressional Parameters

Formulations	Bulk density (g/cm3)	Tapped density (g/cm3)	Carr's Index	Hausner Ratio	Angle of repose (θ)
RF1	0.620 ±0.04	0.845 ± 0.03	15.32 ± 0.06	1.16 ± 0.06	29.55 ± 0.12
RF2	0.640 ± 0.05	0.800 ± 0.05	13.56 ± 0.01	1.27 ± 0.01	29.48 ± 0.10
RF3	0.668 ± 0.02	0.862 ± 0.02	23.62 ± 0.09	1.23 ± 0.04	28.10 ± 0.12
RF4	0.670 ± 0.02	0.699 ± 0.01	25.90 ± 0.03	1.13 ± 0.04	30.11 ± 0.13
RF5	0.759 ± 0.02	0.721 ± 0.03	20.17 ± 0.13	1.28 ± 0.09	31.43 ± 0.17
RF6	0.712 ± 0.04	0.834 ± 0.05	23.70 ± 0.11	1.22 ± 0.11	29.56 ± 0.15
RF7	0.790 ± 0.05	0.642 ± 0.05	21.44 ± 0.10	1.18 ± 0.01	30.44 ± 0.10
RF8	0.567 ± 0.04	0.929 ± 0.02	22.08 ± 0.09	1.19 ± 0.04	27.09 ± 0.13

POST-COMPRESSIONAL PROPERTIES:

THICKNESS, DIAMETER AND HARDNESS:

Thickness was in range of 4.2 ± 0.02 to 4.4 ± 0.06. The hardness was in range of 6.4 to 9.1 Kg/cm^2. The friability was found to be in the range of 0.23 ± 0.014 to 0.76 ± 0.087. Data are in table 3.

PHYSICO-CHEMICAL PROPERTIES:

DRUG CONTENT:

Drug content was in range of 96.21 ± 0.15 to 99.67 ± 0.13, which reflects good drug content uniformity. Results are in Table 3.

Swelling Index:

It was in range of 58.75 ± 0.78 to 71.20 ± 0.56. Results are in Table 3.

Table 3: Post-Compressional & Physico-Chemical Properties

Formulations	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Swelling index (%)
RF1	4.4 ± 0.01	11.8 ± 0.04	7.2 ± 0.03	0.48 ± 0.035	96.21 ± 0.15	58.75 ± 0.78
RF2	4.4 ± 0.02	11.7 ± 0.06	6.4 ± 0.05	0.41 ± 0.033	99.45 ± 0.19	60.40 ± 0.21
RF3	4.4 ± 0.01	11.9 ± 0.03	9.1 ± 0.07	0.44 ± 0.076	99.67 ± 0.13	61.80 ± 0.27
RF4	4.4 ± 0.03	12.6 ± 0.02	8.1 ± 0.08	0.27 ± 0.067	97.79 ± 0.11	71.20 ± 0.56
RF5	4.3 ± 0.06	12.4 ± 0.03	8.3 ± 0.05	0.76 ± 0.087	99.50 ± 0.15	70.80 ± 0.41
RF6	4.3 ± 0.04	12.7 ± 0.09	8.5 ± 0.03	0.23 ± 0.014	97.50 ± 0.24	68.50 ± 0.50
RF7	4.3 ± 0.02	12.3 ± 0.08	7.5 ± 0.01	0.25 ± 0.086	98.45 ± 0.27	69.38 ± 0.47
RF8	4.4 ± 0.06	11.9 ± 0.04	7.8 ± 0.04	0.57 ± 0.032	97.21 ± 0.14	58.60 ± 0.32

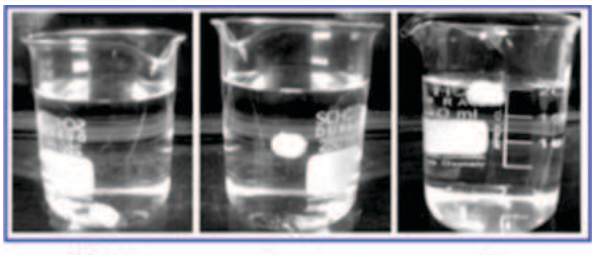

Fig 2: In-vitro Buoyancy Study of Floating Tablet

Invitro Dissolution Studes:

Invitro dissolution studies were carried out for Floating tablets using USP XXIII dissolution test apparatus-II at 50rpm, 900ml of 0.1N HCl used as dissolution media. Results are shown in table 4 & in figure 3.

Table 4: Invitro Release Data Of Floating Tablets: RF1-RF8

Timings	RF1	RF2	RF3	RF4	RF5	RF6	RF7	RF8
30min	23.26 ±0.70	17.50 ±0.18	18.74 ±0.22	5.19 ± 0.63	8.30 ± 0.21	10.00 ± 0.10	10.17 ±0.23	8.81± 0.76
1 hr	29.89 ±0.40	27.53 ±0.23	29.69 ±0.34	10.32 ± 0.23	17.01 ± 0.88	18.11 ± 0.34	29.16 ±1.15	16.08 ±0.48
2 hr	37.47 ±0.98	42.57 ±087	43.42 ±0.11	16.56 ± 0.83	23.96 ± 0.10	24.66 ± 0.39	45.41 ±0.64	25.83 ±0.66
3 hr	46.52 ±0.11	50.90 ±0.36	51.26 ±0.35	21.90 ± 0.30	31.68 ± 0.32	32.89 ± 0.63	53.91 ±0.38	37.11 ±0.70
4 hr	57.63 ±0.74	61.97 ±0.47	63.80 ±0.25	33.89 ± 0.41	39.90 ± 0.43	42.14 ± 0.48	62.19 ±0.76	44.22 ±0.56
5 hr	60.98 ±0.46	69.81 ±0.12	71.74 ±0.18	39.63 ± 0.44	47.83 ± 0.44	48.22 ± 0.66	65.86 ±0.33	54.26 ±0.58
6 hr	66.45 ±0.58	77.83 ±0.69	78.47 ±0.87	53.12 ± 0.78	54.69 ± 0.65	55.50 ± 0.74	71.34 ±0.73	68.10 ±0.54
7 hr	74.41 ±1.10	85.80 ±0.23	86.36 ±0.05	64.89 ± 0.43	65.70 ± 0.67	66.96 ± 0.96	78.93 ±0.65	75.30 ±0.31
8 hr	82.98 ±0.87	92.40 ±0.14	93.78 ±0.40	73.63 ± 0.51	74.00 ± 0.12	75.14 ± 0.41	87.11± 0.73	81.90 ±0.79
9 hr	91.57 ±0.69	99.90 ±0.78	99.90 ±0.50	85.67 ± 0.77	83.76 ± 0.78	84.78 ± 0.52	99.84 ±0.82	86.43 ±0.34
10 hr	99.99 ±0.41	99.90 ±0.78	99.90 ±0.50	93.54 ± 0.17	94.90 ± 0.98	95.50 ± 0.80	99.84 ±0.82	90.19 ±0.91
11 hr	99.99 ±0.41	99.90 ±0.78	99.90 ±0.50	100.00 ± 0.03	99.99 ± 0.00	99.99 ± 0.00	99.84 ±0.82	99.91 ±0.85
12 hr	99.99 ±0.41	99.90 ±0.78	99.90 ±0.50	100.00 ± 0.03	99.99 ± 0.00	99.99 ± 0.00	99.84 ±0.82	99.91 ±0.85

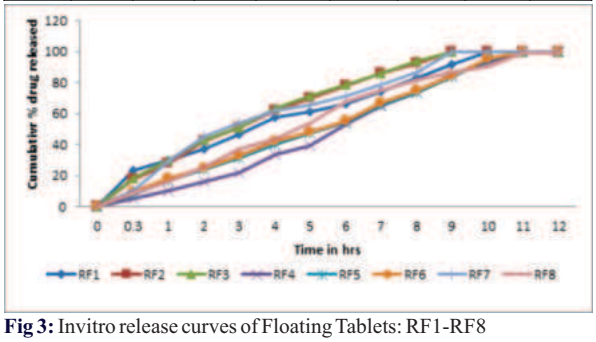

Fig 3: Invitro release curves of Floating Tablets: RF1-RF8

CONCLUSION:

- It is evident that, the formulation retained for longer periods of time in the stomach and provides controlled release of the drug.
- Floating tablets of Ritonavir can be developed to increase gastric residence time and thereby increasing its bioavailability.
- Formulated FDDS tablets gave satisfactory results for various parameters.
- As the amount of polymer in the tablet formulation increases, the drug release rate decreases and as the concentration of gas generating agent increases, the drug release increases and at the same time floating lag time decreases.
- $NaHCO_3$ has predominant effect on the buoyancy lag time, while HPMC K4M, has predominant effect on total floating time and drug release.
- Sodium alginate and Xanthan gum have given extra adhesion property.

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