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Original Article

FORMULATION AND *IN VITRO* EVALUATION OF RITONAVIR FLOATING TABLETS BY MELT GRANULATION TECHNIQUE

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ABSTRACT

Objective: The purpose of this study was to formulate Ritonavir floating matrix tablets by melt granulation technique in order to prolong its gastric residence time thereby increasing its bioavailability.

Methods: The Ritonavir tablets were prepared by melt granulation technique, using carriers such as Gelucire 43/01, Gelucire 50/02 and Geleol pellets alone or in combinations. Ethyl cellulose was used as drug release rate retarding agent and sodium bicarbonate was used as gas generating agent. The prepared granules were subjected to pre and post compressional parameters. The formulations were optimized on the basis of matrix integrity, duration of floating, swelling behavior and *In vitro* drug release.

Results: The drug-excipients compatibility studies were performed by FT-IR and the study revealed that there is no drug excipients interaction. A combined matrix system containing Gelucire 43/01: Gelucire 50/02 with 1:1 concentration along with HPMC K 15 M shows good drug release pattern with less floating lag time and increased floating duration.

Conclusion: The *in vitro* drug release pattern of Ritonavir floating tablets was fitted to different kinetic models which showed the highest regression for Zero order kinetics with Higuchi mechanism.

Keywords: Gelucire 43/01, Gelucire 50/02, Geleol pellets, Swelling behavior

INTRODUCTION

Gastro retentive drug delivery systems help prolongs the overall gastrointestinal transit time and improves the oral bioavailability of the drugs that are having site specific absorption from the stomach, i.e., the upper part of small intestine. Therefore, different approaches have been proposed to retain the dosage form in the stomach including bioadhesive system, swelling and expanding systems, floating systems and delayed gastric emptying devices [1-3]. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time of the dosage form and sustained drug release [4]. Ritonavir is human immunodeficiency virus (HIV) protease inhibitor used at the antiretroviral agent, and its biological half-life is 3-5 h [5]. Ritonavir requires multiple daily doses in order to maintain adequate plasma concentrations. Therefore, it would be a suitable model candidate for gastro retentive formulation.

The gastro-retentive drug delivery systems can be retained in the stomach and assist in imposing the oral sustained delivery of the drug that has absorption window in a particular region of gastric tract [6]. These systems help in the continuous release of the drug before it reaches the absorption window thus ensuring optimal bioavailability.

Gelucire 43/01 and 50/02 and Geleol were used as carrier forming materials and hydroxypropyl methylcellulose (HPMC) and EC are used as controlled release polymers [7, 8]. Sodium bicarbonate is used as gas generating agent. Gelucires are a family of vehicles derived from mixtures of mono-, di-, and triglycerides with polyethylene glycol (PEG) esters of fatty acids. Gelucire are available with a range of properties depending on their hydrophilic lipophilic balance (HLB 1-18) and melting point (33OC-65OC) range [9-11]. Gelucire containing only PEG esters (Gelucire 55/18) are generally used in the preparation of fast-release formulations while Gelucire containing only glycerides or a mixture of glycerides and PEG esters (Gelucire 54/02, 50/13, 43/01) are used in the preparation of sustained-release formulations. The main objective of the present study is to formulate gastro retentive Ritonavir drug delivery systems by melt granulation method using carriers such as Gelucire 43/01, Gelucire 50/02 and Geleol pellets alone or in combinations.

MATERIALS AND METHODS

Materials

Gelucire (43/01 and 50/02) and Geleol were obtained from Gattefosse (St Priest, Cedex, France) as gift samples. HPMC 15 K, ethyl cellulose, and other excipients were purchased from S. D fine chemicals.

Table 1: Formulation of floating ritonavir tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ritonavir	100	100	100	100	100	100	100	100	100	100	100	100
Gelucire 43/01	50	---	---	75	---	---	100	---	---	50	---	50
Gelucire 50/02	---	50	---	---	75	---	---	100	---	50	50	---
Geleol pellets	---	---	50	---	---	75	---	---	100	---	50	50
HPMC K15	80	80	80	80	80	80	80	80	80	80	80	80
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	64	64	64	39	39	39	14	14	14	39	39	39
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

HPMC K15-Hydroxy propyl methyl cellulose, MCC-Microcrystalline cellulose

Preparation of ritonavir floating tablets [12-14]

Gelucire (43/01and 50/02) and Geleol were melted in a china dish at their melting points, and a required quantity of Ritonavir was added to the molten mass. Previously prepared mixture containing HPMC K15, sodium bicarbonate, ethyl cellulose, microcrystalline cellulose were added to drug-Gelucire (43/01 and 50/02) and Geleol mixture. Here, Sodium bicarbonate was added as gas generating agent. It was mixed to prepare uniform mass and sieved through 44 mesh. Lastly, talc and magnesium stearate were added. The lubricated blends were compressed using rotary tablet press.

Evaluation methods for ritonavir floating tablets

1. *In vitro* buoyancy studies

The prepared Ritonavir floating tablet was placed in 900 ml of 0.1 N HCL in a vessel maintained at 37±0.5^{0}C and stirred at 50 rpm in a US Pharmacopeia (USP) type II dissolution test apparatus, Mumbai, India). The percentage of floating granules up to 12 h was determined, and the floating times were measured by visual observation.

2. *In vitro* drug release studies [15]

The release of drug from granules containing the different drug to lipid proportions with and without the release rate modifier was investigated. Studies were performed in triplicate using a (USP) type II dissolution test apparatus with an agitation speed of 50 rpm in 0.1 N HCL maintained at 37±0.5 ^{0}C. At appropriate time intervals, the samples were withdrawn and assayed spectrophotometrically at 256 nm after filtration through Whatman filter paper and with suitable dilutions. The methodology for *in vitro* dissolution was kept the same for all the batches prepared.

3. Selection of lipid carrier

The preliminary screening was performed to select the best lipid carrier among Gelucire 43/01, and Gelucire 50/02 and Geleol. Formulations were prepared using various drug-to-carrier ratios (1:0.5, 1:0.75 and 1:1). The selection of polymers was based on tests for floating behavior *and in vitro* drug release studies.

4. Kinetic modeling of drug release [16, 17]

The dissolution profile of all the batches was fitted to zero-order, first-order, Higuchi, Korsmeyer and Peppas to ascertain the kinetic modeling of drug release.

RESULTS AND DISCUSSION

Ritonavir floating tablets were developed to increase the gastric residence time of the drug so that they can be retained in the stomach for a longer time and help in the controlled release of the drug to a minimum of 12h.

Preformulation studies

Compatibility among drug and optimized polymer i.e. Gelucire 43/021 and Gelucire 50/02 were assessed by performing IR Spectroscopic studies. There was no interaction between the drug and polymers were observed as, the principle peaks of the drug were found unaltered in the IR Spectra. Granules of various formulations containing drug and meltable binder were evaluated for angle of repose, bulk density, tapped density and Carr's index. All formulations were found to be in the acceptable range.

Post compressional parameters

Each formulation was evaluated for parameters such as weight variation, drug content, hardness, friability, floating behavior and *in vitro* drug release. The weights and friability of all formulations were within the range according to IP. Weight lose in the friability test was less than 0.6% in all the cases. The hardness was in the range of 2.1±0.2 to 3.0±0.3 Kg/cm^2, which was due to the use of waxy polymers; it also indicated that the increase in carrier content increases the crushing strength of tablets.

***In vitro* dissolution studies of prepared tablets**

All Formulations were subjected to *in vitro* dissolution study. All Tablets retained their integrity throughout the study and released the drug in controlled manner as shown in the fig. 1.

Three batches of formulations (F1, F2, and F3) as shown in table 1 were prepared using 14% of polymers Gelucire 43/01, 50/02 and Geleol respectively while the same optimum amount of sodium bicarbonate (8%) used. From the evaluation results, it was observed that the three formulations failed to release the drug up to 12 h, indicating less concentration (14%) of lipoidal polymer. Whereas F6 contained 20% concentration of geleol which didn't satisfactory sustained drug release.

Less floating lag time and more floating duration were obtained in the case of the formulations containing different concentrations of Gelucire 43/01 (F4, F7, F10 and F12). The Gelucire 43/01 in combination with Gelucire 50/02 and Gelucire 43/01 in combination with Geleol were present in the formulation batches F10 & F12 respectively. This implicates that with an increase in the concentration of lipoidal polymer more floating duration was achieved. The formulations containing Gelucire 50/02 either individually has shown to extend the drug release with an increase in its concentration. In case of F10 formulation, better results containing Gelucire 50/02 in a combination of Gelucire 43/01 was observed.

F3, F6, F9 contained Geleol individually in increasing concentration; it was observed that the drug release was also sustained with concentrations. In F11 and F12, the satisfactory drug release, floating lag time and floating duration were obtained, where geleol was present in combination with Gelucire 50/02 and 43/01 respectively. F11 and F12 formulations were less in comparison with F10 formulation in terms of floating lag time and floating duration.

Among all formulations, tablets of batch F10 released 98% of a drug within 12 h, which was according to the need for the therapy, which contains 28 % of Gelucire 43/01 and Gelucire 50/02 in combination which was the highest amount of polymer. Hence, it was decided to keep total polymer concentration at 28% for acceptable formulation in further study.

Drug content and floating studies

The drug content was in the range of 90.66±1.03 to 98.83±0.56 % which reflects good uniformity in drug content among different formulations. The time taken for the tablets to rise to the surface and float is the floating lag time. The gas generated is trapped and protected within the gel, formed by hydration of the polymer, thus decreasing the density of the tablet. As the density of the tablet falls below 1, the tablet became buoyant. The floating lag time ranged between 55 sec to 22 min.

Table 2: *In vitro* drug release of prepared floating tablets of ritonavir

Time (H)	Cumulative % of drug release (n=3) mean±SD					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	28.7±0.23	39.6±0.45	21.23±0.23	16.82±0.35	18.65±0.59	22.45±0.59
2	56.8±1.35	62.3±0.01	52.03±0.542	49.83±0.47	32.19±1.23	40.60±0.51
4	86.2±0.21	77.7±1.37	89.62±0.29	64.2±1.21	52.21±1.56	69.54±0.84
6	91.1±0.32	96.2±0.42	98.63±0.36	76.8±0.26	70.22±0.28	80.28±0.54
8	---	---	---	89.62±0.774	83.3±0.87	99.32±0.60
10	---	---	---	97.3±1.35	92.28±0.49	---
12	---	---	---	---	---	---

The hydrophobic meltable material in all the formulations imparted sufficient integrity to the tablets. HPMC K15 (hydrophilic) was selected as a matrixing agent considering its widespread applicability and excellent gelling activity in sustained release formulations. Sodium bicarbonate generates CO_2 gas in a presence of hydrochloric acid present in the dissolution medium. Generated gas is trapped and protected within a gel formed by hydration of HPMC K15; thereby decreasing the density of the tablet becomes buoyant.

Table 3: *In vitro* drug release of prepared F7-F12 floating tablets of ritonavir

Time (H)	Cumulative % of drug release (n=3) mean±SD					
	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
1	19.82±1.88	14.26±1.45	6.83±0.54	32.19±0.56	23.64±0.88	14.26±0.98
2	22.45±0.89	20.42±0.45	20.33±0.22	41.1±0.23	38.13±0.61	21.62±0.87
4	27.56±0.62	28.51±1.89	23.64±1.03	58.92±0.70	47.05±1.20	54.53±1.23
6	40.75±0.35	33.74±1.32	26.97±1.99	65.74±1.06	57.14±1.35	61.9±1.56
8	56.9±1.64	54.23±0.51	32.53±1.23	78.88±1.22	67.84±1.65	64.03±1.99
10	64.86±1.05	65.71±0.54	49.06±1.45	85.66±0.87	70.09±1.24	78.89±1.54
12	70.1±0.94	69.7±1.03	57.06±1.03	98.67±0.47	82.26±1.23	81.23±1.89

Table 4: Drug content and floating studies of F1-F12 formulations

Formulation code	Drug content (%) mean±SD (n=3)	Swelling index (%)	Floating studies	
			Floating lag time	Floating duration (hrs)
F1	94.2±0.23	70.03	20 min	4
F2	95.06±0.54	75.70	22 min	5
F3	96.78±0.21	69.54	20 min	3
F4	96.89±0.89	80.18	55 Sec	12
F5	92.03±0.23	77.89	5 min	10
F6	95.58±0.41	76.58	40 Sec	8
F7	91.78±0.65	79.08	90 Sec	12
F8	95.62±0.28	74.56	2.2 min	10
F9	90.66±1.03	68.87	1.2 min	11
F10	92.16±0.54	69.21	45 Sec	12
F11	98.83±0.56	80.23	1.5 min	10
F12	94.01±0.66	78.68	2 min	10

Release kinetics

The optimized formulation F10 was found to have following typical zero order kinetics, which clearly indicated by their relatively higher "r" values compared to the first order regression coefficient values and follows Higuchi diffusion as release model and korsmeyer-peppas model and entire exponent 'n' values were found to be in between 0.5-1, indicating that all the formulations were following non-fickian mode of drug release.

Table 5: Pharmacokinetic modeling of ritonavir floating tablets

Formulation code	Relative regression coefficient values (r)					n
	Zero order	First order	Higuchi	Erosion	Korsemeyer Peppas	Korsemeyer Peppas
F1	0.887	0.976	0.901	0.882	0.942	0.656
F2	0.877	0.944	0.807	0.87	0.979	0.479
F3	0.931	0.966	0.781	0.929	0.947	0.87
F4	0.895	0.951	0.818	0.89	0.899	0.698
F5	0.963	0.98	0.851	0.959	0.996	0.702
F6	0.954	0.816	0.635	0.949	0.987	0.706
F7	0.961	0.976	0.89	0.954	0.918	0.55
F8	0.972	0.965	0.859	0.967	0.958	0.654
F9	0.949	0.937	0.843	0.944	0.914	0.737
F10	0.907	0.827	0.688	0.899	0.992	0.444
F11	0.898	0.969	0.931	0.889	0.984	0.569
F12	0.904	0.969	0.922	0.9	0.952	0.732

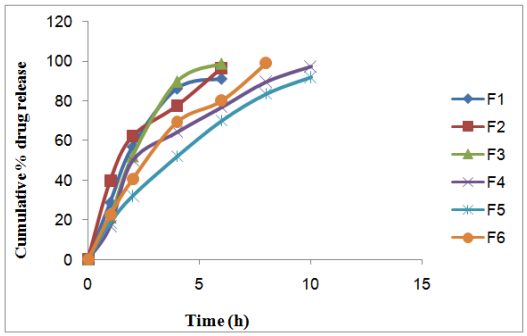

Fig. 1: *In vitro* dissolution plots of F1 to F6

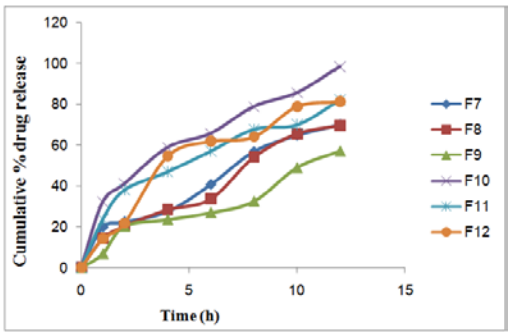

Fig. 2: *In vitro* dissolution plots of F7 to F12:

CONCLUSION

In present study controlled release floating matrix tablet of Ritonavir was successfully prepared utilizing Melt Granulation technique with appropriate hardness and thickness. The *in vitro* drug release studies of prepared Ritonavir tablets were studied separately according to their proportions (1:0.5, 1:0.75, 1:1 and their combinations) using 0.1N HCl as dissolution media. Floating was successfully achieved at the taken concentration of Sodium Bicarbonate and HPMC K15. In terms of lipidic polymers a combination of Gelucire 43/01 and Gelucire 50/02 in a ratio of 1:1 to the drug (F10) was appropriate, which showed least floating lag time and highest floating duration. Among all the formulations, formulation F10 showed promising results releasing 98.67% of the drug in 12Hrs with a floating lag time of 55 sec and total floating time of 12 h.

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CONFLICTS OF INTERESTS

Declare none

REFERENCES

1. Bulgarelli E, Forni F, Bernabei MT. Effect of matrix composition and process conditions on casein-gelatin beads floating properties. Int J Pharm 2000;198:57-65.
2. Singh BN, Kim KH. Floating drug delivery system: an approach to the controlled drug delivery via gastric retention. J Controlled Release 2000;63:235-59.
3. Nur AO, Zhang JS. Captopril floating and/or bioadhesive tablets: design and release kinetics. Drug Dev Ind Pharm 2000;26:965-9.
4. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled-release system for gastric retention. Pharm Res 1997;14:815–9.
5. Kumar K, Shah MH, Ketkar AR, Kadam SS, Paradkar A. Effect of drug solubility and different excipients on floating behavior and release from glyceryl mono-oleate matrices. Int J Pharm 2004;272:151-60.
6. S Sarojini, R Manavalan. "An overview on various approaches to gastro retentive dosage forms". Int J Drug Dev Res 2012;4:1-13.
7. Dasharath M Patel, Natavarlal M Patel, Viral F Patel, Darshini A Bhatt. Floating granules of rantidine hydrochloride-gelucire 43/01: formulation optimization using factorial design. AAPS PharmSciTech 2007;8:E1-E7.
8. Dennis AB, Farr SJ, Kellaway IW, Taylor G, Davidson R. *In vivo* evaluation of rapid release and sustained release gelucire capsule formulations. Int J Pharm 1990;65:85-100.
9. Sutananta W, Craig DQM, Newton JM. The effects of aging and thermal behaviour and mechanical properties of pharmaceutical glycerides. Int J Pharm 1994;111:51-62.
10. Ainaoui A, Ouriemchi EM, Bidah D, EI Amram MK, Vergnaud JM. The process of drug releases with oral dosage forms with lipidic gelucire matrix. J Polym Eng 1997;17:245-57.
11. Ainaoui A, Vergnaud JM. Modeling the plasma drug level with oral dosage forms with lipidic gelucire matrix. Int J Pharm 1998;168:155-62.
12. Shyam Shimpi, Bhaskar Chauhan, KR Mahadik, Anat Paradkar. Preparation and evaluation of diltiazem hydrochloride-gelucire 43/01 floating granules prepared by melt granulation. AAPS PharmSciTech 2004;5:1-6.
13. Mahaparele PR, Kasture PV, Deshmukh SS, Kuchekar BS. Sustained release matrices of metoprolol succinate using compritol 888 ATO and precirol ATO 05. J Pharm Res 2006;5:10-4.
14. Paradkar AR, Maheswari M, Chauhan MB. Sustained release matrices of Metformin hydrochloride and glyceryl behenate. Indian Drugs 2004;41:350-3.
15. Patel NM, Soniwala MW. Influence of release enhancer on the release of Vanlafaxine hydrochloride from glyceryl behenate matrix tablet. Indian Drugs 2008;45:98-104.
16. Richard W Korsmeyer, Robert Gurny, Eric Doelker, Pierre Buri, Nikolaos A Peppas. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm 1983;15:25-35.
17. Peppas NA. Analysis of fickian and non-fickian drug release from polymers. Pharm Acta Helv 1985;60:110-1.