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Formulation and Evaluation of Ritonavir Floating Tablets.

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ABSTRACT

The aim of present research work was to formulate gastro retentive floating tablets containing Ritonavir. The floating tablets of Ritonavir was formulated by direct compression technique using natural, semi-synthetic and synthetic polymers such as gellan gum, HPMC K4M, and carbopol 971p. Sodium bicarbonate was used as gas generating agent. FTIR studies revealed that there is no interaction between the drug and the polymers used in the formulation. Prepared Ritonavir tablets were evaluated by various quality parameters including weight variation, hardness, friability, drug content, tablet density, floating test, swelling index, *in-vitro* drug release and showed satisfactory results. Formulations F2, F5, F6 showed satisfactory drug release of 90.3%, 94.3%, and 97.7% respectively. The optimized batch F6 shows good results and extended drug release.

Keywords: Ritonavir, Floating tablet, gellan gum, carbopol 971p, HPMC K 4M.

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INTRODUCTION

Gastroretentive dosage forms (GRDFs) are designed to be retained in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal (GI) tract.⁽¹⁾ The idea is to prolong the residence time of the drug delivery in the stomach known as gastric residence time (GRT).⁽²⁾ These are low density systems that have sufficient buoyancy to flow over the gastric contents and are buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. As the system is floating on the gastric contents, the drug is slowly released at a specific rate from the system.^(3,4) Drugs that are easily absorbed from the gastrointestinal tract and have a short half-life are eliminated quickly from the blood circulation, so there is a need of frequent dosing to maintain therapeutic concentration of drug. To eliminate this limitation, the oral sustained controlled release formulations have been developed in an attempt to release the drug slowly into the gastrointestinal tract and maintain an effective drug concentration in the blood over long period of time.⁽⁵⁾

Ritonavir is a Protease Inhibitor widely prescribed in anti-retroviral regimen. It blocks the HIV protease, thereby reducing the viral load in the infected individual. Ritonavir was initially developed as an independent antiviral agent.⁽⁶⁾ Ritonavir mainly suffers with low oral bioavailability due to degradation of Ritonavir by the cytochrome P450-3A4 (CYP3A4) isoenzymes in the distal intestine, efflux of the absorbed drug by counter transporter proteins (mainly P-glycoprotein) present in the distal intestine.⁽⁷⁾ Ritonavir is unstable at alkaline pH. It shows pH-dependent solubility and solution stability. pH of Ritonavir is 6.8 and pka is 2.8.^(8,9) Biological Half-life is 3-5 hrs.^(10,11) It is primarily absorbed from stomach because of these characteristics, it was selected for the development of GRDDS.

MATERIALS AND METHOD

Ritonavir was obtained from micro labs Bangalore as a gift sample. Carbopol 971p, gellan gum and HPMC K 4M were purchased from Sai chemicals, Solapur. All chemicals used in the research work were of analytical grade.

Preformulation Studies:

Solubility study of the drug the solubility of Ritonavir was studied in 0.1N HCl at 37 ± 0.5 The amount of the drug dissolved was analyzed spectrophotometrically (Systronics UV-Visible double beam spectrophotometer-2201) at 240 nm after suitable dilutions.

Powder flow property:⁽¹²⁾

The flow properties of powders were determined which are the following: bulk density, tapped density, compressibility index (Carr's index), Hausner's ratio and angle of repose.

Preparation of Ritonavir floating tablets

All the formulations of Ritonavir floating tablets were prepared by direct compression method. Accurately weighed quantities of polymers were taken in a mortar and mixed geometrically. To this required quantity of Ritonavir was added and mixed slightly with pestle. Accurately weighed quantity of sodium bicarbonate was taken separately in a mortar and powdered with pestle. The powder was passed through sieve No. 40 and mixed with the drug blend which was also passed through sieve No. 40. The whole mixture was collected in a plastic bag and mixed for 5 minutes. To this talc and magnesium stearate was added and mixed for 2 minutes. The mixture equivalent to 300 mg was compressed using Remi Karnawati tablet punching machine.

Post compression studies :^(13,14)

Weight Variation:

20 tablets of each formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight (IP. 2007). Specifications of % weight variation allowed in tablets as per Indian Pharmacopoeia.

Thickness:

The thickness and diameter of the tablets was determined using a Vernier caliper

Hardness:

For each formulation, the hardness of 5 tablets was determined using Monsanto hardness tester.

Friability:

Friability was measured with Roche Friabilator. A loss of less than 1 % in weight is generally considered acceptable. Percent friability (% F) was calculated as follows,

$$\% F = (\text{Initial Wt.} - \text{Final Wt.} / \text{Initial Wt.}) \times 100$$

Drug content uniformity:

Accurately weighed quantity of the powdered tablet equivalent to 100 mg of the drug was transferred to 100ml volumetric flask. To this 50 ml of 0.1N Hcl was added then shaken for 5 minutes and make the final volume with 0.1N Hcl up to 100 ml. Then the solution was sonicated for 15 minutes and filtered and then absorbance was determined at 240 nm using UV spectrophotometer (UV- 2201, Systronics).

Fourier-transform infrared (FTIR) spectroscopy:

Drug-polymer compatibility studies were conducted using FTIR spectrophotometer by KBr pellet technique.

Differential scanning calorimetry:

DSC of pure drug and optimized batch was determined.

Swelling studies :⁽¹⁵⁾

The extent of swelling was measured in terms of % of weight gained by the tablet. One tablet from each formulation was weighed and kept in Petridish containing 50ml of 0.1 N HCL solutions. At the end of specified time intervals tablets were withdrawn from petridish and excess buffer blotted with tissue paper and weighed. The % of weight gained by the tablet was calculated by using the following formula

$$\text{Swelling index (\%)} = \frac{M_t - M_0}{M_0} \times 100$$

Buoyancy lag time determination and total Floating time:

The in-vitro buoyancy was determined by the floating lag time. The tablets were placed in a 250 ml beaker containing 100ml of 0.1 N HCL. The time required for the tablet to rise to the surface for floating was determined as the floating lag time and further duration of all tablets was determined by visual observation.

In vitro dissolution studies :⁽¹⁵⁾

In vitro drug release studies were conducted for a period of 12 hrs. using USP XXIV type-II (Paddle) dissolution apparatus at $37 \pm 0.5^\circ\text{C}$ and at 50 rpm using 900 ml of 0.1N Hcl as dissolution medium. 5 ml of sample was withdrawn at predetermined time intervals from the dissolution medium and replaced with fresh medium to maintain the sink condition. Then, the samples were analyzed for Ritonavir by UV visible spectrophotometer (UV 2201 Systronic) at 240nm.

RESULTS AND DISCUSSION:

Table 1: Absorbance for the calibration curve of Ritonavir in 0.1N HCL:

Concentration ($\mu\text{g/ml}$)	Absorbance
0	0
5	0.134
10	0.290
15	0.419
20	0.565
25	0.721
30	0.901

Table 2 Ritonavir standard calibration curve

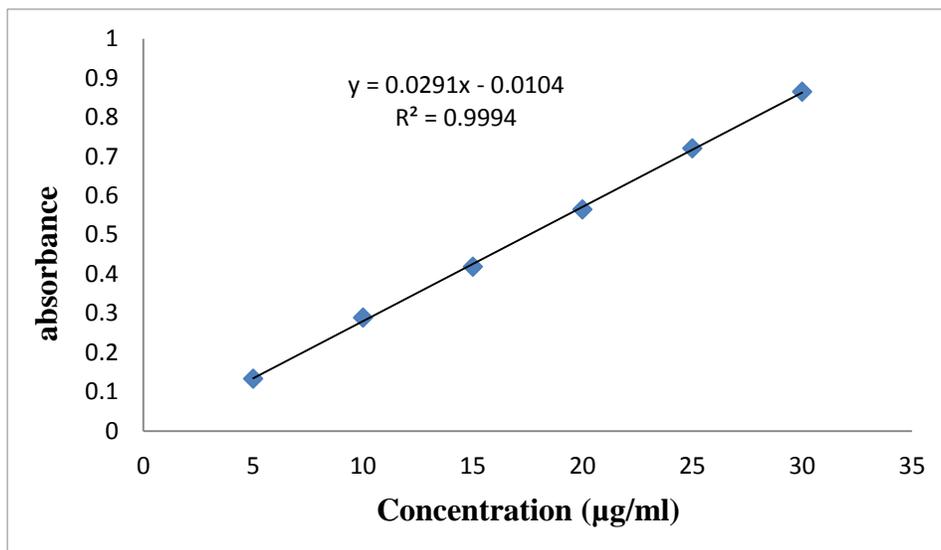


Table 3: Formula for preparing Ritonavir tablet

Ingredients	F1	F2	F3	F4	F5	F6
Ritonavir	100	100	100	100	100	100
Carbopol 971p	30	60	-	-	-	-
Gellan gum	-	-	30	60	-	-
HPMC K4M	-	-	-	-	30	60
Sodium bicarbonate	30	30	30	30	30	30
Magnesium stearate	5	5	5	5	5	5
Talc	5	5	5	5	5	5
PVP K30	10	10	10	10	10	10
MCC	110	90	110	90	110	90
Total	300	300	300	300	300	300

The Precompression Parameters:

The Precompression parameters such as bulk density, tapped density, angle of repose, carr's index and Hausner's ratio were evaluated. The results of these parameters were found to comply with specification of IP.

Table 4: Precompression parameters:

Formulation Code	Bulk density	Tapped density	Hausner's ratio	Carr's index	Angle of repose
F1	0.420	0.588	1.394	28.27	37.4±0.15
F2	0.428	0.600	1.401	28.66	38.9±0.45
F3	0.425	0.600	1.411	29.16	34.2±0.23
F4	0.432	0.624	1.444	30.76	32.8±0.35
F5	0.425	0.603	1.4188	29.51	36.7±0.34
F6	0.446	0.640	1.434	30.31	38.7±0.43

DSC of Ritonavir:

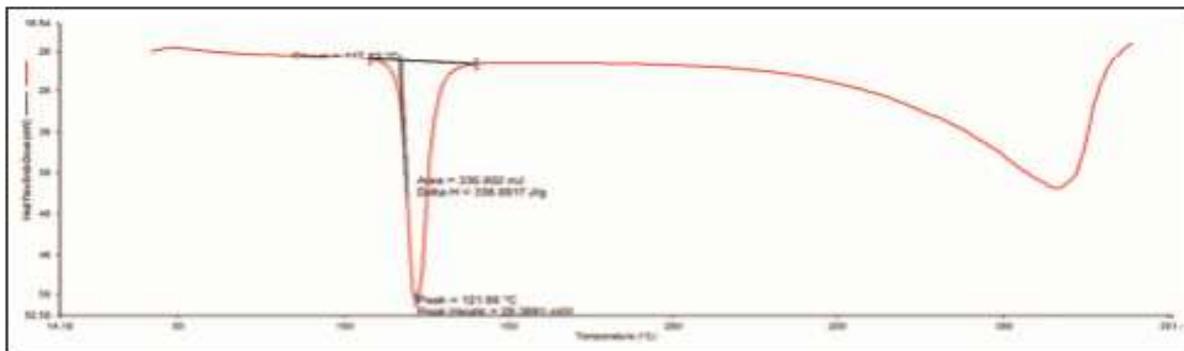


Figure 1: Differential scanning calorimetry for pure Ritonavir

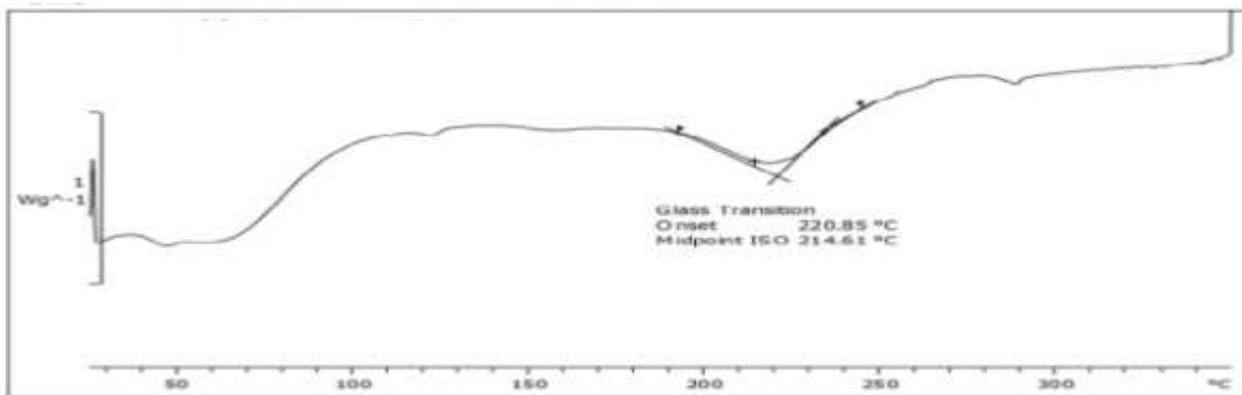


Figure 2: Differential scanning calorimetry for Ritonavir+ HPMC K4M FTIR:

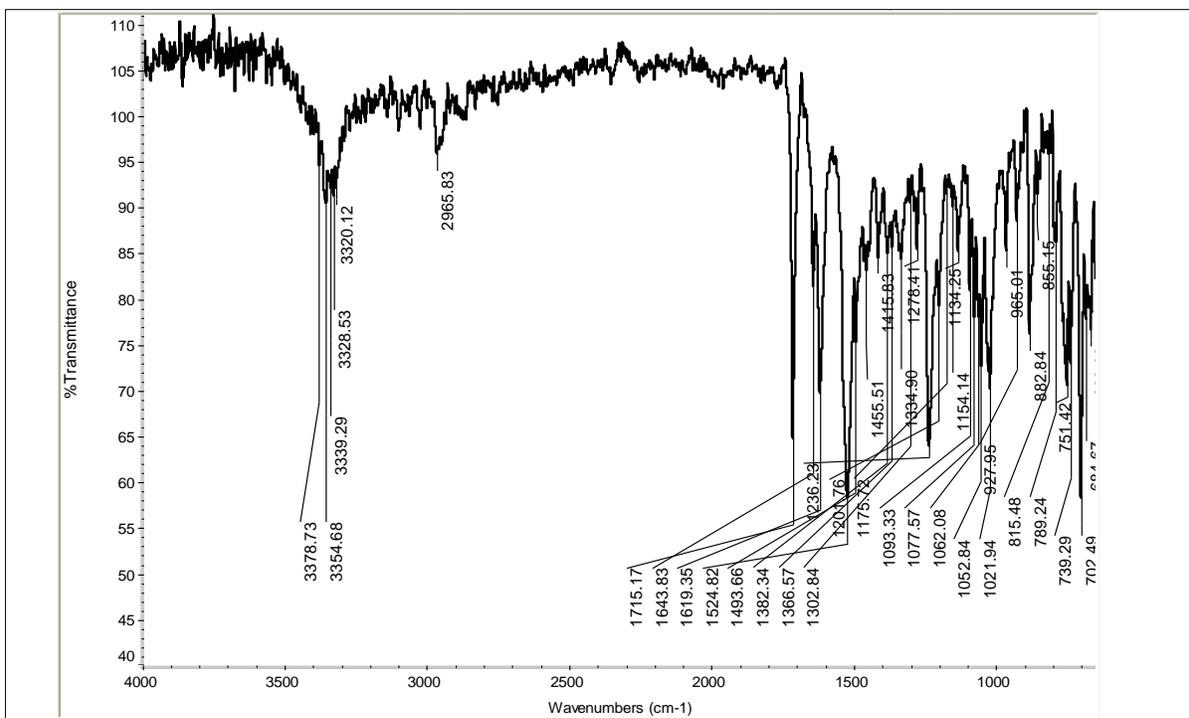


Figure 3: FTIR of pure Ritonavir

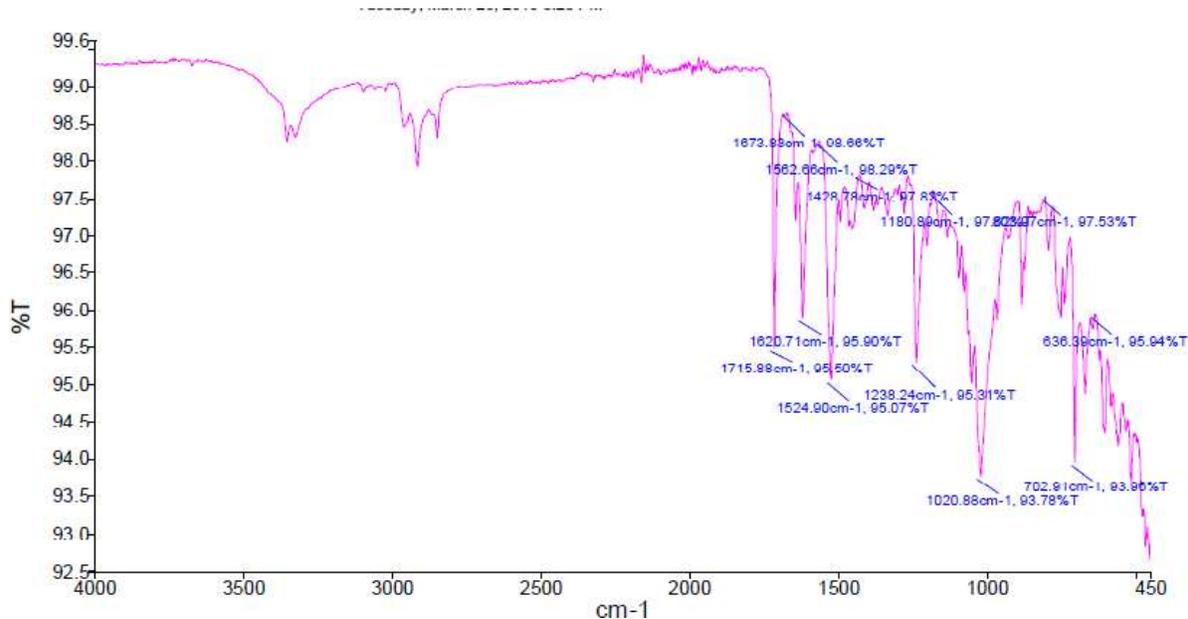


Figure 4: FTIR of carbopol 971p+Ritonavir

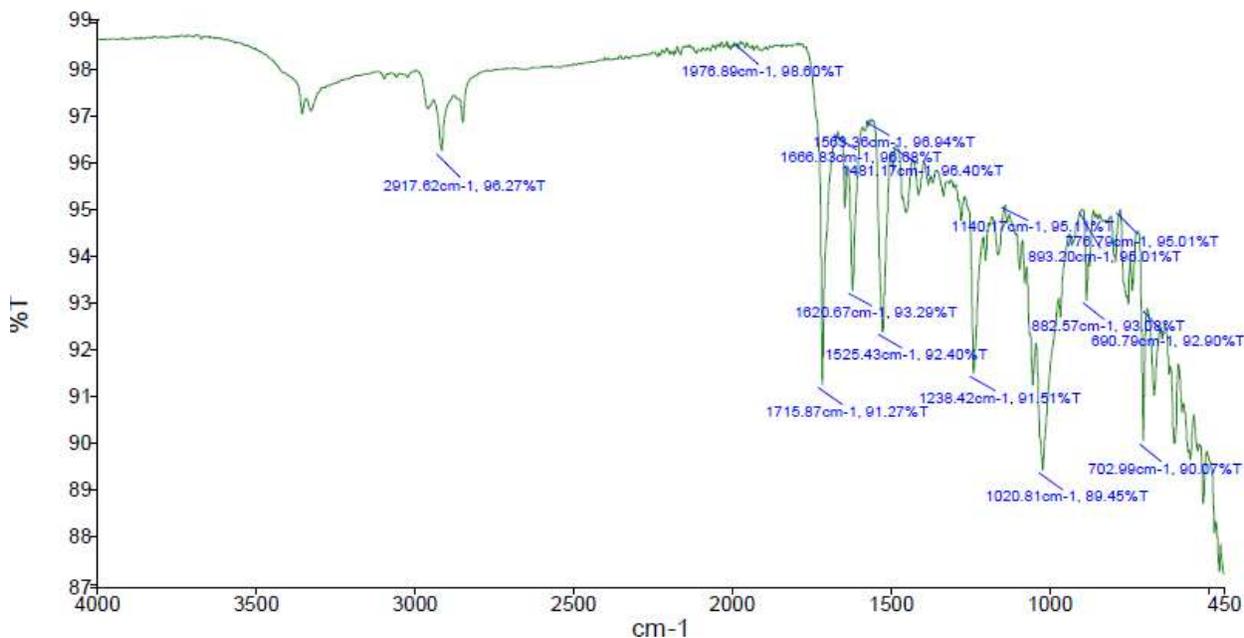


Figure 5: FTIR of Gellan gum+Ritonavir

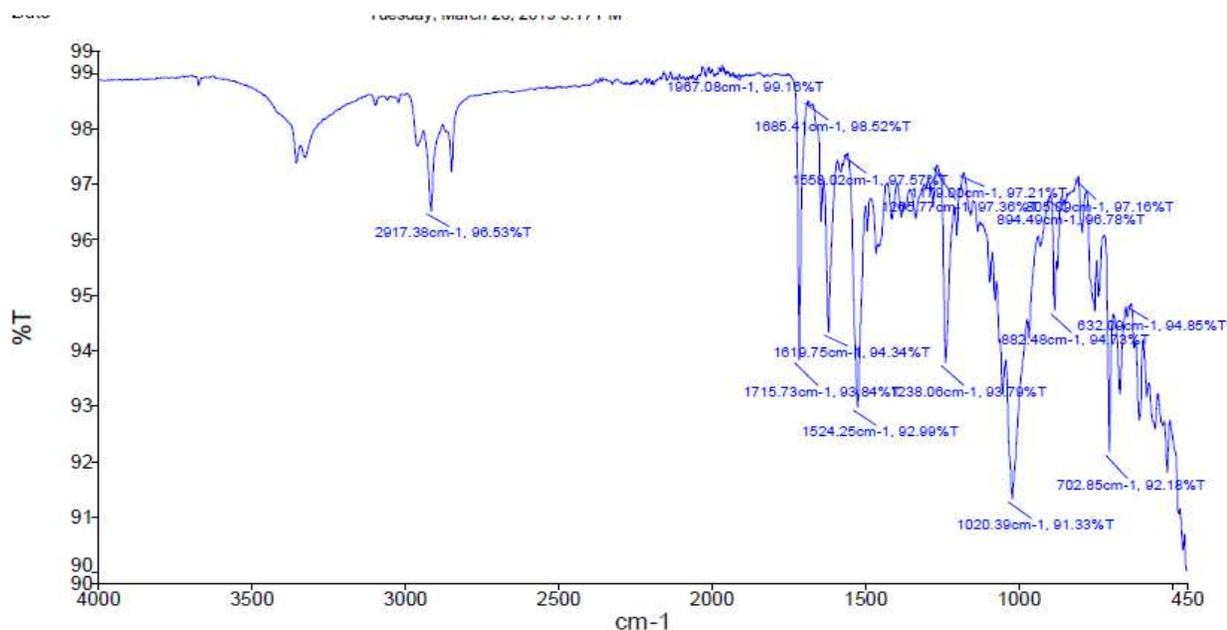


Figure 6: FTIR of HPMC K4M+Ritonavir

Post compression parameters:

Ritonavir Floating tablet was prepared by direct compression using different polymers in different ratios. In these formulations hardness is in the range of 4.5-5.1kg/cm². Weight variation in the range of 298-301mg. friability is in the range of 0.17-0.22%. Thickness is about 3.2-3.9mm. The drug content was found to be in the range of 94.21-98%.

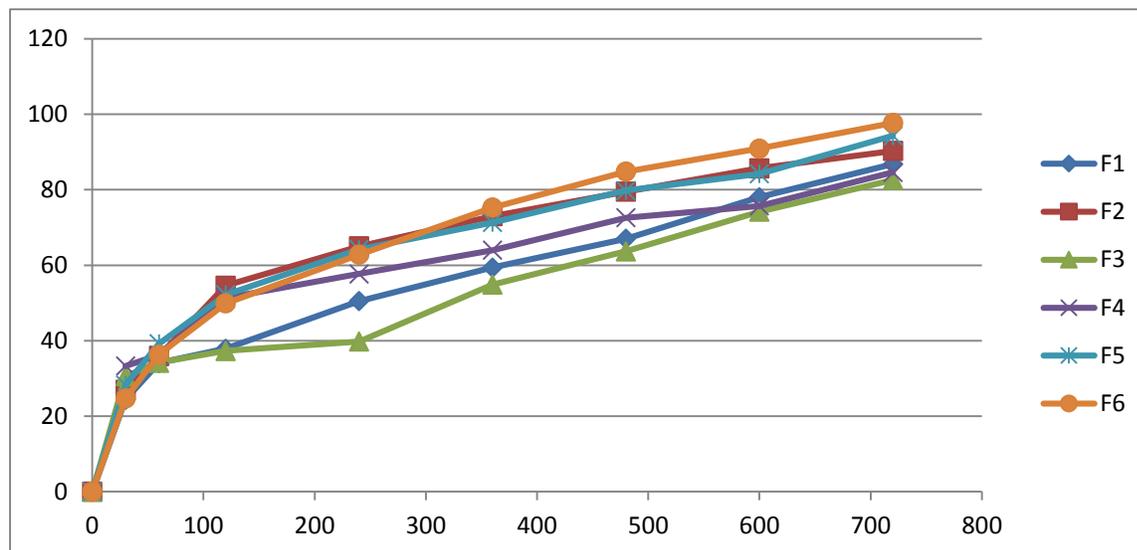
Table 5: Post compression parameters for the Ritonavir tablet:

Formulation	Weight Variation(mg)	Hardness (Kg/cm ²)	Thickness (mm)	Friability (%)	Drug Content
F1	300	4.5	3.8	0.21	96.01
F2	301	4.7	3.9	0.23	94.21
F3	298	4.6	3.6	0.22	95.12
F4	302	4.5	3.7	0.21	94.6
F5	301	5.2	3.4	0.18	97.36
F6	300	5.5	3.5	0.17	98.17

In-vitro Drug release:

Ritonavir floating tablet containing the formulations F1-F6, in which formulation F1 and F2 containing carbopol 971p shows drug release of 86.8% and 90.37% upto 10 hrs. Formulation F3 and F4 containing gellan gum shows drug release is about 82.67% and 84.25% upto 10 hrs. Formulations F5 and F6 containing HPMC K 4M show drug release is about 93.3% and 97.7% above 12 Hrs. Formulations F5 and F6 shows the highest drug release with prolonged period of time.

Table 6: Cumulative % Drug Release



Cumulative % Drug Release Versus Time (Min) Of Ritonavir Floating Tablet.

Table 7: Post compression parameters

Formulation code	Buoyancy lag Time (Sec)	Swelling index (%)	Floating duration (hrs)
F1	26	42.47	10
F2	33	45.15	10
F3	20	62.79	10
F4	24	69.20	10
F5	12	60.3	≥12
F6	14	71.6	≥12

Floating characteristic of Ritonavir tablet:

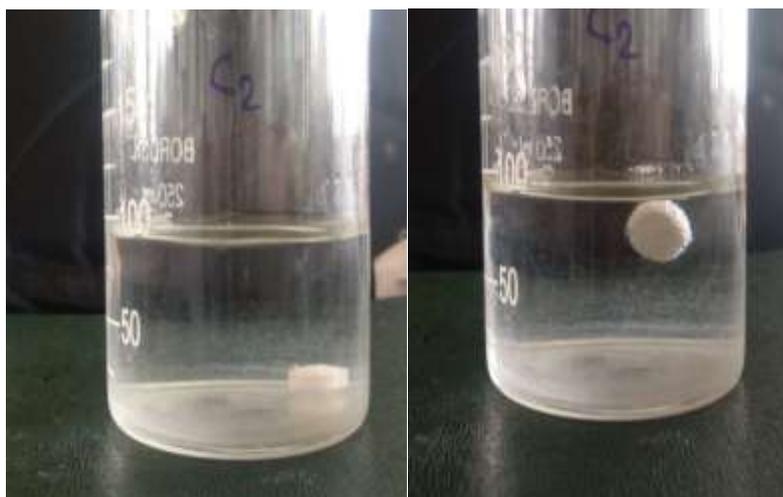


Figure 7: at 0 seconds

Figure 8: after 26 seconds

CONCLUSION

From the result of the study, is concluded that Ritonavir Gastroretentive floating tablets prepared from natural, semi-synthetic and synthetic polymers with different concentration have the ability

to release the drug over prolonged period of time. In comparison to carbopol 971p (F1 and F2) and gellan gum (F3 and F4) HPMC K4M (F5 and F6) shows better drug release. HPMC K4M shows the highest drug release with prolonged period of time. Batch F6 is the optimized batch with highest drug release of 97.7% above 12 hrs.

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