IJPSR (2022), Volume 13, Issue 1 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 24 March 2021; received in revised form, 25 May 2021; accepted, 02 June 2021; published 01 January 2022

FORMULATION AND EVALUATION OF GASTRO RETENTIVE MUCOADHESIVE FILM OF RITONAVIR

P. Shailaja * and G. Loknadh

AU College of Pharmaceutical Sciences, Andhra University, Visakhapatnam – 530003, Andhra Pradesh, India.

Keywords:

Malnutrition, Anaemia, Gastroretentive Multiunit particulate system, Colon targeted t Ritonavir, Gastro retentive mucoadhesive films, AIDS and Bioavailability ablet

Correspondence to Author:
Dr. Pashikanti Shailaja

Assistant Professor,
Department of Pharmaceutical Technology, A. U. College of Pharmaceutical Sciences
Andhra University, Visakhapatnam – 530003, Andhra Pradesh, India.

E-mail: dr.pshailaja@andhrauniversity.edu.in

ABSTRACT: Objective: The research work aims to formulate and evaluate the Gastro retentive mucoadhesive film of Ritonavir using polymers like HPMC K15M, Polyvinyl alcohol, and PEG 400 as a plasticizer by solvent casting method for treatment of AIDS. **Method:** Prepared gastro retentive mucoadhesive films were evaluated for various parameters such as *in-vitro* unfolding behavior of film, Folding endurance, Percent swelling, Drug content, and *in-vitro* drug release studies. **Results:** The release rate of the gastro retentive mucoadhesive films of Ritonavir was found to obey Korsmeyer-Peppas kinetics. After analysis of different evaluation parameters and drug release kinetics. **Conclusion:** Formulation code F4 was selected as a promising formulation for delivery of Ritonavir as a muco-adhesive Gastro retentive film with required *in-vitro* parameters 99.08% drug release at 12th h.

INTRODUCTION: Oral controlled release dosage forms have advantages such as ease of administration, patient compliance and flexibility in formulation. Drug bioavailability of pharmaceutical oral dosage forms is influenced by one important factor *i.e.*, gastric residence time of the dosage form. Several approaches for gastric retention includes high density (sinking system), low density (floating systems), expandable systems, super porous hydrogel systems, mucoadhesive systems and magnetic systems [1-3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(1).464-70

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(1).464-70

An advanced alternative to traditional dosage forms is gastro retentive mucoadhesive drug delivery systems, where a combination of mucoadhesion with the ability to expand by unfolding and swelling for a desired period [4, 5]. Gastro retentive mucoadhesive film is a drug-loaded polymeric film mainly comprised of API, film-forming polymer, mucoadhesive polymer and plasticizer with a suitable solvent [6]. Present work aims to formulate and evaluate the Gastro retentive mucoadhesive film of Ritonavir with desired characteristics.

MATERIALS AND METHODS: The Ritonavir was obtained as a gift sample from Mylan labs. Hydroxy Propyl Methyl Cellulose K15 M, Polyvinyl alcohol, PEG 400 obtained from central drug house private limited. All other reagents used were of pharmaceutical or analytical grade.

Construction of Calibration Curve of Ritonavir:
Preparation of 0.1N HCI: 8.5 mL of Hydrochloric acid was taken in a 1000 mL volumetric flask and to this 200 mL of distilled water was added and the final volume was made up to 1000 mL to get 0.1N HCL.

Preparation of Stock Solutions:
Stock I: 100 mg of ritonavir was taken and a few mL of ethanol was added until it dissolved. To this few mL of 0.1N HCL was added and volume was made up to 100 mL in a 100 mL volumetric flask to produce (1000 µg/mL)

Stock II: From stock I, 10 mL was taken and volume was made up to 100 mL with 0.1N HCL to produce (100 µg/mL) solution. From stock II, aliquots of 2, 4, 6, 8 and 10 mL were taken to obtain working standard solutions of 20-100 µg/mL were prepared in a 10 mL volumetric flask, and the volume was made up to 10 mL by using 0.1N HCL, and the above solutions were measured at 245 nm using double beam UV spectrophotometer. Absorbance values were plotted against the concentration of Ritonavir (µg/mL) [7].

Preparation of Gastro-retentive Mucoadhesive Film: The film was prepared by solvent casting method, in which HPMC K15M and PVA were dissolved in water separately by continuous stirring on a water bath for 10-15 min. Both the solutions were left overnight. Then both the solutions were mixed to this drug solution, and 0.1 mL of PEG 400 was added. The above solution was cast on a Petri plate coated with glycerol, with predetermined dimensions, and dried at 40 ºC for 2 h. Then the obtained films were cut into required dimensions (4 cm × 2 cm) and folded in accordion pattern, and inserted into a 00 size capsule, and are evaluated [9,10].

TABLE 1: FORMULAE FOR GASTRO RETENTIVE FILMS

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Ritonavir (mg)	100	100	100	100	100	100	100	100	100	100
HPMC K15M (mg)	25	50	75	100	25	50	75	100	100	100
PVA(mg)	25	50	75	100	100	100	100	25	50	75
PEG 400 (mL)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Evaluation of Films:
***In-vitro* Unfolding Behavior of the Film:** The prepared polymeric film was folded into 00 capsules. In vitro unfolding study was carried out in 900 mL of 0.1N HCL using USP type I apparatus at a constant temperature of 37 ± 5 ºC at 50 rpm to examine their unfolding behavior. Baskets were removed after an interval of 2 h,4 h and 8 h, respectively [16].

Folding Endurance of Film: The folding endurance of the film was determined by repeatedly folding the film at the same place at three different positions until it breaks at the places of folding [15, 16].

Drug Content: Drug content was determined by dissolving the film in 100 mL 0.1N HCL and kept for 24 h and intermittently shaken to dissolve completely, and the absorbance was measured at 245 nm using UV spectrophotometer [8].

Swelling Index: The swelling properties of the film can be determined by placing the film in USP dissolution test apparatus I in 900 mL of 0.1 N HCL. The film should be removed periodically from the dissolution medium after draining free water by blotting, and film weight gain should be measured on an electronic balance. The Swelling index can be calculated by formula [13].

Swelling index = (swelling wt of film-initial wt of film) / (initial wt of film) × 100

***In-vitro* Dissolution Studies:** *In-vitro* drug dissolution study was carried out in 900 mL 0.1N HCL using USP dissolution apparatus I (Paddle type) at 37 ± 0.5 ºC at 100 rpm. The film was inserted into the capsule and submerged in a dissolution medium. Aliquot of 5 mL was withdrawn at a particular time interval and analyzed using UV spectrophotometer at a given λ max 245 nm. Sink conditions should be maintained throughout experiment [12].

Stability Studies: The film in the capsule was packed in aluminium foil and stored in an ICH stability chamber maintained at 40 ± 2 ºC (75%

±5% RH) for three months. The capsule was withdrawn periodically for evaluating drug content and release kinetics [14].

RESULTS:

Calibration Curve in 0.1N HCI:

TABLE 2: ABSORBANCE VALUES OF RITONAVIR IN 0.1N HCI

Concentration (µg/mL)	Absorbance(n=3) (Mean ± s.d)
20	0.255±0.03
40	0.499±0.02
60	0.682±0.05
80	0.812±0.02
100	0.989±0.01

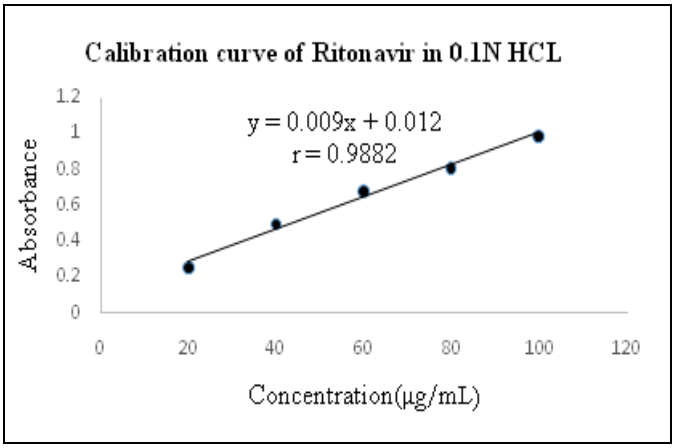

Fig. 1: CALIBRATION PLOT OF RITONAVIR IN 0.1N HCL

In-vitro Tests of Film:

TABLE 3: *IN-VITRO* EVALUATION RESULTS FOR ALL FORMULATIONS (N=3)

Code	Visual Appearance	*In vitro* unfolding behaviour (min) Mean ± S.D (n=3)	% Drug content Mean ± S.D (n=3)	Folding endurance (times ± S.D) (n=3)	Swelling index (%) Mean ± S.D (n=3)
F1	Transparent	15±0.57	89.8±0.23	179±0.56	104.6 ±0.45
F2	Transparent	16±0.57	87.8±0.57	180±0.78	83.16 ±0.62
F3	Transparent	18±1	90.8±0.35	183±0.59	91.25 ±0.89
F4	Transparent	14±0.57	93.8±0.18	187±0.16	108.66±1.24
F5	Transparent	17±0.57	92.8±0.56	188±0.23	107.86±0.65
F6	Transparent	15±0.25	91.8±0.57	189±0.56	85.28±1.17
F7	Transparent	18±0.57	89.8±0.45	187±0.79	96.35±0.95
F8	Transparent	16±0.23	92.8±0.23	182±0.56	111.57±0.42
F9	Transparent	17±0.57	90.8±0.58	190±0.59	85.52±1.05
F10	Transparent	18±1.15	87.8±0.68	185±0.42	91.23±0.32

FIG. 2: VISUAL APPEARANCE OF FILM

FIG. 3: UNFOLDING BEHAVIOUR OF THE FILM

TABLE 4: *IN-VITRO* DISSOLUTION DATA OF F1 TO F4 FORMULATIONS (n=3)

Time (hours)	F1 (Mean ± S.D) n=3	F2 (Mean ± S.D) n=3	F3 (Mean ± S.D) n=3	F4 (Mean ± S.D) n=3
0.08	11.8±0.42	8.8±0.85	9.8±0.23	14.8±0.23
0.16	26.8±0.35	14.8±0.56	13.8±0.56	18.8±0.13
0.25	34.8±0.78	17.8±0.75	26.8±0.78	20.8±0.45
0.5	47.8±0.56	24.8±0.36	29.8±0.89	27.8±0.56
0.75	60.8±0.32	27.8±0.28	34.8±0.75	29.8±0.78
1	71.8±0.89	33.8±0.35	43.8±0.85	36.8±0.66s
2	87.8±0.76	47.8±0.56	49.8±0.46	37.8±0.35
3	88.8±0.86	56.8±0.89	60.8±0.65	41.8±0.26

4	92.8±0.23	66.8±0.75	67.8±0.89	44.8±0.45
5		74.8±0.89	71.8±0.78	57.8±0.75
6		80.8±0.56	77.8±0.58	66.8±0.56
7		96.8±0.23	80.8±0.98	77.7±0.45
8			94.8±0.45	81.8±0.78
9			97.8±0.78	92.8±0.56
10				95.8±0.22
11				96.08±0.78
12				99.08±0.32

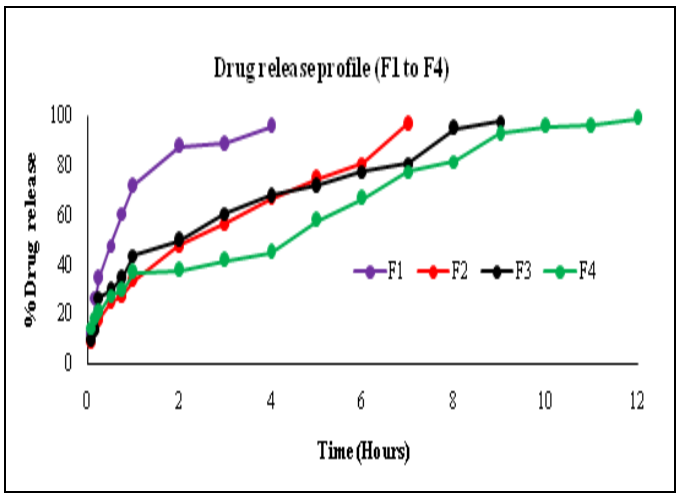

FIG. 4: DRUG RELEASE PLOTS (F1 TO F4)

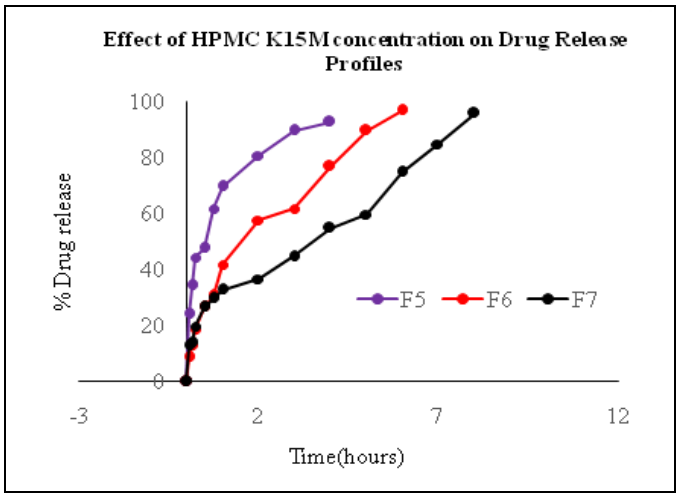

FIG. 5: DRUG RELEASE PLOTS (F5 TO F7)

TABLE 5: *IN-VITRO* DISSOLUTION DATA OF F5 TO F10 FORMULATIONS

Time (hours)	F5 (Mean ± S.D) n=3	F6 (Mean ± S.D) n=3	F7 (Mean ± S.D) n=3	F8 (Mean ± S.D) n=3	F9 (Mean ± S.D) n=3	F10 (Mean ± S.D) n=3
0.08	24.1±0.53	8.8±0.13	12.8±0.25	13.8±0.56	11.8±0.23	14.8±0.12
0.16	34.5±0.26	12.8±0.56	13.8±0.75	17.8±0.75	16.8±0.45	19.8±0.23
0.25	44.4±0.33	18.8±0.45	19.8±0.55	21.8±0.85	23.8±0.78	22.8±0.33
0.5	47.8±0.56	26.8±0.35	26.62±0.75	26.8±0.26	28.8±0.95	27.8±0.45
0.75	61.8±0.78	30.8±0.89	29.8±0.83	30.8±0.54	32.8±0.45	32.8±0.56
1	69.8±0.45	41.8±0.76	32.8±0.45	39.8±0.64	41.8±0.23	38.8±0.67
2	80.8±0.44	57.8±0.56	36.8±0.87	42.8±0.23	44.8±0.36	43.8±0.89
3	89.8±0.56	61.8±0.78	44.8±0.56	43.8±0.66	57.8±0.44	45.8±0.91
4	92.8±0.21	76.8±0.86	54.8±0.78	58.8±0.48	60.8±0.78	56.8±0.23
5		89.8±0.75	59.79±0.95	67.8±0.87	65.8±0.12	61.8±0.56
6		96.8±0.45	74.8±0.56	70.8±0.99	71.8±0.35	72.8±0.89
7			84.8±0.75	79.8±0.78	80.8±0.42	84.8±0.78
8			95.8±0.45	87.8±0.45	87.8±0.55	87.8±0.45
9				90.8±0.52	90.8±0.68	90.8±0.95
10				94.8±0.75	93.8±0.91	92.8±0.96
11				96.3±0.75	95.83±0.75	96.83±0.75
12				98.1±0.35	97.53±0.56	98.23±0.57

TABLE 6: CORRELATION COEFFICIENT AND K VALUES OF ZERO-ORDER AND FIRST ORDER PLOT

Code	Zero order (r)	$K_{0\ (\%/hr)}$	First order (r)	$k_{t\ (hr^{-1})}$
F1	0.8775	21.73	0.9847	0.85
F2	0.9847	11.74	0.8049	0.85
F3	0.9648	9.76	0.9223	0.38
F4	0.9889	7.99	0.9411	0.29
F5	0.9096	19.50	0.9946	0.72
F6	0.9720	14.82	0.9617	0.41
F7	0.9908	10.35	0.8929	0.14
F8	0.9845	8.70	0.8885	0.33
F9	0.9728	8.54	0.9908	0.18
F10	0.9846	8.58	0.9654	0.29

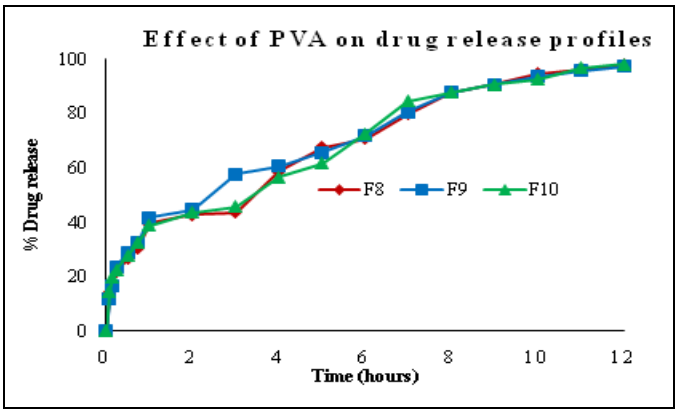

FIG. 6: DRUG RELEASE PLOTS (F8 TO F10)

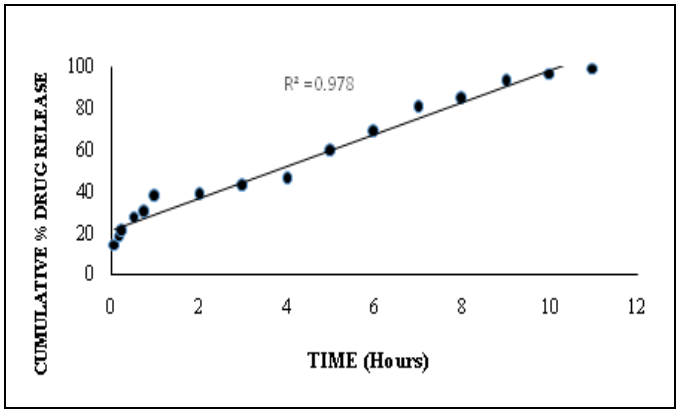

FIG. 7: ZERO-ORDER PLOT OF OPTIMIZED FORMULATION

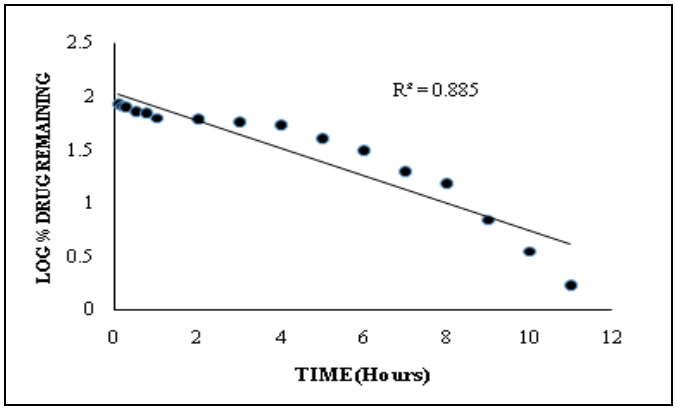

FIG. 8: FIRST ORDER PLOT OF OPTIMIZED FORMULATION

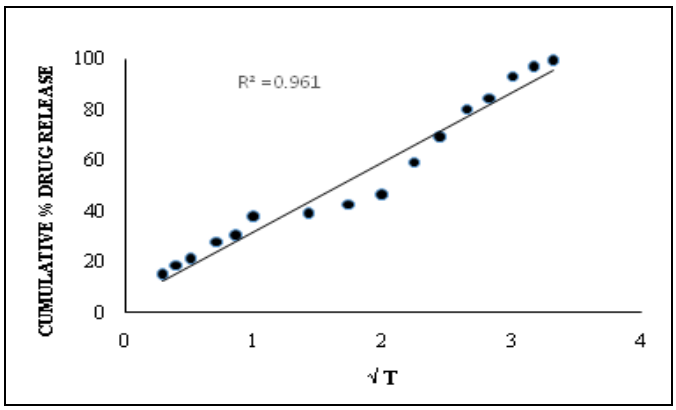

FIG. 9: HIGUCHI PLOT OF OPTIMIZED FORMULATION

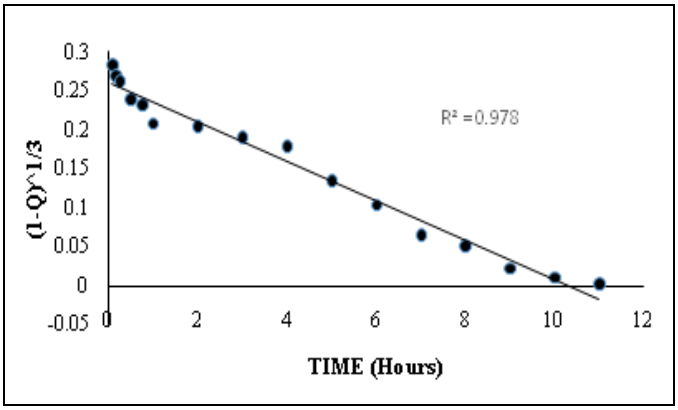

FIG. 10: HIXON-CROWELL PLOT OF OPTIMIZED FORMULATION

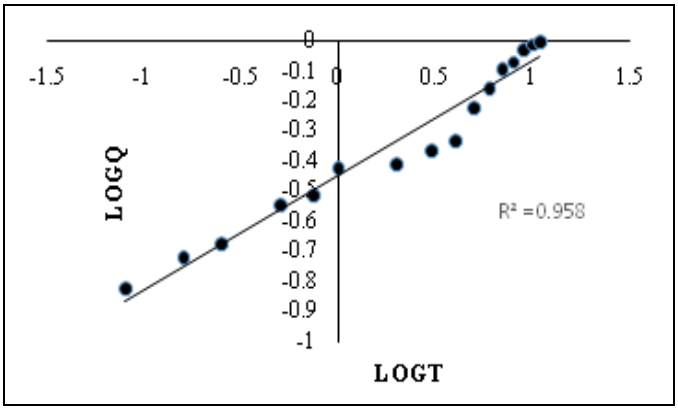

FIG. 11: KORSEMEYER-PEPPAS PLOT OF OPTIMIZED FORMULATION

TABLE 7: CORRELATION COEFFICIENT VALUES OF HIGUCHI, KORSEMEYER-PEPPAS AND HIXON-CROWELL PLOT

Formulation Code	Higuchi Plot (r)	Korsemeyer-Peppa's Plot (r)	n	Hixon- Crowell Plot (r)
F1	0.9548	0.9886	0.512	0.8777
F2	0.9970	0.9978	0.522	0.9847
F3	0.9918	0.9942	0.589	0.9648
F4	0.9805	0.9889	0.631	0.9507
F5	0.9721	0.9959	0.838	0.9096
F6	0.9846	0.9959	0.738	0.9720
F7	0.9780	0.9957	0.638	0.9908
F8	0.9914	0.9925	0.823	0.9845
F9	0.9950	0.9985	0.738	0.9728
F10	0.9895	0.9928	0.722	0.9846

DISCUSSION: The Gastro retentive muco-adhesive film was prepared by solvent casting method, by trial and error method. Several ratios of Ritonavir: HPMC K15M, Polyvinyl alcohol ranges from 0.25 to 5 was performed, and ratios range were fixed based on the thickness of the film. Based on the above selection criteria, 4 ratios were fixed *i.e.,* 1:0.25, 1:0.5, 1:0.75, and 1:1 (F1-F4), and the above ratios of films were cast and optimized. In vitro parameters of all the formulations (F1-F11) such as folding endurance was found to be in the range of 179:185 times, drug content in the range of 87% - 93%, and the swelling index was found to be in the range of 85% - 111% and *in-vitro* unfolding behaviour was found to be within 14-18 seconds for all the formulations, *in-vitro* maximum drug release was found to be in the range of 4 h – 12 h based on the concentration of HPMC K15M.

Based on the above optimization process F4 was selected as it showed maximum drug release at 12 h and the drug content was found to be 93% and in vitro unfolding behavior as well as appearance and folding endurance of the film showed required characteristics. It was observed that as the HPMC K15M concentration is increased with an increase in the prolonged activity, as PVA concentration increased, there is no effect on the drug release.

CONCLUSION: Based on the above studies, it is concluded that F4 formulation (1:1 ratio) showed the highest drug release within 12 h of 10 formulations prepared. It was observed that the concentration of polymer played a key role in drug release *i.e.,* as the concentration increases, release rate decreases. From the above results, the present research work revealed that the gastro retentive mucoadhesive is an advanced alternative to traditional gastro retentive dosage forms.

AUTHORS CONTRIBUTIONS: All the authors have contributed equally.

ACKNOWLEDGMENT: The drug sample was provided by Mylan Laboratories, and excipients like Hydroxyl Propyl Methyl Cellulose K15 M, Polyvinyl alcohol, PEG 400 were obtained from Central Drug House Pvt. Ltd. The remaining study of work was carried out in Andhra University College of Pharmaceutical Sciences.

CONFLICTS OF INTEREST: The author(s) declare(s) that there is no conflict of interest.

REFERENCES:

1. Shireesh KR and Chandra BS: Formulation and pharmacokinetic evaluation of ritonavir floating tablets in the management of AIDS. International Journal of Pharmaceutical Sciences and Drug Research 2018; 10 (6): 492-96.
2. Shifana M, Sivakumar R, Harsha KJ and Haribabu Y: Formulation design and optimization of expandable gastro retensive film for controlled release of propranolol hydrochloride. Saudi Journal of Medical and Pharmaceutical Sciences 2018; 4(7): 835-41.
3. Srikanth P, Hemalatha S and Suggala VS: Formulation development and in-vivo radiographic studies of diltiazem hydrochloride loaded floating capsules prepared by modified pulsincap technology. International Journal of Pharmaceutical Sciences and Research 2019; 10(5): 2550-64.
4. Kamlapurkar KA, Manmat BR, Ghurghure SM, Sagar SS and Imran NM: Formulation and Evaluation of Ritonavir Floating Tablets American Journal of PharmTech Research 2019; 9(2): 321-31.
5. Kulkarni N, Kulkarni M, Rathod J and Dhole NS: Formulation and evaluation of gastro-retentive floating microspheres: a systematic review. International Journal of
6. Pharmaceutical Sciences and Research 2020; 11(11): 5404-16
7. Dsouza L and Koland M: Bilayer film type of unfolding drug delivery system for the dual release of proton pump inhibitor and H2 receptor antagonist. Asian Journal of Pharmaceutics. 2016; 10 (2):76-85.
8. Thavva V and Baratam SR: Formulation and evaluation of terbinafine hydrochloride microsponge gel. International Journal of Applied Pharmaceutics 2019; 11: 78-85.
9. Bonthagarala B, Dasari V and Kotra V: Enhancement of solubility and dissolution rate of BCS class II drug ritonavir using liquisolid technique. Int J of Pharma Sciences and Research 2019; 10(5): 2430-38.
10. Chowdary KPR and Rao KSP: Formulation Development of Pioglitazone Tablets Employing β Cyclodextrin-Poloxamer 407-PVP K30: A Factorial Study. Scholars Research Library 2011; 3(6): 24-30.
11. Shakuntla V and Kalpana N: Unfolding type gastro retentive film of cinnarizine based on ethyl cellulose and hydroxyl propyl methyl cellulose. International Journal of Biological Macromolecules 2014; 6(4):347-52.
12. Patel TB and Patel TR: Design and development of novel mucoadhesive gastro retentive formulation of glipizide. Int J of Research in Ayurve and Pharmacy 2014; 5(5): 625-31.
13. Srinivasa RB and Vijaya RJ: Formulation and evaluation of floating matrix tablets of levofloxacin hemihydrate using hydroxypropyl methylcellulose k4m to treat helicobacter pylori infection. Asian Journal of Pharmaceutical Clinical Research 2018; 11(6): 148-51.
14. Padma P, Rajalakshmi AN and Ilaveni P: Formulation and evaluation of mucoadhesive microspheres of an anti-migraine drug. Journal of Drug Delivery and Therapeutics 2018; 8: 465-74.
15. Syed. E and Sai K: Preparation and evaluation of floating microspheres of ritonavir. International Journal of Research in Pharmacy and Chemistry 2013; 3(4): 834-41.

16. Pathak A, Mishra A and Mishra P; Formulation and evaluation of gastro retentive mucoadhesive film of captopril. Pharmacia 2013; 2(1): 31-38.

17. Harsoliya M and Patel V: Formulation of floating microspheres of ritonavir by cross linking technique: Int Journal of Pharma and Biol Archives 2012; 3(1): 108-11.

How to cite this article:
Shailaja P and Loknadh G: Formulation and evaluation of gastro retentive mucoadhesive film of ritonavir. Int J Pharm Sci & Res 2022; 13(1): 464-70. doi: 10.13040/IJPSR.0975-8232.13(1).464-70.