Available online on http://www.ijhacr.com

International Journal of Health Advancement and Clinical Research (tz) 2024; 2 (1); 8-14

Original Research Article

Formulation and Evaluation of Extended-Release Tablets of Ranolazine

Subhash Chandra [1], Vijay Sharma [2], N. Ravindra[3], Sunil Kumawat [4]

[1]Research Scholar, Goenka College of Pharmacy, Lachhmangarh, Sikar.

[2]Professor, Goenka College of Pharmacy, Lachhmangarh, Sikar.

[3] Professor, Goenka College of Pharmacy, Lachhmangarh, Sikar.

[4]Associate Professor, Goenka College of Pharmacy, Lachhmangarh, Sikar.

Received: 13-01-2024 / Revised: 16-02-2024 / Accepted: 29-02-2024
Corresponding author: Subhash Chandra
Conflict of interest: Nil

Abstract:

The purpose of pharmaceutical formulations such as extended-release tablets is to allow the gradual and prolonged absorption of medications into the body. Compared to immediate-release formulations, they provide a number of benefits, such as less dosage frequency, less variation in drug concentration, better patient compliance, and maybe fewer adverse effects.This project aims to develop and test Ranolazine Extended Release Matrix tablets that can prolong the drug's release profile up to 24 hours. The results will be compared to the invitro release profile of the commercially available formulation. twelve formulations (F1-F12) were prepared with the utilization of various polymers and then compared with the innovator's formulation. The formulation (F12) consisting of HPMC K100M, Stearic acid, and Carbopol 974p exhibited a drug release of 99% within 24 hours, which is similar to the innovator product and is regarded as the optimized formulation. The optimized formulation was determined to have a similarity factor of 64.3.

Key Words: Key words: Prolonged absorption, Matrix tablet, Carbopol 974p.

Introduction

Oral administration is the preferred method for administering medications due to its ease of use and the fact that the gastrointestinal system allows for more flexibility in designing dose forms compared to other routes. The terms "Sustained release," "prolonged release," "modified release," "extended release," or "depot" formulations are used to describe drug delivery systems that are specifically designed to achieve or prolong the therapeutic effect by continuously releasing medication over an extended period of time following the administration of a single dose.[1] There are several factors that contribute to the appeal of certain pharmaceutical formulations: Enhances the absorption of the medication, decreases the need for frequent administration to maintain optimal blood levels, minimizes fluctuations in drug concentration and associated adverse effects, and perhaps enhances targeted drug delivery. [2]

Extended-release tablets play a pivotal role in modern pharmacotherapy by providing controlled and sustained drug release, leading to enhanced therapeutic efficacy and improved patient adherence. Extended-release tablets are a type of pharmaceutical formulation designed to deliver drugs into

the body gradually over an extended period. They offer several advantages over immediate-release formulations, including reduced dosing frequency, minimized fluctuations in drug concentration, improved patient compliance, and potentially fewer side effects.[3,4]

These tablets are engineered to release the active ingredient slowly and consistently over time, maintaining therapeutic levels in the bloodstream. This sustained release can be achieved through various mechanisms, such as matrix systems, reservoir systems, osmotic systems, or combination systems, each tailored to the specific characteristics of the drug and the desired release profile.

Evaluation parameters of Extended-release tablets of ranolazine

Weight variation test

A digital balance was employed to calculate the average weight of 20 randomly chosen tablets from each formulation. The weight of every tablet had been individually estimated using the same method and then compared to the average weight.[5]

Hardness

The hardness test is conducted to quantify the tablet's mechanical resistance. The tablet should possess sufficient durability to endure the stress of packaging and transportation. The Electro lab digital hardness tester has been used to determine the hardness of tablets. The pills were assessed for their hardness, and the average hardness was determined. The unit of measurement is often given in kilopascals (kp) or kilograms per square centimeter (kg/cm^2). [6]

Thickness

The thickness of each batch was measured using a digital vernier scale for 20 pre-weighed tablets. The average thickness, measured in millimeters, was then determined. The tablet's thickness is mostly determined by its hardness and might serve as an initial control parameter.[7,8]

Friability percentage

Tablets' resistance to cracking and abrasion during shipment and packing is shown by the friability test. In most cases, a friability rating of less than 1% is ideal for traditional tablet designs. The starting weight was recorded after 10 tablets had been taken if their weight was equal to or greater than 650 mg. The Roche friabilator was used to spin the tablets 100 times at 25 rotations per minute. The tablets were reweighed after being dusted. [9]

The Tablets were deemed compliant if they lost less than one percent of their weight.

The percentage of friability is determined by the formula, which is given as the loss of weight.

$$\%\ Friability = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100$$

Drug Content

Five tablets had been weighed and crushed. A quantity of powder corresponding to 50 mg of the chosen medicine was placed in a 250 ml volumetric flask along with 250 ml of a diluting solution (0.1N HCl). The mixture was then subjected to sonication for a duration of 15 minutes. Transfer 4 milliliters of the solution from the previous step into a 200 milliliter volumetric flask and fill it up with a diluting medium. Create a standard solution that has the same concentration as the test solution, using the same diluting medium. The solutions were ultimately passed through a Whatman filter paper number 40. Subsequently, the samples were analysed using the U.V spectrophotometric technique. [10]

***In-vitro* dissolution study**

The *in vitro* dissolution study used USP dissolution test apparatus type II (paddle). Each of the six dissolution flasks contained one tablet in 900 ml of dissolution medium, maintained at 37 ± 0.5°C. At specified intervals, solution portions were withdrawn midway between the medium surface and rotating blade, at least 1 cm from the vessel wall. These samples were filtered through a

0.45 µm membrane filter, diluted with dissolution medium, and measured in 1 cm cells using a spectrophotometer, with dissolution medium as blank. The % drug dissolved from Ranolazine tablets was then calculated. [11,12]

Calculation of similarity factor

The equation proposed by Moore and Flanner is as follows:

$$f_2 = 50 \times \log \{[1+(1/n) \Sigma | R_t - T_t |^2]^{-0.5} \times 100\}$$

Where f_2 is similarity factor, n is the number of observations, wt is optional weight, R_t is percentage drug dissolved from reference formulation, and T_t is percentage drug dissolved from test formulation.

Results and Discussion

The physical criteria such as hardness, its thickness, weight variation, and friability were all examined in all formulations, and they were all determined to be within the limitations set by the pharmacopoeia. A table containing the test findings was prepared. All of the formulations had drug contents that were within the allowed range

Table 1: Data of post compression studies of the prepared tablets

Formulation code	Weight variation(mg)	Thickness (mm)	Hardnes (kg/cm^2)	Friability	Drug content
F 1	1350.8±1.02	8.2±.02	15.0±0.2	0.16%	98.01%
F 2	1349.6±0.74	8.3±.02	17.1±0.3	0.12%	99.40%
F 3	1350.1±1.09	8.4±.02	16.1±0.4	0.15%	101.50%
F 4	1350.6±0.21	8.4±.02	18.2±0.2	0.13%	99.41%
F 5	1350.9±1.29	8.2±.02	17.6±0.6	0.15%	98.51%
F 6	1350.7±1.26	8.5±.02	16.0±0.7	0.14%	99.37%
F 7	1350.8±0.98	8.4±.02	17.0±0.4	0.16%	99.65%
F 8	1350.7±0.87	8.6±.02	18.0±0.4	0.15%	99.71%
F9	1350.8±0.78	8.2±.02	17.4±0.6	0.14%	98.45%
F10	1350.5±0.67	8.5±.02	16.6±0.3	0.16%	99.57%
F11	1350.7±0.32	8.6±.02	17.8±0.2	0.15%	99.52%
F12	1350.8±0.54	8.5±.02	18.0±0.3	0.14%	99.85%

Table 7.10: *In vitro* release profiles of F1-F4 with Innovator formulations

Time interval (Hrs.)	Cumulative % Drug dissolved				
	F-1	**F-2**	**F-3**	**F-4**	**Innovator**
0.5	27.9	40.2	29.8	11.5	17
2	58.1	57.9	56.7	21.3	35
4	80.6	69.3	65.4	32.7	48
6	89.7	76.4	75.4	41.8	52.7
8	99.7	88.6	86.9	50.23	59.1
10		93.9	92.4	58.7	65.5
12		99.2	100.7	64.4	71
16				71.4	80.32
20				78.6	89.6
24				90.1	99

In-vitro drug release data and profiles

The results of the Invitro dissolution studies showed that the type of polymer used has an impact on the pattern of drug release. Batches containing Carbopol 974p (F1), Stearic acid (F2), and Methocoel K4M (F3) exhibited a significantly higher rate and extent of drug release. On the other hand, the drug release from F4 (Methocoel K100M) was lower due to its higher viscosity and the reduced permeability of water through Methocoel K100M**.**

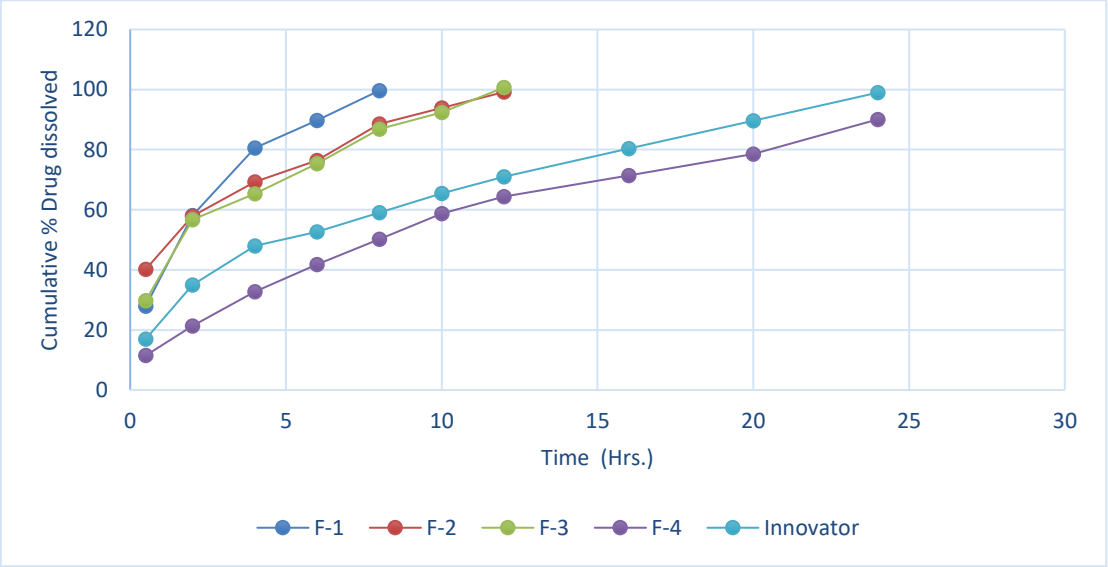

Fig. 1: *In vitro* release profiles of F1-F4 with innovator formulations

Table 7.11: *In vitro* release profiles of F5-F10 with innovator formulations

Time Interval (hrs)	Cumulative % drug dissolved						
	F-5	**F-6**	**F-7**	**F-8**	**F9**	**F10**	**Innovator**
0.5	24.04	20.82	18.01	14.28	7.6	10.2	17
2	46.81	40.10	35.83	30.01	19.9	23.6	35
4	65.02	55.72	51.20	43.06	30.4	35.7	48
6	73.98	67.47	65.65	59.78	42.7	49.7	52.7
8	83.83	77.86	76.54	71.85	47.7	53.6	59.1
10	94.68	89.44	88.17	77.85	54.3	66.7	65.5
12	108.9	97.01	96.93	86.76	58.7	72.9	71
16			100.1	95.05	67.6	81.3	80.32
20				98.78	75.9	89.3	89.6
24					81.2	92.6	99

In formulations F5 and F6, Carbopol 974p and Methocoel K100M were combined as release retardant polymers. In F5, with a combined polymer concentration of 13%, drug release extended to 10 hours, while in F6, with a concentration raised to 15%, release extended to 12 hours. Due to Carbopol 974p's pH dependency, at lower pH values, the polymer matrix is less swollen, allowing faster drug release. In formulations F7 and F8, Carbopol 974p and stearic acid were combined, with constant Carbopol concentration. In F7, release extended to 16 hours, while in F8, with

increased stearic acid, release extended to 20 hours, showing stearic acid's superior release profile compared to Carbopol. Subsequent trials used Methocoel K100M and stearic acid, but in F9 and F10, the drug release profile was more retarded than desired. Therefore, further trials involved the combination of these three polymers

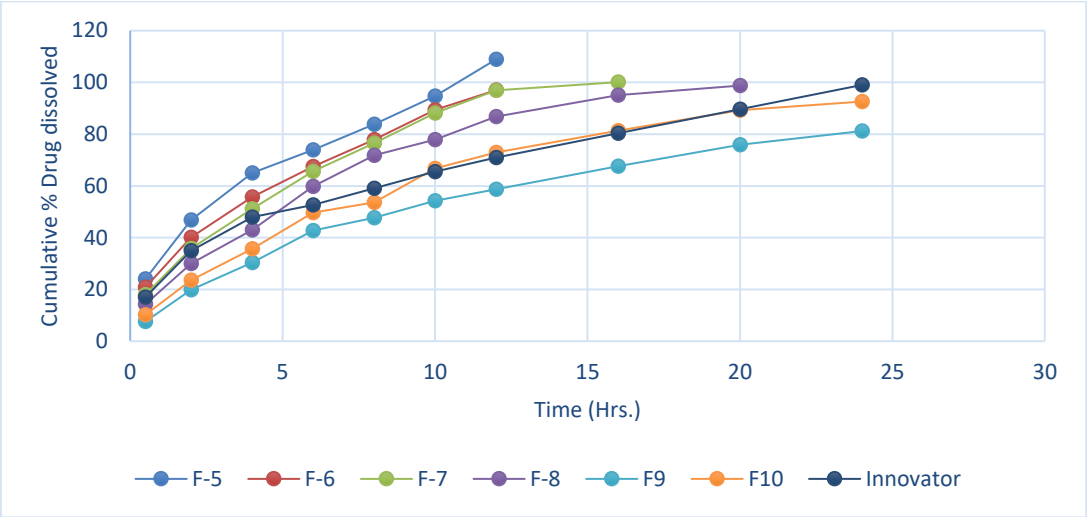

Fig. *In vitro* release profiles of F5-F10 with innovator formulations

Table 7.12: *In vitro* release profiles of F11,F12 with innovator formulations

Time interval	Cumulative % of drug dissolved		
(Hrs.)	F-11	F-12	Innovator
0.5	15.6	13.8	17
2	39.3	26.7	35
4	59.2	43.3	48
6	70.6	54.67	52.7
8	78.4	61.7	59.1
10	84.6	69.4	65.5
12	89.8	76.7	71
16	93.5	84.6	80.32
20	97.4	95.2	89.6
24	101	99.2	99

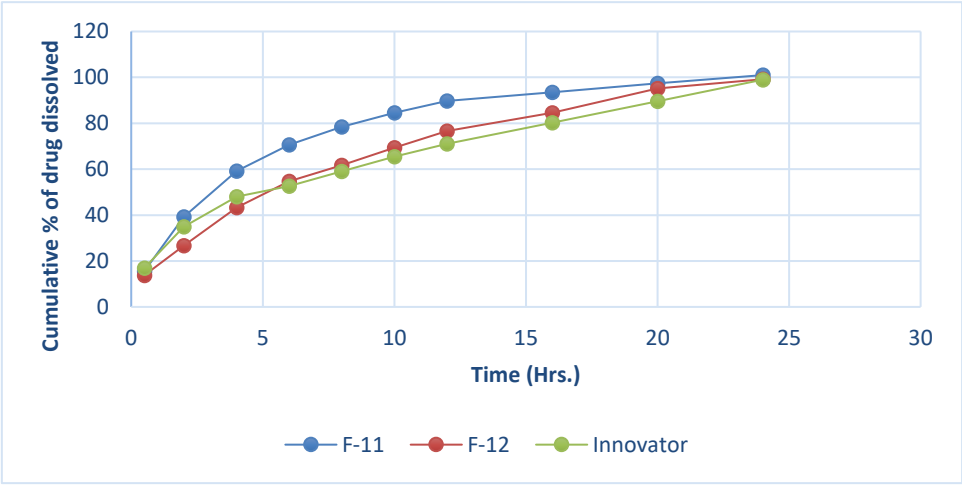

Fig : *In vitro* release profiles of F11,F12 with innovator formulations

In F11, combination of Carbopol 974p(90mg), stearic acid(130mg), Methocoel K100M (50mg) were used to form polymer matrix. Here the release was extended upto 24hrs and initially,the release was almost similar to innovator but at later time points the release was faster compared to innovator and the similarity factor was found to be 41.6. In F12,same combination of polymers were used in same concentration but about 2% Methocoel K100M was used extragranularly. Here drug release was similar to Innovator and the similarity factor was found to be 64.3.

Conclusion

The current research set out to replicate the innovator's success in producing and evaluating Ranolazine extended release matrix tablets utilising certain polymers to produce extended release for up to 24 hours. After being made using the wet granulation process, the tablets were tested for assay, friability, hardness, weight variation, and invitro drug release, among other post compression characteristics. Every one of the parameters fell inside the permissible limits. F12, the optimised formulation including HPMC K100M, Stearic acid, and carbopol 974p, demonstrated 99% drug release in 24 hours, matching that of the innovator. A similarity factor of 64.3 was determined for the optimised formulation.

References

1. Gupta PK and Robinson JR. Oral controlled release delivery. Treatise on controlled drug delivery., 1992; 93(2): 545-555……Jantzen GM and Robinson JR. Sustained and Controlled-Release Drug Delivery systems. Modern Pharmaceutics., 1995; 121(4): 501-502.
2. Madhusudhan P and Nazeer S. Extended-release formulation. International Journal of Pharmacy and Technology. 2010; 2: 625-684.
3. Chandra, S., Sharma, V., & Kumawat, S., Extended-Release Tablets: An Overview. International Journal of Health Advancement and Clinical Research (tz),2023; 1(4): 85–89.
4. Fukui S, Yano H, Yada S, Mikkaichi T, Minami H, Design and evaluation of an extended-release matrix tablet formulation; the combination of hypromellose acetate succinate and hydroxypropylcellulose, Asian Journal of Pharmaceutical Sciences, 2017; 12(2):149-156.
5. B. Babu Rao, P. Harish, Saikat Das, T. Ashwin Kumar, V. Raman Koundinya. Formulation Development and In-Vitro Evaluation of Extended Release Tablets Containing Losartan Potassium. Asian J. Pharm. Res., 2013; 3(4):181-188.
6. Sharma R, Bansal M, Garg A, Agarwal V, Sharma D, Formulation and Evaluation of Sustain Release Matrix Tablet of Aceclofenac. International Journal of Health Advancement and Clinical Research (tz), 2023;1(1):6-11.
7. Nandhakumar S, Sugreevudu G, Harikrishnan N, Formulation design and Evaluation of Extended-Release Tablets of Oxybutynin for Effective Management of Overactive Bladder Syndrome. Research Journal of Pharmacy and Technology. 2021; 14(12):6558-4.
8. Sunil Kumar, Anil Kumar, Vaibhav Gupta, Kuldeep Malodia, Pankaj Rakha. Oral Extended Release Drug Delivery System: A Promising Approach. Asian J. Pharm. Tech., 2012; 2(2): 38-43.
9. Sharma P P, Sharma S, Khokra S L, Sahu R K, Jangde R, Singh J, Formulation, development and evaluation of sustained release matrix tablets containing salbutamol sulphate, Pharmacologyonline2, 2011; 1197-1203.
10. D Vamshidhar Reddy, Ambati Sambashiva Rao. A Review on Oral Extended Release Technology.

Research J. Pharm. and Tech.,2015; 8(10): Page 1454-1462.

11. Pagar H B, Shinde U P, Barhate S D, Bari M M, Janjale M V, Agrawal Y S. Formulation and evaluation of indomethacin sustained release matrix tablets. Inventi Rapid NDDS. 2011;4.
12. Mandal S, Ratan GN, Mulla JS, Thimmasetty J, Kaneriya A. Design and In Vitro evaluation of gastro retentive sustained release tablets of tizanidine hydrochloride. Int New Drug Deliv. 2010;2(4):144-152.