



Research Paper

Formulation and in vitro evaluation of sustained release matrix tablets of Rimopride Citrate Dihydrate

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ARTICLE INFO

ARTICLE HISTORY

Received 06 January, 2024
 Received in revised form 12 January, 2024
 Accepted 16 January, 2024
 Available online 19 January, 2024

Key words:

Rimopride Citrate Dihydrate,
 Sustained release

ABSTRACT

Drugs are most frequently administered by oral route. Although a few drugs taken orally are intended to be dissolved in the mouth, nearly all drugs taken orally are swallowed. A few drugs such as antacids are swallowed for their local action in the gastrointestinal tracts. Hence the above study demonstrated that combination of HPMC K4M and HPMC K15M can be used to formulate sustained release matrix tablets of Rimopride Citrate Dihydrate. This can sustain the drug release up to 24 hours as per standard dissolution profile. This can be expected to reduce the frequency of administration and decrease the dose – dependent side effects associated with repeated administration of conventional Rimopride Citrate Dihydrate dihydrate tablets.

The cumulative drug release of innovators brand (MOZA SR, Intas Pharmaceuticals) of sustained release tablet of Rimopride Citrate Dihydrate were compared for in vitro dissolution study. The formulation F9 matrix tablet releases the drug appropriately in comparison of innovators brand. The cumulative drug release at the end of 24th hour from formulation F9 (98.01%) and the cumulative drug release at the end of 24th hour from innovators brand was (97.30%).

The in vitro drug release result indicates that formulation F9 released more drug than innovators brand and hence more drug is available at the absorption site from formulation F9 as compared to innovators brand, hence the formulation F9 has better bioavailability than innovators brand of Rimopride Citrate Dihydrate sustained release matrix tablet and also the sustained release matrix tablet was found to be beneficial in terms of reduction in frequency of administration. The formulation F9 best suited with zero order release kinetics (corr.coefficient = 0.943) than the first order release kinetics (corr. Coefficient = 0.910). The formulation F9 follows Higuchi model of drug release kinetics (corr. coefficient = 0.41).

The Korsmeyer peppas drug release kinetics showed correlation coefficient (0.926) and release exponent (n) 0.724 which indicates that the drug release mechanism is non-fickian diffusion. Hence it can be concluded that once daily sustained release matrix tablet of Rimopride Citrate Dihydrate having short half life, was found to exert a satisfactory sustained release profile which may provide an improved bioavailability, increased therapeutic efficacy and patient compliance.

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Drugs are most frequently administered by oral route. Although a few drugs taken orally are intended to be dissolved in the mouth, nearly all drugs taken orally are swallowed. Of these, most are taken for the systemic drugs effects that result after absorption from the various surfaces along the gastrointestinal tracts. A few drugs such as antacids are swallowed for their local action in the gastrointestinal tracts.¹

A few drugs such as antacids are swallowed for their local action in the gastrointestinal tracts. Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, cost-effective manufacturing process and flexibility in dosage form. Oral sustained release dosage forms have been developed and studied to restrict these systems to specific regions of the gastrointestinal tract as well as to improve the pharmacological activity and to reduce toxic effects²⁻³. The majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal milieu⁴⁻⁵.

Sustained Release Concept

A sustained release product may be considered one in which a drug is initially made available to the body in an amount sufficient to cause the desired pharmacological response as rapidly as is consistent with the properties of the drug determining its intrinsic availability for absorption; and one which provides for maintenance of activity at the initial level for a desirable number of hours in excess of the activity resulting from the usual single dose of drug⁶⁻⁷. An alternative approach is to administer the drug repetitively using a constant dosing interval, as in multiple-dose therapy. For the oral route in this case the drug blood level reached and time required to reach that level depend on the dose and dosing interval. There are several potential problems inherent in multipledose therapy. The drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for certain disease state⁸.

The objective of this evaluation was to create and test Rimopride Citrate Dihydrate supported discharge lattice medicines using only hydrophilic polymer hydroxypropyl methylcellulose (HPMC) of two specified thickness grades: HPMC K4M and HPMC K15M.

2.MATERIALS AND METHOD

Preformulation studies

Prior to development of any dosage form, it is essential that certain fundamental physical and chemical properties of the drug molecule and other derived properties of the drug powder are determined. This information will dictate many of subsequent events and possible approaches in formulation development. This first learning phase is called as preformulation⁹.

Drug excipient compatability study by FTIR spectroscopy

The FTIR spectra of pure Rimopride Citrate Dihydrate, Rimopride Citrate Dihydrate with HPMC K4M, HPMC K15M and Rimopride Citrate

Dihydrate with HPMC K4M, HPMC K15M, Lactose, Magnesium stearate, Talc, Aerosil were analyzed for compatibility study.

The instrument was operated under dry air purge and the scans were collected at scanning speed 2mm/sec with resolution of 4cm-1 over the region 4000-400cm-1. The scans were evaluated for the presence of principle of peaks of drug, shifting and masking of drug peaks and appearance of new peaks due to polymer interaction¹⁰.

Preparation of standard calibration curve

100 mg of Rimopride Citrate Dihydrate was accurately weighed and transferred into 100 ml volumetric flask. It was dissolved and diluted to volume with purified water to give stock solution containing 1000µg/ml. The standard stock solution was then serially diluted with purified water to get 10ug/ml of Rimopride Citrate Dihydrate The λ_{max} was found to be 274 nm using UV Spectrophotometer. The absorbance values were plotted against concentration (µg/ml).

Materials used for Dry granulation

Materials	Actual Quantity (gm/1000 tablets)	Sieve no
Materials for dry mixing		
Rimopride Citrate Dihydrate	10.77	24#
Lactose IP/BP	37.05	24#
HPMC K4M	20.00	24#
HPMCK15M	25.00	24#
Talcum	0.50	40#
Magnesium Stearate IP/BP	0.50	40#
Aerosil IP/USP	0.10	40#
Materials for dry lubrication		
Rimopride Citrate Dihydrate	4.23	24#
Talcum	0.50	40#
Magnesium Stearate IP/BP	0.50	40#
Aerosil IP/USP	0.10	40#

Table No.1 Physicochemical evaluation of tablet

Tablet thickness

Thickness and diameter were measured using a calibrated dial caliper. Three tablets of each formulation were taken randomly and thickness was measured individually¹¹.

Hardness test:

To determine tablet hardness, Monsanto hardness tester was used. Tester barrels feature compressible springs between plungers. Contacting the tablet with the lower plunger yields a zero reading. Using a threaded bolt, the upper plunger is pressed against a spring to break the tablet. To indicate spring compression, a pointer rides a barrel gauge. The fracture force is recorded and its zero force is subtracted⁹. It was Kg/cm2 hardness.

Friability test:

The most popular and commercially available friability apparatus is the Roche Friabilator, in which approximately 6g (w_0) of dedusted tablets are subjected to 100 free falls i.e the apparatus revolves at 25rpm dropping the tablets through a distance of 6 inches in a rotating drum and are then reweighed (w). the friability, f , is given by: $f = 100 \cdot (1 - w_0/w)$

Values of f from 0.8 to 1.0% are regarded as the upper limit of acceptability.

Kinetics of In vitro drug release

To investigate the manner of medicine release from tablets, the discharge data was broken down with the accompanying numerical models:

Zero order kinetics

$$(Q = K_0t)$$

It represents a system in which Drug release frequency is independent of concentration. C is the total amount of drug released in time t , and K_0 denotes the zero order release constant.

First order kinetics

$$\log Ct = \log C_0 - K_1t/2.303$$

This description pertains to drug release frequency from systems in which the release frequency is influenced by concentration.

Ct denotes the quantity of drug released at time t , C_0 represents the initial drug concentration, and K_1 represents the first-order release constant.

Higuchi kinetics

$$W = K_2 t^{1/2}$$

It refers to drug release from systems in which the solid drug is disseminated in an insoluble matrix and Direct correlation exists between the rate of drug release and the rate of drug diffusion.

W is the total amount of medication released during time t , and K_2 is the Higuchi dissolving constant.

Hixson Crowell kinetics.

$$(100 - W)^{1/3} = 100^{1/3} - K_3t$$

This concept elucidates the release mechanism in systems where it relies on the alteration of tablet surface area and diameter over time. It primarily applies to systems that degrade or deteriorate over time. K_3 is the release constant, and W is the total amount of medication dissolved at time t . Korsmeyer and Peppas equation

$$Mt / M_\infty = K_4t^n$$

The subsequent equation signifies the drug release from the polymeric system when the release mechanism deviates from Fickian diffusion. F is the total quantity of medication dissolved at time t , K_4 is the release constant, and n is the exponent dictating the drug release mechanism.

Stability study

Pharmaceutically stable containers/closures meet physical, chemical, microbiological, medicinal, and toxicological needs during shelf life. For

temperature, humidity, and light-sensitive medicinal medications and items, stability tests recommend storage, retesting, and shelf-lives.

12-month long-term testing at $25^\circ\text{C} \pm 2^\circ\text{C} / 60\% \text{ RH} \pm 5\% \text{ RH}$. Testing took place over 6 months at $40^\circ\text{C} \pm 2^\circ\text{C} / 75\% \text{ RH} \pm 5\% \text{ RH}$. Our study examined the stability of chosen formulations at 40°C and 75% RH for 3 months. Polyethylene-lined aluminium tablet stability test. Decators maintained 75% RH samples¹².

3. RESULT AND DISCUSSION

Physical properties	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk Density [gm/ml]	0.434	0.435	0.433	0.431	0.435	0.439	0.428	0.422	0.438
Tapped Density [gm/ml]	0.625	0.626	0.631	0.628	0.630	0.634	0.623	0.615	0.623
Compressibility index	31.45	32.60	31.02	31.26	30.95	30.75	31.30	31.38	30.69
Hausner's ratio [HR]	1.39	1.40	1.44	1.45	1.448	1.444	1.46	1.467	1.452
Angle of repose	34°33"	34°18"	32°64"	33°75"	32°42"	32°05"	31°47"	32°55"	33°32"
Observation	Miserable Flow rate	Miserable Flow rate	Miserable Flow rate	Miserable Flow rate	Miserable Flow rate	Miserable Flow rate	Miserable Flow rate	Miserable Flow rate	Miserable Flow rate

Table No.2 Physical parameters of granules before dry granulation

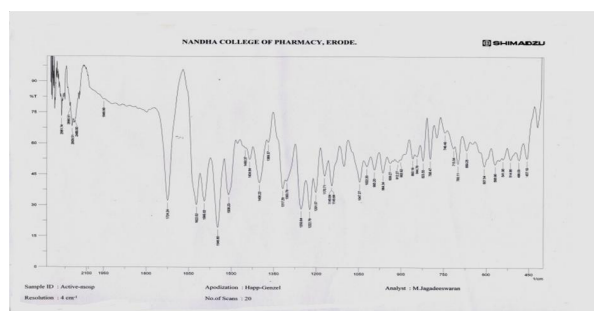


Figure No.1 FTIR Spectra of Rimopride Citrate Dihydrate

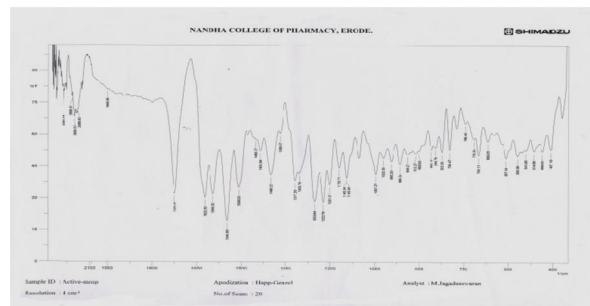


Figure No.2 FTIR Spectra of Rimopride Citrate Dihydrate with HPMC K4M and HPMC K15M

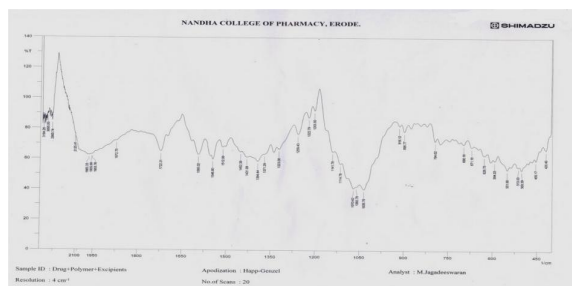


Figure no.3 FTIR Spectra of Rimopride Citrate Dihydrate with two different grades of hydroxypropyl methyl cellulose polymer

Interpretation of FTIR Spectra

Sr .N o	Functional groups presents in Rimopride Citrate Dihydrate	Standard FTIR range	Observed Peak
1	C=O (in ketone)	1705-1725	1724.11
2	C-N (vibrations)	1000-1400	1400.20, 1434.94, 1450.37
3	C-H	700-850	607, 669, 700, 715, 746, 798
4	C-Cl	800-600	700.11
5	C-F	1000-1400	1201.57

Evaluation of tablets

The tablets from each batch of factorial design were evaluated for uniformity of weight, thickness, hardness, friability and the results were reported in table no --. The tablets showed good weight uniformity as indicated by the low value of Relative Standard Deviation (RSD<1%). The tablet thickness were found in the range of 3.90 ± 0.01 mm to 4.00 ± 0.01 mm. the tablet hardness varied from -- to --. The tables pass the friability test, as all the batches were within the pharmacopoeial limit¹³. (F<1%).

Formulations	Uniformity in weight (mg)	Thickness variation (mm)	Hardness (kg/cm ²)	Friability (%)
F1	98.4	3.16	5.20	0.103
F2	98.90	3.21	4.40	0.210
F3	99.02	3.15	4.60	0.141
F4	99.97	3.12	5.30	0.158
F5	99.89	3.20	4.60	0.21
F6	99.74	3.08	4.70	0.265
F7	99.37	3.22	5.30	0.106
F8	98.59	3.15	4.90	0.150
F9	99.98	3.13	5.20	0.160

Table No. 3 Post compression parameters of Rimopride Citrate Dihydrate

Time (hrs)	Average percentage drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	40.07	41.89	38.99	45.54	42.01	35.00	30.82	25.06	24.3
4	65.0	60.04	59.37	78.53	63.0	53.23	47.11	44.11	41.9
7	96.22	89.93	85.0	97.0	86.72	79.09	72.40	66.29	58.20
12	--	97.02	98.89	--	98.58	97.66	84.21	79.56	74.10
16	--	--	--	--	--	--	97.0	98.01	83.50
24	--	--	--	--	--	--	--	--	98.6

Table No.4 Dissolution Profiles of Formulation F1-F9.

Duration	Hardness(kg/cm)	Friability (%)
After one month	5.20	0.160
After two months	5.20	0.160
After three months	5.19	0.161

Time in hours	Cumulative percentage drug release		
	1 st month	2 nd month	3 rd month
0	0	0	0
1	24.1	24.0	23.98
4	41.8	41.6	41.52
7	58.2	58	57.97
12	74	73.8	73.65
16	83.3	83	82.95
24	98.4	98.3	97.82

Table No. 5-6 Stability data

4. CONCLUSION

Matrix tablet of Rimopride Citrate Dihydrate were prepared by dry granulation method by using various excipient. During this phase of investigation various factors that likely to affect the performance of the sustained release was studied. Dry granulation method was formulated. Granules were evaluated for tests such as Bulk density, Tapped density, Compressibility Index and Hausner ratio before being punched as tablets¹⁴. Tablets were tested for weight variation, thickness and friability, in-vitro dissolution test were performed & % drug release was studied. Dissolution tests were performed and percentage drug release was calculated. Dissolution profile of Formulation-F7 was optimized based on evaluation parameters.

In the dissolution modelling all the developed formulations followed Higuchi-Peppas drug release. The optimized formulation-F7 followed zero order drug release¹. The developed formulation was tested for its stability for three month and found to be stable. In this research, HPMC was found to play a great role in controlling release of drug Rimopride Citrate Dihydrate sustained Release tablets from the matrix system for the treatment of gastrointestinal agents.

Accordingly, it can be concluded that the formulation is robust in the performance is less likely to be affected by the various factors studied

5.CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

6. ACKNOWLEDGEMENT

We are highly grateful to our Honorable Chairman, TKR college of Pharmacy, Telangana state for providing the necessary facilities to carry out this research work.

7. REFERENCE

1. The Remington. The Science and Practice of Pharmacy. 20th edition, (2006), Vol. I Mack Publishing Company. 903-913,939-941
2. S. P. Vyas, Roop K. Khar, Controlled Drug Delivery, Concepts and Advances, 1st .edition (2000),
3. Howard C. Ansel, Pharmaceutical dosage forms and drug delivery systems, sixth edition (1995), 215.
4. D. M. Brahmanekar, Sunil B. Jaiswal, Biopharmaceutics and Pharmacokinetics, 1st edition (1995), 336, 337, 348.
5. Leon Lachman, Herbert A, Lieberman, The Theory and Practice of Industrial Pharmacy, 3 rd edition. Indian edition Varghese publishing house, Bombay, (1990), 317,318,319,
6. Herbert A, Lieberman, Leon Lachman, Pharmaceutical Dosage Forms; Tablets volume 1, 2nd edition (2005), 195,196.
7. Herbert A, Lieberman, Leon Lachman, Pharmaceutical Dosage Forms; Tablets volume 3, 2nd edition (2005), 199,238,239,240.
8. Herbert A, Lieberman, Leon Lachman, Pharmaceutical Dosage Forms; Tablets volume 2, 2nd edition (2005), 246,274.
9. M. Victoria Velasco, James L. Ford, Philip Rowe and Ali R. Rajabi-Siahb, Journal of Controlled Release, Volume 57, Issue 1,(1999),75-85.
10. M..P.Danckwerts, International Journal of Pharmaceutics, Volume 112, Issue 1, (4.November1994), 37-45.
11. Outi Honkanen,et.al, European Journal of Pharmaceutical Sciences, Volume 15,issue5, (June2002),479-488
12. Eur J Gastroenterol Hepatol. (2001 May); 13 suppl1: S43-7
13. T.Ramchandrar, & D, R. (2023). Design Prepare and characterization of Pregabalin loaded solid lipid Nanoparticles . Frontier Journal of Pharmaceutical Sciences and Research, 6(3), 37–41.
14. Naoyuki Yoshida, Discovery Research Laboratories, Daiippon pharmaceuticals co. Ltd, Enoki-cho, Suita, Osaka, Japan, Folia Pharmacol.Jpn (Nippon Yakurigaku Zasshi) (1999), 113 (5), 299-307.