International Journal of Scientific Research and Engineering Development-– Volume 7 Issue 6, Nov-Dec 2024

Available at www.ijsred.com

RESEARCH ARTICLE OPEN ACCESS

Formulation, Development and Invitro Evaluation of Nicorandil Extended Release Tablets

Alladi Saritha[1], Sanjana[1]

Professor, SSJ College of Pharmacy, Hyderabad-500075

Email:alladis1@gmail.com

ABSTRACT

The nicorandil extended release tablets are prepared by wet granulation method using different polymers in varying combinations.. Compatability studies were carried out and found that drugs and excipients are compatible with each other.post compression parameters were carried out found to be within the limits. Tablet blends were prepared and micromeritic studies were carried out are found to be within the limits. The dissolution data of all formulations reveals that as combination of Compritol, Carbopol showed increases the percentage drug release was found to be increased Formulation (F8) containing combination of Compritol, Carbopol934P shows that the 98.5% drug release was found in 24hrs .

Keywords: nicorandil, dissolution ,zero order, extended release tablets, Similarity factor.

INTRODUCTION

To overcome such problems, controlled release and extended release delivery are receiving considerable attention from pharmaceutical industries worldwide. Despite presence of varied routes of drug administration, oral route remains the preferred route of choice. This route provides maximum patient compliance, is relatively simple to formulate for the formulator and convenient for the patient to administer the drug (1,2,3)

The aim of the present study was to develop a extended release film coated tablets of nicorandil drug and these were compared with that of marketed tablets. The basic approach is to select suitable excipients carbopol974 and compritol to formulate extended release formulation of Nicorandil drug (4,5). The present study focus on formulation and evaluation of extended release matrix tablets of Nicorandil drug for chronic angina.

EXPERIMENTAL

Preparation of film coated Nicorandil extended release tablets:

Nicorandil is sifted through # 40 sieve and mixed thoroughly in a poly bag. Microcrystalline cellulose (Avicel pH 101), carbopol 934 and Compritol passed through # 40 sieve and collected in poly bag.The sifted material transferred into the rapid mixer granulator and mixed for 15 minutes by setting impeller at slow rpm.(7,8)

Binder solution was prepared by dissolving povidone k30 in purified water.After completion of addition of binder solution, wet granulate was raked and kneaded till to get wet granulate with desired consistency is reached Sifted the dried granules through # 20 sieve and collected the oversized granules separately. Aerosil was sifted through # 60 sieve, added to the granular blend and mixed for 5 minutes.Granules prepared from above process are subjected for making of tablets. Tablets were compressed using compression machine with lubricated blend, employing appropriate punch tooling (9,10).

Table No. 1 Preparation Of Nicorandil Film Coated Tablets (Mg/Tab):

	F1	F2	F3	F4	F5	F6	F7	F8
Nicorandil	20	20	20	20	20	20	20	20
Carboxy methyl cellulose	81	67	53	25	46	39	32	25
Compritol	70	70	70	70	84	91	98	105
Carbopol 934	14	28	42	70	35	35	35	35
P.H_2O	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Poly vinyl pyrrolidine	10	10	10	10	10	10	10	10
Aerosil	5	5	5	5	5	5	5	5
Opadry yellow	15	15	15	15	15	15	15	15
Total weight	695	695	695	695	695	695	695	695

EVALUATION OF TABLET BLEND:

Bulk Density:

It is the ratio of given mass of powder and its bulk volume determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduating cylinder.The powder sample under test was screened through sieve no 18 and 10 mg of pure drug was accurately weighed and filled in a 100 ml graduated cylinder and the powder was leveled and the unsettled volume (V_O) was noted. Bulk density was calculated in g/ml by the formula:

Bulk density (BD) = W/V_b

W=Weight of the powder

V_b=Volume of powder

Tapped Density:

The powder sample under test was screened through sieve no.18 and 10 mg of pure drug was filled in 100ml graduated cylinder of tap density tester (electrolab, ETD 1020). The mechanical tapping of the cylinder was carried out using tapped density tester at a normal rate of 250 drops per minute for 500 times initially and the initial tapped volume (V_i) was noted. Tapping was proceeded further for additional 750 times and volume was noted. The difference between two tapping volumes was calculated.

Tapped density (TD) = W/V_t g/ml

W=Weight of the powder ;

V_t = final tapped volume

Angle of Repose (θ):

It is a direct measure of flow property of powders. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal. Angle of repose was determined using funnel to pour the powder on the surface from a fixed height of 2cm. Circumference was drawn with a pencil on the graph paper and the radius of base of a pile was measured at 5 different points and average was taken for calculating Angle of repose using following formula.

Angle of repose (θ) =Tan^{-1} (h/r)

Where, h = height of pile

r = radius of the base of the pile

θ = angle of repose

Compressibility Index:

Compressibility index (% Compressibility): Carr's index i.e., % compressibility indicates the flow property and packing ability of the tablet. It is determined by measuring both the bulk and tapped density of a powder. When the % compressibility ranges from 5 to 16, the materials have acceptable flow property and packing ability. Compressibility Index was calculated using following equation:

$$\text{Carr's index} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} X100$$

Hausner's Ratio:

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

EVALUATION OF ROLANZEPINE TABLETS

Weight Variation:

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation were calculated. The test for weight variation is passed only if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown.

$$\% \text{ Deviation} = \frac{(\text{Individual weight} - \text{Average weight})}{\text{Average weight}} X100$$

Thickness:

The thickness of tablets was determined by using digital vernier calipers. Ten individual tablets from each batch were used and the results averaged. It should be in a range of ±5% variation of a standard value. The results were expressed in **mm**.

Hardness:

Ten tablets from each batch were selected and hardness was measured using Digital hardness tester to find the average tablet hardness or crushing strength.

Friability:

The friability values of the tablets were determined using a roche friabilator. It is expressed in %. 20 tablets were initially weighed (initial weight) and transferred to friabilator. Friabilator was operated at 25 rpm for 4 min. Percentage friability was calculated using the following equation.

$$\% \text{ friability} = \frac{\text{intial weight - final weight} \times 100}{\text{initial weight}}$$

Friability of tablets less than 1% was considered acceptable.

In Vitro Dissolution Test (As per U.S.P):

The Dissolution studies of the prepared tablets were carried using Electro lab apparatus II. Dissolution was performed in 900 ml of 0.1N HCL acid for 2hrs & phosphate buffer of pH 6.8 at 37 ± 0.5°C at 50 rpm upto 24hrs.

Medium	:	0.1N HCL pH 1.2 for 2h pH 6.8 Phosphate buffer from 0.5h to 24h.
Volume of medium	:	900 ml.
Apparatus	:	USP II (Paddle) apparatus
RPM	:	50
Temperature	:	37± 0.5^0c
Sample points	:	2 hour
Sample volume	:	5 ml
Replacement volume	:	5 ml

Comparison with Marketed Formulation.

(1) Similarity factor (f2):

As the name specifies, it stresses on the comparison of closeness of two comparative formulations. Generally similarity factor in the range of 50-100 is acceptable according to USFDA. It can be computated using the formula

$$f2= 50\times\log \{[1+ (1/n) \Sigma_{t=1}^{n} (R_t-T_t)^2]^{-0.5} \times 100\}$$

Where, n is the number of dissolution sample times,

R_t and T_t are the individual or mean percent dissolved at each time point t, for the reference and test dissolution profiles respectively.

(2) Difference factor (f1):

Difference factor focuses on the difference in percent dissolved between reference and test at various time intervals. It can be mathematically computed by using the formula:

$$f1= \{[\Sigma_{t=1}^{n} |R_t-T_t|] / [\Sigma_{t=1}^{n} R_t]\} \times 100$$

Similarity factor of 50-100 ensures sameness of two products Difference factor of 0-15 ensures minor difference between two products.Prior to in vivo study, comparison of in vitro dissolution profiles using similarity and difference factors may be the promising surrogate.

RESULTS AND DISCUSSION

Evaluation of Tablet Blend:

Tablet blend was evaluated for micromeritic parameters showed that for all trial batches. bulk density and tapped density for the tablet blend were in the range of 0.313- 0.495 gm/ml. The angle of repose for the formulations was found to be in the range of 25.47°to 32.13°. Compressibility index was found within the range of 11.59-14.22% which is within the specified limit of good flow properties. Angle of repose was less than 28 and Carr's index values were less than 15 and Hausner's ratio values were less than 1.25 for the pre-compression blend of all the batches indicating good flow properties.

Table No.2 Evaluation of Pre-Compression Parameters:

S. No	Batch No.	angle of repose(°)	Bulk density(g/ml)	Tapped density (g/ml)	C.I	Hausner's ratio
1	F1	28.23	0.495±0.01	0.562±0.05	11.92±0.08	1.13±0.01
2	F2	25.51	0.389±0.02	0.445±0.03	12.58±0.03	1.14±0.02
3	F3	27.12	0.390±0.02	0.450±0.04	13.34±0.04	1.15±0.05
4	F4	32.13	0.495±0.09	0.587±0.11	15.27±0.06	1.18±0.12
5	F5	29.23	0.389±0.11	0.440±0.08	11.59±0.07	1.13±0.02
6	F6	26.48	0.391±0.07	0.462±0.12	14.22±0.03	1.18±0.01
7	F7	26.81	0.373±0.10	0.430±0.01	13.26±0.01	1.15±0.05
8	F8	25.13	0.394±0.10	0.450±0.03	12.45±0.02	1.14±0.01

Mean ± S.D, n=6 ;

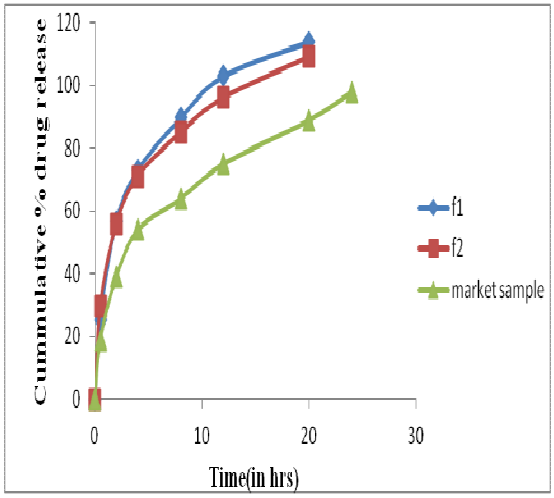
C.I- Compressibility Index

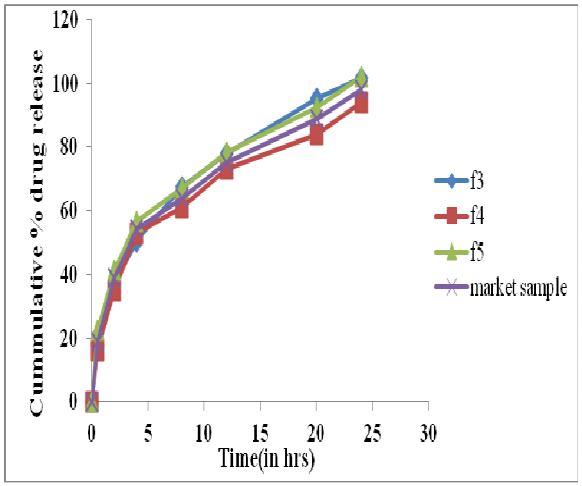
EVALUATION OF POST-COMPRESSION PARAMETERS

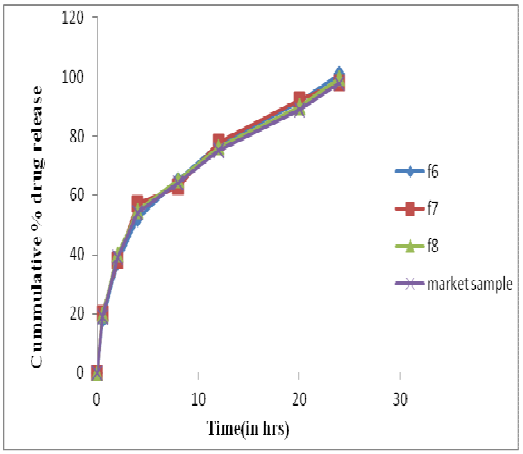
Batch No.	Average weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
F1	695±1.44	8.51±0.01	7.5±0.02	0.23±0.05
F2	695±1.38	8.54±0.06	7.8±0.05	0.21±0.06
F3	695±1.35	8.12±0.03	8.2±0.01	0.20±0.05
F4	695±1.43	8.42±0.02	9.0±0.06	0.19±0.03
F5	695±1.49	8.58±0.08	9.4±0.08	0.20±0.08
F6	695±1.39	8.31±0.19	9.2±0.01	0.23±0.05
F7	695±1.41	8.47±0.11	9.5±0.02	0.21±0.06
F8	695±1.44	8.49±0.14	9.3±0.04	0.20±0.05
Ranexa	695 mg	8.18±0.12	9.2±0.03	< 1%

The prepared extended tablets were tested with respect to weight variation, hardness, thickness, and friability. The thickness of the tablets in the range of 8.18 to 8.58 mm weight variation in the range of 695 mg. Formulations trials from F1 to F8 have thickness with ±5% variation of standard value and hardness was found within the range 7-9.5 kg/cm^2.Friability was less than 1% which was acceptable.Average weight of all the tablets was around 695±7.5%. All the tablets of different batches complied with the official requirements for weight variation, hardness and friability.

IN VITRO DISSOLUTION STUDIES :







The comparative dissolution profile of all formulations showed prolonged drug release for 24 hrs making the formulation ingredients suitable for sustained release formulation. The in-vitro drug dissolution studies were conducted for marketed product and optimised formulation.

Formulations F1 to F2 to which 70mg of compritol, 14, 28 mg of carbopol were added respectively to each formulation which showed more than 85% of drug release within 12hrs which confirms within the limits by USP, which states that not less than 80% of labeled amount of nicorandil was released in 24hrs.

- For formulations F3 to F4 to which 42&70 mg of carbopol and 70 mg of carbopol was added showed in vitro drug release more than 90% within 20hrs.For formulations F5 to F8 to which 35 mg of carbopol934P and compritol concentration was increased from 11% to 15% were added showed in vitro drug release more than 95% within 24hrs. This shows that combination Compritol, Carbopol934P increased the percentage release of the drug.
- By observing in vitro drug release kinetics nicorandil extended release tablets higuchi's order which have highest linearity (r^2= 0.991).From table similarity factor for F8 formulation was found to be more i.e., 75.82 compared to other formulations and difference factor was found to be less i.e., 1.4578 compared to other formulations.
- Based on the drug release rate for formulation (F8) has similar release rate with that of innovator, so F8 was taken as optimized formula.
- Therefore F8 formulation said to be comparable with that of marketed product

Table No. 5 release kinetics of Nicorandil Formulations

Formulations	Zero order	First order	Higuchi	Peppas	"n" value
F1	0.818	0.984	0.977	0.975	0.435
F2	0.782	0.980	0.959	0.982	0.348
F3	0.869	0.986	0.989	0.994	0.442
F4	0.835	0.960	0.973	0.976	0.440
F5	0.837	0.981	0.976	0.993	0.377
F6	0.861	0.911	0.986	0.991	0.432
F7	0.835	0.959	0.974	0.984	0.403

F8	0.838	0.945	0.976	0.986	0.402
Market sample	**0.819**	**0.926**	**0.977**	**0.986**	**0.407**

When the optimised formulation F8 subjected to First Order, Zero Order, Higuchi models .Drug release data was best explained by Higuchi's equation, as the plots showed the highest linearity(r^2 =0.989).the corresponding plot (log cumulative percent drug release vs log time) for the Korsmeyer-peppas equation indicated a good linearity with the (r^2 = 0.991). The diffusion exponent n was 0.35-0.43, which appears to indicating a fickian diffusion

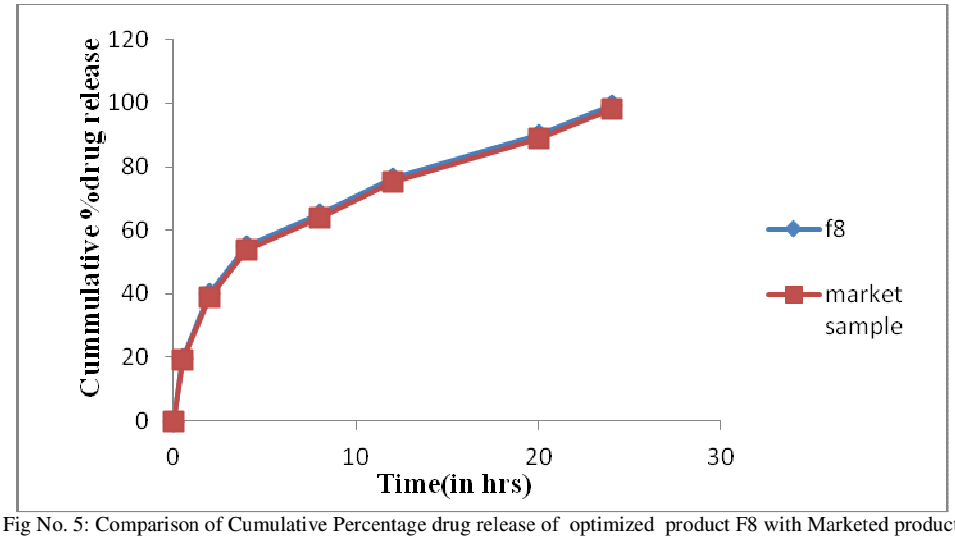


Fig No. 5: Comparison of Cumulative Percentage drug release of optimized product F8 with Marketed product

Table No. 6: Simiarity factor Analysis

	MARKETED	**TEST**			
Time (in hrs)	**R_t**	**T_t**	**[R-T]**	**$[R-T]^2$**	
0	0	0	0	0	
0.5	19	19.7	0.7	0.49	
2	39	40	1	1	f2=75.82
4	54	54.9	0.9	0.81	f1=1.689
6	64	65	1	1	
12	75	76.3	1.3	1.69	
20	89	90	1	1	
24	98	99.5	1.5	2.25	
SUM	438		7.4	8.24	

Similarity factor of optimized formulation with marketed formulation was found to be 75.82.

Conclusion

From the above experimental result, it can be concluded that film coated nicorandil extended release tablets can be prepared by wet granulation method using different polymers in varying combinations. Carbopol934P increases the percentage drug release was found to be increased. Formulation (F8) containing combination of Compritol, Carbopol934P shows that the 99.5% drug release was found in 24hrs and found similar with that of marketed preparation.

7. BIBLIOGRAPHY

1. Rang H.P; M.M.Dale; J.M.Ritter; R.J.Flower. "The Heart In: Pharmacology". 5thEdition; Informa Healthcare, USA,2008; Volume 1; pg no:270-271.
2. Leon Shargel, Susanna Pong, Andrew B.C., Applied Biopharmaceutics and Pharmacokinetics,Modified-Release Drug Products, 535 Fifth Edition,2004
3. Shargel L, Kanfer I. Generic Drug Product Development of solid oral dosage forms. Winley Inter Science 2010: 1-16.
4. S.P Vyas; R.K.Khar. "controlled drug delivery concepts and advances. In: Targeted & Controlled Drug Delivery System".1st Edition; India Binding House, Noida; Pg No:387-416
5. Alladi saritha, Nalini shastri , Sadanandam, Anantha Lakshmi.Enhancement of Dissolution and Anti-inflammatory Activity of Meloxicam by Spherical Agglomeration Technique. J. Pharm. Sci. & Res. Vol.4(1), 2012, 1657-1661
6. Sastry, Srikonda, Nyshadham, Janaki. International Publication Number WO 2006/074398 A2. 2006 July 13.
7. Saritha,Nansri Saha. Design and evalution of HPMC matrix floating tablets of doxazosin . International Journal of Scientific Research and Engineering Development-– Volume 7 Issue 1, Jan-Feb 2024
8. Katzhendler I, Mader K, Friedman M. Structure and hydration properties of hydroxypropyl methylcellulose matrices containing naproxen and naproxen sodium. *Int J Pharm* 2000:161-179.
9. Hand book of pharmaceutical excipients, 6th edition-Raymond Rowe C Rome,Paul J Shesky ; . Science and practice, *Royal Pharmaceutical Society of Great Britain London*,Pg no:110-113.
10. Michel F, Rousseau, MD, PhD, Division of Cardiology, University of Louvain, Avenue Hippocrate 10/2800, B-1200 Brussels, Belgium.

