FORMULATION DEVELOPMENT AND *INVITRO* EVALUATION OF RANOLAZINE EXTENDED RELEASE TABLETS

Alladi saritha and Rebecca sanjana
SSJ College of Pharmacy, Hyderabad-500075

Abstract:
The ranolazine extended release tablets can be prepared by wet granulation method using different polymers in varying combinations. Tablet blends were prepared and micromeritic studies were carried out for those blends and found to be within the limits. 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. Also dissolution data of all formulations reveals that as combination of Compritol, 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 innovator. On comparing R^2 with innovator, formulation (f8) shows similar results with marketed formulation
Key words: *ranolazine, extended release tablets, Compritol, Carbopol934P*

Corresonding author:
Alladi Saritha,
Associate Professor,
SSJ College of Pharmacy,
Hyderabad-500075
Email:alladis1@gmail.com

QR code

INTRODUCTION:

An ideal drug delivery system should able to deliver an adequate amount of drug, preferably for an extended period of time, for its optimum therapeutic activity. Most drugs are inherently not long lasting in the body and require multiple daily dosing to achieve the desired blood concentration to produce therapeutic activity [1, 2]. 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 [3, 4]

The aim of the present study was to develop a pharmaceutically stable and quality improved formulation of extended release film coated tablets of ranolazine drug and these were compared with that of marketed tablets The basic approach is to select carbopol974 and compritol to formulate extended release formulation of Ranolazine drug (5,6). The present study outlines a systemic approach for formulation and evaluation of extended release matrix tablets of Ranolazine drug for chronic angina.

MATERIALS AND METHODS:

Ranolazine was a kind gift sample from strides labs pvt ltd, Bangalore, India. Compritol, Carbopol934Pfrom Research lab fine chem. Industries (Mumbai). Povidone, titanium di oxide SD fine chemicals, Mumbai.Ethanol and all solvents used were analytical grade.

EXPERIMENTAL
Preparation of film coated ranolazine extended release tablets:

Ranolazine 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 1: Preparation of Ranolazine Film Coated Tablets (Mg/Tab):

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Ranolazine	500	500	500	500	500	500	500	500
Avicel PH 101	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$_2$O	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Povidone K 30	10	10	10	10	10	10	10	10
Aerosil	5	5	5	5	5	5	5	5
Titanium di oxide	15	15	15	15	15	15	15	15
Total weight	695	695	695	695	695	695	695	695

EVALUATION OF TABLET BLEND:

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.

$$\text{Angle of repose } (\theta) = \text{Tan}^{-1}(h/r)$$

Where, h = height of pile
r = radius of the base of the pile
θ = angle of repose

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.

$$\text{Tapped density (TD)} = W/V_t \text{ g/ml}$$

W=Weight of the powder   ;
V_t = final tapped volume

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:

$$\text{Carr's index} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \times 100$$

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.

$$\% \text{ Deviation} = \frac{(\text{Individual weight} - \text{Average weight})}{\text{Average weight}} \times 100$$

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.

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

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. the samples were withdrawn at periodical intervals and the absorbance was observed at 271nm and thepercentage of drug release was determined.

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 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

Table 3: Evaluation of Post-Compression Parameters:

Batch No.	Average weight (mg)	Thickness (mm)	Hardness (kg/cm²)	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.

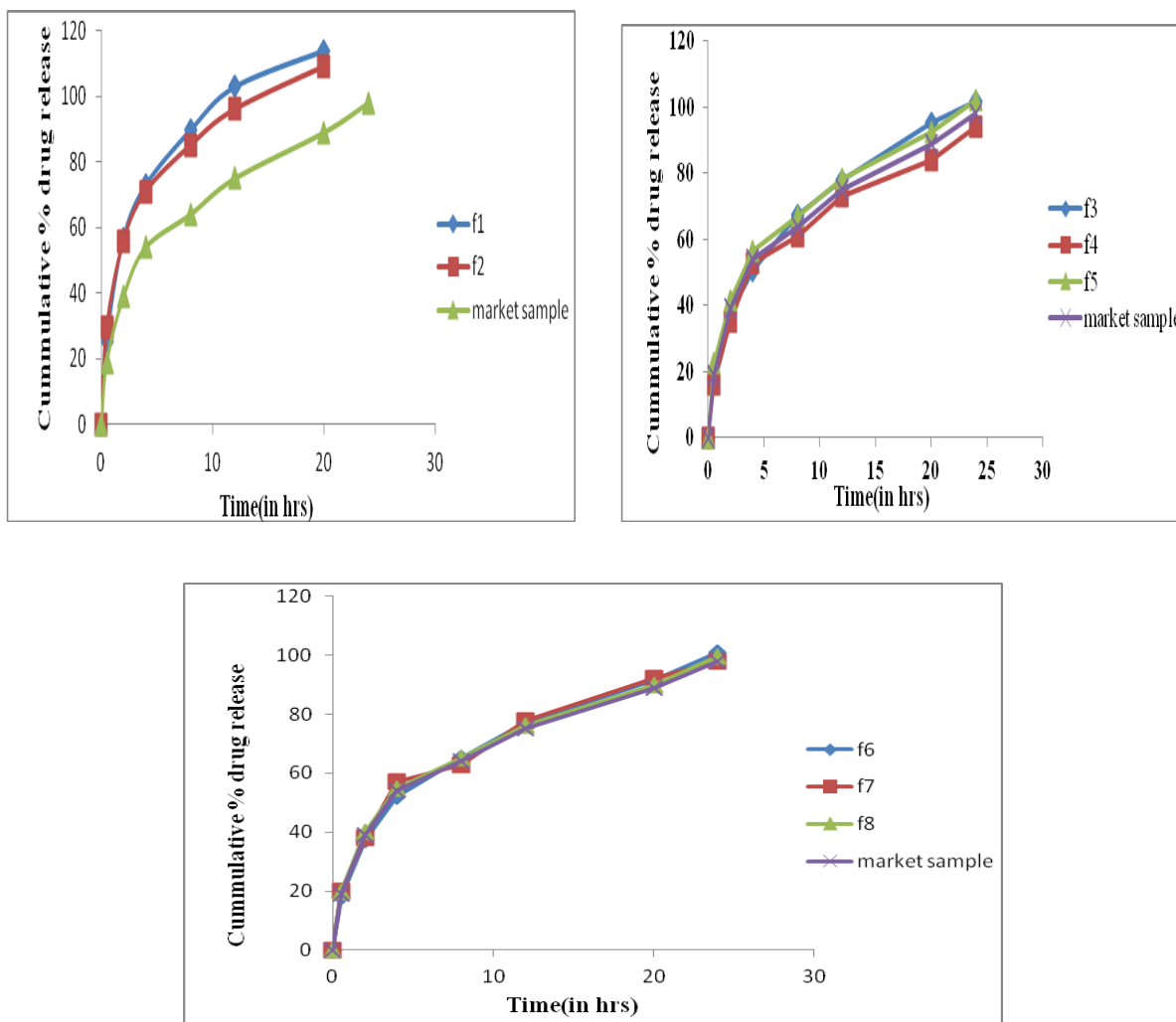### *IN VITRO* DISSOLUTION STUDIES:

Fig.1: *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 ranolazine 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.

- Based on the drug release rate for formulation (F8) has similar release rate with that of innovator, so F8 was taken as optimized formula.By observing in vitro drug release kinetics ranolazine 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. Therefore F8 formulation said to be comparable with that of marketed produc

Table 4: Release kinetics of Ranolazine 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 fickian diffusion

CONCLUSION:

From the above experimental result, it can be concluded that film coated ranolazine 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.

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