Research Article

# Formulation and Development of Sustained Release Matrix Tablet of Ranolazine

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**ABSTRACT**

Ranolazine is an anti-anginal drug used to treat chronic stable angina in adults. The main drawback with normal conventional dosage form is that the solubility of Ranolazine is relatively high at the lower pH (4.5 and below) and highly variable hepatic first pass metabolism following oral administration, with systemic bio-availability of 76% and Ranolazine also has a relatively short plasma half life of 2.5±0.5 hrs. in this investigation sustained release tablet were prepared by using partially neutralized pH- Dependent polymer HPMC90SH 4000SR, HPMC K4M, HPMC 15Cps and combination of polymer (HPMC K4M and HPMC 15Cps). By using different concentration of HPMC90SH 4000SR, HPMC K4M and HPMC 15Cps will better the dissolution rate and tablets were prepared by wet granulation method. Prepared tablets were evaluated for thickness, uniformity of weight, hardness, friability, drug content, invitro drug release. The invitro release of Ranolazine sustain release tablets was studied in 900 ml of 0.1 N HCl as dissolution medium using a USP dissolution paddle assembly at 50 rpm and 37±0.5$^0$C for 2 hrs, then release studies were conducted in pH 7.4 phosphate buffer for 24 hrs optimized formulation (F2) released 99.08% of drug for 24 hrs. The optimized formulation was subjected to stability studies for three month at 40$^0$C temperature with 75±5% RH and showed there was no significant change in drug content, physiochemical parameters and release pattern.

**Keywords:** HPMC 15Cps, HPMC90SH 4000SR, HPMC K4M, ranolazine, sustain release tablet

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## INTRODUCTION

Angina pectoris is a symptom of an underlying heart condition. It means that the heart is not getting enough blood and as a result, not enough oxygen. This decrease of oxygen being delivered to the muscle of the heart happens if one or more coronary arteries are narrowed or blocked, a condition called Atherosclerosis.

Blood enters the heart through two blood vessels. These are known as the coronary arteries and they supply the heart muscle with the blood, oxygen and nutrients it needs to keep beating. Normally, the coronary arteries deliver enough blood so that the heart muscle gets the amount of oxygen it needs to work properly. However, in coronary heart disease these arteries become narrowed which reduces the amount of blood that can pass through arteries causes blood can't get to the heart muscle fast enough and the heart complains with pain. This pain is known as angina. It is more likely to occur during exertion (for example, walking or climbing stairs) when the heart muscle needs more blood and oxygen as it works harder [1].

This is defined as those allow at least a two-fold reduction in dosing frequency, as compared to the drug presented in a conventional form, such as a solution or a prompt drug releasing conventional solid dosage form.

Drug efficacy generally depends upon the ability of the drug to reach the target in sufficient quantity to maintain therapeutic levels for the desired time period. Orally administered drugs must

overcome several obstacles to reach their desired targets. Before orally administered drugs enter the general circulation of the human body, they are absorbed into the capillaries and veins of the upper gastrointestinal tract and are transported by the portal vein to the liver. The pH and enzymatic activities found in gastrointestinal fluids may inactivate the drug or cause the drug to dissolve poorly. In addition, following their absorption in the intestine, orally administered drugs are often subject to a "first pass" clearance by the liver and excreted into bile or converted into pharmacologically inactive metabolites. Decreased bioavailability of orally administered drugs is a consequence of this 'first pass effect [2-4].

Many drugs, being weak bases, acids or salts thereof demonstrate pH-dependent release from extended release formulation, for example coated pellets. At the low pH in the stomach, weakly basic drugs are freely soluble resulting in fast release rates. However, the release rate can decrease dramatically once the dosage forms reach the higher pH- regions of the intestinal tract. Differences in the release rate in different parts of the gastrointestinal tract may cause in vivo variability and bioavailability problems.

The main aim of this study is to overcome the problem of pH-dependent release of a weakly basic drug and to achieve pH-independent release of this drug from extended release formulations and thus increase the bioavailability of this drug.

The aim of this work is to evaluate the in-vitro performance of sustained release matrix tablets of Propranolol. HCl for pH-independent release utilizing various extended release polymers and organic acids as pH-modifiers which modulates acidic microenvironment in intestinal fluid and thus enhance the local solubility and release of weakly basic drug in high pH environment.

## MATERIALS AND METHODS

**Materials:** Ranolazine was procured from the F&D department of RICHER Pharmaceuticals ltd., Hyderabad, India. Excipients such as HPMC K4M, HPMC 15 cps, HPMC 90SH, Lactose monohydrate, Magnesium stearate, were obtained from SD Fine Chemicals, Mumbai.

**Methods:**

**Preparation of standard curve of Ranolazine:**

The samples of different concentration were analyzed at 272 nm using UV-Spectrophotometer against pH 7.4 phosphate buffer as blank. [5]

**Drug excipient compatibility studies:**

Drug excipient interaction was studies by FTIR spectroscopy. The spectra were recorded for pure ranolazine and with excipient mixture. Drug excipient interactions were studied by FTIR spectroscopy. The spectra were recorded for ranolazine physical mixture of excipient and physical mixture of drug with excipient using FTIR-spectrophotometer from KBr pellets. The scanning range was 400-4000cm -1

**Formulation development:**

**Preparation of sustain release tablet by wet granulation method: [6]** Eight different formulations were prepared by wet granulation method by different type of sustained release polymers. These polymers are highly soluble at low pH and are soluble at basic pH thereby increasing the matrix permeability and thus maintaining local solubility of the basic drug at pH. These formulations were prepared for the selection of polymers which provides the sustained release of drug and remains the formulation intact in the acidic medium.

**Different steps involved in Preparation of Ranolazine 1000mg SR tablets blend are:**

- ***Dispensing & Shifting*:** Ranolazine and lactose monohydrate were weighed in required quantity and shifted through # 40 mesh.
- ***Dry Mixing*:** Mix then transfer into a mortar.
- ***Binder preparation*:** Dissolve required amount of povidone in purified water.

- ***Method (Wet Granulation)*:** Add binder solution slowly to the above mix and knead thoroughly until wet mass is formed and pass the wet mass through sieve # 10.
- ***Drying*:** Keep that wet granules in tray dryer at temperature of $50^0$c until LOD of 1-2% is reached.
- ***Shifting*:** After drying pass the granules through # 20 mesh.

***Pre-lubrication*:** For F1, F2, F3, F4 Weighed required quantity of Lactose monohydrate and HPMC 90SH 4000SR and shift through # 40 mesh and for F5, F6, F7 weighed required quantity of Lactose monohydrate and HPMC K4M and shift through # 40 mesh and for F8 weighed required quantity of Lactose monohydrate, HPMCK4M and HPMC15cps and shift through # 40 mesh and add to the dried granules and mix it for 15 minutes.

**Table 1: Composition of sustained release matrix tablets of ranolazine**

| S. N. | Category | Ingredients | Qty. taken |
|---|---|---|---|
| 1 | Anti-Anginal | Ranolazine | 1000 mg |
| 2 | Sustained release polymers | • HPMC K4M<br>• HPMC 15CPS<br>• HPMC 90 SH | 40 % |
| 3 | Binder | Povidone | 20 % |
| 4 | Diluent | Lactose | Q.S to 100% |
| 5 | Lubricant | Magnesium stearate | 1-2% |

**Table 2: Composition of sustained release matrix tablets prepared by different type of polymers**

| INGREDIENTS (mg) | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ | $F_6$ | $F_7$ | $F_8$ |
|---|---|---|---|---|---|---|---|---|
| **Ranolazine** | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 |
| **Lactose monohydrate** | 365 | 290 | 215 | 140 | 290 | 215 | 140 | 110 |
| **Povidone** | 45 | 45 | 45 | 45 | 45 | 45 | 45 | 45 |
| **Purified water** | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |
| **HPMC90SH 4000SR** | 75 (5%) | 150 (10%) | 225 (15%) | 300 (20%) | --- | --- | --- | --- |
| **HPMC K4M** | --- | --- | --- | --- | 150 (10%) | 225 (15%) | 300 (20%) | 300 (20%) |
| **HPMC 15Cps** | --- | --- | --- | --- | --- | --- | --- | 30 (2%) |
| **Magnesium Stearate** | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| **Target Weight (in mg)** | **1500** | **1500** | **1500** | **1500** | **1500** | **1500** | **1500** | **1500** |

**Evaluation of sustain release tablet of Ranolazine:**

Evaluation was performed to assess the physiochemical properties and release characteristics of developed formulation.

**Precompression parameters:**

**Angle of Repose (θ): [7]**

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose.

$\tan \theta = h / r$

$\theta = \tan^{-1} (h/r)$

Where, θ is the angle of repose

h is height of pile

r is radius of the base of pile

Different ranges of flow ability in terms of angle of repose are given in (**Table 3**).

**Table 3: Standard value of powder flow property test**

| S. No. | Angle of Repose | Powder Flow |
|---|---|---|
| 1 | <25 | Excellent |
| 2 | 25-30 | Good |
| 3 | 30-40 | Passable |
| 4 | >40 | Very Poor |

**Bulk density: [8, 9]**

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 5 g of powder from each formulation was introduced into a 10 ml measuring cylinder. Initial volume was observed, the cylinder was allowed to tap. The tapping was continued until no further change in volume was noted. Bulk density is calculated by using formula:

Bulk density (ρb) = Bulk volume of the powder/Weight of the powder

Tapped density (ρt) = Tapped volume of the powder/ Weight of the powder

**Compressibility Index (Carr's Consolidation Index):**

The Carr's index of the powder was determined by using formula:

Carr's index (%) = [(TBD -LBD) × 100]/TBD

Where, LBD = weight of the powder/ volume of the packing

TBD = weight of the powder/tapped volume of the packing

**Table 4: Grading of the powders for their flow properties according to carr's index**

| S. No. | Carr's index | Type of flow |
|---|---|---|
| 1 | 5-15 | Excellent |
| 2 | 12-18 | Good |
| 3 | 18-23 | Fair to passable |
| 4 | 23-35 | Poor |
| 5 | 33-38 | Very poor |
| 6 | >40 | Very very poor |

**Post compression parameters:**

**Hardness:**

The resistance of tablets to shipping or breakage under the conditions of storage, transportations and handling before usage depends on its hardness. The hardness of tablet was measured by Pfizer hardness tester. The hardness was measured in terms of $Kg/cm^2$

**Friability:**

Roche friabilator was used for testing the friability. Ten tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

Friability (f) = (1 - W0/ W) x 100

Where'W0 'is weight of the tablets before the test and

'W' is the weight of the tablet after the test.

**Weight variation test: [8]**

Twenty tablets from each formulation were selected randomly and weighed individually average weight was determined. Individual tablets weighed were then was compared with average weight.

The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The percentage deviation in weight variation is shown in (**Table 5**).

**Determination of drug content/ Uniformity of drug content:** Ten tablets were finely powdered. Quantity of the powder equivalent to 1000 mg of Ranolazine was accurately weighed and transferred to 100 ml volumetric flask containing 50 ml of 7.4 pH phosphate buffer. It was allowed to stand for 6 hrs with intermittent sonication to ensure complete solubility of the drug. The solution was made up to volume with 7.4 pH phosphate buffer and the

mixture was centrifuged. 1 ml of the supernatant liquid was suitably diluted, filtered and analyzed for Ranolazine content at 272 nm by double UV-visible spectrophotometer.

**Table 5: Percentage deviations in weight variation according to USP**

| Average weight of a tablet | Percentage deviation |
|---|---|
| 130 mg or less | **±**10 |
| More than 130 mg and less than 324 mg | ±7.5 |
| 324 mg or more | ±5 |

**In-vitro dissolution studies: [10, 11]**

In-vitro dissolution study was performed by using USP dissolution test apparatus (Apparatus 1, Paddle type) at 50 rpm for 2hr in 0.1 N HCl (900 ml).Then the dissolution medium was replaced with pH 7.4 phosphate buffer and tested for next 24 hrs. At the end of different time period withdrawn 5ml of sample at the specified time interval and again fill with 5ml of dissolution medium, Collect and filter it with whatman filter paper and use this solution as sample

**Stability studies for optimized formulation:**

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a re-test period for the drug substance or a shelf life for drug product and recommended storage conditions. In general, a drug substance should be evaluated under storage condition (with appropriate tolerances) that test its thermal stability and if applicable, its sensitivity to moisture. Three types of storage conditions are used i.e. Long term, Accelerated and where appropriate, Intermediate (**Table 6**).

**Table 6: General guideline for stability study**

| Study | Storage conditions | Minimum time period covered by data at submission |
|---|---|---|
| **Long term** | 25±2°C/60±5% RH or 30±2°C/65±5% RH | 12 months |
| **Intermediate** | 30±2°C/65±5% RH | 6 months |
| **Accelerated** | 40±2°C/75±5% RH | 6 months |

**RESULTS AND DISCUSSION**

**Preparation of standard curve of Ranolazine:**

Calibration curve of Ranolazine was prepared in Methanol at determined wavelength 272nm. The calibration curve was linear between 10 to 200 µg/ml concentration ranges. The $R^2$ and slope were found to be 0.9994 and 0.006.

**Compatibility study**

FTIR spectra of Ranolazine, HPMC, Lactose monohydrate, HPMC K4M and core tablet of with Ranolazine is shown as follows.

**Micromeritic Properties:**

**Angle of Repose:**

The angle of repose was in the range of 22°.77' to 27°.39' indicating the good flow properties (**Table 8**).

**Carr's Index:**

Compressibility index was carried out, it found between 14.39% to 15.16% indicating the powder blend has the required flow property for compression (**Table 8**).

**Hausner's ratio:**

Hausner's ratio was calculated for the blend, it found between 1.165 - 1.77 indicating. Powder blend has the required flow property for compression (**Table 8**).

**Table 7: Calibration curve of Ranolazine concentration vs absorbance (µg/ml)**

| S. N. | Concentration in µg/ml. | Absorbance at 272 nm |
|---|---|---|
| 1. | 0 | 0 |
| 2. | 10 | 0.047 |
| 3. | 20 | 0.104 |
| 4. | 40 | 0.232 |
| 5. | 60 | 0.353 |
| 6. | 80 | 0.497 |
| 7. | 100 | 0.621 |
| 8. | 120 | 0.7 |
| 9. | 140 | 0.85 |
| 10. | 160 | 0.93 |
| 11. | 180 | 1.078 |
| 12. | 200 | 1.177 |

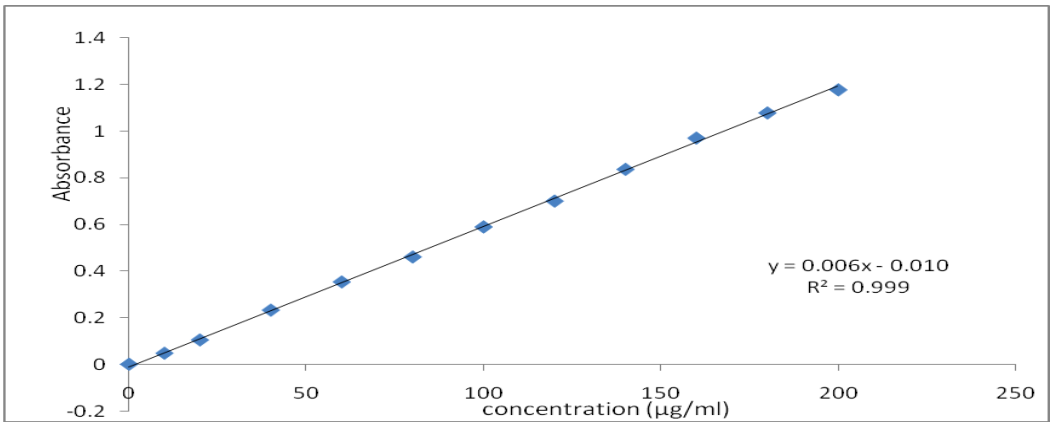


**Figure 1: Standard calibration curve of Ranolazine**

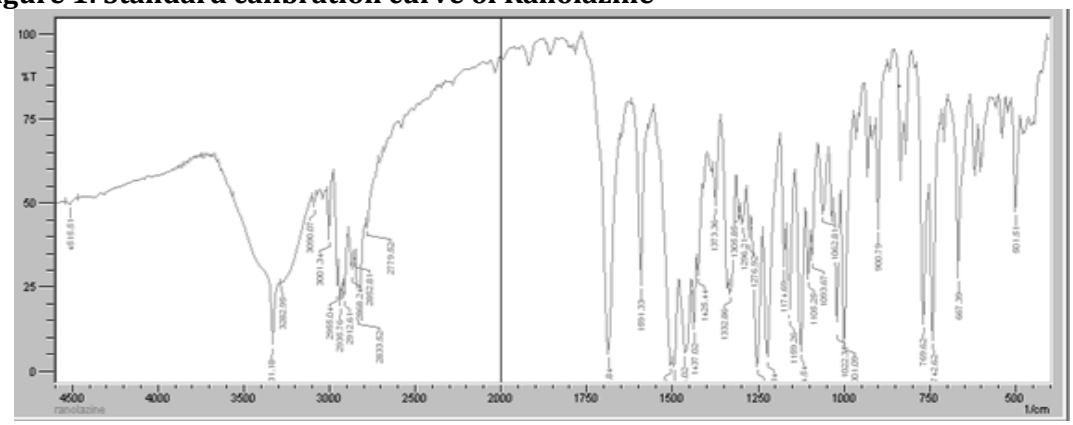

**Figure 2: IR spectra of pure drug (Ranolazine)**

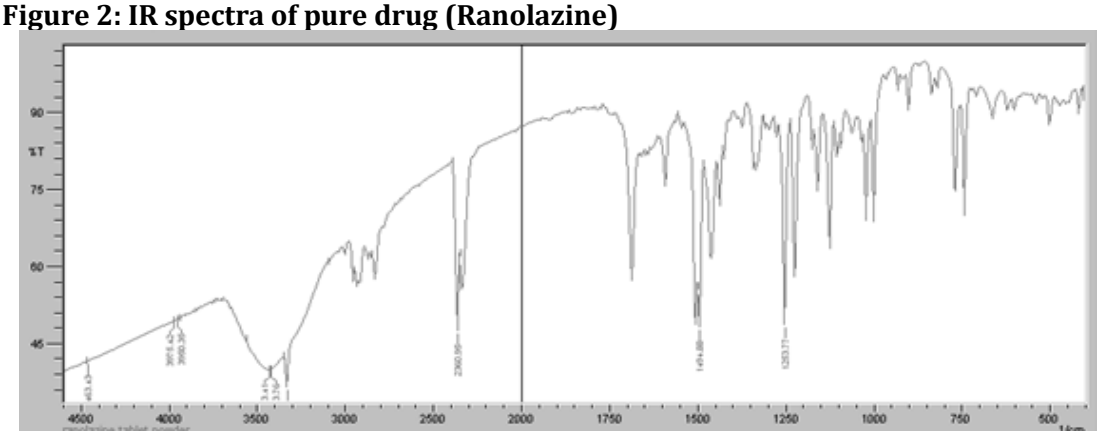

**Fig: 3 FT-IR study of Ranolazine with lactose monohydrate**

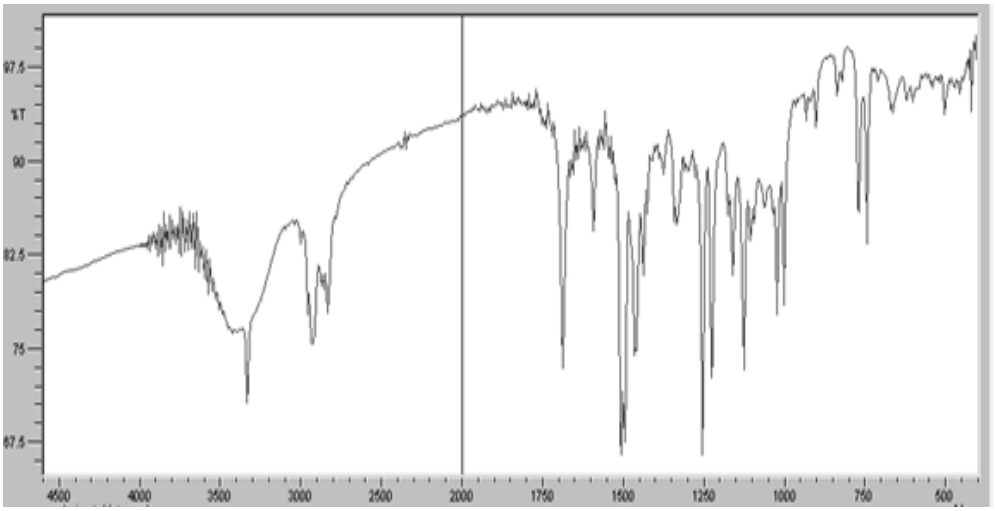

**Figure 4: FT-IR study of Ranolazine with HPMC K4M**

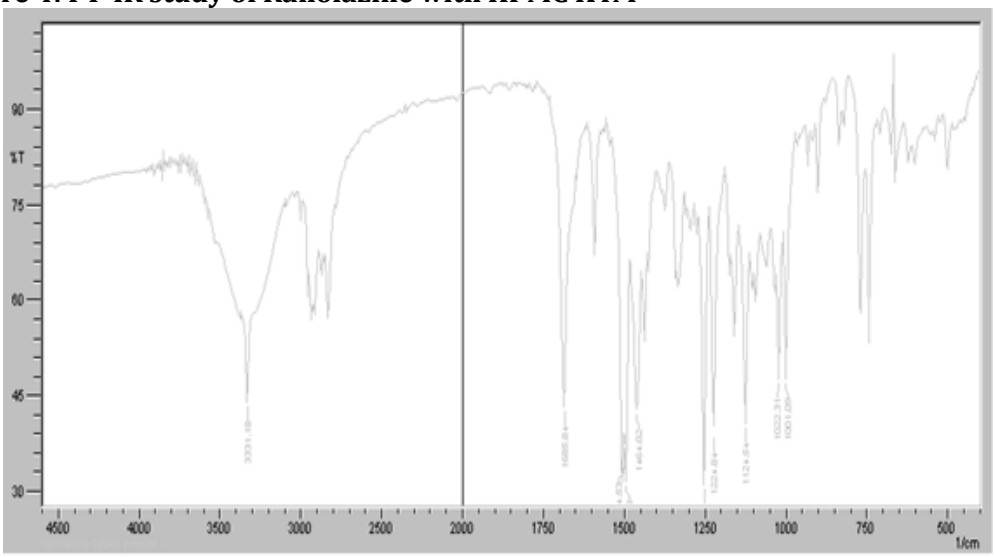

**Figure 5: FT-IR study of Ranolazine with HPMC 15 CPS**

**Table: 8 Results of angle of repose, Hausner ratio &% compressibility**

| Formulations | Angle of repose (θ) | Compressibility Index or Carr's Index (%) | Hausner's ratio |
|---|---|---|---|
| $F_1$ | $26^0.86'$ | 15.16 | 1.165 |
| $F_2$ | $25^0.28'$ | 14.39 | 1.167 |
| $F_3$ | $24^0.49'$ | 15.00 | 1.176 |
| $F_4$ | $27^0.39'$ | 15.92 | 1.175 |
| $F_5$ | $22^0.77'$ | 14.39 | 1.167 |
| $F_6$ | $25^0.15'$ | 15.01 | 1.176 |
| $F_7$ | $25^0.02'$ | 14.31 | 1.166 |
| $F_8$ | $25^0.52'$ | 15.04 | 1.177 |

**Evaluation of sustained release matrix tablets of Ranolazine:**

The prepared sustained release matrix tablets of Ranolazine were subjected to physical parameters i.e. Thickness, Weight variation, Hardness, Friability and Content Uniformity %. All pH-independent sustained release matrix tablets comply for all the physical parameter. The results are as follow:

**Hardness test**

The measured hardness of core and coated tablets of each batch ranged between 8-12 kg/cm$^2$ (table 9). This ensures good handling characteristics of all batches.

**Friability test**

The values of friability test were tabulated in table 9. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

**Weight variation test**

The percentage weight variations for all formulations were tabulated in table 9. All the formulated (F1 to F8) tablets passed weight variation test as the % weight variation was within the in house specification limits of ± 1% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

**Drug content uniformity**

The percentage of drug content for F1 to F8 was found to 95% to 99% of Ranolazine, it complies with in-house specifications. The results were shown in (**Table 9**).

**Table 9: Results of physical parameter**

| Formulations* | Thickness (mm) | Weight variation (mg) | Hardness (kg /cm$^2$) | Friability (%) | Drug uniformity (%) |
|---|---|---|---|---|---|
| **$F_1$** | 7.10±0.02 | 1499.5± 5 | 8-9 | 0.094 | 96.16 |
| **$F_2$** | 7.11±0.01 | 1500.5± 3.5 | 10-12 | 0.093 | 95.10 |
| **$F_3$** | 7.06±0.04 | 1501.5 ± 4 | 9-10 | 0.045 | 98.36 |
| **$F_4$** | 7.08±0.03 | 1498 ± 6 | 9-10 | 0.043 | 97.8 |
| **$F_5$** | 7.10±0.02 | 1501 ± 5 | 10-11 | 0.098 | 98.2 |
| **$F_6$** | 7.10±0.01 | 1503 ± 4.5 | 8-9 | 0.093 | 97.84 |
| **$F_7$** | 7.07±0.03 | 1498.5± 4 | 10-12 | 0.096 | 97.01 |
| **$F_8$** | 7.12±0.01 | 1502± 3 | 9-10 | 0.046 | 99.02 |

**In-vitro dissolution studies:**

Generally for sustained release products, dissolution medium is buffer (pH 6.8 to 7.5) on the basis that dosage form will remain in intestine longer time after gastric emptying. But drugs like Ranolazine formulated as matrix tablets contained within a pH dependent polymer. Ranolazine is highly soluble at low pH and exhibits limited solubility at intestinal pH levels. By testing in 0.1N HCl one can look at the rate of release from the dosage with solubility not being an issue. Any active released should be in solution and can therefore be analyzed. Testing this way can be more discriminative, allowing seeing unique release characteristics of the dosage form. Dissolution profiles of all formulations were compared by percentage of drug release verses time. From dissolution results it was confirmed that formulation F8 was showing good dissolution profile.

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**Table: 10 Dissolution profiles of F1- F8 formulations**

| Time | 1$^{st}$ hour | 4$^{th}$ hour | 12$^{th}$ hour | 24$^{th}$hour |
|---|---|---|---|---|
| **F1** | 40.012±0.02 | 85.024±0.06 | 93.075±0.03 | 97.015±0.03 |
| **F2** | 31.053±0.04 | 78.061±0.03 | 95.048±0.01 | 98.078±0.03 |
| **F3** | 25.041±0.05 | 78.043±0.03 | 88.093±0.03 | 95.046±0.01 |
| **F4** | 18.043±0.03 | 56.026±0.02 | 88.048±0.03 | 96.058±0.02 |
| **F5** | 41.012±0.02 | 83.071±0.04 | 92.036±0.03 | 98.066±0.05 |
| **F6** | 28.071±0.01 | 72.075±0.06 | 90.069±0.05 | 98.052±0.02 |
| **F7** | 17.062±0.02 | 60.053±0.07 | 82.092±0.04 | 88.082±0.03 |
| **F8** | 42.035±0.01 | 86.042±0.03 | 96.025±0.02 | 99.032±0.01 |

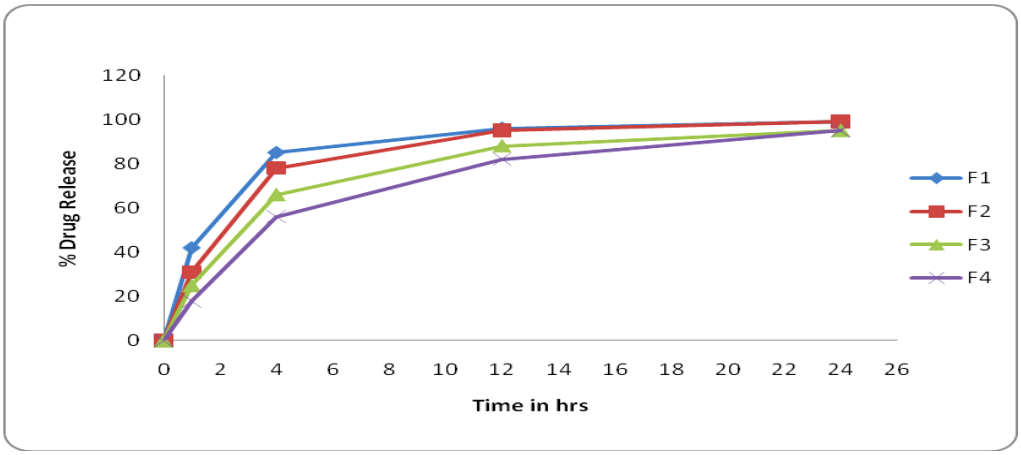


**Figure 6: Representing % drug release of ranolazine sr tablets of trials F1-F4 formulated with METOLOSE 90SH 4000SR of different concentration**

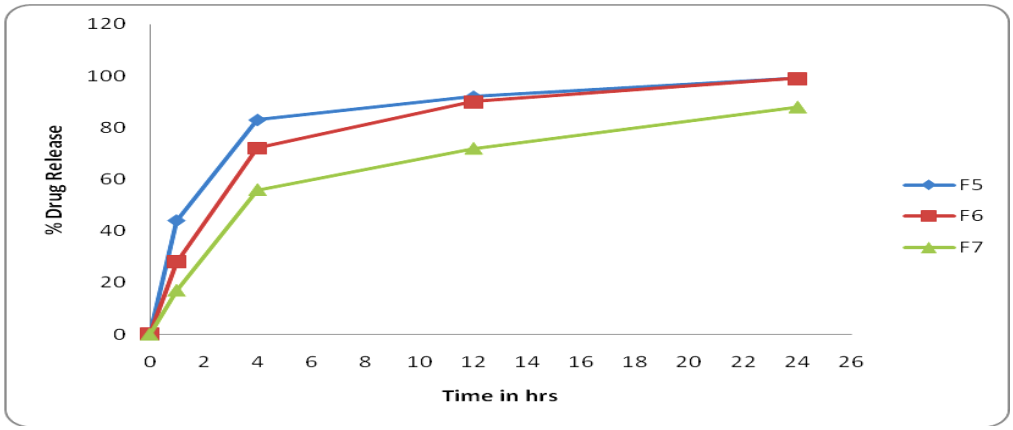


**Figure 7: Representing % drug release of Ranolazine SR tablets of trials F5-F7 formulated with HPMC K4M of different concentration**

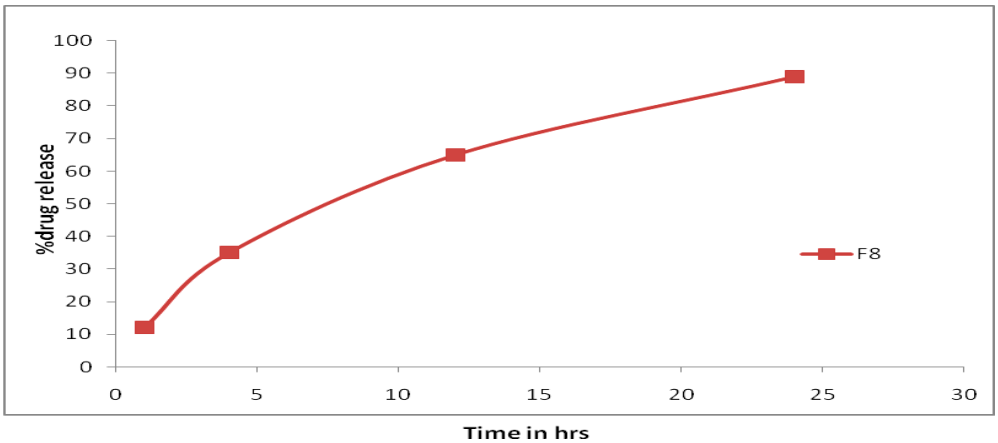


**Figure 8: Representing % drug release of Ranolazine SR tablets of trial F8 formulated with HPMC K4M & HPMC15CPS**

**Stability studies of final formulation:**
According to ICH guidelines, 3 months accelerated stability study at 40±2°c and 75±5% RH optimized formulation (F8) was carried. It showed negligible change over time for parameters like appearance, drug content, dissolution and assay etc., No significant difference in the drug content between initial and formulations stored at 40±2°c & 75±5% RH for 3 months. Results were tabulated in (**Table 11**).

**Table: 11 Intermediate time stability studies**

| Test | Limits | Initial | 3 Months |
|---|---|---|---|
| Appearance | Orange colored, Capsule shaped, Sustained release tablets | Satisfactory | Satisfactory |
| Average weight | About 1540mg | 1541 mg | 1540.2 mg |
| Hardness | 8 – 12 kg/cm$^2$ | 10kg/cm$^2$ | 10.5 kg/cm$^2$ |
| **Dissolution** 1st hour | Not more than 30% | 15% | 9.1% |
| 4th hour | Between 30-60% | 42% | 12.5% |
| 12th hour | Not less than 60% | 66% | 34.2% |
| 24th hour | Not less than 80% | 85% | 73.6% |
| **Assay** Each tablet Contains Ranolazine | 980 mg to 1100 mg (98.0%-110% of the labeled amount) | 987.2 mg (98.72%) | 992.0mg (99.2%) |
| Remarks | Complies | Complies | Complies |

## CONCLUSION

Ranolazine is used for the treatment of Angina pectoris, which has a short Elimination half-life of 1.4-1.9 hours. Its dose is 500 to 1000 mg daily in divided doses.

In the present study, an attempt was made to prepare matrix tablets of Ranolazine by wet granulation method using different hydrophilic polymers as matrix material. Combination of polymers like HPMC K4M and HPMC 15 Cps are better to control drug release among the various formulations prepared, formulation F8 showed better drug release profiles formulation studied. The release of drug from the combination of polymers (HPMC K4M and HPMC 15 Cps) containing Lactose monohydrate was found to be governed by diffusion controlled process.

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