ORIGINAL ARTICLE

# Effect of different polymers on release of ranolazine from extended release tablets

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An extended release tablet provides prolonged release of drug, maintains the desired concentration of drug in plasma and thereby reduce dosing frequency, improve patient compliance and reduce the dose-related side-effects. Ranolazine is indicated for the chronic treatment of angina in patients who have not achieved an adequate response with other anti-anginal agent. The present investigation was undertaken to design the extended release tablets of ranolazine employing different polymers as matrix forming agents using direct compression technique. Formulated tablets were evaluated for weight variation, hardness, friability, drug content, swelling index and *in vitro* release studies. The drug release followed first order kinetics and controlled by both erosion and diffusion mechanism. It is concluded that the desired drug release pattern can be obtained from the formulation containing 9.8% w/w eudragit and 39.2% w/w metallose offered relatively much slow release of ranolazine compared with other formulations. The selected formulation showed a similarity factor 76 when comparing *in vitro* dissolution data of the commercial formulation ranozex 500.

***Key words:*** *Anti-anginal, diffusion mechanism, direct compression technique, matrix forming*

## INTRODUCTION

Extended release drug delivery technology can provide smooth plasma levels of the drug over a longer period of time, reduce dosing frequency and improve patient compliance.[1] Ranolazine is indicated for the treatment of chronic angina. Unlike other anti-anginal medications such as nitrates and beta blockers, ranolazine does not significantly alter either the heart rate or blood pressure. Hence, it is of particular use in individuals with angina that is not responsive to maximal tolerated dose of other anti-anginal medication.[2] The biological half-life of ranolazine is 7 h. Cellulose ethers (hydroxyethyl cellulose [HEC] and hydroxypropyl cellulose [HPC]) are commonly employed as the hydrophilic, swellable and erodible matrix polymers for orally administered types of controlled release systems.[3,4] Ethyl cellulose and cellulose acetate were used as release retardant binder for controlled release formulation.[5-7] In this study, attempts were made to study the influence of polymers on release profiles of extended release tablets of ranolazine. Extended release tablets of ranolazine are designed to reduce the frequency of administration. Several research papers were published on ranolazine extended release formulations. However, research work on ranolazine extended release formulations containing the selected polymers were not published. So, studies were undertaken to develop these formulations and the results are reported here.

## MATERIALS AND METHODS

Ranolazine, metallose, eudragit, ethylcellulose, were procured from NATCO Pharmacy Pvt. Ltd., Kothur. Hydroxypropyl methylcellulose (HPMC), cellulose acetate, HEC, HPC, hydrochloric acid (Hcl), talc, magnesium stearate from SD Fine chemicals, Mumbai. Analytical balance (Shimadzu, Mumbai), bulk density apparatus (Thermonik, Mumbai). Hot air oven (Thermonik, Mumbai). Rotary compression machine (Cadmach, Mumbai) Pfizer hardness tester (Shimadzu, Mumbai) friabilator dissolution apparatus ED-21 electolab, Mumbai, ultra violet (UV) visible spectrophotometer (Shimadzu, Mumbai).

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## PREPARATION OF RANOLAZINE TABLETS

All the formulation was prepared according to the composition showed in the Table 1. Ranolazine and polymer were triturated well and moistened with water to form a damp mass. The damp mass is passed through American society of testing and materials (ASTM) 12 to obtain granules. The granules thus obtained were dried at 60°C. The dried granules were re sieved through ASTM 16 mesh and lubricated with talc and magnesium stearate. The granules were compressed by employing 12 mm round shaped die with Cadmach CMS 25 tableting machine.

## PRE COMPRESSION EVALUATION OF GRANULES

### Angle of repose

The angle of repose of granules was determined by the fixed funnel method.[8] The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter and the height of the powder cone were measured and angle of repose was calculated using the following equation.

$\tan\theta = h/r$ where h and r are the height and radius of the powder cone respectively.

## BULK DENSITY AND TAPPED DENSITY

Both BD and TD were determined. The granules (2 g) free from aggregates were introduced into a 10 ml measuring cylinder. The initial volume was observed and the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 s intervals. The tapping was continued until no further change in volume was noted. BD and TD were calculated using the following formulas:

BD = weight of the powder/volume of the packing
TD = weight of the powder/tapped volume of the packing.

**Table 1: Composition of ranolazine tablets**

| Ingredients | Quantity per single tablet in mg | | | | | | |
|---|---|---|---|---|---|---|---|
| | F-1 | F-2 | F-3 | F-4 | F-5 | F-6 | F-7 |
| Ranolazine | 500 | 500 | 500 | 500 | 500 | 500 | 500 |
| Ethyl cellulose | 100 | - | - | - | - | - | - |
| Cellulose acetate | - | 100 | - | - | - | - | - |
| Hydroxyethyl cellulose | - | - | 100 | - | - | - | - |
| Hydroxyproyl cellulose | - | - | - | 100 | - | - | - |
| Eudragit RL 100 | - | - | - | - | 100 | - | - |
| Eudragit RS 100 | - | - | - | - | - | 100 | - |
| Metallose 90 SH 10000 | 400 | 400 | 400 | 400 | 400 | 400 | 400 |
| Magnesium stearate | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Talc | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Total weight | 1020 | 1020 | 1020 | 1020 | 1020 | 1020 | 920 |

## COMPRESSIBILITY INDEX

Compressibility index of the granules was determined by Carr's compressibility index:

$$\text{Carr's index} = ([TD\text{-}BD]\ TD)/100 \quad (1)$$

## POST COMPRESSION EVALUATION OF TABLETS

The formulated tablets were evaluated for the following physicochemical characteristics.

## WEIGHT VARIATION

Formulated matrix tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation[9,10] was calculated by using the following formula:

$$\%\text{weight variation} = \frac{\text{average weight-individual weight}}{\text{average weight}} \times 100 \quad (2)$$

## HARDNESS

Hardness of the tablet was determined using the Pfizer harness tester. The tablet was placed in the tester and the pressure was applied until the tablet ruptures to record the hardness.

## FRIABILITY

The Roche friabilator was used to determine the friability of the tablets. 20 pre-weighed tablets were placed in the apparatus, operated for 100 revolutions and then the tablets were reweighed. The percentage friability[11] was calculated according to the fallowing formula:

$$\text{Friability} = \frac{\text{initial weight-final weight}}{\text{initial weight}} \times 100 \quad (3)$$

## DRUG CONTENT OF RANOLAZINE

Totally 20 tablets of each formulation were collected and powdered. Powder equivalent to 100 mg ranolazine was weighed, solubilized in sufficient quantity of methanol, diluted suitably with 0.1 N Hcl and the absorbance was measured by using Shimadzu double beam spectrophotometer (UV-1700) at 271 nm.[12]

## SWELLING INDEX

The tablet was weighed ($w_0$) and placed in dissolution medium containing distilled water maintained at 37°C. At per determined time intervals, the tablet was withdrawn and blotted to remove excess water and weighed ($w_t$).

The percentage swelling index was calculated with the fallowing formulae.[13]

$$\text{Swelling index} = 100 \times (w_t - w_0)/w_t \quad (4)$$

Where
$w_t$ = final weight of tablet
$w_0$ = initial weight of tablet

## *IN VITRO* DISSOLUTION STUDIES FOR RANOLAZINE TABLETS

The *in vitro* dissolution studies were conducted for all the ranolazine tablets formulations using USP dissolution apparatus 2 (basket TDT-08l, Electro lab, Mumbai). Dissolution test was carried out for a period of 24 h using 0.1 N Hcl (900 ml) as dissolution media. At appropriate time intervals (0.5), 5 ml samples were withdrawn and replaced with the same volume of dissolution medium. The absorbance of this sample was measured at 271 nm against blank using Shimadzu (UV-1700) double beam spectrophotometer to determine the drug released from the tablets.

## KINETICS AND MECHANISM OF DRUG RELEASE

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models:

$$\text{Zero order: } C = K_0 t \quad (5)$$

$K_0$ - zero order release rate constant
t - time in hours

$$\text{First order: } \text{Log } c = \log C_0 - K_t/2.303 \quad (6)$$

$C_0$ –initial concentration of drug
k - first order release rate constant.

To evaluate the mechanism of drug release from ranolazine extended release tablets, data of drug release were plotted in Korsmeyer *et al*. equation:

$$Mt/M8 = kt^n$$

Where
Mt/M8 - The fractional solute release,
t - Release time in hours,
k Kinetic constant characteristics of the drug/polymer system.

## RESULTS AND DISCUSSION

The extended release tablets containing ranolazine were formulated with a view to extend drug release up to a period of 24 h. The extended release formulations may be designed as diffusion controlled, dissolution controlled or combination of both. In this investigation, the combination and diffusion and dissolution phenomena were employed. Hydrophilic polymers such as HPMC and hydrophobic polymers ethyl cellulose, cellulose acetate, eudragit were used to retard the drug release. The formulations were prepared with wet granulation technique by employing metallose alone and in combination with other polymers. All the granules prepared as per the composition given in Table 1 were subjected to micromeritic properties. The observed Carr's index was found to be <15 and indicating excellent flow properties and hence they were compressed to form tablets the resulting tablets were evaluated for various quality control tests and the results were presented in Table 2. To study the influence of polymer on the kinetics and mechanism of drug release, the formulated tablets were subjected to *in vitro* drug release studies and the observed data is shown in Figure 1.

The drug release fallowed zero order kinetics ($r^2 > 0.9876$) and various *in vitro* release parameters such as release rate, $t_{50}$, $t_{90}$ were calculated and depicted in Table 3. The mechanism of drug release was observed to be the combination of diffusion and erosion, as the exponential coefficient of the Peppas[14] equation was in between 0.5 and 1. It was also observed that the incorporation of hydrophobic polymers into the hydrophilic polymers retarded the release of ranolazine from extended release formulations. The formulation containing 9.8% w/w eudragit RL 100 and 39.2% w/w metallose (F-6) offered relatively much slow release of ranolazine compared to other formulations. Further the release profiles observed from the selected formulation was compared with the marketed formulation. The similarity factor was found to 76. Hence this formulation was found to be much appropriate to achieve the control release of ranolazine.

## CONCLUSION

In the present investigation, attempts were made to

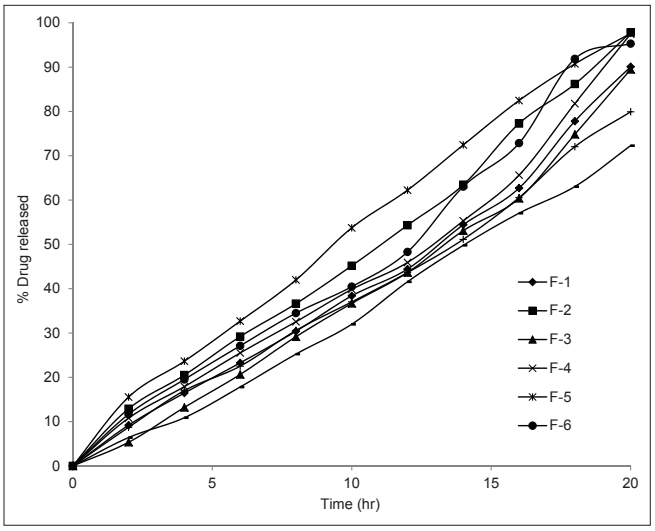


**Figure 1:** *In vitro* release profile of ranolazine tablets formulated with various polymer

**Table 2: Physical characteristics of ranolazine tablets**

| Physical formulation | Average weight | Drug content | Hardness (kg/cm²) | Friability | Swelling index |
|---|---|---|---|---|---|
| F-1 | 1028.41±0.45 | 99.98±0.87 | 8.4±0.78 | 0.79±0.056 | 71.34±0.034 |
| F-2 | 1025.94±0.76 | 101.98±0.35 | 8.9±0.48 | 0.67±0.043 | 68.67±0.076 |
| F-3 | 1028.69±0.96 | 98.78±0.58 | 8.6±0.73 | 0.83±0.032 | 69.78±0.036 |
| F-4 | 1028.69±0.76 | 101.11±0.75 | 8.5±0.87 | 0.69±0.58 | 55.89±0.54 |
| F-5 | 1021.89±0.36 | 98.98±0.38 | 8.9±0.25 | 0.86±0.38 | 67.89±0.38 |
| F-6 | 1023.33±0.26 | 99.98±0.38 | 8.3±0.57 | 0.79±0.48 | 66.89±0.23 |
| F-7 | 923.98±0.76 | 99.98±0.15 | 8.9±0.78 | 0.89±0.054 | 78.09±0.067 |

**Table 3: *In vitro* release kinetics observed from ranolazine tablets**

| Formulation | Correlation coefficient ($r^2$) | | | | Release kinetics | | | Exponential coefficient ($n$) |
|---|---|---|---|---|---|---|---|---|
| | Zero order | First order | Higguchi | Peppas | $K_0$ (mg/h) | $T_{50(h)}$ | $T_{90(h)}$ | |
| F-1 | 0.9896 | 0.7310 | 0.8854 | 0.9864 | 23.182 | 13.1 | 20.0 | 0.9093 |
| F-2 | 0.9970 | 0.8137 | 0.9149 | 0.9898 | 22.314 | 11.2 | 19.0 | 0.8162 |
| F-3 | 0.9876 | 0.7369 | 0.8898 | 0.9844 | 23.688 | 13.5 | 20.2 | 0.8419 |
| F-4 | 0.9853 | 0.9743 | 0.9311 | 0.9762 | 23.781 | 12.7 | 19.3 | 0.6774 |
| F-5 | 0.9947 | 0.8683 | 0.9407 | 0.9866 | 24.369 | 9.8 | 17.8 | 0.7474 |
| F-6 | 0.9931 | 0.8369 | 0.9001 | 0.9828 | 21.652 | 12.5 | 18.7 | 0.8252 |
| F-7 | 0.9959 | 0.8376 | 0.9011 | 0.9930 | 22.852 | 13.7 | 21.8 | 0.9112 |

formulate ranolazine extended release tablets to provide effective drug release for 24 h. The formulation containing 9.8% w/w eudragit and 39.2% w/w metallose offered relatively much slow release of ranolazine compared with other formulations. Further the release profiles observed from the selected formulation was compared with the marketed formulation. The similarity factor was found to 72.

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