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DESIGN AND *IN VITRO* EVALUATION OF SUSTAINED RELEASE TABLETS OF RANOLAZINE

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ABSTRACT

Sustained-release drug delivery system containing Ranolazine (an anti-anginal drug) with different ratios of pH dependent polymer, Eudragit L100-55 was designed by wet granulation method. The physicochemical compatibility of the drug and polymers were studied by FTIR spectrophotometer and found to be compatible. The *in vitro* release of Ranolazine SR tablets was studied in 900 ml of 0.1N HCl as dissolution medium using a USP dissolution paddle assembly at 50 rpm and 37±0.5°C. The promising formulation with concentration of Eudragit L100-55 polymer 12.5% showed better release of 99.78±0.99% after 24 hours. It showed Zero-order release with linearity (r=0.9447 to 0.9895). The similarity factor (*f2* values) was used for the comparison of *in vitro* release study of the best formulation of SR tablets and marketed ER product of Ranolazine. The *f*2 values found to be 77.29. Based on the similarity factor (*f2* values), the F4 formulation of SR tablets can be considered as optimized formulation in comparison with marketed ER product's drug release profile. To study the mechanism of drug release from the oral SR tablets of Ranolazine, the release data were fitted to the well-known exponential equation (Korsmeyer/Peppa's equation) and 'p' values found to be 0.73-0.78. This indicates that the release of drug follows non - fickian transport. Hence the present study indicates that the formulation F4 of the oral sustained release tablets of Ranolazine provides a better option for development of oral SR tablets of Ranolazine for once-daily administration.

INTRODUCTION: Ranolazine was approved by the US FDA in January 2006 for the treatment of chronic stable angina in patients who have had an inadequate response to traditional anti-anginals. It differs from traditional anti-anginal drug therapies in that its anti-ischemic effects are independent of a hemodynamic effect (e.g. heart rate and/or blood pressure). The presently preferred route of administration for Ranolazine is oral. A typical oral dosage form is a compressed tablet, a hard gelatin capsule filled with a powder mix or granulates, or a soft gelatin capsule (soft gel) filled with a solution or suspension.

Conventional oral dosage formulations are not ideally suited to Ranolazine because the solubility of Ranolazine is relatively high at the low pH that occurs in the stomach. Furthermore Ranolazine also has a relatively short plasma half-life. The high acid solubility property of Ranolazine results in rapid drug absorption and clearance, causing large and undesirable fluctuations in plasma concentration of Ranolazine and a short duration of action, thus necessitating frequent oral administration for adequate treatment [1, 2, 3, 4]. There is therefore a need for administering Ranolazine in an oral dosage form once or twice daily that provides a drug delivery system which control the release profile and inhibit rapid release of the drug from the formulation during its residence in the stomach (where the pH is-below about 4.5) and which promotes the release of a therapeutic amount of drug from the dosage form in the lower gastrointestinal tract (where the pH is generally greater than about 4.5).

A most preferred copolymer is methacrylic acid copolymer, Type C, USP (which is a copolymer of methacrylic acid and ethyl acrylate having between 46.0% and 50.6% methacrylic acid units). Such a copolymer is commercially available as Eudragit L100-55 (as a powder) [5]. Sustained-release formulation of Eudragit L100-55 can be an alternative for administration of such drugs. Sustained-release drug delivery system can increases the patient compliance, effectiveness of therapy and reduce the chances of adverse effect and hypersensitivity reactions by maintaining the plasma drug concentration at the same level with in therapeutic range for the required period of time. Therefore, the basic objective of the study was to design and *in vitro* evaluation of sustained-release tablets of Ranolazine for effective treatment of angina-pectoris.

MATERIALS AND METHODS:

Materials: Ranolazine, Eudragit L100-55, Isopropyl alcohol and Dichloromethane were received as a gift sample from Micro Labs, Tamil Nadu, India. Micro crystalline cellulose was received from Merck (India) Ltd., Mumbai and Magnesium Stearate was received from Indian Research Product, Tamil Nadu, India.

Instruments: Digital Balance-Ohaus Precision Standard, Tablet hardness tester-Monsanto, Friability tester-Electrolab, Vernier Caliper-Mitutoyo Corporation- Japan, Dissolution apparatus USP XXIII-Electro lab, Mumbai, Double beam UV Spctrophotometer- Schimadzu Pharmaspec 1700,; Rotary tablet punching machine- Kambert, FT-IR Spectrophotometer- Schimadzu FT-IR 8400 S

Preformulation studies [6]: Study was carried out by using infrared spectrophotometer to find out if there is any possible chemical interaction of Ranolazine with Eudragit L100-55, Micro crystalline cellulose, and Magnesium stearate. Weighed amount of drug (3 mg) was mixed with 100 mg of potassium bromide (dried at 40 to 50^{o}C). The mixture was taken and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned in Schimadzu FTIR 8400S spectrophotometer. The same procedure was repeated for the polymer and the physical mixture of drug and the polymer.

Preparation of standard curve [7]: Ranolazine was estimated spectrophotometrically at 272 nm by using 0.1 N HCl as solvent. 100 mg of Ranolazine was accurately weighed and dissolved in 0.1N HCl (20ml) and then made up the volume to produce 100ml with 0.1N HCl. From this stock solution 1 ml was taken and diluted to 100 ml with 0.1N HCl. Several dilutions were made from this stock solution, to obtain a concentration range of 1-10 µg/ml. The absorbance was measured at 272 nm using 0.1N HCl as blank and plotted to get the calibration curve.

Preparation of sustained-release tablets of Ranolazine [8, 9, 10, 11]: Six batches (F1-F6) of Sustained-release tablets each containing 500 mg of Ranolazine were prepared by wet granulation method employing variable concentrations (5.0%-17.5%) of polymer (Eudragit L100-55) as pH-dependent binder for sustaining the release of drug, microcrystalline cellulose as diluent and magnesium stearate as lubricant. In the formulation of granules, Isopropyl alcohol and Dichloromethane were used as granulating agent (**Table 1**).

TABLE 1: FORMULAE OF RANOLAZINE SUSTAINED-RELEASE TABLETS

Ingredients (mg/tab)	F1 5.0*%	F2 7.5*%	F3 10*%	F4 12.5*%	F5 15*%	F6 17.5*%
Ranolazine	500	500	500	500	500	500
Microcrystalline cellulose	104.8	88.8	72.8	56.8	40.8	24.8
Eudragit L100-55	32	48	64	80	96	112
Magnesium stearate	3.2	3.2	3.2	3.2	3.2	3.2
Isopropyl alcohol and Dichloromethane	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Total weight of the tablet is 640 mg; * indicates the percentage of Eudragit L 100-55 polymer used

Accurately weighed quantity of Ranolazine, microcrystalline cellulose, and Eudragit L 100-55 were screened through 40 mesh sieve and then blended together in a mortar for about 10 minutes. Mixture of Isopropyl alcohol and Dichloromethane (1:1) was added as a granulating agent to the blend with constant mixing for about ten minutes. The wet mass was then passed through 16 mesh sieve to obtain uniform granules and air dried. Then the dried granules were screened through 20 mesh sieve. Then magnesium stearate was added to the above dried granules and thoroughly mixed for about 2 minutes. Then the lubricated granules were compressed with eight station rotary tablet machine (Cadmach, India) using 12 mm flat circular beveledged punches to an average weight of about 640 mg/ tab.

Physico chemical Evaluations [12, 13, 14, 15]: Prepared sustained release tablets of Ranolazine were evaluated for their thickness, hardness, weight variation, friability, drug Content uniformity, *in vitro* release study and mechanism of drug release. Thickness of the tablet was measured by using dial caliper (Mitutoyo, Japan). Hardness test was carried out by using Monsanto hardness tester. The friability was determined by using Roche friabilator. Content uniformity studies are used for controlling batch-to-batch variation and it was determined by Schimadzu Pharmaspec 1700 UV Vis-Spectrophotometer at 272nm using 0.1N HCl as a medium.

***In vitro* release study** [16, 17]: The release of Ranolazine from prepared SR tablets (F1-F6) were studied in 900 ml of 0.1N HCl for first 2 hours and followed by pH 7.4 Phosphate buffer as dissolution medium using USP XXIV dissolution apparatus at 50 rpm and 37±0.5^{o}C. Samples were withdrawn at specific time intervals, filtered and analyzed by UV-Visible spectrophotometer at 272nm. An equal volume of fresh dissolution medium was replaced to maintain the sink condition. Cumulative percentage of drug release was calculated. The promising formulation selected on the base of drug release study.

Comparative *In vitro* release study with marketed product [16, 17]: The promising formulation F4 was selected on the basis of drug release study and compared with marketed tablet of Ranolazine ER. Finally for the optimization of the promising formulation the similarity factor (*f2* values) was used for the comparison of *in vitro* release study between promising formulation of sustained release tablets and marketed ER product of Ranolazine [18].

Mechanism of drug release [19, 20, 21]: In order to understand the mechanism of drug release from the prepared formulations, the data were treated according to first order release (Log cumulative percent drug remaining versus time), Higuchi's (Cumulative percent drug released versus square root of time), and Korsmeyer equation / Peppa's model equations (Log cumulative percent drug released versus log time) and zero order (cumulative amount of drug released versus time).

RESULTS AND DISCUSSION: The main goals of treatment in angina pectoris are relief of symptoms, slowing progression of the disease, and reduction of future events, especially heart attacks and ofcourse death. All the results related to design and *in vitro* evaluation of oral sustained release tablets of Ranolazine and its comparative *in-vitro* drug release study with marketed ER product of Ranolazine were analysed and the Ranolazine SR tablet seem to be a successful formulation.

Preformulation studies: There is no appearance or disappearance of any characteristics peaks. This shows that there is no chemical interaction between the drug, polymer and excipient used in the tablets. The presence of peaks at the expected range confirms that the materials taken for the study are genuine.

Preparation of standard curve: Standard Curve of Ranolazine was determined by plotting absorbance (nm) verses concentration (mcg/ml) at 272nm and it is follows the Beer's law (1microgram to 10 micrograms). The study also revealed better regression values (0.9987).

Tablet Thickness: The thickness of the tablets ranged from 3.9 to 4.1 mm (**Table 2**). The mean thickness was uniform in all formulations.

Hardness test: The hardness of all batches ranged from 7.5-8.5 Kg/cm^2 (**Table 2**).

Friability test: The percentage friability of all batches ranged from 0.047 % to 0.094 % (**Table 2**).

Weight variation test: The percentage weight variations for all formulations are present in **Table 2**. All the formulations (F1-F6) passed weight variation test as per the Pharmacopoeias limits of 5%.

Drug content uniformity: Drug content was found to be uniform among the all formulations and ranged from 99.234±0.463 to 99.530±0.410 (**Table 2**).

TABLE 2: PHYSICOCHEMICAL EVALUATIONS

Formulation	Thickness (mm)	Hardness (Kg/cm^2)	Weight Variation (mg)	Friability (%)	Content Uniformity (%)
F1	4.00±0.071	7.6±0.223	640.47	0.062	99.355±0.361
F2	4.06±0.055	7.9±0.418	640.65	0.047	99.234±0.463
F3	3.98±0.084	8.0±0.353	639.715	0.047	99.530±0.410
F4	4.04±0.054	8.1±0.418	641.125	0.062	99.425±0.314
F5	4.00±0.100	8.2±0.273	641.64	0.078	99.477±0.354
F6	3.98±0.084	8.2±0.273	641.080	0.094	99.443±0.489

All values are expressed as mean ± S.D, n= 10

***In vitro* release study:** The drug release was seen till 16, 18 and 20 hours from the formulations F1, F2 and F3 respectively. Here the results of *in vitro* drug release from the formulations were not satisfactory. But in fourth trial (formulation F4) the *in vitro* drug release was found to be satisfactory as F4 formulation released the total drug in 24 hours. Then for the confirmation of the satisfactory result of the formulation F4 two more trials (F5 and F6) were used. In these trials the rate of drug release decreased in comparison to above formulations (**Table 3 and Fig. 1**). The results of different trials (F1-F6) proved that formulation F4 is the promising/best formulation. The concentration of Eudragit L100-55 played important role in the *in vitro* drug release from the formulation. The release of drug continuously decreased when the concentration of polymer Eudragit L100-55 increased (F1 to F6). In fourth trial (formulation F4) the *in vitro* drug release was found to be satisfactory.

TABLE 3: *IN VITRO* RELEASE PROFILE

Time (hrs)	*Cumulative Percentage of Drug Release						
	F1	F2	F3	F4	F5	F6	Marketed
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
0.5	19.87±0.98	17.58±0.14	14.98±0.47	12.34±0.20	11.41±0.23	11.41±0.23	12.99 ± 0.25
1	28.72±0.55	25.63±0.54	23.59±0.44	22.14±0.46	19.37±0.52	19.37±0.52	23.64 ±0.10
2	36.21±0.20	34.00±0.70	32.25±0.27	28.00±0.81	26.98±0.76	26.98±0.76	28.81 ±0.69
4	44.18±0.80	42.11±0.62	44.40±0.54	38.18±0.36	32.12±0.63	32.12±0.63	39.47 ±0.32
6	55.34±0.21	55.20±0.65	53.30±0.97	41.78±0.81	39.65±0.32	39.65±0.32	42.58 ±0.19
8	63.77±0.64	62.74±0.53	61.49±0.42	51.95±0.22	42.59±0.46	42.59±0.46	52.48 ±0.36
10	77.28±0.43	73.41±0.25	70.40±0.70	59.03±0.51	50.47±0.60	50.47±0.60	60.11 ±0.06
12	85.48±0.25	81.35±0.37	79.26±0.47	64.00±0.14	58.78±0.74	58.78±0.74	69.73 ±0.80
14	90.37±0.27	88.44±0.31	85.82±0.97	73.11±0.99	63.91±0.60	63.91±0.60	75.47±0.48
16	99.17±0.13	95.67±0.48	90.02±0.82	80.87±0.50	69.77±0.31	69.77±0.31	82.02±0.41
18	-	99.60±0.59	95.26±0.30	86.15±0.84	73.47±0.41	73.47±0.41	88.96±0.64
20	-	-	99.66±0.13	93.28±0.60	79.69±0.65	79.69±0.65	95.97±0.62
22	-	-	-	97.71±0.16	83.41±0.27	83.41±0.27	99.44±0.18
24	-	-	-	99.78±0.99	88.57±0.29	88.57±0.29	104.74±0.39

All values are expressed as mean ± S.D, n= 3

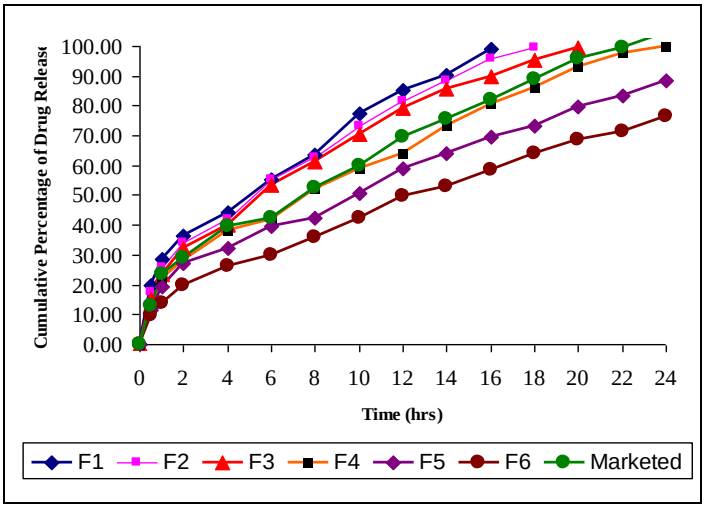

FIG. 1: *IN VITRO* RELEASE PROFILE

Comparative *In vitro* release study with marketed product: The total drug release from the marketed ER product was 104.74% after 24 hours. It was compared with the promising/best formulation of sustained release tablets (F4) to find out the similarity in drug release till 24 hours (**Table 4 and Fig. 2**). The similarity factor (*f2* values) was used for the comparison of *in vitro* release study between promising/best formulation of sustained release tablets and marketed ER product of Ranolazine. The *f*2 values found to be 77.29 (**Table 5**). FDA has set a public standard of *f*2 value in the range 50-100 to indicate similarity between two dissolution profiles.

So, the result of the similarity factor (f2 values) indicates that the promising/best formulation of sustained release tablets can be consider as optimized formulation in comparison with marketed ER product's drug release profile.

Table 4: RANOLAZINE SR (F4) Vs MARKETED ER PRODUCT

Time (hrs)	*Cumulative Percentage of Drug Release	
	F4	Marketed
0	0.00±0.00	0.00±0.00
0.5	12.34±0.20	12.99 ± 0.25
1	22.14±0.46	23.64 ±0.10
2	28.00±0.81	28.81 ±0.69
4	38.18±0.36	39.47 ±0.32
6	41.78±0.81	42.58 ±0.19
8	51.95±0.22	52.48 ±0.36
10	59.03±0.51	60.11 ±0.06
12	64.00±0.14	69.73 ±0.80
14	73.11±0.99	75.47±0.48
16	80.87±0.50	82.02±0.41
18	86.15±0.84	88.96±0.64
20	93.28±0.60	95.97±0.62
22	97.71±0.16	99.44±0.18
24	99.78±0.99	104.74±0.39

All values are expressed as mean ± S.D, n= 3

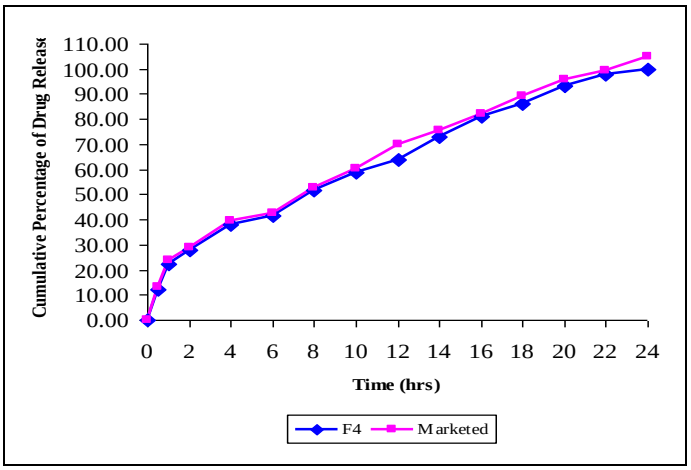

FIG. 2: *IN VITRO* RELEASE OF RANOLAZINE SR (F4) VS. MARKETED ER PRODUCT

TABLE 5: APPLICATION OF SIMILARITY FACTOR FOR COMPARATIVE *IN VITRO* RELEASE PROFILE OF RANOLAZINE SR (F4) WITH MARKETED ER PRODUCT

Time in hrs	* Cumulative % Drug release	
	Marketed Product	F4
0	0.00±0.00	0.00±0.00
4	39.47 ±0.32	38.18±0.36
8	52.48 ±0.36	38.18±0.36
16	82.02±0.41	80.87±0.50
24	104.74±0.39	99.78±0.99

*f*2 value = 77.29; * All values are expressed as mean ± S.D, n= 3

Mechanism of drug release: To know the mechanism of drug release from these formulations, the data were treated according to first-order release, Higuchi's, and Korsmeyer equation/Peppa's model equations along with zero order (cumulative amount of drug released versus time). The regression coefficient for the zero-order plots found to be 0.98-0.99 (**Table 6**).

TABLE 6: KINETIC PROFILE OF FORMULATIONS (F1-F6) AND MARKETED ER PRODUCT

Formulation Code	Zero Order	First Order	Higuchi		Koresmeyer *et al.*
	Regression Coefficient (R^2)	Regression Coefficient (R^2)	Regression Coefficient (R^2)	n	Regression Coefficient (R^2)
F1	0.9899	0.9687	0.9908	0.76	0.9751
F2	0.9893	0.9314	0.9957	0.77	0.9882
F3	0.9826	0.9631	0.9972	0.78	0.9921
F4	0.9908	0.8765	0.9898	0.75	0.9873
F5	0.9907	0.9725	0.9901	0.73	0.9786
F6	0.9950	0.9905	0.9871	0.74	0.9855
Marketed ER Product	0.9915	0.9021	0.9895	0.75	0.9758

The resultant 'n' values found to be 0.73-0.78. The study indicates that the release of drug follows anomalous (Non - Fickian) transport which implies that the drug release from the tablet follows both dissolution and diffusion mechanisms.

CONCLUSION: The study was undertaken with an aim to design oral sustained-release tablets of Ranolazine for once-daily administration for the therapy of chronic angina. It can be concluded that the present study indicates that the oral sustained release tablets of Ranolazine provides a better option for development of a once-daily formulation of the drug. Success of the *In vitro* drug release studies recommends the product for further in vivo studies, which may improve patient compliance.

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