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Development of extended release matrix tablets of Ranolazine containing polyacrylic and ethylcellulose polymers

Jagdish Bidada[1], Indrajeet Gonjari[2], Akshay Bhusari[3], Chandrakant Raut[1], Amar Dhule[4]

[1]*Department of Biopharmaceutics, Government College of Pharmacy Karad, Satara (MS) India*
[2]*All India Council of Technical Education (AICTE), New Delhi 01*
[3]*Sai Adventium pharma Ltd. Pune, Maharashtra.*
[4] *Rajashri Shahu College, Latur(MS)India*

ABSTRACT

Ranolazine is an anti-anginal drug with extensive 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 hours. Ranolazine, used in management therapy of anginal disorders, has been incorporated into monolithic matrices whose excipients were mixtures at different ratios of a acrylic resin (Carbopol 971 P) hydrophilic & pH-dependent nature and an ethylcellulose (Ethocel N20/N50), water-insoluble and pH-independent polymers. Technological characterization (drug particle morphology, mean weight, diameter, thickness, hardness and friability of tablets) was carried out and in vitro drug release behaviour was measured using the USP Type II (Paddle) apparatus. The effect of varying the Carbopol–Ethocel ratio, as well as the drug–polymeric matrix ratio, was evaluated by simple factorial design using two independent factors. The results showed the suitability of Carbopol–Ethocel mixtures as matrix-forming material for ranolazine Extended release formulations. Combination of the swelling properties of Carbopol 971 P with the plastic properties of the more hydrophobic Ethocel N20/N50 allowed suitable modulation of ranolazine release. Mathematical analysis of the release kinetics indicated that the nature of drug release from the matrix tablets was dependent on drug diffusion and polymer relaxation and therefore followed non-Fickian or anomalous release. The developed extended release matrix tablets of Ranolazine prepared with monolithic matrices release up to 12 hours. The factorial study indicates a good correlation coefficient (0.98317). The effect was dependent on both the independent factors of hydrophilic and hydrophilic polymer.

Keywords: Ranolazine; Carbopol; Ethocel; Sustained release; Matrix tablet.

INTRODUCTION

Ranolazine is indicated for the treatment of chronic angina in patients who have not achieved an adequate response with other anti-anginal drugs. Its novel mechanism of action increases oxygen

supply to the myocardium without compromising hemodynamic status. [1] Ranolazine is extensively metabolized in gut and liver and its absorption is highly variable. The apparent terminal half-life of poorly soluble ranolazine is 2.5±0.5 hours. The marketed preparation has 500 mg or 1000 mg active ingredient and administered twice daily. Hence judicious selection of release retarding excipients is necessary for achieving constant in vivo release.

Sustained-release oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects.[2]Among the different approaches studied with this aim, matrix systems still appear as one of the most attractive from both the economic as well as the process development and scale-up points of view.[3]Moreover, it has been shown that the suitable combination of more types of polymers as matrix-forming materials enables appropriate modifications of the release characteristics of the drug from the dosage form.[4] Hydrophilic polymer matrix systems are widely used for designing oral controlled drug delivery dosage forms because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance.[5]The polymers selected for the present study was Carbopol 971 P and ethyl cellulose. These polymers provide ph-dependant &pH independent respectively drug release to oral dosage forms that can be used for formulating the sustained-release dosage forms. [6]

Suitability of Carbopol 971 P (a copolymeric methacrylic acid resin) and Ethocel N20/N50 (an ethylcellulose), alone or in combination, as polymeric materials matrix tablets able to adequately extend drug release. Although acrylic resins [4] and ethylcellulose [7, 9] have been widely used as sustained release materials for matrix systems, to our knowledge the properties of their mixtures have not yet been evaluated. The influence of varying the Carbapol–Ethocel ratio and/or the drug–polymeric matrix ratio on drug release behaviour has been investigated. The technological properties of the tablets obtained with the different formulations were also examined.

MATERIALS AND METHODS

Drug: Ranolazine (Macleods Pharmaceuticals Ltd., India); Polymers: EC N20/N50 (Hercules wellingtion, USA), Carbopol 971 P (Degussa India Pvt. Ltd). Other excipients: Lactose IP (Schreiber Dynamics), Microcrystalline cellulose (Ming Tai Chemical co. Ltd., Taoyuan Hsien, Taiwan), Magnesium Stearate (Nitika chemicals, Mumbai), Colloidal Silicon dioxide (Degussa, India). Reagent: Hydrochloric Acid (HPLC grades). KH_2PO_4, Sodium hydroxide, Sodium chloride and other chemicals were either analytical reagents grade.

Formulation of Matrix Tablets

Matrix tablets with a theoretical weight of 680 mg were manufactured with the aim of achieving a described extended-release formulation over a 12-hr release period. The general formulation used in the study is ranolazine shown in Table 1. Batch size of the formulations ranged from 0.5–2.0 kg yielding 1000–4000 tablets. Ranolazine, Lactose, Carbopol 971 P were sifted through No.40 mesh and weighed accurately. The above material were loaded into the RMG and mixed at slow speed impeller for 15 minutes and granulated using Binder solution of ethyl cellulose in IPA and methylene dichloride. The wet mass was passed through No. 10 Sieve. The wet mass was loaded for Drying in tray Dryer at 55-60°C until moisture content was not more than 2.0%. The date, time, temperature and moisture content was recorded. Moisture content was checked at 105°C. The dried material was sifted through No. 20 sieve and the sifted granules were collected

into polythene bag and packed properly. Colloidal Silicon Dioxide, magnesium stearate were sifted through No.60 mesh and sifted materials (except magnesium stearate) were collected in to a polythene bag and mixed for 5 minutes. Magnesium Stearate was added and mixed for further minute at slow speed. Lubricated granules were compressed using table compression machine(General Mechanical Industries, Mumbai) equipped with 17.5 mm x 8.0 mm capsule shaped (plain) punches and die. All the preparations were stored in airtight containers at room temperature for further study.

Table 1. Factorial Design Of Matrix Tablet

Batch. No.	X1, X2	Carbopol 971 P	Ethyl cellulose N20/N50
C1	-1, -1	55	50/0
C2	-1, 0	55	25/25
C3	-1, +1	55	0/50
C4	0, -1	70	50/0
C5	0, 0	70	25/25
C6	0, +1	70	0/50
C7	+1, -1	85	50/0
C8	+1, 0	85	25/25
C9	+1, +1	85	0/50

Table 2. Formulation Batches C1-C9

Ingredient	C1	C2	C3	C4	C5	C6	C7	C8	C9
Ranolazine	500	500	500	500	500	500	500	500	500
Lactose	30	30	30	15	15	15	0	0	0
Micro crystalline cellulose	15	15	15	15	15	15	15	15	15
Carbopol 971P	55	55	55	70	70	70	85	85	85
Ethyl cellulose N20	50	25	0	50	25	0	50	25	0
Ethyl cellulose N50	0	25	50	0	25	50	0	25	50
Colloidal Silica (Aerosil-200)	10	10	10	10	10	10	10	10	10
Total weight	680	680	680	680	680	680	680	680	680

All Qty in Mg

Characterization of Granules

Prior to compression, lubricated granules were evaluated for their characteristic parameters. Moisture content was determined using Halogen moisture analyzer (Mettler-Toledo). Angle of repose was determined by funnel method. Bulk density and tapped density were determined by cylinder method, and Carr's index (CI) was calculated using the following equation. [9]

$$CI = (TD-BD) \times 100/TD$$

Where, TD is the tap density and BD is the bulk density.

Characterization of Tablets

The properties of the compressed matrix tablet, such as hardness, friability, weight variation, and content uniformity were determined using reported procedure briefly [10]; hardness was determined by using Monsanto hardness tester. Friability was determined using Roche friability testing apparatus. Weight variation and uniformity of drug content were performed according to the Official procedures. Uniformity of weight was determined by weighing 20 tablets

individually, and the drug was extracted in water. The drug content was determined as described for granules.

In vitro release study

Release studies were carried out for extended release Ranolazine formulations using USP dissolution apparatus (Electrolab Pvt. Ltd., India) Dissolution studies were conducted using USP type II (paddle) method at 100 rpm for 12 h. The dissolution medium was 0.1 N HCl and the temperature were maintained at 37°c ± 0.5^0C. The amount of drug dissolved in the medium was determined by HPLC (Jasco PU 2080 Plus) at 272 nm.

Kinetic Analysis of Dissolution Data

To study the mechanism of drug release from the matrix tablets, the release data were fitted to zero-order, first-order, and Higuchi equation.[11]These models fail to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore, the dissolution data was also fitted to the well-known exponential equation (Korsmeyer equation), which is often used to describe the drug release behaviour from polymeric systems. [12]

$$\text{Log } (M_t/M_f) = \text{Log } k + \text{Log } t$$

Where, M_t is the amount of drug release at time t; M_f is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet; and n is the diffusional exponent indicative of the mechanism of drug release.

To clarify the release exponent for different batches of matrix tablet, the log value of percentage drug dissolved was plotted against log time for each batch according to the Equation above. A value of n = 0.45 indicates Fickian (case I) release; Case II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled drug release. [13]

Model independent Analysis

The difference and similarity factors, commonly known, as f1 and f2 fit factors are model independent pair wise comparisons originally reported by Moore and Flanner [14].These parameters are currently recommended for use in most guidance documents[15]published by regulatory agencies for the comparison of dissolution profiles. The regulatory requirement as set by the FDA specifies that a minimum of 12 dosage units from each manufactured batch should be tested with suitable sampling times. In order to see whether the dissolution curves of the matrices of optimized batches and marketed product for different time intervals could be considered similar, difference (*f*1) and similarity (*f*2) factors proposed by Moore and Flanner[14]and implemented by FDA CDER were calculated according to the following equations:

$$f_1 = \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \times 100$$

$$f_2 = 50 \times \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

Where R_t & T_t are % drug release of reference & test at time 't' respectively

Determination of Swelling Behaviour

The swelling behaviour of matrix tablets was determined by the method reported by Al-Taani and Tashoush. [16] Matrix tablet was introduced into the dissolution apparatus under the standard set of conditions as specified for determination of in vitro drug release. The tablets were removed using a small basket and swollen weight of each tablet was determined. Swelling was calculated according to the following formula, where S is the weight of the matrix after swelling; and T is the initial weight of the matrix.

$$\% \text{ Swelling} = (S-T)/T \times 100$$

Stability Study of matrix Tablet

Stability studies are an integral part of the drug development program and are one of the most important areas in the registration of Pharma products. 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 enables recommended storage conditions, re-test periods and shelf lives to be established. Stability assessment started with studies on the substance to determine degradation products and degradation pathway. On the ICH Harmonized Tripartite Guidelines on Stability testing of New Drug substances and products, fundamental recommendations are summarized. [17]

According to the ICH guideline, long term (12 months) and accelerated stability studies (at least 6 months) have to be carried out.

It is up to the applicant to decide whether long term stability studies are performed at 25°C ± 2°C/60% RH ±5% RH or 30°C ± 2°C/65% RH ±5% RH . If 30°C ± 2°C/65% RH ±5% RH is the long-term condition, there is no intermediate condition. If long term studies are conducted at 25°C ± 2°C/60% RH ±5% and significant change occurs at any time during 6 months testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria.

For drug products packaged in impermeable containers (Aluminium tubes), semi permeable container (LDPE pouches, bottles etc), drug products intended for storage in a refrigerator, in a freezer and below –20°C, the study, storage condition and minimum time period covered by data at submission, are different not like as in general case.

Joel Davis test

According to Joel Davis Test, if the product holds up for 3 months under accelerated condition i.e. 40°C and 75% RH (chemical stability, dissolution, physical characteristics), then in an ANDA, the generic company will be given a two year expiration date but must follow up with real time data to substantiate the dating. The method is however, also used by ethical companies in the development of new drug entities. If the product does not pass the Joel Davis test, then conventional stability testing at room temp for prolonged periods (eighteen months) must accompany the NDA or the ANDA to satisfy the stability requirements of the submission.

RESULT AND DISCUSSION

The composition of different matrix tablets using factorial design is summarized in Table 1. The granules for matrix tablet were prepared according to the formula given in Table 2 and characterized with respect to angle of repose, moisture content, bulk density, and total drug content (Table 3). Angle of repose was less than 30° for all the batches of granules indicating

satisfactory flow behaviour. Moisture content of less than 2% indicates optimum drying of granules.

Table 3. Granules Property

Trial No.	Bulk Density[$]	Tapped Density[$]	Compressibility Index[$]	Hausners Ratio[$]	Angle of Repose[$]	Loss on drying
C1	0.339±0.0163	0.381±0.011	10.968±1.652	1.124±0.0207	30.333±0.577	1.4
C2	0.335±0.0079	0.367±0.014	8.751±2.371	1.097±0.028	26±1	1.7
C3	0.355±0.0236	0.385±0.024	7.794±2.103	1.085±0.025	31.667±0.577	1.5
C4	0.333±0.0108	0.374±0.005	11.055±2.422	1.125±0.0307	30.667±0.577	1.8
C5	0.353±0.0042	0.382±0.008	7.651±2.258	1.083±0.026	28.667±1.155	1.6
C6	0.346±0.0105	0.374±0.01	7.576±0.537	1.082±0.006	30.333±0.577	1.8
C7	0.353±0.0210	0.385±0.010	8.353±3.197	1.092±0.038	28±0	1.7
C8	0.362±0.0221	0.395±0.022	8.528±1.512	1.093±0.018	30.333±0.577	1.2
C9	0.335±0.0088	0.369±0.007	9.302±1.259	1.103±0.015	28.667±0.577	1.4

$- All values are mean ± SD, n=3

All examined formulations gave tablets with good and reproducible technological properties. Table 4 shows the data obtained from each lot of examined tablets. As can be seen, all tablet lots showed good weight, thickness, and diameter uniformities and no significant differences were observed with varying formulation composition. Tablet hardness, instead, was strongly influenced in formulations containing Ethocel to those with carbopol as polymeric matrix. However, hardness always remained within acceptable limits to give good handling properties without breakage or excessive friability problems, thus confirming the excellent compactability properties of these polymers which allowed extended release even in the absence of other excipients.

The release pattern of Ranolazine ER tablets from marketed formulation and from different batches of formulated batches are illustrated in figure 1. Carbopol is used in proportion of 55,70, and 85 mg with Ethylcellulose N20/N50 in proportion of 50/0,25/25 and 0/50 and different batches are formulated and drug release for 1,4,8,12 hours is shown in figure 1 . All batches (C1-C9) showed more than 80% drug release in 12 hours. All batches showed more than 80% drug release in 12 hours. Batch C9 contains showed release 24.50 % at 1hour.

Table 4. Ranolazine ER Tablet Property

Trial No.	Thickness[$]	Hardness[$]	Friability*	Uniformity of weight(¥)	Assay
C1	5.813±0.012	8.133±0.11547	0.2	679.85±2.539	99.37
C2	5.837±0.055	9.5±0	0.04	680.4±3.378	98.42
C3	5.803±0.005	9.467±0.057735	0.2	680.15±4.912	98.83
C4	5.740±0.05	8.133±0.11547	0.04	680.45±4.084	97.72
C5	5.807±0.012	8.1±0.1	0.012	680.2±3.995	100.25
C6	5.8167±0.015	7.967±0.057735	0.02	680.4±3.299	99.33
C7	5.8067±0.012	8.0667±0.11547	0.1	680.85±3.391	98..68
C8	5.803±0.006	8.033±0.057735	0.2	680.65±3.297	99.45
C9	5.817±0.006	8.067±0.11547	0.05	679.85±3.498	99.4

*$- All values are mean ± SD, n=3 ¥- All values are mean ± SD, n=20, *n=10*

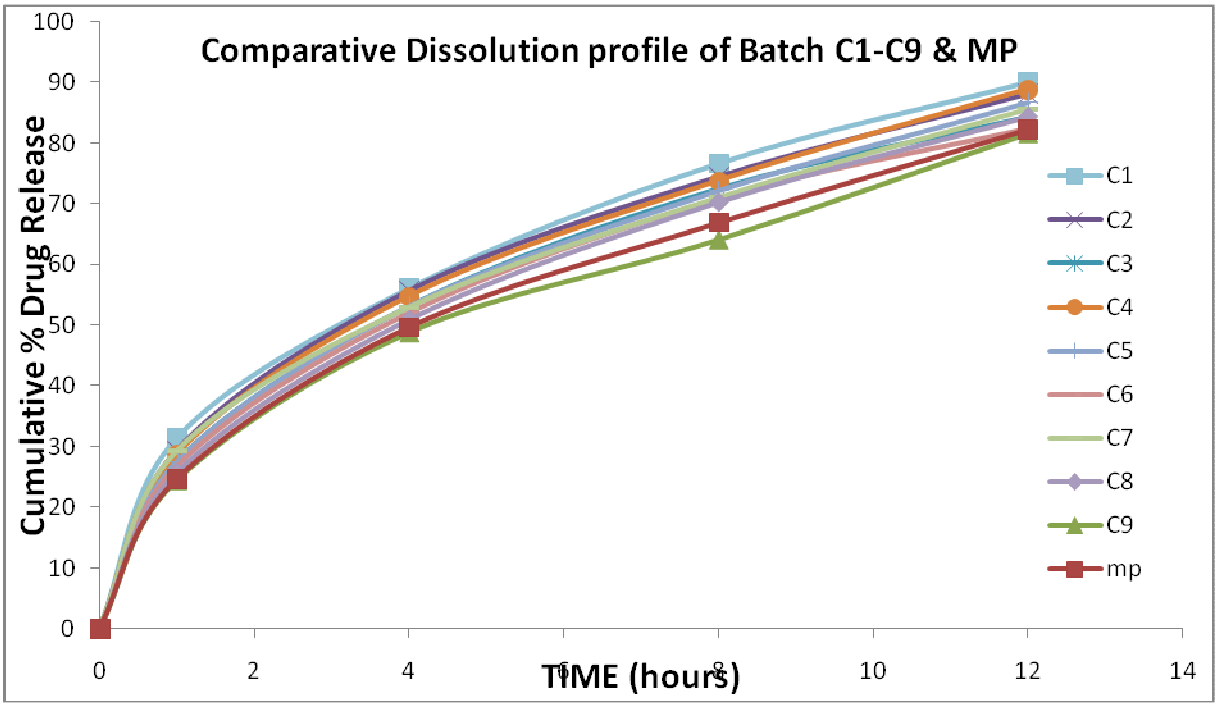

Figure 1. Comparative Dissolution profile of Ranolazine ER tablet Batch C1-C9 & Marketed Preparation (MP)

At low pH (5.0 or less), less than 10% of the Carbopol® acid groups will be ionized, resulting in relatively little stiffening by electrostatic charge repulsion, and relatively little swelling compared to fully neutralized Carbopol® polymer systems. In this regime, hydrogen bonding to polysaccharides or directly to proteins is probably the major mechanism for bioadhesion.

Drug release mechanism from carbopol polymer is processed as the external surface of the tablet is hydrated, it also forms a gelatinous layer upon hydration; however, this gel layer is significantly different structurally from the traditional matrix tablet. The hydrogels are not entangled chains of polymer, but discrete microgels made up of many polymer particles, in which the drug is dispersed. The crosslink network enables the entrapment of drugs in the hydrogel domains. Since these hydrogels are not water soluble, they do not dissolve, and erosion in the manner of linear polymers does not occur. Rather, when the hydrogel is fully hydrated, osmotic pressure from within works to break up the structure, essentially by sloughing off discrete pieces of the hydrogel. It is postulated that as the concentration of the drug becomes high within the gel matrix and its thermodynamic activity or chemical potential increases, the gel layer around the tablet core actually acts almost like a rate-controlling membrane, resulting in linear release of the drug.

In order to study the drug release mechanism of the examined tablets, the dissolution profiles were analysed according to the zero-order, first-order, Higuchi's square root equations, Hixson crowel cube root law, Korsmeyer Peppas, Baker Lonsdale Model**,** (Table 5). In all cases, the most suitable mathematical model for describing our experimental data was the Higuchi equation indicating that diffusion was the main factor controlling the drug release rate and that the release mechanism was not significantly influenced by formulation variations. A high value of correlation coefficient (r^2 = 0.998, n=0.477) suggested good correlation between in vitro-in vivo data. The effect of varying the polymeric matrix composition is shown in Fig. 2, where are reported the release profiles of ranolazine, as a function of time, from matrices containing a

drug–polymeric matrix ratio. As can be seen, a progressive decrease of ranolazine dissolution rate was observed with increasing the % of Ethocel N20/N50 in the polymeric matrix.

Tablet 5. Release kinetic Study of matrix tablet*

Kinetic Release Model		C1	C2	C3	C4	C5	C6	C7	C8	C9	MP
Zero Order	r^2†	0.887	0.888	0.889	0.898	0.902	0.890	0.892	0.909	0.915	0.911
First Order		0.809	0.808	0.808	0.809	0.808	0.808	0.809	0.808	0.807	0.808
Higuchi Model		0.995	0.996	0.996	0.998	0.998	0.996	0.996	0.979	0.998	0.999
Hixson Crowel Cube Root Law		0.4973	0.976	0.970	0.980	0.979	0.967	0.972	0.999	0.975	0.976
Korsmeyer-Peppas		0.999	0.999	0.999	0.997	0.999	0.998	0.999	0.999	0.997	0.999
Baker Lonsdale Model		0.820	0.823	0.826	0.834	0.838	0.826	0.824	0.847	0.852	0.849
n" Release Exponent§		0.430	0.443	0.454	0.453	0.462	0.457	0.429	0.479	0.477	0.481
F1		13.92	10.93	6.34	10.26	7.26	3.9	6.9	3.54	1.88	1
F2		59.31	64.42	74.50	65.59	72.50	81.77	73.88	84.47	90.57	100

**Analyzed by the regression coefficient method.*
†Correlation coefficient Fickian.
MP-Marketed preparation
§Diffusional exponent indicative of the mechanism of drug release.

Model-independent approaches, two fit factors that compare the dissolution profiles of a pair of drug products were applied to the dissolution data. These fit factors directly compare the difference between percent drug dissolved per unit time for a test and a reference product (Marketed formulation). The fit factors are denoted f1 (difference factor), and f2 (similarity factor). The dissimilarity (f1) and similarity (f2) factors were shown in the table no. 5**.** It has been observed that in batch C9 dissimilarity (f1) factor was 1.88 (much below 15) while the similarity (f2) factor was 90.57 (much above 50) indicating that the developed tablet formulation has in vitro dissolution profile identical to the marketed product, and that the developed batches possesses greater possibility of passing the in vivo bioequivalence test.

Concentration of Carbopol was found to be a dominant factor than concentration of EC N20/N50 Figure 2 showed that the release was retarded up to 12 hours with higher carbopol concentration batches. Release of drug was found to be more retarded as the concentration of Ethyl cellulose increased. The interactive term (X_1X_2) shows linearity in the effect of drug retardation. The 'n' values are less than 0.5, which indicate the non-fickian release i.e. initially there is rapid release, which is followed by tailing off overtime. The dissolution profile was found to be of matrix type. The factorial study indicates a good correlation coefficient (0.98317). The effect was dependent on both the factors.

The factorial equation is for Concentration of Polymer and drug release as follows:

$$Y = 86.504 - 1.914\ X_1 - 2.6916\ X_2 + 0.407\ X_1X_2 - 0.3845\ X_1^2 + 0.766X_2^2$$

Where- X_1 –Concentration. Of polymer I

X_2 –Concentration. Of polymer II

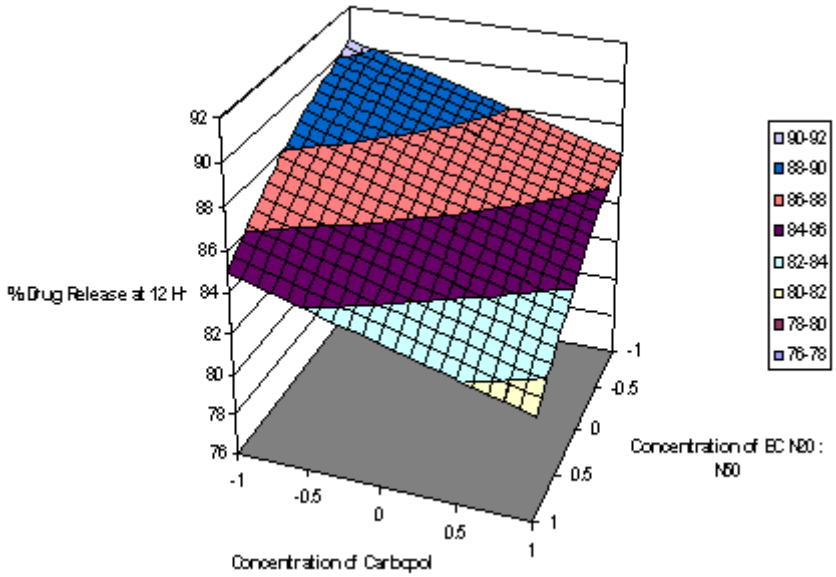

Figure 2. Analysis of concentration of polymer and drug release

The swelling behavior of matrix was determined by the above given method. Figure 3 represents the swelling index as function of time. It is clear that matrix underwent both swelling and erosion at the same time after placement in dissolution media. Swelling occurs at the same time after placement in the dissolution apparatus media since swelling occurred simultaneously in the matrix. Constant release can be obtained in such type of matrices. The increase in path length due to swelling was compensated by continuous release of matrix.

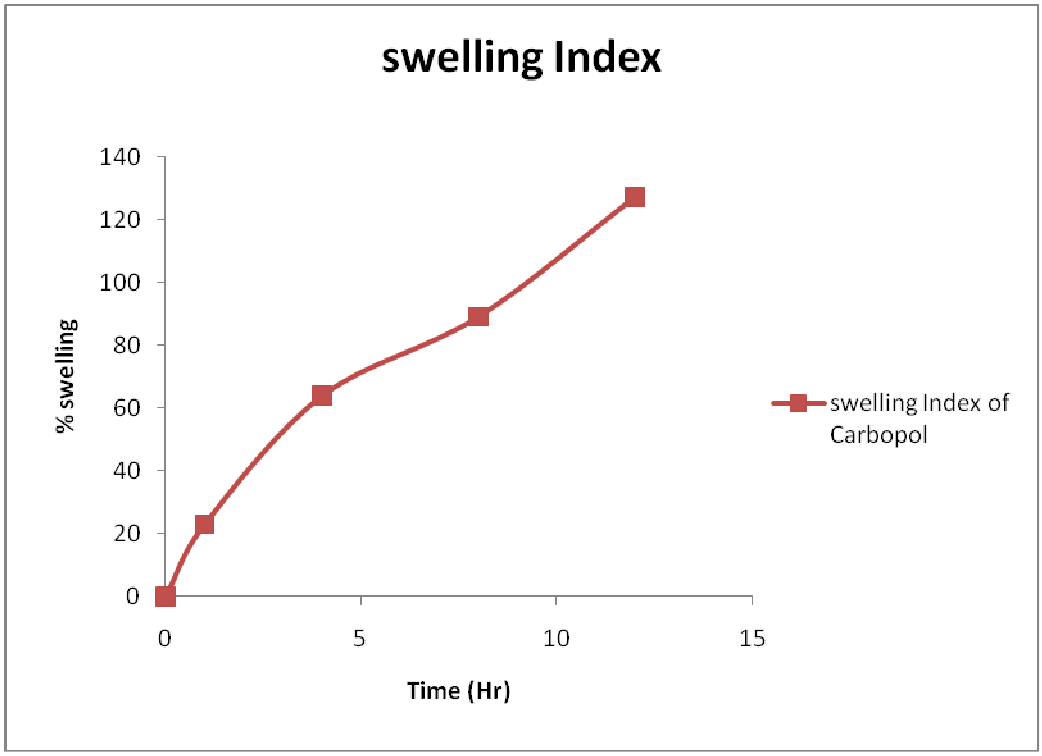

Figure 3. Graph of % swelling as function of time for Optimized Batch

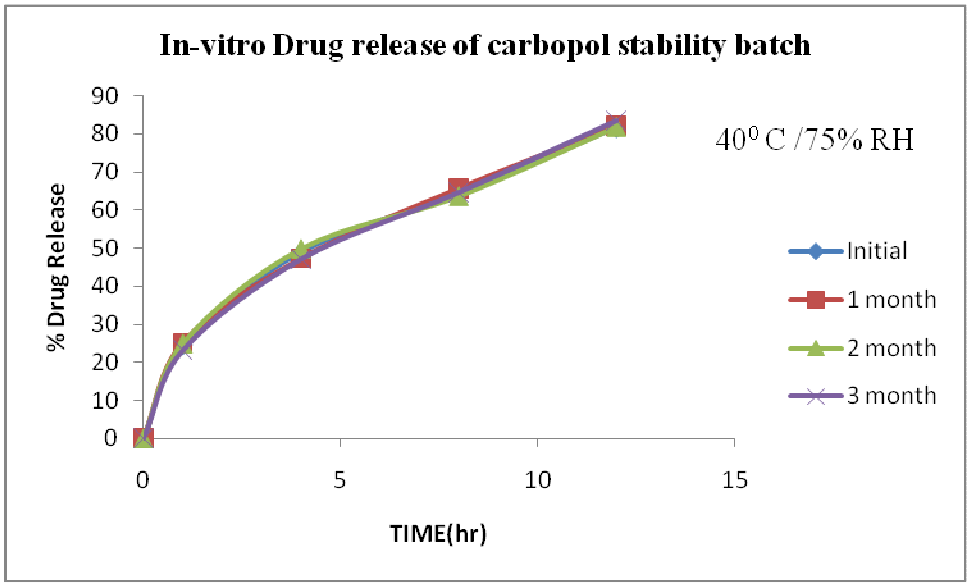

Figure 4. Dissolution of stability Batch Ranolazine ER Tab after1, 2, 3 months of storage at 40^0 C and 75% RH

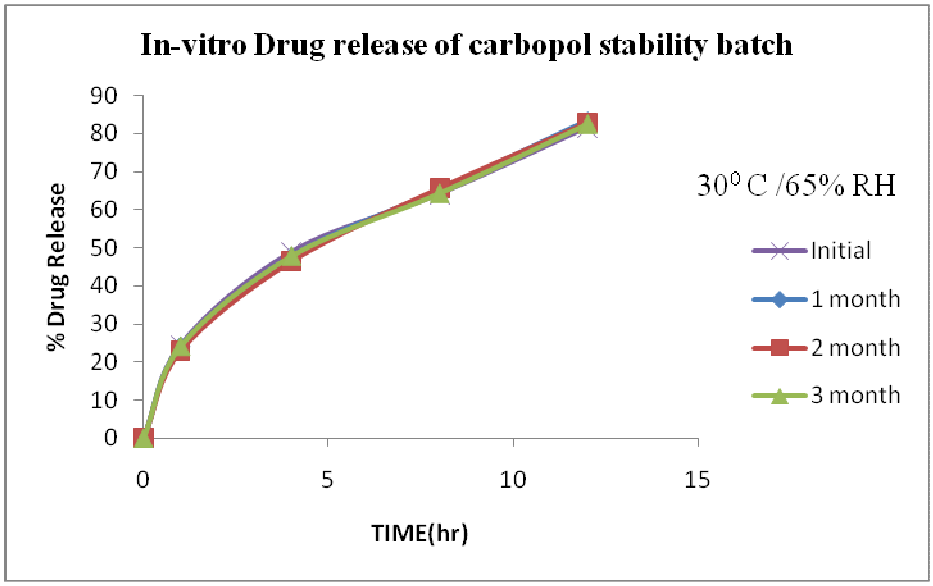

Figure 5. Dissolution of stability Batch Ranolazine ER Tab after1, 2, 3 months of storage at 30^0 C and 65% RH

Table 6. swelling Index of optimized Batch

Time	C9
0	0
1	23.02
4	63.94
8	89.16
12	127.25

Formulation Batch C9 gave desirable release and is optimized formulations and hence this batch was charged for stability studies. The stability studies were carried out under specific conditions of temperature and humidity: 40^{0}C&75% RH and 30^{0}C &65%RH.The study was conducted over a period of 3 months. The results indicate that no remarkable changes in physical appearance and in vitro dissolution profiles were found.

CONCLUSION

Extended release matrix tablets of Ranolazine were prepared by factorial design using carbopol and ethyl cellulose. Variation of polymer amount and viscosity grade significantly affected drug release from prepared matrix tablets. Higher amount of polymer decreased drug release rate and extent irrespective of its type. Release rate of the drug from the matrix tablets was significantly influenced by the concentration of carbopol used than concentration of EC N20/N50.

The 'n' values are less than 0.5, which indicate the non-fickian release i.e. initially there is rapid release, which is followed by tailing off overtime. The dissolution profile was found to be of matrix type. The factorial study indicates a good correlation coefficient (0.98317). A high value of correlation coefficient (r^2 = 0.998, n=0.477) suggested good correlation between in vitro-in vivo data.

Results of the present study,altogether demonstrated that combination of both hydrophilic and hydrophobic polymers could be successfully employed for formulating sustained-release matrix tablet of ranolazine .The investigated extended release tablet of ranolazine was capable of maintain constant plasma drug concentration through 12 hours. However Extensive *in vitro in vivo* correlation studies on similar formulations are essential to establish a successful formulation from the biopharmaceutical viewpoint.

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