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Research Article

MODULATORY EFFECT OF POLYMER TYPE AND CONCENTRATION ON DRUG RELEASE FROM SUSTAINED RELEASE MATRIX TABLETS OF RANOLAZINE: A COMPARATIVE RELEASE KINETIC STUDY

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ABSTRACT

Objective: Ranolazine (RZ), antianginal drug indicated for the treatment of chronic stable angina pectoris, was formulated into sustained-release matrix tablets and optimized to improve patient compliance and achieve controlled release over a certain period.

Methods: Different formulations were prepared by wet- and melt-granulation techniques. Excipients at different ratios as Eudragit® L100-55, Methocel™ E5, Avicel® PH-101, and carnauba wax powder were used to develop a ternary polymeric matrix system for the controlled delivery of RZ. The prepared formulations were subjected to granulometric and characteristic studies. Comparative dissolution and release kinetic studies of the selected formulation and the reference product, Ranexa® extended-release film-coated tablets, Gilead Sciences, Inc., USA, were further carried out to ensure product similarity.

Results: The optimum pH-dependent to pH-independent polymers ratio was 1:1.3 (w/w). Extragranular carnauba wax in a concentration of 32.50 mg/tablet (2.50 gm% w/w) was the key excipient in controlling drug release kinetics by forming waxy matrix granules which prevent rapid dissolution. Modulation of the microenvironmental pH using a potent alkalinizing agent was very effective for controlling drug release patterns in different dissolution media from pH 1.2–6.8.

Conclusion: The release of RZ from the matrix tablets was controlled for a period of 24 h, and thereby expected to provide patient compliance with minimal side effects.

Keywords: Sustained release, Ranolazine, pH-independent polymer, pH-dependent polymer, Film-former carnauba wax, Microenvironmental pH modulation, Wet-granulation, Melt-granulation.

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INTRODUCTION

Chronic stable angina pectoris (CSAP) is the most prevalent manifestation of coronary artery disease that impairs quality of life, and reduces life expectancy, particularly among the elderly. In most of the European countries, it affects up to 5% of population over the age of 40 years. Approximately, 20,000–40,000 individuals of every million population are suffering from CSAP [1]. It is characterized by discomfort in the chest or in adjacent areas, such as jaw, shoulder, back or arms, and usually elicited by exertion or emotional stress [2]. Clinically, CSAP is mainly caused by an imbalance between myocardial oxygen supply and myocardial oxygen consumption [1,2].

The first-line pharmacological treatment of CSAP includes short-acting nitrates for chest pain relief, as well as β-blockers and Ca^{2+} antagonists for controlling heart rate and symptoms [3]. However, despite the effectiveness of the current treatment regimen, episodes of CSAP may persist or even get worse. Moreover, a combination of antianginal drugs can cause many gastrointestinal and cardiovascular side effects on long-term use [4,5]. Therefore, the development of a new antianginal drug with favorable antiarrhythmic properties is a promising approach.

Ranolazine (RZ) is a relatively new class of antianginal drugs that were approved in 2006 by the US Food and Drug Administration, and in 2008 by the European Medicines Agency for the use in patients with CSAP who are symptomatic on β-blockers, Ca^{2+} antagonists or nitrates [6]. RZ (Fig. 1) is a racemic mixture of two enantiomeric forms [7], chemically described as 1-piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl], with the empirical formula of $C_{24}H_{33}N_3O_4$, and a molecular weight of 427.545 g/mol [8]. It is described as white to off-white solid powder, very slightly soluble in water (756 mg/L at 25°C) [8]. RZ was first introduced as immediate release dosage forms, then discontinued, and replaced by extended-release dosage forms because of the very short terminal elimination half-life of immediate release RZ, which was ranging from 1.4 to 1.9 h after oral administration [9].

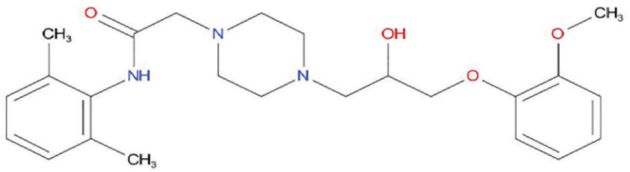

Fig. 1: The chemical structure of ranolazine

At present, RZ is marketed under the brand name of Ranexa® film-coated tablets, manufactured by Gilead Sciences Inc., USA, as extended-release dosage forms, with dosing of 500–1000 mg twice daily, prolonged absorption phase, maximal plasma concentrations (C_{max}) typically observed 4–6 h after oral administration, and terminal elimination half-life averaged ~7 h after multiple dosing to steady-state [8,10,11]. Nevertheless, the cost of Ranexa® extended-release film-coated tablets is high, starting from $212.50 for 500 mg, and $452.43 for 1000 mg [12]. The high cost of Ranexa® extended release film coated tablet may be either due to its superior content of high-functionality excipients and functional film coating system or due to the novelty of the manufacturing process.

Sustained release drug delivery systems (SRDDS) were designed to control drug release profiles at predetermined rates to achieve the desired drug concentration either in blood plasma or at target sites for a specific period. More specific, SRDDS were developed for those drugs that are rapidly absorbed from the gastrointestinal tract, having a shorter half-life, eliminated quickly from the blood circulation, and showing narrow absorption window [13,14]. SRDDS are advantageous over other modified release drug delivery systems in respect of offering better patient compliance, maintaining constant plasma drug concentration level, reducing chances of toxicity, and once a day drug therapy, which, in turn, reducing the overall cost of treatment [15].

The incorporation of a high-dose drug into SRDDS that releases the drug steadily over a specific period is a big challenge and requires careful selection of excipients, formulation, and process parameters. Therefore, the aim of this research was to develop a sustained-release polymeric matrix system containing a high dose of RZ as an active ingredient. In the previous relevant studies, Asaduzzaman *et al.* [16] prepared sustained-release matrix tablets of RZ by wet-granulation technique, using Methocel™ K4M CR only as a dissolution retardant. Uddin *et al.* [17] also prepared sustained-release matrix tablets of RZ by wet-granulation technique, using a combination of high viscosity grades of hydroxypropyl methylcellulose (HPMC) as Methocel™ E50, Methocel™ K100 LV CR, Methocel™ K4M CR, and Methocel™ K15M CR. Alternatively, Rahman *et al.* [18] prepared sustained-release matrix tablets of RZ by direct compression technique, using Eudragit® L100-55 and a high viscosity HPMC grade (Methocel™ K15M CR) as dissolution retardants. However, these formulations were optimized for 8–12 h, using high viscosity HPMC grades and functional coating systems. In our study, RZ sustained-release matrix tablets were prepared by wet- and melt-granulation techniques, using a blend of pH-dependent (Eudragit® L100-55 copolymer), pH-independent (Methocel™ E5 and Avicel® PH-101), and film-forming (carnauba wax) polymers at different ratios and concentrations, aiming at controlling the release of RZ for a period of 24 h. In addition, modulation of the microenvironmental pH using a potent alkalinizing agent as sodium hydroxide (NaOH) was relatively essential to control the release of RZ from the polymeric matrix system in different dissolution media. Comparative dissolution and release kinetic studies against the reference product, Ranexa® extended-release film-coated tablets (Gilead Sciences, Inc., USA) were further carried out at various physiologically relevant pH to mimic gastric and intestinal conditions.

MATERIALS AND METHODS

Materials

RZ was purchased from Aurobindo Pharma Ltd., India; Eudragit® L100-55 copolymer (an anionic copolymer of methacrylic acid and ethyl acrylate) was purchased from Evonik Industries, Germany; Methocel™ E5 Premium LV (also known as hypromellose, a low viscosity HPMC of 5 cP) from Dow Chemical Company, USA; Avicel® PH-101 (microcrystalline cellulose of particle size ~50 μm) from FMC Corporation, USA; carnauba wax powder, and magnesium stearate from Sigma-Aldrich, Germany. NaOH, potassium phosphate monobasic anhydrous, sodium acetate trihydrate, glacial acetic acid, and hydrochloric acid were kindly supplied by October Pharma, Egypt. Ranexa® extended-release film-coated tablets were purchased from Gilead Sciences, Inc., USA, and used in our study as a reference product. All reagents and solvents used were of analytical grades and purchased from Sigma-Aldrich, Germany.

Methods

Preparation of matrix granules by wet-granulation technique

Matrix granules of RZ, Eudragit® L100-55, Methocel™ E5, Avicel® PH-101, and carnauba wax were prepared at concentrations, as shown in Table 1. A granulating solution of NaOH was prepared by dissolving NaOH in purified water, and then mixed with a powder mixture of RZ, Eudragit® L100-55, Methocel™ E5, and Avicel® PH-101 to form a wet mass. The wet mass was dried at 50°C using a lab drying oven (Thermo Fisher Scientific, USA) until the moisture content was lower than 2%, then sieved using a sieve of mesh size 500 μm (Haver and Boecker®, Germany), remixed with extragranular carnauba wax powder and re-sieved, followed by mixing with magnesium stearate lubricant for 1–2 min. The matrix granules were stored in a desiccator over $CaCl_2$ at 0%RH and 25°C until compression into tablets.

Preparation of matrix granules by melt-granulation technique

Matrix granules of RZ, Eudragit® L100-55, Methocel™ E5, Avicel® PH-101, and carnauba wax powder were prepared at concentrations, as shown in Table 1. Intragranular carnauba wax powder was melted at 80°C in a Petri-dish, then mixed with RZ, and allowed to cool until a solid mass was formed. The solid mass was crushed, sieved using a sieve of mesh size 800 μm (Haver and Boecker®, Germany), then mixed with dried granules of Eudragit® L100-55, Methocel™ E5, and Avicel® PH-101 (initially prepared by wet-granulation using NaOH solution as a granulating solution), and re-sieved using a sieve of mesh size 500 μm, followed by mixing with magnesium stearate lubricant for 1–2 min. The matrix granules were stored in a desiccator over $CaCl_2$ at 0%RH and 25°C until compression into tablets.

Tableting process

The matrix granules were compressed into tablets using a single punch tablet press (Erweka®, Germany), with an oblong shape punch (8.6 mm × 23 mm). The hardness of all tablets was set to be around (30 – 32 kP). The average weight of tablets was within the range of 1300 mg ± 5%.

Characterization of granules and the prepared tablets

Angle of repose (θ)

The angle of repose (θ) is often determined by the fixed funnel and free-standing cone method. In this method, a funnel is fixed at a certain height on a white graph paper placed onto a flat horizontal surface. The powder sample is gradually passed through the funnel till the apex touched the tip of the funnel; thereafter, the radius of the base of the conical pile is determined. The θ can be calculated using the following equation 1 [19]:

Table 1: Formulation composition of RZ sustained-release matrix tablets

Ingredient (mg)	Formula code									
	Wet-granulation technique					Melt-granulation technique				
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
RZ	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
Eudragit® L100-55	143	143	143	130	104	143	143	143	130	104
Methocel™ E5	39	39	65	52	65	39	39	65	52	65
Avicel® PH-101	69.90	50.40	28.95	56.90	69.90	30.90	8.90	1.90	9.40	22.40
Carnauba wax	26.00	23.50	27.95	32.50	32.50	65.00	65.00	55.00	80.00	80.00
Magnesium stearate	13.00	35.00	26.00	19.50	19.50	13.00	35.00	26.00	19.50	19.50
Total tablet weight (mg)	1300	1300	1300	1300	1300	1300	1300	1300	1300	1300

RZ: Ranolazine

$$\text{Tan}\,\theta = \frac{h}{r} \quad (1)$$

Where h and r are the height and radius of the base of the conical pile, respectively.

Weight uniformity

Weight uniformity was evaluated according to the European Pharmacopeia [19], where 20 tablets from each formula were individually weighted. The percentage of weight variation was calculated using equation 2. The average weight of tablets was within the range of 1300 mg ± 5%.

$$\text{Weight uniformity} = \frac{(\text{Individual weight} - \text{Average weight})}{\text{Average weight}} \times 100 \quad (2)$$

Tablet hardness

Tablet hardness for ten tablets per formula was separately measured using the hardness tester (Erweka® TBH 100, Germany) [19]. The hardness of all tablets was set to be around (30–32 kP).

Tablet friability

Tablet friability was evaluated according to the European Pharmacopeia [19], where 20 tablets from each formula were accurately weighed, then placed in the friabilator chamber (Erweka® TA100, Germany), and allowed to rotate at 25 rpm for 4 min. Tablets were collected, gently cleaned, and re-weighted. The percentage of weight loss in tablets, as a reference of friability, was calculated using equation 3. Tablets pass the test if not more than 1% of the weight of the tablets was lost.

$$\textit{Frability} = \frac{(W_o - W_f)}{W_o} \times 100 \quad (3)$$

Where W_0 is the initial weight of tablets, and W_f is the final weight of tablets.

Tablet thickness and diameter

Tablet thickness and diameter were measured using a micrometer (Mitutoyo, Japan). A total of three tablets from each formula were separately measured. Tablet thickness and diameter were within the range of (7 mm ± 0.2) for tablet thickness, (23 mm ± 0.2) as length (L), and (8.6 mm ± 0.2) as width (W) for tablet diameter.

Content uniformity

A total of six tablets from each formula were dissolved individually and diluted with 0.1N HCl (pH 1.2) to the appropriate volumes. The resulting solutions were filtered through 0.45-µ membrane filter paper (Whatman® membrane filters, SIGMA-Aldrich, USA). The absorbance was measured at 272 nm using a ultraviolet (UV) spectroscopy (Shimadzu® UV-visible spectrophotometer 1601/PC, Japan) [16,20].

***In-vitro* and comparative dissolution**

Three dissolution media were selected for *in-vitro* dissolution studies; namely, 0.1N HCl (pH 1.2), acetate buffer solution (pH 4.5), and phosphate buffer solution (pH 6.8), representing gastric and intestinal conditions. The selected formula (F5) was placed in a vessel containing 900 mL of each dissolution media maintained at a temperature of 37°C±0.5°C, then installed onto a dissolution tester (Hanson-Vision® Classic 6, USA) equipped with USP apparatus II (paddle mode) with a paddle rotation speed of 50 rpm [16].

Comparative dissolution studies of the selected formula (F5), described as sustained-release matrix uncoated tablets, and Ranexa® extended-release film-coated tablets (Gilead Sciences, Inc., USA) were further carried out in triplicate. Dissolution profiles of the selected formula were compared with the reference product, Ranexa® extended release film coated tablets (Gilead Sciences, Inc., USA), using the similarity (f_2) and difference (f_1) factors, defined by the following equations 4 and 5, respectively [21]:

$$f_2 = 50\log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad (4)$$

$$f_1 = \left\{\frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n} R_t}\right\} \times 100 \quad (5)$$

Where n is the number of sampling time-points, R_t and T_t are the mean percent dissolved of the reference product and the prepared tablets, respectively, up to each time point t. f_2 represents a logarithmic transformation of the sum-squared error of the difference between the reference and the test products overall time-points. To consider similar dissolution profiles, f_2 values should be higher than 50. Alternatively, f_1 defines the percent difference between 2 curves at each time point and represents a measurement of relative error between curves. f_1 values should be lower than 15 [21].

Drug release kinetics

To study the drug release kinetics, the data obtained from *in-vitro* drug release studies were evaluated using the following mathematical models.

Zero-order release kinetics

In zero-order release kinetics, the cumulative amount of drug release is directly proportional to time, as described by the following equation 6:

$$C = (K_o\, t) \quad (6)$$

Where K_0 is the zero-order rate constant expressed as concentration per time, and t is the time per h.

A graph of drug concentration versus time would yield a straight line with a slope equals to K_0 and intercept the origin of the axes. This model is applied for film-coated matrix tablets with low drug solubility, such as osmotic-controlled release tablets.

First-order release kinetics

It is expressed as Log cumulative percentage of drug undissolved versus time, as described by the following equation 7 [22]:

$$\text{Log } C = (\text{Log } C_o - K_t/2.303) \quad (7)$$

Where C is the amount of drug not dissolved at the time (t), C_0 is the drug concentration at t equals to 0, and k_t is the corresponding release rate constant.

This model is used to describe the drug release pattern of water-soluble drugs from porous matrix systems.

Higuchi square root release model

The Higuchi release model is expressed as the cumulative percentage of drug release versus square root of time, as described by the following equation 8 [23]:

$$Q = (K_H t^{½}) \quad (8)$$

Where Q is the amount of drug dissolved at the time (t), and K_H is the Higuchi constant.

As a result, the drug release rate is proportional to the reciprocal of the square root of time. This model is applied for modified release matrix systems containing water-soluble drugs.

Hixson-Crowell cube root release model

Hixson-Crowell cube root model explains the possible changes in drug release pattern with the surface area and diameter of the prepared tablets [24]. It is expressed as the cube root of the initial concentration minus the cube root of the percentage of drug undissolved in the matrix system versus time, as described by the following equation 9 [24]:

$$(Q_o^{\frac{1}{3}} - Q_t^{\frac{1}{3}} = K_{HC}.t) \quad (9)$$

Where Q_0 is the initial amount of the drug in the prepared tablets, Q_t is the amount of drug release at the time (t), and k_{HC} is the rate constant for Hixson-Crowell cube root model.

Korsmeyer–Peppas equation

It is a simple, semi-empirical model relating exponentially the drug release to the elapsed time, as described by the following equation 10 [25]:

$$\frac{Q}{Q_o} = Kt^n \quad (10)$$

Where Q/Q_0 is the fraction of drug released at the time (t), (K) is the constant comprising the structural geometric characteristics, and (n) is the diffusion exponent that depends on the release mechanism.

If (n=0.45), the release mechanism follows Fickian diffusion (case I); (0.45 < n < 0.89), the release mechanism is non-Fickian (anomalous case); while if (n>0.89), the release mechanism is super Case II transport. Case II transport generally refers to the erosion of polymeric chains, while non-Fickian (anomalous case) refers to a combination of both diffusion and erosion mechanisms [25].

This model is applied for polymeric dosage forms when the release mechanism is unknown, or more than one release mechanism is involved in the dosage form preparation.

Analysis of dissolution data

Two parameters, namely, mean dissolution time (MDT) [26] and dissolution efficiency (DE) [27] were used to further compare the release profiles of the selected formula (F5) and the reference product, Ranexa® extended-release film-coated tablets (Gilead Sciences, Inc., USA).

MDT

MDT is calculated from the dissolution data using the following equation 11 [26]:

$$MDT = (n/n+1)\ K^{(-1/n)} \quad (11)$$

Where (n) is the release exponent, and K is the release rate constant.

A higher MDT value refers to higher retaining efficacy of the polymer, and *vice versa* [26].

DE

DE is defined as the area under the dissolution curve within a time range of (t_1–t_2) and can be calculated using the following equation 12 [27]:

$$DE = \frac{\int_{t_1}^{t_2} y dt}{y_{100} \times (t_2 - t_1)} \times 100 \quad (12)$$

Where y is the drug percent dissolved at the time (t).

Formulations are considered equivalent if the difference in between their dissolution efficiencies and the reference product is within (± 10%) [27].

Accelerated stability studies

Accelerated stability studies were carried out according to the International Council for Harmonization guidelines for stability studies; at 40°C and 75% RH for 6 month [28]. The selected formula (F5) was stored in high-density polyethylene (HDPE) bottles as the marketed product and placed into a stability chamber. Tablets were evaluated in terms of appearance, thickness, diameter, hardness, friability, and *in-vitro* drug release.

Statistical analysis

Data were collected and coded before analysis. All data were expressed as mean±SD. All statistical analyses were made using ANOVA, followed by Tukey Kramer test at p>0.05 using GraphPad Instat® Software.

RESULTS AND DISCUSSION

Pre-formulation and preliminary studies

Flowability and handling characteristics of the prepared matrix granules were evaluated by the fixed funnel and free-standing cone method to determine the angle of repose (θ), which typically showed good flow properties with θ ranged from 33° to 35° for wet-granulation formulations, and 31° to 33° for melt-granulation formulations.

Different pharmaceutical technologies and formulation strategies were preliminarily screened for the preparation of RZ sustained-release tablets, such as direct compression using conventional and high-functionality excipients, dry-granulation, and wet-granulation using pH-independent polymers only, but only wet- and melt-granulation techniques using a blend of multifunctional polymers with controlled microenvironmental pH, showed the best results in terms of *in-vitro* drug release and comparative dissolution (data not shown). The basic principle of the wet-granulation technique relies on holding powder particles together using an aqueous, alcoholic, hydroalcoholic, or buffered binder solution, while the melt-granulation technique is based on incorporating a melt binder in the tablet preparation [29,30]. F1-F5 formulas were prepared by wet granulation technique, using Eudragit® L100-55, Methocel™ E5, and Avicel® PH-101 intra-granularly, and carnauba wax powder extra-granularly, while F6-F10 formulas prepared by a melt-granulation technique using carnauba wax powder intra-granularly, and Eudragit® L100-55, Methocel™ E5, and Avicel® PH-101 extra-granularly. However, F6-F10 formulas showed undesirable *in-vitro* drug release results, whereas tablets completely disintegrated and released the drug within 8 h. This may be attributed to the low concentration of carnauba wax in comparison to RZ. Besides, in case of increasing the concentration of carnauba wax, the total tablet weight would be higher than 1800 mg, since the optimal experimental ratio between carnauba wax and RZ was 0.5:1 (w/w), which is considered unfavorable for patient acceptability, safety, and access. Furthermore, the uses of pH-dependent (Eudragit® L100-55) and pH-independent (Methocel™ E5 and Avicel® PH-101) polymers in higher concentrations exceeding the concentration of film-forming polymer (carnauba wax) were relatively essential to form a stable ternary polymeric matrix system with controlled release properties. Therefore, F1-F5 were selected for further comparative studies.

Evaluation of the prepared tablets

The prepared tablets were evaluated in terms of the weight uniformity, hardness, friability, thickness, diameter, and content uniformity, as shown in Table 2.

Table 2: Characterization of the prepared tablets

Method	Formula code	Weight (mg) (Mean±SD) (n=20)	Weight variation (%RSD)	Hardness (kP) (Mean±SD) (n=10)	Friability (%) (Mean±SD) (n=20)	Thickness (mm) (Mean±SD) (n=3)	Diameter (L) × (W) (mm) (Mean±SD) (n=3)
Wet- granulation	F1	1300±0.08	1.44	33.3±0.07	0.09±0.03	7.00±0.09	(23±0.09) × (8.6±0.12)
	F2	1300±0.10	1.68	33.0±0.06	0.11±0.10	7.23±0.11	(23±0.05) × (8.6±0.22)
	F3	1300±0.17	1.73	30.8±0.05	0.12±0.09	7.00±0.03	(23±0.04) × (8.6±0.14)
	F4	1300±0.09	1.40	32.1±0.02	0.10±0.06	7.00±0.02	(23±0.04) × (8.6±0.20)
	F5	1300±0.18	1.81	30.8±0.02	0.12±0.11	7.00±0.02	(23±0.02) × (8.6±0.21)
Melt- granulation	F6	1300±0.33	3.69	34.6±0.22	0.05±0.08	7.01±0.02	(23±0.03) × (8.6±0.09)
	F7	1300±0.28	4.50	35.3±0.40	0.04±0.07	7.02±0.06	(23±0.02) × (8.6±0.08)
	F8	1300±0.40	4.19	34.8±0.67	0.07±0.11	7.03±0.05	(23±0.03) × (8.6±0.10)
	F9	1300±0.48	5.63	33.7±0.83	0.08±0.13	7.03±0.09	(23±0.04) × (8.6±0.09)
	F10	1300±0.63	5.90	33.1±0.91	0.10±0.15	7.02±0.08	(23±0.03) × (8.6±0.10)

The percentages of weight variations in the prepared tablets ranged from 1.40 to 5.90%, which fall within the acceptable weight variation range of (± 5%). The hardness values ranged from 30.80 to 35.30 kP, which complied with the set range of 30–32 kP as in case of formulations prepared by wet-granulation technique, while tablets prepared by melt-granulation technique showed a little bit higher hardness values due to the presence of carnauba wax powder intra-granularly, which increases the physical resistance and porosity of tablets by forming a porous microstructural matrix. The friability values of the prepared tablets ranged from 0.04 to 0.12%, which are acceptable, hence tablets pass the test if not more than 1% of the weight of the tablets was lost. The tablet thickness ranged from 7.00 to 7.23 mm, with diameters of 23 mm±0.2 as length (L), and 8.6 mm±0.2 as the width (W), which are accepted orally. Content uniformity of the prepared formulations ranged from 95.18 to 98.57%, with RSD values ranging from 0.288 to 0.890, which were within the set range of 90–110% [16,20].

The effect of microenvironmental pH modulation (pH^M) on dissolution behavior

Microenvironmental pH modulation (pH^M) is a promising approach to modify the release rates of pH-dependent and ionizable drugs. In general, in case of dissolution-enhancement, and for a weakly basic drug that is primarily deprotonated and non-ionized in intestinal fluid, an acidifying agent is preferably used to enhance the drug dissolution rates by decreasing the pH^M of the dosage form, while in case of a weakly acidic drug, an alkalizing agent is used to increase the drug dissolution rates by increasing the pH^M of the dosage form. Conversely, in controlled-release, an alkalizing agent is commonly used to control the dissolution rates of a weakly basic drug by further increasing the pH^M of the dosage form, while in case of a weakly acidic drug, an acidifying agent is preferable to use [31-33].

In addition, the Noyes-Whitney's equation typically described the relationship between the dissolution rate and the solubility of the drug in both phases; the diffusion layer and the surrounding medium, as shown in equation 13 [34]:

$$\frac{dC}{dt} = \frac{D.S}{h} \times (C_{ss} - C_b) \quad (13)$$

Where dC/dt is the rate of dissolution, D is the diffusion coefficient of the drug substance, S is the effective surface area of drug particles, h is the diffusion layer thickness, C_{ss} is the concentration of saturated solution at the solid surface, and C_b is the bulk concentration.

Hence, drug diffuses out from the solid dosage form surface; the microenvironment is the diffusion layer which is formed around the dissolved drug particles. For hydrophilic polymeric matrix systems, the initial stage of the drug release process involves drug diffusion from the surface of the solid dosage form, along with other water-soluble components. Since the gel layer is formed, the saturated solution of water-soluble components entrained within the hydrated polymer gel layer is referred to as microenvironment [34].

Based on the principles of Noyes-Whitney's equation, the pH of the diffusion layer affects the dissolution rates of weakly acidic and basic drugs. Thus, the addition of a pH-modifier leads to alter the concentration of the drug at the excipient-drug interface, change the boundary layer thickness, and hence enhance or retard the drug dissolution rates, depending on the type and concentration of pH-modifier [32,33].

Furthermore, according to Korsmeyer–Peppas equation (10) to investigate the mechanism of drug release [25], an exponent (n) value of 0.45 indicates that the release mechanism is mostly diffusion-controlled (Fickian release), while in case of (n) value of 0.89, indicating that the release mechanism is primarily swelling-controlled (Case II transport or purely relaxation-controlled), and if (n) value in between of 0.45 and 0.89, indicating anomalous transport release kinetics (a combination of pure diffusion and Case II transport). In fact, Korsmeyer–Peppas equation can elucidate whether the addition of pH-modifier alters the drug dissolution rates or not. Whereas controlled release formulations composed of the drug substances and polymers, without pH-modifiers, commonly exhibit zero-order release kinetics (Case II transport or purely-relaxation controlled), but by the addition of pH-modifiers results in anomalous transport release kinetics. Depending on the type and concentration of pH-modifier, a higher pH-modifier concentration leads to decrease the (n) value, increase the release constant (K) value, and subsequently increase drug diffusivity, and *vice versa* [32,33].

On the other hand, the release rate of pH-modifier, and the extent of pH^M maintenance in the dosage form play significant roles in controlling drug dissolution from the dosage form, whereas the release rate of pH-modifier is proportional to the drug release rate and follows the same drug release mechanism [35-37], while the extent of pH^M maintenance in the dosage form correspondingly reflects the solubility of pH-modifier, hence pH-modifiers with high water solubility tend to dissolve immediately in the penetrating medium, then quickly diffuse out. In turn, pH-modifiers with low saturation solubility are more likely to stay inside the dosage form in sufficient amounts for an extended period to maintain a certain pH level of poorly water-soluble drugs [32,33]. Accordingly, pH^M of the dosage form can be ideally modulated if the pH-modifier is present inside the tablet matrix with proper concentration. Therefore, the proper selection of pH-modifier type and concentration is quite crucial for understanding the drug release pattern and mechanism from such pH-modulating systems.

RZ is a very slightly water-soluble, pH-dependent drug with 3 pKa values of 13.4 (acidic), 6.91 (basic), and 2.91 (basic) [8]. Therefore, modulation of the pH^M inside the dosage form to yield a pH-dependent sustained release of the functional polymers was a prerequisite to control the release of RZ from the polymeric matrix. Due to the basicity and low solubility of RZ, particularly in alkaline pH, a potent alkalinizing agent

as NaOH was sequentially added to control the pH^M of the dosage form. Hence, the mechanism of pH-modifier in controlling the pH^M can be quantitatively evaluated by pH^M determination or examination of pH-modifier release methods [32,33], whereas pH^M determination method is clearly observed as a function of time at different fractional dimensions of tablets [31], the dissolution-modulated behavior of RZ was initially evaluated in the suitable media; 0.1N HCl (pH 1.2), at three consecutive time-points, followed by evaluated in phosphate buffer solution (pH 6.8), and analyzed spectrophotometrically at 272 nm. Basically, the ideal pH^M modulation mainly occurs when the release rate of pH-modifier is similar to or slower than the drug release rate during the dissolution process. For instance, in case of the suitable media; 0.1N HCl (pH 1.2), at 30 min time-point, the percentage of RZ released was 16.53%, indicating that 83.47% of NaOH remained in the tablet matrix; at 2 h time-point, the percentage of RZ released was 34.33% (percentage increased by ~50%); while at 4 h time-point, the percentage of RZ released was 46.15% (percentage increased by ~25%), indicating that 53.85% of NaOH still remained in the tablet matrix, which was sufficiently effective to modulate the pH^M of the dosage form during the rest of the dissolution process. We may, therefore, conclude that the release rate of NaOH was almost similar to the release rate of RZ. On the other hand, to determine the optimum concentration of NaOH, experimental formulations were sequentially prepared by different concentrations of NaOH ranging from 0.1 to 0.9% (w/w), and evaluated separately in two different dissolution media; 0.1N HCl (pH 1.2) and phosphate-buffered solution (pH 6.8). Consequently, the percentages of RZ released were gradually decreased with increasing the concentration of NaOH until a constant release (plateau) was obtained at both dissolution media. As a result, NaOH in a concentration of 9.1 mg/tablet (0.7 gm% w/w) was found to be sufficiently effective in controlling the dissolution behavior of RZ in all dissolution media.

The modulatory effect of polymer concentration and type on drug release

The modulatory effect of polymer concentration and type on drug release from sustained-release matrix tablets of RZ was further investigated, as shown in Table 3. Eudragit® L100-55 copolymer is an anionic copolymer of methacrylic acid and ethyl acrylate initially dissolves at pH level above 5.5 (i.e., Eudragit® L100-55 inhibits the release of RZ from the matrix tablets in the stomach where pH level below 5.5 and promotes its release in the lower gastrointestinal tract where pH level above 5.5), while Methocel™ E5 is a non-ionic, pH-independent hydrophilic polymer of HPMC with good absorption, swelling, and controlled release properties, Avicel® PH-101 is a pH-independent hydrophilic polymer of microcrystalline cellulose with good adhesive and cohesive properties [38]. The release process from the hydrophilic polymeric matrix of Methocel™ E5 and Avicel® PH-101 is a dynamic process, involving a sequence of polymeric transformation as polymer wetting, hydration, gel formation, swelling, and finally polymer dissolution. However, the release mechanisms involved in controlling drug release from hydrophilic polymer matrix systems are interchangeable, and primarily influenced by other factors, such as physicochemical properties of polymers, pH-modifier solubility and the design of the dosage form, the key mechanism relies on the presence of water-soluble polymers inside the tablet matrix, which gradually hydrate on the outer

Table 3: Modulatory effect of polymer concentration and type on drug release

Formula code	Experimental ratio (w/w)			Film-forming polymer (g%)	Comparative dissolution		
	pH-dependent polymer	pH-independent polymer			f_2		
	Eudragit® L100-55	Methocel™ E5	Avicel® PH-101	Carnauba wax	pH 1.2	pH 4.5	pH 6.8
F1	1.3	1.0		2.00	72	52	45
		0.36	0.64				
F2	1.6	1.0		2.25	48	93	49
		0.44	0.56				
F3	1.5	1.0		2.50	46	70	36
		0.69	0.31				
F4	1.2	1.0		2.50	64	87	47
		0.48	0.52				
F5	1.0	1.3		2.50	59	72	57
		0.48	0.52				

f_2 refers to similarity factor; comparative dissolution was carried out against the reference product, Ranexa® extended release film coated tablets (Gilead Sciences, Inc., USA).

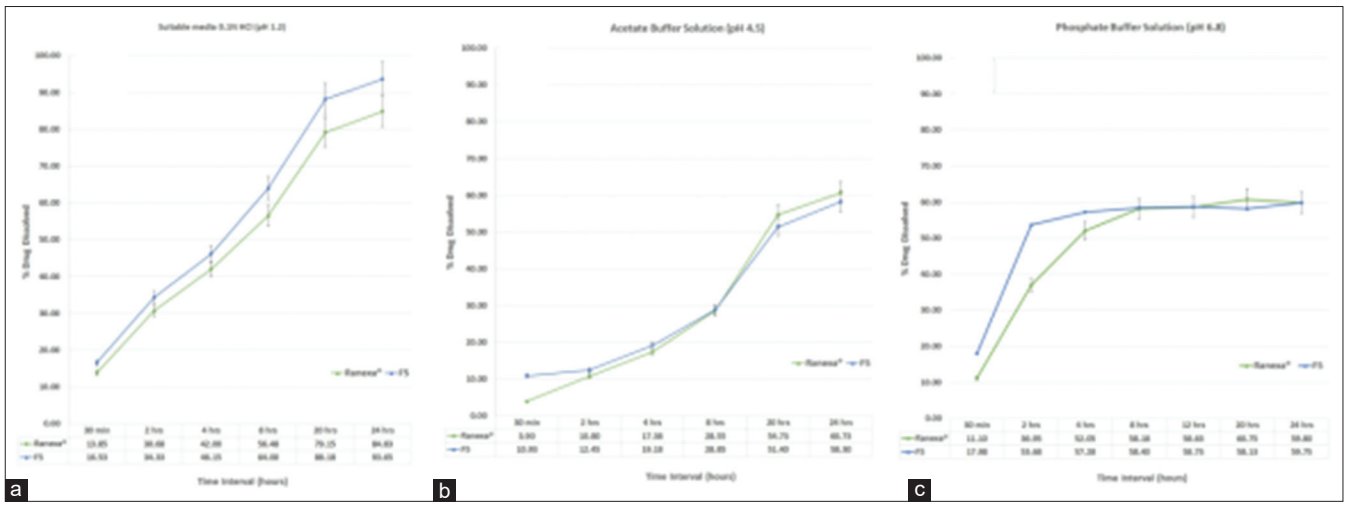

Fig. 2: Ranolazine sustained release profile from F5 and Ranexa® extended-release film-coated tablets (Gilead Sciences, Inc., USA); (a) at suitable media: 0.1N HCl (pH 1.2), (b) at ABS (pH 4.5), (c) at PBS (pH 6.5)

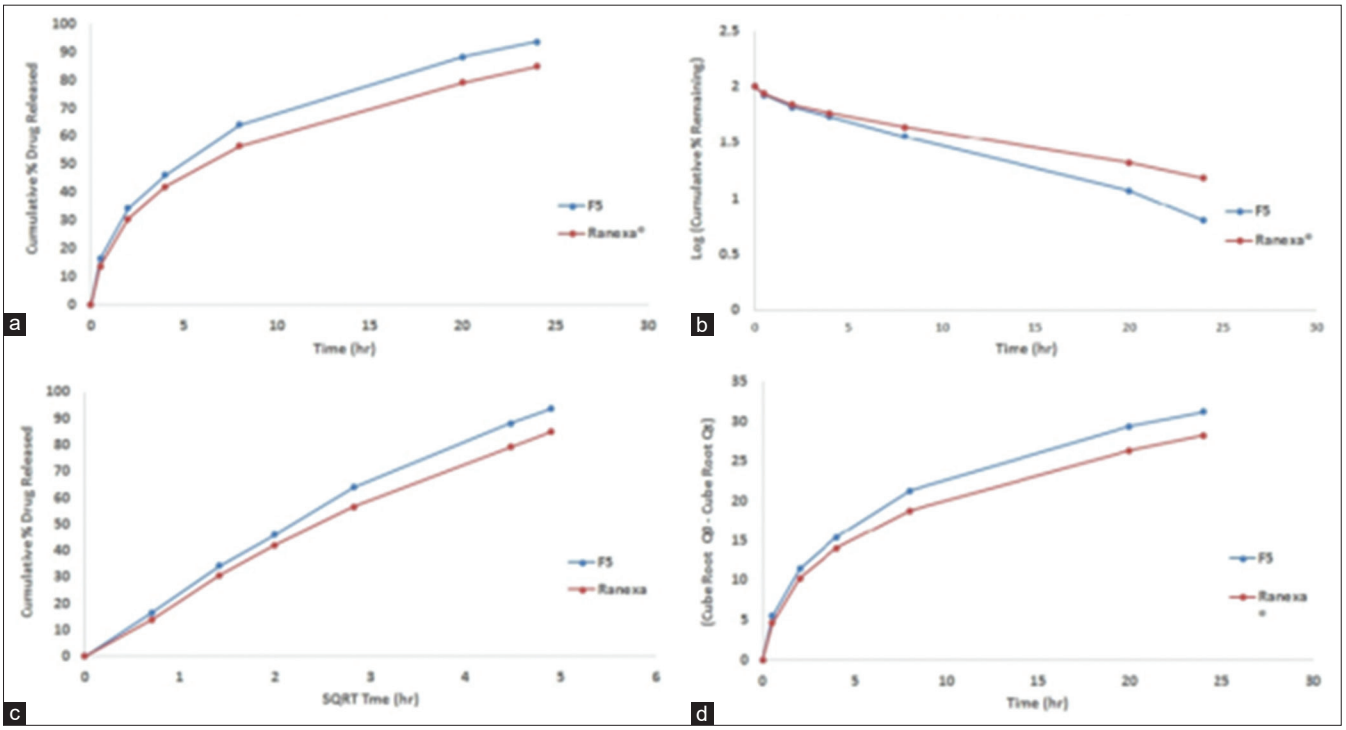

Fig. 3: Release kinetics of F5 formula and Ranexa® extended-release film-coated tablets (Gilead Sciences, Inc., USA); (a) at zero-order release, (b) at first-order release, (c) at Higuchi release model, at (d) Hixson-Crowell release model

surface of the matrix structure to form a gel layer. Accordingly, the drug substance is naturally released from the hydrophilic matrix system by diffusion through the gel layer, and by the rate of tablet erosion [39,40]. Alternatively, carnauba wax is a hydrophobic wax polymer with a melting point of 80–88°C, exhibits good plasticizing and barrier properties. It is characterized by the formation of highly porous matrix granules with a large surface area, which allows diffusion to occur spontaneously [38]. To form a stable ternary polymeric matrix system, a combination core of pH-independent, pH-dependent, and film-forming polymers was evaluated together in different ratios and concentrations (Table 3). From these results, we may conclude that the optimum ratio between pH-dependent (Eudragit® L100-55) and pH-independent (Methocel™ E5 and Avicel® PH-101) polymers was 1:1.3 (w/w), with an extragranular film-forming carnauba wax in a concentration of 32.50 mg/tablet (2.50 g% w/w). Based on the aforementioned results, F5 formula was selected for further *in-vitro* and comparative dissolution studies against the reference product.

***In-vitro* and comparative dissolution**

The cumulative percentage release of RZ from the selected formula (F5) compared to the marketed product, Ranexa® extended-release film-coated tablets (Batch no.: AE2765BA, Expiry date: 06/2020) is shown in Fig. 2. As shown in Table 4, f_2 value (similarity factor) is close to 50 on comparing F5 to Ranexa® extended-release film-coated tablets, while f_1 (difference factor) is lower than 15, indicating that the two dissolution profiles are considered similar.

Table 4: Similarity (f_2) and difference (f_1) factors on comparing F5 formula to Ranexa® extended-release film coated tablets

Factor	0.1N HCl (pH 1.2)	Acetate buffer solution (pH 4.5)	Phosphate buffer solution (pH 6.8)
f_2	59.09	72.10	56.97
f_1	11.68	9.39	9.43

Drug release kinetics and analysis of dissolution data

The data obtained from *in-vitro* drug release were evaluated using zero-order release kinetics (Fig. 3a), first-order release kinetics (Fig. 3b), Higuchi release model (Fig. 3c), and Hixson-Crowell release model (Fig. 3d). Kinetically, as shown in Table 5, F5 formula was found to follow first-order release kinetics and Higuchi release model, but best fitted to first-order release kinetics with a coefficient of determination or R-squared (R^2) equals to 0.9925, followed by Higuchi release model with an R^2 equals to 0.9873. This finding was to some extent in accordance with other reported works by Asaduzzaman *et al.* [16] and Rahman *et al.* [18]. The good first-order R^2, which is close to unity, was mainly due to the drug load, porous matrix structure and release mechanism, i.e., the first-order plot of F5 formula showed good linearity, indicating that the amount of drug released is dependent on the matrix drug load and matrix porosity. This may be attributed to the presence of extragranular carnauba wax, which increases tablet porosity and matrix pore size. Moreover, the release profile of F5 formula showed well-fitting with Higuchi release model, indicating that the drug is released by diffusion mechanism due to the presence of cellulosic polymers in high concentrations. In turn, Ranexa® extended-release film-coated tablets showed well-fitting with Higuchi release model with an R^2 equals to 0.9887, followed by first-order release kinetics with an R^2 equals to 0.9834. This may be attributed to the functional coating system and less or non-porous matrix structure of Ranexa® tablets. In spite of the fact that controlled release drug delivery systems exhibit a constant concentration (plateau) and zero-order release kinetics, in sustained and extended-release drug delivery systems, the drug release behavior would be over an extended period of time, and thereby zero-order release kinetics would not be attained, except in the case of osmotic-controlled release oral delivery systems [12,13,41].

To further identify the release mechanism of RZ drug substance from the polymeric matrix tablets, Korsmeyer–Peppas equation was applied by fitting the dissolution data (up to 60% of drug release) into Korsmeyer–Peppas model [25]. As shown in Table 6, F5 formula showed an exponent (n) value of 0.472 with a (K) equals to 24.070 and R^2 equals to 0.9997, indicating that the release mechanism follows anomalous transport release kinetics, i.e., a combination of pure diffusion and Case II transport. In a diffusion-controlled release, the solvent transport rate of diffusion is higher than the process of polymeric chain relaxation. Hence, absorption equilibrium and release pattern occur rapidly on the surface of polymeric

Table 5: Y-equation (Y = aX + b) and coefficient of determination (R^2) of F5 formula and Ranexa® extended-release film-coated tablets

Formula code	Zero-order release kinetics		First-order release kinetics		Higuchi release model		Hixson-Crowell release model	
	Y-equation	R^2	Y-equation	R^2	Y-equation	R^2	Y-equation	R^2
F5	Y=3.360X+20.900	0.8677	Y=−0.046X+1.944	0.9925	Y=18.944X+4.808	0.9873	Y=1.120X+6.967	0.8677
Ranexa®	Y=3.048X+18.383	0.8724	Y=−0.032X+1.932	0.9834	Y=17.152X+3.864	0.9887	Y=1.016X+6.128	0.8724

matrix structure, leading to a condition of time-dependent. In addition, the matrix tablets undergo swelling-controlled, indicating that the polymer relaxation also plays a significant role in the drug release. However, the effect of drug diffusion was higher than the effect of polymer relaxation as the (n) value was closer to 0.50. In turn, Ranexa® extended-release film-coated tablets showed an exponent (n) value of 0.474 with a (K) equals to 21.359 and R^2 equals to 0.9986, indicating that the release mechanism also follows anomalous transport release kinetics. This finding was in accordance with other reported works by Asaduzzaman *et al.* [16] (Higuchi release model, and non-Fickian/anomalous transport release kinetics), Rahman *et al.* [18] (Higuchi release model, and non-Fickian/anomalous transport release kinetics, and Uddin *et al.* [17], which they evaluated four different grades of cellulosic polymers, namely, Methocel™ E50, Methocel™ K100 LV CR, Methocel™ K4M CR, and Methocel™ K15M CR and concluded that the drug release rate from the tablet matrix was significantly influenced by the proportion and viscosity grade of HPMC, where the release rate was dependent on diffusion and polymer relaxation in cases of higher proportion and grades of HPMC, while in cases of lower proportion and grades, the release rate was governed by Fickian diffusion. Furthermore, increasing the proportion of polymers would significantly increase the (n) value, leading to shifting the release mechanism from Fickian to non-Fickian transport [17].

To evaluate the retarding efficacy of the polymer on drug release, MDT was determined [27]. A higher MDT value refers to higher retaining efficacy of the polymer material, and *vice versa* [17]. As shown in Table 6, MDT values of F5 formula and Ranexa® extended-release film-coated tablets were found to be almost similar, indicating the medium polymer retarding efficacy of these formulations. For further dissolution profiles' comparison, the dissolution efficiencies (DE%) of F5 formula and Ranexa® extended-release film-coated tablets were evaluated [26].

Table 6: Drug release rate parameters of Korsmeyer–Peppas equation for F5 formula and Ranexa® extended release film coated tablets

Release parameters	K	n	SSD	R^2	MDT (h)	DE (%)
Formula code						
F5	24.070	0.472	1.644	0.9997	4.720	71.88
Ranexa®	21.359	0.474	4.556	0.9986	4.804	70.96

Rate constant (K); release exponent (n); SSD: sum of the squared difference; coefficient of determination (R^2); MDT: mean dissolution time; DE: dissolution efficiency

In general, formulations are considered equivalent if the difference in between their dissolution efficiencies and the reference product is within (±10%) [27,42]. As shown in Table 6, the difference of DE% between F5 formula and Ranexa® extended-release film-coated tablets is less than 10%, indicating that both formulations are equivalent. Furthermore, the dissolution efficiencies of F5 formula and Ranexa® extended-release film-coated tablets were higher than 70%, confirming the similarity between those formulations.

Accelerated stability studies

The results of accelerated stability studies of F5 formula (Table 7) showed that there were no significant changes in the appearance, assay or dissolution profiles of the prepared tablets, no degradation products were detected, and friability of the tablets, when stored in HDPE bottles, remained unchanged.

CONCLUSION

A sustained-release dosage form of RZ was successfully formulated and optimized using a blend of pH-dependent, pH-independent, and film-forming polymers, aiming at controlling the drug release rates for a period of 24 h. Modulation of the microenvironmental pH using a potent alkalinizing agent was very effective in controlling the release profiles of RZ from the matrix tablets in different dissolution media. Extragranular carnauba wax was the key excipient in controlling the drug release pattern by forming waxy granules with a porous microstructural matrix which prevent rapid dissolution.

The prepared tablets are advantageous over the marketed product by being in the form of sustained-release uncoated tablets, where no functional coating system is required, and manufactured by the wet-granulation technique using conventional excipients, hence no need for high-functionality excipients or high-tech machinery for scale-up production. Besides, the ternary polymeric matrix system is more stable and showed sustained release profiles for a period of 24 h. Further bioequivalence studies are requested for the proof of concept.

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Table 7: Characterization of F5 formula after 6 month of storage

Formula code	Weight uniformity (RSD%)		Hardness (kP) (Mean±SD) (n=10)		Friability (%) (Mean±SD) (n=20)		Thickness (mm) (Mean±SD) (n=3)		Diameter (L) × (W) (mm) (Mean±SD) (n=3)	
F5	Initial	After 6 month	Initial	After 6 month	Initial	After 6 month	Initial	After 6 month	Initial	After 6 month
	1.81	2.11	30.8±0.02	30.22±0.66	0.12±0.11	0.26±0.44	7.00±0.02	7.00±0.09	(23±0.02) × (8.6±0.21)	(23±0.14) × (8.6±0.46)
	***In-vitro* drug release after 8-h at 0.1N HCl (pH 1.2) (%) (Mean±SD) (n=3)**				***In-vitro* drug release after 20-h at 0.1N HCl (pH 1.2) (%) (Mean±SD)(n=3)**				***In-vitro* drug release after 24-h at 0.1N HCl (pH 1.2) (%) (Mean±SD) (n=3)**	
	Initial		After 6 month		Initial		After 6 month		Initial	After 6 month
	64.00±3.71		62.40±2.14		88.18±1.10		85.90±1.45		93.65±1.00	91.78±0.84

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AUTHORS CONTRIBUTIONS'

All the authors have contributed equally.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interests.

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