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ORIGINAL ARTICLE

Formulation and Evaluation of Rizatriptan Benzoate Sublingual Tablet to Treat Migraine

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ABSTRACT
Migraine is a neurological condition marked by intense headaches, nausea, and heightened sensitivity to light and sound, necessitating prompt therapeutic intervention for optimal management. This study aimed to develop and assess Rizatriptan Benzoate sublingual tablets to facilitate expedited medication release, swift onset of action, and enhanced patient adherence in migraine treatment. Sublingual tablets of rizatriptan benzoate were manufactured via the direct compression technique, employing superdisintegrants like crospovidone and croscarmellose sodium at varying dosages. The formulations were assessed for parameters. Batch F9 emerged as the best optimised formulation, exhibiting satisfactory tablet attributes including hardness, minimal friability, and consistent medication content. The formulation demonstrated rapid wetting and disintegration in under 30 seconds, signifying that tablets dispersed swiftly under sublingual circumstances. In vitro dissolution experiments shown that over 99% of the medication was released within 10 minutes, signifying its immediate availability for absorption. The kinetic investigations of drug release demonstrated that the optimised formulation followed first-order kinetics, characterised by high regression coefficients, signifying concentration-dependent drug release. The study determined that Rizatriptan Benzoate sublingual tablets have rapid pharmacological action, superior dissolving, heightened bioavailability, and higher patient adherence, rendering them a viable choice for the effective treatment of acute migraine episodes.
KEYWORDS: *Rizatriptan Benzoate, Sublingual Tablet, Migraine, Croscarmellose Sodium, In-vitro Drug Release.*

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INTRODUCTION

Migraine is a neurological condition with a series of headache attacks. A wide range of issues related to the autonomic nervous system. Symptoms include photophobia, vomiting, visual abnormalities, and various neurological symptoms. An untreated migraine attack can disrupt or diminish the quality of life for those with migraines for 4-72 hours. This can be achieved by parenteral delivery, which may not be applicable in all cases. A non-parenteral and convenient sublingual formulation of the drug has been developed for sublingual administration, which results in a rapid absorption into systemic circulation and consequently a fast onset of action [1-3]. The thin sublingual mucosa is responsible for the quick onset of effect. The sublingual mucosa is 190 µm thick, whereas the buccal mucosa is 500-800 µm thick, and the high vascularization of the sublingual mucosa causes high plasma drug concentrations due to better absorption of the drug. The patient is apprehensive about the drug being installed sublingually. To absorb fluids independently with an efficiency of more than 200 µL. The drug is flushed out through the saliva and the drug for sublingual administration is washed out. It leaves the mouth cavity and goes into the gastrointestinal tract. The formulation should remain in contact with the wet surface of the sublingual mucosa to enhance interaction with the formulation as salivation will wash it off the mucosal surface. However, to overcome this limitation, some bioadhesive polymers, including chitosan are added in formulations [4,5]. Rizatriptan benzoate (RTB) belongs to a new class of drugs called selective and potent 5-HT1B and 5-HT1D receptor agonists. It is prescribed for the treatment of acute migraine (with or without aura) to help with the symptoms of migraine, including pain, nausea and photophobia (or

phonophobia). The half-life of Rizatriptan is 2-3 hours. It is somewhat permeable in the body and highly soluble and therefore is classified in BCS-III, Biopharmaceutical Classification System. The absorption is fast (up to 90%) and the absolute bioavailability is low. That is, almost 47% is due to the high first-pass effect when administered orally [2,7,8]. The aim of our research is to prepare RTB sublingual tablet which will be able to avoid first pass metabolism and will possess a rapid action. Bioadhesive polymers such as chitosan, combined with superdisintegrants Croscarmellose Sodium (CCS) and Crospovidone were used to formulate RTB sublingual tablets. The dissolution is largely uniform, and, at the same time, encourages the continued contact with the sublingual mucosa [9]. The tablets thus prepared were then evaluated on their physiological parameters such as in vitro dissolution study.

MATERIAL AND METHODS

Materials

All the subsequent materials were purchased from commercial sources and used in the formulation. Swapnroop Drugs & Pharmaceuticals has acquired the drug 'Rizatriptan Benzoate'. Further excipients were obtained from the various manufacturers such as Croscarmellose and Crospovidone (Chempure Pvt Ltd) and Lactose, Chitosan, Talc, Magnesium stearate and Aspartame (SD Fine Chemicals Pvt Ltd) Pune, Maharashtra, India.

Equipment uses

The equipments purhased from commercial sources for formulation are digital weigh balance (Shimadzu, Japan), single rotary compression machine (Lab Press 8 station), disintegration tester (Electro lab), dissolution apparatus (Electro lab TDT 08L), UV-VIS spectrophotometer (Jasco V630) and glassware (Borosil).

Drug-Excipients Interactions

To test the compatibility of the drug and excipient, FTIR spectrometry was used. FTIR spectra of the drug alone and drug-excipient physical mixtures (1:1 w/w) were obtained from a Shimadzu instrument in Japan [11,12].

DSC Analysis

analyses were carried out to examine the thermal properties and compatibility of Rizatriptan Benzoate with some polymers. There was a very sharp endothermic peak at 184°C – this was the melting point of the pure compound. Thermogram changes showed interactions with polymers: Crospovidone and Croscarmellose Sodium. But there were no significant interactions with excipients such as Crospovidone, Croscarmellose Sodium. The results showed that there are some polymers that can be compatible with Rizatriptan Benzoate while some should be considered carefully in the formulation process [12,13].

Formulation of Sublingual Tablet of Rizatriptan Benzoate

The tablets of Rizatriptan Benzoate are made using the direct compression method. For the sublingual pill the Direct Compression method was chosen, based on the flow parameters, the particle qualities, and the compressibility. The quantity of all the components (Rizatriptan Benzoate, Croscarmellose Sodium, Crospovidone, chitosan and aspartame) were precisely weighed as per the formulation specifications. Agglomerates were removed from each component by passing through a #60 mesh sieve to ensure uniformity in particle size distribution. The medicine and excipients (except for the lubricant and glidant) were then added to an appropriate container and mixed thoroughly for 10-15 minutes to form a homogeneous mixture. The lubricant, magnesium stearate, and glidant, talc, were sifted through a #80 screen before adding to the powder blend.

Table 1: Composition of 12 runs with different composition and different concentration of Croscarmellose and Crospovidone

Ingredients	**Batches**											
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Rizatriptan Benzoate	5	5	5	5	5	5	5	5	5	5	5	5
Croscarmelose Sodium	**2**	**3.5**	**5**	**2**	**3.5**	**5**	**2**	**3.5**	**5**	**3.5**	**3.5**	**3.5**
Ccrospovidon	**2**	**2**	**2**	**3.5**	**3.5**	**3.5**	**5**	**5**	**5**	**3.5**	**3.5**	**3.5**
Chitosan	10	10	10	10	10	10	10	10	10	10	10	10
Aspartame	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Lactose	76.0	74.5	73.0	74.5	73.0	71.5	73.0	71.5	70.0	73.0	73..0	73.0

The liquid was added in a slow manner in order to achieve uniform dispersion in it without over-lubrication, and it was mixed for 2-3 minutes. The powder mixture was then compressed into tablets

using a Lab Press, 2-Station, single punch tablet compression machine with flat faced 2 mm punches. The formulated tablets were collected and stored in sealed containers in a controlled atmosphere for further evaluation. The complete composition of all 12 formulations (NF1 - NF12) is given in the table 1 [14,15].

Pre-compression Parameters

Angle of repose

The angle of repose is found out via the following methods: Fixed funnel method. The method is based on pouring the powder from a funnel at a given height (H) on a horizontal surface and forming a pile of powder in the shape of a cone. The angle of repose (θ) is found by:tan θ = H/RT R is the radius of measured base.his method is based on measuring the flow properties of powder. Angles less than 5 degrees are okay for flow [14,15].

Bulk Density

A known weight of powder was put into a 50 mL graduated cylinder and the initial volume was read without tapping to get the loose bulk density (LBD). Tapped bulk density (TBD) was determined by tapping the cylinder up to a constant volume.

These latter were computed with the following formulas:

Mp = mass of powder in grams, Volume of powder sample = Vp (ml)

The mass of the powder (tbd) is divided by the taped volume.

These properties can be used to describe the flow and packing properties of powders.

Compressibility index of Rizatriptan Benzoate powder

Carr's compressibility index and wells were utilised to determine compressibility.

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

Hausner's ratio

It can be calculated by the ratio (tapped density/bulk density). The Hausner's ratio is the ratio of Tapped density to Bulk density.

Tablet compression and characterization of compressed tablet

The powder mixture with Rizatriptan Benzoate was lubricated with magnesium stearate and talc. In order to make sublingual tablets, a formulation containing a 5 mg drug was compressed in a rotary tablet machine, with a 2 mm punch.

Post compression evaluation of Rizatriptan Benzoate Sublingual tablet

The tablets were described fast as per the recipe and Weight of 20 tablets was checked using electronic balance. P 1996. Roche type friabilator was used to test 18 tablets (10 tablets) for 4 minutes at 25 rpm. Monstanto hardness tester was used to measure the hardness of 10 tablets of each formulation. The thickness of 10 tablets was measured using Vernier-Electronic's calliper. The disintegration test was employed for recording the time for a complete disintegration of the tablet [16,17].

Drug content of sublingual tablet

10 pills were weighed and crushed in mortar and pestle. Each 10 cc of phosphate buffer pH 6.8 was used to dilute 10 mg equivalent of Rizatriptan Benzoate powder. The sample was filtered and the amount of the drug was determined by UV spectrophotometry at 223 nm.

Dissolution study of sublingual tablet

The fast-disintegrating sublingual tablets were tested in vitro in USP dissolution device type II. The dissolution media used was 900ml of phosphate buffer (6.8 pH) and the tablet was dissolved in a dissolution flask. The flask was kept at a constant temperature, 370 ± 0.50°C, in a constant temperature bath. The motor was set at the desired speed (50 rpm) and 2, 4, 6, 8 and 10 minutes' worth of fluid was collected to determine the quantity of medication in the fluid [18,19].

Optimization of Sublingual tablet of Rizatriptan Benzoate

The design expert software was used for optimization of formulation of controlled release Rizatriptan Benzoate 5 mg. (CCD) was used as a standard protocol, which was based on the pre formulation study, with α = 1. The amount of study HPMC K100M and Eudragit Rs were used as independent factors and hardness and cumulative % drug release at 24 hr. act as dependent variable. Chose the middle point of the plane, (0,0). Knows how to summarise 9 run studies [25].

Table 2: Levels of independent variables

Variable	Low (-1)	High (+1)
Croscarmellose Sodium	2	5
Crospovidone	2	5

Drug release kinetic study

In vitro release study was performed using various kinetic models, namely zero-order, Hixson, first-order, Higuchi and Korsmeyer-Peppas. The interpretation was carried out and recorded according to the values of the regression coefficient [20-23].

RESULTS AND DISCUSSION

Physical compatibility of drug excipients

The peaks at ~3128cm-1, ~1610cm-1 and ~662cm-1 were characteristic peaks of N-H stretching, aromatic C=C stretching and C-H bending vibrations in Rizatriptan benzoate respectively. The excipients Croscarmellose sodium and Crospovidone, which are characteristic of these substances, could be seen in their FTIR spectra in accordance with the corresponding functional groups in the specified substances.The spectra of physical mixture of medication and excipients showed all the key characteristic peaks of Rizatriptan benzoate without any notable shift or disappearance or production of new peaks. It suggests that the medicine can be compatible with the selected excipients by the correlation of the spectra. (Figure 1 illustrates)

Differential scanning calorimetry analysis

The exhibited a strong and well-defined endothermic peak at around 184°C which corresponded to melting point. This is the maximum intensity as a result of the purity and crystal structure of the drug.The DSC thermogram of the tablet formulation revealed a wide endotherm at 150°C which is less than the pure drug itself. The difference in melting temperature to lower value and the broadening of the peak is suggestive of a decrease in crystallinity of the medication.

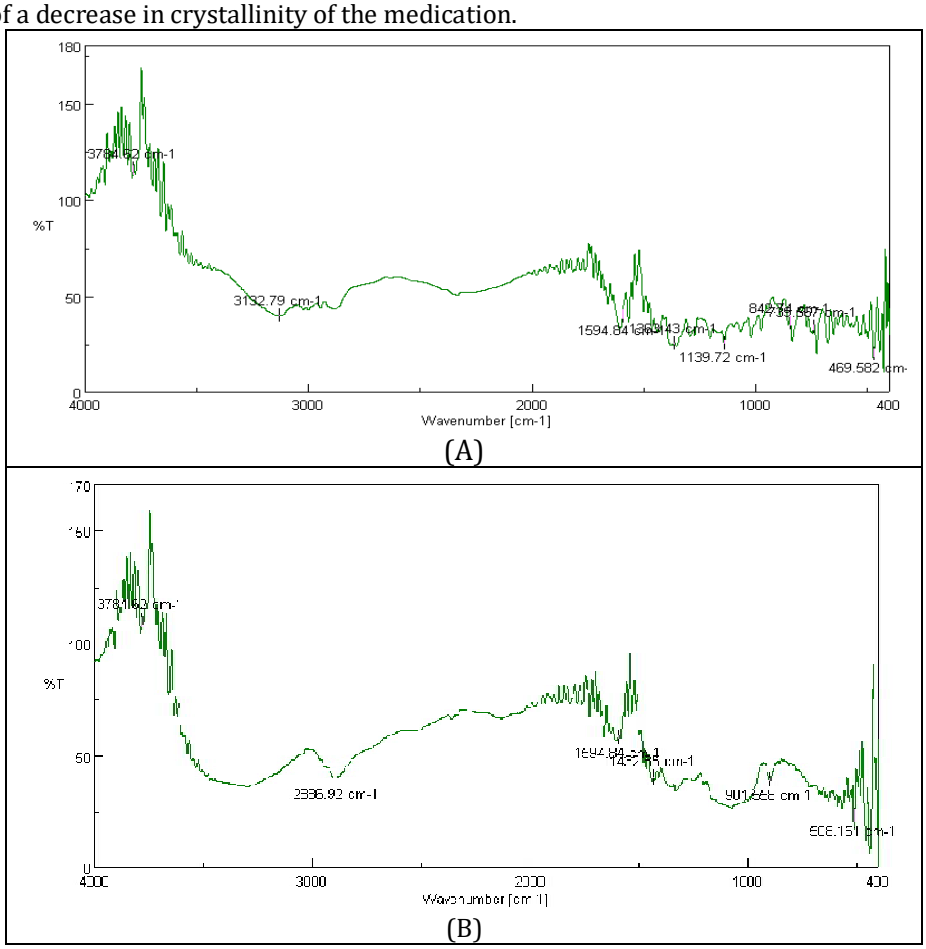


Figure 1: FTIR of (A) Pure Rizatriptan Benzoate and (B) Rizatriptan with polymers

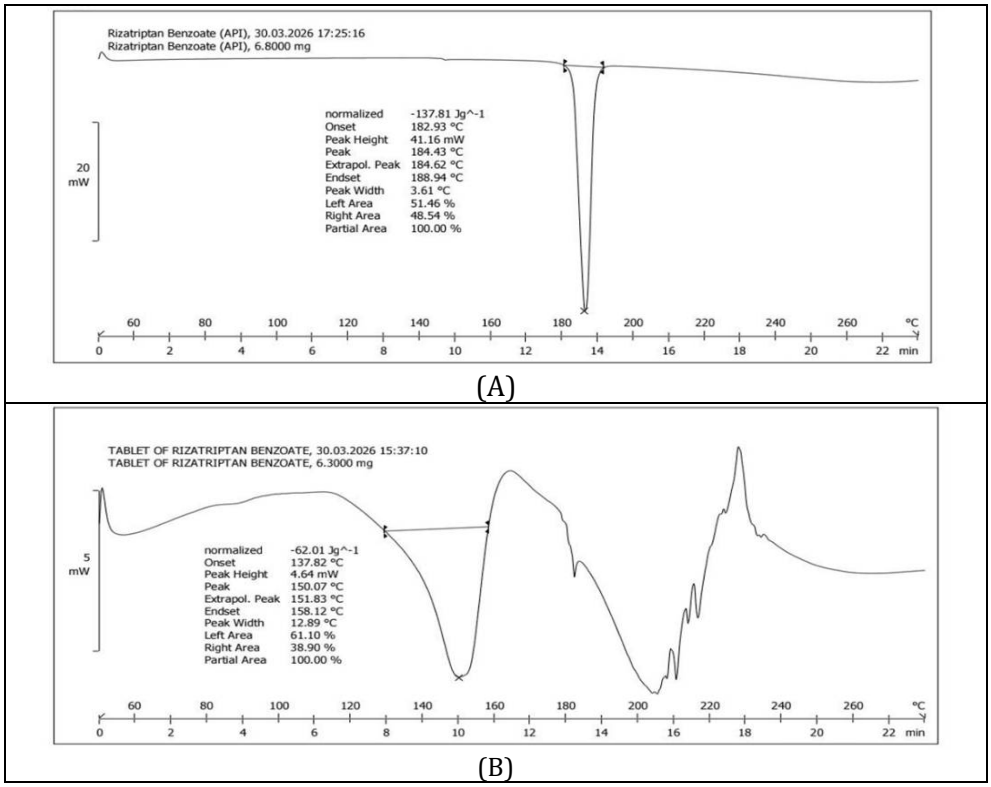


Figure 2: DSC thermogram of (A) Pure Rizatriptan Benzoate & (B) Rizatriptan Benzoate Tablet

Pre-compression study

All batches prior to compression had good flow properties. All the results obtained were found to be acceptable for the angle of repose (26.50 – 29.60), bulk density of the material (0.44 – 0.48 g/cm3), tapped density of the material (0.52 – 0.54 g/cm3), Carr's index (11.1% – 15.4 %), and Hausner ration (1.12 – 1.18) which indicated that the material flowed well (Table 3).

Table 3: Pre compression study.

Batch	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (θ)
F1	0.44	0.52	15.4	1.18	29.6
F2	0.45	0.53	15.1	1.17	29.1
F3	0.45	0.52	13.5	1.16	28.7
F4	0.46	0.53	13.2	1.15	28.2
F5	0.46	0.52	11.5	1.13	27.9
F6	0.47	0.53	11.3	1.13	27.5
F7	0.47	0.53	11.3	1.13	27.1
F8	0.48	0.54	11.1	1.12	26.8
F9	0.48	0.54	11.1	1.12	26.5
F10	0.47	0.54	13.0	1.15	26.9
F11	0.46	0.53	13.2	1.15	27.4
F12	0.45	0.53	15.1	1.17	28.0

Values are expressed as mean ± SD; n = 3.

Post-compression analysis

The average weight of tablets was between 99 and 101. The prepared tablets of all the formulations were relatively strong with regard to its pharmaco-technical criteria, with a thickness of the tablet of 2.5 mm to 2.7 mm. The friability of the tablets obtained after producing the sublingual tablets 0.31-0.45 % were in the above range. Hardness of the tablets was determined, and it was found to be within the range of 2.3-2.6 kg/cm2. The range of the drug content of the tablets tested was 96.2 ± 1.8 to 100.8 ± 0.7 of the stated value, and the drug content standard was met (Table 4).

Table 4: Post compression study of sublingual tablet.

Batch	Avg. Weight (mg)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Wetting Time (sec)	Disintegration time (sec)	Water absorption ratio (%)	Drug Content (%)
F1	101	2.7±0.03	2.5	0.42	48	13	48.6±2.1	96.2±1.8
F2	100	2.7±0.04	2.3	0.45	45	15	52.4±2.0	97.4±1.6
F3	100	2.6±0.05	2.5	0.41	38	16	56.2±1.9	98.1±1.5
F4	100	2.6±0.02	2.5	0.40	36	14	60.8±1.8	98.9±1.3
F5	99	2.6±0.03	2.5	0.38	34	17	65.5±1.6	99.3±1.2
F6	99	2.5±0.04	2.6	0.34	30	13	70.2±1.5	99.7±1.1
F7	99	2.5±0.03	2.4	0.36	27	18	75.8±1.4	100.1±1.0
F8	101	2.5±0.02	2.5	0.32	24	15	80.6±1.2	100.4±0.9
F9	100	3.5±0.03	2.4	0.31	22	12	86.4±1.0	100.8±0.7
F10	101	2.6±0.04	2.3	0.33	26	16	82.1±1.1	100.2±0.9
F11	99	2.6±0.03	2.4	0.37	33	13	76.9±1.3	99.6±1.1
F12	99	2.7±0.05	2.6	0.40	44	17	71.4±1.5	99.0±1.3

Assay of *In-vitro* drug release

in-vitro drug release tests of Rizatriptan Benzoate sublingual tablets were conducted by extracting 5 mL samples at intervals of 0, 2, 4, 6, 8, 10, 12, and 15 minutes. The samples were examined with a UV spectrophotometer at 223 nm. The results indicated a fast drug release, exceeding 90% within 10 minutes and approaching 100% within 15 minutes. The fast-dissolving profile demonstrates the formulation's appropriateness for sublingual delivery and prompt alleviation of migraine symptoms. (Figure 3).

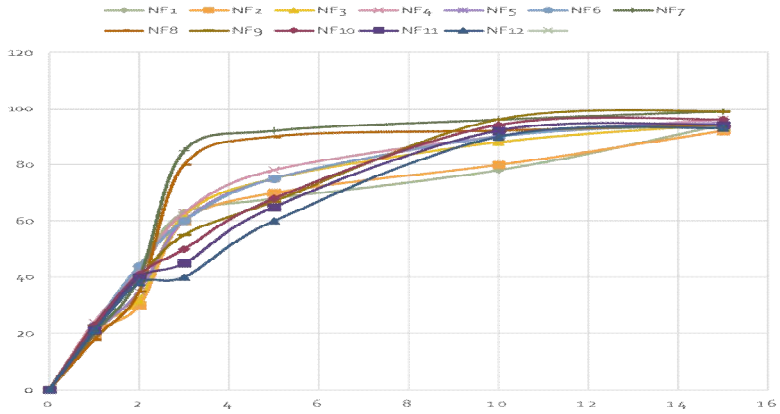


Figure 3: Cumulative % drug release profiles of Rizatriptan Benzoate Sublingual formulation as per experimental design.

Optimization of tablet

Disintegration Time (Y1)

Disintegration Time (Y1) Model Significance: The quadratic model is highly significant with a p-value < 0.0001. Factor Impact: Both superdisintegrants showed a pronounced negative effect, meaning increasing their concentration significantly reduces disintegration time. Dominant Factor: Factor A (Croscarmellose Sodium) has a much higher F-value (376.16) compared to Factor B (117.36), indicating it is the primary driver for rapid disintegration.

Y=16.60-9.25A 5.17B + 0.125 AB + 5.31A2 + 3.26B2

Wetting Time (Y2)

Wetting Time (Y2) Model Significance: The quadratic model is highly significant ($p < 0.0001$) with an F-value of 147.52. Factor Impact: Similar to disintegration, higher levels of A and B lead to a significant decrease in wetting time. Dominant Factor: Factor A showed a superior effect (F482.15) over Factor B (F 125.92). Regarding the quadratic terms:

- $A^2$was statistically significant with F = 24.27 and p = 0.0160, indicating a nonlinear effect of HPMC K100M on drug release.
- $B^2$was not significant (F = 3.88, p = 0.1434), suggesting a weaker curvature effect for Eudragit RS100.

The residual error was low (5.95), confirming good agreement between experimental and predicted values.

Y_2 = 14.46-6.034 - 3.08B + 0.0000AB + 3.1642 + 2.21B2

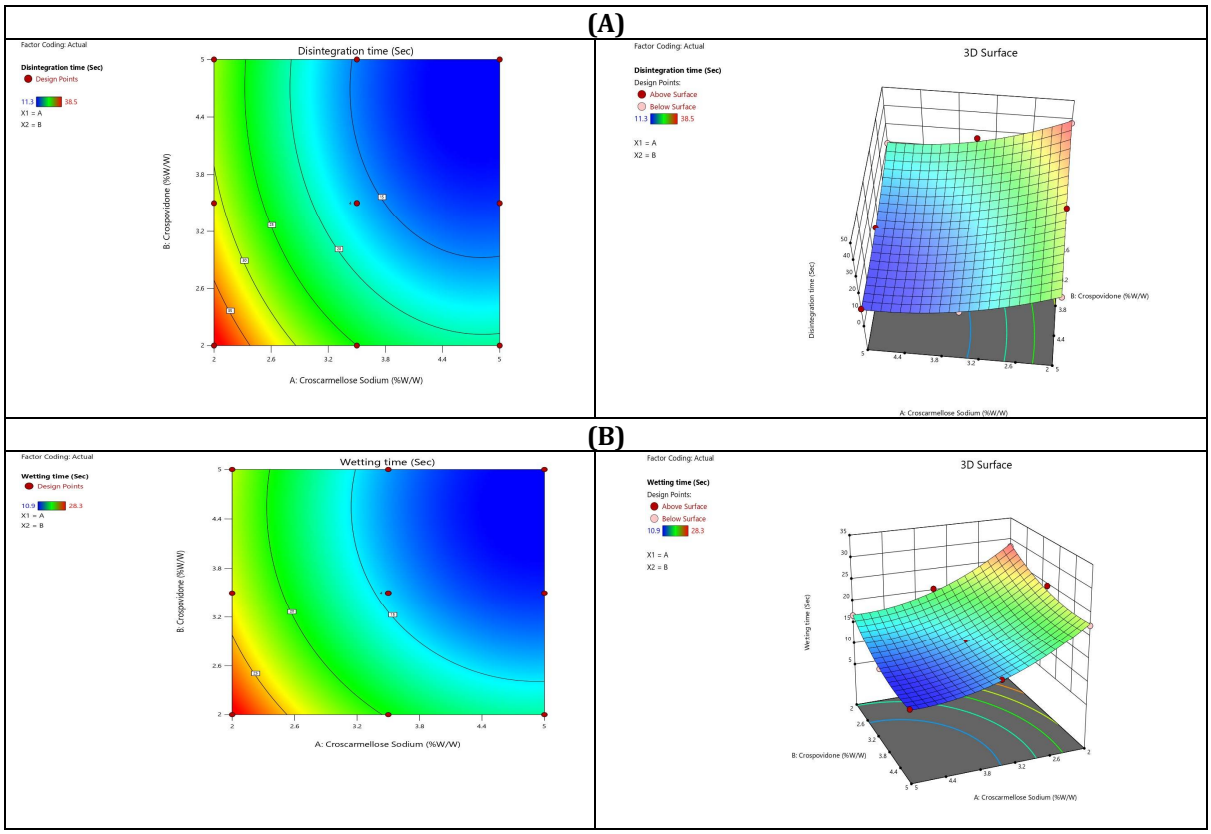
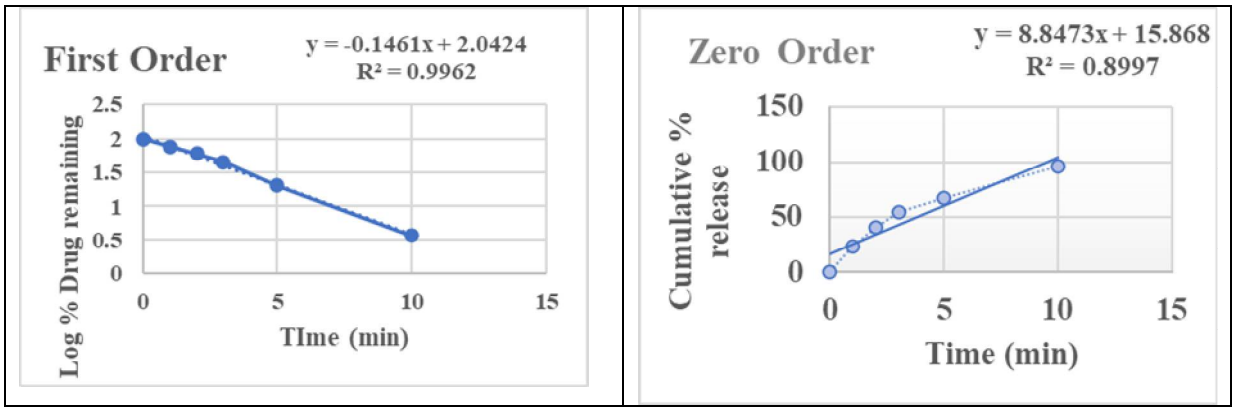


Figure 4. (A) Contour Plot and 3D surface graph of Disintegration Time (Y1); (B) Contour Plot and 3D surface graph of Wetting Time(Y2).

The 3D response surface plot illustrates the effect of Croscarmellose Sodium (A) and Crospovidone (B) on the wetting time of Rizatriptan Benzoate sublingual tablets. Wetting time decreased with increasing concentrations of superdisintegrants, indicating improved water uptake and faster tablet wetting. The curved surface indicates a significant interaction between the two formulation variables on the response.

Drug Release Kinetic Study

The Zeroth order, First order, Higuchi, Korsmeyer–Peppas and Hixson–Crowell models were used to investigate the drug release kinetics of Rizatriptan Benzoate sublingual tablets for the dissolving data. The regression coefficient (R^2) values were calculated for each model to determine the best model suitable for the prediction. Rizatriptan Benzoate Sublingual Tablets showed an appropriate match. The in-vitro drug release profile of the formulations showed that the developed formulation NF9 showed the best performance according to first order kinetic model. The data obtained for the drug release rate of the NF9 formulation were best fitted to the first-order model (R2 = 0.9762), showing a higher correlation coefficient in comparison to the other models.



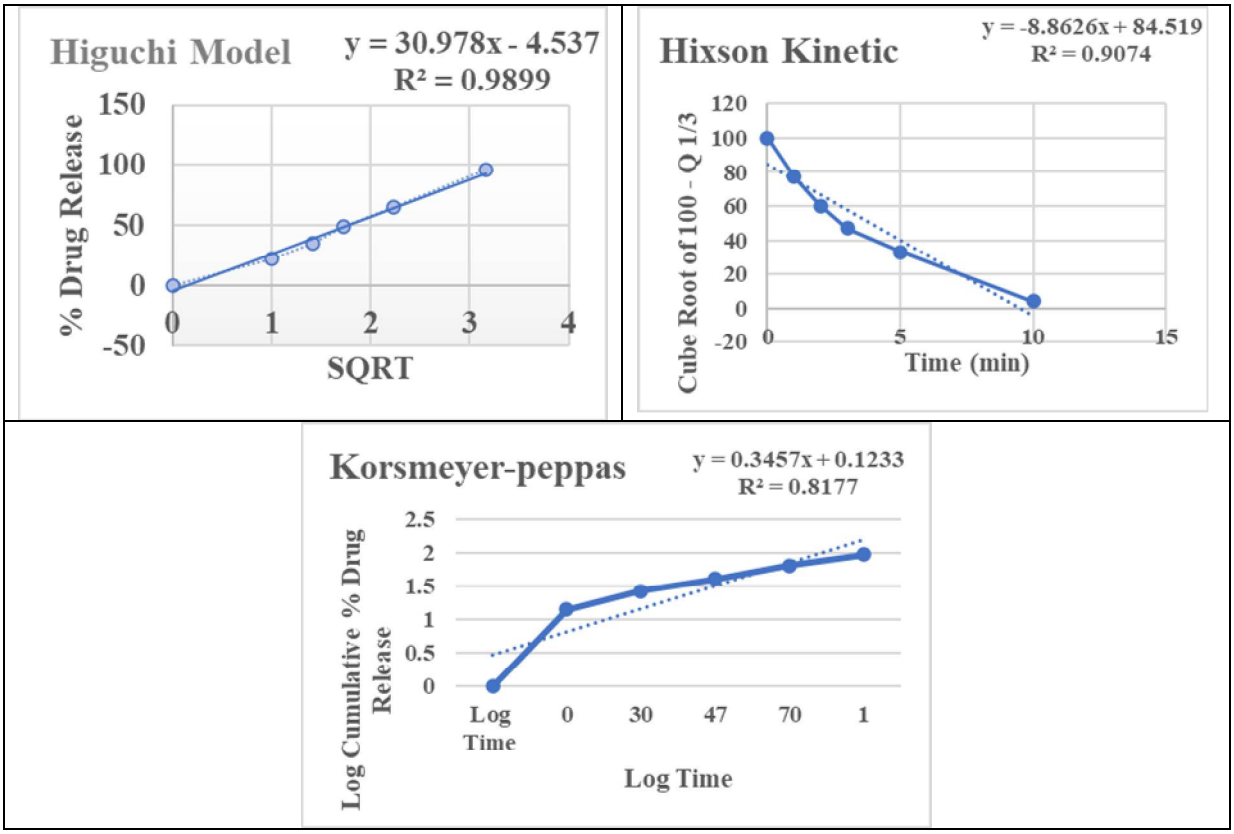


Figure 6: Drug release kinetic modeling of rizatriptan benzoate sublingual tablets (NF9 formulation) showing the fitting of dissolution data to Zero-order, First-order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas models for evaluation of the drug release mechanism and kinetics.

Cell Cytotoxicity Study

HEK293 cells were grown in (MEM) supplemented with non-essential amino acids (NEAA) and foetal bovine serum (FBS) at 37°C under 5% CO_2 atmosphere. A 96-well plate was used to inoculate cells and incubate them for 24 hours. The media was removed and cells were exposed to different concentrations of Rizatriptan Benzoate; cells that were not exposed were used as control cells. MTT reagent was added after 24 hours of incubation and again incubated for 4 hours for formazan crystal formation. A solution which is able to make the crystals dissolve was added [24,25]. The absorbance was measured and quantitated at 570 nm and % cell viability and IC_{50} were calculated. The MTT test was performed on HEK293 cells to evaluate the cytotoxicity of Rizatriptan Benzoate at various concentrations (5-500 µg/mL) after 24 hours' incubation. Rizatriptan Benzoate showed greater than 90% cell survival at lower concentrations (5–100 µg/mL), indicating that there was no cytotoxicity. At higher concentrations (250–500 µg/mL) a dose-dependent decrease in cell viability was observed. The IC_{50} value (~157 µg/mL) suggests that the drug is compatible and non-toxic at therapeutic levels.

Percent Cell Survival (%) = Absorbance of Test/Absorbance of Control ×100

Table 5: MTT assay results showing percent cell survival of rizatriptan benzoate on HEK-293 cells at

Concentration (ug/mL)	Absorbance	Average	% Cell Survival	Average % Cell Survival	St. Error
CTRL	0.421	0.439	95.827	100.000	6.333
5	0.466	0.409	106.070	93.096	8.068
10	0.345	0.409	78.528	93.172	0.612
25	0.452	0.444	102.883	101.138	0.932
50	0.375	0.416	85.357	94.689	5.983
100	0.376	0.433	85.584	98.634	6.897
250	0.254	0.280	57.815	63.809	5.881
500	0.298	0.342	67.830	77.769	6.727
IC50 VALUE	**152.7292**				

Values are expressed as mean ± n = 3

Varying Concentrations

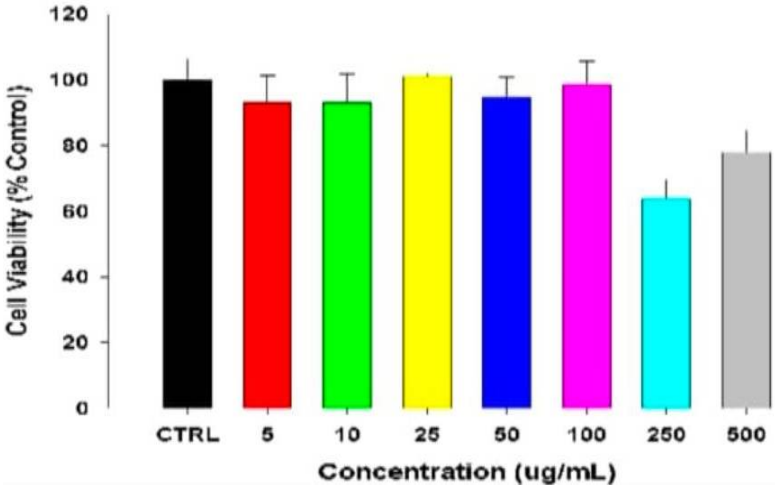


Figure 7: Cytotoxicity of Rizatriptan Benzoate on HEK-293 Cells Assessed by MTT Assay**.**

DISCUSSION

The pre-compression assessment of all formulations (F1–F12) exhibited acceptable flow properties. The angle of repose measurements was under 30°, signifying excellent flowability of the powder mixture. This observation was corroborated by Carr's Index values of 11.1–15.4% and Hausner's Ratio values of 1.12–1.18, all of which fall within acceptable parameters for direct compression. FTIR and DSC analyses verified the lack of substantial interaction between Rizatriptan Benzoate and the chosen excipients, demonstrating favourable compatibility and stability of the formulation components. The formulated sublingual tablets displayed satisfactory post-compression properties, with hardness between 2.3 and 2.6 kg/cm^2 and friability values ranging from 0.31 to 0.45%, indicating sufficient mechanical integrity. Among all formulations, formulation F9 exhibited greater performance. It demonstrated a rapid disintegration time of 12 seconds, rendering it extremely appropriates for sublingual delivery. The drug content exhibited uniformity, guaranteeing dose consistency. Dissolution studies indicated swift drug release across all formulations; yet, formulation F9 attained the maximum release, with over 99% of the medication liberated within 15 minutes. The release kinetics analysis demonstrated that the formulation adhered to first-order kinetics, evidenced by a R^2 value of 0.9962, indicating that the drug release rate was dependent on concentration. The fast disintegration and dissolution properties of formulation F9 are due to the synergistic action of the superdisintegrants croscarmellose sodium and crospovidone. These characteristics facilitate expedited medication absorption via the sublingual route, hence improving treatment efficacy and patient adherence during severe migraine episodes.

CONCLUSION

This study effectively designed and assessed sublingual tablets of Rizatriptan Benzoate for expedited migraine treatment. Preformulation and compatibility analyses validated the appropriateness of the medication and excipients for formulation development. All formulations demonstrated satisfactory physicochemical qualities; however, formulation F9 was recognised as the optimised formulation due to its exceptional tablet characteristics, quick disintegration, homogeneous drug content, and improved dissolution profile. The optimised formulation released roughly 99% of the medication after 15 minutes, adhering to first-order release kinetics. The stability investigations indicated that the formulation maintained stability during accelerated storage settings. The use of croscarmellose sodium and crospovidone significantly improved tablet disintegration and medication release. The formulated Rizatriptan Benzoate sublingual tablet is a viable alternative to traditional dosage forms by delivering rapid start of action, increased bioavailability, higher patient adherence, and successful management of acute migraine episodes.

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