Original Article

Formulation Development and Optimization of Bioenhanced Sublingual Tablets of Rizatriptan Benzoate to Combat Migraine

Manish Kumar Singh[1,*], Rupa Mazumder[1], Swarupanjali Padhi[1], Dinesh Kumar Singh[2]

[1]Noida Institute of Engineering and Technology (Pharmacy Institute), Greater Noida, Uttar Pradesh, INDIA.
[2]Jubilant Generics Limited, Sector-59, Noida, Uttar Pradesh, INDIA.

ABSTRACT

Introduction: The drugs belonging to BCS class III, create various challenges for the development of sublingual dosage form due to poor absorption through sublingual mucosa. The sublingual drug delivery is suitable for potent drugs only and prevents the first-pass metabolism of drugs, leading to its direct absorption into the systemic circulation. **Objectives:** The purpose of the present research was to formulate a fast-dissolving sublingual tablet and enhance the permeability of rizatriptan benzoate to combat acute migraine. The work is based on a comparative selection of the optimum bioenhancer among sodium laurel sulphate and sepitrap 80. **Materials and Methods:** The bioenhanced sublingual tablet of rizatriptan benzoate was prepared by wet granulation technique using fluidized bed processor (FBP) equipment. A 2^3 full factorial design was followed for the optimization of the process, by varying three independent factors at two levels and studying their effects on three dependent variables. The Design-Expert software version 10 was used to carry out the design of experiment (DoE) trials. The optimized formulation was subjected to stability studies for 3 months as per the International Conference of Harmonization (ICH) guidelines. **Results:** The formulation S-3, exhibited the shortest *in vitro* disintegration time of 9 sec; dissolution study showed 100% drug release in 10 min; the highest *in vitro* percent permeability of 77.28% 90 min and highest *ex vivo* permeation of 82.28% of the drug in 90 min, were observed as compared to that of the control formulation. The values associated with the evaluation parameters, disintegration time, dissolution, and permeability of the optimized formulation, were found to be within the accepted range as found in the stability studies. **Conclusion:** The use of polyplasdone XL and sepitrap 80 could be promising for developing a fast-release sublingual tablet with improved permeability and bioavailability, especially with drugs having low permeability.

Key words: Sublingual tablets, Rizatriptan benzoate, Migraine, Wet granulation, polyplasdone XL, Sepitrap 80, *Ex vivo* permeability.

INTRODUCTION

In the late 1970s, oral-dissolving drug-delivery systems had been first introduced as an alternative to conventional tablets. Sublingual drug delivery produces quick onset of action, better bioavailability, and maximizes dissolution properties. The benefit of the sublingual system is that the drug can directly reach the bloodstream and bypass the enzymatic degradation in the liver and stomach. The above benefits lead to enhanced bioavailability of the drug in the blood, as compared to that with conventional tablets. This type of formulation brings great benefit in the case of pediatric, geriatric patients, and non-compliant patients.[1] In addition, the anatomical structure and chemical nature of the sublingual mucosa and availability of blood supplying veins to the sublingual area of mouth play a vital role in drug permeation and in attaining desired plasma drug concentrations.[2,3] The major problems associated with orally ingested tablets are first-pass metabolism, bioavailability, and the onset of drug action. The presence

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Correspondence:
Dr. Rupa Mazumder
Professor and Dean, Noida Institute of Engineering and Technology (Pharmacy Institute), 19 Knowledge Park – II, Institutional Area, Greater Noida-201306, Uttar Pradesh, INDIA.
E-mail: rupa_mazumder@rediffmail.com

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of thin sublingual mucosa compared to the buccal mucosa allows the fast absorption of drug substances and rapid onset of action.[3-5] Medically, many drugs are administered through sublingual routes, such as cardiovascular drugs, steroids, some barbiturates, benzodiazepines, opioid analgesics, nifedipine, etc.[6] The drug absorption from the sublingual route is affected by permeability of the membrane, dosage form design, and physiochemical nature of the drug(s). Major challenges for the development of fast dissolving sublingual tablets are associated with drugs having poor permeability through the biological membranes. Migraine is a common type of headache disorder characterized by a unilateral headache and other symptoms such as nausea, vomiting, gastrointestinal disturbances, photophobia, and phonophobia.[7] Rizatriptan benzoate is a potent drug and considered more effective than the traditional triptans for the treatment of acute migraine attacks.[1] Triptan category of drugs, such as rizatriptan benzoate, sumatriptan, and so on, are used as the first-line drugs for managing moderate to severe migraines.[8,9] Rizatriptan is a new generation anti-migraine drug, which is a serotonin 5HT 1D receptor agonist that inhibits both dural vasodilatation and inflammation and is very helpful in reducing migraine symptoms.[10] It has been seen that a lack of serotonin level in the body usually causes migraine as well as depression. Generally, low levels of serotonin cause vasodilation and the introduction of rizatriptan inhibits vasodilation. The available oral disintegrating tablets (ODT) and conventional tablets of rizatriptan benzoate in the market show some drawbacks regarding the low bioavailability related to the low rate of its absorption (T_{max}). Hence, sublingual rizatriptan can deliver fast-acting, non-invasive relief from migraine attacks and thereby, overcome the challenges associated with permeability problems.

Therefore, the present work was designed to formulate bioenhanced sublingual tablets of rizatriptan benzoate, using super disintegrants, ensuring fast disintegration, better dissolution, and better permeability of the drug.[11] This research work is based on the optimization of the amount of the super disintegrant, polyplasdone XL (crospovidone XL) to check its effects on the disintegration time (DT) and selection of the best bioenhancer from sodium lauryl sulphate (SLS) and sepitrap 80, a novel permeability enhancer. Sepitrap 80 (brand name) contains polysorbate 80 (45-65%) and magnesium aluminometasilicate (35-55%). Sepitrap 80 also enhances the solubility of the active ingredient attributing to its enhanced bioavailability.

MATERIALS AND METHODS

Materials

Rizatriptan benzoate was obtained as a gift sample from Jubilant Generics Limited, Noida and the Sepitrap 80 was procured from Seppic Pvt. Ltd., Mumbai. The other excipients, polyplasdone XL, silicon dioxide, mannitol (Pearlitol 25C and SD 200), povidone K30, SLS, colloidal silicon dioxide (Aerosil 200), peppermint flavor, aspartame, and stearyl fumarate, were gifted by Jubilant Generics Limited, Noida.

Methods

Preformulation studies

In the preformulation studies, a physical evaluation of the drug and excipients was carried out. The objective of the study was to select suitable excipients for the drug, for the development of the formulation under study. The preformulation study involved the following steps:

Identification of drug and excipients

The characterization of the drug and excipients used in the study was performed using Fourier transform infrared (FTIR) spectrophotometer (Perkin, Japan) in the range between 1 cm^{-1} to 4000 cm^{-1}. Pellets were prepared for analysis in FTIR by dispersion of the API and excipients in KBr through compression, and the corresponding graphs were recorded.[12]

Physical compatibility

Separate mixtures of the drug with each excipient in 1:1 ratio were prepared. Each mixture was divided into two portions, kept separately in closed vials, and labeled properly; then one part of each mixture was kept at 40±2°C/75±5% RH for 1 month and the second part was kept at room temperature.[13]

Selection of dissolution media for dissolution study

The drug was weighed (50 mg) and added to each of 20 ml of a selected solvent such as distilled water, 0.1N HCl, pH 4.5 acetate buffer, and phosphate buffer pH 6.8, in different glass vials, agitated and kept on a water bath set at 37°C for 24 hr. The solution was filtered and the filtrate was tested with the help of UV-spectrophotometer at 226 nm for the quantitative estimation.[14]

Determination of flow property of the blends of formulations (S1 - S11)

The flow properties of the API along with the excipients are important for deciding the process to be adopted for tablet compression. The poor flow of the powder and blends affects the compression of the tablets and can

lead to erroneous assay and a lack of uniformity in the distribution of the drug.

The flow properties of the blends of the various formulations (S1 – S11) were obtained by measuring their bulk densities, tapped densities, angles of repose, Carr's compressibility indices, and Hausner's ratios, as discussed below.[15,16]

Bulk density and tapped density[15]

It was measured by the tapped density apparatus (Electrolab, India) with the help of a graduated cylinder. Samples were weighed and transferred into a measuring cylinder and measured their bulk volumes, followed by the measurement of tapped densities of the blends using a tapped density apparatus. USP 2 method was selected for determining the tapped density of the samples, expressed as g/mL using the given formula:

Bulk Density (D_b) = Mass of Samples / Occupied Bulk Volume

Tapped Density (D_t) = Mass of Samples / Occupied Tapped Volume

Compressibility index (Carr's index)[15]

Carr's index, frequently used in the preformulation studies to find out the flowability of powder/granules, was determined by the given formula:

$$\% \text{ Carr's Index} = [(D_t - D_b) \times 100] / D_t$$

Hausner's ratio[16]

The Hausner's ratios (HRs) of samples were calculated using the given formula:

$$\text{Hausner's Ratio (HR)} = D_t / D_b$$

Angle of repose[16]

By using a simple funnel, angles of repose of the prepared formulation blends were determined. The funnel was held at a height of 25 cm from the base using a burette stand. Samples were introduced from the top of the funnel and were allowed to flow downwards until a maximum height "h" was received. By using a scale, the diameter of the heap, d, was measured and the angles of repose were calculated using the following formula:

$$\text{Angle of Repose } (\theta) = \tan^{-1}(h/r),$$

where h = height of the sample and r = radius of the heap obtained.

Preliminary trials for selection of excipients

Diverse preliminary trials were performed for the selection of the concentrations of the diluents (mannitol 25C and Mannitol 200 SD), super disintegrant (crospovidone XL) and permeation enhancer (Sepitrap 80 and SLS), and other excipients, such as lubricating agent, glidant, flavoring agent, and so on. The objective of the preliminary trials was the selection of excipients' grades and concentrations so that they will produce optimum results. Initial two trials, T-1, and T-2 were undertaken to develop a formulation of sublingual tablets and to resolve the basic problems of tablets during compression, such as sticking, capping, and weight variation. The trial T-3 was taken to resolve the problem associated with blend uniformity. Trials T-4 to T-6 were undertaken to optimize the amount of the super disintegrant (polyplasdone XL) to check their effects on DT. Later on, trials T-7 and T-8 were undertaken to bring about the optimum dissolution of the drug by optimizing with mannitol 25C, and trial T-9 was selected for further permeability studies. After the selection of the amounts of the excipients and their grades as a part of the formulation development, various trials were considered to optimize the concentrations as shown in Table 1. After the achievement of optimum results, the formulation was developed using the QbD approach.

Experimental design[17-19]

Formulations of the sublingual tablet of rizatriptan benzoate were prepared according to 2^3 factorial designs by varying three independent factors at two levels and studying their effects on three dependent variables for the optimization process. Eleven trials were finalized using DoE, three of them being selected as central trials. Variables were selected based on a literature survey. The dependent variables were *in vitro* dissolution rate, disintegration time, and permeability, whereas the independent variables were mannitol 25C, crospovidone XL, and sepitrap 80 (Table 2). The Design-Expert R software version 10 had been used for the data analysis. The results obtained after optimization and the number of trials used are mentioned in Table 3.

Quality target product profile (QTPP) of the sublingual tablet to develop QbD approach

QTPP is a set of characteristics of the drug product which is to be set for the desired qualities of the drug product before starting the formulation. Accompanying properties might be chosen as QTPP because of the writing audit which may impact the sublingual tablet to convey medical viability and productivity. The target quality profiles of tablets that have been selected are considered to have a high degree of impact on sublingual

Table 1: Composition of preliminary trials formulation.											
Intra-granular part											
S.NO	**Ingredients**	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**	**T10**
1	Rizatriptan Benzoate	14.53	14.53	14.53	14.53	14.53	14.53	14.53	14.53	14.53	14.53
2	**Polyplasdone XL**	20	20	20	16	14	12	12	12	12	12
3	Silicon dioxide	20	20	10	10	10	10	10	10	10	10
4	Mannitol 25 C	112.97	110.97	53.18	53.18	53.18	53.18	63.18	73.18	73.18	73.18
Binder											
5	Povidone	10	10	10	10	10	10	10	10	10	10
6	Purified water	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s
Extra-granular part											
7	Mannitol 200 SD	--	--	77.79	77.79	77.79	77.79	67.79	57.79	52.79	52.79
8	Polyplasdone XL	--	--	--	4	6	8	8	8	8	8
9	Sodium Laurel Sulphate	--	--	--	--	--	--	--	--	5	--
10	Sepitrap 80	--	--	--	--	--	--	--	--	--	5
11	Peppermint Flavor	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
12	Aspartame	8	8	8	8	8	8	8	8	8	8
13	Colloidal Silicon dioxide	2	2	2	2	2	2	2	2	2	2
14	Sodium Stearyl Fumarate	2	4	4	4	4	4	4	4	4	4
Total weight (mg)		**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Table 2: Independent variables with three center points and two Levels.				
Critical Materials Attributes (CMA)				
Component	**Name**	**Minimum (mg)**	**Centre point (mg)**	**Maximum (mg)**
A	Polyplasdone XL	10	15	20
B	Mannitol 25 C	60	70	80
C	Sepitrap 80	5	10	15

dosage forms, such as dissolution rate, DT, and percent permeability.

Selection of variables by preliminary trial batches

Based on the observation of preliminary trials, excipients that majorly impact the productivity of sublingual tablets were considered as formulation variables. The independent variables which would impact the critical quality attributes (CQA) of rizatriptan sublingual tablets were mannitol 25C, polyplasdone XL, and sepitrap 80, the concentrations of which are mentioned in Table 2. The dependent variables were evaluated for dissolution rate, DT, and percent permeability.

Preparation of bioenhanced sublingual tablet of rizatriptan benzoate

Rizatriptan being moderately bitter and showing poor flow properties, to mask its bitter taste and improve the flow properties, wet granulation method[19] was adopted for the development of the bioenhanced sublingual tablets. For granulation, an FBP (Glat GPCG 1.1) of 4 liters was used. In this process, all the excipients and API were weighed accurately and separately. API, crospovidone XL, mannitol 25C, and silicon dioxide were shifted through ASTM #40 sieve and collected in polybags. Intermediate granules were blended for 5 min with hand rotation in polybags. Povidone was dissolved in the required amount of purified water using a mechanical stirrer and it was stirred continuously until a clear solution was obtained. The sieved materials were transferred into FBP and a binder solution of povidone was sprayed to granulate the content in the FBP. After the granulation was achieved content was dried in the FBP at bed temperature, not more than 60°C for about 1 hr, till the loss on drying (LOD) of dry granules was not more than 2.5%. Dried granules were passed through ASTM #40 sieve and collected in a polybag. All

Table 3: Composition of optimized sublingual tablet formulation S1-S11.

S.no	Ingredients	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11
Intra-granular												
1	Rizatriptan Benzoate	14.53	14.53	14.53	14.53	14.53	14.53	14.53	14.53	14.53	14.53	14.53
2	Crospovidone XL	5	5	5	5	5	5	5	5	5	5	5
3	Silicon dioxide	10	10	10	10	10	10	10	10	10	10	10
4	Mannitol 25C	80	70	80	60	60	70	60	60	80	70	80
Binder solution												
5	**Povidone**	10	10	10	10	10	10	10	10	10	10	10
6	**Purified water**	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s
Extra-granular												
7	**Mannitol 200 SD**	55.97	55.97	35.97	75.97	55.97	55.97	75.97	55.97	35.97	55.97	55.97
8	**Polyplasdone XL**	5	10	15	5	15	10	5	15	15	10	5
9	**Sepitrap 80**	5	10	15	5	15	10	5	15	15	10	5
10	**Peppermint Flavor**	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
11	**Aspartame**	8	8	8	8	8	8	8	8	8	8	8
12	**Colloidal Silicon dioxide**	2	2	2	2	2	2	2	2	2	2	2
13	**Sodium Stearyl Fumarate**	4	4	4	4	4	4	4	4	4	4	4
Total weight (mg)		200	200	200	200	200	200	200	200	200	200	200

the extra granules of excipients were shifted through ASTM #40 sieve, except sodium stearyl fumarate, and collected in the same polybag. The blend was mixed in a Conta blender for 15 min and after that sodium stearyl fumarate which was passed through ASTM #60 sieve, was added and again blended for 5 min. The top spray method was selected for spraying the binder solution, during granulation. At last, the blend was ready for compression, the composition of the formulation being presented in Table 3. The parameters of FBP, such as inlet temperature (°C), bed temperature (°C), blower speed, spray rate (g/min), and atomization were set up at 40-65°C, 28-35°C, 20-25 rpm, 7-10 g/min and 1atm, respectively. The methods of preparation were similar for preliminary trials and optimized batches. The tablets were prepared by 16 stations tablet compression machine (Cadmach, Ahmedabad).

Evaluation of bioenhanced sublingual tablets

The evaluations of the developed sublingual tablets were carried out for friability, thickness, hardness, weight, content uniformity, wetting time, DT, *in vitro* drug release, *in vitro* permeability, and *ex vivo* permeability.

The various evaluation parameters for sublingual tablets are disused below:

Weight variation[20]

After compression, 20 tablets from each batch were selected and the average weight was calculated. The results obtained after calculation might not deviate from limits as given in the Indian Pharmacopeia (IP), 1996.

Thickness[15]

Vernier caliper was used for measuring the thickness of the tablets. In this process, three tablets were selected from each batch and the average thickness of the tablets was noted.

Hardness Test[21]

During this test, ten tablets were selected randomly from each batch and determined the hardness of each tablet. A hardness tester (Electrolab Machines, India) was used to determine the hardness of the tablets.

Friability Test[20]

For determination of friability, 20 tablets from each batch were taken and weighed properly, then placed in the Roche friabilator (Electrolab, India) and rotated for 4 min at 25 rpm. The collected tablets were again weighed and the percent friability (must lie within 1%) was calculated as per the given formula.

$$\text{Percentage Friability} = \left\{ \frac{(\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100 \right\}$$

Blend uniformity

For the determination of drug blend uniformity (BU), a blend equivalent to one tablet weight was weighed from the blend, and a solution of concentration 1 µg/ml was prepared in phosphate buffer pH 6.8. The drug content was estimated by using a UV-visible spectrophotometer (UV-1601, Shimadzu) at 226 nm.

Assay[22,23]

For determination of the drug content uniformity, 20 tablets were weighed randomly and crushed with a mortar and pestle. Single dose equivalent to 10 mg of rizatriptan, was weighed from the crushed powder and prepared a solution of 1µg/ml concentration in phosphate buffer pH 6.8. The drug content of the given sample was estimated by using a UV-visible spectrophotometer at 226 nm.

Wetting time[24]

The wetting time of the prepared tablets was determined by using a simple Petri dish and a Whatman number 1 filter paper. The filter paper was cut and placed over the Petri dish and then 10 ml buffer solution (pH 6.8) was poured into it. Each tablet was kept in the dish containing the solution and allowed to get wetted. The time was noted till the water was absorbed to the upper surface of the tablets.

Disintegration time[25]

For the determination of DT, six tablets were randomly taken from separate batches and placed in six cylindrical glass tubes of disintegration tester (Electrolab, India) at 37±0.5°C, in purified water. The maximum time was noted for complete disintegration of each tablet.

In vitro drug release studies[26]

For determination of *In vitro* drug release, a dissolution test apparatus (Electrolab, India) type II (paddle method) was selected as per the United States Pharmacopeia (USP) and deaerated water was used as the medium. The basket was filled with 900 mL of deaerated water maintained at 37±0.5°C temperature and rotated at 50 rpm. The compressed tablets were placed in the baskets and samples were withdrawn at given intervals of time (2 min, 5 min, 10 min, and 15 min). The drug content was analyzed by using a UV-visible spectrophotometer at 226 nm. During this entire process, the sink condition was maintained by replacing samples with an equal quantity of fresh deaerated water in the vessel.

In vitro permeation study[22,27]

The *in vitro* permeation study was carried out to find out the permeability of the drug across the membrane. For this study, an open-ended tube was selected and one side of this tube was sealed with egg membrane obtained from the egg and its other side was kept open for introducing the drug solution. The donor compartment of the apparatus was filled with the formulation from which the drug permeated into the receiver compartment (beaker). The temperature and stirrer speed of the receiver compartment was maintained at 37°C and 50 rpm, respectively, for mixing the solution in it. The receiver compartment was filled with a 200 ml buffer solution (pH 6.8). Then the whole setup of the open-ended tube was dipped into the receiver compartment. The samples were withdrawn at a specified time from 5 min to 90 min at constant intervals of time, from the beaker, and the drug content was estimated by using a UV-visible spectrophotometer at 226 nm.

Ex vivo permeation study[22,27]

For determination of the *ex vivo* permeability of the drug, the buccal mucosa of the goat had been selected. The buccal mucosa was brought from the local slaughterhouse, Khoda, Noida. The buccal mucosa was excised from the buccal cavity and cleaned properly. The open-ended tube was selected for *ex vivo* permeation study, whereas one side of this tube was sealed with goat mucosa obtained by the above procedure and the other side was kept open for introducing the drug solution. The donor compartment of the apparatus was filled with the drug solution (rizatriptan) and which permeated into the receiver compartment (beaker). The temperature and stirrer speed of the receiver compartment was maintained at 37°C and 50 rpm, respectively, for mixing the solution. The receiver compartment was filled with a 200 ml buffer solution (pH 6.8). Then the whole setup of the open-ended tube was dipped into the receiver compartment. The samples were withdrawn at a specified time from 5 min to 90 min at constant intervals of time, from the beaker and the drug content was estimated by using a UV-visible spectrophotometer at 226 nm.

Stability studies[28]

The objective of the stability studies was to check the quality of the product after storage for a specified duration of time. The best formulation from all the batches was subjected to stability studies for 3 months at accelerated stability conditions (40±2°C/75%±5% RH) and kept in a humidity chamber. The samples were evaluated for various tablet parameters as discussed above.

RESULTS AND DISCUSSION

Preformulation studies

Selection of the dissolution medium

The solubility of rizatriptan benzoate in different media, such as distilled water, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer, was found to be more than 50 mg/ml, whereas, in 0.1N HCl, it was found to be 36.3 mg/ml. The highest dose of rizatriptan benzoate is 30 mg per day. Based on the solubility data, distilled water was selected as the dissolution medium, and 30 mg of the drug was found to be soluble in less than 250 ml of the selected medium, which meant that the sink condition would be maintained in 900 ml of the selected medium.

Determination of flow property of APIs and blend of formulations (S1 - S11)

The API had been found to have poor flow property as per the results of the compressibility index (%) and Hausner's ratio, but the blends from each batch had been found to have good flow properties.

The Micromeritic properties of the API and its blends have been recorded in Table 4 which also depicts the BU of the optimization batches, S1 to S11.

Identification of drug by FTIR

The drug was identified by using FTIR. The spectra obtained from FTIR complied with the original drug and confirmed that it was rizatriptan benzoate (Figure 1).

Physical compatibility

The physical mixtures of the drug and excipients were found to be unaltered and no sign of change in color, texture, and odor was observed after completion of the stability period. The drug and excipients were found to be physically compatible, as observed in Table 5.

Observation preliminary trials

The objective of the preliminary trials was to select the excipients' grades and concentrations so that they could further produce optimum results. The T-1 formulation containing 2 mg of sodium stearyl fumarate as a lubricating agent, was found to possess a sticking problem during compression. The sticking problem was resolved in T-2 batch after increasing the amount of sodium stearyl fumarate up to 4 mg, but the BU was found to be out of limits. To solve this problem, different grades of mannitol, such as mannitol 200 SD, were introduced in the extra granular portion of T-3 batch and the BU was found to be under limits. The DT of T-4 was found to be above 2 min; thus, to reduce the disintegration time, polyplasdone XL was added in different amounts in the extra granular part along with its intragranular portion. The DTs of T-5 and T-6 formulations were found to be 60 s and 35 s, respectively, but the percentage drug release of T-6 batch was found to be 65% in 5 min, while the limits of the dissolution rate of rizatriptan benzoate were not less than 80% in 5 min. Hence, to solve this problem, the amount of mannitol 25C was optimized as given in T-7 and T-8, and the percentage drug release was found to be 75% and 83%, respectively, in 5 min. After the achievement of dissolution and DT under control, batch T-8 was found to be ready for further study of permeability. Permeation enhancers, such as SLS and sepitrap 80, were introduced in the extra granular portion of the formulation. The *in vitro* percentage permeability of batch T-9 containing SLS as the permeability enhancer was found to be 48.14% in 90 min. However, the *in vitro* percentage permeability of the formulation T-10 was found to be 53.14%, which was greater than that of the T-9 batch. Hence, based on the *in vitro* percentage permeability results, SLS was

Table 4: Micromeritic properties of APIs blend of all formulations.

APIs/ Formulation	Bulk density (g/ml)	Tap density (g/ml))	Compressibility index (%)	Hausner's ratio	Angle of repose	Blend Uniformity (%)
Rizatriptan benzoate	0.378g/ml	0.619g/ml	38.88%	1.636	30.29	--
S1	0.378	0.619	38.88	1.636	28.75	98.30
S2	0.351	0.401	12.00	1.142	28.70	99.10
S3	0.380	0.454	16.29	1.188	28.79	99.18
S4	0.382	0.460	16.95	1.204	29.30	101.10
S5	0.372	0.420	11.42	1.129	29.89	100.04
S6	0.402	0.470	14.46	1.169	28.17	97.08
S7	0.391	0.470	16.80	1.202	39.80	99.90
S8	0.370	0.411	09.97	1.111	29.19	97.34
S9	0.350	0.400	12.50	1.142	29.47	100.04
S10	0.381	0.441	13.60	1.157	29.17	99.24
S11	0.390	0.461	15.10	1.182	29.17	97.25

excluded as a permeability enhancer for further studies and sepitrap 80 was being carried out for permeability studies.

Physical evaluation of tablets

The evaluated average weight, friability, hardness, thickness, and wetting time of the prepared tablets have been reported in Table 6.

The average weight was found to be between 199 to 203 mg and the value was within the prescribed limits. The observed thickness was between 3.42-3.55 mm, hardness, in the range of 19-25 N, and friability % in the range of 0.46-.58% was observed for the tablets from all the prepared batches (S-1 to S-11). The percentage of drug content was found to be in the range of 98.5% to 102.4%; wetting time ranging between 03 to 28 seconds and the appearance of the wet tablets were recorded in Figure 2.

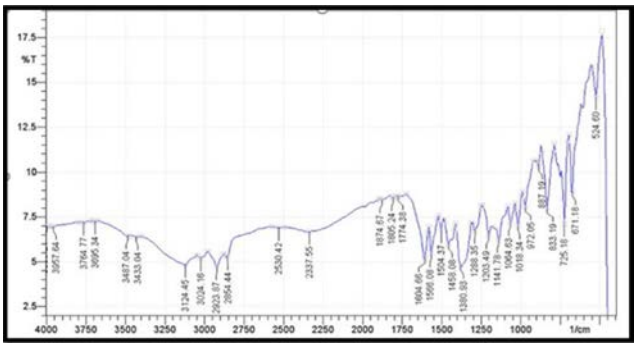

Figure 1: FTIR spectra of rizatriptan benzoate.

In vitro disintegration time

The specification of disintegration time for fast dissolving tablets is under 2 min as per the USP guidelines.

The objective of this research was to develop a bioenhanced fast-dissolving rizatriptan benzoate tablet with a disintegration time of 20 s or less. The disintegration time ranged between 9 s to 48 s for all the formulations, as shown in Figure 3. The formulation S-3 showed less disintegration time (9 s) as compared to the other formulations. This formulation contained 10 percent polyplasdone XL that reduced the DT to 9 s. However, formulation S-4 contained 5% polyplasdone which showed a disintegration time of 48 s. The above results confirmed that polyplasdone XL concentration had a visible effect on disintegration time.

Table 5: Physical compatibility study of drug and excipients.

S. No	Composition	Physical description and Conditions				
		Initial	Normal room temperature		40±2°C / 75±5%RH	
			15 days	30 Days	15 Days	30 Days
1.	Rizatriptan benzoate (RZB)	Clear White Powder	Changeless	Changeless	Changeless	Changeless
2.	Crospovidone XL	Clear White Powder	Changeless	Changeless	Changeless	Changeless
3.	RZB + Crospovidone XL	Clear White Powder	Changeless	Changeless	Changeless	Changeless
4	Silicon Dioxide	White to Gray Powder	Changeless	Changeless	Changeless	Changeless
5.	RZB + Silicon Dioxide	White to Gray Powder	Changeless	Changeless	Changeless	Changeless
6.	Povidone	White Powder	Changeless	Changeless	Changeless	Changeless
7.	RZB +Povidone	White Powder	Changeless	Changeless	Changeless	Changeless
8.	SLS	White Powder	Changeless	Changeless	Changeless	Changeless
9.	RZB +SLS	White Powder	Changeless	Changeless	Changeless	Changeless
10.	Sepitrap 80	White Powder	Changeless	Changeless	Changeless	Changeless
11.	RZB + Sepitrap 80	White Powder	Changeless	Changeless	Changeless	Changeless
12.	Mannitol SD 200	Clear White Powder	Changeless	Changeless	Changeless	Changeless
13.	RZB + Mannitol SD 200	Clear White Powder	Changeless	Changeless	Changeless	Changeless
14.	Aspartame	White Powder	Changeless	Changeless	Changeless	Changeless
15.	RZB + Aspartame	White Powder	Changeless	Changeless	Changeless	Changeless
16.	Mannitol 25 C	White Powder	Changeless	Changeless	Changeless	Changeless
17.	RZB + Mannitol 25 C	White Powder	Changeless	Changeless	Changeless	Changeless
18.	Aerosil 200	Clear White Powder	Changeless	Changeless	Changeless	Changeless
19.	RZB + Aerosil 200	Clear White Powder	Changeless	Changeless	Changeless	Changeless
20.	Peppermint	White Powder	Changeless	Changeless	Changeless	Changeless
21.	RZB + Peppermint	White Powder	Changeless	Changeless	Changeless	Changeless
22.	Sodium Stearyl Fumarate	Clear White Powder	Changeless	Changeless	Changeless	Changeless
23.	RZB+ Sodium Stearyl Fumarate	Clear White Powder	Changeless	Changeless	Changeless	Changeless

Table 6: Physical evaluation of compressed tablet.						
Formulation code	**Avg weight (mg)**	**Thickness (mm)**	**Hardness (N)**	**Friability (%)**	**Assay (%)**	**Wetting Time (s)**
S1	201	3.45	22	0.55	98.5	28.00
S2	201	3.36	21	0.46	99.1	12.00
S3	200	3.45	19	0.58	99.9	03.00
S4	199	3.43	22	0.48	101.3	21.00
S5	199	3.43	20	0.56	99.8	20.00
S6	200	3.45	22	0.53	102.4	12.00
S7	201	3.42	21	0.53	99.3	06.00
S8	202	3.45	21	0.52	99.2	03.00
S9	203	3.54	23	0.58	99.0	24.00
S10	199	3.55	25	0.57	100.6	12.00
S11	200	3.58	22	0.56	99.4	04.00

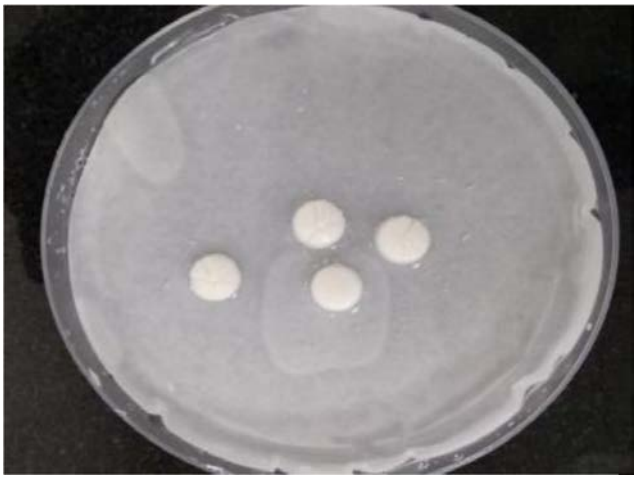

Figure 2: Appearance of tablets during wetting procedure.

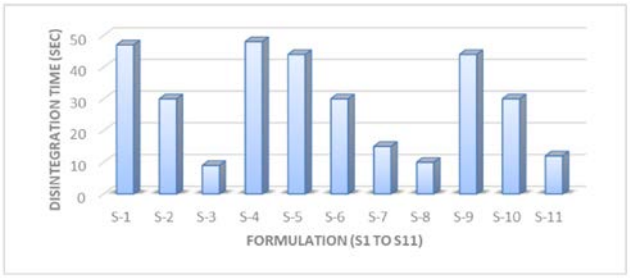

Figure 3: *In-vitro* disintegration time of formulation S1 to S11.

In vitro drug release studies

The *in vitro* drug release of formulations S-1 to S-11 in 10 min were 98%, 97%, 99%, 96%, 95%, 96%, 97%, 97%, 96%, 96% and 97%, respectively (Figure 4). Almost complete dissolution could be seen in 10 min for all the developed formulations. The dissolution profiles of all the formulations differed only in the

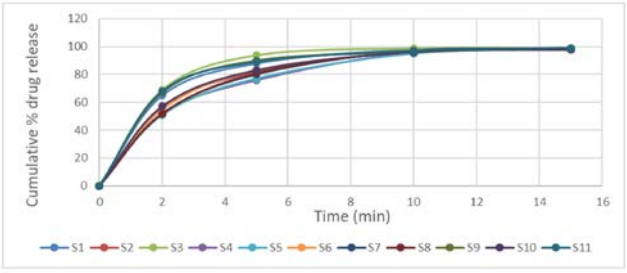

Figure 4: *In-vitro* cumulative percent drug release of S-1 – S-11 batches.

initial time point of dissolution (2 and 5 min). The batches S-4, S-5, S-7, and S-8 showed less drug release in 2 min, *i.e.*, 52 %, 51%, 52%. and 52%, respectively, whereas, they showed drug release of 76%, 77%, 70%, and 81%, respectively, in 5 min. All these batches contained the least concentration of mannitol 25C (60 mg), whereas the batches S-3, S-9, and S-11 showed maximum drug release of 94%, 90%, and 89%, respectively, in 5 min and 99%, 96%, and 97% in 10 min, respectively, and they contained 80 mg of mannitol 25C. Thus, mannitol 25C showed its effect in the initial point of dissolution. Later on, the rates of drug release from the above-mentioned formulations were found to be almost similar. The polyplasdone XL also showed some effects on dissolution and it could be seen in 5 min of the data of batches S-4, S-5, S-7, and S-8. Among these, the batches S-5 and S-8 contained the maximum amount of polyplasdone XL (20%) which showed a maximum drug release in 5 min as compared to S-4 and S-7, as the latter two formulations contained the least amount of polyplasdone XL (10%). The S3 batch showed a maximum percentage drug release of 100% and S-4 showed the minimum drug release in 10 min.

In vitro permeation study

The *in vitro* permeation study was carried out using egg membrane for control and other batches. The *in vitro* percentage permeability of S1 to S11 formulations were found to be 46.14%, 61.76%,77.28%, 44.94%, 74.08%, 61.76%, 45.95%, 76.48% 75.28%, 61.76%, and 46.95%, respectively, in 90 min (Figure 5). Formulation S3 showed maximum percentage permeability, as this formulation contained a maximum amount of sepitrap 80 (15 mg). This formulation also had a high amount of Polyplasdone XL and mannitol 25C, which also showed some impact on it. However, S4 showed the least percentage permeability of about 43.24% in 90 min because of the presence of the least amount of sepitrap 80 in the formulation. The control formulation which didn't contain any type of permeation enhancer showed 40.31% *in vitro permeability* in 90 min, which was less than that of S4. This result had indicated that sepitrap 80 influenced the permeability of the drug in the sublingual dosage form.

Ex vivo permeation study

The *ex vivo* permeability study was carried out using goat mucosa as the permeability membrane. The percentage permeability of S1 to S11 formulations were 53.14%, 67.76%, 82.28%, 50.24%, 78.08%, 67.76%, 52.95%, 79.08%, 80.28%, 67.76% and 53.95%, respectively, as recorded in Figure 6. The formulation S3 showed maximum percentage permeability of 82.28% (Figure 4) across goat mucosal membrane, as the batch contained a maximum amount of sepitrap 80 (15 mg) and polyplasdone XL (20 mg). The control formulation which contained no permeability enhancer showed 44.21% permeability. The S4 formulation provided the least percentage permeability of 52.24%, as it contained only 5 mg sepitrap 80, comparably very less than that in S-3, which contained 15 mg of sepitrap 80. The S2 batch containing 10 mg of sepitrap 80 showed 67.76% permeability at 90 min. The results obtained from the various formulations prepared confirmed that the permeability enhancers had a prominent role in the permeability of the drug and they enhanced the percentage permeability of the drug upon increasing their concentrations within a limited range.

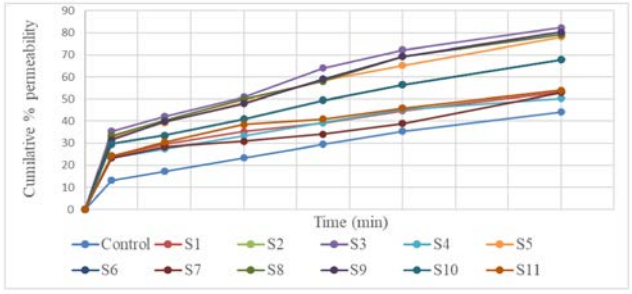

Figure 5: *In-vitro* cumulative percent permeability of control and S-1– S-11 batches.

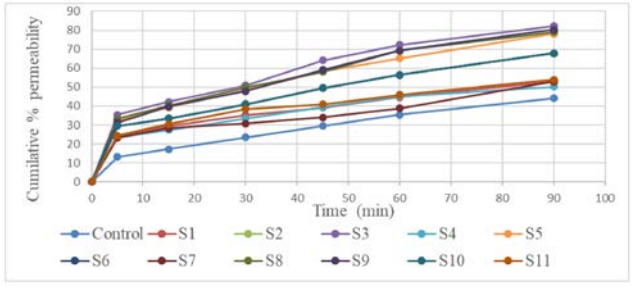

Figure 6: *Ex vivo* cumulative percent permeability of Control and (S1– S11) batches.

Comparison of control and other batches based on percentage permeability

Based on the results obtained, Figure 7 shows the comparative permeation profile of rizatriptan sublingual tablets with different concentrations of sepitrap 80 in the formulations.

The control formulation did not contain any type of permeation enhancer. The S1, S2, and S3 contained 5 mg, 10 mg, and 15 mg sepitrap 80, respectively, as permeation enhancers. The comparative data was calculated at 5, 30, and 90 min of time intervals for the selected formulations. The results declared that percentage permeability had increased by increasing the amount of sepitrap 80. However, the control batch and S-3 showed 45.31% and 82.28% permeability, respectively, at 90 min. This proved that sepitrap 80 showed their effect on the permeability of rizatriptan from the developed sublingual tablets.

Optimization results

The results of the full factorial study have been depicted in the following sub-sections:

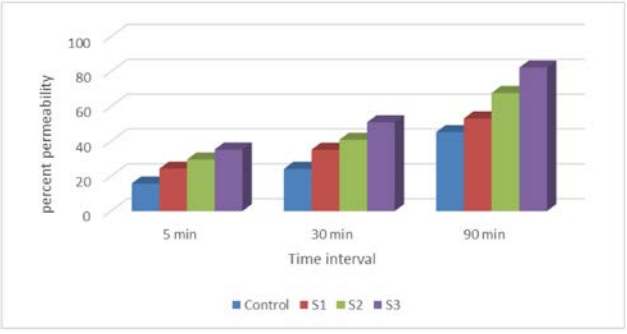

Figure 7: Comparative data of percent permeability of Control with different batches.

Table 7: ANOVA for Response-1 factorial model.						
Analysis of variance table (Partial sum of squares – Type 3						
Sources	**Sum of Squares**	**Df**	**Mean square**	***F*- value**	***p*-value Prob> *F***	
Model	1007.50	4	251.87	136.82	<0.0001	Significant
A-Mannitol 25 C	946.13	1	946.13	513.94	<0.0001	
B- Polyplasdone XL	36.13	1	36.13	19.62	0.0044	
AB	15.13	1	15.13	8.22	0.0286	
AC	10.12	1	10.12	5.50	0.0574	
Residual	11.05	6	1.84			
Lack of Fit	6.38	4	1.59	0.68	0.6665	Not significant
Pure Error	4.67	2	2.33			
Cor Total	1018.55	10				

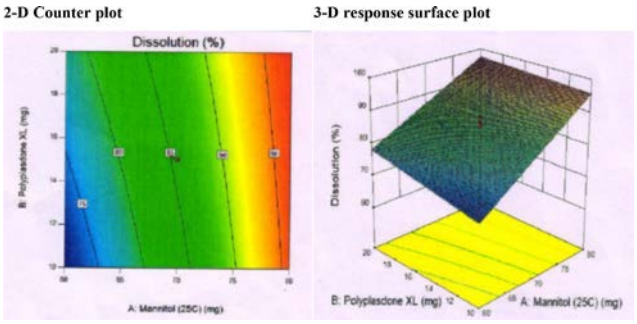

Figure 8: 2-D Counter plot and 3-D response surface plot of response-1 dissolution.

A. Response – 1 dissolution (%)

Table 7 shows the analysis of variance (ANOVA) report for the selected factorial model. The F-value of 136.82 clarifies that the model is significant. It has been found that there is only a 0.01% chance to occur large *F*-value due to noise. The Prob>*F* values obtained are less than 0.05, which means that the model terms are significant. Factor A and B are significant model terms and Prob>*F* values of more than 0.05 confirm that the model terms are insignificant. The fitted equation obtained for the selected model is given below:

Independent variables: Mannitol 25°C

Standard deviation: 1.36, mean value: 63.18, C.V. %: 1.58

R-square value: 0.9864, Adj *R*-square value: 0.9830, Pred *R*-square value: 0.9797

Response surface analysis

The 3D response surface plot and 2D counter plot analyses indicate that the effect of mannitol 25C concentration is highly prominent on % dissolution. An increase in the concentration of mannitol 25C increases the dissolution rate as observed for 5 min (Figure 8). On the other hand, the effect of polyplasdone XL concentration has been found to be negligible. Moreover, the effect of sepitrap is also found to be insignificant on the dissolution profile of the drug under study.

B. Response - 2: disintegration time (DT)

An ANOVA for the selected factorial model (disintegration time) is shown in Table 8. The F-value of 82.90 clarifies that the model is significant. It is found that there is only a 0.01% chance to occur large *F*-value due to noise. The Prob>*F* values obtained are less than 0.05, which means that the model terms are significant. Factor B is a significant model term and Prob>*F* values more than 0.05 confirm that the model terms are insignificant. The fitted equation obtained for the selected model is given below:

Independent variables: polyplasdone XL

Standard deviation: 6.91, mean value: 39.27

R-square value: 0.9540, Adj *R*-square value: 0.9424, Pred *R*-square value: 0.9280

Response surface analysis

The 3D-response surface plot and 2D counter plot analyses indicate that the effect of polyplasdone XL concentration is highly prominent on disintegration time; an increase in its concentration decreases the disintegration time, as observed in Figure 9. On the other hand, the effect of concentration of mannitol 25C is found to be negligible. Further, the effect of sepitrap 80 is also found to be insignificant on the dissolution profile.

C. Response - 3: permeability (%)

An ANOVA for the selected factorial model (permeability %) is shown in Table 9. The model is significant as *F*-value was found to be 290.12 compared to noise. Only 0.01% chance has been found to occur large *F*-values due to noise. The Prob>*F* values are less than 0.05, which means that the model terms are significant. Factor C is a significant model term and the value of Prob>*F* more than 0.05 confirms that

Table 8: ANOVA for response-2 factorial model.						
Analysis of variance table (Partial sum of squares – Type 3						
Sources	**Sum of Squares**	**D_f**	**Mean square**	***F*- value**	***p*-value Prob> F**	
Model	7910.50	2	3955.25	82.90	<0.0001	Significant
B- Polyplasdone XL	7812.50	1	7812.50	163.75	<0.0001	
C- Sepitrap 80	98.00	1	98.00	2.05	0.1.897	
Residual	381.68	8	47.71			
Lack of Fit	381.68	6	63.61	1.62	0.5421	Not significant
Pure Error	0.000	2	0.000			
Cor Total	8292.18	10				

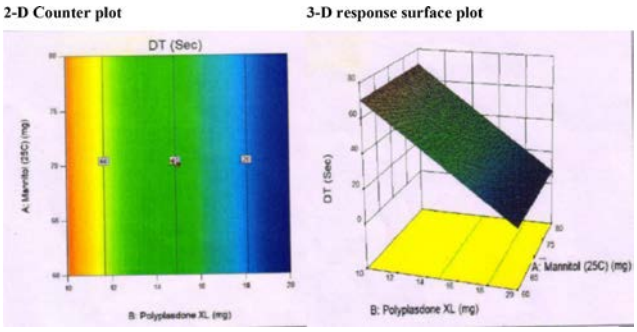

Figure 9: 2-D Counter plot and 3-D response surface plot of response-2 DT.

the model terms are insignificant. The fitted equation obtained for the selected model is given below:

Independent variables: Sepitrap 80

Standard deviation: 2.25, Mean value: 63.18, C.V.%: 3.56

R-square value: 0.9864, Adj R-square value: 0.9830, Pred R-square value: 0.9797

Response surface analysis

The 3-D response surface plot and 2-D counter plot analyses indicate that the effect of sepitrap 80 has been highly prominent on % permeability; the increase in the concentration of sepitrap 80 has increased the % permeability, as observed in Figure 10. On the other hand, the effect of polyplasdone XL concentration on drug permeability has been found to be negligible. Moreover, the effect of Mannitol 25C has also been found to be insignificant on permeability.

Optimization and validation of DoE model

The optimized and validated critical material attribute (CMA) values as per the desired CQA criteria have been enlisted in Table 10. The objective has been to obtain the studied ranges of CMAs meeting the desired criteria of CQAs (Table 10). The overlay plot shows the optimized solution of all the independent variables over CQAs results (Figure 11).

The design space obtained shows operating ranges for factor A (67 to 80 mg), factor B (18 to 20 mg) at a fixed value of factor C (11.74 mg), and suggested optimal formulation composition containing A: 73.5 mg, B 19 mg, and C: 11.74 mg.

Stability studies

The optimized sublingual tablet formulation was subjected to stability studies and the results so obtained, have been depicted in Table 11. The results of the drug content, DT, and dissolution rates after 3 months in the stability chamber were found similar to that of the control samples (normal temperature). Hence, it can be concluded that the prepared tablets are stable under such conditions.

CONCLUSION

We attempted to design and develop the bioenhanced sublingual tablet of rizatriptan benzoate to combat migraine in the present research work. The main objectives behind the work were the enhancement of percentage permeability of the drug, fast drug release, bypassing the effect of first-pass metabolism, and achieving patients' compliances. The present research work reflects the comparative permeability enhancer property of two different excipients (SLS and Sepitrap 80) in the formulation. Disintegration time affects the drug release as well permeability of the drug. Higher the DT, lower the drug release, and vice versa. The study showed that the formulation containing polyplasdone XL in the intra-granular as well as extra-granular parts is more beneficial than the formulation (Table 1) developed with the incorporation of the entire amount polyplasdone XL in the intra-granular part. Divided concentrations of polyplasdone XL in two different parts of a formulation lower the DT more effectively than the formulation containing the complete amount of polyplasdone XL in one part. The available dosage form of this drug in the market has been facing some

Table 9: ANOVA for Response-3 factorial model.						
Analysis of variance table (Partial sum of squares – Type 3						
Sources	**Sum of Squares**	**D_f**	**Mean square**	***F*- value**	***p*-value Prob> F**	
Model	2929.25	2	1464.63	290.12	<0.0001	Significant
A- Mannitol 25 C	3.13	1	3.13	0.62	0.4541	
C- Sepitrap	2926.13	1	2926.13	579.63	<0.0001	
Residual	40.39	8	5.05			
Lack of Fit	34.39	6	5.73	1.91	0.3828	Not significant
Pure Error	6.00	2	3.00			
Cor Total	2969.64	10				

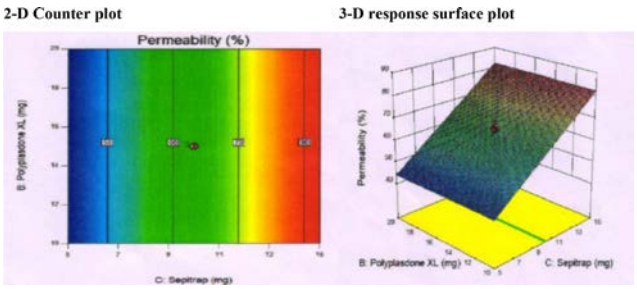

Figure 10: 2-D Counter plot and 3-D response surface plot of reponse-3 permeability (%).

Table 10: Validation DOE model for CMAs and CQAs.				
CMAs				
Factor A (mg)		Factor B (mg)	Factor C (mg)	
72.56		19.16	11.74	
CQAs				
CQAs	**Predicted mean**	**Actual mean**	**95 % CI (Low)**	**95 % CI (High)**
Dissolution %	89.837	89.99	84.6354	86.6374
Disintegration time (sec)	12.6106	12	34.4702	44.0753
Permeability %	70.5703	69.99	61.6196	64.744

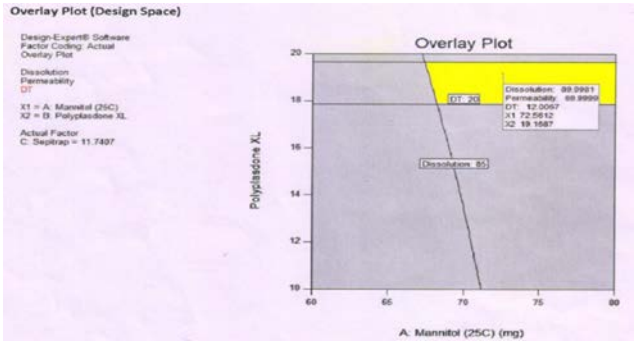

Figure 11: Overlay plot for independent variables and their responses on CQAs.

issues, such as less bioavailability due to first-pass metabolism, degradation of the drug in the stomach pH, and slow drug release. This drug is highly soluble in the aqueous medium but has a low permeability, which increases the dose frequency resulting in reduced patient compliances. Hence, to resolve all these problems, the development of a sublingual dosage form was the best possible option in solid dosage forms.

The results obtained from the study showed that the problem associated with the low bioavailability of the drug has been resolved as the drug is presently formulated for its sublingual delivery incorporating a bioenhancer and a super disintegrant in the fast release novel formulation to overcome the problems associated with migraine.

The SLS used in the formulations understudy was excluded as permeability enhancers because it provided less percentage permeability than that by Sepitrap 80 at the same concentration. Hence, sepitrap 80 was finally selected as the permeability enhancer and the formulations containing sepitrap 80 were subjected to DOE trials. The developed tablets from the various optimized batches were then evaluated for physical and chemical parameters. The *in vitro* disintegration time, *in vitro* percent drug release, *in vitro* permeability (%), and *ex vivo* permeability (%) of all the batches were found to be in between (9 - 45) sec, 97% - 99%, 44.94% - 77.28%, and 50.24% - 82.28% respectively. The *in vitro* and *ex vivo* permeabilities (%) of batch S-3 at 90 min were found to be 77.28% and 82.28% respectively; DT was reported to be 9 sec and the formulation showed 100% drug release in 10 min. A stability study was also performed for the best batch (S-3) at 40ºC/75% RH for three months following ICH guidelines and no such deviation was observed from the initial products. It had further been found from the study that the excipients like mannitol, silicon dioxide, sodium stearyl fumarate, aerosol 200, polyplasdone XL, aspartame, sepitrap

Table 11: Stability study of best formulation- Evaluation parameters.					
S. No	**Parameters**	**Initial**	**First Month**	**Second Month**	**Third Month**
1.	Thickness (mm)	3.31	3.31	3.31	3.31
2.	Hardness (N)	19	18	19	20
3.	Drug content (% w/w)	100.41	100.17	99.937	99.83
4.	Friability (%w/w)	0.27	0.31	0.38	0.39
5.	Average Weight (g)	199	199	199	199
6.	Disintegration Time (Sec)	09.00	09.20	09.45	10.45
7.	Wetting Time (Sec)	03.00	04.00	04.00	04.00
8.	*In vitro* % cumulative percent drug release in 10 min	99.00	98.82	98.05	97.64
9.	*In vitro* permeation study (% cumulative release in 90 min)	77.28	76.02	75.06	74.23
10.	*Ex vivo* permeation study (% cumulative release in 90 min)	82.28	81.37	79.43	77.07

80, and SLS were the ideal excipients used for the preparation of sublingual tablets of rizatriptan. Hence, the S-3 batch of the prepared formulations was justified as the optimized formulation of the prepared sublingual tablets of rizatriptan used for combating migraine.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

BU: Blend uniformity; **FBP:** Fluidized bed processor equipment; **DoE:** design of experiment; **QbD:** Quality by Design; **DT:** Disintegration Time; **FTIR:** Fourier Transform Infrared; **SLS:** Sodium laurel sulphate; **QTPP:** Quality Target Product Profile; **CQA:** Critical quality attributes; **USP:** United States Pharmacopeia; **NMT:** Not more than; **LOD:** loss on drying; **IP:** Indian Pharmacopeia; **ANOVA:** Analysis of Variance; Critical materials attributes.

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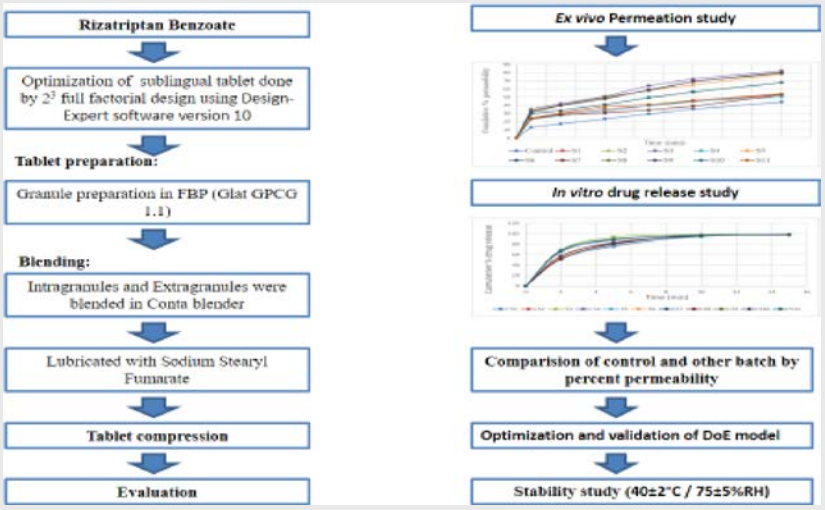
PICTORIAL ABSTRACT



SUMMARY

- Rizatriptan is a new generation anti-migraine drug, which is a serotonin 5HT 1D receptor agonist and used as a first line drug for managing moderate to severe migraines. Sublingual tablet of rizatriptan can provide fast-acting, non-invasive relief from migraine attacks and thereby, overcome the challenges associated with the permeability problems of the drug.
- Therefore, the present work was designed to formulate bioenhanced sublingual tablets of rizatriptan benzoate, using super disintegrants, ensuring fast disintegration, better dissolution, and better permeability of the drug.
- The research work is based on the comparative study and selection of the optimum bioenhancer among sodium laurel sulphate and Sepitrap 80 based on permeability studies.
- The bioenhanced sublingual tablet of rizatriptan benzoate was prepared by wet granulation technique using fluidized bed processor (FBP) equipment.
- A 2^3 full factorial design was followed for the optimization of the process, by varying three independent factors at two levels and studying their effect on three dependent variables. Eleven runs were carried out, out of which three were identified as the central points. The Design-Expert software version 10 was used to carry out the design of experiment (DoE) trials. The optimized formulation was subjected to stability studies for 3 months as per the International Conference of Harmonization (ICH) guidelines.
- The use of polyplasdone XL and Sepitrap 80 can be promising for the development of fast-release formulations of sublingual tablets with improved permeability, especially with drugs having low permeability.

About Authors

Mr. Manish Kumar Singh has completed Master of Pharmacy in Pharmaceutics from Noida Institute of Engineering and Technology (Pharmacy Institute), Greater Noida, UP, and his area of interest is modified drug release and nanotechnology. He is presently working in F&D as Research Associate in Medley Research Centre, Mumbai.

Dr. Rupa Mazumder is working as Professor, Dean and HOD Pharmaceutics in the Noida Institute of Engineering and Technology (Pharmacy Institute), Greater Noida, UP, and has a total teaching and research experience of more than 25 years. Prof. Mazumder has served various reputed academic organizations, like Birla Institute of Technology (BIT), Mesra, Ranchi, and School of Pharmacy & Technology Management (SPTM), NMiMS University, Mumbai. She has guided 19 Ph.D. scholars in the field of Pharmaceutics, Microbiology and Natural Products. Dr. Mazumder has more than 250 publications in reputed national and international journals and conferences. Her major research work is on formulations related to novel drug delivery systems with the view of inclusion of new drug molecules obtained from natural sources and drug molecules and their derivatives synthesized chemically.

Mrs. Swarupanjali Padhi is working at the Noida Institute of Engineering and Technology (Pharmacy Institute), Greater Noida, UP, as Assistant Professor in the Department of Pharmaceutics. Her field of interest is development of formulations in novel drug delivery systems. She has published her research work in various reputed SCI and Scopus indexed journals.

Mr. Dinesh Kumar Singh has completed his Master of Pharmacy in Pharmaceutics and he is presently working as Senior Research Scientist in Jubilant Generics Ltd., Noida, UP.

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