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Research Article

FORMULATION OF RIZATRIPTAN BENZOATE SUBLINGUAL TABLETS PREPARED BY DIRECT COMPRESSION WITH DIFFERENT BIOADHESIVE POLYMER: *IN VITRO* AND *EX VIVO* EVALUATION

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ABSTRACT

Objective: The current investigation deals with formulation and evaluation of fast disintegrating sublingual tablets of rizatriptan benzoate (RTB) to produce its intended therapeutic effect for acute treatment of migraine. When the drug is given by sublingual route, it overcomes the first pass metabolism and quick entry of drug in systemic circulation is obtained. It would result in fast pharmacological response hence faster relief from migraine which is an important criterion in migraine therapy.

Methods: In this study, RTB sublingual tablets were prepared using direct compression process using various bioadhesive polymers such as sodium carboxymethyl cellulose, hydroxyl propyl methyl cellulose-K4M, and chitosan at various concentration ranging 0.5-5% w/w along with sodium starch glycolate (SSG) or cross carmellose sodium (CCS) as super disintegrants at different concentration ranging 2-8% w/w.

Results: The tablets disintegrated quickly and dissolution tests conclude that RTB was released from the formulation within the compendial limits. The formulations batches (A_8 and B_8) containing 2% w/w chitosan along with 2% w/w SSG or CCS which disintegrate rapidly and show high dissolution and *ex vivo* permeation were selected as optimized formulations.

Conclusion: The results obtained from the study showed that the bioavailability problem of the drug has been solved as the drug is given by sublingual route and it directly enters into systemic circulation. Furthermore, the formulation overcomes the problems associated with migraine attack as fast disintegrating technology is used.

Keywords: Rizatriptan benzoate, Migraine, Bioadhesive polymers, Sublingual tablet.

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INTRODUCTION

Migraine is a brain disorder which is by recurrent attacks of headache and various problems related to autonomic nervous distinguished system such as sensitivity to light (photophobia), nausea, visual disturbances, and other neurological symptoms. The quality of life of migraineur is significantly affected by an untreated migraine attack with 4-72 hrs of duration. According to several surveys, patients routinely experience the ill effects of the migraine attack as bring the most extreme they have ever experienced. In such cases, a quick onset of pharmacological responses required from drugs [1,2]. This can successfully be accomplished by parenteral administration, yet this technique may not generally be helpful for the patient. Therefore, a non-parenteral and convenient dosage form have been developed, i.e., sublingual dosage form in which drug is administered beneath the tongue from where it immediately reaches the systemic circulation thus providing quick onset of action [2-4]. The reason behind this quick onset of action is due to thin sublingual mucosa (190 μm) as compared to buccal mucosa (500-800 μm) and abundance of blood supply in sublingual region which results in high plasma drug concentration due to maximum drug absorption [5]. One issue related with sublingual medication conveyance is the way that the patient tends to automatically swallow fluids more prominent than 200 μL and quick disposal of drugs because of the flushing activity of salivation because of which the drug to be distributed using the sublingual course is expelled from the oral cavity and enters the gastrointestinal tract. To ensure a more intense contact of the formulation with the sublingual mucosa, the formulation should adhere to the moist surface of mucosa and should resist the flushing action of saliva. To overcome this disadvantage, certain bioadhesive polymers such as chitosan, sodium carboxymethyl cellulose (NaCMC), and hydroxyl propyl methyl cellulose-K4M (HPMC-K4M) were used in formulations [6-10].

The rizatriptan benzoate (RTB) is a potent and selective 5-$HT_{1B/1D}$ receptor agonist. It is used for treating acute migraine with and without aura and minimising migraine symptoms, including pain, nausea, and photophobia or phonophobia. The half life of rizatriptan is 2-3 hrs and absorption is rapid up to 90%, but absolute bioavailability is low, i.e., 47% because of high first pass effect when taken orally [11,12].

The objective of our study is to develop RTB sublingual tablets which bypass the first pass metabolism and accomplished the quick onset of activity. The RTB sublingual tablets were prepared using bioadhesive polymers such as chitosan, NaCMC, and HPMC-K4M along with superdisintegrants sodium starch glycolate (SSG) and cross carmellose sodium (CCS). Bioadhesive polymers are used in low concentration so that characteristics of sublingual tablets such as disintegration and dissolution is not affected significantly and simultaneously it provides long contact to sublingual mucosa [13]. These developed tablets were then evaluated on the basis of physiochemical parameters, *in vitro* dissolution and *ex vivo* permeation study.

MATERIALS AND METHODS

Materials

Rizatriptan is obtained as a gift sample from SMS Pharmaceuticals, Hyderabad. The bioadhesive polymers Chitosan was purchased from Shanghai Biochemicals Pvt. Ltd., India. HPMC-K4M was purchased from

CDH Pvt. Ltd, New Delhi, India. NaCMC and Spray-dried mannitol were purchased from Signet Chemical Corporation Pvt. Ltd, Mumbai. The superdisintegrants SSG and CCS were being purchased from and Loba Chemie Pvt. Ltd, Mumbai, India. Microcrystalline cellulose (MCC) was purchased from Arihant Trading Co., Mumbai, India, and magnesium stearate was purchased from S.D. Fine Chem. Ltd, Mumbai, India.

Formulation of rizatriptan sublingual tablets

Sublingual tablets of RTB were processed by direct compression method. Accurate amount of all the ingredients except magnesium stearate were passed over mesh #60 and mixed homogeneously using geometric dilution. At last, magnesium stearate was added to lubricate and mixed well. The blended material was directly compressed by a four station tablet punching machine fitted with 6 mm flat faced punch and die set. The compression force and mass of all tablets were kept stable with each tablet containing RTB equivalent to 5 mg of rizatriptan. The compositions of different formulations are given in Tables 1-3. The concentration of superdisintegrants was optimized on the basis of disintegration time from the formulation batches as shown in Table 1. After optimizing the concentration of superdisintegrants, the type and concentration of bioadhesive polymers was then optimized as given in Tables 2 and 3. Batches containing SSG as superdisintegrant were coded as "A" while batches containing CCS as superdisintegrant were coded as "B."

Determination of physicochemical parameters of tablets containing bioadhesive polymer

The drug content uniformity of the formulation was determined by dissolving the powdered tablet in 0.1 N NaOH solution and sonicated for 20 minutes in ultra sonicator bath. The solution was then filtered using 0.45 µm nylon filter, and the filtrate was subjected to necessary dilutions and the analysis was done by ultraviolet (UV)-spectrophotometer at 226 nm.

By using digital vernier caliper, the thickness of the tablets of all the prepared batches was carried by placing it perpendicular to the diameter. Measurement was done of ten tablets for each batch (n=10). Allowable variation mentioned in literature is ± 5% [14].

Weight variation test was performed by weighing 20 tablets which were selected randomly from each batch, and the individual tablet weights were then compared with the calculated average weights. The percentage weight variation of each batch was then calculated.

Hardness is performed to evaluate mechanical shock and friability test is to check the impact of friction and shocks, which may frequently cause tablet to chip, cap or break. Hardness of tablet of each batch was measured with the help of Monsanto hardness tester. It was expressed in kg cm^{-2} and study was performed in replicate of 10. Friability test was done by placing preweighed sample of tablets with approximately weight of 6.5 g in the Roche type friabilator, which was subjected to 100 revolutions. After rotations, the tablets were dedusted and the percent friability was then calculated by reweighing the tablets.

Wetting time

The wetting time of the tablets was assessed (n=6). This trial impersonates the activity of saliva in contact with the formulation. A Whatman channel paper plate collapsed once oppositely was set in a Petri dish of 7.7 cm in breadth. 8 ml of water with the water solvent color, i.e., rhodamine B was placed on the channel paper in the Petri dish. The tablet was then deliberately kept on the channel paper and time for full wetting was measured. The presence of color on the surface of tablet was taken as a sign of full wetting [15].

***In vitro* disintegration time**

In vitro disintegration time was calculated for tablets of each batch using disintegration apparatus in 6.8 phosphate buffer being maintained at 37±0.5°C [16].

***In vitro* dissolution studies**

Dissolution study of tablets of various batches was performed in 900 ml of pH 6.8 phosphate buffer as a media maintained at 37±0.5°C using

Table 1: Formulation composition of rizatriptan sublingual tablets for optimizing the concentration of superdisintegrants

Component	Quantity (mg/tab)							
	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
RTB	7.25	7.25	7.25	7.25	7.25	7.25	7.25	7.25
SSG	2	4	6	8	-	-	-	-
CCS	-	-	-	-	2	4	6	8
SDM	61.43	60.03	58.63	57.23	61.43	60.03	58.63	57.23
MCC	26.32	25.73	24.98	24.38	26.32	25.73	24.98	24.38
CSD	2	2	2	2	2	2	2	2
MS	1	1	1	1	1	1	1	1
Total weight	100	100	100	100	100	100	100	100

RTB: Rizatriptan benzoate, SSG: Sodium starch glycolate, CCS: Cross carmellose sodium, SDM: Spray dried mannitol, MCC: Microcrystalline cellulose burst, CSD: Colloidal silicon dioxide, MS: Magnesium stearate

Table 2: Formulation composition of rizatriptan sublingual tablets containing 2% w/w SSG as superdisintegrants and variable concentration of different bioadhesive polymers

Component	Quantity (mg/tab)								
	A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8	A_9
RTB	7.25	7.25	7.25	7.25	7.25	7.25	7.25	7.25	7.25
NaCMC	0.5	2	5	-	-	-	-	-	-
HPMC-K4M	-	-	-	0.5	2	5	-	-	-
Chitosan	-	-	-	-	-	-	0.5	2	5
SSG	2	2	2	2	2	2	2	2	2
SDM	61.08	60.03	57.40	61.08	60.03	57.40	61.08	60.03	57.40
MCC	26.18	25.73	24.83	26.18	25.73	24.83	26.18	25.73	24.83
CSD	2	2	2	2	2	2	2	2	2
MS	1	1	1	1	1	1	1	1	1
Total weight	100	100	100	100	100	100	100	100	100

RTB: Rizatriptan benzoate, NaCMC: Sodium carboxymethyl cellulose, HPMC-K4M: Hydroxy propyl methyl cellulose-K4M, SSG: Sodium starch glycolate, CCS: Cross carmellose sodium, SDM: Spray dried mannitol, MCC: Microcrystalline cellulose burst, CSD: Colloidal silicon dioxide, MS: Magnesium stearate

Table 3: Formulation composition of rizatriptan sublingual tablets containing 2% w/w CCS as superdisintegrants and variable concentration of bioadhesive polymers

Component	Quantity (mg/tab)								
	B_1	B_2	B_3	B_4	B_5	B_6	B_7	B_8	B_9
RTB	7.25	7.25	7.25	7.25	7.25	7.25	7.25	7.25	7.25
NaCMC	0.5	2	5	-	-	-	-	-	-
HPMC-K4M	-	-	-	0.5	2	5	-	-	-
Chitosan	-	-	-	-	-	-	0.5	2	5
CCS	2	2	2	2	2	2	2	2	2
SDM	61.08	60.03	57.40	61.08	60.03	57.40	61.08	60.03	57.40
MCC	26.18	25.73	24.83	26.18	25.73	24.83	26.18	25.73	24.83
CSD	2	2	2	2	2	2	2	2	2
MS	1	1	1	1	1	1	1	1	1
Total weight	100	100	100	100	100	100	100	100	100

RTB: Rizatriptan benzoate, NaCMC: Sodium carboxymethyl cellulose, HPMC-K4M: Hydroxy propyl methyl cellulose-K4M, SSG: Sodium starch glycolate, CCS: Cross carmellose sodium, SDM: Spray dried mannitol, MCC: Microcrystalline cellulose burst, CSD: Colloidal silicon dioxide, MS: Magnesium stearate

USP Type II (paddle type) dissolution assembly kept at 50 rpm. 5 ml of the sample was taken at different time interval, i.e., 2, 5, 10, 15 and 20 minutes and replaced with the same volume of fresh buffer. The samples were then filtered through 0.22 µm nylon filter, and drug content was analyzed using UV visible spectrophotometer at wavelength of 226 nm. Six replicates were taken to ensure high confidence on result for the dissolution studies [17].

***Ex vivo* permeation studies**

Ex vivo permeation of all the formulation batches was conducted through porcine oral mucosa (ventral surface of tongue) using Franz diffusion cell. Porcine oral mucosa was chosen as a most appropriate model for the permeation study due to its similarity to the human oral mucosa as far as histological attributes, biochemical structure, and penetrability and also the accessibility and lower cost. The mucosa was extracted and trimmed uniformly from the sides, washed in pH 6.8 phosphate buffer and utilized instantly. The mucosa was mounted between the donor and receptor compartments of Franz diffusion cell. The receptor compartment of the diffusion cell was loaded with pH 7.4 phosphate buffer kept up at 37±0.5°C and hydrodynamics were kept up utilizing magnetic stirrer. The donor compartment was loaded with 2 ml of pH 6.8 phosphate buffer. The RTB tablet of given batch was placed in donor compartment. 3 ml sample from receptor compartment were withdraw at suitable time interval (2, 5, 10, 20, 30, 45, 60, 90,105 and 120 minutes), which was then replaced with 3 ml of fresh pH 7.4 phosphate buffer. The permeation studies were carried out up to 2 hrs (120 minutes) because the freshly excised porcine oral tissue can remain alive for 2 hrs at 37±0.5°C [18,19]. Three replicates for each batch were taken for all permeation studies. The permeability coefficient (K_p) was calculated using equation (1) where J_{ss} is the steady state flux and C_v is the total volume in donor compartment. J_{ss} was obtained from the slope of the linear portion of the plot between the cumulative amount of Rizatriptan permeated per unit area and time.

$$Kp = J_{ss}/C_v \quad (1)$$

Differential scanning calorimetry (DSC)

The molecular state of the drug was assessed by DSC analysis of placebo tablet, physical blend of drug and excipients, Rizatriptan sublingual tablet, and pure drug using a DSC (DSC 6, Perkin Elmer, USA). All the samples were warmed in hermetically fixed aluminum container with a temperature scope of 35°C-394°C at a steady rate of 10.0°C for every min under nitrogen cleanse at 20 ml/minutes [20].

Accelerated stability studies

Optimized formulations (A_8 and B_8) packed in aluminum foil were subjected to accelerated stability study for 3 months as per ICH norms by keeping it in stability chamber kept at a constant temperature of 40°C±2°C and relative humidity of 75%±5% RH [21]. For 3 months, samples were taken at regular time interval of 1 month and analyzed for the change *in vitro* drug release and drug content by procedure stated earlier. Tests were performed in triplicate and mean value of the observed values was noted along with standard deviation.

RESULTS AND DISCUSSION

Determination of physicochemical parameters

The resulted physical properties of sublingual tablets were compared and are shown in Tables 4-6.

Drug content uniformity test for all the prepared batches was performed as per USP guidelines, and the results were found to be on compliance with USP guidelines. Content uniformity of batches containing SSG varies from 98.02% to 102.43% while in case of CCS containing batches it varies from 98.36% to 104.32% [14].

Thickness analysis of tablet was performed as per procedure mentioned in literature [12]. Observed variation among different batches was lying in acceptable limits of ±5%.

Weight variation test was performed as per as USP monograph. All the tablets were found to lie within acceptable weight variation limit of ±10% with respect to average weight [14].

Tablets require certain quality or hardness and a friability so as to withstand mechanical shock of handling in dealing with in assembling, packaging and dispatching. Sufficient hardness and friability are additionally required for buyer acknowledgment [12]. Prepared tablets were found to be in compliance with friability limits (<1%) mentioned in literature [14]. Hardness was also analyzed for all the batches using Monsanto hardness tester and were found to be in acceptable limit (3-6 kg/cm^2), which is required to keep up the integrity of tablet.

Wetting time

There was no significant difference in wetting time between batches with and without bioadhesive polymers. The wetting time values for the prepared tablets of all the formulation batches were found to be in the range of 12-38 seconds. The wetting time was less with 2% w/w NaCMC (A_2 and B_2), 5% w/w HPMC-K4M (A_6 and B_6), and 5% w/w chitosan (A_9 and B_9). It was observed that as the concentration of NaCMC in batches (A_3 and B_3) was made more or <2% w/w the time taken for wetting was increased. In case of batches containing chitosan and HPMC-K4M as the concentration of bioadhesive polymer decreased below 5% w/w the wetting time was increased. The results of wetting time for various batches are shown in Table 7.

***In vitro* disintegration time**

The optimized concentration of superdisintegrants was used to optimize the type and concentration of bioadhesive polymers as per Tables 2 and 3. In this study, disintegration time for batches containing SSG 2% w/w as superdisintegrants varies between 12 and 37 seconds and for batches containing CCS 2% w/w as superdisintegrant varies between 14 and

Table 4: Physicochemical analysis of batches containing superdisintegrant SSG and CCS in different ratio

Batch code	Weight variation (mg) (n=20)	Hardness (Kg/cm^2) (n=10)	Thickness (mm) (n=10)	Content uniformity (%)	Friability (%)
C_1	101±3.11	4.8±0.11	3.1±0.04	99.61	0.12
C_2	100±3.04	4.5±0.09	3.2±0.03	98.42	0.19
C_3	101±4.13	4.9±0.38	3.1±0.05	98.21	0.34
C_4	100±3.92	4.9±0.21	3.0±0.04	102.02	0.23
C_5	102±4.37	4.6±0.18	3.0±0.06	99.68	0.31
C_6	106±4.24	5.5±0.43	3.0±0.03	103.11	0.27
C_7	101±3.91	5.2±0.60	3.0±0.05	99.46	0.44
C_8	100±4.19	4.5±0.33	3.0±0.04	104.32	0.21

The results of weight variation, hardness, thickness are reported in mean±SD, SSG: Sodium starch glycolate, CCS: Cross carmellose sodium, SD: Standard deviation

Table 5: Physicochemical analysis of batches containing SSG (2% w/w) and bioadhesive polymers

Batch code	Weight variation (mg) (n=20)	Hardness (Kg cm^2) (n=10)	Thickness (mm) (n=10)	Content uniformity (%)	Friability (%)
A_1	100±3.11	5.2±0.38	3.0±0.04	98.02	0.34
A_2	100±3.31	4.1±0.32	3.2±0.03	99.71	0.27
A_3	101±4.62	4.3±0.44	3.1±0.06	101.24	0.43
A_4	102±3.76	5.6±0.40	3.0±0.04	99.51	0.18
A_5	101±4.20	4.5±0.28	3.0±0.05	102.43	0.19
A_6	100±3.01	4.9±0.61	3.0±0.03	99.56	0.47
A_7	103±3.99	4.6±0.53	3.2±0.03	98.34	0.17
A_8	100±4.76	5.1±0.31	3.1±0.05	101.42	0.22
A_9	102±3.69	4.7±0.56	3.0±0.04	99.83	0.36

The results of weight variation, hardness, thickness are reported in mean±SD. SSG: Sodium starch glycolate, SD: Standard deviation

Table 6: Physicochemical analysis of batches containing CCS (2% w/w) and bioadhesive polymers

Batch code	Weight variation (mg) (n=20)	Hardness (Kg cm^2) (n=10)	Thickness (mm) (n=10)	Content uniformity (%)	Friability (%)
B_1	102±4.71	4.2±0.47	3.0±0.05	101.39	0.25
B_2	100±3.90	4.1±0.32	3.2±0.03	98.71	0.28
B_3	100±3.45	4.3±0.63	3.1±0.06	98.36	0.17
B_4	101±3.52	4.6±0.42	3.0±0.04	103.01	0.34
B_5	103±3.85	4.7±0.07	3.0±0.04	104.04	0.18
B_6	104±4.47	5.1±0.26	3.0±0.03	98.91	0.34
B_7	100±3.93	5.2±0.17	3.0±0.05	99.56	0.41
B_8	100±3.77	5.8±0.44	3.2±0.06	103.35	0.17
B_9	101±2.38	4.6±0.36	3.1±0.04	99.50	0.14

The results of weight variation, hardness, thickness are reported in mean±SD, SD: Standard deviation, CCS: Cross carmellose sodium

38 seconds as shown in Table 7. According to USP guidelines, sublingual tablets should disintegrate in <2 minutes in USP disintegration apparatus equipped with basket rack assembly without plastic disk [13]. Thus, all the batches pass the *in vitro* disintegration test. The rapid and sudden disintegration of tablets might be due to spray dried mannitol, MCC burst and due to the presence of superdisintegrant (SSG or CCS).

In vitro dissolution test

The dissolution profile of RTB in all the formulations is shown in Figs. 1 and 2. As mentioned in literature, within 15 minutes the amount of drug dissolved from a sublingual tablet should be more than 80% [15]. As a result, all batches comply with the above-mentioned criteria, as all the formulation showed above 80% release within 10 minutes. Quick release of the drug from the formulations can be clarified on the basis of various factors. First, the assembling strategy can be a standout among the most imperative parameters for the quick dissolution. The tablets formulated using direct compression method disintegrates into rizatriptan particles rather than granules that straightforwardly come into contact with dissolution liquid and displays nearly quicker release. From all the polymers containing formulations, the formulation A_8, A_9, B_8 and B_9 containing 2% w/w and 5% w/w chitosan showed the most extreme drug release. The chitosan generally inundates water when it comes in contact with the fluid and burst because of the pressure applied by the capillary action thereby show immediate disintegration of the dosage form.

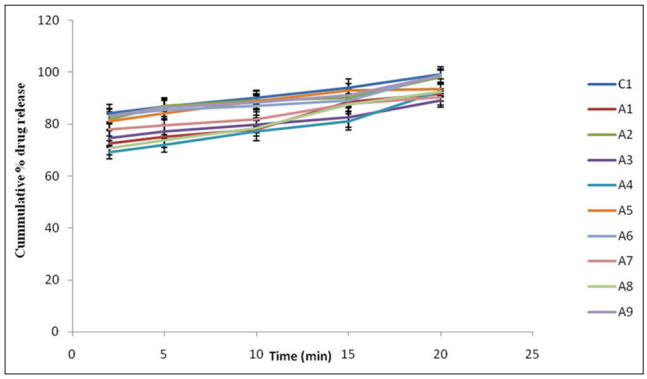

Fig. 1: Dissolution profile of sublingual tablets of rizatriptan benzoate containing sodium starch glycolate 2% w/w with and without bioadhesive polymers

Ex vivo permeation studies

All the batches were further analyzed by performing *ex vivo* permeability studies through porcine oral mucosa procured from local slaughter house, Jalandhar. The percentage of drug permeated from the formulations after 120 minutes in the vicinity of 23.55% and 27.95%. Low and

Table 7: *In vitro* disintegration time and wetting time of sublingual tablets of RTB

Batch code	Disintegration time (seconds)	Wetting time (seconds)
C_1	22±3.22	17±0.56
C_2	34±4.76	23±0.42
C_3	41±6.34	29±0.59
C_4	35±4.67	26±0.37
C_5	19±2.83	15±0.41
C_6	39±7.31	29±0.54
C_7	38±5.35	33±0.23
C_8	42±1.59	28±0.47
A_1	32±3.98	27±0.58
A_2	23±9.37	19±0.60
A_3	34±1.57	26±0.33
A_4	48±2.87	25±0.54
A_5	29±10.01	37±0.51
A_6	25±1.99	14±0.56
A_7	34±5.72	31±0.38
A_8	47±8.34	24±0.46
A_9	27±9.47	12±0.45
B_1	35±4.76	23±0.50
B_2	21±7.38	19±0.49
B_3	34±2.66	33±0.53
B_4	46±6.41	38±0.55
B_5	48±3.77	29±0.38
B_6	24±4.90	17±0.49
B_7	36±6.45	36±0.37
B_8	43±2.56	21±0.58
B_9	26±7.55	13±0.52

For all the batches disintegration and wetting time is reported in mean±SD. SD: Standard deviation, RTB: Rizatriptan benzoate

Table 8: Drug release parameters for permeability studies carried out on porcine mucosa (n=3)

Batch	Released (%)	J_{ss} (µg/cm² hr)	K_p (cm/hr)
C_1	23.68±4.22	157.3±11.91	62.92±5.78
C_5	23.55±3.45	157.8±17.87	63.12±3.98
A_1	24.18±1.98	159.5±23.12	63.92±9.77
A_2	25.72±0.87	247.9±13.67	99.16±4.54
A_3	23.67±0.56	171.4±15.65	68.56±6.87
A_4	26.42±1.65	256.8±14.76	102.72±7.45
A_5	25.66±0.59	279.4±12.68	111.76±3.26
A_6	25.41±0.98	282.2±16.34	112.88±11.20
A_7	27.91±2.54	285.9±22.87	114.36±6.56
A_8	25.26±1.76	414.9±11.87	165.96±8.52
A_9	27.95±3.45	348.7±16.87	139.48±4.52
B_1	24.88±0.67	199.1±12.87	79.64±3.65
B_2	25.97±0.98	253.5±19.98	101.4±6.56
B_3	25.03±0.34	194.7±14.56	77.88±7.72
B_4	25.69±2.56	255.4±16.78	102.16±8.66
B_5	25.44±1.65	268.1±13.65	107.24±2.76
B_6	25.99±0.93	273.1±18.55	109.24±1.65
B_7	25.32±2.54	324.2±10.66	129.68±5.81
B_8	25.68±1.49	410.3±19.77	164.12±9.62
B_9	25.07±3.68	357.6±14.76	143.04±7.48

The results of permeation value are reported in mean±SD. SD: Standard deviation

moderate release of drug can be credited to little volume (2 ml) in donor compartment due to which the tablets swell. The resulted swollen particles of the tablets have porosity, and the drug discharge through them happens due to dispersion from the openings made by the porosity of matrix. In *in vivo* conditions, the force being applied by the tongue to the tablet can inhibit swelling and promotes disintegration of tablet and release of drug from the formulation. Then again, Chitosan and HPMC-K4M formulations (A_4-A_9 and B_4-B_9) showed higher drug release and increased steady state flux (J_{ss}) and permeability coefficient (K_p) values

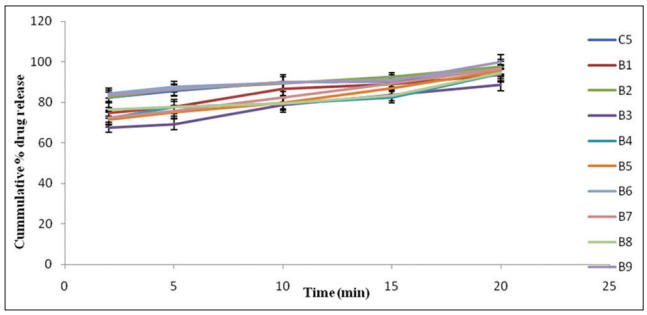

Fig. 2: Dissolution profile of sublingual tablets of rizatriptan benzoate batches containing cross carmellose sodium 2% w/w with and without bioadhesive polymers

contrasted with NaCMC formulations shown in Table 8. Maximum value of J_{ss} and K_p was observed for A_8 and B_8 batch having 2% w/w chitosan.

DSC

The DSC thermogram of the samples, i.e., pure drug, placebo (tablet), physical mixture of RTB with excipients, and optimized RTB sublingual tablet were studied. The endothermic peak of pure drug was found at 164°C whereas in optimized RTB sublingual tablet and physical mixture of RTB with excipients the endothermic peak was observed at 165°C. The size of peak is small because of the reason that measure of RTB in sublingual tablet and physical blend with drug was about 20%. It demonstrates that drug is present in crystalline form in all the formulations. The presence of peak at 138.8°C on all samples except the pure drug was due to the addition of excipients (Fig. 3).

Accelerated stability studies

There were no physical changes in the appearance and color of tablet. After subjecting the optimized formulation (A_8 and B_8) to the accelerated stability studies, the results were shown Tables 9 and 10 and Fig. 4. It was found that in percentage drug content and *in vitro* drug release there were no major changes. Hence, the formulation was found to be stable.

CONCLUSION

Our research has been made to overcome problem associated with poor drug bioavailability of RTB by giving the drug by sublingual route which will bypass first pass effect; thus drug bioavailability will be enhanced. All batches were made by direct compression method. SSG and CCS were used as superdisintegrants in various concentrations, and an optimum concentration (2%w/w) of superdisintegrants was selected based on disintegration time. Along with these superdisintegrants various bioadhesive polymers such as Chitosan, HPMC-K4M, and NaCMC were used as in different ratio, i.e., 0.5% w/w, 2% w/w, and 5% w/w in tablets so as to enhance the residence time of drug containing particles and overcome the flushing action of saliva. Their concentration was optimized in such a way that they will provide adhesion of generated particles after disintegration of tablet without significantly effecting the disintegration time of tablet. Various parameters were evaluated for each batch such as weight variation, thickness, content uniformity, drug content, *in vitro* dissolution test, and *in vitro* disintegration test. The result of these tests has been found in acceptable range as per USP 2007. The formulation containing 2% w/w and 5% w/w chitosan, i.e., A_8, A_9, B_8 and B_9 has shown good dissolution as compared to other batches. The permeability value of formulation containing 2% w/w and 5% w/w of chitosan and HPMC-K4M (A_5, A_6, A_8, A_9, B_5, B_6, B_8 and B_9) was found to be maximum. The formulation with 2% w/w of chitosan (A_8 and B_8) was selected as optimum formulation as it not only will give effective result such as permeation, dissolution, and disintegration but it is also economical as compared to higher amount of its percentage, i.e., 5% w/w used for batches A_9 and B_9. Accelerated stability studies of optimized formulations (A_8 and B_8) reveals that designed formulations are stable on storage and are capable to give reproducible results.

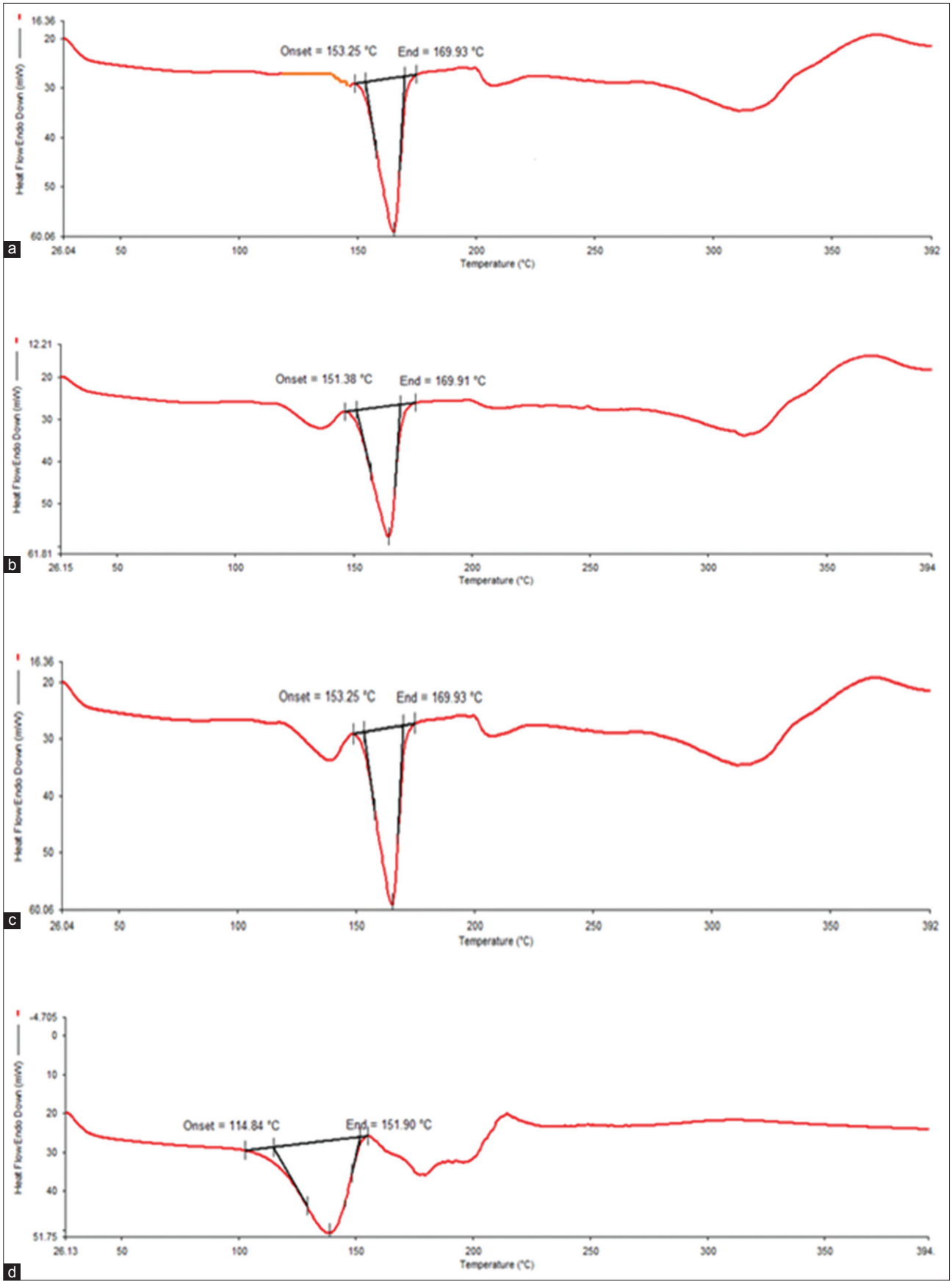

Fig. 3: Differential scanning calorimetry thermogram of (a) pure drug, (b) physical mixture of drug and excipients, (c) rizatriptan benzoate sublingual tablet and (d) placebo tablet

Table 9: Accelerated stability studies for batch A_8

Parameter	Temperature maintained at 40±2°C; RH maintained at 75±5% RH			
	Initial	After 1 month	After 2 months	After 3 months
Drug content (%)	99.89±3.24	99.82±3.19	99.76±3.16	99.69±2.27
% drug release after 20 minutes	99.31±2.15	99.23±3.21	99.18±2.18	99.16±2.25

RH: Relative humidity

Table 10: Accelerated stability studies for batch B_8

Parameter	Temperature maintained at 40±2°C; RH maintained at 75±5% RH			
	Initial	After 1 month	After 2 months	After 3 months
Drug content (%)	99.89±2.24	99.82±3.19	99.76±3.16	99.69±2.27
% Drug release after 20 minutes	99.91±3.27	99.86±2.21	99.71±3.18	99.68±3.25

RH: Relative humidity

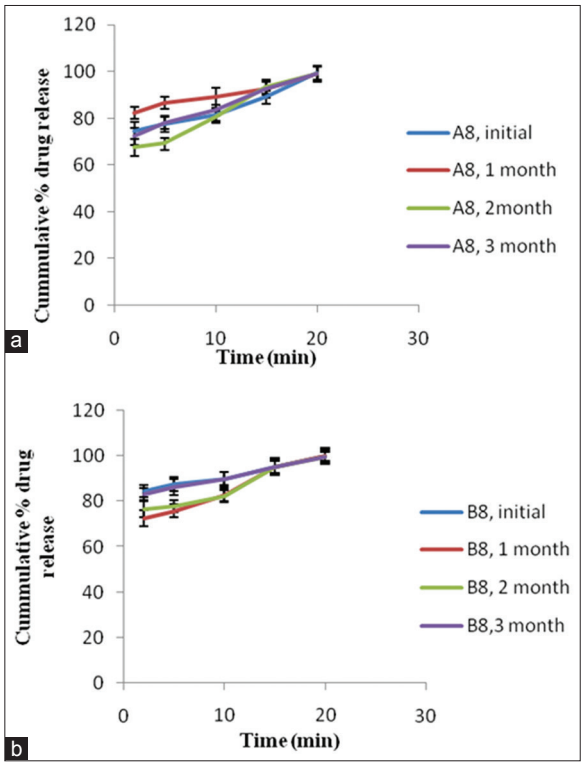

Fig. 4: Percentage drug release of (a) optimized formulation A_8 at various time intervals (b) optimized formulation B_8 at various time intervals

Future prospective of the present project comprises *in vivo* evaluation of the developed formulation in suitable animal model using suitable analytical technique which could not be done during present work due to time constraint and availability of sophisticated instrumentation.

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