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Development of Oral Disintegrating Tablet of Rizatriptan Benzoate with Inhibited Bitter Taste

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Abstract: The purpose of this research was to mask the bitter taste of Rizatriptan benzoate (RB) and to formulate an oral disintegrating tablet (ODT) of the taste-masked drug. Taste masking was done by mass extrusion with aminoalkylmethacrylate copolymer, Eudragit EPO, in different ratios. The drug: polymer ratio was optimized based on bitterness score and RB -polymer interaction. Taste masking was evaluated by checking the *in vitro* release of RB in simulated salivary fluid (SSF) of pH 6.8 and by sensory evaluation in human volunteers. Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) were performed to identify the physicochemical interaction between RB and the polymer. For formulation of rapid- disintegrating tablets of RB, the batch that depicted optimum release of RB in SSF, was considered. ODTs of Rizatriptan Benzoate were prepared by using superdisintegrants namely, sodium starch glycolate, crospovidone and croscarmellose sodium using the direct compression method. The tablets were evaluated for hardness, friability, wetting time, *in vitro* disintegration time. The optimum formulation was selected and the tablets were evaluated for thickness, drug content, content uniformity and mouth feel, in vivo disintegration time, *in vitro* drug release at pH 1.2 and 6.8 and stability study. Eudragit EPO was able to mask the bitter taste of Rizatriptan benzoate effectively in 1:1 ratio by mass extrusion method. FTIR and DSC data revealed absence of RB-polymer interaction. ODTs containing crospovidone (5% w/w) depicted minimum disintegration time. Taste evaluation of ODT in human volunteers revealed considerable taste masking, with all 6 volunteers, reporting the taste of ODTs as good in comparison with RB. Thus, results conclusively demonstrated successful taste masking and rapid disintegration of the formulated tablets in the oral cavity with adequate dissolution. The research work suggests a rapid, simple and cost effective mass extrusion method for formulation of ODT of Rizatriptan benzoate.

Key words: Taste masking · Oral disintegrating tablet · Rapid-disintegrating tablets · Rizatriptan benzoate · Eudragit EPO · Superdisintegrants

INTRODUCTION

Migraine is a chronic and incapacitating neurological disorder characterized by pulsating headaches usually restricted to one side, lasting for 4-48 hours. Although the specific cause of migraine is currently unknown, the mechanisms involved in the pathophysiology of migraine are well understood. The neurotransmitter serotonin appears to be intimately involved in the pathogenesis of migraine; levels of serotonin fall during the onset of a migraine attack and serotonin agonists relieve attacks [1]. Many of the approved treatments, specifically for treating migraines, act through serotoninergic mechanisms. These include the traditional ergotamine-based medication and the newer 5-HT1B/1D receptor agonist (triptan) treatments that selectively target particular serotonin-receptor subtypes [2].

Rizatriptan benzoate (RB) is one of the more clinically effective and therefore cost-effective oral triptans available for the acute treatment of migraine.

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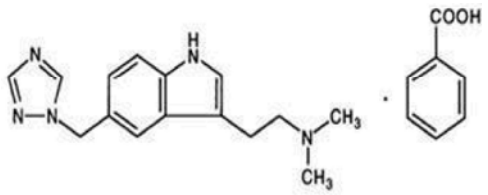


Fig. 1: Rizatriptan benzoate

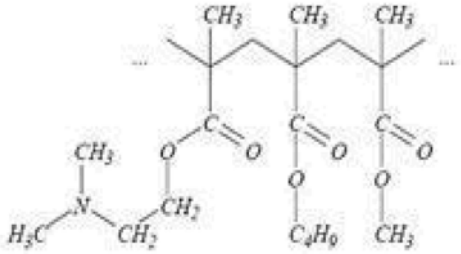


Fig. 2: Eudragit EPO

Rizatriptan benzoate (Figure 1) is an orally active serotonin 5-HT1 receptor agonist that potently and selectively binds to 5-HT1B/1D subtypes. It has greater oral bioavailability than sumatriptan and is rapidly absorbed [3]. Its bitter taste is its main drawback [4-6]. It is important to mask the unpalatable taste of a drug in order to improve the product quality as well as patient compliance, especially in the children and the elderly population [7].

The general objective of taste masking is to minimize drug release in the oral cavity from the time of the onset of tablet disintegration until the time that it (such disintegrated mass) is swallowed. It is therefore important to find methods of forming drug carrier combinations which would release negligible amounts of drug in the oral cavity, yet provide a rapid and complete release in the gastric region [8, 9].

Eudragit L and S polymers are poly (methacry1ic methyl methacrylate)s, which are soluble in water at pH values above 6 and 7, respectively; and are suitable for enteric coating and GI targeting of drug. Eudragit RS and Eudragit RL are used for formulating the time controlled drug delivery systems, due to their permeability and pH independent swelling nature. Eudragit E(R) (Figure 2) is a cationic copolymer, based on dimethyl aminoethyl methacrylate and neutral methacrylic esters, soluble up to pH 5; however it is swellable and permeable above pH 5.8. It is a copolymer of (2-dimetylaminoethyl) methacrylate, butyl methacrylate and methyl methacrylate in the ratio of 2:1:1. Eudragit E(R), an acid-soluble polymer, was selected for the taste masking [10-13].

Oral Disintegrating Tablets (ODTs), a type of drug delivery system, are solid unit dosage forms, which disintegrate rapidly in the mouth without chewing and in absence of water. ODTs are widely used for pediatric, geriatric and institutionalized patients due to their ease of administration [14]. The current commercially available ODT of Rizatriptan benzoate (MAXALT-MLT(R), USA) is prepared by lyophilization [15]. However; the ODTs formed by lyophilization may have low mechanical strength and may exhibit-poor stability at higher temperatures and humidity. In addition, freeze-drying is a capital intensive process [14]. Therefore, the simple and economical method of mass extrusion of the drug with Eudragit EPO was utilized to mask the bitter taste of rizatriptan benzoate. Although Eudragit polymers have been researched extensively for their taste masking ability and are used commonly for controlling the drug release or for the GI targeting, yet a Eudragit based, commercial taste masked product doesn't exist. The current research work uses Eudragit EPO for masking the bitter taste of rizatriptan benzoate.

The objective of this investigation was to mask the bitter taste of RB by preventing its release at salivary pH yet allowing release to occur under the acidic conditions of stomach (pH 1.2) and to develop a ODT of RB by the direct compression method.

MATERIALS

Rizatriptan Benzoate was procured as a Gift Sample from Cipla Ltd Mumbai (India). Eudragit EPO was a kind Sample from Evonik Degussa Ltd. Mumbai (India). Sodium starch glycollate USP (Primojel(R)), croscarmellose sodium USP (Ac-Di-Sol(R)) and crospovidone USP (Polyplasdone XL(R)) were gifted by Shreya Life Sciences, Aurangabad (India). The following excipients, gifted by Shreya Life Sciences, Aurangabad (India), Pearlitol(R) SD 200, sodium stearyl fumarate, sodium saccharin and peppermint oil were used for preparing the ODTs. All other ingredients used were of analytical grade.

METHODS

Preparation of Taste-Masked Granules of Rizatriptan Benzoate: The bitter taste of rizatriptan benzoate was masked by using Eudragit EPO by using the mass extrusion method [16]. The drug was thoroughly mixed with powdered Eudragit EPO, in weight ratios of 1:1, 1:2, 1:3, in a glass pestle mortar for 10 minutes. The mixture of drug and polymer (4gm, 6gm, 8gm of the weight ratios

1:1, 1:2, 1:3 respectively) was added slowly to 3, 5 and 7ml of 10% ethanol in water, till a gel was obtained. The prepared gel was pressed manually through a glass syringe 18G×1/2" flat cup hypodermic needle. After extrusion of the gel, the ethanol was removed by evaporation by leaving the gel overnight at room temperature. Subsequently the solidified gel was crushed into granules using pestle and mortar. The drug: polymer granules P1, P2, P3, corresponding to drug: Eudragit weight ratios of 1:1, 1:2, 1:3 respectively, were sieved through 2 sieves, number 22 and 44 (having nominal mesh aperture 710 µm and 355 µm) [17] and the granules collected on sieve number 44 were evaluated for taste masking.

Determination of Threshold Bitterness Concentration of Rizatriptan Benzoate: The bitter taste threshold value of rizatriptan benzoate was determined [18] by a single blind study, based on taste recognition by six volunteers from whom informed consent was obtained. A series of rizatriptan benzoate standard solutions of different concentrations (50, 75, 100, 125, 150, 175 and 200 µg/ml) were prepared in phosphate buffer pH 6.8 (ionic strength of phosphate buffer pH 6.8 is 0.252). Starting with the lower concentration, the volunteers were instructed to place 1ml of the standard solution on the center of the tongue. The solution was retained in the mouth for 30 seconds and then the mouth was thoroughly rinsed with distilled water. The next highest concentration was tasted after 10 minutes. The threshold value was selected from standard solutions of rizatriptan benzoate as the lowest concentration that produced the sensation of bitter taste in human volunteers.

Characterization of Taste Masked Granules of Rizatriptan Benzoate for in vitro Evaluation of Taste Masking, Flow Properties and Molecular Properties: *In vitro* taste of batch P1, P2 and P3 and also of drug; polymer physical mixture (PM) was evaluated [19] by determining drug release in phosphate buffer solution pH 6.8. Taste masked granules, equivalent to dose of rizatriptan benzoate (10mg), was placed in 5 ml of phosphate buffer pH 6.8 solution and was allowed to stand for 1 and 2 minutes. The amount of drug released was determined by UV spectroscopic method (JASCO V-630, Japan) at 225 nm. The UV spectroscopic method, for determination of RB in phosphate buffer solution pH 6.8 at 225 nm, was developed and validated in our laboratory. The regression equation for calibration curve of RB in phosphate buffer pH 6.8 was $y = 0.2489x + 0.0012$ ($r^2 = 0.9993$).

Drug release [20] from the taste masked granules of rizatriptan benzoate, equivalent to dose, was determined in USP Type II apparatus (Electrolab TDT, Mumbai, India) at 50 rpm at 37± 0.5°C and 0.1 N hydrochloric acid as the dissolution medium, analyzing 5ml of appropriately diluted sample at 225 nm. The regression equation for RB in 0.1 N hydrochloric acid was $y = 0.223x + 0.021$ ($r^2 = 0.9990$).

Physical properties of the taste masked granules (batch P1, P2, P3) such as bulk density, tapped density, compressibility index, Hausner's ratio and the angle of repose [21] were determined. Bulk density was determined by the IP method I; tapped density was determined by tapping the sample 500 times.

Molecular properties of taste masked granules were studied by Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared Spectroscopy (FTIR). Thermal behavior of rizatriptan benzoate and taste masked granules of rizatriptan benzoate (1:1) was recorded using a Differential Scanning Calorimeter (Shimadzu DSC TA 60 WS) at the scanning rate of 20°C/min over a temperature range of 100 to 200°C. Infrared (IR) spectra of these samples were obtained by potassium bromide disc method (JASCO FTIR-4100, Japan) in the range of 4000 to 400 cm^{-1}.

Selection of Superdisintegrants and Formulation of Oral Disintegrating Tablets (ODT): Tablets, containing taste masked granules P1 and Pearlitol$^{(R)}$ SD 200 as the diluent along with the superdisintegrants in various concentrations, (Table 3) were prepared by using direct compression. Tablets were directly compressed using 4 kg/cm^2 on a Karnavati Mini Press II 8-station 'D' tooling tablet press. (Rimek Mini Press-II, Karnavati Engineering Ltd., Mumbai, India) The superdisintegrant, that yielded the least disintegration time, was used in the final formulation of the tablets.

Evaluation of Oral Disintegrating Tablets

Wetting Time: A piece of tissue paper folded twice was kept in a culture dish (internal diameter 6.5 cm) containing 6ml of phosphate buffer at pH 6.8. A pre-weighed tablet was placed on the paper and the time for complete wetting was measured [22].

Tablets were also evaluated for hardness [23] and friability [22] with Monsanto hardness tester (Veego, Mumbai) and Friability test apparatus (Veego, Mumbai) respectively.

***In vitro* Disintegration Time:** A tablet was placed [24] in each of the six tubes of the disintegration test

apparatus (Remi Equipments, Mumbai, India) containing phosphate buffer pH 6.8 as the immersion liquid; a disk was added to each tube. The time (in seconds) required for complete disintegration of the tablets with no palpable mass remaining in the apparatus was measured.

Characterization of ODT of Batch R8: The powder blend of batch R8 was evaluated for flow properties such as angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio.

Physical Appearance and Thickness: Tablets from batch R8 were evaluated for color and shape. The thickness and diameter of five tablets was measured using Vernier Calipers [25].

Drug Content: Drug content was determined [23, 26] by powdering a pooled sample of 10 tablets of batch R8 and dissolving the blend equivalent to 145.3 mg of rizatriptan benzoate in 50 ml of 0.1 N hydrochloric acid. The solution was filtered through Whatman filter paper No. 41, suitably diluted and the drug content was analyzed by UV spectroscopy at 225 nm. The UV spectroscopic method, for determination of RB in phosphate buffer solution pH 6.8 at 225 nm, was developed and validated in our laboratory.

Content Uniformity: The content of active ingredient of ODTs of batch R8 was determined [26] from each of 10 dosage units selected randomly. Each tablet was powdered and dissolved in 50 ml of 0.1N hydrochloric acid. The solution was filtered, suitably diluted and the drug content was analyzed by UV spectroscopy at 225 nm.

***In Vivo* Disintegration Time:** In vivo disintegration of ODTs of batch R8 [16] was performed on 6 healthy human volunteers, from whom informed consent had previously been obtained. One tablet was held in the mouth after pre-rinsing the mouth with water. The time required for complete disintegration of the tablet, as reported by the volunteers, was recorded.

***In Vitro* Dissolution Study:** In vitro dissolution study was performed [20] on tablets from batch R8 in 900 ml of 0.1 N hydrochloric acid and, separately, in phosphate buffer pH 6.8, using USP Type II apparatus at 50 rpm at 37± 0.5°C. Samples were suitably diluted and analyzed at 225 nm.

***In Vivo* Taste Masking Evaluation of Oral Disintegrating Tablet of batch R8 and Mouth Feel:** In vivo taste masking evaluation of batch R8 oral disintegrating tablet was performed [25] on the healthy human volunteers. Informed consent for participation in the test was obtained. The volunteers were requested to taste the taste masked ODTs by keeping the tablets in the mouth till it disintegrated and to rank its taste on a scale of perception ranging from 0-5. For comparison, the drug substance was also subjected to taste evaluation by the panel. The disintegrated material was held in the mouth for another 60 seconds and then spat out. The mouth was rinsed with water without swallowing the disintegrated material and, finally, the mouth feel was recorded. The human volunteers were asked to give their opinion about the feeling of smoothness or grittiness of the dispersion on a numerical scale ranging from 0 to 3 where 0, 1, 2 and 3 indicating no, slight, moderate and high roughness, respectively.

Stability Study: The oral disintegrating tablets of batch R8 (30 in number) were wrapped in an aluminum foil and placed in a Stability chamber (Thermolab, India) controlled at 40±2°C/ and 75±5% relative humidity for a period of 2 months [25]. At the end of 2 months, the content of rizatriptan benzoate was determined, also the apparent changes in tablet characteristics such as color and physical characteristics were observed.

RESULTS AND DISCUSSION

Determination of Threshold Bitterness Concentration of Rizatriptan Benzoate: All the volunteers felt the sensation of bitterness, after 30 seconds at the concentration of 150 µg /ml. Therefore it was concluded that the threshold concentration of rizatriptan benzoate, that triggered the sensation for bitter taste, was 150 µg /ml.

Characterization of Taste Masked Granules of Rizatriptan Benzoate: Table 1 depicts the drug release from the taste masked granules P1, P2, P3 and drug: polymer physical mixture PM, at the end of 1 and 2 minutes. The observed drug release, in phosphate buffer pH 6.8 from the batch P1 taste masked granules (drug: polymer ratio is 1:1) at the end of 2 minutes, was 131.16 µg /ml, which was less than the threshold bitterness concentration of rizatriptan benzoate of 150 µg /ml. Hence the taste masked granules batch P1, in the ratio 1:1 of drug to Eudragit EPO, was evaluated for

Table 1: *In Vitro* taste masking evaluation of taste masked granules of batch P1, P2, P3

Batch Code	Drug release (µg/ml) 1 minute	Drug release (µg/ml) 2 minute	% Drug release 1 minute	% Drug release 2 minute
P1	111.25±1.60	131.16±1.90	5.55±0.050	6.56±0.06
P2	92.42±2.75	105.73±2.52	4.621±0.09	5.29±0.08
P3	72.92±1.90	84.80±1.27	3.65±0.070	4.24±0.04
PM	326.48±3.75	622.20±4.19	16.28±0.730	31.12±1.39

Table 2: Flow properties of taste masked granules P1, P2, P3

Sr. No.	Parameter	P1	P2	P3
1	Bulk Density (g/cm^3)	0.5±0.0	0.526±0.0	0.526±0.0
2	Tapped Density (g/cm^3)	0.555±0.0	0.6±0.02	0.612±0.02
3	Compressibility Index (%)	9.9±0.0	12.3±3.05	14.07±3.05
4	Hausner's Ratio	1.11±0.0	1.14±0.04	1.16±0.04
5	Angle of Repose	29° 28'±0.39	30° 96'±0.43	32° 54'±0.47
6	Flowability	Excellent	Good	Good

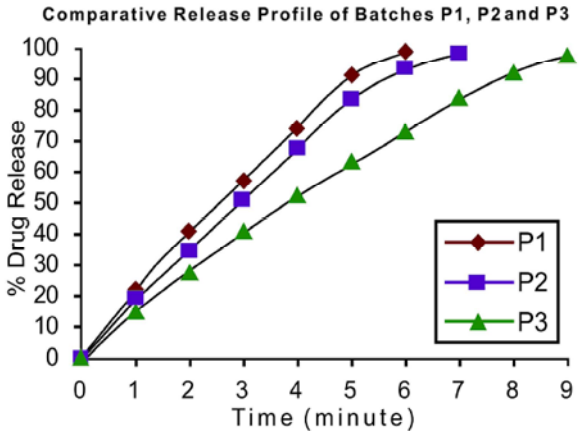


Fig. 3: Comparative Release Profile of Batches P1, P2 and P3 in 0.1 N hydrochloric acid

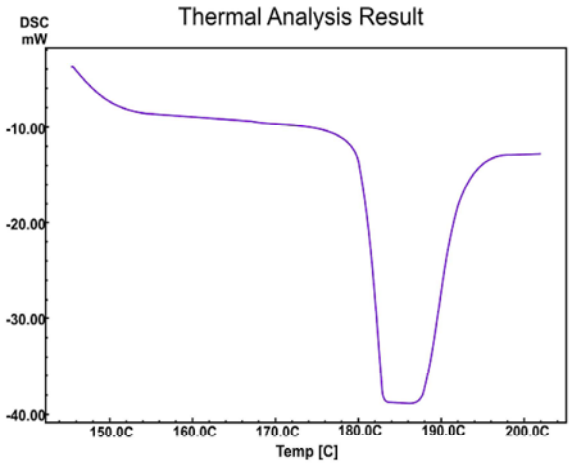


Fig. 4: DSC thermogram of rizatriptan benzoate

optimum taste masking in further studies. These findings are similar to those of Mahamuni *et al*. [27]. *In vitro* dissolution results (Figure 3) indicated good dissolution since greater than 97% of drug release was observed at 6, 7 and 9 minutes for taste masked granules P1, P2 and P3 respectively (98.74±0.58%, 98.28±0.11%, 97.33±0.55%) in o.1 N hydrochloric acid. *In vitro* dissolution of drug: polymer physical mixture and ODT of drug: polymer physical mixture revealed 98.67 ±0.39 % and 98.82±0.41 % drug release, at the end of 4 minutes.

The taste masked granules of batch P1 showed excellent flowability and compressibility (Table 2) and batch P2, P3 showed good flowability since angle of repose was observed to be less than 35°.

The FTIR spectra of drug, Eudragit E, physical mixture and taste masked granules batch P1 were studied. There were no major changes in the FTIR spectra of the taste masked granules batch P1 indicating the absence of any chemical interaction in between RB and the polymer. (Results are not revealed).

Thermal behavior of pure drug and taste masked granules batch P1 are depicted in Figure 4 and 5. The characteristic endothermic peak of drug, corresponding to the melting point, was observed at 182°C. DSC of taste masked granules depicted an endothermic peak at 185°C indicating complete miscibility of drug with polymer. No significant difference in DSC pattern of drug and taste masked granules batch P1 suggested absence of interaction in between the drug and the polymer.

The primary criteria, for the selection of the optimized batch, were the efficiency of taste masking, % drug release and degree of flow properties.

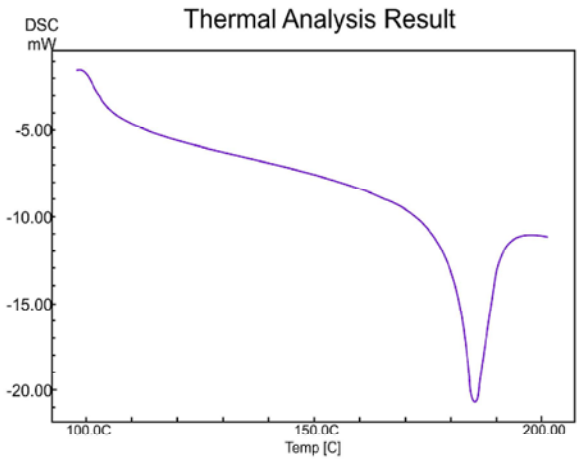


Fig. 5: DSC thermogram of taste masked granules of rizatriptan enzoate

Since batch P1 showed acceptable flow properties, faster drug release i.e. 98.74 % drug release within 6 minutes as compared to batch P2 and P3 and taste was masked at a lower polymer concentration, further experimentation was carried out on batch P1.

Selection of the Superdisintegrant: Initially tablets containing superdisintegrants in the concentrations 2, 3, 4 and 5% w/w were tested for disintegration time, wetting time, hardness and friability. The disintegration times of (Table 4) the tablets followed the order crospovidone (CP) « sodium starch glycollate (SSM) « croscarmellose sodium (CCM). Tablets formulated with 5% crospovidone (batch R8) disintegrated in 44 seconds. Tablets formulated with 5% sodium starch glycolate (batch R4) and croscarmellose sodium (batch R12) disintegrated in 57 seconds and 65 seconds respectively. The probable reason for delayed disintegration of the tablets with CCM and SSG might be due to their tendency to gel more than CP. This result is consistent with the findings of Shagufta Khan *et al.* [28] in their studies with an orodispersible tablet of ondansetron hydrochloride.

Increased concentrations of the crospovidone were found to reduce the disintegration time. The reason may be the highly porous structure of crospovidone, allowing it to draw large amounts of water, by a water wicking mechanism, into the porous network of the tablet. Due to this, though, crospovidone swells immediately but to a

Table 3: Formulations of oral disintegrating tablet of taste masked granules of batch P1

Ingredient	Quantity (%)
Taste Masked Granules (P1)	14.53
Superdisintegrant	2 to 5
Pearlitol(r) SD200	77.97 to 80.97
Sodium saccharin	1
Sodium stearyl fumarate	1
Peppermint	0.5
Total	100

All tablets contained 14.53% of taste masked granules of batch P1

Table 4: Evaluation of properties of ODTs containing superdisintegrants

Batch	Disintegrant	Disintegrant % w/w	Diluent % wt/wt	Disintegration Time (sec)	Wetting Time (sec)	Hardness (kg/cm^2)	Friability (%)
R1	*SSG	2	80.97	87±2.36	108±1.41	2.83±0.40	0.403
R2	SSG	3	79.97	78±2.13	99±1.78	2.75±0.27	0.465
R3	SSG	4	78.97	64±1.78	86±1.72	2.62±0.20	0.513
R4	SSG	5	77.97	57±2.31	77±2.16	2.58±0.20	0.544
R5	** CP	2	80.97	81±1.64	97±1.47	2.91±0.58	0.482
R6	CP	3	79.97	69±2.16	84±1.75	3.0±0.440	0.419
R7	CP	4	78.97	54±1.54	75±1.47	3.08±0.37	0.357
R8	CP	5	77.97	44±1.41	67±1.67	3.20±0.24	0.294
R9	***CCM	2	80.97	92±2.42	110±1.96	2.95±0.33	0.497
R10	CCM	3	79.97	84±1.51	101±1.94	2.87±0.44	0.543
R11	CCM	4	78.97	72±1.16	92±1.96	2.79±0.24	0.606
R12	CCM	5	77.97	65±1.54	79±1.87	2.66±0.25	0.698

*SSG - Sodium starch glycolate **CP - Crospovidone ***CCM - Croscarmellose sodium

lesser extent, yet it rapidly absorbs water into its network without forming a gel [29-31]. The tablets, containing 5% w/w croscarmellose sodium demonstrated increased disintegration time. Croscarmellose sodium swells to a larger extent upon contact with water. The fibrous nature of croscarmellose sodium allows intra-particulate as well as extra-particulate wicking of water even at low concentrations. However, croscarmellose sodium is made by cross linking (etherification) of sodium carboxymethylcellulose, which greatly reduces its water solubility, while permitting the material to swell and absorb water in amounts of several times its own mass without losing its fibrous structure. Such hydration makes croscarmellose sodium more viscous and adhesive, when used at the higher concentrations. This can be the possible reason for the increase of disintegration time of the tablets made with croscarmellose sodium [29]. Hence, crospovidone (5% w/w) was selected as the optimum concentration for the formulation of ODTs. Table represents the chemical structure and the properties of the superdisintegrants. Table 8 depicts various properties of the most frequently used superdisintegrants. Table 9 depicts the chemical structure of superdisintegrants.

Evaluation of Oral Disintegrating Tablets: Hardness of formulated batches R1-R12 (Table IV) was found to vary from 2.58 kg/cm^2 - 3.20 kg/cm^2. Less hardness of ODT of rizatriptan benzoate, as compared to the hardness of uncoated oral tablets, may be attributed to absence of microcrystalline cellulose (MCC) in the R1-R12 formulations. Haware *et al*. [29] reported the same results for promethazine hydrochloride ODTs prepared by using mannitol and avicel P 102 as diluents. The tensile strength of promethazine oral disintegrating tablets was found to vary from 0.484±0.11 to 0.559±0.17 N/mm^2. MCC is known as a potent dry binder as the particles have a large number of free hydroxyl groups. Thus the interaction forces, at contact points between particles, may be strong hydrogen bonds between hydroxyl groups, causing increased tablet hardness.

The friability of formulated tablets (Table 4) was observed to be 0.294-0.689 % which is considered to be acceptable for withstanding normal shipping and handling. We have observed higher values for hardness in case of ODTs formulated with crospovidone. The observation is consistent with the findings of Gohel M [35].

The tablets formulated with crospovidone presented with greater hardness yet lesser disintegration times when compared with tablets formulated with sodium starch glycolate or with croscarmellose. Iman Saad Ahmed [36] *et al.* has observed the same phenomenon in case of lyophilized oral disintegrating tablet of nimesulide. Bulk and tapped density of CP are lower as compared to bulk and tapped density of CCM or SSG, perhaps because of its porous structure [30-34]. Greater hardness of batches R5-R8, formulated with CP, may be attributed to reduction in porosity of CP. The ODT was formulated by direct compression of powdered admixture of taste masked granules of RB, Pearlitol and superdisintegrants in powder form. The intense particle particle bond formation, in powdered superdisintegrant CP, may be responsible for improved hardness of the ODT [37].

In the wetting time study (Table 4), it was observed that the tablet containing crospovidone 4% w/w (batch R8) was fully hydrated after 67 seconds of contact with

Table 5: Characterization of powder blend of ODT of batch R8

Sr. No.	Parameter	Result	Interpretation
1	Bulk Density (g/ml)	0.484±0.02	----------
2	Tapped Density (g/ml)	0.536±0.03	----------
3	Angle of Repose	28° 17'±0.36	Excellent flow
4	Compressibility index (%)	9.6±0.40	Excellent flow
5	Hausner's ratio	1.10±0.0	Excellent flow

Table 6: Evaluation of compressed tablet of batch R8

Sr. No.	Evaluation Parameters	Result
1	Physical Appearance	White colored, 8±0.0 mm in diameter, round concave faced
2	Thickness (mm)	3.9±0.22
3	*In Vivo* Disintegration Time (Seconds)	31±1.78
4	Mouth Feel	Cooling sensation, Pleasant
5	Drug Content (%)	99.80±0.68
6	Content Uniformity (%)	99.47±2.05

Table 7: *In Vitro* drug release of ODT of batch R8 in 0.1N HCl and phosphate buffer pH 6.8

Sr. No.	Time (minutes)	0.1 N HCl	Time (minutes)	Phosphate buffer pH 6.8
1	0	0	0	0
2	1	7.02±0.80	5	5.78±0.33
3	2	18.99±0.76	10	7.53±0.45
4	3	32.22±0.67	15	8.85±0.37
5	4	43.13±0.83	30	9.55±0.31
6	5	58.60±0.86	45	10.04±0.17
7	6	71.27±0.65	60	10.52±0.30
8	7	84.40±0.92	-------	----------
9	8	93.09±0.57	-------	----------
10	9	97.12±0.57	-------	----------
11	10	96.71±0.49	-------	----------
12	15	96.34±0.73	-------	----------

Table 8: Properties of superdisintegrants [30-34]

Name of the Superdisintegrant	Avg Particle size (µm)	Surface Area (m^2/g)	Bulk Density (g/mL)	Tapped Density (g/mL)	Flowability Index	Degree of Cross linking	Degree of substitution
1. Polyplasdone XL							
Type A	130-150	0.7	0.28	0.36	50	High	-----
Type B	30-50	1.4	0.33	0.48	44		
2. Ac-Di-Sol	50	0.7	0.46	0.72	31	0.6	0.85
3. Primojel	50	0.2	0.76	0.92	58	0.25-4	0.23-0.32

Table 8: Properties of superdisintegrants [30-34]

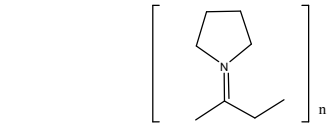
Name of the Superdisintegrant	Ionic Natu Re	Particle shape	Swelling pressure (kPa)	Time to reach 90% max swelling pressure (sec)	Swelling volume (L/Kg)	Hydration Capacity g water/g of polymer	pH dependant swelling
1. Polyplasdone XL							
Type A	Noni oinc	Highly porous	110	21.9	5.8	4.4	Not pH dependent
Type B	Noni onic	& granular					
2. Ac-Di-Sol	Anionic	Fibrous & non-porous	271	88.1	13.5	12.1	Swells less at acidic pH
3. Primojel	Anionic	Spherical & non-porous	158	75	23.6	18.3	Swells less at acidic pH

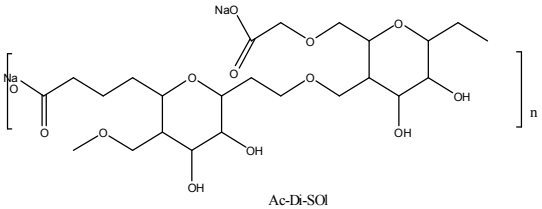
phosphate buffer pH 6.8, whereas the tablets, formulated with sodium starch glycolate and croscarmellose sodium, remained dry and hard. This finding of a correlation between wetting and disintegration time was similar to the results of Iman Saad Ahmed *et al*. [36].

Characterization of ODT of Batch R8: Tablets of batch R8 depicted the best physical properties (Table 4) accompanied with the fastest disintegration time and, therefore, batch R8 ODTs were evaluated for other parameters like flow properties, general appearance, thickness, *in vivo* disintegration time, *in vitro* dissolution time, drug content, content uniformity and mouth feel (Table 5 & 6). The angle of repose, compressibility index and Hausner's ratio of the powder blend of batch R8 were observed to be 28° 17', 9.6 and 1.10 respectively, indicative of acceptable flow properties for tablet manufacture.

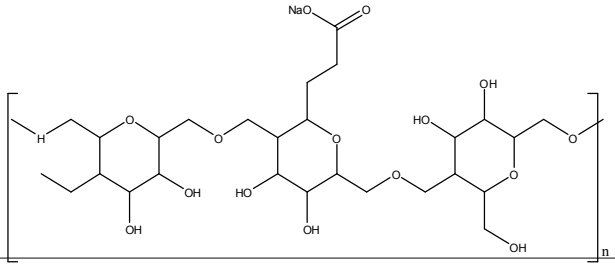
The dissolution study (Table 7) of the optimized tablet revealed rapid release of drug (97.12 % of drug within 10 minute). It indicated the formation of matrix tablet of rizatriptan benzoate. (Figure 6). These results were consistent with the findings of Lourenco *et al*. [38]. The dissolution profile of the tablet in phosphate buffer pH 6.8 (Figure 7) showed that, at the end of 30 minutes, less than 10% of drug was released. Because, the drug release rate from the ODT was similar with that for the taste masked granules of batch P1, it seems reasonable to conclude that direct compression did not affect those attributes of the taste masked granules responsible for the release of the drug.

Table 9: Chemical structure of superdisintegrants





Ac-Di-SOl



Primogel

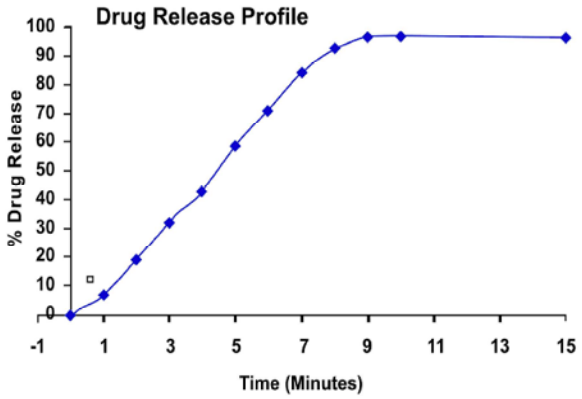


Fig. 6: *In vitro* drug release of batch R8 in 0.1 N hydrochloric acid

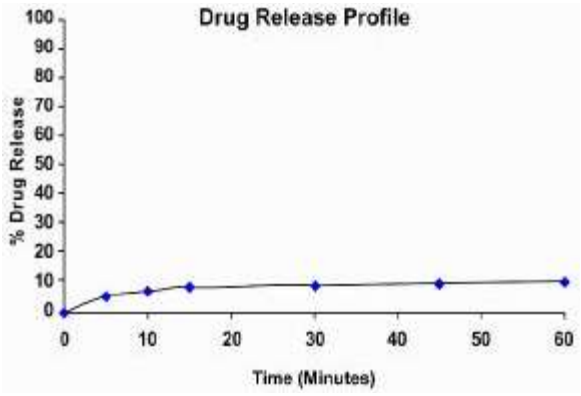


Fig. 7: *In vitro* drug release of batch R8 in phosphate buffer pH 6.8

***In Vivo* Taste Masking Evaluation of Oral Disintegrating Tablet of R8:** The taste masking study in human volunteers of both the ODT and of taste masked granules revealed significant masking of the bitter taste of rizatriptan benzoate. All the 6 volunteers reported that the ODT of taste masked granules as being 'good' on the perception scale whereas 4 volunteers reported drug substance as 'bitter' and 2 volunteers reported drug substance as being 'very bitter' on the perception scale. Moreover all the volunteers experienced a good mouth feel of the formulated rizatriptan benzoate ODT. Thus sensory evaluation of the optimized batch R8 significantly improved its palatability.

Stability Study: The stability study did not show any significant drug loss or changes in the mechanical strength or in colour and disintegration time of the tablets at the end of 2 months. The ODT of rizatriptan benzoate was therefore considered to be stable under ambient storage conditions for 2 months.

CONCLUSION

The study conclusively demonstrated complete taste masking of Rizatriptan benzoate and rapid disintegration and dissolution of ODT. Taste masking by

mass extrusion method may be an economical and efficient method for currently marketed, lyophilized ODTs of Rizatriptan benzoate.

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