IJPSR (2011), Vol. 2, Issue 4 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 05 December, 2010; received in revised form 18 February, 2011; accepted 02 March, 2011

DEVELOPMENT AND EVALUATION OF MELT- IN- MOUTH TABLETS BY SUBLIMATION TECHNIQUE

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Keywords:

Melt- In- Mouth tablets,

Rizatriptan Benzoate,

Sublimation,

Ammonium bicarbonate,

Camphor,

Direct compression,

Porous tablets

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ABSTRACT

In the present study Rizatriptan benzoate, which is the bitter drug requires taste, masking. β- Cyclodextrin is used in taste masking, which improves the patient compliance and also increases the rate of dissolution. Solid dispersion of drug and β- Cyclodextrin were prepared which was optimised in 1: 8 ratios, which gave satisfactory results for taste masking. This was then characterised using Differential scanning colorimetry (DSC), X-ray diffraction (XRD) and Infra Red (IR). The prepared solid dispersion was then formulated into tablets using varying concentrations (0-30%) of sublimating agents. The sublimating agents used were camphor and ammonium bicarbonate. The formulated powder blend was evaluated for angle of repose, bulk density, tapped density, Carr's index. These powder properties showed good flowability. Tablets were formulated by direct compression. The sublimation process produced pores into the tablets, which allowed easy penetration of dissolution media followed by rapid release of the drug, which is the major aim of melt-in-mouth tablet dosage form. The tablets were evaluated for hardness, friability, disintegration time (*in vitro, in vivo*), drug content and dissolution. The tableting properties showed that hardness and friability were within the range. Drug content was found to be 97.79 %. The *in vitro* and *in vivo* disintegration time was within the range 18- 45 and 21-49 seconds respectively. Dissolution showed 100 % release rate within 0.5-2 minute.

INTRODUCTION: We often see that patient find difficulty in swallowing the conventional tablets especially the geriatrics, paediatric patients, and patients suffering from various diseases, are the major problems. Hence, it is the necessary criterion to develop a dosage form that will provide rapid and quick action. Thus, the development of Melt-In-Mouth tablets, which disintegrates rapidly without the need of drinking water providing convenience of administration, patient compliance and quick onset of action [1, 2]. These tablets are prepared by sublimation method using camphor and ammonium bicarbonate as sublimating agents along with mannitol provided porous tablets that on administration disintegrates in the oral cavity, without the need of swallowing or intake of water and also rapid drug release rate.

The fast dissolving tablets prepared contains insoluble excipients and gave a rough texture [3], which is overcome by Melt-In-Mouth tablets, which were porous and gave a pleasant mouth feel improving the patient compliance.

Rizatriptan Benzoate is an antimigraine agent used in treatment of migraine associated with severe one-sided throbbing headache, which is followed by intense pain. Hence to provide quick action there was a need to develop melt in mouth tablets. It is a 5-Hydroxy Tryptamine $_{(1B/1D)}$ [5HT $_{(1B/1D)}$] receptor agonist used in Melt-In-Mouth tablet providing quick action [4].

MATERIALS AND METHODS:

Materials: Rizatriptan Benzoate is procured from Ranbaxy Labs. Ltd. β- Cyclodextrin, Mannitol, camphor and ammonium bicarbonate were obtained from Emcure Pharmaceuticals Ltd.

Methods:

Preparation of taste masked granules [5, 6]: β- Cyclodextrin was used for taste masking and also improving the solubility. In this method the taste masking was done by preparing the solid dispersion of drug and β- Cyclodextrin by addition of water to prepare slurry, which was then allowed to dry in oven at 60°C.

Characterization of rizatriptan benzoate and β- cyclodextrin:

- **Infra Red (IR) Study:** The drug, polymer and drug polymer solid dispersion was subjected to Fourier Transform Infra Red (FTIR) studies to check drug polymer interaction using FTIR (SHIMADZU 8400 S). The KBr disk method was used for preparation of sample.

- **Differential Scanning Colorimetry (DSC) Study:** The drug, polymer and drug polymer solid dispersion was subjected to DSC study. DSC was performed on a METTLER DSC 30. First 10-30 mg of sample was weighed into aluminum crucible. Rizatriptan Benzoate, β- Cyclodextrin and Rizatriptan Benzoate with β- Cyclodextrin solid dispersion were analyzed by heating at scanning rate of 20°C/minute over a temperature range 40 to 250°C**.**

- **X-ray Diffraction (XRD) Study:** Rizatriptan Benzoate, β- Cyclodextrin and Rizatriptan Benzoate with β- Cyclodextrin were subjected to powder XRD using P.W. 1729, X-Ray Generator, Philips, Netherland. To study X-Ray Diffraction pattern, the sample was placed into aluminum holder and the instrument was operated between initial and final 2θ angle of 5-50° respectively in an increment of 0.4°2θ.

- **Taste evaluation [7]:** Taste evaluation was done by a panel of 10 human healthy volunteers (age 20-25 years) using time intensity method. Research was carried out in accordance with standard institutional guidelines. Study was carried out using informed consent of all the human volunteers under the approval of institutional human experimentation committee. Taste evaluation was done by a

panel of 10 members using time intensity method. Sample equivalent to normal dose was held in mouth for 10 sec., bitterness levels were recorded instantly and then after 10 sec, 1, 2, 5, and 15 minutes. Volunteer's opinion for bitterness values were rated by giving different score values. That is 0: no bitterness, 1: acceptable bitterness, 2: slight bitterness, 3: moderately bitterness, 4: strong bitterness.

Descriptive statistics mean and standard deviation were calculated for all variables. Paired t- test was applied using INSTAT software. Value $P<0.05$ has been considered as statistical significant level.

Formulation design of melt-in-mouth tablets by sublimation method [8, 9, 10]**:** For development of rizatriptan benzoate melt-in-mouth tablets by sublimation technique 8 formulations were prepared with varying concentrations of ammonium bicarbonate and camphor (0 to 30% w/w) which were added to the tableting component. Ingredients after sifting through sieve no. 40 were thoroughly mixed for 10 min. Tablets were compressed on 8mm round concave punch on 16-station rotary tablet machine (Cadmach). The compressed tablets were then subjected to sublimation at 60°C for 6 hrs in vacuum oven. Tablets were evaluated for various quality control parameters. Batch sizes for all the formulation were 50 tablets.

Evaluation of mixed powder blend of drug and excipients [11]**:** Evaluation of mixed blends of drug and excipients were carried out for all the formulations for angle of repose, bulk and tapped density, % compressibility and flowability.

Evaluation of melt-in-mouth tablets: The formulated melt-in-mouth tablets were evaluated for different parameters like thickness, uniformity of weight, hardness, water absorption ratio, *in vitro* and *in vivo* disintegration time.

- **Thickness:** Thickness of the tablets was determined using a thickness gauge (Mitutoyo, New Delhi, India). Five tablets from each batch were used, and average values were calculated.

- **Weight variation test** [12]**:** To study weight variation 20 tablets of each formulation were weighed using an electronic balance (Schimadzu), and the test was performed according to the official method.

- **Drug content:** Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets were weighed and extracted in water and concentration of drug was determined by measuring absorbance at 227.5nm by Ultra Violet (UV) spectrophotometer (Schimadzu 1601)

- **Hardness and friability** [13]**:** For each formulation the hardness and friability of 6 tablets were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche Friabilator (LabHosp Mumbai, India) respectively.

- **Disintegration time** [14]: *In vitro* disintegration time of 6 tablets from each formulation was determined by using Digital Tablet Disintegration Apparatus (Veego Scientific, Mumbai, India). *In vitro* disintegration test was carried at 37$\pm$2°C in 900ml distilled water. *In vivo* disintegration time of tablet was checked in healthy human volunteers by putting a tablet on tongue and time required for complete disintegration was checked.

- **Dissolution studies** [15]: The *in vitro* dissolution studies were carried out using USP apparatus type II (VGA Scientific 6DA Apparatus) at 100rpm. The dissolution medium used was distilled water (900 ml) maintained at 37°C. Aliquots of dissolution media were withdrawn

at different intervals, for Rizatriptan benzoate by measuring absorbance at 227.5nm by UV spectrophotometer. The dissolution experiments were conducted in triplicate.

- **Scanning Electron Microscopy (SEM)**: SEM studies were carried out for the tablets prepared before and after sublimation.
- **Stability studies:** Stability study was conducted by storing the tablets at 40±2^{o}C/75 ±5% RH for three months. The content and dissolution behaviour from dissolving tablets were tested monthly for three months.

RESULT AND DISCUSSION: Rizatriptan benzoate: β-cyclodextrin (1: 1 to 1: 12) solid dispersions were prepared by slurry method to mask the bitter taste of the drug. Panel of 10 members using time intensity method were evaluated for the taste masking of drug. The ratio of drug: β- cyclodextrin for taste masking was optimised to 1: 8. The data in **Table 1** indicates the taste evaluation of drug: β-cyclodextrin (1: 8) solid dispersion.

TABLE 1: VOLUNTEERS OPINION TEST FOR RIZATRIPTAN BENZOATE BEFORE AND AFTER TASTE MASKING (n= 10)

Time (secs)	Before taste masking Mean ± SD	After taste masking Mean ± SD
10	2.3***± 0.48	0.5***± 0.84
60	3.3***± 0.48	0.3***± 0.69
120	3.4***±0.51	0.2***±0.31
300	3.8***±0.42	0
600	3.8***±0.42	0
900	4.0***± 0.0	0

P< 0.001***; P< 0.01**; P< 0.05*; e*ach reading is a mean of ten determinations ± SD*

The optimised drug: β- cyclodextrin (1: 8) solid dispersion was characterized by FTIR, DSC and X-ray diffraction. The interaction between the drug and the carrier often lead to identifiable changes in IR profile of the solid dispersion. The drug and the solid dispersion were subjected to IR analysis in order to evaluate possible solid-solid interaction between the drug and β- cyclodextrin. The data was compared with the standard spectrum of drug and the characteristics peaks associated with specific structural characteristics of the molecule and their presence/absence in β- cyclodextrin as well as the solid dispersion were noted.

The IR spectra of the solid dispersion (**fig. 1**) showed that there was no significant evidence for interaction between drug and β- cyclodextrin. Peaks of both drug as well as β- cyclodextrin were observed and interpreted.

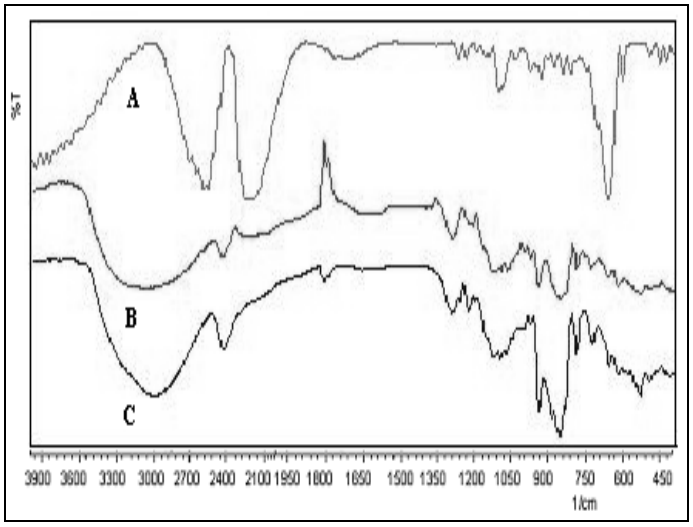

FIG. 1: INFRARED SPECTRUM FOR A) RIZATRIPTAN BENZOATE; B) β- CYCLODEXTRIN; C) RIZATRIPTAN BENZOATE: β- CYCLODEXTRIN

The DSC of drug: β- cyclodextrin (1: 8) did not show any interaction of drug and β- cyclodextrin. Pure drug and pure β- cyclodextrin shows melting point at 180°C and 256°C respectively. Rizatriptan benzoate and β cyclodextrin (1:8) in their solid dispersion showed melting point at 179°C and 254°C respectively (**Fig. 2**).

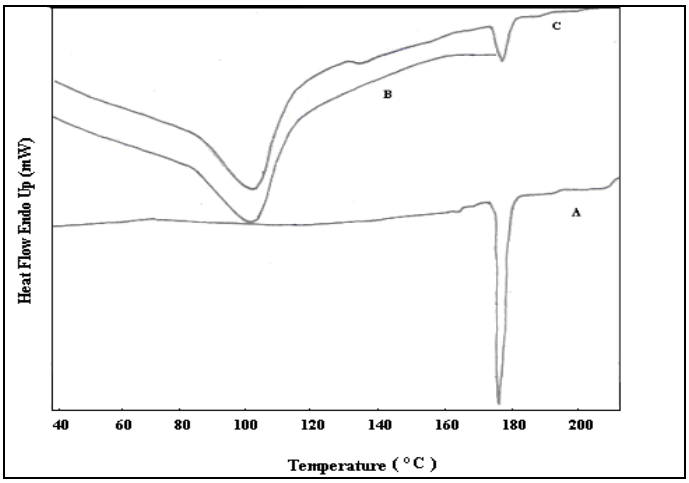

FIG. 2: DIFFERENTIAL SCANNING CALORIMETRY FOR A) RIZATRIPTAN BENZOATE; B) β- CYCLODEXTRIN; C) RIZATRIPTAN BENZOATE: β- CYCLODEXTRIN

The X-ray diffraction pattern of drug: β-cyclodextrin (1: 8) showed no defined peak; this implies the absence of apparent crystallinity in the solid dispersion. However the pure drug powder showed typical peak of rizatriptan benzoate, conforming the satisfactory sensitivity of the method (**fig. 3**).

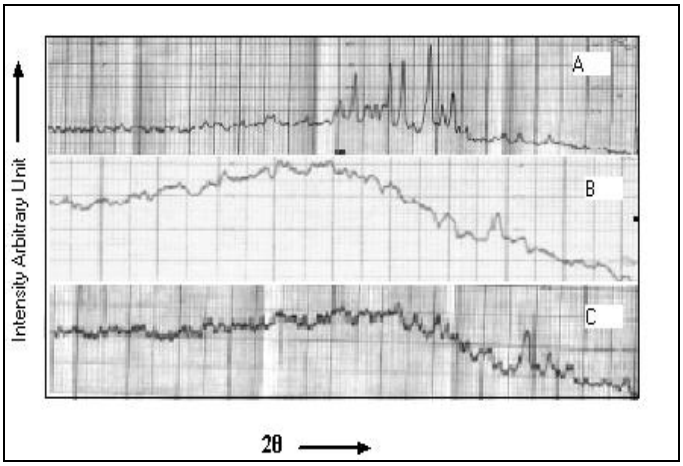

FIGURE 3: POWDER X- RAY DIFFRACTION PATTERN FOR; A) RIZATRIPTAN BENZOATE; B) β- CYCLODEXTRIN; C) RIZATRIPTAN BENZOATE: β- CYCLODEXTRIN

The SEM studies showed that the tablet produced is porous in nature, which can be easily identified as seen in **figures 4, 5, 6 and 7** which shows the difference between tablets before and after sublimation.

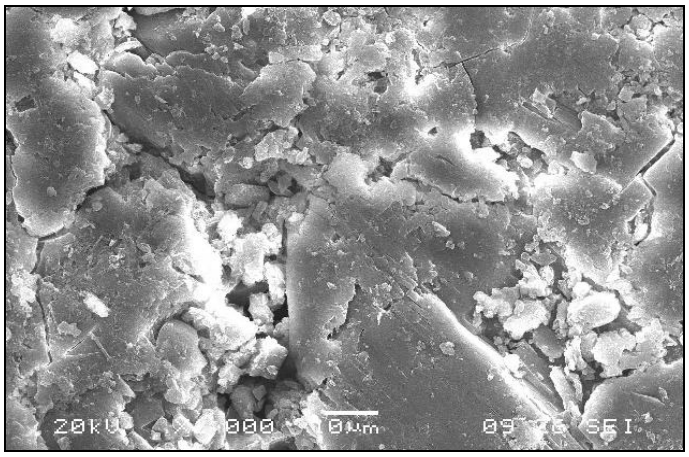

FIG. 4: SEM OF TABLET CONTAINING AMMONIUM BICARBONATE AFTER SUBLIMATION

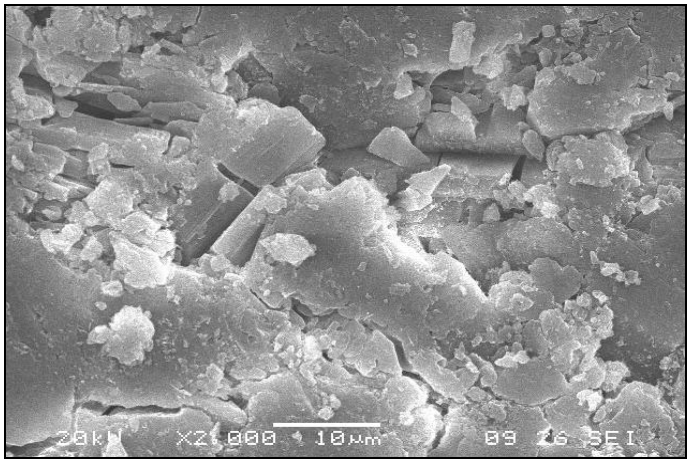

FIG. 5: SEM OF TABLET CONTAINING CAMPHOR AFTER SUBLIMATION

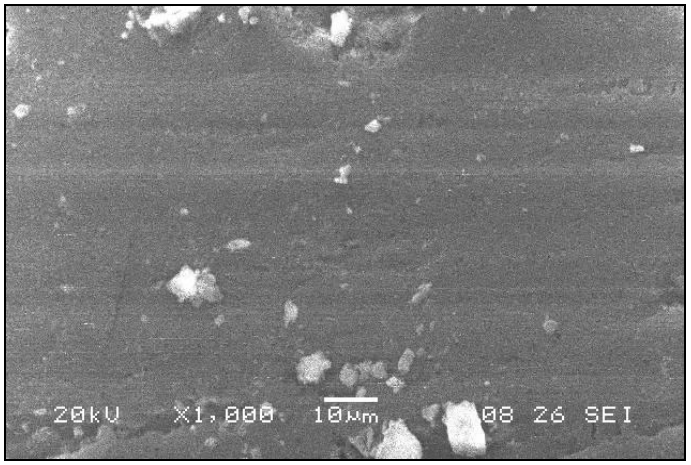

FIG. 6: SEM OF TABLET CONTAINING AMMONIUM BICARBONATE BEFORE SUBLIMATION

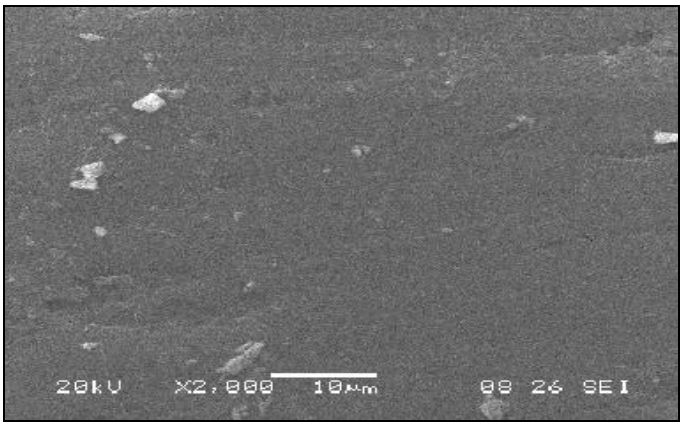

FIG. 7: SEM OF TABLET CONTAINING CAMPHOR BEFORE SUBLIMATION

In the present study various sublimating agents were used and were evaluated using various parameters. After confirming the absence of interaction in the solid dispersion; drug: β-Cyclodextrin (1:8), complex was used in designing of the formulations. The melt-in-mouth tablets of rizatriptan benzoate were prepared by using various sublimating agents.

All the formulations were shown in (**Table 2**). Melt-in-Mouth tablets were prepared using varying concentration of sublimating agents from 0% -30 % of the weight of tablets. The formulations were given as E1, E2, E3, E4 and F1, F2, F3, F4 respectively. Tablets were prepared by direct compression method using Sixteen-station punch tablet machine (Cadmach, India).

TABLE 2: DESIGN OF FORMULATION USING AMMONIUM BICARBONATE AND CAMPHOR

Name of Ingredient	Quantity (mg)							
	E1 (0%)	E2 (10%)	E3 (20%)	E4 (30%)	F1 (0%)	F2 (10%)	F3 (20%)	F4 (30%)
Rizatriptan Benzoate	7.27	7.27	7.27	7.27	7.27	7.27	7.27	7.27
β- Cyclodextrin	58.16	58.16	58.16	58.16	58.16	58.16	58.16	58.16
Camphor	-	-	-	-	-	17.5	35	52.5
Ammonium Bicarbonate	-	17.5	35	52.5	-	-	-	-
Mannitol (Pearlitol SD 200)	100.82	83.32	65.82	48.32	100.82	83.32	65.82	48.32
Aspartame	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Strawberry flavor	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75
Magnesium stearate	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75
Aerosil	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75
Total	175	175	175	175	175	175	175	175

From **table 3,** it was observed that all the formulations have angle of repose between ranges 13- 23°. This was higher than control formulation. Also, the percentage compressibility was found within the range of 9-16. The powder blend of all the formulations has good flowability. Evaluation parameters for powder blend like angle of repose, bulk density, tapped density, percentage compressibility were within limit. Drug and solid dispersion showed good flow properties.

Evaluation of tablets by prepared by sublimation method: As shown in **table 4**, there was no decrease in mean weight of tablet formulations E1 and F1 that does not contain ammonium bicarbonate and camphor. The mean weight of the formulation E2 and F2 (containing 10% of ammonium bicarbonate and camphor respectively) before sublimation was 176.1±0.562 mg and 174.5±0.745 mg and that after sublimation of volatile component were 158.9±0.142 mg and 158±0.215 mg.

TABLE 3: POWDER PROPERTIES OF CONTROL FORMULATION AND FORMULATION CONTAINING AMMONIUM BICARBONATE AN CAMPHOR (n=3)

Formulation Properties	E1	E2	E3	E4	F1	F2	F3	F4
Angle of Repose (^{0})	12±0.1245	18±1.0452	23±1.245	17±0.5631	12±0.1245	19±0.4315	13±0.1579	22±0.1245
Bulk Density (g/cm^3)	0.4127±1.2030	0.4718±1.0231	0.4566±0.2435	0.4191±0.7856	0.4127±1.2030	0.5071±0.1546	0.4626±1.4563	0.4218±1.946
Tapped Density (g/cm^3)	0.4535±1.4631	0.5302±1.9976	0.5058±1.6533	0.4936±0.5522	0.4535±1.4631	0.6088±0.5487	0.5146±0.5374	0.4936±1.5567
% Compressibility	8.99±0.5497	11.01±1.4697	9.72±1.3396	15.1±1.4752	8.99±0.5497	16.7±0.8462	10.11±0.6184	14.54±1.7823
Porosity (%)	6.88±0.7985	10.53±0.1548	7.7±0.4558	15.9±1.5768	8.88±0.7985	16.22±1.7856	10±1.4618	13.95±0.9431
Flowability	Excellent	Good	Good	Good	Excellent	Good	Good	Good

TABLE 4: TABLET WEIGHT BEFORE AND AFTER SUBLIMATION

Formulation code	Amount of ammonium bicarbonate/Camphor added	Tablet (mg)	Tablet (mg)	Residual amount of Ammonium bicarbonate/Camphor
		Before sublimation	After sublimation	
E1	0	175 ± 0.112	175 ± 0.456	0
E2	17.5	176.1 ± 0.562	158.9 ± 0.142	0.3
E3	35	173.7 ± 0.501	140.1 ± 0.821	1.4
E4	52.5	174 ± 0.084	124.2 ± 0.069	2.7
F1	0	175 ± 0.896	175 ± 0.384	0
F2	17.5	174.5 ± 0.745	158 ± 0.215	1
F3	35	173.3 ± 0.245	140.2 ± 0.958	1.9
F4	52.5	176.4 ± 0.341	126.5 ± 0.357	3.1

The mean weights of the formulations E3 and F3 (containing 20% of ammonium bicarbonate and camphor respectively) before sublimation were 173.7±0.501 mg and 173.3±0.245 mg and after sublimation of volatile component were 140.1±0.821 mg and 140.2±0.958 mg.

The mean weights of the formulations E4 and F4 (containing 30 % of ammonium bicarbonate and camphor respectively) before sublimation was 174±0.084 mg and 176.4±0.341 mg and after sublimation of volatile component was 124.2±0.069 mg and 126.5±0.357 mg. The decrease in mean weights of tablets in the formulations corresponded to weight of ammonium bicarbonate and camphor added to the tablets as evident from the residual value of ammonium bicarbonate and camphor after sublimation of tablets.

Thus, it was concluded that almost all the ammonium bicarbonate and camphor have sublimated from the compressed tablets.

Disintegration time in oral cavity: Table 5 shows that there was no change in disintegration time of tablets in oral cavity for formulation E1, F1. But disintegration time of tablets in oral cavity for

formulations E2, E3, E4 and F2, F3, F4 was found to be decreased after sublimation. Rapid disintegration was achieved in case of formulation F4 containing 30% camphor.

This rapid disintegration of tablets in oral cavity is contributed to pores, which are created in the tablet upon sublimation of ammonium bicarbonate and camphor after sublimation from the compressed tablets. This enhanced porosity allowed the saliva to penetrate into tablet and resulted into quick disintegration of tablet.

This clearly indicates that there is significant difference in disintegration value for formulations E2, E3, E4 and for formulations F2, F3, F4. While for formulation E1 and F1 there is no significant statistical difference.

TABLE 5: DISINTEGRATION TIME IN ORAL CAVITY BEFORE AND AFTER SUBLIMATION

Formulation	Disintegration time in oral cavity (sec)	
	Before sublimation	After sublimation
E1	70.33 ± 1.241	70.33 *± 0.147
E2	58 ± 0.512	49.33** ± 1.098
E3	44 ± 1.963	27.33** ± 1.578
E4	52 ± 2.568	21.66** ± 1.963
F1	79.66 ± 0.187	79.66* ± 1.874
F2	45 ± 0.178	27.33** ± 0.861
F3	51 ± 1.594	22.66** ± 1.554
F4	49 ± 0.178	14.33** ± 0.496

Each value represents disintegration time ± SD for 6 tablets; *P<0.05, **P>0.05

Tableting properties: Tablets prepared by direct compression and then sublimation were subjected to quality control test like weight variation, friability, hardness, disintegration time and drug content, which was analyzed by UV spectrophotometeric method at 227.5nm using distilled water. Results were compared with marketed formulation of rizatriptan benzoate.

Formulations with ammonium bicarbonate as volatilizable component showed a greater degree of weight variation when compared with formulation containing camphor. Yet this weight variation was within the limit specified as per Indian Pharmacopoeia (I.P.) 1996. Hardness of tablet increased with decrease in amount of volatilizable components. Friability of tablet decreased with decrease in amount of volatilizable component. All the formulations except E1 and F1 (control tablet) showed extremely low disintegration time.

Amongst all formulations, formulations E3, E4 (containing 20%, 30% of ammonium bicarbonate respectively), F3 and F4 (containing 20%, 30%, of camphor respectively) emerged to be the most satisfactory exhibiting disintegration time of 23.33± 0.9693 and 18.33±0.7554 sec and 18.66±0.4233 and 12.33±0.7412 sec respectively. Hardness of all the tablets ranges from 2.59 to 4.8 kg/cm^2. Drug content of 96.57 to 99.14% w/w. Friability was found to be 0.13 to 0.79%.

Hence, all the quality control parameters of the best formulations E3, E4 and F3, F4 was well within the limit prescribed by I.P. with dramatic decrease in disintegration time. Rapid disintegration of tablets in oral cavity is contributed to the pores created in the tablet upon sublimation of volatilizing component from the compressed tablet although all the formulation with higher content of ammonium bicarbonate and camphor showed extremely low disintegration time than marketed formulation.

They also exhibit higher friability, lower hardness and dull appearance. The problems mentioned were not exhibited by tablet formulations E3 and F3 as shown in **table 6**.

TABLE 6: TABLETTING PROPERTIES OF CONTROL FORMULATION AND FORMULATIONS CONTAINING AMMONIUM BICARBONATE AND CAMPHOR (n=3)

Tableting Properties	E1	E2	E3	E4	F1	F2	F3	F4	Marketed Formulations
Weight variation	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes
Hardness (kg/cm²)	5.4±0.1852	4.86±0.5542	4.06±0.9423	3.57±0.0147	5.2±0.8852	4.53±0.4412	4.03±0.4475	2.59±0.5079	3.5±0.0659
Friability (%)	0.14±0.0556	0.24± 0.6895	0.35±0.5122	0.68±0.1649	0.18±0.4318	0.13±0.7193	0.33±0.4751	0.79± 0.4478	0.72±0.5596
Drug content (% w/w)	97±0.0984	98.23±0.9551	96.57±0.7861	99.14±0.6652	97.92±0.4522	97.84±0.5596	98.63±0.02891	98.41±0.8456	Passes
Disintegration time *In vitro* (sec)	62.66±0.1457	45.33±0.4436	23.33±0.9693	18.33±0.7554	71.66±0.5537	22.33±0.4386	18.66±0.4233	12.33±0.7412	80±0.9942
In vivo (sec)	70.33±0.8124	49.33±0.9612	27.33±0.6625	21.66±0.9431	79.66±0.5531	27.33±0.4578	22.66±0.8457	14.33±0.7542	125±0.6431

Dissolution profile for tablets containing ammonium bicarbonate and camphor: Dissolution profile for tablets prepared by E1, E2, E3, and E4 formulations has shown in **figure 8**. From data it was observed that 100% drug release occurred within 0.5-2 min while the tablets prepared by F1, F2, F3, and F4 formulations which were shown in **figure 9**. From the data it was observed that 100% drug release occurred within 0.5-1 mins.

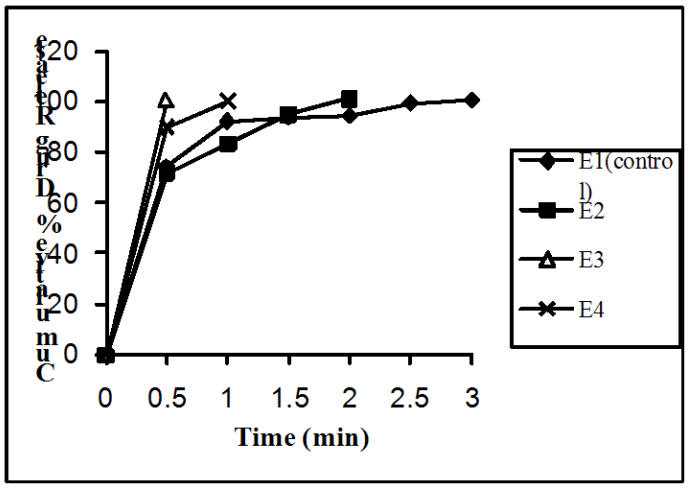

FIG. 8: DISSOLUTION PROFILE OF TABLET CONTAINING AMMONIUM BICARBONATE

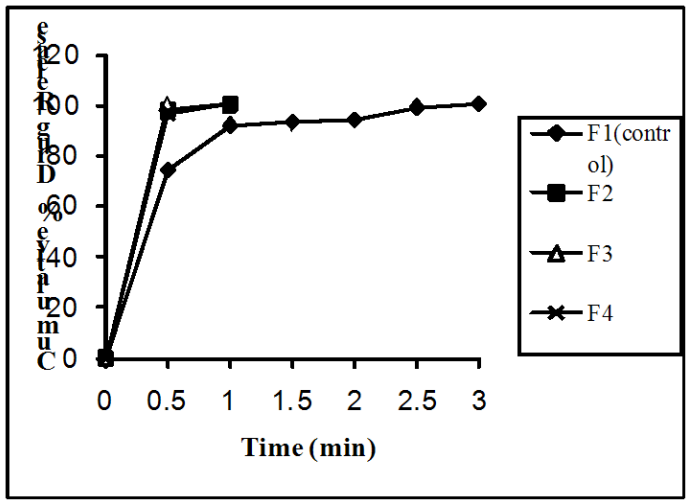

FIG. 9: DISSOLUTION PROFILE OF TABLETS CONTAINING CAMPHOR

Dissolution profile of marketed tablet: It was observed that 100% drug release of the marketed tablet was found to be within 4 min, as shown in **figure 10**, which was quite high than tablet prepared by using various superdisintegrants.

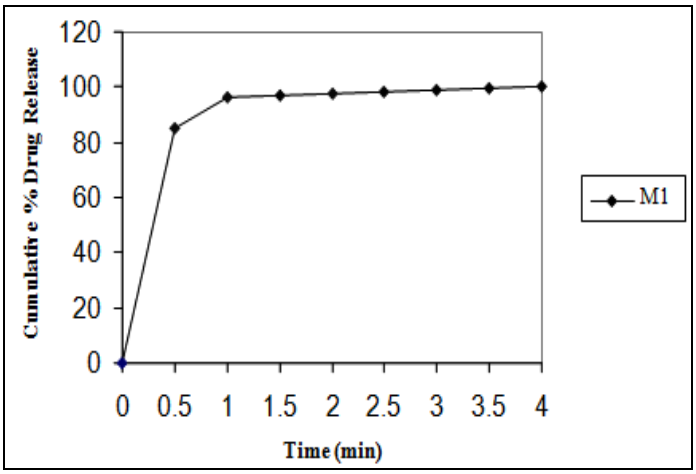

FIG. 10: DISSOLUTION PROFILE OF MARKETED TABLET

Stability studies: During storage of the tablets at 40±2°C/75 ±5% RH for three months, the tablets were tested for their contents and dissolution behaviour monthly. It was observed that the content from the tablets remained same, while the dissolution release rate of tablets decreased with time. This is due to slight increase in hardness of tablets followed by decrease in disintegration time as well as decreased in dissolution release rate.

CONCLUSION: Solid dispersion prepared by using β- cyclodextrin effectively masked the taste of Rizatriptan benzoate. Solid dispersion gave good flowability and there was no interaction between drug and β- cyclodextrin. Tablets prepared using sublimating agents were porous in nature and showed faster disintegration and dissolution, which is the major aim.

ACKNOWLEDGEMENT: We are very grateful to Ranbaxy Labs. Ltd., for providing Rizatriptan Benzoates, Emcure Pharmaceuticals for providing mannitol and ammonium bicarbonate. Authors also wish to thank the faculty of Physics University of Pune, Maharashtra, India.

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