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Design and evaluation of fast dissolving tablets for rizatriptan benzoate

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ABSTRACT

Rizatriptan Benzoate is potent anti migraine drug having agonist activity at the 5-hydroxytryptamine (5-HT) 1B and 5-HT 1D receptor. It commonly used for relief of headaches in treatment of migraine. Conventional tablets of RZT are not capable of rapid action, which is required for immediate relief from migraine pain. The aim of present work is to formulate and evaluate fast dissolving tablets of Rizatriptan Benzoate prepared by effervescent and sublimation methods using effervescent agents like sodium bicarbonate & citric acid, super disintegrants like Cross carmellose sodium, Avicel P^H 112 as diluents and menthol as sublimating agent. The prepared tablets were evaluated for uniformity of weight, thickness, friability, content uniformity, hardness, disintegration time, wetting time and for in vitro drug release. Further the tablets were characterized by fourier transform infra red spectroscopy and differential scanning calorimetry. Among all the formulations the tablets prepared by sublimation methods using menthol and Cross carmellose sodium as super disintegrant and Avicel P^H 112 as diluents showed faster disintegration and rapid drug release.

Keywords: Rizatriptan Benzoate, Cross carmellose sodium, Avicel P^H 112, sublimation

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INTRODUCTION

Fast dissolving tablets are solid dosage form containing medical substances which disintegrate rapidly, usually within few seconds when placed upon tongue requiring no additional water to facilate swallowing[1,2].This novel dosage form is suitable for all age groups, particularly children, elderly and patient who are ill and have difficulty in swallowing conventional tablets and capsules. Current approaches of making fast disintegrating tablets are maximizing the porous structure of the tablet matrix by incorporating appropriate disintegrating agents and or highly water-soluble excipients in tablet formulation. Direct compression is the easiest way of manufacturing tablets. Disintegration and solubilization of the directly compressed tablets are based on action of disintegrants, water-soluble excipients and effervescent agents. In many cases, the disintegrants play a major role in disintegration and dissolution process of FDTs made by direct compression.

In today's era many people are suffering from migraine. Migraine [3] is a one sided throbbing headache followed by neurological and visual disturbances. Attack may prolong for long period. Rizatriptan benzoate is an antimigraine agent. It is 5HT1B/1D receptor agonist used in treatment of migraine. It is the first online drug, which is most effective as compared to other triptans. Quick onset of action is necessary in order to protect the patient from migraine attack. The present study is aimed to design such a dosage form for rizatriptan benzoate, which is able to deliver drug as rapidly as possible so that onset of action is quick and patient does not require water for swallowing.
In sublimation method, the rapid disintegration of the tablets is achieved by creation of pores in the tablets up on sublimation of volatile components added in the tablets. The saliva will enter these pores and cause the rapid

disintegration of the tablets in the oral cavity. The porous structure is responsible for the faster water uptake, Hence it facilitates wicking action in bringing about faster disintegration [4, 5].

Direct compression is one of the techniques requires the incorporation of a super disintegrants into the formulation the use or highly. The basic approach used in development of FDT was the use of super disintegrants like cross linked Croscarmellose Sodium, Microcrystalline Cellulose, Crospovidone etc. which provide instantaneous disintegration of tablet after placed on tongue, thereby releasing the drug in saliva. In the present work Rizatriptan benzoate fast dissolving tablets were prepared by direct compression method using super disintegrants like sodium starch glycolate, microcrystalline cellulose as diluents and menthol as sublimating agent.

However the formulation development of pharmaceuticals is focused on design of new drug delivery system to improve patient compliance. Hence it is necessary to individualize the drug therapy to optimize the drug concentrations and manufacturing technology for patient oriented drug delivery system.

MATERIALS AND METHODS

Rizatriptan bezoate was obtained as a gift sample from apotex pharma ltd, Bangalore. Sodium bicarbonate was obtained from qualigens fine chemicals, Mumbai. Methanol & Citric acid were obtained from High-pure fine chem., Chennai. Crosscarmellose sodium and Crosspovidone was obtained commercially from S.D fine chem, ltd., Mumbai.

PREPARATION OF FAST DISSOLVING TABLETS BY SUBLIMATION METHOD:
Accurately weighed quantity of Rizatriptan benzoate, subliming agents (menthol), super disintegrating agents (Crosscarmellose sodium and Crosspovidone), micro crystalline cellulose and mannitol were mixed and passed through the sieve # 44. Finally talc was added as lubricating agent. The powder mixture was subjected to compression into tablets using a 10 station rotary tablet compression machine. After compression tablets were heated in a hot air oven at 60°C until constant weight was obtained to ensure the complete removal of volatilizable component to make the tablet porous.

PREPARATION OF FAST DISSOLVING TABLETS BY EFFERVESCENT METHOD:
Accurately weighed quantity of Rizatriptan benzoate, gas generating agents (sodium bicarbonate & citric acid), super disintegrating agent, micro crystalline cellulose and mannitol were mixed and passed through the sieve # 44. Finally talc was added as lubricating agent. The powder mixture was subjected to compression into tablet using a 10 station rotary tablet compression machine.

EVALUATION OF PREPARED FAST DISSOLVING TABLETS
Physical parameters such as weight variation, hardness, friability and disintegration were evaluated for prepared tablets [6]. The prepared fast dissolving tablets were further evaluated for physical parameters like drug content, wetting time, water absorption ratio, and moisture uptake studies and for invitro dissolution studies.

The moisture uptake study was carried out by keeping 10 tablets along with calcium chloride in a desiccators maintained at 37˚C for 24hrs to ensure complete drying of the tablets. The tablets were then weighed and exposed to 75% RH, at room temperature for 2 weeks. The required humidity can be achieved by keeping saturated sodium chloride solution in the desiccators for 24hrs. The tablets are reweighed and the percentage increase in weight was recorded. If the moisture uptake tendency of a product is high, it requires special dehumidified area for manufacturing and packing of the tablets [7].

Wetting time is carries out by taking 5 circular tissue papers of 10cm diameter were placed in a petridish with 10cm diameter. 10mL of water containing Amaranth, water soluble dye was added to the petridish. One tablet was carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet was noted ad wetting time [8]. Disintegration times of fast dissolving tablets were carried out by the method given by Gohl. For this a petridish was filled with 10mL of water and the tablet was carefully placed in the centre of petridish and the time taken for the tablet to completely disintegrate into fine particles was noted.

***In vitro* dissolution:**

Dissolution studies on each formulation were performed in a calibrated 8 station test apparatus (LAB INDIA) equipped with paddles (USP apparatus II method) employing 900ml of 6.8P^H as a dissolution medium. The paddles were operated at a 50 rpm and the temperature was maintained at 37±0.5°C throughout the experiment. Samples were withdrawn at regular intervals for 30 min and replaced with equal volume of same dissolution medium to maintain the constant volume throughout the experiment. Samples withdrawn at various time intervals were suitably diluted with same dissolution medium and the amount of drug released was estimated by ELICO double beam spectrophotometer at 229nm. The dissolution studies on each formulation were conducted in triplicate.

CHARACTERIZATION OF FAST DISSOLVING TABLETS

Fourier transforms infrared spectroscopy

The FTIR spectra of Rizatriptan benzoate, Polymer and formulations F2, F6 & F8 were obtained using Brucker FTIR spectrophotometer to study the interaction between drug and carrier in films. The samples were prepared in KBr discs (2 mg sample in 200 mg KBr) and the sampling range was 400-4000 cm^{-1} and the resolution was 4 cm^{-1}. The FTIR spectra were shown in Figures 2to5

Differential scanning calorimetry

Differential scanning calorimetry measurements were performed on Rizatriptan benzoate, Polymer and formulations F2, F6 & F8**)** using differential scanning calorimeter (METTLER TOLEDO INDIA Pvt Ltd Make DSC 1 with eSTAR software). The samples were placed in a sealed aluminum crucible and evaluated with a heating rate of 20°C/min at a temperature range of 20-2300°C. The thermograms were recorded and were shown in Figures 6 to 9.

RESULTS AND DISCUSSION

Fast dissolving tablets were prepared by effervescent and sublimation methods using effervescent agents (sodiumbicarbonate), sublimating agents (menthol) at different concentrations were found to be stable and suitable for increasing the dissolution rate of Rizatriptan Benzoate. The compositions of various tablet formulations are given in **table 1**. All batches of tablets were compressed under identical conditions to minimize the processing variables. Then the compressed fast dissolving tablets were further evaluated for physical parameters such as weight uniformity, hardness, friability and drug content. These studies revealed that all the tablet formulations were found to be stable and meeting I.P specified limits weight uniformity, friability and drug content. The hardness of all the tablet formulations was in the range of 3.0 to 3.5 kg/cm2. Weight uniformity of all the tablet formulations were in the range of 200 ± 3 mg/tablet. Friability losses of all the tablet formulations were negligible and were in the range of 0.1 to 0.2%. Drug content estimated for all the tablet formulations was highly uniform with less than 2.5% variation**.**

Dissolution studies were performed on all the tablet formulations by using U.S.P paddle method (apparatus II).based on the data obtained from the dissolution studies, various parameters such as DE30% , first order and zero order and Hixon Crowell release rate constants were estimated. The dissolution parameter DE30% was estimated by employing trapezoidal rule to the dissolution profiles.

The dissolution profiles of Rizatriptan benzoate fast dissolving tablets were shown in figure 1**.** The *in vitro* dissolution and kinetic parameters were given in table 2. The drug from various tablet formulations were released at a faster rate compared to pure drug. Formulations F2, F6 and F8 prepared by effervescent and Sublimation method using Crosscarmellose sodium as superdisintegrant found to release 99% in 30 min and were suitable for fast dissolving tablets. FTIR and DSC studies of Rizatriptan benzoate formulations were done to know any drug and excipient interactions.

The possible interaction between the drug and the carrier was studied by FTIR spectroscopy. IR spectra of pure rizatriptan showed characteristic peaks at CH3, CH2 stretch at 2915cm-1, C=C stretch at 1604cm-1, NH bend at 1271cm-1, C-N stretch at 1139 cm-1. FTIR spectra of the optimized formulations displayed all the characteristic bands of drug, without any significant spectral shift. This suggested that there was no potential chemical interaction between the components of the formulations. The FTIR spectra were given in figure 2-5.

DSC analysis was performed for the pure drug and for formulations F2, F6 and F8. DSC thermogram for pure venlafaxine shows onset of peak at 183 ^{0}c, where as DSC thermograms of optimized formulations F2, F6 and F8 showed onset of peaks at 183^{0}C, 190^{0}C and 185^{0}C indicated that there was no drug and polymer interaction. The thermograms were shown in figures 6-8. The results indicated that there were no drug and excipient interactions.

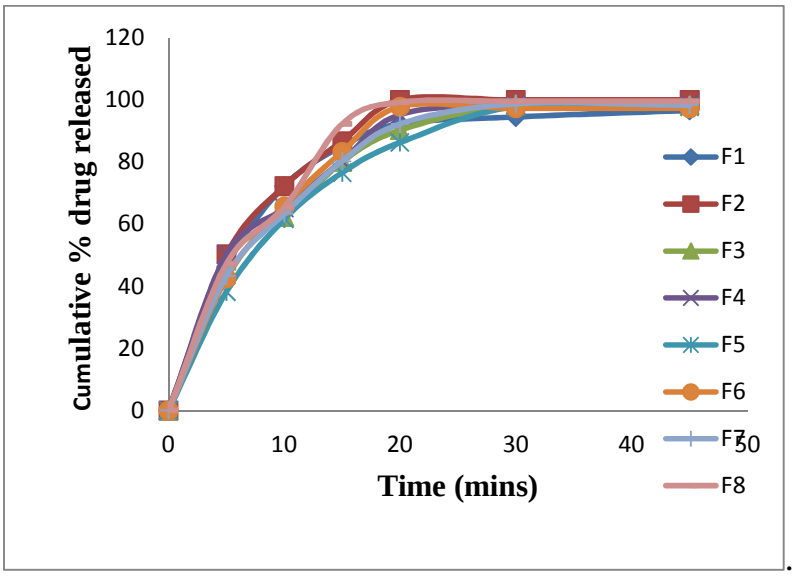

Figure 1: Drug Release profiles of Rizatriptan Benzoate Fast dissolving Tablets

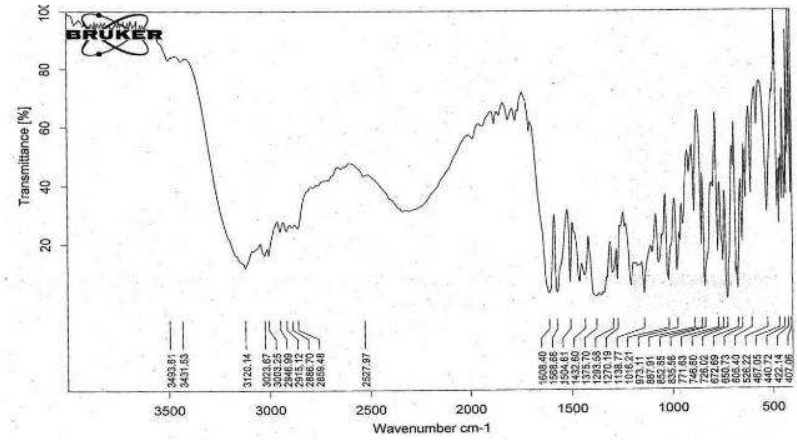

Figure 2: FTIR Spectrum of Rizatriptan Benzoate Pure Drug

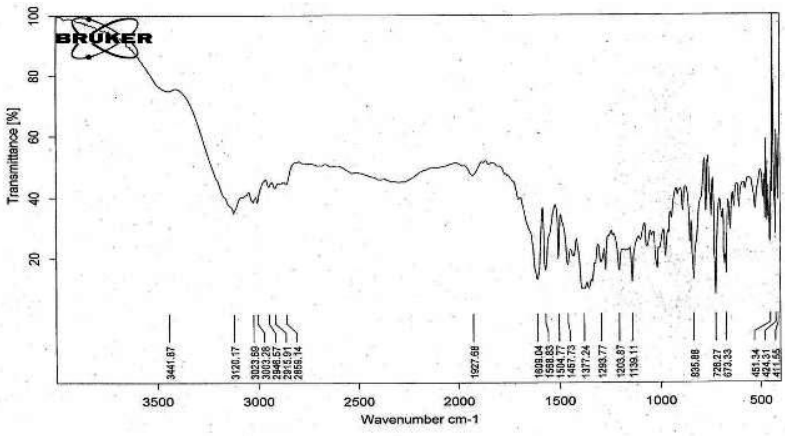

Figure 3: FTIR Spectrum of F2 Formulation

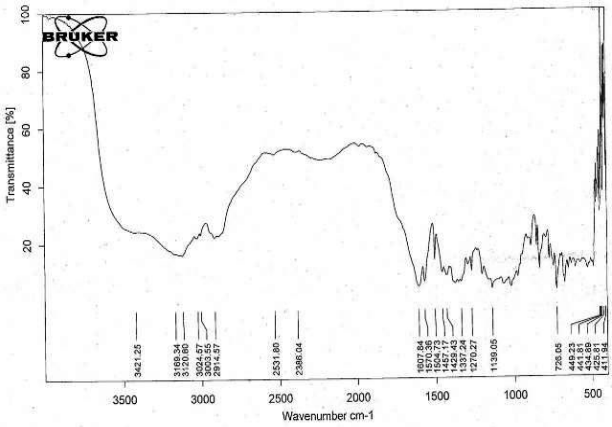

Figure 4: FTIR Spectrum of F6 Formulation

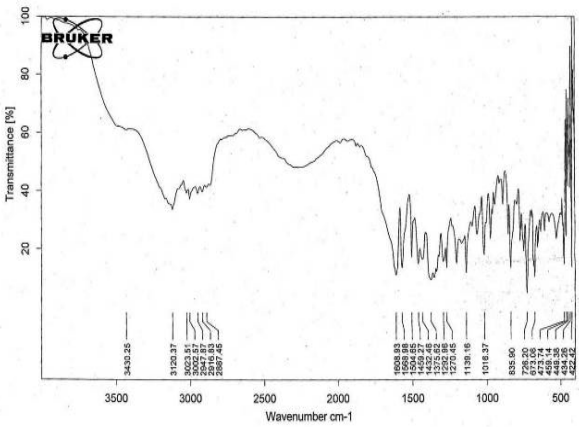

Figure 5: FTIR Spectrum of F8 Formulation

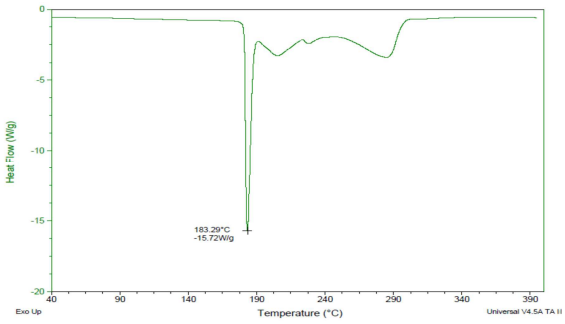

Figure 6: DSC Thermogram of Pure drug

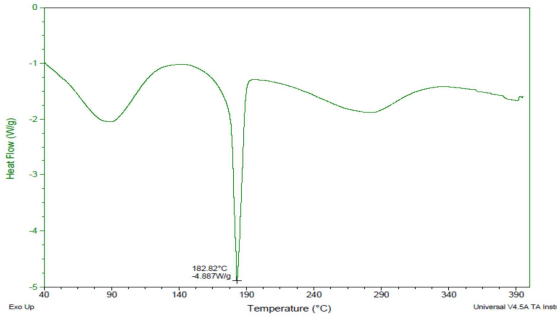

Figure 7: DSC Thermogram of Formulation F2

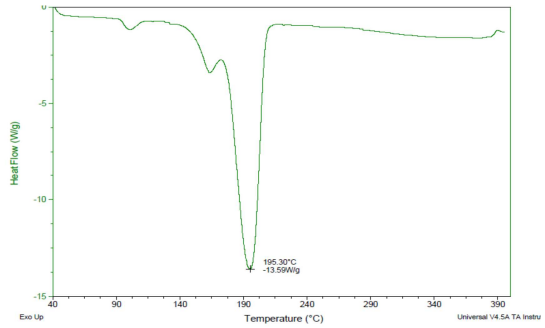

Figure 8: DSC Thermogram of formulation F6

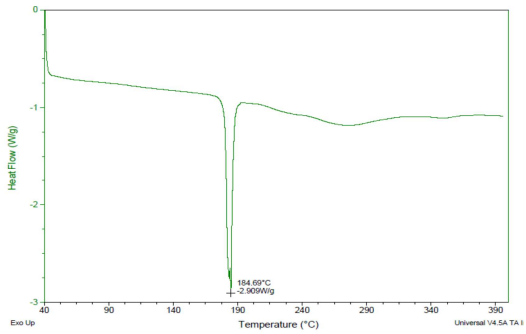

Figure 9: DSC Thermogram of formulation F8

Table No1: Composition of Rizatriptan Benzoate Fast Dissolving Tablets

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8
Drug	10	10	10	10	10	10	10	10
Sodium bi-carbonate	20	30	20	30	-	-	-	-
Menthol	-	-	-	-	30	40	30	40
Calcium silicate	-	-	-	-	-	-	-	-
Crosscarmellose sodium	10	20	10	20	20	20	-	-
Mannitol	80	80	80	80	60	60	60	60
Crosspoviodine	-	-	-	-	-	-	20	20
Avicel	78	58	58	28	78	68	78	68
Xantham gum	-	-	20	30	-	-	-	-
Talc	2	2	2	2	2	2	2	2
Total	200	200	200	200	200	200	200	200

Table No 2: Dissolution Parameters of Various Fast Dissolving Tablets of Rizatriptan Benzoate

Formulation	DE 30%	Zero Order		First Order		Hixson crowell	
		K (mg/min)	R^2	K_1 (min^{-1})	R^2	K_H ($mg.min^{1/2}$)	R^2
F1	31.36	1.783	0.808	0.176	0.847	0.025	0.941
F2	33.25	1.729	0.844	0.159	0.995	0.035	0.979
F3	31.36	1.846	0.979	0.099	0.914	0.0312	0.87
F4	35.68	1.81	0.902	0.104	0.903	0.0313	0.831
F5	19.61	1.989	0.826	0.193	0.908	0.031	0.875
F6	28.96	1.928	0.844	0.186	0.782	0.031	0.668
F7	36.1	1.92	0.832	0.175	0.878	0.0321	0.831
F8	26.1	1.911	0.937	0.191	0.916	0.035	0.824

CONCLUSION

From the present study, it is concluded that the tablets of Rizatriptan benzoate prepared by effervescent technique using sodium bicarbonate as effervescent agent and menthol as sublimating agent are suitable for fast dissolving formulations. Effervescent technique would be an alternative approach to use of more expensive adjuvant and sophisticated instruments in the formulation of mouth dissolving tablets. The prepared tablet gives benefit in terms of patient compliance, rapid onset of action, increased bio-availability, low side effect and good stability which make these tablets popular as a dosage form for the treatment of migraine.

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