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Formulation, Development and Evaluation of fast disintegrating tablets of Rizatriptan benzoate using novel adjuvants

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ABSTRACT: RZT 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. Marketed freeze dried tablet of RZT is available. Freeze drying is cumbersome and it yields a fragile and hygroscopic product. Thus, the aim of the present investigation is to formulate orally disintegrating tablets (ODTs) of Rizatriptan using simple and cost effective dosage forms. Approach used was use of superdisintegrants to prepare tablets. Tablets were prepared by direct compression using superdisintegrants such crospovidone, croscarmellose sodium, and sodium starch glycolate with incorporation of diluents like lactose, MCC and mannitol. Tablets of RZT prepared using crospovidone with MCC exhibited the least friability and disintegration time (s). To decrease the disintegration time further, modified diluents like spray dried lactose, Avicel PH 102 and Orocell 200.used along with the superdisintegrants for the preparation of ODTs. Tablet prepared using orocell showed good disintegration but shows less dispersion. Further trial was done in combinations of Orocell with Avicel PH 102. Among them Avicel PH 102 and orocell in 35:65 ratio showed less time of disintegration and rapid dissolution.

KEYWORDS: Orally disintegrating tablets, Rizatriptan benzoate, Orocell.

INTRODUCTION

- There has been an increased demand for more patient compliance dosage forms since last decade, these potentiated developments of new technologies. Now a day's development of new drug is a very costly and time consuming process, so efforts has been made by researcher for development of novel dosage forms of existing drug and the production of more cost effective dosage forms**.** Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available. However, it is not preferred for many patient groups such as the geriatric, pediatric and who are mentally retarded, uncooperative, nauseated patients[1]. To fulfill these requirements, pharmaceutical technologists have developed a novel oral dosage form known as Orally Quick Disintegrating (ODTs) tablets which disintegrate rapidly in saliva, usually in a matter of seconds, without the need of water[1].
- ODT products have been developed for numerous indications ranging from 1) Migraines, for which rapid onset of action is important 2) Mental illness, for which patient compliance is important for treating chronic indications such as depression and schizophrenia[2].
- RZT is potent anti migraine drug having agonist activity at the 5-hydroxytryptamine (5-HT) 1B and

5-HT 1D receptor subtypes provides relief of headaches for treatment of migraine. It undergoes rapid absorption but bioavailability is 45% due to its first pass metabolism. It has half-life of 2 - 3 hours. Thus, it will take more time for onset of action in conventional tablets for severe migraine attack. About 10% of children and adolescents suffer from migraine. So, it is preferred to formulate dosage forms which dissolve within minute and give fast relief from pain and minimize first pass metabolism and finely increase bioavailability[3].

- In market RZT is available in freeze dried dosage form which gives rapid disintegration. Main disadvantage of this method is very costly method, process is not feasible and product is highly sensitive to moisture. Freeze drying is cumbersome and it yields a fragile and hygroscopic product[4].
- In the present work tablets were prepared by direct compression using superdisintegrant Cross povidone with advanced adjutants Orocell, Spray dried lactose and microcrystalline cellulose. Due to spherical technologies of Orocell has excellent flow, Superior strength, outstanding disintegration performance, leaving taste with cooling sensation. Orocell 200 is having 90% mannitol with (<315µm)[5]. Avicel PH 102 diluent due to its granular nature so, give excellent flow and good dispersibility[6]. Spray dried lactose free flowing grade of lactose having good compressibility and water dispersibility[7]. Main aim of research is to obtain very cost effective approach with fast disintegration, increased effectiveness using promising adjuvant for fast release.

EXPERIMENTAL

Materials

Rizatriptan benzoate, Primogel, Ac-di-sol and Kollidon were received as gift sample from Torrent Research Centre (Ahmedabad, India) Avicel PH102 and spray dried lactose were obtained as gift sample from Lincoln Pharmaceuticals, Orocell received as gift sample from PharmaTransSanaQ Mumbai. Talc, Aerosil and Magnesium stearate were procured from Apex Chemicals (Ahmedabad, India).Aspartame and Sucralose purchased from Hi-media lab, Mumbai.

Methods

Preparation of ODT: - All the ingredients are weighed accurately and pass from sieve 100#. Mixed uniformly and lubricated sufficiently and directly compressed in rotary tablet machine using 6 mm concave punch (Rimech, Ahmedabad, India). Tablet formulation contains 10 mg of drug and amount of superdisintegrants were varied from 0-5%. Diluents used are spray dried lactose, Avicel PH 102 and Orocell are used in single and in combination with suitable colour , flavour and sweeteners.
(The formulation composition are given in table)

Evaluation

Weight Variation[8]

Randomly, twenty tablets were selected after direct compression but and the mean weight was determined. None of the tablets should deviate from the average weight by more than ±10%.

Wetting time[9]

The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10-cm diameter was placed in a petridish with a 10-cm diameter. Ten milliliters of water containing eosin, a water-soluble dye, was added to the petridish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time. The wetting times were measured according to the method described by Gohel et al.

In vitro Disintegration[9]

The disintegration time was measured using a modified disintegration method (n = 5). For this purpose, a petridish (10-cm diameter) was filled with 10 mL of water. The tablet was carefully put in the center of the petri dish and the time for the tablet to completely disintegrate into fine particles was noted.

In vitro Dissolution Test[8]

Dissolution test was examined in water (900 ml,37 ± 0.5°C) using a dissolution test apparatus (USP TDT 06 PL, Electrolab, Mumbai) with a paddle rotation at 50 rpm. After placing a tablet containing 10 mg of RZT in 0.1 N HCl, the solution was filtered through a cellulose acetate filter of 0.2m m pore size. Samples were withdrawn at different intervals like 1, 2, 3, 4, 6, 8, 10, 20, 30 min and diluted suitably using 0.1 N HCl and analyzed at 280 nm for cumulative drug release using (UV-2450, Shimadzu Corp., Japan) spectro photometer.

Drug content[8]

Twenty tablets were weighed and powdered. An amount of the powder equivalent to 10 mg of RZT was dissolved in 100 ml of 0.1 N HCl, filtered, diluted suitably and analyzed for drug content at 280 nm using UV-Visible spectrophotometer (UV grade- Shimadzu, Japan).

Hardness[8]

The crushing strength of the tablets was measured using a Monsanto hardness tester. Three tablets from

each formulation batch were tested randomly and the average reading was noted.

Friability[8]

The friability of a sample of 10 tablets was measured using a Roche Friabilator (Electrolab). Twenty preweighed tablets were rotated at 25 rpm for 4 minutes. The tablets were taken out, dedusted and reweighed. The percentage friability of the tablets was measured as per the following formula,

Percentage friability = ((Initial weight – Final weight) / Initial weight) x 100

In vivo disintegration time[10]

The in vivo disintegration time was measured in six human volunteers. A tablet was placed on the tongues of the volunteers and time required for complete disintegration in the mouth was noted and also taste and mouth feel was observed.

Stability Studies[11]

The stability studies of formulated tablets were carried out at 40^0C and 75% RH using a stability chamber for one month. The effects of temperature and time on the physical characteristics of the tablet were evaluated for assessing the stability of the prepared formulations. The different parameters that were studied are disintegration time, hardness, friability, drug content and dissolution rate.

Table: 1 Formulations composition for selection of superdisintegrants

Ingredients*	Formulations**					
	I	**II**	**III**	**IV**	**V**	**VI**
RZ	**10**	10	10	10	10	10
Kollidon	**2**	5	-	-	-	-
SSG	**-**	-	2	5	-	-
Crosss carmelose Na	**-**	-	-	-	2	5
MCC	**82**	85	82	85	82	85
Disintegration time (Sec)	**85 sec**	90 sec	120 sec	105 sec	137 sec	126 sec

Weight variation < 10 %, hardness is between 3-4.5 kg/cm^2, friability < 1

Table: 2 Formulations composition of ODT of RZT using different diluents

Ingredients*	Formulations**				
	A	**B**	**C**	**D**	**E**
RZ	10	10	10	**10**	10
Kollidon	-	-	-	**2**	2
Avicel PH 102	84	-	-	**41**	-
Sp. dried lactose	-	84	-	**-**	41
Orocell 200	-	-	84	**41**	41

*All the batches contain 3% of Aspartame, 1% magnesium stearate 2 % Aerosil with addition of color and flavor. Total weight of tablet is 100 mg. ** All the quantities are in mg.

Table: 3 Evaluation parameter of given formulations

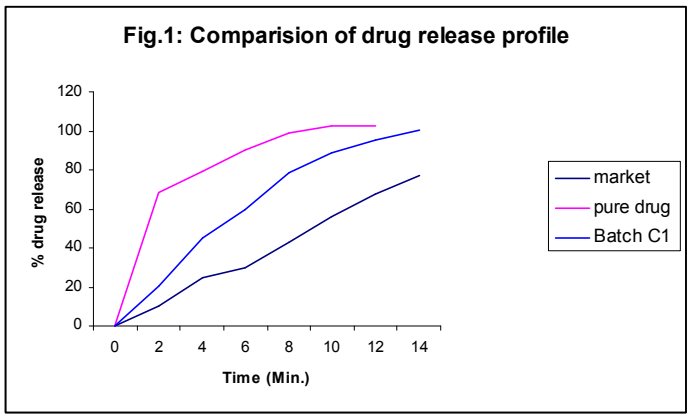
Formulation	A	B	C	D	E
% drug content	100.2±0.6	99.54±0.5	101.2±0.4	**101.2±0.7**	99.68±0.6
Hardness (Kg/cm^2)	3.5±0.01	3.8±0.002	4±0.005	**3.5±0.03**	3.5±0.04
Friability (%)	0.45±0.012	0.55±0.014	0.38±0.017	**0.14±0.015**	0.64±0.011
Wetting time	60±4.5	85±2.5	55±2.8	**45±3.5**	58±3.4
In vitro D.T time	90 ± 3.4	150 ± 2.4	77 ± 1.8	**52 ± 2.5**	65± 3.1
In vivo D.T time	120±2.3	186±1.4	90±2.5	**65±1.6**	80±1.8

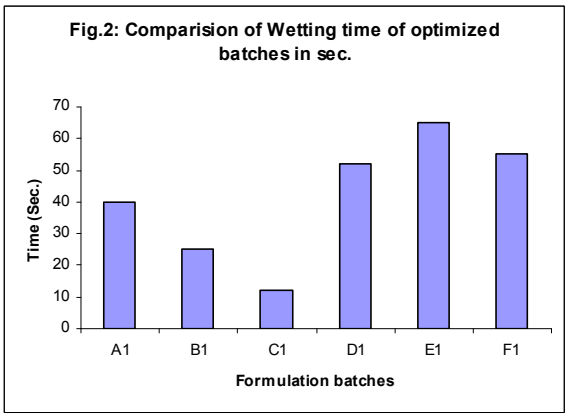
Note: All the batch are within the limit of weight variation <10%.No of tablet used are n=6. Wetting time, In vitro D.T time and In vivo D.T time is given in sec.

Table: 4 Formulations composition for selection of different ratio

Ingredients*	Formulations**						
	A1	**B1**	**C1**	**D1**	**E1**	**F1**	**G1**
RZ	10	10	10	10	10	10	10
Kollidon	2	2	2	2	2	2	2
Avicel PH 102	-	16.4	28.7	41	53.3	65.6	82
Orocell 200	82	65.6	53.3	41	28.7	16.4	-
Wetting time	40±2.4	25±1.8	12±2.8	35 ± 1.5	52±2.6	65±3.2	55±2.8
Disintegrations time	85±3.6	39±3.5	20 ±1.8	52 ± 2.5	73±2.2	80±1.6	80±2.3

*All the batches contain 3% of Aspartame, 1% magnesium stearate 2 % Aerosil with addition of color and flavour. Total weight of tablet is 100 mg.
** All the quantities are in mg.





RESULT AND DISCUSSION

Fourier transfer infrared spectroscopy: FTIR spectra of the pure drug showed significant bands at 3430 cm^{-1} NH strech, 2938, 2888 cm^{-1} CH3, CH2 stretch, 1608, 1505 cm^{-1} C= C and C =N stretch, 1569 cm^{-1}NH bend, 1446, 1377 cm^{-1}CH2, CH3 bend, 1271, 1140, 1016 cm^{-1}C–N stretch cm^{-1}, which indicates groups is match with structure of drug and confirm the purity of the drug. Preliminary trials were taken using various superdisintegrants like Ac-Di-Sol, Primogel and Kollidon in various concentrations from 0, 2, 5% of each one using MCC as diluents. But From all superdisintegrants Kollidon have showed minimum DT of 85 sec in 2% and 90 sec. in 5% compared to other two. Due to difference of 5 sec it is preferred to use 2% Kollidon with modified diluents in further trials. An objective of this method is to develop cost effective dosage forms.

Batch A, B, and C are prepared without addition of superdisintegrants using diluent like avicel, spray dried lactose and orocell respectively. Drug content, weight variation and Friability are within the limit as per IP std. All of them showed higher DT but from them Batch C showed less DT of 77 sec. Addition of Aerosil resulted in appreciable decrease in friability. It was also showed that spray dried lactose having more wetting and disintegration time than orocell and avicel. So, batches containing Orocell are used for further studies.

Orocell having less dispersibility it had given creamy texture. So, Batches D, E were prepared in combination of Orocell with avicel and spray dried lactose in 50: 50 ratio to increase dispersibility. Batch D showed less DT time of 52 sec and fast dissolution rate compared to E. Hardness of tablet was found between 3.13 - 4.06 kg/cm^2. Friability of tablet was found below 1% indicating good mechanical resistance. So, Avicel is preferred for further optimization of disintegration time and drug release profile. So, different combinations of Orocell and Avicel are selected for further study and batches A1-G1 were prepared. In batch C1 showed excellent result of wetting time (12±2.8 sec.) and DT (20 ±1.8 sec.) and dissolution rate profiles is 100.57% within 20 min. with good mouth sensation and less gritteness and give smooth texture in mouth in presence of 2 % of Kolidon. All the parameters are improved in combination then individual diluents.

The stability study of optimized batch was carried out at 40°C-75% RH. The tablets were found to be stable at such condition and other parameters were found to be unaffected.

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