

DEVELOPMENT OF DIRECTLY COMPRESSIBLE CO-PROCESSED EXCIPIENTS FOR ORALLY DISINTEGRATING TABLETS USING ROTARY EVAPORATION METHOD

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ABSTRACT

Objective: The objective of this research was to co-process tablet excipients by rotary evaporation method to create mixtures that can help in achieving direct compression, optimum disintegration time along with required hardness and friability in formulation of orally disintegrating tablets.

Methods: The co-processing of lactose with other excipients was done by rotary evaporation method using water as solvent. The co-processed excipients were evaluated for precompression and postcompression properties. To check the effect of solvent, the lactose- sodium starch glycolate (SSG) mixture which was found to be best, was co-processed using methanol and water: methanol (1:1) as solvent systems. Placebo tablets were prepared and evaluated. These three coprocessed excipients were used in formulation of orally disintegrating tablets (ODTs) using Zolmitriptan as a model drug and tablets were evaluated for various parameters.

Results: The precompression properties of processed lactose had shown significant increase in compressibility. When co-processing of lactose was done with other excipients using water as solvent, lactose- SSG co-processed mixture had shown best result compared to other co-processed excipients. When lactose- SSG mixture was co-processed with methanol and water: methanol (1:1) as solvent, its compressibility was not improved that much as with water alone. This was further evident from the evaluation of ODTs of Zolmitriptan.

Conclusion: The co-processed mixture of lactose & SSG prepared by rotary evaporation method using water as solvent had shown best properties among all co-processed mixtures which was proved by its use in ODTs of Zolmitriptan.

Keywords: Direct compression, orally disintegrating tablets, Co-processing, Rotary evaporation

INTRODUCTION

Oral route of drug administration is perhaps the most appealing route for the delivery of drugs [1]. Of the various dosage forms administered orally, the tablet is one of the most preferred dosage form because of its ease of manufacturing, convenience in administration, accurate dosing, better stability compared with oral liquids, and because it is more tamper proof than capsules [2]. Over the decade, the demand for the development of orally disintegrating tablets (ODTs) has enormously increased as it has notable impact on the patient compliance. ODTs are designed to disintegrate rapidly on contact with saliva and enable oral administration without water or chewing, these formulations offer increased convenience and ease of administration with the potential to improve patient compliance, particularly in certain populations, where swallowing of conventional solid oral dosage forms presents difficulties [3-5]. Direct compression is one of the popular techniques for preparation of these dosage forms of its easy implementation, use of conventional equipment along with commonly available excipients, limited number of processing steps and cost effectiveness. For allowing disintegration of ODTs in the oral cavity, ODTs are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may increase the cost of the product [6]. Although simple in terms of unit process involved, the direct compression process is highly influenced by powder characteristics such as flowability, compressibility and dilution potential. No single material is likely to exhibit all the ideal characteristics. The platform for the manipulation of excipient functionality is provided by co-processing. In co-processing two or more excipients interact at the sub-particle level, the objective of which is to provide a synergy of functionality improvement as well as masking the undesirable properties of individual components. Various techniques for preparation of co-processed excipients are roller compaction, wet granulation, spray drying, hot melt extrusion, solvent evaporation etc [7]. Rotary evaporation method was selected because intimate contact between excipients throughout removal of solvent is possible without need of stirrer, removal of solvent at faster rate at lower temperature compared to conventional solvent evaporation

method and recovery of solvent. Lactose was selected because its poor compressibility [2, 8] hinders its use in designing ODT. After Rotary evaporation of lactose using water as a solvent, its precompression properties were remarkably improved. Using this as basic research line, lactose was co-processed with other excipients. Zolmitriptan was selected as model drug because it is a selective agonist of serotonin (5-hydroxyl triptamine; 5-HT) triptan derivatives used as an antimigraine drug which act as 5HT_{1B/1D} receptor agonist. It is widely used in migraine therapy [9].

MATERIALS AND METHODS

MATERIALS

Zolmitriptan was obtained as a gift sample from Emcure Pharmaceuticals limited. Lactose, Croscarmellose sodium, Sodium starch glycolate and Crospovidone were purchased from Research Lab Fine Chem Industries. All other reagents were of laboratory grade.

METHODS

- a) **Processing of lactose with water as a solvent by using rotary evaporator** 5 g of lactose was added into 20 ml of water. Water was evaporated at 80°C using rotary evaporator (Heidolph, Germany) at 150 rpm under vacuum. The dried powder was removed and passed through sieve no.16.
- b) **Co-processing of lactose with different excipients by using rotary evaporator** Co-processing of lactose-crospovidone (97:3), lactose- sodium starch glycolate (SSG) (97:3), lactose-croscarmellose sodium (97:3), lactose-PVP (90:10) and lactose-PVP-crospovidone (87:10:3) was done as per procedure mentioned above. Co-processing of lactose-SSG was also done using methanol (at 60°C at 150 rpm) and water: methanol (1:1) by same method mentioned above.
- c) **Evaluation of processed and co-processed excipients**
 - i. **Precompression properties**

Carr's compressibility index The Carr's compressibility index was calculated by calculating the tapped and bulk density using the 10

ml measuring cylinder. Compressibility is calculated by the formula [10],

$$C = 100 \times \left(1 - \frac{\rho_B}{\rho_T}\right)$$

Where ρ_B is the freely settled bulk density of the powder, and ρ_T is the tapped bulk density of the powder. Carr's index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability.

Hausner's Ratio The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. It is calculated by the formula,

$$H = \frac{\rho_T}{\rho_B}$$

Hausner's ratio greater than 1.25 is considered to be an indication of poor flowability.

ii. Post compression Properties

Hardness

Hardness was measured using Monsanto Hardness Tester.

Friability Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25rpm and dropping a tablet at height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were de-dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula [11]

$$F = \frac{\text{Initial weight of tablets} - \text{Final weight of tablets}}{\text{Initial weight of tablets}} \times 100$$

Table 1: Formulation chart of ODT of Zolmitriptan

Ingredients (mg/tablet)	Formulation code				
	F ₁	F ₂	F ₃	F ₄	F ₅
Zolmitriptan	5	5	5	5	5
Lactose	194	-	-	-	-
SSG	6	6	-	-	-
Processed Lactose	-	194	-	-	-
Co-processed lactose-SSG (Water)	-	-	200	-	-
Co-processed lactose-SSG (Methanol)	-	-	-	200	-
Co-processed lactose-SSG (Water: Methanol {1:1})	-	-	-	-	200
Magnesium Stearate	5	5	5	5	5
Total	210	210	210	210	210

f) Evaluation of tablet

Hardness, Disintegration Test and Friability were done with the same method mentioned above. Other parameters were done as per following procedure

Diameter and Thickness It was measured by using vernier caliper.

Weight variation

The USP weight variation test is run by weighing 20 tablets individually, and comparing individual weight to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit [2].

% drug content 20 tablets were taken and triturated. Powder equivalent to 5 mg of drug was taken and dissolved in 0.1 N HCl. Solution was filtered using whatman filter paper. With further dilution, spectrophotometric determination was carried out at 222 nm and by using calibration curve equation, drug content was determined.

Dissolution test

Dissolution test was carried out in 0.1 N HCl by using USP dissolution apparatus for 30 min. A tablet was placed in dissolution

Disintegration Test

The disintegration time of six randomly selected tablets from each tablet batch were evaluated in purified water at $37 \pm 1^\circ\text{C}$ using disintegration apparatus. The time for each tablet to completely disintegrate and pass into solution was noted and the mean value was calculated.

iii. FTIR study

This study was done to check the interaction of excipients with the solvents by using SHIMADZU IRAffinity-1 FTIR spectrophotometer.

d) Preformulation Study

Identification of drug by IR

The identification of drug was done by FTIR study.

Determination of λ_{max}

Accurately weighed 50 mg of drug was dissolved in 0.1 N HCl. Further, dilutions were made with 0.1N HCl to get concentration of 1 ppm and scanned in the range of 200-400 nm by using UV spectrophotometer (JASCO V-630 Spectrophotometer).

Preparation of Calibration curve

1 ppm to 5 ppm solutions of the drug were made in 0.1 N HCl and absorbance was noted at 222nm.

e) Formulation of ODT of Zolmitriptan

Orally disintegrating tablets of Zolmitriptan were prepared by direct compression method. The co-processed mixtures of lactose- SSG (97:3) prepared by using water, methanol and water: methanol (1:1) as solvents, processed lactose prepared by using water as solvent and physical mixture of lactose and SSG were used in different formulations. Magnesium stearate was used as lubricant.

medium (500 ml) which was rotated at a speed of 50 rpm by means of a paddle. A temperature of $37 \pm 0.5^\circ\text{C}$ was maintained throughout the study [13].

RESULTS AND DISCUSSION

Evaluation of co-processed excipients

Carr's index and Hausner's ratio of processed lactose were significantly different from unprocessed lactose which showed increase in compressibility. Also it was compressed at relatively less pressure. Carr's index and Hausner's ratio of co-processed excipients were less indicating their directly compressible nature. The co-processed excipients were compressed at less pressure. Compressed tablets showed good hardness, less friability with disintegration time within limit except the co-processed lactose-PVP tablet which failed to disintegrate within specified limit. In co-processing with PVP, complete recovery of product is not possible as it was sticking to the wall of round bottom flask. Lactose- SSG using water as solvent co-processed mixture was selected for further study as it showed most promising result with best hardness and less friability among all. When same mixture was co-processed with methanol as solvent, no significant changes in precompression and postcompression properties were observed compared with physical mixture whereas with methanol : water (1:1), its precompression

and postcompression properties were improved but less than that with water alone. All the results were as shown in Table 2. FTIR

study had shown no chemical interaction of lactose & SSG with solvents as shown in Fig.1, Fig. 2, Fig. 3 & Fig.4.

Table 2: Evaluation of Processed and Co-processed excipients

Co-processing Medium (Solvent)	Name of the co-processed / processed excipients	Precompression properties		Post compression properties		
		Carr's index	Hausner's ratio	Hardness (Kg)	Friability (%)	Disintegration time (Seconds)
No Medium	Lactose	31.03	1.45	Tablets were not formed due to less compressible nature of excipient.		
Water	Processed lactose	14.66	1.17			
	Lactose + Crospovidone	13.75	1.159	3	0.67	20
	Lactose + SSG	11.25	1.167	3.2	0.51	24
	Lactose + Croscarmellose Sodium	12.91	1.148	2.6	0.85	18
	Lactose + PVP	15.55	1.184	4.2	0.42	> 900 (15 min.)
	Lactose + Crospovidone + PVP	18.23	1.203	3.7	0.51	38
No medium	Lactose + SSG	23.86	1.258	2.2	1.45	25
Methanol	Lactose + SSG	19.23	1.238	2.6	1.21	28
Water: Methanol (1:1)	Lactose + SSG	19.21	1.23	3.4	0.71	27

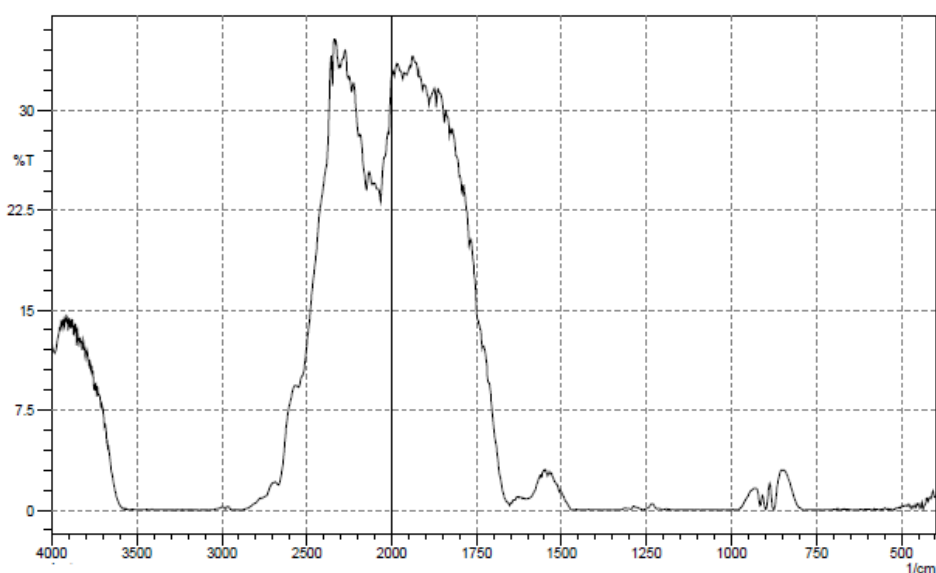


Fig. 1: FTIR spectra of physical mixture of lactose and SSG

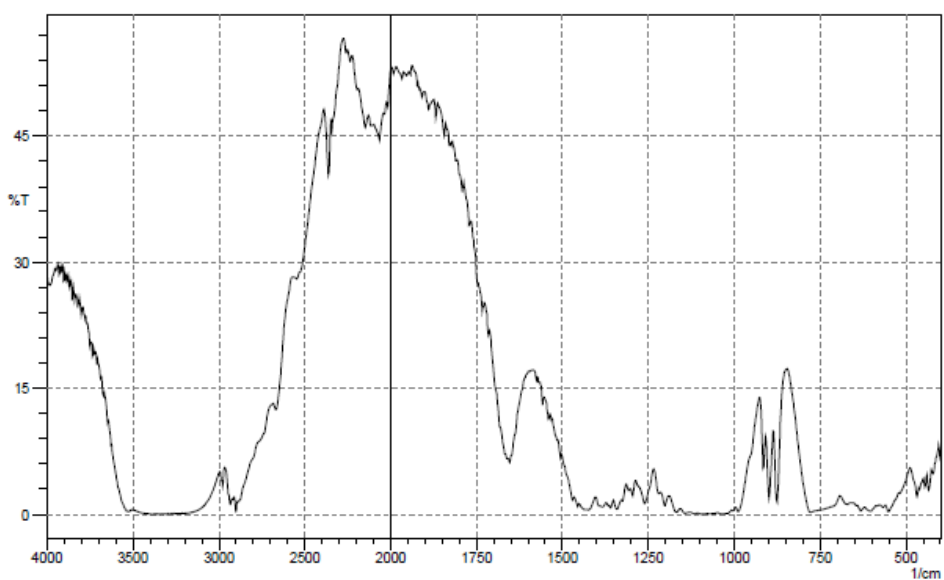


Fig. 2: FTIR spectra of co-processed mixture of lactose and SSG using water as solvent

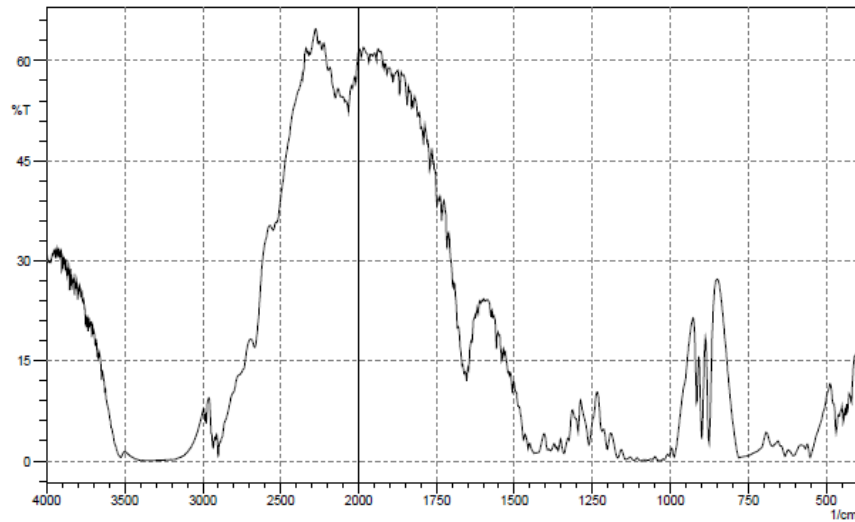


Fig. 3: FTIR spectra of co-processed mixture of lactose and SSG using methanol as solvent

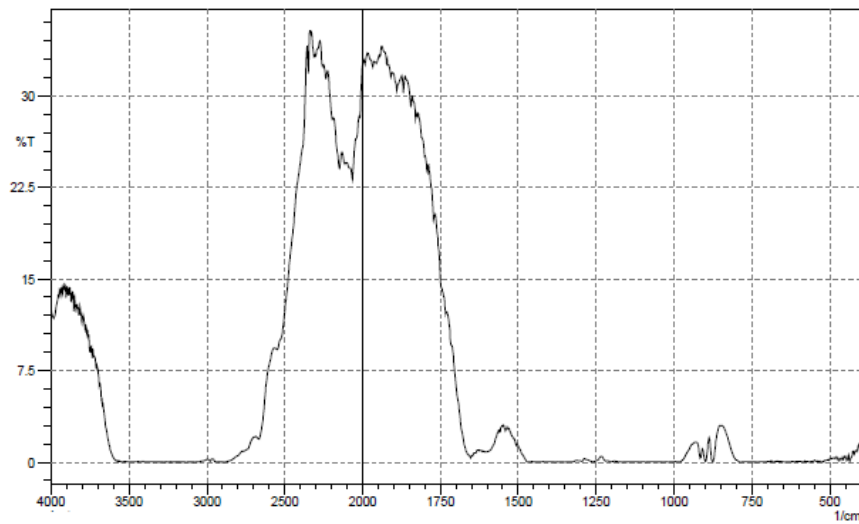


Fig. 4: FTIR spectra of co-processed mixture of lactose and SSG using water: methanol (1:1) as solvent

Preformulation study

IR spectra of Zolmitriptan had shown all the major peaks of drug (Fig.5). λ_{max} of the drug was found to be 222 nm (Fig. 6) and its calibration curve was as shown in fig.7.

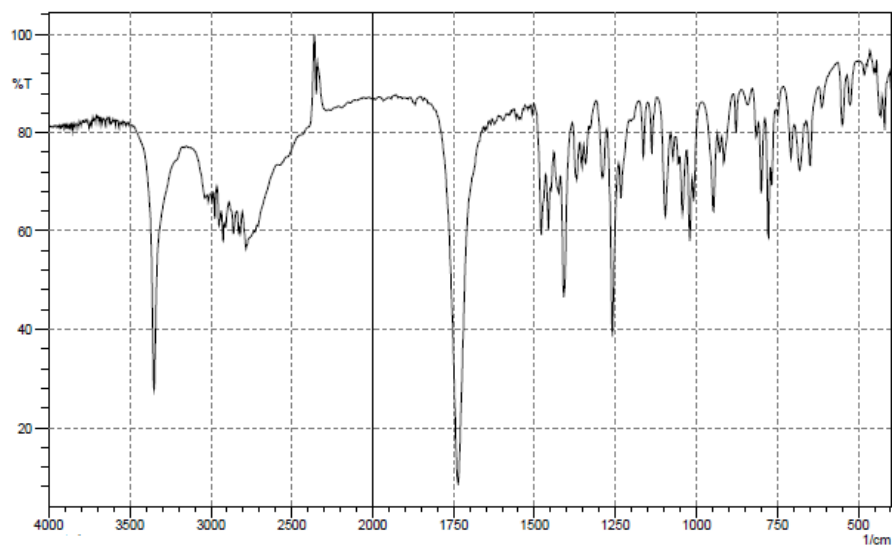


Fig. 5: FTIR spectra of Zolmitriptan

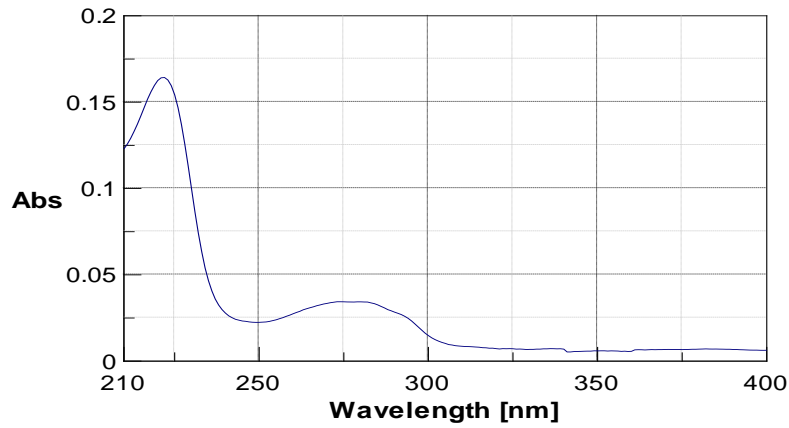


Fig. 6: UV spectra of Zolmitriptan

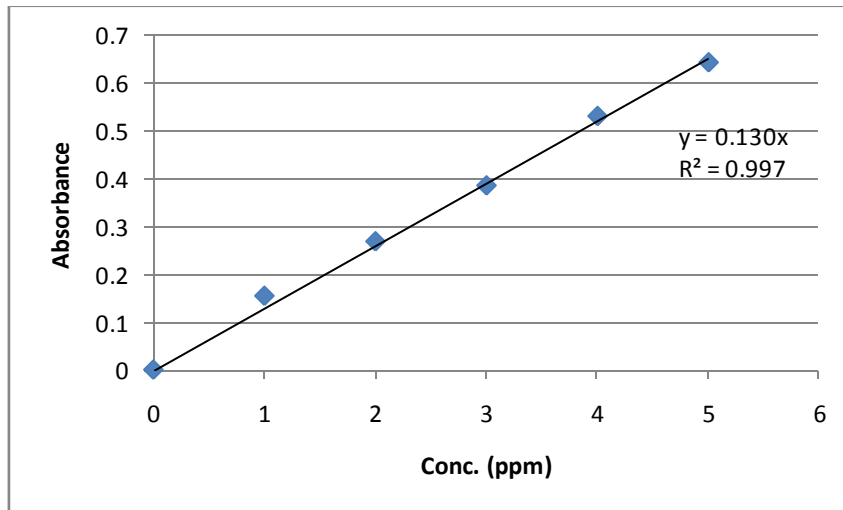


Fig. 7: Calibration curve of Zolmitriptan

Evaluation of ODT of Zolmitriptan

Among all the batches, F₃ had shown best hardness and less friability compared to other batches when all the tablets were compressed at same pressure. Uniformity in thickness and diameter of tablets were

observed. Disintegration time was found to be within limit for all the batches with minimum time shown by F₁ as it was less hard. Weight variation and % drug content was found to be within limit. All the batches had shown complete drug release within 30 min (Fig. 8). All the Results were shown in Table 3.

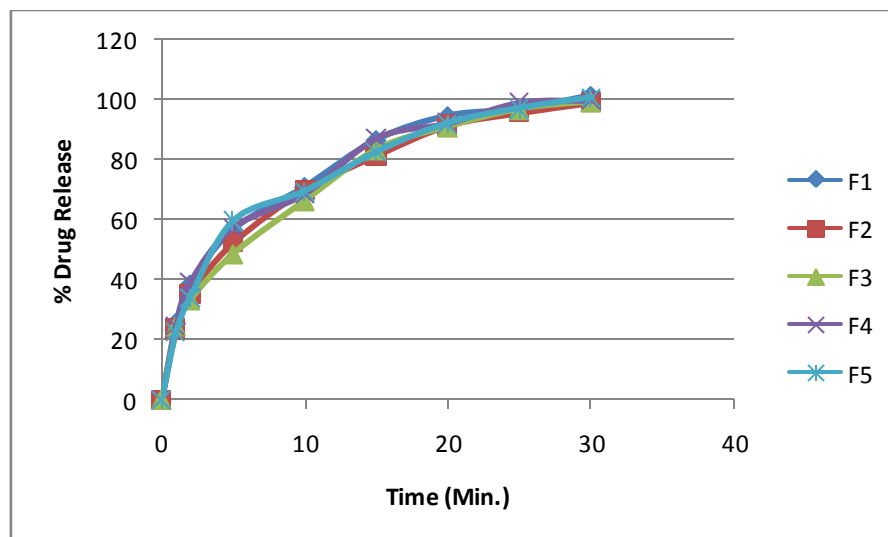


Fig. 8: Dissolution study of ODT of Zolmitriptan

Table 3: Evaluation of ODT of Zolmitriptan

Parameter	Formulation code				
	F ₁	F ₂	F ₃	F ₄	F ₅
Diameter (mm)	7.24±0.02	7.24±0.02	7.24±0.02	7.24±0.02	7.24±0.02
Thickness(mm)	4.18±0.02	4.18±0.02	4.18±0.02	4.18±0.02	4.18±0.02
Weight variation (mg)	210±2	209±1	210±1	210±2	209±1
% Friability	1.34	1.04	0.65	0.89	0.74
Hardness (kg/cm ²)	2.0	2.6	3.6	2.8	3.3
Disintegration time (sec.)	16	19	24	21	24
% Drug content	98.83	101.49	99.59	100.91	100.23

CONCLUSION

The processed lactose prepared by rotary evaporation using water as solvent has shown improved compressibility. The co-processed mixture of lactose & SSG prepared by rotary evaporation method using water as solvent has shown best properties among all co-processed mixtures which is proved by its use in ODT of Zolmitriptan. In future, different co-processed mixtures of various excipients can be prepared by using different solvents using rotary evaporation method.

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