Research Article **CODEN: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: **www.ijrpns.com**

FORMULATION AND EVALUATION OF TASTE MASKING ORAL DISINTEGRATING TABLETS OF ZOLMITRIPTAN

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ABSTRACT

Zolmitriptan is a new serotonergic agonist of the 5-$HT_{1D/1B}$ receptor with anti-migraine property and belongs to the class of the triptans. It is extremely bitter in taste. The purpose of this research was to develop a bitterless orally disintegrating tablet of poorly soluble drug like zolmitriptan. Taste masking was done by complexing Kyron T-134 in different ratios. Three super disintegrants like Sodium starch glycolate, Crospovidone, Low substituted hydroxypropyl cellulose were used. Prepared tablets were evaluated for different properties like Drug content, hardness, friability, wetting time, water absorption ratio, disintegration time and *In-vitro* dissolution studies. The different formulations showed disintegration time between 39 to 52 seconds. Drug release showed between the range of 5 to 30 minutes. Among all the formulations, F9 with Low substituted hydroxypropyl cellulose at a concentration of 4% showed 98.09% drug release within 30 minutes. Thus F9 was considered as best among the other formulations. The tablets showed enhanced dissolution hence better patient compliance. Kinetic analysis (r^2) of release data based on best curve-fitting method for selected ODT of Zolmitriptan showed first order kinetics indicating that the drug release depends upon its concentration.

KEYWORDS

Zolmitriptan, Kyron T-134, Superdisintegrants, Oral disintegrating tablets and Disintegrating time.

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INTRODUCTION

Rapidly disintegrating tablets (RDT) are defined as a solid dosage form containing medicinal substances that disintegrate within a matter of seconds when placed upon the tongue. In the European Pharmacopoeia, RDT are defined as tablets that can be placed in the mouth where it disperses rapidly before swallowing.

Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly, and is

also seen in swallowing conventional tablets and capsules[2] Hence, FDDTs (Fast-dissolving/disintegrating tablets), disintegrate and/or dissolve rapidly in the saliva remarkably fast, within a few seconds, without the need of water or chewing and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast disintegrating tablets, as they may take up to a minute to completely disintegrate RDTs can be achieved by various conventional methods like direct compression, wet granulation, molding, spray drying, freeze drying and sublimation. In order to allow fast disintegrating tablets to dissolve in the mouth, they are made of both very porous and soft molded matrices or compressed into tablets with very low compression force. However, the function and the concept of all these dosage forms are similar. Undesirable taste is one of the important formulation problems that are encountered with many drugs. Administration of bitter drugs orally with an acceptable level of palatability is a key issue for health providers. Proven methods for bitterness reduction and inhibition have resulted in improved palatability of oral pharmaceuticals. Taste masking is an essential requirement for fast dissolving tablets for commercial success. Ion exchange resins have been increasingly used to the taste masking of bitter taste drug and help to prepare RDT. Ion exchange resins are solid and suitable for solubilised high molecular weight poly electrolytes that can exchange their mobile ions of equal charge with the surrounding medium reversibly and stotiometrically. They are available in desired size ranges. Kyron T-134 was used as an ion exchange resin for taste masking of bitter drugs. The polymer was mixed with the drug in different ratios, i.e., drug- resin granules were lubricated and used for compression as required.

Zolmitriptan is a novel serotonin 5-$HT_{1D:1B}$ receptor agonist is being investigated for the acute oral treatment of migraine.

MATERIAL AND METHODS

Preparation of drug-resinate complex

The method used for making the taste of zolmitriptan was complexed with ion exchange resin such as kyron T-134 as for the following procedure.

Step 1: Drug and resonate were accurately weighed in required ratio.

Step 2: Then slurry of resin was made in sufficient quantity of demineralised water and stirred for half an hour at 500 RPM, in order to allow the polymer structure to swell uniformly.

Step 3: The drug was added slowly under stirred conditions to step 2.

Step 4: The drug resin mixture was continuously stirred for 6 to 8 hours at 500 to 600 RPM and volume was made up to 100ml.

Preparation of drug-resinate granules and lubrication

After the drug resin mixture were stirred for the required time, the drug resonates were thoroughly washed with demineralised water for several times then filtered by using whatman filter paper and dried. The powdered drug resinate particles are wetted, made into damp mass. Then passed through sieve no. 60 and dried at 60^{o}C for 30minutes. These granules were taken in a polyethylene bag along with other excipients and mix for 15 minutes. Then finally add talc (glidant) and blend for 5 minutes. Then it is subjected into pre compression parameters followed by direct compression.

EVALUATION PARAMETERS

Pre-formulation studies

Fourier Transform Infrared Spectroscopy

The fourier transform infrared analysis was conducted for the structure characterization. FTIR spectra of the pure drug, polymers and formulations were recorded by using BRUKER FTIR instrument. Approximately 1mg of sample were mixed with 100mg of spectroscopic grade KBr pellets, samples were scanned in the IR range from 1000-3500cm^{-1}.

Pre-compression studies of fast dissolving tablets

Bulk density

Bulk Density is the mass of the powder per volume bulk volume of the drug .Bulk Density is determined by filling the graduated measuring cylinder with 50gms of active pharmaceutical ingredient (APIs) and noting down the volume occupied by them. It is calculated by using the formula:

Bulk Density = $\frac{M}{V_0}$

Where, M = weight of the powder

V_0 = apparent volume of powder blend in the cylinder

Tapped density

Tapped density is the ratio between a given mass and the volume of the powder after tapping for some fixed number of taps. Electro lab tapped density tester is used for determining the tapped density of the powder for 750 taps. Tapped density is found from the formula;

Tapped density = $\frac{M}{V_f}$

Where, M = weight of the powder

V_f = Final volume of the powder blend in the cylinder

Angle of repose

Angle of repose was determined by using the funnel method. The powder was poured from a funnel that can be raised vertically until a maximum height (h) was obtained. The radius of the heap was measured. The angle of repose can be calculated as:

$$\Theta = \tan^{-1} h/r$$

Where, h=height of the pile

r=radius of the pile

Carr's Index

The flow property of the active pharmaceutical ingredient (APIs) is can be inferred from the value of compressibility index or Carr's index. This can be measured from the Bulk density and Tapped density. Results are shown in Table

Carr's Index = $\frac{(\text{Tapped density} - \text{Bulk Density}) \times 100}{\text{Tapped density}}$

When the values of Carr's index are less than 15% the powder possesses good flow properties and when it is more than 25% it indicates poor flow.

Hausner's ratio

It is the ratio of tapped density and Bulk density. It is a measure of the frictional resistance of the blend. The ideal range of Hausner ratio is 1.0-1.18.

Hausner's ratio = $\frac{\text{Tapped density}}{\text{Bulk density}}$

Post compression studies of zolmitriptan oral disintegrating tablets

Hardness

Hardness is an indication to measure the strength and force require to break the tablet. The hardness of the tablet is measured using a Monsanto hardness tester and the tester consists of a barrel containing a compression spring held between two plungers. The tablet was placed in contact with the lower plunger and a zero reading was taken. The upper plunger was then forced by turning a threaded bolt until the tablet fractured, as the spring was compressed, a pointer moved along a gauge in the barrel to indicate the force which is a measure of hardness in kg/cm^2 is expressed in kg/cm^2.

Thickness

Thickness is measured by using "vernier callipers" 3 tablets are taken and are placed between the two upper jaws and the thickness was measured as replicate of three sets. After adjusting the callipers to zero reading the +ve or –ve the correction value is noted and values are estimated.

Weight variation

Ten tablets from each batch were weighed in digital balance and average weight was determined and standard deviation was calculated. Not more than two of tablets must differ from the average weight and not more than the percentages.

Friability

Roche friabilator is used to find out the friability of the tablets. In friability testing done to know the loss of weight of tablets and to withstand abrasion and shock. For tablets with an average weight of 0.65g or less take a sample of whole tablets with an average accurately the required number of tablets. Place the tablets in the drum and rotate it. Remove

the tablets, remove any loose dust from them and weigh them accurately. The test is run only once unless the results are difficult to interpret or if the weight loss is greater than the targeted value, in which case, the test is repeated twice and the mean of the three tests is determined. A maximum loss of weight not greater than 1% present is acceptable for most tablets.

Mouth feel test or Taste evaluation

The Mouth feel is critical and patient must feel the product is pleasant .One tablet from each batch was tested for sensation by placing the tablet on the tongue the human volunteers are used for evaluation of mouth feel. Taste evaluation was done by using time intensity method taste was recorded instantly after 10 Sec placing on the tongue which was continued up to 1, 2, 3, 4, 5, minutes respectively volunteer an opinion for taste were rated by giving different score values as follows:

Drug content uniformity

The test for uniformity of single dose preparations is based on the assay of the individual contents of the active substance of a number of single dose units to determine whether the individual contents are set within limits with reference to the average content of the sample. Determine the content of active ingredient in each 10 dosage units taken at random using the method given in the monograph or by another suitable analytical method.

The preparation complies with the test if each individual content is 85 to 115% of the average outside these limits or if one individual content is outside the limits of 75 to 125% of average content.

If one individual content is outside the limits of 85 to115%. Some of the average content, but within the limits of 75 to 125% repeat the determination using another 20 dosage units. The preparation complies with the test if not more, than the weight of the individual contents of the total sample of 30 dosage units is outside 85 to 115% of the average content and more is outside the limits of 75 to 125% of the average content.

Disintegration

Disintegration is the time taken by the tablet to break up into smaller particles. The disintegration test is carried out in an apparatus containing a basket assembly with 6 glass tubes of length 7.75 cm and diameter 2.15mm, a # 10 mesh sieve is present at the bottom. The basket is raised and lowered 28 to 32 times per minute. The medium maintained at 37± 2^0C. Six tablets were placed in each of the tubes and the time required for the complete passage of tablet fragments to the mesh (#10) was considered as the disintegration time of the tablet.

Dissolution

Dissolution study was performed in 900ml P^H 6.8 phosphate buffer using USP type 2 paddle apparatus at 50 RPM for 30 minutes (37±0.5^{0}C). Aliquots of the dissolution medium (5ml) were withdrawn at specific time intervals (0, 5, 10, 15, 20, 25, 30 minutes) and replaced immediately with equal volume of fresh medium. The samples were filtered and analyzed for drug content by measuring absorbance at 283nm. The drug concentration was calculated and expressed as a cumulative percent drug release.

RESULTS AND DISCUSSION

Drug - Excepient compatibility studies

It is clear from the FTIR spectrum that the major absorption bands of the pure drug are observed in the spectrum with negligible variation in their positions. These observations clearly indicated that, there is no interaction of the drug with the polymer and other excipients.

FORMULATION OF ZOLMITRIPTAN ORAL DISINTEGRATING TABLETS

Oro dispersible tablets were prepared using zolmitriptan and kyron T-134 complexes which were prepared by physical mixture method, variable concentrations of super disintegrants and other excipients.

Table No.1 Standard calibration data of zolmitriptan

S.No	Concentration(µg/ml)	Absorbance
1	5	0.11
2	10	0.223
3	15	0.339
4	20	0.436
5	25	0.550

Table No.2: Formulation of drug-resinate complex ratio and its % drug release

S.No	DRUG AND KYRON T- 134 RATIO	% DRUG LOADED IN DRUG-RESIN COMPLEX
1	1:1	92.84
2	1:2	98.10
3	1:3	95.34

From the above observations drug loading efficiency was more to Drug- resin complex of 1:2 ratio hence it is taken for formulation of ODT

Table No.3: Composition of zolmitriptan: Kyron T-134 complex (1:2) oral disintegrating tablets for single formulation (mg) (Batch Size = 1000 tablets)

S.No	Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	DRC (1:2) Equivalent to 5mg	15	15	15	15	15	15	15	15	15
2	Sodium starch glycolate	4	5	6	-	-	-	-	-	-
3	Crospovidone	-	-	-	4	5	6	-	-	-
4	Low-substituted hydroxyl propyl cellulose	-	-	-	-	-	-	4	5	6
5	Microcrystalline cellulose	124	123	122	124	123	122	124	123	122
6	Talc	2	2	2	2	2	2	2	2	2
7	Magnesium Stearate	2	2	2	2	2	2	2	2	2
8	Sucralose	2	2	2	2	2	2	2	2	2
9	Vanilla Flavor	1	1	1	1	1	1	1	1	1
10	Total weight	150	150	150	150	150	150	150	150	150

Table No.4: Results of flow properties of different formulations of zolmitriptan

Formulation code	Angle of repose(Ɵ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio
F1	28.3	0.398	0.459	13.22	1.153
F2	29.6	0.416	0.458	9.170	1.100
F3	27.4	0.408	0.450	9.333	1.102
F4	29.6	0.411	0.446	7.847	1.085
F5	28.3	0.396	0.442	10.40	1.197
F6	27.02	0.401	0.448	10.49	1.117
F7	28.3	0.393	0.438	10.27	1.114
F8	29.2	0.408	0.452	9.734	1.107
F9	27.02	0.404	0.442	8.597	1.094

Table No.5: Thickness, diameter, hardness, friability, weight variation and *i*n vitro disintegration time

Formulation code	Thickness (mm)	Diameter (mm)	Weight variation(mg)	Friability (%)
F1	3.02	9.00	147.4	0.6
F2	3.01	9.00	146.1	0.61
F3	2.98	9.00	146.1	0.53
F4	2.99	9.00	149.5	0.68
F5	2.97	9.00	148.95	0.67
F6	2.99	9.00	148.45	0.58
F7	3.03	9.00	144.85	0.60
F8	2.96	9.00	146.9	0.7
F9	2.95	9.00	148.2	0.53

Formulation code	Hardness (kg/cm^2)	Wetting time(sec)	Water absorption ratio (%)	*In-vitro* disintegration(sec)	Drug content uniformity (%)
F1	3.27	42	62	52	98
F2	3.63	35	63	50	99.1
F3	3.55	34	69	48	98.7
F4	3.43	35	55	51	98.57
F5	3.47	33	51	48	98.32
F6	3.24	31	58	42	98.13
F7	3.33	38	63	48	98.89
F8	3.37	31	65	41	98.99
F9	3.42	28	64	39	99.15

Table No.6: Taste evaluation and mouth feel test for best formulations (F9)

Volunteers	Time (min)			
	1	2	3	4
1	1	0	0	4
2	0	4	4	4
3	0	0	4	4
4	0	0	4	4
5	1	0	0	4

Volunteers opinion for taste were related by giving different score values
0 = good
1 = tasteless
2 = slightly bitter
3 = bitter
4 = pleasant

Table No.7: *In-vitro* drug release data of formulation F-01 to F-09

Time (min.)	Formulation code(cumulative % Drug release)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	33.81	35.72	37.36	34.63	39.27	41.45	48.54	50.72	51.27
10	36.73	37.56	45.75	37.82	41.12	50.41	57.26	63.00	69.82
15	37.75	38.58	57.85	40.21	45.17	63.23	64.13	72.08	77.57
20	39.86	41.79	70.27	44.80	48.41	71.76	65.30	80.38	86.73
25	41.72	43.11	79.65	49.41	53.32	81.97	70.84	85.19	95.39
30	42.49	45.26	86.09	54.86	60.43	89.44	71.50	87.56	98.09

Table No: 8

Formulation code	Zero order R^2	First order R^2	Higuchi model R^2	Korsmeyer peppas R^2	Hixon crowel R^2
F9	0.813	0.996	0.977	0.847	0.989

From the above observations Kinetic analysis (r^2) of release data based on best curve-fitting method for selected ODT of Zolmitriptan the Drug release showed First order kinetics (R^2=0.996) indicated that the drug release depends upon its concentration.

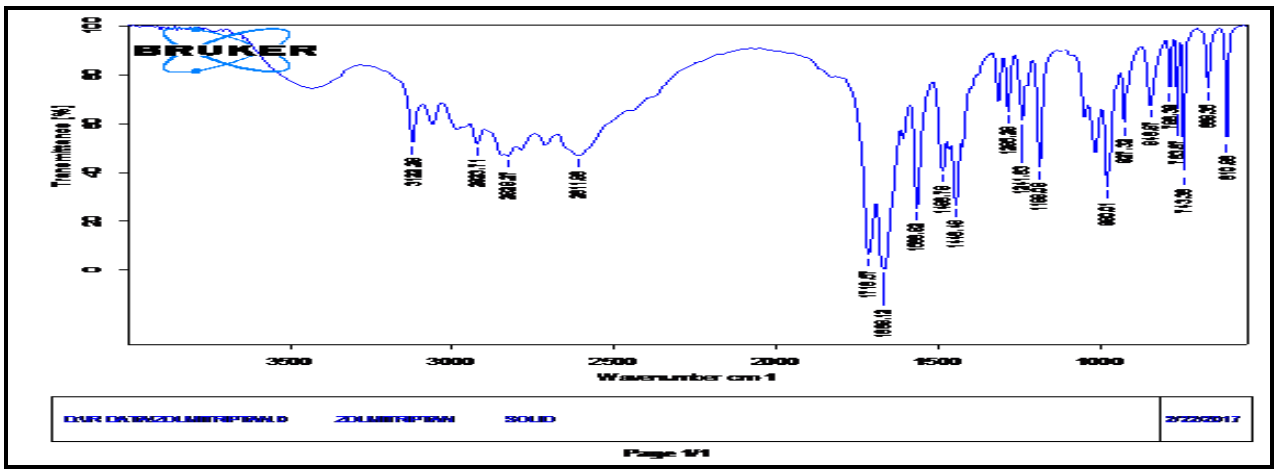

Figure No.1: FTIR spectra of pure drug Zolmitriptan

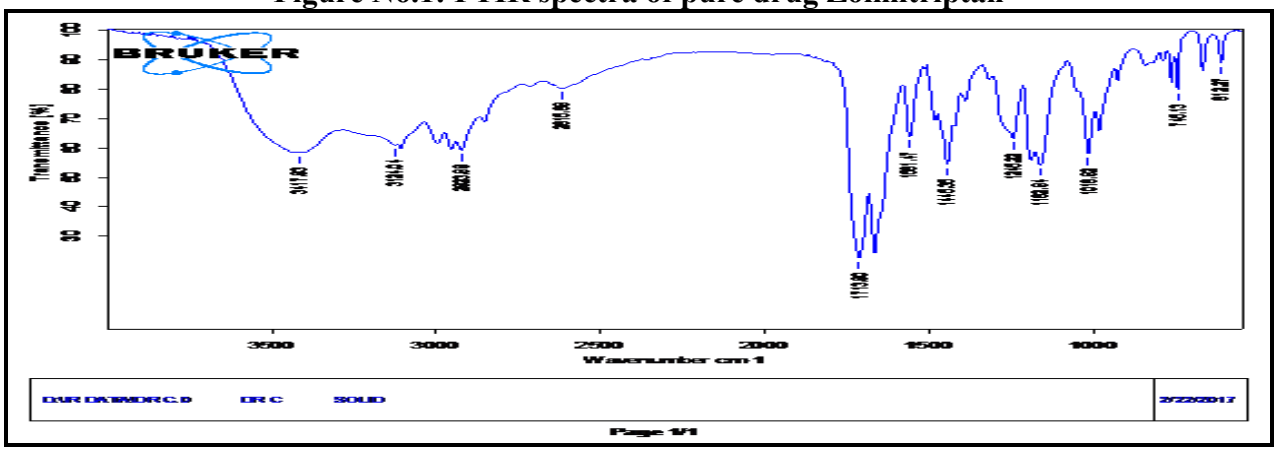

Figure No.2: FTIR of drug resin complex

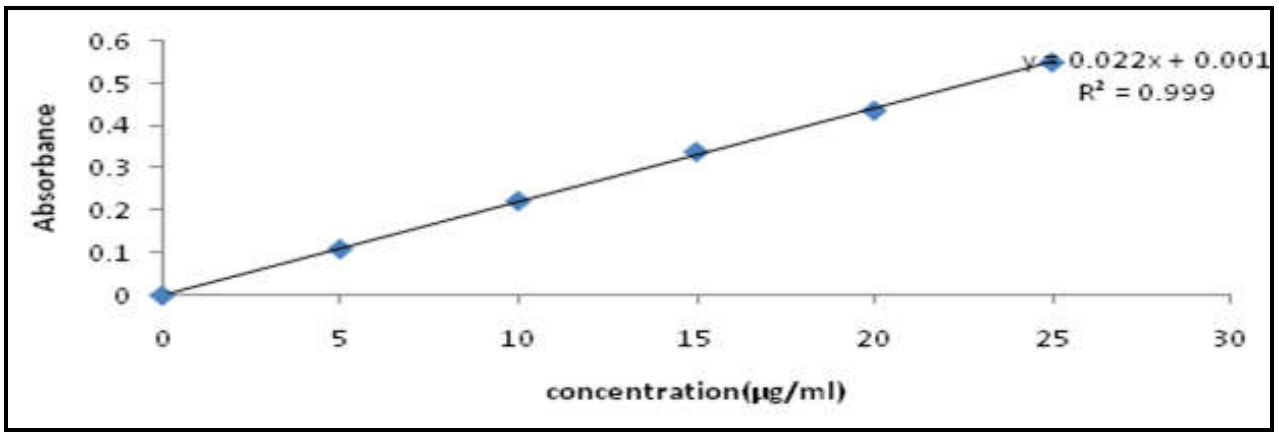

Figure No.3: Standard Calibaration Curve of Zolmitriptan

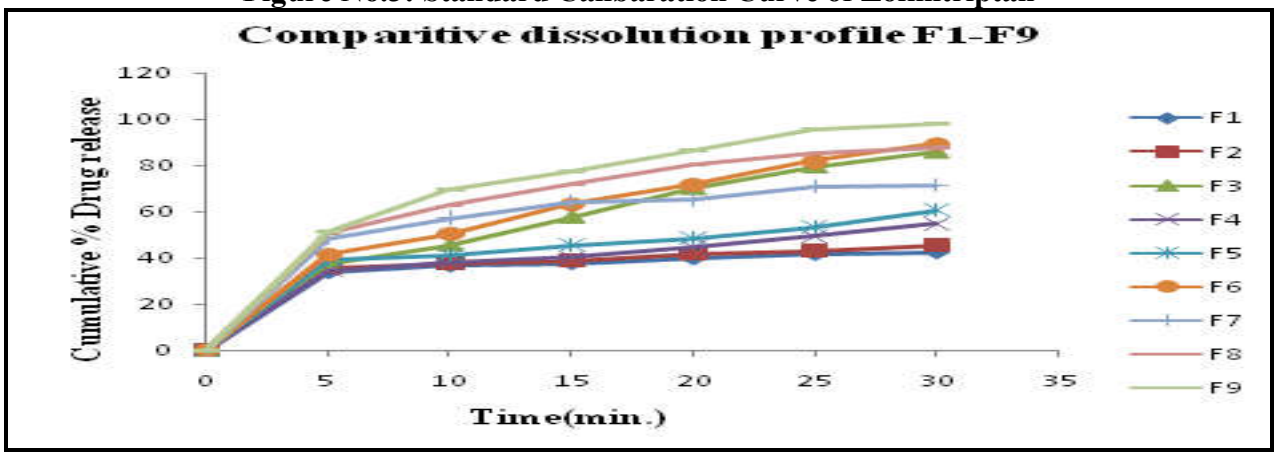

Figure No.4: Different Dissolution kinetic parameters of optimized formulation F9

CONCLUSION

In the present research investigation work undertaken, an attempt was made to explore the use of ion exchange resin as a taste masking agent and superdisintegrant in the formulation of taste masking oral disintegrating tablet of Zolmitriptan. The purpose was to enhance patient compliance and provide rapid onset of action. Kyron T-134 was used as an ion exchange resin for taste masking of bitter drugs. The polymer was mixed with the drug in different ratios, i.e.., drug- resin granules were lubricated and used for compression as required. Results showed that the bitterness was masked with 1:2 ratio. The trail number F9 has high percent cumulative drug release. FTIR studies showed that all the functional groups present in 1:2 ratio of drug – resin complex and that of the final formula containing low substituted hydroxypropyl cellulose along with that of the individual structures. Hence, they are compatible with each other. Trails were taken with different super disintegrating agents to get less disintegration. Hence, from the present research investigation, it was concluded that the taste masking ion exchange resin Kyron T-134 proved to be useful as a taste masking agent for bitter drugs like zolmitriptan as well as super disintegrating agent. The superdisintegrant like low substituted hydroxypropyl cellulose is effectively reducing the disintegrating time less than 40 seconds. Good mouth feel was achieved by using suitable sweetener and flavouring agent. Thus, we are able to achieve our objective of preparing highly compatible orally disintegrating tablets of zolmitriptan, with minimum excipients and simple method of manufacture.

ACKNOWLEDGEMENT

The authors wish to express their sincere gratitude to Department of Pharmaceutics, Santhiram College of Pharmacy, Nandyal, Kurnool, Andhra Pradesh for providing necessary facilities to carry out this research work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Pavankumar K *et al.* Formulation and evaluation of taste masking oral disintegrating tablets of zolmitriptan, *International Journal of Research in Pharmaceutical and Nano Sciences,* 7(4), 2018, 129-138.