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FORMULATION AND IN-VITRO EVALUATION OF ZOLMITRIPTAN ORO-DISPERSIBLE TABLETS

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Abstract:
The purpose of this research was to develop Oro-dispersible tablets of Zolmitriptan.Orally disintegrating tablets offers a solution for pediatrics, geriatrics; psychiatric or mentally ill people and those have difficulty in swallowing Tablets/capsules resulting in improved patient compliance.Zolmitriptan is a synthetic tryptamine derivative and is used for the treatment of migraine. The aim is to formulate orally disintegrating tablets of Zolmitriptan by using different Superdisintegrants like Crosspovidone, croscarmellose sodium and sodium starch glycolate with different concentrations of 2%, 3% 4% while microcrystalline cellulose, lactose aerosil magnesium stearate used as fillers. Tablets were prepared by direct compression method. The tablets were evaluated for hardness, thickness, friability, and weight variation and disintegration time, drug content and %drug release studies were performed. Tablets containing Crosspovidone, as disintegrant with 4% showed 100% release within 15mins.
Keywords: *Zolmitriptan, orally disintegrating tablets, Crosspovidone.*

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INTRODUCTION

Recent advances in novel drug delivery aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for ease of administration and to achieve better patient compliance. Oral drug delivery has been known for decades as the most widely utilizes route of administration among all the routes that have been explored for the systemic delivery of drugs. The reason that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the food stuffs that are ingested daily. Fast dissolving tablets are gaining prominence as new drug delivery systems. These dosage forms dissolve or disintegrate in oral cavity within a minute without the need of water or chewing. It has been reported that Dysphagia [1] (Difficulty in swallowing) is common among all age groups and more specific in paedatric, geriatric population along with institutional patients and patients with nausea, vomiting and motion sickness complications[2].Orally disintegrating tablets (ODT) [3] with good taste and flavor increase the acceptability of bitter drugs by various groups of population. Often people experience inconvenience in swallowing conventional tablets and capsules when water is not available, in the case of motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic conditions and bronchitis. For these reasons, tablets which can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention.

Zolmitriptan is a bitter drug that is primarily used in the treatment of migraine. It helps to relieve headache, nausea, vomiting and sensitivity to light/sound. It is a serotonin (5-HT1) agonist, the half-life of zolmitriptan is 2.5 to 3 hrs and it undergoes hepatic metabolism, the absolute oral bioavailability is about 40 to 50%. So, in order to improve the bioavailability and masking the bitter taste of the drug we have prepared taste masked fast disintegrating tablets of zolmitriptan, that disintegrate in the oral cavity upon contact with saliva and there by improve therapeutic efficacy by using synthetic super disintegrants [4, 5].

MATERIALS AND METHOD

Zolmitriptan (NIVON specialties Munmbai) sodiumstarch glycolate, Crospovidone, croscarmellose sodium (S.D. Fine Chemicals Ltd, Mumbai) , Amberlite IPR88 (Premier chems, Nagpur), MCC (Avicel PH-102)(Strides Arco labs, Bangalore),Magnesium stearate, Lactose (S.D. Fine Chemicals Ltd, Mumbai),Aerosil(H.D. Pharmachem, Ahmedabad),Hydrochloric acid(SD Fine Chemicals Ltd, Mumbai.), Sodium hydroxide (Merck specialities Ltd, Mumbai.), Potassium dihydrogen phosphate (Merck specialities Ltd, Mumbai.) .

Method:

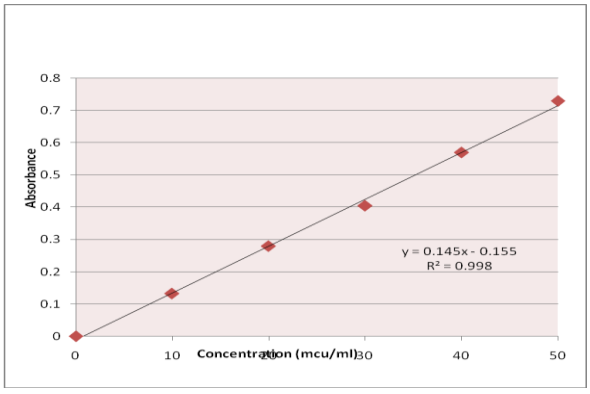
An UV-VIS spectrophotometric method was used for the estimation of Zolmitriptan in this work. A stock solution of Paroxetine HCl (1000µg/mL) was prepared in 0.1N HCL and the absorbance of Paroxetine hydrochloride was measured at 208nm using Elico UV-VIS spectrophotometer SL 150. As the dissolution studies were carried out in 0.1 N HCl buffer [6] , the standard concentrations were prepared using the same medium for dilution in the range of 10-50µg/mL of drug which obeyed Beer's law and calibration curve was constructed. The calibration data was given in table 1 and curve was shown in figure 1.

Table 1: Calibration curve data of Zolmitriptan in 0.1N HCl buffer

s.no	Concentration	absorbance
1	10	0.132
2	20	0.279
3	30	0.405
4	40	0.569
5	50	0.729

A= -0.024, B=0.01484, r=0.9998

Fig 1: Calibration curve of Zolmitriptan in 0.1N HCl buffer



Drug Excipients Compatibility Study (Physical observation)

The pure drug along with its formulation excipients were subjected to compatibility studies, the results of the physical observation were shown in the following table 1.

Table 2: Results of Drug Excipient Compatibility studies

s.no	Excipients	1st week	2nd week	3rd week
1	Amberlite IPR88	no reaction	no reaction	**no reaction**
2	Cross povidone	no reaction	no reaction	**no reaction**
3	Sodium starch glycolate	no reaction	no reaction	**no reaction**
4	Croscarmellose sodium	no reaction	no reaction	**no reaction**
5	Microcrystalline Cellulose	no reaction	no reaction	**no reaction**
6	Magnesium Stearate	no reaction	no reaction	**no reaction**
7	lactose	no reaction	no reaction	**no reaction**
8	**Aerosil**	**no reaction**	**no reaction**	**no reaction**

Formulation of Zolmitriptan:

The oral disintegrating tablets of Zolmitriptan were prepared using Crospovidone, Croscarmellose sodium and sodium starch glycolate, used as super disintegrants microcrystalline cellulose and lactose are used as diluents, Aerosil and magnesium stearate used as flow promoter .The composition of each batch shown in Table-3.Direct compression technique was selected for this formulation of ODT tablets, because porous nature is more in direct compression blend than wet granulation blend, so it will give faster disintegration, in this process all the ingredients were together passed through sieve no 40. The blends are mixed for 5mins. The final blend was compressed into tablets by using 8mm flat bowled edge punches with break line.

Table 3: Formulae of Orodispersible Tablets of Zolmitriptan

Formulation	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)	F7(mg)	F8(mg)	F9(mg)
Ingredients									
Zolmitriptan	5	5	5	5	5	5	5	5	5
Amberlite IPR88	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Microcrystalline cellulose	67.3	66.3	65.3	67.3	66.3	65.3	67.3	66.3	65.3
Lactose	20	20	20	20	20	20	20	20	20
Crospovidone	2	3	4	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	2	3	4	-	-	-
SSG	-	-	-	-	-	-	2	3	4
Aerosil	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Sodium saccharine	2	2	2	2	2	2	2	2	2
Magnesium stearate	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Peppermint flavour	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total	100	100	100	100	100	100	100	100	100

Evaluation Parameters of Zolmitriptan ODT:

Solubility Studies

Solubility studies were conducted in various solvents and different pH solutions. The solubility of API was determined by dissolving the drug in 250 ml of buffer. For this purpose Purified water, organic solvents, 0.1 N HCL solution, pH 6.8 phosphate buffer and pH 7.4 phosphate buffers were used. Maximum amount of the drug was dissolved in 250 ml of medium and was kept untouched for 12 hrs. Later on the insoluble drug was filtered off and the solution was analyzed to find out the solubility.

Evaluation of Pre Compression Parameters of the Powder [7, 8]

Prior to compression, materials were evaluated for their flow and compressibility parameters. Flow properties of powders were determined by angle of repose, Compressibility index and Hauser's ratio

Evaluation of Post Compressional Parameters of the Tablets [7, 8]

Physical appearance

The physical appearance of the compressed tablets involves the measurement of a number of attributes like tablet shape, smoothness, chipping, cracks, surface texture, color etc.

Thickness

Thickness was determined for 20 pre-weighed tablets of each batch using a digital Vernier scale and the average thickness was determined in mm**.** The tablet thickness should be controlled within a ± 5%variation of a standard.

Weight Variation

20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The tablets meet the USP specifications if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits

Hardness:

The hardness of Dothiepin hydrochloride ODTs was measured with a Monsanto hardness tester (M/s Campbell Electronics, model EIC-66, India). For each batch 3 tablets were tested.

Friability:

For each formulation 10 tablets were weighed, placed in Friabilator (M/S Campbell Electronics, India) and were subjected to 100 rotations in 4 min. The tablets were reweighed and friability was calculated along with mean and the standard deviation.

$$Friability = \frac{W_1 - W_2}{W_1} \times 100$$

Where "W1*"* is the initial weight and "W_2*"* is the final weight of the tablets.

Wetting Time:

Five circular tissue papers of 10cm diameter are placed in a petridish. Ten milliliters of water soluble dye solution is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time.

Disintegration Time

Disintegration time is the time taken by the tablet to breakup into smaller particles. The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes of 7.75 cm in length and 2.15 mm in diameter, the bottom of which consists of a #10 mesh sieve. The basket is raised and lowered 28-32 times per minute in a medium of 900 ml which is maintained at 37±20^{o}C. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the mesh (# 10) was considered as the disintegration time of the tablet. The disintegration time that patients can experience for oral disintegrating tablets ranges from 15 to 30 seconds.

Dissolution studies

Dissolution is a process by which the disintegrated solid solute enters the solution. The test determines the time required for a definite percentage of the drug in a tablet to dissolve under specified conditions.

Method: The dissolution test was carried out in USP Apparatus Type II(paddle) with 0.1 N Hydrochloric acid as the dissolution medium. The samples were drawn at 5, 10, 15 and 20 mins. Fresh volume of the medium was replaced with the withdrawn volume to maintain the sink conditions. Samples withdrawn were analyzed for the percentage of drug released.

***In-vitro* release kinetics [9, 10, 11]:**

Dissolution data of above formulations was fitted in Zero order, First order equations.

Zero-Order Kinetics-

Zero order as cumulative amount of drug released vs time,

$\mathbf{C = K_0 t}$

Where K_0 is the zero-order rate constant expressed in units of concentration/time and *t* is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axis.

First order kinetics-First order as log cumulative percentage of drug remaining vs time,

$$\mathbf{log\ C = log\ C_0 - K\ t / 2.303}$$

Where C_0 is the initial concentration of drug, K is the first order constant, and t is the time.

RESULTS AND DISCUSSION

The Zolmitriptan API (10µg/ml) was scanned in the UV between 200-400nm, Observed that at 208 nm shows maximum absorbance. Calibration curve of Zolmitriptan was carried out at 208 nm of 10, 20, 30,40, 50µgm/ml was shown in table-1 Figure-1. Drug Excipient Compatibility was investigated and shown in table:2 Results of pre-compression and post compression parameters were shown in Table-4 and 5.anddissolution profiles of formulations F_1 to F_9 shown in table:6 and comparative dissolution profiles plotted shown in figure-2,3,4.

F_1, F_4, F_7 and F_{10} batches were formulated using crosspovidone as super disintegrants at different concentrations of 5% and 10%respectively. F_{10} batch with 10% crosspovidone showed better results. The results indicate that crosspovidone showed concentration dependent disintegration.

F_2 , F_5, F_8 and F_{11} batches were formulated using croscarmellose sodium as superdisintegrant at different concentrations of 5% and 10% respectively. F_{11} batch with 10% croscarmellose sodium showed better results. The results indicate that croscarmellose sodium showed concentration dependent disintegration.

F_3, F_6, F_9 and F_{12} batches were formulated using sodium starch glycolateas superdisintegrant at different concentrations of 5% and 10%respectively. F_{12} batch with 10% sodium starch glycolate showed better results. The results indicate that sodium starch glycolate showed concentration dependent disintegration.

Table 4: Precompression Properties of Zolmitriptan API

Formulation code / Parameters	Bulk Density gm/cc	Tapped Density gm/cc	Hausners ratio	% Compressibility /carrs index (%)	Angle of Repose (degrees)	Porosiy (%)
F1	0.5	0.625	1.25	20	18.17	20
F2	0.52	0.55	1.057	15.45	19.24	11.2
F3	0.45	0.55	1.22	18.18	20.42	18.2
F4	0.5	0.62	1.24	19.35	22.34	20
F5	0.46	0.55	1.195	16.36	19.17	18.2
F6	0.56	0.69	1.23	18.84	20.24	16.7
F7	0.53	0.59	1.113	12.01	19.17	15.3
F8	0.52	0.62	1.192	16.12	18.24	11.2
F9	0.5	0.62	1.25	19.35	22.26	20

Table 5: Results of Post Compressional Parameters

Formulation code / Parameters	Weight variation	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Content uniformity (%)
F1	99.21	3.00	0.210	0.12	99.92
F2	99.5	3.01	0.213	0.15	98.3
F3	99.11	3.02	0.212	0.14	100.01
F4	99.36	3.00	0.212	0.19	98.5
F5	99.81	3.03	0.214	0.19	98.9
F6	100.8	3.02	0.213	0.10	100.02
F7	99.01	3.01	0.210	0.11	98.6
F8	101	3.03	0.212	0.14	100.01
F9	99.90	3.01	0.213	0.12	99.2

Formulation code / Parameters	Disintegration time (Sec)	Disintegration time in Modified method	Wetting time (sec)
F1	24	26	28
F2	20	22	24
F3	16	18	20
F4	28	31	32
F5	21	24	25
F6	18	21	22
F7	30	33	35
F8	26	24	30
F9	27	21	26

Table 6: Dissolution study of Zolmitriptan Oral Disintegrating Tablets

Time (min)	Cumulative Percentage Drug Release (%)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
5	55.42	65.34	70.43	52.43	61.53	72.19	50.23	60.21	65.26
10	62.57	72.90	89.45	61.89	70.82	86.13	60.96	68.90	70.19
15	76.24	90.56	100.01	74.21	84.90	92.39	72.10	75.17	82.83
20	90.06	100.0	100.02	86.12	90.31	100.01	80.43	85.62	95.84

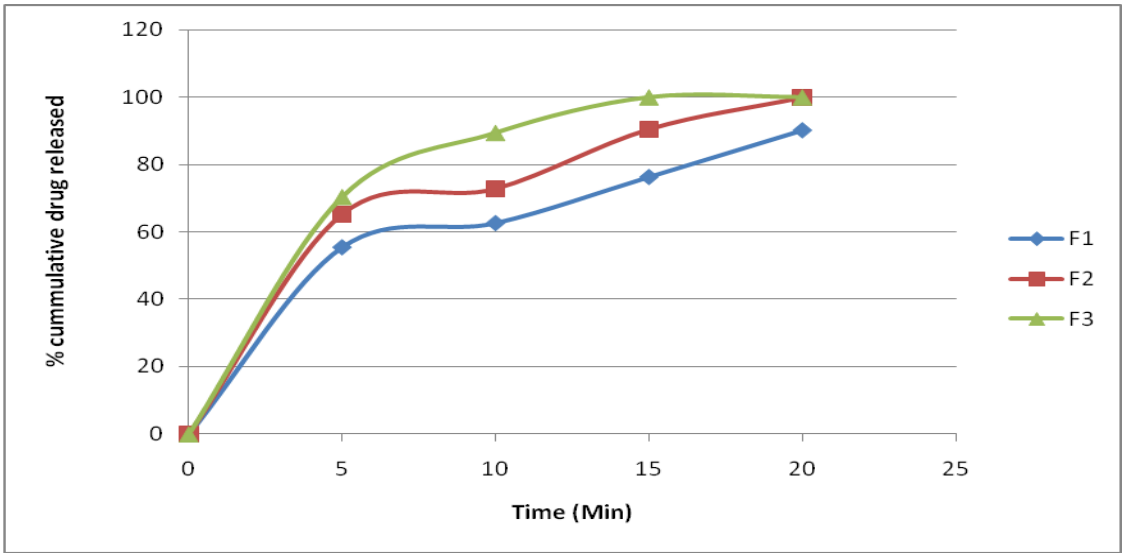


Fig. 2: Drug Release Profile of Tablets Containing Crospovidone as Super disintegrants

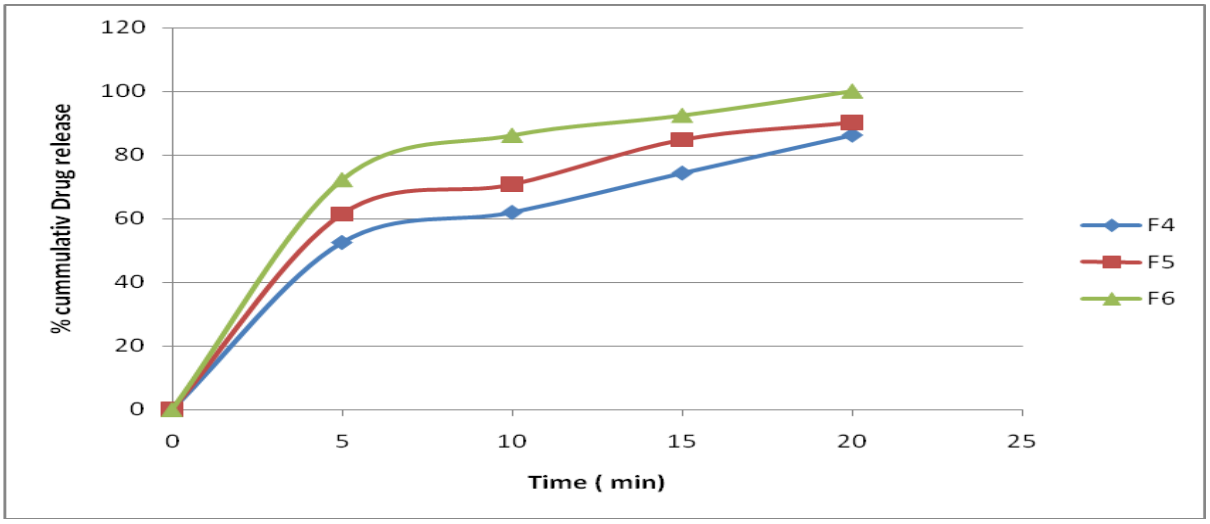


Fig.3: Drug Release Profile of Tablets Containing Croscarmellose Sodium as Superdisintegrant

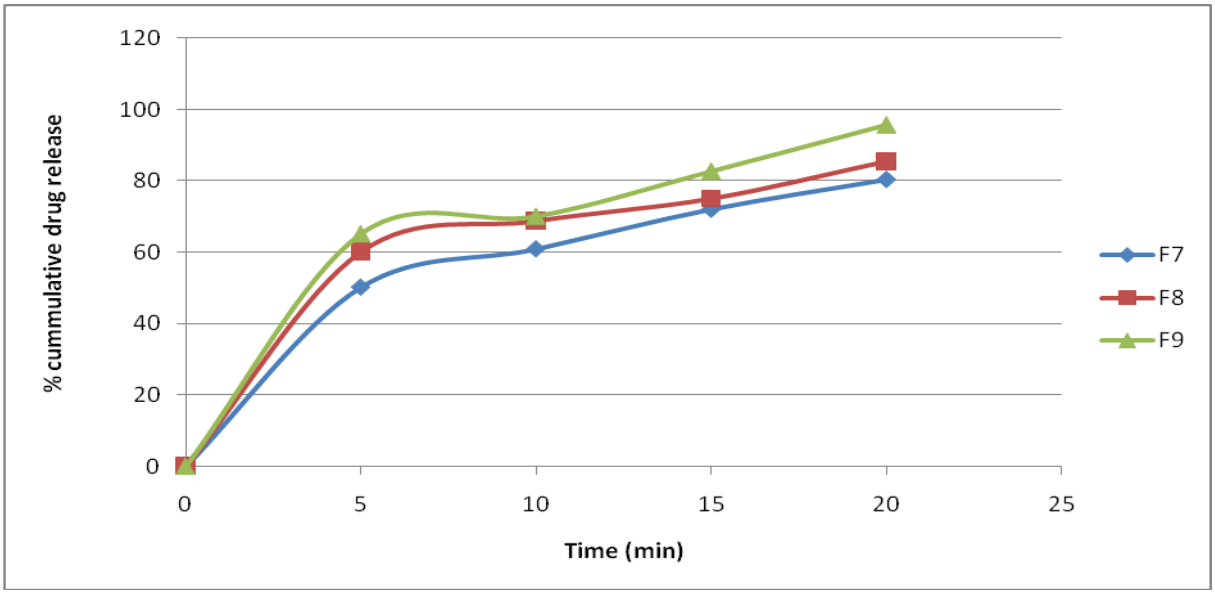


Fig.4 Drug release profile of tablets containing sodium starch glycolate as super disintegrants

***In Vitro* Release Kinetics:**

By studying the release kinetics of zolmitriptan from the orally disintegrated tablet, as the formulations did not follow a zero-order release pattern. When the data were plotted according to the zero-order equation, the formulations showed regression values between 0.738 and 0.852, and the data were plotted according to the first-order equation, the formulations showed a fair linearity, with regression values between 0.853 and 0.998. Release kinetics of zolmitriptan followed a first-order release pattern.

Table 7: Different kinetic models of Zolmitriptan ODT's (F1-F9)

FORMULATION CODE	ZERO ORDER	FIRST ORDER
	R^2	R^2
F1	0.850	0.909
F2	0.823	0.871
F3	0.746	0.892
F4	0.852	0.954
F5	0.793	0.978
F6	0.738	0.998
F7	0.835	0.993
F8	0.762	0.949
F9	0.796	0.853

SUMMARY

Orally disintegrating tablets of Zolmitriptan was prepared by direct compression method by using super disintegrant like crosspovidone, croscarmellose sodium and sodium starch glycolate, designated as 9 different types of formulations (F_1 to F_9). F_1 , F_2 and F_3 tablets were prepared with crospovidone,F_4,F_5 and F_6 with croscarmellose sodium andF_7,F_8, and F_9 with Sodium starch glycolate at different concentrations of 2%,3% and 4% respectively. Tablets were evaluated for weight variation and thickness, disintegration time, in vitro dissolution, wetting time. The in vitro disintegration time of the best fast disintegrating tablets was found to be within 16 seconds.

F_1 , F_2 and F_3 batches were formulated using crosspovidone as superdisintegrants at different concentrations of 2%, 3% and 4%respectively. F_3 batch with 4% crosspovidone showed better invitro drug release profiles. F_4, F_5 and F_6 batches were formulated using croscarmellose sodium as superdisintegrants at different concentrations of 2%, 3% and 4% respectively. F_6 batch with 4% croscarmellose sodium showed better invitro drug release profiles. F_7, F_8 and F_9 batches were formulated using sodium starch glycolate as superdisintegrants at different concentrations of 2%, 3% and 4%respectively. F_9 batch with 4% sodium starch glycolate showed better invitro drug release profiles.

Hence when compared to all the formulations .F_3 (crospovidone 4%), F_6 (croscarmellose 4%) and F_9 (Sodium starch glycolate 4%) shows better results. Among these three formulations (F_3, F_6 and F_9), The F_3 formulation with 4% crosspovidone was found to be the best formulation, superior in activity.

Tablets containing crosspovidone (4%) exhibit quick disintegration time than tablets containing croscaremellose sodium and sodium starch glycolate.

The fast disintegrating tablets of Zolmitriptan with shorter disintegration time, and sufficient hardness could be prepared using crosspovidone and other excipient at optimum concentration.

CONCLUSION

Zolmitritan is used to treat migraine[12]. They are formulated as oral disintegrating tablets which show better patient acceptability and compliance with improved efficacy when compared with conventional dosage forms. Direct compression was the preferred technology for the preparation of oral disintegrating tablets of Zolmitriptan. Based on the preliminary studies various formulation trials (F_1-F_9) were carried out with different concentrations of Superdisintegrants, filers and lubricants. From the various formulations it was concluded that the formulation F_3 was finalized as the optimized formula. Formulation F_3 showed satisfactory results with various physicochemical evaluation parameters and release characteristics.

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