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Research Article

Pharmaceutical Sciences

FORMULATION AND *INVITRO* EVALUATION OF ZOLMITRIPTAN SUBLINGUAL TABLETS

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ABSTRACT

Worldwide, migraines affect more than 10% of people. Chronic migraines occur in approximately 1.4 to 2.2% of the population. The mucosa has a rich blood supply and provides rapid absorption for drugs than oral route. The Zolmitriptan is a serotonin ($5HT_{1B/1D}$) agonist used for the treatment of migraine with or without aura. The half-life of zolmitriptan is 2.5 to 3 hours and it undergoes hepatic metabolism, the absolute oral bioavailability is about 40 to 50% because of hepatic metabolism. So it causes poor bioavailability of zolmitriptan by oral route, so there is a need to increase its bioavailability by formulating it into sublingual dosage form. Hence Zolmitriptan is a suitable drug for buccal dosage forms for fast and better therapeutic profile than oral route. The aim of this study is to increase the bioavailability of zolmitriptan for the potential emergency treatment of migraine pain. An attempts have been made to prepare fast dissolving tablets of zolmitriptan using superdisintegrating agents like crosscarmellose sodium and Crosspovidine. Twelve formulations were developed with two different mucoadhesive polymers (HPMC E-50 and chitosan). They were prepared by direct compression method. Tablet weight variation, hardness, friability, thickness, wetting time, percentage of drug content, disintegrating time and dissolution times were evaluated for each formulation and the results were found satisfactory. By comparing the above twelve formulations F9 (10% chitosan+ 8% cross providence) shows a less disintegration time (6Sec) and more dissolution percentage (98.47± 0.42) at 10 min. So the formulation F9 is prerequisite for rapid management of migraine.

KEY WORDS

zolmitriptan, migraine, sublingual, chitosan.

INTRODUCTION

Worldwide, migraines affect more than 10% of people. Rates of migraines are slightly lower in Asia than in Western countries. Chronic migraines occur in approximately 1.4 to 2.2% of the population. Migraine is a neurovascular disorder, where there is an interaction between the intracranial nerves and blood vessels[1].

Migraine is characterized by pulsating headache, usually restricted to one side, which comes in attacks lasting 4-48 hours and is often associated with nausea, vomiting, sensitivity to light and sound, vertigo, loose motions and other symptoms[2].

In this case, a rapid onset of pharmacological effect is often desired from drugs. This can effectively be achieved by parenteral administration, but this method may not always be convenient for the patient and patient with migraine generally suffer from nausea and vomiting, so oral treatment can also inconvenient or could fail. Therefore, there is growing interest in developing new, non-parenteral, reliable and convenient dosage forms using administration route where a rapidly dissolved drug is immediately absorbed into systemic circulation[3,4].

In the present study, zolmitriptan is the drug of choice, because it elicit its action rapidly and continuously.

This research work is undertaken to develop fast disintegrating sublingual tablets of Zolmitriptan prepared by direct compression technique. The proportions of superdisintegrants and excipients in the formulations was varied.

MATERIALS AND METHODS

Zolmitritan was a gift sample from Aurobindo Pharma Ltd. Hyderabad, India. Polymers like HPMC, Chitosan, superdisintegrants like crospovidone, crosscarmellose sodium, excipients like Avicel 102 (Microcystalline cellulose), citric acid, magnesium stearate, mannitol and talc were obtained from Drug India Pvt. Ltd.

Formulation of different batches

The main aim of the present study was to formulate different batches using two various superdisintegrants in varying concentrations. So different batches of formulations was planned accordingly. According to that F1, F2, F3 - (with Crospovidone (2%,4%,6%) + HPMC E- 50(10%)), F4,F5,F6 - (with Crosscarmelose sodum (2%,4%,6%) + HPMC E-50(10%)) F7, F8, F9 - (with Crospovidone (2%,4%,6%) + Chitosan (10%)), F10, F11, F12 - (with Cross carmelose sodum (2%,4%,6%) + Chitosan (10%)) were formulated. The slight bitter taste of the drug was masked using Mannitol (35%) and citric acid (3%) as *the* sweetening and flavoring agents, shown in **Table No.1**.

Table 1: Formulations of Different Batches (F1-F12)

Ingredients (mgs)	FORMULATION CODES											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Zolmitriptan	4	4	4	4	4	4	4	4	4	4	4	4
Mannitol	70	70	70	70	70	70	70	70	70	70	70	70
HPMC E 50	20	20	20	20	20	20	--	--	--	--	--	--
Chitosan	--	--	--	--	--	--	20	20	20	20	20	20
Crospovidone	8	12	16	--	--	--	8	12	16	--	--	--
Croscarmellose sodium	--	--	--	8	12	16	--	--	--	8	12	16
MCC	82	78	74	82	78	74	82	78	74	82	78	74
Magnesium sterate	6	6	6	6	6	6	6	6	6	6	6	6
Talc	4	4	4	4	4	4	4	4	4	4	4	4
Citric acid	6	6	6	6	6	6	6	6	6	6	6	6

FORMULATION METHOD

The drug and the excipients were passed through sieve No 40 except lubricant. Weighed amount of drug and exicipients were mixed in geometric dilution method. The blend was further lubricated with Magnesium stearate (pre-sieved through sieve no 80) and the powder blend is subjected to drying for removal of moisture content and was compressed by direct compression method by using flat faced punches in cadmach 16 punches tablet punching machine. Round punches measuring 8.7 mm diameter were used for compression. Tablet of 200mg was prepared by adjusting hardness and volume screw of compression machine properly. A total number of 12 formulations were prepared and evaluated.

EVALUATION PARAMETERS FOR SUBLINGUAL TABLETS

General appearance[5]

The general appearance of tablets, its visual identity and overall 'elegance' is essential for consumer acceptance, control of lot-to-lot uniformity and general tablet-to-tablet uniformity and for monitoring the production process. The control of general appearance involves measurement of attributes such as a tablet's size, shape, colour, presence or absence of odour, taste, surface textures, physical flaws and consistency.

Uniformity of Thickness[5,6]

The thickness of individual tablets may be measured with a vernier calliper, which permits accurate measurements and provides information of the variation between tablets. Tablet thickness should be

controlled within a ± 5% variation of a standard value. In addition, thickness must be controlled to facilitate packaging.

Weight variation[7]

Weight variation test was performed for twenty tablets from each batch using an electronic balance and average values were calculated.

Hardness (Crushing load) [8,9]

Tablet hardness is measured by Monsanto hardness tester. A tablet is placed in the hardness tester and load required to crush the tablet is measured.

Friability[8,9]

Friability is a crucial parameter for evaluation of sublingual tablets. Roche friabilator is used to determine the friability by following procedure. Pre weighed tablets are placed in the friabilator. Friabilator consist of a plastic chamber that revolves at 25 rpm. The tablets are rotated in the friabilator for 4 minutes. At the end of test tablets are dusted and reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as:

$$\% \text{ Friability} = \frac{\text{Loss in weight}}{\text{Initial weight}} \times 100$$

Wetting time[9,10]

The initial process in the disintegration of a sublingual tablets involves water uptake and wetting of the tablet. So determination of wetting time is also important. A Petri-dish containing 6 ml of distilled water is taken and a tissue paper folded twice is placed in it. A tablet containing a small quantity of amaranth colour is placed on this. Time required for the upper surface of the tablet to become complete red is the wetting time.

Water absorption ratio[9, 10]

A pre weighed tablet (W_a) is placed in a petridish in the similar way as described in the wetting time test. When the tablet has absorbed water completely, it is removed and weight is noted (W_b). Water absorption ratio R is calculated as:

$$R = \frac{Wa - Wb}{Wb} \times 100$$

***In vitro* Dispersion Time**[11-14]

Tablet was added to 10ml of buffer solution (pH 6.8) and time required for complete dispersion was measured. Three tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

Disintegration Time (DT) [11-14]

Disintegration times of the prepared FDSTs were determined with six tablets in distilled water at 37 ± 0.5°C using a disintegration tester. The disintegration time was defined as the time necessary for the FDST to completely disintegrate until no solid residue remains or only a trace amount of soft residue remains on the screen31. All results are presented as mean value ± SD (*n* = 6).

Drug Content Uniformity [11]

Twenty tablets were selected randomly and powdered. A quantity of this powder corresponding to one tablet was dissolved in 100 ml of 6.8 pH phosphate buffer, stirred for 15 min and filtered. 1 ml of the filtrate was diluted to 100 ml with 6.8 pH phosphate buffer. Absorbance of this solution was measured at 223nm using 6.8 pH phosphate buffer as blank and content of drug was estimated.

Assay calculation: The amount of drug present was calculated by given formula,

$$\text{Drug content} = \frac{\text{Spl abs. x Std. wt. x Std. dil.}}{\text{Std. abs. x Spl. wt. x Spl. dil.}} \text{ x Spl. Purity}$$

Dissolution test[12-14]

The dissolution of Zolmitriptan sublingual tablets were carried in USP Type 2 paddle apparatus. The dissolution medium (6.8 pH phosphate buffer) was maintained at a temperature of 37 ± 0.5°C with a paddle rotation speed at 50 rpm. At 2 minutes interval, a 5-mL sample was withdrawn and replaced by phosphate buffer pH 6.8; these samples were assayed for zolmitriptan content by Shimadzu UV spectrophotometer at 223nm.

RESULTS AND DISCUSSION

Flow Properties:

Zolmitriptan along with other excipients were evaluated for bulk density, tap density, angle of repose, compressibility and Hausner ratio, before proceeding to direct-compression. The physical parameters are recorded in **Table 3**.

Angle of repose: 25 to 30 indicating good.

Compressibility index: 15 to 17 indicating good

Hausner ratio: 1.17 to 1.2 indicating good.

Table 2: FT-IR Spectra of zolmitriptan and with exipients				
IR Spectral Peaks for various functional groups [wavelength (cm^{-1})]				
Components	**O-H_{def}**	**C-H $_{str\ aromatic}$**	**N-H_{def}**	**C-O_{str}**
Zolmitriptan	1410	1458	1560	1259
Zolmitriptan + Mannitol	1412	1458	1559	1259
Zolmitriptan + HPMC E 50	1409	1458	1561	1258
Zolmitriptan + Chitosan	1409	1459	1560	1259
Zolmitriptan + Crospovidone	1418	1462	1559	1259
Zolmitriptan + Croscarmellose sodium	1409	1458	1559	1259
Zolmitriptan + MCC	1409	1458	1559	1259
Zolmitriptan + Magnesium stearate	1409	1458	1558	1259
Zolmitriptan + Talc	1411	1458	1560	1259

Table 3: Preformulation characteristics of Zolmitriptan sublingual tablets					
Formulation	**Bulk density (g/cc)**	**Tapped density (g/cc)**	**Hausner ratio**	**Compressibility index (%)**	**Angle of repose (ɵ)**
F1	0.391	0.463	1.18	15.55	27.54
F2	0.375	0.442	1.17	15.15	29.00
F3	0.379	0.446	1.17	15.02	27.42
F4	0.380	0.450	1.20	15.55	25.82
F5	0.392	0.466	1.18	15.87	27.00
F6	0.374	0.440	1.17	15.00	26.75
F7	0.371	0.441	1.18	15.87	25.82
F8	0.376	0.444	1.18	15.31	26.20
F9	0.370	0.438	1.18	15.52	28.35
F10	0.381	0.452	1.19	15.70	27.43
F11	0.377	0.449	1.19	16.03	29.56
F12	0.384	0.461	1.20	16.70	30.01

Table 4 : Post formulation characteristics of Zolmitriptan sublingual tablets					
Formulation	**Thickness[a] (mm)**	**Weight variation[b] (mg)**	**Hardness[a] (kg/cm^2)**	**Friability[a] (%)**	**Wetting time[c] (sec)**
F1	3.83±0.02	198±0.49	3.9±0.16	0.32	26±0.4
F2	3.84±0.009	199±0.56	3.8±0.08	0.27	25±0.7
F3	3.84±0.01	200±0.58	4±0.18	0.15	23±0.2
F4	3.82±0.02	197±0.63	3.8±0.27	0.24	28±0.7
F5	3.82±0.01	199±0.84	3.9±0.15	0.13	26±0.4
F6	3.71±0.01	201±0.77	3.7±0.25	0.28	24±0.8
F7	3.77±0.02	200±0.90	3.8±0.40	0.19	17±0.6
F8	3.80±0.01	202±0.88	4.1±0.20	0.19	14±1.4
F9	3.72±0.02	198±0.87	3.9±0.15	0.31	9±0.4
F10	3.90±0.02	200±0.73	3.8±0.18	0.21	13±0.5
F11	3.87±0.01	197±0.68	3.9±0.27	0.26	12±0.8
F12	3.82±0.02	199±0.55	3.9±0.31	0.17	11±0.3

a Mean ± S.D., n = 10 tablets, b Mean ± S.D., n = 20 tablets, c Mean± S.D., n=6 tablets

Table 5: Post formulation characteristics of Zolmitriptan sublingual tablets				
Formulation	**Water absorption ratio[a] (%)**	***In-vitro* dispersion time[a] (sec)**	**Disintegration time[a] (sec)**	**Drug content (%)**
F1	43	20±0.42	18±0.5	99.5±0.5
F2	20	18±0.45	17±0.6	98.83±1.04
F3	31	12±0.71	15±0.3	101.48±0.5
F4	28	31±0.75	18±0.5	98.62±1.51
F5	24	15±0.75	16±0.7	97.59±0.52
F6	19	13±0.69	15±0.3	100.11±1.78
F7	26	20±0.42	11±0.4	98.18±0.86
F8	28	18±0.64	10±0.8	96.23±1.22
F9	33	11±0.78	6±0.6	101.05±1.58
F10	25	30±0.44	12±0.9	99±0.87
F11	19	28±0.31	11±0.5	102±0.45
F12	23	25±0.59	9±0.4	100±0.61

a Mean ± S.D., n = 6 tablets.

Table 6: Cumulative % drug release for formulations (F1 – F12)

	Cumulative % drug release [a]				
TIME (MIN)	**2**	**4**	**6**	**8**	**10**
F1	71.73±1.13	74.02±1.50	76.95±1.52	81.84±0.24	84.78±0.71
F2	78.25±0.74	81.68±0.69	86.90±0.46	90.97±1.40	92.93±0.28
F3	85.75±0.25	88.26±0.64	91.95±0.66	92.60±0.89	93.42±0.69
F4	69.12±1.21	71.08±1.71	72.06±0.45	73.85±0.71	76.13±1.24
F5	73.04±0.18	73.69±0.37	77.60±1.37	78.74±0.66	80.86±0.80
F6	77.93±1.19	80.37±1.19	82.98±0.72	86.08±0.65	87.22±1.35
F7	82.00±1.62	86.41±1.40	88.85±1.62	89.50±1.34	91.30±0.90
F8	83.96±0.74	87.38±0.63	89.99±0.75	91.79±1.09	93.91±0.89
F9	88.69±0.57	92.60±0.62	94.40±0.52	96.51±0.316	98.47±0.42
F10	79.72±0.75	80.86±0.71	81.6±1.21	83.15±1.12	86.90±0.76
F11	81.52±1.47	83.96±1.56	86.24±0.39	88.04±0.27	90.97±0.87
F12	83.15±0.52	85.26±0.16	92.60±0.43	92.93±0.99	94.40±0.738

a Mean ± S.D., n = 6 tablets.

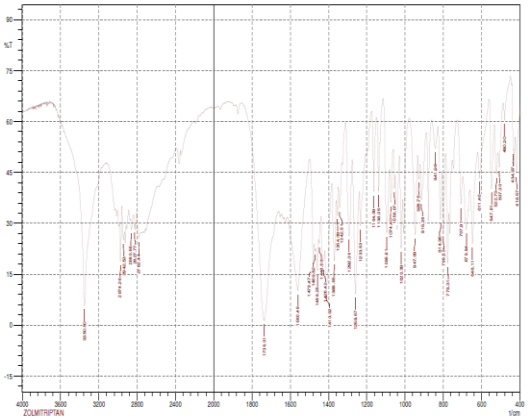

Fig 1: FT-IR spectra of Zolmitriptan

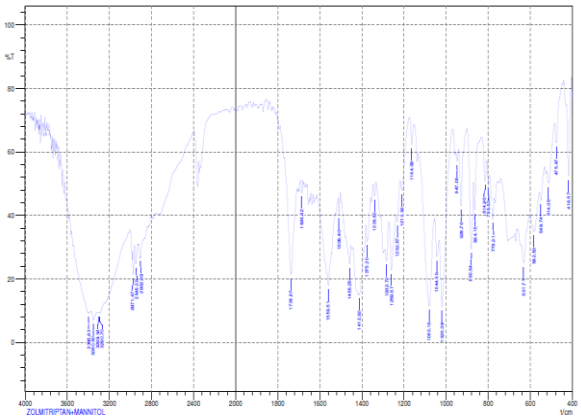

Fig 2: FT-IR spectra of Zolmitriptan + Mannitol

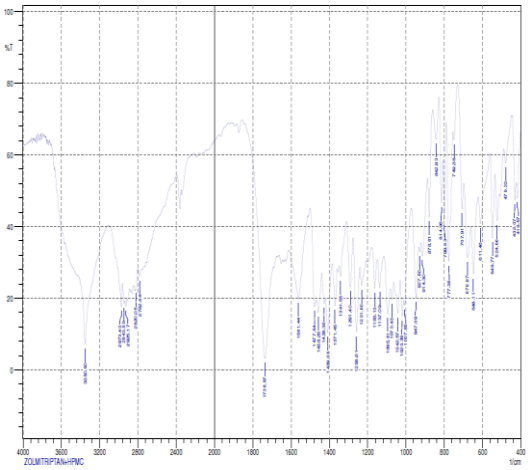

Fig 3: FT-IR spectra of Zolmitriptan + HPMC- E50

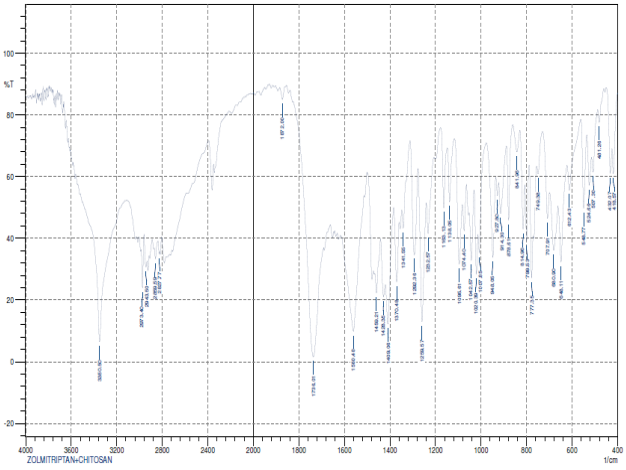

Fig 4: FT-IR spectra of Zolmitriptan + Chitosan

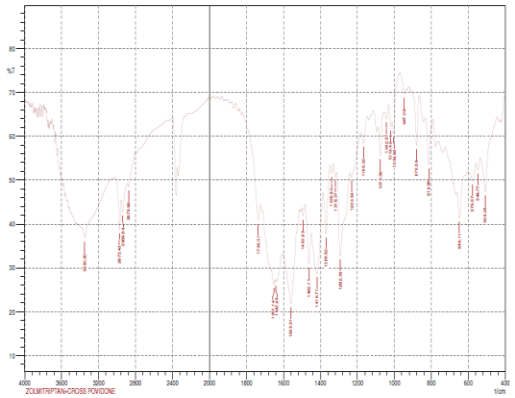

Fig 5: FT-IR spectra of Zolmitriptan + Crospovidone

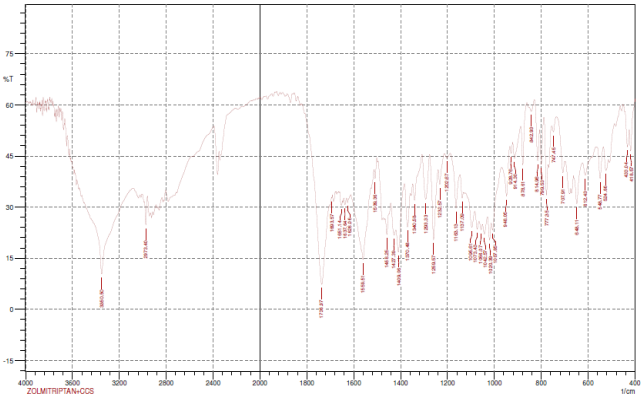

Fig 6: FT-IR spectra of Zolmitriptan + CCS

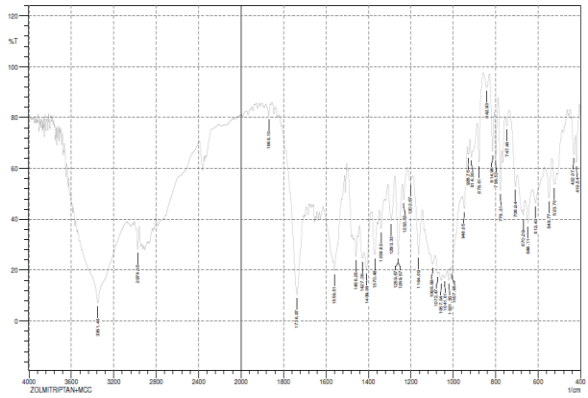

Fig 7: FT-IR spectra of Zolmitriptan + MCC

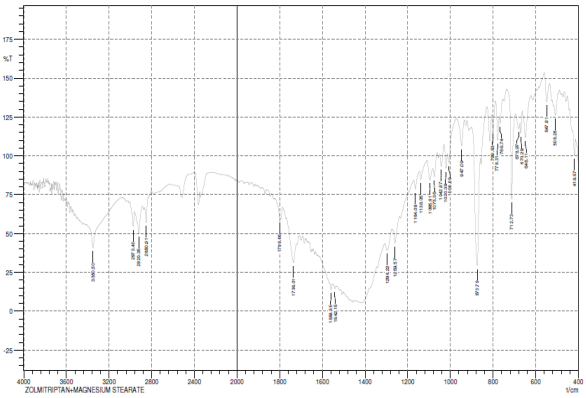

Fig 8: FT-IR spectra of Zolmitriptan + Mg.sterate

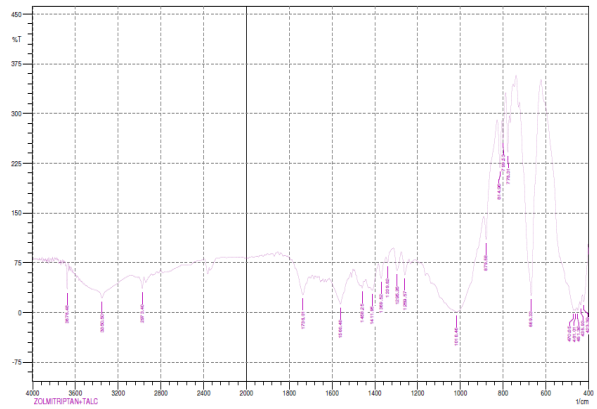

Fig 9: FT-IR spectra of Zolmitriptan + Talc

Wetting time Images

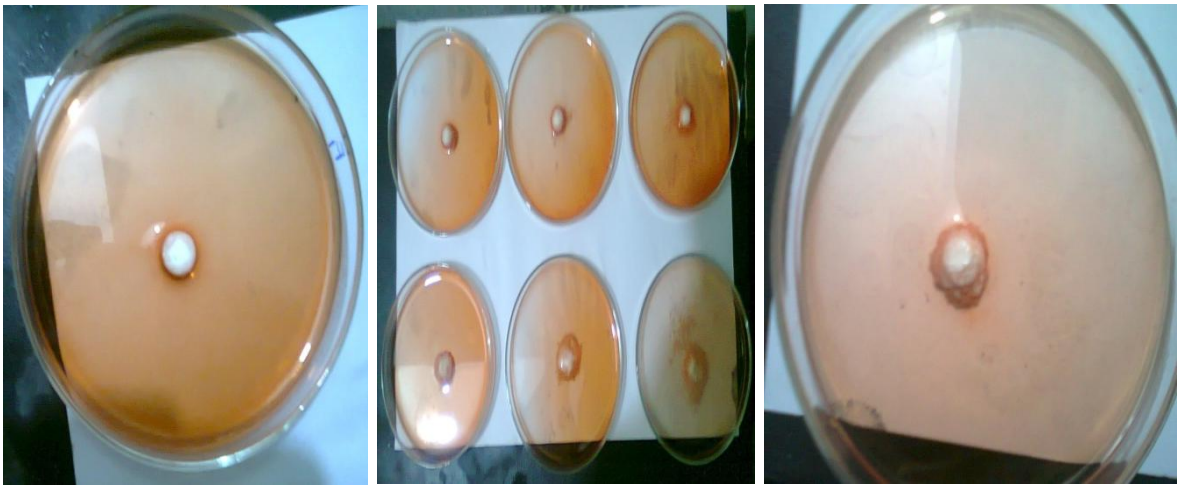

Fig 10: Wetting time images of Zolmitriptan sublingual formulations

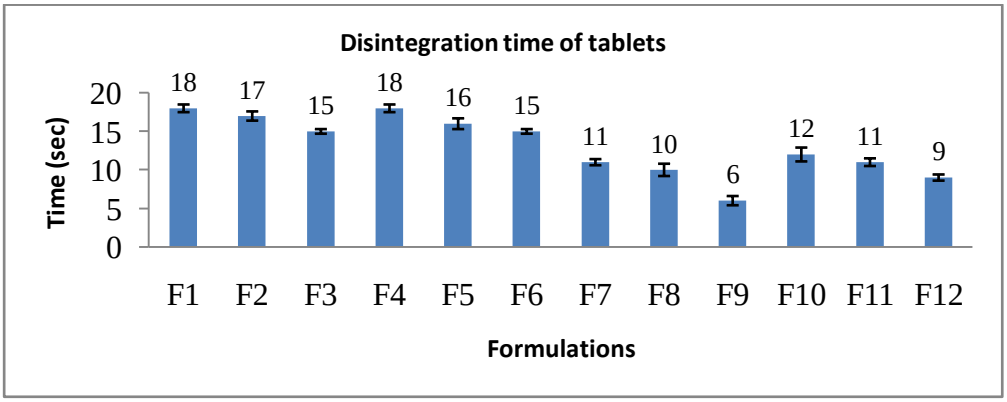

Fig 11: Disintegration time of Zolmitriptan sublingual formulations

EVALUATION STUDIES

The important parameters in the production of tablets were evaluated and reported in **Table 4 and Table 5**. The weight variation of the tablets was within the range. The thickness varied from 3.71± 0.01 mm to 3.84±0.009 mm. The hardness varied from 3.7±0.25 kg\cm^2 to 4.1±0.20 kg\cm^2 found satisfactory. The friability test was passed. The wetting time was ranged from 9±0.4 sec to 28±0.7 sec (**Fig 10**). The water absorption ratio was varied from 19% to 33%. The *In-vitro* dispersion time was within limits. The percent content uniformity was 96.23±1.22 % to 102±0.45 % and therefore was satisfactory. The Disintegration time varied between 6±0.6 sec to 18±0.5 sec and found to be satisfactory (**Fig: 11**).

Dissolution Studies

Based on the objectives of the present investigation, the tablets were evaluated for release of Zolmitriptan. Dissolution studies were attempted. Since the delivery system was Sublingual, Phosphate buffer pH 6.8 solution was used as dissolution medium. The results are shown in **Table 6** and **Figures 12-15**.

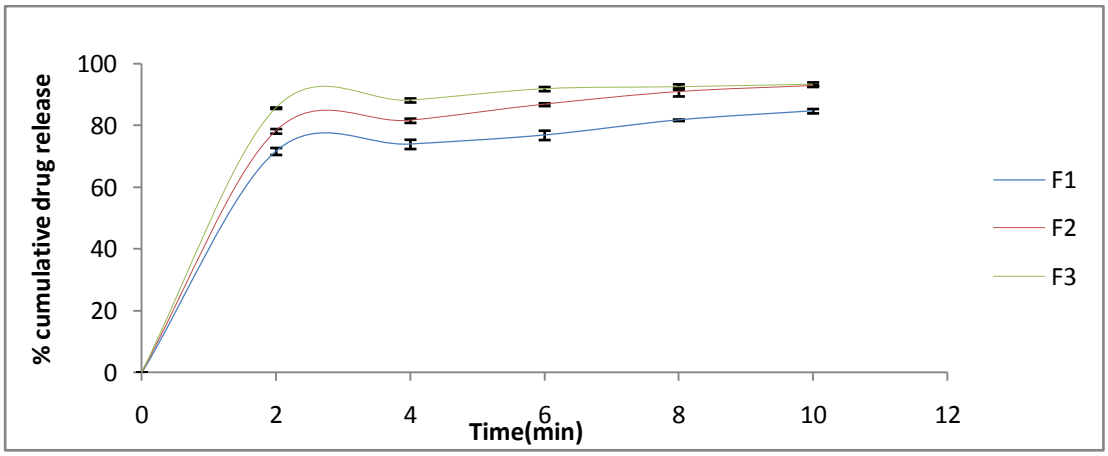

Fig 12 : Drug release of Zolmitriptan sublingual formulations of HPMC E-50 with varying concentrations of Crospovidone

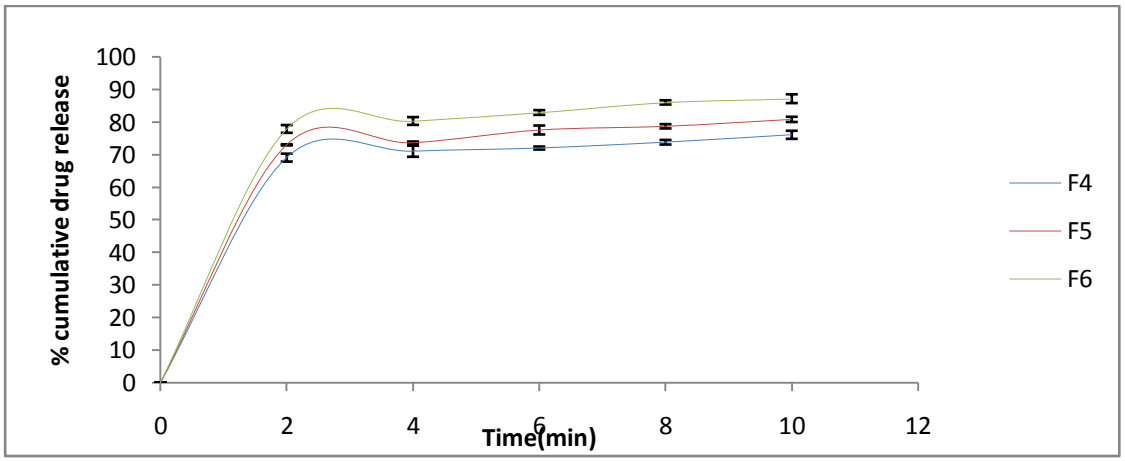

Fig 13: Drug release of Zolmitriptan sublingual formulations of HPMC E-50 with varying concentrations of Croscarmellose sodium.

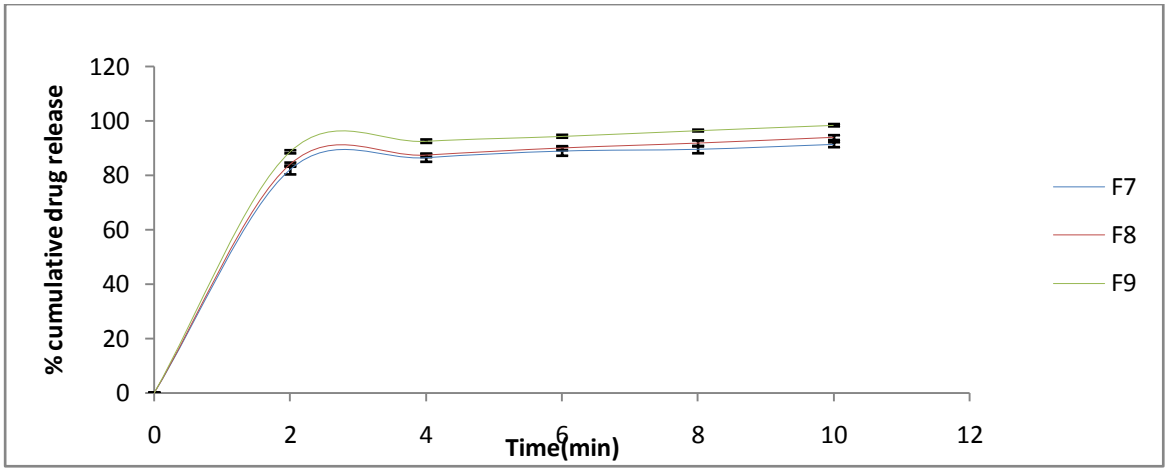

Fig 14: Drug release of Zolmitriptan sublingual formulations of Chitosan with varying concentrations of Crospovidone

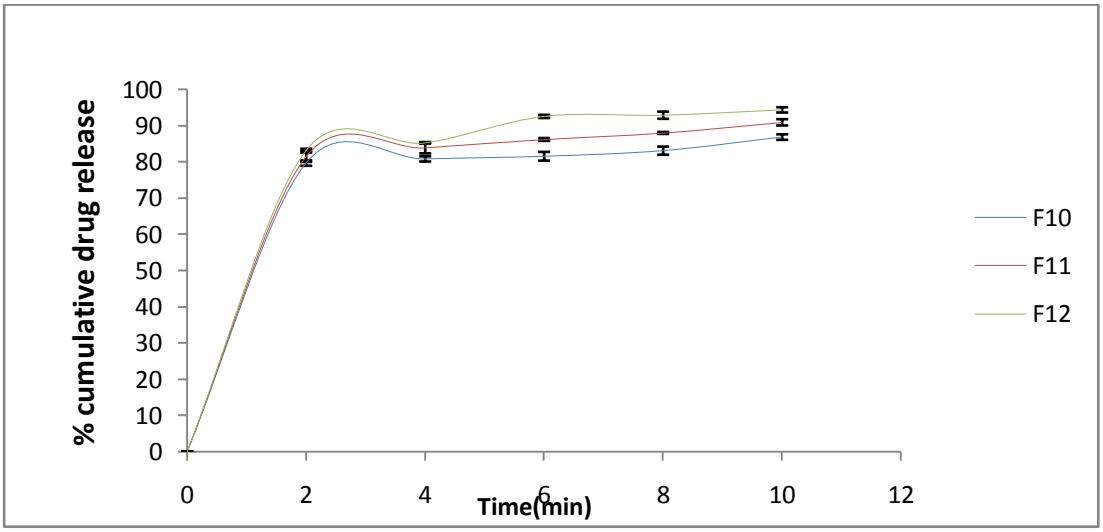

Fig 15: Drug release of Zolmitriptan sublingual formulations of Chitosan with varying concentrations of Croscarmellose sodium.

Formulations F1, F2, F3 which contained HPMC + increasing concentrations of Crosspovidone have recorded drug release 84.78% ± 0.71, 92.93% ± 0.28, 93.42% ± 0.69 respectively within 10 min. Formulations F7, F8, F9 which contained Chitosan + increasing concentrations of Crosspovidone have recorded drug release 91.30%± 0.90, 93.91%±0.89, 98.47% ±0.42 respectively, at the end of 10 min. Formulations F4, F5 and F6 which contained HPMC + increasing concentrations of Crosscaramellose sodium have recorded drug release 76.13% ±1.24, 80.86% ± 0.80, 87.22% ± 1.35 respectively within 10 min. Formulations F10, F11, F12 which contained Chitosan + increasing concentrations of Crosscaramellose sodium have recorded drug release 86.90% ± 0.76, 90.97% ± 0.87,94.40% ± 0.73 respectively, at the end of 10 min.

The dissolution data reveals that the rate of dissolution was increasing linearly with increasing concentration of superdisintegrant. Comparing the effect of two different super disintegrants with HPMC E-50 and Chitosan as mucoadhesive polymer, Crosspovidone gave better release with in 10 min. By using the mucoadhesive polymers HPMC E-50 and Chitosan with the two superdisintegrants, the chitosan combination gives better release profiles. So the combination of chitosan and crosspovidone is the

best combination for sublingual release of zolmitriptan.

CONCLUSION

The combination of chitosan and crospovidone is the best combination for sublingual release of Zolmitriptan. This combination gave fast moisture absorption, dispersion, and disintegration and better dissolution profiles. The rate of dissolution is directly proportional to the concentration of super disintegrant.

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