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FORMULATION AND EVALUATION OF ZOLMITRIPTAN POROUS TABLET BY USING SUBLIMATING AGENTS

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ABSTRACT

Tablets may be defined as solid unit pharmaceutical dosage forms containing drug substance with or without suitable excipients and prepared by either compression or molding methods. Zolmitriptan is a selective agonist of serotonin (5-hydroxytryptamine; 5-HT) type 1B and 1Dreceptors. In this study immediate release monolithic tablets of Zolmitriptan using sublimation technique. Immediate release tablets of Zolmitriptan were prepared by the direct compression technique using subliming agents like camphor and Crospovidone as superdisintegrant are used. The sublimation technique is mainly used to ensure burst release by forming porous tablet matrix so that it does swell and entrap Zolmitriptan which results in fast absorption of Zolmitriptan. Subliming agents are sublimed from the tablets by drying in hot air oven at 60oC for 12 hrs. The formulations were evaluated for weight variation, hardness, friability, drug content, wetting time, and *in vitro* dissolution.

KEYWORDS

Zolmitriptan, Immediate release tablets, Serotonin, Super disintegrant and Crospovidone.

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INTRODUCTION[1,2]

Tablets may be defined as the solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or moulding methods. They have been in wide spread use since the latter part of the 19th century and their popularity continues. The term compressed tablet is believed to have been first used by “JOHN WYETH”. Tablets remain popular as a dosage form because of the advantages afforded both to the manufacturer and the patient.

Properties of tablets

The attributes of an acceptable tablet are as follows:

1. The tablet must be sufficiently strong and resistant to shock, abrasion, should withstand handling during manufacturing, packing, shipping, and use. Hardness and friability tests measure this property.
2. Tablet must be uniform in weight and in drug content of the individual tablet. This is measured by the weight variation and content uniformity tests.
3. The drug content of the tablet must be bioavailable. This property is measured by the dissolution test. Accurate bioavailability can be obtained from the drug levels in the blood after its administration.
4. Tablets must be elegant in appearance, characteristic shape, color and other markings necessary to identify the product.

Tablets must retain all these functional attributes which include drug stability and efficacy.

MATERIALS AND METHODS[3,4,5]

Zolmitriptan, Polyvinyl pyrrolidone, microcrystalline cellulose, Crospovidone, Croscaramelose sodium, Sodium starch glycolate, Camphor and Magnesium stearate.

Formula for the Zolmitriptan Porous Tablet tabulated in the Table No.1.

Precompression characteristics

Before going to the formulation the powder flow properties like Bulk density, Tapped density, True density, Angle of Repose, Compressibility index and Hausner's ratio were performed and the results were tabulated in the Table No.3.

Bulk Density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve#20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. It is expressed in g/ml and is given by

$$D_b = M/Vb$$

Where,

M is the mass of powder

Vb is the bulk volume of the powder.

Tapped Density

It is the ratio of the total mass powder to the tapped volume of the powder. It was determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10cm at 2 second intervals. The tapping was continued until no further change in volume was noted.

$$D_t = M/Vt$$

Where,

M is the mass of powder

Vt is the tapped volume of the powder.

Angle of Repose

It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined by the following formula.

$$\text{Tan } \theta = h/r$$

Therefore $\theta = \text{Tan}^{-1} h/r$

Where,

θ = Angle of repose

h = height of the cone

r = Radius of the cone base.

Compressibility Index

The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index.

$$\text{Carr's compressibility index (\%)} = [(D_t - D_b) X 100] / D_t$$

Where,

D_t is the tapped density

D_b is the bulk density

Hauser's Ratio

Hausner's ratio is an indirect index of the ease of powder flow. It is calculated by the following formula.

$$\text{Hausner's ratio} = D_t/D_b$$

Where, Dt is the tapped density,

Db is the bulk density.

Post Compression Studies

Tablet Thickness Test

Randomly 10 tablets were taken from each formulation trial batch and their thickness was measured using a Venire caliperse.

Weight Variation Test

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

Measurement of Tablet Hardness

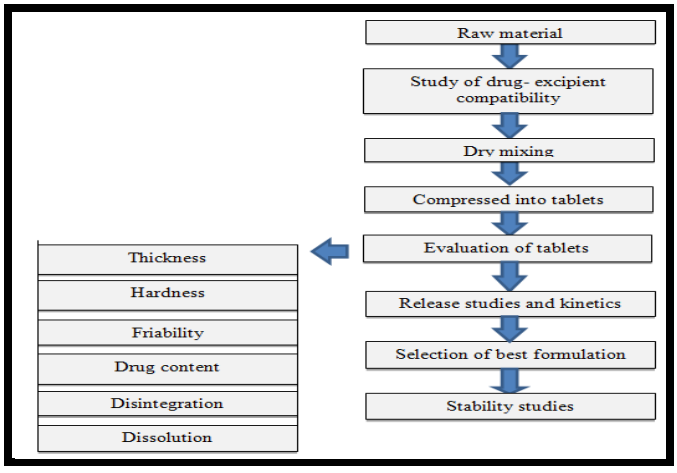
The hardness of tablet is an indication of its strength. The force is measured in kg and the hardness of about 3-5 kg/cm^2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation was determined by Monsanto hardness tester.

Friability Test

It is measured of mechanical strength of tablets. Roche Friabilator is used to determine the friability by following procedure. Twenty tablets were weighed and placed in Roche Friabilator where the tablets were exposed to rolling and repeated shocks resulting from free falls within the apparatus. After 100 revolutions, tablets are removed, dedusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

% Friability = (loss in weight / Initial weight) X 100

METHODOLOGY



Post compression results were showed in the Table No.4.

Dissolution parameters

Medium: 0.1N HCL, 900ml.

Apparatus: USP Type I (Basket).

Rotation speed: 50 RPM

Temperature: 37±5^{o}C.

Time: 2, 4, 6, 8, 10, 12 and 14 min.

Dissolution results are tabulated in the Table No.6.

RESULTS AND DISCUSSIONS

All the formulations were evaluated for bulk density, tapped density, % compressibility, hausner's ratio and angle of repose. The results of % compressibility, hausner's ratio and angle of repose were found to be between 12-20, 1.11-1.26 and 30-40 respectively. These results show that the formulations have fair to very good flow properties.

From the Table No.4, it is observed that the thickness, hardness, friability, weight variation and content uniformity of the porous tablets before drying were in the passable range. The F1 - F9 formulations containing camphor as the subliming agent didn't show much effect on the disintegration time whereas the formulations. The disintegration of F6 formulation was found to be of 2'.9"mins which is satisfactory.

DISCUSSION

Immediate release tablets of Zolmitriptan were formulated by direct compression method using Camphor as subliming agents, Microcrystalline cellulose as diluents, Povidone as binder, CCS, CP as super disintegrant, Magnesium stearate as lubricant.

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and excipients were studied as shown in Figures No.6.4 and 6.5. The peaks obtained in the spectra's of each formulation correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components.

The blends were analyzed for parameters such as Sieve analysis, Bulk density, Tapped density,

Compressibility index and Hausner's ratio and the results were found to be within limits.

Bulk density and tapped density values were found to be within limits. Compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area and cohesiveness of material. The powdered blend has required flow property.

After compression, all the tablets were dried at 60^{o}C for 12hrs and were evaluated for various parameters like weight variation, hardness, thickness, friability, disintegration and *in-vitro* drug release.

All formulations were found to have good hardness so they were taken for further studies. The measured hardness of tablets of each batches are in the range of 6 to 6.5kp.

Tablets mean thickness were almost uniform in all formulations and were found to be in the range of 2.40 mm to 2.6mm.

Friability values are found to be less than 1% in all the cases and considered to be satisfactory.

The total weight of each formulation was maintained constant and the weight variation of the tablets was within limits of 5%.

All the tablets passed the pharmacopoeial specifications for disintegration of Zolmitriptan porous tablets within 3 minutes.

The first trial (F1) was performed by direct compression using 15% of camphor as subliming agent and it was observed that the disintegration time of the product was on higher side. The reason behind this is due to closure of pores of the granules at the time of compression. In order to overcome these problem next trials (F2, F3) were planned using higher concentrations of super disintegrants.

In formulations (F2, F3) containing 15% camphor 6%, 8% of SSG as super disintegrants the disintegration time was found to be around 3mins and the *in-vitro* drug release was not satisfactory as they showed only 90% drug release in 14mins. In order to overcome this problem, the next trials (F4, F5) were planned by incorporating higher concentrations of super disintegrants (4% CCS, 6% CCS) and the results showed disintegration time around 3minsand the *in-vitro* drug release. Both the formulations F4 and F5 exhibited *in-vitro* drug release of 90 % in 14mins.

The trials (F6, F7) were planned using 15% camphor as sublimating agent and 8% CCS, 4% CP as super disintegrants to improve the dissolution rate and the results showed disintegration time around 20sec for F6 and 47sec.

The next trials (F8, F9) were carried out containing 15% camphor 6%, 8% CP in F8, F9 in the formulations. The tablets were evaluated for various parameters.

The optimized formulation F6 containing 15% of camphor showed *in-vitro* drug release of almost 98.06% of Zolmitriptan in 12mins and the disintegration time was found to be 20sec. The tablets loaded for stability at 40^{o}C and 75% RH for 1 month and 3 months respectively did not show much effect on the dissolution and drug content and are within the limits as per ICH guideliens therefore ensuring that the formulation F6 is a stable formulation.

Table No.1: Composition of Formulations

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Zolmitriptan	5mg	5mg	5mg	5mg	5mg	**5mg**	5mg	5mg	5mg
2	Camphor	30mg	30mg	30mg	30mg	30mg	**30mg**	30mg	30mg	30mg
3	Microcrystalline cellulose	148	144	140	148	144	**140**	148	144	140
4	Polyvinyl pyrrolidone	6mg	6mg	6mg	6mg	6mg	**6mg**	6mg	6mg	6mg
5	Sodium starch glycolate	8mg	12mg	16mg	-	-	-	-	-	-
6	Croscarmellose sodium	-	-	-	8mg	12mg	**16mg**	-	-	-
7	Crospovidone	-	-	-	-	-	-	8mg	12mg	16mg
8	Mg.stearate	3mg	3mg	3mg	3mg	3mg	**3mg**	3mg	3mg	3mg
9	Total weight	200mg	200mg	200mg	200mg	200mg	**200mg**	200mg	200mg	200mg

Table No.2: Table showing the bulk density of the API's

S.No	Material	Bulk density (gm/mL)	Tapped density (gm/mL)	Compressibility index (%)	Hausner's ratio	Angle of repose	Flow property
1	Zolmitriptan	0.472gm/mL	0.510gm/mL	24.62 %	1.32	38^0C	passable

Table No.3: Pre-compression parameters for formulation batches

S.No	Formulation code	Bulk density (gm/cc)	Tapped density (gm/ml)	Compressibility index (%)	Hausner's ratio	Angle of Repose (θ)	Flow property
1	F1	0.72±0.045	0.87± 0.01	17.126±0.6	1.206±0.06	36.62±0.21	Fair
2	F2	0.71±0.043	0.873±0.04	19.714±0.7	1.251±0.04	37.46±0.11	Fair
3	F3	0.41±0.045	0.483±0.5	15.113±0.8	1.178±0.08	38.32±0.31	Fair
4	F4	0.45±0.045	0.52 ± 0.09	15.60±0.2	1.15±0.02	28.06±0.31	Very good
5	F5	0.45±0.045	0.50 ± 0.07	12.23±0.6	1.11±0.04	27.58±0.15	Very good
6	F6	0.44±0.044	0.50 ± 0.09	12.58±0.8	1.13±0.08	28.44±0.11	Very good
7	F7	0.45±0.045	0.52 ± 0.04	15.19±0.1	1.15±0.06	28.36±0.13	Very good
8	F8	0.44±0.044	0.52± 0.01	15.48±0.6	1.18±0.08	28.52±0.19	Very good
9	F9	0.45±0.045	0.51 ± 0.04	13.48±0.8	1.13±0.09	29.32±0.19	Very good

Table No.4: Evaluation parameters of formulations of porous tablets before drying

S.No	Formulation code	Thickness ± S.D. (mm)	Hardness ±S.D. (KP)	Friability (%)	weight variation (mg)	Drug content (Zolmitriptan) (%)	Disintegration Time ± S.D. (min)
1	F1	2.6±0.05	6.00±1.5	0.54	200±5.60	99.13±0.53	3.2±0.35
2	F2	2.59±0.07	6.100±1.3	0.45	198±5.45	96.27±0.64	3.3±0.30
3	F3	2.57±0.06	6.400±1.2	0.35	195±8.10	97.63±0.55	3.5±0.45
4	F4	2.57±0.10	6.400±1.1	0.41	205±6.00	98.36±0.58	3.4±0.56
5	F5	2.58±0.09	6.300±1.3	0.42	196±7.89	98.33±0.62	3.3±0.35
6	**F6**	**2.57±0.04**	**6.400±1.1**	**0.31**	**195±5.98**	**98.64±0.84**	**2.9±0.23**
7	F7	2.54±0.07	6.500±1.0	0.29	199±2.45	98.76±0.81	3.2±0.31
8	F8	2.56±0.10	6.400±1.3	0.25	197±3.67	97.36±0.94	3.4±0.28
9	F9	2.52±0.08	6.500±1.2	0.31	199±4.87	98.44±0.84	3.4±0.15

Table No.5: Evaluation parameters for formulations of porous tablets after drying

S.No	Formulation code	Thickness ±S.D.(mm)	Hardness ± S.D. (Kp)	Average weight variation (mg)	Drug content (Zolmitriptan)(%)	Disintegration Time ± S.D.
1	F1	2.6±0.05	3.7±1.0	165±1.19	99.26±0.45	1min 10sec
2	F2	2.59±0.07	3.8±1.2	163±1.93	96.38±0.56	43sec
3	F3	2.57±0.06	4.1±1.7	166±1.82	97.03±0.61	32sec
4	F4	2.57±0.10	4.1±2.0	166±1.27	98.26±0.55	57sec
5	F5	2.58±0.09	4.2±1.5	163±1.67	98.29±0.42	36sec
6	**F6**	**2.57±0.04**	**3.9±1.0**	**162±1.92**	**98.60±0.68**	**20sec**
7	F7	2.54±0.07	4.1±1.3	166±1.60	98.71±0.78	47sec
8	F8	2.56±0.10	3.8±1.0	164±1.89	97.40±0.84	30sec
9	F9	2.52±0.08	3.9±1.2	164±1.24	98.25±0.79	25sec

Table No.6: *In vitro* Release Profile of Zolmitriptan from formulations F1-F9

S.No	Time (min)	Cumulative % drug release								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	2	14	16	25	18	23	39	12	18	23
2	4	25	30	39	33	40	56	28	32	39
3	6	37	45	56	46	59	72	39	44	50
4	8	58	60	68	58	67	86	50	59	68
5	10	69	72	79	71	80	98	63	74	77
6	12	80	85	90	89	95	102	78	83	96
7	14	91	93	98	95	99	---	90	99	102
8	16	103	99	---	102	---	---	98	103	---

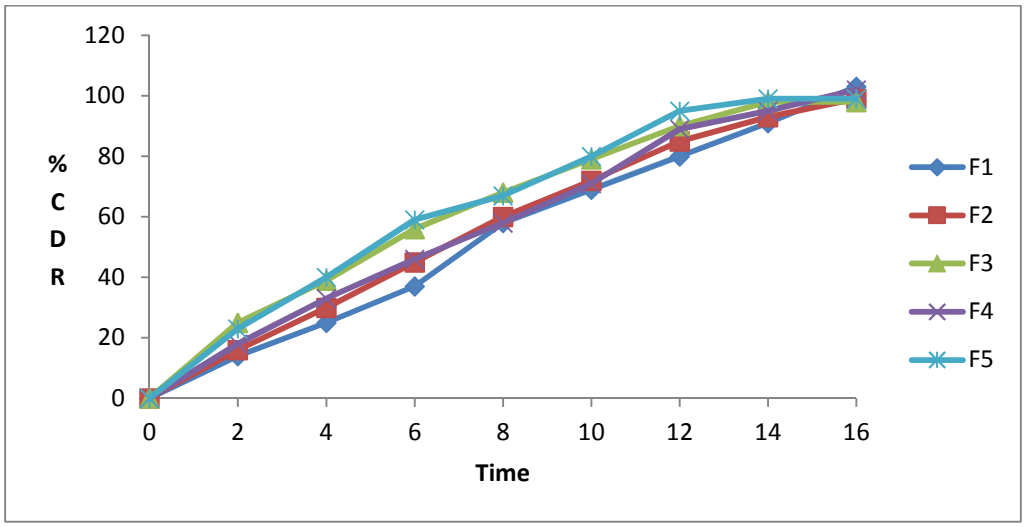


Figure No.1: *In-vitro* Release Profile of Zolmitriptan from formulations F1-F5

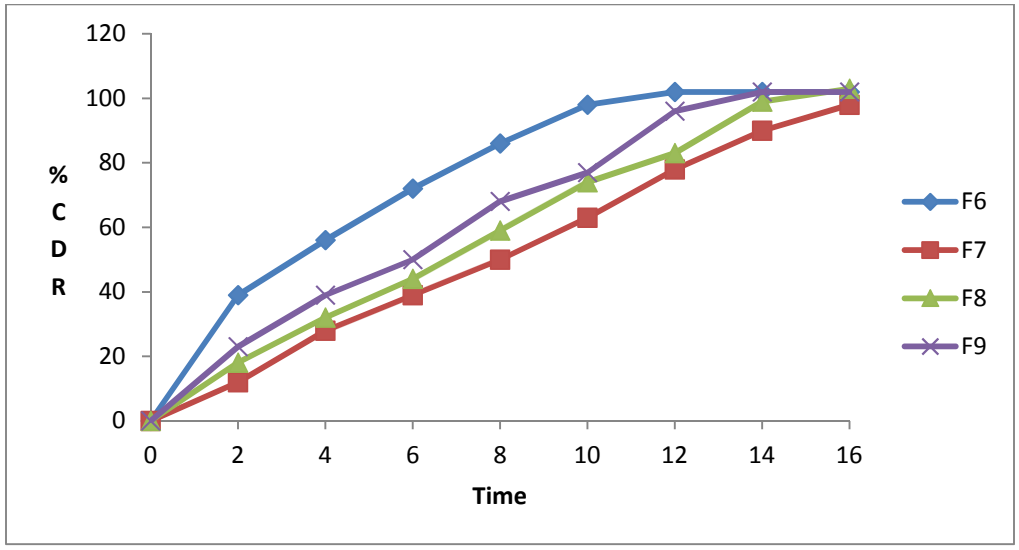


Figure No.2: *In-vitro* Release Profile of Zolmitriptan from formulations F6-F9

CONCLUSION

This dissertation work was done with an aim to design an immediate release oral dosage of Zolmitriptan and evaluation of the tablets for various parameters including in vitro drug release studies. Zolmitriptan tablets were formulated by using microcrystalline cellulose as lubricant, camphor as subliming agents, Crospovidone, SSG and CCS as super disintegrant, Povidone as binder and magnesium stearate as lubricant. The powdered blend were compressed into tablets and were analyzed for the parameters such as average weight, disintegration time, friability, thickness, weight variation, hardness, moisture content and drug content. The formulation F6 is formulated by using subliming agents and super disintegrants where it can ensure burst release of the drugs so that there release cannot be interlinked. The formulation F6 containing 15% of camphor showed disintegration time of less than 30seconds after drying. Camphor as subliming agent was found to be most effective of all other subliming agents as it had showed drastic effect on the drug release. All other parameters viz: Hardness, Thickness, Weight variation and drug content were also found to be within limits. The dissolution profiles and drug content of the tablets were found to be satisfactory even after subjecting the tablets to stability studies at 40^{o}C and 75% RH for 1 month and 3 months respectively. The formulation F6 and process can be easily scaled up and can be easily employed in large scale production because the process is simple, cost effective and precise and also yields reproducible good result that involves complex process for manufacturing the tablets.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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