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Der Pharmacia Lettre, 2013, 5 (2):324-332
(http://scholarsresearchlibrary.com/archive.html)

Der Pharmacia Lettre
Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

Formulation development and evaluation of oral disintegrating tablets of zolmitriptan

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ABSTRACT

Orally disintegrating tablets (ODTs) are getting popularity over conventional tablets due totheir convenience in administration and suitability for patients having dysphagia (difficulty in swallowing). There is an increasing demand for more patient compliant dosage form and a novel method is the development orally disintegrating tablets which dissolve or disintegrates instantly on the patient tongue or buccal mucosa. It is suited for tablets undergoing high first pass metabolism and is used for improving bioavailability with reducing dosing frequency to minimize side effect and make it more cost effective. Zolmitriptan is a selective serotonin receptor agonist .Zolmitriptan , the absolute bioavailability is only approximately 40% due to extensive hepatic first pass metabolism (CYP1A2-mediated). Hence the main objective of the study was to formulate oral disintegrating tablets of Zolmitriptan to achieve a better dissolution rate and further improving the bioavailability of the drug. Orally disintegrating tablets prepared by direct compression and using Supertab11SD, Avicel PH 102, Crospovidone, Ac-Di-Sol, Sodium starch glycolate, Aspartame , Magnesium stearate were prepared and evaluated for the precompression parameters such as bulk density, compressibility, angle of repose etc. The prepared batches of tablets were evaluated for hardness, weight variation, friability, disintegration time and in-vitro dissolution profile and found satisfactory. Among the three groups, F9 Formulation as the best formulation and showed maximum dissolution rate with drug release.

Keywords: Zolmitriptan, Superdisintegrants and Orally disinintegrating tablets.

INTRODUCTION

The tablet is the most widely used dosage form because of its convenience in terms of self -administration, compactness and ease in manufacturing. However, many patients especially children and elderly have difficulty in swallowing tablets and capsules and consequently unable to take medicine as prescribed. Almost 50% of the population is affected by such problem, resulting in the high incidence of non compliance and infective therapy. To overcome such problems, fast disintegrating tablets or orally disintegrating tablets have emerged as an alternative dosage forms. Oral disintegration tablets are the novel technology for administration of the drug through the oral route. ODT's are solid unit dosage forms, which disintegrate or dissolve rapidly in the mouth without chewing and water. Many patients find it difficult to swallow like pediatric and geriatric and those people who are travelling or little access to water and some patients who are mentally ill like schizophrenia they are also did not take medicine, oral disintegrating tablets solve these problems. An Oral disintegration tablets is a solid dosage form that disintegrates and dissolves in the mouth without water within 60 seconds or less. orally disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. Additionally, pediatric patients may suffer from ingestion problems as a result of underdeveloped muscular and nervous control. ODTs may show increased oral bioavailability. It provides good

stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients. Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets offer an advantage for populations who have difficulty in swallowing. It has been reported that Dysphagia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications. ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population. "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." ODT products have been developed for numerous indications ranging from migraines (for which rapid onset of action is important) to mental illness (for which patient compliance is important for treating chronic indications such as depression and schizophrenia). Orally disintegrating tablets have been found to be the choice for Psychiatric as well as patient suffering from stroke, thyroid disorder, Parkinson's diseases and multiple sclerosis, patients with nausea, vomiting and motion sickness. These systems may offer superior profile with potential mucosal absorption thus increase the drug bioavailability. These systems are also called melt-in-mouth tablets, Rapidmelts, porous tablets, Orodispersible, quick dissolving or rapidly disintegrating tablets[1-7].

MATERIALS AND METHODS

Materials :Supertab11SD, Avicel PH 102, Crospovidone, Ac-Di-Sol, Sodium starch glycolate, Aspartame and Magnesium stearate from the gift of Active pharma labs, Hyderabad.

Methodology:

Standard calibration curve of zolmitriptan

Solutions ranging from 5 to 25 µg/ml were prepared using 0.1 N Hcl); separately, absorbance was measured for each solution at λ max of 220 nm using Shimadzu UV/ visible 1700 spectrophotometer, graph was plotted for absorbance versus concentration of Zolmitriptan.(Table 1,Fig.1)

Formulation development

Formulation of oral disintegrating tablets of Zolmitriptan 5mg were carried out by direct compression technique. The procedure has been described as follows (Table.2):

As the drug substances are hygroscopic the amount of drug substance weighed may not be equivalent to the desired weight (because of the presence of moisture).Therefore the quantity of substance to be weighed was calculated as follows;

$$\text{Quantity of substance} = \frac{\text{Strength X Assay purity X LOD purity}}{\text{Assay of substance X(100-LOD)}}$$

Procedure for F-1

Zolmitriptan, Supertab11SD, Avicel, Crospovidone, Aspartame were weighed, sifted through #40 mesh and blended in the polybag for 10 min.Mg stearate passed through #80 mesh whichch was added to the above blend and lubricated for 5 min in te poly bag From the final blend tablets were compressed using 6.4 mm round flat shaped punches.

Procedure for F-2 and F-3

In this trail concentration of crosspovidone increased gradually and evaluate parameters.

Zolmitriptan, Supertab11SD, Avicel, Crospovidone, Aspartame were weighed, sifted through #40 mesh and blended in the polybag for 10 min.Mg stearate passed through #80 mesh whichch was added to the above blend and lubricated for 5 min in te poly bag.From the final blend tablets were compressed using 6.4 mm round flat shaped punches.

Procedure for F-4 :

In this trail Superdisintegrant crosspovidone was replaced by cross carmellose sodium initially low concentrations and evaluate parameters. Zolmitriptan, Supertab11SD, Avicel, Cros carmellose sodium, Aspartame were weighed, sifted through #40 mesh and blended in the polybag for 10 min.Mg stearate passed through #80 mesh whichch was added to the above blend and lubricated for 5 min in te poly bagFrom the final blend tablets were compressed using 6.4 mm round flat shaped punches.

Procedure for F-5 & F-6
In this trail concentration of Cros carmellose sodium increased gradually and evaluate parameters.Zolmitriptan, Supertab11SD, Avicel, Cros carmellose sodium, Aspartame were weighed, sifted through #40 mesh and blended in the polybag for 10 min.Mg stearate passed through #80 mesh whichch was added to the above blend and lubricated for 5 min in te poly bag

From the final blend tablets were compressed using 6.4 mm round flat shaped punches.

Procedure for F-7 :
In this trail Superdisintegrant was cross carmellose sodium replaced by Sodium starch glycolate initially low concentrations and evaluate parameters. Zolmitriptan, Supertab11SD, Avicel, Cros carmellose sodium, Aspartame were weighed, sifted through #40 mesh and blended in the polybag for 10 min. Mg stearate passed through #80 mesh whichch was added to the above blend and lubricated for 5 min in te poly bagFrom the final blend tablets were compressed using 6.4 mm round flat shaped punches.

Procedure for F-8 & F-9
In this trail concentration of Sodium starch glycolate increased gradually and evaluate parameters.Zolmitriptan, Supertab11SD, Avicel, Cros carmellose sodium, Aspartame were weighed, sifted through #40 mesh and blended in the polybag for 10 min. Mg stearate passed through #80 mesh whichch was added to the above blend and lubricated for 5 min in te poly bag.From the final blend tablets were compressed using 6.4 mm round flat shaped punches.

Evaluation of Blend
Angle of repose
The internal angle between the surface of the pile of blend and the horizontal surface is known as the angle of repose. The Angle of repose was known by passing the blend through a funnel fixed to a burette stand at a particular height (4 cm). A graph paper was placed below the funnel on the table. The height and radius of the pile was measured. Angle of repose of the blend was calculated using the formula:

$\theta = \tan^{-1} (h / r)$

h = Height of the pile
r = Radius of the pile

Bulk density
Bulk density is used as a measure to describe packing materials or granules.Bulk density is the ratio of given mass of powder and its bulk volume. It was determined by transferring an accurately weighed amount of powder sample to the graduated cylinder with the aid of a funnel. The initial volume was noted. Ratio of weight of the sample to the volume it occupied was calculated.

Bulk density = W/V_0 g/ml

W= Mass of the blend
V_0 =Untapped volume

Tapped density
Tapped density was measured by transferring a known quantity of blend into a graduated cylinder and was placed on the tapped density apparatus. The initial volume was noted. The apparatus was set for 500, 750 and 1250 taps. The tapped density was determined as the ratio of mass of the blend to the tapped volume.

Tapped density=W/V_f g/ml

W= Mass of the blend
V_f = Tapped volume

Compressibility index
It is the propensity of a powder to be compressed. It is measured by tapped density apparatus for 500, 750 and 1250 taps for which the difference should be not more than 2%. Based on the apparent bulk density and tapped density the percentage compressibility of the blend was determined using the following formula.

% Compressibility = $[(V_0 – V_f) / V_0] X 100$

OR

% Compressibility = [(Tapped density – Bulk density) / Tapped density] X 100

Hausner ratio
It indicates the flow properties of the powder. The ratio of tapped density to the bulk density of the powders is called Hausner ratio.

Hausners ratio= Tapped density / Bulk density

Loss on drying
The Loss on drying test is designed to measure the amount of water and volatile matters in a sample when the sample is dried under specified conditions. The loss on drying of the blend (1.5g) was determined by using electronic LOD (helium lamp) apparatus at 105°C.

Evaluation of Tablets
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, colour, embossing, debossing 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 thickhness 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

Average weight of tablet (mg)	% difference
130 or less	10 %
From 130 to 324	7.5%
> 324	5%

Hardness test
The crushing load which is the force required to break the tablet in the radial direction was measured using a Schluenzier hardness tester. The hardness of 10 tablets was noted and the average hardness was calculated. It is given in kp or kg/cm^2.

Friability
In friability testing the tablets are subjected to abrasion and shock. It gives an indication of the tablets ability to resist chipping and abrasion during transportation and shipping. If the tablet weight is ≥ 650 mg 10 tablets were taken and initial weight was noted. For tablets of weight less than 650 mg the number of tablets equivalent to a weight of 6.5 g were taken. The tablets were rotated in the Roche Friabilator for 100 revolutions at 25 rpm. The tablets were dedusted and reweighed. The percentage friability should be not more than 1%w/w of the tablets being tested.

The percentage friability is expressed as the loss of weight and is calculated by the formula:

% Friability = $[(W_0—W_f) / W_0] \times 100$

W_0 = Initial weight of tablets
W_f = Final weight of tablets

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 ± 2^0C. 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 5 to 30seconds.

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.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, 20 30, min. Fresh volume of the medium were replaced with the withdrawn volume to maintain the sink conditions. Samples withdrawn were analyzed for the percentage of drug released.

Dissolution Parameters

Dissolution Apparatus : USP Apparatus Type II (Paddle)
Dissolution Medium : 0.1N Hydrochloric acid
Volume : 500 ml
Temperature : 37±2° C
Rpm : 50
Sampling Intervals (min) : 5, 10, 15,20, 30 min

Stability Studies

Selected formulation is subjected to stability studies as per 40°C / 75% RH for 2 months. Sample are taken and analyzed at time interval(Table.9 and 10).

RESULTS AND DISSCUSION

Table 1.Standard graph of Salbutamol Sulphate in 6.8 Buffer Solution at λ max 220nm

Sl. No.	Concentration (mcg/ml)	Absorbance
1.	00	0.00
2.	05	0.035
3.	10	0.070
4.	15	0.105
5.	20	0.138
6.	25	0.170

Table.2.Formulation development of Zolmitriptan oral disintegrating tablets

Ingredients (mg)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Zolmitriptan	5	5	5	5	5	5	5	5	5
Supertab11SD	97	97	97	97	97	97	97	97	97
Avicel PH 102	19.6	18.3	17	19.6	18.3	17	19.6	18.3	17
Crospovidone	3.9	5.2	6.5	-	-	-	-	-	-
Ac-Di-Sol	-	-	-	3.9	5.2	6.5	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	3.9	5.2	6.5
Aspartame	2	2	2	2	2	2	2	2	2
Peppermint	1	1	1	1	1	1	1	1	1
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight (mg)	130	130	130	130	130	130	130	130	130

Table.3. Precompression parameters of various formulations

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index	Hausner Ratio	Angle of repose(θ)	% LOD
F1	0.384±23	0.545±11	31.25±11	1.41±33	41.52±58	1.75±51
F2	0.362±29	0.485±25	25.36±62	1.33±58	40.61±39	1.80±35
F3	0.380±45	0.530±50	28.30±55	1.39±19	48.42±65	1.75±11
F4	0.371±56	0.493±30	24.74±81	1.32±38	37.41±45	1.50±01
F5	0.360±25	0.462±84	22.07±25	1.66±76	33.92±28	1.47±17
F6	0.419±69	0.477±67	12.26±19	1.14±52	24.28±71	1.37±55
F7	0.417±56	0.471±55	11.49±43	1.13±68	22.32±69	1.33±63
F8	0.416±89	0.475±72	12.44±28	1.13±72	25.54±50	1.20±21
F9	0.428±21	0.456±35	18.22±66	1.25±44	24.56±38	1.19±49

All the values were Expressed in mean ±SD no of tra ils (n)=3

Table.4.Evaluation parameters of Zolmitriptan ODTs

Formulation Code	Average weight (mg)	Thickness (mm)	Hardness (kp)	Percentage Friability (%)	Disintegration Time (sec)
F1	131.2±0.12	3.71±0.54	3.8±0.16	0.63±0.10	80±0.88
F2	130.6±0.25	3.65±0.23	4.2±0.52	1.22±0.25	71±0.95
F3	132.3±0.35	3.69±0.38	4.0±0.16	1.50±0.35	65±0.89
F4	131.8±0.33	3.68±0.72	4.3±0.19	0.78±0.65	59±0.96
F5	129.8±0.22	3.72±0.61	4.3±0.75	0.90±0.42	54±0.97
F6	129.6±0.19	3.66±0.12	4.4±0.16	1.75±0.39	50±0.90
F7	132.0±0.15	3.65±0.28	4.0±0.22	0.32±0.44	30±0.99
F8	130.5±0.30	3.72±0.34	4.2±0.70	0.45±0.29	25±0.91
F9	130.2±0.14	3.70±0.67	4.0±0.15	0.68±0.37	21±0.88

All the values were Expressed in mean ±SD no of tra ils (n)=3
Dissolution studies for Reference product Zomig ZMT 5mg tablets

Table.5.Drug release of Reference product

S.NO	Time (min)	Drug release (%)
1	0	0
2	5	96.9
3	10	97.9
4	15	98.9
5	20	100.2
6	30	100.2

Table.6.Cumulative % Drug release Zolmitriptan oral disintegrating tablets

Time(Min)	Formulations		
	F1	F2	F3
0	0	0	0
5	91.1±0.025	91.8±0.033	92.3±0.064
10	91.3±0.083	93.1±0.045	94.5±0.046
15	92.6±0.065	95±0.086	97.0±0.086
20	92.8±0.052	96.3±0.075	98.6±0.074
30	93.4±0.045	97.1±0.061	99.9±0.054

Table.7.Cumulative % Drug release Zolmitriptan oral disintegrating tablets

Time(Min)	Formulations		
	F4	F5	F6
0	0	0	0
5	92.8±0.025	93.8±0.033	92.6±0.064
10	94.0±0.083	95.1±0.045	94.0±0.046
15	95.2±0.065	95.6±0.086	97.8±0.086
20	97.1±0.052	96.8±0.075	98.2±0.074
30	99.2±0.045	97.9±0.061	99.5±0.054

Table.8.Cumulative % Drug release Zolmitriptan oral disintegrating tablets

Time(Min)	Formulations		
	F7	F8	F9
0	0	0	0
5	95.3±0.029	96.8±0.053	97.3±0.074
10	96.2±0.063	97.0±0.065	98.5±0.066
15	97.5±0.055	97.2±0.086	99.6±0.016
20	97.9±0.082	98.6±0.065	100.5±0.054
30	99.8±0.025	99.8±0.031	101.5±0.024

Table .9 Stability study data

PARAMETERS TESTED	**STORAGE CONDITIONS**		
	INITIAL	**40^0C±2^0C / 75% ±5% RH**	
		1st month	**2nd month**
Description	White coloured flat faced	No change	No change
Average weight (mg)	130.5	1001	1002
Thickness(mm)	3.79	3.80	3.81
Hardness (kp)	4.0	3.9	3.5
% Friability	0.51	0.61	0.56
Disintegration time (sec)	20	20	22

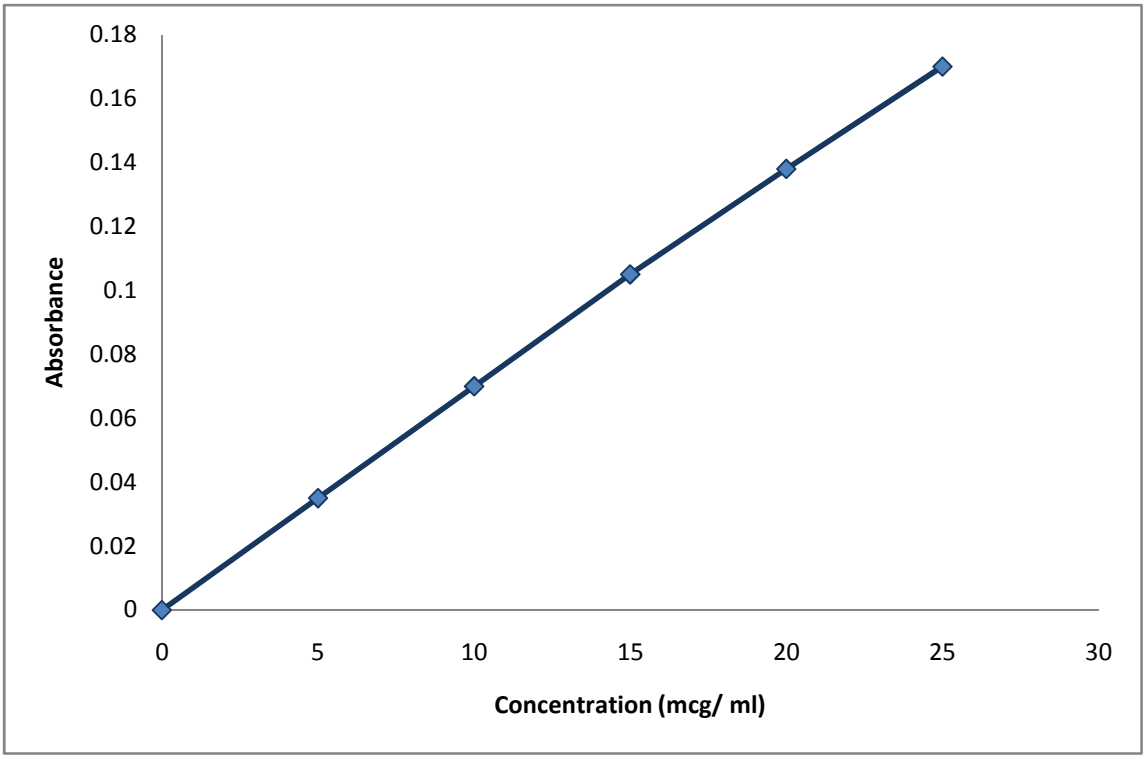

Fig.1. Standard graph of zolmitriptan in 0.1N Hcl at 220 nm

Table.10.Dissolution data of stability study sample (Cumulative percentage of drug release)

Time Interval(min)	Initial	$40^0C \pm 2^0C$ / 75% ±5% RH	
		Ist month	2 nd month
0	0	0	0
5	95.2	95.3	95.7
10	97.5	97.7	96.8
15	98.3	98.3	97.7
20	99.2	99.1	98.9
30	99.8	99.4	99.4

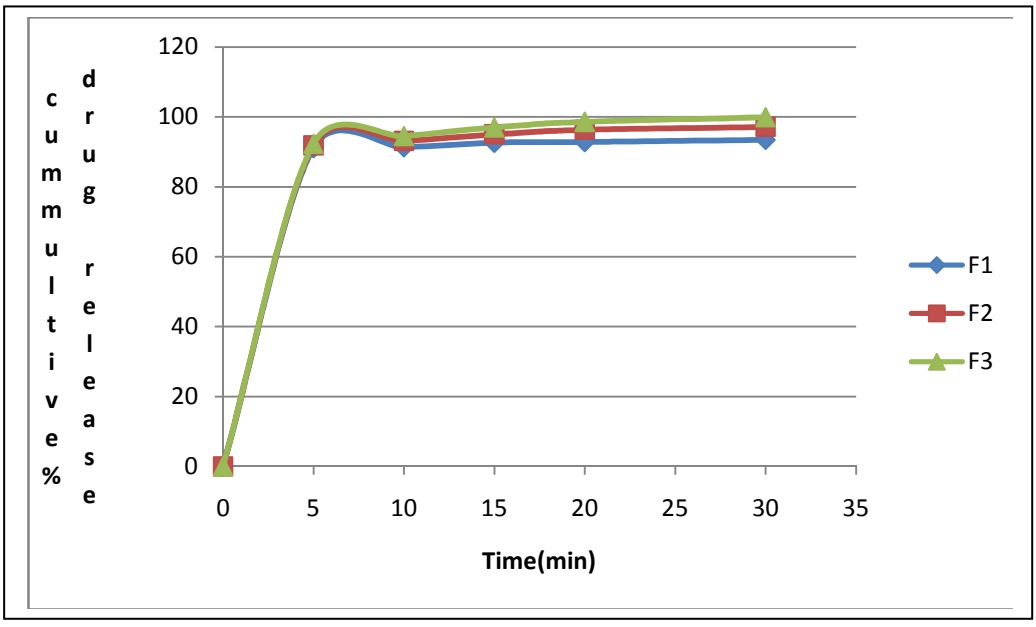

Fig.2. Dissolution profile of various formulations(F1-F3)

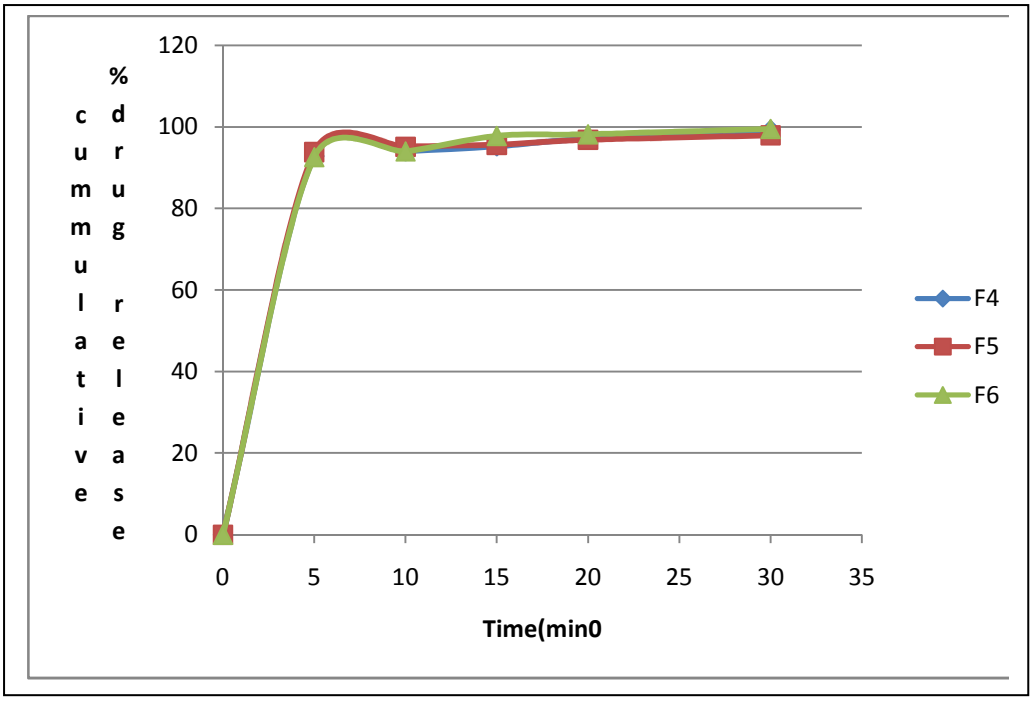

Fig.3. Dissolution profile of various formulations(F4-F6)

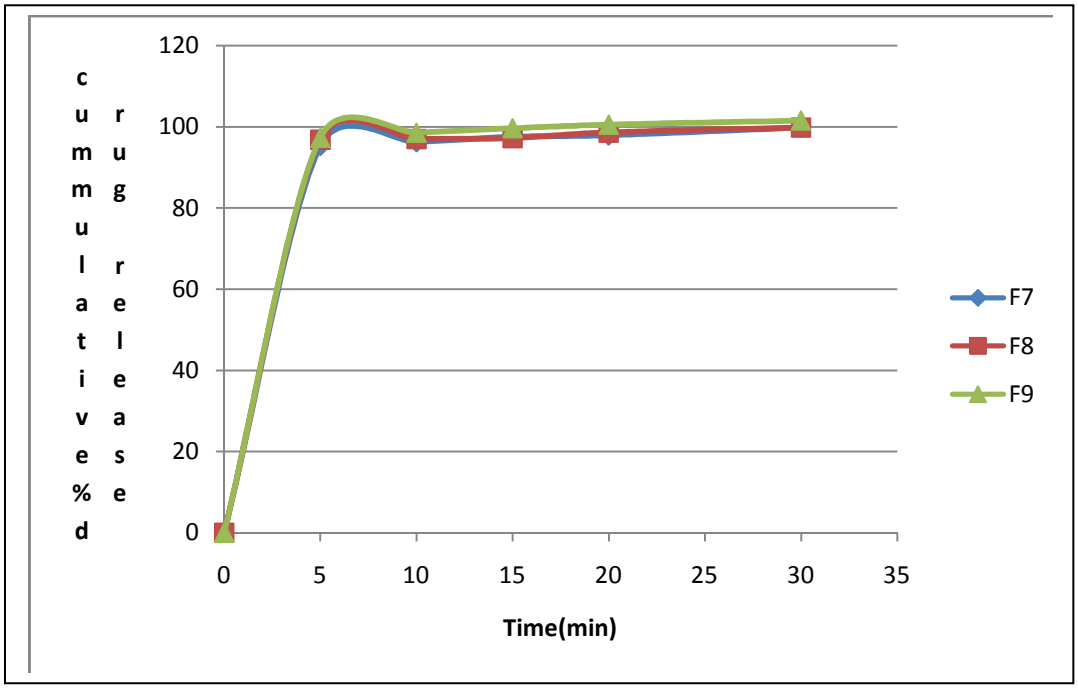

Fig.4. Dissolution profile of various formulations(F7-F9)

CONCLUSION

F1 was carried out using supertab 11SD as a diluent, crospovidone (3%) as superdisintegrant & mg.stearate (1.15%).In this trail disintegration time was very high. ***Conclusion of trail*** *:* optimization of disintegration time of tablet in next trail.

F2 was carried out using supertab 11SD as a diluent, crospovidone (4%) as superdisintegrant & mg.stearate (1.15%). In this trail disintegration time was very high with loss of friability. ***Conclusion of trail*** *:* In this trail disintegration time of tablet in next trail and decrease the friability**.**

F3 was carried out using supertab 11SD as a diluent, crospovidone (5%) as superdisintegrant & mg.stearate (1.15%). In this trail disintegration time was high with loss of friability was very high.***Conclusion of trail :*** optimization of disintegration time of tablet in next trail and decrease the friability**.**

F4 was carried out using supertab 11SD as a diluent, Ac-di-sol (3%) as superdisintegrant & mg.stearate (1.15%). In this trail disintegration time was very high. ***Conclusion of trail :*** optimization of disintegration time of tablet in next trail.

F5 was carried out using supertab 11SD as a diluent, Ac-di-sol (4%) as superdisintegrant & mg.stearate (1.15%). In this trail disintegration time was very high with loss of friability.***Conclusion of trail :*** In this trail disintegration time of tablet in next trail and decrease the friability**.**

F6 was carried out using supertab 11SD as a diluent, Ac-di-sol (5%) as superdisintegrant & mg.stearate (1.15%). In this trail disintegration time was high with loss of friability was very high.***Conclusion of trail :*** optimization of disintegration time of tablet in next trail and decrease the high friability loss.

F7 was carried out using supertab 11SD as a diluent, Sodium starch glycolate (3%) as superdisintegrant & mg.stearate (1.15%). In this trail disintegration time was very high.***Conclusion of trail :*** optimization of disintegration time of tablet in next trail.

F8 was carried out using supertab 11SD as a diluent, Sodium starch glycolate (4%) as superdisintegrant & mg.stearate (1.15%). In this trail disintegration time was good. ***Conclusion of trail :*** disintegration time of tablet is further improved in next trail.

F9 was carried out using supertab 11SD as a diluent, Sodium starch glycolate (5%) as superdisintegrant & mg.stearate (1.15%). In this trail disintegration time was good. ***Conclusion of trail :*** In this trail disintegration time of tablet was good and friability with in the limits and has good dissolution profiles compared to reference product.

Acknowledgements
Director, Active Pharma Labs, Hyderabad is duly acknowledged for providing necessary facilities. The authors also express their thanks to Gitam institute of pharmacy, Vizag,AP.

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