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Research Article

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Evaluation and Optimization of Olmesartan medoxomil tablet using Synthetic and Natural superdisintegrants

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ABSTRACT

The present investigation was carried out with the aim to formulate and evaluate Fast/mouth dissolving tablet of Olmesartan medoxomil by direct compression method. Olmesartan medoxomil is the novel anti-hypertensive drug having specific angiotensin II type 1 antagonist activity and used in the management of acute and chronic hypertension. Mostly hypertension found in geriatric patients who face difficulty in swallowing (dysphagia). Olmesartan medoxomil drug have major problem of solubility in biological fluids and first pass metabolism, which results into poor bioavailability (26%) after oral administration. In the present work We had developedfast dissolving tablet of Olmesartan medoxomil 20 mg, using synthetic and natural superdisintegrants like, Sodium starchglycolate, Croscarmellose, Crospovidone and Plantagoovatamucilage in different concentrations (5, 7.5 and 10mg). The taste of drug was masked usingaspartame as sweetening agent, Mannitolused as bulk forming agent. Other excipients used are talc as a Glidant, and Magnesium stearate as lubricant. The prepared formulation batch of tablets were evaluated for weight variation, tablet thickness, hardness, friability, drug content, wetting time, in vitro dispersion time and in-vitro dissolution study and the batch F12 was observed as optimized. Effect of disintegrant on disintegration behaviour of tabletwas evaluatedin artificial saliva and the compatibility study was carried out using Infrared spectroscopy.

Keywords: *Fast dissolving tablets, Olmesartan medoxomil,Plantagoovatamucilage, Superdisintegrants.*

INTRODUCTION

Now a day fast dissolving tablets are gaining more importance in the market. Currently these tablets are available in the market for treating many disease conditions. More is concern is on hypertension, migraine, dysphasia, nausea and vomiting, Parkinson's disease, schizophrenia, pediatric emergency[1-4]. These are the target conditions with the scope for formulations such as fast dissolving tablets. The patient with above conditions show convenience with fast dissolving tablets over conventional tablets because of ease of administration, swallowing, pleasant taste and availability in several flavors[5]. The paediatric and geriatric patients are of particular concern. To overcome this, dispersible tablets[6] and fast-disintegrating tablets[7] have been developed. Most commonly used methods to prepare these tablets are; freeze-drying/lyophilization[8], tablet molding[9] and direct-compression methods[10]. Lyophilized tablets show a very porous structure, which causes quick penetration of saliva in to the pores when placed in oral cavity[11]. The main disadvantages of tablets produced are, in addition to the cost intensive production process, a lack of physical resistance in standard blister packs and their limited ability to incorporate higher concentrations of active drug. Molded tablets dissolve completely and rapidly. However, lack of strength and taste masking are of great concern[12]. Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablets[13].

Olmesartan medoxomil is chemically (5-methyl-2-oxo-2H-1,3-dioxol-4-yl)methyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-({4- [2- (2H -1 ,2,3,4-tetrazol-5-yl) phenyl] phenyl}methyl)1H imidazole -5 carboxylate[14]. Olmesartan medoxomil is a prodrug of Olmesartan – a compound that inhibits binding ofangiotensin II to the AT1 – receptor. Olmesartan medoxomil is hydrolyzed to Olmesartan during absorption from the gastrointestinal tract. It is mainly used in the treatment of hypertension. The typical dose of Olmesartan medoxomil is 20 mg per day in patients who are not volume depleted. Tablet formulation containing 20 mg and 40 mg Olmesartan medoxomil are available in market[15].

In the present study, an attempt was made to develop fast dissolving tablets of Olmesartan medoxomil using natural and synthetic superdisintegrants to improve its bioavailability.

MATERIALS AND METHODS

Olmesartan medoxomil was received as gift sample from Micro Labs, Banglore, India,Microcrystalline cellulose from Zydus Research center, Ahmedbad, India, Cross povidone and Croscarmellosefrom DMV International, Mumbai, India and Spray dried mannitolfrom Indchem International, Mumbai India. All other excipients, chemicals, reagents and solvents used are of either analytical or Pharmacopoeial grade.

Direct compression method is used for the preparation of fast dissolving tablets by Single punch machine.

ISOLATION OF MUCILAGE

The seeds of *plantago ovate* were soaked in distilled water for 48 hrs and then boiled for fewminutes so that mucilage was completely released into water. The material collected was squeezed through muslin cloth for filtering and separating out the marc. Then, an equal volume of acetone was added to the filtrate so as to precipitate the mucilage. The separated mucilage was dried (in oven at temperature less than 600º C), powdered, sieved (# 80)and stored in a desiccator until use.

PREPARATION OF TABLETS

Fast dissolving tablets of Olmesartan medoxomil were prepared by direct compression method. The different batches designed are as shown in table no. 1. All the excipients are screened through sieve no 80 separately, weighed and mixed properly in geometric order. Lubricant and glidant were added and the blend/ mixture thus obtained were compressed using 9 mm punch into tablets of 200 mg on a single punch machine (Hardik, Ahmedabad).

Table no. 1: Composition of all the formulation designed (F1 to F12)

Sr. No.	Ingredients/formulation batch(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Olmesartan	20	20	20	20	20	20	20	20	20	20	20	20
2	SSG	6	8	10	-	-	-	-	-	-			
3	Crosscarmellose	-	-	-	6	8	10	-	-	-			
4	Crosspovidone	-	-	-	-	-	-	6	8	10	-	-	-
5	PO	-	-	-	-	-	-	-	-	-	6	8	10
6	Aspartame	2	2	2	2	2	2	2	2	2	2	2	2
7	MCC	40	40	40	40	40	40	40	40	40	40	40	40
8	Mag. Stearate	2	2	2	2	2	2	2	2	2	2	2	2
9	Talc	2	2	2	2	2	2	2	2	2	2	2	2
10	Mannitol	128	126	124	128	126	124	128	126	124	128	126	124
Total (mg)		200	200	200	200	200	200	200	200	200	200	200	200

EVALUATION OF BLEND

The powder blend was evaluated for follow pre-compression parameters.

Pre-compression Parameters

7.4.1 Derived properties

Preformulation testing is an investigation of physical and chemical properties of a drug substances alone and when combined with excipients. It is the first step in the rational development of dosage forms. The overall objective of preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage form.

7.4.2 Angle of Repose

The blend was poured through a funnel that can be raised vertically until amaximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose was calculated using the following formula

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

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

Where, θ = Angle of repose

h = height of the cone,

r = Radius of the cone base

Table no. 2:Correlation between angle of repose andflow property

Sr. No.	ANGLE Of REPOSE (θ^0)	FLOW PROPERTY
1	<20	Excellent
2	20-30	Good
3	30-40	Passable
4	>34	Very poor

7.4.3 Bulk Density

Apparent bulk density (P_b) was determined by pouring blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined. The bulk density was calculated by using the following formula:

$$\mathbf{P_b = M/V_b}$$

Where,

P_b = Bulk Density

M = Weight of sample in gm

V_b = Final volume of blend in cm

7.4.4 Tapped Density

It is the ratio of total mass of the powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Tapping was done up to time there is no further movement of volume was noted. The tapped density was calculated by using the following formula

$$\mathbf{P_t = M/V_t}$$

Where,

P_t = Tapped Density

M = Weight of the sample in gm

V_t = tapped volume of blend in cm

7.4.5 Carr's index or % compressibility

The simplest way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I) which was calculated as follows:

$$\mathbf{I = P_t - P_b / P_t \times 100}$$

Where,

I = Carr's index or % Compressibility

P_t = Tapped density

P_b= Bulk density

Table No. 3: Relationship between % compressibility and flow ability

Sr. No.	% COMPRESSIBILITY	FLOW ABILITY
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair Passable
4	23-35	Poor
5	33-38	Very Poor
6	<40	Very Very Poor

7.4.6. Hausner ratio

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

$$\textbf{Hausner ratio} = P_t/P_b$$

Where,

P_t = Tapped density,

P_b = Bulk density

Table No. 4: Hausner's ratio as an Indicator of Powder Flow Properties

Sr. No.	Hausner's Ratio	Type of flow
1	<1.18	Excellent
2	1.19-1.25	Good
3	1.3-1.5	Passable
4	>1.5	Very poor

7.5 EVALUATION OF TABLET

The compressed tablet were evaluated for following parameters.

7.5.1 Hardness

Hardness was determined by using Monsanto hardness tester. Hardness of three tablets from each batch of different formulation was tested.

7.5.2 Friability

The friability of tablets was determined using Roche Friabilator. Olmesartan medoxomil mouth dissolving tablets were transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes i.e. 100 revolutions. The tablets were deducted and weighed again. The percentage friability was calculated by,

$$F = \frac{W_{initial} - W_{final}}{W_{final}} \times 100$$

% Friablity of tablets less than 1% is considered acceptable.

7.5.3 Thickness

Thickness was measure by Verniercalliper scale in triplicate manner.

7.5.4 Weight variation

Twenty tablets were randomly selected from each formulation and weighed individually to check for weight variation. The following percentage deviation in weight variation according to IP was allowed.

Table No. 5: Weight Variation Specification as per IP.

Average weight of Tablet	% Deviation
80 mg or less	± 10
80mg-250mg	± 7.5
250 mg or more	± 5

The total weight of Olmesartan medoxomil fast dissolving tablet was 200 mg, hence a maximum deviation of ± 7.5 % was considered.

7.5.5 Wetting Time

Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue. Wettingtime is closely related to the inner structure of the tabletsand to the hydrophilicity of the excipient. A piece of tissuepaper folded double was placed in a petri plate (internaldiameter is 10 cm) containing 10 ml of water. The tablet wasplaced on the paper and the time for complete wetting of thetablet was measured in seconds.

7.5.6 Water absorption Ratio

A small piece of tissue paper folded twice was placed in a small petridish containing 6ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then reweighed. Water absorption ratio, R was determined by using following formula were given

$$R = Wa - Wb / Wb \times 100$$

Where, Wa=The weight of tablet after water absorption,

Wb=The weight of tablet before water absorption.

7.5.7 In-vitro Dispersion time Test

In Vitro dispersion time was measured by dropping a tablet in a beaker containing 50 mlof Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected andIn Vitro dispersion time was performed.

7.5.8 Content uniformity

20 tablets were crushed and powder equivalent to 20 mg of Olmesartan medoxomil and dissolve in 100 ml of Phosphate buffer stirred and filtered. 1 ml of the solution was diluted to 10 ml with phosphate buffer pH 6.8 and the absorbance was taken at 257 nm with the help of UV Spectrophotometer. The amount of drug present in each formulation was determined by UV spectroscopy.

7.5.9 In vitro disintegration test

One tablet is introduced in to one tube of disintegration apparatus IP and a disc is added into the tube. The assembly is suspended in the beaker containingphosphate buffer pH 6.8 and the apparatus is operated until the tablet disintegrated. To be in compliance with the IP standards, Fast dissolving tablets must disintegrate within 1 minute when examined by the disintegration test for tablets.

7.5.10 Taste/ Mouth sensation

Mouth-feel is critical, and patients should receive a product that feels pleasant. One tablet from each batch was tested for the sensation by placing the tablet on the tongue. The healthyhuman volunteers were used for evaluation of mouth feel. Taste evaluation was done by apanel of 5 members using time intensity method. Sample equivalent to dose of drug was heldin mouth for 10 secs. Taste were recorded instantly and then after 10 secs, 1, 2, 4and 6minutes. Volunteer's opinion for the taste were rated by giving different score values i.e. 0 =good, 1= tasteless, 2 = slightly bitter, 3 = bitter, 4 = awful.

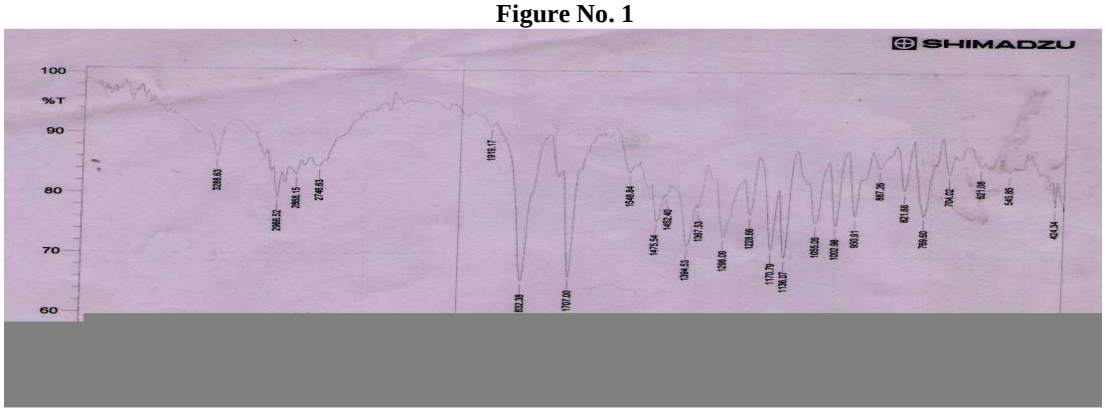
7.5.11 In-Vitro Dissolution Study

In vitro dissolution study was performed in 900 ml Phosphate buffer pH 6.8 using USP Type II (paddle) apparatus at 30 rpm for 30 minutes (37 ± 0.5^0C). Aliquots of the dissolution medium (10 ml) were withdrawn at specific time intervals and replaced immediately with equal volume of fresh medium. The samples were filtered through whatmann filter paper and analyzed for drug content by measuring the absorbance at 257 nm. Drug concentration was calculated from the standard calibration curve and expressed as cumulative percent drug dissolved. The Cumulative percentage drug release was plotted against time to determine the release profile.

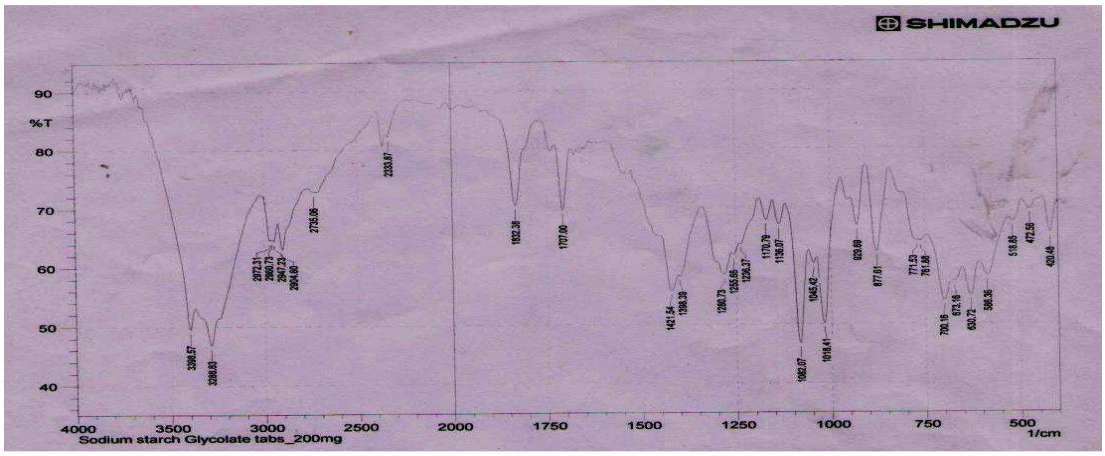
FTIR studies

The Fourier-transform infrared spectra of Olmesartan medoxomil and mixture superdisintegrantswith other excipients were obtained by using FTIR spectroscopy–5300 (Shimadzu Japan). Samples were prepared by KBr pressed pellet technique. The scanning range was 400 -4600 $cm^{-1}$and the resolution was 4 cm^{-1}. The spectra obtained are shown below:

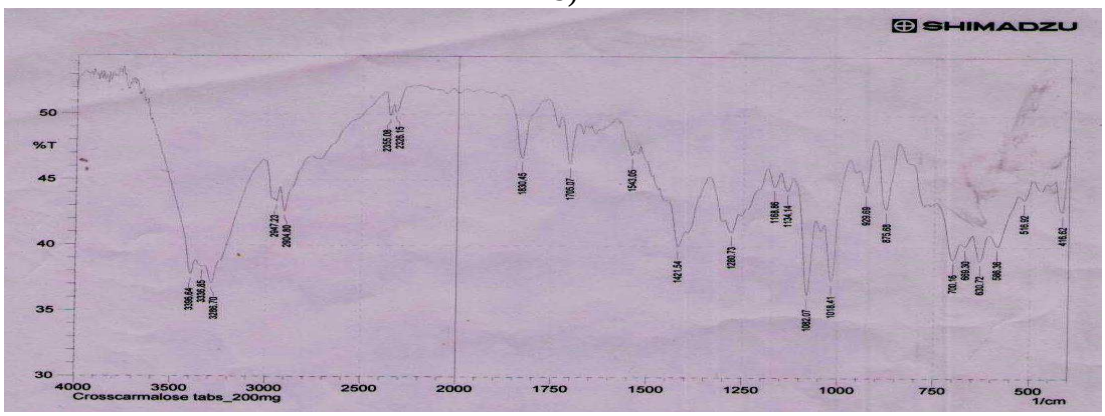
Figure No. 1



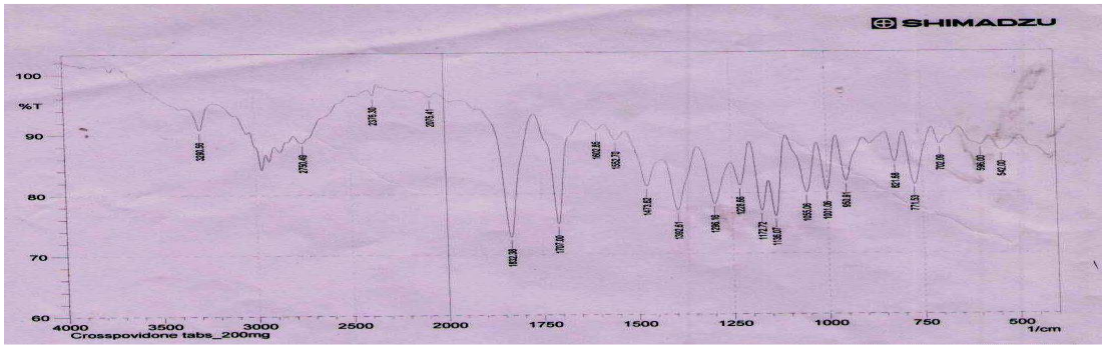
a)



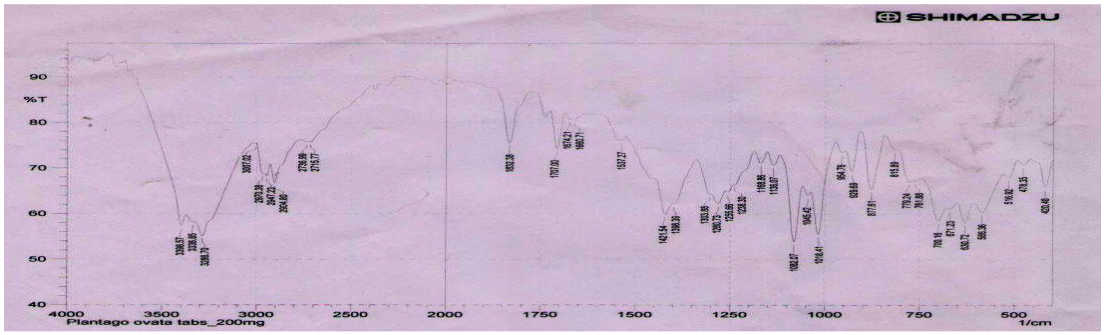
b)



c)



d)



e)

IR Spectrum of a) Olmesartan, b) F3, c) F6, d) F9 and e) F12

RESULTS AND DISCUSSION

Before preparation of tablet to make conform the physico-chemical properties and solubility of Olmesartan medoxomil are determined as shown in Table no. 6 and 7. Parameters are found to be within limit as given in Official book. FTIR studies revealed that there was no physico-chemical interaction between Olmesartan medoxomil and other excipients. The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing properties are given in Table 8. The data obtained from post-compression parameters in all the formulations, friability is less than 1%, indicated that tablets had a good mechanical resistance. Hardness of the tablets was found to be in the range of 3.1 to 3.69 kg/cm^2.Drug content was found to be in the range of 97.90 to 101.8 %, which is within acceptable limits.In vitro dispersion times were found to be in the range of 19.20 to 42.66 sec. The water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water, were found to be in the range of 55.83 to 96.60 % and 18.86 to 36.50 sec respectively are given in Table no. 10. The dissolution profiles of formulations are shown in Table no. 11. The dissolution profiles of all formulations are shows the release of drug 99 % within 30 min. The formulations F9 and F12 shows 100% drug release within 20&15 min respectively. Compare to synthetic superdisintegrantsformulations with *Plantagoovata* formulations shows faster release of drug, this is due to more swelling property of *Plantagoovata* mucilage. In case of formulation F12, the 98 % and 100 % of drug release was found within 15 and 20 min is shown in Fig. 5.

Table no. 6: Preformulation studies of Olmesartan medoxomil

EXPERIMENTAL	PROPERTY STUDY	RESULTS
Organoleptic properties	**Colour**	White to light yellowish-white powder
	Odour	Metallic
	Taste	Metallic slightly bitter
	Nature	Hygroscopic and Light sensitive
Identification of Drug Sample	**Melting Point**	177^{0}C

Table no. 7: Solubility of Olmesartan medoxomil

Water	Methanol	Phosphate buffer pH 6.8
Insoluble	Soluble	Sparingly Soluble

Table no. 8:Preformulation studies of different formulations

Formulation Code	Angle of repose* (Degree) ± SD	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Hausner,s Ratio
F1	22.33 ± 0.41	0.425	0.506	16.00	1.19
F2	22.17 ± 0.29	0.434	0.512	15.23	1.17
F3	22.45 ± 0.22	0.425	0.493	13.79	1.16
F4	21.59 ± 1.22	0.421	0.481	12.47	1.14
F5	21.34 ± 1.26	0.421	0.476	11.59	1.13
F6	21.10 ± 1.38	0.425	0.481	11.64	1.13
F7	21.87 ± 0.82	0.430	0.512	16.02	1.19
F8	22.56 ± 0.41	0.425	0.50	15.00	1.18
F9	22.01 ± 0.69	0.434	0.493	11.82	1.13
F10	22.83 ± 0.19	0.430	0.487	11.86	1.13
F11	22.82 ± 0.42	0.425	0.493	13.79	1.16
F12	22.39 ± 0.77	0.430	0.487	11.84	1.14

Table no. 9: Evaluation result of FDT's from batch F1-F12

Formulation code	Evaluation Parameters			
	Thickness ± S.D. (mm)	Avg. Weight Variation ± S.D. (mg)	Hardness ± S.D. (kg/cm^2)	Friability (%)
F1	4.24 ± 0.13	200.5 ± 0.38	3.25 ± 0.21	0.59 ± 0.02
F2	4.36 ± 0.04	201.1 ± 0.59	3.20 ± 0.16	0.52 ± 0.03
F3	4.24 ± 0.11	201.4 ± 1.51	3.69 ± 0.16	0.66 ± 0.02
F4	4.18 ± 0.08	200.1 ± 1.28	3.65 ± 0.27	0.48 ± 0.01
F5	4.12 ± 0.13	200.2 ± 0.94	3.25 ± 0.16	0.56 ± 0.03
F6	4.22 ± 0.09	199.6 ± 1.14	3.35 ± 0.16	0.54 ± 0.07
F7	4.28 ± 0.09	200.2 ± 0.83	3.38 ± 0.16	0.40 ± 0.02
F8	4.17 ± 0.08	200.4 ± 1.14	3.10 ± 0.16	0.59 ± 0.01
F9	4.30 ± 0.16	201.0 ± 0.70	3.30 ± 0.16	0.66 ± 0.02
F10	4.18 ± 0.18	200.6 ± 0.89	3.36± 0.16	0.30 ± 0.21
F11	4.03 ± 0.11	201.6 ± 1.14	3.45 ± 0.16	0.36 ± 0.05
F12	4.11 ± 0.14	200.2 ± 0.83	3.65 ± 0.16	0.29 ±0.01

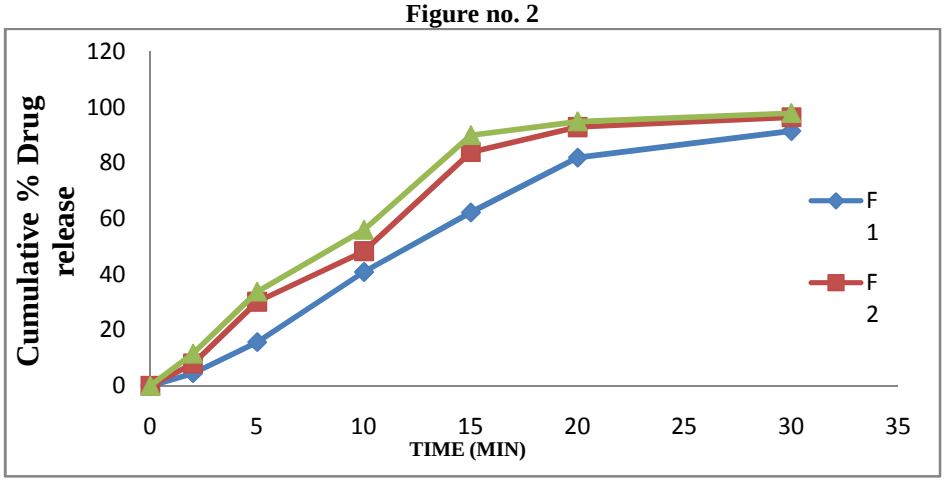
Table no. 10: Evaluation results of FDT's from batch F1-F12

Formulation Code	Evaluation parameters				
	Dispersion Time (sec)	Disintegration Time (sec)	Wetting time (sec)	Water absorption ratio (%)	Content of active ingredients %
F1	42.66 ± 4.10	48.33 ± 1.24	36.50 ± 0.05	55.83 ± 0.76	98.48 ± 0.82
F2	39.33 ± 0.94	42.00 ± 1.63	32.50 ± 0.45	66.13 ± 1.04	99.25 ± 1.76
F3	35.66 ± 1.63	32.33 ± 2.86	27.53 ± 0.25	71.93 ± 1.13	100.2 ± 1.62
F4	39.16 ± 1.04	41.33 ± 2.49	32.46 ± 0.56	69.60 ± 0.36	99.15 ± 1.58
F5	30.50 ± 1.32	34.66 ± 1.15	27.90 ± 0.55	75.53 ± 2.50	97.90 ± 1.66
F6	24.50 ± 0.86	28.33 ± 1.52	23.00 ± 0.52	82.86 ± 0.41	99.12 ± 1.58
F7	33.66 ± 0.76	36.16 ± 1.60	30.63 ± 0.51	76.06 ± 1.18	99.81 ± 0.25
F8	23.76 ± 0.25	29.33 ± 1.52	24.00 ± 0.45	88.99 ± 0.59	99.31 ± 0.98
F9	21.90 ± 0.45	24.66 ± 3.06	21.10 ± 0.52	94.60 ± 1.21	101.8 ± 0.52
F10	30.73 ± 0.76	36.33 ± 2.08	29.16 ± 0.80	78.55 ± 0.99	98.30 ± 1.52
F11	23.61 ± 0.44	27.33 ± 1.52	23.66 ± 0.30	91.03 ± 0.51	97.95 ± 1.84
F12	19.20 ± 0.26	22.16 ± 1.25	18.86 ± 0.51	96.60 ± 1.08	99.60 ± 0.82

Table No. 11. Percent Cumulative Drug Release Profile of all formulations (F1-F12)

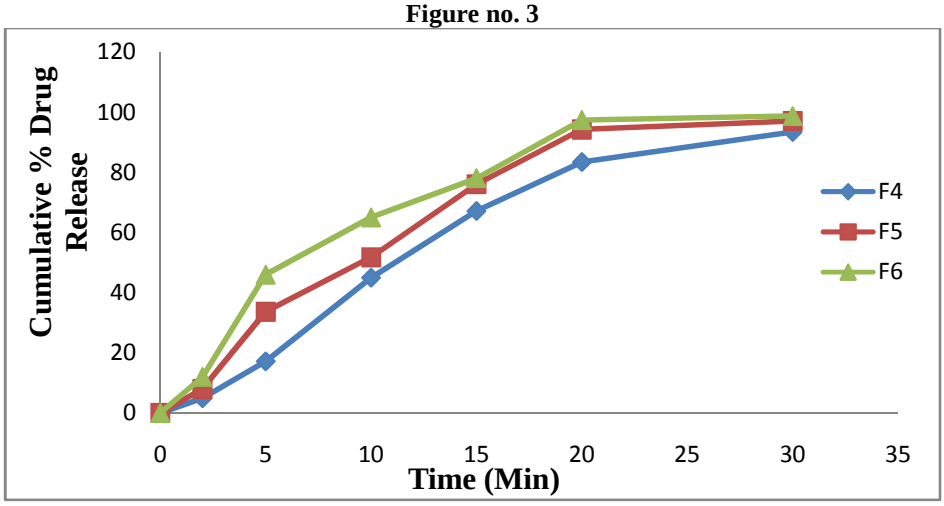
Formulations	Cumulative Percent Drug Release Time (min.)						
	0	**2**	**5**	**10**	**15**	**20**	**30**
F1	0.000	4.520	15.668	40.881	62.243	81.942	91.487
F2	0.000	7.976	30.182	48.354	83.902	92.896	96.409
F3	0.000	11.589	33.789	55.996	89.946	94.887	97.885
F4	0.000	4.833	17.128	44.957	67.112	83.436	93.456
F5	0.000	7.942	33.617	51.750	76.011	94.223	97.065
F6	0.000	11.936	45.983	64.997	78.026	97.334	98.705
F7	0.000	6.726	35.263	56.336	83.230	95.385	98.213
F8	0.000	11.068	42.548	65.676	84.742	97.543	99.197
F9	0.000	13.847	56.289	71.790	88.603	99.036	99.525
F10	0.000	8.463	35.334	66.016	80.208	98.373	99.197
F11	0.000	11.242	49.418	77.734	95.823	99.368	99.535
F12	0.000	13.847	51.308	80.960	98.341	100.032	100.181

Figure no. 2



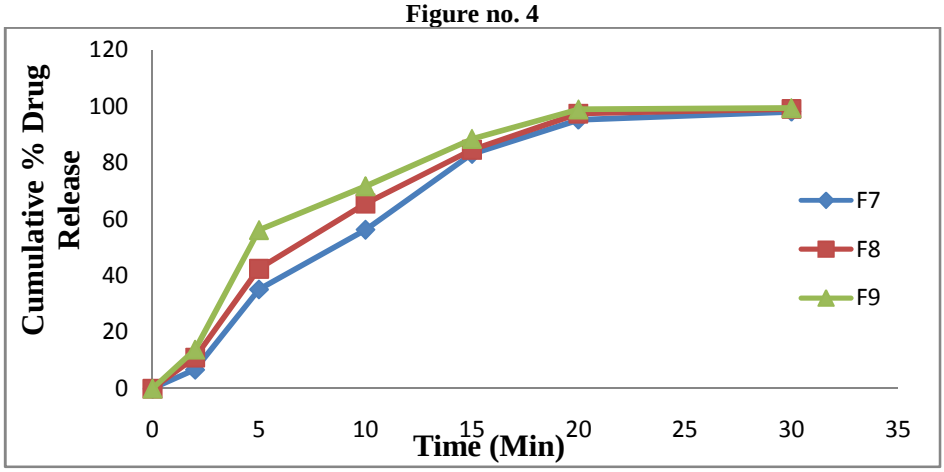
Cumulative % Drug release of F1, F2 and F3 Batches.

Figure no. 3



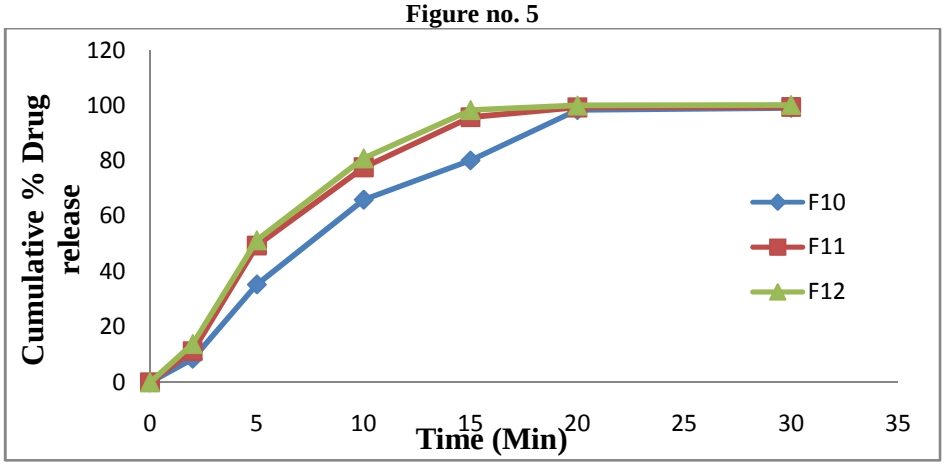
Cumulative % Drug release of F4, F5 and F6 Batches.

Figure no. 4



Cumulative % Drug release of F7, F8 and F9 Batches.

Figure no. 5



Cumulative % Drug release of F10, F11 and F12 Batches.

CONCLUSION

The present work revealed that the natural superdisintegrant, *plantagoovata*mucilage showedbetter disintegrating and dissolution property than the most widely used syntheticsuperdisintegrants in the formulation of fast dissolving tablets

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