Comparative Study on Effect of Natural and Synthetic Super disintegrants in the Formulation of Fast Dissolving Tablets containing Promethazine Hydrochloride

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Abstract

Objective: To formulate promethazine HCl as fast dissolving tablets (FDTs) by using different natural and synthetic superdisintegrant.

Methods: An attempt was made to extract the *Plantago ovata* (ispaghula) mucilage, *Aegle marmelos* (bael) mucilage, dehydrated banana powder and evaluated it for various physicochemical characterizations. The swelling index, melting point, moisture absorption, loss of drying, stability, pH was determined respectively. FDTs of promethazine hydrochloride was formulated by direct compression technique using different concentration (5-15%) of *Plantago ovata* (ispaghula) mucilage, *Aegle marmelos* (bael) mucilage, dehydrated banana powder as natural superdisintegrant, and compared with renowned and sodium starch glycolate as synthetic superdisintegrant. The formulated tablets were evaluated for post-compression parameters like thickness, hardness, friability, weight variation, wetting time, content of active ingredient (%), in-vitro disintegration, in-vitro dispersion, and in-vitro dissolution**.**

Result: The formulated tablets were evaluated for various physical tests like weight variation, friability, hardness, thickness and results complied with the limits. Among all the formulations F3 containing *Plantago Ovata* with a concentration of 15% produce the least disintegrating time 18.00 sec and dispersion time 29.00 resulting in higher drug release rate 95.43% in 12 minutes. Hence it is considered an optimized formulation. The present study revealed that the *Plantago ovata* as a natural superdisintegrant showed better disintegrating properties than the most widely used synthetic superdisintegrant like sodium starch glycolate in the formulation of FDTs.

Conclusion: The result suggested that the *Plantago ovata* act as a good super disintegrating agent.

Keywords: Promethazine HCl, super disintegrants, fast dissolving tablets, direct compression, *Plantago Ovata,* sodium starch glycolate.

Introduction:

The majority of dosage forms are administered by the oral route, which is the preferred and most common one. It develops most preferred method of administration due to the benefits it provides, including safety, convenience, pain avoidance, and improved patient compliance [1]. Almost all of oral medicinal dose forms, like regular tablets and capsules, are designed to be ingested whole or chewed. Children, bedridden patients, and elderly patients have trouble ingesting these dosage forms as a result. Orally disintegrating tablets, which dissolve or disperse in saliva within a few seconds without water, have been developed as novel drug delivery techniques to solve this issue.

United States of America Food and Drug Administration (USFDA) defines FDT as "A solid dosage form containing medicinal substances or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon a tongue" [2-4].

Some of the major ingredients are encapsulated into the tablet formulation which helps to break up the tablet or capsule into smaller fragments called as slugs and thus are named as Super disintegrants [5]

Therefore, the present study deals with a novel idea of preparing superdisintegrant from Aegle Marmelos (Bael fruit) gum. Aegle Marmelos (Indian Bael) fruit contains a gummy material containing highly branched nature of Terminal units of Galactose, Arabinose, Rhamnose and Galacturonic acid.[6] The carboxylic nature of the gum is responsible for the disintegrating activity. Aegle marmelos is used as an antifertility agent, to cure diabetes and cholesterol levels. This novel idea of using the natural superdisintegrant is helpful in increasing rate of disintegration by rapid drug release. Moreover, rate of drug absorption as well as bioavailability also enhances. Some of the known natural super disintegrants contain Isapghula Husk Mucilage (Plantago ovata) Aloe Vera, Guar gum, Lepidiumsativum mucilage, Hibiscus Rosa Sinensis and Fenugreek fruit mucilage [7,8]

Promethazine HCl, the active material used in the present study, is a H1 receptor antagonist of the phenothiazine class, and serves as one of the most important prophylactics against motion

sickness. In addition to the general disadvantages of tablets named above, a major drawback of the Promethazine HCl therapy, in the form of conventional tablets, is the necessity of drug administration more than 1 h before the commencement of the actual embark [9]. This may in some cases cause unnecessary medication, as motion sickness is not absolute, or give rise to therapy failure.

Therefore, the purpose of the present study was to develop a fast-dissolving tablet of promethazine hydrochloride (PM-HCl) by direct compression and to mask the intensely bitter taste of the PM-HCl. Such tablet should disintegrate rapidly in the saliva without need of water (Traveller Friendly Drug Delivery System), release the drug instantly for immediate therapeutic effect, and be of acceptable taste.

Materials and method:

Promethazine HCl (Akums Drug Pvt. Ltd. Haridwar, U.K. India), Sodium Starch Glycolate (Loba chemei. Pvt. Ltd. Mumbai, Maharashtra), Microcrystalline cellulose (Loba chemei. Pvt. Ltd. Mumbai, Maharashtra), Mannitol (Loba chemei. Pvt. Ltd. Mumbai, Maharashtra), Lactose (Loba chemei. Pvt. Ltd. Mumbai, Maharashtra), Magnesium stearate (Loba chemei. Pvt. Ltd. Mumbai, Maharashtra), Talc (Loba chemei. Pvt. Ltd. Mumbai, Maharashtra). other reagents and chemicals used were of analytical grade

Isolation of natural polymers:

Isolation of Plantago ovata mucilage: The seeds of Plantago ovata were soaked in distilled water for 48 hours and boiled for a few minutes. The collected material was squeezed through muslin cloth to separate them. Then, an equal volume of acetone was added to the filtrate for the precipitation of the mucilage.

The separated mucilage was dried at 40C in a tray dryer. The dried mucilage was powdered and sieved in sieve no # 80. The resultant powder was stored in a desiccator and used for the present study [10,23].

Isolation of Aegle Marmelos mucilage: For the isolation of mucilage, fruits/seeds were soaked in distilled water for 48 h and then boiled for 1 h for complete release of mucilage into water. The material was filtered by squeezing in a muslin cloth to remove marc.

Then, an equal volume of acetone was added to filtrate to precipitate the mucilage. The mucilage was separated and dried in oven at a temperature [11].

Isolation of dehydrated banana powder: The collected fresh whole bananas were cleaned for any debris and weighed. The skin peeled bananas were dipped in ethanol in 5 minutes. Then banana was weighed and squashed to paste, this paste was added with citric acid (2-3%) to remove the sticky nature. Then water is separate by centrifugation and processing. The pressed mass is subjected to drying in tray-dryer. The dried substances were milled and screened in sieve (#80) to get fine powder [12,24].

Preparation of preliminary tablet: Fast disintegrating tablet of promethazine HCl were prepared by direct compression method because of their several advantages:

1. Easiest way to manufacture tablets.

2. Use of conventional equipment.

3. Use of commonly available excipient.

4. Limited number of processing steps.

Physicochemical characterization of natural super disintegrants:

The purified and dried extracted gum powder was evaluated for its micrometric properties, viscosity, solubility studies, swelling index and loss on drying.

Swelling index:

The study was carried out by using a 100 mL stoppered graduated cylinder. The initial bulk volume of 1 g of Powder was noted. Water was added in sufficient quantity to ensure 25 mL of uniform dispersion by vigorously shaking every 10 min for 1 h and then allowed to stand for 24 h. The dispersion was stored at room temperature and the sediment volume of the swollen mass was measured after 24 h

Swelling index=100*(V2-V1/V1)

Where, V1=Initial volume of material before hydration; V2=Volume of hydrated material

Loss on drying:

The loss on drying technique is used to determine high levels of moisture or solvents present in the sample. The material sample was weighed (W1) and heated in an oven for 2 h. It was cooled in the dry atmosphere of desiccators and then finally weighed (W2).

% Loss on drying=[(W1-W2)/W1]100

Where, W1=Initial weight of the powder; W2=Final weight of the powder.[13]

Table 1: Physicochemical characterization of natural super disintegrants

Method Employed	Plantago Ovata (Ispaghula)	Dehydrated Banana Powder	Aegle Marmelos (Bael Fruit)
Swelling index	65± 1.521	57 ± 1.521	63± 1.521
Capillary fusion method	139 ± 1.121˚C	88 ± 1.023ºC	93± 1.527ºC
Moisture Absorption	2.76 ± 0.7843%	2.89± 0.7443%	2.67± 0.7827%
Loss of drying	1.79 ± 0.3570%	0.991± 0.0013%	7.1± 0.1231%
Stability (ºC)	137˚C	112ºC	129ºC
pH	5.9 ± 0.021	7.16 ± 0.023	6.3± 0.032

Determination of λmax:

A solution of Promethazine HCl containing conc. 10µg/ml was prepared in distilled water and UV spectrum was taken using Shimadzu (UV-1800) spectrophotometer. The solution was scanned in the range of 200-400 nm.

Derivation of drug spectrum: The prepared stock solution of promethazine HCl (10µg/mL) in Distilled. water represented maximum wavelength peak (λmax) at 247 nm and absorbance at λmax was found to be 0.8717. The peak report after the practical assessment.

Procedure for Calibration of Promethazine HCl in distilled water:

Preparation of stock solution:

Promethazine hydrochloride 100 mg was dissolved in water 100 ml (1000µg/ml) Stock solution I. From this solution 10 ml was pipetted and diluted with water up to 100ml (100µg/ml Stock solution II was prepared.

Preparation of sample solution:

From Stock solution II 1 ml was pipetted and diluted with water up to 10ml (10µg/ml).

From Stock solution II was carried out taking 0.2, 0.4, 0.6, 0.8, 1 ml and made up to 10 ml to obtain the concentration of 2, 4, 6, 8, 10 µg/ml respectively. The absorbance was measured at 247 nm against the respective blank solution using UV visible spectrophotometer 1800. The standard

curves were plotted by putting the known concentration on X- axis and the obtained absorbance on Y- axis.

Formulation of promethazine hydrochloride fast dissolving tablets:

In present study, 12 different formulations (F1-F12) of drug-excipient blend were prepared. Fast dissolving tablets of Promethazine Hydrochloride were prepared by Direct compression method, by using *Plantago Ovata*, *Aeglo Marmelos*, Dehydrated Banana Powder as natural superdisintegrant and Sodium Starch Glycolat*e* as synthetic superdisintegrant in different ratios and directly compressible mannitol, lactose as diluents to enhance the mouth feel. Magnesium stearate and talc as a lubricant, Microcrystalline cellulose as a binder.

Table 2: Formulation of promethazine HCl fast dissolving tablets prepared by direct compression method

Ingredients (mg)	Formulation code and quantity											
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Promethazine HCl	25	25	25	25	25	25	25	25	25	25	25	25
***Plantago Ovata* seed mucilage**	10	20	30	-	-	-	-	-	-	-	-	
***Aegle Marmelos* Mucilage**	-	-	-	10	20	30	-	-	-	-	-	
Dehydrated Banana Powder	-	-	-	-	-	-	10	20	30	-	-	-
Sodium Starch Glycolate	-	-	-	-	-	-	-	-	-	10	20	30
Microcrystalline Cellulose	95	85	75	95	85	75	95	85	75	95	85	75
Mannitol	50	50	50	50	50	50	50	50	50	50	50	50
Lactose	10	10	10	10	10	10	10	10	10	10	10	10
Magnesium Stearate	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
Total weight of each tablet	200	200	200	200	200	200	200	200	200	200	200	200

All the ingredients were passed through #60 mesh separately. The drug and mannitol were mixed by small portion of both each time and blending it to get a uniform mixture and kept aside.

Then, the ingredients were weighed and mixed in geometrical order and tablets were compressed at 8mm size to get a tablet of 200 mg weight using a tablet machine (Karnawati 8 station). The tablets were prepared according to the formulae shown in table 2[14]

Evaluations studies of tablets:

Pre-Compression Studies: [15-19]

Bulk and tapped densities:

Weighed quantity of powder blend (M= 10 g) was taken in a graduated cylinder and the bulk volume (Vb) was determined. The measuring cylinder containing known mass of powder blend was tapped for fixed number of times with an interval of 2 seconds between each tap (50 times)

and the final tapped volume (Vt) occupied in the cylinder and the weight of the blend (M = 6 g) was noted. Bulk densities and tap densities were calculated as follows**:**

$$\textit{Bulk density} = [M/Vb]\ g/mL$$

$$\textit{Tapped density} = [M/Vt]\ g/mL$$

Angle of repose:

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The angle of repose determination of drug-excipient blend was carried out by fixed funnel method. A sufficient amount of blend (7g) was poured through a funnel which was fixed at an appropriate height to form a cone. The tip of the funnel was held close to the growing cone and slowly raised as the pile grew in order to minimize the impact of falling particles. The height and the radius of the formed cone was measured. The angle of repose was calculated as follows: -

$$\tan\theta = h/r\ ,\ \text{so}\ \theta = \tan^{-1} h/r$$

Where θ = angle of repose, h= height of pile, and r = radius of the base of pile.

Carr's compressibility index: It is the indicator of powder compressibility and flowability. It is the measure of cohesiveness, density indices, and particle size of a powder material.

The less compressible a material, the more flowable it is. It is calculated as follows:

***Compressibility Index* = [(Tapped density- Bulk density/ Tapped density) x 100] %**

Hausner's ratio:

It is an indirect index of ease of powder flow. It is calculated as follows:

***Hausner's ratio* = Tapped density / Bulk density**

Post Compression Studies [20-22]

Evaluation of tablets All the tablets were evaluated for different physical parameters as Organoleptic properties, weight variation, hardness, friability, disintegration time, wetting time, drug content and in vitro dissolution study.

Thickness:

The thicknesses of the formulated tablets were measured by using Vernier callipers.

Weight variation:

The formulated tablets were tested for weight uniformity. For these 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet's weight was then compared with average weight to ascertain whether it was within permissible limits or not.

% Weight variation = Average weight Average Weight-Individual weight ×100

Hardness:

The hardness of tablets was measured using Pfizer type hardness tester. Three tablets were selected from each formulation randomly and their hardness was measured. The mean SD of hardness values were calculated.

Friability:

The friability of the tablets was determined by using Roche friabilator. The weight of 20 tablets (initial weight) was subjected to friabilator at 25 revolutions per 4 min. Tablets were then dedusted, reweighed (final weight) and percentage loss was calculated.

Friability is obtained by the following formula

% Friability = Initial weight Initial weight-Final weight ×10

Table 3: Pre-compression parameter of formulation prepared by direct compression method

Formulation code	Angle of repose (º)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio
F1	28.02±1.64	0.796±0.026	0.859±0.015	12.81±1.15	1.19±0.01
F2	29.13±1.73	0.743±0.002	0.832±0.008	14.91±1.71	1.14±0.04
F3	27.32±0.69	0.776±0.010	0.734±0.022	15.65±1.15	1.23±0.03
F4	25.88±1.04	0.872±0.034	0.812±0.010	10.15±1.40	1.13±0.02
F5	23.77±0.63	0.802±0.017	0.898±0.007	12.87±1.43	1.17±0.04
F6	24.13±2.73	0.782±0.011	0.822±0.010	11.56±0.63	1.19±0.04
F7	23.61±0.73	0.851±0.013	0.902±0.008	11.32±1.05	1.16±0.03
F8	24.54±1.09	0.789±0.021	0.876±0.007	14.14±0.93	1.18±0.02
F9	25.16±0.35	0.661±0.030	0.826±0.013	11.36±0.59	1.22±0.03
F10	26.45±0.76	0.726±0.002	0.798±0.017	10.87±0.80	1.19±0.04
F11	29.23±0.64	0.798±0.009	0.857±0.011	11.38±0.98	1.21±0.02
F12	30.31±0.70	0.805±0.004	0.848±0.076	12.30±0.80	1.20±0.04

Table 4: Organoleptic Characteristics of formulated tablets

Characteristic	Description
Appearance / Texture	Smooth and clean evenly coloured tablets
Colour	Cream
Shape	Circular
Odor	Faint smell
Taste	Appreciably sweet

Table 5: Post-compression parameters of formulated tablets

Formulation code	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight variation (mg)
F1	2.24±0.01	3.61±0.38	0.59±0.043	198.23 ± 0.38
F2	2.43±0.07	3.40±0.33	0.47±0.014	197.24 ± 0.27
F3	2.58±0.02	3.13±0.65	0.46±0.024	200.60 ± 0.67
F4	2.32±0.05	3.21±0.25	0.44±0.039	198.12 ± 1.18
F5	2.65±0.01	3.24±0.31	0.54±0.015	199.10 ± 0.62
F6	2.87±0.05	3.34±0.72	0.52±0.039	202.60 ± 0.75
F7	2.43±0.05	3.22±0.22	0.66±0.045	201.03 ± 1.18
F8	2.21±0.04	3.29±0.30	0.58±0.010	199.75 ± 1.10
F9	2.52±0.03	3.10±0.38	0.60±0.035	199.86± 1.13
F10	2.49±0.06	2.86±0.35	0.54±0.011	200.46± 1.16
F11	2.62±0.05	3.26±0.70	0.68±0.19	198.86± 1.58
F12	2.32±0.03	3.88±0.25	0.70±0.011	199.22± 0.65

In vitro disintegration test:

In vitro disintegration time was determined by using disintegration test apparatus without a disk for six tablets. The disintegration medium was 900 mL of distilled water kept at (37.0±0.5) °C and stirred at a rate of (30±2) r/min. The time was measured in seconds for complete disintegration of the tablet with no palpable mass remaining in the apparatus. The test was carried out in triplicate.

In-vitro dispersion time:

Three tablets from each formulation were randomly selected and a dispersion time study was performed. Tablets were separately added to 10 ml of water and the time required for complete dispersion was measured.

Wetting time and water absorption ratio:

A double folded tissue paper was placed in a Petri dish. 6 mL of water containing a water-soluble dye (eosin) was added to the Petri dish. A tablet (pre-weighed) was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablet

was noted as the wetting time. The wetted tablet was then weighed and the water absorption ratio (R) was determined by using the equation:

$$R=100\ (Wb-Wa)/Wb$$

Where Wa and Wb are the weights of the tablet before (dry weight) and after water absorption (wet weight) respectively.

Content of active ingredient: Five tablets from each batch were weighed and crushed with a pestle in a mortar. The fine powder was weighed to obtain 100mg and transferred to 250 ml conical flask containing 100 ml of 0.1 N HCl stirred for 45 min in a sonicator. The solution was filtered dilutions were prepared and analyzed by UV spectrophotometer at 247 nm and drug content was determined. As per I.P., out of 10 tablets, not more than one tablet should deviate outside range 90-110% and none outside 85-115% of the average value shown as table 7

Table 6: Water absorption ratio, Wetting time, In-vitro Dispersion and In-vitro Disintegration time

Formulation code	Water absorption ratio (%)	Wetting time (sec)	In-vitro Dispersion time (sec)	In-vitro Disintegration time (sec)
F1	89.35±2.94	34.00±3.00	37.00±4.00	23.00±1.00
F2	87.34±2.54	26.00±2.00	34.00±4.00	20.00±2.00
F3	94.53±3.00	21.00±1.00	29.00±3.00	18.00±3.00
F4	80.15±1.98	32.00±3.00	31.00±1.00	24.00±3.00
F5	83.20±2.30	29.00±3.00	35.00±3.00	22.00±2.00
F6	89.11±2.90	25.00±2.00	38.00±1.00	20.00±1.00
F7	87.34±2.45	38.00±3.00	33.00±1.00	27.00±3.00
F8	90.44±3.01	32.00±2.00	39.00±2.00	24.00±1.00
F9	86.15±2.01	30.00±3.00	34.00±4.00	22.00±1.00
F10	89.34±2.80	34.00±3.00	36.00±3.00	23.00±2.00
F11	91.56±3.00	29.00±2.00	31.00±4.00	21.00±1.00
F12	93.17±3.05	26.00±1.00	30.00±2.00	19.00±1.00

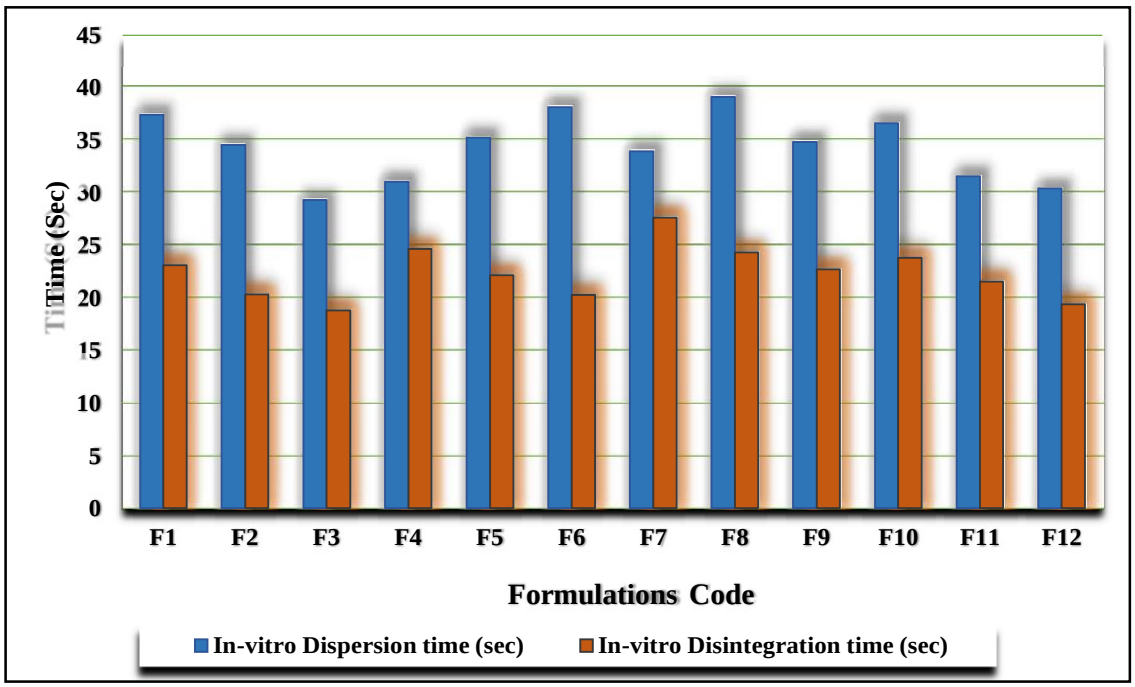

Fig.1 In-vitro Dispersion and In-vitro disintegration time

Table 7: Content of active ingredient (%)

Formulation code	Content of active ingredient (%)
F1	98.04±0.66
F2	97.23±0.26
F3	100.78±0.16
F4	99.91±0.56
F5	99.57±0.47
F6	98.83±0.72
F7	97.56±0.38
F8	100.23±0.28
F9	98.56±0.81
F10	99.35±0.28
F11	99.87±0.86
F12	98.69±0.38

In-vitro dissolution or % cumulative drug release:

The dissolution rate was studied by using USP type II paddle dissolution apparatus, in 900 mL of phosphate buffer 0.1N HCl at (37.0±0.5) °C at 50/min. The aliquot of the dissolution medium was withdrawn at regular time intervals and the same volume of pre-warmed (37.0±0.5) °C fresh dissolution medium was replaced. The samples were filtered and drug content of Promethazine HCl in each sample was analyzed after suitable dilution by Shimadzu UV-spectrophotometer 1800 at 247 nm.

Table 8: % Cumulative drug release

Formulations code	Time (min)					
	2	**4**	**6**	**8**	**10**	**12**
F1	45.72±1.23	59.98±0.76	72.50±0.68	79.39±0.57	84.92±0.44	91.43±0.98
F2	42.63±1.12	56.80±0.74	68.47±0.62	75.65±0.71	89.78±0.81	91.17±0.61
F3	41.43±0.43	47.98±0.53	62.12±0.81	79.43±0.95	88.90±1.00	95.43±1.10
F4	34.67±0.23	46.12±0.67	59.54±0.65	71.78±0.78	80.78±1.15	83.39±1.30
F5	36.19±0.34	44.78±1.45	61.63±1.00	74.20±1.32	82.20±0.78	84.82±1.34
F6	36.46±0.87	44.87±1.15	58.40±0.37	71.65±0.62	82.87±0.47	87.12±0.31
F7	37.23±0.76	46.98±0.43	59.80±1.32	73.54±1.12	82.85±0.63	86.47±0.57
F8	35.28±0.73	47.32±0.54	60.22±0.32	73.29±0.65	84.65±1.34	89.17±1.25
F9	37.13±1.00	43.76±0.62	59.98±0.91	72.50±0.47	84.43±1.27	91.27±0.61
F10	38.28±0.40	49.32±0.67	66.65±1.00	72.22±0.37	79.67±0.78	85.65±1.32
F11	34.86±0.51	46.19±1.32	62.32±0.78	74.63±0.23	83.20±0.28	92.87±0.87
F12	39.34±0.54	45.72±0.62	59.65±0.091	71.32±0.43	86.41±1.32	92.34±1.12

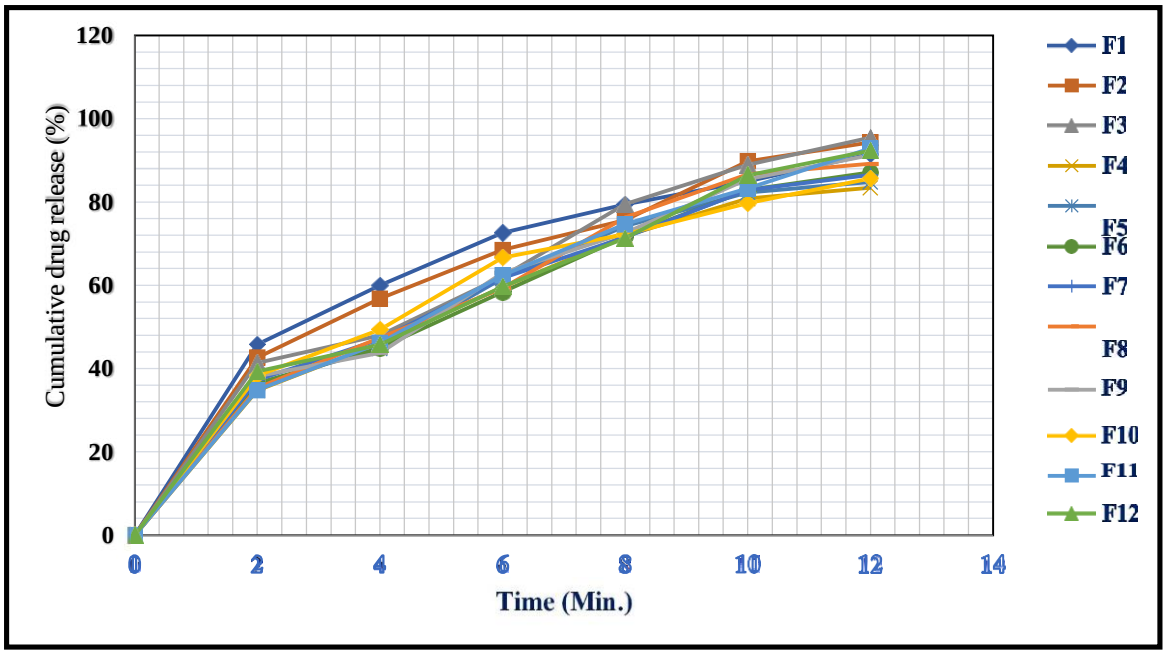

Fig.2 % Cumulative drug release

Results:

The bulk density and tapped density of powder blend has been evaluated. The angle of repose for the entire formulation blend was found to be in the range 23.61 to 30.31. formulation with natural super disintegrants (Plantago ovata, Aegle Marmelos, Deh. Banana powder) (F1-F12) as a disintegrants show angle of repose value ≤26.45-30.5. Hausner's ration was found to be in the range 1.13-1.23 and that indicated that all formulation has good flow properties. The batches showed low hardness 2.86 and higher 3.81. F12 show higher friability and F4 show low friability (0.46%). All parameter shows weight variation, thickness, disintegration time (sec) within standard limit. All formulation was subjected to dissolution. From all the above observation it was concluded that the formulation F3 contain Plantago ovata 15% found to be better formulation in term of rapid dissolution and but maximum % drug release was found to be 95.43% of formulation F3 with Plantago ovata (15%). Hence it is considered as optimized formulation. The present study revealed that the Plantago ovata as a natural superdisintegrant showed better disintegrating property than the most widely used synthetic superdisintegrant like sodium starch glycolate in the formulation of FDTs.

Conclusion:

The selection of an ideal optimized batch of fast dissolving tablets was made after consideration of evaluation parameter by dissolution study, disintegrating time and wetting time. The batch F3 fast dissolving tablets was selected as an ideal batch as its dissolution, disintegration time

and wetting time were best among all the formulation. It showed the maximum In-vitro cumulative % release of drug 95.43%.

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