European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 07, Issue 09 , 2020

USE OF NATURAL SUPERDINTEGRANTS IN FORMULATIONOF FAST DISINTEGRATING TABLET OF ATENOLOL

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ABSTRACT:

The fundamental idea in the development of FDT is to use superdisintegrants which help tablet to immediately disintegrate when place on tongue and allow to release the drug into saliva. Through the application of superdisintegrants, fast dissolving tablets are swiftly dissolved or disintegrated. The solubility speed of the drug product impacts the absorption rate. The faster the medication dosage form dissolves in solution, the faster the clinical action is absorbed and started. In FDT, ideally a drug or dosage form should dissolve or disintegrate within 60 seconds in the saliva. The goal of this study was to use natural disintegrants to make a fast-disintegrating tablet of Atenolol. Microcrystalline cellulose was used as a diluent, aspartame was used as a sweetener, and Natural super disintegrant was used to make the tablets. Isapghula mucilage and banana powder were utilised as superdisintegrants in this investigation. In this formulation, natural superdisintegrant were employedin 2%, 4%, 6%, and 8% concentration. Based on the findings, it can be stated that the tablet formulation containing 6% Isapghula mucilage (i.e., 12 mg in each tablet, formulation code FI3) and 8% of banana powder (i.e., 16 mg in each tablet, formulation code FB4) had a faster and higher drug release viz. 98.02% and 96.75% respectively during the in-vitro dissolution study.

Keywords: Atenolol, Banana powder, Fast disintegrating tablet, Isapghula mucilage, Natural superdisintegrant.

I. INTRODUCTION:

As a new medicine delivery technology, fast disintegrating tablets (FDTs) are gaining popularity. When come in contact with saliva in oral cavity these dosage forms, dissolve or disintegrate within a minute without the use of water or chewing (Prakash et al., 2011). The

fundamental technique in developing FDT is the use materials such as carboxy methyl cellulose, sodium starch glycolate, polyvinylpyrollidone, that immediately decompose the pill after putting on the tongue, releases the medication into the saliva. FDTs are helpful in delivering drugs to children and the elderly (Gupta et al., 2014).

Fast disintegrating drug delivery system (FDDS) combines the benefits of both liquid and traditional tablet formulations while also providing additional benefits over both traditional dose forms. They combine the ease of ingesting of a tablet formulation with the convenience of a liquid format (Masih et al., 2017). FDDS enables far more precise dosage than the principal oral liquid alternatives. Patients who are dysphasic, geriatric, paediatric, travelling, or psychotic will benefit from this part of the formulation. Those who are unable or unwilling to consume traditional oral formulations.

Fast dissolving tablets (FDTs), which dissolve in the mouth without chewing and require additional water consumption, have gotten a lot of press in the recent decade. The term orodispersible tablet was recently coined by the European Pharmacopoeia to describe a tablet that disintegrates or disperses in the mouth in less than 3 minutes before swallowing (Kumar et al., 2014). Patients can easily consume such a tablet since it disintegrates into smaller granules or melts in their tongue from a hard solid gel-like structure. It might take anywhere from a few seconds to nearly a minute for good FDT to disintegrate (Preis, 2015). Neuroleptics, Cardiovascular, Analgesic, and Antiallergic drugs are all good candidates for this system. When a tablet is placed on the tongue, it quickly disintegrates, releasing a medication that disperses or dissolves in the saliva. As a result, the medicine has a faster start of action and a higher bioavailability than traditional tablet dose forms. FDTs are manufactured using a variety of technologies, all of which are based on enhancing porosity in the tablet by adding superdisintegrants or water-soluble excipients (Hirani et al., 2009).

Oral administration is widely recognised, accounting for 50-60% of all dose forms, and is also the most widely utilised due to a variety of benefits including stability, ease of administration, accurate dosage, self-medication, and patient compliance. As a result, the most prevalent formulations are oral solid dosage formulations (Bennadi, 2013).

Superdisintegrants are an agent that are commonly used in tablet formulations to help break apart the compacted mass into primary particles, allowing the active components to dissolve or release more easily when the tablet is placed in a fluid environment. They support the tablet matrix's moisture penetration and dispersion (Pahwa and Gupta, 2011)The main function of disintegrant is to counteract the tablet binder's efficiency and the physical forces that act during compression to shape the tablet. To improve disintegration processes, new materials known as "superdisintegrants" have recently been developed. Another type of superabsorbing material with custom-made swelling qualities is superdisintegrants. These materials are designed to swell quickly rather than absorb large amounts of water or aqueous fluids (Markl and Zeitler, 2017). They are physically dispersed throughout the matrix of the dosage form and expand when exposed to moisture. These new drugs dissolve more quickly and have greater mechanical strength at lower concentrations. About 1-10 percent by weight concentration of superdisintegrant is usually incorporated in tablet to make it to fast disintegrating tablet. Effective superdisintegrants increase the compression and compatibility of high-dose medication formulations without affecting mechanical resistance. Their particles are small and permeable, enabling them, without leaving a discomfort or a gelling, to dissolve rapidly in the tongue (Bhowmik et al., 2018).

II. MATERIAL AND METHODS:

Materials:

Atenolol was procured as a gift sample from Shreya life sciences Pvt. Ltd. Aurangabad, Maharashtra. S.D. Fine Chemicals provided the sodium starch glycolate (SSG) and

microcrystalline cellulose (MCC). ICPA Health Care Products Ltd., Ankaleshwar, Gujarat, provided a gift sample of crospovidone, immediately compressible mannitol. Navketan Pharma, Aurangabad, Maharashtra, provided magnesium stearate as a gift sample. Dagdu Teli Chandwadkar Trading Company in Nashik, Maharashtra, provided the isapgol. A genuine fruit vendor sold me a fresh banana. Analytical grade chemicals and reagents were utilized for the said research work.

Methods:

Preparation of Isapghula Mucilage:
Plantago ovata seeds (as shown in figure 1A), were steeped in distilled water for 48 hours before being cooked for a few minutes. To separate the materials, they were squeezed through muslin fabric. The filtrate was then treated with an equivalent volume of acetone to precipitate the mucilage. In a tray drier, the separated mucilage was dried at 40°C. Sieve no. 80 was used to sieve the powdered mucilage. The resulting powder was kept in a desiccator and used in this study (Kumar et al., 2017).

Preparation of Banana Powder:
Fresh whole bananas (as shown in figure 1B), were gathered and weighed after being cleaned of any debris. In 5 minutes, the skinned bananas were soaked in ethanol. The banana was then weighed and squished into a paste, which was then mixed with citric acid (2-3%) to remove the sticky properties. After that, centrifugation and processing are used to separate the water. The compacted bulk is next dried in a tray dryer. To obtain fine powder, the dry ingredients were ground and filtered in a sieve #80 (Soni and Raju, 2015).

Figure 1: Plantago ovata seed (A), Fresh whole banana and powder (B)

Estimation of the Atenolol using UV spectrophotometry:
Stock solution preparation:
Weighed quantity (10 mg) of atenolol, transferred to a 100 mL volumetric flask. Add methanol to dissolve the drug. The concentration of prepared solution was 100 µg/ml and the flask shaken well during preparation of stock solution (Kumare et al., 2013).

Absorption maxima of atenolol using UV spectrophotometry:
Absorption maxima was performed on UV spectrophotometer (Shimadzu 800 double beam), in phosphate buffer pH 6.8 as a blank, a sample of 100 µg/ml drug solutions from 200 to 400 nm. 275 nm was found to be the maximum wavelength (Mane et al., 2019).

Preparation of standard curve:
Accurately weighed quantity of 10 mg of atenolol was carefully added in a 10 ml volumetric flask. Solubilized in 1 ml methanol, add sufficient quantity of methanol in volumetric flask to make 10 ml, the resulting solution is 100 µg/ml. The standard solution was diluted suing phosphate buffer pH 6.8to get the dilutions5, 10, 15, 20, 25 µg ml (Kori et al., 2013).

Preformulation studies:
Fourier transform infrared spectroscopy (FT-IR) study: To check at any interactions between the drug and the polymer that was utilised including sodium starch glycolate (SSG), microcrystalline cellulose (MCC), crospovidone, directly compressible mannitol, Isapgol mucilage, banana powder, magnesium stearate and talc. Infrared spectra of KBr pellets taken with a Bruker infrared spectrophotometer. The IR spectra of the pure Atenolol and its physical combination was studied using FT-IR (Yadav et al., 2010).
Differential scanning calorimeter (DSC) studies: Thermograms of pure atenolol and its formulation were obtained using DSC (Mettler Star SW 8.10) throughout a temperature range of 35-300°C at a heating rate of 10°C/minutes. The sample, which was precisely weighed at 2.0 mg, was hermetically sealed in an aluminium pan. To maintain an inert atmosphere, nitrogen gas was purged at a rate of 10 ml/minute (Sarfraz et al., 2015).

Excipient selection and optimization of concentration:
The time of disintegration is the most important feature in optimization of fast disintegration tablet development. Fast disintegrating tablets were prepared with a wide range of excipients (binders and superdisintegrants) and then evaluated to ascertain whether the prepared tablets passed in various in process quality control tests including friability, hardness and disintegration time. The combination with the fastest disintegration time, maximum hardness and the lowest friability has been chosen for future research. The tablets were made using direct compression (Bhusnure et al., 2015).
In all of the aforesaid formulations, weighed quantities of pharmaceuticals, as well as optimal concentrations of superdisintegrant and binder, as well as excipients, were combined in a dry and clean mortar in a geometric sequence. After that, the mixture was sieved no. 60 for direct compression. The powder mixture was then compressed into tablets using a multi punch tablet compression machine with a 6mm punch. These fabricated tablets were evaluated.

Preparation of atenolol fast disintegrating tablets:
Using direct compression method, Atenolol rapidly dissolving tablets were prepared. With the exceptions of granular excipients that were instantaneously compressible, all other excipients were processed individually through #60 mesh. The components were then weighed, geometrically mixed, and compressed into 200 mg tablets on a 12-station rotating tablet compression machine using 8 mm flat face-round tool. For each of the designed formulations a lot of 90 tablets was prepared. The composition of various formulation is shown in Table 1.

Table 1: Formulation Composition for Atenolol FDT

Ingredient(s)	Formulation code and quantities(mg)							
	FB1	**FB2**	**FB3**	**FB4**	**FI1**	**FI2**	**FI3**	**FI4**
Atenolol	50	50	50	50	50	50	50	50
Banana Powder	4	8	12	16	--	--	--	--
Isapgol Mucilage	--	--	--	--	4	8	12	16
MCC	110	106	102	98	110	106	102	98

SSG	5	5	5	5	5	5	5	5
Crospovidone	5	5	5	5	5	5	5	5
Talc	4	4	4	4	4	4	4	4
Magnesium Stearate	2	2	2	2	2	2	2	2
Mannitol	20	20	20	20	20	20	20	20
Total weight (mg)	200	200	200	200	200	200	200	200

MCC- Microcrystalline Cellulose, SSG- Sodium Starch Glycolate

III. RESULT AND DISCUSSION:

Pre-compression evaluation of Atenolol FDT formulations:

The angle of repose, bulk and tapped density, Hausner's ratio, and compressibility index of lubricated granules of each formulation were determined as shown in table 2, before feeding into a tablet compression machine to determine flow characteristics and compressibility (Pingale and Ravindra, 2013).

Angle of repose: The funnel method was used to determine the angle of repose of API powder. The angle of repose is the maximum angle that can be made between the surface of a pile of powder and the horizontal plane. The powder mixture was precisely weighed and poured into the funnel. The funnel's height has been decreased to 2.5 centimetres above ground level. Allow the powder combination to flow freely through the funnel and onto the surface. The powder cone's diameter is measured three times to get an average value.

The equation is used to calculate the angle of repose:

$$\text{Angle of Repose } (\theta) = \tan^{-1}\left[\frac{h}{r}\right]$$

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

Bulk density determination: The mass to volume ratio of an untapped powder sample determines a substance's bulk density (including inter particulate void volume). The powder (W) is weighed and placed in a graduated measuring cylinder to calculate the volume (V0). The formula used to compute bulk density is given below:

$$\text{Bulk density (BD)} = \left[\frac{W}{V_0}\right]$$

Where, W=Powder weight, V_O=Powder volume.

Tapped density determination:The tapped density is obtained by mechanically tapping a graduated cylinder containing the sample until only a minor volume change is seen. The powder sample weighing 25 gm was screened using sieve No.18, and the weight of the sample was placed in a 100 mL graduated cylinder. A tapped density tester was used to mechanically tap the cylinder 500 times at a nominal rate, and the tapped volume Vo was recorded. When the difference between two tapping volumes is less than 2%, Vf is tapped volume. The blend volume was used to compute the tapped density, Hausner's ratio, and Carr's Index. The unit of bulk density and tapped density is g/ml.

The formula used to calculate tapped density is given below:

$$\text{Tapped density (TD)} = \left[\frac{W}{V_f}\right]$$

Where, W=Powder weight, V_O=Powder volume.

Carr's index: Carr's index is described by the term compressibility. It's a metric for how compressible a powder is. It is linked to relative flow rate, cohesion, and particle size in an indirect way. The formula for calculating Carr's index was:

$$\text{Carr's Index (\%)} = \frac{(\text{Tapped Density} - \text{Bulk Density}) \times 100}{\text{Tapped Density}}$$

Hausner's ratio: Hausner's ratio, which indicates the flow properties of the powder, is calculated using the ratio of tapped density to bulk density.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table 2: Pre-compression evaluation of Atenolol granules (n=10, Mean ± SD)

Formulation code	Angle of repose	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Compressibility index (%)
FB1	29.83 ± 0.33	1.562 ± 0.33	1.923 ± 0.18	1.231 ± 0.29	18.750 ± 0.11
FB2	25.46 ± 0.21	1.650 ± 0.22	2.083 ± 0.38	1.312 ± 0.14	19.412 ± 0.14
FB3	23.89 ± 0.41	1.689 ± 0.19	2.008 ± 0.15	1.153 ± 0.11	13.240 ± 0.31
FB4	26.97 ± 0.57	1.695 ± 0.26	1.992 ± 0.26	1.175 ± 0.34	14.915 ± 0.27
FI1	24.72 ± 0.81	1.712 ± 0.39	2.179 ± 0.16	1.245 ± 0.21	19.655 ± 0.41
FI2	28.51 ± 0.92	1.661 ± 0.08	1.887 ± 0.18	1.136 ± 0.19	11.960 ± 0.35
FI3	27.18 ± 0.29	1.667 ± 0.51	1.873 ± 0.18	1.119 ± 0.17	10.009 ± 0.29
FI4	28.73 ± 0.42	1.278 ± 0.18	1.812 ± 0.67	1.254 ± 0.15	19.987 ± 0.18

Post-compression evaluation of atenolol FDT's: Prepared tablets were evaluated for various parameters including thickness, weight uniformity, hardness, friability, water absorption ratio, in-vitro disintegration time, in-vitro dispersion time and drug content (Patel and Pingale, 2014). The results of these parameters are summarized in table 3 and 4.

Thickness: With a Vernier calliper (Mitutoyo 500-196-30-Advanced), the thicknesses of the tablets were measured, and average values were calculated using 20 tablets from each batch.

Uniformity of weight: Each tablet in a batch should be the same weight, and weight deviations should be within the pharmacopeia's allowed acceptable range. A Mettler Toledo AB analytical balance, model AB104-S, was used to determine weight uniformity. The weight variation was determined using a sample of ten tablets.

Hardness:The tablet's hardness reflects its durability. A hardness tester (Erweka, TBH 425) was used to determine the hardness of 10 tablets from each batch.

Friability: Using the friability test instrument, the friability of 10 tablets for each formulation was determined (Electrolab, EF-2W).

Table 3: Post-compression evaluation of Atenolol tablets (n=10,Mean ± SD)

Formulation code	Thickness (mm)	Weight (mg)	Hardness (kg/cm^2)	Friability (%)
FB1	1.91 ± 0.08	198.23 ± 1.74	4.15 ± 0.01	0.47± 0.23
FB2	1.89 ± 0.14	199.64 ± 0.99	4.09 ± 0.05	0.38 ± 0.19
FB3	1.94 ± 0.21	199.18 ± 2.56	3.99 ± 0.03	0.43 ± 0.19
FB4	1.88 ± 0.19	198.96 ± 2.89	4.07 ± 0.02	0.35 ± 0.22
FI1	1.87 ± 0.13	200.32 ± 2.52	4.11 ± 0.03	0.43 ± 0.29
FI2	1.89 ± 0.08	198.46 ± 2.44	4.03 ± 0.05	0.41 ± 0.11
FI3	1.91 ± 0.11	199.63 ± 3.22	4.08 ± 0.07	0.39 ± 0.56
FI4	1.91 ± 0.23	199.12 ± 1.67	4.06 ± 0.09	0.41 ± 0.81

Water absorption ratio: An accurately weighed tablets and placed in a 7-cm-diameter Petri dish filled with 7 mL of red dye solution. The time was recorded when the entire upper surface of a tablet was wetted, and the tablet was weighed again. The following equation was used to compute the water absorption ratio:

$$R = \frac{100(W_a - W_b)}{W_b}$$

Where Wb is the weight of a tablet before wetting and Wa after it.
In-vitro Disintegration Time: The rapid disintegration of the FDTs was caused by saliva entering the tablet pores, causing superdisintegrants to expand and provide enough hydrodynamic pressure for the tablet to disintegrate quickly and completely.
In-vitro Dispersion Time:As the concentration of superdisintegrants rises, the wetting time/dispersion time decreases. The water absorption ratio increases as the concentration of superdisintegrants increases, while disintegration time decreases.
Drug Content: The drug content was found to be between 88.98±1.02 and 97.68±1.23, showing that the drug was distributed uniformly in the formed tablets according to pharmacopoeia specifications.

Table 4: Post-compression evaluation of Atenolol tablets (n=06, Mean ± SD)

Formulation code	Wetting time (sec)	Water absorption ratio	Dispersion time (sec)	In-vitro disintegration time (sec)	Drug content ((%)
FB1	43 ± 2.1	80.57 ± 0.67	42.43 ± 1.47	27.95 ± 1.00	82.56 ± 1.02
FB2	48 ± 1.9	84.74 ± 0.84	43.21 ± 1.89	28.32 ± 1.25	86.67 ± 1.73
FB3	50 ± 1.6	91.43 ± 0.18	39.41 ± 1.65	29.12 ± 1.98	92.01 ± 1.84
FB4	52 ± 1.8	88.23 ± 0.49	42.67 ± 1.98	28.45 ± 1.50	96.75 ± 1.32
FI1	53 ± 2.6	84.37 ± 0.31	39.31 ± 1.25	31.47 ± 1.25	84.23 ± 1.25
FI2	54 ± 1.7	86.48 ± 0.36	41.52 ± 1.34	28.11 ± 1.50	92.53 ± 1.28
FI3	52 ± 1.2	84.36 ± 0.42	38.61 ± 2.12	35.45 ± 1.00	98.02 ± 1.23
FI4	51 ±1.5	4.49 ± 0.23	7.87 ± 0.09	598.2 ± 1.67	96.21 ± 1.57

In-vitro drug release: Formulations FB1 containing superdisintegrant Banana powder (2%) and FB2 containing superdisintegrant Banana powder (4%) had release rates of 82.56 percent and 86.67 percent, respectively. Formulations FB3 containing superdisintegrant Banana (6%) and FB4 containing Banana (8%) had release rates of 92.01 percent and 96.75 percent, respectively. Formulation FI1 containing superdisintegrant Isapghula (2%) and FI2 containing superdisintegrant Isapghula (4%) showed a release of 84.23 percent and 92.53 percent, respectively, while FI3 containing superdisintegrant Isapghula (6%) and FI4 containing superdisintegrant Isapghula (8%) showed a release of 98.02 The resulting formulations FB4 and FI3 had the highest release rates of 96.75±1.61and 98.02±1.01percent, respectively, as depicted in table 5.

Table 5: In-vitro drug release of Atenolol from various formulations

Time (min)	Formulation code and % drug release							
	FB1	FB2	FB3	FB4	FI1	FI2	FI3	FI4
1	19.25	20.68	22.32	24.32	20.12	22.23	24.95	23.87

	±1.11	±1.78	±0.93	±1.13	±1.03	±1.04	±1.48	±1.72
3	31.74 ±1.26	32.56 ±0.98	34.56 ±0.74	39.23 ±1.37	32.75 ±1.73	35.23 ±1.18	40.56 ±1.57	38.36±1 .61
5	48.31 ±1.25	51.12 ±1.17	53.42 ±1.59	55.31 ±1.43	49.21 ±1.34	50.32 ±1.39	56.79 ±1.34	55.01 ±1.43
10	69.12 ±1.76	71.65 ±1.73	75.65 ±1.64	80.21 ±1.73	70.23 ±1.09	73.18 ±1.21	81.21 ±1.07	78.32 ±1.70
15	82.56 ±1.98	86.67 ±1.19	92.01 ±1.74	96.75 ±1.61	84.23 ±1.13	92.53 ±1.31	98.02 ±1.01	96.21 ±1.17

The formulations FB4 and FI3 (containing 16 mg, or 8%, and 12 mg, or 6%, of banana powder and Isapghula, respectively) were chosen because they have good effects with a high percentage.

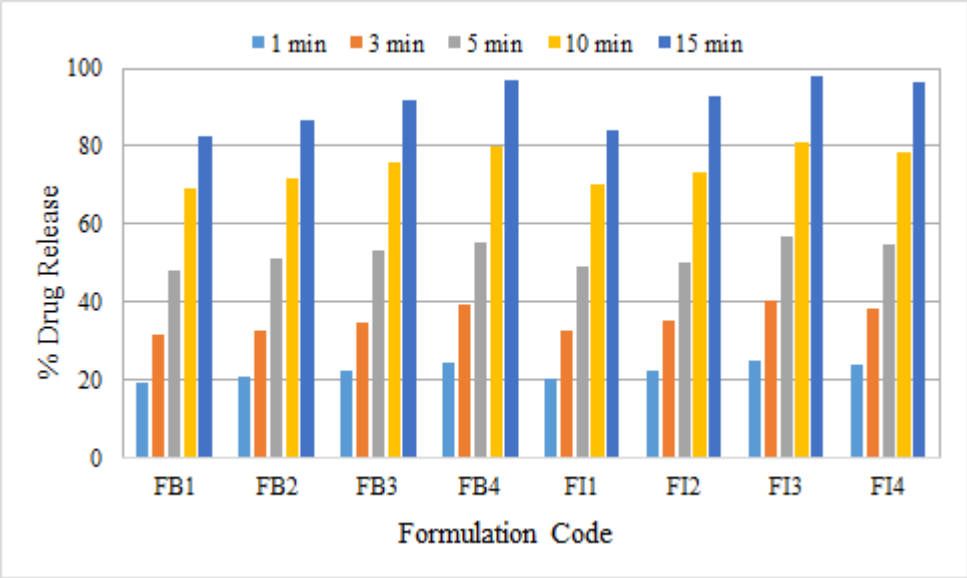

Figure 2: Cumulative Release (%) of Atenolol

Kinetic Release: Models for analysing dissolution data that can be applied mathematically. The models provided in this paper include both empirical and semi-empirical models for evaluating dissolution rate data. The use of these models allows the mechanism and type of drug release that can be predicted from mouth dissolving tablets to be elucidated. To study the mechanism of drug release, data from in vitro release tests (FB1 to FB4 and FI1 to FI4) was fitted to various kinetic models, including Zero-order, First-order, Higuchi's, and Korsmeyer-Peppas. Table 6 summarizes the applicability of all of these equations. The rate constants were also determined using the slope of each model's plot. The dissolving data of all formulations were fitted into the Korsmeyer-Peppas equation to determine the exact process. With slope (n) values, all formulations exhibited good linearity R2. ‘n' is the release exponent in the Korsmeyer-Peppas model, which indicates the drug release mechanism. The n values are greater than 0.54, indicating an abnormal drug delivery pathway.

Table 6: Kinetic Value Obtained from In-vitro Release Profile of Atenolol FDT

Formulation	R2				n-value
	Zero order	First order	Peppas	Higuchi	Peppas
FB1	0.941	0.976	0.991	0.973	0.590
FB2	0.931	0.983	0.983	0.983	0.583
FB3	0.973	0.987	0.989	0.971	0.576
FB4	0.983	0.971	0.993	0.992	0.541
FI1	0.939	0.989	0.989	0.983	0.593
FI2	0.968	0.979	0.991	0.986	0.561
FI3	0.987	0.993	0.996	0.993	0.549
FI4	0.971	0.971	0.987	0.987	0.573

Stability study:

Short-term stability tests on the promising formulations (FB4 and FI3) were conducted by storing the tablets (in amber coloured rubber stoppered vials) at 40°/75 percent relative humidity for three months. The tablets were visually evaluated at one month, two months, and three months (initial, middle, and final durations) for any physical changes, changes in drug content, and in-vitro dispersion time.

IV. CONCLUSION:

After considering the assessment parameters of dissolution study, disintegration time, and wetting time, an excellent batch of fast disintegrating tablets was selected. Batch FB4 and FI3 fast disintegrating tablets (containing 16 mg, or 8%, of banana powder and 12 mg, or 6%, of Isapghula, respectively) were chosen as the best batch because of their dissolution, disintegration time, and wetting time. The maximal in-vitro cumulative percentage release of the drug was 996.75 ±1.61 and 98.02 ±1.01 respectively.

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