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Formulation and Evaluation of Fast Disintegrating Tablets of Atenolol Using Natural and Synthetic Superdisintegrants

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ABSTRACT

Oral disintegrating tablet (ODT) is defined as "A solid dosage form containing medical substances or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue". The aim of the present research is to formulate Atenolol fast disintegrating tablets. Atenolol is β1- cardio selective adrenergic receptor blocker, widely used in the treatment of hypertension, angina pectoris, arrhythmias and myocardial infarction. It works by slowing down the heart and reducing the work load of the heart. The conventional tablets of atenolol are reported to exhibit fluctuations in the plasma drug levels after administration. Atenolol fast disintegrating tablets were prepared by using direct compression method using Synthetic as well as Natural superdisintegrants like sodium starch glycolate, Cross carmellose sodium and Miriabilis jalapa starch. The prepared tablets were characterized for their hardness, weight variation, disintegration time, wetting time, water absorption ratio friability, and in vitro dissolution studies. The ability of the tablet to release the drug faster depends on the concentration and type of superdisintegrants. In this study the fast disintegrating tablets containing Cross carmellose sodium, Sodium starch glycolate and Miriabilis jalapa starch as the super disintegrant in the ratio of 1:2:3 Shows better release of drug. About 97.92% of the drug was released from the tablets in 10mins. Therefore, based on the physico chemical properties, in vitro drug release profile F9 formulation containing Miriabilis jalapa starch is optimized as the best formulation.

Keywords: Fast Disintegrating Tablets, Superdisintegrants, Atenolol, *Miriabilis jalapa* starch, In vitro evaluation.

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INTRODUCTION

Fast disintegrating drug delivery system (FDDTS) are a new generation of formulation which combine the advantages of both liquid and conventional tablet formulation and at the same time offer added advantages over both the traditional dosage forms. They provide the convenience of tablet formulation and allow the ease of swallowing provided by a liquid formulation. FDDS provides much more accurate dosing than the primary alternative oral liquids. This segment of formulation is especially designed for dysphasic, geriatric, pediatric, travelling and psychotic patients. Who are unable to swallow or refuse to swallow conventional oral formulations. Dysphagia or problem in swallowing is common in all age groups. Common complaints about the problem in swallowing tablets in the order of frequency of complaints are surface, dosage form, size and also taste of tablet. During the last decade fast disintegrating tablets (FDT) disintegrate in mouth without chewing and extra water intake has drawn a great deal of attention. The FDT is also called as fast melting, fast dispersing orodispersible tablet, rapid dissolve, and rapid melt tablet. Recently, the European pharmacopoeia adopted the term orodispersible tablet for a tablet that disintegrate or disperse in less than 3 minutes in mouth before swallowing. Such a tablet disintegrate into smaller granule or melts in mouth from a hard solid gel-like structure, allowing easy swallowing by patients. The disintegration time for good FDT varies from several second to about minute. Suitable drug candidate for such system include Neuroleptics, Cardiovascular, Analgesic and Antiallergics. Such a tablet disintegrates rapidly when it placed on tongue, drug is released that disperses or dissolved in the saliva. Which result in rapid onset of action and greater bioavailability of drug than those observed from conventional tablet dosage form. Various technologies are utilized for fabrication of FDTs and these techniques are based on the increasing of porosity by addition of superdisintegrants or water soluble excipients in the tablet.

The oral route of administration have wide acceptance up to 50-60% of total dosage forms and also considered as the most widely employed route of administration due to its

wide range of advantages like stability, ease of administration, accurate dosage, self medication and patient compliance. Hence oral solid dosage forms are mostly preferred. Among all the dosage forms, the tablet dosage form is the most popular, because of ease of transportability and lower manufacturing cost. The disadvantage of oral dosage forms such as Dysphasia or difficulty in swallowing can be overcome by developing rapidly disintegrating and dissolving tablet dosage forms which dissolve in saliva and does not require water for swallowing. The faster the drug into solution, quiker the absorption and onset of clinical effects. Some drugs are absorbed from the mouth, pharynx, esophagus, as the saliva passes down into the stomach.

Superdisintegrants:

Disintegrating agents are substances routinely included in the tablet formulations to aid in the break-up of the compacted mass into the primary particles to facilitate the dissolution or release of the active ingredients when it is put into a fluid environment. They endorse moisture penetration and dispersion of the tablet matrix. The major function of disintegrants is to oppose the efficiency of the tablet binder and physical forces that act under compression to structure the tablet. Recently new materials termed as "superdisintegrants" have been developed to improve the disintegration processes. Superdisintegrants are another version of superabsorbing materials with tailor-made swelling properties. These materials are not planned to absorb significant amounts of water or aqueous fluids, but planned to swell very fast. They are physically dispersed within the matrix of the dosage form and will expand when the dosage form is exposed to the wet environment. These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. Superdisintegrants are generally used at a low level in the solid dosage form, typically 1-10 % by weight relative to the total weight of the dosage unit. Their particles are generally small and porous, which allow for rapid tablet disintegration in the mouth without an objectionable mouth-feel from either large particles or gelling. The particles are also compressible which improves tablet hardness and its friability. Effective superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high- dose drugs.

MATERIAL AND METHODS

Atenolol was obtained gift sample from Medrich.Ltd.Benglore, Crosscarmelose sodium, Sodium starch glycolate and microcrystalline cellulose were from S.D. Fine Chemicals. Other chemicals used were analytical grade.

Table 1: List of chemical used with their suppliers

Sr.No.	Materials	Suppliers
1	Atenolol	Medrich Ltd. Benglore
2	Mannitol	S.D. Fine Chemicals, Mumbai
3	Microcrystalline Cellulose	S.D. Fine Chemicals, Mumbai
4	Sodium Starch Glycolate	S.D. Fine Chemicals, Mumbai
5	Crosscarmelose Sodium	S.D. Fine Chemicals, Mumbai
6	Miriabilis Jalapa Starch	Natural source
7	Aspartame	S.D. Fine Chemicals, Mumbai
8	Magnesium Stearate	S.D. Fine Chemicals, Mumbai
9	Talc	S.D. Fine Chemicals, Mumbai

Preparation of Natural Superdisintegrant: Miriabilis jalapa Starch

The seeds were collected from some of gardens of Sangola. These were washed with water to remove dust and dirt particles and dried in oven at 60^0 C for 7 hrs. After drying the seeds were stored. The seeds were crushed by Mortar and Pestle into coarse powder.

Hydrolysis –Acidic hydrolysis.

Analytical method for estimation of the Atenolol drug (UV method)

Preparation of stock solution

Atenolol 10 mg were weighed and transferred to 100 ml volumetric flask and dissolve in methanol. The flask was shaken and volume was made to mark with methanol to give a solution containing 100 µg/ml.

UV absorption maxima of atenolol

UV scanning done for 100 µg/ml drug solutions from 200-400 nm in phosphate buffer pH (6.8) as a blank using shimadzu 800 double beam UV spectrophotometer. The wavelength maximum was found to be at 275 nm.

Preparation of standard curve: Atenolol 10 mg were accurately weighed and solubilized by using 1 ml methanol in 10 ml volumetric flask and phosphate buffer added to make up the volume so as to give stock solution of 100µg/ml. The standard solutions were diluted with phosphate buffer pH 6.8 to obtain various dilutions (5, 10, 15, 20, 25µg ml) in standard volumetric flask.

Drug-Excipients Compatibility: Drug-Excipients compatibility studies form an important part of Preformulation studies. The interaction between the drug and excipients are determined after a specific time period by using suitable analytical techniques like IR.

Infrared Absorption Spectroscopy: To investigate any possible interaction between the drug and polymer used (Sodium starch glycolate, Crosscarmelose sodium, Miriabilis jalapa starch, microcrystalline cellulose, Magnesium stearate and Talc). Infrared spectra recorded on Bruker infrared spectrophotometer in KBr pellets. IR spectrum of pure drug (Atenolol) and its physical mixture was carried out by using FT-IR.

Preparation of fast disintegrating tablets of atenolol: Fast disintegrating tablets of Atenolol were prepared by Direct Compression Method. All the ingredients except granular directly compressible excipients were passed through #60mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 200mg by using 8mm flat face round tooling on 10 station rotory tablet compression machine. A batch of 90 tablets was prepared for all designed

formulations. The formulation designs have been shown in (table.2)

RESULT AND DISCUSSION

In the present investigation pre-formulation studies was estimated on the drug and superdisintegrants. Crosscarmelose sodium, Sodium starch glycolate and Miriabilis jalapa Starch in different conc. 6mg, 12mg, and 18mg were added to formulate 200 mg Atenolol Fast disintegrating tablets. Direct compression technique was applied in formulating fast disintegrating tablets.

Table 2: Formulation table of fast disintegrating tablets:

Ingredients	Formulation code and quantities(mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Atenolol	50	50	50	50	50	50	50	50	50
Mannitol	100	94	88	100	94	88	100	94	88
Microcrystalline cellulose	35	35	35	35	35	35	35	35	35
Sodium Starch Glycolate	6	12	18	-	-	-	-	-	-
Crosscarmellose Sodium	-	-	-	6	12	18	-	-	-
Miriabilis Jalapa Starch	-	-	-	-	-	-	6	12	18
Aspartame	3	3	3	3	3	3	3	3	3
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4
Total (mg)	200	200	200	200	200	200	200	200	200

Characterization of drug

Determination of Organoleptic Properties: Physical appearance of Atenolol was evaluated by various organoleptic properties like appearance, color, odor as shown in **Table 3.**

Table 3: Interpretation of physical properties of Atenolol

Sr. No.	Physical properties	Interpretation
1	Appearance	Crystalline
2	Color	White
3	Odor	Odorless

Determination of Solubility Profile: Atenolol was soluble in methanol and other solubility profile results were shown in **Table 4.**

Table 4: Solubility profile of atenolol in different solvent

Sr.No.	Solvent	Solubility
1	Methanol	Freely soluble
2	Ethanol	Sparingly soluble
3	Isopropanol	Slightly soluble
4	Acetic acid, DMSO	Soluble

Determination of Melting Point: Melting point of Atenolol determined by Capillary fusion method. Shown in **Table 5.**

Table 5: Melting point of atenolol

Method Employed	Experimental value
Capillary fusion method	158^{0}C

Determination of Calibration Curve: Atenolol In phosphate buffer pH 6.8 solution yield characteristic curve when scanned in the UV range between 200-4000 nm. The λmax for Atenolol in phosphate bufferpH6.8 solution was finalized at 275 nm.

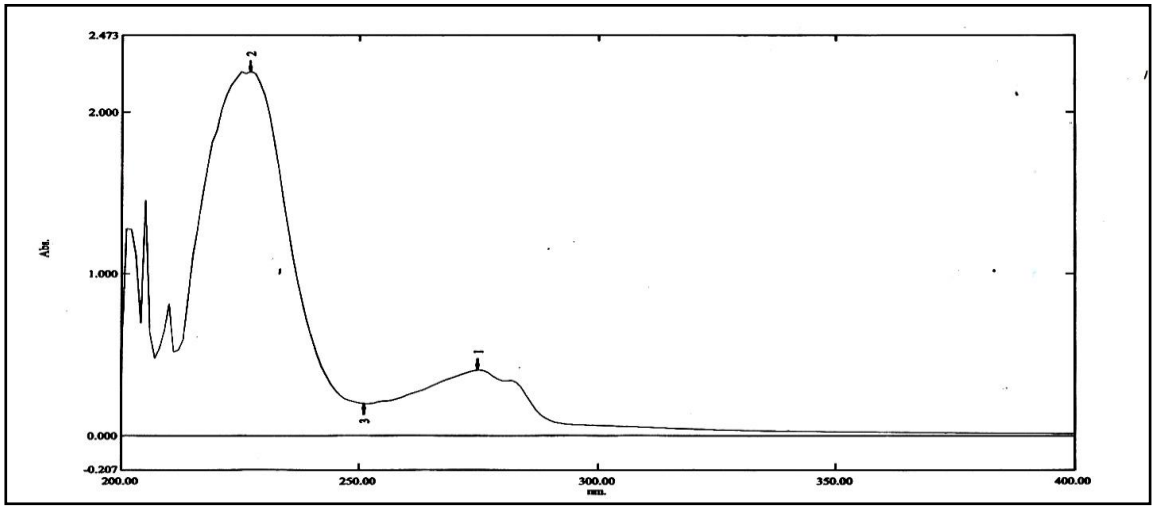

Figure 1: Standard spectra of atenolol in phosphate buffer pH 6.8

The standard plot data of Atenolol in respective buffer determined at λmax is given in Table 6. This data was used for construct the calibration curve Figure 2. This showed linear relationship with respect to absorbance values with the correlation coefficient.

Table 6: Standed plot data for atenolol

Concentration in (µg/ml)	Absorbance
0	0.000
5	0.111
10	0.232
15	0.314
20	0422
25	0.537

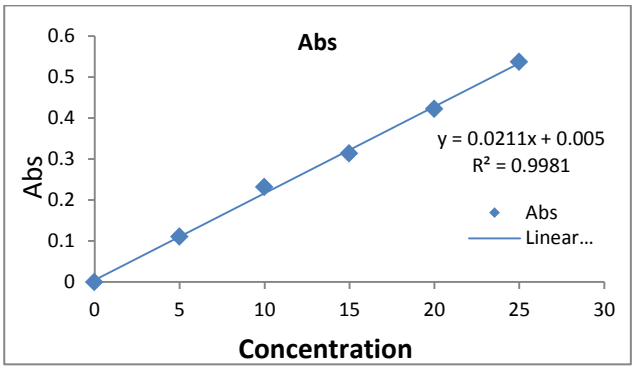

Figure 2: Standard plot of Atenolol

FT-IR Study:

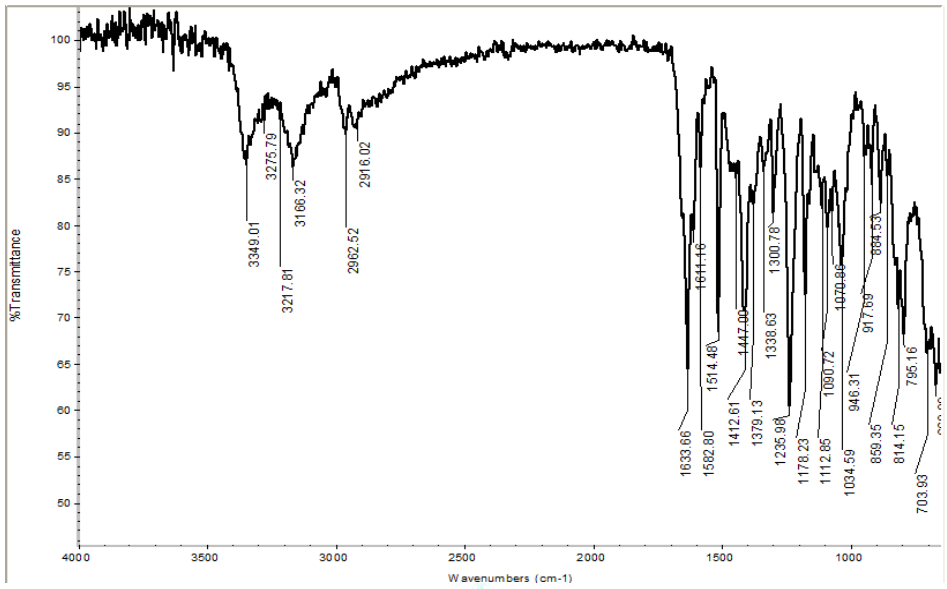

Figure 3: FT-IR Spectra of atenolol

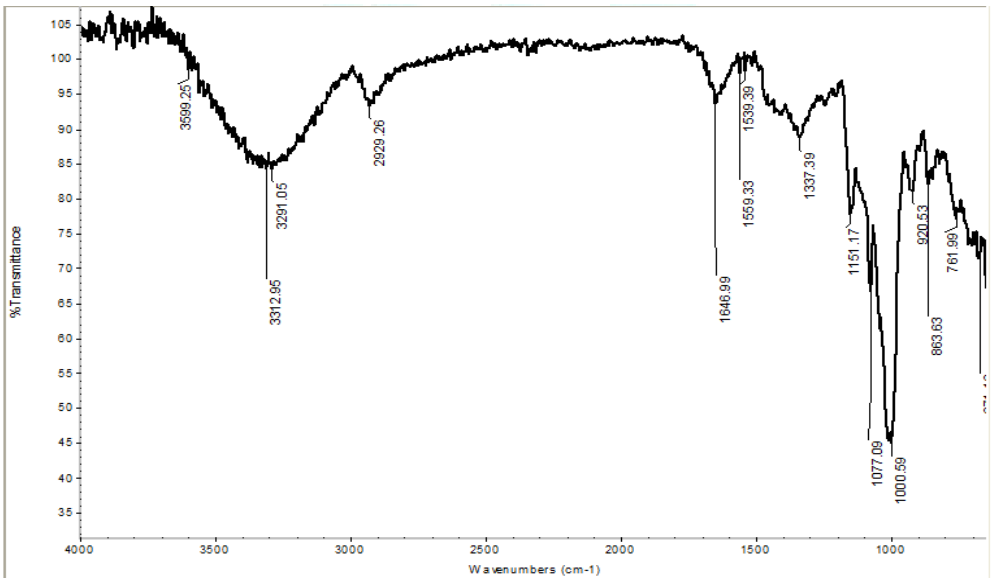

Figure 4: FT-IR Spectra of Miriabilis jalapa starch

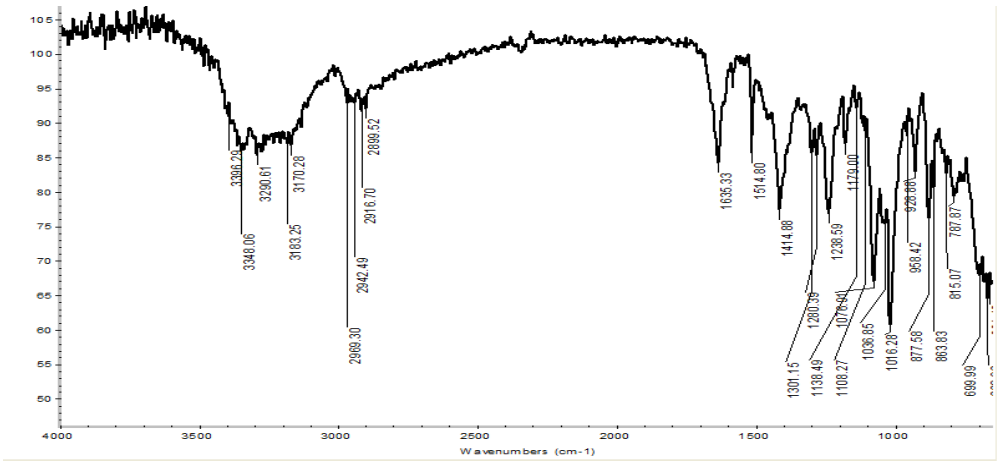

Figure 5: FT-IR Spectra of F1 batch

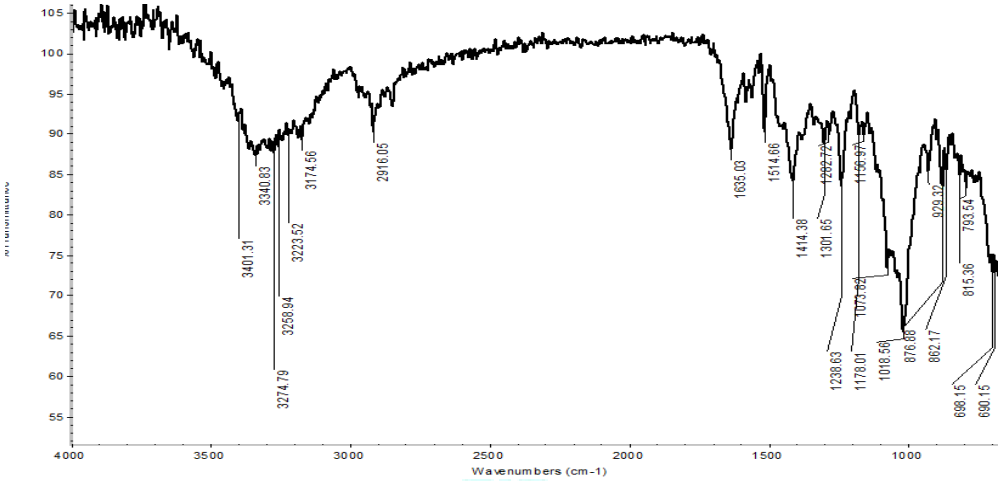

Figure 6: FT-IR spectra of F4 batch

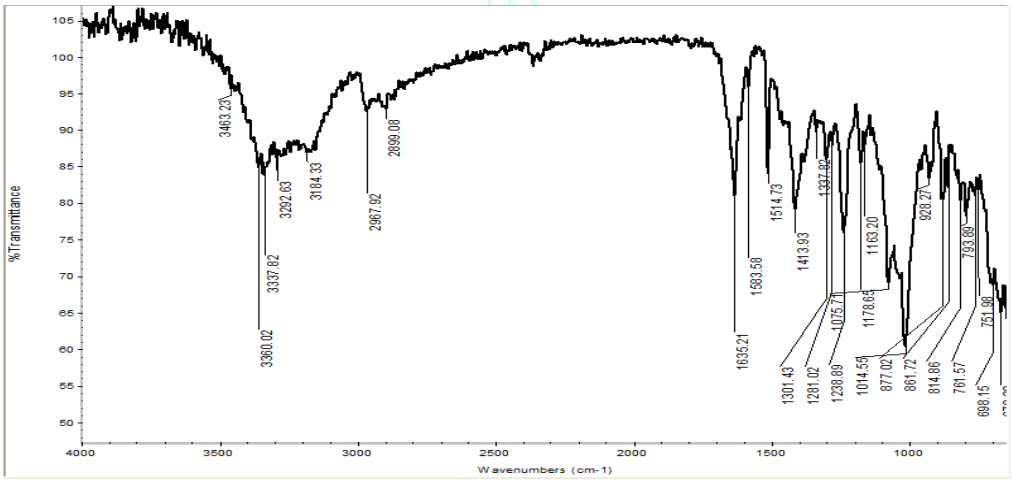

Figure 7: FT-IR Spectra of F7 batch.

Comparison of the peaks of functional groups observed in IR spectra of compatibility studies.

Table 7: IR spectra of compatibility studies of drug and excipient

IR Spectra	**Peak of functional groups[Wavelength(cm^{-1})]**				
	OH Stretch	N-H Stretch	C=O	C=C Conjugated(Aromatic)	C-H Stretch
Reference Std	3368	3198-3071	1666	1614	2870
Atenolol	3349	3166	1633.66	1611	2916.02
Sodium starch glycolate	3367.92	3294.08	1592.03	1492.03	3228.95
Crosscarmelose sodium	3355	3222	1632	1607.29	3166
Miriabilis jalapa starch	3312.95	3291.05	1646	1559	2929

Table 8: IR spectra of compatibility studies of drug and formulation batches

IR Spectra	Peak of functional groups[Wavelength(cm^{-1})]				
	OH Stretch	N-H Stretch	C=O	C=C Conjugated(Aromatic)	C-H Stretch
Reference Std	3368	3198-3071	1666	1614	2870
Atenolol	3349	3166	1633.66	1611	2916.02
F1batch	3348.06	3183.25	1535.33	1514.80	2899.52
F4 batch	3340.83	3174.56	1635.03	1514.66	2916.05
F7 batch	3337.82	3184.33	1635.21	1583.58	2899.08

Phytochemical Screening of the Powder: The basic Phytochemical screening tests for carbohydrates, alkaloids, steroids, flavonoids, saponins, tannins and phenols were carried out and shown in Table 9. The tests indicated the absence of alkaloids, steroids, flavonoids, saponins, tannins and phenols. Only carbohydrates were found to be present.

Table 9: Determination of purity of Natural polymer

Sr. No	Test of Phytoconstituent	Result
1	Test for steroids: Libermann – Burchard	Absent
2	Test for Carbohydrates: Molisch test, Barfoed's test, Benedicts test Present	Present
3	Test for Saponins: Foam test Absent	Absent
4	Test for Flavonoids :Shinoda test, Zinc/HCl reduction test Absent	Absent
5	Test for Tannin/phenol:ferric chloride test, gelatin test	Absent

Table 10: Identification test for carbohydrates:

Sr.No	Test	Observation	Inference
1	Fehling test: 2ml test solution +2ml fehling solution+boiled for 10 minute.	A red precipitate is formed	Reducing sugar present
2	Benidict test: To 5 ml of benidict solution adds 1 ml of test solution and shakes each other. Shake the tube in boiling water bath and heat for 3 min. Remove the tube from heat and allow to cool.	Formation of green, red, yellow precipitation	Reducing sugar is present

Tablet Formulation: Drug along with calculated concentration of superdisintegrant and other excipients were mixed together and compressed by direct compression method using 8mm punch in multi compression machine. Before compression the pre-compression parameters were also determined.

Pre-compression Parameter of Tablet: The characterization of mixed blends was done for determination of mass volume relationship parameters. The evaluated parameters were bulk density, tapped density, Hausner's ratio, compressibility index and angle of repose. The bulk density of blend varied between 0.37-0.49 g/cm3. The tapped density was found in the range of 0.44-0.58 g/cm3. By using these two density data, Hausner's ratio and compressibility index was calculated. The powder blends of all formulation had Hausner's ratio of less than 1.18 indicating good flow characteristics. Blends having value of compressibility index less than 25% were considered as free flowing ones. The values for compressibility index were found between 12.24-17.24. The flow ability of the powder was also evidenced by the angle of repose. The angle of repose below 35 ^{0}. Range indicates good flow properties of powder. Lower the friction occurring within the mass, better the flow rate. The angle of repose was found to be in range 22.27- 27.10^0. The results for characterization of blend are shown in Table 11. The mixed blends were then compressed using rotary tablet punching machine to obtain the fast disintegrating tablets.

Table 11: Precompression parameters of powder blend:

Formulations	Angle of repose (0^0)	Loose bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carrs index (%)	Hausners ratio
F1	24.98	0.43	0.49	12.24	1.13
F2	26.56	0.41	0.48	14.58	1.17
F3	25.21	0.47	0.55	14.54	1.17
F4	25.33	0.49	0.58	17.24	1.18
F5	22.27	0.39	0.46	15.21	1.17
F6	24.12	0.40	0.47	14.89	1.17
F7	26.39	0.44	0.51	13.72	1.15
F8	27.10	0.37	0.44	15.90	1.18
F9	24.01	0.48	0.56	14.28	1.16

Post compression parameter:

Post Compression Parameter of Tablet Uniformity of Thickness: The crown diameters of all the formulations were found to be uniform (6mm).Thickness of all the formulations was in the 3.38±0.05mm to 4.00±0.3mm (± 5 % of the average thickness of 10 tablets).

Weight Uniformity: As the percentage weight variation was within the pharmacopoeial limits of ±7.5%. It is related to tooling of the compression machine, head pressure, machine speed and flow properties of the powder. Inconsistent powder or granulate density and particle size distribution are common sources of weight variation during compression.

Hardness: In all the formulations, hardness test indicated good mechanical strength, as the hardness of the FDTs was found in the range of 2.2±0.15 to 3.6±0.25 kg/cm2.High hardness values increase the disintegration time and reduced dissolution values. By exploiting the correlation between hardness, disintegration, dissolution, friability, percentage defective and weight variation, improves the quality of the tablets.

Friability: Friability was observed less than 1%, indicated that FDTs had a good mechanical resistance. It is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping.

Water Absorption Ratio: The capacity of disintegrates to swell in presence of little amount of water were found to be in the range of 69.36±0.35-95.52±0.16 %. The water absorption ratio that is the up taking of water was very fast and the ratio was found higher.

In-vitro Disintegration Time: This rapid disintegration of the FDTs was due to the penetration of saliva into the pores of the tablet, which lead to the swelling of superdisintegrants to create enough hydrodynamic pressure for quick and complete disintegration of the tablet.

In-vitro Dispersion Time: The wetting time/dispersion time decreases with increase in the concentration of superdisintegrants. It was observed that as the concentration of superdisintegrants increases water absorption ratio increases and disintegration time decreases.

Drug Content: The drug content was found to be within the range of 95.71±1.1 to 98.78±0.93 indicating uniform distribution of drug in the formulated tablets as per pharmacopeia specification.

Table 12: Post compression parameters: Uniformity of thickness, hardness, friability, weight variation

Formulation code	Uniformity of thickness(n=3)(mm)	Hardness(n=3)(kg/cm³)	Friability (n=3) (%)	Weight variation(n=3)(mg)
F1	3.46±0.02	2.9±0.15	0.59	198±05
F2	3.73±0.3	2.8±0,47	0.49	200±05
F3	4.00±0.03	3.6±0.25	0.34	201±03
F4	3.43±0.03	2.2±0.15	0.48	199±05
F5	3.69±0.1	3.2±0.6	0.39	201±05
F6	3.44±0.04	2.9±0.4	0.36	200±05
F7	3.38±0.05	2.6±0.6	0.58	198±04
F8	3.71±0.04	3.2±0.15	0.60	201±1.0
F9	3.48±0.08	3.1±0.4	0.51	200±1.0

***Represents values expressed as mean SD**

Table 13: water absorption ratio, dispersion time, in vitro disintegration time, drug content uniformity

Wetting time(n=3)(sec)	Water absorption ratio(n=3)	Dispersion time(n=3)(sec)	Invitro disintegration time(n=3)(sec)	Drug content uniformity (n=3)(%)
48±1.6	81.69±0.13	45.66±2.0	33.00±1.0	96.85±1.7
51±1.6	78.47±0.24	37.51±1.0	24.66±1.5	98.06±0.88
50±2.6	85.56±0.39	28.39±1.0	28.66±0.57	96.14±0.85
45±2.6	91.47±0.37	33.15±1.0	31.33±0.57	98.38±1.3
48±0.8	95.48±0.27	25.46±2.0	20.32±1.5	95.71±1.1
53±0.8	79.41±0.15	44.32±2.0	19.33±1.5	97.35±1.8
62±2.7	69.36±0.35	33.36±1.0	25.33±1.5	96.07±1.2
51±2.8	84.46±0.33	42.98±2.0	17.35±0.57	97.41±1.8
47±0.8	95.52±0.16	25.00±1.0	15.00±1.0	98.78±0.93

***Represents values expressed as mean SD**

In-vitro Release Studies: The comparative drug release was shown in Table 14. And in (Figure 8, 9,10and11). Formulations F1 containing superdisintegrant Sodium starch glycolate (6mg), and F2 containing superdisintegrant sodium starch glycolate (12mg) showed a release of 82.28% and 85.07%, F3 containing superdisintegrants Sodium starch glycolate (18mg) while F4 containing Crosscarmelose sodium (6%) showed a release of 92.14% and 85.05%. Formulation F5 containing superdisintegrant Cross carmelose sodium (12mg) and F6 containing super disintegrant Crosscarmelose sodium (18mg) showed a release of 90.00% and 94.71% while F7 containing superdisintegrant Miriabilis jalapa starch (6mg) while F8 containing superdisintegrant (12 mg) Miriabilis jalapa starch showed a release of 93.02% and 94.28% respectively and F9 containing superdisintegrants Miriabilis jalapa starch(18mg) showed a release of 97.92% were selected for preparation of fast disintegrating tablet. Resultant formulation F9 showed best release of 97.92%. The formulation F9, which have good results with high percentage, was selected.

Table 14: In vitro dissolution studies:

Time in minutes	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	52.28	54.35	57	51.42	55.28	59.14	61.28	62.75	64.50
4	56.14	58.92	61.92	60.65	61.50	64.28	67.92	70.50	73.07
6	64.07	65.78	74.12	67.71	70.71	77.14	79.28	81.24	83.35
8	76.71	78.02	81.42	81.24	83.35	86.14	88.28	89.78	92.35
10	82.28	85.07	92.14	85.05	90.00	94.71	93.02	94.28	97.92

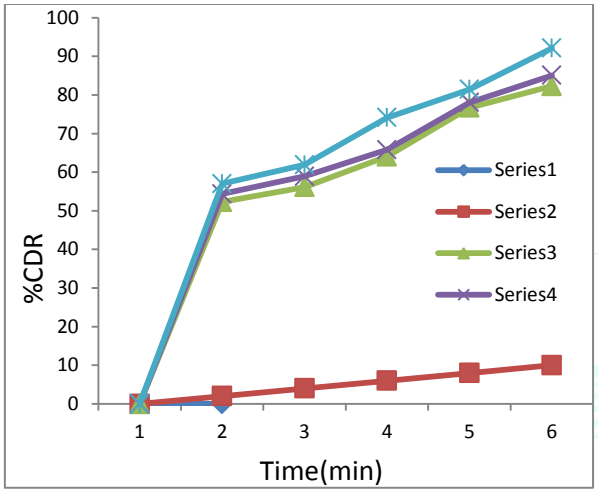

Figure 8: Comparative in vitro release profile of Atenolol fast disintegrating tablets for formulation F1-F3.

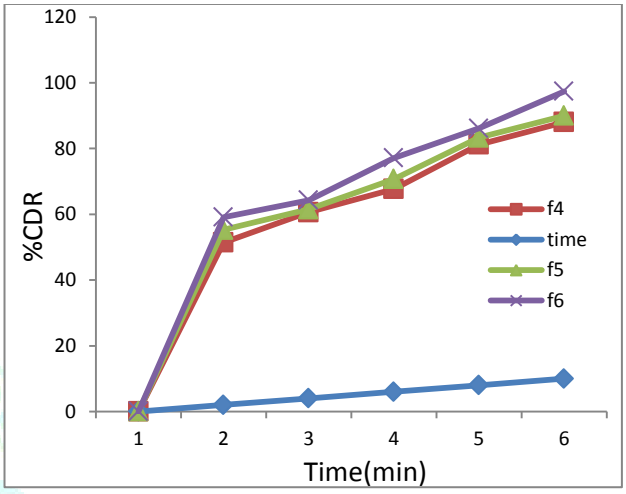

Figure 9: Comparative in vitro release profile of Atenolol fast disintegrating tablets for formulation F4-F6.

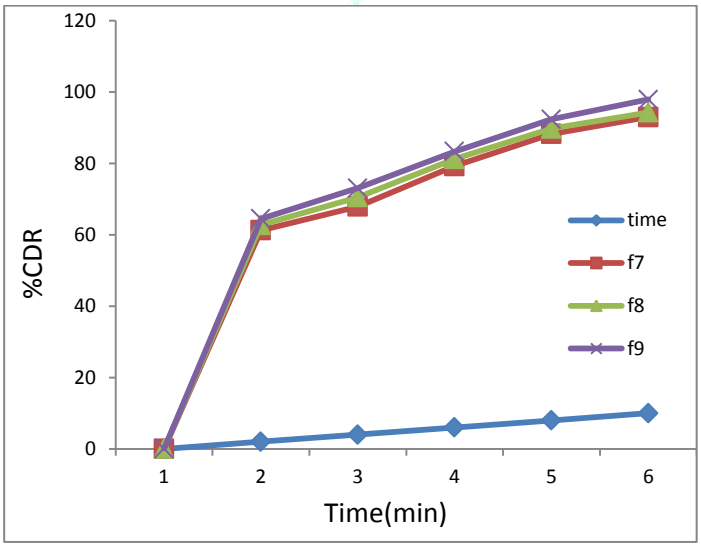

Figure 10: Comparative in vitro release profile of Atenolol fast disintegrating tablets for formulation F7-F9.

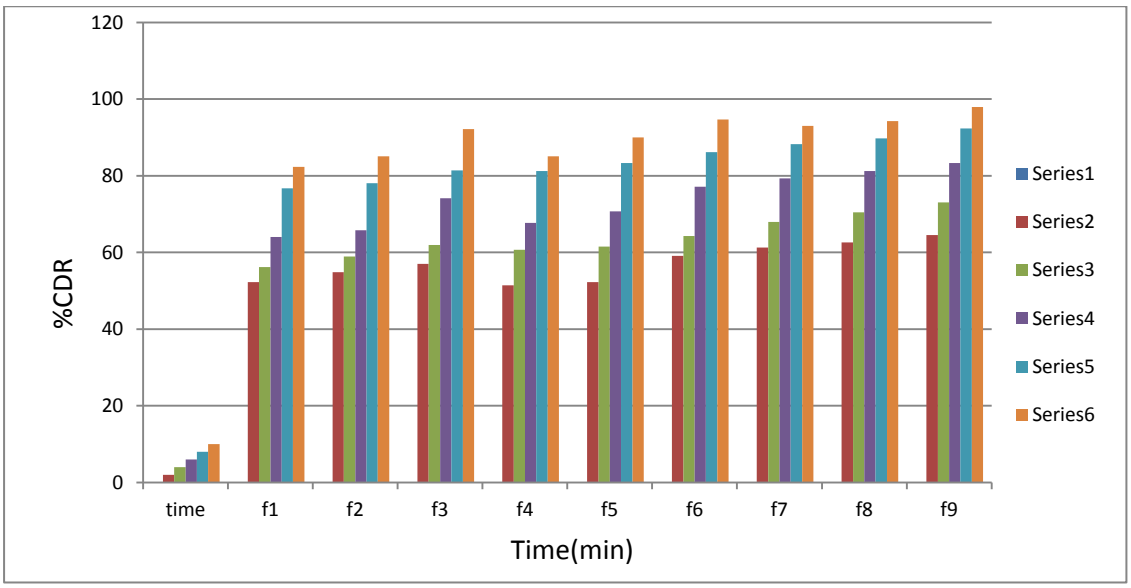

Figure 11: Graphical representation of In vitro drug release profile of Atenolol fast disintegrating formulation for F1-F9.

Stability study:

Short-term stability studies on the promising formulation (F9) were carried out by storing the tablets (in amber colored rubber stoppered vials) at 40°/ 75% Relative humidity over a period 3 months. At interval of one month, the tablets were visually examined for any physical changes, changes in drug content and In-vitro dispersion time.

CONCLUSION

The present study conclusively indicates that the formulation F9 (Miriabilis jalapa Starch 18mg as a superdisintegrants) is very much promising as fast disintegrating tablets of Atenolol with an In vitro dispersion time of 25±1.0secs, wetting time of 47±0.8 secs and water absorption ratio of 95.52±0.16% and In-vitro fast dissolution profile of 97.92% within 10 minutes.

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