

Arabinoxylan from *Plantago ovate* (Husk) a Novel Binder and Superdisintegrant

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ABSTRACT: The aim of the present investigation was to evaluate the binding and disintegrating properties of arabinoxylan isolated from Ispaghula (*Plantago ovata*) husk. Atenolol and atorvastatin orodispersible tablet F1, F2 and F3 were prepared by direct compression method using arabinoxylan (12, 9, 6) mg as superdisintegrant, and F4 and F5 containing 12 mg Ispaghula husk and 12 mg sodium starch glycolate, respectively. Metformin tablets were prepared by wet granulation method F1 containing starch as binder, F2 containing arabinoxylan as binder and F3 containing arabinoxylan as binder and as superdisintegrant. Prepared tablets were evaluated for precompression parameters such as compatibility studies, bulk density, tapped density, angle of repose, Hausners ratio and Cars index and post compression parameters such as weight variation, hardness, thickness, diameter, wetting time, water absorption ratio disintegration time drug release and moisture uptake studies. Attempts were done to trace the possible disintegrant mechanism of arabinoxylan. FTIR spectra of physical blend of atenolol, atorvastatin, metformin with arabinoxylan confirmed the compatibility of excipient with formulation ingredients. All the formulations of atenolol, atorvastatin satisfied the limits of redispersion with a dispersion time of less than 60 sec. F1 showed minimum disintegration time 4 sec providing the evidence of arabinoxylan an excellent superdisintegrant when compared with F4 containing Ispaghula husk with disintegration time 30 sec and F5 contains sodium starch glycolate having disintegration time of 35 sec. Minimum wetting time of 17 sec and high water absorption ratio of F1 formulation confirmed the arabinoxylan as swelling disintegrant. The results of metformin tablet indicate that arabinoxylan could be useful to produce tablets with desired characteristics for specific purposes, and could be used as an alternative substitute binder and superdisintegrant in pharmaceutical industries. These studies provide a strong evidence for usefulness of arabinoxylan as binder and superdisintegrant and a good alternative to natural and synthetic superdisintegrant.

Key words: Orodispersible, arabinoxylan, superdisintegrant, binder

INTRODUCTION

Pharmaceutical industry is striving to satisfy the therapeutic needs of patients by the use of innovative materials and techniques in drug product design. In drug development in addition to active drug excipients play a major role, excipients included in tablet dosage form are diluent, binder, disintegrant, lubricant and glidant.¹

Binders are added to add cohesiveness to powders thereby providing the necessary bonding to form granules which under compaction form a compact mass as tablet. Binders are usually selected

on basis of previous experience, particular product needs, literature or vendor data or the preference of individual scientists or manufacturing unit.²

Disintegrants are the hydrophilic substances which swell by absorbing water in the gastrointestinal tract which leads to swelling and hence disintegration of tablet into smaller fragments facilitating the breakup of a tablet after oral administration.³

Excipients from natural sources have been preferred over synthetic one because of their safety, biodegradability and low cost.⁴ Certain excipients in formulations such as native corn starch act both a binder and disintegrant. As a binder, the starch is converted to a paste before adding it to the wet granulation. As a disintegrant, it is added dry to the powder blend.⁵

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Ispaghula (*Plantago ovata*) plant is grown in Indo-Pak subcontinent, this plant is generally cultivated as a 'Rabi' or post rainy season crop (October - March).⁶ Ispaghula husk consist of dried seeds of the plant. It contains 20-30% mucilages which are present in the epidermis of seeds. Ispaghula seeds and husk mucilages are highly branched acidic arabinoxylan that are chemically polysaccharides.⁷ Its husk and isolated mucilage have number of pharmaceutical applications as they are used as binder, thickening agent, superdisintegrant and also used in the design of sustained release formulations.⁸ However a little works has been done on exploring the pharmaceutical applications of arabinoxylan isolated from husk.

Certain disorders such as hypertension and hypercholesterolemia frequently coexist and may require concomitant therapy.⁹ Borghi *et al.*¹⁰ found that patients taking concomitant statin and antihypertensive therapy could experience a reduction in B.P. that was not possible by using these therapies alone. In severe cardiovascular problems the combination therapy of atorvastatin and atenolol may be useful and effective.¹¹ Combined bilayered tablet of atenolol and atorvastatin have been formulated by Dey *et al.*¹², but orodispersible tablet of this combination have not yet been formulated.

The present investigation is designed to evaluate the use of arabinoxylan as superdisintegrant in the design of orodispersible tablet of atenolol and atorvastatin and to compare its effects with husk and other synthetic superdisintegrant. This study also explores the disintegrating and binding properties of arabinoxylan in metformin tablet in comparison with starch and sodium starch glycolate.

MATERIALS AND METHODS

Atenolol, atorvastatin and metformin were obtained as gift from Warrick Pharmaceuticals, Islamabad, Pakistan. Ispaghula husk was purchased from local market of Sargodha, Pakistan. All other chemicals like sodium starch glycolate, talc, microcrystalline cellulose and saccharine sodium starch, magnesium stearate were of analytical grade.

Isolation of arabinoxylan. Arabinoxylan was isolated from the husk by method of Shazia *et al.*¹³ 100 g of Ispaghula seed husk was soaked in 5 liters of distilled water over night. Sodium hydroxide aqueous solution (2.5%) was added to the mixture to adjust the pH 12 and after stirring of two to three minutes the husk was separated from the gel by vacuum filtration. Sample was coagulated with concentrated acetic acid at pH 3. The gel obtained was washed several times with distilled water over a period of 2-3 days until the pH remained constant and freeze dried for 1 week. The yield of gel was about 45%.

Preparation of orodispersible tablets of atenolol and atorvastatin. Orodispersible tablets of atenolol and atorvastatin were prepared by direct compression method in which all the ingredients required for preparation of mouth disintegrating tablets were passed through mesh 60 separately. Then all ingredients were weighed and mixed by tumbling in a polythene bag and compressed by using 8 mm round flat punches on 10 station rotary tablet machine.¹⁴ Six formulations (F1, F2, F3, F4, F5, F6) of orodispersible tablets were compressed containing different superdisintegrants as shown in Table 1.

Table 1. Formulation of atenolol & atorvastatin tablets.

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Atenolol	50	50	50	50	50	50
Atorvastatin calcium	5	5	5	5	5	5
Arabinoxylan	12	9	6	-	-	-
Ispaghula husk	-	-	-	12	-	-
Sodium starch glycolate	-	-	-	-	12	-
Mg-stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Microcrystalline cellulose	76	79	82	76	76	82
Saccharine sodium	3	3	3	3	3	3
Total weight	150 mg					

Formulation of metformin tablets. Metformin tablet was prepared by wet granulation method.¹⁵ Metformin and all excipients were weighed and passed through 1.0 mm sieve and mixed for 10 minutes. Purified water was used as granulating fluid to form wetted mass of formulation wetted mass was then granulated by passing through a 25 mm sieve. Granules were then dried in an oven at 40 °C for 1 hr. Dried granules were passed through 1 mm screen. Finally 1% w/w of superdisintegrant and 2% w/w of lubricant added and compressed as tablet. F1 contains starch as binder, F2 arabinoxylan as binder and F3 arabinoxylan as binder and as superdisintegrant.

Table 2. Formulation of metformin tablet.

Ingredients	F1	F2	F3
Metformin	500	500	500
Starch	31.25	-	-
Arabinoxylan (binder)	-	31.25	31.25
Sodium starch glycolate	12.5	12.5	-
Arabinoxylan (superdisintegrant)	-	-	12.5
Microcrystalline cellulose	93.75	93.75	93.75
Magnesium stearate	6.25	6.25	6.25
Total weight	650 mg		

Evaluation of mixed blend of drugs and excipients

FTIR Studies. The FTIR spectra were recorded for pure drugs atenolol, atorvastatin, metformin and their physical mixture with arabinoxylan. The pellets were prepared in KBr press (2 mg sample in 200 mg KBr) under a hydraulic pressure of 150 kg/cm².¹⁶

Bulk density, tapped density. Bulk density was measured by method I of United state Pharmacopeia¹⁷. For atenolol atorvastatin tablet 100g of powder containing drug and all excipients passed through sieve 60 and mixed in polyethylene bag by tumbling added in a dry 250-mL cylinder without compacting. For metformin tablet granules were treated according to above mentioned method. Powder was leveled without compacting and apparent volume, V_o , to the nearest graduated unit was noted. Bulk density was then calculated in g per ml, by the formula: $(M) / (V_o)$

Tapped density was measured according to method I of United state pharmacopeia.¹⁷ Mixed blend of drug and excipients passed into a dry 250-

mL glass graduated cylinder (readable to 2 mL) without compacting, apparent volume V_o was noted.

Cylinder was tapped initially 500 times by raising the cylinder and allowing it to drop under its own weight and tapped volume V_a was noted. The tapping was repeated additional 750 times and noted the tapped volume, V_b . V_b is considered the final tapped volume V_f if the difference between two volumes is less than 2%.

The tapped density was calculated in g per mL, by the formula: $(M) / (V_f)$

Measures of powder blend compressibility.

The compressibility index and Hausner ratio are the simple, fast and most commonly used methods for powder flow determination.

Compressibility Index was calculated by the formula:

$$\frac{100(V_o - V_f)}{V_o}$$

Hausner Ratio was calculated by the formula:

$$\frac{V_o}{V_f}$$

Angle of repose. The angle of repose, of premixed blend of active and excipients was measured according to the fixed funnel and cone method¹⁸. According to this method graph paper placed on a flat horizontal surface and a funnel was clamped with its tip 2 cm above paper. The powder was carefully poured through the funnel until the cone thus formed just reached the tip of the funnel. The height (h), of the powder cone and the mean diameter (D), of the base of the powder cone was determined and the angle of repose calculated using the equation:

$$\tan \theta = 2h / D$$

In-vitro evaluation of the prepared tablets.¹⁹

Weight variation test. Twenty tablets were selected randomly from each formulation and weighed on electrical weighing balance (Shimadzu, Japan). The average weight was calculated by dividing total weight with number of the tablets. The weight variation range was established by ± 7.5 mg

for atenolol and atorvastatin and ± 5 for metformin tablet.

Tablet hardness. Tablets were selected from each formulation and placed horizontally between two arms of the digital hardness tester (Pharma Test Germany). After breakdown of each tablet the hardness value was noted. Average of three values was determined.

Tablet thickness and diameter. In determining thickness and diameter of the tablets, tablets were placed vertically between two arms of the digital apparatus (Pharma Test Germany) and values were noted from screen of instrument.

Friability. Friability of the tablets was calculated by using Roche Friabilator (Pharma Test Germany). Twenty tablets were selected, weighed on electronic weighing balance (Shimadzu, Japan) and their weight was noted as initial weight. Tablets were placed in the drum of Friabilator. The Friabilator was operated at a speed of 25 rpm for 4 minutes. After 4 minutes tablets were removed, dedusted and re-weighed in order to determine final weight of the tablets.

Friability of the tablets was calculated by using following formula

$$\text{Friability (f)} = (1 - W_o/W) \times 100$$

W_o = Weight of tablets before the test

W = Weight of tablets after the test

The weight loss should not be more than 1%.

Tablet disintegration. One tablet was placed in each tube of disintegration apparatus (Pharma Test Germany). Buffer solution of pH 6.8 was placed in the basket and temperature was maintained at $37^\circ\text{C} \pm 2^\circ\text{C}$. pH of the solution was confirmed by pH meter (Jenway 3510 Felsted, Dunmow Essex). The time required for complete disintegration of the tablets was noted.

Wetting time and water absorption ratio. The WT of the tablets was evaluated ($n = 5$) by a slight modification of method of Doijid *et al.*²⁰ Five circular tissue paper of 10 cm placed in petridish 10 cm in diameter. A small volume of 10 ml water soluble dye like eosin solution added to the petridish. The tablet was carefully placed on the filter paper at t

$= 0$ and the time for complete wetting were measured. The appearance of the dye on the surface of the tablet was taken as a sign for complete wetting.

The wetted tablet was then weighed and water AR was calculated according to formula given below

$$\text{AR} = (W_a - W_b)/W_b$$

Where W_a and W_b are the tablet weights after and before wetting.

Moisture uptake studies. 5 tablets of each formulation F1, F2, F3, F4, F5 of atenolol atorvastatin were placed in desiccator for 24 hours. Tablets then weighed and exposed to 75% humidity at room temperature for 2 weeks. Tablets were weighed and % increase in weight was recorded.

In-vitro drug release / dissolution studies. *In vitro* drug release studies of atenolol atorvastatin orodispersible tablets were performed in phosphate buffer of pH 6.8. USP type-2 apparatus (Pharma Test Germany) was used and operated with a speed of 50 rpm at 37°C . Samples were withdrawn at an interval of 3 minutes until complete dissolution results. The amount of the sample withdrawn was replaced by 6.8 pH buffer solution. The samples were analyzed for atenolol and atorvastatin calcium at wavelengths 243 and 225 nm respectively on UV-visible spectrophotometer (Pharma Spec 1700 Shimadzu Japan) after dilution and filtration to study the release of drug from different formulations.²¹ For metformin tablet dissolution media was phosphate buffer of pH6.8 paddle speed 50 rpm and samples were taken at 5 minute interval and absorbance taken at 233 nm.

RESULTS AND DISCUSSION

The search for new excipients such as binder and superdisintegrant from natural sources is the major research era now a days. The main criteria for selection of any binder or superdisintegrant are its compatibility with other ingredients of formulations. FTIR spectra shown in figure 1 and 3 showed the compatibility of arabinoxylan with atenolol, atorvastatin and metformin as no shift of bands and no additional peaks were observed.

Since, the flow properties of the powder mixture are important as they assure the uniformity of mass of

the tablets¹⁴, the flow of the powder mixtures were analyzed before compression to tablets, table 1 showed precompression parameters of orodispersible tablet (atenolol and atorvastatin), F1, F2, F3 had angle of repose 40, 36, 38, respectively H.R 1.31 and C.I. 24 indicating passable flow according to flowability scale of USP, while powder mixtures of F4 and F5 containing ispaghula husk and sodium starch glycolate as superdisintegrant were poor flowing with angle of repose 44 and 50 and H.R. 1.42, 1.51 and C.I. of 29.62 and 33.96.

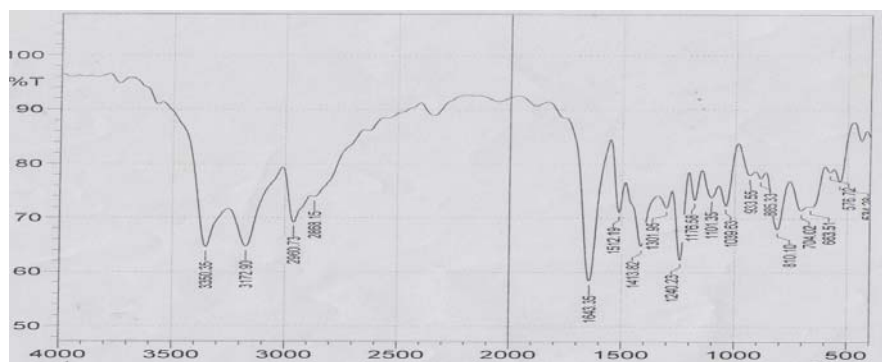
Metformin tablet powder of F1 and F2 showed good flow properties with angle of repose 34, 36 H.R 1.1 and C.I. 9.09 and 10 as shown in table 6, while

F3 showed passable flow properties according to USP scale.

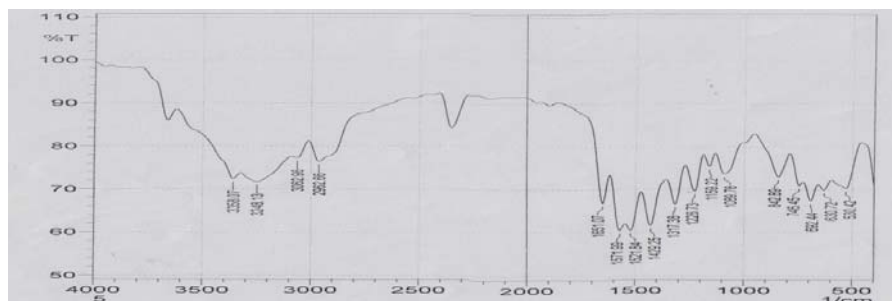
Postcompression parameters of orodispersible tablet of atenolol and atorvastatin are shown in table 4 and in figure 2 and metformin tablet in table 7. All the five formulation have the hardness, thickness and diameter according to specifications and showed friability less than 1% which showed good mechanical strength F1 showed minimum disintegration time 4 sec providing the evidence of arabinoxylan an excellent superdisintegrant when compared with F4 containing ispaghula husk with disintegration time 30 sec and F5 sodium starch glycolate 35 sec.

Table 3. Precompression parameters of atenolol and atorvastatin tablets.

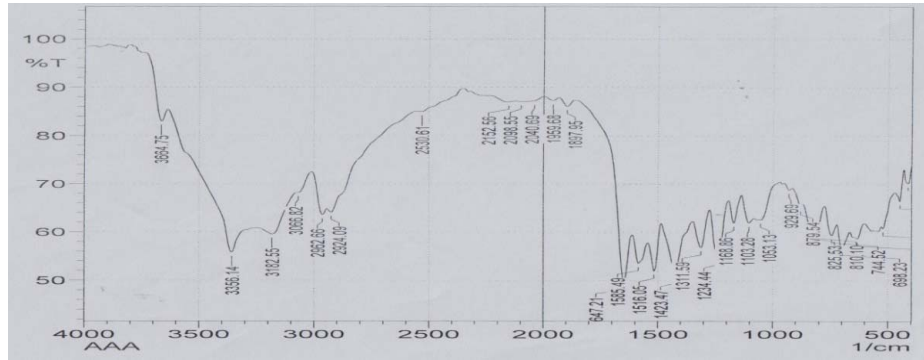
Code	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (($^{\circ}$))	Hausner's ratio	Carr's index (%)
F1	0.38 ± 0.01	0.5 ± 0.01	40 ± 1	1.31	24.00
F2	0.38 ± 0.00	0.5 ± 0.01	36 ± 1	1.31	24.00
F3	0.38 ± 0.00	0.5 ± 0.01	38 ± 0.5	1.31	24.00
F4	0.38 ± 0.01	0.54 ± 0.01	44 ± 2	1.42	29.62
F5	0.35 ± 0.01	0.53 ± 0.01	50 ± 0.5	1.51	33.96



a) Atenolol



b) Atorvastatin



c) Atenolol, atorvastatin and arabinosylan

Figure 1. FTIR spectra of atenolol, atorvastatin and physical blend of drugs with arabinosylan.

Table 4. Postcompression parameters of orodispersible tablets of atenolol and atorvastatin.

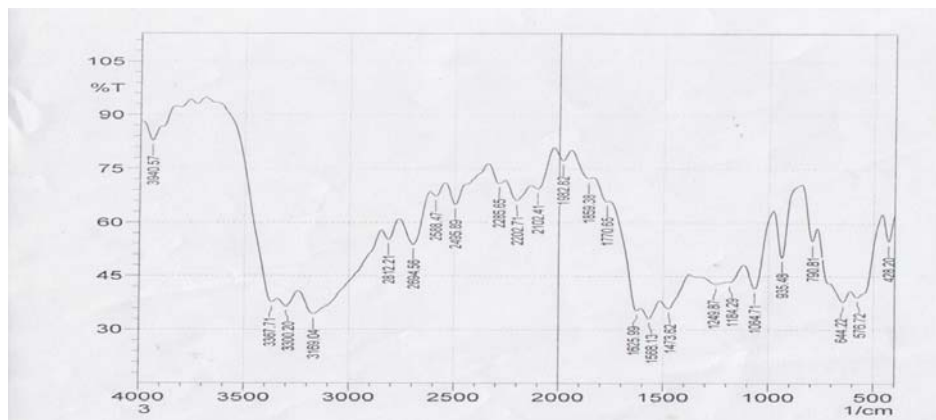
Parameters	Wt. variation (mg)	Diameter (mm)	Hardness Kg/cm ²	Thickness (mm)	Friability (%)	Disintegration time (Sec)
F1	143.6 ± 0.15	6.84 ± 0.04	2.9 ± 0.1	2.89 ± 0.01	0.61 ± 0.01	4 ± 1.00
F2	140.89 ± 0.11	6.85 ± 0.01	2.8 ± 0.0	3 ± 0.02	0.72 ± 0.01	6 ± 1.00
F3	142.8 ± 0.21	6.9 ± 0.00	3 ± 0.1	2.9 ± 0.01	0.51 ± 0.00	8 ± 1.00
F4	149.2 ± 0.18	6.91 ± 0.01	3 ± 0.2	2.9 ± 0.00	0.52 ± 0.02	30 ± 1.53
F5	148.03 ± 0.12	6.85 ± 0.02	3.2 ± 0.2	3.0 ± 0.01	0.51 ± 0.01	35 ± 1.00

Table 6. Precompression parameters of metformin tablets.

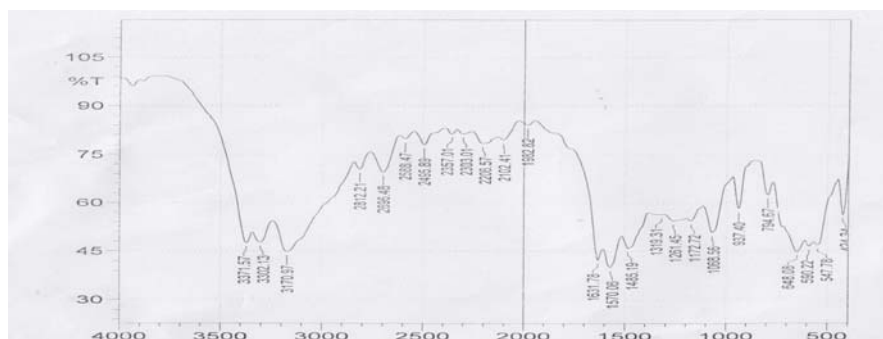
Code	Bulk density g/ml	Tapped density g/ml	Angle of repose (°)	Hausner's ratio	Carr's index %
F1	0.35 ± 0.01	0.39 ± 0.01	34 ± 2	1.1	9.09
F2	0.52 ± 0.00	0.58 ± 0.01	36 ± 0.5	1.1	10
F3	0.45 ± 0.01	0.6 ± 0.00	41 ± 1	1.33	25

Table 7. Postcompression parameters of metformin tablets.

Parameters	Wt. variation (mg)	Diameter (mm)	Hardness (Kg/cm ²)	Thickness (mm)	Friability (%)	Disintegration* time (min)
F1	645 ± 0.15	11 ± 0.5	6.0 ± 0.1	5.1 ± 0.1	0.91 ± 0.01	14 ± 1.00
F2	647 ± 0.21	10.7 ± 1	5.5 ± 0.3	5.1 ± 0.0	0.84 ± 0.01	4.5 ± 1.50
F3	644 ± 0.21	10.6 ± 0.3	6.0 ± 0.1	5.1 ± 0.1	0.88 ± 0.00	2.5 ± 1.00



a) Metformin



(b) Metformin and arabinoxylan

Figure 3. FTIR spectra of metformin (a) and physical blend of metformin with arabinoxylan (b).

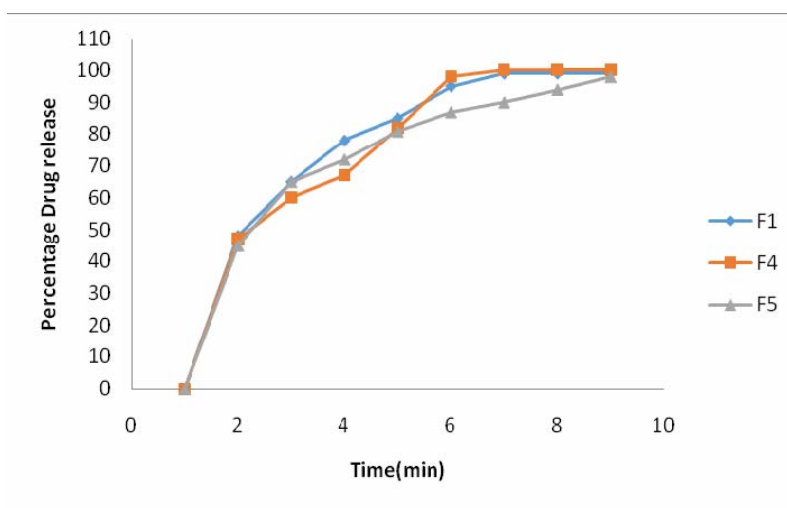


Figure 4. *In vitro* release profile of atenolol from orodispersible tablets.

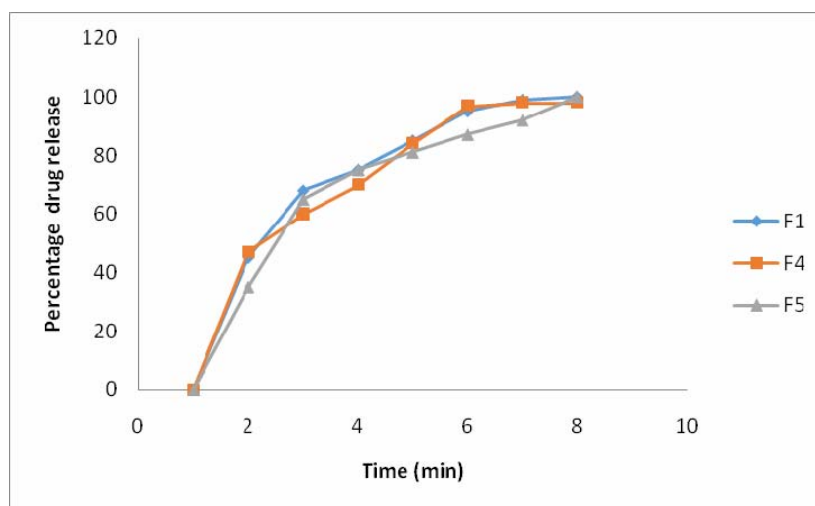


Figure 5. Release profile of atorvastatin from orodispersible tablets.

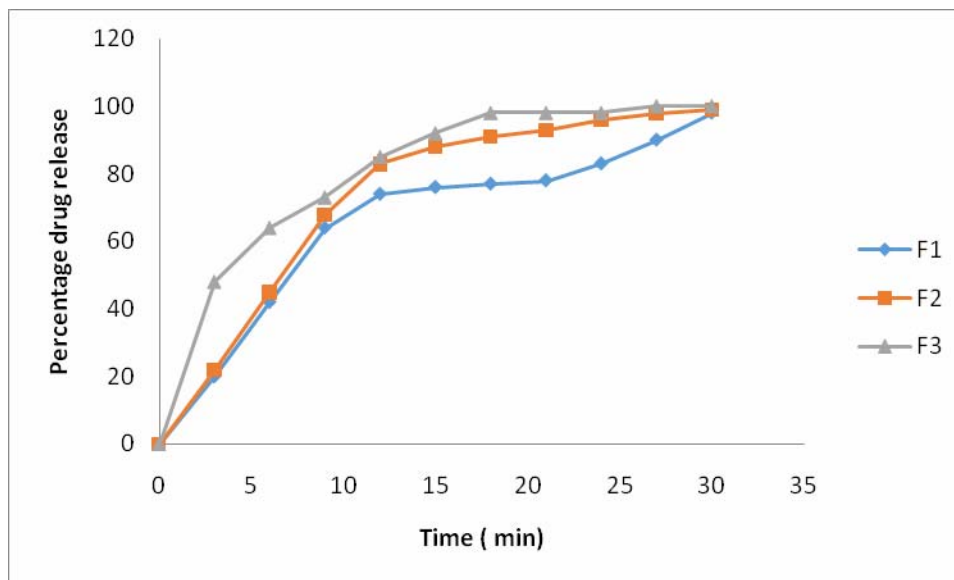


Figure 6. *In vitro* release profile of metformin tablets.

The disintegration mechanism of the arabinoxylan and ispaghula husk was determined by wetting test and water absorption ratio. Both disintegrants were classified as the swellable disintegrant as they showed significant swelling on contact with water and this was evident in our results as F1 formulation showed swelling ratio of 1.946 within minimum wetting time of 17 sec, F4 1.088 swelling ratio with 26 sec of wetting time as shown in figure 2. Arabinoxylan isolated from husk has high swelling index and average water retention value of 8100% as determined Jayme and Roffael²² and most probably this was reason that F1 showed minimum disintegration time. F5 containing sodium starch glycolate in spite of showing maximum water absorption ratio 2.11 and wetting time of 26 sec showed maximum disintegration time among all other superdisintegrants this behaviour of sodium starch glycolate was in accordance with literature²³.

Moisture uptake studies confirmed the stability of all formulation in the presence of moisture. All metformin tablet formulations satisfied the limits of hardness, thickness and diameter, all the tablets were within specification for friability i.e. less than 1%. F1 (containing starch as binder and sodium starch glycolate as superdisintegrant) showed the disintegration time of 14 minutes. F2 (containing

arabinoxylan as binder and sodium starch glycolate as superdisintegrant) showed disintegration time of 4.5 minutes while F3 (containing arabinoxylan both as binder and superdisintegrant) showed disintegration time of 2.5 minutes, this study further strengthen our finding that arabinoxylan a better superdisintegrant than sodium starchglycolate and ispaghula husk.

In vitro release profile of orodispersible tablet of atenolol atorvastatin showed that F1 and F4 showed almost 98% -100% drug release of both atenolol and atrovastatin within 18 minutes while in F5 98% of atenolol release in 24 min and 100 % atrovastatin release in 21 minutes. In metformin tablet F1 showed 98% release in 30 minutes, F2 99% release in 30 minutes, and F3 showed rapid drug release almost 98% in 18 minutes.

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