- Short communication

Preparation and *In vitro* Evaluation of Orally Disintegrating Tablets (ODTs) of Alprazolam

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Orally disintegrating tablets (ODTs) are different from other conventional oral tablets in terms of rapid disintegration of the tablet on the tongue rather than swallowing. This is convenient and advantageous for the patients who face difficulties in swallowing for instance, pediatric, geriatric, bedridden, physically and mentally retarded, psychiatric patents. Moreover, fast disintegration of orally disintegrating tablets leads to faster dissolution and absorption, producing rapid onset of action.[1-3]

Alprazolam is short acting banzodiazepine anxiolytic which is used in the treatment of anxiety and panic disorder.[4] It is rapidly absorbed after oral administration having the onset of action in 0.7 to 1.8 hours with absolute bioavailability of 80 to 100%. The elimination half-life is 9 to 16 hours and 80% of drug binds to serum protein, mainly albumin.[5]

Alprazolam conventional oral tablets are available in 0.25 mg and 0.5 mg tablet in Bangladesh. However no orally disintegrating tablet is available in market of Bangladesh. Besides, alprazolam ODT is only available in USA as brand Niravam which is manufactured by SCHWARZ Pharma.[6] Therefore, the aim of this present study is to formulate orally disintegrating tablet of alprazolam by using various concentrations of different superdisintegrants such as croscarmellose sodium, sodium starch glycolate and crospovidone to compare and evaluate their effects on various quality parameters of the tablets.

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To formulate alprazolam ODT**,** active pharmaceutical ingredient and other excipients were measured individually according to the proposed formulation shown in table 1 and blended in mortar and pestle for 10 minutes. Then the mixture was passed through a 40 number mesh size aperture and collected. Finally, the blend was compressed using rotary punch machine. Total nine batches of alprazolam ODT were prepared by direct compression method.

Pre-compression parameters of the formulation mixture such as angle of repose[7,8], Carr's index and Hausner's ratio were evaluated for ensuring proper flow property of powder mix[9]. Prepared nine batches (A1-A3, B1-B3 and C1-C3) were evaluated by performing weight variation test, friability test, hardness test, measurement of diameter and thickness, wetting time, dispersion time, dissolution study and potency test.

Ten randomly selected tablets from each batch were weighed individually and all together by electric balance. The average weight and the percentage deviation of the tablets were then calculated. As per US Pharmacopoeia (USP), the acceptable limit of weight variation is ±10% for tablet weight of less than or equal to 130 mg.[10,11] For hardness testing, three tablets from each batch were taken and placed vertically in a digital hardness tester.[12] The machine was then pressed and the breaking point of the tablet was noted. Generally, the acceptable value of crushing strength for tablet is 2-3 kg/cm^2. For friability testing, three alprazolam tablets from each

batch were weighed individually and then placed in a Roche friabilator at 25 rpm/min for 4 minutes. The final weight was calculated and % friability was measured.[12,13]According to the specification, the % friability value must be less than or equal to 1%.To measure diameter and thickness, three tablets were taken from each batch individually and measured by digital slide calipers and average diameter and thickness were calculated.

For wetting time calculation, a piece of tissue paper folded twice was kept in a petri dish of 5.7 cm inner diameter, containing 6 ml of purified water. One tablet from each batch was placed on the tissue paper and allowed to wet completely. The time required for complete wetting of the tablet was then noted.[12,14] Dispersion time was calculated by taking one tablet from each batch and kept individually in the center of a petri dish (5.7 cm diameter) which was previously filled with 9 ml of phosphate buffer solution simulating the pH of saliva. Then the time required for the tablet to completely disintegrate into fine particles was noted.[12]

Dissolution test was performed using USP type-II apparatus and 900 ml of phosphate buffer (PH 6.8) as the dissolution medium. Three tablets from each batch were taken for this test and the dissolution apparatus was set at 50 rpm and 37ºC ± 0.5ºC for 40 minutes. Five ml of aliquots were periodically withdrawn and filtered. The sample volume was replaced with an equal volume of fresh dissolution medium. Then, 0.2 ml of filtrate solution was taken and made 10 ml for 50 times dilution by using phosphate buffer of pH 6. Finally, the samples were analyzed spectrophotometrically at 260 nm.[11, 15]For potency testing, one tablet from each batch was taken and crushed with a mortar and pestle. The powder sample equivalent to 10mg of alprazolam was weighed and dissolved in suitable quantity of phosphate buffer (pH 6.8). The volume was adjusted to 100ml with the phosphate buffer (pH 6.8). The drug content was analyzed using UV spectrophotometer at 260 nm.[10, 16]

The data obtained from angle of repose indicated excellent flow property of the powder bed of nine batches. Carr's index and Hausner ratio showed good flow property of the formulation, according to the specification[17].

Weight variation, diameter and thickness test, hardness, friability test of all nine batches showed less deviation which clearly indicates batch uniformity meeting the specification of USP. The results of wetting time and dispersion time showed that all the batches are in the specification. Among the nine batches, batch A3 and C2 showed lowest wetting time (22 seconds) and A1 showed lowest dispersion time (2.18 minutes). The results of pre-compression and physicochemical parameters of nine batches are shown in table 2.

Table 1. Formulation of alprazolam orodispersible tablet (all amounts taken in mg)

Ingredients	A1	A2	A3	B1	B2	B3	C1	C2	C3
Alprazolam	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Cross-povidone	5	3.13	6.25	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	5	3.75	8.75	-	-	-
Crosscarmellose sodium	-	-	-	-	-	-	2.5	1.25	6.25
Microcrystalline cellulose	80	80.94	79.38	80	80.63	78.13	81.25	81.88	79.38
Sodium saccharine	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Aerosil	0.625	0.625	0.625	0.625	0.625	0.625	0.625	0.625	0.625
Mannitol	28.88	29.81	28.25	28.88	29.5	27	30.13	30.75	28.25
Pre-gelatinized starch	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25

Table 2. Pre-compression and physicochemical parameters of the prepared batches.

Parameter	A1	A2	A3	B1	B2	B3	C1	C2	C3
Pre-compression parameters									
Angle of repose (^{0})	17.74	18.39	27	29.25	25.7	27.26	23.66	18.39	23.25
Carr's index (%)	12.12	13.15	13.15	7.4	14.64	19.51	26.67	8.18	11.62
Hausner's ratio	1.14	1.15	1.15	1.08	1.17	1.24	1.36	1.09	1.13
Physicochemical parameters									
Weight variation	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Friability (%)	0.26	0.08	0.26	0.27	0.41	0.14	0.13	0.1	0.52
Hardness (kg/cm^2)	2.92	2.63	3.67	5.39	4.17	4.86	2.71	2.27	3.41
Diameter (mm)	7.057	7.073	7.057	7.07	7.05	7.09	7.043	7.097	7.083
Thickness (mm)	3.32	3.23	3.44	3.18	3.29	3.68	3.27	3.55	3.42
Wetting time (sec)	31	33	22	29	33	31	35	22	27
Dispersion time (min)	2.18	3.5	2.44	3.45	3.29	3.35	2.45	2.34	3.1

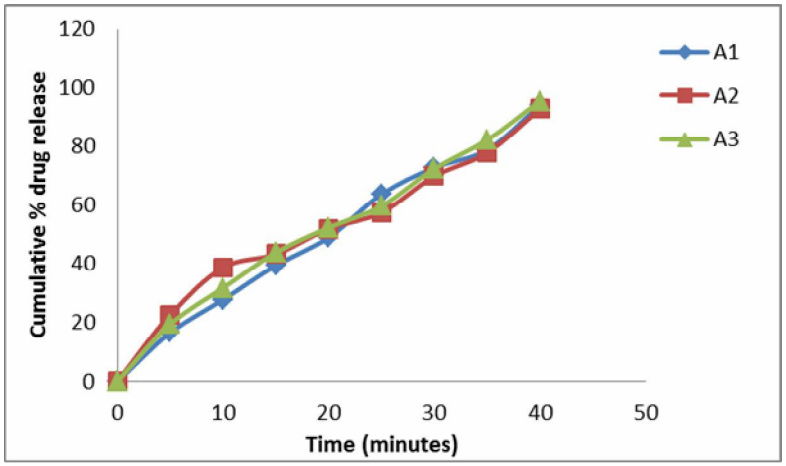

Figure 1. *In vitro* drug release profile of batch A1-A3.

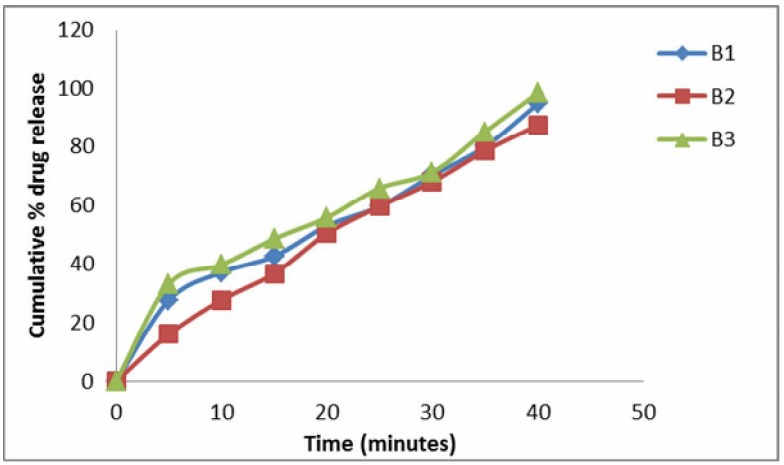

Figure 2. *In vitro* drug release profile of batch B1-B3.

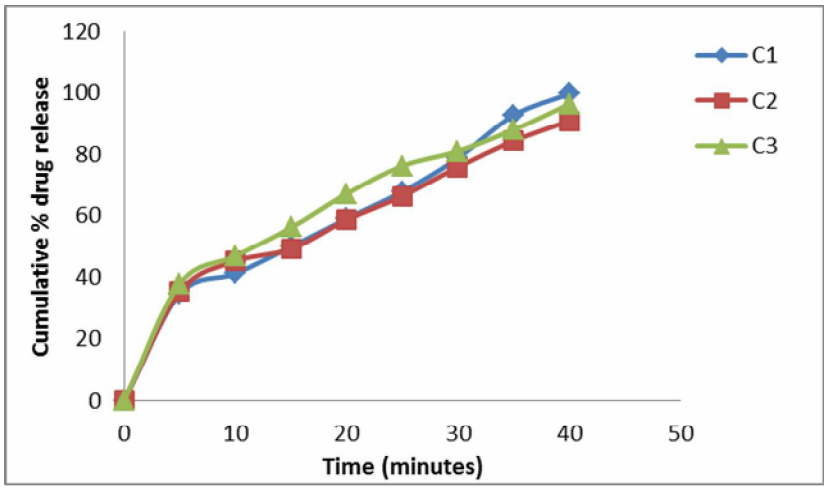

Figure 3. *In vitro* drug release profile of batch C1-C3.

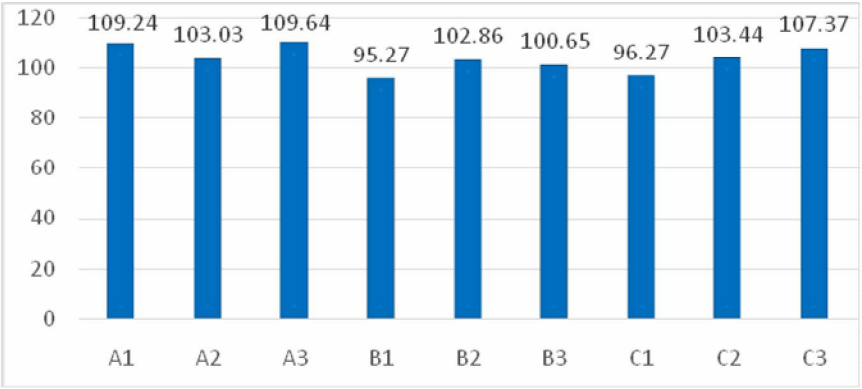

Figure 4. Potency (%) of prepared formulations.

After performing dissolution study, it has been found that all the batches except B2 showed more than 90% of drug release in 40 minutes. Therefore, from the experiment it can be claimed that, croscarmellose sodium at 2.5, 4 and 5% concentrations (range 0.5-5% w/w), sodium starch glycolate at 3%, 4% and 7% concentrations (range 2-8% w/w) and crospovidone at 1%, 2% and 5% (range 2-5% w/w) concentrations can be used for formulating alprazolam orally disintegrating tablets. In vitro drug release profile of batches (A1-Ac, B1-B3 and C1-C3) is shown in figures 1, 2 and 3. Comparing the data obtainedform the dissolution study of nine batches, it is evident that Batch C1-C3 using crospovidone as superdisintegrant showed excellent percent drug release (34.39-99.61%) in 40 minutes.

According to the specification, the acceptable potency range for drug potency is not less than 90 % and not more than 110% for most low dose drugs. Figure 4 shows the result of the potency test and it has been found that all the batches met this specification (95.27 - 109.64%) and batch A3 had the highest drug content.

The study of formulating and evaluating nine different batches of alprazolam orodispersible tablets using three different superdisintegrants draws a comparison among the batches on different quality

parameters. It can be concluded that, among the nine batches, batch C shows satisfactory result as an orally disintegrating formulation of alprazolam using crospovidone as superdisintegrant.

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