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FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLET OF AZITHROMYCIN BY DRY GRANULATION METHOD USING SUPER DISINTEGRANTS.

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ABSTRACT

The task of developing immediate release tablet is accomplished by using a suitable diluents and super-disintegrants. Faster disintegration of the tablet administered orally minimizes absorption time and improves its bioavailability in less time. Immediate Release tablet of Antibiotic drug is formulated using dry granulation using super disintegrant croscarmellose sodium. Azithromycin is Antibiotic drug is used to treat STDs due to Chlamydia and gonorrhoea, community-acquired pneumonia, pelvic inflammatory disease, pediatric otitis media and pharyngitis, and Mycobacterium avium complex (MAC) in patients with advanced HIV disease. One of the important studies included in the present investigation is of study on process parameter effect on performance of the Immediate Release tablets. The effect of selected process parameters on critical properties of immediate release (IR) tablets were studied, like effect of disintegration time, friability, dissolution profile.

Key words: Immediate release, Azithromycin, Croscarmellose sodium

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INTRODUCTION

Many patients especially children and elderly have difficulty in swallowing tablets and capsules and consequently unable to take medicine as prescribed. Almost 50% of the population is affected by such problem, resulting in the high incidence of non compliance and ineffective therapy. Most pharmaceutical forms for oral administration are formulated for direct ingestion, or for chewing, or for prior dispersion and/or dissolution in water; some of them are absorbed in the mouth (sublingual or buccal tablets). To obviate the problems associated with conventional dosage forms, orally immediate release tablets have been developed, which combine hardness, dosage uniformity, stability and other parameters, with extremely easy administration, since no water is required for swallowing the tablets and they are thus suitable for geriatric, pediatric and traveling patients^{1,2,3}.

Pharmaceutical products designed for oral delivery and currently available on the prescription and over-the-counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption. Disintegrating agents are substances routinely included in tablet formulations and in some hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids. Super-disintegrant improves disintegrant efficiency resulting in decreased use levels when compared to traditional disintegrants^{4,5,6}.

Azithromycin is Antibiotic drug of macrolide class is used to treat STDs due to Chlamydia and gonorrhea, community-acquired pneumonia, pelvic inflammatory disease, pediatric otitis media and pharyngitis, and Mycobacterium avium complex (MAC) in patients with advanced HIV disease. Elimination half life is 68 hrs and orally absorption is about 40%⁷.

MATERIAL AND METHODS

Materials used in this study were obtained from the different sources. Gift sample of Azithromycin was obtained from Alembic research center, vadodara, India, Calcium hydrogen phosphohydrogen phosphate anhydrous were gifted from Signet Chem. Ltd, Mumbai, Super disintegrating agent Croscarmellose sodium was obtained from FMC, Sodium lauryl sulfate and Magnesium stearate were obtained from Cogniz ,India.

Formulation approach: Dry Granulation method^{8,9,10,11,12,13}

Drug and Di-calcium hydrogen phosphate were dispensed and passed through 30 #. Sift Pregelatinised starch and Croscarmellose sodium through # 30 and blend of above step for dry mixing for 5 min. Transfer the pre mixed blend obtained from above step, to the hopper of roll

and start compaction. Set the pressure gauge of the machine so as to get suitable slug hardness. Separate the retained good slug using sifter fitted with 12 # sieve and re compact the fines. Repeat the cycle till suitable good slug obtained. The slug was then pass through 1 mm screen, for uniform sizing of the granules. Then % yield was calculated and from that amount of extra granular excipients to be added was calculated. Blending was carried out in cone blender with Sodium lauryl sulfate and magnesium stearate for 5 min. Compression was carried out in tablet compression machine. Formulation for different batch was shown in Table 1.

Table 1: Formulation of tablet by dry granulation method

Batch No.	F1	F2	F3	F4	F5
Ingredients	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab
API	275.0	275.0	275.0	275.0	275.0
Di-calcium hydrogen	110	85.0	90.0	155.0	155.0
Pregelatinised starch	25.0	25.0	25.0	28.0	26.0
Croscarmellose sodium	12.0	11.0	11.0	9.0	11.0
Di-calcium hydrogen	40.0	70.0	65.0	-----	-----
Sodium lauryl sulfate	2.00	3.00	3.00	2.00	2.00
Magnesium stearate	11.0	11.0	11.0	11.0	11.0
Total Weight	480	480	480	480	480

EVALUATIONS:

1. Micromeretics parameters^{14, 2, 3}

Bulk Density (BD):

Weigh accurately 25 g of granules, which was previously passed through #20 sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V_0). Calculate the apparent bulk density in gm/ml by the following formula

$$\text{Bulk density} = \text{Weight of powder} / \text{Bulk volume}$$

Tapped density(TD):

Weigh accurately 25 g of granules, which was previously passed through #20 sieve and transfer in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times initially and measure the tapped volume (V_1) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tapped volume (V_2)

to the nearest graduated units. If the difference between the two volumes is less than 2% then final the volume (V₂). Calculate the tapped density in gm/ml by the following formula.

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped volume}}$$

Carr's Index: The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

$$\text{Carr's Index} = \frac{[(\text{TD}-\text{BD}) * 100]}{\text{TD}}$$

Hausner's Ratio

The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material.

$$\text{Hausner's ratio} = \text{TD/BD}$$

2. Physical parameters^{14, 15, 2, 3}

Hardness:

Tablets require certain amount of strength or hardness and resistance to friability, to with stand mechanical shocks of handling in manufacture, packaging, and shipping. The most widely used apparatus to measure tablet hardness (crushing strength) is the Schleuniger hardness tester.

Friability:

Friability is related to tablets ability to withstand both shocks and abrasion without crumbling during manufacturing, packing, transportation and consumer handling. Friability can be evaluated by means of friability test apparatus. Acceptable limit was not more than 1.0% of three samples.

Method: accurately weighed 6.5 gm of tablet and transfer into Friabilator and subjected to 100 revolutions in 4 minutes. Dedusted tablets were reweighed (final wt).

$$\% \text{ Friability} = \frac{(\text{Initial Weight} - \text{final weight})}{(\text{Initial weight})} \times 100$$

Thickness:

Ten Tablets were selected at random from individual formulations and thickness was measured by using Vernier caliper scale, which permits accurate measurement.

In-vitro disintegration test

The test was carried out on 6 tablets using Tablet disintegration tester. Distilled water at $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$ was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

***In-vitro* dissolution test.**

The release rate of Azithromycin from immediate release tablets was determined using British pharmacopoeia dissolution testing apparatus I (paddle method). The dissolution test was performed using 900 ml of pH 5.0, 6.8, at $37 \pm 0.5^{\circ}\text{C}$ and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at 5, 10, 15, 20, 30, 45 and 60 min. The samples were replaced with fresh dissolution medium of same quantity. Absorbance of these solutions was measured at 210 nm using a Shimadzu UV-1601 UV/Visible double beam spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

RESULT AND DISCUSSION

Preformulation Study of granules:

Density was poor for API as well formulation F1-F4 for various aspects such as flow and weight variation of tablets but finalized density was achieved in F5 which is good for tablet preparations. Result was shown in Table 2

Table 2: Pre-formulation Study of granules

Parameters	F1	F2	F3	F4	F5
Bulk Density	0.553	0.539	0.501	0.549	0.571
Tapped Density	0.678	0.648	0.650	0.662	0.66
Carr's index	18.4	16.32	22.92	17.06	13.4
Hausner Ratio	1.22	1.202	1.30	1.20	1.15

Physical parameters of tablets

Average wt of tablet was found for F1 to F5 formulation in the range of 478 to 481. The thickness was found uniformly for different formulation. For friability capping was found in F1 and F2 formulation. Disintegration time for F1 to F5 formulation from 0.50 to 4 min and % purity was found in the range. Result was shown in Table 3.

***In-Vitro* release study**

The release rate of Azithromycin from immediate release tablets was determined using British pharmacopoeia dissolution testing apparatus I (paddle method). The dissolution test was

performed using 900 ml of pH 5.0, 6.8, at 37 ±0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at 5, 10, 15, 20, 30, 45 and 60 ml.

Rpm was set 50.r.esult was shown in Figure 1 and 2

Table 3: Physical parameters of tablets

Trials	Avg. Tab Wt.(mg)	Thickness (mm)	Hardness in Kp	% Friability	D.T. (min)	Assay (%)
F1	478	5.50 to 5.55	15 to 16	Capping	0.50	98.0
F2	481	5.52 to 5.58	14 to 16	Capping	1 to 1.30	97.5
F3	480	5.57 to 5.60	14 to 16	0.154	2.25 to 3.20	98.7
F4	481	5.58 to 5.60	14 to 17	0.118	2.05 to 3.15	98.0
F5	481	5.57 to 5.60	14 to 16	0.021	3 to 4	99.2

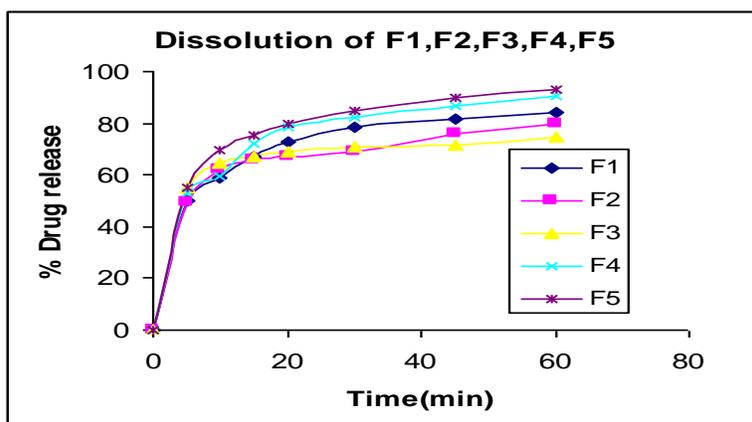


Figure 1: Dissolution of trail batches F1, F2, F3, F4, F5 in pH 5.0

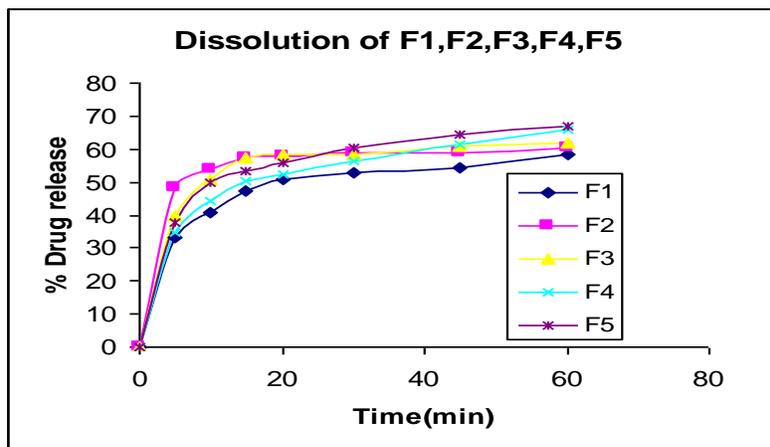


Figure 2: Dissolution of trail batches F1, F2, F3, F4, F5 in pH 6.8

CONCLUSIONS

The prepared granules were evaluated for bulk density, tapped density, Carr's index and Hausner's Ratio. It was found that blend had Carr's index from 13% to 18% and Hausner's Ratio from 1.15 to 1.22, which indicate that ready for compression blend was good flow property and compressibility property. Total formulations were prepared using different grade of DCP, Pregelatinised starch, Croscarmellose sodium in different ratios along with lubricant and wetting agent. The tablets were evaluated for thickness, disintegration, hardness, friability, drug release, wt. variation and assay. The thickness of the tablet varied from 5.45 to 6.20 mm. The disintegrating time was found to be between 3 to 4 min. The hardness was in range of 14 to 16 Kp. Assay for different batches were found to be varied from 97 to 98.2 ± 0.5 indicating the uniformity in drug content within tablets.

The optimized formulation F5 was evaluated for *in vitro* drug release in pH 5.0, 6.8 for 60min using BP type II dissolution apparatus at 50 rpm. Hence Antibiotic drug can be successfully formulated as an immediate release tablet by dry granulation method.

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