International Journal of Current Trends in Pharmaceutical Research

Journal Home Page: www.pharmaresearchlibrary.com/ijctpr

Research Article **Open Access**

Design and *In-Vitro* Characterization of ORO Dispersible Tablets of Azithromycin

H. Padmalatha*

HOD, Pharmaceutical analysis and QA, Gyana Jyothi College of Pharmacy, Boduppal, Hyderabad.

A B S T R A C T

The goal of this project is to formulate Oro-dispersible tablet of Azithromycin that is intended to disintegrate rapidly into the oral cavity and form a stabilized dispersion. A direct compression method was failed to formulate dispersible tablet of Azithromycin so wet granulation method was used. In all the formulations, water was used as a granulating agent. Avicel was used as diluents. Aspartame was used as a sweetening agent. Magnesium stearate and Aerosil were used as lubricant and glidant respectively. FT-IR studies were utilized to obtain the compatibility of the drug and excipients. In preliminary study different super disintegrants Croscarmellose sodium (CCS), Sodium starch glycolate (SSG) and Crospovidone (CPVP) were evaluated for physicochemical parameters of tablet. The simplex lattice design was utilized using amount of intra-granular concentration of super disintegrants, Sodium starch glycolate (A), Croscarmellose sodium (B) and Crospovidone (C) were selected as independent variable. The Hardness (R_1), Disintegration time (R_2), Friability (R_3) and Wetting time (R_4) were selected as dependent variables. A total of 11 formulations with 4 replicas was obtained and optimized. From response surface plot of disintegration time, wetting time, friability and hardness it was found that lower disintegration time of tablets could be obtained when C and B are kept at optimum level. Stability study of final batch showed no significant changes in tablet properties.

Keywords: Azithromycin; Oro-dispersible tablet; Optimization; Disintegration time; FT-IR; Simplex lattice; Wetting time.

A R T I C L E I N F O

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Article History: Received 19 January 2016, **Accepted** 21 February 2016, **Available Online** 15 March 2016

***Corresponding Author**
H. Padmalatha
HOD Pharmaceutical analysis and QA,
Gyana Jyothi College of Pharmacy,
Boduppal, Hyderabad.
Manuscript ID: IJCTPR2840

PAPER-QR CODE

Citation: H. Padmalatha. Design and *In-Vitro* Characterization of ORO Dispersible Tablets of Azithromycin. *Int. J. Curnt. Tren. Pharm, Res.*, 2016, 4(2): 55-62.

1. Introduction

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS make a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance.

Ideal properties of a mouth-dissolving tablet:

Though nothing or nobody is ideal or perfect in this world, yet there are certain limits or characteristics that judge the nearness to perfection. A mouth-dissolving tablet should:

- Not require water or other liquid to swallow.
- Easily dissolve or disintegrate in saliva within a few seconds.
- Have a pleasing taste.
- Leave negligible or no residue in the mouth when administered.
- Be portable and able to tolerate the transportation stress.
- Be able to be manufactured in a simple conventional manner within low cost.
- Be less sensitive to environmental conditions like temperature, humidity etc.

Advantages of Mouth dissolving tablet:

1. No need of water to swallow the tablet.
2. Can be easily administered to pediatric, elderly and mentally disabled patients.
3. Accurate dosingas compared to liquids.
4. Dissolution and absorption of drug is fast, offering rapid onset of action.
5. Bioavailability of drugs is increasedas some drugs are absorbed from mouth, pharynx and esophagus through saliva, passing down into the stomach.
6. Advantageous over liquid medication in terms of administration as well as transportation.
7. First pass metabolism is reduced, thus offering improved bioavailability and thus reduced dose and side effects.
8. Free of risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.
9. Suitable for sustained/controlled release actives.

Criteria for Fast dissolving Drug Delivery System:

The tablets should

- Not require water to swallow but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasant mouth feel.
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.
- Allow the manufacture of the tablet using conventional processing and packaging equipments at low cost.

Salient Feature of Fast Dissolving Drug Delivery System:

1. Ease of Administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.
2. No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
3. Rapid dissolution and absorption of the drug, which will produce quick onset of action.
4. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is increased.
5. Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.
6. Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.
7. The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
8. New business opportunity like product differentiation, product promotion, patent extensions and life cycle management.
9. Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid onset of action required.
10. An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
11. Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

2. Materials and Methods

Materials:

Azithromycin, Crospovidone, Sodium starch glycolate, Croscarmellose sodium, Avicel, Sodium lauryl sulphate, Aspartame, Aerosil, Magnesium stearate.

Methodology:

Determination of UV Absorption maxima:

Azithromycin solution was prepared in 0.1 N HCL and diluted suitably. The UV spectrum of the solution was taken on Shimadzu 1700 UV/Vis double beam Spectrophotometer (Japan). The solution exhibited UV maxima at 210.0 nm.

Preparation of Standard Calibration Curve of Azithromycin:

100 mg of Azithromycin was accurately weighed and dissolved in little amount of ethanol and prepare the final

volume up to 100 ml with 0.1 N HCl (pH 1.2) to prepare stock solution. The 1 ml of stock solution was further diluted with 0.1 N HCl (pH 1.2) in 100ml to get 10 µg/ml (working standard). Then 2,4,6,8 and 10 ml of working standard was taken in 10 ml standard volumetric flask and made up the volume with 0.1N HCl to prepare 2 µg, 4 µg, 6 µg, 8 µg and 10 µg drug per ml solution. Then the absorbance was measured in a UV spectrophotometer at 210 nm against 0.1 N HCl (pH 1.2) as blank.

Tablet formulation:

Formulation of Preliminary Trials of Azithromycin Dispersible Tablet by Direct- Compression: Composition of preliminary trials for Azithromycin Dispersible Tablet by direct compression. All the ingredients were passed through 40-mesh sieve. Required quantity of drug and excipients mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-12 station with 8 mm flat punch, B tooling. Each tablet contains 100 mg Azithromycin and other pharmaceutical ingredients.

Formulation of Preliminary Trials of Azithromycin Dispersible Tablet by granulation: Composition of preliminary trials for Azithromycin Dispersible Tablet by wet granulation shown in table 4.5. Drug is passed through 100 # sieve. All the powders were passed through 60-mesh sieve. Mixture was granulated using water and granules were made passing through 8 # sieve. Granules were dried at 70^{o}C about 10 – 15 min. After drying extragranular part is added, magnesium stearate as lubricant and Aerosil as glidant and mixed in polybag for 5 min. Final blend was passed through 24 # mesh sieve. The blend was compressed using 12 stations 'B' tooling compression machine, 8 mm flat Punch. Each tablet contains 100 mg Azithromycin.

Evaluation parameters:

Pre-compression parameters:

Bulk Density (D_b): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume.

Tapped Density (D_t): It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus).

Angle of Repose (Θ): The friction forces in a loose powder can be measured by the angle of repose (q). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane

Hausner ratio:

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \frac{D_t}{D_b}$$

Where, D_t is the tapped density, D_b is the bulk density.

Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Post compression parameters:

Weight variation:

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P.

Hardness:

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2.

Thickness:

Three tablets were selected randomly from each batch and thickness was measured by using Vernier Caliper.

Friability (F):

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at the height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed.

Wetting time:

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient.

In-Vitro drug release:

Release of the drug *in-vitro*, was determined by estimating the dissolution profile.

Dissolution test:

USP II Paddle apparatus was used and paddle was allowed to rotate at 50 rpm, acid buffer 0.1N HCL (pH 1.2, 900 ml) was used as a dissolution medium.

3. Results and discussions

Results: Standard Calibration curve of azithromycin:

Pre-formulation studies:

Pre-formulation studies were carried out by mixing the drug with various excipients in different proportions reveals that no any significant change appear in the powder mixer at all mentioned conditions, so no any incompatibilities are there between drug and excipients.

Result of Preliminary Trials of Direct Compression:

In present investigation attempt was made to prepare dispersible tablet formulation of Azithromycin using super disintegrant by direct compression. In preliminary study, different batches were prepared as per the composition. All the batches were evaluated as per the standard evaluation parameter. The powder flow property in batch T-1 is very poor. And tablet is show the defect of capping. In batch T-2 flow is slightly improved but it's still poor and capping problem is still continue. In batch T-3 still flow property is not improved.

Result of Preliminary Trials of Wet granulation:

In present investigation attempt was made to prepare dispersible tablet formulation of Azithromycin using super disintegrant by wet granulation to improve flow property and remove capping. In preliminary study, different batches were prepared as per the composition given in table 5.3. All

the batches were evaluated as per the standard evaluation parameter as per section 4.6.8. Different evaluation parameter was also studied. Hardness of preliminary batches was found 3 to 5 kg/cm^2, Disintegration time 17 to 30 sec and friability 0.1 to 0.4%. The cumulative percentage release of batch W-1, W-2 and W-3 between 70 to 95%. Batch W-3 gives better drug release action compare to other.

Table 1: Concentration and absorbance obtained for calibration curve of Azithromycin in 0.1 N hydrochloric acid buffer (pH 1.2):

S. No	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.198
3	20	0.396
4	30	0.601
5	40	0.804
6	50	0.998

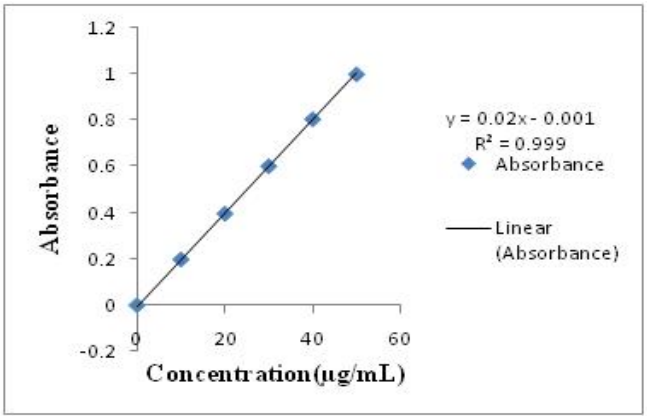
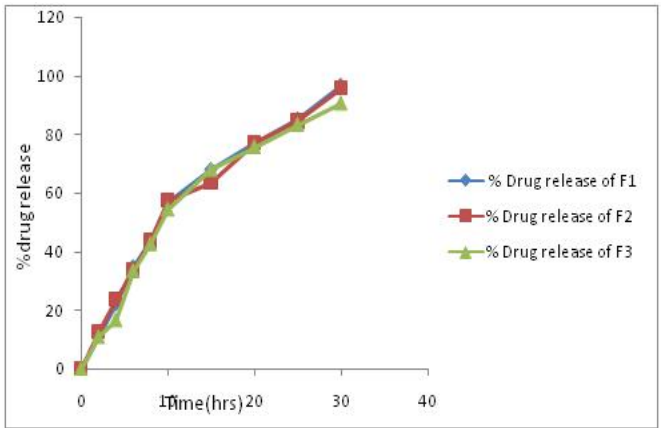
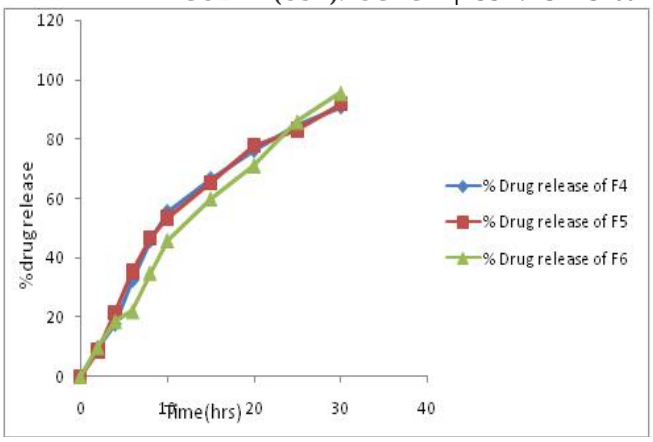


Figure 1: Standard Calibration Curve of Azithromycin

Table 2: Physical parameter of preliminary trials by direct compression

Parameter	T-1	T-2	T-3
Bulk Density (gm/cm^2)	0.31	0.34	0.3
Tap Density (gm/cm^2)	0.63	0.59	0.49
Angle of Repose	Very poor	Poor	Poor
Tablet defect	Capping	Capping	Capping





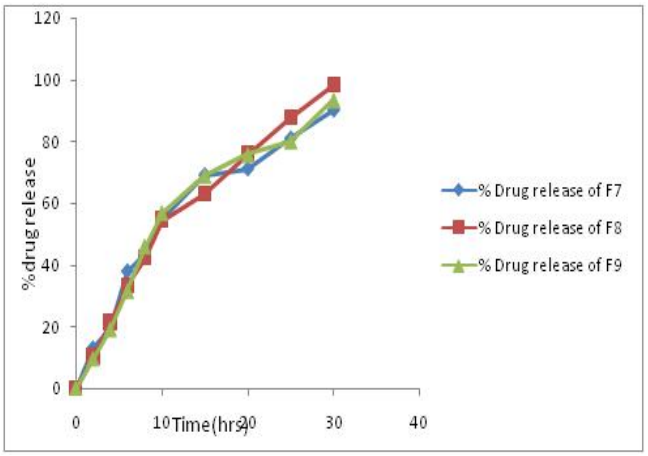


Figure 2: Result of Evaluation of Azithromycin Dispersible Tablet Using Mixture

Discussion:

The present study was carried out to develop oro-dispersible tablets of Azithromycin by direct compression and granulation method. Hence it was necessary to find suitable excipients with good compatibility and disintegrating ability.

Standard Calibration Curve of Azithromycin:

It was found that the estimation of Azithromycin by UV spectrophotometric method at λ_{max} 210.0 nm in 0.1N Hydrochloric acid had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2-10 µg/ml. The regression equation generated was y =0.007x + 0.001.

Pre-formulation studies:

Pre-formulation studies were carried out by mixing the drug with various excipients in different proportions and kept for a month at different temperature and humidity conditions reveals that no significant change appear in the powder mixer at all mentioned conditions, so no incompatibilities were observed between drug and excipients.

Tablet formulation:

Formulation of Preliminary Trials of Azithromycin Dispersible Tablet by Direct- Compression:

The preliminary trials of Azithromycin by direct-compression method reveals that the flow properties of the powder blend is showing the poor flow property and also the tablet defects like capping is observed in these

preliminary formulation so there was need of obtaining the granulation method which may overcome these defects.

Formulation of Preliminary Trials of Azithromycin Dispersible Tablets by granulation:

In granulation method Crospovidone, Croscarmellose sodium and Sodium starch glycolate were used as super-disintegrants. In all the formulations, aqueous granulating agent was used to attain adequate hardness. Avicel was used as diluent. Aspartame was used as a sweetening agent. Magnesium stearate and Aerosil were used as lubricant and glidant respectively.

Evaluation Parameters for Fast Dissolving Tablets of Azithromycin:

Pre-compression parameters:

The values for angle of repose were found in the range of 25°-30°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.41±0.006 to 0.50±0.007 (gm/cc) and 0.50±0.030 to 0.58±0.003 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 13.06% to 18.18%. The Hausner ratio fall in range of 1.14 to 1.22. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Post compression Parameters:

Weight variation test: Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet. The average weight of the tablet is approximately in range of 197±0.920 to 202.5±0.980, so the permissible limit is ±7.5% (185-215 mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test: Hardness of the three tablets of each batch was checked by using Pfizer hardness tester. The results showed that the hardness of the tablets is in range of 3.00±0.000 to 4.00±0.000 kg/cm^2, which was within IP limits.

Thickness:

Thickness of three tablets of each batch was checked by using Vernier. The result showed that thickness of the tablet is raging from 3.56±0.005 to 3.64±0.010.

Friability:

Tablets of each batch were evaluated for percentage friability. The average friability of all the formulations lies in the range of 0.30±0.005 to 0.51±0.005% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Wetting time:

The average wetting time of all the formulations was obtained in the range of 11-24 seconds. The formulation F3 showed maximum wetting time of 24.66±0.577 seconds and the formulation F10 had showed minimum wetting time of 11.33±0.577 seconds. On comparing super disintegrants, the formulation containing SSG take more wetting time than Ac-Di-Sol and Crospovidone. Wetting is related to the inner structure of the tablets and hydrophobicity of the components. This may be due to the fact that SSG is disintegrated by swelling mechanism leading to longer wetting time. Crospovidone and Ac-Di-Sol perform their disintegration by wicking through capillary action and fibrous structure respectively with minimum gelling [2].

In vitro disintegration time: Tablets of each batch were evaluated for in vitro disintegration time. The results showed that the disintegration time of prepared tablets were in the range of 12.66±0.577 to 30.33±0.577 seconds. The tablets of batch F10 prepared using 3.33% of Crospovidone showed the faster disintegration time of 12.66±0.577 seconds. These trials indicated that amongst the disintegrants used Crospovidone and Ac-Di-Sol were better disintegrants to formulate fast dissolving tablets of Azithormycin than Sodium starch glycolate.

In vitro dissolution studies:

Finally, the tablets were evaluated for *in-vitro* dissolution studies in acid buffer (pH-1.2). Formulations F1, F2, F6, F8, F9 showed more than 90% of drug release within 30 min, whereas in formulation F3, F4, F5, F7 showed 75-90% of drug release within 30 min. This result exhibit a direct relationship between concentration of super-disintegrants and drug release. Among the various formulations tablets of batch F8 prepared with 3.33% crospovidone showed 98.07±0.129 release of drug within 30 min.

Table 3: Formulations of preliminary trials

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Azithromycin	100	100	100	100	100	100	100	100	100
Sodium starch glycolate	10	20	30	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	10	20	30	-	-	-
Crospovidone	-	-	-	-	-	-	10	20	30
Avicel	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Aspartame	20	20	20	20	20	20	20	20	20
Mg. Stearate	5	5	5	5	5	5	5	5	5
Aerosil	5	5	5	5	5	5	5	5	5
Total wt	200	200	200	200	200	200	200	200	200

Table 4: Physical parameter of Azithromycin dispersible tablet using mixture design:

Pre-compression parameters:					
Formulations	**Bulk Density (gm/cm^2)**	**Tap Density (gm/cm^2)**	**Carr's Index (%)**	**Hausner ratio**	**Angle of Repose(Θ)**
F_1	0.45±0.005	0.55±0.002	18.18	1.22	27.91±0.890
F_2	0.47±0.006	0.55±0.010	14.54	1.17	28.23±0.580

F_3	0.50±0.007	0.58±0.003	13.79	1.16	29.34±0.680
F_4	0.46±0.003	0.55±0.005	16.36	1.19	26.71±0.260
F_5	0.50±0.007	0.58±0.003	13.79	1.16	29.34±0.680
F_6	0.47±0.006	0.55±0.010	14.54	1.17	28.23±0.580
F_7	0.50±0.007	0.58±0.003	13.79	1.16	29.34±0.680
F_8	0.41±0.006	0.50±0.030	18	1.21	26.78±0.410
F_9	0.41±0.006	0.50±0.030	18	1.21	26.78±0.410

*Values are mean±SD, n=3.

Table 5: Physical parameter of Azithromycin dispersible tablets

	Post-compression parameters:					
FD	**Weight variation (mg)**	**Hardness (kg/cm^2)**	**Thickness (mm)**	**Diameter (sec)**	**Friability (%)**	**Wetting time (sec)**
F_1	203±1	2.76±0.01	6.12±0.01	4.5±0.7	0.420	99±0.12
F_2	204±2	2.74±0.04	6.14±0.02	4.2±0.5	0.341	99±0.3
F_3	201±1	2.71±0.01	6.01±0.01	3.6±0.6	0.363	100±0.1
F_4	204±2	2.80±0.06	6.03±0.03	4.8±0.5	0.561	100±0.3
F_5	205±3	2.81±0.04	6.04±0.04	3.8±0.4	0.482	99±0.6
F_6	204±1	2.74±0.05	6.09±0.05	4.4±0.6	0.513	99±0.4
F_7	199±1	2.76±0.03	6.11±0.03	5 ± 0.1	0.412	98±0.9
F_8	200±2	2.71±0.04	6.09±0.06	4.6±0.2	0.432	99±0.1
F_9	200±3	2.73±0.03	6.03±0.02	4.0±0.3	0.512	100±0.1

*Values are mean±SD, n=3

Table 6

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	11.09	12.56	10.87	9.78	8.76	9.90	12.89	10.21	9.54
4	21.89	23.65	16.54	17.65	21.54	18.54	19.83	21.30	19.01
6	34.67	33.54	33.46	32.45	35.46	21.90	37.89	33.34	31.57
8	43.98	43.56	42.56	45.78	46.76	34.89	43.87	42.32	45.93
10	56.76	57.54	54.46	55.67	53.46	45.86	54.70	54.56	56.86
15	67.87	63.34	67.89	66.76	65.46	59.90	69.03	62.89	68.95
20	76.86	77.12	75.75	76.23	77.87	71.09	71.02	75.76	75.67
25	85.12	84.43	83.34	84.56	83.21	85.87	80.91	87.64	80.09
30	96.57	95.67	90.65	90.87	91.89	95.47	90.07	98.17	93.40

4. Conclusion:

In the present work, an attempt has been made to develop oro disintegrating tablets of Azithromycin. The result of physical parameter of preliminary trials by direct compression showed poor flow property and capping also observed after compression. So aqueous wet-granulation method was utilized. It was found that friability of tablets were affected by SLS, in absence of SLS friability was increased. Without the SLS, the binder was not able to form the proper bridges between the drug particles to form strong granules. Amongst the various combinations of diluents and disintegrants used in the study, tablets that were formulated (wet-granulation) using Crospovidone (3.33%), Croscarmellose sodium and Sodium starch glycolate (each 0.83%) exhibited quicker disintegration of tablets than compared to those other combination of disintegrants in different concentration. The effectiveness of super-disintegrants was in order of CPVP>CCS>SSG. Formulation F8 was the optimized formulation having least disintegration time as well as other parameters was in acceptable range. The stability studies revealed that there was no significant change in tablet properties with aging at different storage conditions. Based on the optimization results it is concluded that the objective of formulating Orally Disintegrating Tablets containing Azithromycin has been achieved with success.

Scope for further studies:

1. To Optimize DT as Less as Possible using combination of two different super-disintegrant in same formulation and also to increase drug release within 1 0min.
2. To decrease particle size of drug by Micronization and thus increasing the contact surface area of Drug particle in suspension and to increase its solubility to improve bioavailability.
3. The work can be extended to study the effect of compression pressure, shape and diameter of the tablet and size of particles (based on mesh screen).

Summary:

The present dissertation work is an attempt to select the best possible diluent- disintegrant combination to formulate rapidly disintegrating tablets of Azithromycin, which disintegrates in matter of seconds in the oral cavity, thereby reducing the first-pass metabolism and the time of onset of

pharmacological action. Crospovidone, Croscarmellose sodium and Sodium starch glycolate were used as super-disintegrants. In all the formulations aqueous granulating agent was used as a binding agent to attain adequate hardness. Avicel was used as diluent. Aspartame was used as a sweetening agent. Magnesium stearate and Aerosil were used as lubricant and glidant respectively. Aqueous Wet-granulation method was employed to formulate the tablets, because direct compression showed tablet defects like capping and poor flow of powder blend. The pre-compression parameters like bulk density, tapped density, Carr's index and angle of repose were determined. All the 9 formulations showed acceptable flow properties.

The post-compression parameters of the tablet like the hardness, thickness, friability and weight variation, disintegration time, wetting time, and *In-vitro* release were carried out and the values were found to be within IP limits. The percentage drug content of all the tablets was found to be between 97.12±0.280% and 99.25±0.670% of Azithromycin, which was within the acceptable limits. From the data obtained, it is observed that Amongst the various combinations of diluents and disintegrants used in the study, tablets that were formulated (wet granulation) using Crospovidone (3.33%), Croscarmellose sodium and sodium starch glycolate (each 0.83%) exhibited quicker disintegration of tablets than compared to those other combination of disintegrants in different concentration. The effectiveness of super-disintegrants was in order of CPVP>CCS>SSG.

5. Acknowledgement

The authors sincerely acknowledge the KP Labs (A Diviison of Karthikeya Drugs & Pharmaceuticals Private Limited), Kotahpet, Hyderabad, for providing Drugs and support to carry out this research work.

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