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Formulation and In-Vitro Evaluation Of Azithromycin Mouth Dissolving Tablets Using Superdisintegrants

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ABSTRACT

Since last decade, it has been observed that the demand for mouth dissolving tablets [1] has been growing, especially for elderly and children who have swallowing difficulties. Azithromycin is a semi synthetic macrolide antibiotic chemically related to azithromycin and clarithromycin. It is effective against a wide variety of bacteria. Azithromycin prevents the bacteria from growing by interfering with their ability to make proteins. It is commonly used for tonsillitis, laryngitis, bronchitis, Pneumonia and Sinusitis and several sexual transmitted infectious diseases. The main criteria for mouth dissolving tablets are to disintegrate or dissolve rapidly in oral cavity with saliva in 15sec to 60sec with need of water. The disintegrants used should fulfill the criteria by disintegrating the tablets in specified time limit. In the present investigation variety of super disintegrants like Ac-Di-sol, SSG, Crospovidone were selected and tablets were prepared by direct compression method [2-3] in different concentration like 4%, 6% and 8% respectively. The prepared tablets were evaluated [4-5] for weight variation, hardness, friability, *in vitro* disintegration time, wetting time, *in vitro* dissolution study, etc. Formulation F-7 shows the lowest disintegration time (6.8sec) and wetting time (13.1sec). *In vitro* dissolution studies [6-7] revealed that formulation F-7 containning 4% w/v Crospovidone showed 98.88% drug release at the end of 15 minutes.

Keywords: Azithromycin, *In-vitro* disintegration time, Mouth dissolving tablets, wetting time.

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INTRODUCTION

Mouth dissolving tablets disintegrate or dissolve in saliva and are swallowed without the need for water. They are beneficial to swallowing tablets and capsules. Thus difficulty is particularly experienced by pediatric and geriatric patients. Various techniques such as freeze drying, sublimation, spray drying, moulding, mass extrussion and direct compression method have been reported for preparation of mouth dissolving tablets. [8-9]

Azithromycin is a semisynthetic macrolide antibiotic. It is chemically related to erythromycin and clarithromycin. It is effective against a wide variety of bacteria such as Hemophillus influenza, Streptococcus, Pneumoniae, Mycoplasma Pneumoniae, Staphylococcus aureus, mycobacterium avium and many others. Azithromycin prevents bacteria from growing by interfering with their ability to make proteins. Due to differences in the way proteins are made in bacteria and humans, the macrolide antibiotics do not interfere with production of proteins in humans. It is an unusual antibiotic in that it says in the body for quite a while (has a longer half life) allowing for once a day dosing and for shorter treatment courses for most infections.

MATERIALS AND METHODS

Azithromycin, Crospovidone and Ac.Di.Sol were received as a gift sample from Ranbaxy Laboratories Limited, India. Aerosil from Genuine Chemical Company,India. Talc procured from CDH, India. Magnesium Stearate from Ferro, USA. Kaolin, Sodium Saccharine from M/s Lab Chemicals, India. MCC procured from CDH, India, Mannitol and Potassium dihydrogen orthophosphate were procured from S.D. Fine Chem, India.

Compatibility study

The drug excipient compatibility study was performed by subjecting the drug excipient blend to FT-IR analysis (Jasco, Japan).

Preparation of Azithromycin Tablets using direct compression

Azithromycin, Crospovidone, mannitol, magnesium stearate, Potassium dihydrogen orthophosphate and talc were weighed accurately. The drug & the diluents were mixed by taking small portion of both & blending it thoroughly to get uniform mixture & kept aside. [10-11] All the ingredients were mixed geometrically along with disintegrating agents. Lubricants were added & mixed well. The powder blend was compressed using die of 9mm size to get tablet using tablet punching machine (Cadmach, India, Single punch).

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Table 1 Formulation compilation of Azithromycin mouth dissolving tablets:

NAME OF INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Azithromycin	100	100	100	100	100	100	100	100	100	100
Ac.Di.Sol	10	15	20	-	-	-	-	-	-	-
SSG	-	-	-	10	15	20	-	-	-	-
Crospovidone	-	-	-	-	-	-	10	15	20	-
Aerosil	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5	5
Kaolin	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5
Sodium saccharine	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Mannitol	27.5	27.5	27.5	27.5	27.5	27.5	27.5	27.5	27.5	27.5
MCC	79.5	74.5	69.5	79.5	74.5	69.5	79.5	74.5	69.5	89.5
TOTAL	250	250	250	250	250	250	250	250	250	250

Evaluation of powder blend

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. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by $D_b = M/ V_b$, Where M is the mass of powder V_b is the bulk volume of the powder.

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 (Macro scientific works, India) and the tapped volume was noted. Tapping was continued until the difference between successive volumes was less than 2%. It is expressed in gm/ml and is given by $D_t = M / V_t$, Where, M is the mass of powder, V_t is the tapped volume of the powder.

Angle of repose (θ)

The frictional forces in a loose powder blend were measured by the angle of repose (θ). 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.

$$\tan (\theta) = h / r$$
$$\theta = \tan^{-1} (h / r)$$

Where, θ is the angle of repose, h is the height in cm, r is the radius in cm.

The powder blend was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel.

Carr's index (I) % compressibility

It indicates powder flow properties. It is expressed in percentage and is given by

$$I = [(D_t – D_b)/D_t] X 100$$

Where, D_t is the tapped density of the powder and D_b is the bulk density of the powder.

Hausner ratio

Hausner ratio is an indirect index of ease of powder flow.

It is calculated by the following formula.

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

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).

EVALUATION OF AZITHROMYCIN MOUTH DISSOLVING TABLET

Diameter (Size) and Thickness

Tablets from each formulation were selected and their diameter and crown thickness was measured. Individual tablets are measured by sliding caliper scale.

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

Tablets require a certain amount of strength or hardness to withstand mechanical shocks of handling in manufacture, packaging and shipping.

Method: The Monsanto hardness tester was used above said parameter

Friability (F)

Tablets were tested for friability using Roche friabilator. This is important to know the mechanical strength of the tablet while handling.

Method: Ten tablets were weighed initially and transferred to the friabilator (Roche). The instrument was set at 25 rpm for four minutes. The resulting tablets were reweighed and percentage loss was calculated using the formula.

$$\frac{\text{(Initial weight – Final weight)}}{\text{Initial weight}} \times 100$$

The percentage loss should be within the limits of 0.1%-0.9%.

In vitro disintegration time

The disintegration test for tablets was carried out in disintegration test Apparatus (Electrolab, India). The limit for mouth dissolving tablet should not be more than three minutes at 37° ±0.5 0C.

Method

The device contains 6 glass tubes that ·are 7.5 cm long, 2 cm in internal diameter and a wall thickness of 2 mm. To test for disintegration time one tablet was placed in each tube and the basket rack was positioned in a 1 litre beaker of water maintained at 37° ±0.5° C. such that the tablet remained 2.5 cm below the surface of the liquid on their upward movement and descended not closer than 2.5 cm from the bottom of the beaker. A standard motor driven device was used to move the basket assembly up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles/minutes. Time taken for tablet to disintegrate completely was noted.

Moisture uptake studies

Three tablets were taken from each formulation & weighted. (w_i); which was kept out at Room temperature for 2 weeks. Then it was kept in dessicator for one day and again weighed (w_f) Moisture uptake % = $(w_i-w_f)/(w_f) \times 100$

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Wetting time & water absorption ratio

One circular tissue paper of 10cm diameter was placed in a petridish with a 10cm diameter. 10millilitres of water soluble dye eosin solution was added to petridish. Tablet placed on surface of tissue paper and time required for water to reach the upper surface of tablet was wetting time. (I.P. - Eosin solution: - A 0.5 % w/v solution of Eosin in water)

Water absorption ratio

Weight of tablet before keeping in petridish noted. (w_b) Wetted tablet from petridish is reweighed (w_a) $R = 100(w_a-w_b)/w_b$

In-vitro dispersion time

It is measured by dropping a tablet in a beaker containing sorenson's buffer pH6.8 (in 10ml) Three tablets from each formulation were randomly selected & invitrodispersion time was performed.

Uniformity of dispersion

According to European pharmacopoeia, two tablets were placed in 100ml water and allowed to disperse. Smooth dispersion produced which passed through sieve with a mesh size of 710 m = 22 sieve.

Drug content

Content uniformity test was done to assure uniform potency of tablets.

Method

20 tablets were weighed and powdered. A quantity equivalent to 100mg of azithromycin was transferred to the 10ml volumetric flask and volume made up-to 10ml with methanol and filtered. 0.5ml of the above filtrate was transferred into 25ml volumetric flask and made up-to 25mlwith 7.4 Phospate buffer. The samples were analysed for the drug content at 209 nm using U.V. Visible Spectrophotometer (Jasco, Japan) against 7.4 phosphate buffer blank.

In Vitro dissolution Study

In vitro dissolution study of various formulations were carried out with 7.4 phosphate buffer (Type II, Electrolab, India)

Method

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900ml of 7.4 phosphate buffer was placed in the vessel and temperature was maintained at 37±0.5° C. Azithromycin dihydrate (100mg) was added to dissolution medium at 100rpm. 2 ml sample was taken from the dissolution medium at regular time interval. After each sampling of 2ml, 7.4 Phosphate buffer was added to maintain sink condition. Further the sample were analysed for the drug content at 209 nm using U.V. visible spectrophotometer using 7.4 Phosphate buffer as blank.

RESULTS

Compatibility study

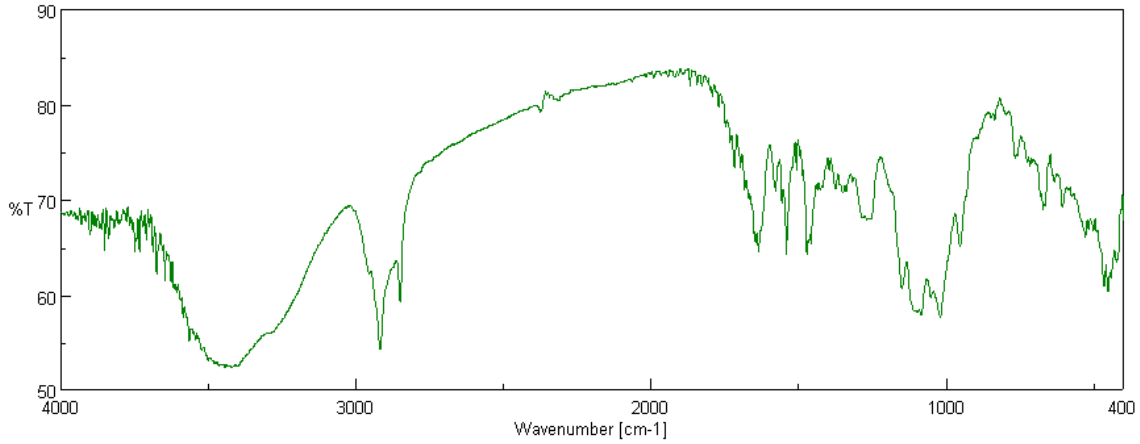

Fig 1: FT-IR spectra of drug and excipients

Table -2 physicochemical properties of powder blend

PARAMETERS	RESULTS
Bulk density	0.29 gm/cc
Tapped density	0.63gm/cc
Compressibility index	51.67 %
Hausner's ratio	2.15
Angle of repose	35.55^0

Table -3 physicochemical parameters of Azithromycin tablets

FORMULATION.	WT. VARIATION	HARDNES (KG/CM^2)	FRIABILITY (%)	DRUG CONTENT (%)
F1	248.88±.94	2.5±0.02	0.5±0.1	94.13±.01
F2	248.71±0.26	2.5±0.02	0.5±0.1	90±0.01
F3	248.69±0.35	2.5±0.02	0.5±0.1	96.52±0.01
F4	248.82±0.73	3.1±0.1	0.6±0.1	91.31±0.01
F5	247.41±0.88	3.1±0.1	0.5±0.1	97.61±0.01

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F6	246.6±0.78	3.1±0.1	0.53±0.15	93.92±0.01
F7	249.66±0.30	2.49±0.01	0.9±0.1	97.74±0.01
F8	247.77±0.25	2,49±0.01	0.3±0.1	94.09±0.01
F9	248.74±0.35	2.49±0.01	0.3±0.1	95.61±0.01
F10	247.86±1.65	3.1±0.1	0.3±0.1	93.70±0.01
F (Marketed)	248.98±0.01	2.1 ± 0.01	0.3 ± 0.1	95.6±0.01

Table 4: physical parameters of mouth dissolving tablets

FORMULATION.	WETTING TIME (SEC)	WATER ABSORPTION RATIO (%)	INVITRO DISPERSION TIME (SEC)	DISINTEGRATION TIME (SEC)	UNIFORMITY OF DISPERSION
F1	18.9±0.01	46±0.10	13±0.1	8.8 ± 0.1	Passes
F2	20.58±0.01	43.2±0.15	14.2± 0.1	8.3±0.1	Passes
F3	19.9±0.01	54.4±0.30	14.9± 0.1	8.8±0.1	Passes
F4	22.8±0.25	33.6±0.25	13.7±0.1	12.4±0.1	Passes
F5	28.8±0.1	31.1±0.15	14.1±0.1	14.0±0.2	Passes
F6	26.3±0.20	30.4±0.5	13.0 ± 0.1	12.3±0.1	Passes
F7	13.1±0.02	64.4±0.15	8.6 ± 0.1	6.8±0.1	Passes
F8	14.0±0.02	34.4±0.1	8.8 ± 0.1	7.2±0.1	Passes
F9	32.0 ±0.1	33.6±0.152	8.9 ± 0.1	7.9±0.1	Passes
F10	34.8±0.59	35.2±0.20	25.2± 0.1	16.7±0.1	Passes
F (Marketed)	20.05±0.1	45 ±0.1	31.33±0.1	19.0±0.1	Passes

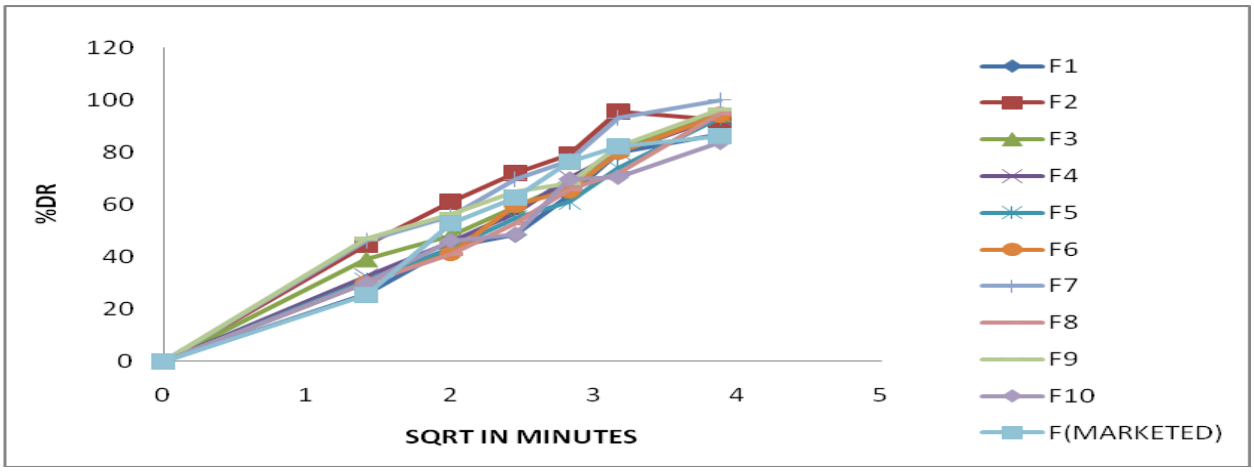

Fig: In-vitro dissolution comparison of formulations with marketed product

DISCUSSION

Azithromycin is an semisynthetic macrolide antibiotic which prevents the bacteria from growing by interfering their ability to make proteins. Organoleptic characteristics of pure drug (Azithromycin) showed that the drug is white crystalline powder which is extremely bitter in taste. The FT-IR spectra analysis of drug and excipients revealed that

the characteristic peaks of azithromycin (C=O stretching at 1729 cm^{-1} and O-H stretching at 3495 & 3560 cm^{-1}) were remained intact. There were no new peaks found. Hence drug excipient compatibility was confirmed by FT-IR study. The Spectroscopy study using UV-Visible spectrophotometer of pure drug with different mediums like Phosphate7.4buffer and 0.lN HCI showed that maximum wavelength was found to be 209 nm and 207 nm respectively. From the Compressibility index and Angle of repose values it was concluded that the pure drug is having very poor flow properties. Sieve analysis of drug shows that 99.9% drug retained on sieve. In- *Vitro* dissolution studies of Azithromycin was carried out in *7.4* phosphate buffer using paddle at 100 rpm which shows that 87.04% drug release in 60minutes. Azithromycin mouth dissolving tablets were prepared by direct compression method using various superdisintegrants like Ac.DiSol, SSG & Crosspovidone in various concentrations like 4%, 6% and 8% respectively. Weight variation was found within the specification of the IP limits. Average weight of all formulation was found in the range of 246.6 to 249.66mg. Hardness & friability of all formulation were within acceptable limits. Hardness of tablets prepared by direct compression was in the range *2.49* to 3.1kg/cm^2.The friability of all formulation was found to be less than 1.0% and hence the tablet with lower friability may not break during handling on machines or shipping.The content uniformity of all the formulations was found in the range of 90 to 97.74%. In *vitro* Disintegration time is very important for mouth dissolving tablets which is desired to be less than 60 seconds. The rapid disintegration may be due to the rapid uptake of water from the medium, swelling, burst effect and thus promoting bio availability. Formulation F7 showed less disintegration time of 6.8 seconds as compared to other formulations. Wetting time is used as an indicator from the ease of tablet disintegration in buccal cavity. It was observed that wetting time of tablets was in the range of 13.1 seconds to 34.8 seconds. It was observed that type of disintegrant affected the wetting of the tablets. Among all the formulation F7 shows highest water absorption ratio and less in-vitro dispersion time. In-vitro dissolution studies of F7 formulation i.e. 4% w/v at different time interval showed the maximum dissolution rate of 98.88% drug release in 15min. All the formulation follows Higuchi order release kinetics. From the overall observations, formulation F7 containing 4% w/v crospovidone was considered to be the best formulation, comparison to all other formulations in order to improve disintegrants/dissolution of the drug in Oral cavity & hence better patient compliance & effective therapy used in the management of motion sickness.

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