International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol. 3, No.3, pp 1479-1484, July-Sept 2011

Formulation and Evaluation of Enteric coated tablets of Azithromycin dihydrate

Ajit Patil*, Santosh Payghan, John Disouza

Department of Pharmaceutics,Tatyasaheb Kore College Of Pharmacy,Warananagar,Kolhapur -416113.

***Corres.author: ajitpatil202@gmail.com**
8605189295

Abstract: The present study was an attempt to formulate and evaluate enteric coated tablets for azithromycin dihydrate to reduce the Gastrointestinal tract side effects.Three formulations of Core tablets were prepared and one who shows rapid disintegration (below three minutes) was selected for enteric coating . Enteric coat was employed by using different polymers such as HPMC-55, Eudragit, Ethyl cellulose in different ratios .Combination of HPMC-55 and ethyl cellulose (10:1.5) exibited better dissolution ,disintegration, hardness and friability properties .This study concluded that enteric coated tablets of azithromycin dihydrate can be prepared by using combination of polymers studied and we can reduce the GI tract side effects.
Keywords: Azithromycin dihydrate, HPMC-55 ,Eudragit L-30 D-55, Ethyl cellulose, Evaluation.

INTRODUCTION:

Azithromycin is semi-synthetic macrolide antibiotic obtained from erythromycin –A. Azithromycin differs from erythromycin by the addition of a methyl-substituted nitrogen atom into the lactone ring. Azithromycin is a first and most important member of new class of antibiotics known as azalides. These modifications in structure result in better gastrointestinal tolerability and tissue penetration. In addition, there is a decreased risk of interaction with other drugs metabolized by the cytochrome P-450 enzyme system, and increased half-life. All macrolides inhibits RNA-dependent protein synthesis by reversibly binding to the 50 S ribosomal subunits of susceptible microorganisms. Thus, RNA-dependent protein synthesis is suppressed, and bacterial growth is inhibited.Hence macrolides are bacteriostatic in nature[1,2,3] .

Azithromycin have activity against gram-positive organisms also offers increased gram-negative coverage over erythromycin and clarithromycin. It also shown good activity against H. influenzae. However, it has variable activity against the family Enterobacteriaceae. Nonetheless, Salmonella and Shigella species have been shown to be susceptible, as have other diarrheal pathogens such as Yersinia and Campylobacter. Its unique feature is an excellent activity against sexually transmitted pathogens, especially Chlamydia trachomatis and can use also in the patients with weak immune responce like in childrens then in HIV, gonorrhea ,non -gonococcal urethritis. An azithromycin is generally used in middle ear infections , tonsillitis ,throat infections, laryngitis, throat infections, bronchitis ,pneumonia, typhoid etc. But instead of all these positive effects to patients , an azithromycin is having some side effects also. When, the patient is frequentally taking azithromycin (in case of weak immune system diseases and sexually

transmited diseases) it shows some side effects like nausea ,loose stool-diarrhoea, abdominal pain, headeach,vomiting, unexplained rashes , pilling of skin, abnormal swelling, blood in stool etc.and all these side effects are related with upper GI tract[4,5].

So, we tried to formulate such an enteric coated formulation which release the drug only in alkaline pH near 6.8. Which leads to cross these side effects and drug will release safely.For the same purpose we have selected different ratios of polymers (HPMC-55,Eudragit,Ethyl cellulose) in combine form and we studied there dissolution ,disintegration characteristics. Within this study we found that ethyl cellulose and HPMC-55 gives a promicing results.In case of , HPMC-55 and eudragit not any significant ratio had given a proper results as we want .The coat did not remain intact for more than 90 minutes and same case was found with ethyl cellulose and eudragit [18,20].

MATERIALS AND METHODS :

Azythromycin dihyadrate and HPMC–55 (USV limited, Govandi, Mumbai.), Ethyl cellulose, magnesium stearate ,talc , Polyvinyl chloride,cross carmalose and lactose. All other additives were procured commercially. In vitro analysis of the prepared tablets was carried out as per the requirements of enteric coated tablets as specified in official pharmacopoeia.

Preparation of core tablets[6,7] :

The core tablets were prepared by direct compression method. All the ingredients were mixed and passed through sieve no. 60(250 microns) to get uniformally distributed and uniform sized particles.Then after sieving process the mixture is put for the compression on 8 station tablet punching machine using 10 mm diameter biconvex round shape die and punches . One batch of fourty tablets were prepared . Detailed composition of azythromycin core tablets is given in **Table 1.**

Preparation of enteric coated tablets[6,7,8] :

Although the composition of a core tablet is same the coating polymers were different (HPMC-55,Ethyl cellulose,Eudragit) and different ratios as given in **Table 2.**

Table 1: Composition of core tablet formulation

Ingredients (mg)	E1	E2	E3
Azithromycin	250	250	250
Cross-carmalose	5	10	15
Lactose	100	100	100
Talc	12.5	12.5	12.5
Magnesium stearate	10	10	10

Table 2 : Composition of enteric coating

Ingredients	Quantity (mg)		
	F1	F2	F3
HPMC-55	100	100	100
PVP	40	40	40
Eudragit	0	0	15
Ethyl cellulose	0	15	0
Talc	3	3	3
Mg stearate	4	4	4

EVALUATIONS OF ENTERIC COATED TABLETS [8,9,10]:

Hardness :

The tablet crushing strength was tested by commonly used Pfizer tablet hardness tester. A tablet is placed between the anvils and the crushing strength, which causes the tablet to break, was recorded.

Friability:

Tablet strength was tested by Roche friabilator. Preweighed (Model: ED-2,
Electrolab) tablets were given 100 revolutions in 4 min and were dedusted. The percentage weight loss was calculated by reweighing the tablets.

Uniformity of weight:

Randomly selected twenty tablets from all the three formulations were weighed individually and together on electronic balance (Metteler Toledo electronic balance: Model P G 03-S) .The average weight was noted .

Disintegration time:

Disintegration time was determined using the disintegration apparatus USP (Electrolab, Bangalore, India) in 0.1N HCl for 2 h and then in phosphate buffer pH 6.8 for 1 hour maintaining the temperature at 37 ± 2°C .

Drug content studies :

The drug content in tablets were determined by randomly choosing ten tablets from all three enteric coated formulations and powdered using mortar & pestle. A quantity equivalent to 250 mg of azithromycin it was weighed and dissolved in methanol (diluted if necessary) ,then absorbance was taken on 215 nm on (UV 150-02, Double beam spectrophotometer, Shimadzu Corp., Japan) at wavelength 215 nm.

In vitro Dissolution tests[11,12,13] :

Drug release profile was evaluated in vitro, using a dissolution test apparatus . The USP XIII Type II (paddle type) method (TDT-08L, Electrolab, Mumbai, India.) was selected to perform the dissolution profile of azithromycin enteric coated tablets .The dissolution of enteric coated tablet is performed into 0.1N HCL for 2 hours and then the phosphate buffer pH 6.8 for 1 hour. The temperature was maintained at 37 ± 0.5°C and a constant paddle rotation speed of 100 rpm. Samples (5 ml) were withdrawn at regular intervals and filtered. The samples were analyzed by UV spectrophotometer (UV 150-02, Double beam spectrophotometer, Shimadzu Corp., Japan) at wavelength 215 nm.

Drug release kinetics [14,15,16,17,19]:

The drug release kinetics by different kinetic models for the optimum formulation (F2) was also studied.

Drug release kinetics :

Cumulative % drug release:

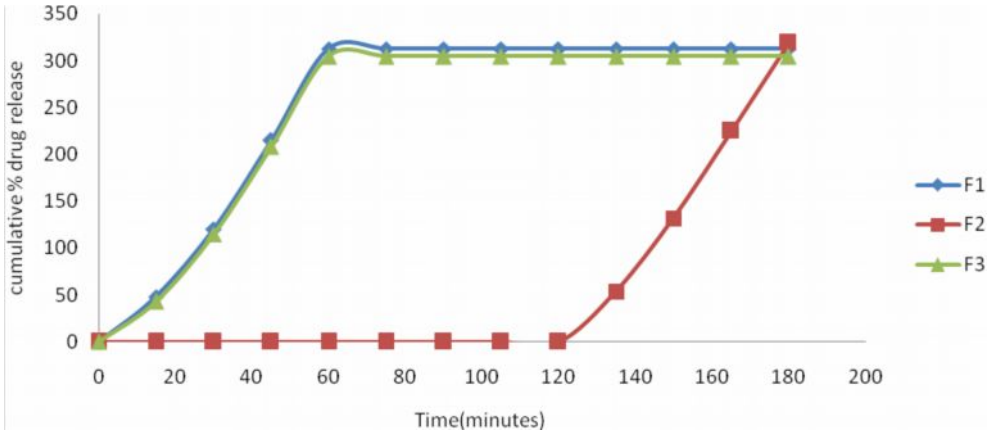

Figure:1 Comparison between dissolution studies of F1,F2 and F3 formulations.

Release kinetic models:

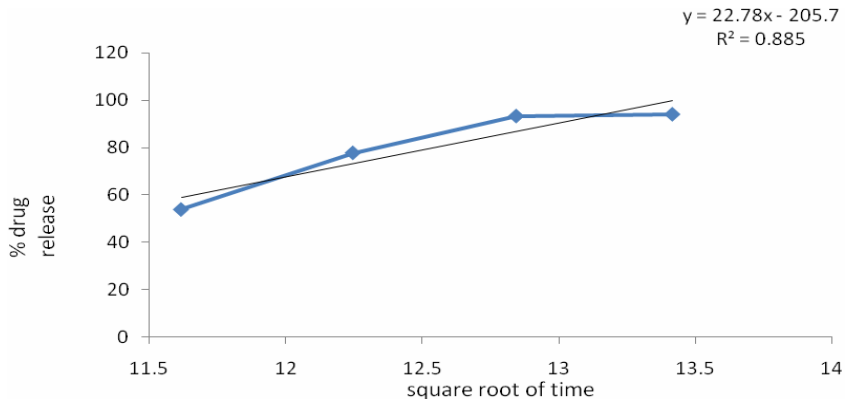

Figure:2 Higuchi Plot of percent drug release verses square root of time.

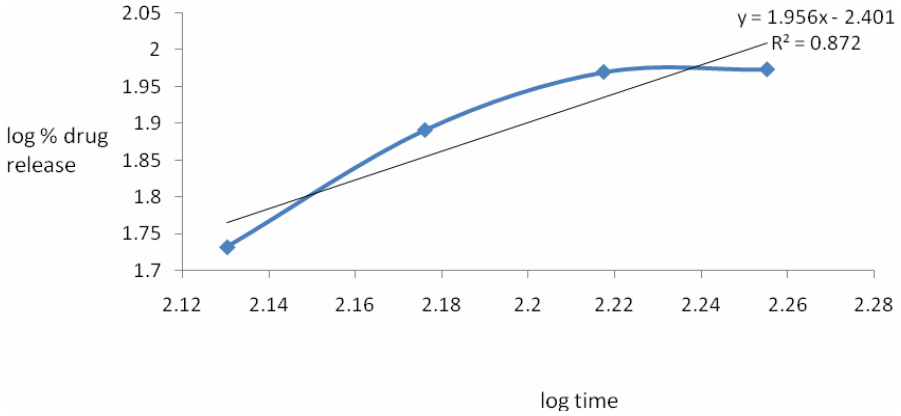

Figure:3 Korsemayer Peppase plot log % drug release verses log time.

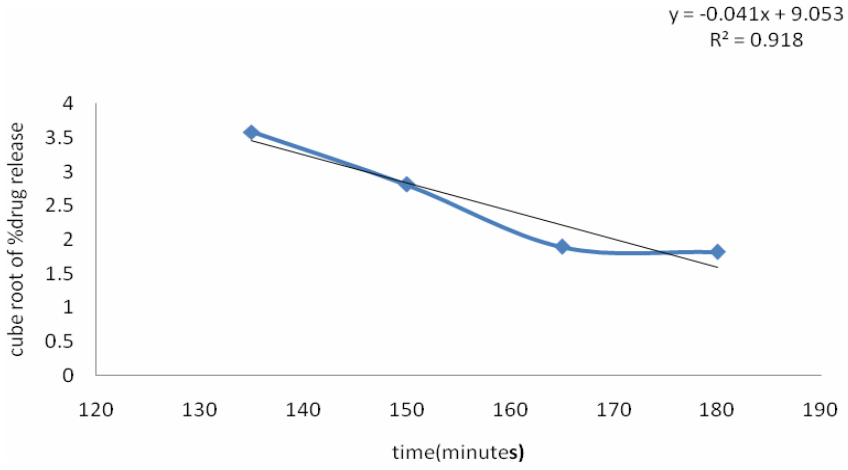

Figure:4 Hixon Crowell cube root plot of cube root of % drug release verses time.

RESULT AND DISCUSSION :

As mentioned above the azithromycin drug is having many side effects which are related with the upper gastrointestinal tract ,means stomach and duodenum mainly . These side effects are mainly due to the stimulation of motiline receptors . These receptors are present in the stomach and duodenum . generally the function of these motiline receptors are to motivation of Gastro intestinal smooth muscles , so that the food present in the Gastro intestinal tract can move or transit from stomach to intestine. When a patient administering an azithromycin which is of azalide group molecule , at that time there is excessive stimulation of these motiline receptors . Due to this stimulation the patient suffers from nausea ,loose stool-diarrhoea, abdominal pain, headeach, vomiting, unexplained rashes , pilling of skin , abnormal swelling like side effects .

The purpose of formulation of the enteric coated tablets of azythromycin is to delay the release of drug and to allow release in lower part of gastrointestinal tract . The reason behind this delaying of release is , to prevent the contact of azithromycin with the motiline receptors of upper gastro intestinal tract.So by releasing the drug in lower gastrointestinal tract(ileum and large intestine) we can safely administer azithromycin without side effects and without altering its absorption .

Three different core tablets were prepared each with varying concentrations of disintegrating agent(cross-carmalose). Then the other excepients like lactose(diluent) ,magnesium stearate(lubricant) and talc(glident) were used . The Prepared tablets were subjected to disintegration test at pH 6.8 phosphate buffer and the tablet which disintegrated within 3 minutes is selected for further enteric coating(E3). All the other tests like hardness ,friability,weight variation were employed for this core tablet(E3) .The enteric coating was applied with the consideration of transit time of food or dosage form from stomach to jejunum of small intestine(2hrs) and from percent release verses time plot shows that formulation F2 shows good and predictable release.

Enteric coating was applied using various polymers like ethyl cellulose , hydroxyl propyl methyl cellulose phthalate (HPMC -55), and eudragit . The best combination we found that was of ethyl cellulose and HPMC-55 (F2) , the coating was remain intact for two hours in the acidic pH 0.1 N HCL and disintegrated completely in the phosphate buffer pH 6.8 within half an hour . Combination HPMC -55 and the eudragit (F3) (10:1.5) was not intact more than one and half hour in the 0.1 N HCL, also HPMC-55(F1) was not remain intact in 0.1N HCL for more than one hour. So, the combination of HPMC -55 and ethyl cellulose(F2) (10:1.5) was best for the enteric coating , which have given hardness(4-5kg) ,friability(0.8-1) ,weight variation(490±10), content uniformity, percent drug release and disintegration and dissolution within officially specified limits (Table 3).

From the kinetic models the we found that ,Hixon crowell cube root model was best fitted for release kinetics of azithromycin enteric coated tablet.(Table 4)

Table 3: Characteristics of azithromycin enteric coated formulations.

Parameters	Formulations		
	F1	F2	F3
Hardness (kg)	3.02	4.58	3.5
Weight variation	554	550	557
Friability(% loss)	3.5	0.5	1.9
Drug release(%)	Fail	94	Fail
Disintegration(0.1NHCL)(min)	50	100	70
Disintegration (pH6.8)(min)	3	6	5
Dissolution (min)0.1 N HCL	65	120	90
Dissolution (min) 6.8 pH phosphate buffer	5	8	7

Table 4 : kinetic model describing slop,Intercept and R^2 values.

Kinetic Model	Slop	Intercept	R^2 value
Higuchi model	22.78	205.7	$R^2 = 0.885$
Hixson Crowell cube root model	1.956	2.401	$R^2 = 0.872$
Korsemayer Peppas model	0.041	9.053	$R^2 = 0.918$

CONCLUSION :

From all above studies , we concluded that , by using combination of HPMC-55 and ethyl cellulose(10:1.5)(F2) we can apply effective enteric coat to the rapid disintegrating core tablet . Other formulations HPMC-55(F1) and HPMC-55 and eudragit (10:1.5)(F3) are also shows enteric coating effects but not effective like that of HPMC-55 and ethyl cellulose(10:1.5) (F2) formulation . So, by this way we can prevent the side effects of azithromycin in upper gastrointestinal tract using HPMC-55 and ethyl cellulose(10:1.5)(F2) enteric coating formulation.

REFERENCES :

1. Jose Mantego-Santiago Garcia-Granda*,Miguel Bayod-Jasanada et al. An easy and general method for quantifying azithromycin dehydrate in matrix of amorphous azithrmycin.ARKIVOC 2005(ix)321-331.
2. Djokic, S.; Kobrehel, G. U.S. Patent 1985, US 4 517 359.
3. Bright, G.M. U.S. Patent 1984, US 4 474 768.
4. Bright, G.M.; Nagel, A.A.; Bordner, J.; Desai, K.A.; Dibrino, J.N.; Nowakowska, J.; Vincent, L.; Watrous, R.M.; Sciavolino, F.C.; English, A.R. *J. Antibiot.* 1988, *XLI*, 1029.
5. Anroop B. Nair, Rachna Gupta et al. Formulation and evaluation of enteric coated tablets of pronon pump inhibitor. Journal of basic and clinical pharmacy 2010;001:215-264.
6. Sumit Charkborty, Sibaji Sarkar et al Formulation development and evaluation of pantoprazole enteric coated tablets. International journal of Chemtech Research 2009;1:663:666
7. Rabia Bushra ,Muhmmad Harris Shoib et al. Enteric coating of ibuprofen tablets using an aqueous dispersion system. Brazilian journal of pharmaceutical sciences .2010;46:99-105.
8. S.Bozdag ,S.Calis and M. Summu. Formulation and stability evaluation of enteric coated omeprazole formulations S.T.P.PHARMA SCIENCES.1999;9:321-327.
9. Lee TW., Robinson JR., In Remington:The science and practice of pharmacy;Gennaro, Ed.; Lippincott Williams and Wilkins: Baltimore; 2000; (2); 903-929.
10. L. Lachman, H.A. Liberman, J.L. Kanig.Theory and practice of industrial pharmacy.3rd Edn, Varghese Publishing House,Mumbai: 296 – 302, (1991).
11. Fukui E, Miyamura N, Uemura K, et al. Preparation of enteric-coated timed-release press-coated tablets and evaluation of their function by in vitro and in vivo tests for colon targeting. Int J Pharm. 2000; 204: 7-15.
12. Johnson DA. Review of esomeprazole in the treatment of acid disorders.Expert Opin Pharmacotherapy. 2003; 4: 253-264.
13. Sinha VR, Kumria R. Coating polymers for colon specifi c drug delivery:A comparative in vitro evaluation. Acta pharm. 2003; 53: 41-47.
14. Brunton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics, New York, McGraw Hill, 2006.
15. Biswas BK, Islam, S, Begum F,et al. In vitro release kinetic study of esomeprazole magnesium from methocel K15M and methocel K100 LVCR matrix tablets. Dhaka Univ J Pharm Sci. 2008: 7: 39-45.
16. Bladh N, Blychert E, Johansson K, et al. A new esomeprazole packet (sachet) formulation for suspension: in vitro characteristics and comparative pharmacokinetics versus intact capsules/tablets in healthy volunteers. Clin Ther. 2007; 4: 640-649.
17. Xie Y, Xie P, Song X, et al. Preparation of esomeprazole zinc solid dispersion and study on its pharmacokinetics. Int J.Pharm. 2008; 360: 53-57.
18. Durriya Hashimat, M Harris shoaib , Zafar alamMehmood, development of entericoatedflurbiprofen tablets use in opadry/acryl –eze system – atechnical mode, AAPS Pharm SecTech , March 2008 , vol 9 (1) , 116 .
19. Bardou, Marc; Martin, Janet, Pantoprazole: from drug metabolism to clinical relevance, Expert Opinion on Drug Metabolism and Toxicology,April 2008 Volume 4 (4), 471 – 483 .
20. Murthy KS, Kubert DA, Fawzi MB. In vitro release characteristics of hard shell capsule products coated with aqueous- and organic-based enteric polymers. J Biomater Appl. 1988; 3: 52-79.

*****