



FORMULATION DEVELOPMENT AND EVALUATION OF DELAYED RELEASE DOXYCYCLINE TABLETS

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ABSTRACT

The main purpose of this work is to develop small intestine targeting tablets of doxycycline hydrochloride by wet granulation method and enteric coating of tablets (conventional standard coating technique). This drug is universal antibiotic and can be targeted to the specific site of absorption by enteric coating using pH dependant polymers. Polymers like Eudragit and HPMC Phthalate are selected where dissolution is above pH 6 and pH 6.4 respectively. Preformulation studies like angle of repose, bulk density, tapped density, porosity, Carr's index, Hausner's ratio were performed. Six batches (F1 to F6) were formulated and evaluated for hardness, friability, weight variation, drug content, disintegration and in-vitro dissolution. Among the six batches, batch F4 was showing 94% drug release and was considered to be best formulation.

Keywords: polymers, enteric coated tablets, doxycycline hydrochloride tablets.

INTRODUCTION

Enteric coated tablets are solid unit dosage forms meant for oral administration and are designed to bypass the stomach¹ and release the drug in small intestine. Doxycycline delayed release tablets are prepared by wet granulation method and coated using different polymers like Eudragit and HPMC to delay the release. Doxycycline² is an universal antibiotic use to treat gram negative infections where the susceptible organism was strongly proven to be present and also used to treat different microbial infections. It is a tetracycline antibiotic³. Its half life is around 12 to 24 hours and 80% of the dose is absorbed through small intestine. The pH of small intestine in different regions was found to be 5 to 7 PH in duodenum, 6 to 7 PH in jejunum and 7 PH in ileum⁴. Eudragit and HPMC phthalate polymers⁵ are selected where the dissolution properties are above PH 6.0 and PH 6.4

respectively. Polymers coating solution concentrations are designed to develop the targeting action of doxycycline in small intestine.

The aim of proposed work was to formulate and characterize enteric coated tablets⁶ of doxycycline for delayed release of drug in small intestine for treatment of different infections.

MATERIALS AND METHODS

Materials used

Doxycycline hydrochloride, dicalciumphosphate, microcrystalline cellulose, starch, lactose, PVP-K-30, sodium starch glycolate, eudragit-L100, HPMC phthalate-55, isopropyl alcohol, methylene chloride, titanium dioxide, talc, magnesium stearate, methyl paraben, propyl paraben were used as depicted in Table 1 & 2.

Table 1: Formulation of doxycycline HCl enteric coated tablets

S.No	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
1	Doxycycline hydrochloride	100	100	100	100	100	100
2	Dicalcium phosphate	45.9	45.9	45.9	45.9	45.9	45.9
3	Microcrystalline cellulose	10.2	10.2	10.2	10.2	10.2	10.2
4	Starch	35.7	35.7	35.7	35.7	35.7	35.7
5	Lactose	52.4	52.4	52.4	52.4	52.4	52.4
6	PVP-K-30	7.332	7.332	7.332	7.332	7.332	7.332
7	Sodium starch glycolate	21.5	21.5	21.5	21.5	21.5	21.5
8	Titanium dioxide	1.01	1.01	1.01	1.01	1.01	1.01
9	Talc	3.06	3.06	3.06	3.06	3.06	3.06
10	Magnesium stearate	0.24	0.24	0.24	0.24	0.24	0.24
11	Methyl paraben	0.5	0.5	0.5	0.5	0.5	0.5
12	Propyl paraben	0.046	0.046	0.046	0.046	0.046	0.046
13	Aerosil	0.51	0.51	0.51	0.51	0.51	0.51

Table 2: Coating solution materials

S.No	Ingredients	F1 (gm)	F2 (gm)	F3 (gm)	F4 (gm)	F5 (gm)	F6 (gm)
1	Eudragit-L 100	-	-	-	25	35	45
2	HPMC Phthalate	25	35	45	-	-	-
3	Isopropyl alcohol	225	225	225	225	225	225
4	Methylene chloride	225	225	225	225	225	225
5	Talc	2.55	2.55	2.55	2.55	2.55	2.55
6	Titanium dioxide	0.83	0.83	0.83	0.83	0.83	0.83
7	Sunset yellow lake	1%	1%	1%	1%	1%	1%

Method of manufacturing enteric coated tablets⁶

Wet granulation method⁷

All the ingredients including drug and other excipients⁸ are mixed using cad mach miller except lubricant, then binder solution is added and passed through suitable sieve and granules are allowed to dry. Then lubricant is added to the dried granules and again sifted then compressed into a tablet using tablet compressor-Clit-CJD-3(23 stations).

Enteric coating method

Enteric coating of the compressed tablets is achieved by standard coating pan technique. Coating solutions of HPMC phthalate and Eudragit L 100 polymers prepared separately with plasticizers in three different concentrations respectively. These solutions are applied over tablets using spray gun at appropriate pressure. The coated tablets are primarily dried using heat blower and secondarily dried in tray drier.

PREFORMULATION STUDIES

Angle of repose⁹

Angle of repose has been used as indirect methods of quantifying powder flow ability, because of their relationship with inter particle cohesion. A static heap will slide when the angle of inclination is large enough to overcome frictional forces and stop when gravitational forces balance the forces. The sides of heap will make an angle with horizontal which is called angle of repose.

$$\text{Angle of repose} = \tan^{-1} h/r$$

Where h is height of pile and r is radius of pile.

Bulk density¹⁰

Bulk density is given by the mass "m" of the powder occupying a known volume 'v' according to the relationship.

$$P_b = (M/V)g/cc$$

It depends on particle size, shape, tendency of particle to adhere.

Tapped density

Weighed powder sample was transferred to a graduated cylinder and was placed on tapped density

apparatus, was operated for a fixed number of taps (100).It is the ratio of weight of sample to tapped volume.

$$\text{Tapped density} = \text{mass/tapped volume}$$

Porosity

The porosity of voids and of the powder is defined as the ratio of void volume to the bulk volume of the packaging.

$$E = (V_b - V_p) / V_b = 1 - (V_p / V_b)$$

Carr's Index

Based on the apparent bulk density and the tapped density , the percentage compressibility of the bulk drug was determined by using the following formula.

$$\% \text{Compressibility} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

Hasner's Ratio

The ratio of tapped density to bulk density of the powders is called the Hasner's ratio.

Evaluation of delayed release doxycycline tablets

Hardness test¹¹

Pfizer hardness tester was used for the determination of hardness of tablets.

Thickness and diameter

Thickness and diameter of the tablets were recorded during the process of compression using vernier callipers.

Friability

Two tablets were accurately weighed and placed in the friabilator (VEEGO- tablet Friabilator) and operated for 100 revolutions. The tablets were dedusted and reweighed. The tablets that loose less than 1% weight were considered to be compliant.

Weight variation

10 tablets were selected randomly from the lot and weighed individually to check for weight variation.

Disintegration test¹²

Tablets were taken and introduced one tablet in each tube of (VEEGO-microprocessor based) disintegration

apparatus and placed in 1-litre beaker and the time of disintegration was recorded. The study was done at room temperature and disk was no used.

Drug content¹³

10 tablets were weighed and powdered. Powder equivalent to 100mg of doxycycline hydrochloride was weighed and dissolved in 6.8 pH phosphate buffer. Different concentrations of drug were prepared and analyzed spectrophotometrically (UV- 1700 Shimadzu Corporation, Japan).

Dissolution studies¹⁴

The in vitro dissolution study was carried out in the USP dissolution apparatus {LABINDA-DISSO 2000 digital tablet dissolution apparatus (BASKET TYPE)}. 900 ml of the dissolution medium (6.8 pH phosphate buffer) was taken in covered vessel and the temperature was maintained at 37±0.5 degrees c.

The speed of paddle was set at 100 rpm. Sampling was done at regular intervals. For each sample 10 ml of the dissolution medium was withdrawn and same amount was replaced. The sample was filtered and diluted with 6.8 phosphate buffer and then analyzed in UV spectrophotometer (UV-1700 Shimadzu Corporation, Japan). The absorbance was measured at 352 nm and % drug release was calculated.

RESULTS AND DISCUSSION

Several technologies have been used in the development of enteric coated tablets and in the present investigation delayed release tablets of doxycycline were prepared by wet granulation method followed by enteric coating. Flow properties of the powder, resistance to particle to particle movement can be judged by using angle of repose. This measurement gives qualitative and quantitative assessment of internal cohesive and frictional force under low levels of external load as might be applied in mixing and tablet compression¹⁵. Values for the angle of repose were found in the range of 23.2 – 25.26°. The compressibility falls in the range of 19.35 to 26.80% and the Hausner's ratio was in the range of 1.24 to 1.36. Hence prepared blends showed good flow properties. All the tablets were prepared under similar conditions and all the formulations have all the required qualities.

The values of pre-compressional parameters evaluated were found to be within prescribed limits indicating good flow properties.

The data obtained for post compressional parameters such as weight variation, friability, hardness, are shown in Table 3.

Table 3: Post compressional parameters

Formula	Weight	Variation	Thickness (mm)	Hardness (kg/m ²)	Friability (%)	Assay (%)
DF1	3.1	5.0	3.98	6	0.654	
DF2	3.3	3.6	4.14	8	0.524	
DF3	4.8	4.9	4.17	7	0.429	103.68
DF4	3.6	3.5	3.92	6	0.761	
DF4	3.5	3.8	4.10	7	0.325	
DF5	4.0	3.9	4.13	7	0.458	

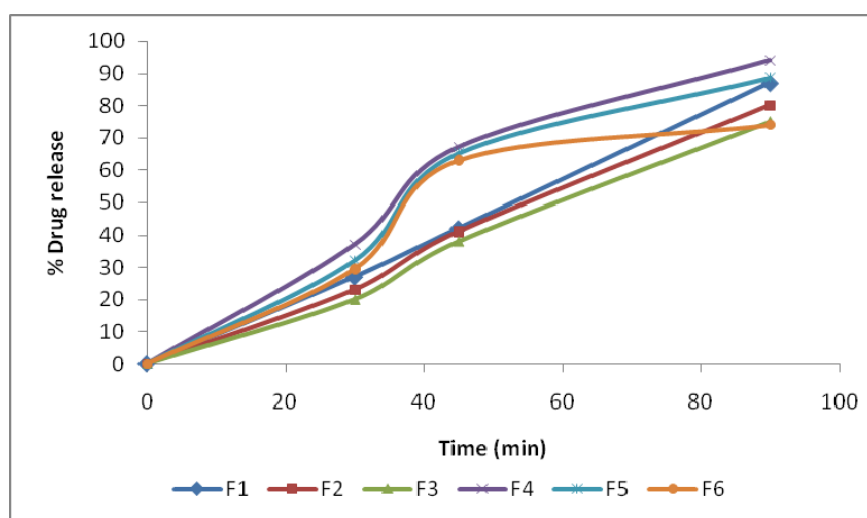


Fig. 1: Comparative Dissolution Profile of Formulations

Hardness was found to be in the range of 2-8kg/cm² in all the formulations indicating good mechanical strength. In all the formulations the friability value is less than 1% giving an indication that tablets formulated are mechanically stable% weight variation was within the limits. Drug content was known by performing assay and it was found to be between 90% to 110% and it was within the limits (shown in table 3). The disintegration of different formulations complies with the pharmacopeia specifications. The dissolution of DF1, DF2, DF3, DF4, DF5, and DF6 showed % drug release of 87%, 80%, 75%, 94%, 88.5%, and 74% respectively at the end of 90 min.

The present work was made to develop delayed release tablets containing Doxycycline hydrochloride tablets. Doxycycline trial batches DF1 TO DF3 were formulated using HPMC P-55 and batches DF4 toDF6 were formulated using Eudragit L100 as enteric polymers in three different concentrations to optimize delayed drug release profile.

In case of trial batches DF1-DF3, it was observed that the drug release profile of DF1 (5% HPMC P-55) showing better enteric release of 87% at the end of 90 min and among DF4-DF6 DF4 (5%Eudragit L100) showing drug release of 94% at the end of 90 min.DF4 batch was considered to be the best enteric formula and further studies can be carried out and finally ready to be marketed.

REFERENCES

1. Leon Lachman, Herbert A, Liberman, Joseph L.Kaing, The theory and practice of industrial pharmacy,Varghese publishing house, Bombay, 3rd edition, 293-295.

2. Seth.S.D.Text book of Pharmacology 1999, 2nd edition,568-569.
3. Rang.H.P, Dale.M.M, Ritter.J.M, Pharmacology, London, 1986, 3rd edition,728-729
4. Tripathi.K.D, Essentials of medical pharmacology, Jaypee publishers Ltd, Delhi,5th edition,668,670-673.
5. Ijeoma F, Uchegbu, Adreas G, Schotzlein, Polymers in drug delivery, 2006, Newyork, 37 & 43.
6. United states pharmacopoeia,2005, 700.
7. Markel dekker, Dilip MP, Hand book of pharmaceutical granulation technology, 1989, Newyork, 1989, 237-260.
8. Rowe rc, Sheskey PJ, Weeler PJ, Editors, Hand book of pharmaceutical excepients, 4th edition, London and Washington DC , The pharmaceutical press , 2003.
9. Jaimini M, Rana AC, Tanwar YS. Formulation and Evaluation of Famotidine Floating Tablets. Current Drug Delivery 2007, 4, 51-55.
10. Reddy LH, Ghose B, Rajneesh, Fast dissolving drug dlivery system, A review of literature, Indian J Pharm Sci, 1997, 59(4), 331-336.
11. Sreenivas S.A, Gadad AP Formulations &Evaluation of ondansetron HCL directly compressed mouth disintegrating tablets, Indian drugs, 2006, 43(1), 35-38.
12. Ziyaur R, Mushir A, Khar RK, Design and Evaluation of bilayer floating tablets of captopril, acta pharm, 2006, 56, 49-57.
13. Rockville MD, USP, 27th revision, USP convention Inc 2004, 2302.
14. Indian Pharmacopoeia, 4th edition, New Delhi, Controller of Publications; 1996, A-80, 82.
15. Abdelbary G, Eouani C, Prinrerre P, Joachim J, Reynier JP, Piccerelle PH.Determination of the invitro Disintegration profile of Rapidly Disintegrating tablets and Correlation with Oral Disinteration.International journal of Pharmaceutics 2004 ; 292 ; 29-41.