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Formulation and evaluation of doxycycline hydrochloride delayed release enteric coated tablets

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ABSTRACT

The present study was undertaken with an aim to formulate doxycycline hydrochloride delayed release tablets. Successful delivery of drugs specifically to the intestine requires the protection of drug from being released in stomach. This drug is universal antibiotic and can be targeted to the specific site of absorption by enteric coating using pH dependant polymers. The present study demonstrates that the doxycycline hydrochloride compression coated tablets could be targeted to intestine using pH dependent polymers. Preformulation studies like angle of repose, bulk density, tapped density, porosity, Carr's index, Hausner's ratio were performed. Enteric coating was carried out using different polymers like Eudragit L-30 D-55, hydroxy propyl methylcellulose phthalate, cellulose acetate phthalate and acryl-EZE® to achieve 5% weight gain and 9 % weight gain. These batches were evaluated for hardness, friability, weight variation, drug content, disintegration and in vitro dissolution.

Keywords: polymers**,** enteric coated tablets, doxycycline hydrochloride tablets. acryl-EZE®, Eudragit L 30 D 55.

INTRODUCTION

Enteric coated tablets are solid unit dosage forms meant for oral administration and are designed to bypass the stomach [1] and release the drug in small intestine. Doxycycline delayed hydrochloride release tablets are prepared by dry mix method and coated using different polymers like L-30 D-55, hydroxy propyl methylcellulose phthalate, cellulose acetate phthalate and Acryl-EZE®. Doxycycline [2] 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 an tetracycline antibiotic. Its half life is around 18 to 22 hours and 80% of the dose is absorbed through small intestine [3].

A number of enteric coating polymers are available and capable of protecting the drug core from the aggressive environments of the stomach [4-7]. Being soluble at higher pH values, these polymers dissolve in the intestine and release the core for ready action. These polymers include several synthetic polymers like polymethacrylates (Eudragits), cellulose acetate phthalate (CAP), hydroxy propyl methyl cellulose phthalate (HPMCP). The aim of the present study was to compare the suitability of these renowned polymers to develop enteric coated tablets of doxycycline for treatment of different infection.

MATERIALS AND METHODS

A. Materials used

Doxycycline hydrochloride, Microcrystalline Cellulose (PH 102), Pregelatinized Maize Starch (Starch 1500), Colloidal Anhydrous Silica, Magnesium Stearate, polymethacrylates (Eudragits), cellulose acetate phthalate (CAP), hydroxy propyl methyl cellulose phthalate (HPMCP), Triethyl citrate, Talc, Isopropyl alcohol, Dichloromethane, Purified water.

Table 1 Formulation of Doxycycline hydrochloride enteric coated tablets (core)

Sr. No.	Ingredients	Theoretical Qty/tab (mg)
	Batch No.	**D**
1.	Doxycycline hydrochloride	100.000
2.	Microcrystalline Cellulose (PH 102)	131.000
3.	Pregelatinized Maize Starch (Starch 1500)	14.500
4.	Colloidal Anhydrous Silica	0.500
5.	Magnesium Stearate	4.000
	Total (Average weight)	250.00

Table 2 Coating solution materials (enteric coating)

Sr. No.	Batch.No.	D1	D2	D3	D4	D5	D6	D7	D8
	Weight gain	5 % w/w				9 % w/w			
1	Eudragit L 30 D 55	12.5	-	-	-	14.625	-	-	-
2	Hypromellose phthalate	-	12.5	-	-	-	14.625	-	-
3	Cellulose acetate phthalate	-	-	12.5	-	-	-	14.625	-
4	Acryl eze	-	-	-	12.5	-	-	-	14.625
5	Triethyl citrate	1.875	1.875	1.875	1.875	3.375	3.375	3.375	3.375
6	Talc	2.5	2.5	2.5	2.5	4.5	4.5	4.5	4.5
7	Iso propyl alcohol	-	q.s.	q.s.	-	-	q.s.	q.s.	-
8	Dichloromethane	-	q.s.	q.s.	-	-	q.s.	q.s.	-
9	Purified water	q.s.	-	-	q.s.	q.s.	-	-	q.s.

B. Method of manufacturing enteric coated tablets dry mix method

Co-Sift Ingredient doxycycline hydrochloride, Microcrystalline Cellulose (PH 102), Pregelatinized Maize Starch (Starch 1500), Colloidal Anhydrous Silica through 40 #.

Mix the above sifted material in blender (25 liters) for 5 minutes at 24 RPM. Sift Magnesium stearate through 40 # and mix with above mixed blend in blender (25 liters) for 5 minutes at 24 RPM.

Compression
The granules were mixed with drug and compressed on a 10-station tablet machine (Cadmach, Ahmedabad, India) using 8.73 mm (11/32) biconvex round shaped die and punches. Three batches were prepared for each formulation. The detailed compositions of Doxycycline HCl core tablet formulations are given in Table 1.

C. Preformulation studies
Angle of repose [8]
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.

Angle of repose=tan-1h/r

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

Bulk density [9]
Bulk density is given by the mass "m" of the powder occupying a known volume 'v' according to the relationship.

Pb =(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.

Tapped density=mass/tapped volume

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.

%Compressibility= tapped density-bulk density/tapped density X100

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

D. Evaluation of delayed release doxycycline hydrochloride tablets (core)

Hardness test [10]

Dr.Scheluenger's 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 test [11]

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.

E. Preparation of enteric coated tablets

The core tablets were enteric coated with different enteric coating material such as Eudragit L-30 D-55, hydroxy propyl methyl cellulose phthalate, cellulose acetate phthalate and acryl-EZE. The detailed compositions of Doxycycline hydrocloride enteric coated tablet formulations are shown in Table 2.

Drug content [12]

10 tablets were weighed and powdered. Powder equivalent to100mg of doxycycline hydrochloride was weighed and dissolved in6.8 pH phosphate buffer. Different concentrations of drug were prepared and analyzed spectrophotometrically (UV- 1700 Shimadzu Corporation, Japan).

F. In vitro dissolution tests

Drug release profile was evaluated in vitro using a dissolution test apparatus (Electro Lab, TDT-08L, Mumbai, India). The USP XIII Type II (paddle type) method was selected to perform the dissolution profile of Doxycycline. The dissolution for all the formulations was carried out according to US Pharmacopoeia [13] for 2 h in 0.1N HCl and then media was changed into phosphate buffer pH 6.8. The temperature was maintained at 37 ± 0.5°C and a constant paddle rotation speed of 100 rpm. Samples (10 ml) were withdrawn at regular intervals and filtered through membrane filter (pore size 0.22 μm). 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.

Table 3 Preformulation parameters

Sr.No.	Test	Result
1	Angle of repose	22.1 – 27.7
2	Bulk density	0.44 gm/ml
3	Tapped density	0.63 gm/ml
4	Carr's Index	30.16
5	Hasner's Ratio	1.43

Table 4 Core tablet evaluation

Sr.No.	Test	Result
1	Weight variation	245 mg – 256 mg
2	Average weight	251 mg
3	Hardness	90 N (70 N – 110 N)
4	Thickness	4.25 mm (4.20 mm – 4.31 mm)
5	Diameter	8.73 mm (8.72 mm – 8.74 mm)
6	Friability	0.131 % w/w
7	Disintegration test	3 minutes to 7 minutes
8	Drug content	99.6 %

Table 5 Dissolution profile comparision (enteric coated tablet)

Dissolution media	0.1 N HCl	Phosphate buffer pH 6.8					
Times in minutes	120	5	10	15	20	30	45
B.No.	% Cumulative drug dissolved						
D1	31.1	-	-	-	-	-	-
D2	25.3	-	-	-	-	-	-
D3	18.7	-	-	-	-	-	-
D4	37.3	-	-	-	-	-	-
D5	5.1	10	29	55	80	98	98
D6	0.9	6	23	47	77	97	99
D7	0	0	21	46	69	94	97
D8	4.8	11	25	59	82	95	97

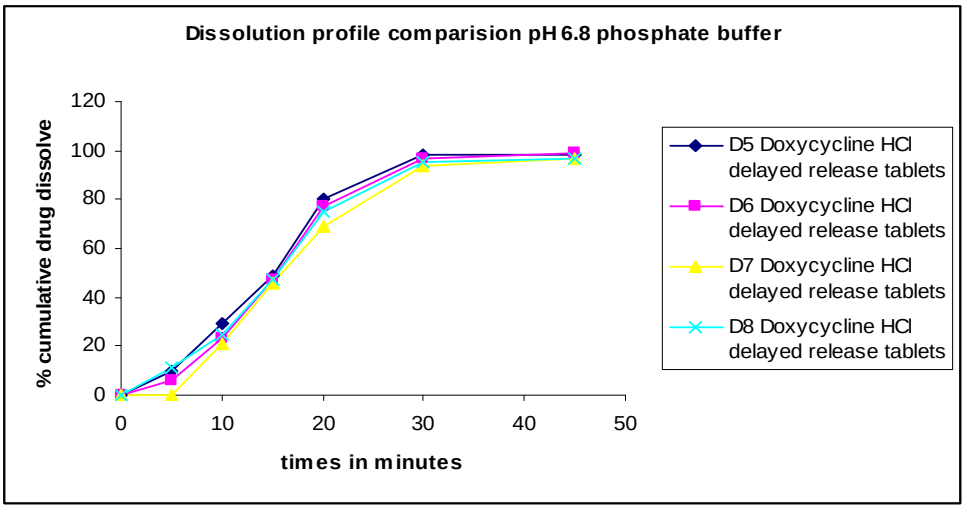

Figure 1 Dissolution profile comparison

RESULTS AND DISCUSSION

Several technologies have been used in the development of enteric coated tablets and in the preset investigation delayed release tablets of doxycycline hydrochloride were prepared by dry mix method then compression 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 compression [14].Values for the angle of repose were found in the range of 22.1 – 27.7 □ . The compressibility falls around 30.16 % and the Hausner's ratio was around 1.43. 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 4. Hardness was found to be in the range of 70 N to 110 N 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 (Table 8). The disintegration of different formulations complies with the pharmacopeia specifications.

In the current study we have selected four enteric coating materials i.e., Eudragit L-30 D-55, hydroxy propyl methylcellulose phthalate, cellulose acetate phthalate and Acryl EZE. In general, these substances are anionic polymers or copolymers which are insoluble in acidic media but acquire water solubility at near neutral pH values due to ionization of functional groups along the polymer chain. In most applications, Eudragit L30 D55 dispersions require the addition of a suitable plasticizer and detackifier such as triethyl citrate and talc, respectively, for proper film forming properties and ease of processability [15]. Hence triethyl citrate and talc were incorporated in the formulations. Four formulations were enteric coated to achieve 5% weight gain using the different enteric coating materials selected. The characteristics of the enteric coated tablets are presented in Table 2. The formulations failed the disintegration test in 0.1 N HCl, hence, four more formulations were prepared with greater amount of enteric coating material (weight gain of 9%). It is evident from Table 5 that the increase in the enteric coating weight (up to 9 %) resulted in non disintegration of the tablets in the acid media (0.1 N HCl) during the study period (2 h). The observed data is in agreement with the reported data showing the potential of these polymers to prevent disintegration in acidic media [16, 17] .

Dissolution analysis was employed to assess the effect of the enteric coat composition and coverage levels on the release of the formulations. *In vitro* drug release was carried out for formulations with 9 % weight gain of enteric coated tablets (D4-D8) in 0.1 N HCl for 2 h followed by phosphate buffer (pH 6.8) for 45 mins. Figure 1 compares the dissolution profile of enteric coated esomeprazole tablets prepared using different coating materials (8% weight gain) in different buffers. It is evident from the figure that all the four formulations demonstrated excellent physical resistance to the acid medium with the acid uptake value between 0.27-2.87% in 2 h. Altering the media to basic (phosphate buff er-pH 6.8) leads to rapid release of the

esomeprazole from all the formulations evaluated. This observation is anticipated, as these enteric coated polymers have shown the similar effect in earlier reports [18-20].

CONCLUSION

Enteric coating was done using four different enteric coating materials (Eudragit L-30 D-55, hydroxy propyl methylcellulose phthalate, cellulose acetate phthalate, Acryl-EZE) to achieve 5% weight gain. Evaluation of these tablets indicated that the coated tablets failed the dissolution test in 0.1 N HCl. However, formulations which were enteric coated to 9% weight gain could pass the dissolution test carried out at pH 1.2. By looking here the dissolution profile of same tablets in pH 6.8 phosphate buffer the formulation with Batch No. D5 and D8 coating layer dissolve faster then the formulation with Batch No. D6 and D7. The formulation with Batch No. D5 and D8 containing Eudragit L 30 D 55 shows better results compare to the formulation containing hypromellose phthalate and cellulose acetate phthalate. Formulation with Batch No. D5 and D8 remain intact in 0.1 N HCl and dissolve fast in pH 6.8 phosphate buffer.

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