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FORMULATION DESIGN AND EVALUATION OF DOXYCYCLINE HYCLATE FILM COATED TABLETS

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ABSTRACT

The main purpose of this work is to develop Doxycycline hyclate film coated tablets are prepared by Direct compression and Dry granulation methods. In the present work, efforts have been made to develop doxycycline hyclate film coated tablets using disintegrants and film formers to mask the hygroscopic nature of the drug. Polymers like hypromellose and ethyl cellulose as film formers. Preformulation studies like angle of repose, bulk density, tapped density, porosity, Carr's index, Hausner's ratio wereperformed. 10 batches were formulated and evaluated for hardness, friability, weight variation, drug content, disintegration in-vitro dissolution and stability studies. Among the six batches, batch F6 was showing 99.8% drug release and was found to be stable and considered to be best formulation.

KEYWORDS: polymers, film formers, film coated tablets, doxycycline hyclate tablets.

INTRODUCTION

Film coating is disposition of a thin film of polymer surrounding the tablet core. Doxycycline hyclate film coated tablets are prepared by Direct compression and Dry granulation methods usind different polymers like hypromellose and ethyl cellulose. Doxycycline [1] 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. Doxycycline is a synthetic (man-made) antibiotic [2] derived from tetracycline. The absolute bioavailability of doxycycline administered orally at a dose of 100-200mg is 90-100%. Polymers coating solution concentrations are designed to develop film coated tablets. The aim of proposed work was to formulate and characterize film coated tablets of doxycycline hyclate for treatment of different infections.

MATERIALS AND METHODS

Doxycycline hyclate, Microcrystalline cellulose, Lactose monohydrate, Crospovidone, Povidone, starch, talc, magnesium stearate, hypromellose, ethyl cellulose, propylene glycol, etc. were depicted in Table 1 and 2.

Table.1: Formulation development of doxycycline hyclate film coated tablets (F1-F10)

INGREDIENTS	Batch no: (mg/tab)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
DOXYCYCLINE HYCLATE	107.65	107.65	107.65	107.65	107.65	107.65	107.65	107.65	107.65	107.65
MICROCRYSTALLINE CELLULOSE	154.85	-	56.14	83.05	58.64	58.36	60.14	63.14	61.94	58.36
LACTOSE MONOHYDRATE	-	163.6	110.71	83.05	90.96	87.54	90.21	92.46	92.91	87.96
POVIDONE	7.5	13.5	9	9	12	12	12	9.5	7.5	12
CROSPOVIDONE	9	7.5	-	-	9	9	10.5	9	10.5	9
STARCH	10.5	-	9	9	6	9	6	10.5	9	9
TALC	7.5	6	4.5	6	7.5	6	7.5	7	6	6
MAGNESIUM STEARATE	1.5	0.75	2.25	0.75	1.5	1.5	2.25	-	3	1.5
Aerosil	-	-	0.75	1.5	2.25	0.75	0.75	0.75	1.5	0.75
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total	300	300	300	300	300	300	300	300	300	300

Table 2: Coating solution materials

		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Hypromellose 15cps	7.50	-	-	-	-	-	-	-	-	-	-
Ethyl cellulose	1.50	-	-	-	-	-	-	-	-	-	-
Titanium dioxide	1.50	-	-	-	-	-	-	-	-	-	-
Talc	1.0	-	-	-	-	-	-	-	-	-	-
Sun set yellow	0.25	-	-	-	-	-	-	-	-	-	-
Propylene glycol	2.0	-	-	-	-	-	-	-	-	-	-
Isopropyl alcohol	0.6	-	-	-	-	-	-	-	-	-	-
Methylene chloride	0.8	-	-	-	-	-	-	-	-	-	-

Method of manufacturing Film coated Tablets

Direct compression method: All the ingredients including drug and other excepients8 except lubricant are mixed and transferred into poly bag, and passed through suitable sieve

and granules are allowed to dry. Then lubricant is added to the dried granules and again then compressed into a tablet using tablet compressor.-

Dry granulation method: Film coating is achieved through various steps: sifting of raw materials, preparation of binder solution, dry granulation, drying, final blending, compression, coating.

PREFORMULATION STUDIES

Angle of repose [3]

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 [4]

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

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= (Vb-Vp)/Vb=1-(Vp/Vb).

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

Hausner's Ratio

The ratio of tapped density to bulk density of the

powders is called the Hasner's ratio.

Evaluation of film coated tablets of doxycycline hyclate

Hardness test [5]

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 Roche 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 [6]

Tablets were taken and introduced one tablet in each tube of disintegration apparatus and placed in 1-litre beaker and the time of disintegration was recorded. The study was done at room temperature and were noted and compared with I.P. standard.

Dissolution studies [7]

The in vitro dissolution study was carried out in the USP 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+or-0.5 degrees c. The speed of paddle was set at 75 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).The absorbance was measured at 276 nm and % drug release was calculated.

STABILITY STUDIES

The final formulation F6 tablets were placed in high density polyethylene (HDPE) container and kept in stability chamber. These studies were carried out for 1 month at storage conditions of 25±2°c / 60±5% RH. After completion of one month time, the samples were withdrawn and checked out for the in-vitro drug release and drug content in order to determine the stability of the product.

RESULTS AND DISCUSSION

TABLE 3: PRE-FORMULATION STUDIES FOR FORMULATIONS (F1-F10)

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index (%)	Hausner's ratio	Moisture content (%)	Angle of repose (°)
F1	0.443±0.03	0.568±.03	22.11±1.28	1.282±0.05	0.42	31.4±0.05
F2	0.449±0.04	0.558±0.04	20.53±1.33	1.242±0.09	0.53	32.3±0.06
F3	0.432±0.03	0.558±0.02	23.42±1.25	1.292±0.08	0.47	31.2±0.09
F4	0.488±0.05	0.643±0.03	24.10±1.37	1.317±0.04	0.54	27.2±0.08
F5	0.473±0.03	0.579±0.04	18.30±1.39	1.224±0.05	0.62	28.9±0.07
F6	0.461±0.04	0.532±0.05	13.34±1.36	1.154±0.06	0.38	29.3±0.04
F7	0.467±0.06	0.560±0.03	16.60±1.28	1.199±0.04	0.57	24.6±0.09
F8	0.463±0.02	0.583±0.02	20.58±0.98	1.259±0.02	0.43	24.8±0.03
F9	0.484±0.04	0.571±0.04	15.23±1.17	1.118±0.04	0.48	26.3±0.04
F10	0.469±0.03	0.559±0.02	16.10±1.26	1.192±0.03	0.55	27.3±0.08

TABLE 4: POST COMPRESSIONAL PARAMETERS

FORMULATION CODE	THICKNESS OF TABLETS (mm)	HARDNESS OF TABLETS (Kg/cm^2)	FRIABILITY OF TABLETS (%)	AVERAGE WEIGHT OF TABLETS (mg)	DISINTEGRATION TIME (min)	Assay (%)
F1	4.52±0.014	3.13±0.13	0.812±0.023	295.9±0.13	9.32±0.06	92.6±0.20
F2	4.58±0.018	5.62±5.62	0.998±0.054	310.4±0.17	11.19±0.54	96.9±0.18
F3	4.62±0.017	3.34±0.20	1.016±0.041	307.5±0.13	9.57±0.05	95.4±0.19
F4	4.64±0.014	7.12±0.16	0.967±0.033	308.7±0.18	18.02±0.08	97.8±0.17
F5	4.57±0.016	4.64±0.15	0.513±0.053	310.2±0.17	10.24±0.07	98.1±0.25
F6	4.71±0.015	4.98±0.17	0.397±0.017	309.2±0.19	8.12±0.09	99.9±0.23

F7	4.78±0.013	5.27±0.13	0.412±0.026	311.9±0.16	10.58±0.08	97.8±0.22
F8	4.69±0.006	5.09±0.06	0.597±0.031	312.3±0.12	9.39±0.02	98.8±0.16
F9	4.74±0.008	6.32±0.10	0.416±0.021	310.7±0.17	9.48±0.05	99.5±0.19
F10	4.68±0.007	5.29±0.15	0.579±0.028	309.7±0.16	8.51±0.04	98.7±0.18

TABLE 5: IN-VITRO DISSOLUTION PROFILE OF ALL FORMULATIONS (F1-F10)

FORMULATION CODE	CUMULATIVE PERCENTAGE DRUG RELEASE AT TIME POINTS IN MIN				
	0	**30**	**45**	**60**	**90**
F1	0	34.6	51.3	71.2	84.2
F2	0	32.4	49.3	70.8	82.9
F3	0	35.2	51.0	69.8	84.7
F4	0	42.9	51.3	74.6	88.4
F5	0	40.7	59.3	80.1	91.4
F6	0	56.8	81.3	93.6	99.8
F7	0	40.9	62.3	86.9	95.8
F8	0	47.6	62.4	79.6	93.5
F9	0	50.4	77.6	86.3	94.9
F10	0	50.9	78.6	88.3	97.5

TABLE 6: STABILITY STUDIES OF DOXYCYCLINE HYCLATE FILM COATED TABLETS OF FORMULATION F6 AFTER ONE MONTH.

PARAMETER	INITIAL	AFTER 1 MONTH
Colour & Appearance	Sun set yellow, round shaped tablets	Sun set yellow round shaped tablets
Assay (%)	99.8	99.8±0.17
Average weight (mg)	309.3	309.1±0.14
Thickness (mm)	4.62±0.006	4.62±0.007

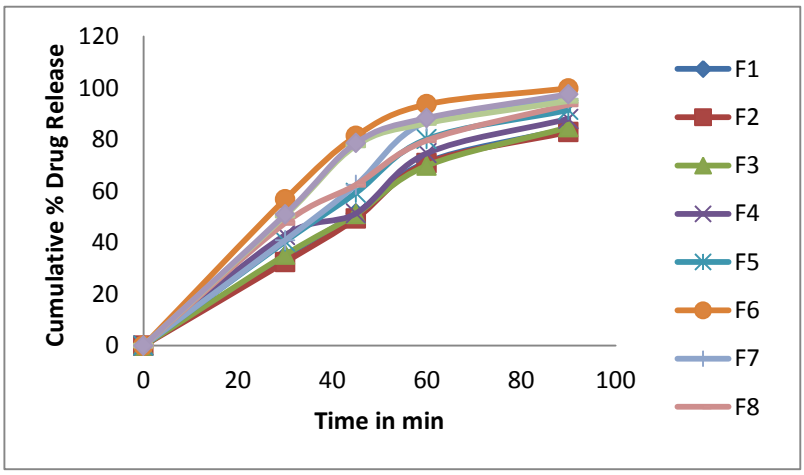

Fig. 1: Comparative Dissolution Profile of Formulations

DISCUSSION

Film coated tablets of Doxycycline hyclate were successfully prepared by direct compression and dry granulation methods .Formulations were evaluated for pre and post compression parameters. The compatibility studies for the drug and excipients used in the formulation were carried out. No characteristic physical changes were observed. The granules of different formulation were evaluated for angle of repose, bulk density and tapped density, compressibility index, Hausner's ratio. The results showed that all formulations of the granules were within limits and thus it confirmed that the granules have good flow property except F1, F2, F3 & F4. In these formulations microcrystalline cellulose and lactose monohydrate were incorporated unequally during granulation, have poor compressibility index. The results of post compression parameters such as thickness, disintegration time, hardness, friability, in-vitro drug release, weight variation and drug content for the prepared formulations were within the limits. The stability studies has been carried out for the best formulation F6 at 25±2°c & 60±5% RH as per the ICH guidelines for one month. The percentage drug release and drug content were not altered with the standard, so the prepared formulation was found to be stable. In the present work, efforts have been made to develop doxycycline hyclate film coated tablets using disintegrants and film formers to mask the hygroscopic nature of the drug. The results showed that the in-vitro drug release was depend on concentration of disintegrants and binders used. The best formulation F6 containing 3% crospovidone & starch showed minimum (8.12 min) disintegration time and maximum (99.8%) in-vitro drug release profile as compared to other formulations.

SUMMARY & CONCLUSION

Film coated tablets of doxycycline hyclate were formulated by direct compression and dry granulation methods with good release profile for specific period of time up to 90min.

Compatibility studies were carried out for the physical mixture and the drug was found to be compatible with all excipients used in different formulations.

The granulation was compressed into tablets and subjected for film coating and were analysed for the parameters such as average weight, friability, thickness, hardness, disintegration and assay.

Formulation containing crospovidone & starch (9mg) each shows rapid rate of disintegration and dissolution when compared with other formulations.

The in-vitro dissolution profiles of F1 to F10 were found to have different percentage of drug release. The disintegration time for F6 tablets was relatively low and dissolution profile was greater than other formulations at the end of 90min. When compared to other formulations, F8 shows better release profile and concluded that F8 was better formulation product.

F6 formulation shows better drug release when compared to other formulations.

The stability studies were conducted for F6 tablets for 1 month, which were found to be stable and concluded that formulation F6 was better stable product with good quality.

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