FORMULATION AND EVALUATION OF DOXYCYCLINE SUSTAINED-RELEASE TABLETS

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***ABSTRACT:** The objective of the present study was to develop sustained release tablets of Doxycycline. Doxycycline is a potent hydrophilic anti bacterial agent. The sustained release tablets were prepared by direct compression method using hydroxyl propyl methylcellulose, Sodium alginate in various concentrations. The powder showed satisfactory flow properties and compressibility. The powders for tableting were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and Hausner's ratio etc. The powder blend showed satisfactory flow properties. The tablets were subjected to thickness, weight variation test, drug content, hardness, friability and in-vitro release studies. All the formulations showed good results which were compliance with Pharmacopoeial standards. All the four formulations showed acceptable pharmacopoeial standards. The result of formulation F2 sustained the release of Doxycycline up to 8 hrs.*
***Key words:** Doxycycline, sustained tablets, Hydroxyl propyl methyl cellulose, direct compression technique, FTIR studies, in vitro rug release*

I. INTRODUCTION

Oral route has been the predominantly adopted due to its convenience for drug delivery. This route is considered significantly in the pharmaceutical field, due to its flexibility in formulating the dosage form than other routes[1]. This route of delivery depends on factors such system type, the disease, the diseased person and the duration of treatment and the characteristic property of the active medicament. Almost all the oral controlled drug delivery systems follow diffusion or dissolution mechanism of drug release in the GIT.The oral route can be utilized to target the required receptor region[2]. This targeting concept is to achieve the patient compliance when compared to normal conventional dosage form. This is achieved by altering the pharmacokinetic parameters and improved pharmacodynamics. Oral route has been used in ancient period also due to its convenience and among all route of delivery. For any medicine the oral route would be the primary choice due to its flexibility in drug delivery systems.[3] Oral route of administration has been used as either conventional or novel drug delivery system. Many advantages including patient willingness to accept and ease of administration. Sustained release system types given for oral route include virtually every at the present time now the theoretical mechanism[4]. This is due to the manufacturing of dosage form is more flexible, since constraint, like sterility problem and harmful effects at site of administration are reduced. Perhaps, it is easy to develop different dosage forms by customary those developed for administration through oral route.[5] The objective of the present study was to develop sustained release tablets of Doxycycline. Doxycycline is a potent hydrophilic anti bacterial agent. The sustained release tablets were prepared by direct compression method.

II.MATERIALS AND METHODS

Doxycycline was collected as a gift sample from Hetero labs, Hyderabad and various excipients and polymers were purchased from AR chemicals, Hyderabad.

Drug excipient compatibility studies[6]

Any potential interaction between drug and excipients can affect the physical or chemical properties of drug, bioavailability and stability of dosage form. Hence, it is important to check and confirm that the selected formulation components are in good compatibility with drug and do not compromise its stability and safety. The principle involved in the IR spectroscopy is measuring the energy difference between the excited and ground states of a molecule. Fourier transformed infrared spectroscopy (FTIR) analysis used for identifying the functional groups

with their means of attachment thus helps assess the drug excipients interaction in terms of polymerization, cross-linking as well as drug loading in the formulation. FTIR was carried out to evaluate the interaction of excipients with the drug. For pure powdered drug KBR pellet method was used and for physical mixture, polished sodium chloride salt plates were used to check the interaction between the components of the formulation.

2.1 MATERIALS AND METHODS

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Formulation development

Table-1: Composition of Doxycycline floating tablets

S.NO.	INGREDIENTS	F1	F2	F3	F4
1	Doxycycline	200	200	200	200
2	HPMC K15	50	100	-	-
3	Sodium alginate	-	-	50	100
4	Microcrystalline cellulose	245	195	245	195
5	Magnesium stearate	3	3	3	3
6	Talc	2	2	2	2
7	Total weight	500	500	500	500

Direct compression method:

Pre weighed ingredients were passed through Sieve no. 40 mesh separately and collected. Ingredients were mixed in geometrical order and thoroughly mixed in a polythene bag for 15 minutes to get a uniform mixture. Talc and magnesium stearate were added to the powder mixture and compressed on a 16- station rotary tablet compression machine using 10mm round flat face punch.

Evaluation studies[7,8,9]

Bulk Density

Bulk densities of all types of granules were determined by pouring gently some amount of sample through a glass funnel into a 10 ml graduated cylinder. The volumes occupied by the sample were recorded. Bulk density was calculated:

Bulk density = weight of sample taken /volume noted

Tap density

Tapped densities of all types of granules were determined by pouring gently some amount of sample through a glass funnel into a 10 ml graduated cylinder. The cylinder was tapped from a height of 2 inches until a constant volume was obtained. Volumes occupied by the sample after tapping were recorded, and tapped density was calculated

Tapped density = weight of sample taken / tapped volume

Where,

V_o = initial volume

V_f = final volume.

Compressibility index

% compressibility was determined by the Carr's compressibility index

Carr's index = Tapped density - Bulk density / Tapped density X 100

Hausner's ratio

Hausner's ratio = Tapped density / Bulk density

Angle of repose

The angle of repose of granules was determined by funnel method. A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm. over the platform. About 10 g of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the steam of the funnel. A rough circle was drawn around the pile base, and the radius of the powder cone was measured.

$\tan\theta = h/r$

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

Evaluation of tablet[10,11,12]

Weight variation

To find out weight variation 20 tablets of each formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight. The test was performed according to the official method

Thickness

The thickness and diameter of tablets were important for uniformity of tablet size. The thickness and diameter of the tablets was determined using a Vernier caliper. Ten tablets from each type of formulation were used and average values were calculated.

Hardness

For each formulation, the hardness of 10 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm2 . Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm^2.

Friability

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of preweighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. A loss of less than 1 % in weight is generally.

The percentage friability was measured using the formula,

% F = {1-(Wo/W)} ×100

Content Uniformity

Twenty tablets were powdered in a mortar. An accurately weighed quantity of powdered tablets equivalent to100 mg of Doxycycline was extracted with pH 6.8 phosphate buffer and the solution was filtered through whatmann filter paper. The absorbance was measured at 268 nm after suitable dilution.

***In- Vitro* Release study**

Drug release was assessed by dissolution test under the following conditions: n = 3, USP type I dissolution apparatus (Basket method) at 100 rpm in 900 mL of phosphate buffer pH 6.8 throughout the dissolution up to 12 hours, maintained at 37°C ± 0.5°C. An aliquot (5mL) was withdrawn at specific time intervals and replaced with the same volume of pre warmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered through whatmann filter paper and drug content in each sample was analyzed by UV-Visible spectrophotometer at 268 nm

Stability studies

To assess the drug and formulation stability, stability studies were done according to ICH guidelines. The optimized formulation was subjected to stability study at 40±2ºC and 75±5% RH for 90days. The samples were evaluated for physical changes, hardness, friability, drug content and percentage drug release during the stability studies.

III.RESULTS AND DISCUSSION

Drug - excipient compatibility studies (FT-IR)

The compatibility between the drug and other excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-lipid mixture, which confirmed the absence of any chemical interaction between the drug, lipid and other chemicals.

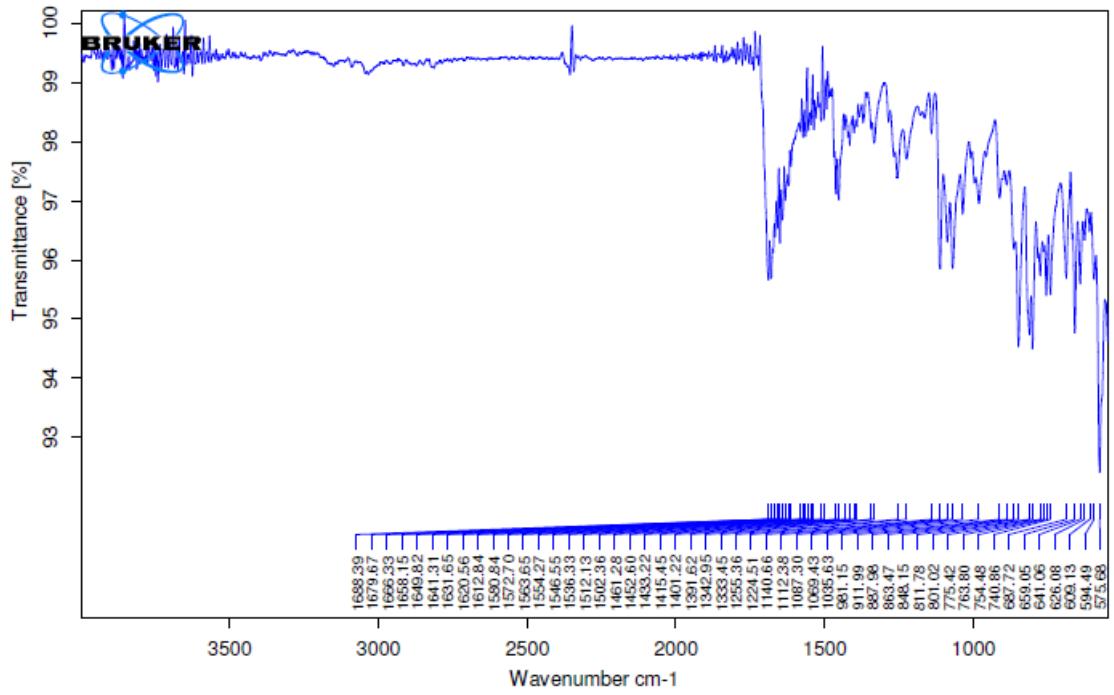

Fig- 1: FTIR Studies of Pure Drug

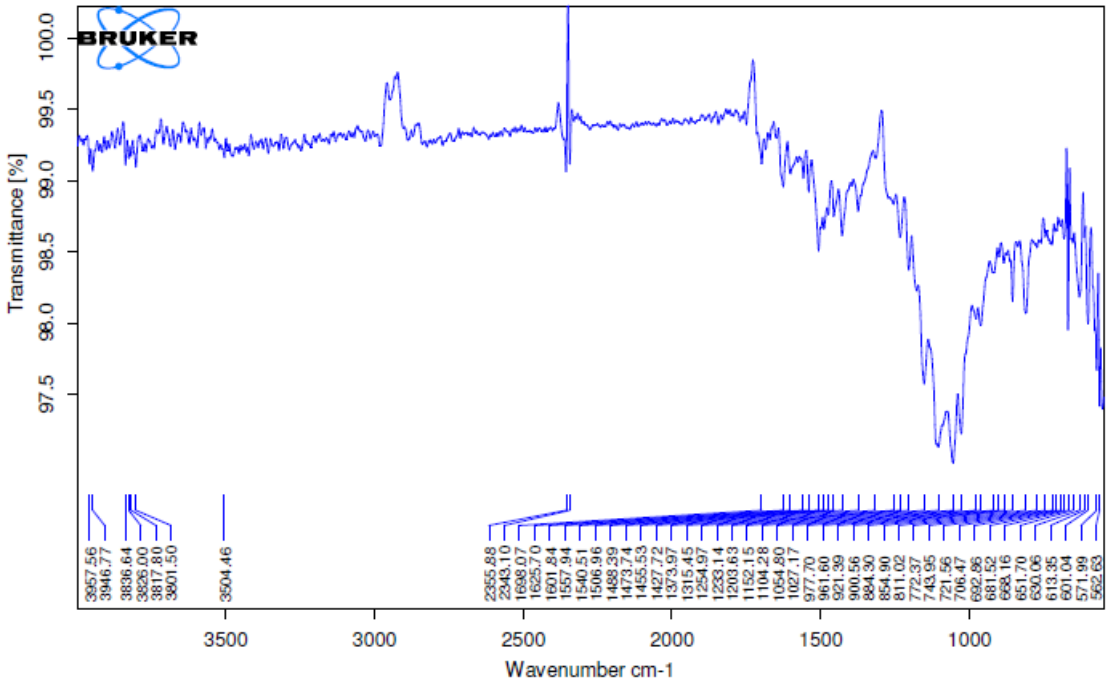

Fig-2: FTIR Studies of physical mixture of drug and excipients

Evaluation studies

Pre compression parameters

Bulk Density: The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.419-0.432.

Tapped density: The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.521-0.543.

Angle of repose: The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 27 ^{0} to 31 ^{0}

Compressibility index: Compressibility index was carried out, it found between 10% to 20.70% indicating the powder blend have the required flow property for compression.

Table-2: Results for pre compression parameters

F. no	**Bulk density**	**Tapped density**	**Compressibility index**	**Hausner ratio**	ANGLE OF REPOSE (0)
F1	0.419	0.529	20.79	1.26	31^0
F2	0.426	0.530	19.62	1.24	29^0
F3	0.430	0.540	20.37	1.25	30^0
F4	0.419	0.521	19.57	1.24	27^0

Post compression parameters

Weight variation:

All the formulated (F1 to F4) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness:

Tablets mean thickness were uniform in F1 to F4 formulations and were found to be in the range of 4.26 mm to 4.55 mm.

Hardness:

The measured hardness of tablets of each batch ranged between 5.15 to 5.27 kg/cm^2 .This ensures good handling characteristics of all batches.

Friability:

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity:

The percentage of drug content for F1 to F4 was found to be between 91.55% and 97.29 % of Doxycycline, it complies with official specifications.

Table-3: Physical parameters of tablets of each formulation

F. No.	**Weight variation (mg)**	**Thickness (mm)**	**Hardness (kg/cm^2)**	**Friability (%)**	**Drug content (%)**
F1	499	4.55	5.21	0.42	91.55
F2	500	4.48	5.22	0.48	97.29
F3	501	4.32	5.19	0.50	91.55
F4	500	4.46	5.27	0.51	95.25

In-vitro Dissolution Study

All the four formulation of prepared matrix tablets of Doxycycline were subjected to in-vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for the 8 hrs.

Table-4: Dissolution Profile of F1 to F8

Time (hrs.)	**F_1**	**F_2**	**F_3**	**F_4**
0	0	0	0	0
1	19.12	18.20	17.11	20.10
2	22.45	25.30	23.11	31.45
3	32.80	35.32	33.76	49.90
4	42.63	44.65	43.23	56.70

5	58.21	59.28	52.11	65.16
6	63.35	68.55	65.22	72.22
7	78.26	80.10	75.16	82.26
8	92.25	98.12	91.12	94.50

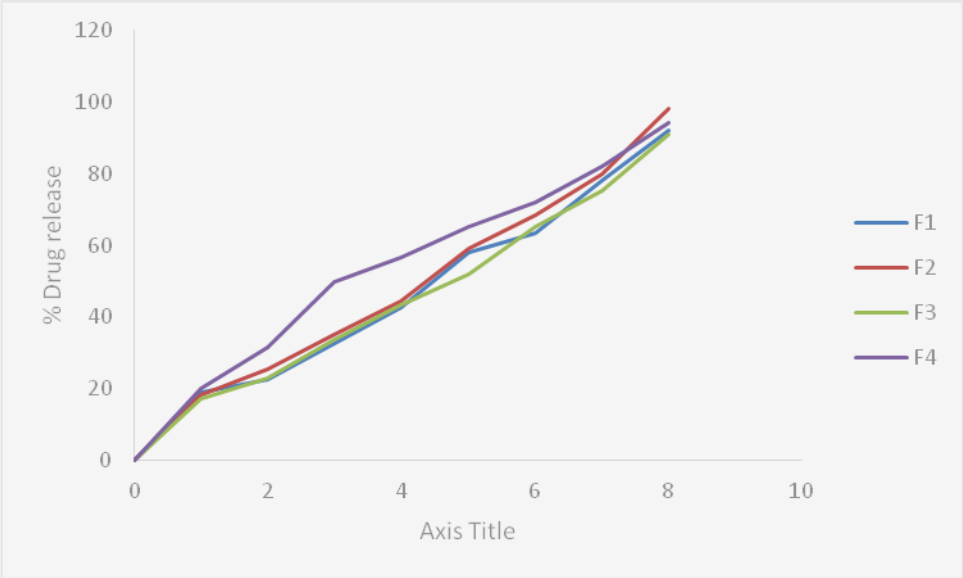

Fig-3: Dissolution profile of (F1-F4) Formulations

Stability studies

Sustained release tablets of Doxycycline formulated in the present study were subjected to accelerated stability studies. Stability studies of the prepared formulations were performed at ambient humidity conditions, at room temperature, at 40^{o}c and 2-8^{o}c for a period up to 90 days. The results revealed that no significant changes in appearance, drug content, hardness, friability, and in vitro release for F2 formulation. When it was stored at the three storage conditions. However there was slight variation in invitro release when it is stored at 2-8^{o}c, there was no change when it is stored at 40^{o}c and room temperature.

Table-5: Results of stability studies of optimized formulation F-2

Formulation Code	Parameters	Initial	1st Month	2nd Month	3 rd Month	Limits as per Specifications
F-2	**25^{0}C/60%RH % Release**	98.12	98.08	97.82	97.03	**Not less than 85 %**
F-2	**30^{0}C/75% RH % Release**	98.12	98.02	97.15	96.99	**Not less than 85 %**
F-2	**40^{0}C/75% RH % Release**	98.12	97.99	97.05	96.73	**Not less than 85 %**

CONCLUSION

This study deals with the investigation carried out with the objective of developing oral sustained release formulation of Doxycycline using polymers. Preparation of tablet by direct compression technique was found to be more effective in sustaining the release of drug. Drug content for all formulations were found to be complies with pharmacopoeial standards. Formulation F2 containing HPMC and sodium alginate with drug release 98.12% for 8 hrs. The controlled and efficient drug delivery system developed in the present study will maintain the plasma Doxycycline levels better, which will overcome the drawbacks associated with the conventional therapy. The drug release from the tablets was sufficiently sustained of the drug from tablets was confirmed. Based on the in-vitro drug release data, the formulation F2 it was concluded as best formulation. In conclusion the present study

demonstrated the successful preparation of sustained release tablet of Doxycycline.

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