ejpmr, 2015,2(5), 1738-1750

SJIF Impact Factor 2.026

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 3294-3211

EJPMR

FORMULATION AND EVALUATION OF MINOCYCLINE HYDROCHLORIDE EXTENDED RELEASE MATRIX TABLETS

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Article Received on 16/08/2015 **Article Revised on 06/09/2015** **Article Accepted on 28/09/2015**

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ABSTRACT

The present study was aimed to formulate and evaluate minocycline hydrochloride (MIN) extended release matrix tablets, using natural polymers like Guar gum and Tara gum, individually and in combination in order to maintain MIN concentration in the blood over a period of time (24 hrs). Totally, seven formulations and *in-vitro* drug release studies were carried out in 0.1N HCl up to 2 hrs and in pH 7.4 buffer for remaining 22 hrs respectively. Based on the *in-vitro* drug release profiles, formulations F7 (combination of Guar and tara gum-12.5%:12.5%) resulted in extended delivery of MIN (61.59%) for a period of 24 hours. Formualtion F6 containing guar gum at 37.5%w/w showed a 71.5 % release of MIN at the end of 24 hrs. Mathematical treatment of the *in vitro* drug release data suggests that, all the formulations fitted into first order release kinetics. Drug release from the matrix occurred by combination of two mechanisms, diffusion of drug from tablet matrix and anamolous transport, which was reflected from Higuchi's model and Korsmeyer peppas equation. Overall, combinatiomn of guar and tara gums significanlty slowed the release of MIN form tablets.

KEYWORDS: Minocycline hydrochloride, Guar gum, Tara gum, extended release, matrix tablets.

INTRODUCTION

Minocycline hydrochloride (MIN) is a semi synthetic tetracycline antibiotic, which has been primarily indicated for the treatment of *Acne vulgaris*, where its success has been attributed

to a combination of its bacteriostatic and anti-inflammatory activities.[1] But its use is limited due to acute vestibular adverse events (AVAEs). In order to lower overall systemic exposure to reduce unwanted side effects, a study was initiated to develop an extended release dosage form of minocycline,[2] It has a half life of >12 hrs.[3] The drug is freely soluble in water.[4] and hence judicious selection of release retarding excipients is necessary to achieve a constant *in vivo* input rate of the drug.[5] The matrix tablets composed of drug and the release retarding material (polymer), offers the simplest approach in designing an extended-release system.[6] Number of studies shows the use of hydrophilic matrices to formulate the controlled release dosage forms of different drugs.[7-11] Because of their simplicity and cost-effectiveness, hydrophilic gel matrix tablets are widely used for oral controlled release dosage forms. Hydrophilic polymers form a gel like structure around the tablet core which controls the drug release.

Although minocycline has relatively long plasma half life, conventional dosage forms and traditional delayed release dosage forms containing minocycline require frequent dosing(every 6 to 12 hrs) on a daily basis resulting in variations in plasma concentrations throughout the course of treatment and ultimately poor patient compliance. Hence, in the present work, an attempt has been made to develop extended-release matrix tablets of minocycline using natural polymers such as Tara gum and Guar gum, alone and in combination, and to study the *in vitro* release characteristics and kinetics of the prepared formulations. The kinetics of the dissolution process was studied by the application of four kinetic equations to the dissolution data namely, the zero-order, the first-order, the Higuchi-square root, Korsmeyer-Peppas equation.

MATERIALS AND METHODS

Minocycline hydrochloride was received as a gift sample from Dr.ReddyLaboratories, Hyderabad, India. Microcrystalline cellulose was obtained from Indian research products, Chennai. Magnesium stearate and talc were obtained from Sd fine chemicals Ltd, Mumbai. Guar gum and Tara gum were obtained from Merck Specialities Pvt Ltd, Mumbai.

Solubility determination

The solubility of the Minocycline was determined in various solvents by adding an excess amount of drug to 10 ml of solvent in 25ml stoppered conical flasks. The flasks were kept at 25± 0.5ºC on a rotary flask shaker for 72 hours to reach equilibrium. The equilibrated samples were removed from the shaker and centrifuged at 4000 rpm for 15 minutes. The

supernatant was taken and filtered immediately using a 0.45µ nylon disc filter. The filtered samples were diluted suitably and assayed for drug measuring absorbance at 265nm for pH 1.2 and 245.4 nm for water, pH 6.8, pH 7.4. Shaking was continued until three constructive estimations were same. The solubility experiments were run in triplicate.

Fourier Transform Infrared spectroscopy (FT-IR)

Samples were analyzed using an ATR-FTIR spectrometer (Bruker, Germany). ATR spectra were measured over the wave number range of 4000-500 cm^{-1} at a resolution of 1.0 cm^{-1}. The powder or film sample is simply placed onto the ATR crystal and the sample spectrum is collected. The sample is then cleaned from the crystal surface and the accessory is ready to collect additional spectra. ATR analysis is less complicated than using KBr pellets, it is fast and a very small amount of the sample is needed.

Preformulation Studies

Angle of Repose

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel (2-4cm) was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. Angle of repose was determined by measuring the height of the cone of powder and radius of the heap of the powder. The angle of repose was calculated using the following equation.

$$\theta = Tan^{-1} \frac{h}{r}$$

Where, θ = angle of repose, h = height of the cone,

Bulk density (D_b)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

$$D_b = M/V_0$$

Where, M is the mass of powder, V_0 is the Bulk volume of the powder.

Tapped density (D_t)

Tapped density was determined by using graduated cylinder. An accurately weighed sample was carefully added to the graduated cylinder with the aid of funnel. The initial volume was noted and the sample was tapped on a horizontal base. Tapping was continued until no further reduction in sample volume was observed. Volume was noted and tapped density is calculated by using the following formula.

$$D_t = M/V_0$$

Where, M is the mass of powder, V_0 is the Bulk volume of the powder.

Carr's Index (I)

It indicates the ease with which a material can be induced to flow and powder compressibility. It is expressed in percentage and is given by

$$I= (D_t-D_b)/ D_t \times 100$$

Where, D_t is the tapped density of the powder, D_b is the bulk density of the powder.

Compressibility Index and Hausner's ratio (H)

In recent years the compressibility index and the closely related Hausner's ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of the bulk density, size, shape, surface area, moisture content and cohesiveness of the materials. Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of the powder.

$$\text{Compressibility Index} = (1-V/V_0) \times 100$$

Where, V = volume of powder blend before tap, V_0 = volume of powder blend after 100 tappings.

Hausner's ratio (H) is a number that is correlated to the flow ability of a powder. The Hausner's ratio is related to the Carr's Index by the formula

$$H = 100/ (100-C)$$

Hausner's ratio also expressed as,

$$H = D_t / D_b$$

(or)

Hausner's ratio = tapped density/ bulk density

Formulation and Evaluation of Minocycline Hydrochloride Tablets

In the present investigation extended release tablets of Minocycline hydrochloride were prepared using different rate controlling polymers by direct compression method as per formulae given in Table. 1 and evaluated for drug content, uniformity of weight, hardness, friability, and dissolution properties.

Direct compression method

Compressed tablets of Minocycline hydrochloride using different polymers (Guar gum, Tara gum) were prepared by direct compression method as per formulae given in table. Accurately weighed quantities of API, polymer was passed through sieve no #40 and remaining ingredients were added to the blend in a polybag and mixed for 10 minutes. The resulting powder blend was compressed on single punch tablet press (Cadmach, India) using 12mm round punches to a hardness of 6-7 kg/cm^2.

In each case twenty tablets were prepared. The tablets were stored in a tightly closed container and evaluated for following characteristics in triplicate.

Table. 1: Formulae used for the development of Minocycline hydrochloride extended release tablets

INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7
Minocycline hydrochloride	50	50	50	50	50	50	50
Tara gum	25	50	75	-	-	-	25
Guar gum	-	-	-	25	50	75	25
Micro crystalline cellulose (MCC)	117	92	67	117	92	67	92
Magnesium state	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4
Total weight	200mg	200mg	200mg	200mg	200mg	200mg	200mg

Evaluation of Minocycline Hydrochloride Tablets

Weight variation

The weight variation test was conducted by weighing 20 randomly selected tablets individually, calculating the average weight and comparing the individual tablet weights to the average.

Hardness

The Hardness of the tablets was measured with a Monsanto hardness tester (M/s Campbell Electronics, model EIC-66, India). The results reported were average value with standard deviation of 10 tablets for each formulation.

Friability

For each formulation 10 tabs were weighed, placed in Friabilator (M/S Cambell Electronics, India) and were subjected to 100 rotations in 4 min. The tablets were reweighed and Friability was calculated along with mean and the standard deviation.

$$Friability = \frac{W_1 - W_2}{W_1} \times 100$$

Where "W_1" is the initial weight and "W_2" is the final weight of the tablets.

Drug content uniformity

Five tablets were weighed and powdered in a mortar. Accurately weighed tablet powder samples equivalent to 10 mg of Minocycline hydrochloride tablets was transferred to a 10ml volumetric flask, and the drug was extracted into 10ml methanol. This solution was filtered through a Whatman No.1 filter paper and collected in to a 10ml volumetric flask. The solution was suitably diluted and the absorbance was measured at 265 nm and 245.4nm. The estimations were carried out in triplicate.

In vitro dissolution studies

The tablet samples were subjected to *In-vitro* dissolution studies using USP Type II dissolution apparatus at 37±0.5°C and 50 rpm speed. To mimic the Gastrointestinal conditions, as per the official recommendation of USFDA, 900 ml of 0.1 N HCL was used as dissolution medium for initial 2hr and 7.4pH phosphate buffer for next 22 hrs. Aliquot equal to 5ml was withdrawn at specific time intervals (1hr, 2hrs, 3hrs, 4hrs, 6hrs, 8hrs, 10hrs, 12hrs, 24hrs) and replaced with fresh buffer. The aliquots were diluted and drug release was determined spectrophotometrically at a wavelength of 265 nm and 245.4nm for 0.1N HCL and 7.4pH phosphate buffer respectively by comparing with the standard calibration curve.

Study of Release Kinetics and Release Mechanisms

The various release kinetic equations in which the experimental data can be fitted and drug release rate can be predicted as a function of some variable (example time) are mentioned below. The suitability of equation is judged on the basis of best fit to the equation using statistical indicators like R^2 value.

Zero Order Equation

This equation describes the systems where the release rate is independent of the concentration of the dissolved species. The dissolution data are fitted into the zero order equation:

$$X = X_0 - K_0t$$

Where, X = Amount of drug released at time t, X_0 = Amount of drug released initially

K_0 = Zero order rate constant

A graph of concentration vs. time would yield a straight line with a slope equal to K_0 and the intercept at the origin of the axes. The zero order plots is derived from plotting the cumulative percent drug dissolved vs. time.

First Order Equation

The first order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species.

Release behavior generally follows the following first order release equation:

$$\ln X = \ln X_0 - K_1t$$

Where, M is the amount of drug undissolved at time t,

M_0 is the amount of drug undissolved at t = 0 and

K_1 is the corresponding release rate constant.

A graph of log concentration of drug remaining vs. time yields a straight line with a negative slope.

Higuchi Square Root Law

The Higuchi square root equation describes the release from systems where the solid drug is dispersed in an insoluble matrix, and the rate of drug release is related to the rate of drug diffusion. A form of the Higuchi Square Root Law is given by equation:

$$Q = K_s\sqrt{t}$$

Where, Q = Amount of drug dissolved at time t, K_s = Higuchi rate constant.

Korsemeyer Peppas Equation

The Korsemeyer's equation, which derived from, the linear line of log cumulative percentage vs. log time curve, is

$$M_t/ M_\infty = Kt^n$$

Where Mt and M∞ are the absolute and the cumulative amount of drug released in time t and infinite time; k is a constant incorporating the structural and geometric characteristics of the device and 'n' is the release exponent which is indicative of the mechanism of release. This is also known as the power law.

Exponent 'n' of the power law and drug release mechanism from polymeric controlled delivery systems of different geometry.

Exponent, 'n'			Drug release mechanism
Thin Film	Cylinder	Sphere	
0.5	0.45	0.43	Fickian diffusion
0.5<*n*<1.0	0.45<*n*<0.89	0.43<n<0.85	Anomalous transport
1.0	0.89	0.85	Case-II transport (follows zero order)

From the above it is clear that when the exponent 'n' takes a value of 1.0, the drug release rate is independent of time. This case corresponds to zero order release kinetics. For slabs, the mechanism that creates the zero order release is known to polymer scientists as case-II transport. Here the relaxation process of the macromolecules occurring up on water imbibitions in to the system is the rate-controlling step. The value of n=0.5 indicates drug release is Fickian in nature. Thus, equation has two distinct physical meanings in the two special cases of n=0.5 (indicating diffusion-controlled drug release) and n=1 (indicating swelling- controlled drug release). Values of n between 0.5 and 1.0 can be regarded as an indicator for the super position of both phenomena (anomalous transport). It has to be kept in mind that the two extreme values for the exponent n, 0.5 and 1.0 are only valid for slab geometry. Power Law is more comprehensive in describing the drug release as compared to Higuchi.

RESULTS AND DISCUSSION

Solubility studies

The order of solubility of Minocycline HCl was Water>7.4pH buffer>6.8pH buffer>0.1N HCl. But in the present investigation the dissolution studies were carried out in 0.1 N HCl for the initial 2 hrs and later in 7.4 pH buffer to mimic the in-vivo conditions. The drug showed its highest solubility in water. The results were given in table 2 and shown in Fig. 1.

Table 2: Solubility determination of Minocycline HCL

S.no	Medium	Solubility(mg/ml)
1	Water	39.85± 0.23
2	1.2 Ph	24.57±0.43
3	6.8 pH	28.46±0.41
4	7.4 pH	36.66±0.31

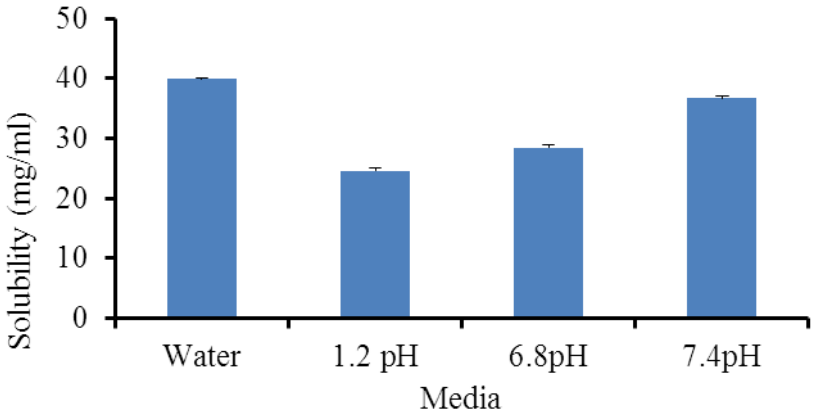

Fig. 1: Solubility of Minocycline HCl in Different media

FTIR Studies

To investigate the possibility of chemical interaction between drug and polymer FTIR spectra of pure Minocycline HCl and polymers were analyzed over the range. The IR spectrum of pure Minocycline HCl in Fig. 2 & 3 showed strong absorption bands at wave numbers as given in Table 3 below.

Table 3: Showing FTIR spectral wave numbers and functional groups of Minocycline hydrochloride.

Functional group present	Reference wave number	Peak observed at wave number (cm^{-1})
N-H bend	1650-1580	1593.61
C-C stretch (in-ring)	1500-1400	1473.34
C-O stretch	1320-1000	1307.57
C-N stretch	1250-1020	1220.89
N-H wag	910-665	864.15

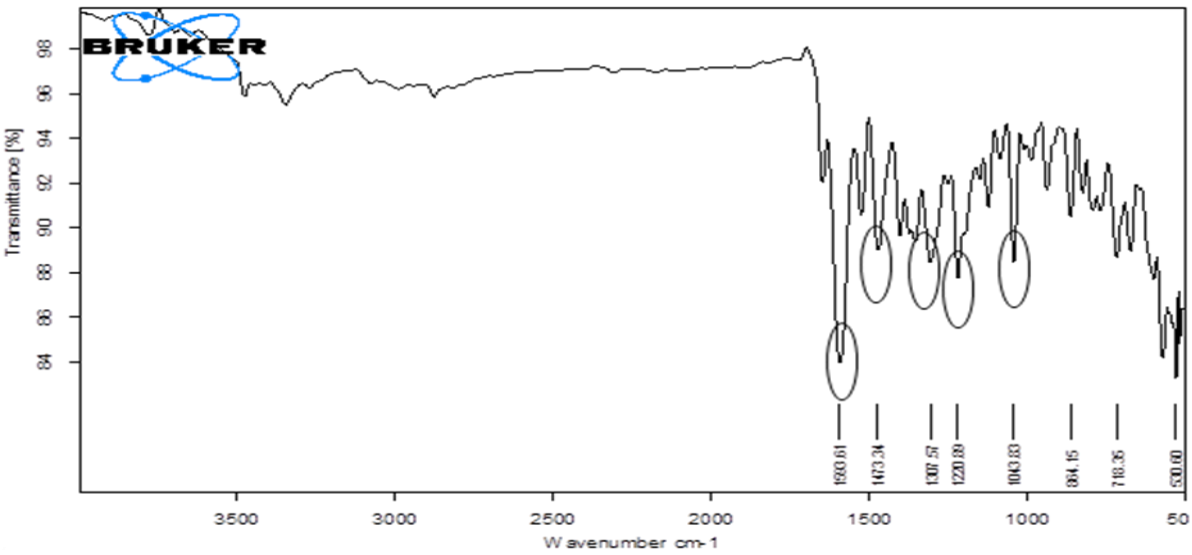

Fig. 2: FT-IR spectra of Minocycline HCl

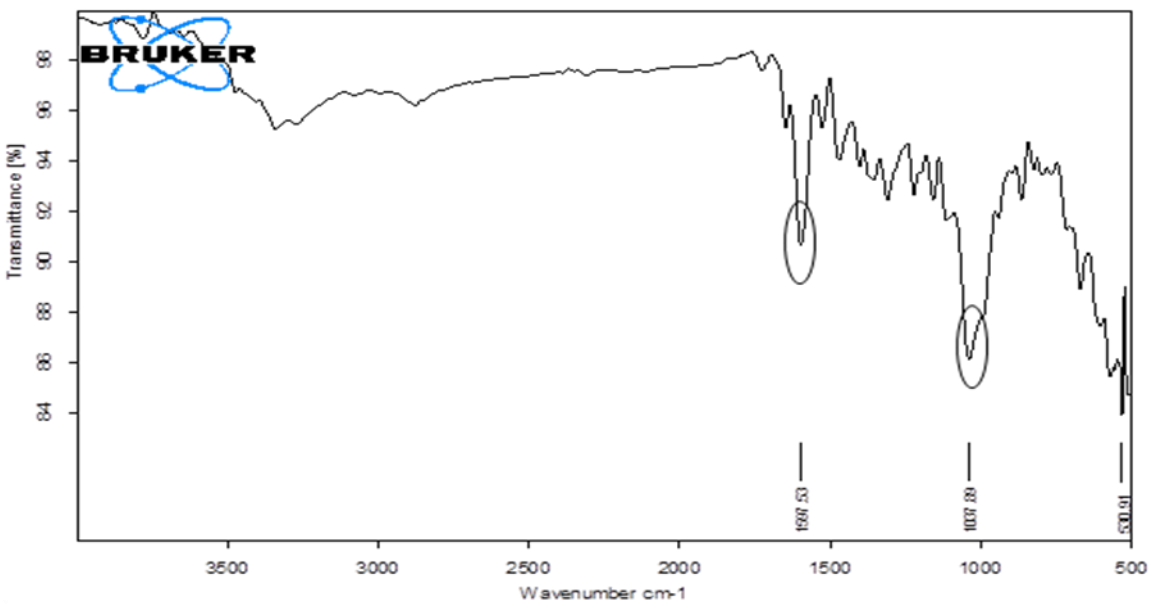

Fig. 3: FT-IR spectrum of formulation (Drug + Guar gum+ Tara gum + Excipients)

Preparation and evaluation of Minocycline HCl extended release tablets

In the present investigation extended release matrix tablets of Minocycline HCl was prepared by direct compression method and evaluated for weight variation, friability, hardness and dissolution. Different natural polymers like Guar gum, Tara gum were used as rate retarding polymers. Magnesium stearate was used as lubricant.MCC was used as fillers in different formulations to adjust the weight of the tablet.

Evaluation of Tablet formulations

Evaluation of Pre-compression parameters of directly compressible powder blends:

All the powder blends were evaluated for flow properties such as carr's index, angle of repose, bulk density, tapped density, compressibility index, haussner's ratio and flowability prior to the compression of tablets. The flow properties of the prepared powder blends were good and found to be within the limits.

Evaluation of Post compression properties of extended release matrix tablets

All the prepared tablets were subjected to evaluation of post compressional parameters like weight variation, hardness, friability, *in-vitro* disintegration time, drug content, wetting time. All the prepared tablets were found to exhibit satisfactory tablet characteristics and were within the limits. The results were given in Table 4 & 5.

Table 4: Pre- compression parameters

Powder Blend	Angle of Repose (θ)	Bulk density(ρ_b) (g/mL)	Tapped density(ρ_t) (g/mL)	Compressibility index (%)	Hausner's ratio	Flowability
Pure drug	40.1	0.814	1.09	25.9	1.26	Poor
F1	24.5	0.771	0.816	4.16	1.02	Good
F2	23.8	0.842	0.852	2.34	1.05	Good
F3	24	0.669	0.733	9.15	1.09	Good
F4	23.2	0.679	0.763	10.4	1.13	Good
F5	25	0.698	0.813	13.93	1.15	Good
F6	24.8	0.576	0.664	12.21	1.17	Good
F7	23.6	0.722	0.811	12.07	1.14	Good

Table 5: Post compression properties of all formulations

Parameters / Formulations	Hardness (kg/cm^2) ± S D	Percent Friability	Weight Variation ± SD	Drug content (mg/tab) ± SD
F1	6.37 ± 0.05	0.7	200 ± 0.14	50 ± 1.25
F2	6.70 ± 0.10	0.8	200 ± 0.12	48 ± 1.98
F3	6.57 ± 0.15	0.6	200 ± 0.15	49 ± 1.67
F4	6.81 ± 0.10	0.6	200 ± 0.10	50 ± 1.25
F5	6.20 ± 0.10	1.2	200 ± 0.04	50 ± 0.98
F6	6.37 ± 0.12	0.7	200 ± 0.06	50 ± 0.65
F7	6.81 ± 0.08	0.9	2000 ± 0.08	49±0.54

Invitro dissolution studies

The in vitro dissolution studies revealed that the formulations F1-F3 were formulated using varying concentrations of Tara gum showed a drug release of 98.9%, 95.9% and 78.1% respectively at the end of 24hrs with MCC as diluent. Formulations F4-F6 containing various concentrations of Guar gum with a drug release of 80.34%, 73.48% and 71.55% respectively at the end of 24hrs with MCC as diluent and found to have better extended drug release when compared to Tara gum. Whereas, formulation F7 was considered as an optimized formulation containing combination of Tara gum(12.5%) and Guar gum(12.5%) with a drug release of 61.59% at the end of 24hrs with MCC as diluent have shown better controlled/extended drug release when compared to individual concentrations of Tara gum and Guar gum.

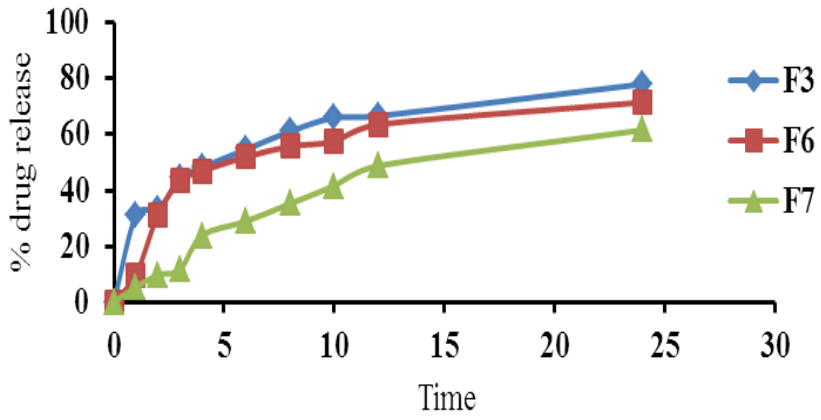

Fig. 4: Comparative Dissolution Profile of Formulations F3, F6, F7

Invitro release kinetics

The dissolution data was fitted into release kinetic profiles to assess the mechanism of drug release. The formulations were found to follow First order release kinetics .Higuchi's plot for F7 showed that the drug release was by diffusion and on extending the 60 % dissolution data in peppas plot with ' n ' value 0.827 indicating the drug release was by anomalous transport.

The Rate Constant and Regression values for all the formulations

Formulation	Zero order		First order		Higuchi		Peppas	
	K	R^2	K	R^2	K_H	R^2	n	R^2
F1	10.75	0.926	0.463	0.706	41.27	0.903	0.822	0.947
F2	3.178	0.786	0.125	0.977	20.41	0.917	0.654	0.841
F3	2.014	0.808	0.056	0.9229	12.90	0.939	0.320	0.965
F4	2.077	0.825	0.060	0.947	13.25	0.951	0.327	0.979
F5	2.188	0.612	0.055	0.773	14.83	0.796	0.505	0.831
F6	2.086	0.646	0.048	0.809	13.93	0.815	0.542	0.775
F7	2.506	0.875	0.040	0.946	15.66	0.967	0.827	0.958

CONCLUSION

Hence from the present investigation it was concluded that, extended release matrix tablets of Minocycline HCl were developed successfully with natural polymer such as Guar gum & Tara gum and extended release diluent such as Microcrystalline cellulose by using direct compression.

ACKNOWLEDGEMENT

The authors are thankful to Dr.Reddy's Laboratories Hyderabad, for providing Minocycline hydrochloride as gift sample for carrying out research work. The authors are also thankful to

Management, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, for providing all the facilities required for the completion of the research work successfully.

REFERENCES

1. Eady EA, Cove JH, Holland KT, Cunliffe WJ. Superior antibacterial action and reduced incidence of bacterial resistance in minocycline compared to tetracycline treated acne patients. Br J Dermatol., 1990; 122: 233-44.
2. Plott RT, Wortzman MS. Key bioavailability features of a new extended release formulation of minocycline hydrochloride tablets. Cutis., 2006; 78: 6-10.
3. Dollery C. Therapeutic Drugs. Edinburgh: Churchill Livingstone; 1991; 2, pp. M203-6.
4. Chambers HF. Protein Synthesis Inhibitors and Miscellaneous Antibacterial agents. In: Brunton LL, Lazo KS, Parker KL, editors. The Pharmacological Basis of Therapeutics, 11th ed. New York: McGraw-Hill Professional., 2005. pp. 1173-87.
5. Raghuram KR, Mutalik S, Reddy S. Once-Daily sustained-release matrix tablets of nicorandil: Formulation and *In Vitro* Evaluation. AAPS PharmSci Tech., 2003; 4: 61.
6. Nellore RV, Rekhia GS, Hussain AS, Tillmand LG, Augsburger LL. Development of metoprolol tartrate extended-release matrix tablet formulations for regulatory policy consideration. J Control Release., 1998; 50: 247-56.
7. Meshali MM, El Sayed GM, Syed EL. Preparation and evaluation of theophylline sustained release tablets. Drug Develop Ind Pharm., 1996; 22: 373-6.
8. Nath BS, Venkatesh, Hiremath D. Formulation and evaluation of sustained release dosage form of theophylline using a combined hydrophobic and hydrophilic matrix. Indian J Pharm Sci., 2000; 62: 33-6.
9. Hajare AA, More HN, Dsouza JI. Design and evaluation of sustained release tablets of diltiazem hydrochloride. Indian Drugs., 2004; 41: 175-6.
10. Behl AK, Dhake AS. Formulation and release characteristics of sustained release ofloxacin Tablets. Indian Drugs., 2005; 42: 316-8.
11. Holte O, Onsogen E, Myrvold R. Sustained release of water soluble drug from directly compressed alginate tablets. Eur J Pharm Sci., 2003; 20: 403-7.