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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF SR MATRIX TABLETS OF PEFLOXACIN

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ABSTRACT

The basic objective in dosage form design is to optimize the delivery of medication to achieve the control of therapeutic effect in the face of uncertain fluctuation in the system in which drug release takes place. This is usually concerned with the maximum drug availability by attempting to attain a maximum rate and extent of drug absorption, however; control of drug action through formulation also implies controlling the bioavailability to reduce drug absorption rates. So in the present study, an attempt has been made to formulate sustained release matrix tablets of Pefloxacin. Tablets were prepared using a direct compression method employing natural sustained release polymer such as Xanthum gum in different concentrations. The tablets were evaluated for physical characteristic like hardness, weight variation, friability and drug content. *In-vitro* release of drug was performed in phosphate buffer pH 6.8 for fourteen hours, percent friability 0.22 % and disintegration time 2.20 h. All the physical characters of the fabricated tablet were within the acceptable limits. The data obtained from *in vitro* dissolution studies were fitted in different models viz. Zero order, first order, Higuchi and Korsmeyer-Peppas equation. It was also observed that the highest correlation was for Korsmeyer- Peppas profile ($R^2 = 0.9938$). A value of n for all matrices studied here was ranged between 0.4339 to 0.4840; indicating an anomalous behavior corresponding to swelling, diffusion and erosion mechanism.

Keywords: Pefloxacin, xanthan gum, sustained release matrix tablets, cumulative drug release.

INTRODUCTION

Pefloxacin is 1-ethyl-6-fluoro-7- (4-methyl- 1-piperazinyl)-4-oxo- 1,4-dihydro-3-quinolone carboxylic acid and the dihydrate mesylate salt is used for the tablet and injection formulations¹. Pefloxacin has a plasma half-life of about 8-13 h and is also extensively metabolized, the principle metabolite being N-demethyl pefloxacin, otherwise known as norfloxacin (NOR). Pefloxacin is used for the treatment of diseases of the skin and various kinds of urinary tract infections. It is given by mouth or by intravenous infusion in the treatment of susceptible infections. Doses are expressed in terms of the equivalent amount of pefloxacin and are usually 400 mg twice daily by mouth or by intravenous infusion. Pefloxacin has bacterial activity against enterobacteriaceae, *Pseudomonas aeruginosa*, haemophilus, neisseria, staphylococci and *Mycobacterium leprea* and has been tried in the treatment of leprosy². Pefloxacin a C_{max} of 6.0-6.5 mg/l following a 600 mg dose. Food does not reduce the absorption of ofloxacin, ciprofloxacin, pefloxacin, and lomefloxacin to a clinically important extent. The magnitude of the reduction in theophylline clearance varies between the fluoroquinolones, with a 64 % decrease in theophylline clearance with enoxacin and a 30 % decrease with ciprofloxacin or pefloxacin³. Pefloxacin elimination is markedly delayed in cirrhotic patients due to a decrease in pefloxacin total clearance of more than 70 %. The volume of distribution is also decreased. Dosage adjustment may be necessary with pefloxacin in cirrhotic patients⁴. The place of Pefloxacin in this new and expanding class of 4-quinolone antibacterial drugs have

yet to be defined and it appears to be well-tolerated and useful drug for the treatment of serious infections in hospitalized patients⁵.

MATERIALS AND METHODS

Pure drug Pefloxacin was purchased from Hunan Goldliloo Pharmaceutical Co. Ltd., China, Xanthum gum and Microcrystalline cellulose (PH 101) was purchased from S. D. Fine Chemical Ltd. Mumbai, India Magnesium stearate was purchased from Thomas Baker Pvt. Ltd., Mumbai. Stearic acid) was purchased from Central Drug House (P) Ltd. New Delhi, India. PVP 90-F and PVP K-30 was purchased from BASF, India. The chemicals and reagents used are of analytical grade.

Excipient compatibility study by HPLC method

Preparation of Pefloxacin and excipient blend

Binary physical mixtures of pefloxacin and various excipients were prepared in a ratio of 1:1 w/w (all in triplicate). 100 mg of both Pefloxacin and excipient (Xanthan gum, microcrystalline cellulose, stearic acid and magnesium stearate) was weighed into 5 ml screw vials. Binary mixtures were mixed with a glass capillary tube and the tip of the tube was broken and left inside the vials. The vials were closed with a screw cap. Samples were kept at 50 °C in stability chamber for one week, with control of pefloxacin without excipients.

Standard calibration curve of Pefloxacin

Calibration samples (5, 10, 15, 20, 25 µg/ml) and validation samples (7, 12, 17 µg/ml) all in triplicate were

prepared by appropriate dilution of working stock solution. UV absorbance value of calibration samples and validation samples were recorded against water as reference at $\lambda = 288$ nm in double beam spectrophotometer.

Standard calibration curve of Pefloxacin and excipients

50 mg pefloxacin and 50 mg each of xanthan gum, microcrystalline cellulose and 4 mg magnesium stearate were accurately weighed into 100 ml volumetric flask. Firstly dissolved in some amount of water, then the volume was made up with water. The solution was filtered through Whatman grade no. 1 (11 μ m pore size). From above stock solution, standards were prepared containing pefloxacin in the concentration range 5 to 25 μ g/ml in triplicate. UV absorbance value of their sample was recorded against distilled water as reference at $\lambda = 288$ nm in double beam spectrophotometer. Percent error and relative standard deviation were calculated. The effect of excipient on the specificity of UV method determined by calculating concentration of pefloxacin in solution of drug excipient from a standard calibration curve of pefloxacin

Preparation of Tablets

The granules were prepared by the wet granulation method. All the formulations were made for batch size of 50 g. All ingredients were passed through sieve # 40. All ingredients except magnesium stearate and stearic acid were taken in mortar pestle and properly mixed. After 10 to 15 min of mixing 10 ml of stearic acid solution was gradually added while mixing the powder. Additional water (5-10 ml) was added as to make wet mass suitable for granulation. Wet mass was screened through sieve # 20 into dry trays and trays were kept in the dryer at 40°C. The percent moisture content of the granules was periodically checked by moisture balance and granules were removed from the dryer when the residual moisture level reached in 1 to 2 % w/w.

Evaluation of Tablets

Pre-compressional evaluation

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends/granules. There are many formulation and process variables involved in mixing and granulation that can affect the characteristics of blends/granules produced. The various characteristics of blends tested are as given below:

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ , is in equilibrium with the gravitational force⁶.

$$\tan \theta = \frac{h}{r}$$

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

Where θ = Angle of repose, h = height of the cone,
r = Radius of the cone base

Bulk density

Density is defined as weight per unit volume. Bulk density (ρ_b) is defined as the mass of the powder divided by the bulk volume and is expressed as gm/ml. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together⁶.

$$\rho_b = \frac{M}{V_p}$$

Where ρ_b = Bulk Density, M = Weight of sample in g,

V_p = Volume of sample in ml

Tap density

It is the ratio of the total mass of the granules to the tapped volume of the granules. It can be calculated by following formula and it is expressed in g/ml⁶.

$$\rho_t = \frac{M}{V_t}$$

Where ρ_t = Tap Density, M = Weight of sample in g,

V_t = Tap volume of sample in ml

Percent compressibility

It is calculated by following formula,

$$C = \left[\frac{\rho_t - \rho_b}{\rho_t} \right] \times 100$$

Percent compressibility and flow ability of blends is shown in Table 3.

Hausner's Ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner's Ratio} = \frac{\rho_t}{\rho_b}$$

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Post-compressional evaluation

General appearance

The general appearance of a tablet, its visual identity and overall 'elegance' is essential for consumer acceptance. Tablets are evaluated for its size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws, consistency and legibility of any identifying marking⁶.

Weight variation

The weight variation test provides limits for the permissible variations in the weights of individual tablets,

expressed in terms of the allowable deviation from the average weight of a sample. 20 whole tablets are weighed and average weight is calculated⁶.

Tablet thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Thickness of tablets was measured using a vernier caliper. Tablet thickness should be controlled within a $\pm 5\%$ variation of standard values⁶.

Tablet hardness

The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in kg and the hardness of about 6-7 kg is considered to be satisfactory for sustained release matrix tablet⁶.

Friability

It is a measure of mechanical strength of tablets. Roche friabilator is used to determine the friability. A maximum loss of weight (from a single test or from the mean of the three tests) not greater than 1.0 percent is acceptable for most tablets. If obviously cracked, chipped or broken tablets are present in the sample after tumbling, the sample fails the test. It expressed in percentage as⁶

$$\text{Percent Friability} = \frac{\text{Loss in Weight}}{\text{Initial Weight}} \times 100$$

Conventional compressed tablets that lose less than 1.0% of their weight are generally considered acceptable⁷.

Percent drug Content

Randomly selected twenty tablets are powdered. Equivalent of powerful drug is transferred to the volumetric flask. Volume of the flask is made up with water. Test samples are prepared by dilution. Test solution filtered through Whatman grade no. 1 (11 μm pore size). Test solutions are analyzed in UV-viz. spectrophotometer and absorbance is recorded. Percent drug content is calculated by following formula⁶.

$$\text{Percent drug content} = \left[\frac{\text{Theoretical wt of drug} \times \text{Observed wt of drug}}{\text{Theoretical wt of drug}} \right] \times 100$$

In vivo dissolution test

In vitro drug release studies from the prepared matrix tablets were conducted using USP type II apparatus at 37°C at 50 RPM. Dissolution mediums used were 900 ml of phosphate buffer of pH 6.8. The release rates from matrix tablets were conducted in phosphate buffer pH 6.8 for further time periods. The samples were withdrawn at desired time periods from dissolution media and the same were replaced with fresh dissolution media of respective pH. The samples were analyzed by UV spectrophotometer. The amounts of drug present in the samples were calculated with the help of appropriate calibration curves constructed from reference standards.

Drug dissolved at specified time periods was plotted as percent release versus time curve⁸.

In vitro drug release characterization models: Mathematical Models (Kinetic modeling)

There are number of kinetic models, which described the overall release of drug from the dosage forms. Because qualitative and quantitative changes in a formulation may alter drug release and *in vivo* performance, developing tools that facilitate product development by reducing the necessity of bio-studies are always desirable. In this regard, the use of *in vitro* drug dissolution data to predict *in vivo* bio-performance can be considered as the rational development of controlled release formulations⁹.

Dependent-model method (Data analysis)

Zero order release kinetics

This model refers to the process of constant drug release from a drug delivery device such as oral osmotic tablets, transdermal systems, matrix tablets with a low-soluble drug and other delivery systems. In its simplest form, zero order release can be represented as

$$Q = Q_0 + K_0 t$$

Where, Q = the amount of drug released or dissolved (assuming that release occurs rapidly after the drug dissolves), Q_0 = the initial amount of drug in solution (it is usually zero), and K_0 = the zero order release constant. The plot made: cumulative % drug release vs. time (zero order kinetic model)¹⁰

First order release kinetics

This model has been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. The rate laws predicted by the different mechanisms of dissolution both alone and in combination, have been discussed by Higuchi. This relationship can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water soluble drugs in porous matrices. However, the earliest equation expressing dissolution rate in a quantitative manner was proposed by Noyes and Whitney as

$$\frac{dc}{dt} = k (C_s - C_t)$$

Where, $\frac{dc}{dt}$ is the rate of change in concentration with respect to time and k is the rate constant

The integrated form of the equation is:

$$\int \left[\frac{C_s}{(C_s - C_t)} \right] = kt$$

$$\text{Log } C = \text{Log } C_0 - \frac{kt}{2.303}$$

Where, C_0 is the initial concentration of drug and K is first order constant¹⁰

Higuchi model

Higuchi developed models to study the release of water soluble and low soluble drugs incorporated in semisolid

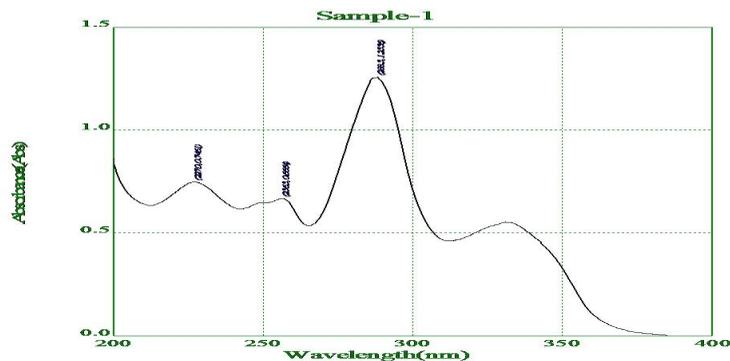


Figure 4: Pefloxacin spectra in water as a solvent by UV spectrophotometer

Table 1: Absorbance and concentration value of calibration sample of pefloxacin in UV ($\lambda = 288$ nm, solvent: water)

Conc. (µg/ml)	Absorbance			Mean		
	A	B	C			
5	0.3613	0.3454	0.3388	0.3485		
10	0.7418	0.7066	0.7226	0.7237		
15	1.1196	1.2010	1.1151	1.1452	Slope	0.073
20	1.4511	1.4918	1.4779	1.4736	Intercept	0.003
25	1.7692	1.8438	1.7848	1.7993		

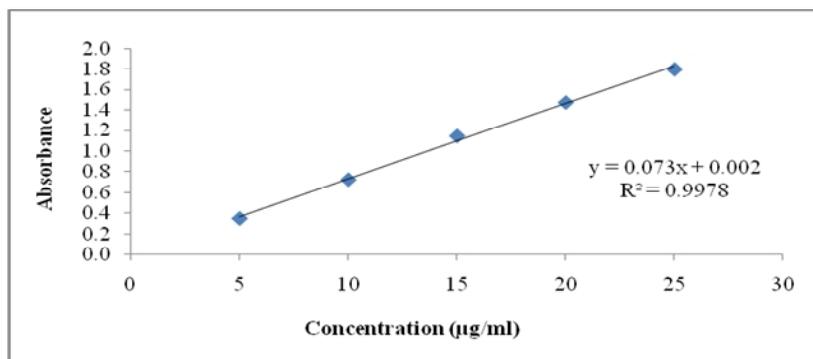


Figure 5: Calibration curve of pefloxacin in UV ($\lambda = 288$ nm, solvent: water)

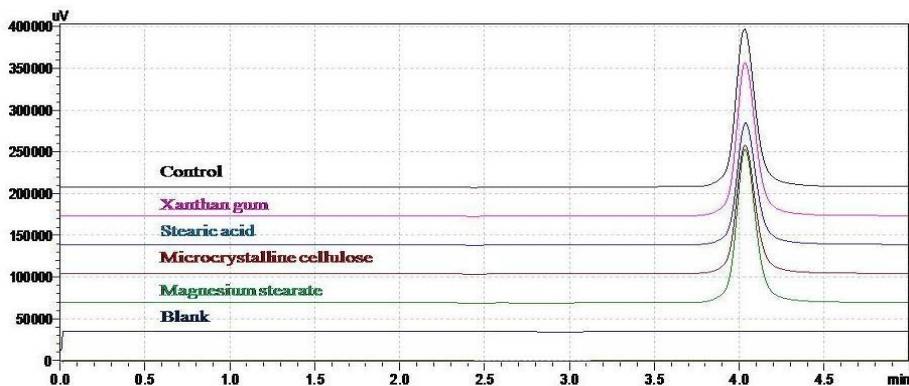


Figure 6: HPLC chromatogram of samples of drug excipient compatibility study (λ_{max} 288 nm, solvent: water)

Table 2: Drug excipient interaction study data of pefloxacin with all excipient in HPLC ($\lambda = 288$ nm, Solvent: water)

Excipient (with Drug)	Theoretical Conc. ($\mu\text{g/ml}$)	Area			Mean	Cal. Conc. ($\mu\text{g/ml}$)	% Recovery	RSD (Precision)
		A	B	C				
Xanthan gum	15	885861	895258	882567	887895	13.97	6.86	0.74
Stearic acid	15	947968	946258	948020	947415	14.93	0.45	0.11
Microcrystalline cellulose (PH 101)	15	942946	943754	941258	942786	14.86	0.95	0.14
Magnesium stearate	15	932658	933062	942189	942370	14.75	1.00	0.58
Eudragit EPO	15	936739	947734	956577	947017	14.93	0.50	1.05
Malt dextrin	15	938840	970929	951022	953597	15.03	-0.21	1.70
PVP 90-F	15	962646	952244	946293	953721	15.01	-0.23	0.87
PVP K-30	15	932121	958071	946499	945564	14.90	0.65	1.37
HPMC E-5	15	915845	891379	898172	901799	14.19	5.37	1.40
Control	15	947925	946398	948874	947732	14.94	0.42	0.13

Table 3: Evaluation data of granule of SR matrix tablets of pefloxacin

Formulation	Angle of Repose	Bulk Density (g/ml)	Tapped Density (g/ml)	Percent compressibility	Hausner's ratio
F ₁	40.554	0.568	0.962	40.96 (Very, very poor flow)	1.694 (Good flow)
F ₂	42.071	0.555	0.895	37.99 (Very poor flow)	1.613 (Good flow)
F ₃	40.813	0.462	0.735	37.14 (Very poor flow)	1.591 (Good flow)
F ₄	25.608	0.419	0.614	31.76 (Very poor flow)	1.465 (Good flow)
F ₅	25.263	0.435	0.547	20.48 (Fair-passable flow)	1.257 (Good flow)
F ₆	26.115	0.396	0.490	19.18 (Fair-passable flow)	1.237 (Poor flow)
F ₇	27.322	0.410	0.534	23.22 (Poor flow)	1.302 (Good flow)
F ₈	27.492	0.390	0.515	24.27 (Poor flow)	1.321 (Good flow)

Post-compressional evaluation of Tablets

Table 4: Physical parameters of different formulation of SR matrix tablets of pefloxacin

Formulation	Weight Variation \pm % ^a	Mean Thickness (mm)	Hardness (kg)	Friability (% w/w)	Percent Drug Content	Disintegration Time (h)
F ₁	499.5 \pm 0.10	4.22	6.5	0.48	96.59	1.05
F ₂	500.2 \pm 1.25	4.23	6.0	0.37	98.93	1.17
F ₃	520.2 \pm 0.04	5.66	7.0	0.23	96.08	1.23
F ₄	500.3 \pm 0.05	5.49	6.5	0.31	97.75	1.25
F ₅	505.5 \pm 0.20	4.28	7.0	0.20	96.10	1.30
F ₆	530.7 \pm 0.13	5.68	6.5	0.33	98.12	1.41
F ₇	541.5 \pm 0.10	5.72	6.5	0.16	97.46	1.55
F ₈	570.3 \pm 0.06	5.91	7.0	0.22	99.14	2.20

^aAverage of 20 tablets \pm maximum deviation of any of tablet from average value

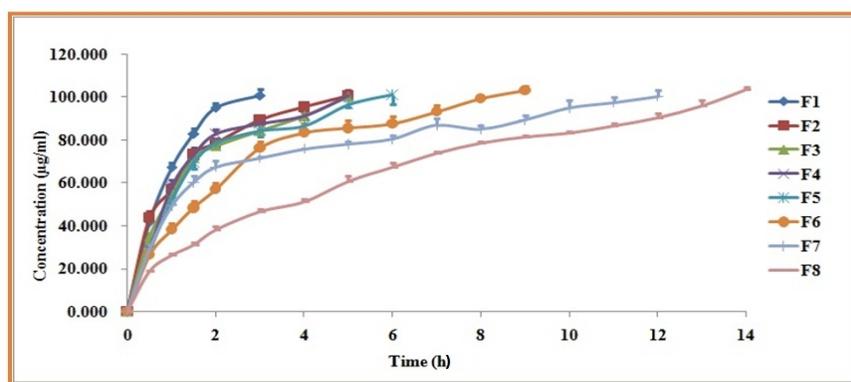


Figure 7: Dissolution profile of different batches of pefloxacin SR matrix tablets

Table 5: Coefficient of determination values for fitting of dissolution data into various equations along with exponent (n) value of Peppas model fit

Formulation	Zero order	First order	Higuchi	Peppas	
	r ²	r ²	r ²	r ²	n
F ₁	0.6780	0.6795	0.9732	0.9793	0.4339
F ₂	0.5725	0.5743	0.9715	0.9909	0.3909
F ₃	0.6652	0.6667	0.9825	0.9877	0.4431
F ₄	0.4847	0.4865	0.9509	0.9736	0.3750
F ₅	0.4322	0.4341	0.9201	0.9513	0.3680
F ₆	0.3930	0.3949	0.9177	0.9566	0.4020
F ₇	-0.2104	-0.2077	0.7508	0.9660	0.2620
F ₈	0.7085	0.7096	0.9932	0.9938	0.4840

CONCLUSION

HPLC and UV analytical methods for pefloxacin were validated for linearity, accuracy, precision and specificity for pefloxacin. All Excipients tested in drug excipient study were compatible with drug. Granules for optimized formulation had good flow property as measured in terms of angle of repose, Hausner's ratio, percent compressibility. The final selected tablet had good sustained release property (14 hours). Drug release data was best fitted to Korsmeyer-Peppas. Exponent term in this kinetic model had value of that indicated release was Fickian.

DISCUSSION

Result of drug release indicated that the addition of xanthan gum was not capable to produce the sustain release. Addition of stearic acid retarded the drug release from the tablet in concentration dependent manner. With the increase in percentage of xanthan gum and stearic acid, the tablet matrix is greater and thus the drug release rate was found to be less. The optimized batch was selected on the basis of sustained release (14 hours) percent friability 0.22 % and disintegration time 2.20 hours. *In-vitro* dissolution release profile (Figure 7) shows that F₈ releases the drug more than 80 % within 10 hours, further on the basis of disintegration time F₈ was selected as optimized formulation. The data obtained from *in vitro* dissolution studies were fitted in different models viz. Zero order, first order, Higuchi and Korsmeyer-Peppas equation. It was also observed that highest correlation was found for Korsmeyer- Peppas profile (R² = 0. 9938). A value of n for all matrices studied here was ranged between 0.4339 to 0.4840; indicating an anomalous behavior corresponding to swelling, diffusion and erosion mechanism

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