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Formulation and evaluation of controlled release matrix tablets of norfloxacin using natural gums

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ABSTRACT

Norfloxacin is a synthetic broad-spectrum antibacterial drug. Norfloxacin exhibits high antimicrobial activity against a wide variety of Gram negative and Gram-positive bacteria. The aim of the present study is to formulate controlled release matrix tablets of Norfloxacin using the natural gums. Tablets were formulated by wet granulation technique. The prepared granules were subjected to evaluate pre formulation parameters such as angle of repose, compressibility index, bulk density, tapped density, compressibility index and Hausner's ratio. The prepared tablets were evaluated for parameters like average weight, hardness, friability, drug content and dissolution studies. In our present study, the effect of Guar Gum, Xanthan gum and pectin with norfloxacin is studied. The pre-compression and post compression parameters were found to be satisfactory. Among all the formulation, formulation NF 3 showed satisfactory results with various physicochemical evaluation parameters by using guar gum as a natural gum. The *in vitro* release profiles of the drug could be best expressed by Zero order as the plots showed high linearity (R2 = 0.999). The results of the present study showed that norfloxacin may be formulated as controlled release matrix tablets by using the natural gum guar gum.

Keywords: Norfloxacin, Antibacterial, Pre compression, Post compression, Guar Gum, Xanthan Gum, Pectin.

1. INTRODUCTION

In recent years, significant interest has focused on hydrophilic polymers in the design of oral controlled drug delivery systems, due to their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance. The synthetic hydrophilic polymers well thought-out as release retardants are pretty expensive; in addition biodegradability is open to discussion when compared with natural polymers[1].

During the past two decades tremendous growth in the development of drug delivery systems using matrices based on natural gum. Natural gums are biodegradable and non-toxic, which moisturize and swell in contact with aqueous media, and this has been used for the preparation of various dosage forms [2].

Norfloxacin (1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3 quinoline carboxylic acid) is a synthetic broad-spectrum antibacterial drug. The drug is used for the treatment of urinary tract infections. Development of bacterial resistance to currently available antibiotics due to the lack of patient compliance suggests an appropriate dosing of antibacterial drugs, such as quinolone drug's norfloxacin is very slightly soluble in water. Norfloxacin exhibits high antimicrobial activity against a wide variety of Gram negative and Gram-positive bacteria, including gentamicin resistant *Pseudomonas aeruginosa* and β-lactamase positive *Neisseria gonorrheae* [3].

Excellent therapeutic effects have been shown in the treatment of respiratory, biliary and urinary tract infections. Norfloxacin is photosensitive. Prolonged exposure of bulk drug under direct sunlight or under fluorescent light results in the formation of ethylenediamine degradate. Their main activity is against Gram-negative bacteria, but it is also active in Gram-positive cocci. They are prescribed for a myriad of infections such as bladder infection, ophthalmic

infection, and also for some cases of sexually transmitted diseases such as uncomplicated gonorrhea [4].

Hence, to reduce the frequency of administration and to improve patient compliance, an attempt has been made to formulate the controlled-release matrix tablets of Norfloxacin using natural gums like xanthan gum, pectin and Guar gum.

2. MATERIALS AND METHODS

Norfloxacin was generously gifted by Orchid Labs Ltd, Chennai. Microcrystalline cellulose, Lactose (Paxmy speciality chemicals, Chennai), Guar gum, xanthan gum, Pectin, Magnesium stearate and Talc were commercially procured from SD fine chemicals, Mumbai were used for this study. All other ingredients used were of analytical grade.

2.1. Formulation of tablets

Formulation of Norfloxacin tablets were prepared by wet granulation method employing various excipients as mentioned in the table 1. Weighed quantities of Norfloxacin, polymers (Guar gum, Xanthan gum and pectin), MCC and starch were separately passed through sieve no. #40 and mixed well. Then the powder mass was triturated well and the granules were prepared by wet granulation technique using starch paste (10% w/v) as binder. The wet mass was passed through sieve no. #20 and dried at 60°C. The moisture content was maintained in the granules between 2 – 5% for better compression. the prepared granules were resieved and are lubricated with talc and magnesium stearate (2:1 ratio). The granules were punched to get tablets of average weight 800mg for Norfloxacin matrix tablets using 12.7mm punches in 16 station tablet machine.

2.2. Characterization of granules

The granules were evaluated for their characteristics parameters such as angle of repose, bulk density, compressibility index and Hausner's factor [5-8].

2.2.1. Angle of Repose

This angle is defined as the static angle of repose and is a common way of explaining flow characteristics of powder granulation. In most pharmaceutical powders and granules, the angle of repose values range from 25-40°, with lower values indicating better flow characteristics. The angle of repose is defined as the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

$$\text{Tan } \theta = h/r$$

Where,

h and r are the height and radius of the powder cone

2.2.2. Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A known amount of granules from each formula, previously lightly shaken to break any agglomerates formed was introduced into a graduated measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own height onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in the volume was noted. LBD and TBD were calculated using the following formulas.

LBD = Weight of the powder/volume of the packing

TBD = Weight of the powder/tapped volume of the packing

Table - 1: The formulation composition of norfloxain matrix tablets

Ingredients	Quantity per Tablet in mg											
	NF1	NF2	NF3	NF4	NF5	NF6	NF7	NF8	NF9	NF10	NF11	NF12
Norfloxacin	400	400	400	400	400	400	400	400	400	400	400	400
Guar gum	160	200	240	280	-	-	-	-	-	-	-	-
Pectin	-	-	-	-	160	200	240	280	-	-	-	-
Xanthan	-	-	-	-	-	-	-	-	160	200	240	280
MCC	92	72	52	32	92	72	52	32	92	72	52	32
Starch	92	72	52	32	92	72	52	32	92	72	52	32
Talc	10	10	10	10	10	10	10	10	10	10	10	10
Magnesium stearate	06	06	06	06	06	06	06	06	06	06	06	06

2.2.3. Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index which was calculated by using the following formula:

Carr's index (%) = [(TBD-LBD) ×100]/TBD

2.2.4. Hausner's Factor

Hausner found that the ratio DF/DO was related to interparticle friction and, as such, could be used to predict powder flow properties. It is calculated by using the following formula:

Hausner's Factor = DF/DO

Where, DF is Tapped bulk density and DO is Loose bulk density.

2.3. Evaluation of tablets [9-13]

2.3.1. Thickness

Thickness mainly depends on die filling, physical properties of materials to be compressed under compression force. There may be a small variation in the thickness of individual tablets in a batch. The thickness was measured by using vernier calipers. The thickness of 6 tablets was measured and the average thickness was calculated.

2.3.2. Hardness

The hardness of a tablet is indication of its strength. It is tested by measuring the force required to break the tablet across the diameter. The force is measured in kg and the hardness of about 4 kg is considered to be satisfactory for uncoated tablets. Monsanto hardness tester is used for this purpose. The hardness of 6 tablets was measured and the average hardness was calculated.

2.3.3. Friability test

Friability test is carried out to assess the ability of the tablet to withstand abrasion in packing, handling and transport. Electrolab friability tester was used for finding out the friability of the tablet. A number of tablets (6) were weighed accurately and placed in the chamber of the apparatus. After 100 rotations, the tablets were taken out from the apparatus, re-dusted and weighed. The loss in weight indicates the friability of the tablets. A maximum friability of 1% is acceptable for tablets as per Indian Pharmacopoeia (IP). Percentage friability was determined by using the formula given below:

% friability = (W1 - W2 / W1) × 100

Where, W1 = weight of tablets before test; W2 = weight of tablets after test

2.3.4. Weight variation test

Twenty tablets were selected randomly and weighed individually. The average weight was calculated and compared with the individual tablet weight. Not more than two of the individual tablet weight should deviates from the average weight by more than the percentage.

2.3.5. Drug content

The drug content in the formulations of Norfloxacin was estimated by using RP-HPLC method. The HPLC equipment consisted of Shimadzu LC 2010A HT HPLC system, Princeton SPHER column C18 (250 mm × 4.6 mm, i.d 5µ) using mobile phase consisting of 20 mM disodium hydrogen orthophosphate:acetonitrile (pH 3.0, ratio 95:5) with UV detection at 254 nm. The internal standard used was prochlorperazine. The retention times of prochlorperazine and Norfloxacin were 6.2 and 8.9 min, respectively. The linearity for Norfloxacin is 0.25-2.0 g/ml.

2.3.6. *In vitro* drug release

Drug release from the tablets was studied using USP dissolution apparatus (Electrolab TDT-081, India), type I (basket method). A tablet was placed inside a basket and immersed in a dissolution vessel (n= 6) containing 900 ml of pH 7.4 buffer, used as dissolution media at 37±0.5^{0}C and stirred at a speed of 100 rpm. The amount of drug released after every hour up to 12 hrs was determined using UV visible spectrophotometer (Shimadzu Corporation, 1601, Japan) at 294 nm.

2.3.7. Kinetics of drugs release [14-16]

Kinetics of drug release is studied by plotting the data obtained from *in vitro* release in various kinetics models.

2.3.7.1. Zero Order Kinetics

The graph was plotted as cumulative % drug release Vs Time where the drug release rate is independent of its concentration.

$$C = K\theta t$$

Where, Kθ = Zero order rate constant expressed in units of concentration/time.

t = Time in hours.

2.3.7.2. First order Kinetic model

The graph was plotted as log cumulative % of drug remaining Vs Time, where release rate is concentration dependent

$$\text{Log } C = \log C0 - Kt / 2.3030$$

Where, C0 = Initial concentration of drug

K = First order constant

t = Time in hours.

2.3.7.3. Higuchi kinetics

Higuchi describes the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion. The graph was plotted as cumulative % drug released Vs square root of time.

$$Q = Kt1/2$$

Where, K = Constant reflection design variable system.

t1/2 = Time in hours.

Hence, drug release rate is proportional to the reciprocal of square root of time. If the plot yields a straight line, and the slope is one then the particular dosage form is considered to follow Higuchi kinetics of drug release.

2.3.7.4. Hixson-crowell erosion equation

It describes the drug release with changes in the surface area and the diameter of particles the data were plotted using the Hixson and crowell rate equation. The graph was plotted by cube root of % drug remaining in matrix Vs time.

Q0.

$$1/3 – Qt$$

$$1/3 = KHC\ t.$$

Where, Qt = Amount of drug released in time t

Q0 = Initial amount of drug in tablet.

KHC = Rate constant for Hixon crowell rate equation.

2.3.7.5. Korsmeyer-Peppas equation

To find out the mechanism of drug release, it was further plotted in peppas equation as log cumulative % of drug released Vs log time.

$$Mt / M\alpha = Kt\ n,$$

$$Log\ Mt / M\alpha = log\ K + n\ log\ t$$

Where, Mt / Mα = Fraction of drug released at time t

K = Kinetic rate constant

t = Release time

n= Diffusion exponent indicative of the mechanism drug release.

This model is used to analyze the release of pharmaceutical polymeric dosage forms when the release mechanism is not known or more than one type of release phenomenon was involved. The n value could be obtained from slope of the plot of log cumulative % of drug released Vs log Time.

2.4. Stability studies as per the ICH guidelines

Developed matrix tablets were packed in High Density Poly Ethylene (HDPE) containers and were subjected to stability studies at the following different temperature and humidity conditions as prescribed by the International Conference on Harmonization (ICH) [17-20].

25 °C with 60 % RH

40 °C with 75 % RH

Samples were withdrawn at 1, 2 and 3 months intervals and evaluated for their physical properties and in vitro drug release.

3. RESULTS AND DISCUSSION

Bulk Density for norfloxacin blend was found to be in the range of 0.421 to 0.526. Tapped density for granules were found to be between 0.476 and 0.632. Compressibility index and Hausner's ratio were obtained in the range of 8.59 to 16.77 and 1.09 to 1.20 respectively. Angle of repose was observed in the range of 25.12° to 29.36° (Table 2).

Table 2: Flow properties of Tablet Blend

Formulations	Angle of Repose	Bulk Density	Tapped density	Compressibility Index	Hausner's Ratio
NF 1	26.17°	0.441	0.508	13.18	1.15
NF 2	26.24°	0.448	0.512	12.50	1.14
NF 3	25.12°	0.459	0.504	8.59	1.09
NF 4	29.36°	0.526	0.632	16.77	1.20
NF 5	29.16°	0.510	0.604	15.56	1.18
NF 6	27.24°	0.479	0.558	14.16	1.16
NF 7	25.56°	0.452	0.516	12.40	1.14
NF 8	29.19°	0.492	0.588	16.33	1.19
NF 9	27.43°	0.497	0.584	14.89	1.17
NF 10	26.48°	0.481	0.556	13.48	1.15
NF 11	25.46°	0.421	0.476	11.55	1.13
NF 12	28.46°	0.498	0.596	16.10	1.19

Table - 3: Physical Characteristics of Norfloxacin matrix tablets					
Formulations	Average weight (Mg)	Thickness (mm)	Hardness (Kd/cm²)	Friability	Drug Content (%)
NF 1	806±2.8	2.8± 0.02	5.8 ± 0.12	0.23	96.29
NF 2	824±1.6	2.6± 0.01	5.8 ± 0.14	0.31	97.72
NF 3	800±1.8	2.2± 0.02	6.5± 0.17	0.16	99.75
NF 4	820±1.4	3.1± 0.01	5.1± 0.12	0.27	93.05
NF 5	812±2.2	3.2± 0.02	5.2 ± 0.21	0.44	94.76
NF 6	808±3.1	3.1± 0.01	5.2± 0.08	0.51	95.32
NF 7	816±2.1	3.1± 0.02	5.9 ± 0.16	0.28	97.91
NF 8	821±1.3	3.3± 0.01	5.9 ± 0.12	0.52	91.46
NF 9	809±2.4	2.9± 0.02	5.8 ± 0.14	0.36	97.91
NF 10	814±1.7	3.2± 0.01	5.1 ± 0.10	0.22	96.27
NF 11	818±1.5	3.1± 0.02	5.2 ± 0.18	0.34	93.02
NF 12	823±0.8	3.5± 0.01	5.0 ± 0.13	0.53	90.98

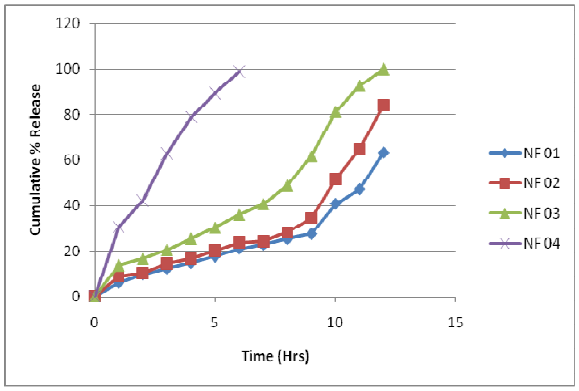

Figure - 1: Comparative *in vitro* release profile of norfloxacin matrix tablets containing guar gum in different concentration.

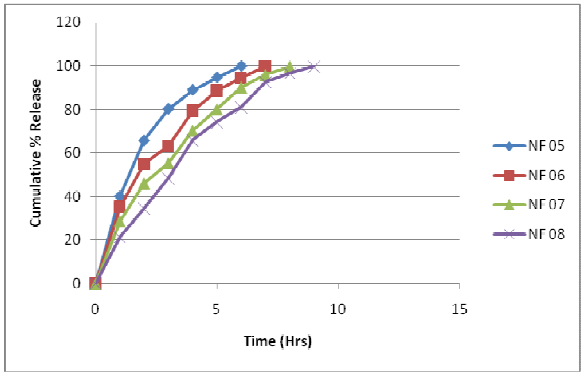

Figure - 2: Comparative *in vitro* release profile of norfloxacin matrix tablets containing pectin in different concentration.

3.1. Post-compression parameters

Prepared blends were compressed and these compressed tablets were evaluated for Average weight, thickness, friability, hardness, drug content and dissolution. The average percentage deviation of 20 tablets of each tablet was less than 3%. The thickness and hardness of the tablet ranged from 2.2 – 3.5 mm and 5.0 – 6.5 kg/cm2 respectively. The percentage friability of all batches ranged from 0.16 to 0.53 %W/W. The drug content percentage was ranged from 90.08 to 99.75 (Table 3). The dissolution profile of Norfloxacin matrix tablets with various natural gums are shown in figure 1 to 3.

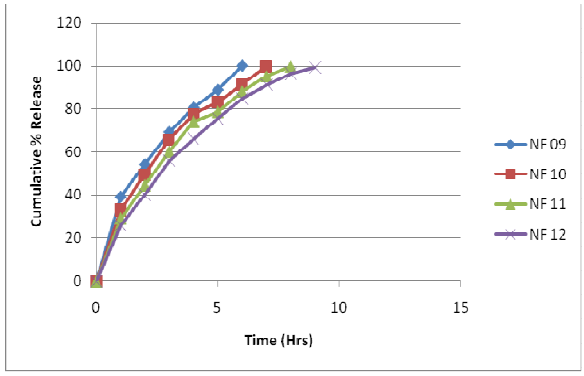

Figure - 3: Comparative *in vitro* release profile of norfloxacin matrix tablets containing xanthan gum in different concentration.

3.2. Release kinetics study

The kinetics of drug release was determined based on korsmeyer - peppas equation obtained by *in vitro* dissolution data to various kinetics models. Accordingly the R2 value was found to be 0.999 for Zero order, 0.984 for first order, 0.993 for Higuchi, 0.997 for korsmeyer-peppas and 0.845 for Hixson-crowell cube root plot. The R2 value of korsmeyerpeppas was close to 1 and n value was found to be 0.671.

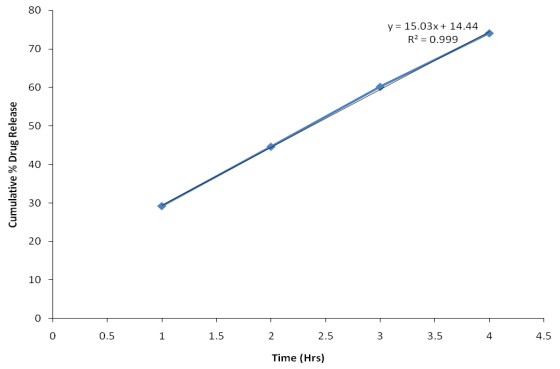

Figure - 4: Zero order release model of Norfloxacin matrix formulation (NF 3).

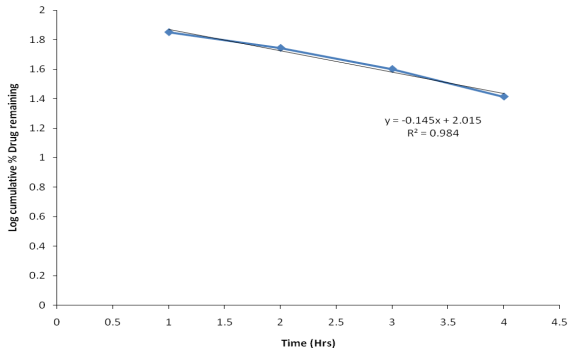

Figure - 5: First order release model of Norfloxacin matrix formulation (NF 3).

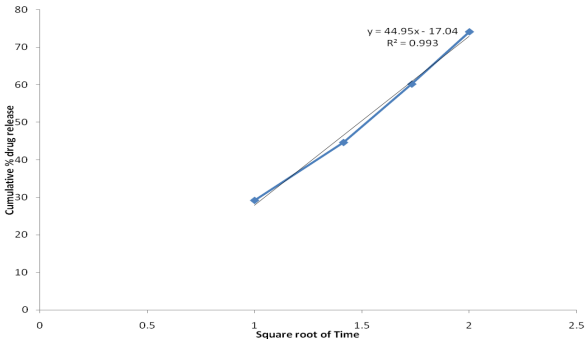

Figure - 6: Higuchi release model of Norfloxacin matrix formulation (NF 3).

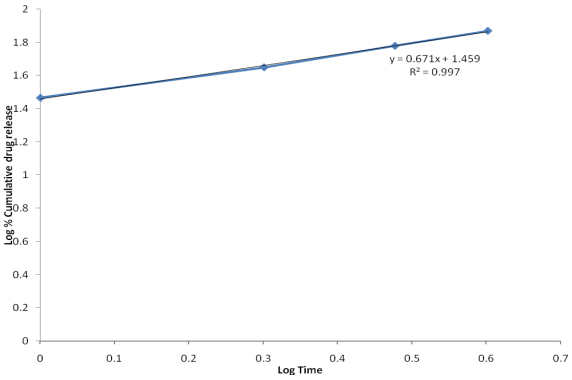

Figure - 7: Korsmeyer – Peppas model of Norfloxacin matrix formulation (NF 3).

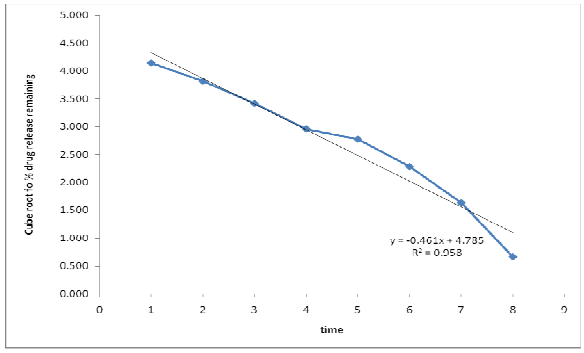

Figure - 8: Hixson – Crowell model of Norfloxacin matrix formulation (NF 3).

3.3. Stability studies

Stability studies were conducted for the formulation NF 3. The stability study was performed at 40±2°C/75±5%RH for a specific time period. The tablets were analyzed for hardness, drug content and *in vitro* drug release. The overall results showed that the formulation is stable at above mentioned storage conditions shown in table 4.

Table - 4: Stability data of Norfloxacin matrix formulation NF 3

Test	Stability Results (40 ± 2º C / 75 ± 5%RH)			
	Initial	1st Month	3rd Month	6th Month
Hardness	6.5 ± 0.17	6.4 ± 0.15	6.4 ± 0.18	6.3 ± 0.14
Drug Content (%)	99.75	99.69	99.63	99.58
Drug Release (%)	99.97	99.91	99.86	99.96

3. CONCLUSION

The objective of the present research work was to formulate and evaluate the controlled release matrix tablets of Norfloxacin using natural gums. The formulated tablets showed better patient acceptability and compliance. Wet granulation technique was the preferred technology for the preparation of Norfloxacin tablets. Based on the preliminary studies, various formulation trials (NF 1 to NF 12) were carried out with different concentration natural gums like guar gum, pectin and xanthan gum.

From the various formulations it was concluded that the formulated batch of NF 3 was finalized as the optimized formula. Formulation F5 showed satisfactory results with various physicochemical evaluation parameters like hardness, thickness, friability, drug content. The drug release kinetics of the optimized formulated followed Zero order kinetics and the drug release as per n value of Korsmeyer-peppas is non-fickian

diffusion. The stability studies indicated that the formulated tablets were found to be stable. Therefore, it is concluded that the NF 3 trial was satisfactory formulation that could perform therapeutically, with improved efficacy and better patient compliance.

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