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Research · December 2019

DOI: 10.31838/ijpr/2020.SP1.103

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ISSN 0975-2366

DOI: https://doi.org/10.31838/ijpr/2020.SP1.103

Research article

Formulation and Evaluation of Floating Tablet of Norfloxacin

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Received: 12.10.19, Revised: 12.11.19, Accepted: 12.12.19

ABSTRACT

The oral route is considered as the most promising route of drug delivery. Several approaches have been attempted in the preparation of gastro-retentive drug delivery systems. These include floating systems, swell able and expandable systems, high density systems, bio adhesive systems, altered shape systems, gel forming solution or suspension systems and sachet systems. Floating systems have low bulk density so that they can float on the gastric juice in the stomach. The problem arises when the stomach is completely emptied of gastric fluid. In such a situation, there is nothing to float on. It shows absorption window in stomach area, which makes it suitable candidate for gastro retentive dosage forms. The aim and objective of the study is to develop a floating tablet of Norfloxacin to minimize the frequency of dosing by increasing dissolution and sustained release action up to 12 hrs by single unit dosage. Floating tablet of Norfloxacin, consist of HPMC K4M and lactose as release retardant polymer and sodium bicarbonate as gas generating agent, were formulated by direct compression method. It was found that formulation containing 245 mg HPMC K4M & PVPk30 of Norfloxacin in 12 hrs with desired floating lag time 1min 48 sec and constantly float on dissolution medium for more than 12 hrs.

Keywords: Norfloxacin, HPMC K4M, PVPk30, Direct compression method.

INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms[1]. One of such difficulties is the ability to confine the dosage form in the desired area of the gastrointestinal tract. To overcome this physiological problem, several drug delivery systems with prolonged gastric retention time have been investigated. Attempts are being made to develop a controlled drug delivery system that can provide therapeutically effective plasma drug concentration levels for longer durations, thereby reducing the dosing frequency and minimizing fluctuations in plasma drug concentration at steady state by delivering drug in a controlled and reproducible manner[2]. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability reduces drug waste and improves solubility of drugs that are less soluble in high pH environment. Gastric retention to provide new therapeutic possibilities and substantial benefits from patients. The controlled gastric retention of solid dosage forms may be achieved by the mechanism of mucoadhesion, floatation, sedimentation, expansion, modified shape systems or by the administration of pharmacological agents, that delaying gastric emptying. Based on these approaches, floating drug delivery systems seems to be the promising delivery systems for control release of drugs. Traditional oral sustained formulations have a drawback that it cannot release a drug at specific site[3]. The sustained release product is designed to release the drug over the entire gastrointestinal tract. Hence, clinical acceptable sustained release dosage forms of Norfloxacin. The floating drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability[2]. Weakly basic drugs and their salts exhibit a drop in aqueous solubility at high pH condition (intestinal region), result in low and incomplete release of drugs from sustained release formulation. The bioavailability of these drugs can be improved by creating an acidic micro-environmental pH using some organic acid in the intestinal pH or by making the

formulation to remain for longer period of time in the stomach as these drugs are better soluble in the acidic pH[4]. Norfloxacin, a weakly basic drug is selected for this study.

MATERIAL AND METHODOLOGY

List of materials is as mentioned in Table 1.Floating tablets containing Norfloxacin were prepared by wet granulation technique using varying concentration of polymer with sodium bicarbonate. Polymer and Norfloxacin were mixed homogeneously using glass mortar and pestle. Isopropyl alcohol was used as granulating agent. Granules were prepared by passing the wet coherent mass through a #16 sieve. The granules were dried in hot air oven at a temperature of 45ºC. Dried granules were sieved through #40 sieve and lubricated with magnesium stearate and talc just 4-5 minutes before compression. Lubricated granules were compressed into tablet compression machine using 12 mm flat round punches to obtain tablets of desired specification.[5]

Table 1:List of Materials

Materials	Supplier/manufacturer	Function
Norfloxacin	Sulab Laboratory, Vadodara	API
Lactose	Sulab Laboratory, Vadodara	Binder
HPMC K 4 M	Sulab Laboratory, Vadodara	Polymer
PVP K 30	Sulab Laboratory, Vadodara	Polymer
Sodium bicarbonate	Sulab Laboratory, Vadodara	Effervescent agent
Citric acid	Sulab Laboratory, Vadodara	Effervescent agent
Magnesium stearate	Sulab Laboratory, Vadodara	Lubricant
Talc	Sulab laboratory, Vadodara	lubricant

Table 2: Factors (independent variables), factor levels and responses (dependent variables) used in 2^2 factorial design

Factors	Types of factors	Levels of factors		Response
		-1	+1	
X_1 = amount of HPMCK4M (mg)	Numeric	180mg	245mg	Y_1 = floating time (hours)
X_2 = amount of PVPK30 (mg)	Numeric	180mg	245mg	Y_2 = lag time (seconds)

Table 3: Composition batches were prepared using 2^2 factorial design

Ingredients	F1	F2	F3	F4
Norfloxacin	200mg	200mg	200mg	200mg
HPMCK4M	180mg	245mg	180mg	245mg
PVPK30	30mg	30mg	15mg	15mg
$NaHCO_3$	80mg	80mg	80mg	80mg
Citric acid	30mg	30mg	30mg	30mg
Mg stearate	10mg	10mg	10mg	10mg
Talc	5mg	5mg	5mg	5mg

Table 4: Pre-compression parameters of batches

Batch Code	Bulk Density (g/ml)	Tapped Density (g/ml)	Angle of Repose (θ)	Carr's Index (%)	Hausner's ratio
Nor/001	0.35±0.03	0.39±0.02	29.89±0.3	10.25±0.02	1.11±0.03
Nor/002	0.39±0.04	0.42±0.01	29.55±0.5	7.14±0.05	1.076±0.05
Nor/003	0.42±0.02	0.45±0.01	26.56±1.2	6.66±0.02	1.071±0.07
Nor/004	0.29±0.03	0.32±0.02	27.47±0.6	9.375±0.04	1.103±0.04

Table 5: Post-compression parameters of preliminary batches

Batch Code	Hardness (kg/cm^2)	Thickness (mm)	% Weight variation	Friability (%)	Drug content (%)	Floating lag time (sec)	Total floating time (hr)
Nor/001	5.2	2.1	1.23	0.74	99.35	182±12	10
Nor/002	4.8	2.05	0.99	0.79	98.59	155±17	10
Nor/003	5	2.08	0.99	0.65	99.47	129±13	12
Nor/004	5.2	2.1	1.23	0.61	98.30	170±06	12

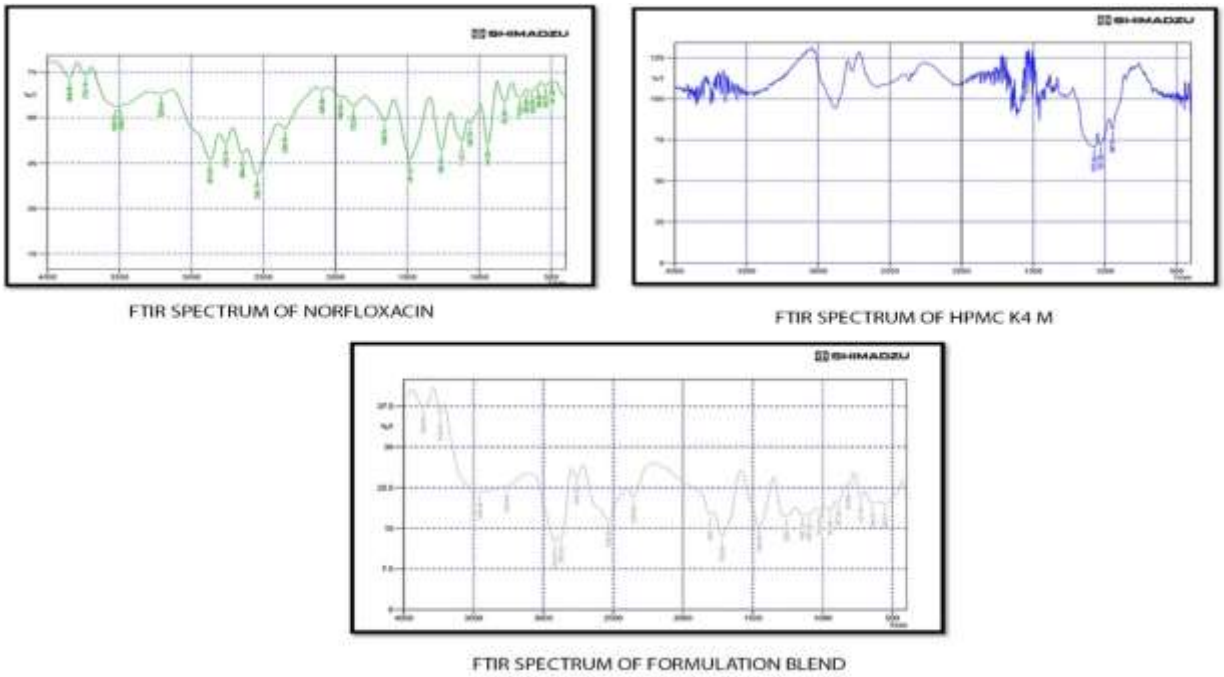

Figure 1: FTIR Spectra

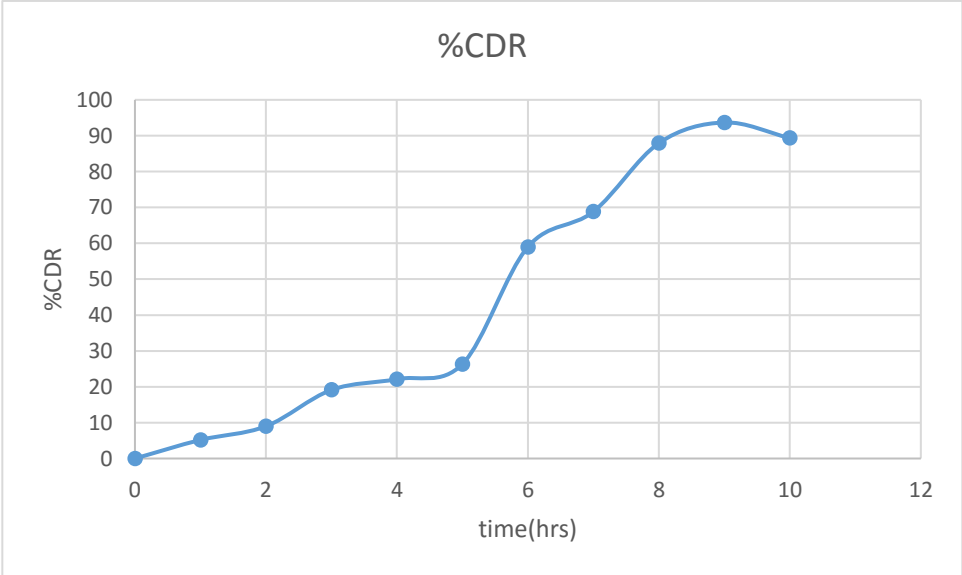

Figure 2: Drug Release of Optimized Batch

PREFORMULATION STUDIES

FTIR study

The identity of the pure Norfloxacin drug sample was studied by scanning the sample in the wave number range 400-4000 cm^{-1} using FTIR spectroscopy by KBr pellet method. The finger print obtained was compared with the reference standard.[6]

Preparation of Standard Curve

Stock solution of Norfloxacin was prepared in 0.1N HCl by first dissolving 10 mg of the drug in 10 ml of 0.1 N HCl and then making up the final volume to 100 ml with 0.1 N HCl.: From the stock solution, 0.5 ml of stock solution was transferred to 10 ml volumetric flask and volume was adjusted to the mark using of 0.1 N HCl to obtain strength of 10μg/ml. The solution was scanned in the UV range of 200-400 nm. Appropriate volumes of aliquots from standard Norfloxacin stock solution were transferred to five separate 10 ml volumetric flask. The volume was adjusted to the mark with 0.1 N HCl to obtain concentrations of 2, 4, 6, 8 and 10 μg/ml.

CHARACTERIZATION

Bulk Density

The bulk density of a powder is dependent on particle packing and changes as the powder consolidates. A consolidated powder is likely to have a greater arch strength than a less consolidated one and may be therefore be more resistant to powder flow. The ease with which a powder consolidates can be used as an indirect method of quantifying powder. Apparent bulk density (gm/ml) was determined by pouring preserved bulk powder into a graduated cylinder via a large funnel and measuring the volume and weight. [7]

Tapped density

Tapped density is the bulk density of a powder which has been compacted by tapping or vibration. Tapped density was determined by placing a graduated cylinder containing a known mass of powder (previously passed through 20# size mesh sieve) on a mechanical tapping apparatus, which is operated for a fixed number of taps (100) or until the powder bed volume has reached to a minimum. The tapped density was computed by taking the weight of drug in cylinder and final volume. [7]

Carr's index

The Compressibility Index of the granules blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a granules and the rate at which it packed down. [7]

Hausner's ratio

The Hausner's ratio is a number that is correlated to the flow ability of a granular material. [7]

$$\text{Hausner's Ratio} = TD / BD$$

Angle of repose

The angle of repose of granules powder was determined by the funnel method. The accurately weight granules were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the granules. The granules were allowed to flow through the funnel freely on to the surface. The diameter of the granules cone was measured and angle of repose was calculated using the following equation. [7]

$$\tan \theta = h/r$$

Where, h and r are the height and radius of the granules cone respectively.

Tablet dimensions

Thickness and diameter of ten tablets were measured using vernier calipers. The extent to which the thickness of each tablet deviated ±5% from the standard value was also measured by using Electronic digital caliper vernier calipers.

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Hardness of the tablet was tested using Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with tablet and a zero reading was taken. The upper plunger was then forced a spring by turning a thread bolt until the tablet fractured. As the spring was compressed, a pointer moved along a gauge in the barrel to indicate the force which is a measure of hardness.[7]

Weight variation

The weight of the tablet being made is routinely measured to ensure that a tablet contains the proper amount of drug. The IP weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablet meet the IP test if not more than 2 tablets are outside the percentage limits. IP official limits of percentage deviation of tablet are presented in the table. In the present study the tablet weight was 200 mg, so more than two of the individual weights of tablet should not deviate from the average weight of tablets by more than ±7.5 %.[8]

Friability

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the

tablet surface. Friability generally reflects poor cohesion of tablet ingredients.

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and placed in the Friabilator. The Friabilator was operated at the speed of 25 rpm for 100 revolutions. The tablets were de-dusted and weighed again (W_{final}). The % friability was then calculated by following formula. [7]

$$F = \{(W_{initial} - W_{final})/ W_{initial}\} \times 100$$

% friability of tablets less than 1% is considered as acceptable.

In vitro buoyancy studies

The in vitro buoyancy studies were performed by placing each of the tablet in a 250 ml of beaker, containing 200 ml of 0.1N HCl (pH 1.2), maintained at 37±0.5°C in a water bath. Physical state of the tablet was observed for more than 12 hours. The time between the introduction of the tablets its buoyancy on the 0.1N HCl (lag time) the time during, which the tablets remains buoyant (total buoyancy time) were determined visually. Three replicates of each formula were performed.[6]

Drug content estimation

Ten tablets were randomly selected and powdered. A quantity of powder equivalent to 7.5 mg of Norfloxacin was accurately weighed and transferred into a 100 ml volumetric flask and dissolved in 0.1 N HCl and the volume was made with 0.1 N HCl (pH 1.2). The flask was shaken on a flask shaker for 24 hours and was kept for 12 hours for the sedimentation of undissolved materials. The solution was filtered through Whatman filter paper. 1 ml of the above solution was transferred to a 100 ml volumetric flask and diluted to 100 ml with 0.1 N HCl and the absorbance was measured at 254 nm using UV spectrophotometer. The percentage of Norfloxacin was determined using previously prepared standard calibration curve. [6, 7]

In vitro drug release studies

Drug release from the tablets was studied using USP dissolution test apparatus I. The tablets were placed in the dissolution vessels fitted with basket. A tablet was placed inside a basket and immersed in a dissolution vessel containing 900 ml of 0.1 N HCl (pH 1.2) used as dissolution media at 37±0.5ºC and stirred at a speed of 100 rpm. The 10 ml of sample was withdrawn at predetermined time interval and fresh dissolution medium was replaced. The collected samples were filtered and were analysed for drug content by using UV visible spectrophotometer at λ_{max} of 276 nm. Finally % drug release at various time interval was calculated. [7, 8]

OPTIMIZATION OF VARIABLES USING FULL FACTORIAL DESIGN

To select ideal proportion of HPMC K4M and PVPK30, factorial design approach was used. This study investigated utility of a 2-factor and optimization process for floating matrix tablets of Norfloxacin. The experimental trials were performed at all 4 possible combinations. Amount of HPMC K4M (X_1) and amount of PVPK30 (X_2) were selected as the independent variables based on the results of preliminary trial batches. The amount of talc and magnesium stearate were kept constant at 2% and 1% w/w respectively. The floating lag time in seconds (Y_1) and % drug release at 12 hour (Y_2) were included as dependent variables. The data is shown in Table 2 & 3.

RESULTS AND DISCUSSION

The FTIR spectrum of pure drug and excipients are shown in Figure 1. From the spectrum it was interpreted that there was no interaction between the drug and the excipients.

The wavelength of maximum absorption (λ_{max}) was found to be 276 nm. This wavelength was used for determination of drug content of formulation. The square of the regression coefficient was found to be 0.9979 indicating linearity.

The graph of absorbance vs. concentration for Norfloxacin in HCl was found to be linear in the concentration range of 2-8 µg/ml at 276.0 nm.

The formulation of floating matrix tablets were developed using Norfloxacin with HPMC K4M and PVP K30 alone and in blend combinations and ratios with sodium bicarbonate and citric acid by direct compression method.

HPMC K4M (hydrophilic) was selected as a matrixing agent considering its widespread applicability and excellent gelling activity in sustained release formulations. Sodium bicarbonate was used as gas generating agent. PVP K30 was employed as binding agent. The talc and magnesium stearate were employed for their glidant and lubricant property. Pre-compression parameters of are provided in Table 4.

The thickness of the tablets was average 2±0.5 mm. The hardness of the floating tablets ranged between 4.6±0.4 to 5.6±1 kg/cm^2 and the percent friability of the prepared tablets was well within acceptable limit (<1%). No significant weight variation was observed between average

weight and individual weights. The results of post-compression parameters are given table. Content uniformity test showed that the percentage of drug content for all the batches were in between 98.00±2.00 to 99.47±1.29. Post-compression parameters of preliminary batches data is provided in Table 5.

As the density of the tablet falls below 1 (density of water), the tablet becomes buoyant. Floating lag time of the tablets was also found to be directly related to polymer concentration. In all the formulations of preliminary trials floating lag time ranged from 129±13 to 305±21 seconds. Tablets containing HPMC K4M exhibited shorter floating lag time as compared to lactose. This might be due to rapid hydration of HPMC K4M as compared to PVPK30. It has also been observed that increased concentration of sodium bicarbonate had shorter floating lag time. The drug release was found to be faster with HPMC K4M as the polymer when compared to lactose. It was also found that the increased concentration of polymer had drug retardant effect in the formulation. It was also revealed that the blend of HPMC K4M and PVPK30 might be exhibit better drug retarding efficiency. The drug retarding efficiency of the formulation was in following order. Thus, from the results obtained from batches, it was decided to optimize the formulations by using blend of HPMC K4M and PVPK30 with sodium bicarbonate in lesser concentration to achieve a sustained drug release for a period of 12 hours. The data of drug release for optimized batch is represented graphically in Figure 2

CONCLUSION

Norfloxacin being a weakly basic drug, shows good absorption in gastric pH condition. It shows hepatic first pass metabolism and thus poor oral bioavailability. Hence, an attempt has been made to retain dosage form in stomach for longer period of time so that one can avoid problem of hepatic metabolism and also due to good solubility of drug in acidic pH, absorption and bioavailability might be enhanced. Characterization of drug and individual excipients confirmed their purity. Moreover, characterization of prepared physical mixtures of drug with polymers indicated the absence of major interaction of the drug and other excipients. Floating tablets can be prepared by using HPMC K4M and PVPK30 by using wet compression method. Results of friability, uniformity of drug content and weight variation for the floating matrix tablets complied with IP specifications. From the results, it can be concluded that HPMC K4M can reduce floating lag time but cannot sustain drug release for longer duration. One can achieve sustain drug action up to 12 hours and thereby dosage frequency can be minimized.

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