Tropical Journal of Pharmaceutical Research March 2023; 22 (3): 469-476
**ISSN:** 1596-5996 (print); 1596-9827 (electronic)


Available online at http://www.tjpr.org
**http://dx.doi.org/10.4314/tjpr.v22i3.2**

**Original Research Article**

# Influence of pH on the release of a once-daily formulation of ciprofloxacin tablets prepared with different polymers

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*Sent for review: 24 October 2022* *Revised accepted: 28 February 2023*

## Abstract

***Purpose:*** *To study the release behaviour of ciprofloxacin hydrochloride tablet matrices prepared with different polymers in dissolution media of different pH.*
***Methods:*** *Different formulations of slow-release matrix tablets of ciprofloxacin hydrochloride were prepared with polymers, namely, ethyl cellulose (Etc), hydroxyethyl cellulose (Hec), hydroxypropyl methylcellulose (Hpc), and Eudragit® L-100 (Eud) using matrix embedding technique. The matrix tablets were characterized and studies of their dissolution profiles were studied in 0.1 N HCl (pH 1.2) and in simulated intestinal fluid (excluding enzymes) of pH 4.0, 6.0, and 7.4.*
***Results:*** *The tablets had the following characteristics: weight, 659.25 ± 7.96 to 661.65 ± 6.53 mg; hardness, 7.05 ± 0.21 to 9.60 ± 0.40 kgf; friability, 0.212 to 0.292 %; and drug content, 91.47 ± 0.53 to 112.50 ± 4.14 %. In batches prepared with ethyl cellulose, Eudragit L-100, and hydroxypropyl methylcellulose, drug release increased with a decrease in pH. However, matrix tablets prepared with hydroxyethyl cellulose displayed the highest drug release at pH 4.0 with $C_{max}$ of 108.75 % and $T_{50\%}$ of 30.86 min; thereafter, drug release decreased with increase in pH. The pattern of drug release was Hec > Hpc > Eud > Etc in most media with more drug release in acidic than at alkaline pH.*
***Conclusion:*** *Release of ciprofloxacin from the formulated matrix tablets was pH-sensitive in vitro. This should be taken into consideration in designing sustained release oral form of ciprofloxacin.*

***Keywords:*** *Sustained release, Matrix tablets, Ciprofloxacin, Ethyl cellulose, Hydroxyethyl cellulose, Hydroxypropyl methylcellulose, Dissolution media*



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## INTRODUCTION

The obvious advantages of oral route make it the most preferred route of drug administration [1]. Sustained release oral preparations because of their characteristics are more cost-effective, less toxic, reduce side effects, and enhance patients' compliance [2]. The gastrointestinal tract's physiological conditions such as motility, pH, ions and enzymes present determine drug release from slow-release preparations [3]. The dissolution medias' pH to a large extent determines the rate and extent of release of

drugs with pH-dependent solubility from sustained release preparations [4]. In addition, polymer type and concentration are also consequential in drug release from extended-release systems. Appropriate selection of polymers is therefore necessary for the formulation of well-characterized and reproducible sustained release systems [5].

Monolithic matrix sustained-release oral tablets have been formulated with hydrophobic and/or hydrophilic polymers. Hydrophobic matrices are suitable for drugs with high solubility [6]. The release of drugs with high solubility has been successfully modulated in hydrophobic matrices such as ethyl cellulose or Eudragit® L-100 matrices [7]. Also, hydroxypropyl methylcellulose and other hydrophilic polymers like hydroxyethyl cellulose have been used as matrix formers. Both are hydrophilic non-ionic derivatives of cellulose ether. They are stable over a wide pH range and their non-ionic nature reduces their interactions with other chemical entities when used in acidic, basic, or electrolytes systems and has reproducible release behaviour [8].

Determination of release profiles of sustained release formulations at different pH is, therefore, necessary to know over which pH range dosage forms release their drugs at a faster rate than required to avoid dose dumping at a particular narrow pH range thus useful in differentiating good formulations from bad ones. Ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, and Eudragit® L-100 have been used individually to sustain the release of drugs [9-10]. The properties of the polymer used affect the behaviour of the active ingredient in a formulation. The polymer used should not however compromise the therapeutic actions of the incorporated drug as it must be compatible with the active ingredient.

Ciprofloxacin is an antibiotic belonging to the class known as fluoroquinolones. It has a wide range of activities against both Gram-negative and Gram-positive bacteria. It is useful in treatment of many sensitive bacterial infections. Ciprofloxacin readily accumulates in the body leading to toxicity because of its high permeability caused by its small molecular size, thus making its sustained release preparations desirable [11].

In this study, hydrophobic and hydrophilic polymers were used as matrices differently to retard ciprofloxacin release from matrix-tablets. The release profiles were studied using aqueous media of different compositions and pH.

## EXPERIMENTAL

### Materials

Eudragit® L-100 (Rohm Pharma, Italy), Ethyl cellulose (high viscosity), hydroxypropyl methylcellulose (high viscosity) and hydroxyethyl cellulose (high viscosity) were obtained from Fluka (Germany); absolute ethanol, concentrated hydrochloric acid, and monobasic potassium phosphate (BDH, England); ciprofloxacin hydrochloride, talc, and magnesium stearate (Jawa, India). Other analytical grade materials were purchased and used in the analysis and evaluation of the tablets.

### Formulation of ciprofloxacin matrix tablets

The granules were made by wet granulation method with ethanol as the granulating fluid to prevent unintended swelling of some polymers which may happen in aqueous granulating fluid [9]. Four polymers namely: hydroxypropyl methylcellulose, Eudragit® L-100, ethyl cellulose and hydroxyethyl cellulose were used differently to formulate 12 batches of the matrix tablets at three concentration levels per polymer. They were formulated to contain 500 mg of ciprofloxacin hydrochloride each. The polymers formed 10, 20, and 30 % w/w of the active ingredients, respectively. Ciprofloxacin hydrochloride was blended with the appropriate quantity of each of the polymer dispersed separately in absolute ethyl alcohol to form a homogenous wet mass. The damp mass was then sieved through 1.7 mm sieve and dried in an oven at 50 $^{o}$C for 1 h. The oven-dried granules were then sieved through 1.0 mm sieve followed by lubrication with magnesium stearate and talc before compression in a single punch Manesty F2 (England) tablet press fitted with 12 mm punches with flat surfaces. Table 1 shows the formula for all of the batches.

### Determination of the matrix tablets characteristics

The tablets were assessed for their crushing strength (hardness), weight uniformity, friability, thickness, porosity, and drug content.

Hardness tester (Mosanto®, Manesty, England) was used to measure the crushing strength of the tablets by observing the load required to crush each tablet.

Uniformity of weight tests was performed on all the batches in accordance with the USP method (USP 40$^{th}$ edition) using Adventurer® digital balance (Ohaus model AR 3130, China) [12].

**Table 1:** Composition of the matrix tablets

| Ing. (mg) | Batch no. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **$Etc_1$** | **$Etc_2$** | **$Etc_3$** | **$Hec_1$** | **$Hec_2$** | **$Hec_3$** | **$Eud_1$** | **$Eud_2$** | **$Eud_3$** | **$Hpc_1$** | **$Hpc_2$** | **$Hpc_3$** |
| Cipr | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |
| Etc | 50 | 100 | 150 | - | - | - | - | - | - | - | - | - |
| Hec | - | - | - | 50 | 100 | 150 | - | - | - | - | - | - |
| Eud | - | - | - | - | - | - | 50 | 100 | 150 | - | - | - |
| Hpc | - | - | - | - | - | - | - | - | - | 50 | 100 | 150 |
| Talc | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| M. ste | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |

**Key:** Ing = ingredients, Cipr. = ciprofloxacin hydrochloride, Etc = ethyl cellulose, Hec = hydroxyethyl cellulose, Eud = Eudragit® L-100, Hpc = hydroxypropyl methylcellulose, M. ste = magnesium stearate

Friability tests were carried out in all the batches using Erweka TA 100 model friabilator (Germany). A set of Vernier callipers was used to measure the tablet diameter and thickness.

The porosities ($E_p$) of the tablets were calculated using Eq 1.

$$E_p = (1\text{-}4w/e_t\pi D^2H)100 \text{ …….. (1)}$$

where w is the tablet weight, $e_t$ represents the particle true density of the compact/tablet material, H is the tablet thickness, and D is the tablet diameter.

Drug content was determined using the spectrophotometric method. Drug content was then calculated using an already prepared calibration curve (Beer's plot) of the standard solutions of the drug.

**Swelling studies**

The swelling behaviour of the matrix tablets was determined in both 0.1 NHCl and simulated intestinal fluid in all the batches.

**Dissolution studies**

Calibration curves (Beer's plots) of ciprofloxacin hydrochloride were prepared first in 0.1 N HCl (pH 1.2) and in simulated intestinal fluids (SIF) without enzymes of pH 4.0, 6.0, and 7.4 at wavelengths of 278, 274, 272, and 270 nm respectively for various pH which corresponded with the wavelength of the maximum absorption of the drug in each dissolution medium. Drug dissolution experiments were carried out in 900 mL of 0.1 N HCl and in simulated intestinal fluids of pH 4.0, 6.0, and 7.4 at 37 ± 1 $^oC$ and a speed of 50 rotations per minute (rpm) using USP type 2 dissolution apparatus [12].

**Determination of drug release kinetics**

The dissolution data were fitted into various release models such as first order, zero order, Korsmeyer-Peppas, and Higuchi models to determine the kinetics and mechanisms of drug release from the matrix tablets as follows:

(i) Zero order as the cumulative amount of drug release) (C) versus time (t)

$$C = K_o t \text{ ……} \quad (2)$$

(ii) First order as the logarithm of cumulative percentage of drug remaining (C) versus time (t).

$$\text{Log } C = \text{Log } C_o - Kt/2.303 \text{ ……} \quad (3)$$

where Co is the initial concentration of the drug.

(iii) Higuchi model as a cumulative percentage (Q) of drug released at a time (t) and $k_H$ is a constant reflecting the design variables of the system. The quantity of drug released is proportional to the square root of time:

$$Q = k_H t^{1/2} \text{……} \quad (4)$$

(iv) Korsmeyer-Peppas: The release data for the first 60% drug release were fitted into Korsmeyer *et al's* equation as log cumulative percentage drug released versus log time.

$$m_t/m_\infty = kt^n \quad \text{……} \quad (5)$$

The value of the exponent (n) is used to characterizes the mechanism of drug release and $m_t/m_\infty$ is the fractional amount of drug released, t is the time, and k is the kinetic constant characteristic of the drug-polymer system. For a cylindrical matrix, n is by Fickian diffusion if $n \leq 0.45$ and non-Fickian release if $n > 0.45 < 0.89$, $n = 0.89$ is case ii release, and $n > 0.89$ is for super case ii release [13].

**Dissolution studies**

The effect of pH on the release of ciprofloxacin hydrochloride was studied by carrying out dissolution tests in 0.I N HCl pH 1.2, and in simulated intestinal fluids of pH 4.0, 6.0, and 7.4.

### Statistical analysis

Data were analysed with Microsoft Excel 2016 while analysis of variance was carried out using IBM SPSS version 21. Tukey *post hoc* tests were used to determine group differences at 95 % level of significance ($p < 0.05$).

## RESULTS

### Characteristics of matrix tablets

The physical appearance, crushing strength, friability, weight uniformity, and content of the active ingredients were within acceptable range and satisfactory. These are shown in Table 2. The tablet hardness for all the batches was in the range of 7 - 10 kgf with a friability of less than 0.3 % which are acceptable for non-disintegrating sustained-release matrix tablets. Also, the content of active ingredients which was within ± 12 % of the labelled amount of the active ingredient is an indication of the reproducibility of the wet granulation method used to prepare the tablets.

The results of the swelling studies showed that there was more swelling in simulated intestinal fluid without enzymes (Figure 1) than in 0.1 N HCl (Figure 2) because the drug is more soluble in an acidic medium than in an alkaline medium.

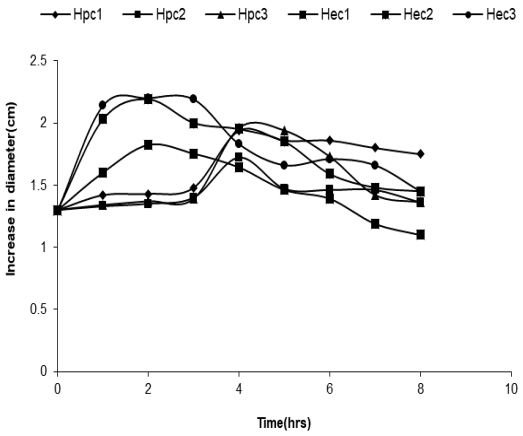


**Figure 1**: Swelling isotherms of hydroxyethyl cellulose (Hec) and hydroxypropyl methylcellulose (Hpc) batches in SIF pH 7.4

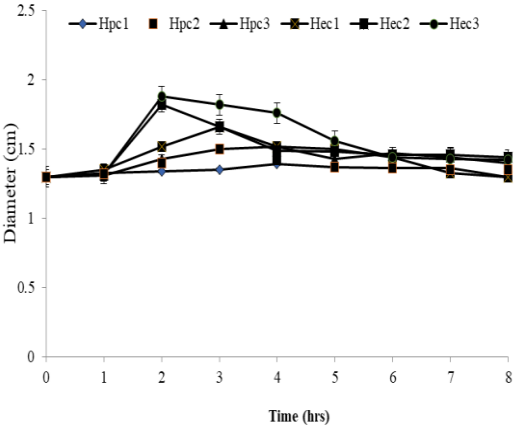


**Figure 2**: Swelling isotherms of hydroxyethyl cellulose (Hec) and hydroxypropyl methylcellulose (Hpc) batches in 0.1 N HCl

**Table 2:** Tablet properties of the ciprofloxacin matrix tablets

| Lot code | Parameters | | | | | |
|---|---|---|---|---|---|---|
| | Mean weight (mg), n=20 | Thickness (mm), n=5 | Hardness (Kgf), n=10 | Friability (%), n=20 | Drug content (%), n=3 | Porosity (%) |
| $Etc_1$ | 564.50±7.45 | 5.170±0.042 | 7.6±0.86 | 0.319 | 104.74±2.47 | 39.09 |
| $Etc_2$ | 621.00±9.41 | 5.450±0.053 | 8.20±0.56 | 0.292 | 99.31±2.47 | 35.48 |
| $Etc_3$ | 659.25±7.95 | 5.700±0.016 | 7.9±0.45 | 0.241 | 111.7±1.04 | 33.52 |
| $Eud_1$ | 550.05±8.61 | 5.195±0.028 | 6.65±1.10 | 0.468 | 97.76±1.68 | 40.93 |
| $Eud_2$ | 615.80±11.04 | 5.260±0.21 | 7.90±1.02 | 0.255 | 112.50±4.14 | 31.65 |
| $Eud_3$ | 659.90±7.38 | 5.500±0.00 | 9.6±0.04 | 0.246 | 96.98±0.95 | 31.03 |
| $Hpc_1$ | 560.05±7.01 | 5.265±0.024 | 8.80±0.78 | 0.394 | 105.05±0.39 | 43.19 |
| $Hpc_2$ | 622.90±8.86 | 5.660±0.021 | 10.00±0.87 | 0.352 | 102.34±0.47 | 43.62 |
| $Hpc_3$ | 661.65±6.53 | 6.170±0.026 | 7.05±0.21 | 0.274 | 91.47±0.53 | 41.90 |
| $Hec_1$ | 551.05±9.59 | 4.921±0.160 | 7.95±0.57 | 0.369 | 100.55±0.15 | 45.90 |
| $Hec_2$ | 612.80±8.82 | 5.315±0.047 | 6.95±0.39 | 0.388 | 91.94±0.53 | 42.50 |
| $Hec_3$ | 661.20±6.57 | 5.540±0.068 | 7.45±0.47 | 0.212 | 102.14±0.61 | 34.39 |

**Key:** Etc = ethyl cellulose, Hec = hydroxyethyl cellulose, Eud = Eudragit® L-100, Hpc = hydroxypropyl methylcellulose

**Dissolution characteristics**

The drug release from the matrix tablets were in most cases dependent upon the concentration of polymer used. In batches prepared with hydroxypropyl methylcellulose drug release decreased with increasing polymer concentrations. The drug release differed significantly among the three concentrations ($Hpc_1$, $Hpc_2$, and $Hpc_3$). In batches prepared with hydroxyethyl cellulose, $Hec_1$ and $Hec_2$ were significantly not different from each other but different from $Hec_3$. In batches prepared with Eudragit L-100, drug release in $Eud_2$ and $Eud_3$ was statistically the same but different from $Eud_1$. In ethyl cellulose batches $Etc_1$ could not achieve sustained release since more than 90 % drug release was observed within the first hour. However prolonged-release was observed in $Etc_2$ and $Etc_3$ in a manner dependent on polymer concentration (Table 3).

**Table 3:** Some ciprofloxacin matrix tablet release parameters in 0.1 N HCl

| Batch | $T_{50\%}$ (min) | $T_{70\%}$ (min) | $C_{max}$ (%) |
|---|---|---|---|
| $Etc_1$ | 30.85 | 41.14 | 102.25 |
| $Etc_2$ | 181.71 | 301.09 | 84.37 |
| $Etc_3$ | - | - | 46.32 |
| $Hpc_1$ | 582.77 | - | 52.84 |
| $Hpc_2$ | - | - | 35.74 |
| $Hpc_3$ | 593.33 | - | 50.19 |
| $Eud_1$ | 54.86 | 102.85 | 101.42 |
| $Eud_2$ | 349.81 | - | 63.62 |
| $Eud_3$ | 343.17 | - | 63.63 |
| $Hec_1$ | 148.87 | 240.00 | 98.27 |
| $Hec_2$ | 148.87 | 310.59 | 99.11 |
| $Hec_3$ | 429.70 | | 65.80 |

**Key:** Etc = ethyl cellulose, Hec = hydroxyethyl cellulose, Eud = Eudragit® L-100, Hpc = hydroxypropyl methylcellulose

**Effect of pH on matrix tablet dissolution**

The batch containing 30 % hydroxyethyl cellulose ($He_3$) had the highest release at pH 4.0 with $T_{50\%}$ at 30.86 min compared to 411.91 min at pH 1.2 and 48 min at pH 6.0 (Figure 3). In other batches, the release of drug reduced with increasing in pH (Figure 4 and Figure 5).

**Kinetics of drug release**

Table 4 shows the results of fitting the release data into various release models. All formulations followed Higuchi release pattern except those prepared with hydroxypropyl methylcellulose $Hpc_1$, $Hpc_2$, and $Hpc_3$ which followed first order release kinetics. Applying the Korsmeyer *et al,* power law indicated that the coefficient n was not more than 0.45 for matrix tablets prepared with hydrophobic polymers i.e., formulations $Eud_1$, $Eud_2$, $Eud_3$, $Etc_2$ and $Etc_3$ while those prepared with hydrophilic polymers were above 0.45. It implied that while drug release was by Fickan diffusion in hydrophobic matrices, that of the hydrophilic polymer tablet matrices were governed by anomalous mechanism i.e., a coupling of more than one mechanism.

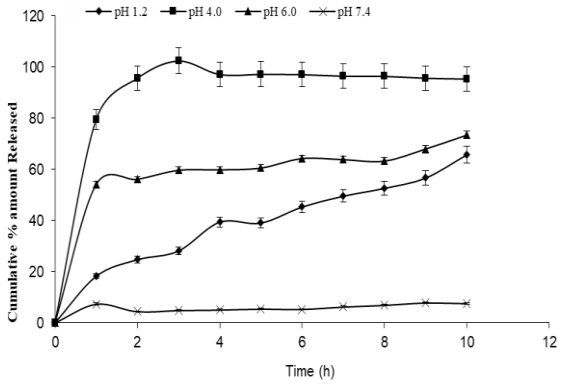


**Figure 3**: Effect of pH on ciprofloxacin release from hydroxyethyl cellulose tablet matrices

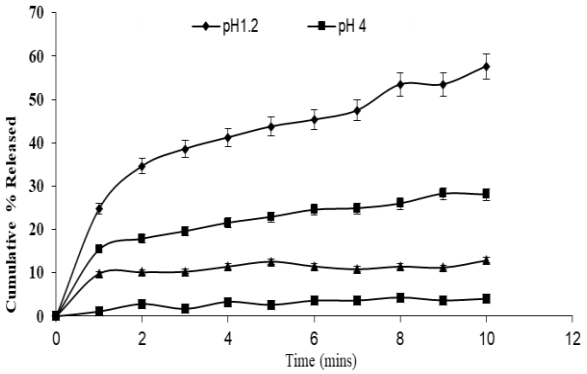


**Figure 4:** Effect of pH on ciprofloxacin release from Eudragit L-100 tablets matrices

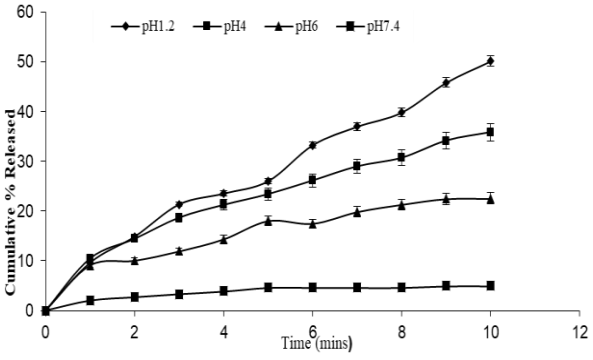


**Figure 5**: Effect of pH on ciprofloxacin release from hydroxypropyl methylcellulose tablet matrices

**Table 4:** Ciprofloxacin release kinetics from various matrices

| Lot no | Drug release model | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Zero Order | | First Order | | Higuchi | | Korsmeyer | |
| | $R^2$ | $K(h^{-1})$ | $R^2$ | $K(h^{-1})$ | $R^2$ | $K(h^{-1/2})$ | $R^2$ | n |
| $Hec_1$ | 0.7504 | 62.10 | 0.9335 | 0.4482 | 0.9700 | 37.63 | 0.9739 | 0.56 |
| $Hec_2$ | 0.7533 | 53.23 | 0.7866 | 0.4322 | 0.9899 | 31.52 | 0.9829 | 0.47 |
| $Hec_3$ | 0.8609 | 35.80 | 0.9645 | 0.0884 | 0.9775 | 19.04 | 0.9785 | 0.55 |
| $Hpc_1$ | 0.9384 | 31.02 | 0.9890 | 0.0713 | 0.9501 | 15.64 | 0.9792 | 0.67 |
| $Hpc_2$ | 0.9444 | 20.10 | 0.9850 | 0.0410 | 0.9546 | 10.41 | 0.9837 | 0.67 |
| Hpc3 | 0.9608 | 23.95 | 0.9883 | 0.0636 | 0.9408 | 13.87 | 0.9892 | 0.69 |
| $Etc_1$ | -1.4472 | 71.60 | 0.0015 | 0.0097 | 0.0093 | 39.10 | 0.0160 | 0.062 |
| $Etc_2$ | 0.6200 | 51.18 | 6.9803 | 0.1654 | 0.9806 | 28.44 | 0.9843 | 0.45 |
| $Etc_3$ | 0.6518 | 30.24 | 0.9754 | 0.0557 | 0.9876 | 15.81 | 0.9807 | 0.45 |
| $Eud_1$ | -0.1163 | 66.21 | 0.6983 | 0.3050 | 0.7498 | 37.79 | 0.8300 | 0.24 |
| $Eud_2$ | 0.4631 | 35.74 | 0.9489 | 0.0820 | 0.9593 | 19.32 | 0.8998 | 0.44 |
| $Eud_3$ | 0.463 | 35.74 | 0.8355 | 0.0670 | 0.8908 | 19.52 | 0.8314 | 0.37 |

**Key:** Etc = ethyl cellulose, Hec = hydroxyethyl cellulose, Eud = Eudragit® L-100, Hpc = hydroxypropyl methylcellulose

## DISCUSSION

The matrix tablets were tested *in vitro* for drug release in media varying pH to simulate the pH of various segments of the gastrointestinal tract. Ciprofloxacin release from tablet matrices was initially high due to high drug release in the first hour owing to the presence of some quantity of drug on the matrix-tablet surfaces followed by sustained drug release. Drug release in $Hpc_1$, $Hpc_2$, and $Hpc_3$ decreased with increasing polymer concentration and pH. hydroxyethyl cellulose and hydroxypropyl methylcellulose are swellable matrix formers and retard drug release by the formation gel layers which prevent the penetration of the dissolution fluid. When a swellable tablet matrix comes into contact with water, it absorbs water and forms a gel layer around the dry core which retard drug release and also prevents wetting of the tablet core and tablet disintegration with kinetics dependent on the polymer's molecular mass, temperature, and solution pH [14]. Higher concentration of the polymers results in gel layers that are more viscous and resistant to drug diffusion thus making the diffusion pathway more tortuous [15].

Formulations prepared with hydroxyethyl cellulose had the highest release at a pH of 4.0 but for other polymers drug release decreased with increasing pH and polymer concentration. This could be a result of the solubility behaviour of hydroxyethyl cellulose. Formulation $Etc_1$ could not sustain the drug release at that polymer concentration but a higher concentration of the polymer $Etc_2$ and $EC_3$ effectively retarded drug release. Drug release in formulations $Eud_1$, $Eud_2$, and $Eud_3$ was dependent also on the drug-polymer ratio however, there was no significant difference in the release behaviours of $Eud_2$ and $Eud_3$ suggesting that further increase in the polymer concentration did not result in decreased drug release. Hydrophobic polymers make the entry of the dissolution medium into the tablet matrices difficult due to their reduced affinity for water thus resulting in retarded drug release. The release kinetics in formulations $Eud_1$, $Eud_2$, $Eud_3$, $Etc_2$, $Etc_3$, $Hec_1$, $Hec_2$, $Hec_3$ followed the Higuchi release model a process dependent on the square root of time $Hpc_1$, $Hpc_2$ and $H_3$ followed first-order release kinetics. The mechanism of drug release as determined by Korsmeyer *et al*, equation is by Fickan diffusion in formulations $Eud_1$, $Eud_2$, $Eud_3$, ($n \leq 0.45$ [13]. The formulations $Hec_1$, $Hec_2$, $Hec_3$, $Hpc_1$, $Hpc_2$, and $Hpc_3$ followed anomalous mechanisms involving diffusion and erosion of the gel layers ($0.45 < n < 0.89$). Erosion of the gel layers in $Hec_1$, $Hec_2$, and $Hec_3$ was faster due higher aqueous solubility of hydroxyethyl cellulose. Out of the four batches containing 30 % by weight of each polymer tested at different pH none could achieve 50 % drug release in 10 h in pH 7.4. Maximum cumulative drug release (Cmax) decreased with increase in pH. The retarded rate of dissolution in an alkaline medium could be as a result of the poor solubility of ciprofloxacin in alkaline pH and the observed increased swelling of the polymer at alkaline pH which increased the diffusion pathway of the drug. Ciprofloxacin being a weakly acidic drug is likely to undergo ionization at a slightly alkaline pH of 7.4.

Improved release of ciprofloxacin hydrochloride in acidic pH has been reported and hence a formulation of ciprofloxacin that could swell so that is retained in a fed stomach was designed [17]. Also, it was reported that ciprofloxacin showed reduced bioavailability from the colon (pH 7.4) in an *in vitro* study of slow-release release ciprofloxacin in intestinal model [18].

## CONCLUSION

Increasing the pH of the dissolution medium has been shown to reduce the release of ciprofloxacin from prepared matrices. This is due to decreasing solubility of the drug and/or increase in swelling of the swellable hydrophilic matrices which increases the diffusion pathway of the drug. Release of ciprofloxacin from the matrices is sensitive to pH and that should be taken into consideration in designing sustained release oral forms of ciprofloxacin.

## DECLARATIONS

### *Acknowledgements*

Authors are grateful to Anthony Ofomata of the Energy Research Centre, University of Nigeria, Nsukka for technical assistance.

### *Funding*

None provided.

### *Ethical approval*

None provided.

### *Availability of data and materials*

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### *Conflict of Interest*

No conflict of interest associated with this work.

### *Contribution of Authors*

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. The work was conceptualized and designed by Prof SI Ofoefule, while data collection and analysis of data were done by JI Ogbonna, RC Omeh, CC Mbah, BC Amadi, CA Ezegbe, and LO Ugorji. The manuscript was written by JI Ogbonna and SI Ofoefule, however, all the authors read the manuscript and approved it for publication.



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