

# Evaluation of a poly (acrylic) acid polymer as a sustained release matrix for ciprofloxacin hydrochloride

Nwachukwu, Nkemakolam<sup>1, \*</sup>, Emeje, O. Martin<sup>2</sup>, Ofoefule, I. Sabinus<sup>3</sup>

<sup>1</sup>Department of Pharmaceutics & Pharmaceutical Technology, University of Port Harcourt, Choba, Rivers State, Nigeria

<sup>2</sup>Department of Pharmaceutical Technology, National Institute for Pharmaceutical Research & Development, Idu, Abuja, Nigeria

<sup>3</sup>Department of Pharmaceutical Technology and Industrial Pharmacy, University of Nigeria, Nsukka, Enugu State, Nigeria

## Email address:

pharmnkem@yahoo.com (Nwachukwu, N)

## To cite this article:

Nwachukwu, Nkemakolam, Emeje, O. Martin, Ofoefule, I. Sabinus. Evaluation of a Poly (Acrylic) Acid Polymer as a Sustained Release Matrix for Ciprofloxacin Hydrochloride. *International Journal of Science, Technology and Society*. Vol. 2, No. 4, 2014, pp. 85-90. doi: 10.11648/j.ijsts.20140204.15

**Abstract:** An evaluation of the sustained release (SR) properties of a polyacrylic acid polymer, Carbopol 971 (CP 971) as matrix in the formulation of ciprofloxacin hydrochloride (CH) tablets was carried out. The CP 971 in concentrations of up to 40 % w/w were wet granulated using ethanol 95% v/v and the dried granules were evaluated for packing, densification and flow properties. The tablets were evaluated for hardness, friability, uniformity of weight and content of active ingredient. The formulations dissolution profiles were tested in 0.1 N Hydrochloric acid (0.1 N HCl, pH 1.3), simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 7.2) without enzymes. Results obtained showed significant retardation ( $p < 0.05$ ) of ciprofloxacin release as the polymer concentration increased. Drug release was significantly different in the three media used with the release rate being faster in SGF than 0.1 N HCl and SIF. This can be attributed to the high solubility of the drug in acidic media. More than 50% of drug content was released within 4 h. Ciprofloxacin tablets containing 20 % w/w was adjudged the best formulation and drug release from the formulation was diffusion controlled (Fickian).

**Keywords:** Poly (Acrylic) Acid, Ciprofloxacin Hydrochloride, Micromeritics, Densification, Sustained Release

## 1. Introduction

Sustained release formulation is a concept that has received a lot of attention since the 1960's because of its inherent advantages over the conventional release dosage forms. These advantages include: reduction of dosage frequency, constant pharmacodynamic response, patient compliance and reduction of side effects of the active ingredient [1, 2]. Orally administered sustained release formulations have their active ingredient gradually released in the gastro-intestinal tract (GIT) on the administration of a single dose [3, 4]. Carbopols are synthetic high molecular weight, white fluffy, acidic hygroscopic powder [5 – 7]. They have been reported as a good performing matrix in oral sustained release tablet formulations [8 – 11]. At low concentrations (1 – 3%) carbopol resins allow normal release of medicaments in tablets but at higher concentrations (5 – 40%), they effect modified release of the medicament [12, 13]. Ciprofloxacin hydrochloride is a

flouroquinolone compound with anti infective/anti bacterial properties [14] and is used in the treatment of susceptible bacterial infections in the gastro-intestinal tract (GIT), ear, nose, and throat infections, dermatitis, exacerbations of cystic fibrosis, and HACEK endocarditis [15]. Ciprofloxacin is rapidly and well absorbed from the GIT [16 – 18]. Its oral bioavailability is about 70% with attainment of peak plasma concentration of 0.5 to 2 h after ingestion of food. It has a biologic half life of between 3.5 to 4.5 h [19] and this property makes it a good candidate for sustained release formulations. It has been reported that oral sustained release CH tablets performed comparably well with the normal release tablet in terms of efficacy [20]. The SR tablet was reported to have the advantage of reduced symptoms of nausea, diarrhoea, and lower treatment costs [20].

### 1.1. Materials

Ciprofloxacin hydrochloride, concentrated hydrochloric acid, sodium hydroxide, stearic acid, ethanol (Sigma Chemical Coy, USA), lactose, sodium chloride (BDH Poole, England), potassium dihydrogen orthophosphate

(Aldreich, USA), talc (May and Baker), Carbopol 971 (G.F. Goodrich, Ohio, USA)

## 2. Method

**Table 1.** Formula for formulation of ciprofloxacin hydrochloride granules

Ingredient	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Ciprofloxacin hydrochloride (mg)	500.00	500.00	500.00	500.00	500.00
Carbopol 971(% w/w)	0.00	10.00	20.00	30.00	40.00
Talc(% w/w)	0.50	0.50	0.50	0.50	0.50
Stearic acid(% w/w)	1.00	1.00	1.00	1.00	1.00
Total weight (mg)	507.50	557.50	607.50	657.50	707.50

### 2.1. Preparation of Granules

Five batches of ciprofloxacin hydrochloride (CH) were prepared with the formula in Table 1. Ciprofloxacin hydrochloride and CP 971 were weighed in each case into a Wedgewood mortar in amounts sufficient to produce 100 tablets. Sufficient quantity of ethanol 95% v/v was used to wet mass the powder blends. Granules were formed from the wet mass by screening through a 1.70 mm stainless steel sieve. Screened granules were dried at 60°C for 1 h in a Memmert® oven (GmbH, Germany). The dried granules were screened using a 1.00 mm stainless sieve. Talc and stearic acid were added extragranularly to lubricate the granules prior to compression.

### 2.2. Evaluation of the Granules

#### 2.2.1. Flow Rate and Angle of Repose

A 10.00 g quantity of ciprofloxacin hydrochloride granules was allowed to flow freely under gravity from a glass funnel of orifice and base diameters of 1.10 cm and 5.50 cm respectively and a fixed height of 15.00 cm above a flat table surface. The time of flow, the height and radius of the granule heap formed were measured and recorded. The flow rate and the tangent of the angle of the powder heap were calculated from Equations 1 and 2 [21].

$$\text{Flow Rate (F R)} = M / F T \text{ (sec)} \quad (1)$$

$$\text{Angle of Repose } (\theta) = \tan^{-1} [h / r] \quad (2)$$

Where M = mass of granules, F.T. = flow time of granules, h = height of granule heap and r = radius of granule heap. Three replicate determinations were made.

#### 2.2.2. Bulk and Tapped densities

A 10.00 g quantity of CH granule was freely poured into a dry 100 mL measuring cylinder and the volume,  $V_b$  noted. Mechanical tapping of the cylinder on a flat surface was done until no further decrease in volume of the granule was observed. This was noted as the tapped volume,  $V_t$ . The bulk and tapped densities were calculated as a ratio of the granule mass and the respective volumes [22] from Equations 3 and 4.

$$\text{Bulk density (D}_b\text{)} = M / V_b \quad (3)$$

$$\text{Tapped density (D}_t\text{)} = M / V_t \quad (4)$$

Where M is mass of granules,

#### 2.2.3. Hausner's Quotient and Carr's Index

Hausner's quotient and Carr's index were calculated from the bulk and tapped density values using Equations 5 and 6 [23].

$$\text{Hausner's quotient} = D_t / D_b \quad (5)$$

$$\text{Carr's index (CI)} = \{1 - D_b / D_t\} \times 100 \quad (6)$$

### 2.3. Compression of Tablets

Talc and stearic acid were added extragranularly. Tablet compression was done with a single punch tableting machine (Manesty, F-3, England) fitted with a 13.5 mm biconvex set of punches to a target weight of 507.50 to 707.50 mg. Compression was done at a constant pressure unit of the tableting machine.

## 3. Evaluation of Ciprofloxacin Hydrochloride Tablets

Evaluation of tablets for weight variation, hardness, friability and dissolution were done 24 h post compression.

### 3.1. Uniformity of Weight

From each batch of the ciprofloxacin hydrochloride tablets twenty tablets randomly selected were weighed singly on an Adventurer® analytical balance [24]. The mean weight, standard deviation and coefficient of variation were calculated. The acceptance and rejection criteria for each tablet batch is as stipulated in the British Pharmacopoeia, BP 2009 [24].

### 3.2. Crushing Strength

Ten tablets randomly selected from each batch of the ciprofloxacin hydrochloride tablets were tested using a Monsanto® tablet crushing strength tester and the values

recorded in Kg/f units. The mean breaking strength and standard deviation were determined for each batch [25].

### 3.3. Friability Test

An Erweka<sup>®</sup> TAR 200 (Erweka<sup>®</sup>, GmbH, Germany) twin drum electronic friabilator programmed to revolve for 4 min. at 25 rpm was used for the friability test. Ten tablets randomly selected were dedusted, collectively weighed and tested. The percentage loss in weight for each batch was calculated from Equation 7 [26].

$$B = 100 [1 - W / W_o] \quad (7)$$

Where B = Friability or % loss in weight,  $W_o$  = initial tablet weight and W = final tablet weight.

### 3.4. Assay of Tablets

This was determined using the BP method. Twenty tablets randomly selected from each batch of tablet formulation were weighed collectively in an Adventurer<sup>®</sup> analytical balance. They were powdered together and a quantity equivalent to the average weight of twenty tablets was dispersed in 80 mL of freshly prepared 0.1 N HCl, filtered and volume made up to 100 mL to obtain a stock solution of 1mg/mL. Dilutions of the stocks were prepared and their ciprofloxacin hydrochloride content was analyzed spectrophotometrically at 278 nm using a JENWAY<sup>®</sup> 6405 UV/Vis spectrophotometer.

### 3.5. Evaluation of Drug Dissolution

The *in vitro* dissolution profiles of CH tablets were carried out using the BP 2009 Paddle method. One tablet was used in each unit of a six station dissolution apparatus (Erweka<sup>®</sup> DT 600, GmbH, Germany) containing 900 mL of the appropriate dissolution media (0.1 N HCl, SGF, or SIF). The paddles were set at  $100 \pm 1.00$  rpm. Five (5 mL) aliquots of the dissolution medium maintained at  $37 \pm 1.0^\circ\text{C}$  were withdrawn at 1 h intervals up to 8 h. Samples were analyzed spectrophotometrically using a JENWAY<sup>®</sup> 6405 UV/Vis spectrophotometer at 278 nm, 279 nm, and 280 nm in 0.1 N HCl, SGF and SIF (without enzymes) respectively. Dissolution test was carried out in two replicates. Analysis of data for each dissolution profile was done by fitting into the appropriate kinetics and release model.

### 3.6. Results and Discussion

Table 2 shows some micromeritic properties of ciprofloxacin hydrochloride granules. The batch that did not contain CP 971 (control batch) had a flow rate of  $5.90 \pm 0.19$  g/s. At 10% w/w CP 971 flow rate was  $6.76 \pm 0.18$  g/s and increased gradually to  $8.00 \pm 0.00$  g/s at 40% w/w CP 971. There was increase from bulk density to tapped density as a result of densification of granules occasioned by tapping which resulted in reduced volume of the granules. The angle of repose was highest for the control batch ( $36.37 \pm 4.74^\circ$ ) and gradually decreased as the polymer concentration increased. The Hausner's quotient values for all batches was  $> 1.25$ .

Table 2. Micromeritic properties of ciprofloxacin hydrochloride granules

Batch	Flow rate {SD $\pm$ (g/s)} *	Angle of repose {SD $\pm$ ( $^\circ$ )} *	Bulk density {SD $\pm$ (g/ml)} *	Tapped density {SD $\pm$ (g/ml)} *	Hausner's Quotient { $\pm$ SD} *	Compressibility index {SD $\pm$ (%) } *
1	$5.90 \pm 0.19$	$36.37 \pm 4.74$	$0.32 \pm 0.00$	$0.50 \pm 0.00$	$1.53 \pm 0.00$	$36.40 \pm 0.00$
2	$6.76 \pm 0.18$	$36.20 \pm 0.62$	$0.32 \pm 0.00$	$0.52 \pm 0.00$	$1.62 \pm 0.00$	$36.43 \pm 0.04$
3	$7.00 \pm 0.17$	$34.10 \pm 4.33$	$0.30 \pm 0.00$	$0.52 \pm 0.00$	$1.73 \pm 0.00$	$38.40 \pm 0.00$
4	$7.66 \pm 0.16$	$32.70 \pm 0.40$	$0.30 \pm 0.00$	$0.46 \pm 0.00$	$1.54 \pm 0.00$	$38.40 \pm 0.00$
5	$8.00 \pm 0.00$	$30.97 \pm 0.57$	$0.36 \pm 0.00$	$0.52 \pm 0.00$	$1.55 \pm 0.00$	$35.70 \pm 0.00$

\*n = 3 where n = number of sampling times and SD = standard deviation.

Table 3. *In vitro* tablet properties.

Batch	Weight variation { $\pm$ CV(mg%)} *	Hardness {SD $\pm$ (Kg/f)} **	Friability {SD $\pm$ ( %)} **
1	$512.65 \pm 3.02$	$6.80 \pm 1.05$	$0.10 \pm 0.00$
2	$554.35 \pm 2.18$	$8.25 \pm 1.05$	$0.03 \pm 0.00$
3	$691.80 \pm 1.60$	$10.70 \pm 1.32$	$0.03 \pm 0.00$
4	$649.40 \pm 1.63$	$12.55 \pm 1.43$	$0.01 \pm 0.00$
5	$695.85 \pm 1.32$	$12.75 \pm 0.75$	$0.00 \pm 0.00$

\*n = 20, \*\*n = 10 where \*n and \*\*n = number of samples

The Carr's index (Compressibility index) ranged from 36.40 to  $38.40 \pm 0.00$ . The angle of repose, Hausner's quotient and Carr's index were relatively high and is

indicative of granules that would not flow well [27]. Such granules would require induced die feeders to ensure uniform flow of granules from the hopper to the die cavity. In the absence of a flow aid, these granules may not produce tablets of uniform size and weight in actual tableting operations involving machine speed and vibrations.

The *in vitro* tablet properties are shown in Table 3. The weight variations ranged from 1.60 to 3.02%. They are adequate in terms weight variations [24]. The crushing strength values ranged from  $6.80 \pm 1.05$  to  $12.75 \pm 0.75$  Kg/f. The crushing strength of the tablets increased with increase in the concentration of the polymer and were above the minimum value of 4 Kg/f [28] Increase in polymer concentration is known to increase bonding

capabilities of granules [29] resulting in tablets with good mechanical properties. Friability values were  $< 1\%$  for all tablet batches. Friability is a measure of the abrasive resistance and values of  $\leq 1\%$  are considered strong enough to withstand objectionable handling and transportation stresses in uncoated tablets [30]. The friability values decreased as the polymer concentration increased.

### 3.7. Assay of Ciprofloxacin Hydrochloride Tablets

Ciprofloxacin hydrochloride tablets at 0%, 10%, 20%, 30%, and 40% w/w of CP 971 had content of active

ingredients as  $94.22 \pm 0.33\%$ ,  $88.96 \pm 0.25\%$ ,  $97.45 \pm 0.18\%$ ,  $91.83 \pm 0.33\%$  and  $95.68 \pm 0.14\%$  respectively. All batches except at 10% w/w passed uniformity of content test for ciprofloxacin hydrochloride tablets as stipulated by the United States Pharmacopoeia, USP [14].

## 4. Drug Release Profiles

The release profiles of ciprofloxacin hydrochloride in 0.1 N HCl are shown in Figure 1.

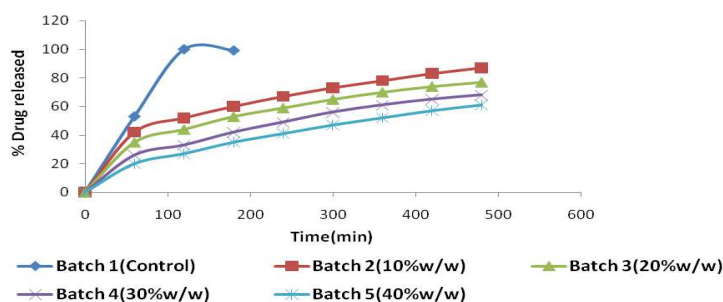


Fig 1. Dissolution profile of Ciprofloxacin hydrochloride tablets in 0.1 N HCl

The control batch as would be expected exhibited the fastest release. All the batches containing CP 971 exhibited a burst release within the first 60 min (1 h) of hydration. More than 50% of the drug content in all the batches were released within the 480 min (8 h) release period and the amount of drug released decreased as the concentration of CP 971 increased. This is evidenced from the time taken for 50% of the drug to be released ( $t_{50}$ ) which were 58, 110, 240, 250, 320 for the control batch, 10%, 20%, 30%, and 40% w/w CP971 respectively in 0.1 N HCl (Table 4). Drug release was gradual after 60 min (1 h) and this is consistent with sustained release preparations. In SGF (pH 1.2) and SIF (pH 7.2), an initial fast release (burst release) also occurred within the first 60 min after which a gradual release of the drug followed (Fig.2). This can be attributed to the gel formed by the matrix after hydration which became a limiting step to the entry of dissolution medium into the tablet core and the subsequent elution of the active drug through the gel formed [31].

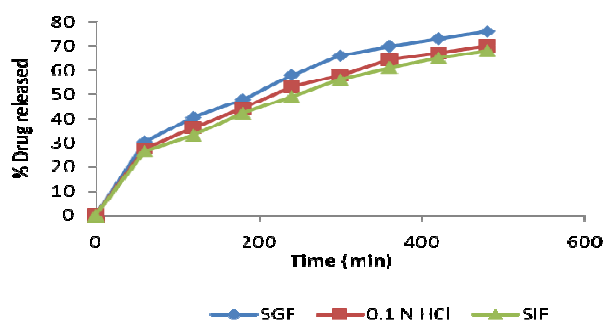


Fig.2. Dissolution profile of Ciprofloxacin hydrochloride tablet at 20% w/w CP 971 in 0.1 N HCl, SGF and SIF

There was faster release of the ciprofloxacin in SGF and 0.1 N HCl than SIF. Ciprofloxacin hydrochloride has high solubility at pH values below 5 and above 10 and has been reported to be highly absorbed in the upper parts of the stomach up to the jejunum [31, 32]. The high release in SGF and 0.1 N HCl could have been enhanced by CP 971. Carbopols are known to exhibit maximum viscosity at pH 6 – 10 while its viscosity is considerably reduced at pH below 3 or above 12 [33, 34]. Furthermore, CH is weakly acidic and is unionized in acidic medium of 0.1 N HCl and SGF. The charge density on the tablets which is dependent on the pH of the dissolution medium can affect drug release. In SGF, protonation causes breakage of hydrogen bonds and this leads to weaker electrostatic interactions. This would cause swelling and disentanglement of the matrix thereby enhancing higher ciprofloxacin release in SGF, while in SIF a slower release occurs as a result of stronger attractive force between phosphate ions and CP 971 [35]. In 0.1 N HCl, the maximum amount of CH ( $C_{max}$ ) released within 8 h decreased with increase in CP 971 concentration. This is expected because increase in the polymer concentration would normally lead to increased viscosity / gelation of the polymer.

Table 4.  $T_{50}$  and  $C_{max}$  of Ciprofloxacin hydrochloride tablets in 0.1 N HCl

Batch/Conc.	$T_{max}$ (minutes)	$C_{max}$ (%)
1 (control)	58.00	101.01
2 (10% w/w CP 971)	110.00	77.20
3 (20% w/w CP 971)	240.00	67.50
4 (30% w/w CP 971)	250.00	61.10
5 (40% w/w CP 971)	320.00	50.90
3 (20% w/w CP 971 in SGF)	220.00	70.80
3 (20% w/w CP 971 in SIF)	275.00	66.00

Where  $C_{max}$  = maximum % of drug released and  $T_{50}$  = time for 50% drug release.

## 5. Kinetics and Mechanism of Drug Release

Table 5 shows the kinetics and mechanism of release. Korsmeyer – Peppas model classifies mechanism of drug release as Fickian (diffusion controlled) if  $n = 0.5$ , non Fickian if  $0.5 < n < 1.0$ , Case II if  $n = 1.0$ , Super Case II if  $n > 1.0$  [36]. The kinetics of release shows that at 10, 20, 30, and 40% w/w CP 971 all batches exhibited a mixture of Zero order, First order and Higuchi square root kinetics. However, Higuchi kinetics was dominant at 10% and 20% w/w CP 971 while First order was dominant at 30% and 40% w/w in 0.1 N HCl. The release mechanism in the same medium show  $n$  values of 0.429, 0.553 and 0.582 respectively for 10, 30, and 40% w/w CP 971, indicating a non Fickian release while at 20% w/w, with  $n$  value of 0.477 the mechanism was diffusion controlled (Fickian).

In SGF and SIF the kinetics was similar to what was obtained 0.1 N HCl. The mechanism of release in SGF and SIF also followed the same pattern as in 0.1 N HCl ( $n = 0.664$  and  $0.611$ ). Thus change in pH therefore did not affect both the kinetics and mechanism of release of the ciprofloxacin hydrochloride tablets. On statistical evaluation using Graph Pad Prism version 5.04 software, it was found that there was significant release ( $p < 0.05$ ) of ciprofloxacin hydrochloride from the tablets at 60, 180, 240, 300, 360, 420 and 480 minutes while an insignificant difference in release ( $p > 0.05$ ) occurred at 120 min in all three media used. The insignificant difference in release at 120 min can be attributed to the activity of the viscous gel layer formed on the tablet periphery which may be thick, strong and very viscous at this sampling time. Drug release from hydrogels is controlled by the degree of cross linking [37].

**Table 5.** Kinetics and mechanism of release of ciprofloxacin hydrochloride tablets.

Batch	Zero order kinetic $r^2$	First order kinetic $r^2$	Higuchi square root Kinetic $r^2$	Korsmeyer - $r^2$	Peppas $n$	Model $K$
0.1 N HCl						
Batch 1(control)	0.8933	1.0000	0.8291	0.8771	0.6378	0.6072
Batch 2(10%w/w)	0.8784	0.9964	0.9994	0.9992	0.4288	0.7381
Batch 3(20%w/w)	0.9382	0.9956	0.9974	0.9978	0.4773	0.5558
Batch 4(30%w/w)	0.9382	0.9788	0.9946	0.9939	0.5528	0.3107
Batch 5 (40%w/w)	0.9483	0.9768	0.9956	0.9968	0.5821	0/1535
Batch 3(20%w/w)SGF	0.9420	0.9768	0.9932	0.9547	0.6635	0.0217
Batch 3(20%w/w)SIF	0.9467	0.9566	0.9703	0.9731	0.6112	0.2060

Where  $r^2$  = correlation coefficient,  $n$  = mechanism of drug release, and  $k$  = kinetic parameter.

## 6. Conclusion

The granules although not free flowing resulted in the production of tablets with good mechanical properties and minimal variation in weight. The dissolution profile showed that the matrix CP 971 exhibited a good control in drug release from the tablets. All batches of the tablets exhibited more than 50% drug release within the 8 h release period. The batch that contained 20% w/w of CP 971 is considered the best in terms of release behavior. Carbopol 971 is considered as a good matrix for the formulation of sustained release ciprofloxacin hydrochloride tablets especially at 20% w/w.

## References

- [1] S.I. Ofoefule and A. Chukwu, 'Use of Acrylic and Metacrylic Acid Derivatives as Sustained Release Matrices for Theophylline Hydrate Tablets', *Pharm. Chim. Boll.* 138, 1999, p. 562.
- [2] S.I. Ofoefule and C. Amanambu, 'Comparative Sustained Release Matrix Capacities of Some Polymer Matrices in Theophylline Hydrate Tablets', *J. Univ. Sci. Tech., Kumasi, Ghana*, vol.18,(2) 1998, p. 47.
- [3] S.J. Carter, In : Cooper and Gunn's Tutorial Pharmacy, Pitman Publishing Inc., Massachusetts, 1976, pp. 282 – 286.
- [4] S.S. Jambhakar and P.J. Breen, Basic Pharmacokinetics, The Pharmaceutical Press, London, 2009, pp. 87- 96.
- [5] S.I. Ofoefule, Textbook of Pharmaceutical Technology and Industrial Pharmacy, Samakin Nig. Enterprises, Lagos, 2005, p.102.
- [6] H.C. Ansel, N.G. Popovich and L.V. Allen, Pharmaceutical Dosage Forms and Drug Delivery Systems, 9 ed., Lippincott Williams and Wilkins, 2010, pp. 257 – 271.
- [7] H.C. Ansel, Introduction to Pharmaceutical Dosage Forms, 4 ed., Lea Febiger, Philadelphia, 1985, p. 170.
- [8] S. Aditya, K. Tartavati, A. Mehta, L.A. Larry and W.H. Stephen, 'Influence of Metacrylic Acid Polymers On The Release Performance of Weakly Basic Drugs From Sustained Release Hydrophilic Matrices'. *J. Pharm. Sci.* vol 93 (9), 2004, pp. 2319 - 2331.
- [9] G. Vjera, G. David and B.S.Andrews, 'Comparison of the Mucoadhesive Properties of Various Polymers', *Adv. Drug Deliv. Rev.* vol. 57, 2005, pp. 1713 - 1723.
- [10] O. Okorie, Some Physicochemical and *In Vitro* Bioadhesive Properties of Deffated Detarium Gum, Quill and Sperr, Ph.D. Thesis (unpublished). Department of Pharmaceutics and Pharmaceutical Technology, University Of Nigeria, Nsukka, Nigeria, 2004,
- [11] D.A. Alderman, A review of cellulose ethers in hydrophilic matrices for oral controlled Release dosage forms. *Int. J. Tech. Prod.Manuf.* vol.5 (3) 1984, pp. 1 - 9.

- [12] S.B. Ganesh, P.L. Safak, K.S. Kaylan and H.S. Neau, Extruded and Spherical Beads Containing Carbopol 974P To Deliver Electrolytes and Salts of Weakly Basic Drugs, *Int. J. Pharm.* 321, 2006, pp. 60 - 71.
- [13] D.A Alderman, A Review of Cellulose Ethers in Hydrophilic Matrices for Oral Controlled Release Dosage Forms, *Int. J. Tech. Prod. Manuf.* 5 (3), 1984, 1 - 9.
- [14] The United States Pharmacopoeia (USP) 32, The United States Pharmacopoeial Convention, Rockville M.D., 2009, p. 1945.
- [15] J.E.F. Reynolds, *Martindale: The Complete Drug Reference*, 37 ed., The Pharmaceutical Press, London, 1982, pp. 265 - 269.
- [16] C. Brattstron, A.S. Maimborg and G. Tyden, 'Penetration of Ciprofloxacin and Ofloxacin into Human Aliograit Pancreatic Juice', *J. Antimicrob. Chemother.* 22, 1988, pp. 213-219
- [17] F.D. Daschner, M. Westenfelder and A. Daihoff, Penetration of Ciprofloxacin into Kidney, Fat, Muscle and Skin Tissues, *Eur. J. Clin. Microbiol.* vol. 5, 1986, pp.212 - 213
- [18] B. Crump, R. Wise and J. Deut, Pharmacokinetics and Tissue Penetration of Ciprofloxacin, *Antimicrob. Agents Chemother.*, vol. 24, 1983, pp. 784 - 786.
- [19] Ciprofloxacin @ <http://home.intelcom.compharm/lennon/orpic.html> downloaded on 2nd May, 2012.
- [20] J.L. Fourcroy, B. Berner, Y. Chiang, M. Cramer, L. Rowe and N. Shore, 'Efficacy and Safety of a Novel Once- Daily Extended Release Ciprofloxacin Tablet Formulation for Treatment of Uncomplicated Urinary Tract Infection in Women', *Antimicrob. Agents Chemother.* vol.40 (10) 2005, pp. 4137 - 4143.
- [21] T.S. Allagh, G.O. Ameh and S.I. Okafor, Formulation and Evaluation of The Physicochemical Properties of *Ageratum conyzoides* (Fam.Asteraceae) Granules and Tablets, *Nig. J. Pharm Sci.*, vol.8 (2) 2009, pp. 18 - 25
- [22] J.N. Staniforth, 'Powder Flow' In: Aulton, M.E., *Pharmaceutics: The Science of Dosage Form Design*, ELBS, Churchill Livingstone, 1988, p.105
- [23] B.S. Neuman, *The Flow Properties of Powders*. Advances in Pharmaceutical Sciences, Academic Press, London, 1967, pp.181 - 188.
- [24] *British Pharmacopoeia*. The Stationary Press London, 2009, Appendix XIIB : A 467 - 468.
- [25] G.S. Banker and N.R. Anderson, *Tablets In : Theory and Practice of Industrial Pharmacy*, Lachman and Lieberman (editors), CBS Publishing House, Bombay 1991, pp.293 - 329.
- [26] N.A. Armstrong, 'Tabletting' In : Aulton M.E.(ed.) *Pharmaceutics : 'The Science of Dosage Form Design'* ELBS, Churchill Livingstone, London, 1990, p. 663
- [27] P.J. Sinko, *Martins Physical Pharmacy and Pharmaceutical Sciences*, 6 ed., Lippincott Williams and Wilkins, Philadelphia, 2011, pp.492 - 515.
- [28] S.I. Ofoefule, *A textbook of Pharmaceutical Technology and Industrial Pharmacy*, Samakin (Nig) Ent. Lagos, 2002, pp 57 - 66.
- [29] B.F. Cooper and E.A. Brecht, *J. Amer. Pharm. Ass. Ed.*, 46 : 1957, 540 - 980.
- [30] *British Pharmacopoeia*, The Stationary Press, London, 2011, Appendix XVIII G
- [31] J. Sun, S. Sakai, Y. Tauchi, Y. Deguchi, J. Chen, R. Zhang and K. Marimoto, Determination of the lipophilicity of two quinolone anti-bacterials : Ciprofloxacin and grepafloxacin in the protonation equilibrium, *Eur. Pharm. Biopharm.* Vol. 54, 2002, pp 51 - 58.
- [32] T.A. Tartaglione, A.C. Raffalovich, W.J. Poynor, A. Espinal-Inapreff and T.M. Kekerling, Pharmacokinetics and Tolerance of Ciprofloxacin After Sequential Increasing Oral Doses. *Antimicrob. Agents Chemother.* Vol. 29, 1986, pp. 62 - 66.
- [33] J.G. Cohen, In: *Analytical Profiles of Drug Substances*. Florey, K.(ed) Academic Press, New York, .1975, p. 180.
- [34] R.B. Theodore, *Liquid Dosage Forms Containing Insoluble Matter In : J.P. Sprawls (ed), 2 nd ed.*, J.B. Lippincott, Philadelphia, 1970, p.212.
- [35] R.W. Korsmeyer and N.A. Peppas, Effect of Morphology of Hydrophilic Polymer Matrices On The Diffusion and Release of water Soluble Drugs, *J. Member. Sci.* vol.9, 1981, pp. 211 - 217.
- [36] N.A. Peppas, Analysis of Fickian and non Fickian drug release from polymers, *Pharm. Acta Helv.* 60 ; 1985, pp. 110 - 111
- [37] S. Lin, J. Menig and L. Lachman, *J. Pharm. Sci.*, 57 : 1968, pp. 2142 - 2144