Available on line www.jocpr.com

Journal of Chemical and Pharmaceutical Research

ISSN No: 0975-7384
CODEN(USA): JCPRC5

J. Chem. Pharm. Res., 2011, 3(2):11-20

Use of Xanthan Gum and Ethylcellulose in Formulation of Metronidazole for Colon Delivery

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ABSTRACT

Matrix tablets were prepared using blends of xanthan gum (XG) and ethylcellulose (EC). Metronidazole was used as a model drug. The ability of the prepared matrices to retard drug release in the upper gastrointestinal tract (GIT) and to undergo enzymatic hydrolysis by the colonic bacteria was evaluated. For this, drug release studies were carried out in the presence and absence of rat cecal content. The overall rate of release of metronidazole from ethylcellulose matrices was significantly higher than from Xanthan gum matrices. These results indicate that XG has higher drug retarding ability than ethylcellulose. Formulations of the model drugs containing 40 % of XG followed zero order kinetics via anomalous or non-fickian release mechanism whereas that containing 30 % XG followed first order kinetics via fickian diffusion. Formulations containing mixture of polymers followed higuchi kinetics via fickian diffusion. Presence of XG alone or in combination retarded the initial release of drugs from the tablets due to high swelling, which made them more vulnerable to digestion by the microbial enzymes in the colon. Optimum release was observed with metronidazole formulation containing XG alone (formulations containing Xanthan gum 30% and XG 40 % respectively) and in combination (formulation containing XG 22.5%:EC 7.5 %) Significance difference was observed between drug release in dissolution medium with and without rat cecal contents for the optimum batches of metronidazole tablets ($P<0.05$).

Key Words: xanthan, Ethylcellulose, metronidazole, cecal content, matrix tablets.

INTRODUCTION

Metronidazole, the drug of choice for intestinal amoebiasis, has to be delivered to the colon for its effective action against entamoeba histolytica. Metronidazole is rapidly and completely absorbed after oral administration of conventional dosage form. Although these tablets provide

minimal amount of metronidazole for local action in the colon which is still effective in treatment of amoebiasis, undesirable systemic side effect occur upon their administration {1}

The manufacture by direct compression of matrix-type tablets using ethylcellulose (EC) as the matrix-forming polymer has been studied {2,3,5,8,9}, and the effect of various formulation and process variables on such tablets has been studied in depth {2,3,5-7,9} .

Ethylcellulose has been used as film and matrix-forming material for sustained-release dosage forms {2–8}.The drug release mechanism from directly compressed ethylcellulose tablets has been elucidated {10}

In the absence of polymer swelling ability, EC compatibility becomes a key factor in such systems, because release kinetics will depend largely on the porosity of the hydrophobic compact {11}. Although EC is considered insoluble, it can take up water {12}. This is because of its hydrogen bond capability with water due to the polarity difference between the oxygen atom and the ethyl group of the polymer {13}.

EC, like other water insoluble polymers used in Drug Delivery System, more often than not requires the incorporation of release modifiers, which creates channel through which drug leaches out, increase the wetting of the hydrophobic barriers of the matrix, or modify the barrier properties of the absorbing membrane.

When in contact with water, ethylcellulose swells and retard drug release. It displays initial surface erosion, which is responsible for the initial fast release. The release rate then decreases because external layers of the tablet become depleted and water must penetrate the deeper layers of the tablet to reach the undissolved drug.

Xanthan gum is a high molecular weight extracellular polysaccharide produced by the fermentation of the gram-negative bacterium *Xanthomonas campestris*. The primary structure of this naturally produced cellulose derivative contains a cellulose backbone (β-D-glucose residues) and a trisaccharide side chain of β-D-mannose- β -D-gluronicacid –**α**-D-mannose attached with alternate glucose residues of the main chain. The terminal D-mannose residues may carry a pyruvate function, the distribution of which is dependent on the bacterial strain and the fermentation conditions. The non-terminal D- mannose unit in the side chain contains an acetyl function. The anionic character of this polymer is due to the presence of both glucuronicacid and pyruvic acid groups in the side chain {14}.

In one of the trials, Xanthan gum showed a higher ability to retard the drug release than synthetic Hydroxypropylmethylcellulose. Xanthan gum and hydroxypropylmethylcellulose were used as hydrophilic matrixing agents for preparing modified release tablets of diltiazem HCI. Hydroxypropylmethylcellulose and Xanthan gum exhibited significant effect on drug release from the tablets prepared by direct compression technique. It was concluded that by using a suitable blend of hydroxypropylmethylcellulose and Xanthan gum desired modified drug release could be achieved {15}.

In another study, the retention and releasing properties of Xanthan gum,desire release profile was achieved in delivery of theophylline {16}.. The matrices made alone with Xanthan gum (X) showed higher drug retention at all concentrations, compared with a galactomannan (G) matrices

used as comparing standard. The matrices prepared by combination of both gums however were able to produce near-zero-order drug release. The XG (conc 8%) tablets provided the required release rate (about 90% at the end of 8 h), with zero-order release kinetics.

The objective of this work was to develop matrix tablets of metronidazole for colon targeted delivery, using natural gum(X G) as cost-effective, nontoxic, easily available, and suitable hydrophilic matrix systems, and ethylcellulose.

EXPERIMENTAL SECTION

Materials used include:Xanthan gum (Jinshi Pharm. Ltd, China), ethylcellulose (GOMBH, Germany), lactose, sodium hydroxide, Hydrochloric acid,metronidazole (BDH, England), absolute ethanol, conc. Hydrochloric acid (BDH, England), monobasic potassium phosphate (Sigma Aldrich, U. S.A).

Preparation of metronidazole matrix powder mixtures

Sufficient quantities of materials were weighed to make provision for up to 440 tablets for 11 batches (40 tablets per batch at a target weight of 500mg each).The individual polymers (Xanthan gum and Ethylcellulose) were included in the formulation in various proportions (10% to 40 % w/w) while their combinations were employed in the ratio of 30%w/w. The drug was geometrically blended with sufficient quantity of lactose and various the polymers as stated in the formulae in table 1, using pestle and mortar. Mixing was maintained for 10 minutes and the powder mixtures stored in well-closed specimen bottles. Compression was achieved at a pressure setting of 12.5 N in a manesty single punch tableting machine fitted with flat-faced punches and compressed to a target weight of 500 ± 10 mg. Each drug compacts were stored in airtight specimen bottles before further evaluations.

Absolute drug content.

Spectrophotometric method was used [17]. Ten tablets of each batch were crushed in a mortar and an amount equivalent to the mean weight of the tablet was placed in a 100ml volumetric flask. This was dissolved in 0.1 N HCl, made up to 100ml and filtered. 5ml of this filtrate was then diluted appropriately and the absorbance determined spectrophotometrically at 250nm for metronidazole. This was carried out in triplicate.

Evaluation of tablet properties

Tablet dimensions

The thickness and diameter of compacts produced from metronidazole was determined using vernier calipers. The mean and standard deviation of five randomly selected tablets from each batch was calculated.

Uniformity of weight

The weight of ten randomly selected tablets of metronidazole was determined individually and collectively. The mean weight and standard deviation were computed.

Crushing strength (hardness test)

The Monsanto hardness tester was used to determine the force required for crushing ten randomly selected tablets from metronidazole batches. Results are reported in kgf mean of individual measurements with standard deviations calculated.

Friability

Five tablets selected randomly from metronidazole batches were dusted and weighed using analytical balance. These were introduced into a friabilator (Roche) and set to rotate at 25±1 r. p. m for 4 minutes after which the tablets were dedusted re-weighed and the percentage friability calculated using equation (17)

Percentage Friability=Weight loss/Initial Weight x 100 % …….. Eqn (17)

Dissolution studies

Preparation of dissolution media

Simulated intestinal fluid (SIF)

6.8g of monobasic potassium phosphate was dissolved in 250ml of distilled water and the resultant solution mixed with 190 ml of 0.2N Sodium hydroxide. The pH was adjusted to 7.4 with 0.2NSodium hydroxide using pH meter, and the final volume made up to 1000ml with sufficient amount of distilled water.

Simulated gastric fluid (SGF)

2.0g of Sodium Chloride was thoroughly mixed with 7.0ml of Hydrochloric acid and the volume made up to 1000ml with distilled water.

Preparation of rat cecal content medium

Wistar rat weighing 150-200g and maintained on a normal diet (soaked gram) were used. Forty-five minutes before the commencement of drug release studies, seven rats were killed by spinal traction. The abdomen were opened, the cecal were traced, ligated at both the ends, dissected, and immediately transferred into pH 7.4 buffer previously bubbled with nitrogen. The cecal bags were opened, their contents were individually weighed, pooled, and suspended in the buffer continuously bubbled with carbon dioxide. These were finally added to the dissolution media to give a final cecal dilution of 4%w/v, respectively. All the above procedures were carried out under carbon dioxide in order to maintain anaerobic conditions.

In-vitro drug release studies

The ability of matrix tablets of metronidazole to remain intact in the physiological environment of stomach and small intestine was assessed by mimicking mouth to colon transit. Drug release studies were carried out using USP XXIII dissolution apparatus (Apparatus 1, 100 rpm, 37.5^{o}C) in 500 ml 0.1 N HCI for 2 h as the average gastric emptying time is 2h.. The dissolution medium was replaced with 500 mL of pH 7.4 phosphate buffer saline (PBS) and the dissolution was continued for 18 h. A 5 ml of the sample was taken at the specified time period (4 h, 5 h, 8 h, 10 h, 12 h, 16 h and 24 h) and analyzed at 250nm for metronidazole using a Shimadu UV Spectrophotometer (Shimadu, Japan with . A 5 ml volume of filtered, fresh dissolution medium was added to make the volume after each sample withdrawal [{18}].

The susceptibility of the matrix tablets to the enzymatic action of colonic bacteria was assessed by continuing the drug release studies in simulated colonic fluids prepared using rat cecal content as described by Sinha et al. [{19}].

Table 1: Metronidazole tablets composition

	XG10%	**XG20%**	**XG30%**	**XG40%**
Drug (g)	8.00	8.00	8.00	8.00
GG(g)	0.80	1.60	2.40	3.20
Lactose (g)	11.20	10.40	9.60	8.80
	EC10%	**EC20%**	**EC30%**	**EC40%**
Drug (g)	8.00	8.00	8.00	8.00
EC(g)	0.80	1.60	2.40	3.20
Lactose (g)	11.20	10.40	9.60	8.80
	XG15%EC15%	**XG7.5%EC22.5%**	**XG22.5%EC7.5%**	
Drug (g)	8.00	8.00	8.00	
GG(g)	1.20	0.60	1.80	
EC(g)	1.20	1.80	0.60	
Lactose (g)	9.60	9.60	9.60	

Table 2: Tablet properties of Metronidazole

Batch	**Weight (mg),n=10**	**Thickness (mm),n=5**	**Hardness (Kgf),n=10**	**Friability (%), n=5**	**Drug content(%), n=4**	**Diameter (mm)n =5**
XG10%	497±6.25	4.92±0.04	4.7±0.54	0.93±0.23	98.80±0.77	12.65±0.01
XG20%	499±4.71	4.89±0.03	5.05±0.44	0.40±0.006	97.35±0.47	12.66±0.02
XG30%	500.8±4.47	4.93±0.04	5.3±0.48	0.40±0.007	100.00±0.85	12.68±0.01
XG40%	497.1±5.76	4.92±0.07	5.5±0.41	0.40±0.006	99±.0.46	12.69±0.02
EC10%	497.7±5.25	4.83±0.06	4.7±0.54	1.03±0.17	98.13±2.95	12.65±0.02
EC20%	496.6±4.27	4.84±0.10	4.75±0.42	0.80±0.33	99.7±1.24	12.66±0.01
EC30%	498.8±4.66	4.94±0.05	4.65±0.47	0.50±0.20	98.5±2.64	12.64±0.02
EC40%	497.6±0.46	4.98±0.02	4.75±0.54	0.81±0.006	99.0±1.40	12.67±0.02
XG15%:EC15%	497.3±5.07	4.93±0.07	4.5±0.41	0.80±0.005	98±0.63	12.67±0.01
XG7.5%:EC22.5%	497.5±6.28	4.90±0.07	4.4±0.47	0.81±0.005	100±0.85	12.67±0.02
XG22.5%:EC7.5%	495.2±5.12	4.97±0.02	4.6±0.39	0.48±0.18	99±1.47	12.68±0.02

Table 3: Some release parameter of metronidazole tablets

Batch	T_{50} (hrs)	T_{70} (hrs)	C_{max} (%)
XG10%	0.90	3.00	82.00
XG20%	1.35	3.00	81.50
XG30%	12.00	-	57.20
XG40%	16.00	-	50.00
EC10%	0.75	1.20	92.60
EC20%	0.77	1.25	90.00
EC30%	0.79	1.35	91.60
EC40%	0.79	1.75	93.00
XG15%:EC15%	0.95	1.6	90.00
XG7.5%:EC22.5%	0.82	1.38	94.70
XG22.5%:EC7.5%	4.00	11.50	77.00

Determination of the release kinetics, mechanism of drug release and statistical data analysis

To investigate the drug release kinetics, data obtained from in vitro dissolution studies were plotted into various kinetic models [20 – 22]

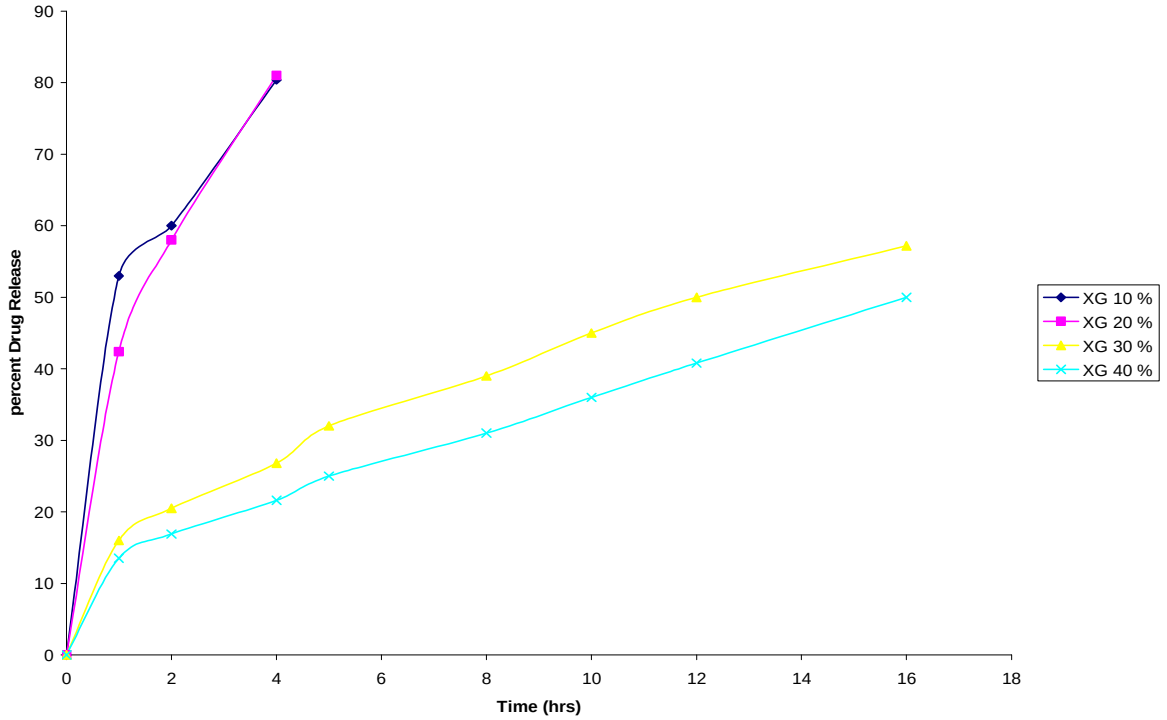

Figure 1: Release profiles for metronidazole batches containing 10% - 40% Xanthan gum

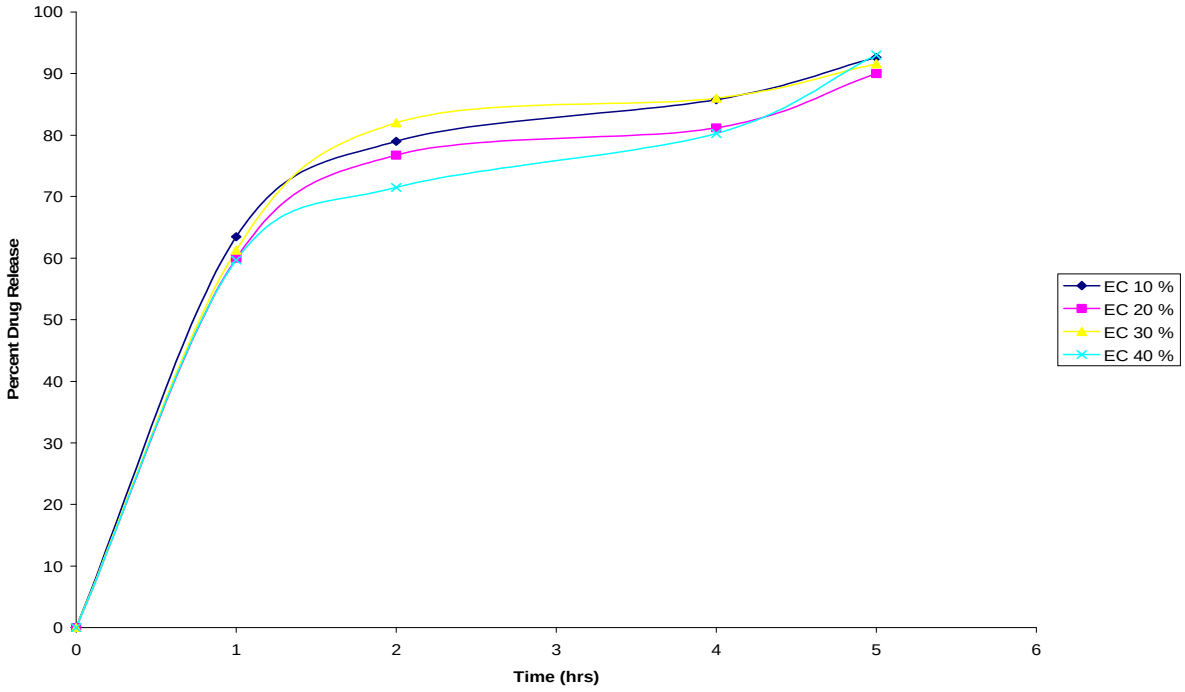

Figure 2: Release profiles for metronidazole batches containing 10% - 40% Ethylcellulose

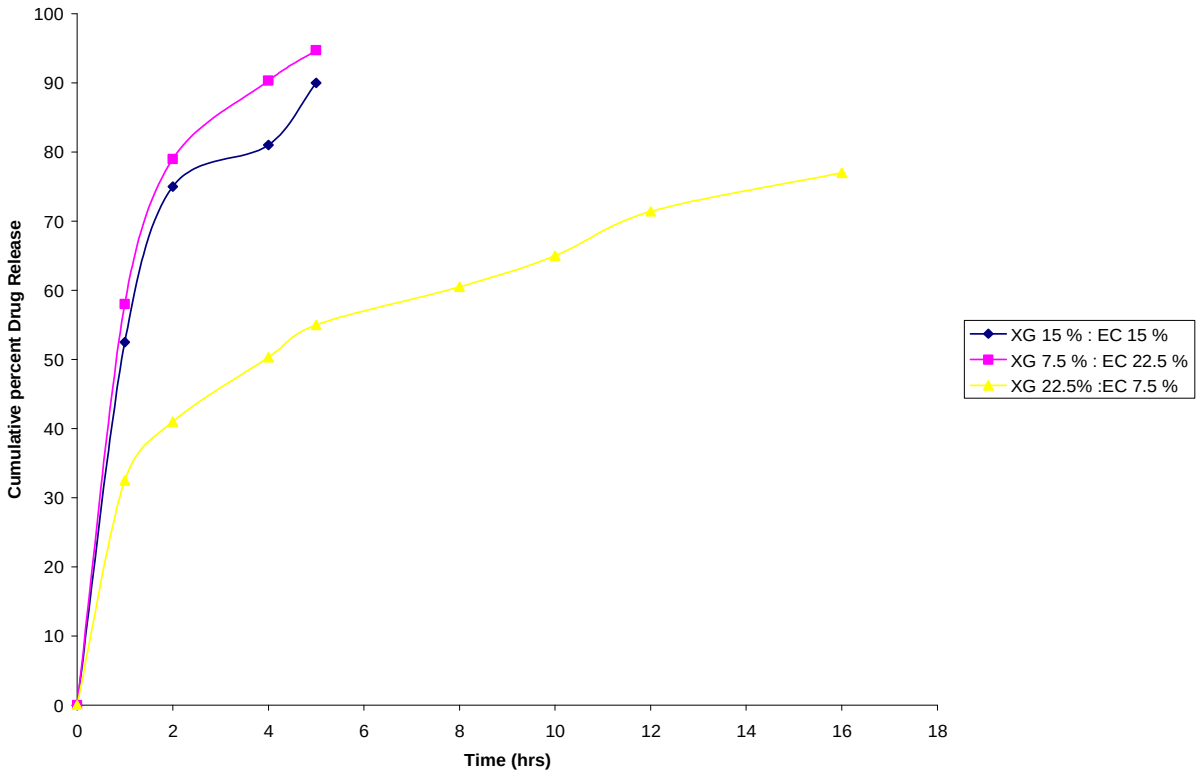

Figure 3: Release profile of Metronidazole Formulations containing Xanthan Gum and Ethylcellulose

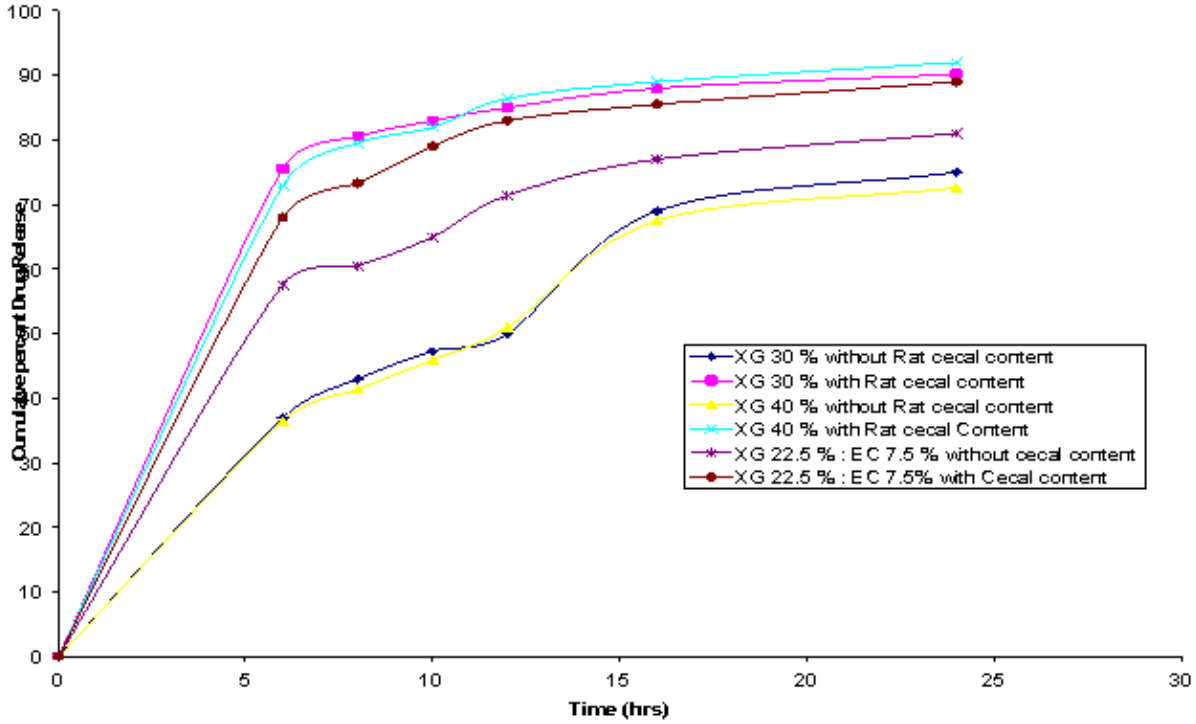

Figure 4: Release profile of Metronidazole in dissolution study with and without cecal content.

Table 4: kinetics and Mechanism of release for metronidazole matrix tablets

Batch	Zero - order	First – order	Higuchi	Korsmeyer	N
XG 30%	0.9827	0.9970	0.9946	0.9915	0.45
XG 40%	0.9982	0.9945	0.9786	0.9776	0.47
XG 22.5%: EC7.5%	0.9388	0.9868	0.9902	0.9961	0.31

The mechanism of drug release was determined by plotting the data for the first 60% drug release in Korsemeyer et al equation [23]

To observe if there was significant difference between drug release with and without rat cecal content medium, data was plotted into Microsoft excel software and student t test performed

RESULTS AND DISCUSSION

Tablet properties of the matrices

Table 2 shows some of the properties of metronidazole matrix tablets. All of them were of good mechanical strength and acceptable friability values. Weight of tablets fall between 495 mg and 500 mg. absolute drug content was within 97% and 99%. These values are within the USP specification for tablets {24}

The hardness and low friability values indicate that the tablets can withstand the stress associated with transportation and dispensing processes.

Dissolution profiles of tablets

The time taken for 50% and 70% of the drug to be released ($T_{50\%}$ and $T_{70\%}$) respectively and the maximum cumulative amount of drug release (C_{max}) were used to characterize the release profiles of the matrix tablets (Tables 3).All the batches except,,XG 30%, XG 40%, XG 22.5%:EC 7.5% were not able to retard the release of the drug beyond 5 hours. Metronidazole batches prepared with ethylcellulose (EC) (10%, 20%, 30% and 40 %) achieved more than 90% drug release within 5 hours. The C_{max} values were comparatively higher than for those batches containing xanthan gum 10 – 40 % ($P < 0.05$). This is because ethylcellulose swells when in contact with dissolution medium and displays initial surface erosion, which is responsible for the initial fast release of the matrix . With other polymers, retardation of drug release increases with increase in polymer concentration.

Xanthan gum had a higher retardation capacity than ethylcellulose ($P < 0.05$).

Drug release kinetics and mechanism of release.

During the test, all the formulations swelled and the outer layer of most of the tablets appeared to be hydrated after being placed in the dissolution medium, with progressive increase in the size of these hydrated matrices, specially visualized for xanthan gum matrices. This was followed by gradual loss of integrity, resulting from hydrodynamic stress induced by the dissolution apparatus.

For matrices containing Xanthan gum, there was an initial burst of xanthan gum erosion from the matrices during the acidic pH, thereafter the erosion slowed considerably.

In order to investigate the release kinetics the dissolution data were fitted into different kinetic models namely zero order, first order and Higuchi models.

Ideally, a sustained release tablet should release the required quantity a drug with predetermined kinetics in order to maintain an effective drug plasma concentration {25}. To achieve this, the tablet should be formulated so that it releases the drug in a predetermined and reproducible manner. Table 4 shows the release Kinetics.

From the results in table 4 metronidazole formulation with Xanthan gum 30% follow First order kinetics with highest linearity(r^2 = 0.9970) via fickian diffusion (n = 0.45). First Order Model describes release from systems where drug release rate is concentration dependent. However the drug release was also found to be close to Higuchi Kinetics (r^2 =0.9946)which describes the release of drugs from an insoluble matrix as a square root of time dependent process based on Fickian diffusion .
However increasing the concentration of gum to 40 % shifts the drug release kinetics to zero kinetics (r^2 = 0.9982 {20} .The Zero order rate describes system where rate of drug release is independent of concentration. The release mechanism unlike XG 30%, follows non-fickian (anomalous) 0.45<n>0.89 [{23}]. The formulation containing 40 % xanthan releases the drug by diffusion in the hydrated matrix and polymer relaxation.

XG 22.5% : EC 7.5 % release the drug by higuchi Kinetics based on fickian diffusion (r^2 =0.9902, n = 0.3)

Drug release studies with and without rat cecal content
The susceptibility of xanthan gum and ethylcellulose, to the enzymatic action of colonic bacteria, was assessed by continuing the drug release studies in rat cecal content medium for 24 h after 5 h of testing in simulated gastric and intestinal fluids.

figures 4 show that the presence of rat cecal content in the dissolution medium resulted in a significant increase in drug release, when compared with control ($P < 0.05$). The cumulative percent release from drug released after 24 h from XG 30 % and XG 40 % increased from 65 % and 60.5 % in the absence of rat cecal contents (control) to 93.4 % and 95 % in the presence of cecal matter (figure 4), respectively, indicating that polysaccharide metabolizing xanthan gum is present in the rat cecal contents. Metronidazole matrix tablets, XG 22.5 %: EC 7.5 % release 81 % of the drug in control while in the presence of rat cecal contents, the cumulative percent drug release was 89%.

The polymers used in the matrices were susceptible to the enzymatic action of colonic bacteria.

CONCLUSION

In conclusion, matrix tablets containing 10 % to 40 % coarse ethylcellulose not suitable for colon targeting as they release most of the drug within 2 to 5 h. The same applies to matrix tablets of the model drug containing 10 to 20 %. Xanthan gum.

However, matrix tablets containing 30 % and 40 % xanthan gum control release of the drug for up to 18 h, and when subjected to *in vitro* studies in the presence of rat cecal content, completely degraded the polymer to release most of the drug. Formulations containing Xanthan gum

22.5%:Ethylcellulose7.5%) also had good retarding ability and were susceptible to colonic bacteria , releasing the remaining part of the drug in the colon.

Acknowledgement
The authors are grateful to the technical staff of Department of pharmaceutical Technology and Raw materials Development, National Institute for pharmaceutical Research and Development (N I P R D), Abuja. The members of Staff of God's Glory Computers Institute, Uyo are also acknowledged.

REFERENCES

[1] martindale. The Complete Drug Reference, 34th Ed., Sean C. Sweetman (Ed), The Pharmaceutical press. **2005**.
[2] Shaikh NA, Abidi SE, Block LH. *Drugs Dev Ind Pharm*. **1987**; 13:1345-1369.
[3] Shaikh NA, Abidi SE, Block LH. *Drug Dev Ind Pharm*. **1987**;13:2495-2518.
[4] Porter SC. *Drug Dev Ind. Pharm*. **1989**;15:1495-1521.
[5] Upadrashta SM, Katikaneni PR, Hileman GA, Keshary PR. *Drug Dev Ind. Pharm*. **1993**;19:449-460.
[6] Katikaneni PR, Upadrashta SM, Neau SH, Mitra AK. *Int J Pharm*. **1995**;123:119-125.
[7] Katikaneni PR, Upadrashta SM, Rowlings CE, Neau SH, Hileman GA. *Int J Pharm*. **1995**;117:13-21.
[8] Pather SI, Russell I, Syce JA, Neau SH. *Int J Pharm*. **1998**;164:1-10
[9] Pollock DK, Sheskey PJ. *Pharm Technol*. **1996**;20:120-130.
[10] Neau SH, Howard MA, Claudius JS, Howard DR. *Int J Pharm*. **1999**;179:97-105.
[11] Durig T, Harcum WW, Lusvardi KM, Skinner GW. Compaction characteristics of high ethoxyl, low viscosity ethylcellulose. Pharmaceutical technology report Wilmington DE. 024.**2003**
[12] Joshi HN, Wilson TD. *J Pharm Sci*. **1993**: 82; 1033-1038.
[13] Agrawal AM, Manek RV, Kolling WM, Neau SH. *AAPS PharmSciTech*.**2003**;4:E60
[14] Bhardwaj TR, Kanwar M, Lal R, Gupta A, *Drug Develop Ind Pharm* **2000**; 26:1035-38.
[15] Gohel MC, Amin AF, Petal KV, Panchal MK. *Boll Chim Farm* **2002**; 141:21-8.
[16] Vendruscolo CW, Andreazza IF, Ganter JL, Ferrero C, *Int J Pharm* **2005**; 296: 1 – 11
[17] Olaniyi A. Principles of drug quality assurance and pharmaceutical Analysis. Masoro, Ibadan, Nigeria **2000**
[18] United States Pharmacopoeial Convention (USP) **1999**, USP 24- NF – 19, Rockville, USA
[19] Sinha, V.R., Mittal,B.R., Bhutani, K. K., Rachna Kumari. *Int J.Pharm*,**2004**;269:101 -108
[20] Hadjiioannou TP, Christian GD, Koupparis MA and Macheras PEb. Quantitative Calculations in Pharmaceutical Practice and Research, VCH Publishers Inc. New York, **1993**. 345-348.
[21] Bourne DWA. Pharmacokinetics *In:* Banker GS, Rhodes CT, Modern Pharmaceutics 4th ed, Marcel Dekker Inc. New York, **2002**. pp. 67-92.
[22] Higuchi T, *J. Pharm. Sci.*, **1963**; 52: 1145-1149.
[23] Korsmeryer RW, Gurny R, Doelker E, Buri P and Peppas NA. *Int. J. Pharm* .**1983**;15: 25-35.
[24] The United States pharmacopoeia, XXIII, 1995 and the National Formulary (18th ed). The USP Convention Inc., Rockville, MD, **1981**, PP, 1790-1791, 1791-1794.
[25] 25 Merchant, H. A ; Shoiab H . M ; Tazeen J ; and Yousuf R. I. *AAPS Pharm. SciTech* **2006** :7 (3) article 78.