American Journal of Advanced Drug Delivery

www.ajadd.co.uk

Original Article

Development and Optimization of Paracetamol Immediate Release and Aceclofenac Controlled Release Bilayer Tablets

M. Sudhakar, Vinay Umesh Rao, Nagraju Samalla*

Malla Reddy College of Pharmacy, Maisammaguda, Post Dhulapally, Secunderabad 500014, India

Date of Receipt- 30/05/2013
Date of Revision- 04/06/2013
Date of Acceptance- 08/06/2013

Address for Correspondence
Malla Reddy College of Pharmacy, Maisammaguda, Post Dhulapally, Secunderabad 500014, India

E-mail:
vinayrao68@gmail.com

ABSTRACT

The objective of the study was to formulate bilayer tablets consisting of Paracetamol (PM) and Aceclofenac (AC). 100% of the dose of PM and 50% of the dose of AC was formulated as a fast disintegrating and rapidly dissolving layer which was overlaid with a controlled release layer containing the balance 50% of the dose of AC. The IR-layer was designed in a way to achieve complete release of the dose within a 30 min and SR-layer was designed to deliver the dose at a constant rate of 4 to 5 mg % /hour. To optimize the composition of the IR layer the level of Croscarmellose sodium (CCS) in the formulation was optimized. For optimizing the SR layer, HPMC K4M, K15M and K100M at different levels were evaluated and the type and concentration of HPMC was finalized. These results indicated that release of the drug from the tablet was influenced by content of super disintegrant and polymer grade and concentration. Formulation containing 1.5 % w/w of CCS in IR-layer and 6 % w/w of HPMC K100M in SR-layer showed desired drug release. Thus bilayer tablets could be a potential dosage form for delivering Paracetamol as immediate release and Aceclofenac in a controlled release manner.

Keywords: Paracetamol (PM), Aceclofenac (AC), Croscarmellose sodium (CCS), HPMC K4M, K15 M, K100 M, bilayer tablets, IR-layer, SR-layer.

INTRODUCTION

Paracetamol (PM) is one of the most popular over-the-counter drugs. It has analgesic and antipyretic properties with weak anti-inflammatory activity and it is used in the symptomatic management of moderate pain and fever. When taken at recommended doses it has an excellent safety profile[1-3]. Paracetamol is often prescribed with Aceclofenac (AC) for greater patient acceptability, increased

potency, multiple activity, fewer side effects and quick relief[4].

AC, [(2-{2,6-dichlorophenyl)amino} phenylacetooxyacetic acid] is a new generation non-steroidal anti-inflammatory drug used in the symptomatic treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. The biological half life of Aceclofenac is 3-4 hours and hence dosing frequency of more than one dose per day is required to maintain its therapeutic effect throughout the day. Administration of conventional Aceclofenac tablets 2-3 times a day will produce side effects such as nausea, vomiting, diarrhea, dizziness, rash, gastric bleeding and gastric ulceration[5-7].

The absorption of AC following oral administration is almost complete. However, it has a very high first pass metabolism and plasma protein binding leading to low oral bioavailability[8]. Hence, in developing a sustained release dosage form for AC, it is important to have a fast release fraction which would allow for sufficient concentration of the drug in the blood stream to produce the anti inflammatory effect and a slow release fraction which would maintain that effect. Hence, the aim of the current work is to develop a bilayer dosage form which would release 50% of the drug within 30 minutes and the balance 50% would then release over a period of 8 to 10 hours.. The target product profile is given in Table 1.

Various concentrations of CCS were used to optimize the IR- layer and different grads of HPMC (K100M, K4M, and K15M) were used to optimize the SR-layer.

MATERIALS AND METHODS

Chemicals and Reagents

Paracetamol USP (PM), Aceclofenac BP (AC), (EMCO Industries, Hyderabad), Croscarmellose sodium (Ac-di-sol, FMC), HPMC K4M, HPMC K15M and HPMC K100M (Methocel, Dow Chemicals), Poly vinyl pyrolidone (PVP K-30, Ashland Specialty Chemicals, US), Microcrystalline Cellulose USP (Avicel PH 102, FMC), Magnesium stearate USP (Ferro), were used. All other chemicals and reagents used were of Analytical Reagent grade from Merck. Purified water USP was used where ever required.

Experimental

Bilayer tablets of 1000 mg weight were prepared by the wet granulation (IR-layer) and direct compression (SR-layer) methods. The composition is given in Table 2.

For IR-layer: Wet granulation: All the ingredients were passed through 20 # screens prior to mixing. PM, AC, Avicel PH 102, CCS were dry mixed in a mortar and granulated by using 10% w/v solution of PVP. When enough cohesiveness was obtained, the granules were dried at 60°C for 2 hours in a tray dryer and there after kept in desiccators for 24 hours at room temperature. The dried granules were sized thru 30# screen and blended with Magnesium stearate prior to compression. (Layer 1)

For SR-layer: Direct compression: All the materials were passed through 20 # screens prior to mixing. AC, Avicel PH102, PVP, and HPMC were bag blended for 15 minutes. Magnesium stearate was added and further blending was done for 5 minutes prior to compression (Layer 2).

The compression was performed manually on RIMEK MINIPRESS –II MT compression machine (Karnavati Engineering, Ahmedabad, India) fitted with 12.5 mm circular die/punch set. The die cavity was manually adjusted to fill 1 gram of total granules. 500 mg of the Layer 1 was manually loaded into the die cavity and pre compressed at low compression force. Weighed quantity of Layer 2 was overlaid on this pre-compressed Layer 1 and the whole tablet was then compressed at a compression

force set to give final tablets of 80 to 120N hardness. The physical properties and assay values for all batches are given in Table 3. The in vitro dissolution profile was conducted in pH 7.4 buffer using USP Type II apparatus [9]. Samples were withdrawn at 10,20,30,60,120,240,360,480,600,720minutes interval and analyzed for % drug dissolved using UV spectrophotometric method. Aliquot of the samples were suitably diluted and the concentration of PM and AC was determined spectrophotometrically by using simultaneous equations (1 and 2**)**:

$A_1=ax_1c_x+ay_1c_y$ **(1)**
$A_2=ax_2c_x+ay_2c_y$ **(2)**

Where
A1 = absorbance of sample at 245 nm,
ax1 = molar absorptivity of PM at 245 nm
ay1 = molar absorptivity of PM at 274 nm
A2 = absorbance of sample at 275 nm
ax2 = molar absorptivity of AC at 245 nm
ay2 = molar absorptivity of AC at 275 nm
Cx = concentration of PM
Cy = concentration of AC

RESULTS & DISCUSSION

The first three trials (F1 to F3) were taken in order to optimize the disintegration time (DT) of the Layer 1 and the dissolution of PM and AC from the immediate release fraction. It was observed than 1.5% of CCS (F2) is required in order to get below 3 minutes DT of Layer 1. Hence this concentration was finalized for all subsequent trials. The formulation containing 1.5% Ac-di-sol (F2) in IR-layer released >85% (Q) of the drug within 20 minutes (Fig 1). Hence this composition of the immediate release layer was finalized for all other formulations. The drug release for PM and AC for F4 to F9 at 30 minutes is shown in Fig 2. Thus the release for PM and AC seems to be independent on the composition of the SR layer and is solely driven by the disintegration of the Layer 1.

The target dissolution profile for AC Sustained release product is such that > 50% of the drug is targeted to release as an immediate release fraction thereby inducing the symptomatic management of pain and inflammation[5]. The balance AC release occurs at a rate which gives nearly complete drug release over 12 hours[9].

The in vitro dissolution profiles for AC from formulations F4 to F9 are shown in Fig 3. The comparative in vitro dissolution values for 1hour (D1), 4 hours (D4) and 8 hours (D8) against the targeted values is shown in Fig 4. This indicates that only in case of F9, dissolution profile is matching to the Target profile. All other formulations are significantly faster than the target profile.

The release rate kinetics for F9 was calculated and was shown to follow the Korsmeyer- Pappas model for defining the kinetics of the drug release (Fig 5). This indicates that the mechanism of drug release from the Bilayer matrix system is primarily by combination of diffusion and swelling[10]. Then total polymer concentration required for optimum drug release is 6% and it is achieved by using HPMC K100M.

CONCLUSION

The present study was undertaken with an aim to design oral tablet of PM immediate and AC controlled release. Results indicated that release of the drug from the tablet was influenced by content of superdisintegrant and polymer matrices. Formulation containing 1.5%w/w CCS in IR-layer and 6% w/w HPMC K100M in SR-layer showed desired drug release. So, bilayer tablets could be a potential dosage form for delivering PM and AC. Success of the *In vitro* drug release studies recommends the product for further in vivo studies.

REFERENCES

1. Scottish Intercollegiate Guidelines Network (SIGN) (2008). "6.1 and 7.1.1". Guideline 106: Control of pain in adults with cancer. Scotland: National Health Service (NHS). ISBN 978 1 905813 38 4
2. Moller, P.; Sindet-Pedersen, S.; Petersen, C.; Juhl, G.; Dillenschneider, A.; Skoglund, L. (2005). "Onset of acetaminophen analgesia: comparison of oral and intravenous routes after third molar surgery". British journal of anaesthesia 94 (5): 642–648
3. Acetaminophen Drugs.com
4. Seyda AKKUS ARSLAN*°, Figen TIRNAKSIZ** Aceclofenac A Nonsteroidal Antiinflammatory Drug: FABAD J. Pharm. Sci., 35, 105-118, 2010
5. S.M. Ashraful Islam*, Hosna Banu and Mostafa Reaj Sahariar, Bilayer tablets of paracetamol and aceclofenac: formulation and evaluation.IJPT; 27-12-2011 ISSN: 0975-766X
6. United States Pharmacopoeia, CD, 30, NF 25, The USP Convention; Rockville 2007.
7. British Pharmacopoeia CD version 2; The British Pharmacopoeia Commission; London; 2009
8. Gonzalez E, Cruz C, Nicolas R, Egido J, Herrero-Beaumont G (1994) Long-term effects of nonsteroidal antiinflammatory drugs on the production of cytokines and other inflammatory mediators by blood cells of patients with osteoarthritis. Agents Actions 41: 171-178.
9. Abul Kalam Lutful Kabir1, Shimul Halder1, Madhabi Lata Shuma and Abu Shara Shamsur Rouf1,Formulation Development and *in vitro* Evaluation of Drug Release Kinetics from Sustained Release Aceclofenac Matrix Tablets using Hydroxypropyl Methyl Cellulose, Dhaka Univ. J. Pharm. Sci. 11(1): 37-43, 2012 (June)
10. Suvakanta Dash*, Padala Narasimha Murthy, Lilakanta Nath and Prasanta Chowdhury. “Kinetic Modeling on Drug Release from Controlled Drug Delivery Systems” Acta Poloniae Pharmaceutica-Drug Research, Vol. 67 No. 3 pp.217-223, 2010.

Table 1. Target Product Profile

S.NO	PARAMETERS	SPECIFICATIONS
1	**Description**	White uncoated bilayer tablets with immediate release Paracetamol 350mg & Aceclofenac 50 mg in one layer and sustained release Aceclofenac 50 mg in another layer.
2	**Average Weight**	1000 mg
3	**Size & Shape**	12.5 mm circular biconvex, 5-6 mm thickness
4	**Hardness**	80-120 N
5	**Disintegration time of IR layer**	Not more than 5 min
6	**Friability**	< 1%
7	**Dissolution Testing** (pH 7.4 Phosphate Buffer)	
	DISSOLUTION TEST SPECIFICATIONS FOR PM	
	TIME (Minute)	MEAN % PM DISSOLVED
	0	0
	30	Not less than 80% (Q)
	DISSOLUTION PROFILE TEST SPECIFICATIONS FOR AC	
	TIME(Hours)	MEAN % AC DISSOLVED
	0	0
	1	55-60
	2	60-75
	4	70-85
	8	>85

Table 2. Unit composition formulae (mg/tablet)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
	IR layer (Layer 1)								
Paracetamol	350	350	350	350	350	350	350	350	350
Aceclofenac	100	100	100	100	100	100	100	100	100
CCS (Ac-di-sol)	10	15	20	15	15	15	15	15	15
MCC pH102	25	20	15	20	20	20	20	20	20
PVP (30-K)	10	10	10	10	10	10	10	10	10
Mg.stearete	5	5	5	5	5	5	5	5	5
	SR layer (Layer 2)								
Aceclofenac	---	---	---	100	100	100	100	100	100
HPMC K4M	60	60	60	40	60	---	---	---	---
HPMC K15M	---	---	---	---	---	40	60	---	---
HPMC K100M	---	---	---	---	---	---	---	40	60
MCC ph102	429	429	429	349	329	349	329	349	329
PVP (30-K)	6	6	6	6	6	6	6	6	6
Mg.stearet	5	5	5	5	5	5	5	5	5

Table 3. Physical Properties and Assay of all batches of Bilayer tablets

Formulations	Thickness	Hardness	Friability	Weight (mg)	DT of LAYER 1	Assay of PM	Assay of AC
F1	5.23 ± 0.10	117 ± 6.82	0. 36%	987.14 ± 3.11	> 300	99.23 ± 0.57	98.30 ± 0.56
F2	5.25 ± 0.14	115 ± 7.56	0.38%	991.19 ± 3.18	120	99.57 ± 0.61	99.12 ± 0.19
F3	5.29 ± 0.09	100 ± 8.93	0.44%	994.15 ± 2.53	120	97.92 ± 0.82	98.02 ± 0.42
F4	5.52 ± 0.10	113 ± 5.93	0.25%	988.23 ± 4.14	100	99.57 ± 0.61	98.42 ± 0.46
F5	5.43 ± 0.12	118 ± 6.42	0.27%	994.42 ± 2.17	130	98.30 ± 0.56	99.05 ± 0.23
F6	5.61 ± 0.09	119 ± 7.34	0.42%	989.36 ± 3.15	120	99.12 ± 0.19	98.58 ± 0.65
F7	5.52 ± 0.10	114 ± 6.78	0.47%	993.65 ± 2.43	110	97.65± 0.56	99.10 ± 0.19
F8	5.60 ±0.08	115 ± 8.21	0.38%	985.76 ± 3.45	135	98.34 ± 0.09	98.04 ± 0.43
F9	5.51 ± 0.10	111 ± 7.34	0.40%	995.14 ± 2.63	115	99.26 ± 0.17	99.13 ± 0.18

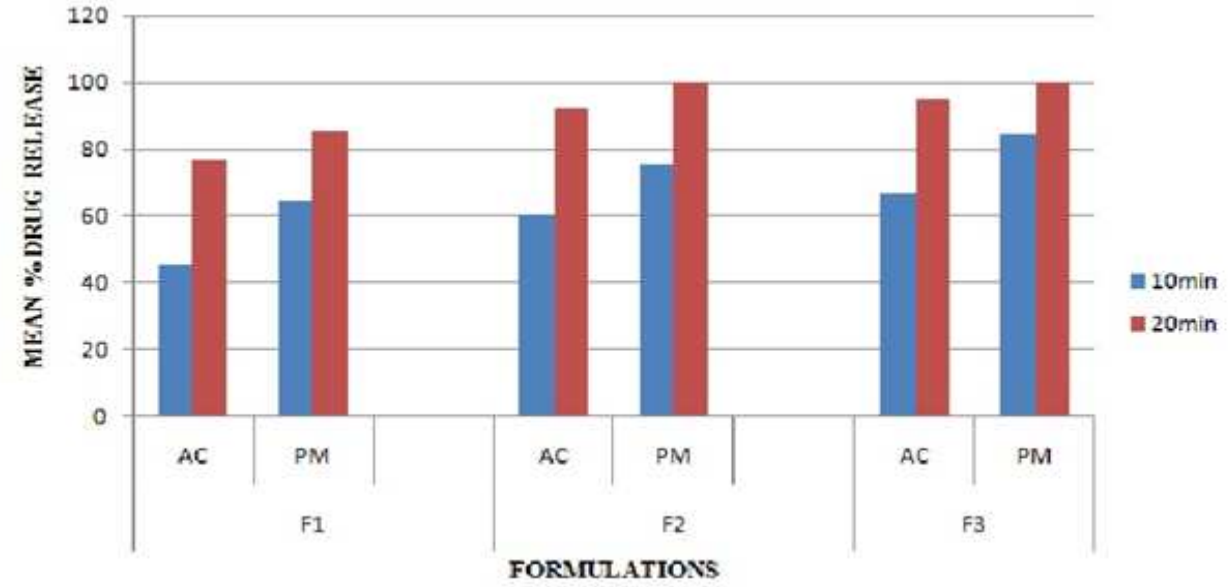

Figure.1. Comparative release of PM & AC at 10 min and 20 min time points

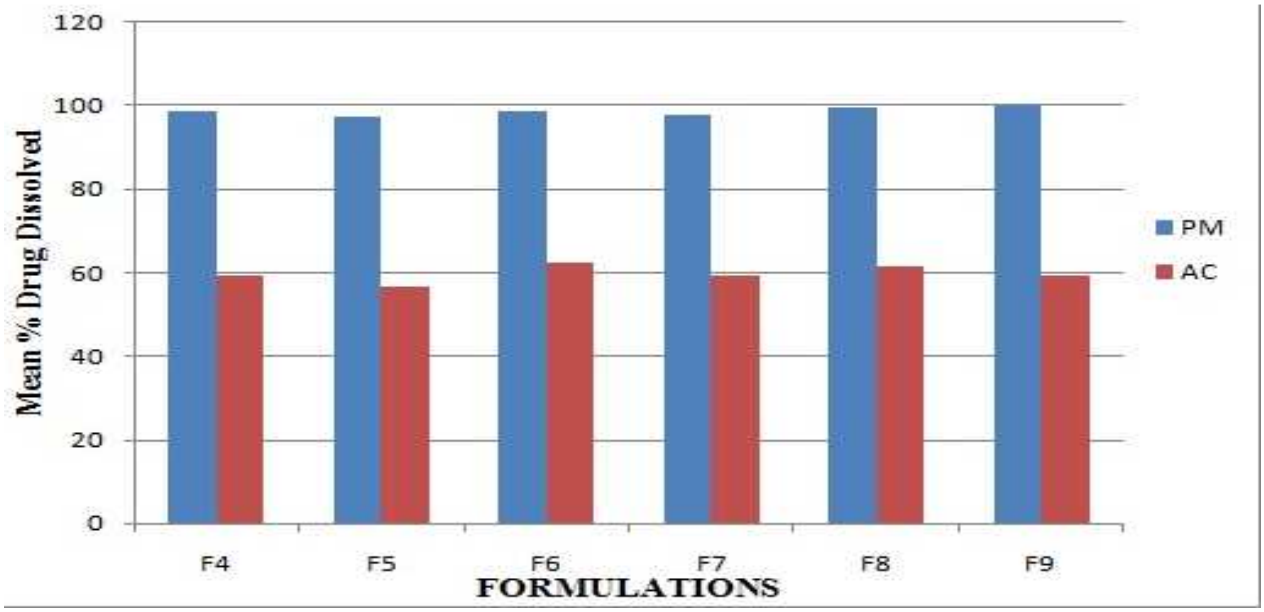

Figure.2. Comparative dissolution values of PM and AC at 30 min time point (F4 to F9)

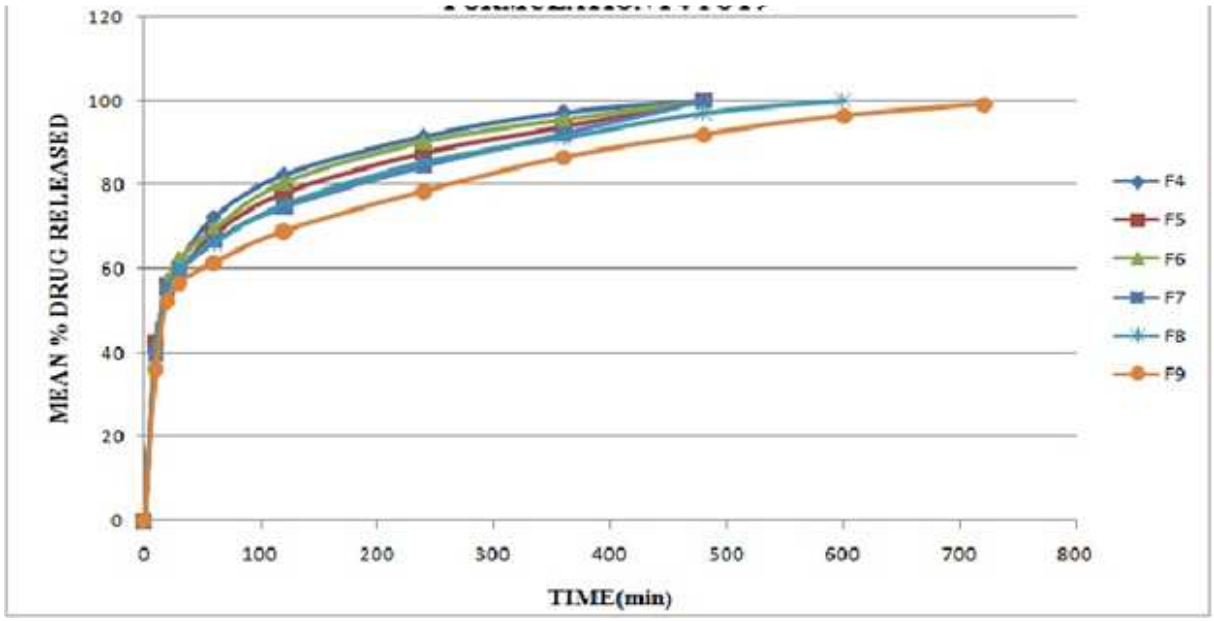

Figure.3. *In Vitro* dissolution profile of AC from formulation F4 to F9

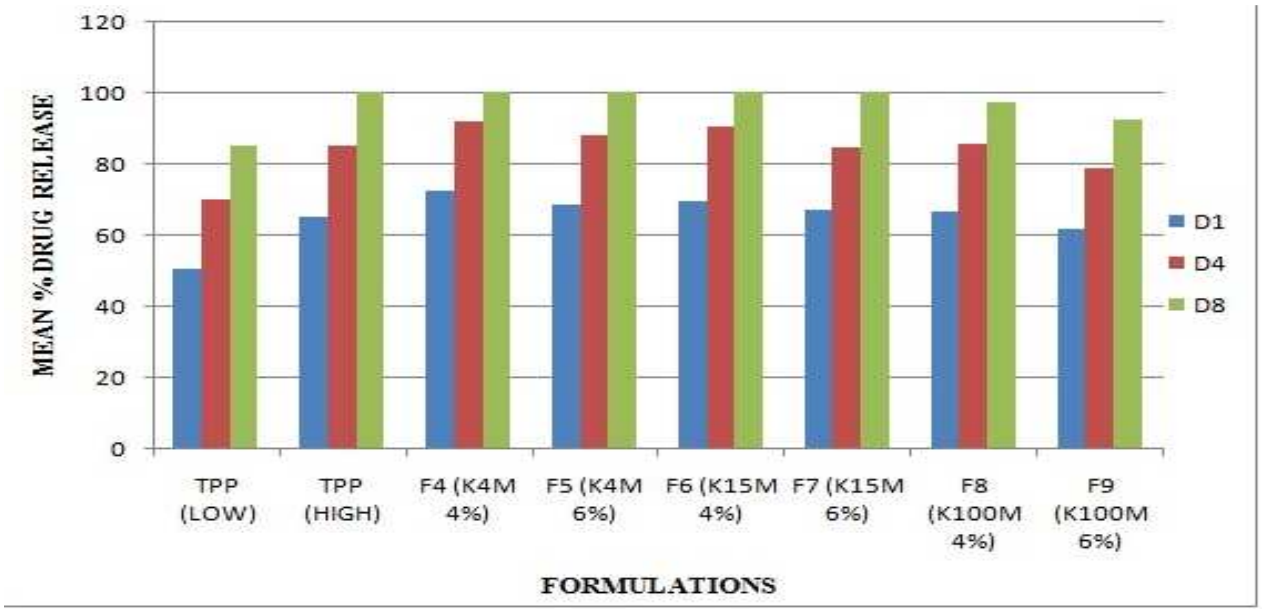

Figure.4. Comparison of AC release rate and extent from F4 to F9

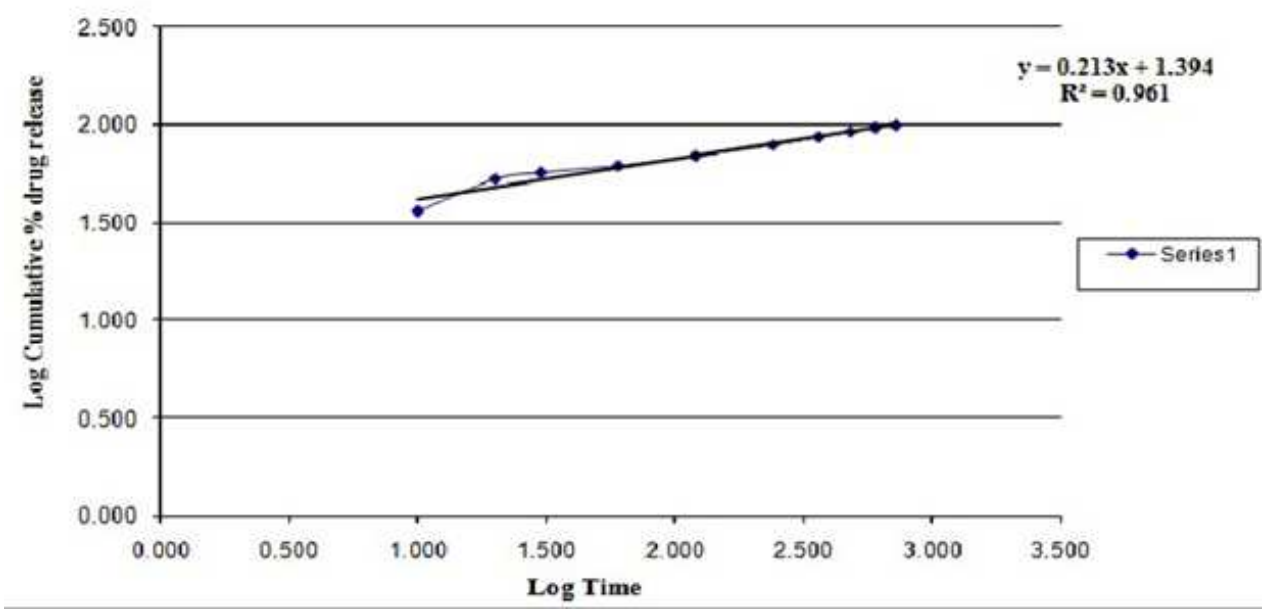

Figure.5. The Korsmeyer-Peppas release rate kinetics for release of AC from formulation F9