Journal of KerbalaUniversity , Vol. 11 No.1 Scientific . 2013

Evaluation diffusion-controlled release of organic species through the LDHs particles based on synthesized and characterized of Mg/Al-Rifampicin- layered double hydroxide nanohybrid .

A. M. Bashi [(a)] , S.M. Hadawi [(b)] , Salam .H .Abdullah* [(c)]

(a) Applied medical science college
University of Karbala
Karbala-Iraq
abbasbashi@yahoo.com

(b, c) Department of Chemistry
College of science
University of Karbala
Karbala-Iraq
h.salam85@yahoo.com

Abstract :

Synthesis of Mg/Al- layered double hydroxides intercalated with rifampicin drug . To obtaining nanohybrid compounds. The method of ion exchange was used with different molar ratio Mg/Al=2,3,4,5, the resulted material was characterized by Fourier transform infrared spectra (FT – IR) ,XRD (X-ray diffraction) the release profiles of the guest anion to phosphate ,sulphate aqueous media, the accumulated release in to phosphate more than sulphate. Release kinetics of Rifampicin has been evaluated with various models such as zeroth order, first order and pseudo- second order as well as Bhaskar equation. It is observed that the release profiles of Rifampicin were governed by pseudo second order. Additionally in this study, novel equations were used and applied for predicting the diffusion of guest anion through LDH nano hybrid particles and applied it for the Rifampicin. These equations were more suitable for diffusion than the previous equation like Bhaskar equation and it's the most convenient.

Keywords: Layered double hydroxides, FTIR-spectroscopy, XRD(X-ray diffraction), rifampicin drug, chemical kinetic controlled release and diffusion.

الخلاصة:

حضرت طبقات مغنيسيوم/ المنيوم ثنائية الهيدروكسيد المقحمة بدواء الرايفامبسين لانتاج المركبات النانوية الهجينة بطريقة التبادل الايوني المباشر بنسب مولية مختلفة (R= 2, 3, 4, 5) . المادة النانوية الناتجة شخصت بواسطة تقنية طيف (FTIR) وطيف حيود الاشعة السينية (XRD). تم دراسة تحررية الانيون العضوي الرايفامبسين في الوسط المائي لايونات الفوسفات والكبريتات حيث وجد ان كمية الانيون العضوي المتحرر في الوسط الحاوي لايونات الفوسفات اكبر من الكبريتات. حركية التحرر لدواء الرايفامبسين قدرت بمعادلات مختلفة من الرتبة الصفرية والاولى والثانية الكاذبة للانتشار بالاضافة الى معادلة باشكار (Bhaskar). يلاحظ ان عملية التحرر تخضع لتفاعل المرتبة الثانية الكاذبة للانتشار. وتم تطبيق معادلات جديدة من المرتبة الثانية الكاذبة للانتشار وهي الاكثر انطباقاً على التنافذ الايوني من بين التجمعات الجزيئية للمركبات النانوية الهجينة مقارنة بمثيلاتها من المعادلات المستخدمة سابقاً.

Introduction:

(Zobir bin Hussein), was synthesized Zn-Al-LDH intercalated with 1-naphthaleneacetate (NAA), by ion- exchange and co-precipitation [(1)],(Jin H. choy) synthesized the Zn-Al-LDH intercalated with indole to get the nanohybrid compound [(2)], (Rong Xu),was synthesized Mg-Al-LDHs intercalated with ibuprofen , by co-precipitation [(3)] , (Sumio Aisawa), was synthesized Mg-Al-LDHs, Zn-Al-LDHs intercalated with L-ascorbic acid , by ion exchange and co-precipitation[(4)] , (Demetrios F.Ghanotakis) was synthesized Mg-Al-LDHs intercalated with gramicidin, amphotericin B , ampicillin and nalidixic acid , by ion-exchange [(5)] .

Rifampicin:. (Rif) is one of the most potent and broad spectrum antibiotics against bacterial pathogens and is a key component of anti-tuberculosis therapy, stemming from its inhibition of the bacterial RNA polymerase (RNAP)[(6)] .

(Rif) is a semi synthetic antibiotic derivative of rifamycin sv. It is a red-brown crystalline powder very slightly soluble in water at neutral PH,freely soluble in chloroform ,soluble in ethyl acetate and methanol . its molecular weight is 822.95 gm/mol and its chemical formula is $C_{43}H_{58}N_4O_{12}$ and

trade name is rifadin and its melting point is(183-188 C) . rifampicin is readily absorbed from the gastrointestinal tract [7].

To limit toxicity effect upon strategy development to improve solubility , particle reduction to a size in nano range is the ideal choice. Thus, we must find out the approach that to make the drug effective with no affect on the drug action . Thus , we have been used layered double hydroxide for prepration of Mg/Al-rifampicin – LDHs by ion exchange method to improved , effectively, removal side effects such as acidity of stomach and highest accumulated amount of rifampicin.

Layered double hydroxides (LDHs) , also known as hydrotacite – like materials , are a class of synthetic two – dimensional nano structured anionic clays, Its structure can be described as containing brucite – like layers , where a fraction of the divalent cations coordination octahedrally by hydroxyl group have been replaced isomorphously by trivalent cations giving positively – charged lattice with charge – balancing anions between the layers , and some hydrogen bonded water molecules may occupy the other remaining free space of the interlayer region [8].

Layered double hydroxides (LDHs) , are a class of host – guest layered solids with the general formula[$M^{II}_{1-x}\ M^{III}_{X}(OH)_2]^{x+}[A^{n-}_{x/n}]^{X-}$ $.mH_2O$, where M^{II} and M^{III} represent di- and tri- valent cations octahedrally coordinated to hydroxyl ions , A^{n-} is the interlayer organic or inorganic anion with negative charge , m is the number of interlayer water . the second formula $X= M^{III}/(M^{II}+M^{III})$ stands for the layer charge density of LDH [9] .

A wide range of host- guest type of materials can be synthesized by ion-exchange method in which the host and guest species are put to gether in the mother liquor , followed by the aging process to form awell – ordered layered nano composite . This type of compound have attracted great attention because it can be made in to various technical applications including slow release of pharmaceuticals and drugs , plant growth regulator , etc .

Several factors are important in the formation of LDHs–based nanocomposites,such as the nature of the cations and its ratio, the PH of the mother liquor during the synthesis , temperature and time of aging as well as the method of synthesizing. these factors will affect the physicochemical properties of the resulting nanocompsites,such as the size of the particals , surface area properties [10].

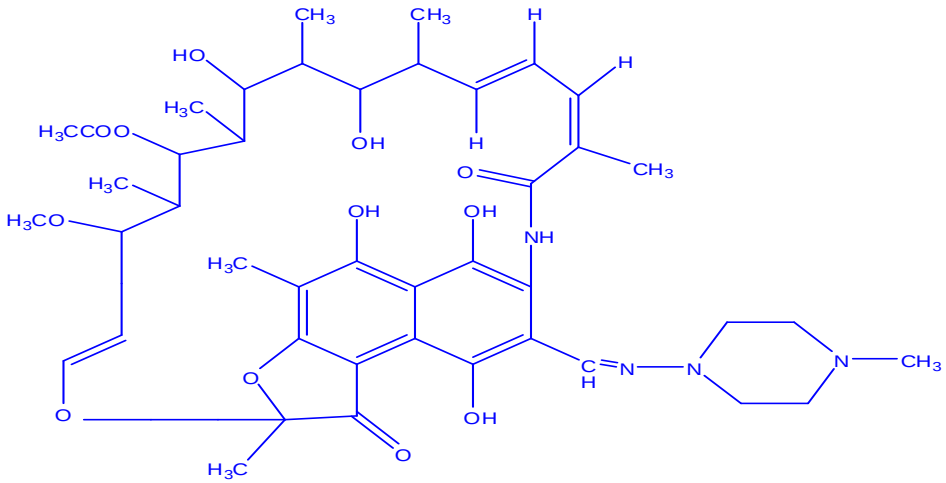


Fig.1 Molecular formula of rifampicin

Experimental section II.

A . Materials

300 mg of rifampicin ($C_{43}H_{58}N_4O_{12}$, molecular weight 822.95 gm/mol) was purchased from pharmaceutical co. ltd , (S.D.I – IRAQ) . $Al(NO_3)_3.9H_2O$ (98%) was purchased from xinbao nice chemical .,NaOH and $Mg(NO_3)_2.6H_2O$ (98%) were purchased from xilong chemical All chemicals were of analytical grade and used without further purification.

B . Prepration of Mg-Al –NO_3- LDHs

Aseries of Mg/Al – LDHs with nominal Mg^{2+}/Al^{3+} molar ratio of 2,3,4 and 5 , were prepared by hydrothermal reaction at 70 C° . The Mg- Al- NO_3- LDHs have been prepared by co- precipitation method from Mg and Al nitrate . Amixed aqueous solution containing 0.1M (1.281 g) Mg (II) and Al(III) R_2=0.05M (0.937 g) , R_3=0.033M (0.618 g), R_4 =0.025M (0.468 g) , R_5=0.02M (0.374 g) were titrated drop wise with NaOH (2M) solution . The PH were a djusted to 10.5 and the mixtures were magnetically stirred at room temperature for 1h . The resulting red-brown precipitate was isolated by filter paper , washed four times with de ionized water , and then dried at 70 C°.

C- Prepration of Mg/Al- rifampicin – LDHs by ion – exchange method

The white precipitate of Mg-Al – NO_3 – LDHs with molar ratio (R_2, R_3, R_4,and R_5) . were dissolved in 50 ml de- ionized water and then drop wise with 100 ppm rifampicin (anion rifampicin that add drops of NaOH (2M) to rifampicin to form anion) . The mixture was magnetically stirred at room temperature for 1 h , and then filtered , washed with de – ionize water four times and then dried .

III. Result and discussion

A . FT-IR spectroscopy

The bands in the spectrum of sample Mg-Al-NO_3-LDHs , also shown in Fig. 2 , it is due to the ν(OH) of the layered double hydroxid mode in the 3552 cm^{-1} . The band 1384cm^{-1} is due to the intercalation of the counter anion (NO_3^-) . the bands between 434-657 cm^{-1} are due to ν(Mg-O) and ν(Al-O) [13]. The FT-IR spectrum of Rifampicin , shown in Figure 2 , has been recorded to be compared with those of the solids prepared. The band at 1712 cm^{-1} can be ascribed to the ν (C=O) mode of the carboxylic group , while that for the amide group is recorded at 1690 cm^{-1} [10] . the bands between 1625-1575 cm^{-1} and 1479 cm^{-1} are due to the ν (C-C) stretching modes of the aromatic rings , those due to the ν (=C-O) of the ether group are recorded at 1255cm^{-1} [11]. the high wave numbers range contains the bands due to ν(OH) , ν(NH), and ν(CH) modes in the 4000-2500 cm^{-1} range , aweek band characteristic of substituted aromatic rings , is recorded close to 2000 cm^{-1} [12] . The bands in the spectrum of sample Mg-Al-Rifampicin-LDHs, also shown in figure 2 , the new bands due to the ν(OH) of the layered double hydroxide mode in the 3429 cm^{-1} [14]. The band at 1716 cm^{-1} can be ascribed to the ν(C=O) mode of the carboxylic group , while that for the amid group is recorded at 1675 cm^{-1}. Upon comparing FT-IR spectra of the hybrids with those of Rifampicin , it is clear that the intercalation reactions are successfully completed without any denaturation of the drug molecules.

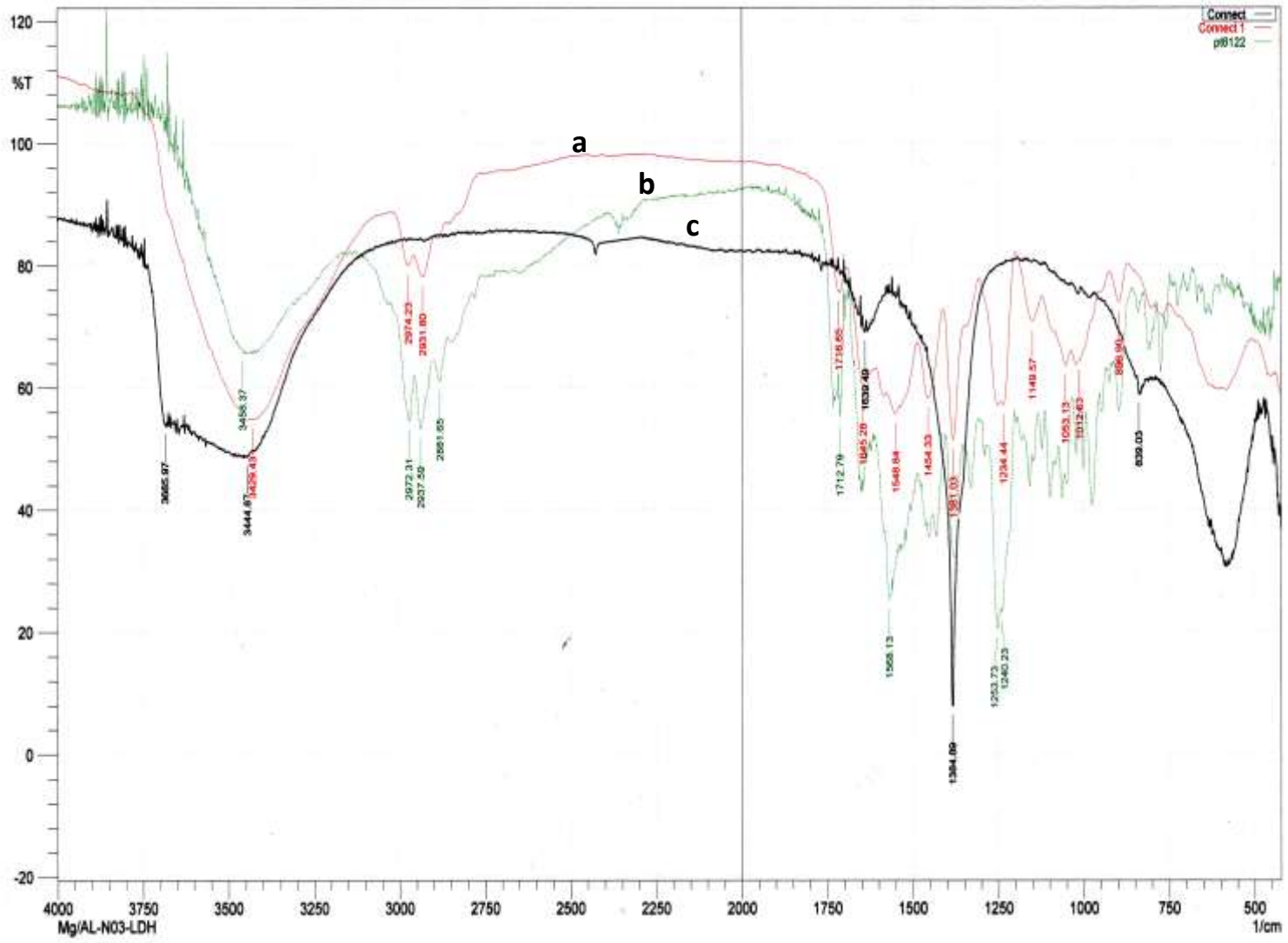


Figure (2). The FT-IR spectra for (a): Mg- Al- Rif- LDHs, (b): Rifampicin, (c): Mg- Al- NO3- LDHs

B- Powder X-ray Diffraction .

Powder X-ray diffraction patterns of the solid obtained that indicate after hydrothermal treatment at 70 Cº a Mg-Al-NO_3-LDHs nanohybrid has been formed "figure 4" for sample Mg-Al-NO_3-LDHs R=5 ion-exchange the basal reflections are recorded at 0.805 nm (003), 0.402nm (006), and 0.262nm (009) , respectively and particle dimension (d_{003}) is 2.415 nm . On the other hand , the basal reflections of sample Mg-Al-Rif-LDH is 1.302nm (003), 0.645nm (006), and 0.349 nm (009), particle dimension (d_{003}) is 3.906 nm . Compared to values of (003), (006), and (009) between paterns of Mg-Al-NO_3-LDHs, and Mg-Al-Rif-LDHs , we find values of (003) diffraction line increase with presence drug as well as (006) and (009), intercalation of drug leads to a significant increase in the interlayer space [(3)].

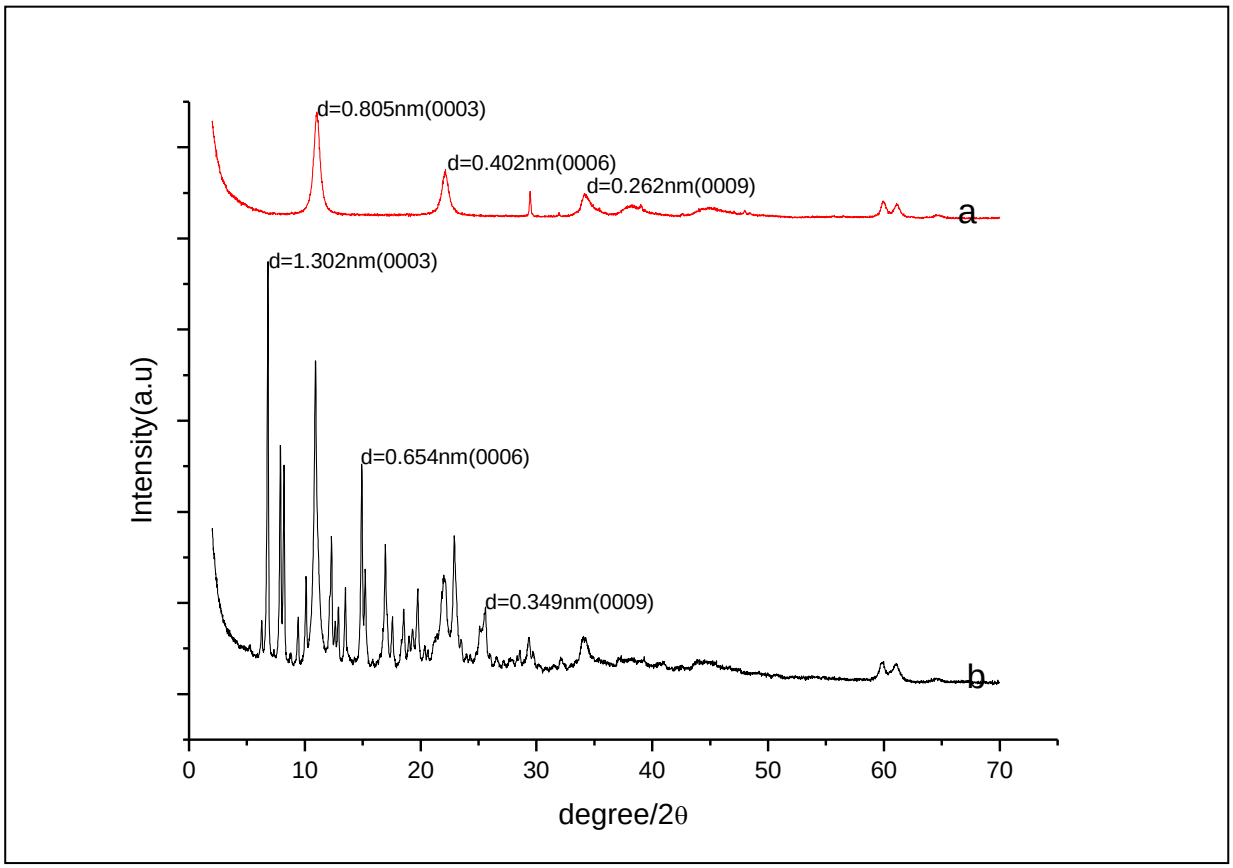


Figure (3). X-ray powder diffraction patterns (a) Mg-Al-NO_3-LDH (b) Mg-Al-Rif-LDH

C. In vitro release of rifampicin-LDHs :

The drug release properties of rifampicin from the nanohybrid interlamellae in to various aqueous media using (0.5 , 0.005) M of Na_2HPO_4 and Na_2SO_4 have been conducted. "figure 4 to7" show the release profiles of drug in to different aqueous solutions . The effects of various aqueous systems on the release of rifampicin were evaluated according to the maximum accumulated release and can be written as follows : phosphate > sulphate.

Figure (4). Release profiles of (Rif) from the interlamellae of Mg-Al- Rif-LDHs , R=2 nanohybrid in to various aqueous systems with different concentrations were containing anions of phosphate and sulphate .

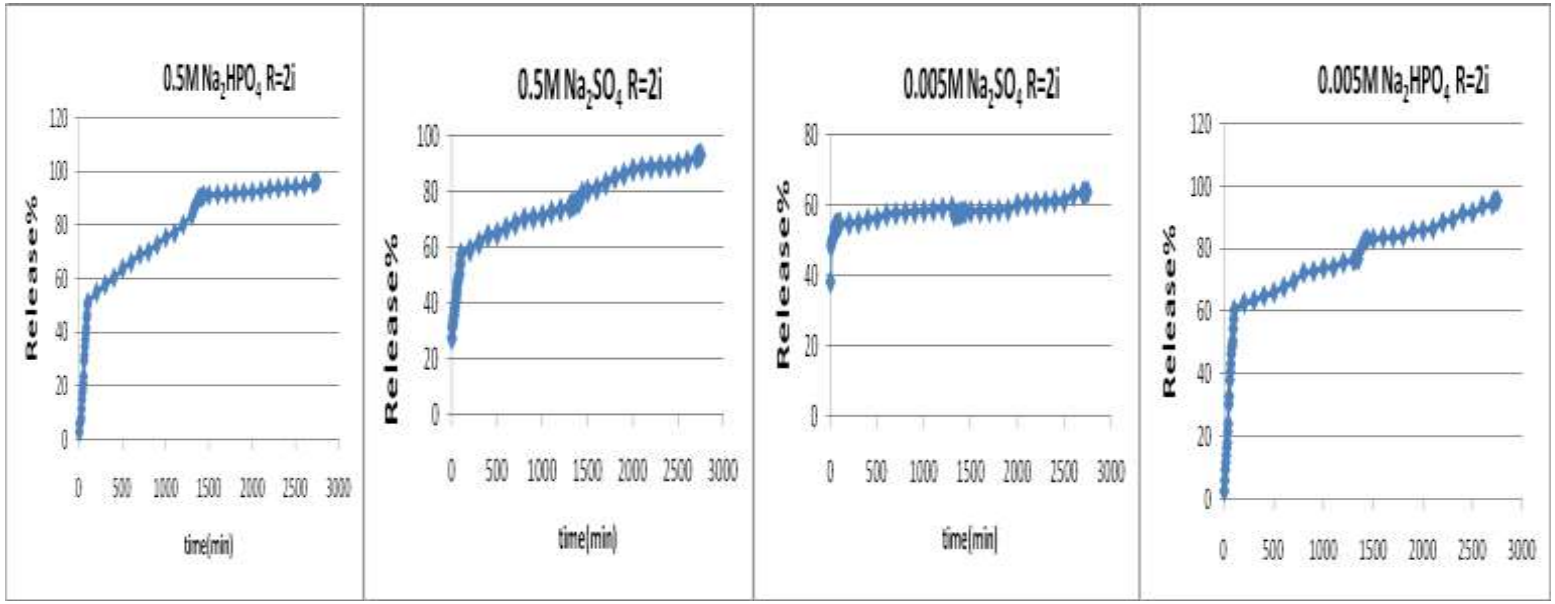


Table 1 . percentage Release, Rate constant(K), Half life ($t_{1/2}$) and correlation coefficients (r^2) obtained from fitting of the release Data of (Rif) from Mg-Al-Rif-LDH nanohybrids into various aqueous solution(Mg/Al=2 ion exchange).

Aqueous solution	Conc.(mol. L^{-1})	Max. Release%	Max. Time(min)	Zeroth order	First order	Bhaskar equation	pseudo second ord.	other parameters for pseudo second ord.	
					r^2			$K\times10^4$ L. $mg^{-1}.min^{-1}$	$t_{0.5}$(min)
Na_2HPO_4	0.5	96	2750	0.778	0.959	0.972	0.993	0.5	116.9
	0.005	95	2750	0.729	0.937	0.933	0.99	1.4	40.5
Na_2SO_4	0.5	93	2750	0.87	0.973	0.945	0.988	7	8.45
	0.005	63.9	2750	0.685	0.95	0.813	0.997	116	0.507

Figure (5). Release profiles of (Rif) from the interlamellae of Mg-Al-Rif-LDHs R=3 nanohybrid in to various aqueous systems with different concentrations were containing anions of phosphate and sulphate (R=3 – ion exchange).

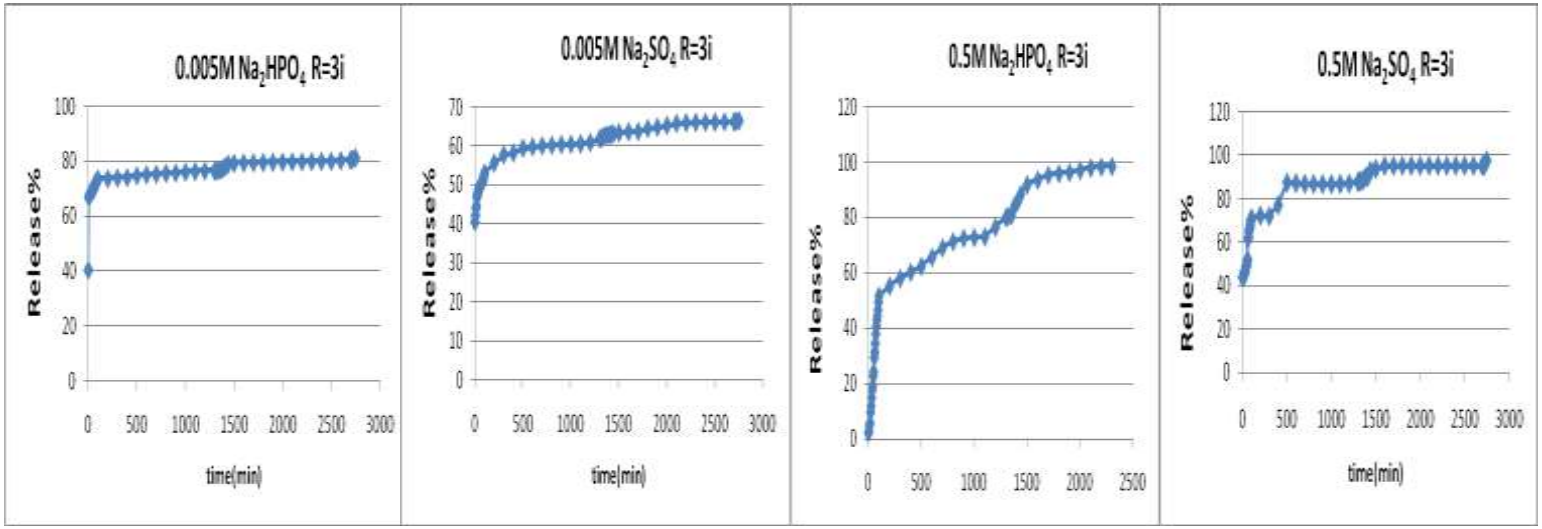


Table 2. Percentage Release, Rate constant(K), Half life ($t_{1/2}$) and correlation coefficients(r^2) obtained from fitting of the release Data of (Rif) from Mg-Al-Rif-LDH nano hybrids in to various aqueous solution (Mg/AL=3- ion exchange).

Aqueous solution	Conc.(mol. L^{-1})	Max. Release%	Max. Time(min)	Zeroth order	First order	Bhaskar equation	pseudo second ord.	other parameters for pseudo second ord.	
					r^2			$K\times10^4$ L. $mg^{-1}.min^{-1}$	$t_{0.5}$(min)
Na_2HPO_4	0.5	98.5	2300	0.794	0.95	0.893	0.995	1.3	43.4
	0.005	81.9	2780	0.511	0.711	0.801	0.999	175	0.338
Na_2SO_4	0.5	97.7	2750	0.728	0.91	0.958	0.998	7.9	7.436
	0.005	66.4	2750	0.809	0.856	0.961	0.998	43	1.352

Figure (6) . Release profiles of (Rif) from the interlamellae of Mg-Al-Rif-LDHs R=4 , the nanohybrids in to various aqueous systems with different concentrations were containing anions of phosphate and sulphate.

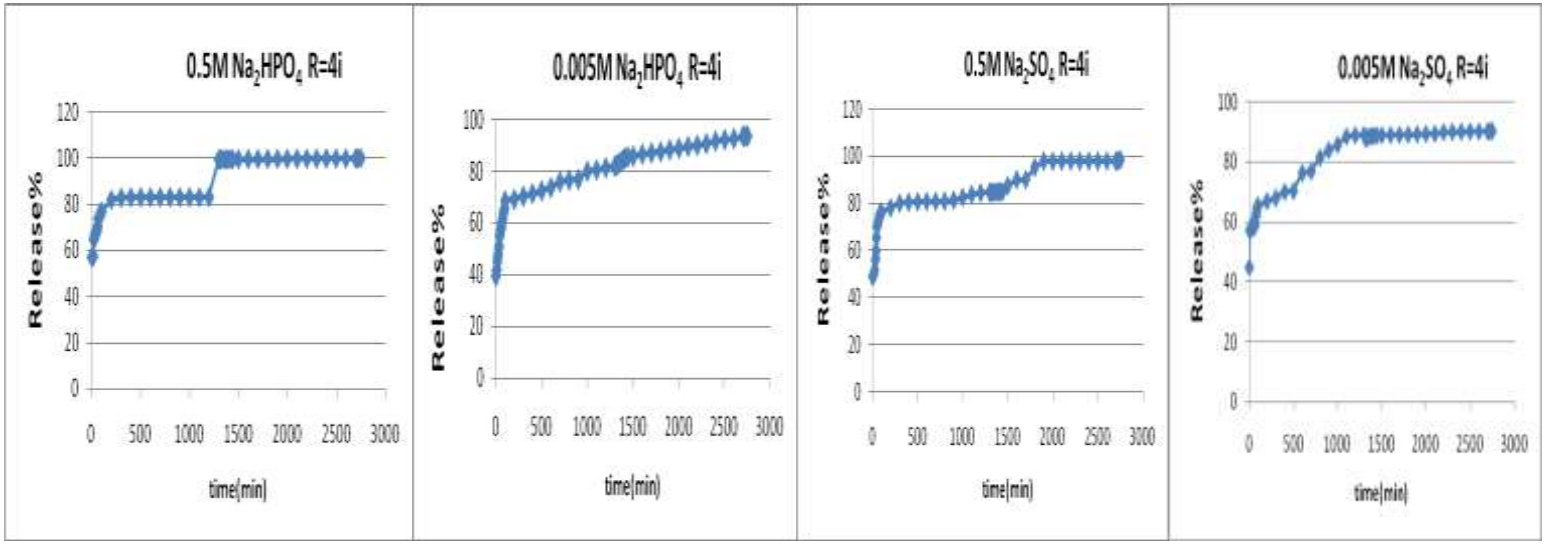


Table 3. Percentage Release , Rate constant (K), Half life ($t_{1/2}$) and correlation coefficients (r^2) obtained from fitting of the release Data of (Rif) from Mg-Al-Rif-LDH nano hybrids in to various aqueous solution (Mg/Al=4- ion exchange).

Aqueous solution	Conc.(mol. L^{-1})	Max. Release%	Max. Time(min)	Zeroth order	First order	Bhaskar equation	pseudo second ord.	other parameters for pseudo second ord.	
					r^2			$K\times10^4$ L. $mg^{-1}.min^{-1}$	$t_{0.5}$(min)
Na_2HPO_4	0.5	99	2750	0.793	0.893	0.826	0.995	1.7	33.4
	0.005	93.5	2750	0.816	0.965	0.969	0.995	14	4.22
Na_2SO_4	0.5	98	2750	0.746	0.885	0.814	0.993	12	4.5
	0.005	90	2750	0.814	0.879	0.959	0.998	19	3.8

Figure (7). Release profiles of (Rif) from the interlamellae of Mg-Al-Rif-LDHs R=5 the nanohybrid in to various aqueous systems with different concentrations were containing anions of phosphate and sulphate .

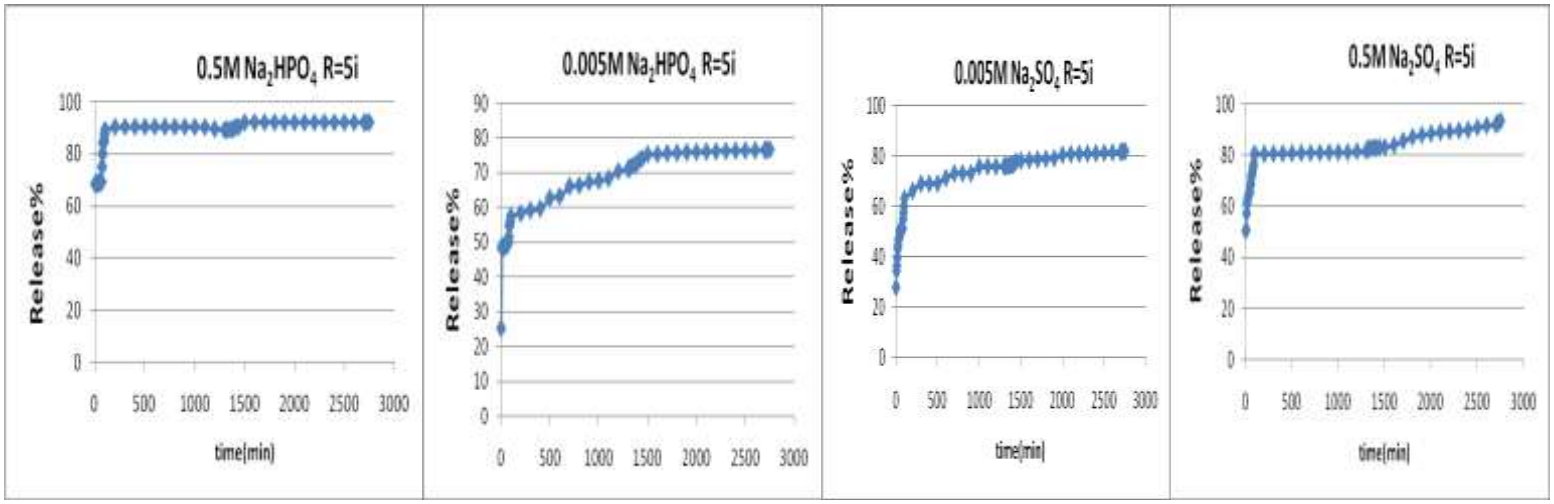


Table 4. Percentage Release, Rate constant(K) , Half life (t1/2) and correlation coefficients(r2) obtained from fitting of the release Data of (Rif) from Mg-Al-Rif-LDH nano hybrids in to various aqueous solution (Mg/Al=5- ion exchange).

Aqueous solution	Conc.(mol. L^{-1})	Max. Release%	Max. Time(min)	Zeroth order	First order	Bhaskar equation	pseudo second ord.	other parameters for pseudo second ord.	
					r^2			$K\times10^4$ L. $mg^{-1}.min^{-1}$	$t_{0.5}$(min)
Na_2HPO_4	0.5	92	2750	0.524	0.611	0.755	0.999	58	1.02
	0.005	76.7	2750	0.802	0.886	0.966	0.998	25	2.3
Na_2SO_4	0.5	93	2750	0.676	0.845	0.861	0.996	50	1.18
	0.005	81	2750	0.723	0.84	0.954	0.998	18	3.5

Finally, according to the release profiles and the amount of Rifampicin (Rif)R=4 intercalated, it is observed that the compound is more convenient “Figure 6” . The results indicate that the amount of Rifampicin intercalated depends on the structure and layer charge , it can be seen that the compounds.

Release Kinetics :

In order to explore the release mechanism , we applied four kinetics were previously mentioned to fit the release kinetic data figure (8-11) and calculated the corresponding linear correlation coefficients(r^2) from the tables (1-4) . compared with the Zeroth order and first order , while pseudo second order kinetic model which is the more fitted model for the release of Rifampicin , which is reflected by the obviously higher linear correlation coefficient of r^2 as in tables (1-4). It is given that the rifampicin molecule is suffered much immobilized when it diffused through the inter particle in the case of Mg/Al-LDHs .

Equation shown (1) can be used to evaluate whether the diffusion through the particle is the rate-limited step. Thus, the release profiles were fitted by Bhaskar equation, to gather with zero order, first- order and pseudo second order equation (in "(2)", "(3)", "(4)") respectively, which is normally used to describe the dissolution, phenomena:

$\ln(Ct/Cf) = - Kt^{0.5}$ …… (1)

$X = Kt + C$ …… (2)

$- \ln (1 - X) = Kt + C$ …….. (3)

$t/Ct = 1/K_2Cf^2 + (1/Cf)t$ …… (4)

(X) is the release percentage of rifampicin at time t (min) and C is a constant. K is a rate constant, Ct the concentration of (Rif) at time t , Cf the final concentration of (Rif).[16]

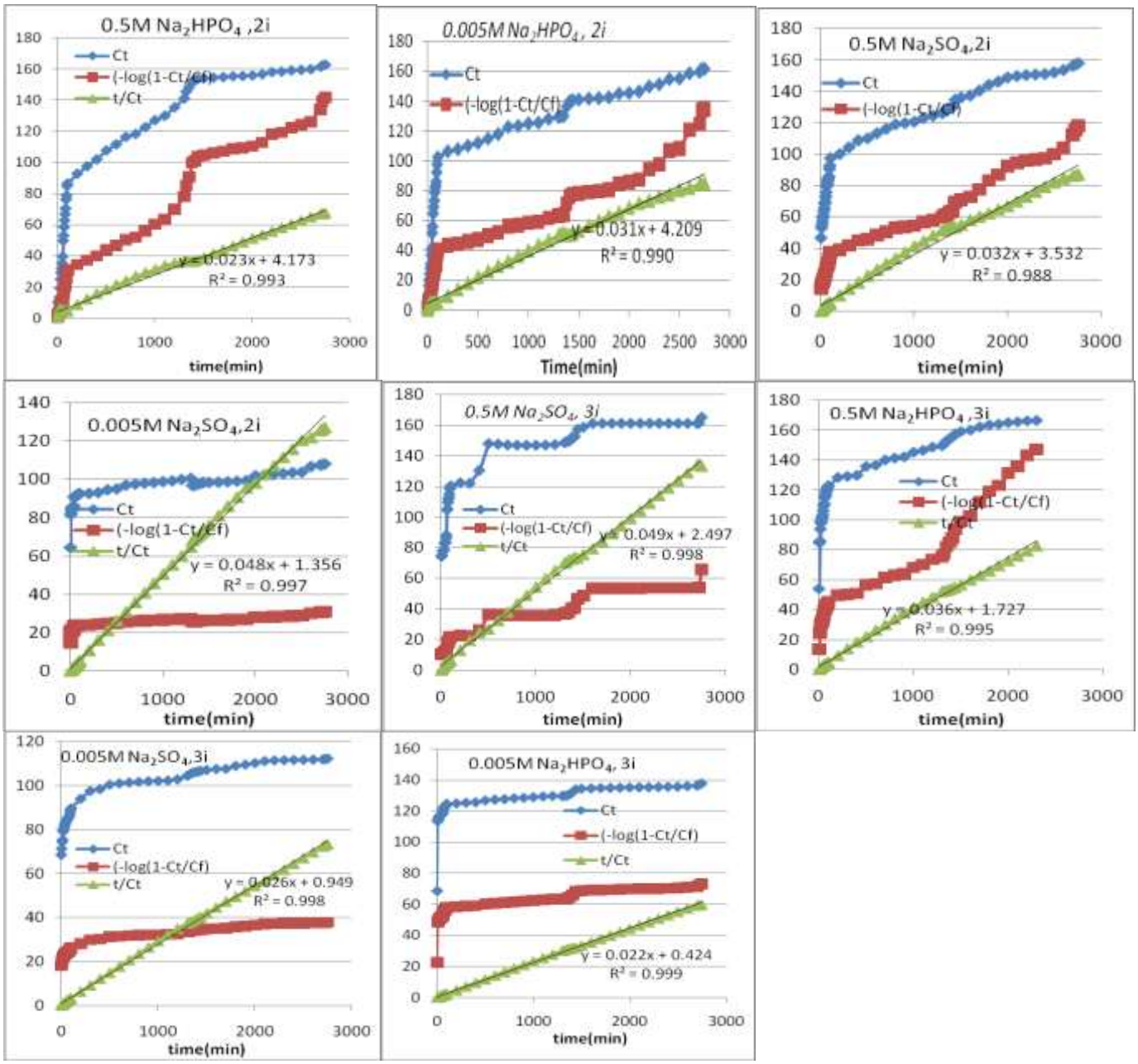


Figure (8). Fitting of the data to the Zeroth ,first and pseudo – second order kinetics for Rifampicin in to different aqueous solutions (Mg/Al=2, 3 ion – exchange) .

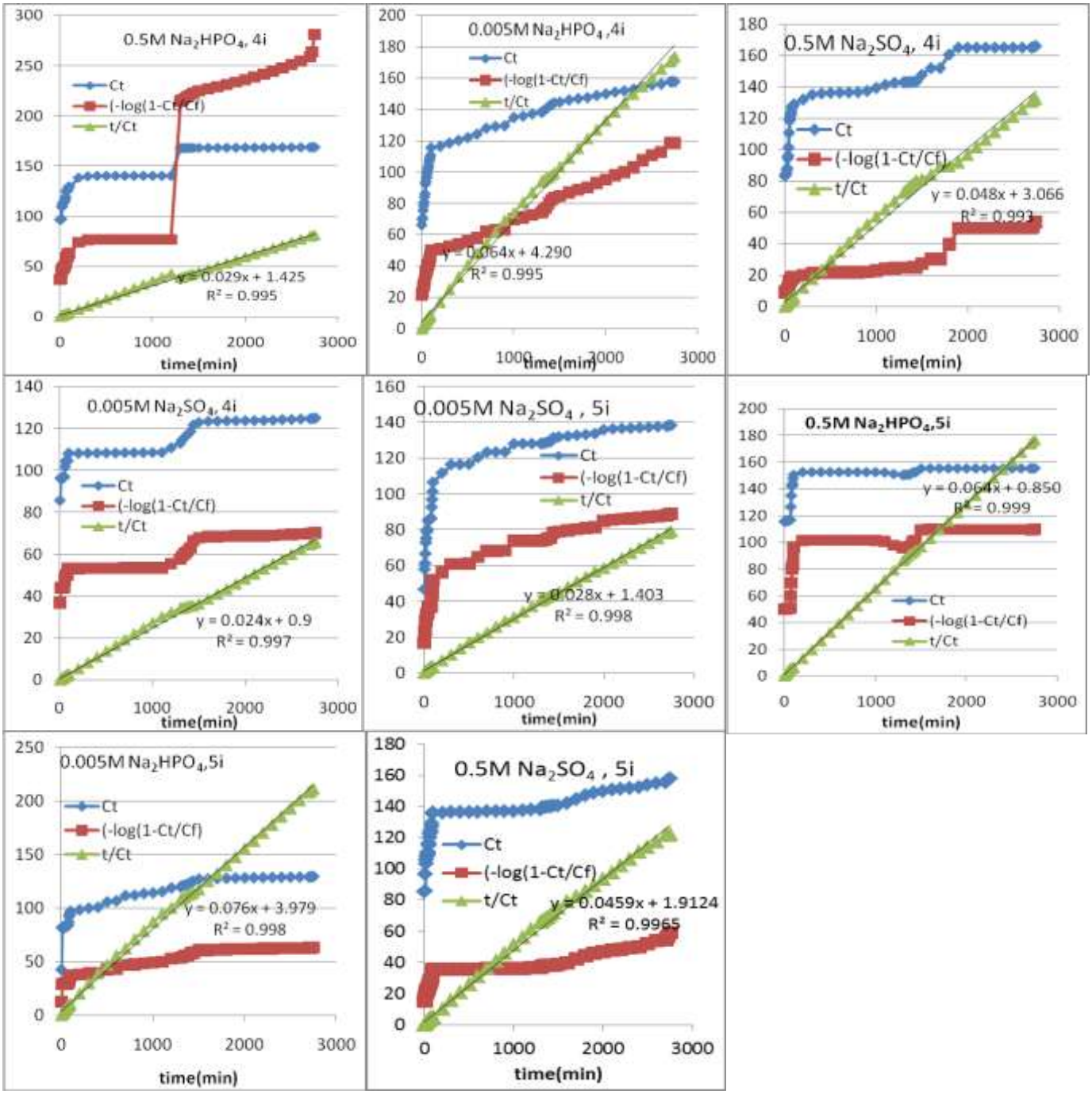


Figure (9) . Fitting of the data to the Zeroth , first and pseudo – second order Kinetics for Rifampicin released in to different aqueous solutions (Mg/Al=4, 5 ion-exchange)

The release of Rifampicin from the inorganic LDH interlamellae involved dissolution of the nanocomposite as well as diffusion of the intercalated anion . The dissolution phenomena take place by ion-exchange process between the intercalated anions and the incoming anion such as phosphate and sulphate anions in the aqueous solution can be better described by pseudo-second order Kinetics because the mechanism of release has been interpreted on the basis of the ion-exchange process between the drug anion intercalated in the lamella host phosphate, or sulphate anions in aqueous solution i.e. depending on two factors : incoming and outgoing anion . In addition , the dissolution time will represent the total time of how long the molecule spends outside the interlamellae host as well as the pseudo-second order model will represent the dissolution as well as diffusion phenomena[15] .

Therefore,in this study,it has been innovated novel equations to evaluate the diffusion of organic species through the LDHs nanohybrid inter particles (equation5 and 6),″ Figure 10-12″and(Table 5).

$$\ln\frac{C_t}{C_f^2 - C_t C_f} = \ln\frac{\mathrm{D}}{\mathrm{n}-1} + (n-1)\ln t \qquad (5)$$

$$\frac{t^m}{C_t} = \frac{m}{KC_f^2} + \frac{t^m}{C_f} \qquad (6)$$

D = the diffusion coefficient , m = the diffusional exponent , (0 < m < 1) and m value calculating from (equation (5))

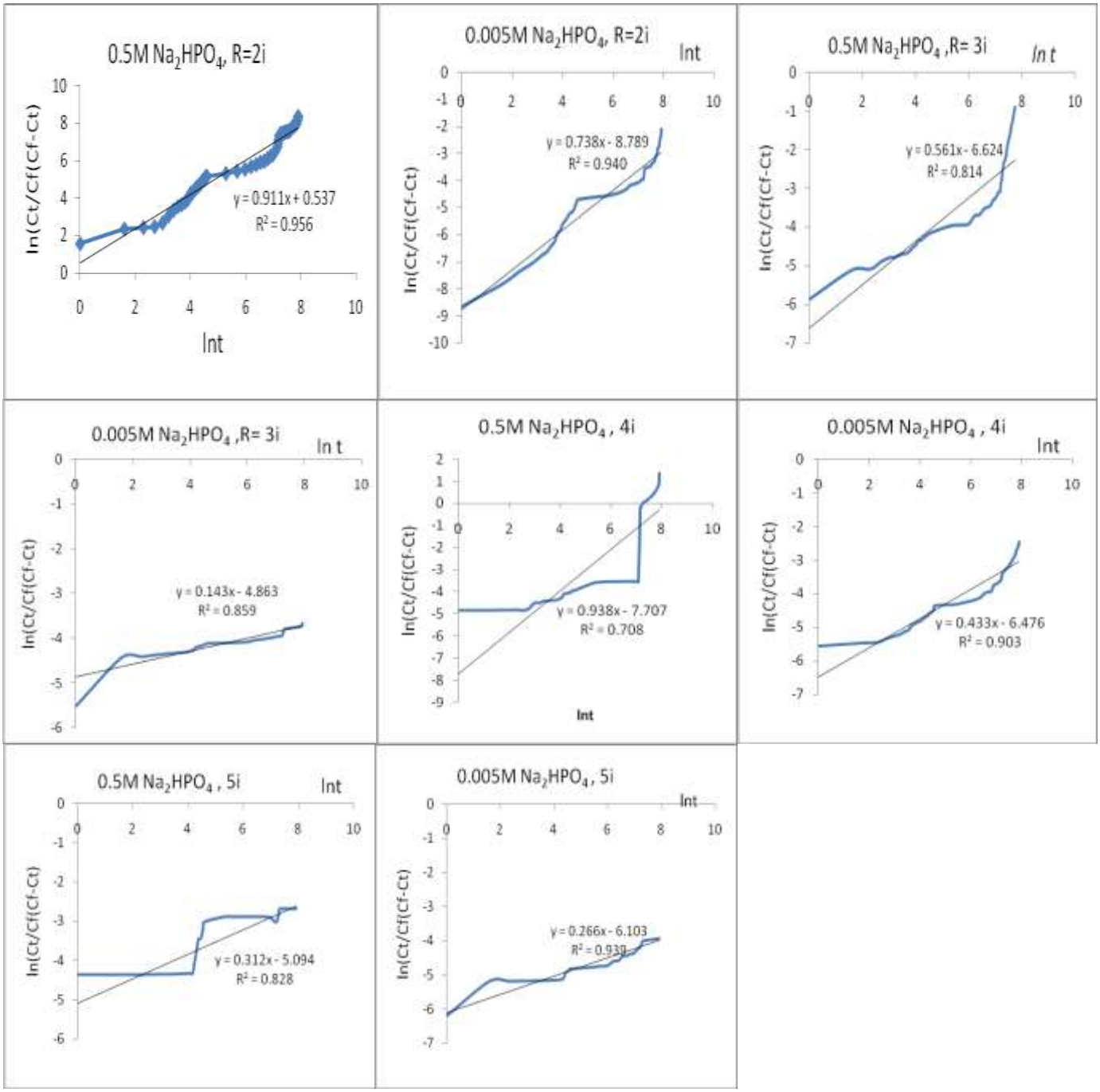


Figure (10) . Plots of $\ln(C_t/((C_f-C_t)C_f))$ versus ln(t), (Mg/Al=2,3,4,5 ion-exchange) in aqueous solution containing anion phosphate .

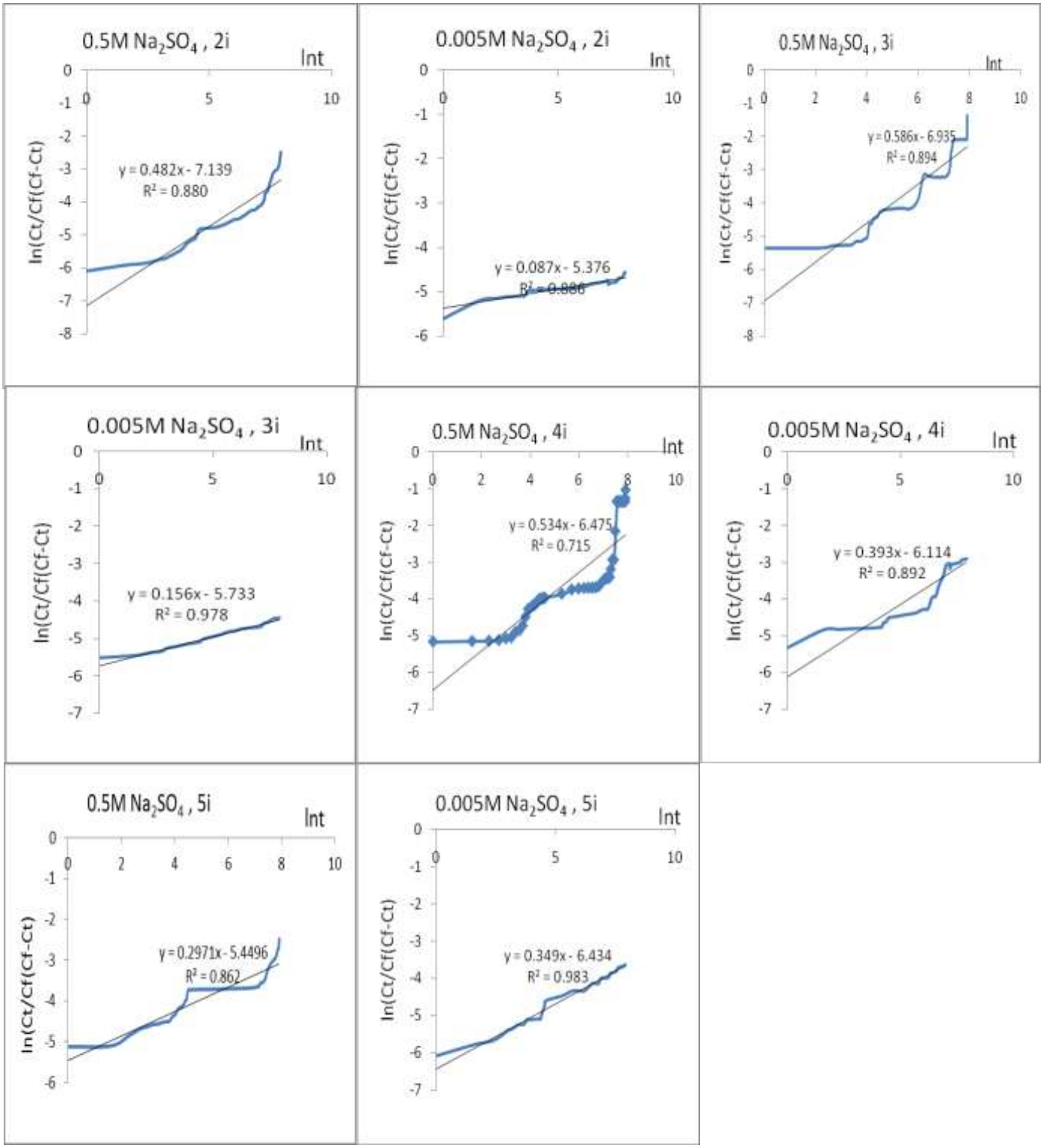
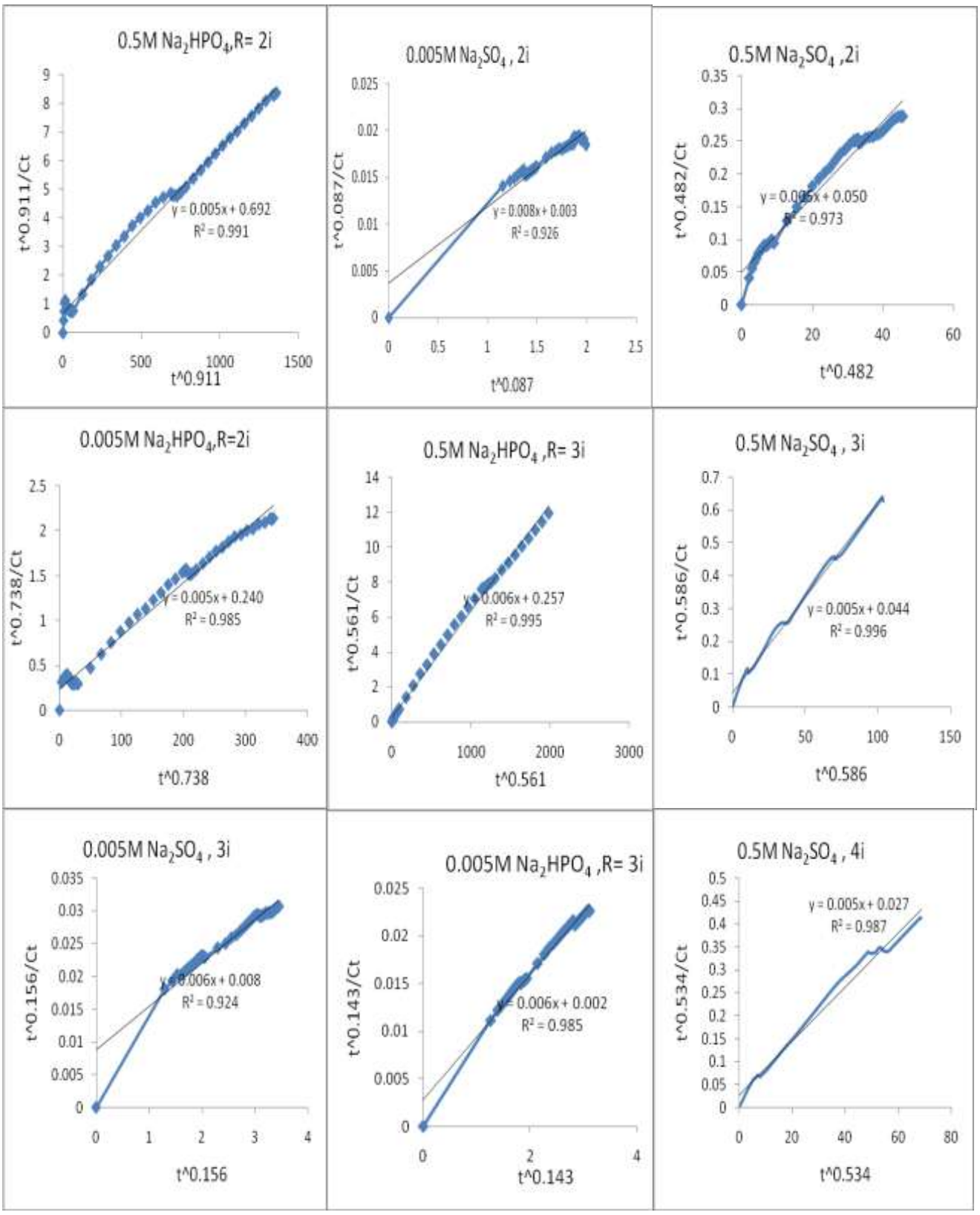


Figure (11) . Plots of ln(Ct/((Cf-Ct)Cf)) versus ln(t) , (Mg/Al = 2, 3, 4, 5 ion- exchange) in aqueous solution containing anion sulphate .


0.5M Na2HPO4,R= 2i
t^0.911/Ct
t^0.911
y = 0.005x + 0.692
R² = 0.991
0.005M Na2SO4 , 2i
t^0.087/Ct
t^0.087
y = 0.008x + 0.003
R² = 0.926
0.5M Na2SO4 ,2i
t^0.482/Ct
t^0.482
y = 0.005x + 0.050
R² = 0.973
0.005M Na2HPO4,R=2i
t^0.738/Ct
t^0.738
y = 0.005x + 0.240
R² = 0.985
0.5M Na2HPO4 ,R= 3i
t^0.561/Ct
t^0.561
y = 0.006x + 0.257
R² = 0.995
0.5M Na2SO4 , 3i
t^0.586/Ct
t^0.586
y = 0.005x + 0.044
R² = 0.996
0.005M Na2SO4 , 3i
t^0.156/Ct
t^0.156
y = 0.006x + 0.008
R² = 0.924
0.005M Na2HPO4 ,R= 3i
t^0.143/Ct
t^0.143
y = 0.006x + 0.002
R² = 0.985
0.5M Na2SO4 , 4i
t^0.534/Ct
t^0.534
y = 0.005x + 0.027
R² = 0.987

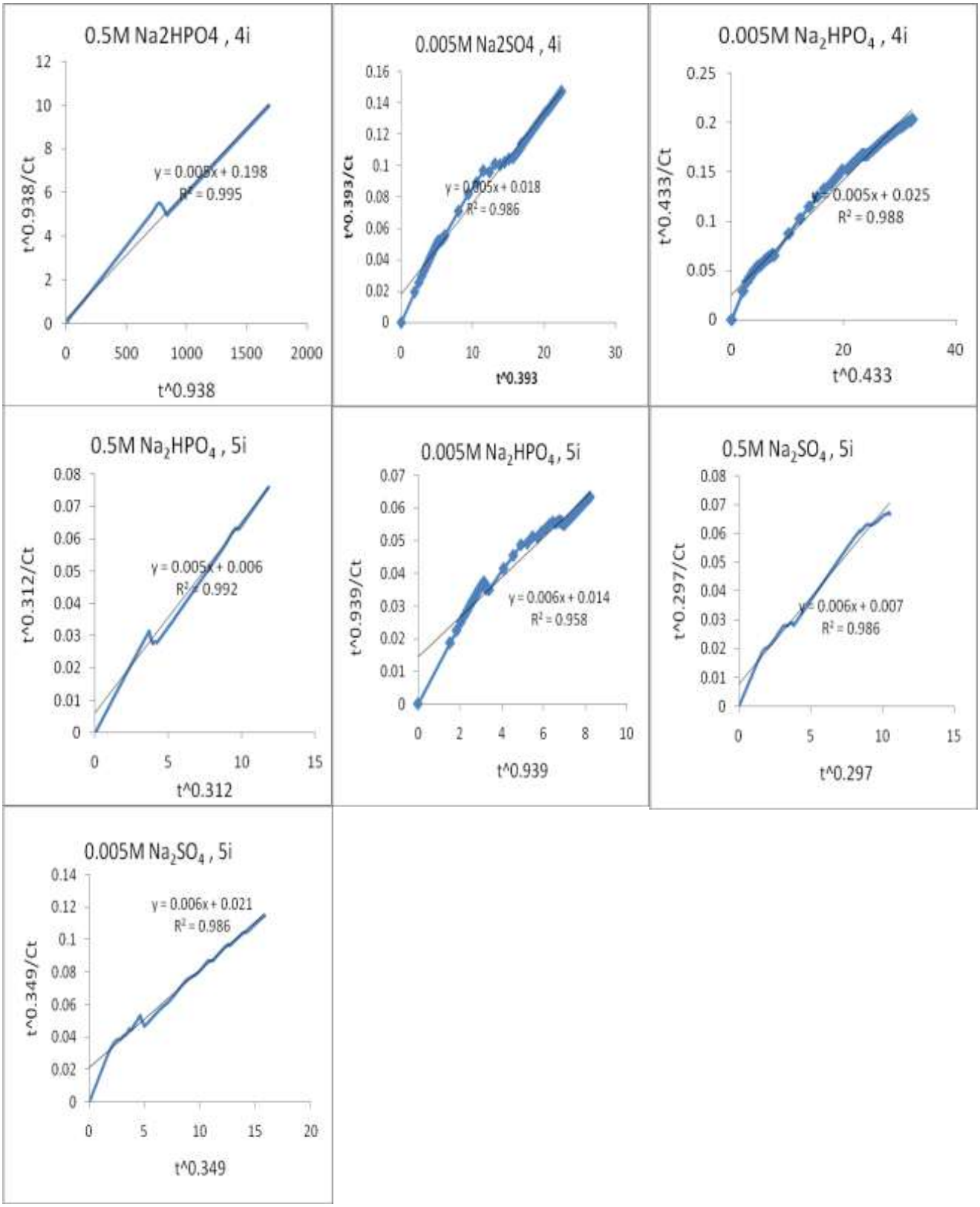


Figure (12) . Plots of (t^m/C_t) versus (t^m), (Mg/Al = 2, 3, 4, 5 ion- exchange) in to various aqueous solution systems with different concentration was containing several anions of sulphate and phosphate .

Table 5 . Rate constant(K), Half Life($t_{1/2}$) and correlation coefficients(r^2) obtained from fitting of the release data of (Rif) from Mg-Al-Rif-LDH Nanohybrid in to various aqueous solution by using equation 1 and 2 (Mg/Al = 2, 3, 4, 5 ion- exchange).

Aqueous solution	Aqueous solution	Concentration ($mol.L^{-1}$)	$K*10^{-4}$ ($L.mg^{-1}.min^{-1}$)	$t_{1/2}$ (min)	m value	r^2 of equation 2
Na_2HPO_4	R2	0.5	0.46	116	0.911	0.991
		0.005	1.07	40.5	0.738	0.985
	R3	0.5	0.764	43.4	0.561	0.995
		0.005	25	0.338	0.143	0.985
	R4	0.5	1.66	33.4	0.938	0.995
		0.005	6	4.22	0.433	0.988
	R5	0.5	18	1.014	0.312	0.992
		0.005	6.6	2.3	0.266	0.958
Na_2SO_4	R2	0.5	3.3	8.45	0.482	0.973
		0.005	10	0.507	0.087	0.926
	R3	0.5	4.6	7.4	0.586	0.996
		0.005	6.8	1.35	0.156	0.924
	R4	0.5	6.9	4.5	0.534	0.987
		0.005	7.6	3.042	0.393	0.986
	R5	0.5	14.8	1.183	0.297	0.986
		0.005	5.8	3.5	0.349	0.986

By comparing the correlation coefficient of equation 5 (Table 5) together with first order equation or Bhaskar equation (Table 1-4) it can be seen that the equation 2 has higher values and it is the best there is . In addition, the novel equation will give us a lot of information like m value that could not be given by any other equation . Finally, from the experimental data in this study , when comparing between correlation coefficient related to first order equation or Bhaskar equation and ″ 2″ for both nanohybrid compounds, we found that the novel equation was more suitable for predicting the rate of diffusion through the LDHs-nanohybrid composite.

References :

1- Zobir bin H., and D. wong,“ synthesis of nanocomposite: 1-Naphthaleneacetate-zinc-aluminuim-layered double hydroxide”, science and environmental studies, Jan. 2002.

2-Jin-HO choy, and S.-HO Hwang,“ Intercalation of functional organic molecules with pharmaceutical, cosmeceutical and nutraceutical functions in to layered double hydroxides and zinc Basic salts”, BUll.korean chem. soc. vol.22,NO.9, (2001).

3- P. Gunawan, and Rong Xu., "Direct control of drug release behavior from latered double hydroxides through particle interactions" , school of chem. 62 nanyang drive , Singapore 637459(2007).

4- Sumio A. , Norihito H. , Satoshi T. , and Hidetoshi H. , "Intercalation behavior of L-ascorbic acid in to layered double hydroxides" , Applied clay science 35, 146-154, (2007).

5- Markos T. and , Demetrios F. , "Intercalation of hydrophilic and hydrophopic antibiotics in layered double hydroxides" , International J. of pharm.(2006).

6- Eliz. A. Campbell, N. Korzhera, A. Mustaev, K. murakami, S. nair, A. Goldfarb and seth A. Darst,“ Structural mechanism for Rifampicin inhibition of bacterial RNA polymerase,” Cell,Vol.104,901-912,March 23, (2001).

7- Laval , and Quebec H7L4A8 , Product MONOGRAPH,″ RIFADIN″ , S-a version 4.0 dated July 23, (2010).

8- Feng Li , and Lihong zhang , David G. Evans ,Clande Forano , Xue Duan,“ Structure and thermal evolution of Mg-Al Layered double hydroxide containing interlayer organic glyphosphate anions,” Thermochimica Acta 424, 15-23 (2004).

9- L. Qin , S. Wang , Rui Zhang , R. zhu , X. sun , and Side yao ,“ Two different approaches to synthesizing Mg-Al-layered double hydroxides as folic acid carriers ,” Journal of physics of solids 69, 2779-2784 (2008).

10- M. Zobir Hussein, S. H. Sarijo , Asmah Hj Yahaya , and Zul Karnain Zainal ,“ The effect of PH on the formation of host-guest type material: Zinc-aluminium – layered double hydroxide-4-chlorophenoxy acetate nano composite ,” Published online 7 February 2007 .

11- D. Pan , H. Zhang , T. Zhang , X. Duan ,“ A novel organic- inorganic microhybrids containing anticancer agent doxifluridine and layered double hydroxides : structure and controlled release properties ,” Chem. Engineering Sci. 65, 3762-3771 (2010).

12- Yu-Jen Chen ,“ The solubility enhancement and the stability assessment of Rifampicin ,Isoniazid and pyrazinamide in aqueous media ,” Athesis submitted in fulfillment of the requirements for the degree of master of science of Rhodes university (2000).

13- Lingna Sun , Changwen Hu , “Facile synthesis via a solvothermal route and characterization of Mg-Al- layered double hydroxide (LDH) 3D micro-nano structure ,” Materials Research Bulletin 46, 1922-1927, (2011).

14- Longchao Du , Baojum Qu , Yuezhong M , Quan Zhu ,“ structural characterization and thermal and mechanical properties of poly (propylene carbonate) / Mg-Al-LDH exfoliation intercalation ,” Composites science and Technology 66, 913-918 (2006).

15- Mohammed Adnan M ,“ Preparation and characterization of Ni/Al nanohybrid with folic acid and suggestion equation to evaluate the diffusion of the active agent ,” a thesis , University of Kerbala / college of science (2012).

16- R. Bhaskar, R. S. R. Murthy, B. D. Miglani, K. viswanathan , "Novel method to evaluate diffusion controlled release of drug from resinate", Int. J. vol. 28, pp. 59- 66, (1986).