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Experimental Study for Loading & Unloading of Cefixime on Activated Carbon as Drug Delivery

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ABSTRACT
Over the past decade, drug carries of various kinds have been used in the field of drug release control operations. It is agreed that drug carries maintain the concentration of drugs within the required range for a long period of time and reduce the toxicity resulting from the use of overdoses and the ability to direct the drug to the affected area. In this research activated carbon was used as an organic carrier in two different sizes (0.6 µm size with surface area 544.4704 m^2/g and 11.042 nm size with surface area 985.6013m^2/g) and cefixime was used as a drug model ,The loading process was based on the adsorption between the surfaces of activated carbon molecules and the drug molecules dissolved in ethanol. The maximum efficiency of the experiments was 73% when the carbon in nanoparticle size and the carrier-to-drug ratio weight were 1.5, The unloading process was studied by studying the mass transfer coefficient and knowing the effect of the variables on its value ,these variables are time and temperature in addition to the PH value of the solution. The highest value of the mass transfer coefficient was obtained at the beginning of the unloading time ,at temperature 37 c° and at PH 1.5 for dissolution medium .added to it proved that when using nanoparticle sizes, the unloaded (release) of the drug is more controlled over time than if the size of the carbon particles and the latter are better than if the drug is pure.

Key words: Drug delivery, activated carbon, cefixime, mass transfer coefficient

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Introduction

The development of a new drug is an enormous step that consumes money, time, and effort, which increases the difficulty in medical research. The priority of any research center in the pharmaceutical industry is to reduce the overall costs and to increase the productivity of the company [1]. A widespread drug route administration type is the Oral drug or (oral route) due to its simplicity, the less patient compliance, and the cheap cost [2]. However, the problem with this type is that the drug degrades before reaching the site of action. The rate of absorption can be increase or decrease depending on different factor such as (food uptake, pH level in the digestive, gastric motility and time of emptying) which causes the treatment of medical to be failed. Moreover, Drugs are harmful in some parts of the human body, such as the stomach mucosa. As a consequence, drug concentration, as well as the drug effectiveness at the site of action, can be very low [3].

To reach the beneficial action of the drug, the administration requires sundry doses along the day with the hazard of forgetting a dose by patients. Also, the variation of the drug concentration in the plasma during the day can be considerable [4]. For example, the treatment with antibiotics or other drugs that require extended time for treatment could face the mentioned problems[5]. One solution is to use the controlled drug delivery systems which are used to embodiment a high drug concentration to achieve the desired profile of drug release through the day[6]. In order to modify the drug delivery process there are different types of delivery systems that can be controlled, such as immediate release, delayed drug delivery, site-specific, and sustained drug delivery systems . In the first two types (quick and delayed drug delivery), the profile of drug release is accelerated in the central system while retarded in the delayed case [7].

The controlled drug delivery systems provide drug release from the dosage form through several hours,this Lead to decreas the time needed to absorb the drug also increase the effectiveness of the drug efficacy while reducing the drug side effects [8,10].The downside of developing controlled drug delivery systems is the high costs high since it requires expensive equipment and particular carriers. [11]. The drug release mechanisms can be clarified by water has penetrated the system, the dissolution of the drug in water, and diffusion of a drug outside the carrier [12].This steps can occur, but in a different rate and order, the level with the lowest rate is the controlling step through which we can predict the mechanics of drug release. [13,15].

In addition to what is mentioned, there are several advantages to the system of drugs loading, including.

- Improved treatment of diseases, through selective accumulation in situ and less accumulation elsewhere.
- Increase the therapeutic value of the drug. [16]
- Maintained the Concentration in desired range for an extended period.
- Delivery the drugs and release around the area.
- reduce the poisoning resulting from the use of doses.[17]

There are several drug carriers, including (liposomes and tubules, polymeric micelles, Dendrimers, Microspheres, Nanostructures and other) [18] in this study was used active carbon. activated carbon has many advantage including (i) Small size (ii) Surface area increases to ratio volume (iv) the delivery of drugs(v)Unique properties of the central nervous system, such as high drug loading, cellular absorption,

thermal deformation [19]. Cefixime has been used as a model drug ,cefixime was an antibiotic of the Cephalosporins family, which is used to treat children and adults suffering from acute infections in the respiratory tract, urinary tract, pharynx, and middle ear. It can also be used to treat patients with Gonorrhea and is one of the treatments that take place in time to get Effect of treatment [20].

There are many previous studies have been used carbon as a drug carrier [21]. systems for nasal and pulmonary delivery studied and used a Nanoparticles composed of biodegradable polymers for their experiment. The result shows fulfilling in the stringent requirements placed on these delivery systems, such as ability to be transferred into an aerosol, stability against forces generated during aerosolization, biocompatibility, targeting of specific sites or cell populations in the lung, release of the drug in a predetermined manner, and degradation within an acceptable period of time.Activated carbon used as a drug carrier, and PA and IBU as types drugs use , which were loaded into AC, with a 44.4 % and 20.7 % loading efficiency for two drugs, Release studies suggested that within 10 min drug release for two PA/AC and IBU/AC complex was complete in the presence of sodium phosphate buffer (pH 5.8)[23] . Carbon nanotubes used as a carrier for 6Mercaptopurine diathesis to cancer disease,CNTs were carboxy functionalized and then loaded with 6MP using the method was named Incipient Wetness impregnation to produce 6MP /MWCNTs complex, a maximum of ~ 65% of the drug was loading, the loaded in nanotubes were shown that the 6MP was release for higher than twenty hours and thus the release was controlled , kinetic emission was found to follow the Hixson Crowell and Zero-Order release model, new strategies was used Carbon nanotubes for their ability to improve bovine availability and systemic detoxification at the site of cancer due to tumor targeting by CNTs[24] .Carbon nanotubes (CNTs) have been used with specific physical and unique chemical properties, Cancer is the most difficult diseases of the present age because its treatment involves the differentiation of healthy cells and infected cells. CNT has the potential to distinguish between them,it was observed that six pulses per second were fired at the 1.4W / CM2 DNA charge occupied Cell-release load is not accompanied by cell destruction and Precise control of therapeutic therapy the increase in local temperature is beneficial, and in the tumor site, there is permeability of the blood vessels,this improves the absorption of drugs in the same place, which increases the effectiveness of chemotherapy[25].

The main objective of this work was to obtain more unloading control of cefixime by prepared a cefixime /AC complex in another meaning loading the drug on carbon molecules and study the change of loading efficiency with the change of the size and quantity of carrier (AC) relative to the amount of the drug, In addition, the effect of the mentioned later factors on the unloading process was studied through the mass transfer coefficient

Methodology and Procedure

The experimental side goes through two stages. The first stage is to get the drugs loaded on the activated carbon molecules through the loading process. The second stage is the unloading process of the drugs, in other words, the emission of the drug from the AC surface through which could study the mass transfer coefficient of the drugs.

Drug loading / Preparations drug-AC sample

Two types was different in particles size from activated carbon used Macro particle size 0.6μ with surface area 544.4704 m2/g purchased from Sigma Aldrich and Nanoparticle size 11.042 nm with surface area 985.6013m2/g purchased from labshop41,cefixime purchased from Cayman company .using different percentages weight drug to weight for both activated carbon types (0.5, 1, 1.5) and calculation of the loading efficiency for all the variables.

Procedure for work

Dissolved the drug in ethanol according to saturation solubility of cefixime (5mg/ml)[22]. Add 1 g from activated carbon to the solution and mixing for 24 hour by the magnetic stirrer at room temperature after this the solution is filtered using Buchner funnel then The remaining material is dried in the oven for 4 hours at 40 Co [23].and the solution from Buchner funnel will be measured the concentration of drug in it by UV spectrometer. This concentration will be multiplied by the volume of the solution to determine the weight of the drug unloaded finally calculate the drug loading efficiency by

$$loading\ eff. = \frac{weight\ of\ drug\ in\ complex}{totat\ weight\ of\ complex} \quad \dots\dots a$$

Simulation solution preparation

The release of drugs measured in two medium PH 1.5 and PH6.5.Therefore acid solution with a pH of 1.5 was prepared from 99% Water injected and 1% hydrochloric acid, and two solutions made from 99% Water injected and 1% methanol100 ml of these solutions were taking in a beaker. And 40 mg of cefixime were taken according to the standard dosage weights of 400mg for the cefixime, which is suitable for the size of the stomach 1000 ml table 2 put the beaker in shaking water bath in three temperature (35,37,39)c^{o} and 50 rpm [24]. Then measuring the concentration at different time.

Study mass transfer coefficient

In this work The experiments were designed by Taguchi (licensing 17.1.0 2013) the number of variables 3, temperature, PH solution and time factors (PH solution two-level (1.5 and 6.5),temperature in co three-level (35,37 and 39) and time in hour three-level(1,3,5)).. the mass transfer coefficient calculate by use eq $\grave{c}$ as shown below, through using 18 run number of experiments for each type of activated carbon.

Table 1 Taguchi design for mass transfer study experiments

Factors	Name	Level values	Column	Level
A	PH	1.5 6.5	1	2
B	TIME(hr)	2 4 6	2	3
C	TEM9(c^o)	35 37 39	3	3

Area was calculated from the surface area of carbon and weight of carbon that calculated from efficiency and weight of drugs used from eq (a) as shown in the table 2.

Table 2 weight of complex used and area calculation

Drug	Weight of drug (mg)	Type AC	eff. %	Weight of complex (mg)	Weight of AC (mg)	Surface area(m^2/g)	Area (m^2)
Cefixime	40	macro	0.68	58.8	18.82	544.4704	10.25
		Nano	0.73	54.79	14.79	985.6013	14.58

Mass transfer coefficient calculation

mass transfer coefficient is best description for the system because it easily correlates the solutions concentration versus time[26].start with mass balance equation

$accumulation\ of\ drug\ in\ solution\ =$
$total\ dissolution\ rate$

$$V\frac{dc_1}{dt} = Aj_1 \quad \ldots\ldots b1$$

But $j_1 = A\,K\,(c_{1sat} - c)$

$$\therefore V\frac{dc_1}{dt} = A\,K\,(c_{1sat} - c_1) \quad \ldots\ldots b2$$

Integrate with boundary condition at (t=0 ,c_1=0)

$$\frac{c_1}{c_{1sat}} = 1 - \exp\left(-\frac{A\,K}{V}t\right) \quad \ldots\ldots c$$

$$K = \frac{V}{A\,t}ln\frac{c_{1sat}}{c_{1sat} - c_1} \quad \ldots\ldots \grave{c}$$

Where:-

A: Area of the particle, m^2

C_{tsat}: Concentration od drug in the surface of the particle (Saturated Solubility of the drug in fluid), $mole/m^3$

C_t: Concentration of drug at the edge of the fluid diffusion layer, $mole/m^3$

J_1: Molar flux rate of drug, $mole/m^2.hr$

K: Overall mass transfer coefficient, m/hr

t: time, hr

V: Volume of solution, m^3

Results and discussion

Loading drug discussion

Cefixime has loaded into blank AC both macro and Nano using the method described above, note from the table3 that there is a difference in the value of the efficiency of loading despite the availability of the same laboratory conditions this difference is due to the difference in the strength of the interaction between alcohol and medicine and the difference of saturation of carbon molecules between experience and other.Since loading is carried out in aqueous conditions, drugs limited solubility in solutions restricts the amount which may be dissolved in the reaction solution. As a result, the concentrations of these drugs was greater than the saturated solubility, the loading process becomes sterile unless the reaction is heated. Loading efficiency reaches a maximum around 24 hours of incubation, after which the loading efficiency no longer increases and in some cases is even lowered.

Table 3 cefixime loading experiment results

Drug	Type of AC	$\frac{W(drug)gm}{W(AC)gm}$	Vol. of ethanol (ml)	W of complex before dray	W of complex after dray	Vol. of sol. Remain (ml)	Cons. drug (g/ml)× 10^{-3}	W drug unload. (g)	W drug loading (g)	eff. %
cefixime	Macro	$\frac{0.5}{1}$	100	3.667	1.147	42	2.46	0.103	0.396	34
		$\frac{1}{1}$	200	4.234	1.234	115	2.1	0.242	0.758	61
		$\frac{1.5}{1}$	300	4.874	1.437	182	2.91	0.53	0.97	68
	Nano	$\frac{0.5}{1}$	100	4.036	1.036	37	1.82	0.067	0.432	41
		$\frac{1}{1}$	200	5.356	1.273	107	1.74	0.186	0.814	63
		$\frac{1.5}{1}$	300	5.904	1.628	159	1.93	0.306	1.193	73

The comparison between the macro and Nano particle size of AC on the loading efficiency was shown in figure 1The loading efficiency was slightly increase when the AC particle size decreases from macro to Nano size at any ratio of W drug / W AC while a maximum loading efficiency at 1.5/1 ratio for both type of AC .

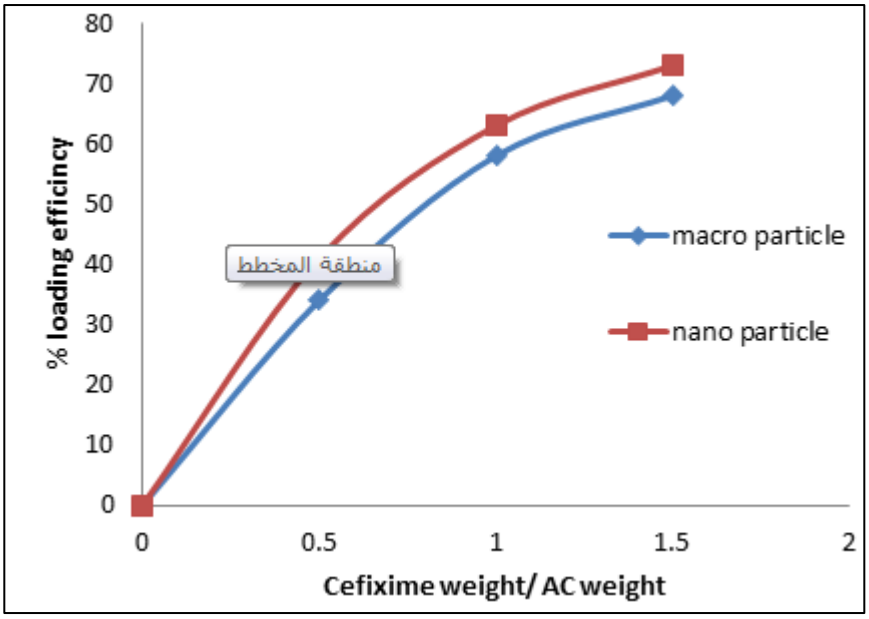

Figure 1: Cefixime loading efficincy behavior

Release drug discussion

drug release from the complex was Incomplete could be due to poor wettability of carbon particles may increase or decrease the emission period and this can be due to the stronger effect of AC porosity on Solubility profiles Compared with the properties of the drug, the higher surface area of the AC pores have the in contact with The media solution, which can lead to faster release; thus, the drug loaded into AC, compared to Pure drugs , preferably faster release also when compared between the macro.AC/drug complex and nano.AC/drug complex.

Figure2 show that at 6 hours ~100% drug release when the drug pure without carbon and >90% release from macro particle activated carbon while the best result release ~80% was from nanoparticle activated carbon .

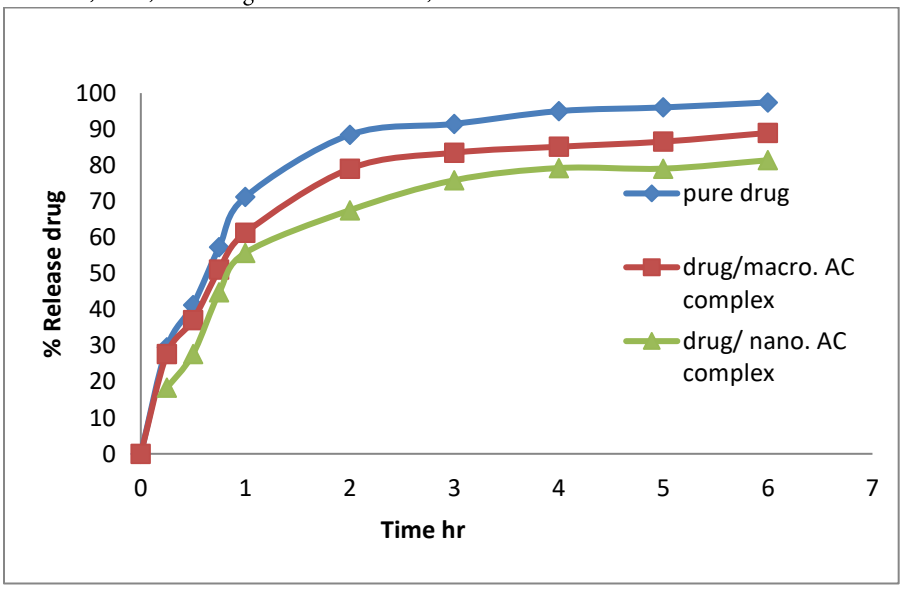

Figure 1 cefxime release pattren in PH1.5 solution at 37c°

Figure3 show that at 6 hours ~100% drug release when the drug pure without carbon and < 70 % release from macro particle activated carbon while the best result release > 70 % was from nanoparticle activated carbon. The Comparative

between figure 2 & 3 show that at PH6.5, the drug release was more control.

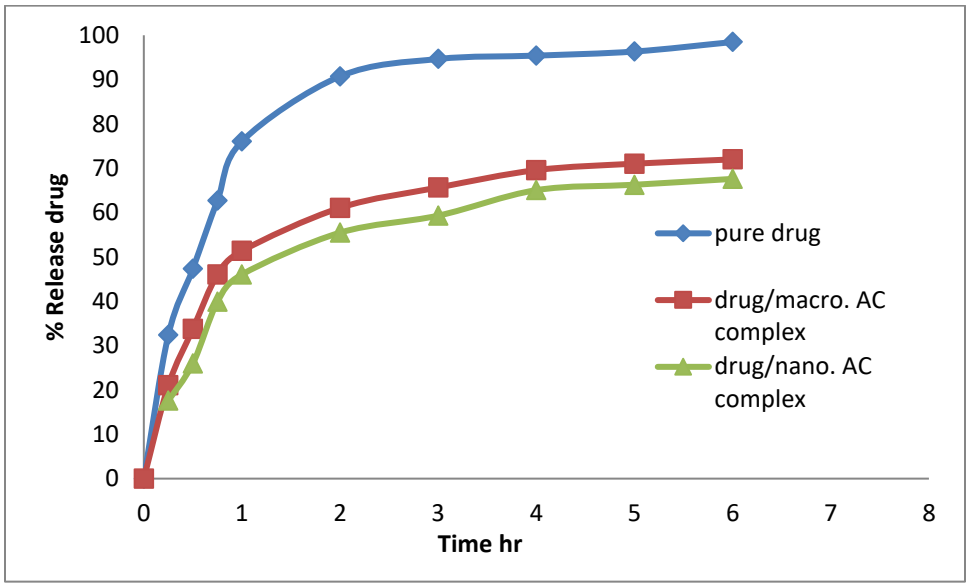

Figure 2 cefixme release pattren in PH6.5 solutionat 37c°

The effect of mass transfer coefficient has was studied on both macro and Nano size particle at different temperature and at different medium, as shown in figures below4-7 the mass transfer coefficient at any temperature has the highest value at the first hour and decreases with time. The maximum value calculated was for 37 C° flowed at 39 C° and 35 C°.

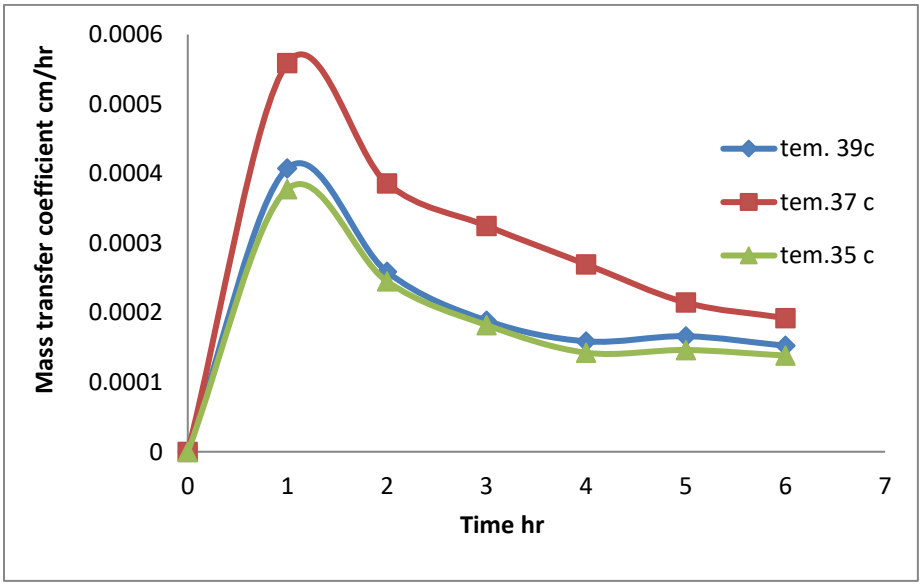

Figure 3 mass transfer coefficient variation with time for cefixime/nano AC sample at PH1.5 solution

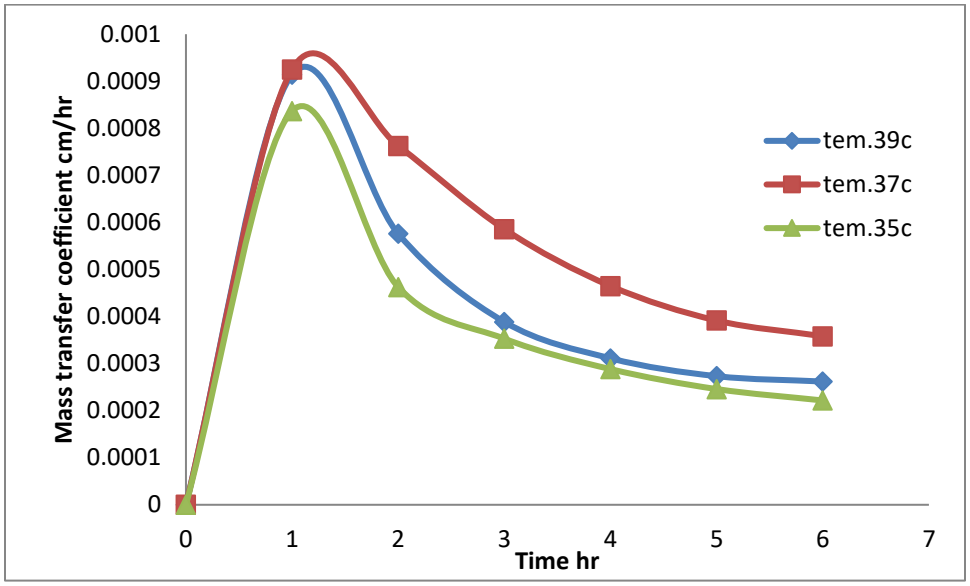

Figure 4 mass transfer coefficient variation with time for cefixime/macro.AC sample at PH1.5 solution

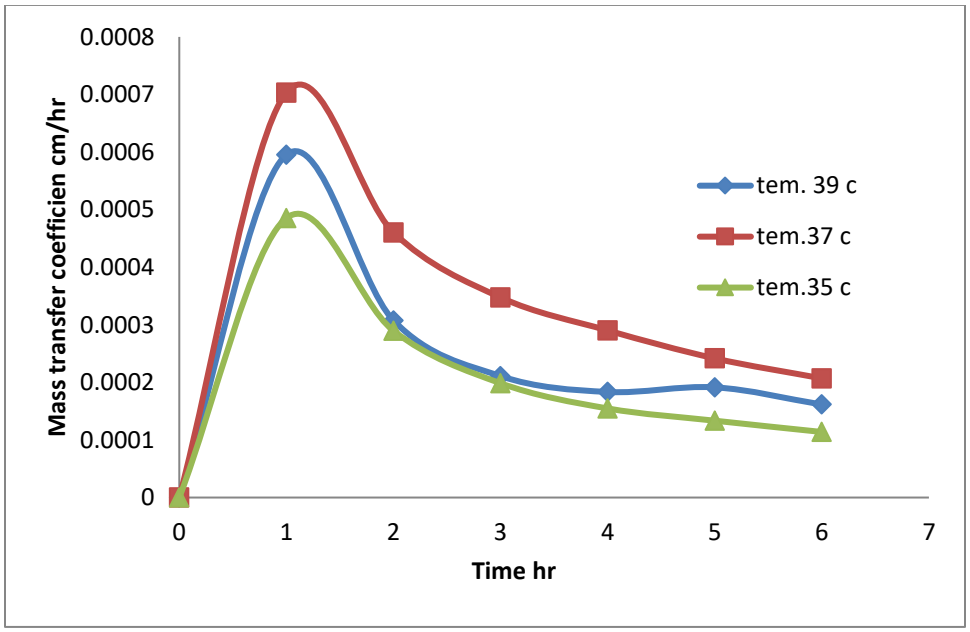

Figure 5 mass transfer coefficien variation with time for cefixime /macro.AC sample at PH 6.5 solution

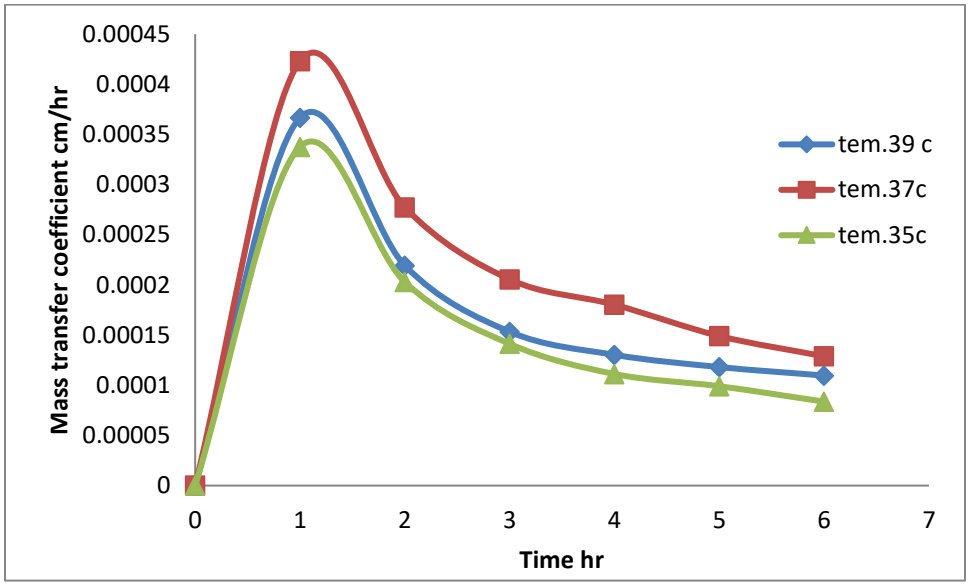

Figure 6 mass transfer coefficient variation with time for cefixime/nanoAC sample at PH 6.5 solution

Figures 8 &9 show the main effect plot .When the line is horizontal, then there is no main effect. Each level of the factor affects the characteristic in the same way and the characteristic average is the same across all factor levels [27]. When the line is not horizontal, then there is a main effect. Different levels of the factor affect the characteristic differently. The larger the difference in the vertical position of the plotted points by comparing the slopes of the lines, you can compare the relative magnitude of the factor effects [28].

-Cefixime/macro.AC sample, The most effective parameter is the time (73.53%) and the least effect is the temperature(6.76%) .

-Cefixime/nano.AC sample, The most effective parameter is the time (79.55%) and the least effect is PH solution (6.18%).

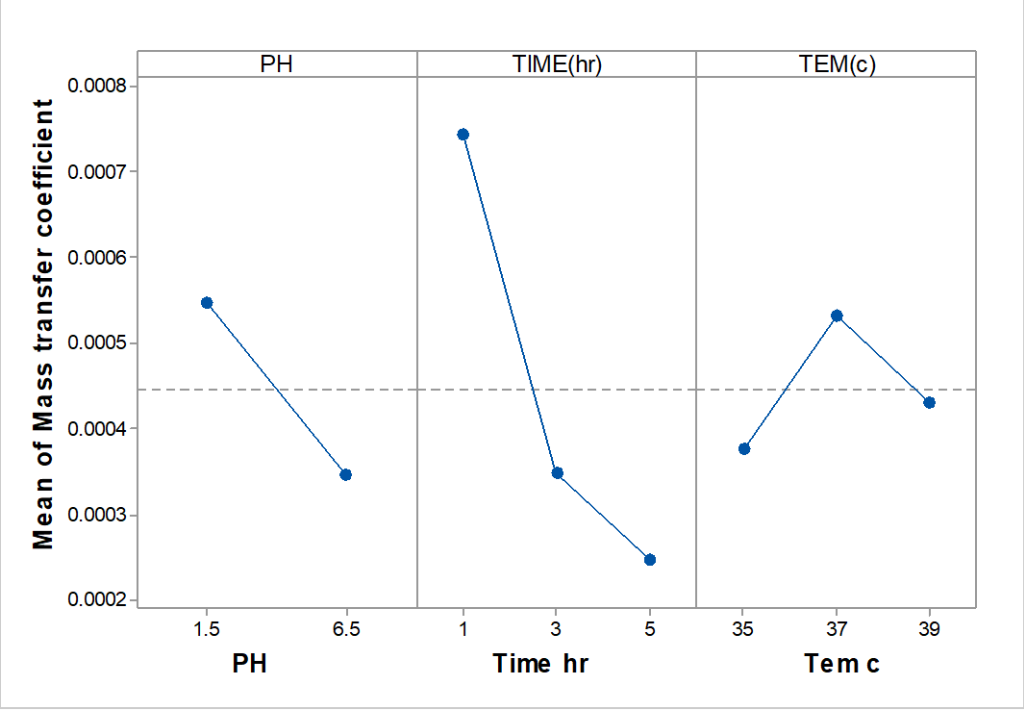

Figure 8: Main effects plot for cefixime / macro AC sample experiments in Taguchi program

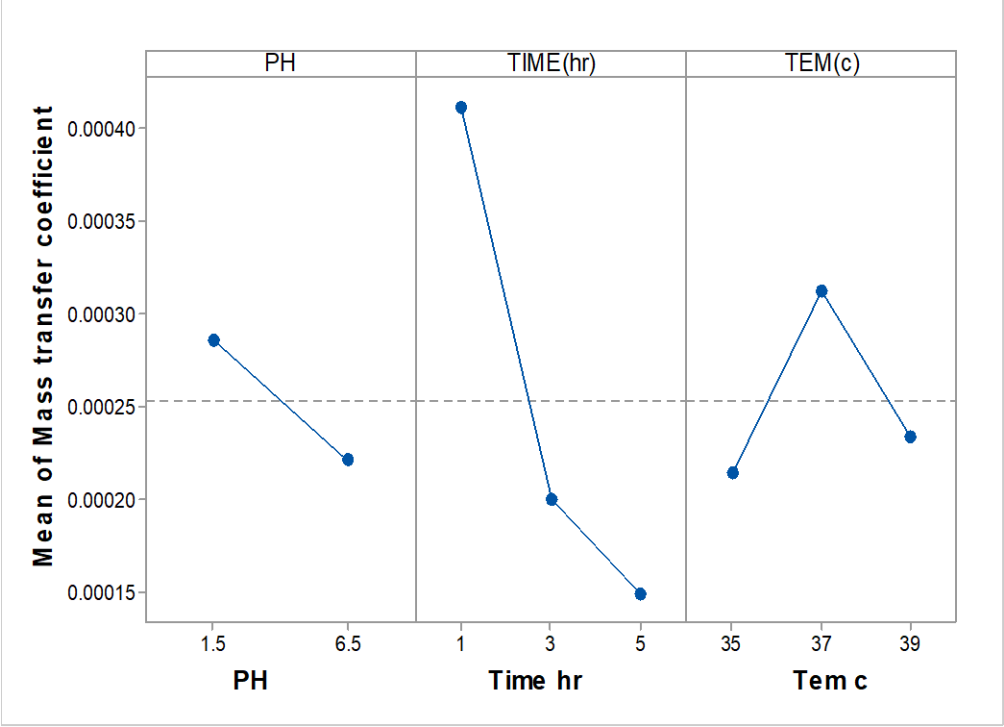

Figure 9: Main effects plot for cefixime / nano.AC sample experiments in Taguchi program

CONCLUSIONS

Cefixime was loading successfully into AC, with a high drug loading efficiency 73% in Nano AC and 68% in macro AC. Surface area is a very important factor affecting the loading efficiency because simply as surface area increased, the chance of adhesion of the drug molecules on the carbon surface increased. Certainly, when smaller the particles size of carbon then greater the surface area so loading efficiency of drugs increased when the particle size of carriers decreased ,maximum loading of drugs occurred when the weight of cefixime more than the weight of activated carbon . The unloading of cefixime was more control when the activated carbon in nanoparticle size that gives more control mass transfer process . highest mass transfer coefficient occurred at temperature 37c^{o} corresponds to the temperature of the human body and when the PH solution was 1.5.

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