Formulation of Alpha Tocopherol Acetate as a Powder Dosage Form by Adsorption

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Abstract :

Alpha-tocopherol acetate is one of the most important vitamin E derivatives,that were used as antioxidants. Adsorbents like kaolin, magnesium carbonate, and microcrystalline cellulose were used successfully to incorporate oily alpha-tocopherol acetate into an acceptable powder dosage form. The results revealed that microcrystalline cellulose as an adsorbents gave the best results with 50% loading capacity at time, 8 minutes before and after incubation period (3 months at 30C°), while kaolin and magnesium carbonate have been shown a significant difference before and after incubation. Addition of 1% w/w magnesium carbonate to the kaolin enhanced the loading capacity by decreasing the time of adsorption from 20 to 6 minutes and 47 to 9 minutes before and after incubation respectively. The study indicated that the best adsorbent to be used in case of oral vitamin E toxicity is microcrystalline cellulose while magnesium carbonate could be used in the formulation for their best adsorption effect.

Key words : Adsorption , Tocopherol Acetate powder

الخلاصة

الفا توكوفيرول اسيتيت كعقار هو واحد من اهم مشتقات فيتامين "هـ" والذي يستعمل بكثرة كمضاد للتاكسد الممتزات مثل الكاؤلين, كاربونات المغنيسيوم و المايكروكرستلاين سلليلوز قد استعملت بنجاح في تقديم الالفا توكوفيرول اسيتيت الدهني على شكل باودر كجرعة دوائية صلبة. لقد اشارت النتائج الى ان المايكروكرستالين سلليلوز هو افضل ممتز للعقار بنسبة تحميل 50% في وقت قارب من 8 دقائق بينما اظهر كل من الكاؤلين و كاربونات المغنيسيوم فرق واضح في نسبة التحميل قبل و بعد فترة الحضانة (ثلاثة اشهر في درجة حرارة 30مئوي).ان اضافة 10% نسبة وزن الى وزن من كاربونات المغنيسيوم الى الكاؤلين قد زاد من نسبة التحميل اعلاه من خلال تقليص فترة الامتزاز من 20 دقيقة الى 6 دقائق , و 47 دقيقة الى 9 دقائق قبل و بعد فترة الحضنة و على التوالي . كما اشارت الدراسة الى ان افضل ممتز يستعمل في حالات التسمم بالفا توكوفيرول اسيتيت هو المايكرو كرستيلاين سلليلوز بينما تفضل كاربونات المغنيسيوم في تركيب الباودر كافضل ممتز.

Introduction :

Sorption is a selective transfer of gas or liquid onto the surface and into the bulk of liquid or solid sorbent[(1)].The substance being adsorbed is called the adsorbate and the substance on which it is adsorbed is called the adsorbent[(2)]. The fine state of subdivision of inert powders confers high adsorptive capacity upon them[(3)]. Adsorption at solid surfaces is involved in nearly every aspect of pharmaceutical development, from formulation design, process development, and manufacturing especially for low-dose drugs in the manufacturing of solid dosage formulations [(4)]. Most of adsorbents differ in their ability of adsorptivity ability besides physical and chemical nature differences like Kaolin, Magnesium carbonate, Pectin, Charcoal, and Microcrystalline cellulose "MCC". Different variety of techniques were used to incorporate oily or liquid drugs in an acceptable pharmaceutical dosage forms using soft gelatin capsules or adsorbent powders, which then can be used as a powdered drug form. The objective of this study was to formulate alpha-atocopherol acetate which is oily derivative of vitamin E series as a solid powder using different adsorbent materials since these vitamin derivatives are difficult to introduce into solid powders or granules dosage form [(5)].

Experimental work :

Materials and Instruments: -

Alpha-tocopherol acetate oily liquid and Microcrystalline Cellulose (Avicel PH 102) Supplied by Samara Drug Industries (SDI). IRAQ , Magnesium carbonate (hydrated) Basic light from B.D.H. Chemicals LTD, Pool, England , Kaolin lave (light) from Prolabo, Rhone-Poulenc, Perroux, S.A. Macon, France , All other reagents were of analytical grade , Sartorius balance AG Gottingen, BL210S, CE, Germany , pH meter, Orchidis Laboratories, France and Hanna instruments type, France , Dissolution apparatus type II, Dis6000, Copley scientific, Nottingham, U.K , U.V. Visible Spectrophotometer, Citra 5, GBC Scientific equipment, U.S.A.

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Methods: -

Characterization of alpha-tocopherol acetate:

10 mg of alpha-tocopherol acetate was dissolved in sufficient amount of absolute ethanol and then diluted to 100ml. The U.V. light absorption was examined between 230nm and 350nm[5].

Formulation of powdered alpha-tocopherol acetate:

Different formulas were prepared, The method was carried out by incorporation equivalent amount of alpha-tocopherol acetate (400mg) as an oily adsorbate in a petridish, then each adsorbent (of formula 1, 2and 3 in table 1) was added into the surface of liquid adsorbate gradually until the oily layer of adsorbate disappeared and dusty powder began to appear, which indicate that the oily adsorbate (alpha-tocopherol acetate) interfere and enclosed by adsorbent powder particles. Additional amount of adsorbent was added until the dual final product become as like as adsorbent parent.

Table (1) Formulas represents alpha-tocopherol acetate as adsorbate with different amounts and types of adsorbents

Formula no.	1	2	3	4	5
Alpha tocopherol acetate	400 mg	400 mg	400 mg	400 mg	400 mg
Kaolin	3000 mg	--	--	3000 mg	
Magnesium carbonate	--	1000 mg	--	34 mg	24 mg
Microcrystalline cellulose (Avicel PH 102)	--	--	2000 mg	–	2000 mg

The weight of final product was determined, then the difference between total amount of final product and the adsorbate (400 mg) represent the weight of adsorbent incorporated in the formula.

Mixing of more than one adsorbent with alpha-tocopherol acetate, (formulas 4 and 5) was used, in which magnesium carbonate concentration was 1% of the total formula [6].

Estimation of angle of repose:

A static heap of powder, with only gravity acting upon it, will tend to form a conical mound by their flowing over a petri-dish from a funnel, The diameter of the static mound (d) and the high of it (h) were measured to determined the angel of repose (θ), as follows [7]:

$$\tan \vartheta = \frac{h}{d}$$

Dissolution study: -

The dissolution characteristics was carried out for the equivalent of 100 mg of alpha-tocopherol from each of the five formulas in a powder form under sink conditions using 900ml of dissolution media of 0.1N HCl (pH=1.2) maintained at 37Cº (± 0.5 Cº) at constant stirring speed (100rpm). Different samples were taken for analysis at specified time intervals (10, 20, 30, 40, 50, 60, 120 minutes), and replaced with the same volume of 0.1N HCL. One milliliter of each sample was diluted to 10 ml by absolute ethanol then filtered. The absorbancy was determined spectrophoto-metrically at their specify 285nm. λmax.

Results and Discussion :-

The scanning of pure alpha-tocopherol acetate oil in absolute ethanol showed maximum absorbance at 285nm[5], which is agree the reported data. while the prepared alpha-tocopherol acetate powders of a different formulas showed best flowability in formulas 1 and 4 (angle of repose 22°-30°) and an acceptable flowability in formula 3 (angle of repose 26°-34°), and bad flowability with formula 2 (with angel of repose >50°) [3]

Dissolution of alpha-tocopherol acetate from adsorbents before incubation period:

The dissolution study for the effect of incorporating of alpha-tocopherol acetate for dissolution study onto kaolin adsorbent before incubation showed that 100% of the drug was released after 10 minutes as shown in figure 1, this may be attributed to the presence of free form (not adsorbed) of the drug in the formula besides to the adsorbed form. In addition, the different polarity between the adsorbate and the adsorbent in the dissolution media[8]. By extending the period of dissolution, it was seen that the amount of drug release was decreased after 10 minutes and reach to about 5% after one hour, this behavior may be referred to the reverse adsorption process that began after 10 minutes by adsorbent (kaolin in figure 1) in acidic media. In addition, the hydrolysis of acetate salt of alpha_tocopherol in acidic pH make the lipophillic property of alpha-tocopherol more than the parent one to leave the surface of kaolin particles.

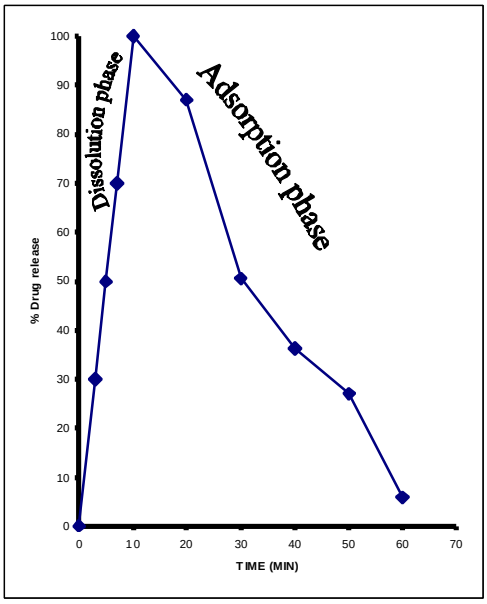

Figure 1: The percent of alpha-tocopherol acetate released from kaolin adsorbent at pH 1.2 before incubation period.

A hundred percent of drug release after (10 min) was also obtained when magnesium carbonate (formula2) and microcrystalline cellulose (formula3) were used as adsorbent as shown in figure 2 and 3, respectively. This indicated that microcrystalline cellulose alone was faster as adsorbent than kaolin and magnesium carbonate because of its intermolecular forces, that will form a cross-linkage between microcrystalline cellulose and alpha-tocopherol acetate [9].

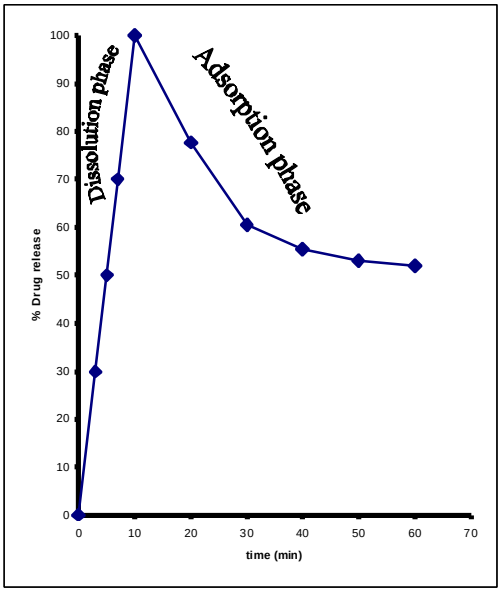

Figure 2: The percent of alpha-tocopherol acetate released from magnesium carbonate adsorbent at pH 1.2 before incubation period.

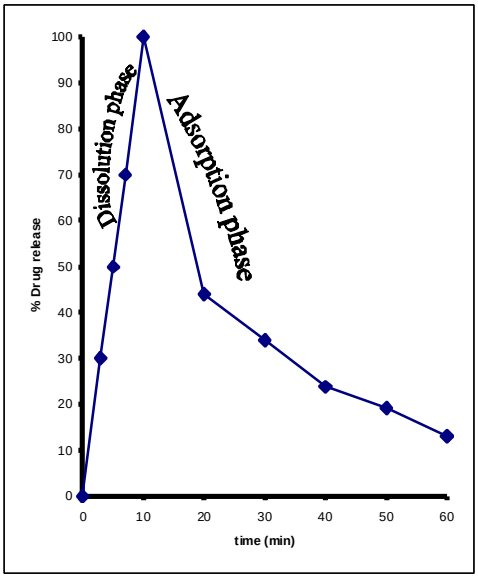

Figure 3: The percent of alpha-tocopherol acetate released from microcrystalline cellulose adsorbent at pH 1.2 before incubation period.

On the other hand magnesium carbonate showed lowest adsorptivity than other adsorbents used, since light magnesium carbonate converted into magnesium chloride in presence of acidic media (pH 1.2), which results in a decrease in the amount of adsorbent ready to utilize their adsorbate amounts, as shown in table 2.

Table 2: The time of 50% release of alpha-tocopherol acetate at two phases for different formula before and after incubation period.

Time for 50 percent release of alpha-tocopherol acetate					
Formula	Adsorbent	Before incubation		After incubation	
		Dissolution phase	Adsorption phase (-time of 100% release)	Dissolution phase	Adsorption phase (-time of 100% release)
1	Kaolin	6 min	20 min	26 min	47 min
2	Magnesium carbonate	6 min	40 min	4 min	14 min
3	Microcrystalline cellulose	6 min	8 min	22 min	8 min
4	Kaolin + magnesium carbonate	6 min	6 min	6 min	9 min
5	Microcrystalline cellulose + magnesium carbonate	6 min	7 min	19.5 min	15 min

In an attempt to utilize these differente adsorptivity of adsorbent used alone, kaolin and microcrystalline cellulose were mixed separately with 1% (w/w) of the total weight magnesium carbonate (formula 4 and 5). It was seen that the time for 50% release of alpha-tocopherol acetate in adsorption phase was 6 and 7 minutes for formula 4 and 5 respectively as shown in figures 4 and 5. These different results may be attributed to the different affinity of alpha-tocopherol acetate to the mixed adsorbents used at certain conditions like temperature and pressure [9].

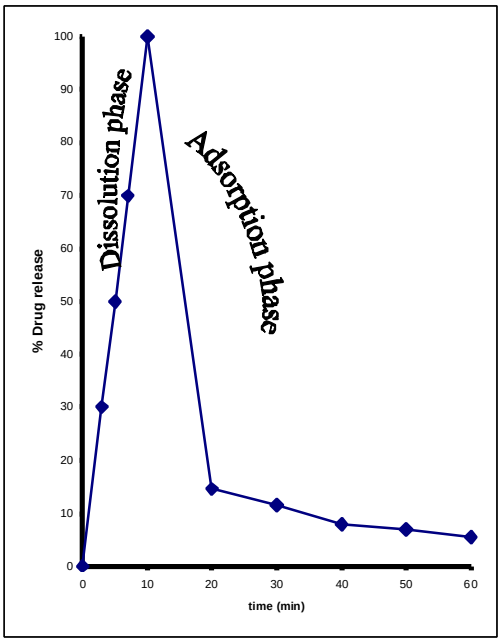

Figure 4: The percent of alpha-tocopherol acetate released from adsorbent mixture of kaolin and magnesium carbonate at pH 1.2 before incubation period.

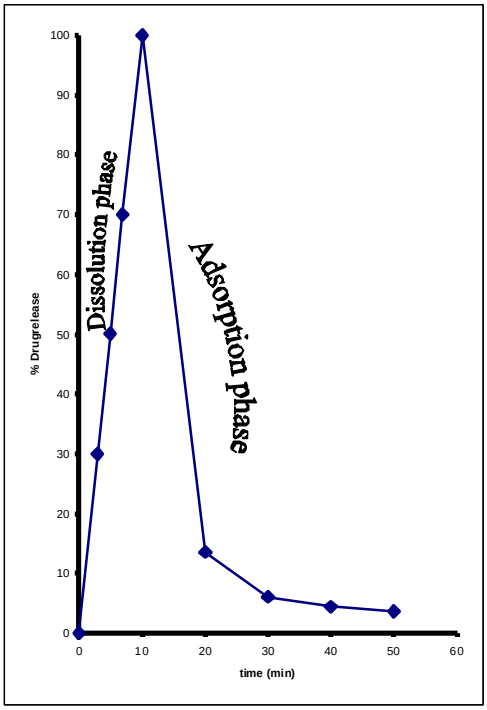

Figure 5: The percent of alpha-tocopherol acetate released from adsorbent mixture of microcrystalline cellulose and magnesium carbonate at pH 1.2 before incubation period.

Langmuir principle as a base for adsorption process can be used to estimate the slope results from the dissolution profile of **(C)**, concentration at equilibrium, versus **C/(x/m)**, as shown in figure 6.According to this base, the smaller the slope is better for adsorption. c/y = 1/ bym + c/ ym where c = equilibrium conc. ' y = amount of adsorbate (mg.) adsorbed per (gm.) of adsorbent" b; empirical affinity (binding constant) , ym, is the amount of adsorbate per unit weight of adsorbent .

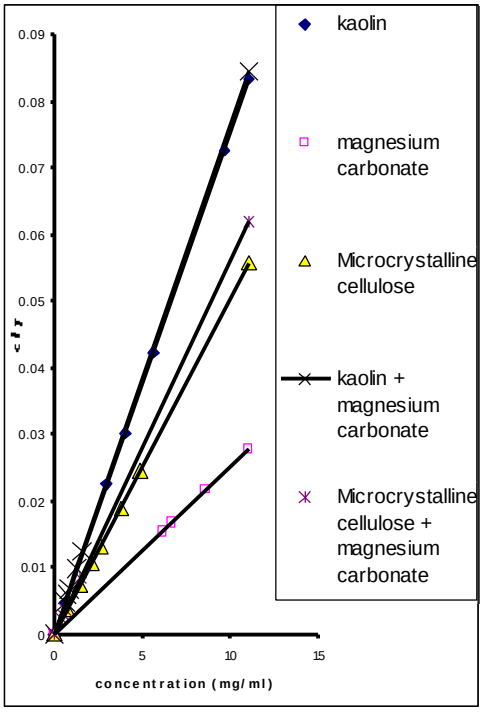

Figure 6: Adsorption of drug on various adsorbents before incubation period

Dissolution of alpha-tocopherol acetate from different adsorbents after incubation period: -

The effect of incubation of alpha-tocopherol acetate as an adsorbate with different adsorbents for 3 months period was studied. It was seen that 100% of alpha-tocopherol acetate release from kaolin in 0.1 N HCl (pH 1.2) takes over 50 minutes compared with 10 and 40 minutes for magnesium carbonate and microcrystalline cellulose, respectively, as shown in figures 7, 8 and 9.

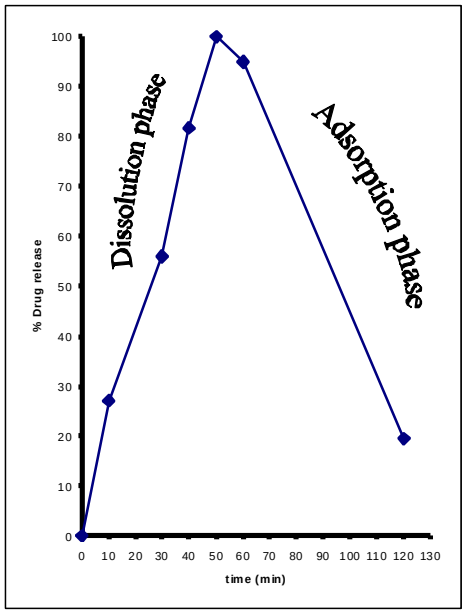

Figure 7: The percent of alpha-tocopherol acetate released from kaolin at pH 1.2 after 3 months of incubation period.

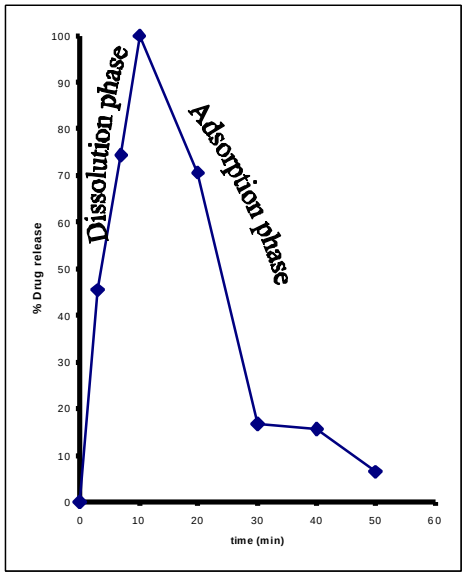

Figure 8: The percent of alpha-tocopherol acetate released from magnesium carbonate at pH 1.2 after 3 months of incubation period.

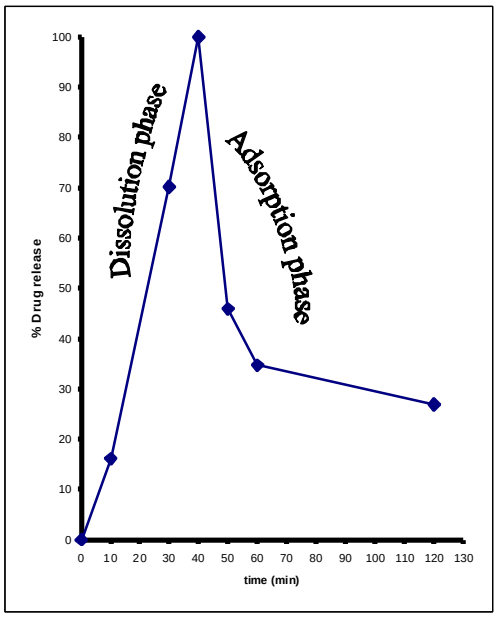

Figure 9: The percent of alpha-tocopherol acetate released from microcrystalline cellulose at pH 1.2 after 3 months of incubation period.

These results differ significantly from those obtained before incubation, this may be attributed to the enough time allowed to alpha-tocopherol acetate to penetrate inside adsorbent particles, beside settlement and equilibrium stabilization of both adsorbent and adsorbate occurred. Meanwhile the difference in 100% release time among different formulas may be attributed to the different affinity of adsorbent used. Kaolin behaved as the best of the other adsorbents used and this may be due to the difference in polarity of both kaolin and alpha-tocopherol acetate[8]. The addition of 1% (w/w) of total weight of magnesium carbonate for both to kaolin and to microcrystalline cellulose, resulted in an increase in 100% of alpha-tocopherol acetate release, as shown in figures 10 and 11.

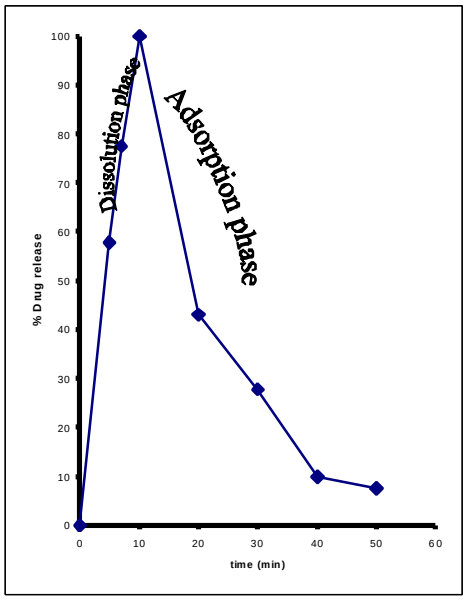

Figure 10: The percent of alpha-tocopherol acetate released from adsorbents mixture of kaolin and magnesium carbonate at pH 1.2 after 3 months of incubation period.

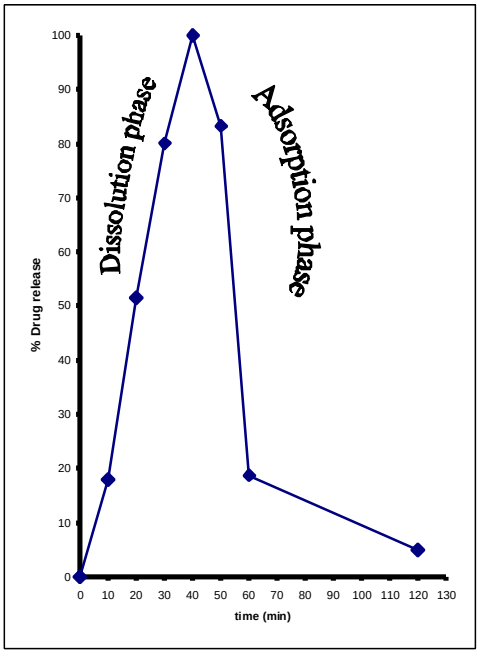

Figure 11: The percent of alpha-tocopherol acetate released from adsorbents mixture of microcrystalline cellulose and magnesium carbonate at pH 1.2 after 3 months of incubation period.

On the other hand, the time for 50% drug release in the adsorption phase for different formulas may be attributed to change in physical property of both alpha-tocopherol acetate and adsorbent used during incubation period. In general, magnesium carbonate enhanced the dissolution phase by its rapid solubility and enhanced the adsorption phase, as in formula 4, due to its higher affinity to alpha-tocopherol acetate [10]. The overall results of adsorption phase indicated that the microcrystalline cellulose when was used alone as an adsorbent was the best one compared to kaolin or magnesium carbonate, while addition of 1% w/w magnesium carbonate to the total weight of formula 1 enhanced the adsorptivity of kaolin. Langmuir plot as a base of adsorptivity indicated that there was a significant difference ($p<0.05$) in the affinity of the alpha-tocopherol and adsorptivity of different formulas with that before incubation, as shown in figure 12 since the adsorptive affinity still constant but the difference was in the presence of free drug in the formulas before incubation that will not found after incubation due to a more contact time between the adsorbent and the adsorbate which will change the loading and then the amount of drug released.

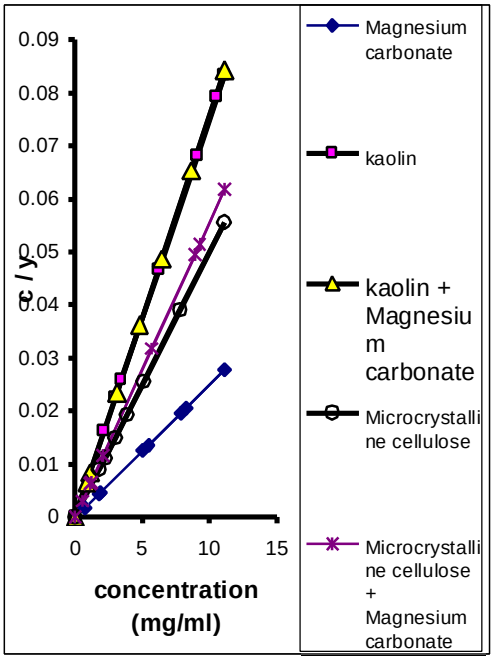

Figure 12: Adsorption of drug on various adsorbents after 3 months of incubation period

Conclusion :-

Based on the results obtained from this study, one can conclude the following:

1. Oily alpha-tocopherol acetate was successfully converted into powdered form that is easy to formulate in a suitable solid dosage form like tablets and powders.

2. Microcrystalline cellulose was the best adsorbent with loading time 50% adsorption 8 minutes before and after incubation, while (kaolin and magnesium carbonate) gave a significant difference before and after 3 months incubation period of prepared alpha-tocopherol powder.

3. Incorporation of 1% of magnesium carbonate to the total weight of kaolin adsorbent enhance the adsorptivity of the resultant powder mixture from 20 to 6 minutes and from 47 to 9 minutes before and after incubation period, respectively.

4. The enhancement of magnesium carbonate as synergistic adsorbent was confined using Langmuir slop as an index for a good adsorption, since magnesium carbonate has slop 0.0025 compared with 0.0075 and 0.005 for kaolin and microcrystalline cellulose respectively.

5. These results can be also conducting in alpha-tocopherol acetate toxicity, since best loading capacity resulted by microcrystalline cellulose while best adsorption effect resulted by magnesium carbonate .

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