Some Variables Affecting Microencapsulation of d–alpha Tocopherol Succinate

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الخلاصة

د – الفا تو كوفيرول سكسونيت هو واحد من أهم الفيتامينات الموجودة والذي هو حالياً يستخدم في هذه الأيام في الغذاء والتغذية نظراً لفعاليته البايولوجية العالية ضد تكونات المتطرف الحر داخل الخلية.
الدراسة الحالية قد توضحت من خلال المواضيع التالية :

- الكبسولات المجهرية لعقار د – الفا تو كوفيرول قد حضرت بمختلف النسب للمادة اللبية والغلاف الخارجي وبنسب 1:1, 2:1 وكذلك 3:1 بطريقة المنتشر الصلب.
- الكبسولات المجهرية والمحضرة بشكل مسحوق وبنسبة مادة لبية إلى الغلاف الخارجي 1:1 قد حضرت بشكل حبوب كجرعة دوائية ذات شكل وصلابة جيدة.
- وجد أن تحرر العقار من الكبسولات المجهرية يزداد كدالة بزيادة المادة اللبية إلى الغلاف الخارجي, سرعة الدوران وكذلك إلى الوسط الهايدروجيني الحامضي.
- أن شكل تحرر العقار لمجموع المادة المتحررة في وسط هايدروجيني حامضي مختلف, يعطي دلالة على استعمال هذا النوع من تحرر العقار كجرعة دوائية طويلة المفعول.
- أن الدراسة قد أعطت حماية جيدة للعقار أعلاه من العوامل البيئية الخارجية.

ABSTRACT

d-alpha tocopherol succinate, (Vit.E) is one of the most important vitamin, that is incorporated in food and nourishment due to its high biological activity against free radical formation inside cells.
This study was illustrated in the followings:
- Microcapsules of d - alpha tocopherol were prepared from different core:wall ratios 1:1 , 1:2 and 1:3 by solid dispersion method using ethyl cellulose (Ethoel ®) polymer .
- The powdered microcapsules with 1:1 core:wall ratio is formulated as tablets with good appearance and hardness.
- The drug release was found to be increased as a function of increasing, core:wall ratio, stirring speed and pH – medium.
- The profile of cumulative different pH – medium release of the drug gives rise an indication of prolonged release dosage form. " during 6hrs. of dissolution"

INTRODUCTION :

Microcapsules consist of a thin wall which can enclose a solid or a liquid core material. The core may also referred to as the nucleus and coating material as the shell[1].
Microcapsule technology is used in a certain process to protect drug from some environmental conditions like physical and chemical interactions including oxidation and some light action[2].
Also a good sustained release has been achieved by microencapsulating poorly water soluble drugs such as oxolamine citrate and amoxicillin[3].
Solid dispersion an easy method for enclosing variable drug particles, is used widely to achieve a good protection for susceptible particles[4] and to control drug release from enclosed drug particles[5].

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Vitamin E, (d – alpha tocopherol succinate) as the only solid type of all vitamin E derivatives, used in medicine as drug therapy besides to its daily body supplement[6].
Tableting of microcapsules has been shown to slow the release significantly and provide prolonged action release, mainly for those prepared with ethylcellulose walls using solvent evaporation method[7].

MATERIALS AND METHODS:

Materials

- d – alpha tocopherol succinate supplied by Samarra Drug Industry (SDI), Iraq.
- Ethylcellulose (46.5% Ethoxy group), (Ethocel) (BDH) Chloroform, Hydrochloric acid form (BDH), Liverpool, England.
- Lactose, Disodium hydrogen phosphate, Methanol, from Riedal De Haen, Ag Seelze, Hanover.
- All other reagents and materials, were of analytical grade.

Methods

Preparation of microcapsules

One gram of hydrophobic substance d – alpha tocopherol succinate was dispersed in a dispersion medium containing 1% (w/v) ethylcellulose polymer in a mixture of 50% (v/v) chloroform:methanol solvent.
The mixture was stirring until homogenous dispersion was obtained, then spread the mixture on a surface of petridish, and allowed for slow evaporation of solvent at room temperature for 4 days[8].
The dried mixture was crushed and pulverized through 18mesh size seive and compressed into 7mm flat tablets.
The same above procedure was carried out for 2 and 3% (w/v) ethylcellulose polymer coating.

Preparation of prolonged action tablets

Five gram of Pulverized granules (18mesh) of 1:1 over wall ratio were mixed with equal quantity of dried lactose as diluent and compressed into 7mm diameter tablets using single flat punch machine each resultant tablet contains 50mg, microcapsules granules, equwalent to 23.3mg d-α- tocopherol succinate (Loading 93.2), 50mg dried lactose and 1mg magnesium stearate as lubricant, the compression force applied was fixed through all the core:wall ratio granules compression.
Then tablet breaking strength was determined by means of Monsanto–Hardness tester.

Dissolution Studies

The dissolution characteristic of d–alpha tocopherol succinate, tabletted and powdered microcapsules were studied at different stirring speed (50, 100 and 150r.p.m) in 900ml of different phosphate buffer medium (pH2, pH4 and pH7).
The total weight of microcapsules is 101mg for both tablet and powdered microcapsules. The dissolution was carried out in a sink condition maintained at 37°C, 10ml of filtered samples were taken for analysis at specified time (for 6 hours), replaced by the same buffer solution, then sample diluted to required volume by methanol and absorbance measured spectrophotometrically by U.V.at λmax 278nm[1].

RESULTS AND DISCUSSION:

Effect of core:wall ratio

The influence of different core:wall ratios are shown by (Fig. 1 and 2) and (Table 1) for the two most promising samples involved powdered and tabletted microcapsules for three different core:wall ratios.

The dissolution of d–alpha tocopherol succinate from microcapsules was increased as a function of core percent increase in the microcapsules, because these microcapsules had thinner wall making penetration of both dissolution medium and the core solution through the walls easier.

Also because of the higher core:wall ratios, there were more particles per microcapsule, resulting in a higher concentration gradient to boost dissolution[9].

The same considerations are controlling factors for dissolution from the tabletted microcapsules. Since the microcapsule wall still has to be penetrated to release the core, the only difference is the compact nature of the tablet as compared with corresponding microcapsules, since compacting microcapsules results in a greatly reduced surface area being available to release[10].

Besides to that, compression of microcapsules results in reducing channel permeation "porosity and tortousity" results in a considerable slowing of the release from the tabletted microcpsules compared with untabletted microcapsules.

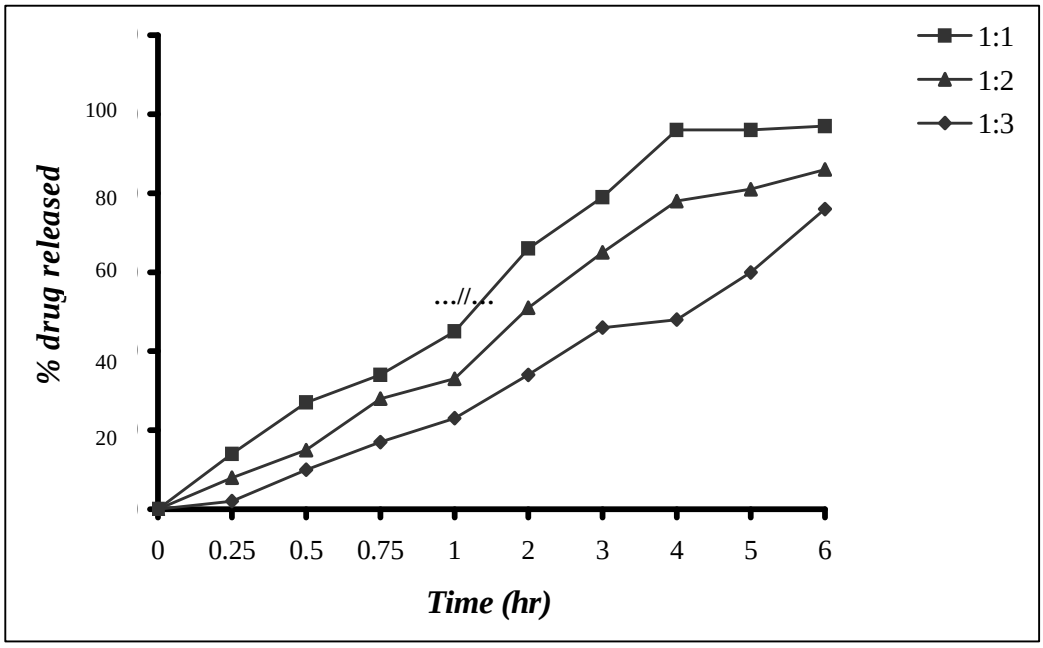


FIGURE 1 . THE EFFECT OF CORE:WALL RATIO ON THE RELEASE OF D – ALPHA TOCOPHEROL SUCCINATE FROM POWDERED MICROCAPSULES AT PH7.

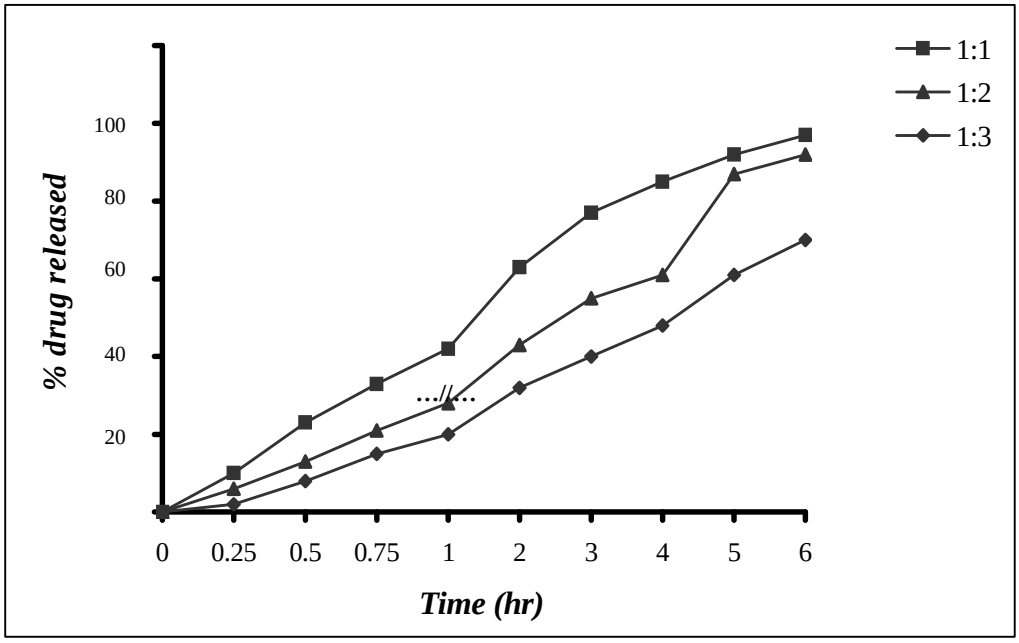


FIGURE 2 . THE EFFECT OF CORE:WALL RATIO ON THE RELEASE OF D–ALPHA TOCOPHEROL SUCCINATE FROM TABLETTED MICROCAPSULES AT PH7.

Table 1 . Percentage of d–alpha tocopherol succinate released from microcapsule (Powder and Tablet).

Time (hr.)	(*) Percent Drug Release					
	Yield% Core:wall Efficiency% (87.8) 1 : 1 (93.3)		Yield% Core:wall Efficiency% (85.1) 1 : 2 (91.2)		Yield% Core:wall Efficiency% (79.7) 1 : 3 (84.5)	
	Powder	Tablets	Powder	Tablets	Powder	Tablets
0.25	14	10	8	6	2	2
0.50	27	23	15	13	10	8
0.75	34	33	28	21	17	15
1.00	45	42	33	28	23	20
2.00	66	63	51	43	34	32
3.00	79	77	65	55	46	40
4.00	96	85	78	61	48	48
5.00	96	92	81	87	60	61
6.00	97	97	86	92	76	70

(*) buffer medium pH_7
(**) $p<0.05$ is significant with corresponding percent of drug release.

Effect of stirring speed

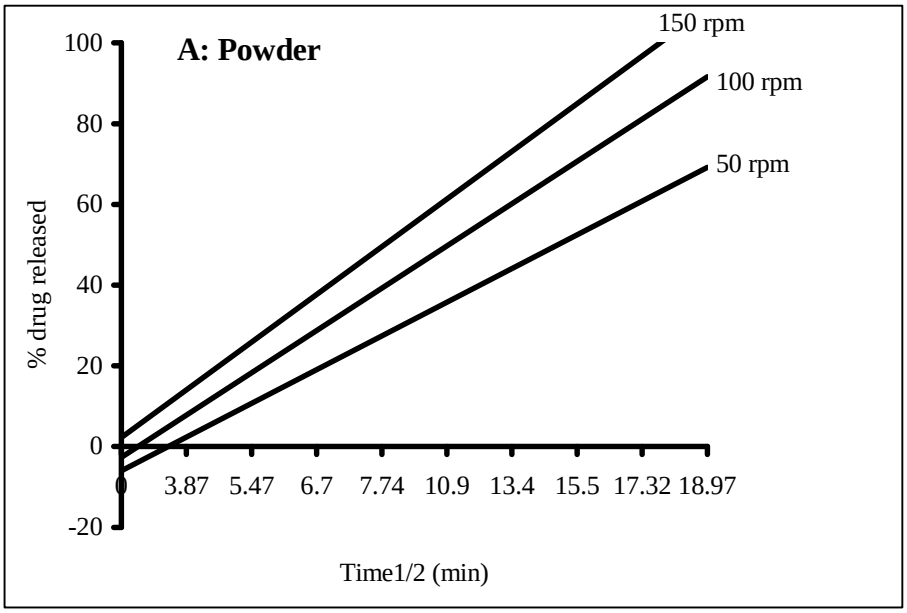
The study of the release of d–alpha tocopherol succinate from microcapsules is shown in (Table 2) for two most promising samples (tablet and powder), the dissolution was carried out at sink condition (the solubility of d–alpha tocopherol is 0.47mg/ml).
It was found that the dissolution of d–alpha tocopherol succinate during first 3 hours up to 80% of the core material, and there was no drug left either in microcapsules powder, after 6 hours or in tablets after 24 hours.

Table 2 . Percentage of d–alpha tocopherol succinate released from powdered and tabletted microcapsules.

Time (hr.)	$(Time)^{1/2}$ (min)	(*) Percent Drug Release(**) "Stirring Speed"					
		(150 RPM)		(100 RPM)		(50 RPM)	
		Powder	Tablet	Powder	Tablet	Powder	Tablet
0.25	3.87	18	12	14	10	5	5
0.50	5.47	33	26	27	23	15	14
0.75	6.7	40	36	34	33	23	22
1.00	7.74	48	42	45	42	40	33
2.00	10.9	65	66	66	63	58	52
3.00	13.4	84	79	79	77	73	59
4.00	15.5	92	88	96	85	73	77

(*) medium pH 7
core:wall 1:1 (Efficiency 93.3%)
particle size 1.0- 1.2mm. (using sieve apparatus)
(**) $p < 0.05$ is significant with corresponding percent of drug release.

The release rates obtained for different stirring speed indicates that diffusion mechanism operates for the release of d–alpha tocopherol succinate, the greater stirring speed used, the shorter the t50% value obtained.
This fact was due to the relative thickness of the boundary layer surrounding individual microcapsules, the time for 50% drug release from the tablet was significantly ($p<0.05$) prolonged in comparison with the release time from microcapsules at the same stirring speed.[11]
It appears that fractional additional of dissolved ethylcellulose produce microcapsules wall which is firstly strong enough to break during tabletting and, secondly prolong the release of the core very well[12].
All the tablets prepared exhibited good physical properties and when used in dissolution tests remained intact at the end of experiment, the dissolution from microcapsules and tablets showed straight line relationship up to 90% when the percent of drug released was plotted against, $(time)^{1/2}$, (Fig. 3) and this indicates that diffusion mechanism of drug release occured.



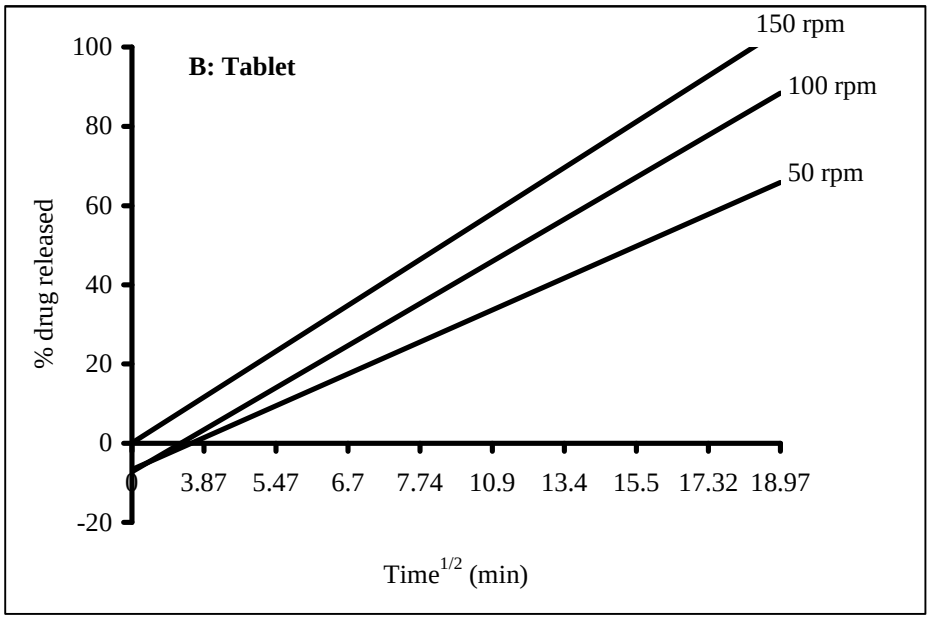


FIGURE 3 . THE PERCENTAGE OF DRUG RELEASE VERSUS ROOT SEQUARE OF TIME AT DIFFERENT STIRRING SPEED (A) POWDERED MICROCAPSULES, (B) TABLETTED MICROCAPSULES.

(Fig. 4) and (Table 3) show the relationship between the crushing strength (hardness) and the core:wall ratio of the tablets, it appears that as the core percent increased, the hardness of tablets increased, this may be referred to low percent of ethycellulose (wall ratio), since ethylcellulose expands after the removal of compression pressure and the bond formed during the compression are relaxed producing less rigid tablet, this relaxation could explain the decrease found in the strength of the tablets as the core:wall ratio increased[13].

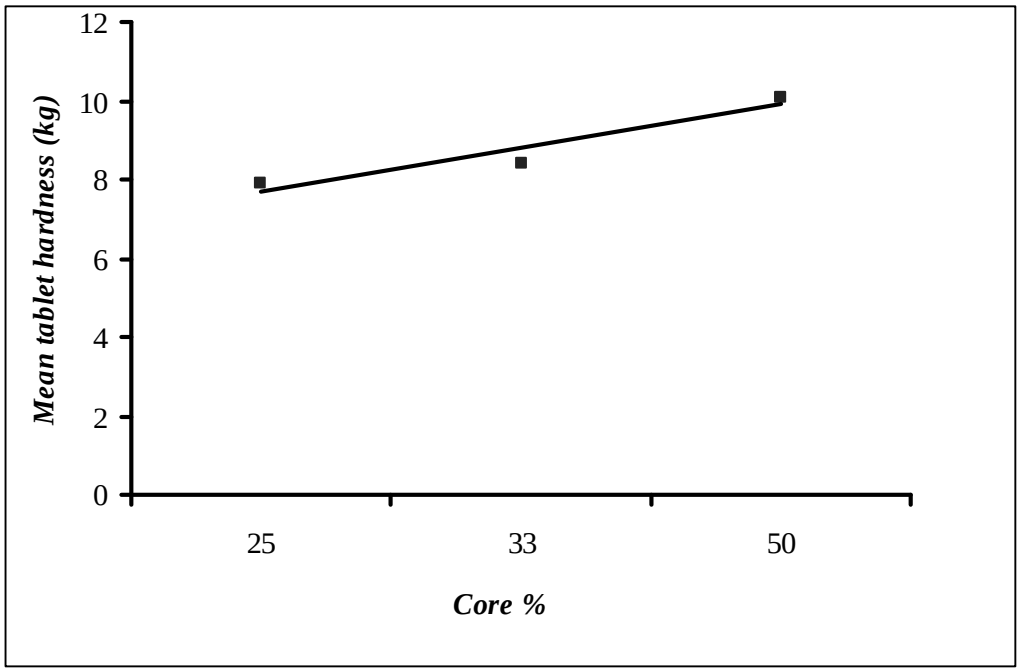


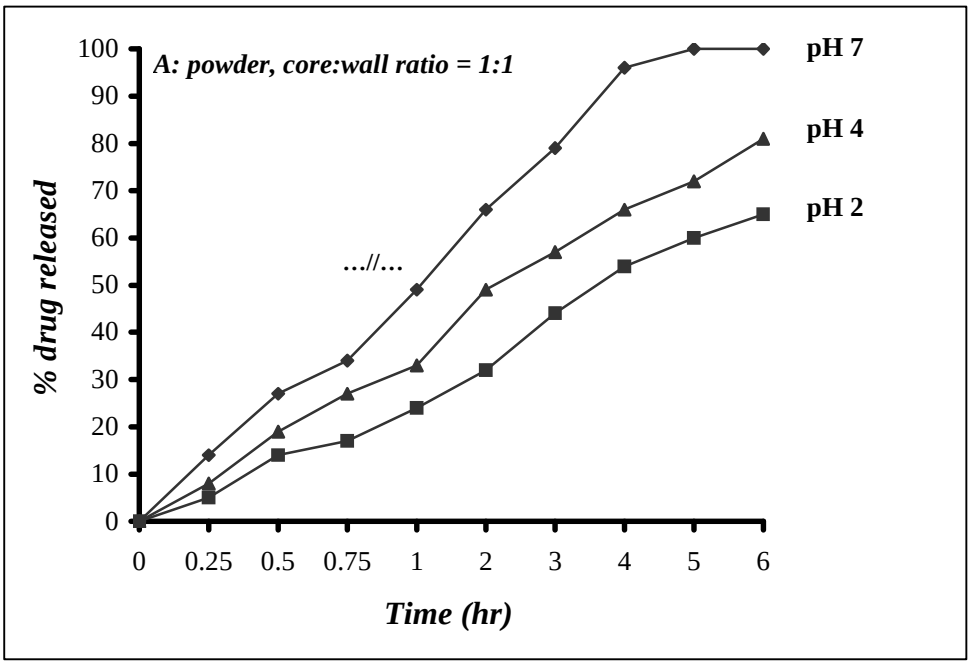
FIGURE 4 . THE EFFECT OF CORE PERCENT OF D–ALPHA TOCOPHEROL SUCCINATE ON THE CRUSHING STRENGTH (HARDNESS).

Table 3 . Effect of increasing core:wall ratio on the hardness of tablets

Core %	Hardness Kg.
50	10.1
33	8.4
25	7.9

Effect of pH – medium

Based on the results obtained from powdered and tabletted microcapsules as shown in (Table 3), and (Figure 5 A and B).



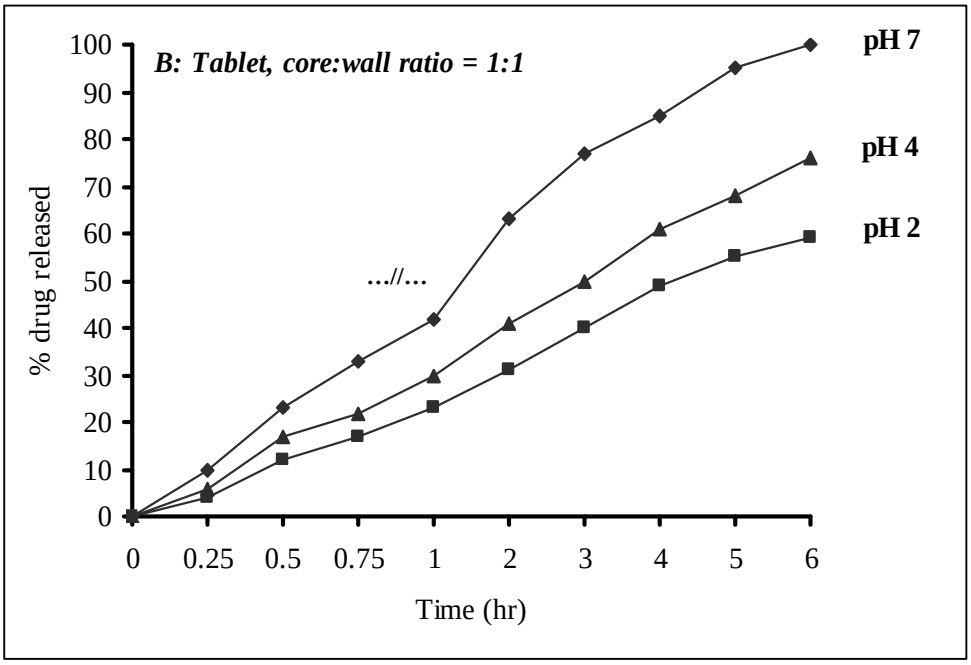


FIGURE 5 . PERCENTAGE OF D–ALPHA TOCOPHEROL SUCCINATE RELEASED FROM (A): POWDERED AND (B): TABLETTED MICROCAPSULES AT DIFFERENT PH FOR 1:1 CORE RATIO, STIRRING SPEED 100 R. P. M.

It appears that from powdered microcapsules, the drug release is increased as a function of pH–medium increased, since about 50% of drug released at the first hour at pH7 compared with 33% and 24% of drug released at pH4 and pH2 respectively, the same result was obtained for tabletted microcapsules, this increasing may be attributed to nature of d–alpha tocopherol succinate which behave like acidic salt derivative where ionization of tocopherol increased and then increased the solubility, while the amount remain which is about 50% takes over about 5 hours to dissolute this 5 attributed to the lower solubility of the drug itself, this mean that the rate limiting step in this dissolution is the solubility of the drug[14].

The later behavior of the drug gives an impression that prolonged release of drug may be obtained and then sustained release delivery dose can be prepared or formulated.

Figure (6) and table (4) showed that the cumulative percent of d–alpha tocopherol succinate released from both powdered and tabletted microcapsules, the results indicated that both types of microcapsules have been behaved as prolonged and extended release pattern in different pH–medium.

This behavior candidate both powdered microcapsules and tabletted microcapsule as extended release dosage form.

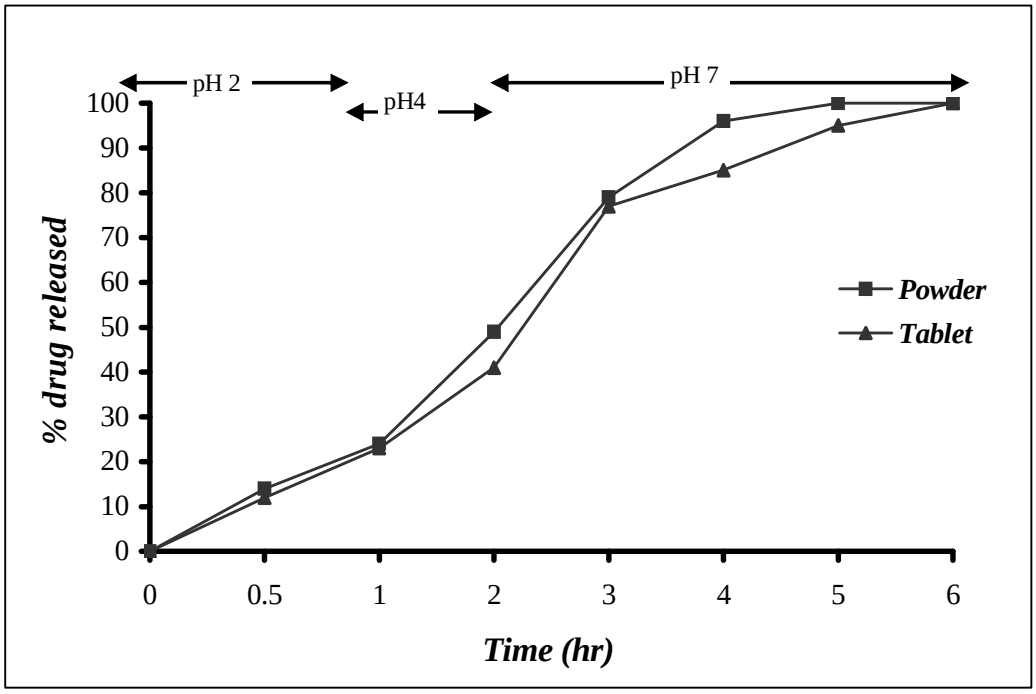


FIGURE 6 . PERCENTAGE OF CUMULATIVE DRUG RELEASED FROM POWDERED AND TABLETTED MICROCAPSULES AT DIFFERENT PH MEDIUM FOR 1:1 CORE:WALL RATIO, STIRRING SPEED 100 R. P.M.

Table 4 . Percentage of d–alpha tocopherol succinate released from powdered and tableted microcapsules at different pH medium.

Time (hr.)	(*) Percent Drug Release(**)					
	Powder			Tablet		
	pH2	pH4	pH7	pH2	pH4	pH7
0.25	5	8	14	4	6	10
0.50	(14)	19	27	(12)	17	23
0.75	17	27	34	17	22	33
1.0	24	33	49	(23)	30	42
2.0	32	(49)	66	31	(41)	63
3.0	44	57	(79)	40	50	(77)
4.0	54	66	(96)	49	61	(85)
5.0	60	72	(100)	55	68	(95)
6.0	65	81	(100)	59	76	(100)

(*) stirring speed (100 r. p. m)
(**) $p < 0.05$ is significant with corresponding percent of drug release.
( ) means cumulative drug release.

CONCLUSIONS

The trials in this study have been succeeded to investigate some variables affecting the release of d–alpha tocopherol succinate from ethylcellulose matrix.
Based on the results obtained, the followings may be concluded:

1- Solid dispersion, by solvent evaporation method can be used as an identical process to coat d–alpha tocopherol succinate and incorporated it into ready compressable granules to formulate prolonged release dosage form.
2- The dissolution of the drug is increased as a function of increasing core:wall ratio, stirring speed and pH–environment.
3- Best tablets were gained, when direct compression of prepared powdered microcapsules, with good appearance and acceptable crushing strength.
4- The cumulative release pattern at a different simulatnous pH medium, for extended period of time give an impression that these powdered and tabletted microcapsules were candidate to formulate a drug as a sustained release dosage form.
5- The study was succeeded to coat the drug from external environmental conditions like moisture, light….. etc "during 6hrs of dissolution".

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