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FORMULATION OF OILY DRUGS IN POWDER FORM USING POROUS SILICAS I. VITAMIN E

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تم دراسة استخدام سليكات الكالسيوم المحتوية على فجوات (فلوريت ر) ونوعين من مسحوق الزجاج ذات فجوات محددة الحجم كحوامل لتحضير فيتامين هـ على هيئة مسحوق حر الانسياب.

وقد استخدم جهاز التحليل الحرارى وميكروسكوب المسح الاليكترونى لدراسة المشتتات المحضرة ، كما تم أيضا قياس خصائص الانسياب ودراسة انطلاق العقار من هذه المشتتات.

وقد أوضحت نتائج التحليل الحرارى وجود جزء من العقار مدمصا ادمصاصا ضعيفا بينما يوجد الجزء الأخر مدمصا ادمصاصا قويا على السليكات ويتناسب الاخير مع مساحة السطح النوعى للسيلكا. وقد أثبتت التجارب أن فلوريت ر أكثر قدرة على ادمصاص العقار بالمقارنة بمسحوق الزجاج.

وقد أعطت مشتتات العقار مع فلوريت ر والمحتوية على كميات من العقار تصل الى ٤٠٪ انسيابا جيدا ، وتجانس المحتوى من العقار وكذلك انطلاق العقار بالكامل فى المحلول المشابه لسوائل الامعاء.

Porous calcium silicate (florite R) and controlled pore glass (CPG 75 & CPG 500) were investigated as carriers to formulate vitamin E in a free flowing powder form. The prepared dispersions were subjected to thermogravemetric analysis (TG), scanning electron microscopic examination, testing of flowability, uniformity of content and in-vitro release of vitamin E.

TG of vitamin E - porous silicas dispersions indicated that vitamin E existed in both lightly and strongly bound state. The latter was directly related to the specific surface area of the carrier. Florite R was found to have a greater ability to hold vitamin E than controlled pore glass. The dispersions prepared using florite R and containing up to 40 % w/w vitamin E showed good flowability, uniformity of content and almost 100 % release of the loaded drug.

INTRODUCTION

Many drugs such as lipophylic vitamins, cod liver oil, clofibrate and valproic acid are available in the form of oils[1]. These drugs are often prepared in the form of soft gelatin capsules[2]. Microencapsulation technique was employed to prepare these drugs in solid powder form suitable for preparation in the form of tablets and capsules[3]. Recently it was reported that fluid extracts can be "solidified" by adsorption on porous silicas[4]. Their availability can be improved by incorporating surfactant into the adsorbates[4,5]. In addition hygroscopic extracts can be stabilized by adsorption onto silica[6]. Conversion of liquid drugs into powdered forms are desirable due to easiness in treating and manufacturing and as an aid to handling or storage[7].

Florite R fits the specification of calcium silicate in USP[8]. It has high oil absorbability and good liquid holding ability[9]. Porous glass has numerous fine pores of 10 to 1000 Å in diameter, and has found many applications e.g. desalting of sea water, in chromatography, as solid support for enzymes and to increase dissolution of insoluble crystalline drugs[10,11]. The physico-chemical properties of drug molecules adsorbed on porous materials are markedly different from those in the crystalline state [12-14].

The aim of the present study was to investigate the utility of porous silicas: Florite R and controlled pore glasses as carriers for uniform distribution of slightly viscous drug,

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vitamin E, in solid free flowing powder form.

EXPERIMENTAL

Materials

- Florite R (Tokuyama soda, Japan). Controlled pore glass (CPG); CPG 75 and CPG 50 (Electro-Nucleonics Ltd., USA). These silicas were used after drying in vacuum at 120° for 3 hours. Their physical properties are shown in Table 1.
- D α - tocopherol (vitamin E), (Esie Pharmaceutical Co., Tokyo, Japan).
- Bile salts (Oxoid Ltd., London).
- All other materials and solvents were of analytical grade.

Equipment

- Thermogravimeter, Du Pont 915 (Du pont Co., USA).
- Aqua counter apparatus, (Hiranuma AQ, Japan).
- Scanning electron microscope, JSM-25 S3 (Jeik co., Japan).
- Dissolution apparatus, USP rotating paddle DT-06 (Erweka FRG).
- Rotary evaporator (Buchi co., Switzerland).

Methods

Preparation of vitamin E dispersions

The dispersions containing various ratios of vitamin E (5 % - 50 % w/w) were prepared as follows: solutions of suitable concentrations (1-5 % w/v) vitamin E in ethanol were prepared. Certain volume of vitamin E solution of appropriate concentration was added to certain weight of the carrier (florite R, CPG 75, CPG 500). The solvent was evaporated under reduced pressure at 35° using a rotary evaporator. The dried samples were kept under vacuum at room temperature in desiccator containing P_2O_5 (0 % relative humidity, RH).

Determination of water content of vitamin E dispersions

Water content of the vitamin E dispersions was determined by Karl Fisher method using Aqua counter. Each experiment was repeated at least three times and the results were averaged.

Thermogravimetric analysis of vitamin E dispersions

Samples of vitamin E dispersions (5-30 % w/w vitamin E) with various silicas were investigated by thermogravimetric analysis using a Du-pont thermogravemeter. Heating rate was 10°/ min and measurements were done under nitrogen gas flow rate of 60 ml/ min. Thermogravemetric analysis was repeated three times for each sample and the values of weight loss corresponding to each stage was estimated and the average was calculated.

Scanning electron microscope

Samples of Florite R and dispersions of vitamin E with Florite R in various ratios were examined by electron scanning microscope. The samples were gold sputter coated prior to examination to render them electrically conductive.

Measurement of flowability

The angle of repose was measured according to the fixed cone method using a glass cylinder with 2.5 cm radius[15]. Each determination was repeated five times and the average was recorded.

Determination of uniformity of vitamin E content in the prepared dispersions

Ten 100 mg samples were taken randomly from each tested dispersion. Each sample was transferred to a 50-ml conical flask containing 20 ml of methanol. The flask was shaken for 10 min, then the volume was adjusted with methanol. The solution was filtered through 0.2 μm membrane filter. One ml of the filtrate was appropriately diluted with methanol. The drug concentration was determined spectrophotometrically at 284 nm. The mean of vitamin E content and standard deviation were calculated for each dispersion.

Determination of *in-vitro* vitamin E release

Release studies were carried out according to USP dissolution test. The dissolution medium

was 300 ml of simulated intestinal fluids containing 0.1 % w/w of bile salts. An accurately weighed sample equivalent to 10 mg of vitamin E was transferred to the dissolution medium adjusted to 37°, which was immediately stirred at 50 r.p.m. At appropriate intervals, 5 ml samples were taken and replaced by the same volume of dissolution medium. Each sample was filtered using 0.2 μm membrane filter. One ml of the filtrate was appropriately diluted with methanol and the drug concentration was determined spectrophotometrically at 284 nm against blank similarly treated. Three samples were tested from each preparation and the results were averaged.

RESULTS AND DISCUSSION

Table 1 shows the specifications of various silicas. Bulk densities were determined by the cylinder method[15],while other values are nominal. Table 2 shows drug content and flowability of various vitamin E dispersions. All these dispersions showed uniformity of vitamin E content. Since Florite R occurred as very fine particles, it showed poor flowability compared to CPGs. Addition of vitamin E in low ratio (5-10 % w/w) may lead to formation of small aggregates of florite R. This in turn may be responsible for the observed improvement of flowability. Further increase in the ratio of oil in the dispersions may lead to formation of larger aggregates that retard flowability. Dispersions prepared with either CPG 75 or CPG 500 using vitamin E in a ratio of 5-30 % w/w gave vitamin E dispersions in powder form. The flowability and uniformity of content were adversely affected as the ratio of the oil in the dispersion was increased. The dispersions containing either CPG 500 or CPG 75 with vitamin E. in a ratio greater than 30 % w/w were in the form of sticky masses. These results were attributed to the lower bulk densities of CPGs compared to florite R (Table 1).

Figure 1 shows scanning electron micrographs of Florite R and its dispersion containing 20 % w/w vitamin E. In case of vitamin E. dispersion with Florite R neither lumps nor oil droplets were observed. This indicated that the oil is adsorbed onto the large surface area of Florite R as a molecular layer.

Table 1: Specification of porous silicas

	Florite R	CPG 75	CPG 500
Mean particle size μm	15-20	200-400	200-400
Sp. surface area m^2/g	140	207	43
Bulk density	0.08-0.12	0.27-0.28	0.41-0.42
Mean pore diameter Å	—	70	564

Table 2: Characterization of vitamin E dispersions with various silicas.

Composition % W/W		%drug content mean(C.V.%)	Angle of repose
Florite R & Vitamin E			
100	–	–	52,5°
95	5	99.71 (1.76)	43,9°
90	10	99.84 (1.98)	42,1°
80	20	99.04 (2.76)	47,3°
70	30	100.61 (3.12)	47,9°
60	40	98.76 (4.68)	49,3°
50	50	101.43 (6.12)	57,2°
CPG 75 & Vitamin E			
100	–	–	30,5°
95	5	99.76 (1.76)	32,7°
90	10	98.74 (2.98)	37,7°
80	20	101.64 (4.15)	46,1°
70	30	103.34 (5.54)	51,7°
CPG 500 & Vitamin E			
100	–	–	34,9°
95	5	99.84 (2.12)	36,7°
90	10	101.26 (3.73)	38,1°
80	20	98.05 (4.65)	47,6°
70	30	99.09 (7.94)	54,2°

C.V. : Coefficient of variation

Thermogravemetric analysis was used to characterize the state of vitamin E in various dispersions. Figure 2 shows the TG curves of various silicas. The observed weight loss was

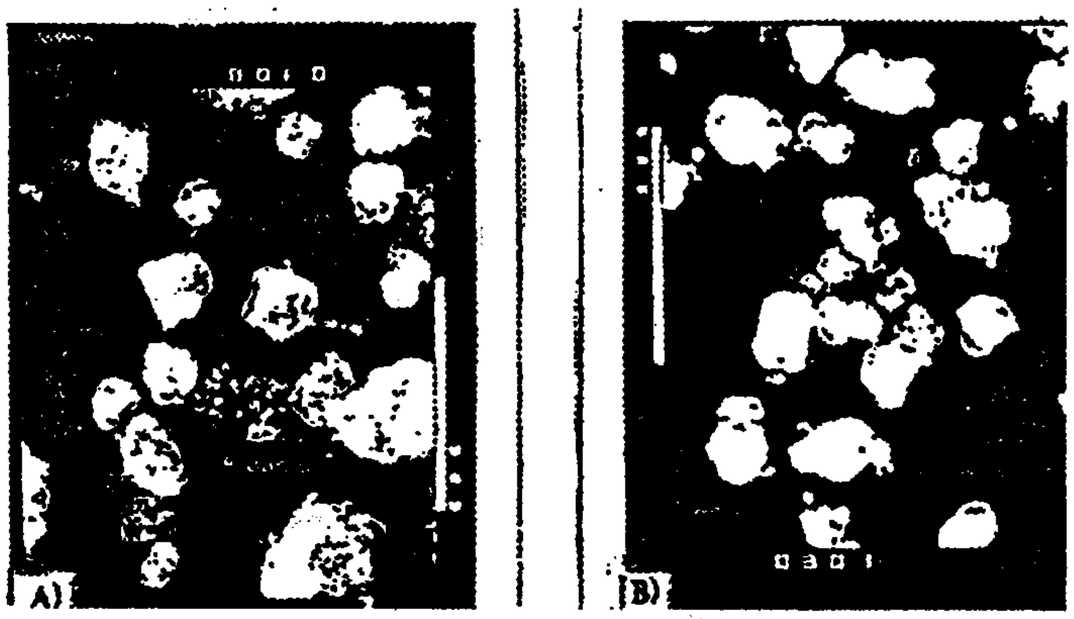

Figure 1:Electron scanning micrographs of vitamin E dispersions with Florite R (magnification 1x450).
A) Florite R B) dispersion of 20 % vitamin E

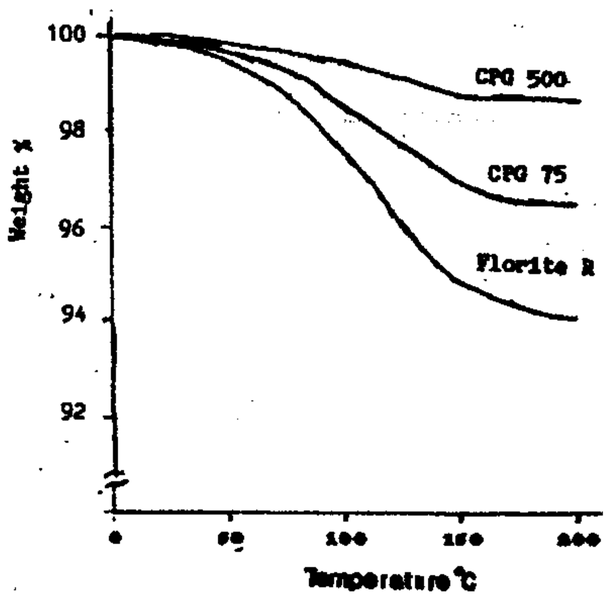

Figure 2: TG curves of various silicas.

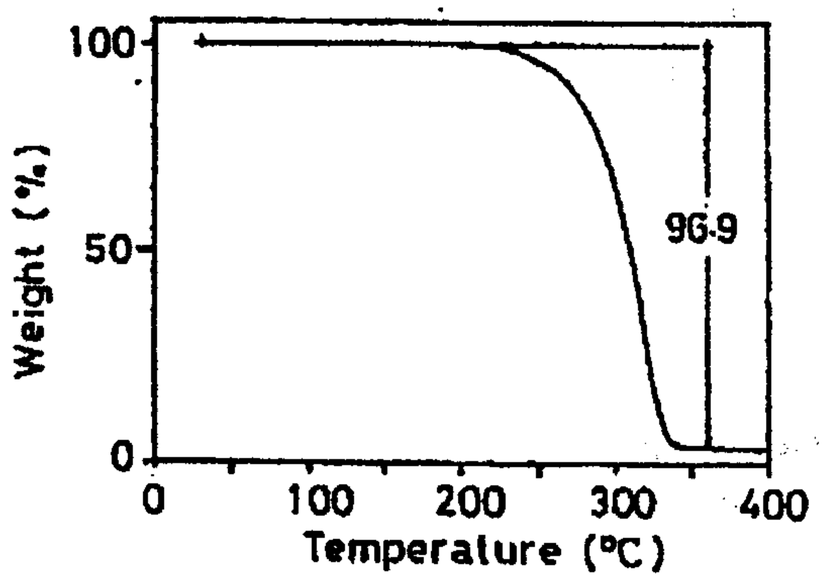

Figure 3: TG curve of vitamin E.

Table 3: Comparison between water content and first stage weight loss of vitamin E dispersion with various silicas.

Composition of dispersion (% W/W)	Water content[a] (% W/W)	First stage weight[b] loss (% W/W)
10 % vit. E & 90 % Florite R	5.46	5.84
10 % vit. E & 90 % COG 75	2.05	2.18
10 % vit. E & 90 % CPG 500	0.76	0.82

[a] Determined by Karl Fisher method.
[b] Obtained from TG curves.

attributed to the loss of both free and adsorbed water. The latter was retained up to 200° as the water molecules were tightly bound to silanol (SiOH) groups of silicas.

Figure 3 shows the TG curve of pure vitamin E. One stage weight loss due to

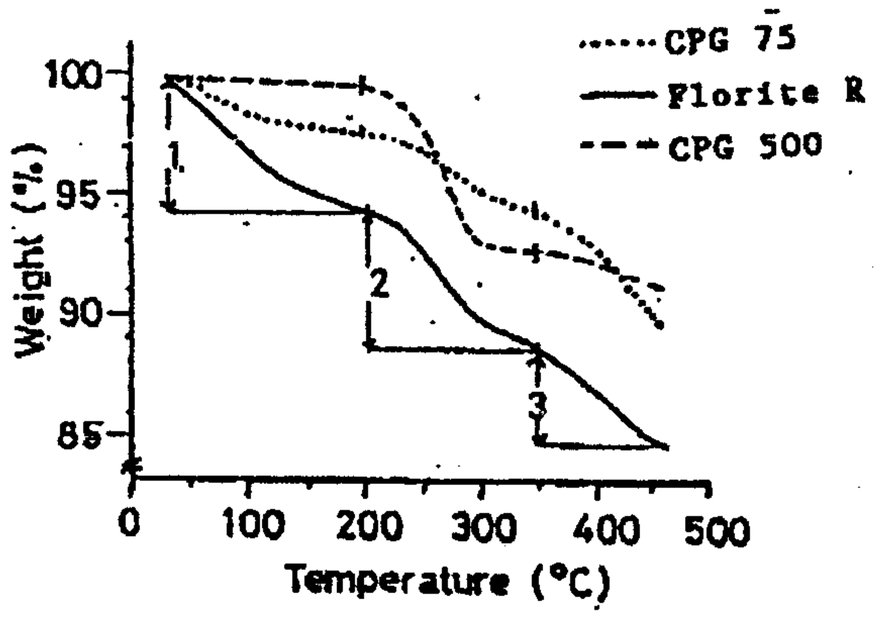

Figure 4: TG curves of 10 % vitamin E dispersions with various silicas.
Stages of wt loss:1-water; 2-weakly adsorbed vitamin E; 3-strongly adsorbed vitamin E.

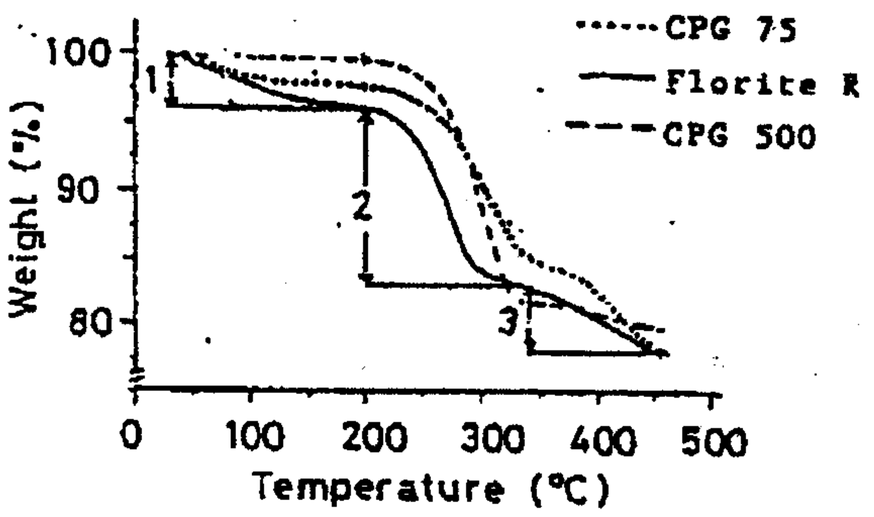

Figure 5: TG curves of 20 % vitamin E dispersions with various silicas.
Stages of weight loss as in Figure 4.

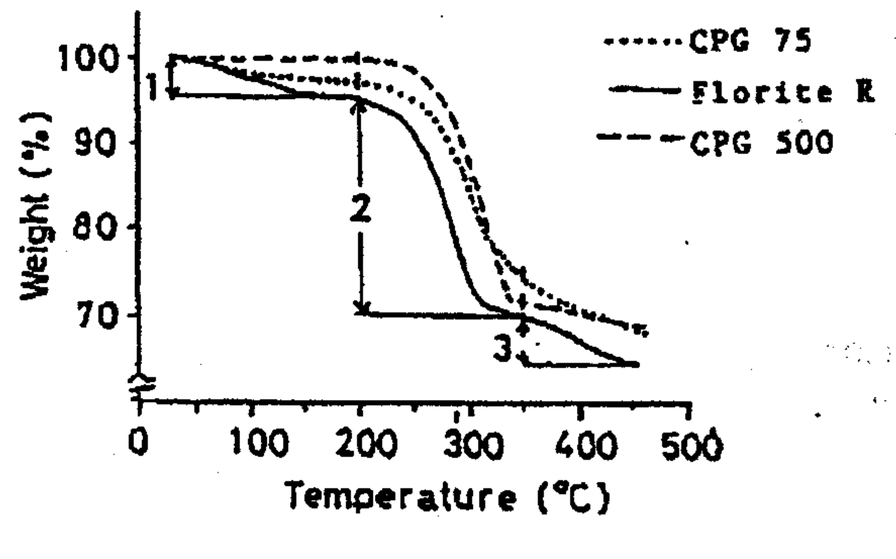

Figure 6: TG curves of 30 % vitamin E dispersions with various silicas.
Stages of weight loss as in Figure 4.

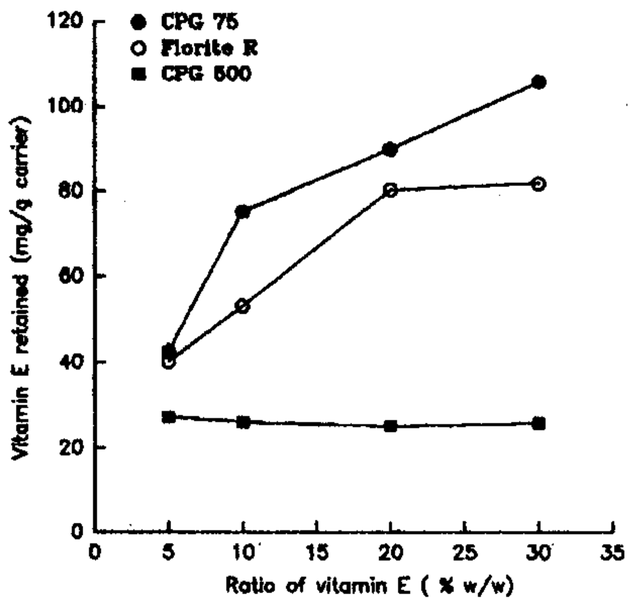

Figure 7: Relation between loading ratio of vitamin E and amount of vitamin E retained after heating its dispersions with various silicas to 350°.

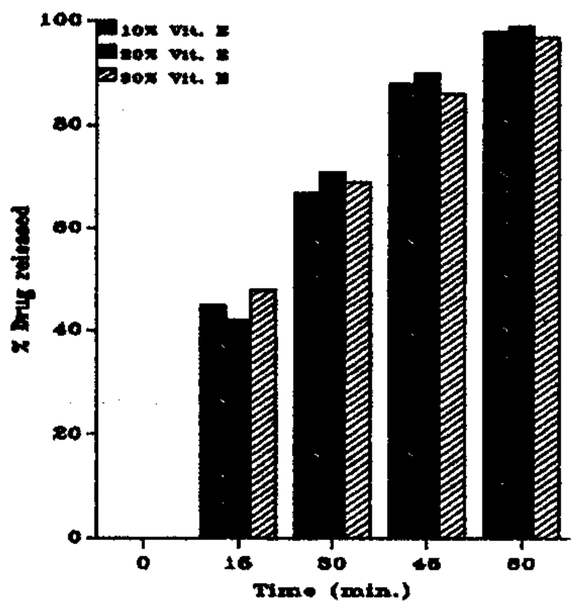

Figure 8: Dissolution profile of vitamin E from its dispersions with Florite R in various ratios in simultated intestinal fluids.

evaporation of vitamin E was observed between 200-300°. Figure 4 shows the TG curves of dispersions containing 10 % of vitamin E and 90% of various silica carriers. All curves showed three stages weight loss. The 1st stage weight loss (occurred between 40-200°) could be attributed to the loss of water content. This was confirmed from the data shown in Table 3.The 2nd stage weight loss which observed between 200-350° was due to evaporation of vitamin E weakly adsorbed into the surface of florite. The 3rd stage weight loss between 350-459° was suggested to be due to evaporation of strongly adsorbed vitamin E. (i.e. entrapped within the pores). Similar TG curves were obtained in case of dispersions containing either 20 or 30 % w/w

Table 4: Mean amount of vitamin E retained after heating its dispersions with various silicas to 350°.

Composition of dispersion (% W/W)		vitamin E retained* (% W/W)	vitamin E retained (mg/g carrier)
vitamin E	Florite R		
5	95	76.26 (2.42)**	40.13
10	90	47.72 (2.09)	53.02
20	80	32.10 (1.94)	80.25
30	70	19.07 (1.69)	81.73
vitamin E	CPG 75		
5	95	80.62 (2.66)	42.45
10	90	67.52 (2.17)	75.10
20	80	35.95 (1.92)	89.88
30	70	24.67 (1.83)	105.72
vitamin E	CPG 500		
5	95	51.85 (2.41)	27.28
10	90	24.78 (1.95)	26.12
20	80	10.35 (2.31)	25.88
30	70	5.87 (2.07)	25.16

* Obtained from TG curves and calculated relative to the original concentration of vitamin E.
** Standard deviations.

vitamin E (Figures 5 & 6). The mean amount of vitamin E retained after heating of each dispersion to 350° (estimated from the corresponding TG Curve) were presented in table 4. Figure 7 shows the relationship between the ratio of the carrier in the dispersion and the amount retained of vitamin E (mg vitamin E/ g carrier) after heating the dispersion to 350°. In case of using CPG 75 as carrier, the amount of the drug retained was increased as the ratio of the drug in the dispersion was increased. Using Florite R as carrier, the amount retained of vitamin E was increased with increasing its ratio in the dispersion up to certain concentration (20 % w/w vitamin E). Further increase in the drug ratio didn't change the amount of drug retained. The amount retained of vitamin E was almost the same when CPG 500 was used as carrier regardless of the ratio of vitamin E in the dispersion. The ability of different silica carrier to retain vitamin E followed the following order:

CPG 75 > Florite R > CPG 500

These results indicated the direct relationship between the specific surface area of the silica carrier and its ability to hold up vitamin E molecules (Table 1). The results also confirm that vitamin E is molecularly dispersed over the extensive surface offered by porous silicas. It was suggested that the drug was physically adsorbed onto the surface of silica (weakly adsorbed) and within the pores (strongly adsorbed). Physical adsorption of the drug took place via hydrogen bonding between silanol groups (Si-OH) located on the surface of silica and phenolic groups of the drug molecules.

Figure 8 shows the dissolution profiles of vitamin E - florite R dispersions in various ratios in simulated intestinal fluids. Almost all the amount of vitamin E loaded onto florite R was released within one hour. There was no significant difference in the rate of vitamin E

released among the dispersions containing various ratios of the drug. The relatively rapid release of the drug from phsioadsorbate was explained by the immediate breakage of the hydrogen bonds after contact of the phsioadsorbate with the aqueous dissolution medium (due to difference in electronegativity between the silicon and nitrogen atom) releasing the free drug.

Conclusion

Florite R was successfully utilized in the preparation of vitamin E in free flowing powder form and in uniform distribution state. Thermogravemetric analysis confirmed the presence of the drug in a molecularly dispersed state.

It was also noticed that porous silica mask the oily taste of the drug. Thus using these dispersions it would be possible to formulate the drug in several oral dosage forms where the dose can be easily controlled. The presence of an oily drug in a dispersed state over the large hydrophilic surface area of porous silica carriers enhances its dissolution rate and hence its absorption and bioavailability.

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