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Vitamin E Microcapsulation by Ethylcellulose Through Emulsion Solvent Evaporation Technique; An Operational Condition Study

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Abstract: Thocopherol (Vitamin E) micro-encapsulation was carried out utilizing the emulsion solvent evaporation (ESOLV) method. Ethyl cellulose (10 cp viscosity grades) was the coating material and the products quality has been characterized by drug loading evaluation and in-vitro drug release analysis. Results showed that the maximum drug loading (0.1 gr/ml) is occurred when the solvent evaporation carries out with about 0.17 Drug/EC ratio, 450 cc of the PVA solution content and 9 cc of Methyl Chloride, in 50-60°C solvent evaporation temperature range. Drug release assessment showed that the drug release rate as a function of microcapsules wall properties is significantly impressed by the thermal curing.

Key words: Microencapsulation · Drug release · Coating, Solvent evaporation · Ethylen cellulose · Bioavailability

INTRODUCTION

Drug bioavailability is pre-dominated by the processes that occur following the drug intake, such as releasing and adsorption. However, the oral route is the most conventional manner for drug delivery many solid pharmaceuticals exhibit low oral bioavailability [1, 2]. Current efforts on drug delivery area include targeted delivery in which the drug is only active on the body target organ, sustained release formulations in which the drug is released over a period of time in a controlled manner and prolonging the drug release from dosage forms and reducing the adverse effects [3, 4]. There are several types of sustained release formulations, include liposomes, drug loaded biodegradable microspheres and drug polymer conjugates [5, 6]. Microencapsulation is a useful technique to postpone the drug release from the dosage forms and remove the undesired effects. Actually, coating an insoluble solid within a special polymer results in eliminating the delivery problems and is generally employed to core material protection, gastric irritation reduction and volatile liquid drugs conservation in the form of pseudo-solids [7-9].

Microencapsulation methods are categorized as the chemical, physico-chemical and physic-mechanical methods, applied based on the drug characteristics. Coacervation, fluidized bed suspension, phase separation, spray drying, pan coating, supercritical expansion and solvent evaporation are commonly used at the lab and commercial scales [10, 11]. Chemical methods are often carried out along with the thermal changes and rarely suggested for the thermal and chemical sensitive materials [12]. Physico-mechanical processes are commercially feasible, in comparison with the other methods. However, thermal and mechanical damages are mostly probable with these methods. Physico-chemical methods such as solvent evaporation are not only operationally mild, but also high efficient, because of taking advantages of the both chemical and physical techniques [13]. Active ingredient (core) and the coating polymers are firstly dispersed in a solvent. Polymer phasing out by a strong solvent leads to form a wall around the drug solid particles [14]. Microencapsulation techniques work properly with the low Tg (Transition Temperature) polymers as well as dose with the high Tg ones. However they often act critical with the high Tg polymers, such as Ethylene Cellules (Tg = 133°C), which is a widely used covering polymer. Therefore, formulation and operational parameters have to be optimized in order to make desirable drug microcapsules [15].

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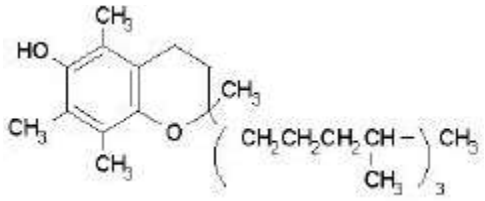

Fig. 1: Tocopherol molecular Formula

Poly-ethyl cellulose (Ethylene Cellulose/ EC) is an insoluble non-toxic polymer and harmless in a view to the environmental concerns, with the extended applications as a coating substance, especially for drug release purposes, where using the soluble substances is impossible. Effect of the molecular weight and concentration on the viscosity, is considered as an important disadvantage to select the coating polymer. In low concentrations and molecular weight, drug covering by the polymer doesn't occur well. On the other hand using a heavy polymer with high concentration, leads to difficult release process. For Ethyl cellulose, molecular weight doesn't affect on the viscosity. So, apart from the microcapsules coalescence, there is no limitation in polymer amount [16].

Vitamin E is a fat-soluble biological antioxidant and detoxifying agent which protects unsaturated fatty acids and membrane structure which was found to be necessary for normal growth maintenance and reproduction. It's deficiency causes myocardial degeneration, muscular dystrophy, encephalacia and liver necrosis, skin collagenosis, red cell haemolysis, cirrhosis of the gall bladder and creatinuria. For adults the daily requirement is 25-30 IU which is equivalent to 25-30 mg of Tocopherol acetate. It aids intestinal absorption of unsaturated fatty acids and other fat-soluble vitamins. Figure 1 shows the Tocopherol chemical structure. Tocopherol shortage generally impacts on the hart and veins activities, neural network and organs reproduction [17, 18].

However studies about vitamin E have been inconsistent, lack of consistency led to the hypothesis that the bioavailability of supplement drugs such as Vitamin E is highly dependent on the supplement consuming way. Blood concentration of Vitamin E has a poor relation to the amount in the body because ingested Vitamin E is rapidly cleared from the blood into the tissues. Dissolution in the gastric liquid is the major limitation of Vitamin E absorption, because it is a lipophilic compound. Low solubility in the gastric liquid results in drug accumulation in the stomach. Therefore the main part of the dosage is probably repulsed before digestion. Microencapsulation protects the Vitamin E as a core and regulates the delivery process [19-22].

Emulsion solvent evaporation is a simple and reproducible method that is often used for drugs microencapsulation with the respecting of the drug thermal resistance [23].

At the current work, Tocopherol microcapsules have been prepared by emulsion solvent evaporation technique using Ethyl cellulose. Methylen chloride and PVA applied as the solvent and external phases. The produced microcapsules were evaluated to measure the drug content and in-vitro drug release.

MATERIALS AND METHODS

Materials: The following chemicals were used as received: Tocophrol (Vitamin E) solution (98 %, Acetate Base, Anuhi Minmetals, China), PVA (PVA 18-17, Switch Industry Development, Hong Kong), Ethyl Cellulose (10 cps, Tianjin Kiayong Chemicals, China), Chloroform (99.6%, Tianjin Kiayong Chemicals, China), Mono potassium Phosphate Powder (99 %, Ruising Chemicals Pte, Singapore), Dichloromethane (99.9 %, Hongzhou Uniwise, China).

Microcapsules Preparation: Thocopherol particles covered by EC have been prepared through the conventional way of emulsification organic solvent evaporation method at the room temperature [24].

A mixture of Thocopherol and EC was dissolved into the Methyl chloride that strongly dissolves the Tocopherol derivatives. The prepared mixture was added slowly (in droplets form) into a PVA (Poly-Venyl Alcohol) solution as the emulsifying external phase. The mixture was stirred by a John Morris magnetic agitator, at a predetermined speed (600 rpm), till the Methyl chloride evaporated entirely and droplets formed microspheres (about 6 h). Agitation process helps to the better distribution in the emulsion [25, 26]. The mixture was filtered by a Whatman paper (no.50) under a light vacuum (by an Abbess Instrument vacuum pump, USA) to separate the microsphere particles. Then the particles were rinsed several times and dried in incubator (Jeio Tech. Korea) for 24 h. Actually the thermal treatment is necessary as the process final step, in order to remove the remained solvent, promote the polymer particles stability and extended drug release enhancement [27, 28].

The test was repeated many times with different amounts of Tocopherol/EC proportion, Solvent, PVA and in different solvent polymerization temperature and the products were analyzed with due regard to the drug loading in order to attain the optimum solvent evaporation condition for Tocopherol microencapsulation by EC.

Drug Loading Yield: A determined amount of dried microcapsules (1 g) was powdered firstly. Then100 ml of a 0.07 N HCL solution was added gradually. The mixture was filtered through a 0.045, Millex-FH (Biognost, Belgium) and the resulted sample was analyzed spectrophotometrically (UV-1800, Shimadzu), at ë= 293. This wavelength doesn't absorb Ethyl cellulose. Each test was performed in triplicate. The standard curves for the Tocopherol were already prepared to present the drug concentration in the solution based on the absorption length.

***In-vitro* Drug Release Study:** Drug release was determined within a paddle apparatus (Vankel 700, Vankel Industries, USA). 40 mg of the microcapsule agglomerates were gradually mixed in with 900 ml of 0.1N HCL and phosphate buffer media (PH=7.4) in a beaker. The mixtures were stirred at 100 rpm and constant temperature (37°C).

Samples (5 ml) were taken at 15 and 30 min and then at 2, 4, 6, 8, 10, 12, 18 and 24 hours, filtered by a 0.045, Millex-FH filter and analyzed spectrophotometrically at ë= 293 to determine the Tocopherol concentration. Results were compared to interpret the gastric medium pH effects on the EC coated Vitamin E microcapsules release rate.

RESULTS AND DISCUSSION

Solvent Evaporation Ingredients Concentration Effect on the Drug Loading Yield: The effect of Drug/ Polymer ration, Dichloromethan and the emulsifier (PVA) concentrations on the microspheres core loading was studied. Results are presented at the figures 2-4 and the optimum concentration amounts are discussed below. Solvent evaporation was performed at 40-45°C at all runs.

Drug/ Polymer Ratio: Different amounts of the EC were used within the 58mg of the Tocopherol, 6ml Methyl Chloride and 400mg PVA solution in solvent evaporation microencapsulation process Fig. 2.

The curve shows that the maximum drug loading occurred in the range of Drug/ EC ratio between 0.16-0.18. At the low EC concentrations (Drug/ EC< 0.15) the microencapsulation efficiency is distinctly low, because of the suspension low viscosity. On the other hand, at the high EC concentrations (Drug/ EC=0.18), polymer phase agglomerates in the early stages of the process and forms a very high viscose medium with the small polymeric pores and inhibits the drug particles penetration.

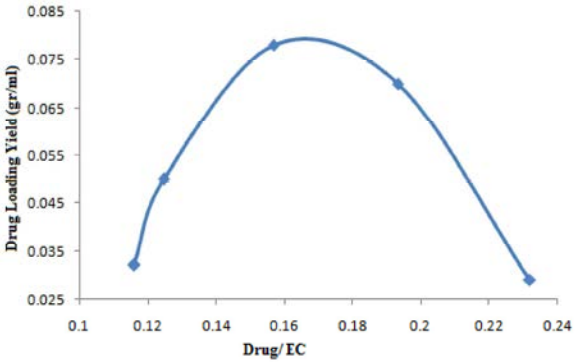

Fig. 2: Effect of Drug/ EC ration on the Microcapsules drug loading. Tocopherol=58 mg, Methylene Chloride= 6ml, PVA+Distilled water= 400mg

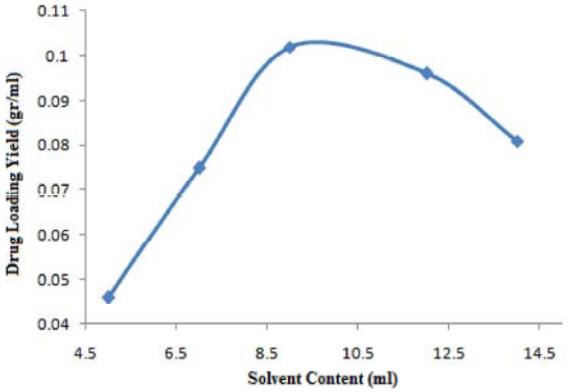

Fig. 3: Effect of Drug/ EC ration on the Microcapsules drug loading. Tocopherol=58 mg, Drug/ Ec= 0.17, PVA+Distilled water= 400mg

Solvent Concentration: Methyl Chloride concentration effect on the microcapsules drug loading was investigated by performing the microencapsulation process with different contents of Methyl Chloride (5, 7, 9, 12 and 14 ml) and the Drug/ EC ratio of 0.17 All the other operational conditions are the same as were in the previous runs.

Figure 3 shows that, in the low solvent content (<8 ml), the most part of the coating material precipitates or remains floating. In high solvent concentrations the coating wall dissolves and drug core releases before the complete microspheres form. The optimum range of Methyl Chloride is 9-10 ml, where as 400 mg PVA solution and 58 g Tocopherol are utilized and the Drug/ EC is equal to 0.17.

PVA Amount Effect: PVA amount influence on the microspheres drug loading, was carried out using 150, 250, 300, 350 and 400 ml PVA in 150 ml distilled water as the emulsifier, within 9ml Methyl Chloride, 58 mg Tocopherol and Drug/EC= 0.17. Results are presented in Fig. 4.

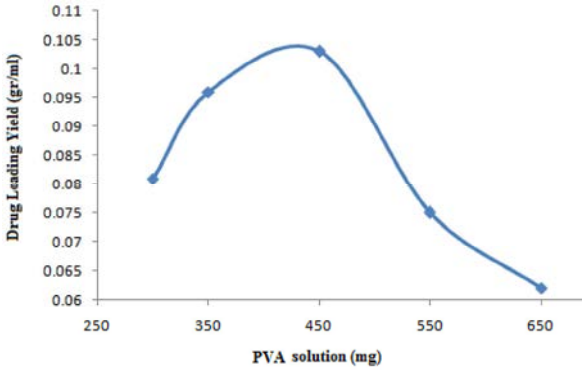

Fig. 4: Effect of Drug/ EC ration on the Microcapsules drug loading. Tocopherol=58 mg, Drug/ Ec= 0.17, Methyl Chloride= 400mg

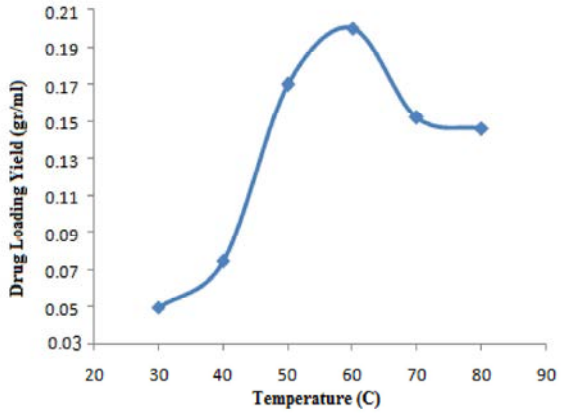

Fig. 5: Effect of Drug/ EC ration on the Microcapsules drug loading. Tocopherol=58 mg, Drug/ Ec= 0.17, PVA+Distilled water= 400mg, Tocopherol= 58 mg

Figure 4 demonstrates that the optimum PVA solution content for forming the Tocopherol- EC microcapsules, at the current condition is about 450 mg (300 mg PVA+ 150 mg distilled water). Results show that low drug loading, at the low PVA content, arises from the droplets joining that leads to the low drug loaded large agglomerates formation. High PVA contents (?300 mg) results in the tiny unstable microspheres formation that release the drug quickly.

Solvent Evaporation Temperature: Temperature effect on the polymerization mechanism and the formed polymer characteristics arises from the solvent behaviour influences by the temperature. Fig. 5 shows the solvent evaporation temperature effects on the Tocopherol loaded EC particles by in 6 different temperatures (40, 50, 60, 70, 80 and 90°C). Drug/EC, Methyl Chloride and the PVA values were determined based on our former testes resulted optimized amounts.

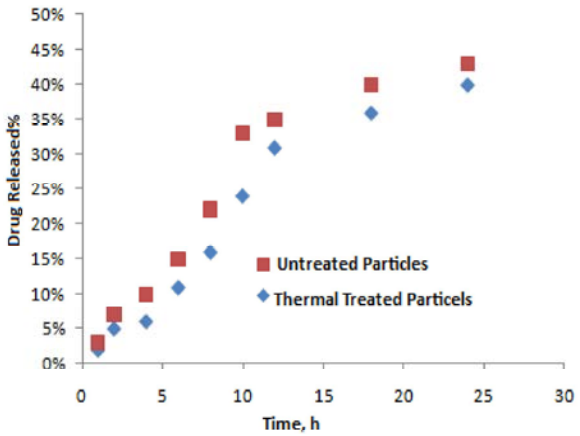

Fig. 6: Thermal treating influence on drug release in 0.1 N HCL, at 80 °C for 24 h

In the low temperatures, Methyl Chloride weak solubility power results in forming the rigid clot segments immediately [29]. At this condition, the loading chance is so low. Solubility power improves by increasing the temperature that leads to the extended EC distribution. EC segments gradually joint to each other by solvent evaporation and large amount of drugs are covered by the EC chains. Evaporation rate increases at the higher temperatures (□60°C), so the EC segments aggregates abruptly that causes decreasing the microcapsules drug loading.

Drug Release Enhancement: Releasing rate for a microencapsulated drug significantly depends on the coating material solubility, structure and characteristics. Solvent evaporation formed particles, should be rinsed and heated to the remained solvent and water elimination. Thermal treatment period and temperature determine the coating wall morphology and properties that influence on the release administrating mechanism consequently. Furthermore, thermal curing of coating wall leads to core adhering to the wall and wall firmness that result in the microcapsule more stability during the storage [30].

Rate of release in 0.1N HCL and simulated gastric juice (pH 7.4 buffer) were compared for two different samples, microencapsulated at the optimized condition (Drug/EC ratio; 0.17, PVA solution content;450cc and Methyl Chloride; 9cc, in 50-60°C solvent evaporation temperature rang). One sample didn't have treated thermally after the evaporation and the other one heated at 80°C for 24 h. Both samples were prepared in the optimized conditions. Results are presented on the figures 7 and 8.

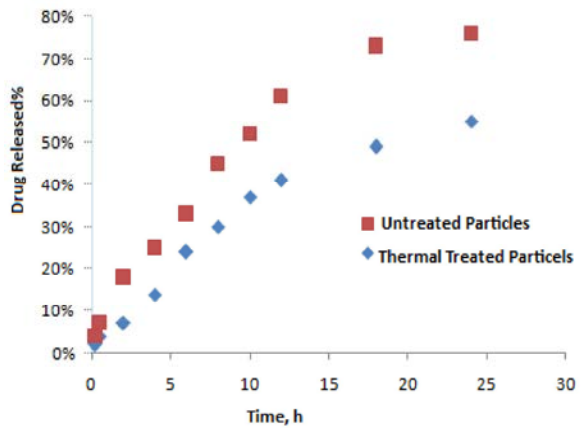

Fig. 7: Thermal treating influence on drug release in gastric juice simulated media, at 80 °C for 24 h

In both low pH and buffer environments the ordinary microcapsules release about 10-20% faster that the thermal heated particles. Therefore the unexpected pH-dependent drug release, which arises from the non-ionic character of the EC, can be due to the residual carboxylic acid groups in the EC or to the presence of the water, remained from the rinsing [31]. It can be emphasize by comparing the untreated particles release data in the figures 6 and 7. During the heating process the solvent and water evaporation completes the coating process and removes the wall pores. Besides, the polymer chains compact more to each other and coating wall becomes rigid that causes slow release procedure (Figures 6 and 7). On the other hand, drug release is dominated by penetration phenomenon in the acidic environments and by polymer solution in the buffers [32]. So, no considerable change is observed in the release rate, for the acidic media, by thermal curing. Instead, there is clear difference between the heat treated particles with the rigid and homogenous coating surface and the ordinary samples release behaviour in the gastric juice simulated media.

CONCLUSION

Loading yield, stability and rate of releasing are the key quality factors of a microencapsulated drug. We have produced an optimized Ethyl Cellulose capsulated Vitamin E through the solvent evaporation method by 9 ml Methyl Chloride, 450 mg PVA solution and 0.17 Drug/EC ratio at 60°C solvent evaporation temperature, with about 0.2 g/ml drug loading. In addition a thermal cured microencapsulated drug, with a firm and uniform thickness wall releases without any influences from the gastric juice chemical condition. On the other hand, an uncured particle is sensitively affected by the gastric liquid acidity.

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