Asian Journal of Chemistry; Vol. 27, No. 10 (2015), 3734-3738

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2015.18958

Preparation of Bioblends Using Spray Dryer and their Applications in Drug Delivery Systems

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Received: 26 December 2014; *Accepted*: 21 January 2015; *Published online*: 22 June 2015; AJC-17336

The importance of the study is to encapsulate L-ascorbic acid in biopolymers in order to obtain (i) enhancing its encapsulation efficiency (ii) increasing drug release ratio using different pH media. Microspheres based on polycaprolactone, polyethylene glycol and chitosan biopolymers are prepared by spray drying technique. Another importance of the study is the encapsulation of L-ascorbic acid which is an essential vitamin for humans. The study includes three different steps. First step is to obtain of low particle size, high surface area and homogeneous drug encapsulation material using spray dryer. Second part is determination of best efficient drug loading conditions. Final part of the study is about drug release experiments and calculation of drug release ratio in different pH media. At the end of studies, we achieved minimum 19.143 ± 0.023 μm particle size with 0.897 m^2/g surface area, 99.13 % maximum drug loading and 93.18 % drug release ratio at 2.8 pH medium.

Keywords: Drug delivery systems, Microencapsulation, Drug loading, Drug release, Spray dryer.

INTRODUCTION

Nowadays, pharmaceutical industry has been focused on some specific biodegradable polymers which are polycaprolactone, polyethylene glycol and chitosan[1]. These polymers have many advantages for drug delivery systems. They are biocompatible and biodegradable polymers; polycaprolactone has porous surface, so drugs can be easily loaded in the polycaprolactone based microspheres. Polyethylene glycol has good stability and it is able to have temporary hydrogen bonding with drugs. Chitosan and chitin are the most biocompatible materials in the world.

Drug encapsulation in colloidal delivery systems is an efficient approach to improve the pharmacokinetics of hydrophilic drugs[2]. These carriers encompass a broad range of dispersion systems ranging from submicron emulsions to colloidal particles, such as bio-based polymeric (polycaprolactone, polyethylene glycol, chitosan, casein and starch) aiming to protect the drug against degradation, sustain drug release, increase patient comfort by avoiding repetitive bolus injections or the use of perfusion pumps and reduce side effects.

Particulate drug carriers can act as delivery vehicles for drugs through various routes of administration[3]. On the other hand, the undesirable adverse effects have to be minimized and therapeutic improvement has to be maximized at the same time for an effective and useful drug delivery tool[4-7]. The only way to obtain improved therapy is that creating very effective drug release in the body and bio-based polymers could provide these vital necessities. Because of these reasons, biodegradable polymers are preferred for drug delivery systems.

Encapsulation may be defined as a process to entrap one substance within another substance, thereby producing particles with diameters of a few nm to a few mm. The substance that is encapsulated may be called the core material, the active agent, fill, internal phase, or payload phase. The substance that is encapsulating may be called the coating, membrane, shell, carrier material, wall material, external phase, or matrix. Two main types of encapsulates might be distinguished, *i.e.*, the reservoir type and the matrix type[8]. The reservoir type has a shell around the active agent. This type is also called capsule, single-core, mono-core or core-shell type. Application of pressure can lead to breakage of the reservoir type of encapsulates and thus to the release of its contents. Poly- or multiple-core type of encapsulates with several reservoir chambers in one particle also exist. The active agent in the matrix type is much more dispersed over the carrier material; it can be in the form of relatively small droplets or more homogenously distributed over encapsulation. Active agents in the matrix type of encapsulates are in general also present at the surface, in contrast to those in the reservoir type[9-12].

It is always a fact that performance of a drug delivery system is about encapsulation and release efficiency. One of

the basic requirements for the controlled and balanced release of the medicament in the body is its ideal spherical shape of polymeric particles and narrow distribution of their sizes. The size and shape of the particles play key role in their adhesion and interaction with the cell[11]. Another important issue for drug delivery systems is that stability at outside and sufficient degradation of drugs inside of human body. To overcome this problem, blending of biopolymer for drug delivery systems could be an enormous alternative because biodegradation rate is easily adjustable by blends of polymers. At these view of points, preparing of a drug which is easily biodegradable, biocompatible inside the body and stable outside the body is the main problem and most important goal for pharmaceutical industry.

Spray drying is the process of contacting an atomized stream to be dried with a gas stream that is at a higher temperature than the liquid stream. The higher temperature of the gas stream causes evaporation of the liquid from the droplets, forming particles. Recently, the use of this process to manufacture hollow, micron and sub-micron particles has also been demonstrated[12-14]. Furthermore, amorphous solid dispersions, soluble complexes, encapsulated systems, solid self-emulsifying systems and nano-dispersions of poorly soluble drugs prepared by spray drying are primary solubilization strategies[15].

On the basis of these remarks, aim of this work is the preparation and characterizations of biodegradable and biocompatible polymer based blends and obtain uniform particle size distribution at the same time. The importance of the study is production of a stable and effective drug encapsulation system using ternary polymer mixture by spray dryer. The main reason of using a ternary polymer mixture is to obtain the best efficiency of a drug material, because a combination of these materials can achieve superior characteristics than each component individually. Another importance of the study is encapsulation of L-ascorbic acid which is essential vitamin for humans. For achieving of the goal our study, we use polycaprolactone, polyethylene glycol and chitosan to prepare drug delivery system and spray dryer was our tool to obtain microspheres. First of all, we evaluate effects of spray drying conditions and composition of the microencapsulating formulation. Secondly, the most uniform distributed particle sized microsphere is selected and drug is loaded to it. L-ascorbic acid is the active ingredient for the study. After that, drug encapsulation and drug release efficiencies are calculated and best drying conditions were determined Drug release experiments are accomplished at different pH values (2.8, 7.4 and 9.6).

EXPERIMENTAL

Polycaprolactone with M_n = 10000 g/mol, M_w = 14000 g/mol and medium molecular weight chitosan are purchased from Sigma-Aldrich. PEG-6000 is a gift from Ashland Inc. L-Ascorbic acid powder (vitamin C) is also obtained from Sigma-Aldrich. Acetic acid (Merck) and formic acid (Merck) are used as solvent agents for polymer mixtures and used without any further purification. Oxalic acid and 2,6-dichloroindophenol sodium salt hydrate are used to determine L-ascorbic acid in UV spectrum.

General procedure: Polymer solutions are fed to spray dryer (Yamato ADL 310 lab scale spray dryer) by a peristaltic pump and first of all, best drying conditions are determined by changing drying temperature (120, 135 and 150 °C) and feed flow rate (3, 6 and 9 mL/min). Atomizer pressure is constant at 1 barg.

Secondly, particle diameter and particle size distribution are determined and L-ascorbic acid in different weight ratios are loaded for each microsphere which had the lowest particle diameter. L-Ascorbic acid loading studies are done by indirect loading of drug to microspheres at 25 °C and 200 rpm. L-Ascorbic acid contents are 5, 10 and 15 wt %, respectively. Encapsulation efficiency is calculated by eqn. 1[12]:

$$\text{Encapsulation efficiency (\%)} = \frac{\text{Final L - ascorbic acid amounts}}{\text{Initial L - ascorbic acid amounts}} \times 100 \quad (1)$$

Liquid phase is analyzed by UV at 518 nm to calculate eqn. 1[19-22]. Drug release calculations are also performed by UV. 0.5 mg blend/1 mL release medium (pH 2.8, 7.4 and 9.6) ratio is used. Drug release is calculated by eqn. 2[8].

$$\text{Drug release (\%)} = \frac{C_t}{C_0} \times 100 \quad (2)$$

where; C_t refers to drug amount in any time and C_0 to drug amount at t = 0.

Detection method: Polycaprolactone + polyethylene glycol + chitosan (PCL + PEG + CH) polymer mixture solutions are prepared by acetic acid-formic acid solutions with 3:7 (v/v) ratios. The value of 3:7 (v/v) acetic acid:formic acid is determined by previous studies[16-18]. Polymer contents in all solutions are 10 wt % and all ternary polymer mixtures are prepared by 1:1:1 (wt/wt) ratio.

Particle size analyzer (Malvern Mastersizer 2000), Mastersizer is used to obtain particle size diameter with distribution. Scanning electron microscopy (SEM-Jeol, JSM-6390 LV) is used to obtain morphological structures of microspheres. Particle morphology is determined by this way. Thermogravimetric analysis or thermal gravimetric analysis (TGA, Perkin-Elmer Diamond TG/DTA) is used to analyze blend structure. Ultraviolet Analysis (UV-UV Mini 1240 SHIMADZU) is used to calculate drug encapsulation efficiency and drug release ratios.

RESULTS AND DISCUSSION

Yields and particle size distributions with standard deviation are shown for all studies in Figs. 1 and 2, respectively. Due to the Fig. 2, Metasizer analyses are done 3 times and particle diameter distribution is determined by standard deviation of the results. Final values demonstrate particle size (μm) with standard mean of PCL-PEG-CH microspheres. Fig. 1 determines that drying efficiency increase by decreasing of flow rates at 120 C and 135 °C; on the contrary drying efficiency increase by increasing of flow rate at 150 °C. The reason of these results is that increasing drying temperature resulted in agglomeration of polymer mixture, so contact time with polymer mixture and drying temperature had adversely effect on diameter distribution[19-21]. Due to these results, 120 °C and 3 mL/min are the best drying conditions because of the lowest particle diameter with 19.143 ± 0.023 μm and highest surface area with 0.897 m^2/g surface area in this study.

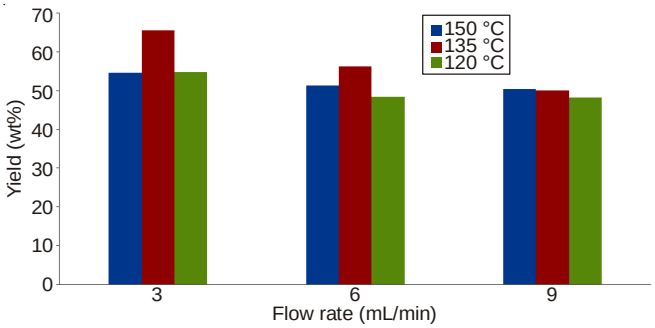

Fig. 1. Yield (wt %) at different drying temperature (°C) and flow rates (mL/min)

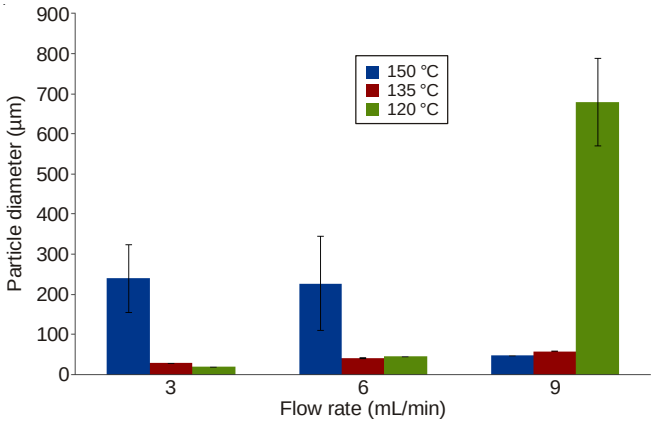

Fig. 2. Particle diameter (µm) with standard deviations at different drying temperature (°C) and flow rates (mL/min)

SEM micrographs are shown in Fig. 3 for 120 °C-3 mL/min, 135 °C-3 mL/min and 150 °C-9 mL/min. It is easily seen that agglomeration increases by increasing of drying temperature. Porous structure of microsphere is also easily shown in all SEM micrographs. This porous structure is an advantage because drug loading capacity of porous spheres is higher than other spherical structures[22].

The sample is placed in furnace and burned in the N_2 atmosphere without O_2 with the ramp 30 °C /min up to 800 °C. Thermal gravimetric analysis scan is obtained from the measurement to determine decomposition temperature and char yield. Thermal gravimetric analysis curves for PCL-PEG-CH bio-blend and L-ascorbic acid loaded bio-blend are shown in Figs. 4 and 5, respectively.

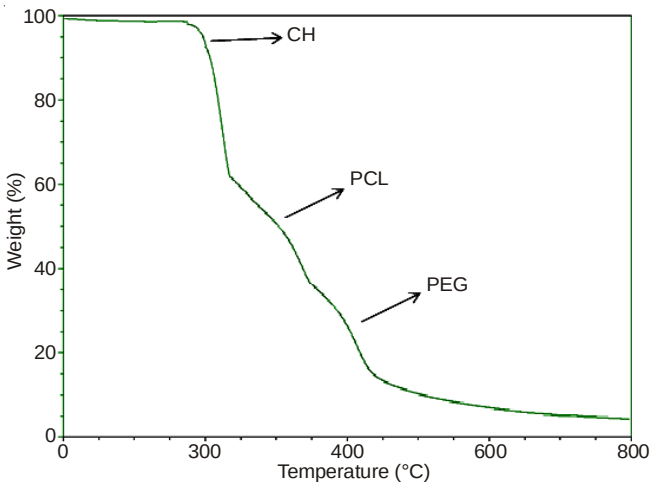

Fig. 4. Thermal gravimetric analysis curve of PCL-PEG-CH microsphere at 120 °C, 3 mL/min

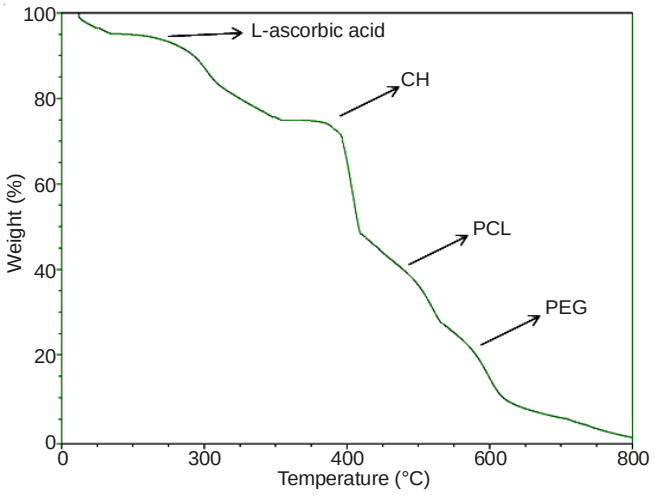

Fig. 5. Thermal gravimetric analysis curve of L-ascorbic acid loaded microsphere

It is seen that TGA curves in Figs. 4 and 5 are blends because thermal degradation curves goes down step by step. Fig. 4 illustrates PCL-PEG-CH blend thermal degradation and it begins about 300 °C with chitosan degradation, following at 350 °C with polycaprolactone degradation and finalized at 400 °C with PEG-6000 degradation. L-Ascorbic acid (Fig. 5) shows that the decomposition starts at around 190 °C. Four

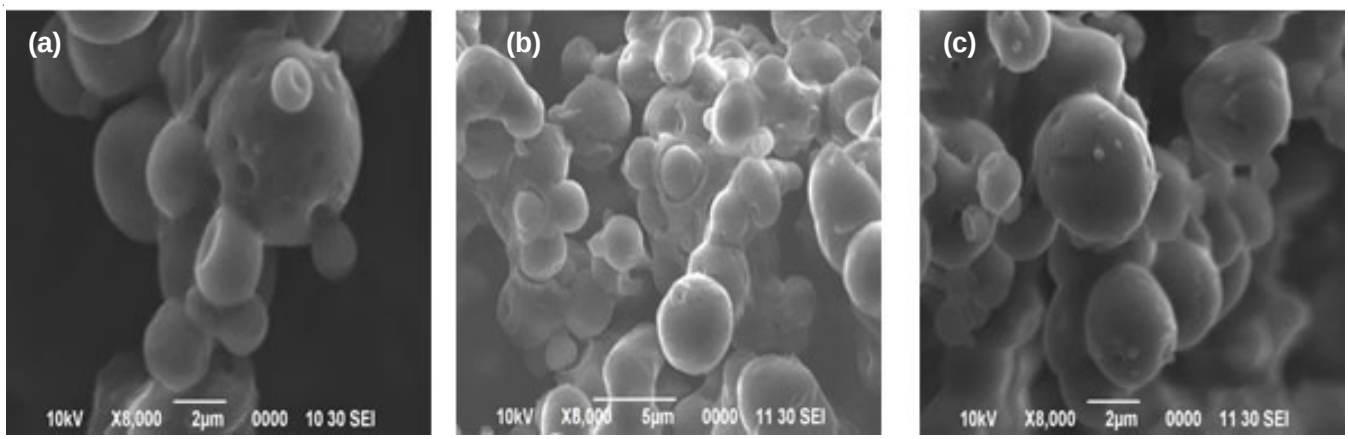

Fig. 3. SEM micrographs (a) 120 °C, 3 mL/min; (b) 135 °C -3 mL/min; (c) 150 °C, 9 mL/min

thermal degradation steps are identified and allocated to the L-ascorbic acid and polymer fractions, respectively, based on the TGA curves.

Drug release studies are performed under three different L-ascorbic acid concentrations (5 wt %, 10 wt % and 15 wt %) with different loading time and PCL-PEG-CH particle amounts. Microsphere obtained at 120 °C and 3 mL/min is used in drug loading studies because this microsphere had the lowest particle diameter and also best distributed particles due to the Metasizer analyses (Figs. 1 and 2). Results are shown in Figs. 6 and 7 for effects of loading time and effects of particle amount, respectively.

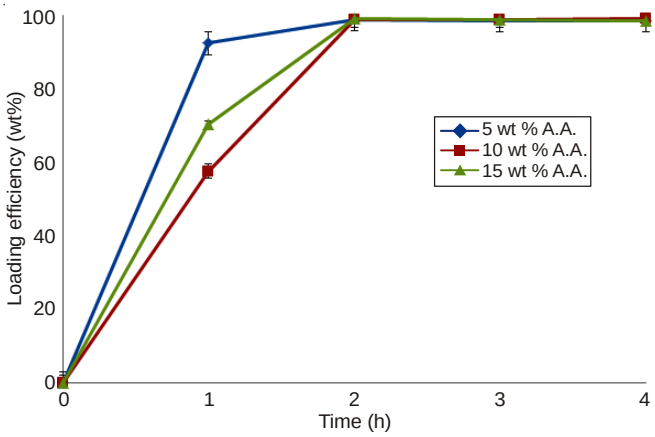

Fig. 6. Effects of drug loading time for L-ascorbic acid on PCL-PEG-CH

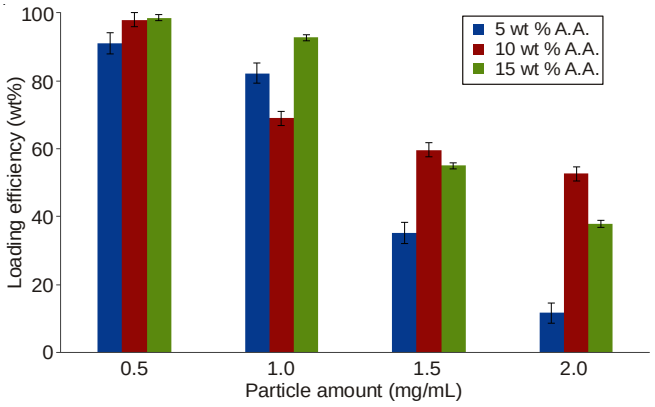

Fig. 7. Effects of particle amount for L-ascorbic acid loading on PCL-PEG-CH

Drug loading experiments are carried out at 25 °C and 200 rpm. Fig. 6 demonstrates that L-ascorbic acid concentrations are rapidly increased in 2 h and stabilized from 2 to 4 h. We achieved significant results in this part and L-ascorbic acid loading is 99.13 wt % due to UV results.

We also determined the effects of particle amount on drug loading efficiency by changing particle amounts from 0.5 mg to 2 mg by increasing of 0.5. Results are showed in Fig. 7. 0.5 mg PCL-PEG-CH in 15 wt % L-ascorbic acid experiment is the most effective study. We also revealed that increasing particle amount decreased drug loading efficiency. The explanation of the result is that increasing particle amount concluded agglomeration of microspheres, so particle surface area is decreased and it affected drug loading efficiency in bad direction.

Drug release studies are performed for the most loaded microsphere obtained in 15 wt % L-ascorbic acid solution by 0.5 mg particle amount. Drug release studies are obtained at three different release medium by changing pH from 2.8 to 9.6 (Fig. 8).

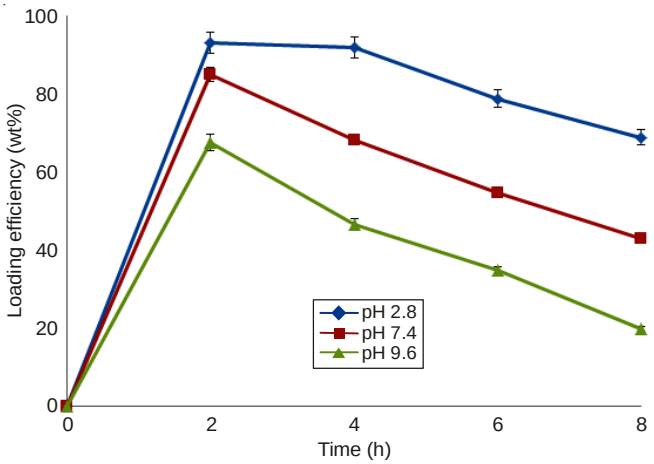

Fig. 8. Drug release studies at different release mediums in 8 h

We achieved peak release points in just 2 h in release mediums and Fig. 8 also illustrated that decreasing pH increased drug release efficiency. Drug loaded microspheres contains PCL-PEG-CH bio-based polymers and particularly interaction of polycaprolactone and chitosan in acidic medium is better than higher pH values[23]. By this way, L-ascorbic acid release remarkably increased in pH 2.8 (max. 93.18 %) as shown in the figure above.

Conclusion

In fact the encapsulation efficiency, loading capacity and drug release behaviour are the most important issues for drug delivery systems. We suggest an alternative solution to solve the problems and these are using spray dryer to reduce particle diameter, to obtain narrow particle size distribution and to produce blends made by ternary polymer mixture to get best performance from the encapsulation material.

We achieved the aim of the study by production of a stable and very effective L-ascorbic acid loaded drug using biodegradable polymer solutions by spray dryer. We also used aqueous solutions of non-toxic solvents in the study. By these ways, we succeeded higher drug loading and drug release efficiency in our study.

Because of unstable and very sensitive L-ascorbic acid, producing vitamin C drugs are really difficult. However, another significant result of our study is achieving 93.18 % L-ascorbic acid release in 2 h.

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