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Research Article

ENCAPSULATION PROTOCOL FOR HIGHLY HYDROPHILIC DRUG USING NON-BIODEGRADABLE POLYMER

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ABSTRACT

Microencapsulation of drugs into solid non-biodegradable polymeric microspheres by solvent evaporation technique remains challenging especially with those having low molecular weight and high hydrophilicity nature. This paper presents an efficient encapsulation protocol for this group of drugs, demonstrated using losartan potassium (LP) as a model compound which is encapsulated into Eudragit RS 100 (ERS) and Eudragit RL 100 (ERL) microspheres. The microspheres were prepared using solvent evaporation technique with an ultimate aim of prolonging drug release. Six formulations were prepared using different drug/polymer ratio. The effects of polymer type and polymer/drug ratios on the size, surface morphology, encapsulation efficiency and the release characteristics of the microspheres were examined. The formulation containing drug/polymer ratio 1:5 in which the ratio between the two polymers (ERS:ERL) is 4:1 was found to be the most appropriate with respect to encapsulation efficiency (94.43 % ± 0.277), drug loading (19.58 % ± 0.417), batch yield (80.40 % ± 1.712), particle size (204.23 ± 8.438) and having highest correlation coefficient (0.9829) amongst all formulation thus providing a desired drug release characteristics. At the optimum stirring speed of 750 rpm, best spherical shaped particles with good surface characteristics were obtained, which were distributed over the size range of 120-270 µm. This proposed method has been successfully used to prepare batches of microspheres having high encapsulation efficiencies.

Key words: Microencapsulation, Eudragit, Losartan potassium, Microspheres, Encapsulation efficiency.

INTRODUCTION

In the recent past, the development of targeted drug delivery systems have received an increasing interest not only for a better treatment of specific local pathologies, but also for the systemic therapy of both conventional and labile molecules as well as a means of achieving chronotherapy for diseases like hypertension[1]. The ability to deliver and have a controlled release of therapeutic agents at injured or targeted disease sites is an important aspect in drug development and regenerative medicine. Such system avoid unnecessary health side effects due to burst effect or overdose, ensuring optimum supply of drug that is required by the biological system for a prolonged period, and cutting down wastage of expensive drugs. Encapsulating the active agents within a polymeric matrix microsphere is a good option to achieve the objective as the polymer can act as the rate-controlling membrane to obtain the desired controlled release[2]. Besides, encapsulation minimizes the deactivation of drugs during the delivery process due to the protection by the polymer shell and this ensures sufficient amount of drug reaching the targeted area. Although so, modern microencapsulation of bioactive substances still continues to be an important area and the effort mostly concentrates on formulation and protocol optimization strategies. The solvent-evaporation method of microencapsulation involves the use of emulsification of a solution containing polymer and drug with an additional medium in which the drug and polymer cannot dissolve.

The aim of this study was to prepare Eudragit microspheres containing highly hydrophilic LP to achieve better encapsulation efficiency and controlled drug release profile suitable for peroral administration. Firstly, we investigated some formulation variables (polymer type, drug: polymer ratio, stirring speed) to obtain spherical particles. Then, the yield of production, particle size distribution, encapsulation efficiency, surface properties and LP release rate from microspheres were investigated. The influences of formulation variables on the microsphere properties were examined and the microsphere formulations suitable to achieve our goal were determined.

MATERIALS AND METHODS

Materials

Losartan Potassium (LP) was collected from Jubiliant Organosys Ltd., India as a free gift sample. Eudragit RS 100 (ERS) and Eudragit RL 100 (ERL) was obtained from Central Drug House (Pvt.) Ltd., Bombay, Magnesium Stearate was obtained from HIMedia Pvt. Ltd., Mumbai and Liquid Paraffin was procured from Merck Ltd., Mumbai, India and all other chemicals were of reagent grade.

Preparation of microspheres

LP microspheres were prepared by solvent evaporation technique[3]. A total of six formulations were prepared taking different drug: polymer ratio. Concisely the polymers ERS and ERL were dissolved in 5 ml of acetone to get a clear solution. The drug LP and Magnesium stearate (30 mg) were added to this mixture and was stirred at the same speed for 30 minutes and then it was kept in the ultrasonic bath until dispersed completely[4]. The resulting dispersion was then poured into a 250 ml beaker containing 150 ml of light liquid paraffin while stirring continuous with a mechanical stirrer at 700 rpm with a blade fitted with a four-blade "butterfly" propeller with a diameter of 50 mm (Lab Digital Stirrer, Remi). Non-polar liquid paraffin was preferred as dispersing medium[5]. Stirring was continued for 3 hours till complete evaporation of acetone. Then the resulted microspheres were collected by filtration under vacuum, washed 4–5 times with 30 ml n-hexane and dried at room temperature (25 °C) for 24 h to get free flowing microspheres[6]. The different batch specifications of LP loaded microspheres are given in Table 2.

RESULTS AND DISCUSSION

SEM characterization of LP loaded Microspheres

The investigation is done on the effects of polymer concentration, thus the inner phase viscosity and the stirring speed of the system on particle formation and particle size, while keeping the other parameters constant. The O/W emulsion is produced by the agitation of two immiscible liquids. The drug substance is dispersed in solution of the polymer. Agitation of the system is continued until the solvent partitions into the aqueous phase and is removed by evaporation. This process results in hardened microspheres which contain the active moiety. Trials were made to prepare microspheres by Solvent evaporation technique in the water phase using acetone/water and alcohol/water systems. Though many formulations were investigated but they did not prove to be satisfactory. Then acetone/liquid paraffin system was used and various formulations (F1, F2, F3, F4, F5 and F6) with different drug: polymer ratios were tried and effect of drug: polymer ratio, stirring speed (500,750 & 1000 rpm) on the particle size of the microspheres were studied after SEM study on prepared microspheres[7] (Fig.1-2).

Table 1: Batch specification of LP loaded microspheres.

Formulation code	D : P	Amount of drug taken (mg)	Amount of polymer taken (mg)	
			ERS	ERL
F 1	1 : 1	100	50	50
F 2	1 : 2	100	100	100
F 3	1 : 3	100	150	150
F 4	1 : 4	100	320	80
F 5	1 : 5	100	400	100
F 6	1 : 6	100	480	120

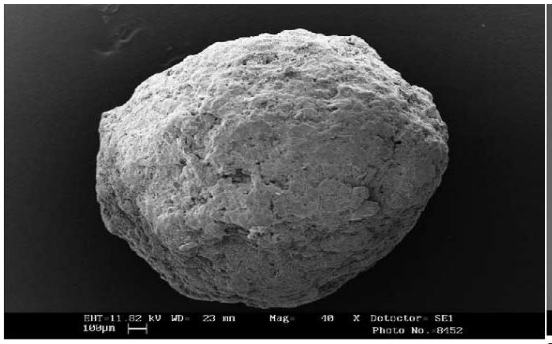

Fig.1: SEM of prepared microsphere without Drug

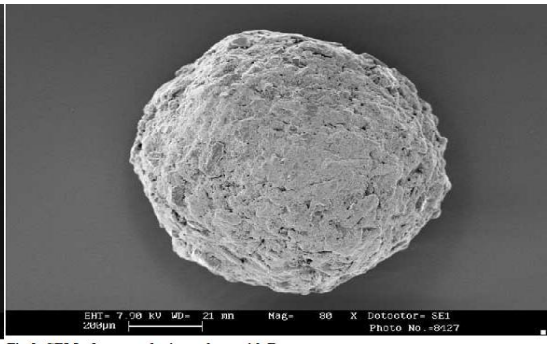

Fig.2: SEM of prepared microsphere with Drug

Effect of the dispersing agent and dispersing medium on loaded microspheres

Magnesium stearate was added to the formulation as a droplet stabilizer to overcome the problem of droplet coalescence during solvent evaporation[8]. The use of magnesium stearate as a dispersion agent decreased the interfacial tension between the lipophilic and hydrophilic phases of the emulsion and further simplified the formation of microspheres. As the solvent evaporated, the viscosity of the individual droplets increased, and highly viscous droplets were observed to coalesce at a faster rate than they could be separated. Magnesium stearate formed a thin film around the droplets and thereby reducing the extent of coalescence, before hardening of the particles, on collision of the droplets. The resultant microspheres were free-flowing, and the use of magnesium stearate was deemed effective.

Liquid paraffin was selected as a bulk or outer phase, since LP and Eudragit RS/RL are only very slightly soluble in liquid paraffin. Acetone has a dielectric constant of 20.7 and was therefore chosen as the dispersed or inner phase, since solvents with dielectric constants between 10 and 40 shows poor miscibility with liquid paraffin[9].

Batch Yield, encapsulation efficiency and Drug loading of loaded microspheres

Yield and encapsulation efficiency remained high at all drug loadings. As polymer content increased, the encapsulation efficiency slightly decreased as seen with the trends for the formulations, F1, F2 and F3 (Fig.3). This can be due to the fact that an increase in polymer content led to an enhancement of the concentration gradient between the emulsion droplets and the continuous phase; as a result increasing the amount of drug partitioning into the continuous phase. Also the fact that the ratio within the polymer ERS and ERL remained 1:1 (ERS:ERL) for F1, F2 and F3 and the polymer ERL being more permeable than ERS due to presence of more quaternary ammonium groups has led to insufficient encapsulation of drug in polymeric matrix. The high encapsulation efficiencies of formulations, F4, F5, F6 in which the ratio between the polymer was kept at 4:1 (ERS: ERL) was found to be remarkably high (F5- 94.43 % ± 0.277) as an increase in the ERS concentration has lead to an increase in the viscosity of the internal phase. When the viscosity of the internal phase is increased, the efficiency of the stirring is reduced and large size microparticles were formed. The increased viscosity as polymer levels increase can impede drug mobility in the droplets, and this was observed as an increase in encapsulation efficiency at high ERS levels. High ERS levels may also lead to rapid polymer precipitation on the droplet surface and rapid microparticle solidification, resulting in the hindering of drug diffusion, effectively trapping it in the particle.

These suggested that the present method was suitable for the preparation of microspheres of a highly water-soluble drug, such as LP. The drug loading was decreased proportionately with increase in amount of added polymer for the formulations, F1, F2 and F3. The same pattern was also observed for next three formulations F4, F5, F6. The effect of drug loading on batch yield, encapsulation efficiency and particle size can be seen in Fig.4.

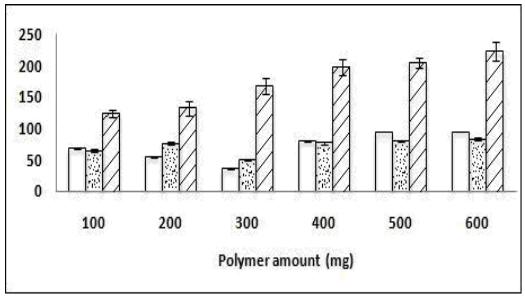

Fig 3: Bar graphs showing effect of polymer amount on □ % Encapsulation efficiency, ▨ % Batch yield and ▨ particle size of LP microspheres

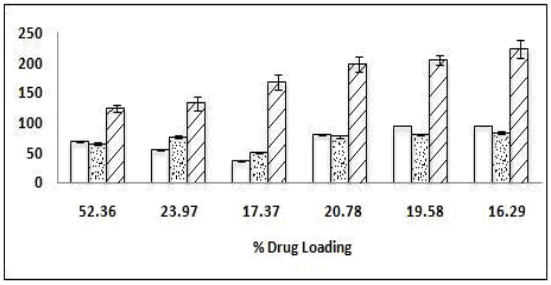

Fig. 4 : Bar graphs showing effect of % Drug loading on □ % Encapsulation efficiency, ▨ % Batch yield and ▨ particle size of LP microspheres

Control of drug-release behavior of microspheres

Examination of the release profiles reveals that drug release was generally faster for LP microspheres produced with the high concentration of ERL polymer despite the apparent similarity in particle size of the microspheres. ERS and ERL are copolymers of partial esters of acrylic and methacrylic acids containing low amounts of quaternary ammonium groups, approximately 5% and 10% for ERS and ERL, respectively. The ERS polymer is water-insoluble, and drug delivery systems prepared from it show pH-independent sustained drug release, attributed to the quaternary ammonium groups. The quaternary ammonium groups in the ERS and ERL chemical structures play an important role in controlling drug release because they relate to water uptake followed by the swelling of the polymers. This is most likely because the number of quaternary ammonium groups of ERS is lower than that of ERL, which renders ERS less permeable.

Compared to all the other formulations, % amount of dissolved drug was higher for F1, F2 and F3 formulation which has the least polymer amount (ERS: ERL= 1:1).

This situation is due to the fact that scarcity of polymer augmented release of the drug and also the thin polymer wall of microspheres as diffusion path led the drug to be easily released in the dissolution medium. The % amount of dissolved drugs of F1, F2 and F3 were not significantly different after the fourth hours. But it is found that, % amount of dissolved drug for F4, F5 and F6 which has the highest polymer amount (ERS: ERL = 4:1) were less than the other formulations. According to the dissolution tests conducted by USP I method, F5 and F6 formulations gave the lowest dissolution rate. Since LP has weak acidic properties, its solubility varies in parts of gastrointestinal tract with different pH values. Dissolution tests were performed separately in two dissolution media with different pH values (1.2 and 7.4) for 12 h by USP I apparatus it is seen that the dissolution profiles were identical at these pH values. After 2 h in 0.1M HCL, the release of LP was restricted to less than 31% for F5. When the pH increased, a rapid LP release was observed from the microparticles prepared at the entire range of polymer concentrations.

Considering the gastrointestinal transit time, release profiles from F1, F2 and F3 seems to be too fast for controlled release. To decrease the release rate ERS and ERL were mixed at different amounts for three microsphere formulations (F4, F5 and F6) in a ratio of 4:1. LP dissolution rates from these microspheres are shown in Fig.5. The amount of LP released in 12 h was between 83-87% for these three formulations. Release rates decreased as the amount of ERS increased considerably.

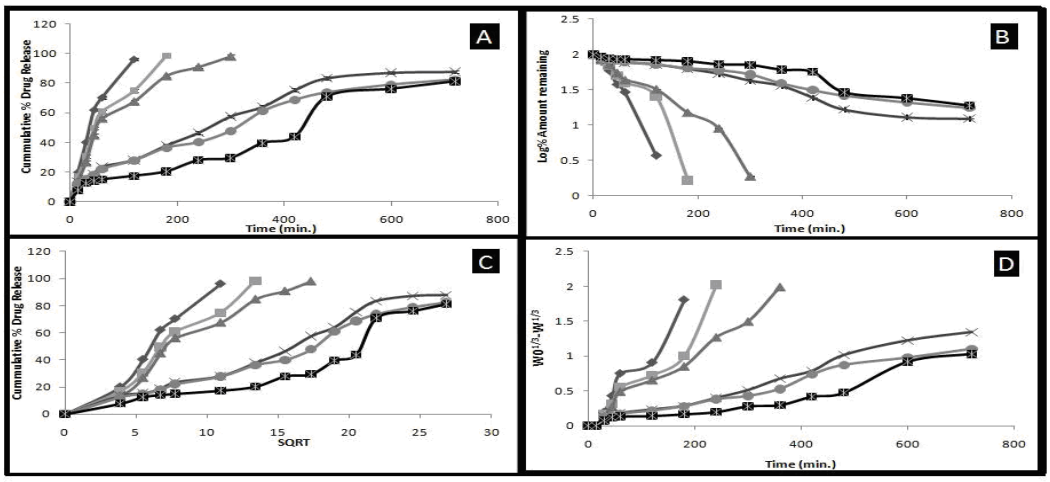

Fig. 5 : Dissolution Graphs (N=3) (A) Zero order Model (B) First Order Model (C) Higuchi Model and (D) Hixon-Crowell model comparing six formulations, F1, F2, F3, F4, F5 and F6

Table 2: Effect of feeding polymer on mean particle size, % yield value, drug loading, encapsulation efficiency of microspheres.

Formulation code	D : P	Amount of Drug taken (mg)		Amount of Polymer taken (mg)	Mean particle size (µm)	Yield Value (%)	Drug Loading (%)	Encapsulation Efficiency (%)
		ERS	ERL					
F 1	1 : 1	100	50	50	123.53 ± 6.372	65.21 ± 1.826	52.36 ± 1.038	68.27 ± 0.581
F 2	1 : 2	100	100	100	132.76 ± 11.807	76.25 ± 2.696	23.97 ± 1.141	54.77 ± 0.743
F 3	1 : 3	100	150	150	167.40 ± 13.079	51.36 ± 1.097	17.37 ± 0.497	35.67 ± 0.456
F 4	1 : 4	100	320	80	198.16 ± 13.046	77.43 ± 2.802	20.78 ± 0.781	80.40 ± 0.347
F 5	1 : 5	100	400	100	204.23 ± 8.438	80.40 ± 1.712	19.58 ± 0.417	94.43 ± 0.277
F 6	1 : 6	100	480	120	222.53 ± 15.302	83.71 ± 2.045	16.29 ± 0.440	95.38 ± 0.305

* Values are average of three readings ± standard deviation.(n=3), D = Drug, P = Polymer

CONCLUSION

This work has successfully demonstrated a direct microencapsulation for low molecular weight and highly water-soluble compounds via solvent evaporation technique, represented by the model molecule of LP. Various engineering factors affecting the microencapsulation process of LP were revealed and discussed accordingly. Key finding in this work was the consideration of having a higher concentration of polymer in the stirring solution during the production process that ensures effective microencapsulation with high encapsulation efficiencies. Drug/polymer ratio and stirring speed of the system were important to obtain spherical particles with smooth surfaces. The yields of preparation and encapsulation efficiencies were very high for all microspheres obtained. LP release rates from microspheres were dependent on the type of polymer used and ratio between the polymers. The drug release profile aimed for p.o. administration could be obtained by adding ERS to ERL and changing the ratio of these polymers. Controlled release without initial peak levels achieved with these microsphere formulations can reduce dosing frequency, decrease side effects and improve patient compliance. Further optimizations and refinements for sure can facilitate the development to utilize the microspheres in real clinical application.

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