

Preparation and Characterization of Polyvinyl Acetate (Kollidon® SR) Microspheres Containing Diclofenac Sodium I: Effect of Stirring Rate and Total Solid Content

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ABSTRACT: Microspheres were prepared by W/O emulsification solvent evaporation technique where Diclofenac Sodium (DS) and Kollidon® SR (KSR) were used as model drug and polymer respectively. Light liquid paraffin (LLP) was used as oil phase and 1% (w/w of the continuum) of span 60 was used for emulsification. Microspheres were prepared using different stirring rate (1500, 2000, 2500, 3000 rpm) and different total solid content of the system (0.08%, 0.16%, 0.24% w/w of the continuum). Microsphere morphology was examined with the help of Scanning Electron Microscope (SEM) and particle size distribution was analyzed by Mastersizer 2000. Larger microspheres were obtained with decreasing stirring rate. Increase in solid content of the system also increased microsphere size. Drug loading was also found to be affected due to these preparative variables. *In vitro* dissolution study was performed in a USP XXX paddle apparatus (type 2). Dissolution media was buffer of pH 7.2, paddle speed was 50 rpm and dissolution temperature was maintained at $37 \pm 0.5^\circ\text{C}$. Release of DS from KSR microspheres was found to follow Higuchi mechanism. DS release was increased with increased stirring rate. But increased solid content of the system resulted in reduced release of DS. Normalized release rate of DS was also found to be affected by these preparative variables. Release rates were found increased with increased stirring rate whereas rates were found decreased with increased solid content of the system.

Key words: Kollidon® SR, Diclofenac Sodium, Microsphere, Solvent evaporation technique.

INTRODUCTION

Microencapsulation is a well-known method that is used to modify and delay drug release from pharmaceutical dosage forms. A popular method for microencapsulation of water insoluble drugs is the solvent evaporation process. Generally, the entrapment efficiency of water soluble drug is low due to drug loss from the organic emulsified polymeric phase before solidification of polymer in

the microspheres.^{1,2} Therefore, optimization of the process may be advantageous for the efficient entrapment of water soluble drugs. In the present investigation, water soluble diclofenac sodium (DS) and water insoluble Kollidon® SR (KSR) were used as model drug and polymer, respectively, for the preparation of microspheres.

Polyvinyl acetate and polyvinyl pyrrolidone (Povidone) based matrix polymer (Kolidon® SR) has already been established as sustained release polymer. This water insoluble polymer (povidone part is water soluble but polyvinyl acetate part is

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water insoluble) can be used in different types of sustained release dosage forms like tablets, pellets, and granules.³ But its excellent flowability and compressibility makes it suitable for sustained release matrix tablet by direct compression.³⁻⁶ However, the main emphasis has been toward the microencapsulation as it has been used for the first time for this purpose in our laboratory and the microencapsulation efficiency of the Kollidon® SR (KSR) has still been evaluated by the same.

Modification of the preparative conditions like emulsifier type and conditions, rate of organic solvent evaporation, continuum pH, core loading, rate of stirring, core solubility etc may all seriously affect the final microsphere characteristics and release kinetics.⁷⁻¹¹ In this paper the effects of stirring rate and total solid content of the system on the KSR microspheres are reported.

MATERIALS AND METHODS

Diclofenac sodium was received as a gift sample from SQUARE Pharmaceuticals, Bangladesh. Kollidon® SR (BASF, Germany), Span 60 (BDH Chemicals Ltd., England), Methanol (MERCK, Germany), Light Liquid Paraffin (MERCK, Germany), Pet Ether of 40-60 (MERCK, Germany) of laboratory grade were also used in the study.

Preparation of Kollidon® SR microsphere. Microspheres were prepared using the emulsification (W/O) and organic solvent evaporation technique¹² which is a slight modification of the Tsai technique.¹³

Light liquid paraffin (LLP) containing 1% (w/w) span 60 was taken in a beaker. DS was suspended in the LLP with the help of a high speed stirrer (Heidolph No. 5011, Heidolph, England). KSR solution with methanol was made with the help of a vortex mixer (DIGISYSTEM LABORATORY INSTRUMENTS INC. Taiwan). This KSR solution was then poured into the DS suspension with continuous stirring. After 2 hours of stirring, hard and spherical sized microspheres were found.

Prepared microspheres were then filtered and washed with petroleum ether (40:60) for several

times until complete removal of the oil phase from the microspheres. A vacuum dryer (VEEGO, India) was used to dry to obtain free-flowing microspheres.

Surface Morphology Study. A Scanning Electron Microscope (SEM) (S-3400N, Hitachi, Japan) was used to observe the surface morphology of the microspheres. SEM image at different magnifications was taken for comparative study.

Particle Size Analysis. Size distribution of the microspheres was analyzed by laser diffraction technique using Mastersizer 2000 (MALVERN, UK). Particle size distribution was measured by Dry Dispersion technique. Volume mean diameter (D [4, 3]) and surface weighted mean diameter (D[3,2]) were used to express average particle size in μm . Specific surface area (m^2/gm) of the microspheres was also determined.

Drug Content. Aqueous solutions of diclofenac sodium (0 to 20 $\mu\text{g}/\text{ml}$) in phosphate buffer (pH 7.2) were prepared and the absorbance was measured by a SHIMADZU UV-VIS Spectrophotometer (UV mini-1240, SHIMADZU CORP., Kyoto, Japan). A linear line was obtained while absorbance values were plotted against concentrations ($R^2 > 0.996$).

Drug loaded microspheres of each batch were finely powdered in a glass mortar. A clear solution of the powder was made using the same buffer (pH 7.2) after proper sonication (POWER SONIC 505, HWASHIN TECHNOLOGY CO., Seoul, Korea). Then the solution was filtered through 0.45 μm filter and analyzed spectrophotometrically for drug content.^{14, 15}

In vitro Dissolution Study. Microspheres of a particular size range were separated with the help of a sieve set (Endecotts Limited, England) for dissolution study. It was carried out in a USP XXX apparatus 2 (Paddle Apparatus) in 900 ml phosphate buffer (pH 7.2) of $37 \pm 0.5^\circ\text{C}$ at a rotational speed of 50 rpm. Dissolution Samples were withdrawn at predetermined intervals and were filtered through 0.45 μm filters. The drug content was determined in the filtrate either directly or after appropriate dilution with the dissolution media.

RESULTS AND DISCUSSION

Microspheres of KSR containing DS were prepared by W/O emulsion solvent evaporation technique where methanol, span 60 and light liquid paraffin (LLP) were used as organic solvent, lipophilic surfactant and oil phase or continuum respectively. Stirring rate and total solid content were two preparative variables. Change in microsphere size, encapsulation efficiency, and release kinetics of DS due to the above two preparative variables have been reported here.

Morphology of the microspheres. Microspheres were hard and free flowing (Figure 1). No significant difference on the surface of the microspheres was appeared due to rpm variation. But lower stirring rate produced larger microspheres. Increased solid content also produced larger microspheres.

Microsphere Size. Microsphere size (both by volume and population) was found to be reduced with increased stirring rate (Table 1). When microspheres were prepared at different stirring rates keeping the KSR and DS amount constant (0.08% w/w of the continuum), it was found that the mean particle size was found decreased with increased stirring rate. This reduction of particle size with increased rate of stirring is a common phenomenon in microencapsulation.¹⁶ With an increased stirring rate a fine emulsion is produced resulting in smaller microspheres. Moreover, the high stirring rate also prevented the fusion of smaller “immature” microspheres which also contributed to the final size of the microspheres. Particle size distribution also showed a unimodal distribution of the smaller microspheres at high stirring rate (Figure 2). In contrast, lower stirring rate showed bimodal distribution of larger particles.

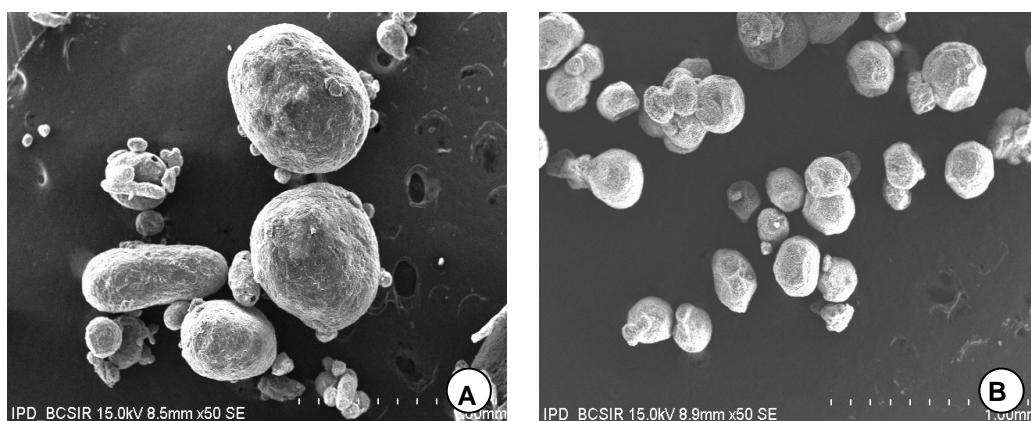


Figure 1. Scanning Electron microscopic image of KSR microspheres containing DS prepared with 1500 rpm (A) and 3000 rpm (B). Core: polymer, 1:1

Table 1. Mean particle diameter, specific surface area (SSA), encapsulation efficiency (EE) and DS release data (in buffer pH 7.2) for KSR microspheres prepared using different preparative conditions.

Variables Studied	Preparative Conditions			Microsphere properties				$t^{1/2}$ release data (K_r/SSA) ^d
	Nominal C : P ratio	Total solid content in LLP (% w/w)	Stirring rate (RPM)	Mean Population Diameter $\mu\text{m} (\pm \text{SD})^a$	Mean Volume Diameter $\mu\text{m} (\pm \text{SD})^a$	SSA ($\text{m}^2/\text{g} \times 10^{-2}$) ^b	EE (percent) ^c	
Stirring Rate (RPM)	1: 1	0.08	3000	395 ± 2.5	423 ± 1.6	1.52	72.32	60.61
	1: 1	0.08	2500	561 ± 2.3	824 ± 1.2	1.31	72.89	55.75
	1: 1	0.08	2000	630 ± 1.8	887 ± 2.01	1.14	75.11	51.86
	1: 1	0.08	1500	863 ± 1.1	1051 ± 1.1	0.995	75.32	46.54
Total solid content	1: 1	0.08	3000	395 ± 2.5	423 ± 1.56	1.52	72.32	60.61
	1: 1	0.16	3000	869 ± 2.3	1014 ± 4.1	1.32	79.55	52.68
	1: 1	0.24	3000	953 ± 3.1	1084 ± 2.2	1.28	82.38	51.52

All the mean microcapsule sizes are the geometric mean and geometric standard deviation (SD) respectively.

^aGeometric mean and geometric SD. ^bSSA = Specific surface area of microcapsules. ^cEncapsulation efficiency is the percentage of theoretical DS content in the microcapsules. ^dRelease rate constant per unit specific surface area (percent release. $\text{hour}^{1/2}/\text{m}^2 \cdot \text{g}^{-1}$)

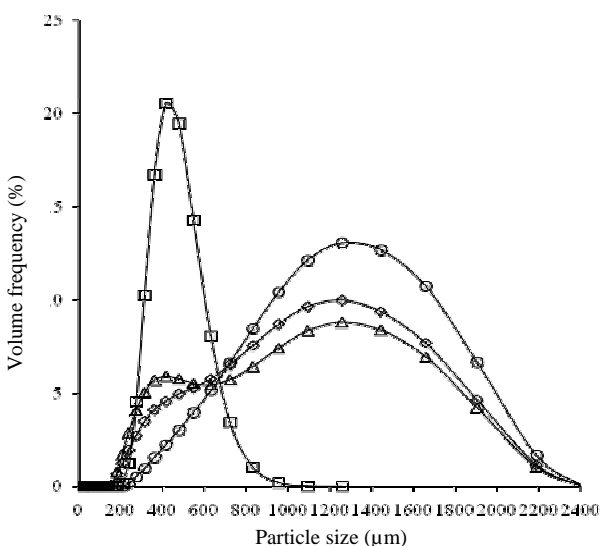


Figure 2. Volume size distribution of KSR microspheres prepared at different stirring rates (RPM). Stirring rate (rpm): 1500, ○; 2000, ◇; 2500, △; 3000, □. Preparative conditions: polymer KSR; C:P is 1:1; total solid content in the system 0.08% (w/w); emulsifier 1 percent w/w span 60.

A linear relation was found between total solid content of the system and microsphere size. As the total solid content was increased, microsphere size was also increased which is also shown in Table 1. This may be explained in the following way. Due to the increase in total solid content, intermolecular collisions between microspheres were increased resulting in fusion of the microspheres into larger particles. Moreover, increased solid content produced a significant increase in viscosity, thus leading to an increase of the emulsion droplet size and finally a higher microsphere size.^{17, 18} A unimodal particle size distributions was observed for all of the batches (Figure 3).

Encapsulation Efficiency. RPM and total solid content variation did not affect the DS loading of the microspheres significantly (Table 1). However, higher stirring rate produced smaller microspheres containing lesser amounts of DS. In case of solid content variation, DS loading was found to be increased with increased solid content of the system.

Release Kinetics. DS release was affected due to different stirring rate. A linear relationship was observed between stirring rate and drug release e.g. drug release was found increased with increased stirring rate (Figure 4). With the higher stirring rate,

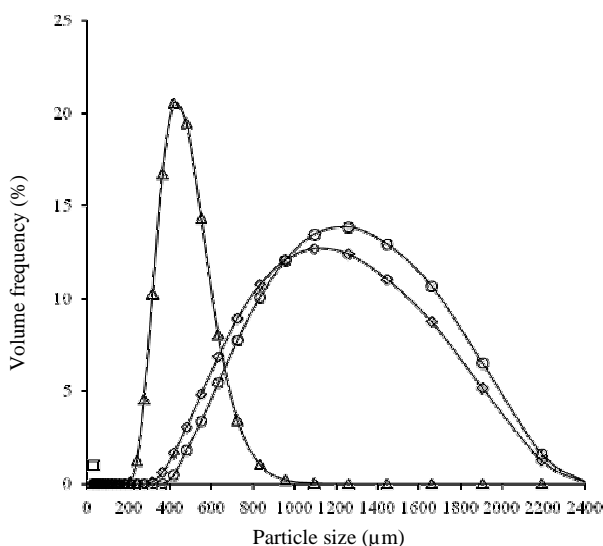


Figure 3. Volume size distribution of KSR microspheres prepared at different percent solid content. Total solid content: 0.24%, ○; 0.16%, □; 0.08%, △. Preparative conditions: polymer KSR; C:P is 1:1; stirring rate (RPM) 3000; emulsifier 1 percent w/w span 60.

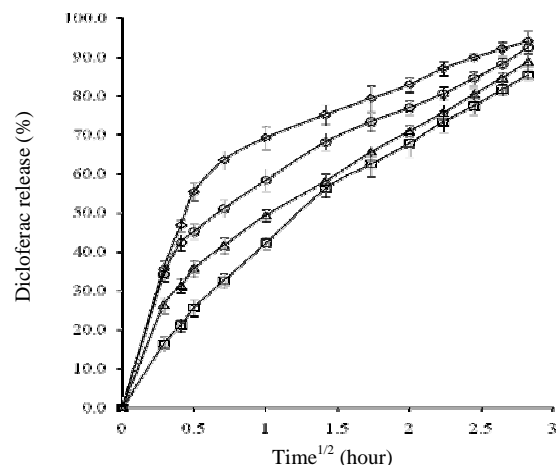


Figure 4. Higuchi plot of the diclofenac sodium release from KSR microspheres (C: P ratio, 1: 1) prepared at different stirring rate. Stirring rates (rpm): 1500, □; 2000, △; 2500, ○; 3000, ◇. Dissolution conditions: buffer pH 7.2, temperature 37 °C, paddle rotation speed 50 rpm

microspheres became smaller. As the stirring rate was increased, fine emulsion was formed which eventually led to the formation of smaller sized microspheres. Microsphere surface area was also increased while stirring rate was increased (Table 1). These two reasons are attributed to the faster release of DS from the microspheres prepared by higher stirring rate. But while the stirring rate was reduced, larger microspheres were formed due to the fusion of

smaller immature microspheres (Figure 1). These larger microspheres then released the drug in a more controlled way. The normalized release rates (K_r/SSA) were also affected due to stirring rate variation. Release rates were found to be increased with decreased stirring rate (Figure 5).

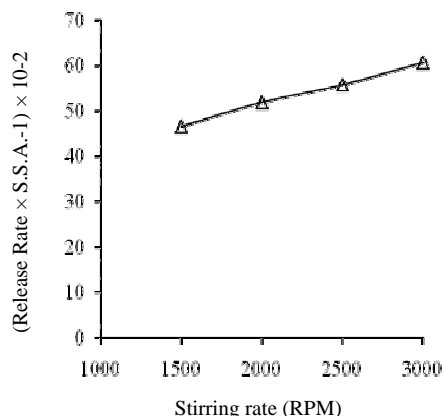


Figure 5. Effect of stirring rate on the normalized release rate ($K_r/S.S.A.$) of DS from the KSR microspheres.

Drug release was also affected significantly due to variation of total solid content of the system. As the solid content of the system was increased, drug release was decreased accordingly (Figure 6). Higher solid content of the system resulted in larger microspheres which ultimately released drug more slowly. Total solid content of the system also affected the normalized release rates of DS. Release rates became larger with increased solid content (Figure 7).

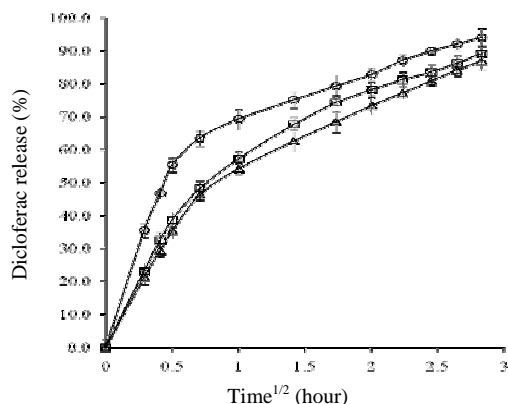


Figure 6. Higuchi plot of the diclofenac sodium release from KSR microspheres (C: P ratio, 1: 1) prepared at different total solid content of the system (percent w/w of the continuum). Total solid contents (% w/w): 0.24%, Δ ; 0.16%, \square ; 0.08%, \circ . Dissolution conditions: buffer pH 7.2, temperature 37 °C, paddle rotation speed 50 rpm

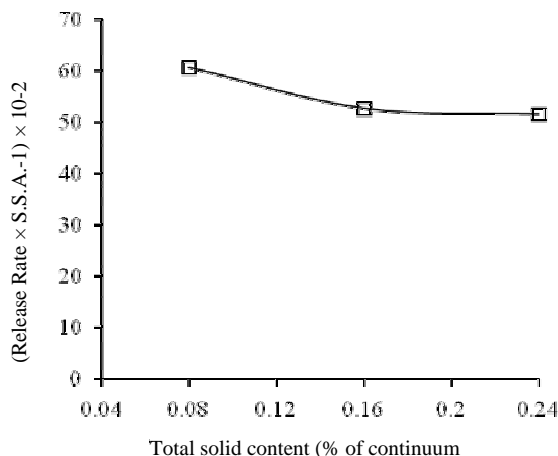


Figure 7. Effect of total solid content (percent w/w of the continuum) on the normalized release rate ($K_r/S.S.A.$) of DS from the KSR microspheres.

CONCLUSION

Microspheres of KSR containing DS were successfully prepared by W/O emulsion solvent evaporation technique and were significantly characterized by different preparative variables like stirring rate and total solid content of the system. KSR microsphere size as well as DS loading in the microspheres was found to be affected by these preparative variables which thereafter directly affect the release kinetics of the drug. Therefore, all preparative variables, as they mutually interact, should be considered together.

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