Preparation and Characterization of Polyvinyl Acetate (Kollidon® SR) Microspheres Containing Diclofenac Sodium II: Effect of core loading

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ABSTRACT: Diclofenac Sodium (DS) loaded Kollidon® SR (Polyvinyl acetate and povidone based matrix retarding polymer) microspheres of different drug loading were prepared using W/O emulsification solvent evaporation technique. Polymeric solution containing the DS was emulsified in light liquid paraffin (LLP) which was initially emulsified by 1% (w/w of the continuum) lipophilic surfactant Span 60. The study was conducted to investigate the effect of different core to polymer ratio (0.5: 1, 1 : 1, 1.5 : 1 and 2 : 1) on microsphere size, encapsulation efficiency and release kinetics of DS. Microsphere size was decreased with increased core loading. However, higher encapsulation efficiency was observed with higher core loading. A square root of time dependent release of DS was observed from the KSR microspheres. Increased core loading caused faster release of DS. Release rates of DS were affected by different DS content in the core. Normalized release rates were also found to be increased with high core loading. Mean dissolution time (MDT) and t_{50} values were also calculated and were found to be affected significantly by different DS loading to KSR microspheres. Low DS loading increased MDT.

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

INTRODUCTION

Polymers have been used in pharmaceutical formulations for various purposes including protection of dosage forms against environmental hazards and hiding bad taste, odor or appearance. The application widely studied today is sustained release dosage forms.

Now a day, polyvinyl acetate and polyvinyl pyrrolidone (Povidone) based matrix polymer (Kolidon® SR) (KSR) is most widely used in the pharmaceutical formulations. For these reasons, it seemed an interesting polymer for the preparation of sustained release dosage forms like tablets, pellets, and granules[1]. Several drugs have been used to prepare sustained release matrix tablet with this polymer [1- 4]. However, this polymer was used in this study to prepare microspheres.

A popular method for microencapsulation is the solvent evaporation process. Both water soluble and water insoluble drugs were used to be encapsulated by this solvent evaporation technique. [5-7] Water soluble diclofenac sodium was used as model drug in this study. 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

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the final microsphere characteristics and release kinetics.[8-12]

The primary aim of this work was to study the effect of core loading on the KSR microspheres in order to facilitate sustained release microencapsulation formulation. The secondary aim was to evaluate the physical characteristics of the prepared microspherers. The first part of this work report will morphology, particles size and entrapment efficiency of the microspheres after preparation. The second part will focus on the drug release kinetics of the diclofenac sodium from KSR microsphere.

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 experiment.

Preparation of Kollidon® SR microsphere. Microspheres were prepared using the emulsification (W/O) and organic solvent evaporation technique[7] 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 in to the DS suspension with continuous stirring. After 2 hours of stirring, hard, 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. To observe the surface morphology of the microspheres, a Scanning Electron Microscope (SEM) (S-3400N, Hitachi, Japan) was used. 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 μg/ml) in phosphate buffer (pH 7.2) were prepared and the absorbance was measured on 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 phosphate 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) at a rotational speed of 50 rpm at 37 ± 0.5ºC in 900 ml phosphate buffer (pH7.2). 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. Core to polymer ratio was considered as preparative variable. Change in microsphere size, encapsulation efficiency, and release kinetics of DS due to different core-polymer ratio have been reported here.

Morphology of the microspheres. Microspheres prepared with different core to polymer ratio were hard and free flowing (Figure 1). But microsphere shape became irregular with increased core loading. In case of 0.5:1 loading, microsphere was spherical in shape (Figure 1A). In contrast, higher core loading (2:1) made the microsphere shape irregular (Figure 1C). Large pores were also observed on the microsphere surface with 2:1 core loading which were absent in case of 0.5:1 core loading.

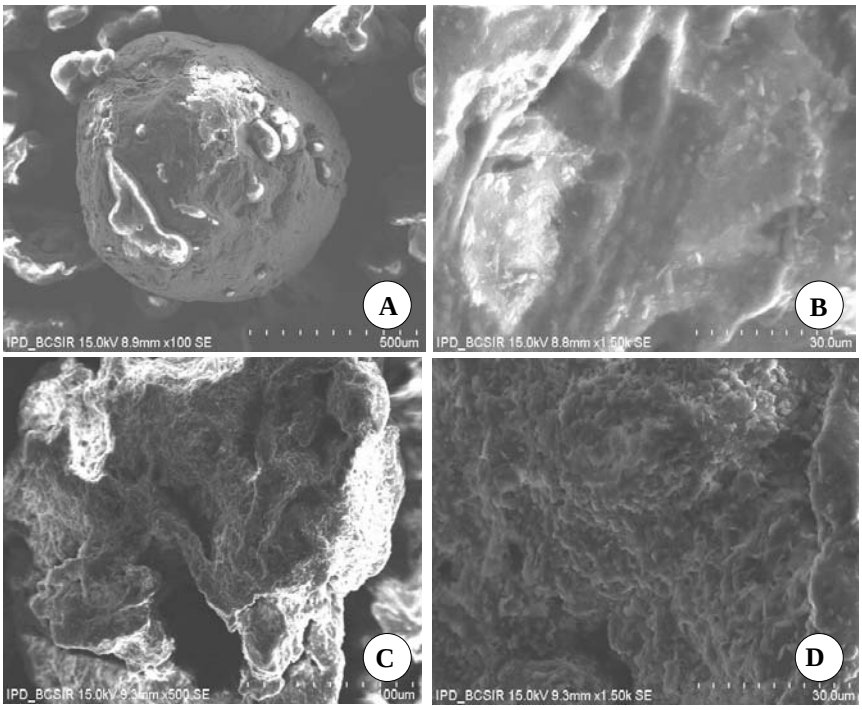

Figure 1. Scanning Electron microscopic image of KSR microspheres containing DS in a core: polymer of 0.5:1 (A, B) and 2:1 (C, D).

Microcapsule Size. Microsphere size (both by volume and population) was found to be reduced with increased core loading (Table 1). The larger microspheres were found in case of lowest core loading (0.5:1) and smaller microspheres were found in case of highest core loading (2:1). High core loading increased the DS content and particle size was to be increased due to this increased solid content of the system. Moreover, increased core load produced smaller microspheres. The smaller microspheres found with higher DS loading could be explained in two ways. Firstly, KSR content was not sufficient to coat excess DS crystals present in the system resulting microspheres having less amount of wall material in the surroundings. Secondly, loosely bonded DS crystals at the surface of the microspheres were dislodged due to intermolecular collision which ultimately made the particle size smaller and irregular. A bimodal particle size distribution (Figure 2) also indicated the presence of large number of smaller sized microspheres along with small number of larger microspheres in case of high DS loading.

Encapsulation Efficiency. The weight of DS theoretically contained in the microspheres was compared with the weight actually obtained from the drug content studies, i.e., the quantity loaded into the microspheres formulated, to get the DS loading

efficiency.[16] Following equation was used for the calculation.

Drug-loading efficiency (%) = (Cp/Ct) × 100 (1)

where, Cp and Ct were the actual and theoretical drug content in DS loaded microspheres, respectively.

Encapsulation efficiency was found to be increased with increased core loading to the KSR microspheres (Figure 3) which is also a common phenomenon. In case of low core loading (C : P is 0.5:1), polymer amount was higher than that of DS and no DS crystals were observed on the surface of the microspheres (Figure 1B). As the core loading was increased, amount of DS became higher compared with KSR amount. This higher amount of DS resulted in encapsulation of DS crystals in the core as well as in the coat. As a result DS crystals were adhered to the microspheres surface which is also seen in figure 1D. Moreover, microspheres were washed with pet ether which was also unable to wash out the DS crystals from the surface. Both of these attributed to the high encapsulation efficiency of the higher core loading microspheres.

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

Variable Studied	Preparative Conditions		Microsphere properties				Release data	
	Nominal C:P ratio	Stirring rate (RPM)	Mean Population Diameter µm (±SD)[a]	Mean Volume Diameter µm (±SD)[a]	SSA (m^2/g X 10^{-2})[b]	EE (percent)[c]	(K_h/SSA)[d]	MDT (hour)[e]
C:P ratio	0.5: 1	3000	551.166 (1.85)	970.700 (1.56)	1.09	57.11	54.92	2.4241
	1: 1	3000	547.047 (1.62)	810.569 (1.23)	1.1	86.01	83.00	1.6605
	1.5: 1	3000	480.388 (2.01)	780.415 (1.92)	1.31	89.23	92.13	0.3279
	2: 1	3000	200.948 (3.65)	360.916 (1.23)	1.35	91.10	94.89	0.1899

All the mean microcapsule sizes are the geometric mean and geometric standard deviation (SD) respectively.
[a] Geometric mean and geometric standard deviation (SD)
[b] SSA = Specific surface area of microcapsules.
[c] Encapsulation efficiency is the percantage of theoretical DS content in the microcapsules.
[d] Release rate constant per unit specific surface area (percent release. $hour^{1/2}$ /m^2. g^{-1}.
[e] MDT = mean dissolution time

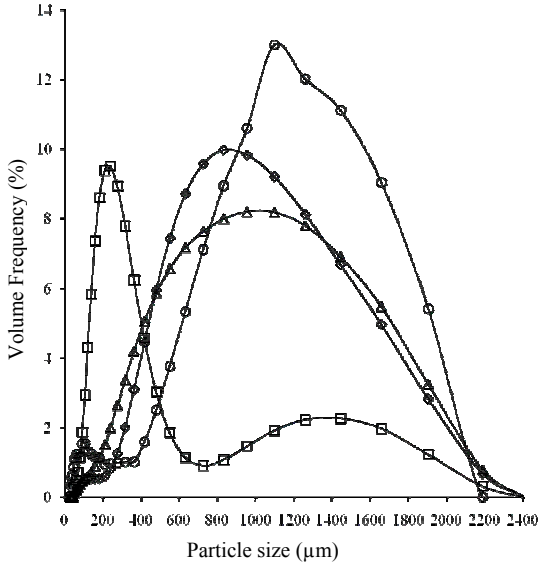

Figure 2. Volume size distribution of different core loaded microspheres. Microspheres C: P ratios: 0.5:1, ○; 1:1, ◊; 1.5: 1, Δ; 2:1, □. Preparative conditions: polymer KSR; stirring rate 3000 rpm; emulsifier 1 percent w/w span 60.

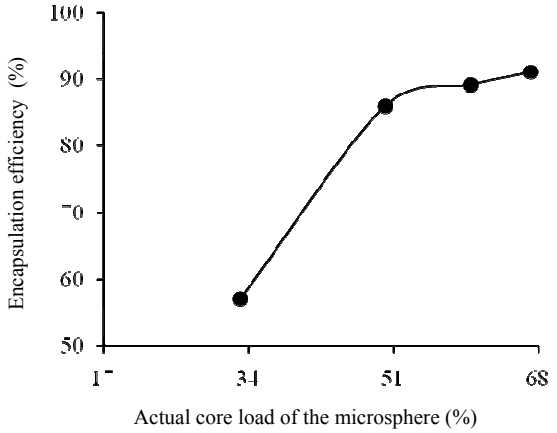

Figure 3. Effect of theoretical DS content on the encapsulation efficiency of KSR microspheres.

Release Kinetics. Release of drug from such matrix type microspheres can be conveniently described by the equation

$$Q = M/A = [DC_m (2C_{tot} - C_s)t]^{1/2}$$

Where Q is the mass (M) of drug release per unit area (A) of surface at time t; C_m = concentration in matrix; C_{tot} = total solid concentration as loading; C_s = total solubility of solute; D = diffusivity.[17] Assuming that the diffusivity and other parameters are constant, the equation may be simplified to

$$Q = K_1 t^{1/2} \qquad \text{where } K_1 \text{ is a constant.}$$

Higuchi also showed a $t^{1/2}$ dependent release from a granular matrix[18] whilst Fessi, Marty, Puisieux and Carlensen presented an equation

$$Q = C_{tot}(Dt)^{1/2}$$

indicating a similar $t^{1/2}$dependent release from a matrix formulation.[19] Similar $t^{1/2}$ dependences have been observed during the release of DS from KSR microspheres.

Figure 4 shows the Higuchi plot of DS release from microspheres prepared with different core to polymer ratio. Almost 70-80 percent drug was released within few minutes of dissolution from high core loading microspheres (1.5: 1 and 2: 1). These microspheres were also unable to sustain the release of DS for up to 8 hours. This might be due to the high DS loading which made the microsphere shape, irregular and surface, porous. Surface also appeared embedded with DS crystals (Figure 1D). On the contrary, relatively less burst release was observed with lower core loading microspheres (0.5: 1 and 1: 1). Even a more sustained release was observed from these microspheres.

The normalized release rate (K_h/SSA) of DS was also found to be reduced with low core loading microspheres (Figure 5). Mean dissolution times (MDT) and t_{50} of DS from KSR microspheres were also calculated. Highest MDT was 2.4241 (hour) for C:P, 0.5:1 whereas lowest MDT was 0.18991 (hour) for C:P, 2:1 (Table 1). A linear relation was also found between percent core loading and t_{50} values of the microspheres. The t_{50} values were found to be decreased with increased DS loading to KSR microspheres (Figure 5).

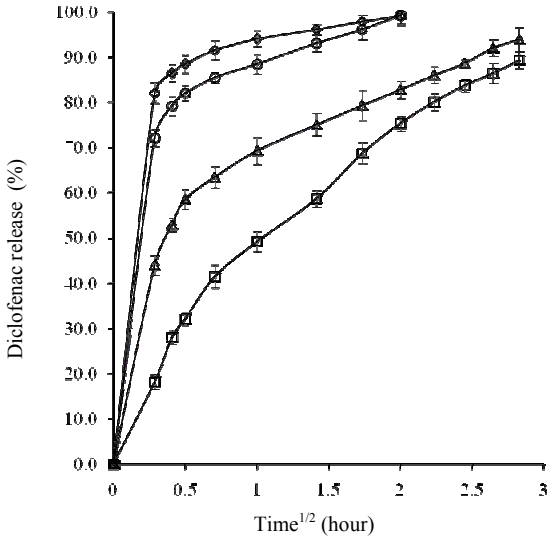

Figure 4. Higuchi plot of the diclofenac sodium release from KSR microspheres prepared at different core to polymer ratio. C: P ratio: 0.5:1, □; 1:1, Δ; 1.5: 1, ○; 2:1, ◊.Dissolution conditions: buffer pH 7.2, temperature 37 ± 0.5 °C, paddle rotation speed 50 rpm.

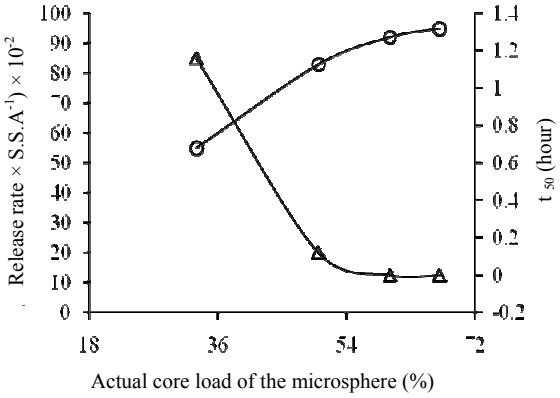

Figure 5. Effect of theoretical DS loading (percent) on the normalized release rate (K_h/S.S.A.) (○) and t_{50} (Δ) of KSR microspheres.

CONCLUSION

Microspheres of KSR containing DS were successfully prepared by W/O emulsion solvent evaporation technique and significantly characterized by different core to polymer ratio. KSR microsphere size as well as DS loading was found to be affected with different core loading. Release kinetics of DS from the KSR microspheres was also affected by different core loading of the microspheres. Therefore,

different core: polymer ratio may be considered as an important preparative variable as it has direct effect on microsphere properties.

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