CHAPTER VIII

UREA-FORMALDEHYDE NANOCAPSULES FOR
CONTROLLED RELEASE OF DICLOFENAC SODIUM

VIII. 1. Abstract

Urea-formaldehyde (UF), polymerized in situ in aqueous media, is a rigid polymer that can be used in the controlled release of bioactive molecules. During the process of polymerization, NSO was encapsulated at three different loadings, which was then replaced by diclofenac sodium (DS), the presence of which was confirmed by FTIR spectra. The nanocapsules thus prepared were evaluated for percentage loading of the drug, particle size and release characteristics. Thermal analysis and x-ray data were obtained to understand the physical nature of the encapsulated drug. The surface characteristics of the nanocapsules were studied by using the scanning electron microscope. Particles in the size range of around 500 nm were obtained. The loading efficiency of NSO was about 90-95 %, whereas for DS, the loading efficiency was only 50-60 %. A complete release of the drug from the matrices occurred in about 24 hours, whereas at 8 hours, only 60 % of the drug was released.

The results of this chapter will be published in Journal of Microencapsulation, (2000), in press.
VIII.2. Introduction

In recent years, a lot of attention has been focused on the development of novel drug delivery systems for both oral and systemic applications using various types of polymers [1-5]. The advantages of such CR preparations containing the non-steroidal anti-inflammatory drugs (NSAID) over their conventional dosage forms have been reported by Chandermun et al [6]. Such formulations minimizes the serious gastric irritant side-effects of the conventional NSAID preparations and also will reduce the dose as well as frequency of administration, and hence, increase the patient compliance, which is paralleled by a reduction in health care costs and better disease management. In this direction, investigations are in progress to prepare the CR formulations containing NSAIDs like diclofenac sodium, indomethacin, etc., using the newer polymeric systems so as to reduce the cost of the final products and to improve their therapeutic effects.

Urea-formaldehyde (UF) is a rigid and slow degradable polymer, which can be prepared by in-situ polymerization in the aqueous media using urea and formaldehyde in an appropriate ratio. Such amino resins produced are the useful wall materials in the preparation of nanocapsules [7]. Hitherto, the UF polymer was used as a matrix material only in the CR of nonpharmaceutical agents like pesticides [8] due to the problems associated with the unfavorable conditions of polymerization, such as higher temperature for the prolonged periods and toxicity associated with the residual monomers [9].

In this chapter, problems associated with the use of UF as a CR device for the pharmaceuticals using diclofenac sodium (DS) as a model drug have been studied by adopting a new technique of reencapsulation. The advantage of UF polymer is that it can be cheaply prepared and the properties of the polymer can be
altered during polymerization from which, the release of the active agent can be controlled [10]. As polymerization involves the unwanted conditions, it was thought of incorporating initially NSO at the time of polymerization and this oil was then completely removed so as to incorporate the drug by incubating the empty capsules in the saturated drug solution. The matrix thus formed was characterized [11-17] by SEM, DSC and by calculating the density of the matrix. The drug distribution and its polymorphic nature was studied by x-ray diffraction. The formulated products are further evaluated for their drug content uniformity and the release pattern.

VIII.3. Experimental

The materials used and the detailed experimental procedures have already been explained in Chapter II under section II.9.

VIII.4. Results and Discussion

VIII.4.A. The Particle Size

The particles produced were analyzed for their sizes using the light scattering method and the mean particle size of 454.8 nm was observed. The particles with sizes ranging from 100 to 800 nm were under 85 % of the total population, but more than 1.0 μm are below 5 % of the total population. SEM photographs of the NSO-loaded and the DS-loaded nanocapsules are shown, respectively in Figs. VIII.1A. From these pictures, it is observed that the particles are spherical in shape and a small collapse on the surface has occurred in the case of the DS encapsulated nanocapsules.
Fig. VI.1. SEM photograph of CA microspheres.
Fig. VI. 2. SEM photograph of Na-Alg microparticles.

Fig. VI. 3. SEM photograph of UF microspheres.
Fig. VIII. 1. SEM of DS-loaded UF nanocapsules.
Fig. IX.1. SEM photograph of Na-Alg beads.
Fig. X.1. SEM of Na-Alg microparticles.
VIII.4.B. Density of the UF Matrix

Density of the UF matrix varied between 1.5 to 1.15 g/cm³, and this depends upon the ratio of urea and formaldehyde (U/F) contents taken. At the U/F ratio of 0.5, the matrix was more rigid and high dense when compared to the matrix formed at the U/F ratio of 1.0. In the case of DS-loaded capsules, density was higher than that of the NSO-loaded capsules and this is due to the collapse of the capsules during replacement of NSO by DS thereby, resulting in a reduction of volume. The density decreased with an increase in % loading and this is due to the increase in volume with increasing loading because the polymer becomes less rigid at higher levels of encapsulation.

VIII.4.C. Percent Entrapment Efficiency

The % entrapment efficiency of NSO as well as DS and the density of nanocapsules containing both NSO and DS are given in Table VIII.1. The results of % entrapment efficiency for both NSO- and DS-loaded particles formed by U/F ratio of 1.0 are lower than the particles formed by U/F ratio of 0.5. It was observed that the % entrapment efficiency for NSO is higher than that of DS in all the systems studied. DS was loaded after the complete removal of NSO and during this process, nanocapsules might have collapsed to some extent (as confirmed by SEM) resulting in a smaller % entrapment efficiency. The difference between % entrapment efficiency of NSO and DS is higher in case of particles produced at the U/F ratio of 0.5. For the NSO encapsulated nanoparticles, the % entrapment efficiency decreased with an increasing NSO loading. On the other hand, for DS, the % entrapment efficiency increased with an increasing loading of NSO.
Table VIII.1. The % Entrapment Efficiency of Active Ingredients and Density of Nanocapsules

<table>
<thead>
<tr>
<th>% Loading</th>
<th>Urea : Formaldehde (molar ratio)</th>
<th>% Entrapment efficiency</th>
<th>Density (g/cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NSO</td>
<td>DS</td>
</tr>
<tr>
<td>20</td>
<td>0.5</td>
<td>81.2 ± 1.5</td>
<td>24.3 ± 0.1</td>
</tr>
<tr>
<td>35</td>
<td>0.5</td>
<td>80.1 ± 1.9</td>
<td>42.7 ± 1.3</td>
</tr>
<tr>
<td>50</td>
<td>0.5</td>
<td>79.8 ± 2.0</td>
<td>58.2 ± 1.3</td>
</tr>
<tr>
<td>20</td>
<td>1.0</td>
<td>71.2 ± 0.5</td>
<td>28.5 ± 0.2</td>
</tr>
<tr>
<td>35</td>
<td>1.0</td>
<td>68.1 ± 1.0</td>
<td>47.0 ± 0.5</td>
</tr>
<tr>
<td>50</td>
<td>1.0</td>
<td>65.8 ± 1.5</td>
<td>60.2 ± 0.9</td>
</tr>
</tbody>
</table>

VIII.4.D. Fourier Transform Infrared Measurements

The FTIR spectra obtained for the pure NSO (curve a), NSO-loaded UF nanocapsules (curve b), empty UF nanocapsules (curve c), pure DS (curve d) and the DS-loaded UF nanocapsules (curve e) are shown in Fig.VIII.2. These measurements are done to confirm the successful encapsulation of NSO, absence of NSO in the empty capsules and reencapsulation of DS, as well as to find out the interactions between DS or NSO with the matrix. These results indicated that the characteristic peaks due to pure NSO (1800, 1750, 1475 and 1400 cm⁻¹) and DS (850, 775, 750, 725, 650 and 570 cm⁻¹) have appeared in the NSO- and DS-loaded UF nanocapsules without any changes in their positions, indicating the successful encapsulation and no chemical interactions. In addition, the NSO- and DS-loaded UF nanocapsules show characteristic peaks due to UF at 775, 1220, 1400, 1600 and 1700 cm⁻¹. The absence of NSO in empty nanocapsules (after complete extraction of NSO from the NSO-loaded UF nanocapsules) was confirmed by the FTIR spectra of the empty UF nanocapsules because of the absence of the characteristic peaks due to NSO.
Fig. VIII. 2: FTIR spectral curves obtained for pure NSO (curve a), NSO-loaded UF nanocapsules (curve b), empty UF nanocapsules (curve c), pure DS (curve d) and DS-loaded UF nanocapsules (curve e).
VIII.4.E. DSC and x-Ray Diffraction Studies

The DSC thermograms of DS (curve a), nanocapsules containing DS (curve b) and UF (curve c) are shown in Fig. VIII.3. The UF exhibits sharp endothermic peaks at 382.02 and 526.82 K, but the DS exhibits sharp endothermic peaks at 324.81 and 383.15 K and the nanocapsules containing DS exhibit sharp endothermic peaks at 381.46 and 525.15 K. Thermogram of the nanocapsules containing DS was almost identical to that of the UF polymer. This indicates that most of the drug was uniformly dispersed at the molecular level in the UF nanocapsules.

The x-ray diffraction patterns of DS (curve a), nanocapsules containing DS (curve b) and UF (curve c) are shown in Fig. VIII.4. Characteristic sharp peaks appeared in the x-ray diffraction (curve a) for pure DS did not appear in the x-ray diffraction (curve b) pattern of the DS-loaded UF matrix and a similar pattern was observed for the UF matrix (curve c). This further confirms the molecular level dispersity of the drug in the nanocapsules.

VIII.4.F. Dissolution Study

Dissolution study of both the formulated and the pure DS was performed to compare the dissolution rates. In order to simulate the GIT conditions, both acidic (0.1N HCl i.e., pH of 1.08 for 3 hours) as well as basic (pH=7.4 phosphate buffer up to 24 hours) media were selected for the dissolution study. There are three factors which affect the release of the drug from the formulations: one is the nature of controlling device i.e., rigidity of the UF matrix, second factor is % loading of DS and third is the media in which dissolution was studied. However, there is no significant release of DS in acidic media for both the pure as well as the
Fig. VIII. 3. DSC thermogram curves obtained for DS (curve a), nanocapsules containing DS (curve b) and UF (curve c).
Fig. VIII. 4. X-Ray diffraction curves obtained for DS (curve a), nanocapsules containing DS (curve b) and UF (curve c).
formulated product because DS, being a salt of the weak acid, is insoluble in acidic media. However, in buffer media, pure DS was completely (>90 %) dissolved in about 6 hours, whereas the formulated products showed only up to 20-40 % release (see Fig. VIII.5).

Higher release rates were observed for DS from the particles produced at a U/F ratio of 0.5 for all the loadings when compared to the particles produced at a U/F ratio of 1.0. The matrix produced at a U/F ratio 0.5 is less rigid and somewhat loose, so that the release rates for the active agents are higher. On the other hand, effect of loading on the release rates is not so significant when compared to the rigidity of the matrix, but with an increase in loading, the higher release rates are observed.

VIII.5. Conclusions

Experimental results suggest that diclofenac sodium can be successfully encapsulated into UF matrix without affecting the chemical nature of the drug. The conditions maintained during polymerization can be varied to control the matrix nature for enhancing the release profile. However, at a U/F ratio of 0.5, the matrix was more rigid and high dense when compared to the matrix formed at a U/F ratio of 1.0. SEM data indicated that the particles produced are spherical in shape with the size range of around 500 nm.

The % loading efficiency of NSO was about 90-95, whereas for the DS, the loading efficiency was only 50-60 %. Initially, higher level of loading of NSO will be favorable to get higher loading of the drug, but the matrix becomes less rigid. The higher release rates were observed for the DS from the particles produced at a U/F ratio of 0.5 in all the loadings when compared to the particles
Fig. VIII. 5. Results of pure DS release (●) and DS from various nanocapsules prepared using UF matrix at a U/F ratio of 0.5 and DS was replaced by NSO from, (*) 20 %, (O) 35% and (♦) 50 %, NSO-loaded nanocapsules and at a U/F ratio of 1.0 and DS was replaced by NSO from, (■)20 %, (□) 35% and (▲) 50 % NSO-loaded nanocapsules.
produced at a U/F ratio of 1.0. Thermal analysis and x-ray diffraction patterns of the compounds indicated that most of the drug was uniformly dispersed at the molecular level in the UF nanocapsules.
VIII. 6. References