Chitosan-based delivery systems for diclofenac delivery: preparation and characterization

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Abstract. The preparation and characterization of novel materials for drug delivery has rapidly gained importance in development of innovative medicine. The paper concerns the uses of chitosan as an excipient in oral formulations and as a drug delivery vehicle for burnt painful injuries. The use of chitosan (CTS) as base in polyelectrolyte complex systems, to prepare liquid release systems as hydrogels and solid release systems as sponges is presented. In this paper the preparation of CTS hydrogels and sponges carrying diclofenac (DCF), as anti-inflammatory drug is reported. The immobilization of DCF in CTS is done by mixing the CTS hydrogel with the anti-inflammatory drug solutions. The concentration of anti-inflammatory drug in the CTS hydrogel generating the sponges was of 57 mg/l, 72 mg/l and 114 mg/l. The CTS sponges with anti-inflammatory drugs were prepared by freeze-drying at -610°C and 0,09 atm. The characterization of the hydrogels and sponges was done by infrared spectra (FTIR) and ultraviolet-visible spectroscopy (UV-VIS). The results indicated the formation of CTS-DCF intermediates. The DCF molecules are forming temporary chelates in CTS hydrogels and sponges and they are compatible with skin or some of biological fluids with satisfactory results.

1. Introduction
The concept of designing a specified delivery system to achieve selective drug targeting has been originated from the perception of Paul Ehrlich, who proposed drug delivery to be as a ‘magic bullet’ [1], where a drug-carrier complex/conjugate, delivers drug(s) exclusively to the preselected target cells in a specific manner. The objective of drug targeting is to achieve desired pharmacological response at a selected site without undesirable interactions at other sites. Among the novel biomaterials, chitin and chitosan are intensively studied due to their many potential applications as pharmaceutical drug carriers. CTS, a natural polysaccharide, is being widely used as a pharmaceutical excipient. CTS comprise a series of polymers varying in their degree of deacetylation, molecular weight, viscosity, pKa etc. The presence of a number of amino groups permits CTS to chemically react with anionic systems, thereby resulting in alteration of physicochemical characteristics of such combinations [2]. Modern biocompatible systems target not only infectious diseases, but also autoimmune disorders, allergies, chronic inflammatory diseases and cancer [3]. The study was aimed to develop and characterize a novel polyelectrolyte complex (PEC) CTS with Tween-80 and oleic acid as drug carrier for controlled drug delivery, with possible use in skin burnt painful injuries. The PEC CTS complexes were prepared by coacervation method using the same ratios of Tween-80, oleic acid and CTS. DCF, used as model drug, is one of the most useful non-steroidal anti-inflammatory drugs (NSAIDs) and is
a practically insoluble compound in acidic solution (pKa 4.0), however, it dissolves in intestinal fluid [4]. Small molecular weight anti-inflammatory drugs that contain chemical groups able to establish temporary physical or chemical bonding with the amino group of the CTS linkage are suitable for the targeted and controlled drug CTS-based delivery systems. In support of this presumption the chemical formulae of CTS and anti-inflammatory DCF drug used in the experiment are illustrated in figures 1-2.

2. Experimental

2.1. Materials
Tween-80 was purchased from Sigma–Aldrich Chemie (Steinhaim, Germany), Diclofenac sodium was obtained by courtesy from Terapia-Ranbaxy SA, Cluj-Napoca. High molecular weight CTS grade (Sigma # 419419) was purchased from Sigma–Aldrich Chemie (Steinheim, Germany). At 86% deacetylation degree it had a 5.99% loss on drying, 0.21% of ashes, and 0.48% of insoluble matter (at 1% in 1% acetic acid) as specified by the manufacturer.

2.2. Preparation of CTS-based PEC solution
CTS hydrogel 0.25% was prepared in double distilled water containing 1% (v/v) acetic acid with continuous stirring, at 30°C, adding at final 2% v/v Tween-80 and 0.2% v/v oleic acid. After 6 h the solution is pale-yellow, with a homogenous consistence and aspect.

2.3. Preparation of CTS-based drug loaded nano/microparticles
To the CTS PEC solution, split in 16 equal volumes, 10 ml each, different quantities of DCF were added to give PEC 1.1, PEC 1.2 and PEC 1.3. The concentration of anti-inflammatory drug in the CTS hydrogel generating the sponges was of 57 mg/l, 72 mg/l and 114 mg/l. The solutions were further stirred for 30 min and then ultrasonically treated in an Elmasonic E60H ultrasonic bath for 10 min. In order to prepare the sponges the hydrogel was freeze-dried in a CHRIST ALPHA 1-4 LD Plus Freeze Dryer, at -60°C and 0.09 atm. Particles from native CTS (NC) were also developed similarly.

2.4. Characterization of PEC
CTS-based polyelectrolyte complex with and without drug were characterized by FTIR (FTIR JASCO 6100 spectrometer) and ultraviolet-visible spectroscopy, UV-VIS (ABLE&JASCO 550V).

3. Spectroscopic analysis of CTS-based DCF loaded materials

3.1. FTIR spectral studies
Figure 3 shows the FTIR spectra of plain CTS, DCF, CTS+DCF (physical mixture) combination and 1.1, 1.2, 1.3 combined microspheres. As it can be seen in the FTIR spectra the maximum at 1100 cm⁻¹ corresponding to the C–O stretching vibration mode in CTS molecule is shifted to the 1108 cm⁻¹ peak due to the steric modifications imposed by the CTS-DCF PEC microspheres. The sharp peak at 1452 cm⁻¹, corresponding to the vibration mode of –CH₃ of DCF molecule, is shifted to 1462 cm⁻¹ which correspond to –NH and C=O stretching vibration, respectively, thereby confirming intermolecular CTS-DCF grafting reaction.
Figure 3. FTIR spectra of plain CTS, DCF, and 1.1, 1.2, 1.3 PEC combined microspheres, 2000-1000 cm⁻¹ spectral region.

The new peak at 1560 cm⁻¹ corresponding to C–N bending vibration further supports the grafting reaction. The other identified vibrations for each sample are presented in table 1.

Table 1. The assignments of the most intense FTIR bands for CTS, DCF and CTS+DCF PEC microspheres.

| Wavenumber (cm⁻¹) | CTS | DCF | CTS+DCF PEC |
|-------------------|-----|-----|-------------|
| 767 vs; 748 vs    | δ(CH) |   |           |
| 1020              | intramolecular C–O stretching |   |           |
| 1050              | intramolecular C–O stretching |   |           |
| 1073              | C–O stretching |   |           |
| 1100              | C–O stretching |   |           |
| 1108              | C–O–C stretching | C–O stretching |   |
| 1145              | C–O–C stretching | O–H bending |   |
| 1355              | amide-III |   |           |
| 1576 vs           | δ(CH₃) |   |           |
| 1579              | amide-II |   |           |
| 1594              | amide-I |   |           |
| 1650              | CH₃ symmetrical deformation | –NH and C=O stretching |   |
| 1380              | CH₃ symmetrical deformation |   |           |
| 1390 s            | ν(COO⁻) |   |           |
| 1410              | CH₃ symmetrical deformation |   |           |
| 1453              | δ(CH₂) |   |           |
| 1453 vs           | –NH and C=O stretching |   |           |
| 1464              | ring str. | C–N bending |   |
| 1506 sh; 1557 s   |   | ν₉(COO⁻) |   |
| 1560              |   | δ(NH)+ring |   |
| 1560              |   | O–H stretching |   |
| 1576 vs           |   | ν(CH) | Aliphatic C–H stretching |
| 1590 s            |   | ν(NH) |   |
| 2845              | C–H stretching |   |           |
| 2919              | C–H stretching |   |           |
| 3440              | O–H stretching |   |           |
| 2920 w; 2980 m    | Aliphatic C–H stretching | ν(CH) | Aliphatic C–H stretching |
| 2929              |   | ν(NH) |   |
| 3085 m; 3040 m    |   |   |   |
| 3260 br; 3388 s   |   |   |   |
| 3450              | amine N–H symmetric stretching |   |   |
3.2. UV-VIS spectroscopy

Figure 4 shows the UV–VIS absorption spectra of CTS and CTS-DCF in 1% dilute acetic acid.

![Figure 4. UV–VIS absorption spectra of CTS and CTS-DCF PEC microspheres in dilute acetic acid solution.](image)

CTS only yields absorption peak at 210 nm. DCF curve has a broad absorption band between 200 nm and 315.6 nm. The spectral absorption at 279.5 nm is specific for CS-DCF PEC microspheres.

4. Conclusions

CTS-DCF polyelectrolyte complex microspheres were prepared and investigated by FTIR and UV-VIS spectroscopy. The results are in agreement to similar data already reported [7, 8]. The increased absorbance at 279 nm and the FTIR shifted vibrational bands can be assigned to the formation of CTS-DCF PEC supramolecular assemblies. Further experiments on the complexation mechanism are in progress in order to elucidate a detailed structure of the complex.

Acknowledgments

This work received financial support from the Romanian Research and Education Ministry under the Core Project PN-09-44 02 01.

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