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Model suspensions of indomethacin "solvent deposited" on cellulose polymers

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The properties of indomethacin "sorbates" with hydrophilic cellulose carriers (optimal drug/carrier ratio 1 : 1 (w/w)) were studied in the solid state and in the form of 0.5% aqueous dispersions. The polymers used were: methyl- (MC), hydroxyethyl- (HEC), hydroxyethylmethyl- (HEMC), hydroxypropyl- (HPC), sodium carboxymethyl- (CMC-Na) and microcrystalline celluloses. It was found that the "solvent deposited" indomethacin, unlike the pure drug, exists predominantly as the α-polymorph, and possesses improved wettability and higher aqueous solubility (the increase was approximately 2–3 times). The indomethacin/cellulose sorbates can be easily transformed into 0.5% aqueous dispersions. The "primary" dispersions were used as a basis for the formulation of new oral suspensions with improved rheological properties and physical stability. The new models behave as non-Newtonian fluids with pseudoplastic flow and good sediment redispersibility after shaking. The indomethacin/carboxymethylcellulose sodium 1 : 1 (w/w) sorbate suspension is the most suitable for future practical application.

1. Introduction

From a biopharmaceutical point of view the potent anti-inflammatory drug indomethacin is a well known example of a problematic drug – e.g. very low aqueous solubility and marked chemical instability in solution, polymorphism, gastric mucosal irritation etc. [1]

Our previous investigations of indomethacin "solvent deposited" on hydroxypropylmethylcellulose, sodium alginate and haemodex (dextran) have shown its advantages over the untreated drug for the formulation of model oral drug suspensions [2, 3]. The positive results were good reasons for us to extend the investigations using other hydrophilic water soluble polymers of the cellulose derivatives group. The objects of the present study were: methyl- (MC), hydroxyethyl- (HEC), hydroxyethylmethyl- (HEMC), hydroxypropyl-, (HPC), sodium carboxymethyl- (CMC-Na) and microcrystalline celluloses.

The aim was to formulate physically stable model aqueous suspensions of indomethacin "solvent deposited" on cellulose carriers.

2. Investigations, results and discussion

2.1. Preparation and properties of indomethacin "sorbates"

The solvent used for preparation of the "sorbates" was ethanol. We have established that ethanol is an appropriate dispersing medium for all the cellulose polymers studied (excepting hydroxypropylcellulose because of its solubility). On the other hand, all the sorbates, irrespective of the type of the cellulose carrier, were solids after evaporation of ethanol and were easily transformed into powders.

Table: Equilibrium solubility of indomethacin sorbates in buffer pH 6.8 at 37 ± 0.1 °C

Cellulose polymer carrier	Indomethacin dissolved (g/100 ml)
Avicel	0.106
Na-CMC	0.117
MHEC	0.158
MC	0.189
HEC	0.199
Untreated indomethacin	0.08

The optimal indomethacin/carrier ratio found for all "sorbates" was 1 : 1 (w/w).

2.2. IR spectral behaviour of indomethacin/cellulose polymer sorbates

The FT-IR spectra recorded (Fig. 1) clearly showed that polymorphic changes take place during the process of indo-

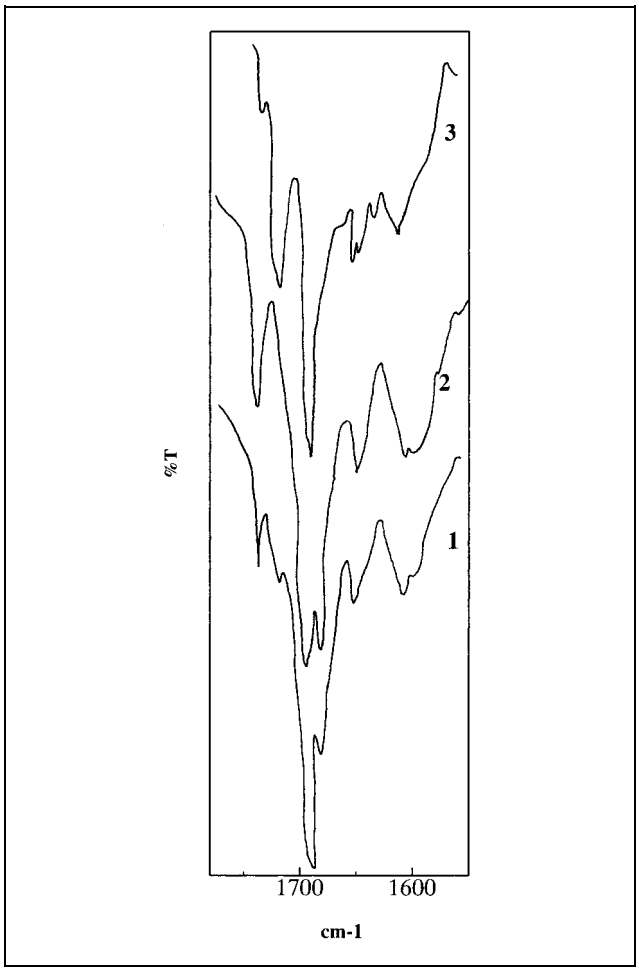

Fig. 1: FT-IR spectra of indomethacin sorbates with cellulose polymers in the region 1780 cm^{-1}–1550 cm^{-1}: **1**: MHEC; **2**: CMC-Na; **3**: HPC

methacin sorbate formation. They support the predominànt existence of an α-polymorph. The absorption bands specific for α-indomethacin [4] appear in the 1550 cm^{-1}–1800 cm^{-1} region at 1734 cm^{-1}, 1690 cm^{-1} and 1651 cm^{-1}, respectively. Some of the main characteristic absorption peaks of gamma-indomethacin can be seen only as very weak or medium vibrations in the spectra of IND/MHEC and IND/HPC sorbates.

It is important to note that none of the spectra showed the characteristic absorption maxima of β-indomethacin [3]. Another finding which is very important from a practical point of view was that the polymer carriers stabilize the α-polymorphic form, which is metastable and more soluble in water. The FT-IR spectra of freshly prepared samples and of samples stored for 6 months under normal conditions were identical. These results are in accordance with the results reported previously in [3].

Obviously, many factors are responsible for the character of the polymorphic transitions of indomethacin during the preparation of sorbates. They need further and more detailed investigations, however.

2.3. Solubility of "solvent deposited" indomethacin

It was established that all the sorbates studied possess higher apparent aqueous solubility than that of non-treated indomethacin (Table 1). The highest solubility was achieved with indomethacin/hydroxyethylcellulose sorbate – the increase was about 2.5 times.

On the other hand, it was found that the solubility of non-treated indomethacin in water not be increased in an aqueous solution of a pure cellulose polymer used in a concentration corresponding to that in the sorbate. This confirms that drug/polymer interactions arise during sorbate preparation, giving higher drug dispersity, stronger adsorption of the drug particles on the polymer surface, and polymorphic transition of γ-indomethacin into the more soluble α-polymorph.

All these changes result in better wettability and higher apparent solubility in water. These properties have a significant effect on the transformation of "solvent deposited" indomethacin into aqueous dispersions as well as on the amount of drug dissolved in the liquid vehicle of the suspension. It was found that between 14% and 28% of indomethacin from the solid phase (the amount depends markedly on the type of polymer carrier) goes into solution. This fact could be of great practical importance for the formulation of oral suspensions of indomethacin.

2.4. Formulation of model oral suspensions of indomethacin sorbates

Preliminary determinations of the viscosity of primary 0.5% aqueous dispersions of indomethacin "solvent deposited" on cellulose polymers, have shown that all the dispersions behave as Newtonian liquids with apparent viscosity in the range 3–7 cP, irrespective of the carrier type. The dispersion of indomethacin/methylcellulose 1 : 1 (w/w) sorbate possessed the highest viscosity (about 2 times higher than that of the other models).

All the aqueous dispersions had unsatisfactory values (below 0.5) for the physical parameter sedimentation volume.

The preliminary results showed the necessity to improve the physical properties of the primary 0.5% indomethacin sorbate aqueous dispersions to meet more completely the current pharmacopoeial requirements for correct oral dosage of drug suspensions. Different physical stabilizers of

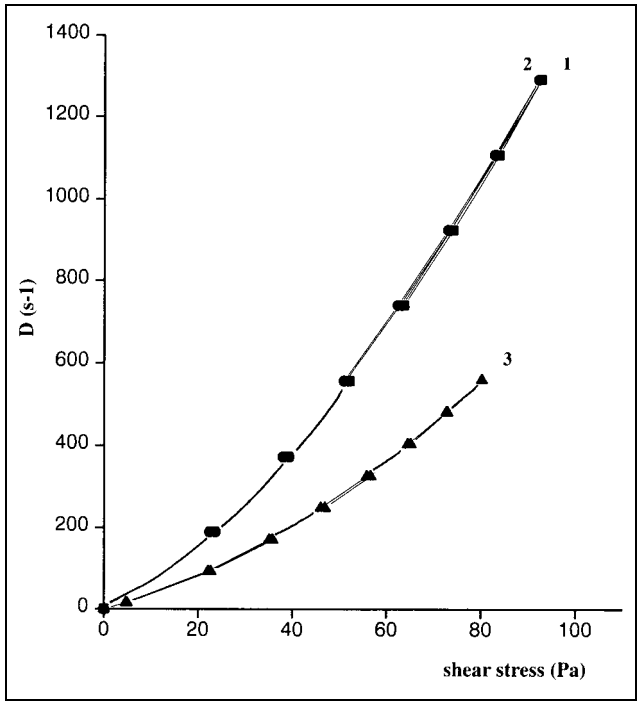

Fig. 2: Rheograms of 0.5% aqueous dispersions of IND/MC 1 : 1 (w/w) sorbate containing physical stabilizers: **1**: MC (1%); **2**: MC (1%) and aerosil (1%); **3**: MC (1.2%) and aerosil (2%)

the classes of thickening-, structure forming- and viscosity increasing agents were investigated. The evaluation of viscosity and physical stability had shown that the models containing the additives aerosil and an additional quantity of polymer (free polymer) are optimal. We also established that the increasing of the aerosil concentration above 2% does not markedly influence the character of the models.

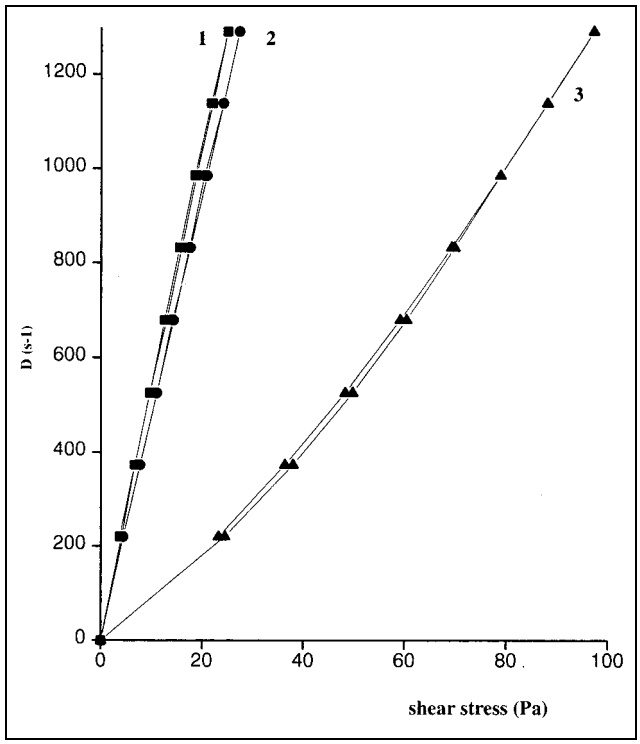

Fig. 3: Rheograms of 0.5% aqueous dispersions of IND/HEC 1 : 1 (w/w) sorbate containing physical stabilizers: **1**: HEC (1%) and aerosil (1%); **2**: HEC (1%); **3**: HEC (2%) and aerosil (2%)

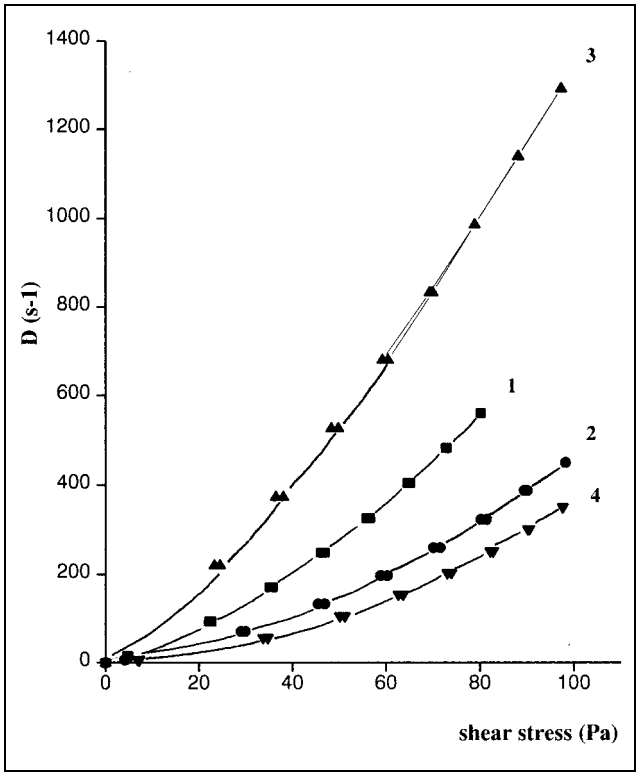

Fig. 4: Rheograms of 0.5% aqueous dispersions of indomethacin sorbates with: **1**: MC; **2**: MHEC; **3**: HEC; **4**: CMC-Na, stabilized with a free polymer (2%) and aerosil (2%)

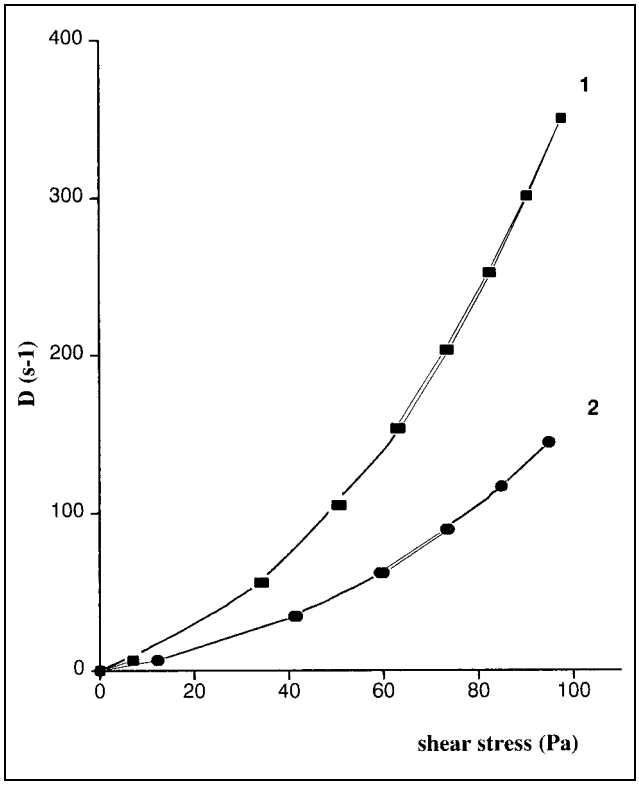

Fig. 5: Rheograms of 0.5% aqueous suspensions of: **1**: indomethacin/CMC-Na 1 : 1 (w/w) sorbate and **2**: indomethacin/CMC-Na 1 : 1 (w/w) physical mixture, stabilized with a free polymer (2%) and aerosil (2%)

The rheograms depicted in Figs. 2, 3 and 4 show that:
– the suspensions are structured but non-thixotropic systems of pseudoplastic flow,
– the type and concentration of the free polymer used as a viscosity-increasing agent, strongly influence flow behaviour. For example, the viscosity of the model with 1% free methylcellulose at $D = 481\ s^{-1}$ is about 1.5 times lower than the viscosity of the model with 1.2% free polymer (Fig. 2). Increasing the polymer concentration up to 2% with indomethacin/hydroxyethylcellulose sorbate results in a 4 fold increase of the structured viscosity at $D = 1138\ s^{-1}$ (Fig. 3).
– the model suspension of indomethacin/carboxymethylcellulose sodium 1 : 1 (w/w) sorbate possessed the best rheological properties (Fig. 4). The viscosity at $D = 350\ s^{-1}$ was $0.279\ Pa \cdot s$ which was about 3 times higher than that of the model with hydroxyethylcellulose recorded at the same shear rate, for example.
Model 0.5% suspensions of 1 : 1 (w/w) physical mixtures of indomethacin/cellulose polymers were also formulated and used for comparison. The rheological study showed that they were more viscous than the corresponding models with indomethacin sorbates. An example is presented in Fig. 5. As can be seen the rheogram of the sample with an indomethacin/carboxymethylcellulose sodium 1 : 1 (w/w) physical mixture lies markedly below that of the sample containing the corresponding sorbate and the viscosity value calculated at $D = 105\ s^{-1}$ for example was about 1.6 times higher. The observed differences in the rheology of the suspensions studied can probably be related to the drug/polymer interactions which take place during sorbate formation.
Another very important fact which was established was that the additives used as physical stabilizers produce an increase in the amount of indomethacin dissolved in the liquid suspension medium. The best result was obtained with the sample containing indomethacin/hydroxyethylcellulose 1 : 1 (w/w) sorbate plus additives – approximately 38% of indomethacin from the solid phase goes into solution.
The sedimentation volume values of the new models were found to be above 0.8 giving very good physical stability.
Thus, the models containing 2% aerosil and 2% free polymer as physical stabilizers (with the model containing methylcellulose the optimal concentration of the latter was lower –1.2%) are optimal and can be considered for further investigations.

2.5. Amount of indomethacin released in vitro at 20th minute ($M_{20'}$)

This parameter was determined as described in the monograph "Indomethacin oral suspension" of USP 23. It should be noted that, irrespective of the cellulose carrier, none of the model sorbate suspensions met the requirement for $Q_{20\,min} \geq 80\%$. On the other hand, the amount of indomethacin released at the 20th minute both from the aqueous dispersion of pure indomethacin and from the suspensions of the corresponding physical mixtures used as samples for comparison, was above 80%.
It can be assumed that the pharmacopoeias experimental conditions used, particulary the direct contact of the sample with a large volume (900 ml) of dissolution medium of pH 7.2, favour the reverse adsorption of indomethacin on the polymer particles. The latter begin to act as a drug "depot" and assure prolonged dissolution of indomethacin. A relatively high initial drug concentration could be related to the amout of the dissolved indomethacin, which is available in the suspension sample. These results and assumptions, however, need to be confirmed *in vivo.*

3. Experimental

3.1. Materials

Indomethacin was kindly donated by Sopharma, Bulgaria. The other additives were purchased as follows: Avicel PH 101, Methocel 1500 cP and hydroxyethylcellulose medium viscosity (Fluka, Switzerland), hydroxypropylmethylcellulose 80–120 cP (Aldrich Chem. Company, USA), sodium carboxymethylcellulose medium molecular mass (Hercules, USA) and Aerosil 200 (Degussa, Germany).

3.2. Methods

3.2.1. Preparation of indomethacin sorbates

Indomethacin "sorbates" with water soluble organic polymers of drug/carrier ratio 0.5 : 1.0-, 1 : 1- or 1 : 2 (w/w) were prepared in 95% ethanol, according to previously described techniques [2].

3.2.2. Spectral study in the IR region

Apparatus – FT IR-810M Shimadzu, Japan. The IR spectra were recorded as suspensions in Nujol.

3.2.3. Preparation of model pharmaceutical suspensions

0.5% Aqueous dispersions (with phosphate buffer pH 6.8 or 7.2 as a dispersion medium) were prepared *ex tempore* from the corresponding powder sorbates as described earlier [2]. The samples were stirred until homogeneity was achieved.

3.2.4. Determination of indomethacin amount dissolved in the model dispersions

The concentration of indomethacin in centrifuged and filtered dispersion samples was assayed by UV spectrometry at 320 nm (Spectronic 21D, Milton-Roy, USA).

3.2.5. Viscosity evaluation

The measurements were made with a Hoeppler Rheoviscometer (DDR) at 20 °C (the constant of the glass tube used was 0.1070 and the weight – 10.0 g) and by a Rheo-Viscosimeter Mettler-RM 180 Rheomat (Mettler Toledo AG, Switzerland) with a measurement system 11.

3.2.6. In vitro release study

This was carried out as described in USP23 in the "Indomethacin oral suspension" monograph. Apparatus – Dissolution tester, Erweka, Germany. The concentration of indomethacin dissolved was determined spectrophotometrically as described above.

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References

1 O'Brien, M.; McGcaulley; Cohen, E.; in: Florey, K. (Ed.): Analytical Profiles of Drug Substances, p. 211, Academic Press Inc., 1984
2 Bogdanova, S.: D.Sc.Thesis, Sofia, 1998
3 Bogdanova, S.; Ford, J.: S.T.P. Pharma Sci. **8,** 1430 (1998)
4 Spychala, S. et al.: Pol. J. Pharmacol. Pharm. **29,** 157 (1977)

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