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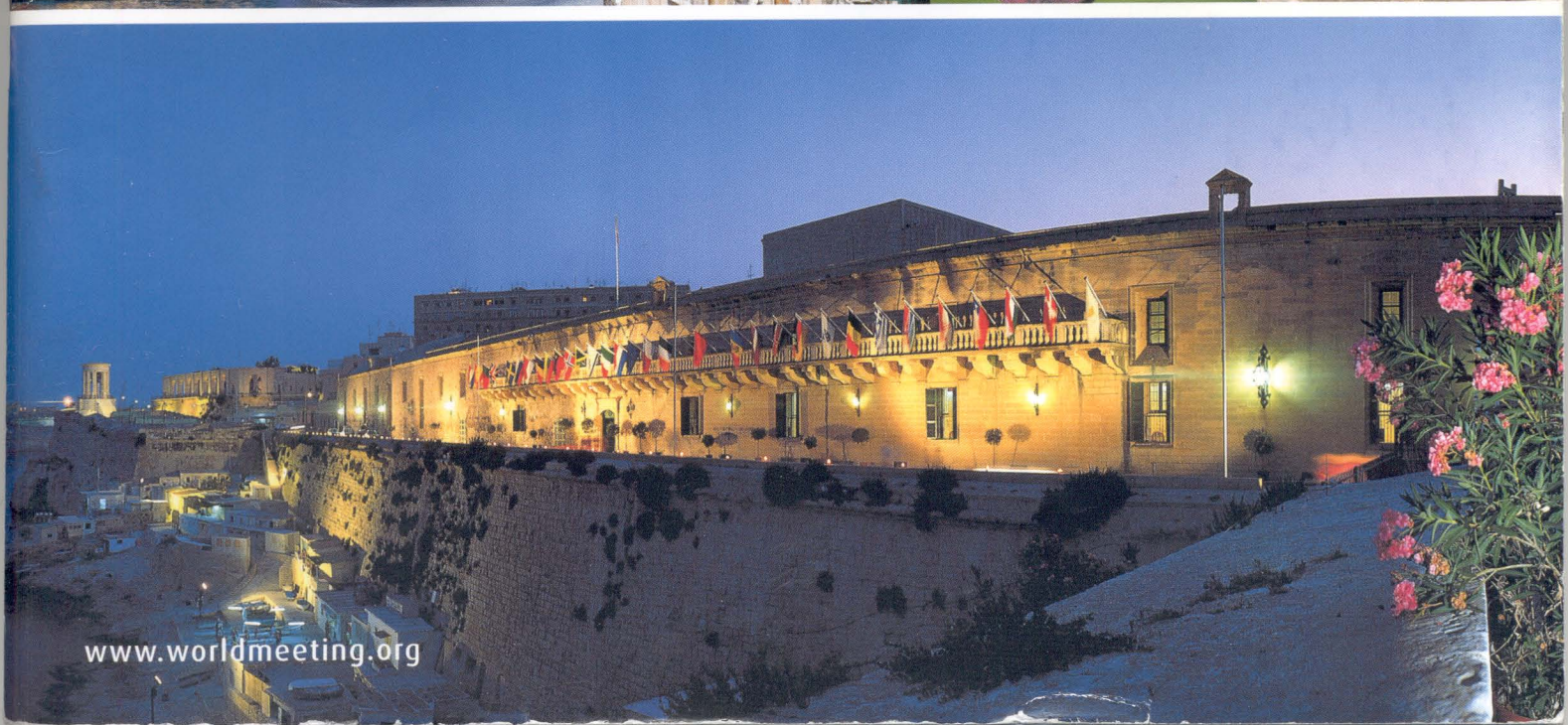

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The use of sound speed measurements in the evaluation of polymers mucoadhesiveness

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INTRODUCTION

The ability of polymers to adhere to soft biological tissues has been used in the last three decades in order to optimise drug delivery in specific body sites and improve systemic drug adsorption. In fact, increased bioavailability and site-specific release was observed for dosage forms able to remain in contact with a certain tissue for a prolonged period of time*[1]*

In the last 20-25 years a very large number of works have been carried out for the development of in-vitro mucoadhesive tests *[2-4]*.

In this work an innovative and simple methodology has been developed and used for the evaluation of mucoadhesive properties by means of sound speed measurements using high resolution acoustic spectroscopy. In systems made of polymers in water, variations in hydration shell of polymeric chains determine changes of dispersions compressibility and this phenomenon can be monitored by sound speed measurements. Two different polymers have been selected, namely PEG 6000 and Carbopol 974 (C974).

These polymers, were analysed either alone or mixed with mucin by using high resolution ultrasound spectroscopy and interactions occurring between polymer-mucin were evaluated through the comparison of experimental and theoretical sound speed values of their water dispersions.

EXPERIMENTAL METHODS

Materials

Carbopol® 974 PNF (Lubrizol Corporation, USA), PEG 6000 (Lipoxol 6000 med powder, Sasol, Germany), and deionised water (obtained by GAMMA 3 s.n.c. Castelverde, CR, Italy).

Sample preparation

2% w/w polymers and mucin samples (stock solutions) were prepared by dispersing the powders in deionised water under magnetic stirring at room temperature. All systems were stored at 5°C for at least 24 hours (4 days for carbopol samples) before the dilute dispersions (of polymers, mucin or mucin-polymers) were prepared and analysed.

Ultrasonic measurements

Ultrasonic velocity was measured using an HR-US 102 high resolution spectrometer (Ultrasonic Scientific, Ireland) fitted with two 1 ml ultrasonic cells. The reference cell was filled with water while the other cell with polymer, mucin and polymer-mucin samples. All the dispersions were analysed at the selected frequencies of 5.2 and 8.2 MHz and temperature control of 37 ± 0.1 °C was achieved using a HAAKE C25P water bath. The limiting resolution was 0.2 mm/sec for ultrasound velocity. In all the following test, sound speed is reported as relative parameter, obtained subtracting the contribution of the pure solvent to the total sound speed ($\Delta U = U_{sample} - U_{solvent}$).

Mucoadhesion study

Dilute dispersions made of mucin, polymer and mucin-polymer mixtures were prepared from stock solutions according to the concentrations reported in Table 1.

Table 1: Analysed samples

System	Concentration (%w/w)		
Mucin		1	
Polymer	1	0.6	0.3
Mucin+Pol	1+1	1+0.6	1+0.3

Mucoadhesion degree (MD) was calculated using the rule of additivity. According to this rule, in a system containing one or more polymers dispersed in water if no interaction occurs between the polymeric chains, the sound speed of the whole system is equal to the sum of the sound speed of each polymer; while, if an interaction occurs the total sound speed measured is lower than the theoretical one. Following this assumption, the MD (%) is calculated using Eq. (1):

$$MD(\%) = \frac{(\Delta U_t - \Delta U_b)}{\Delta U_t} \cdot 100 \qquad (1)$$

Where ΔU_t is the theoretical relative sound speed, equal to the sum of the experimental relative sound speed of mucin and polymer alone and ΔU_b is the experimental sound speed of mucin-polymer blends. A value of 0 % MD indicates no interactions between polymeric chains.

RESULTS and DISCUSSION

The two polymers in study (Carbopol and PEG) were selected for their peculiar mucoadhesive properties. PEG is surely a non mucoadhesive polymer *[2]*, has poor swelling ability and is rapidly dissolved in water; Carbopol is a well known mucoadhesive polymer (independently from the technique used for the evaluation of this feature *[5, 6]*, it swells and is not rapidly soluble in water.

Results of mucoadhesion are reported in figure 1. For PEG-mucin dispersions, values of MD indicated a poor interaction between polymer and mucin resulting always lower than 1.0 %. For the lowest concentration in study (0.3 % w/w) negative values of MD were observed, which theoretically would indicate an increase of the polymers hydration, but they have to be considered as a consequence of the experimental error (all the absolute values for PEG are very close to zero) . Therefore, it was concluded that a MD value around 0.0 ± 1.0 % indicated no interaction between polymer chains.

All Carbopol-mucin systems analysed showed much higher mucoadhesion degree compared to PEG systems, with the exception of the 0.3 % w/w sample showing MD values around zero with a standard deviation of 4.0%. Therefore such concentration was considered not reliable. The results obtained for PEG-mucin and Carbopol-mucin dispersions confirmed the validity of sound speed measurements for mucoadhesiveness analysis when mucoadhesive and non mucoadhesive polymers are analysed.

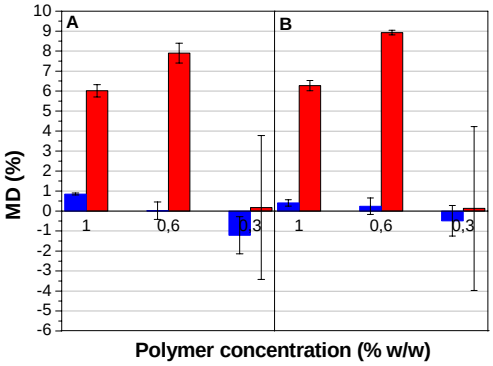

Figure 1: Mucoadhesion degree (%) of the analyzed polymers as a function of their concentrations, calculated at the frequencies of A) 5,2 MHz and B) 8,2 MHz. The mucin amount in each system remains always at a value of 1%. The colors refer to PEG and carbopol respectively.

CONCLUSION

In this work, it was demonstrated that the use of acoustic spectroscopy applied to polymeric dispersions was very effective in discriminating mucoadhesive and non-mucoadhesive systems, failing only for very low polymer-mucin concentrations (i.e. each polymer at 0.3 % w/w). This technique could offer an interesting alternative to traditional methods especially if the studied samples are opaque and in very small amount.

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