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Research Article

Surface Thermodynamics of Mucoadhesive Dry Powder Formulation of Zolmitriptan

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Abstract. Microparticle powders for nasal delivery were formulated to contain the model drug, zolmitriptan, and varying proportions of different polymers. The objective of the study was to investigate the effects of these formulative parameters on the surface chemistry of the spray-dried microparticles and their potential for adhesion to the tested substrates, porcine mucin, and nasal tissue. The polymers used were chitosans of varying ionization states and molecular weights and hydroxypropyl methyl cellulose. The surface energies of the surfaces of the microparticles were determined using contact angle measurements and the van Oss model. The theory of surface thermodynamics was applied to determine the theoretical potential for the different materials to adhere to the substrates. It was found that the drug or polymers alone, as well as the various formulations, were more likely to adhere to mucin than to nasal tissue. Further, there was a trend for higher molecular weight chitosans to adhere better to the substrates than lower molecular weight chitosans. Similarly, adhesion was improved for formulations with a higher content of polymers. These theoretical predictions may be compared with further experimental results and be of use in making informed decisions on the choice of formulations for future expensive bio-studies.

KEY WORDS: chitosan; contact angle; mucoadhesion; surface energy; surface thermodynamics.

INTRODUCTION

The use of powder-based mucoadhesive formulations for nasal drug delivery has been widely discussed in the literature. These formulations, which contain a drug and mucoadhesive materials (usually polymers), tend to improve the bioavailability of the drug by increasing the residence time at the site of absorption or the target site compared to liquid formulations (1,2). The molecular weight, the choice of functional groups, the degree of hydration of the bio/mucoadhesive materials, and their proportions in the formulation all determine the intrinsic properties of the formulation that will eventually affect its performance (3).

Adhesion describes the phenomenon of two surfaces sticking together. If one of the surfaces is a biological substrate, the term bioadhesion is used, and mucoadhesion is used if the substrate is mucus or a mucosal membrane (4). Nasal mucus consists of 95% water, 2.5% glycoproteins, 1–2% electrolytes *etc*. Glycoproteins are responsible for rheological properties of the mucus and contain sialic acid (pK_a= 2.6) and sulfate groups making mucin anionic at neutral pH (5). Although several theories have attempted to explain bioadhesive and mucoadhesive phenomena, explanations based on surface energy thermodynamics are currently popular (3,6). Surface energy thermodynamic models based on acid–base interactions and interfacial tension have been used to predict the bio/mucoadhesive properties of polymers (7–10).

The laws of thermodynamics dictate that all systems undergo changes towards an energetically favorable low free energy state. Accordingly, a powder will adhere to a solid surface if the interfacial free energy of the powder–solid system is lower than the energy states of the separate powder and solid. Therefore, adhesion is energetically favorable only if the free energy of adhesion (ΔG_{adh}) is negative. ΔG_{adh} can be expressed for a system containing a powder, a solid substrate, and a liquid as:

$$\Delta G_{adh} = \gamma_{ps} - \gamma_{pl} - \gamma_{sl} \quad (1)$$

where γ represents the interfacial free energy of the various interfaces: powder–solid (γ_{ps}), powder–liquid (γ_{pl}), and solid–liquid (γ_{sl}). Thus, ΔG_{adh} provides a measure of the affinity between the surfaces.

Various methods have been used to estimate the surface energies of these systems, including contact angle methods, inverse gas chromatography, atomic force microscopy, *etc*. (11–13). Each technique has its own advantages and disadvantages. For example, a typical inverse gas chromatographic

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experiment at infinite dilution, preferentially measures high-energy sites resulting in biased results for surface free energies. On the other hand, contact angle methods might be associated with the change of material integrity in the presence of liquid such as swelling of powder, crystallization of amorphous material, *etc*. However, despite these limitations, good correlations have been observed between surface energy measurements obtained using contact angle methods and the performance of various powders. Contact angle methods have, in fact, been widely used to study the wettability and surface energy of solid powders (7–10,14).

Various approaches have also been suggested for the estimation of surface energy from contact angle measurements. However, the van Oss acid–base (AB) model was chosen for this study because it takes into account the importance of AB interactions in surface and interfacial tension (15–19) and it seems to provide consistent results (18,20,21). In the van Oss model, ΔG_{adh} is divided into two components: the Lifshitz–van der Waals (LW; apolar) component and the AB (polar) component as follows:

$$\Delta G_{adh} = \Delta G_{adh}^{LW} + \Delta G_{adh}^{AB} \tag{2}$$

According to Dupre's equation, ΔG_{adh}^{LW} for the adhesion of a powder to a solid surface in the presence of liquid can be given as follows:

$$\Delta G_{adh}^{LW} = \gamma_{ps}^{LW} - \gamma_{pl}^{LW} - \gamma_{sl}^{LW} \tag{3}$$

where $\gamma_{ps}^{LW} = \left(\sqrt{\gamma_p^{LW}} - \sqrt{\gamma_s^{LW}}\right)^2$.

Similarly, the polar component (ΔG_{adh}^{AB}) for adhesion of a powder to a solid surface in the presence of liquid can be given as:

$$\Delta G_{adh}^{AB} = \gamma_{ps}^{AB} - \gamma_{pl}^{AB} - \gamma_{sl}^{AB} \tag{4}$$

where

$$\gamma_{ps}^{AB} = 2\left(\sqrt{\gamma_p^+\gamma_p^-} + \sqrt{\gamma_s^+\gamma_s^-} - \sqrt{\gamma_p^+\gamma_s^-} - \sqrt{\gamma_p^-\gamma_s^+}\right).$$

The components of the change in free energy of adhesion can be calculated from the interfacial tensions as follows:

$$\Delta G_{adh} = \gamma_{ps}^{LW} - \gamma_{pl}^{LW} - \gamma_{sl}^{LW} + 2\left[\sqrt{\gamma_l^+}\left(\sqrt{\gamma_p^-} + \sqrt{\gamma_s^-} - \sqrt{\gamma_l^-}\right) + \sqrt{\gamma_l^-}\left(\sqrt{\gamma_p^+} + \sqrt{\gamma_s^+} - \sqrt{\gamma_l^+}\right) - \sqrt{\gamma_p^+\gamma_s^-} - \sqrt{\gamma_p^-\gamma_s^+}\right] \tag{5}$$

According to the Young-Dupre equation,

$$(1 + \cos\theta)\gamma_L = 2\left(\sqrt{\gamma_s^{LW}\gamma_l^{LW}} + \sqrt{\gamma_s^+\gamma_l^-} + \sqrt{\gamma_s^-\gamma_l^+}\right) \tag{6}$$

where γ_s^{LW}, γ_s^+, and γ_s^- can be determined for the powder and the solid surface using three liquids with known surface tension components.

The polymers chosen for preparing the bio/mucoadhesive formulations for this study included chitosan and hydroxypropyl methyl cellulose (HPMC) were largely used for preparing bio/mucoadhesive formulations. Chitosan, a natural polysaccharide that is derived from chitin, has impressive mucoadhesive properties (22). These are the result of the positively charged amine group that is found in the chitosan molecule under acidic conditions (pH <6.5). Van der Waals forces, electrostatic attraction, hydrogen bonding, and/or hydrophobic effects also contribute to the mucoadhesive interactions between chitosan and mucin (23). For this reason, chitosan has been widely used for preparing and studying bio/mucoadhesive formulations for various drug delivery applications (2,24–26). However, factors such as chitosan molecular mass and deacetylation degree can influence mucoadhesion properties of the chitosan hydrogel (22,27). In particular, mucoadhesiveness seems to be directly related to the number of free amino groups, which can vary for different chitosan deacetylation degrees and different crosslinking densities. As mucoadhesion requires suitable free chain length for physical entanglement to occur and availability of multiple sites for mucin attachment, chitosan molecular mass is another important factor to be considered. In general, higher molecular masses promote stronger mucoadhesion, but the optimum molecular mass also depends on the flexibility and the conformation of chitosan chains, which must interpenetrate with mucus.

We recently prepared mucoadhesive powders containing chitosan for nasal administration of the antimigraine drug, zolmitriptan (26). The type, molecular weight, and amount of chitosan in these formulations were varied and their solid-state/physicochemical and dissolution properties were studied. The purpose of the study presented here was (a) to investigate the effect of varying the formulation parameters on the surface energies of the resulting powders and (b) to predict the relative affinities of the formulations for mucus and nasal tissue (*i.e.* their bio/mucoadhesive performance) by applying the theory of surface energy thermodynamics.

MATERIAL AND METHODS

Materials

Zolmitriptan (batch number 070701) was purchased from Haorui Pharma-Chem Inc. (New Jersey, USA). Chitosan glutamate Protasan UP G 113 (CG113; Mw, <200 kDa; deacetylation degree, 75–90%) and chitosan glutamate Protasan UP G 213 (CG213; Mw, 200–600 kDa; deacetylation degree, 75–90%) were purchased from NovaMatrix/FMC Biopolymer (Sandvika, Norway). Chitosan base (CB; Mw, 150 kDa; deacetylation degree, >85%) was purchased from SeeLab (Wesselburenerkoog, Germany). Hydroxypropyl methylcellulose (Methocel K4M Premium CR; 19–24% methoxyl content, 7–12% hydroxypropyl content, and 300–5,600 cPs apparent viscosity as a 2% aqueous solution) was obtained from Dow Chemical (Auburn Hills MI, USA). Mucin was purchased from Sigma Aldrich (Stockholm, Sweden). All chemicals (purity >99%) and HPLC grade acetonitrile were purchased from Sigma Aldrich (Stockholm, Sweden) and were used without further purification. Milli-Q water was used in the preparation of the powders. Nasal mucosa was isolated from the snouts of 6- to 12-month-old domestic pigs obtained from a local slaughterhouse in Luleå. Respiratory mucosa was obtained

Table I. Summary of the Types, Molecular Weights, and Amounts of the Polymers Included in the Zolmitriptan Formulations

Sample ID	Polymer	Molecular weight (kDa)	Polymer (% *w/w*)
CG113	Chitosan glutamate	<200	100
CG213	Chitosan glutamate	200–600	100
CB	Chitosan acetate	150	100
HPMC	Hydroxypropyl methylcellulose		100
CG113-Zol1	Chitosan glutamate	<200	30
CG113- Zol2	Chitosan glutamate	<200	50
CG113- Zol3	Chitosan glutamate	<200	70
CG113-Zol4	Chitosan glutamate	<200	90
CG213- Zol1	Chitosan glutamate	200–600	30
CG213- Zol2	Chitosan glutamate	200–600	50
CG213- Zol3	Chitosan glutamate	200–600	70
CG213- Zol4	Chitosan glutamate	200–600	90
CB-Zol1	Chitosan acetate	150	30
CB-Zol2	Chitosan acetate	150	50
CB- Zol3	Chitosan acetate	150	70
CB-Zol4	Chitosan acetate	150	90
HPMC-Zol1	Hydroxypropyl methylcellulose	NA	30
HPMC-Zol2	Hydroxypropyl methylcellulose	NA	50

NA not available

from the inferior nasal concha at the anterior part of the nasal cavity from pig snouts from the same source.

Preparation of Nasal Powders by Spray Drying

The formulations employed in this work are presented in the Table I. Further information on the formulation and preparation of powders by spray drying can be found in our previous article (26). Briefly, drug and polymers to a total weight of 750 mg in ratios described in Table I were dissolved in 250 ml of water adjusted to pH 5.0 using 0.25% acetic acid to aid the dissolution of the components. These solutions were spray dried using a Büchi Mini Spray Dryer B-290 (Büchi Labortechnik AG, Switzerland) with an inlet temperature of 160°C, an aspiration rate of 100%, air flow of 357 Lh^{-1} and a solution feed rate of 5 ml min^{-1}. The resulting powders were sealed in glass vials and stored in a desiccator over silica gel at −15°C before analysis. An amorphous form of the drug was prepared using the melt–cool method. The drug was melted on a laboratory hot plate at 140°C and the resultant molten solid was allowed to cool to room temperature. Chitosans and HPMC were spray dried under similar condition as the formulations. Our previous study confirmed that the chitosan base (CB) was converted to chitosan acetate on spray drying in acetic acid (26). The term CB is thus used to indicate chitosan acetate in this study.

Table II. The Mean Contact Angle Data for the Studied Materials

	Contact angle		
Sample ID	Water	Bromonaphthalene	Formamide
Amorphous drug	23.5	19	21
CG113	49.6	19.8	16.5
CG213	58	20	21
CB	47	13.7	23
HPMC	75	26.2	57
Mucin	62.7	34.1	30.3
Nasal tissue	42.1	66	42.3
CG113-Zol1	24	20	24.1
CG113-Zol2	47.5	19.9	20.1
CG113-Zol3	45	15	21.4
CG113-Zol4	44.3	15.2	21.7
CG213-Zol1	28.7	22	29
CG213-Zol2	49	14.2	28
CG213-Zol3	56.5	17.3	20
CG213-Zol4	49.6	16.8	18
CB-Zol1	30	22.9	23.5
CB-Zol2	31	18	24
CB-Zol3	36	17.8	20
CB-Zol4	45	14	23.5
HPMC-Zol1	53.2	32.4	50.3
HPMC-Zol2	58.6	21.7	49.2

Contact Angles and Surface Energy

The contact angles of water, formamide, and 1-bromonaphthalene with the powder pellets or nasal tissue were determined using the sessile drop method (using KRÜSS EasyDrop). The pellets of spray-dried polymers and formulations and mucin were made by applying 6-ton pressure on the powder for 1 min in an IR press (Graseby Specac). All measurements were carried out at laboratory temperatures (*i.e.* ~23°C). Each measurement was repeated two to three times and the mean value was used in the calculations. The contact angle values were then used to calculate the dispersive and polar contributions to the surface energy of the samples using the van Oss AB method. The values for the dispersive and polar components of

Table III. Surface Energies of Test Liquids Used for Contact Angle Measurements (30,31)

Surface energy γ [mJ m^{-2}]	Water	Bromonaphthalene	Formamide
Total	72.8	44.6	58
(γ^{LW})	21.8	44.6	39
γ^{p} (γ^{AB})	51	0	19
γ^{+}	25.5	0	2.3
γ^{-}	25.5	0	39.6

Table IV. Surface Energy Values Determined Using the Acid–Base Method (Eq. 6)

	Surface energy				
Sample ID	Total	Dispersive	Polar (AB)	Acid (+)	Base (−)
Amorphous drug	52.53	41.95	10.57	0.56	50.18
CG113	55.45	42	13.45	2.4	18.82
CG213	53.21	41.95	11.26	2.79	11.34
CB	54.48	43.34	11.14	1.29	24.02
HPMC	40.6	40.14	0.46	0.01	9.87
Mucin	48.3	37.26	11.04	3.19	9.55
Nasal tissue	46.76	22.06	24.70	3.73	40.83
CG113-Zol1	51.48	41.95	9.53	0.45	50.94
CG113-Zol2	54.9	41.98	12.92	1.88	22.26
CG113-Zol3	54.88	43.09	11.79	1.35	25.75
CG113-Zol4	54.77	43.05	11.71	1.28	26.7
CG213-Zol1	49.29	41.41	7.88	0.31	49.28
CG213-Zol2	52.76	43.25	9.52	0.95	23.84
CG213-Zol3	54	42.61	11.39	2.58	12.56
CG213-Zol4	55.42	42.72	12.71	2.09	19.27
CB-Zol1	52.66	41.15	11.5	0.75	44.29
CB-Zol2	52.51	42.44	10.06	0.58	43.57
CB-Zol3	54.79	42.49	12.3	1.06	35.82
CB-Zol4	54.24	43.29	10.96	1.13	26.63
HPMC-Zol1	38.45	37.94	0.51	0	33.52
HPMC-Zol2	41.76	41.5	0.26	0	24.81

the surface tension of the liquids used for the contact angle measurements are taken from the literature.

RESULTS AND DISCUSSION

In our previous study, chitosan-based microparticles were prepared for nasal delivery. The microparticles were spherical with a narrow size distribution. The formulations were amorphous in nature and varied in their dissolution behavior with the molecular weight and the amount of chitosan used (26). The mucoadhesive behavior of the powders was evaluated using well-established (8–10) models based on thermodynamic theory and contact angle measurements.

Contact Angle Measurements of the Studied Materials

The contact angles of the amorphous form of the drug, spray-dried powders (polymers or formulations), mucin, and nasal tissue are shown in Table II. The contact angle data indicated that the amorphous form of the drug was more

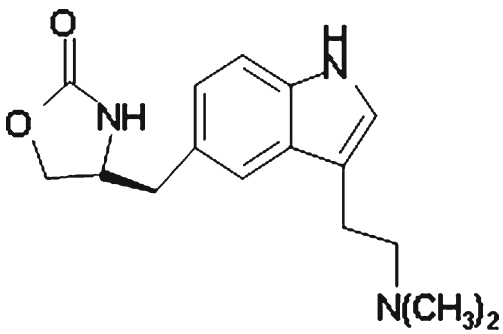

Fig. 1. Chemical structure of zolmitriptan

Table V. Linear Regression Analysis of the Polymer Content of the Formulation and the Dispersive, Acid, and Base Components

	R^2		
Formulations from 0 to 100*w/w* % polymer	Dispersive	Acid (+)	Base (−)
CG113	0.44	0.59	0.73
CG213	0.25	0.78	0.83
CB	0.86	0.82	0.94

hydrophilic than the spray-dried polymers and formulations (26). The wettability of the spray-dried polymers was inversely related to the molecular weight of the chitosan used. HPMC had a wider contact angle with water than any of the chitosans in the study (*i.e.* lower wettability). There was a clear trend for increased amounts of polymer in the formulations to result in decreased wettability (*i.e.* wider contact angles). However, the change in the water contact angle varied with the different polymers; for example, the formulations containing CB were more wettable than formulations containing CG113 or CG213, even with higher proportions of the polymer. Interestingly, the formulations containing HPMC were more hydrophilic than HPMC alone.

Our earlier study indicated that the dissolution rate decreased with increasing polymer content and polymer molecular weight, which correlates well with the wettability trends for these formulations (26). A previous study has also shown a relationship between powder dissolution rate and the wettability of the powders (28).

Surface Energy Results

The surface tensions of the studied liquids are reported in Table III. These liquids are commonly used for the determination of the surface energy of powders; water and formamide are polar and bromonaphthalene is nonpolar. The surface energy dispersive and polar components of the surfaces calculated from the contact angle data are presented in Table IV. The polar component is further divided into acid (electron-acceptor) and base (electron-donor) components. The surface energy results of the drug and the polymers are closer to those of the nonpolar liquids than the polar liquids, which indicates that they are more dispersive than polar in character. The

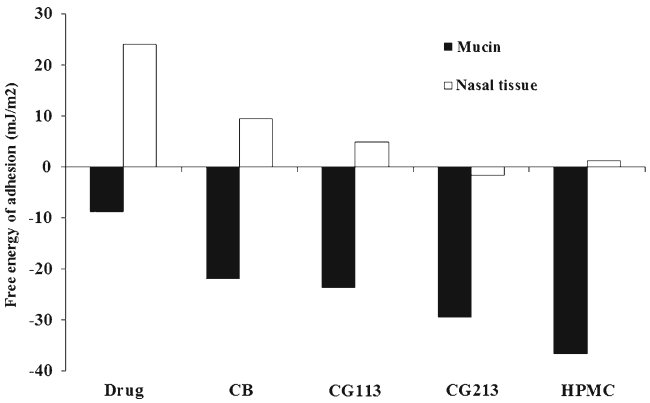

Fig. 2. Adhesive potential of the drug and the spray-dried polymers to mucin and nasal tissue

Table VI. Free Energies of Adhesion Among the Three Phases

Sample ID	Mucin/water/drug			Nasal tissue/water/drug		
	G^{LW}	G^{AB}	G^{total}	G^{LW}	G^{AB}	G^{total}
Amorphous drug	−5.19	−3.58	−8.77	−0.10	24.21	24.11
CG113	−5.20	−18.36	−23.56	−0.10	4.94	4.84
CG213	−5.19	−24.22	−29.41	−0.10	−1.43	−1.53
CB	−5.49	−16.31	−21.80	−0.11	9.56	9.46
HPMC	−4.78	−31.85	−36.64	−0.09	1.37	1.27
CG113-Zol1	−5.19	−3.53	−8.72	−0.10	24.76	24.66
CG113-Zol2	−5.20	−16.58	−21.78	−0.10	7.79	7.69
CG113-Zol3	−5.44	−15.07	−20.51	−0.11	10.57	10.47
CG113-Zol4	−5.43	−14.59	−20.02	−0.11	11.23	11.13
CG213-Zol1	−5.07	−4.75	−9.82	−0.10	20.62	20.52
CG213-Zol2	−5.47	−17.06	−22.54	−0.11	9.88	9.77
CG213-Zol3	−5.33	−23.32	−28.66	−0.10	−0.16	−0.27
CG213-Zol4	−5.36	−18.43	−23.79	−0.10	−2.83	−2.94
CB-Zol1	−5.01	−5.92	−10.93	−0.10	21.23	21.13
CB-Zol2	−5.30	−6.68	−11.98	−0.10	21.17	21.06
CB-Zol3	−5.31	−9.65	−14.96	−0.10	16.61	16.50
CB-Zol4	−5.48	−14.90	−20.38	−0.11	11.38	11.27
HPMC-Zol1	−4.28	−14.96	−19.24	−0.08	18.15	18.07
HPMC-Zol2	−5.09	−20.24	−25.33	−0.10	13.11	13.01

most obvious difference between the drug and the polymers is in the AB surface energy results. The basic nature of zolmitriptan can be explained by the presence of a number of electron-donating sites (ethylamine side chain and carbonyl oxygen in the indol ring) in its structure (Fig. 1). This could be the reason for the more hydrophilic nature of the drug compared with the polymers in this study. Unlike HPMC, chitosans are able to interact with negatively charged sialic acid more easily than the drug, because of their extra electron-acceptor sites.

Effect of Polymer Type and Molecular Weight on Surface Energy

The total surface energy for chitosans is higher than that for HPMC. While there were no significant differences in the dispersive component, the polar contribution was significantly greater for the chitosans than for HPMC. Because HPMC is a non-ionic cellulose, contribution from polar groups was obviously not expected. Earlier studies have shown that charged polymers (*i.e.* cationic and anionic) are more mucoadhesive (29). Thus, the cationic nature of the chitosans provides an edge over HPMC with respect to mucoadhesion. Chitosan acetate has less acidic and more basic components than the other chitosans. It was also found that higher molecular weights of chitosan were associated with more acidic and less dispersive and basic components, which correlates with the increase in the number of positive charge sites.

Effect on Surface Energy of the Proportion of Polymer in the Formulation

The relationship between the surface energy components and the proportion of polymer in the formulations is shown in Table V (using R^2 for linear regression analysis). A poor correlation was observed for the dispersive components of CG113 and CG213, while a better correlation was observed for the acid and basic components. The correlations with all the surface energy components were better for CB. Further, increases in the molecular weight of chitosan led to poor correlations with the dispersive component. The surface

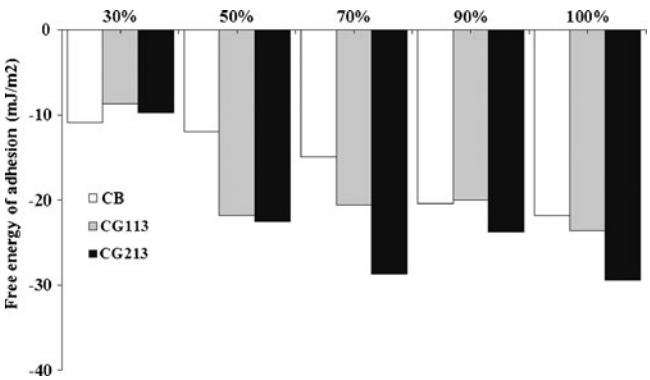

Fig. 3. Potential for the drug and chitosan formulations to adhere to mucin

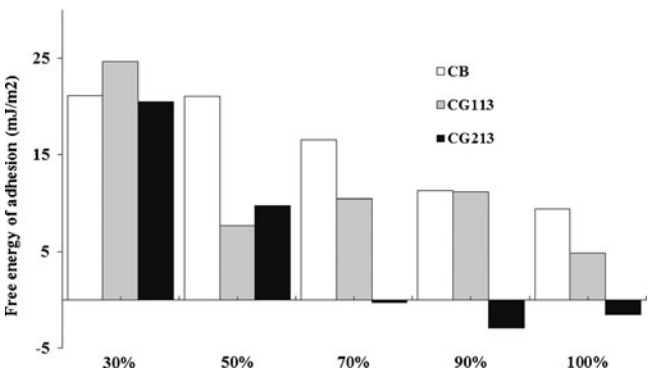

Fig. 4. Adhesion behavior between the drug/chitosan formulations and nasal tissue

energy components for CB were similar to those for the drug, resulting in only a minor impact on the surface energy of the solid dispersions. Further, higher chitosan proportions were associated with moderately increased polarity. The dispersions with higher proportions of polymers had a more balanced surface nature. It can be concluded that polymer content has an impact on the surface chemistry of the drug–polymer particles.

The Free Energy of Adhesion

A negative ΔG_{adh} between the surfaces is essential for adhesion to occur spontaneously. Accordingly, ΔG_{adh} values are inversely related to the potential for adhesion. Figure 2 shows the plot of ΔG_{adh}, showing the potential for the drug and polymers to adhere to mucin and nasal tissue (Table VI).

The ΔG_{adh} for zolmitriptan adhering to mucin or nasal tissue was higher than that for the other materials tested, possibly because of the strong electron-donating character of the drug's surface making adhesion to mucin or nasal tissue energetically unfavorable. ΔG_{adh} values for the chitosans were in the following order: CB > CG113 > CG213, decreasing as the molecular weight of the chitosans increased. The adhesion of HPMC to mucin had the lowest ΔG_{adh}. The ΔG_{adh} between the drug/polymers and mucin was lower than that between the drug/polymers and nasal tissue, indicating stronger adhesion to mucin than to nasal tissue. Spray-dried microparticles of chitosan have been shown to have a strong affinity to mucin, in agreement with our findings (22).

Figures 3 and 4 show plots of ΔG_{adh} for the adhesive potential between formulations containing chitosan and mucin or nasal tissue, respectively. In general, an increase in the polymer content of the formulations resulted in a decrease of ΔG_{adh}. Further, at higher content of polymer (>50%), ΔG_{adh} was lower for higher molecular weight chitosans, following the trend: CB > CG 113 > CG213. ΔG_{adh} values for the interaction between these formulations and mucin were more negative than those for nasal tissue, which indicates that the formulations are more mucoadhesive than bioadhesive. In line with our results, the content of chitosan has been shown to have an impact on the bioadhesive properties of spray-dried formulations in *in vitro* mucoadhesive tests (25). In summary, based on these results, formulations containing 50–70% of CG213 or HPMC appear to be an ideal choice when mucoadhesive formulation for nasal administration is required.

Several *in vitro* methods have been suggested for testing mucoadhesive properties of different materials. Indeed, none of these methods has provided consistent results rather helped in ranking various polymers or formulations by their mucoadhesive properties (3). As shown here, however, a simple, well-established approach based on thermodynamic theory appears to offer successful predictions of the adhesive behavior of powders prior to *in vitro*/*in vivo* studies. In our follow-up manuscripts, we will compare these theoretical predictions with *in vitro*, *ex vivo*, and *in vivo* results.

CONCLUSIONS

The aim of this study was to evaluate the surface energy of different formulations of an antimigraine drug, zolmitriptan, prepared by spray drying. The formulations contained different polymers in varied proportions. It was also our intention to study the theoretical potential for these formulations to adhere to mucin and nasal tissue. Following the van Oss method, contact angle measurements were used to estimate the surface energy components. The free energy of adhesion was determined by application of the theory of thermodynamics in order to estimate the affinity of these materials to the biological substrates.

All the tested materials had higher proportions of dispersive than polar components. The acid component increased as the molecular weight of the chitosans and their content in the formulations increased. In contrast, an inverse relationship was observed with the basic component. The free energies of adhesion between the formulations and mucin were more negative than between the formulations and nasal tissue. The adhesive potential of the materials was favorable when the molecular weight of chitosan and its content in the formulation were increased. This approach offers a guide for the selection of optimal formulation constituents for future complicated, and therefore expensive, *in vitro* or *ex vivo* experiments.

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