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Mucoadhesive Tablets for Buccal Administration Containing Sodium Nimesulide

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The possibility of improving the flux of nimesulide across the buccal mucosa using the drug in the form of a sodium salt was investigated in our study. The salt form may increase to flux across buccal membrane, starting from a suspension; its lower permeation coefficient is compensated by a higher concentration gradient. The salt was inserted into a mucoadhesive tablet for buccal administration. The tablets were designed to prevent the loss of the drug into the saliva by means of a protective layer and placed on the area not in contact with the mucosa. Ten volunteers were used. The in vitro release from mucoadhesive tablets was examined through a porcine buccal mucosa, using a standard Franz cell, modified for present purposes. The advantages of a higher concentration gradient for the flux, related to a higher solubility of the salt, and to a sufficiently high permeation coefficient of the drug, despite the ionized form, could not be completely exploited, because the composition of the formulation destroys the chemical form of the drug.

Keywords Buccal Administration, Carbomer, Mucoadhesive Tablet, Permeation Coefficient, Protective Layer, Sodium Nimesulide, Solubility

Many authors have demonstrated that topical administration of non-steroidal anti-inflammatory drugs (NSAIDs) may be a safe and effective alternative to oral or rectal routes, especially for local disease therapy (Gupta et al. 1996; Sengupta 1998a, 1998b): for instance, buccal therapy can represent a useful tool in controlling acute and chronic stomatitis. This aspect may open new possibilities for the administration of NSAIDs in the oral cavity, particularly for those able to relieve pain in this district.

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Successful topical treatments of oral diseases are rare, due to the constant flow of saliva and the mobility of the involved tissues. Therefore, mucoadhesive formulations, which prolong the residence time and control the drug release toward the buccal mucosa, are expected to overcome these problems, and recently, buccal mucoadhesive tablets were developed containing a variety of drugs (Ceschel et al. 2001a, 2001b; Codd and Deasy 1998; Maggi et al. 1999). Nimesulide was found a convincing candidate for an effective therapy at this level, because of its analgesic activity (Biscarini, Patoia, and Del Favero 1988; Singla, Chawla, and Singh 2000a; Swingle, Moore, and Grant 1976). From a study on pain associated with dental operations, nimesulide was found better than ketoprofen in relieving pain (Pierleoni, Tonelli, and Scaricabarozzi 1993); nimesulide (100 mg per day), as compared with naproxen (250 mg per day), was found to be more effective in reducing pain intensity in patients who underwent maxillofacial surgery (Ferrari Parabita 1993).

In a previous work (Ceschel 2001a) a mucoadhesive tablet was developed containing nimesulide in its acidic form for local administration to the gingival mucosa of the upper jaw. Tablets thus designed ensured the drug release through the mucosa from the mucoadhesive layer, but the dose released was found too low. The aim of this new study was to investigate improving the flux of nimesulide through the buccal mucosa, increasing the solubility of the drug by employing its sodium salt. This idea was supported by the fact that the flux through the buccal mucosa of the nimesulide in its ionized form was found much higher than that of the unionized form. Therefore, the properties of the sodium salt of the drug, extemporarily prepared were exploited. Nimesulide was wet-granulated with lactose and a stoichiometric amount of sodium hydroxide, and the final material was used to prepare tablets with the same formulation previously tested to have a suitable comparison between the two formulations.

MATERIALS AND METHODS

Chemicals

Nimesulide was a gift from Dompè S.p.A. (L'Aquila, Italy); lactose was a commercial sample (Aldrich S.p.A., Milan, Italy); carbomer 941, hydroxypropyl cellulose, carboxymethyl cellulose calcium, povidone K 30, talc, and magnesium stearate (Eigenmann and Veronelli S.p.A., Milan, Italy) were used as supplied.

Preparation of Sodium Nimesulide

Nimesulide was wet-granulated with a preselected amount of lactose and the equivalent quantity of solid sodium hydroxide; a few drops of water were added to facilitate the acid/base reaction and to knead the mass. Granules were obtained by extrusion of the humid paste through a sieve and dried in oven at 40°C for 72 hr.

Manufacturing Tablets

Tablet components for mucoadhesive layer (Table 1) were mixed together, then granules containing the drug, prepared as described above, were added and accurately mixed. The final mixture was slightly compressed in a Korsch single punch tabletting machine (mod. EKO) to obtain an intermediate tablet. Similarly, the components of the protective layer were mixed together. While the composition of the mucoadhesive mixture was kept constant, four different formulations for the protective layer were examined (Table 2).

The selected amount of each formulation was carefully placed over the intermediate tablet and the two parts compressed to obtain the final form. Some technological parameters for the tablets obtained using the four formulations are listed in Table 3. The size and the weight were calculated measuring 10 tablets with an electronic calliper and analytical balance.

Analysis

The concentration of nimesulide, during the release, was determined using an HPLC device (Model 305, Gilson) equipped with a variable-wavelength UV detector (model Spectra 200, Spectra-Physics). A Nova-Pak C18 (150 × 3.9 mm, 4 μm, Waters) column was used. Elution was carried out at room temperature with a mobile phase obtained mixing a buffer solution (di-hydrogen potassium phosphate 0.025 M buffer, adjusted to pH 3 with phosphoric acid) (45%) and Acetonitrile (55%); the injection volume was 10 μl. The flow rate was 1.2 ml/min and the detection was at 230 nm. In these conditions the retention time of nimesulide was 6.58 min.

TABLE 1
Composition of the mucoadhesive layer

Components	Amount mg (%)
Sodium nimesulide	12.26 (20.43)
Lactose monohydrate	10.85 (18.08)
Carbomer 941	10.85 (18.08)
Hydroxypropyl cellulose	10.85 (18.08)
Carboxymethyl cellulose calcium	10.85 (18.08)
Povidone K-30	2.16 (3.6)
Talc	2.418 (3.6)

TABLE 2
Four compositions for the protective layers for the bilayered tablets

		Formulations			
Components		1	2	3	4
Hydroxypropyl cellulose	mg	20.35	44.77	12	22
	%	40.7	40.7	20	20
Carboxymethyl cellulose	mg	20.35	44.77	28.5	52.25
Calcium	%	40.7	40.7	47.5	47.5
Povidone K-30	mg	7.8	17.16	15.3	28.05
	%	15.6	15.6	25.5	25.5
Magnesium stearate	mg	—	—	2.1	3.85
	%	—	—	3.5	3.5
Talc	mg	1.55	3.41	2.1	3.85
	%	3.1	3.1	3.5	3.5

Sodium Nimesulide Solubility Test

Sodium nimesulide suspension, obtained adding an excess of the prepared granules to HPLC-grade water, was heated to 50°C to dissolve the drug and then mantained at 37 ± 0.5°C for 24 hr. Aliquots of about 2 ml of the suspension were filtered through Millipore filters (W-13-2, Tosoh Company), suitably diluted, and then analyzed by HPLC to determine the solubility of the salt in these conditions.

Tissue Preparation

Porcine buccal mucosa, with a fair amount of underlying connective tissue, was surgically removed from the oral cavity of a freshly killed male pig (30–50 Kg) obtained from a local slaughter house (CLAI, Imola, Italy). The buccal mucosa was placed in ice-cold phosphate buffer 0.15 M. The connective tissue of the mucosa was carefully removed using fine-point forceps and surgical scissors. The cleaned buccal mucosa membrane was then placed in ice-cold pH 7.4 phosphate buffer 0.15 M for 12 hr, cut in squared portions, and used in the diffusion cell. The thickness of the porcine buccal mucosa (1.0 ± 0.1 mm) used in the experiments was measured by an electronic calliper (Franz 1975).

In Vitro Permeation Studies from a Sodium Nimesulide Suspension

The in vitro permeation studies were carried out in a standard Franz diffusion cell having 0.64 cm^2 diffusion area (Franz 1975;

TABLE 3
Technological parameters of the final tablets of different formulations

	Formulation			
Parameter	1	2	3	4
Diameter (mm)	9.15 ± 0.25	9.05 ± 0.12	9.12 ± 0.23	9.04 ± 0.15
Thickness (mm)	2.35 ± 0.45	2.46 ± 0.46	2.35 ± 0.56	2.46 ± 0.12
Total weight (mg)	109.56 ± 3.23	171.22 ± 2.28	110.15 ± 6.32	170.33 ± 5.36

Values are a mean of 10 tablets.

Friend 1992): the porcine buccal mucosa was clamped between the donor and receiving compartments. The donor cell (1 ml) was filled with a suspension of ionized nimesulide. The receiving compartment (4.8 ml) was continuously stirred at 600 rpm using a Teflon-coated magnetic stirrer. The whole apparatus was maintained at 37°C by a jacket surrounding the cells and circulating water from a thermostated external bath.

The amount of the drug released and permeated was determined by removing aliquots of 2 ml from the receptor compartments, using a syringe and immediately replacing the same volume of solution. The samples were transferred to volumetric flasks and stored in a refrigerator until their analysis. Sampling schedule was 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hr. All experiments were carried out in triplicate.

In Vitro Release Test

The tests were carried out in the Franz diffusion cell (Figure 1), where the lower compartment was filled with artificial saliva to simulate the oral cavity, whereas the upper compartment was filled with 1 ml of a pH 7.4 phosphate buffer to simulate the blood circulation. The porcine buccal mucosa was clamped with the external surface turned versus the lower compartment. The mucoadhesive layer was placed adherent to the external mucosal surface (lower compartment), while the protective layer was in contact with the artificial saliva. The tablet fitted the circumference of the lower compartment. The solution in the lower compartment was continuously stirred at 600 rpm, using a Teflon-coated magnetic stirrer, to simulate the mechanical movements

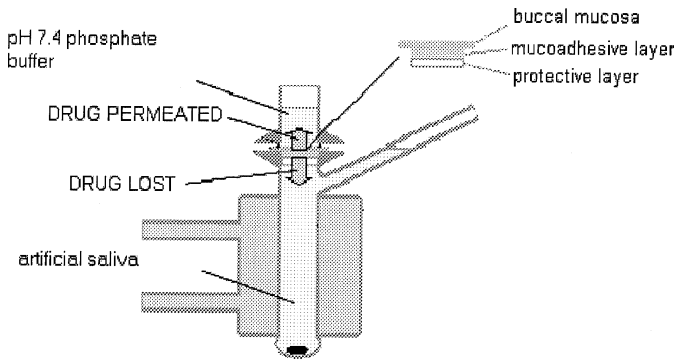

FIG. 1. Structure of the Franz diffusion cell, suitably adapted to present purposes.

of the mouth. The released nimesulide, which had reached the simulated oral cavity (across the faces of the protective layer), was determined by removing aliquots of 2 ml from the lower compartments, as described. All experiments were carried out in triplicate.

Experimental data for this last experiment were fitted with the following equation:

$$\ln M_t/M_\infty = \ln k + n \ln t \quad [1]$$

where M_t/M_∞ is the fraction of drug released at time t (hr), n is the diffusion exponent, and k is the constant apparent release rate (% min^{-1}) (Ritger and Peppas 1987).

In Vitro Permeation Test from the Final Tablets

This test was carried out at the same conditions as described for the in vitro release test. The lower compartment was filled with artificial saliva, while the upper compartment was filled with 1 ml of a pH 7.4 phosphate buffer. The amount of drug permeated through porcine buccal mucosa was determined by extracting the whole solution of the upper compartment. The samples transferred into volumetric flasks were stored in a refrigerator until they were analyzed. Sampling schedule was 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hr for the two compartments. All experiments were carried out in triplicate.

In Vivo Mucoadhesion Test

Then, 10 healthy volunteers were instructed to finish breakfast (consisting of an Italian breakfast) no later than 9.00 am. At 30 min later, the mucoadhesive tablet was placed on gingival region of the right upper canine and fixed for 1 min with a slight manual pressure on the lip; the tablet was let to moisten by the saliva to prevent its sticking to the lip. A standard meal was given in the period of 240–270 min after administration of the tablet. During the experiments the volunteers were allowed to drink water *ad libitum* from 60 min after administration of the tablet. After 480 min administration, the volunteers removed the residual tablet and were asked to record their remarks regarding their experience with the tablet (irritancy, taste, comfort, dry mouth, salivation, and heaviness).

RESULTS AND DISCUSSION

In a previous study (Ceschel 2001a) a mucoadhesive tablet for buccal administration was designed containing nimesulide,

the encouraging results suggested to improve this formulation by increasing the flux of the drug across the mucoadhesive layer. An important parameter to estimate the solubility of the drug was to create a notable concentration gradient promoting the flux. The formation of pharmaceutical salts is widely studied and used, besides other purposes, just to increase the solubility of an acidic and basic drug, even though this step requires further processing of the drug. Nimesulide behaves as an acid, but it differs from most NSAIDs because its acidic function is a sulphonanilide, activated by the presence of a p-NO_2 in the molecular structure, rather than a carboxylic group. This also creates a minor keratinolitic effect. As a consequence the possibility exists to transform the drug into a salt form, as it was previously observed for other drugs of similar structure (for instance, tolbutamide).

Before using the chemical form of a salt for nimesulide in the mucoadhesive formulation, it was necessary to clarify the preparation of the salt and its permeation capacity. The salt was prepared by granulating the acidic drug together with the equivalent amount of sodium hydroxide in the preliminary step of the overall preparation, in the presence of lactose, as an excipient. This way, for possible practical applications of this formulation, additional steps could be avoided.

The nimesulide solubility in the form of sodium salt (associated to lactose) was found to be 2501 ± 1 μg/ml, much higher than the corresponding value of the free acid: 1.98 ± 0.02 μg/ml, obtained at low pH and in the same conditions (Ceschel 2001a). A saturated solution of the salt was used to measure the permeation of ionized nimesulide across a porcine membrane. The permeation is a passive diffusion process that can be described by Fick's law equation:

$$J_s = dQ_r/Adt \qquad [2]$$

where J_s is the steady-state membrane flux in μg/cm^2 per hr; dQ_r is the change in quantity of material passing through the membrane into the receptor compartment expressed in μg; A is the active diffusion area in cm^2; and dt is the change in time.

The permeation profile of nimesulide salt form is represented in Figure 2; for comparison the profile of nimesulide acidic form also inserted (Ceschel 2001a). Table 4 shows the calculated flux values for the suspensions and tablets permeations. It was observed that the flux of the salt is higher than that of the acid, an important result for further advancing of the work; a decisive role is played by the higher solubility of the salt, which ensures a higher concentration gradient in the donor compartment, driving the permeation.

These results support two additional facts. First, an indirect confirmation was obtained of the formation of the salt during granulation: the neat difference between the two profiles support the idea that they are related to two different chemical forms of nimesulide. Second, it was also obtained a direct proof that even in the charged form nimesulide retains a sufficient partition ability to guarantee its absorption.

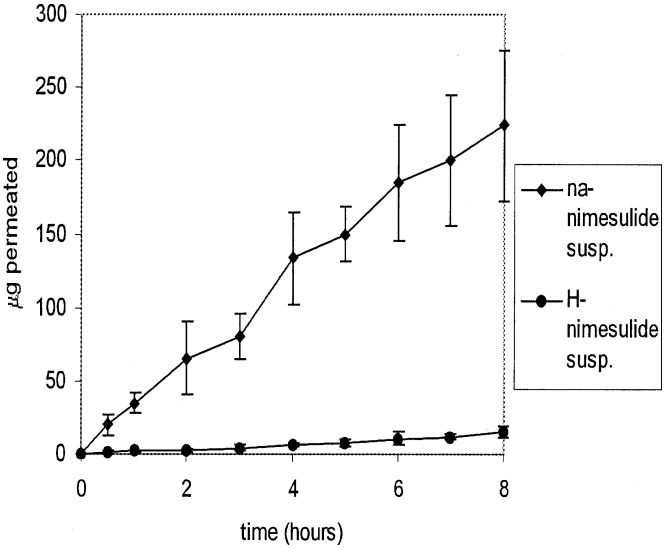

FIG. 2. Nimesulide permeation profiles from suspensions of sodium nimesulide and acidid nimesulide.

To determine the permeability coefficient of the ionized form, the following equation was used:

$$Kp = Js/Cd \qquad [3]$$

where Kp is the permeability coefficient, Js is the flux measured at the steady-time, and Cd is the donor concentration. The permeation constant of the ionized form of nimesulide was found to be 0.0175 cm/hr: this value is sufficiently high to ensure a permeation through the buccal mucosa. The same value for the free acid form (0.6960 cm/hr) is almost 40 times higher and indicates a superior permeation ability of the nimesulide molecule in its acidic form, with respect to the ionized form.

All these results supported the possibility of inserting sodium nimesulide into a mucoadhesive tablet and to obtain an

TABLE 4
Nimesulide fluxes from the (salt and acid) nimesulide suspension and from final tablets containing the salt and acid forms

		J (μg/cm^2 hr)
Flux from the suspension	Salt	43.775 ± 4.154
	Acid	1.379 ± 0.2840
Flux from the protected layer	1 salt	1.925 ± 1.003
	1 acid	1.244 ± 0.0174
	2 salt	1.669 ± 0.123
	2 acid	1.201 ± 0.0186
	3 salt	1.632 ± 0.910
	3 acid	1.383 ± 0.0121
	4 salt	1.586 ± 0.512
	4 acid	1.189 ± 0.0105

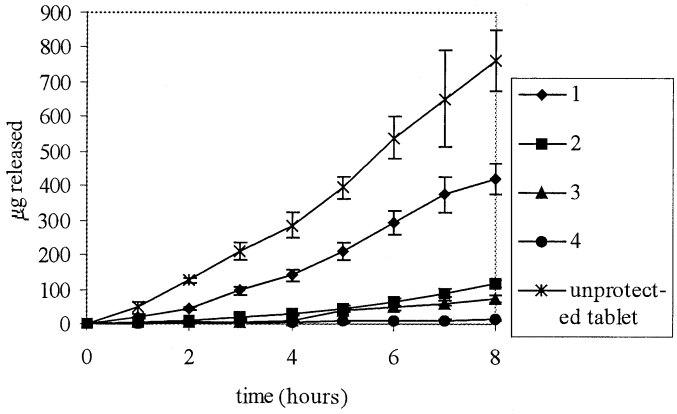

FIG. 3. Release profiles of nimesulide from the protected tablets (1, 2, 3, and 4) and from an unprotected one.

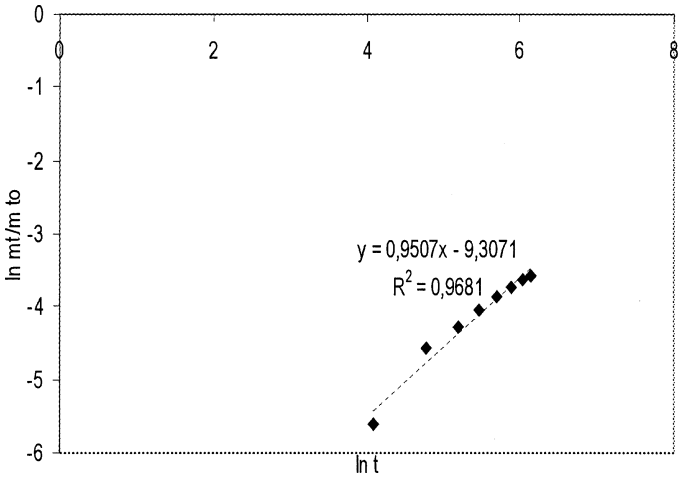

FIG. 4. Release profile of sodium nimesulide from a final unprotected tablet, according to equation 1 (time expressed in minutes).

important absorption of the active agent, when used for buccal administration.

Tablets were then modified to limit the release of the drug from all the face, except that in contact with the membrane: to this purpose four formulations were prepared and tested. Figure 3 shows the release of nimesulide from an unprotected tablet and from tablets protected by four different compositions designed for the protective layer. From the figure, it is evident that the amount to the drug released from unprotected tablets is higher, confirming the necessity of an efficient protective layer. Also the efficacy of the protective layer decreases the release of the drug, but the four formulations are not equivalent.

The amount of nimesulide lost from the protective layer was found very high for formulation 1. For this reason in formulation 2 the protective layer had a double thickness. This modification lowered the amount of drug lost through the protective layer, but it was still at too high values with respect to that permeated through the buccal mucosa. Formulation 3 was therefore changed and this modification lowered the loss of the nimesulide up to 4 hr; this layer was therefore doubled in formulation 4. This modification practically stopped the loss of the drug: after 8 hr the drug lost was $<0.01\%$ of the total amount and formulation 4 was used for further tests.

The tablet enables a prolonged and constant release, as desired for this pharmaceutical form: Figure 4 shows the plot of $\ln M_t/M\infty$ versus ln t. The profile is linear ($r^2 \geq 0.99$): n value of Equation 1 (0.95) indicates a non-Fickian release with a Case II transport, according to Ritger and Peppas (1987). In other words, the dominant release mechanism from the mucoadhesive formulation is the diffusion of the drug through the swelled polymer gel matrix; in addition, the release in a constant mode provides a prolonged effect.

To determine the mucoadhesive potential of different polymers, several techniques are available (Park, Cooper, and Robinson 1987; Ponchel et al. 1987; Peppas and Mikos 1989), mostly involving the measurement of adhesive strength. Because some results (Bouckaert, Lefebvre, and Remon 1993) were not reliable for an in vitro/in vivo correlation, a direct in vivo test was performed using only samples, which showed a good protective behavior. Tablets used for the test revealed adequate comfort and good compliance by the volunteers and no irritation was recorded no case of dry mouth or severe salivation at the place of attachment, or taste alteration, or heaviness were reported. The mucoadhesive layer swelled forming a gel, while the protective layer remained intact; it was not necessary to remove the tablet before the end of the experiment since it did not cause irritation.

Finally release through the mucoadhesive layer was tested directly in contact with the membrane. A surprising side result was that the flux was decisively lower than expected, and this can be clearly seen when the flux obtained from a final tablet (formulation 4) was plotted together with that obtained for the sodium nimesulide suspension (Figure 5). Moreover, the behavior of the tablet containing sodium nimesulide showed only a small difference, when compared with the tablet containing the drug in its acidic form (Table 4).

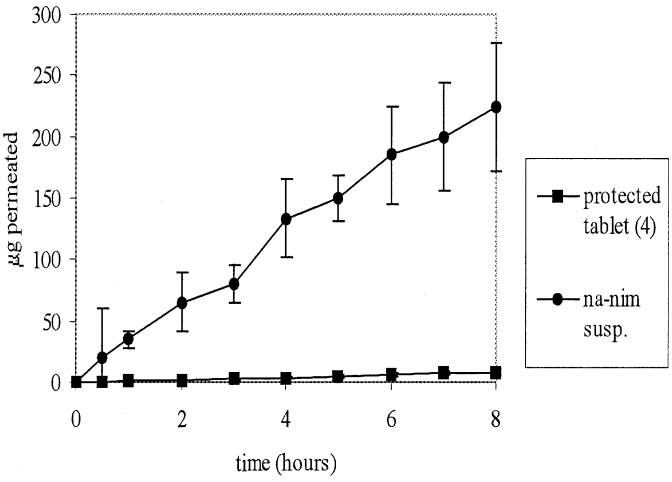

FIG. 5. Permeation profiles of sodium nimesulide from final tablet (formulation 4) and from the sodium nimesulide suspension.

CONCLUSION

Three data emerge from the examination of the overall behavior of tablets:

1. The flux from the salt suspension is much higher than that observed for a suspension, where nimesulide is in the acidic form: the lower permeation coefficient of the ionized form is more than largely compensated by a higher concentration gradient. The main result is that the salt form does not prevent permeation.
2. The permeation from the free suspension is much more efficient than that from the tablets, because it occurs in the absence of any hinderance, related to the formulation (such as the protective layer on one face and the mucoadhesive layer on the other face of the tablet).
3. Final permeation results for sodium nimesulide are of the same order of magnitude as in free acid, when the tablet formulations are concerned, apparently frustrating all the preparatory tests. On one hand, this result was unexpected considering the high parameters obtained (permeation constant and concentration gradient) for the salt form; on the other hand it could have been supposed, because we decided to maintain the same formulation previously chosen for acidic nimesulide. In fact this contains an acidic excipient, such as carbomer, due to its well recognized mucoadhesive ability. This excipient acts as a levelling factor neutralizing the nimesulide anion, when this chemical form diffuses from the inner tablet toward the mucoadhesive layer to permeate.

Carbomer (USPNF XXII) has mucoadhesive properties: by localizing the drug to its site of absorption, the polymer increases the local drug concentration and results in a more rapid and complete bioavailability of the active agent (Singla, Chawla, and Singh 2000b). Beside these important technological properties that make carbomer an important tool of oral mucoadhesive controlled drug delivery systems, its chemical behavior, because of its carboxylic groups, somehow limits its applications related to its interaction with basic or drug in the form of salts. Its acidic structure causes protonation of weak anions or basic center of a drug, thus modifying the starting chemical form and affecting the release. This interaction is not always appreciated in the physical mixtures or after compression into tablets. On the contrary, acid-base reactions are easily evidenced in aqueous solutions. In our case the protonation of the salt represents a clear case of incompatibility between the active agent and the excipient. To explore further the potentiality of the sodium nimesulide to permeation, a different formulation is under study, lacking an acidic component such as carbomer, but maintaining the same adhesive properties.

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