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Preformulation activities of intranasal dosage forms of temazepam

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Abstract

Bioadhesive excipients are used in intranasal drug delivery to prolong the residence time of formulations at the absorption site with the aim of improving the biopharmaceutical properties of the active drug. Bioadhesive starch, obtained by a high energy grinding process starting from a waxy starch (that does not possess any bioadhesive properties), has been employed to prepare different intranasal temazepam-starch formulations. Physico-chemical characterization of these formulations has been performed by means of rheological, thermal, chromatographic and particle size distribution tests both after the preparation processes and during a 6-month storage period in different temperature and relative humidity conditions. All formulations revealed good bioadhesive properties after the manufacturing processes and a good chemical and physico-chemical stability during aging.

Keywords: Intranasal administration; Bioadhesive formulation; Starch; Grinding; Temazepam; Stability

1. Introduction

In recent years, the possibility of using intranasal administration of drugs for systemic medication has received a great deal of attention as an alternative to the parenteral route, mainly for those substances that are poorly absorbed orally or extensively metabolized either in the gastro-intestinal tract itself or are subject to first pass metabolism in the liver.

However some problems are related to this route of administration. Among them, the enzymatic degradation that may occur at the absorption site, and the rapid clearance of nasal formulations from the potential absorption surface in the nose have, of course, a major role in giving low bioavailabilities (Schipper et al., 1991).

In order to promote absorption and improve the bioavailability of an active drug administered by the intranasal route, the physico-chemical state of the drug and the use of particular excipients have to be considered during preformulation activities. The incorporation in a nasal formulation of substances able to decrease mucosal enzymatic degradation, to alter in a reversible way the nasal mucosa permeability or to increase the residence time of the drug at the absorption site, can help

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the formulator in obtaining preparations with good biopharmaceutical performances. For that reason, the use of bioadhesive systems is a solution prolonging the contact time between the formulation and the absorption membrane and, as a consequence, improving the onset and duration of the pharmacological effects (Harris and Robinson, 1990).

Bioadhesion is defined as the ability of a material to adhere to a biological tissue for an extended period of time (Peppas and Buri, 1985; Longer and Robinson, 1987). The drug delivery system is localized on the surface of the biological membrane using natural and synthetic polymers that are able to physically and chemically interact with the surface. The first step of interaction is an intimate contact established between the bioadhesive and the membrane that allows the penetration of the bioadhesive material into the crevice of the tissue surface and the interpenetration of its chains with those of the mucus (Duchene et al., 1988). Other forces of attachment, such as electrostatic interaction, hydrogen bonding and hydrophobic intercalation, are then coupled with the simple mechanical interlocking (Robinson, 1989).

Several polymers have been tested and described in the literature as possessing bioadhesive properties. Among them polyacrylates, cellulose derivatives (Smart, 1984; Lehr, 1990) and, more recently, pregelatinized and modified starch are described in scientific and patent literature for their bioadhesive characteristics.

Pregelatinized starches are thermally modified starches in which the native structure of the grains have been destroyed by means of a technological process (Guyot-Hermann, 1990). Several approaches are described for inducing gelatinization on starches starting from a watery starch suspension, like spray-drying, roll drying and drum drying techniques (Bottenberg et al., 1990). More recently, gelatinization has been obtained by simply milling native starch via a high-energy process (De Ponti et al., 1994).

This pregelatinized starch has been used as excipient in an intranasal formulation containing temazepam, a 1,4-benzodiazepine already marketed for the symptomatic treatment of the compliant of insomnia. Hypnotic drugs are widely used therapeutically to induce and/or to prolong sleep. Administration is generally performed either parenterally or, more usually, orally. When administered orally, these drugs are inefficiently and variably absorbed and the onset of their pharmacological activity greatly depends on the dosage form, e.g. hard or soft gelatin capsules (Fuccella et al., 1972, 1977).

It has been demonstrated that nasal administration of benzodiazepine results in an improved pharmacological activity with respect to oral administration. In fact using suitable nasal carriers it is possible to obtain a faster onset and more pronounced blood concentration of hypnotic than conventional forms of administration (Goldberg, 1988).

The use of a bioadhesive excipient in such intranasal formulations could promote an elevated and more constant hypnotic effect. The aim of this work has been a preformulation study of some intranasal formulations containing temazepam and a bioadhesive starch, obtained with different technological preparation processes.

2. Material and methods

Waxy starch SF04201 was supplied by Cerestar, Milan, Italy and temazepam by Carlo Erba Reagenti, Milan, Italy. The bioadhesive starch (A) used in formulations with temazepam was obtained in our laboratory by grinding the waxy starch SF04201 in a high energy mill.

Hard gelatin capsules size 2 were supplied by Capsugel, Lainate (Milan), Italy. Polypropylene capsules suitable for an original unidose intranasal device for powdery formulations were kindly provided by Bespack, Norfolk, UK. Capsules were sealed in aluminium blisters.

2.1. Preparation techniques

2.1.1. Preparation of bioadhesive starch

A 2-kg portion of waxy starch SF04201 was put in the high energy Sweco Vibro-Energy® mill equipped with 60 kg of cylindrical shaped grinding media (height 12.7 mm, base radius 6.3 mm) made of high density alumina and ground for 6 h.

The material obtained (A) had bioadhesive properties.

2.1.2. Preparation of bioadhesive formulations with temazepam

Four different techniques were evaluated to prepare bioadhesive formulations containing temazepam: grinding, spray-drying, granulation and physical mixing. In each formulation the weight ratio between starch and temazepam was respectively about 3:2.

Grinding

Preparation TEM1: 1 kg of bioadhesive starch (A) was mixed with 0.7 kg of temazepam and the mixture was ground for 1 h using the high energy Sweco Vibro-Energy® mill equipped with 60 kg of cylindrical shaped grinding media (height 12.7 mm, base radius 6.3 mm) made of high density alumina. Preparation TEM2: 1 kg of waxy starch SF04201 was mixed with 0.7 kg of temazepam and the mixture was ground for 6 h under the same conditions used for TEM1.

Spray-drying

Preparation TEM3: 100 ml of a water suspension containing 10 g of waxy starch SF04201 and 6.6 g of temazepam was spray-dried using Lab-Plant SD-04 equipment. The process parameters were set as follows: inlet temperature, 140°C; outlet temperature, 80°C; blower pressure, 1.25 kg/cm^2; nozzle diameter, 0.5 mm; flow rate, 4 ml/min.

Granulation

Preparation TEM4: 180 g of bioadhesive starch (A) and 120 g of temazepam were cosieved and mixed. The mixture was compressed and then reduced to granules by passing through a 80-micron screen.

Physical mixing

Preparation TEM5: 4 g of bioadhesive starch (A) and 6 g of temazepam were cosieved and then mixed in a Turbula mixer for 20 min.

2.2. Analytical methods

2.2.1. Differential scanning calorimetry

Thermal analyses were performed with a Mettler DSC 20 with 40-μl open pans. The scanning rate was 10°C/min using nitrogen as purging gas (50 ml/min).

2.2.2. Thermogravimetry

Thermogravimetric analyses were carried out using a Mettler TG 50 thermogravimeter in alumina pans. The heating rate was 10°C/min using nitrogen as purging gas (100 ml/min).

2.2.3. Particle size distribution analysis

Particle size determinations were performed with a Galai CIS-1 system. Samples were analyzed in silicon suspension at least in triplicate.

2.2.4. Chromatography

HPLC analyses were carried using a Perkin Elmer liquid chromatograph equipped with a Partisphere C18 chromatographic column (length, 250 mm; internal diameter, 4.6 mm; average particle size, 5 μm) under the following experimental conditions: mobile phase methanol/water (+ 1% acetic acid) 60:40, flow rate 1 ml/min and analytical wavelength 232 nm.

2.2.5. Bioadhesion evaluation

In order to evaluate the bioadhesive properties of the preparations, viscosimetric tests were performed on solutions containing the formulation to be tested and on solutions of the formulation plus mucin according to Hassan's method (Hassan and Gallo, 1990). The measurements were carried out on isoviscous solutions.

Rheological tests were performed using a Bohlin CS Rheometer Apparatus equipped with coaxial cylinder and cone plate measuring systems. All measurements were carried out at 37°C at different shear rates (Caramella et al., 1994).

Two commercial polymers were used as standards: one with bioadhesive properties which were already known (pregelatinized starch Cerestar SF12410) and the other with no detectable bioadhesive characteristics (waxy starch Cerestar SF04201).

3. Results

A preliminary evaluation of possible interactions between temazepam and bioadhesive starch (A) was carried out using thermal analysis. A comparison of DSC patterns of temazepam,

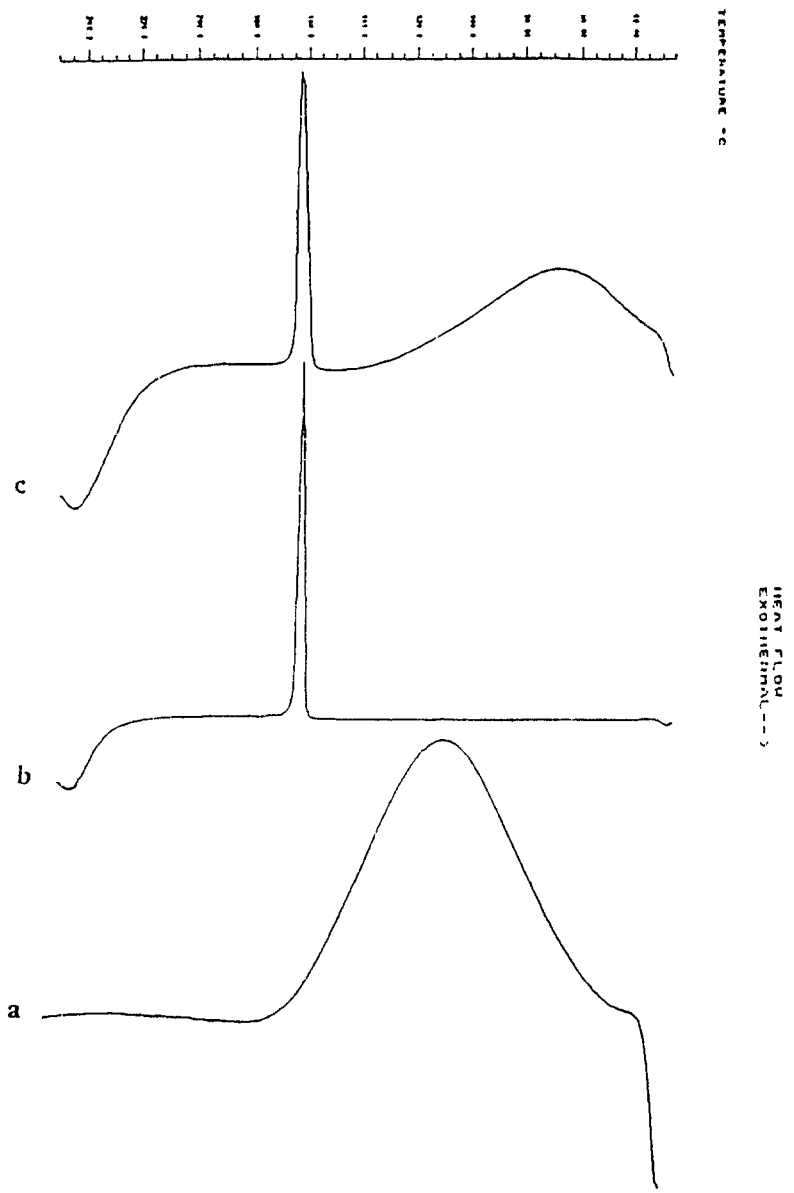

Fig. 1. DSC patterns of (a) bioadhesive starch (A), (b) temazepam and (c) their physical mixture.

bioadhesive starch (A) and their mixture did not reveal any incompatibility, as shown in Fig. 1.

As previously described, preformulation activities considered different preparation techniques. The grinding procedure was used to obtain an intimate mixture between the active drug and the bioadhesive excipient (A), as in the case of preparation TEM1, and also to evaluate the possibility of simultaneously transforming the non-bioadhesive waxy starch into a bioadhesive one and mixing it with temazepam, as in preparation TEM2.

The spray-drying technique was used to promote a solid dispersion of the active drug into the excipient, with the aim of obtaining an intimate mixture, and to study the possibility of operating the gelatinization of waxy starch without starting

from a watery suspension of a precooked and dried starch, as described in the literature.

The granulation process was carried out because it is a widely used procedure in the pharmaceutical industry to obtain a powder with good drug homogeneity and good flow properties, while the physical mixing was performed as a comparison with the other preparation techniques and to study the physical-chemical compatibility between temazepam and the bioadhesive excipient.

The DSC analytical method was also used for dosing temazepam residual crystallinity building up a standard curve on different physical mixtures of the drug with bioadhesive excipient (A). Upon plotting enthalpy changes (J/g) against the drug percentage in the mixture, a linear correlation was found (R^2 = 0.998).

DSC is extremely useful in determining in a quick and accurate way eventual changes in temazepam residual crystallinity that may occur both during manufacturing processes and with aging in different temperature and humidity conditions.

In fact one of the main disadvantages that can be coupled with grinding is the physical transformation of drugs and excipients. As an example, the amorphization of drugs can lead to high dissolution and biopharmaceutical performance due to the high energy activated state of the molecule but these properties may not be maintained with aging. In fact the effect of humidity and temperature could promote the transformation of the drug from an amorphous state into a crystalline one with subsequent decreased dissolution and biopharmaceutical performance. In addition, amorphization can be related to chemical instability of the active drug.

Table 1
Calorimetric analysis results for temazepam-bioadhesive starch (A) formulations

Formulation	Crystallinity (%)
TEM1	89
TEM2	90
TEM3	94
TEM4	99
TEM5	100

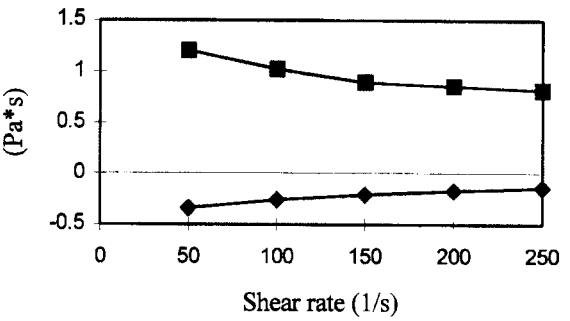

Fig. 2. Rheological synergism (Pa*s) measurements with mucin of waxy starch SF04201 (◆) and bioadhesive starch (A) (■).

In the case of temazepam-starch formulations, DSC analyses proved that manufacturing procedures caused neither crystallinity changes nor a significant amorphization of the active drug, when enthalpy changes of different formulations are compared with respect to the physical mixture as reference (100% crystallinity). Even when a grinding process was used, the quantity of the amorphous form was less than 10% (Table 1).

At the end of the preparation processes, all formulations were also characterized with HPLC, rheological, thermogravimetric and particle size distribution analyses.

Chromatographic determinations of temazepam (mean of 10 samples for each preparation) showed a good chemical strength and homogeneity for all formulations.

Rheological measurements on preparations were made and the data obtained were analyzed according to Hassan's method where the interaction between the material tested and mucus components, in particular mucin, is evaluated.

Hassan theorized that the viscosity of a polymer-mucin mixture could be considered as the resultant of different components like the polymeric viscosity, the mucin viscosity and a bioadhesion component due to the interaction between the two substances. This component is defined 'rheological synergism' and is equivalent to the difference between the mixture viscosity and a theoretical value obtained by the addition of the mucin and polymer viscosities: a positive value of rheological synergism indicates an interaction between mucin and polymer and is considered as an in vitro evaluation of mucoadhesion.

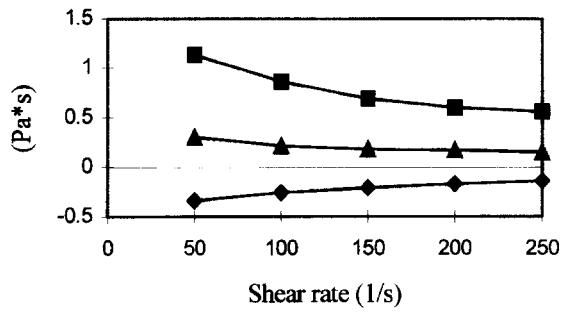

Fig. 3. Rheological synergism (Pa*s) measurements with mucin of formulations TEM1 (■) and TEM2 (▲) in comparison with waxy starch SF04201 (◆).

For preparations obtained with granulation and mixing techniques, both these processes are ineffective in modifying the physical structure of bioadhesive starch, and so the same bioadhesive properties were assumed as the ground waxy starch (A). As shown in Fig. 2, this excipient has a positive interaction with mucin.

The results of rheological analyses showed good bioadhesive properties for preparations obtained using a milling process (Fig. 3). However it has to be noted that the transformation of non-bioadhesive starch into a bioadhesive form is more efficient when the grinding process is performed without the active drug: preparation TEM2 shows a higher interaction with mucin than preparation TEM1, where the waxy starch was ground in the presence of temazepam.

Negative interactions between the spray-dried preparation and mucin revealed no bioadhesive property of this formulation (Fig. 4), indicating

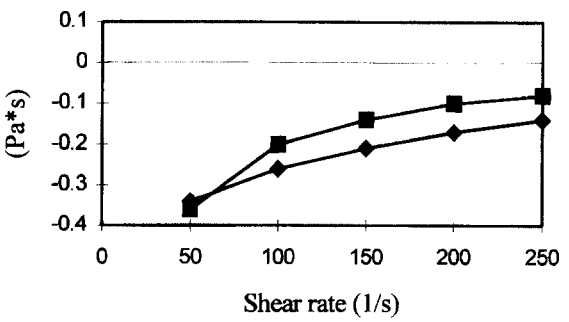

Fig. 4. Rheological synergism (Pa*s) measurements with mucin of formulation TEM3 (■) in comparison with waxy starch SF04201 (◆).

Table 2
Particle size distribution and thermogravimetric analyses for final temazepam-starch formulations

Formulation	Mean diameter (μm)	Water content (%)
TEM1	15.5	5.4
TEM2	9.6	6.1
TEM3	12.3	5.0
TEM4	26.2	6.2
TEM5	7.2	6.4

the ineffectiveness of this technique in inducing the gelatinization of waxy starch starting from a non-precooked and dried material.

The results of particle size distribution and thermogravimetric analyses are reported in Table 2.

The water content of temazepam-starch formulations is between 5 and 6.5% and this is important because adhesion properties are dependent on the degree of hydration of the polymer. The presence of water inside the formulation facilitates the possible interactions with mucosal membranes: bioadhesive polymers exhibit poor adhesive characteristics when dry while their hydration results in the relaxation of the stretched, entangled or twisted molecules, which are able to liberate and expose their adhesive functional groups responsible for bioadhesive interactions.

After their characterization, all preparations were packaged into hard gelatin capsules, which can be used for commonly employed systems for intranasal administration of drugs, and into polypropylene capsules suitable for a specific device for nasal administration of powders and available, at the moment, only as a prototype. Each capsule contained 10 mg of active drug.

Capsules were sealed in aluminium blisters and underwent stability testing under different temperature and relative humidity (R.H.) conditions. During storage, chemical stability and any physico-chemical changes occurring during aging were evaluated.

The chemical stability results (Table 3) showed a good active drug chemical stability without meaningful differences either among the preparations or between the two types of packaging. Chromatographic analyses did not show either correlative substances or degradation products.

Table 3
Chemical stability results (%) of temazepam-starch formulations packaged into (a) hard gelatin and (b) polypropylene capsules stored under different temperature and humidity conditions

Formulation	1 month at 55°C		3 months at 45°C		6 months at 35°C + 75% R.H.	
	(a)	(b)	(a)	(b)	(a)	(b)
TEM1	102	102	102	103	100	99
TEM2	99	99	97	98	99	98
TEM3	100	96	99	97	98	97
TEM4	100	99	97	100	98	96
TEM5	100	100	100	101	98	98

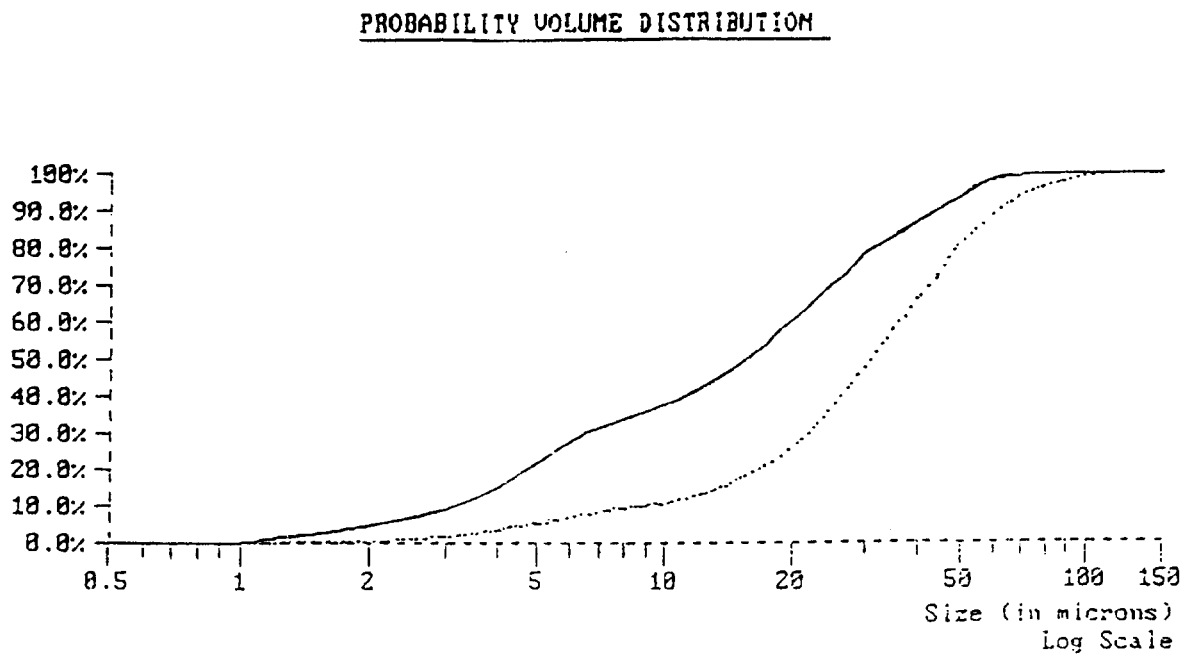

Fig. 5. Particle size distribution curves of preparation TEM1 after manufacturing process (——) and after a storage of 3 months at 45°C (· · ·).

Moreover thermogravimetric and calorimetric analyses did not reveal water content and crystallinity changes during aging not even in high relative humidity conditions.

Compatibility between the active drug and the bioadhesive starch was also confirmed using the DSC technique: no changes in morphological features of peak or in the value of the melting point of temazepam were seen.

Finally, particle size distribution analyses of all preparations were made during aging. Particle size distribution curves of the preparations obtained by spray drying and granulation techniques and stored for 3 months at 45°C are practically the same as at the beginning of the stability test, while in the case of preparations obtained by grinding we noted that the particle size distribution curves were shifted towards larger particle size values. An example is reported in Fig. 5. In these preparations, packaging and/or aging caused agglomeration of the finer portion of mixture components probably

due to a larger superficial area induced by the grinding processes. Despite these variations, the particle size distribution stays in a range compatible with intranasal administration of powders.

4. Conclusion

The possibility of transforming a non-bioadhesive waxy starch into a bioadhesive one by a simple, low cost process like high energy grinding, proves to be very interesting in the pharmaceutical industrial field. This kind of excipient can be used not only for intranasal administration but also when bioadhesive interactions could be important in improving biopharmaceutical performances of a drug formulation.

Bioadhesive starch obtained by grinding can be easily employed in preparation processes widely used in the pharmaceutical industry, to obtain different powdery formulations, as demonstrated with temazepam-starch systems.

Physico-chemical characterization of these preparations showed a good compatibility between the excipient and the active drug and good bioadhesive properties for all formulations, also indicating the possibility of simultaneously transforming a waxy starch into a bioadhesive one and its intimate physical mixing with temazepam using the same grinding process.

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