DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(7), 1159-1169 (1987)

FORMULATION STUDIES OF A NEW NOSCAPINE EMBONATE PREPARATION

V.Haikala, M. Marvola[x] and A. Sothmann
University Pharmacy, Helsinki and
[x]School of Pharmacy, University of Helsinki,
Helsinki, Finland

SUMMARY

Noscapine embonate (1:1), a new noscapine pro drug, was found to be very slightly soluble in water in the approximate pH range 4 to 7. Below this range, the salt began to decompose and release noscapine. When the embonate was suspended in water with polyvidone at pH 5.0 to 5.5, suspensions containing spherical microparticles were produced. Increasing the amount of polyvidone caused the embonate to dissolve completely. Polyvidone had a marked effect on the stability of the suspensions. When 0.5% of polyvidone was used with conventional flavouring agents, the average particle size of the salt was about 2 to 3 μm. No appreciable change in size was observed during a 4 week period. The particles settled slowly and the sediment was easy to redisperse after 6 months' storage. The taste of a formulation containing noscapine embonate and flavouring agents was compared with that of the most popular liquid noscapine hydrochloride preparation in Finland. The formulation developed was significantly more acceptable than the reference preparation ($p<0.01$).

INTRODUCTION

Noscapine is a naturally occurring opium alkaloid of the benzylisoquinoline group. Apart from its antitussive effect, noscapine has no

significant action on the CNS in doses within the therapeutic range. It is widely used in liquid cough medicines as its water-soluble hydrochloride salt, which has a bitter taste. Because taste acceptability is of primary importance in modern medicine, such a formulation may discourage the use of this potent drug.

The aim of this study was to develop a new suspension formulation of noscapine containing the drug as the slightly soluble embonate (1:1), which does not have an unpleasant taste. Polyvidone, a nonionogenic macromolecular dispersing and suspending agent, was used to produce spherical microparticles of the drug and stabilize the suspension.

A patent for this formulation has been applied for[1].

MATERIALS AND METHODS

The polyvidone (Fluka AG) had a mean molecular weight of 40 000. It was used as a 20% solution in water and was freshly prepared before use. The noscapine hydrochloride (Ph.Eur.) was dried before use at 105°C. The embonic acid (Fluka AG) was pure grade and the potassium hydroxide (EKA) of reagent grade. Citric acid, ammonium chloride and hydrochloric acid were of Ph.Eur. grade. The sorbitol solution (AKL-PM) was a 70% solution of sorbitol in water. The liquorice solution was made of extractum glycyrrhizae (Leiras) (500 parts), water (500 parts) and methyl parahydroxybenzoate (1 part). The anise oil was of Ph.Nord. grade. The spiritus menthol (Dispensatorium Fennicum) consisted of 2% menthol in diluted ethanol (62%) (Oy Alko Ab).

Decomposition of noscapine embonate as a function of pH

Noscapine embonate was prepared by dissolving 1 mol of noscapine hydrochloride in dilute hydrochloric acid and 1 mol of embonic acid in dilute potassium hydroxide solution. A yellow precipitate was formed by mixing the two solutions at pH 5.5. After washing the precipitate with water until it was free from chlorides, it was dried at 70°C.

Six 200 mg samples of the dried precipitate were tarnsferred to six 200 ml Erlenmayer flasks. Fifty millilitres of water were added

to each and the pH values were adjusted to 3, 4, 5, 6, 7 or 8 with 0.5 M sodium hydroxide or 0.5 M hydrochlorid acid. The suspensions were agitated for three days at 20°C. The pH of each was checked at least twice a day. After saturation, the suspensions were centrifuged and filtered until clear. Two 1.00 ml samples were taken from each solution and evaporated to dryness on a water bath. Twenty millilitres of 0.1 M hydrochloric acid were added to one of the samples and the same volume of 0.1 M sodium hydroxide solution to the other. The samples were mixed for 20 minutes using a magnetic stirrer. After centrifugation and filtration, the clear solutions were diluted and their absorbances measured spectrophotometrically (Perking-Elmer 550 UV/Vis spectrophotometer) at 260 nm (embonic acid, basic solution) and 211 nm (noscapine, acidic solution) using previously prepared standard curves.

Procedure for preparation of the suspensions

To the basic suspension (see below) were added 10 g (5 g if anise oil or spiritus menthol had been used) of ethanol, varying amounts of polyvidone solutions (0 to 20 g) and water to make total volumes of about 100 ml. The mixtures were homogenized for two minutes. Sorbitol solution and the other ingredients were then added (ammonium chloride (3.4 g) and citric acid (0 to 80 mg) dissolved in small amounts of water; anise oil (0 to 240 mg) and spiritus menthol (1.5 g) dissolved in 5 g of ethanol) to the mixture on a magnetic stirrer. Finally liquorice solution was added and the pH adjusted from 5 to 5.5 using 1 M hydrochloric acid or 1 M sodium hydroxide solution. The total volume was adjusted with water to 200 ml.

The basic suspension was prepared by dissolving 8.55 g of noscapine hydrochloride in water to make a total volume of 1000 ml. Embonic acid (7.38 g) was dissolved in about 45 ml of 1 M potassium hydroxide solution and the total volume was adjusted to 1000 ml with water. Thirty millilitres of the two solutions were mixed using a magnetic stirrer and the pH was adjusted from 5.0 to 5.5 with 0.1 M hydrochloric acid or 0.1 M sodium hydroxide solution.

Sedimentation volumes

Thirteen suspensions (suspensions 1 to 13) were prepared using the procedure described above. These suspensions contained only the

basic suspension, 10 g of ethanol and 0 to 20 g of polyvidone solution. Water was used instead of the other ingredients. The pH of each suspension was adjusted to 5.5. In addition, 5 suspensions were prepared (suspensions 14 to 19) containing the basic suspension, 10 g of ethanol 5 g of polyvidone solution and the flavouring agents (except for liquorice solution) mentioned in the section "Procedure for preparation of the suspensions". One hundred millilitres of each prepared suspension were stored for 4 weeks at room temperature in graduaded cylinders (25 cm x 2.6 cm) and the sedimentation volumes were recorded using the scales of the cylinders.

Cake formation and deflocculation

Twenty-three suspensions containing the basic suspension, 10 g of ethanol, 2.5 to 17.5 g of polyvidone solution, 3.4 g of ammonium chloride, 18 g of liquorice solution, 1.5 g of spiritus menthol and varying amounts of anise oil (0, 30, 60, 120, 240 mg) and citric acid (0, 40, 80 mg) were stored in 200 ml bottles at room temperature. After 3 and 6 months' storage cake formation and deflocculation were evaluated visually, shaking the bottles by hand and observing the times needed for the sediment to redisperse.

Decrease of noscapine concentration at the surface of a typical flocculated formulation

Three identical suspensions were prepared as described in the section "Cake formation and deflocculation". The amount of polyvidone solution was 5 g and the amounts of anise oil and citric acid were 60 and 40 mg, respectively. The pH of the suspensions was adjusted to 5.0. The suspensions were stored for 6 months in 200 ml bottles (150 ml in each bottle) at room temperature. Just before investigation, the suspensions were shaken until they were homogeneous and the bottles were stuck to the working surface to avoid any movement during the experiment. Samples of 1.00 ml were taken slowly using a Finpipette, the top of the pipette being exactly 1 cm below the surface of the suspension. Noscapine was determined by HPLC (Pye Unicam 4010/4020/8251) after decomposition of the salt at pH 1 using a modification of the general method for the determination of opium alkaloids in gum opium[2]. A shorter cyano column (12.5 x 4 mm) was used, with

a mobile phase of 1% ammonium acetate (pH 5.8)-dioxane-acetonitrile (78:11:11). The column eluate was monitored by UV at 313 nm. The flow rate was 1 ml/min. The precision of the analytical method was 0.6% (RSD), as determined using a homogenous suspension (n=6).

Particle growth during storage

Particle growth was studied using an optical microscope (Leitz Wetzlar, Type 307-127.001) and six identical suspensions containing the same ingredients as those mentioned in the section "Decrease of noscapine concentration at the surface of a typical flocculated formulation", except for liquorice solution. Three of the suspensions were stored at 20°C and the other three at 10°C. The diameter of 200 particles in each suspension was measured at intervals of one week, using a calibrated scale incorporated into the microscope. Before sampling, the suspensions were shaken until they were homogenous. The samples were taken from the central region of the 200 ml storage bottles. The particles were classified by determining the numbers of particles in successive size ranges. The smallest class was < 1.9 µm in diameter and the others were multiples of this. Magnifications of x630 and x40 were used.

Taste acceptability

The acceptability of the taste of the suspension containing the ingredients mentioned in the section "Decrease of noscapine concentration at the surface of a typical flocculated formulation" was tested with the help of 20 healthy volunteers (13 female, 7 male, aged 19 to 59 years (mean 41 years)). The taste was compared with that of the most popular liquid noscapine hydrochloride preparation in Finland. The two preparations, which were similar in appearance, were coded A or B and the volunteers tasted them in random order. The taste was evaluated using a scale from 1 to 5 in which 1 was "very bad" and 5 was "very good". The significance of differences between the preparations were tested using Wilcoxon's test.

RESULTS

Decomposition of noscapine embonate as a function of pH

The observed solubility of noscapine embonate after three days' saturation was found to be very poor in the approximate pH range

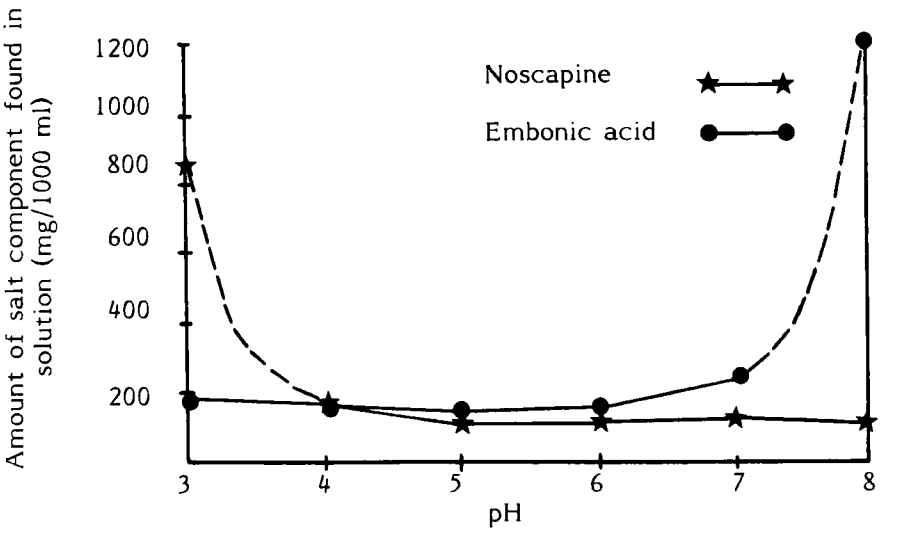

FIGURE 1
Decomposition of Noscapine Embonate as a Function of pH

4 to 7 (Fig.1). Below this range, the salt began to release noscapine. In basic solutions, the embonic acid dissolved.

The analytical method used is partly based on the different degrees of decomposition of the salt in acidic or basic media.

Sedimentation volumes

If polyvidone was not used (Table 1) the result was an unstable suspension with a distinct sediment and a layer at the top of the cylinder. When the concentration of polyvidone was in the range of 0.05 to 1.25, only traces of sediment were observed. Above this range, the volume of sediment increased but, at a concentration of 1.75 the embonate dissolved completely and a clear solution was obtained. Increasing the amount of polyvidone caused the sediment to form again.

The flavouring agents (suspensions 15 to 19) had no evident effect on the volume of the sediment.

Cake formation and deflocculation

No deflocculation was observed in suspensions containing 0.25 to 1.75% of polyvidone and all the flavouring agents except anise oil.

TABLE 1

Effects of Various Polyvidone Concentrations on Sedimentation Volumes of Noscapine Embonate (2.4 mg/ml) after Four Week's Storage in 100 ml Graduated Cylinders.

Concentration of polyvidone (w/v %)	Volume of sediment (ml)
0	2
0.05	Traces[b]
0.10	Traces[b]
0.15	Traces[b]
0.20	Traces[b]
0.25	Traces[b]
0.50	Traces[b]
0.75	Traces[b]
1.00	Traces[b]
1.25	Traces[b]
1.50	3
1.75	0
2.00	1

b Milky suspension with sedimentation volume of less than 0.1 ml.

The time needed to redisperse the suspensions was only a few seconds. If 240 mg of anise oil were used with the other flavouring agents, a hard cake formed and, in most cases, 10 to 20 seconds' shaking was necessary to redisperse the sediment. Cake formation diminished if the amount of anise oil was decreased and the pH waslowered to 5.0 to 5.2.

Decrease of noscapine concentration at the surface of a typical flocculated formulation

The average decrease in noscapine concentration observed after 22 days was only about 13% (Fig. 2). This means that settling of the noscapine embonate microparticles occured slowly, as was to be expected regarding the small particle size.

Particle growth during storage

Although the persistently small particle size limits the value of the results (most of the particles belonged to the smallest class both before and after storage) some interesting observations were made.

Nearly all of the particles were spherical. No particles bigger than about 10 um were present except for some aggregates in samples

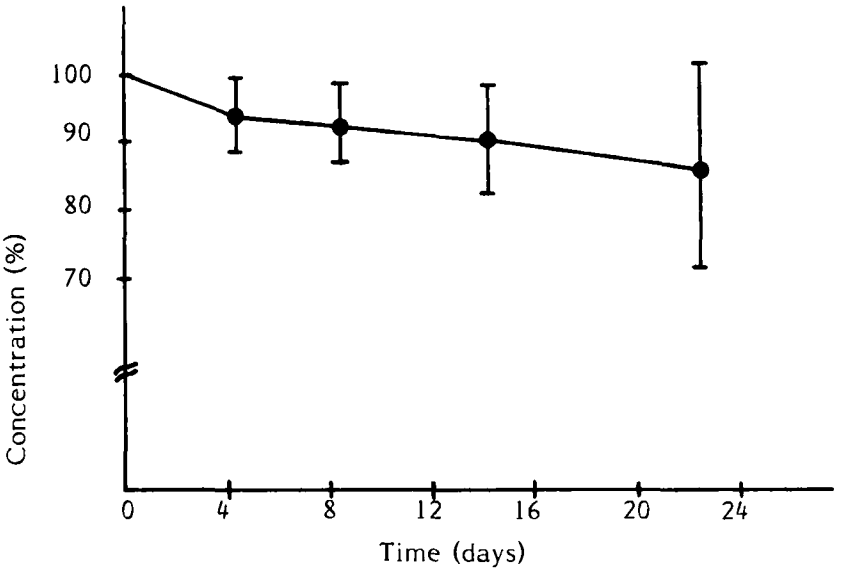

FIGURE 2

Decrease of Noscapine Concentration at the Surface of a Flocculated System

taken after 4 weeks' storage. The average particle size at 20°C was 2.3 μm at the beginning of the test and 2.5 μm after storage. At 10°C, no change in average size (2.3 μm) was observed.

Taste acceptability

The average assessment of the taste of the formulation developed was "good" (Fig. 3) while that of the reference preparation was "bad". Using Wilcoxon's test, the difference is significant ($p<0.01$).

DISCUSSION

The convenient means of suspension preparation used in this study involves precipitation of noscapine embonate at the beginning of the process, followed immediately by the addition of polyvidone and ethanol and homogenization of the mixture to form microparticles of the drug (the ethanol is necessary to prevent foaming). The other ingredients

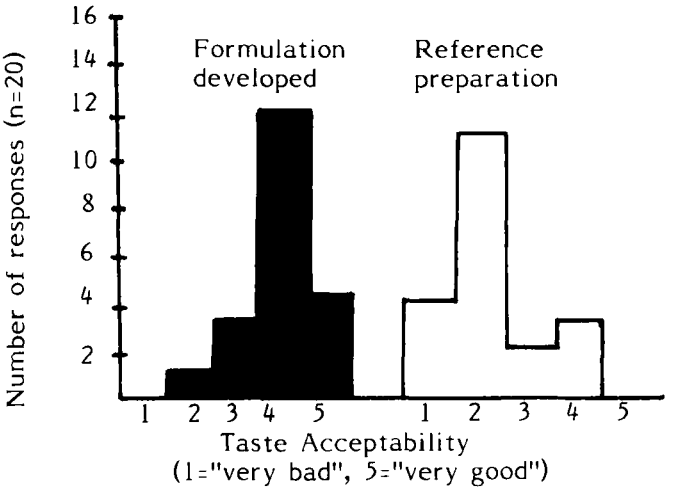

FIGURE 3

Acceptability of a Taste Formulation Developed as Compared with that of the Reference Preparation. The Difference is Significant ($p<0.01$).

are then added as previously described. The small amount of potassium chloride formed during the neutralization stage is not harmful.

A more laborious means of suspension preparation, not used in this study, includes preparation of solid noscapine embonate, which is then dispersed in polyvidone solution using a process similar to that described above. This method is, however, problematic because of the hygroscopicity of noscapine embonate.

Decomposition of noscapine embonate in solution, with release of noscapine, begins at about pH 4. This fact had to be borne in mind when deciding on an appropriate pH for the formulations. Noscapine is also released in the body but the biopharmaceutical properties of the embonate are somewhat different from those of noscapine hydrochloride[3] because of the different physicochemical properties of the two compounds.

Although the solubility of the embonate is very poor in the pH range of 5 to 5.5, which was used in the formulations developed, some of the salt nevertheless dissolves, which gives a slight hint of the bitter

taste typical of noscapine hydrochloride preparations. The solubility can be further reduced by incorporation of anise oil. The amount of anise oil is, however, critical, because too large quantities can deflocculate the system.

Noscapine embonate suspensions containing no suspending or dispensing agents, are physically very unstable. Although no deflocculation occured during a storage period of one year in a preliminary study, accurate dosage and quantitative analysis were impossible because of the rapid sedimentation of the salt. Polyvidone was used to stabilize the system because this macromolecule increases the bioavailability of the aqueous embonate suspension[3].

The observed interaction between noscpine embonate and the macromolecule remained about the same in the concentration range 0.05 to 1.25% of polyvidone but was markedly altered at higher concentrations. Complete dissolution occured at a concentration of 1.75%. The interaction may be a consequence of complex formation. It is well known that polyvidone complexes with aromatic compounds capable of hydrogen bonding. Unfortunately, noscapine embonate, when completely dissolved with the aid of polyvidone, has an upleasant bitter taste, which limits its utility.

The stabilizing effect of polyvidone when used at a concentration of 0.5% is clearly seen in the persistence of the small particle size, which did not increase markedly during storage, and slow settlement, with no difficulty in redispersing the sediment. The high precision of the analytical method also arises from the homogeneity of the system and its small particle size.

A noscapine suspension of acceptable taste was satisfactorily achieved using conventional flavouring agents. Only one of the 20 volunteers considered the taste unacceptable. The fact that noscapine embonate in formulations with polyvidone also exhibits good bioavailability[3] indicates that a liquid antitussive preparation of this kind is a good alternative to conventional noscapine hydrochloride preparations.

REFERENCES

1. Finnish patent application 851052.
2. Yoshifumi Nobuhara, Hiori Hirano, Kensuke Namba and Masahisa Hashimoto, J. Chromatogr., 190, 251 (1980).
3. V. Haikala, A. Sothmann and M. Marvola: Poster at 45th International Congress of Pharmaceutical Sciences of F.I.P., Montreal, 2-6 September 1985