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Heroin: stability and formulation approaches

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Summary

A rapid, selective and sensitive high-performance liquid chromatographic stability indicating assay for heroin and its hydrolysis products was applied to study the stability and kinetics of heroin hydrolysis at its optimal pH in the presence of various pharmaceutical excipients. Heroin hydrolysis involved a two-step sequential mechanism. The pseudo-first-order rate constants have been determined. Buffers catalyzed heroin degradation, while sodium chloride, mannitol or povidone (40,000) had no effect. The physical and chemical stabilities of lyophilized dosage forms containing heroin alone or with excipients: buffer (optimal pH), mannitol, lactose and dextrose were also studied at various temperatures. Phosphate buffer enhanced heroin degradation, while heroin or heroin plus lactose provided stable formulations even at elevated temperatures.

Introduction

Recent emphasis on improving pain relief for terminal cancer patients has resulted in renewed interest in 3,6-diacetylmorphine (diamorphine) hydrochloride (Hardie, 1978; Saunders, 1976; Twycross, 1975, 1977), hereafter referred to as heroin. A rapid, selective and sensitive high-performance liquid chromatographic (HPLC) stability indicating assay (Poochikian and Cradock, 1979) for heroin in the presence of its hydrolysis products (6-monoacetylmorphine and morphine) was

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applied to study the stability and kinetics of heroin hydrolysis. Separation was carried out in aqueous solution at a pH which showed minimal degradation of heroin and eliminated time-consuming extraction procedures.

In the present investigation, the catalytic effect of buffers, the effect of ionic strength of the solution, and the presence of various pharmaceutical excipients on heroin stability in aqueous solutions at its optimal pH about 4.5 (Poochikian and Cradock, 1979), were determined. Subsequently, the information was applied toward formulation of a stable parenteral product.

Since the preliminary results suggested the susceptibility of heroin to hydrolysis, solid dosage forms were required for long-term stability of this drug. The extent of heroin degradation in freeze-dried preparations in the presence or absence of excipients was investigated concurrently at elevated temperature (for convenience). The data concerning these aspects and interactions in the solid state are presented.

Materials and Methods

Reagents

Hydrochloride salts of heroin, 6-monoacetylmorphine and morphine were used as received [1]. The internal standard, 1,8-bis(dimethylamino)napthalene, was from a commercial source [2]. Acetonitrile (HPLC Grade [3]) and distilled water were filtered through 0.50 μm and 0.80 μm solvent-resistant filters [4], respectively. All other chemicals were reagent grade and were used without further purification.

Equipments

A modular high-pressure liquid chromatograph, equipped with a constant-flow pump [5] was used to deliver eluent to a stainless-steel column packed with fully porous 10 μm silica particles bonded with a monomolecular layer of octadecylsilane [6]. Injections were made with a rotary valve injector equipped with a 10 μl injection loop [7]. A variable wavelength ultraviolet detector [8], set at 235 nm, was operated at an attenuation of 0.02 AUFS and the integrator output to the recorder was attenuated 4 times to detect the eluted compounds. The output signals were recorded with a strip chart recorder [9]. Retention times and peak areas of heroin and its hydrolysis products were monitored and quantitated automatically by area measurements using a computing integrator [10].

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[1] National Institute on Drug Abuse, Rockville, MD.
[2] Aldrich Chemicals, Milwaukee, WI.
[3] Fischer Scientific, Fair Lawn, NJ.
[4] Millipore, Bedford, MA.
[5] Model 3500B, Spectra-Physics, Santa Clara, CA.
[6] μBondapak-C_{18}, Waters Ass., Milford, MA.
[7] Valco Inst., Houston, TX.
[8] Model SP 770, Spectra-Physics, Santa Clara, CA.
[9] OmniScribe, Houston Inst., Austin, TX.
[10] System I, Spectra-Physics, Santa Clara, CA.

Chromatographic conditions

The chromatographic mobile phase consisted of 3 volumes of acetonitrile and 7 volumes of 0.015 M potassium dihydrogen phosphate adjusted to pH 3.5 with 2 N phosphoric acid [11]. The column pressure at a flow rate of 1.0 ml/min was about 800 psi. Separations were effected isocratically at ambient temperature. The chromatographic behavior and chromatographic parameters, i.e. the retention volumes, the capacity factors, and the separation factors of the internal standard, heroin and its hydrolysis products have been reported previously (Poochikian and Cradock, 1979). The chromatographic responses for the solutes were linear ($r > 0.999$) in the working concentration range (10–200 μg/ml).

Preparation of solution

Heroin was dissolved in appropriate media to yield a concentration of 1.0 mg/ml. The above solutions were filtered through solvent-resistant filters [4] and promptly dispensed (1.2 ml) in 2 ml flint ampules, sealed and stored at 25 ± 0.1°C and 50 ± 0.1°C. Periodically, 400-μl samples were removed in duplicate and each diluted to 2.0 ml with the mobile phase containing 100 μg/ml of the internal standard. The stability study of each solution at 50 ± 0.1°C was monitored beyond the maximum concentration of 6-monoacetylmorphine.

Preparation of lyophilized samples

Heroin solutions (8.0 mg/ml) containing different amounts of various excipients were prepared and dispensed (2.0 ml) into prechilled flint vials (5 ml). After the contents of the vials were frozen on the prechilled shelf (-35°C) of the freeze-drying unit [12], the products were lyophilized through the following drying cycle. The initial drying was done at -35°C over 24 h. The shelf temperature rose to near 0°C over the next 24 h during which time most of the water was removed. Final drying was carried out at 25°C for an additional 24 h. The pressure throughout the lyophilization process was about 25 μm. Subsequent to freeze-drying, the samples were removed and stored at 50 ± 0.1°C and at room temperature (24 ± 0.5°C).

The freeze-dried samples were reconstituted with distilled water (4.0 ml) and a 100-μl aliquot was diluted to 2.0 ml with the mobile phase containing 42 μg/ml of the internal standard and then immediately subjected to analyses.

Results and discussion

Kinetic studies

Previous studies (Poochikian and Cradock, 1979) indicated that the hydrolysis of heroin proceeded via a two-step sequential mechanism over the pH range studied (3.0 – 8.6). In the present study, the influence of common pharmaceutical additives:

[11] Beckman Zeromatic pH meter, Beckman Instruments, Irvine, CA.
[12] Model 10-800, Virtis, Gardiner, NY.

TABLE I

EFFECT OF BUFFERS ON HEROIN HYDROLYSIS IN AQUEOUS SOLUTION AT VARIOUS TEMPERATURES

Medium	Total buffer conc. (M)	50 ± 0.1°C				25 ± 0.1°C	
		$k_1 \times 10^2$ (day^{-1})	β_{max} [a]	K [b]	$k_2 \times 10^2$ (day^{-1})	$k_1 \times 10^3$ (day^{-1})	t_{90} [c] (days)
Water	–	1.89	0.642	0.223	0.44	1.98	53
Phosphate	0.01	2.79	0.716	0.149	0.42	4.24	24
buffer,	0.10	6.92	0.715	0.150	1.04	10.02	10
pH 4.5	0.50	23.79	0.685	0.181	4.31	34.34	3
Acetate	0.01	2.32	0.713	0.152	0.35	3.94	27
buffer,	0.10	4.22	0.700	0.165	0.70	7.00	15
pH 4.5	0.50	12.47	0.673	0.195	2.43	19.50	5

[a] $\beta_{max} = K^{K/1-K}$ (see Jensen and Lamb, 1964).
[b] $K = k_2/k_1$.
[c] Period of time for 10% disappearance of original heroin concentration.

buffers, mannitol, lactose, polyvinylpyrrolidone and sodium chloride were studied on heroin hydrolysis at the previously determined pH optimum of 4.5 (Poochikian and Cradock, 1979). The degradation of heroin was found to observe pseudo-first-order kinetics with respect to the substrate in all cases. Plots of the logarithm of residual heroin versus time resulted in straight lines ($r > 0.99$). Hydrolysis rate constants (k_1) were computed by the least-squares linear regression method. The second rate constants (k_2) were computed using dimensionless parameters and variables according to the method described by Jensen and Lamb (1964). The hydrolysis intermediate, 6-monoacetylmorphine rose to a maximum value within a certain period of time and decreased in an approximately linear fashion while the concentration of morphine rose gradually after an induction period. The rate constants at 50 and 25 ± 0.1°C plus the t_{90} values (period of time for 10% loss of the initial heroin concentration) at 25 ± 0.1°C in the various media are summarized in Tables 1 and 3. Examination of β_{max} values within each series revealed that the most stable heroin solution had also the highest β_{max} value, indicative of 6-monoacetylmorphine stability. The rate of conversion of heroin to 6-monoacetylmorphine in buffered solutions in general proceeded approximately 7-fold faster than the hydrolysis of 6-monoacetylmorphine to morphine.

Buffer effect

The catalytic effect of phosphate and acetate buffers at pH 4.5, and constant heroin concentration were determined at 25 ± 0.1°C and 50 ± 0.1°C by varying the total buffer concentrations (0.01, 0.1, 0.5 M). The ionic strengths of these solutions were not maintained constant. As will be described in the following discussion, ionic strength did not have a marked effect on the heroin degradation rate under those conditions.

Table 1 presents the results of these studies in terms of degradation pseudo-first-order rate constants and t_{90}. Plots of the rate constants of each of the two steps of heroin hydrolysis versus the total molar concentration of each of the buffers at pH 4.50 showed linear trends with positive slopes. The buffering capacity of each solution was sufficient to maintain constant pH values (± 0.05) over the course of the experiment. Heroin disappearance rate constant in unbuffered solution was slower than in buffered solution at the previously determined optimum pH (Poochikian and Cradock, 1979), and indicated buffer catalysis.

Under the conditions employed, it is clear that the catalysis by phosphate buffers is greater than that by acetate buffers. In both cases, the total observed rate constant is the sum of the catalytic effects of the different buffer species present together with the rate constant of the uncatalyzed reaction. However, no attempts were made in this study to determine the relative catalytic effects of the various buffer components.

Salt effect

The primary salt effect on the heroin degradation was studied at constant heroin concentration and constant temperatures; only the ionic strength was varied by the addition of sodium chloride. The apparent pH of all solutions was about 5.4. No primary salt effect was observed for heroin in solution which covered a range in ionic strength from 0.01 to 0.5 (Table 2). In addition to an evaluation of the effect of sodium chloride on heroin hydrolysis, its influence on the physical stability of heroin solution was also examined. The British Pharmacopeoia (1973) states that 'sodium chloride precipitates diamorphine from solution and is not suitable for adjusting the isotonicity of the injection'. However, we did not observe any precipitate in aqueous solutions containing $\leqq 100$ mg/ml of heroin and 9 mg/ml of sodium chloride.

Excipient effect

In practice, excipients are often present in lyophilized products to provide uniform color, texture, as well as, sufficient strength to the cake to prevent crumbling during storage. Hence, it was of interest to investigate the influence of some excipients (Table 3) on the stability of heroin in solution. In these studies,

TABLE 2

EFFECT OF IONIC STRENGTH ON HEROIN HYDROLYSIS IN AQUEOUS SOLUTIONS AT VARIOUS TEMPERATURES

Sodium chloride conc. (M)	50 ± 0.1°C				25 ± 0.1°C	
	$k_1 \times 10^2$ (day^{-1})	β_{max}	K	$k_2 \times 10^2$ (day^{-1})	$k_1 \times 10^3$ (day^{-1})	t_{90} (days)
0.01	1.69	0.640	0.235	0.40	1.73	60
0.10	1.76	0.625	0.256	0.45	1.75	60
0.50	1.83	0.604	0.288	0.53	1.83	57

TABLE 3

EFFECT OF EXCIPIENTS ON HEROIN HYDROLYSIS IN AQUEOUS SOLUTIONS AT VARIOUS TEMPERATURES

Excipient	50±0.1°C					25±0.1°C	
	Conc.	$k_1 \times 10^2$ (day^{-1})	β_{max}	K	$k_2 \times 10^2$ (day^{-1})	$k_1 \times 10^{-3}$ (day^{-1})	t_{90} (days)
Mannitol	0.01 M	1.59	0.675	0.192	0.31	1.68	63
	0.10 M	1.87	0.665	0.204	0.38	2.08	50
	0.50 M	2.02	0.588	0.249	0.50	2.14	49
Polyvinyl-pyrrolidone	1.0%	1.86	0.633	0.245	0.46	–	–

solutions were prepared at constant temperatures and constant heroin concentration, with varying mannitol concentrations. The apparent pH value of mannitol solutions was constant (about 6.8). The results presented in Table 3 indicate that polyvinylpyrrolidone (1%) or mannitol (0.01, 0.1, 0.5 M) had only minimal effect on the first or second heroin hydrolysis rate constants.

Lyophilized dosage forms

On the basis of solution kinetic data, it was apparent that heroin would not be adequately stable for formulation as 'ready-to-use' solution. However, the 25–50 day t_{90} for heroin hydrolysis at room temperature (Table 1–3) appeared to be compati-

TABLE 4

EFFECT OF BUFFERS ON HEROIN STABILITY IN SOLID STATE [a] AT 50±0.1°C

Buffer	Conc. (M)	Excipient	t_{90} [b] at 50±0.1°C (days)
Phosphate [c]	0.01	–	50
	0.05	–	20
	0.10	–	5
Citrate [c]	0.01	–	120
Phosphate [c]	0.01	Mannitol [d]	48
Phosphate [c]	0.01	Lactose [d]	273
Phosphate [c]	0.02	Glycine [e]	80 [f]

[a] Contains 16 mg heroin hydrochloride in 2 ml lyophilizate.
[b] Period of time for 10% disappearance of original heroin concentration.
[c] pH 5.0.
[d] 76 mg excipient in 2 ml lyophilizate.
[e] 20 mg excipient in 2 ml lyophilizate.
[f] t_{90} at 25±0.1°C was 180 days.

TABLE 5

EFFECT OF EXCIPIENTS ON HEROIN STABILITY IN SOLID STATE [a]

Excipient per vial		t_{90} [b] days (% present at 9 months)		
		25 ± 0.1°C	50 ± 0.1°C	75 ± 0.5°C
Water	–	> 273 (99.5%)	> 273 (97.0%)	273
Mannitol	76.0 mg	> 273 (99.5%)	> 273 (94.0%)	14
Lactose	76.0 mg	> 273 (99.9%)	> 273 (99.4%)	> 273 (96.0%)

[a] Contains 16 mg heroin hydrochloride in 2 ml lyophilizate.
[b] Period of time for 10% disappearance of original heroin hydrochloride.

ble with its use as a buffered or unbuffered formulation with or without excipient(s) that would be constituted as a solution prior to use.

The suitability of heroin in a lyophilized dosage form was examined. The results are summarized in Tables 4 and 5. The freeze-drying process resulted in white cakes which were readily constituted with Sterile Water for Injection. Stability of heroin formulations containing sodium chloride or dextrose were not studied because lyophilized residue did not yield products with acceptable uniform physical appearance.

Although buffers catalyzed heroin hydrolysis in solution, they were incorporated into some lyophilized products to determine any effect in the solid state. However, such freeze-dried products, in the absence or presence of excipients, yielded discolored cakes and/or accelerated heroin degradation within a few months when stored at 50 ± 0.1°C or room temperature. The discoloration of the cakes was dependent upon the phosphate buffer concentration. However, the presence of 0.01 M citrate buffer retarded both the discoloration of the cake and the heroin degradation (Table 4). This observation is in accord with the report that citric acid stabilized sugar containing solutions and prevented darkening of these preparations (Jindra et al., 1979). Furthermore, the HPLC chromatograms of lyophilized heroin samples in the presence of phosphate buffer and mannitol at 50 ± 0.1°C (Table 4) or mannitol alone at 75 ± 0.5°C (Table 5) showed the presence of peaks in addition to those of the heroin hydrolysis products. Physicochemical investigations designed to elucidate the mechanism of the reaction between heroin and excipients in solid state are beyond the scope of this paper.

However, unbuffered freeze-dried preparations in the absence or presence of lactose, when stored at 25 ± 0.1, 50 ± 0.1, or 75 ± 0.5°C for 9 months, resulted in physically and chemically stable products (Table 5). Hence, the data demonstrate strongly that heroin formulated as lyophilized dosage form in the presence or absence of lactose presented no apparent stability problems.

To estimate the loss of original potency of heroin under potential clinical conditions, the stability of the reconstituted solutions at room temperature was monitored for 3 days. Analyses of the freeze-dried samples of heroin alone or heroin in the presence of lactose after constitution with bacteriostatic water for injection [13]

or bacteriostatic sodium chloride injection [13] indicated the presence of at least 98% of the initial heroin concentration. Monoacetylmorphine was the only detectable degredation product. This apparent stability of reconstituted heroin solutions suggests that these dosage forms may be used for multi-dose purposes.

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