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Dissolution kinetics of unstable drugs in two-compartment autoinjectors: Analysis of the individual shaking behaviour and influence of various shaking parameters on the dissolution rate of HI 6 in an automated system

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Abstract

Despite the ubiquitous use of multi-phase drug formulations, detailed investigations on the dispersion kinetics upon shaking are apparently lacking. We were faced with these problems when analysing the operational function of newly developed autoinjectors containing a pharmaceutically unstable nerve agent antidote formulation. For the immediate treatment of organophosphate poisoning, dry/wet autoinjectors have been developed, containing the broad-spectrum cholinesterase reactivator HI 6 dichloride as a powder and atropine in solution. After breaking a separating membrane, HI 6 has to be dissolved by shaking for 5 s prior to injection. Although being crucial for quick dissolution, the mode of shaking has been poorly specified by the two manufacturers. After recording the individual shaking behaviour of 50 volunteers, we constructed a shaking apparatus allowing the imitation of the spontaneous human shaking motion. Mockups of both autoinjector chambers with pneumatic activation, programmed shaking and ejection of the suspension through a filter allowed us to analyse the dissolution progress within seconds. The results with HI 6 dichloride at 5°C showed that complete dissolution was not achieved within 5 s. The dissolution rate was dependent on shaking frequency, height of stroke, inclination of the shaking axis, and the dimensions of the mockups. Upon vertical shaking, a threshold frequency was observed above which the dissolution rate increased abruptly. Horizontal shaking accelerated the dissolution rate and the threshold frequency could be lowered considerably. While HI 6 dichloride did not allow complete dissolution at 5°C, HI 6 dimethanesulphonate was completely dissolved in less than 5 s under shaking conditions as observed with more than 75% of the untrained volunteers.

Keywords: Unstable drugs; Two-compartment autoinjectors; Individual shaking behaviour; Shaking parameters; HI 6

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1. Introduction

Many drug formulations consist of multiphase systems that require vigorous shaking before use to guarantee content uniformity in the dispensed volume. In contrast to the widespread use of these formulations, detailed investigations on the dispersion kinetics upon shaking are apparently lacking. More recently, eye-drop suspensions have attracted particular interest as retarding formulations and have called some attention to the shaking intensity prior to administration. Apt et al. (1979) reported that only 40% of the instructed volunteers were really shaking a corticosteroid eye-drop suspension before use, resulting in erratic delivery. Strobel (1991) found an acceptably uniform availability of indomethacin from eye-drop suspensions only when using a standardised and sufficiently vigorous shaking procedure (20 fast shakes).

Shaking intensities varied markedly among patients and healthy subjects and resulted in differences between expected and observed drug availability from eye-drop suspensions (Diestelhorst et al., 1995; Kwon et al., 1996). To our knowledge, these authors were the first to exactly measure the shaking force and to mimic the manual shaking by a pneumatically driven shaking machine. The range of the typical shaking behaviour and the influence of various parameters such as frequency, stroke height, slope and dimensions of the bottle on the dispersion kinetics, however, have not been analysed as yet.

We were faced with these problems when evaluating the function of newly developed dry/wet autoinjectors that contain the nerve agent antidote HI 6 dichloride and atropine. The use of a liquid formulation of the broad-spectrum acetylcholinesterase reactivator HI 6 (1-(((4-(aminocarbonyl)pyridino)methoxy)methyl)-2-((hydroxyimino)methyl) pyridinium dichloride monohydrate; CAS 34433-31-3) is not practicable because of the instability of the compound at the anticipated concentration (500 mg HI 6 dichloride in 3 ml) (Eyer and Hell, 1985; Eyer et al., 1986; Fyhr et al., 1987; Eyer et al., 1988). Therefore, dry/wet autoinjectors have been developed comprising the oxime as a powder which is dissolved in the atropine-containing solvent immediately before i.m. injection. The autoinjectors are activated by breaking a membrane followed by shaking the device. The commercially available autoinjectors (Astra Tech AB, S-43121 Mølndal, Sweden, and STI International, Frindsbury, Rochester, Kent ME2 4DP, UK) are specified to deliver a dose of some 500 mg HI 6 dichloride and 2 mg atropine sulphate after a shaking time of 5 s only. The recommended shaking motion, however, is not clearly indicated. At any rate, dissolution should be complete within the specified time range independent of the individual shaking behaviour.

The item became even more important when HI 6 dichloride was observed to dissolve quite slowly at low ambient temperatures (Thiermann et al., 1996). Hence, we decided to investigate the dissolution kinetics in more detail. Concerned about the quite artificial kind of agitation in the previous study (magnetic stirring) we decided to investigate the dissolution kinetics of HI 6 dichloride under shaking in comparison with the more soluble HI 6 dimethanesulphonate. Since it is our firm belief that foolproof functioning autoinjectors are required, we felt it urgent to evaluate the influence on the dissolution kinetics of the various shaking parameters as observed with untrained subjects.

To this end, it appeared rational to analyse the individual shaking behaviour of shortly instructed volunteers and to construct a shaking apparatus allowing the imitation of the spontaneous human shaking motion within the range observed. Mockups of both autoinjector chambers allowed pneumatically driven activation followed by shaking for various time intervals and subsequent ejection and filtration through a Millex® filter. The dead-time of the whole procedure was about 2 s.

The results revealed some unexpected facts that also may influence the dispersion efficiency by manual shaking of other multi-phase drug formulations and thus be of broader interest.

2. Materials and methods

2.1. Chemicals

HI 6 dichloride was a generous gift from Astra Tech. HI 6 dimethanesulphonate was prepared from HI 6 dichloride by ion exchange chromatography (Thiermann et al., 1996). The particle size of both HI 6 preparations did not markedly differ, thus allowing comparison of the results. More than 89% of HI 6 dichloride had an apparent diameter from 0.1 to 0.5 mm with an average of 0.25 mm, while 80% of HI 6 dimethanesulphonate was found in the above range with a mean diameter of 0.18 mm.

HPLC analysis revealed that the compound was greater than 99.5% pure. A minor product was suggested to be the deamination product of HI 6 (HI 6 acid $< 0.2\%$; Eyer et al., 1986).

The spectroscopic determination of HI 6 dimethanesulphonate at pH 2 exhibited a maximum at 300 nm $E = 12.0 \times 10^3$ M^{-1} cm^{-1} which agreed with HI 6 dichloride ($E_{300\ nm} = 12.15 \times 10^3$ M^{-1} cm^{-1}).

2.2. Characterization of the shaking motion during activation of dry/wet combination autoinjectors

2.2.1. Recording of the shaking motion

Fifty employees (21 females, 29 males) of our institute were asked to perform the shaking procedure with the dry/wet autoinjectors according to the manufacturers' user instruction. The individual shaking motions were recorded twice per volunteer with a high speed camera (HSV 500, Dedo Weigert Film) from front and side view (shaking time 5 s as indicated; shaking not trained).

To increase the contrast during recording, a black autoinjector model (3.5 cm diam. $\times$ 16 cm, 100 g) with a white stripe was used for shaking. Hand, arm and body were covered by black clothes and a black curtain served as a background. Before starting the shaking procedure, a rod with two white marks (distance 11.5 cm) was presented horizontally and vertically to the camera for calibration.

The records were digitalised in semi-picture form by a digital-controlled VHS videorecorder and an analog/digital converter (Institut für Wasserwesen, Hydromechanik und Hydrologie, Universität der Bundeswehr, Neubiberg). On an average, the pictures were taken every 13 ms and a sequence of 230 pictures was evaluated.

The cartesian coordinates (pixels) of the centre of the white mark and the angular deflection of the stripe from the horizontal axis were determined on the screen.

2.2.2. Periodicity and frequency

The movement of the centre of the white mark followed a sine function ($Y = A + B \times \sin(\omega \times t + \varphi)$; $A =$ baseline; $B =$ amplitude; $2\pi/\omega =$ period of a shaking cycle; $\varphi =$ phase shift, $t =$ time (ms)). Local apices ($Y'(x) = 0$; maximum: $Y''(x' = 0) < 0$; minimum $Y''(x' = 0) > 0$) and points of inflection ($Y'' = 0$) were calculated. The shaking frequency (per minute) was determined from the time measured between two maxima.

2.2.3. Shaking motion

The movement of the autoinjector could be well approximated to an orbit with the cubital joint as the centre and the distance between cubital joint and the centre of the autoinjector as the radius (Fig. 1). Hence, the first shaking cycle (range

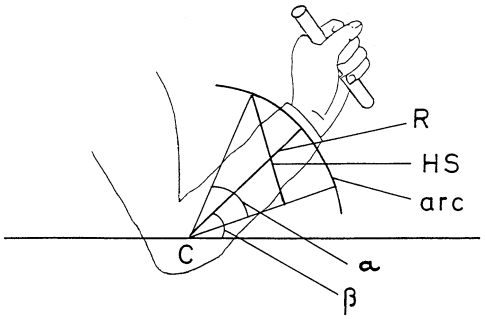

Fig. 1. Scheme of the shaking motion. For sake of simplicity the movement of the autoinjector was assumed to follow an orbit (arc) with the cubital joint as the centre (C) and the distance between C and the centre of the autoinjector as the radius (R). The two points of inversion form the angle α, with $R \times \sin \alpha$ being the height of stroke (HS). The line bisecting angle α and the horizontal axis include angle β which describes the absolute position of the arm at rest.

Table 1
Specifications of the variable parameters of the shaking apparatus

Parameter	Range
Shaking frequency	0–400 min^{-1}
Height of stroke	12–21 cm
Length of connecting-rod	21–26 cm
Inclination from vertical axis	0–45 (90)°

between the first two local minima) which was completely recorded, was fitted to a circular function: $Y = A + \sqrt{R^2 - (X - B)}$; A and B: cartesian coordinates of the circle centre; R: distance measured between cubital joint and the autoinjector model in the hand of each subject. R was a constant in the fitting equation. From these data angular deflection α (Fig. 1) was determined graphically. In seven cases local apices could only be determined by extrapolation (minimum: $n = 7$, maximum: $n = 1$), because the angular deflections were extremely large and outside the screen during shaking. Therefore the theoretical apices were used for determination of angular deflection. The height of stroke ($HS = R \times \sin \alpha$) of a single motion and the arc on the orbit ($arc = 2 \times R \times \pi \times \alpha/360$) were calculated.

2.2.4. Baseline position

The absolute position of the rod was dependent on angle β which describes the position of the arm towards the horizontal axis at rest (Fig. 1). During shaking the autoinjector was moved periodically with $\alpha/2$ in both directions of baseline. Angle β was determined at three points of inflection (lateral shaking) and the mean was calculated for each subject.

2.3. Design and function of the shaking machine

Based on the above analysis, a shaking machine was constructed to imitate the human shaking motion reproducibly and to allow distinct variation of shaking parameters (Table 1).

The apparatus is driven by a 380-V three-phase current motor (16) with a nominal speed of 400 r.p.m. (Fig. 2). The speed can be reduced continuously by a regulator (14) and read from an indicator. The rotation of the shaft is transmitted to the fly-wheel (1) by a V-belt with a 1:1-gear ratio. An eccentric connecting-rod (3) of variable length is fixed on the fly-wheel. The eccentricity can be changed by a sliding block crank (2; variation in height of stroke). The other end of the connecting-rod is fixed to a carriage (4) moving up and down in a dovetail groove (5). A mounting plate (6) on the carriage conveys a vessel system imitating autoinjectors.

For safety reasons, the moving parts of the apparatus are surrounded by a plexi-glass housing (9). The base plate (7) can be mounted on a hinged steel double frame (8) up to a slope of 45° (z-axis). For horizontal shaking, the apparatus is tilted aside (Fig. 2; 90° rotation). The motion of the fixed vessel roughly follows a sine function.

2.4. Vessel system

The vessel mockup (Fig. 3) is fixed on the mounting plate of the shaking device. It consists of three main parts, a solvent chamber (A), a powder chamber (B) and a pneumatically driven valve (C) controlling the ejection of the suspension. The major components are made of plexiglass and fitted by air-tight connections (≥ 6 bar). The upper component of the solvent chamber (A) has an inlet (1) for solvent injection and is connected with a compressed-air line (2) via a manually driven valve (3). In the lower part is a central bore (1 mm diam.) lined with a snug-fitting teflon tubing (6). Its narrow lumen and poor wettability prevents water from dripping into the powder chamber before opening valve (3), and the funnel-shaped bottom allows virtually complete ejection of the fluid. The slant of the bore keeps the powder from intense swirling during solvent injection. From the lateral outlet (8) of the mixing chamber (B) the suspension is forced through a Millex® filter (11; Millipore, Eschborn, Germany, 0.22 mm, 25 mm diam.) into a collecting vessel (13) via a silicon tubing that can be tightly compressed by a pneumatically controlled valve (C). The dead-time of the whole procedure is about 2 s at 4 bar.

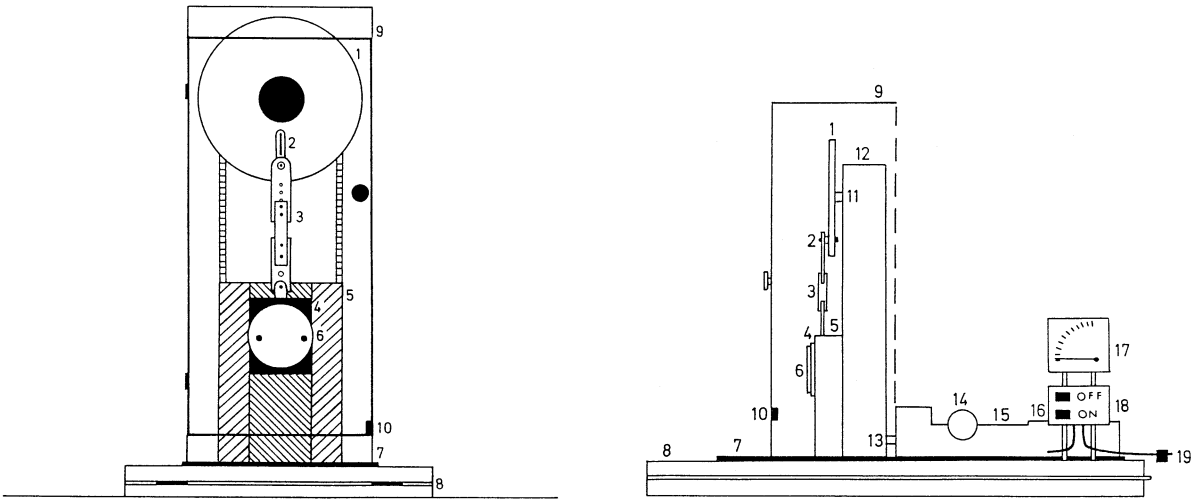

Fig. 2. Shaking machine. 1, Fly-wheel; 2, sliding block crank; 3, connecting-rod; 4, carriage; 5, groove, dovetail-shaped; 6, mounting plate carrying vessel system or autoinjector; 7, base plate; 8, double frame (optional slope variation); 9, plexiglass safety housing; 10, safety switch; 11, driving shaft; 12, beltdrive housing; 13, coupling; 14, speed regulator; 15, gear; 16, motor; 17, speed indicator; 18, switch; 19, mains connection.

The dimensions of the cylindrical mixing chamber were adapted to those of the commercial autoinjectors (Table 2). For the experiments with horizontal shaking, autoinjector mockups with a lateral solvent inlet were used.

2.5. Determination of dissolution kinetics of HI 6 dichloride and HI 6 dimethanesulphonate under various shaking conditions

HI 6 dichloride monohydrate (500 mg; MW 377.2) and 634 mg HI 6 dimethanesulphonate (MW 478.5) were used throughout for the dissolution kinetics in 3.0 and 2.4 ml of tridistilled water with the Astra and STI autoinjector mockups, respectively. All experiments were carried out at 5°C. The standard operation procedure is indicated in Table 3.

To look for the influence of the shaking axis, the machine was inclined by 45° and 90° from the vertical axis. It was made sure that the delivered solvent did not decrease upon inclination.

2.6. Analytical procedures

2.6.1. Photometric determination

HI 6 concentrations were determined in 20 mM phosphoric acid, pH 2, with a UV-265 spectrophotometer (Shimadzu, Duisburg, Germany).

2.6.2. Sieve analysis

Weighed HI 6 dichloride and HI 6 dimethanesulphonate were sieved with a sieve-plate column consisting of 8 ISO 3310-1 sieves (20 cm diam.; aperture: 25, 50, 71, 100, 140, 200, 250 and 500 μm; Retsch, Haan, Germany). The analysis was performed on a Retsch Vibro® sieve shaker. For calculation on a PC, the program Retsch SP 1000 was used.

2.7. Statistics

Data of shaking frequency, height of stroke, arc, a and b were checked for deviation from Gaussian distribution by the method of Kolmogorov-Smirnov (Sachs, 1978). Frequency distribution of normally distributed data was calculated by setting bin width at 10% of arithmetic mean. These data were fitted to the Gaussian distribution function. Correlation of angle α and shaking frequency was investigated by linear regression analysis.

Results are presented as arithmetic means ± S.D., if not otherwise indicated. Coefficients of variation (CV) are given as 100 S.D./mean (%). Significance was tested with Student's t-test (Sachs, 1978). For calculation and graphics a PC was used with GraphPad Prism 2.0 (GraphPad, San Diego, CA) and CSS (StatSoft).

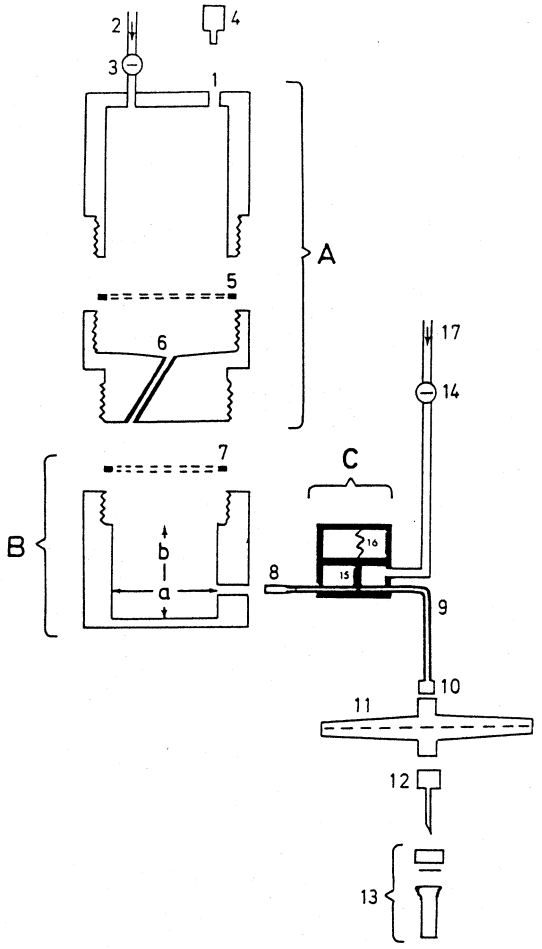

Fig. 3. Vessel system. 1, Inlet for solvent; 2, compressed-air line; 3, manual valve; 4, plug; 5, silicon sealing ring; 6, teflon tubing; 7, silicon sealing ring; 8, Luer lock; 9, silicon tubing; 10, Luer lock; 11, Millex®-Filter; 12, hypodermic needle; 13, collecting vial; 14, manual valve; 15, slider; 16, spring, 17, compressed-air line. a, solvent chamber; b, powder chamber; c, pneumatically driven valve controlling the ejection of the suspension.

Table 2
Dimensions of the mixing chamber in autoinjector mockups

	Astra	STI
Diameter (a)	14.0 mm	11.0 mm
Height (b)	22.9 mm	69.8 mm
Volume	3.53 ml	6.63 ml

3. Results

3.1. Characterization of the manual shaking motion

The periodicity of the shaking motion could be approximated to a sine function with $r^2 = 0.92 \pm 0.13$ (front view) and 0.95 ± 0.03 (side view); $n = 49$ each. The shaking frequency was 217 ± 51 per minute ranging from 102 to 359 per minute. Its frequency distribution (bin width = 21.7 per minute) could be fitted to a Gaussian function with $r^2 = 0.97$.

The autoinjector model was moved at an apparently constant distance (30.7 ± 2.8 cm) from the cubital joint. The cartesian coordinates of the individual shaking motions (side view) allowed good fitting to a circular motion ($r^2 = 0.92 \pm 0.07$;

Table 3
Standard operation procedure to determine the dissolution kinetics of HI 6 under various shaking conditions

- Adjust shaking parameters
- Place pre-weighed HI 6 in the powder chamber
- Screw up the two parts of the solvent chamber
- Couple the solvent chamber with the powder chamber
- Connect the silicon tubing with the outlet of the powder chamber and the Millex® filter attached to the collecting vial
- Fix the vessel system on the mounting plate
- Fill 3.0 ml of water into the solvent chamber and plug up the inlet
- Open the manual valve to force the solvent into the powder chamber
- Immediately start the shaking procedure after complete injection
- Stop shaking after a selected time interval
- Open the pneumatically driven valve to force the suspension through the filter into the collecting vial
- Determine photometrically the HI 6 concentration in the filtrate

$n = 43$). The data of two participants could not satisfactorily be fitted to a circular function ($r^2 < 0.5$), and in five other cases the shaking motion was highly variable.

Angular deflections (α) amounted to $25.2 \pm 10.7°$, ranging from 11 to 53°. The frequency distribution (bin width 2.5°) could be fitted to a Gaussian function with $r^2 = 0.68$. Also height of stroke and arc were normally distributed (means 13.0 ± 4.6 and 13.3 ± 5.4 cm, respectively). Angular deflection, height of stroke and arc were independent of the shaking frequency. The baseline varied intraindividually within a shaking sequence of two to three cycles with CV = 20% and formed an angle of $48 \pm 22°$ towards the horizontal axis. Gaussian function could be fitted with $r^2 = 0.90$.

Differences in the shaking motions of females and males were not detected, albeit differences existed in body height (167.4 ± 5.1 vs 177.3 ± 7.7 cm) and radius (29.6 ± 2.4 vs 31.4 ± 2.7 cm), respectively.

3.2. Kinetics of the dissolution of HI 6 dichloride and dimethanesulphonate at 5°C

To get a first impression of the dissolution process, autoinjector mockups filled with 500 mg HI 6 dichloride and 3 ml of water were shaken under conditions as typically observed in humans. The dissolution kinetics were indistinguishable with both autoinjector types as shown in Fig. 4. Dissolution was complete after 60 s, but reached hardly 2/3 within 5 s. Substitution of the dichloride by the dimethanesulphonate accelerated the dissolution process markedly.

3.3. Effects of different shaking parameters on the dissolution of HI 6 salts

The following experiments were performed with a constant 5-s shaking time. Upon vertical shaking, dissolution was hardly accelerated on increasing shaking frequency up to about 200 per minute at a stroke height of 12 cm. The threshold frequency above which the dissolution rose markedly was 190 and 220 min^{-1} in case of the Astra and STI model, respectively. When the height of stroke was increased to 21 cm the threshold frequency was lower (Astra: 130 min^{-1}; STI: 160 per minute, Fig. 5). Inclination of the assembly also shifted the threshold frequency to lower values, the effect being more marked with the STI mockup (Figs. 6 and 7). It should be noted that the basal concentrations (dissolution before heavy agitation) were generally higher in the Astra model. However, in no case the dissolution of HI

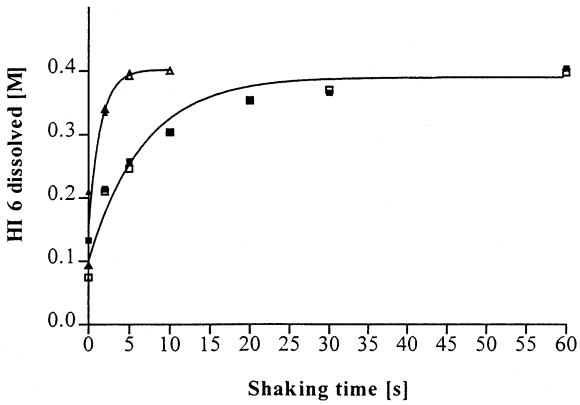

Fig. 4. Dissolution kinetics of HI 6 dichloride and HI 6 dimethanesulphonate in the autoinjector mockups at 5°C. Concentration aimed at 0.4 M. Shaking frequency 180 per minute, height of stroke 12 cm, vertical inclination 45° ($n = 1$). To the data one-phase exponential functions were fitted. □, HI 6 dichloride, STI; ■, HI 6 dichloride, Astra; △, HI 6 dimethanesulphonate, STI; ▲, HI 6 dimethanesulphonate, Astra.

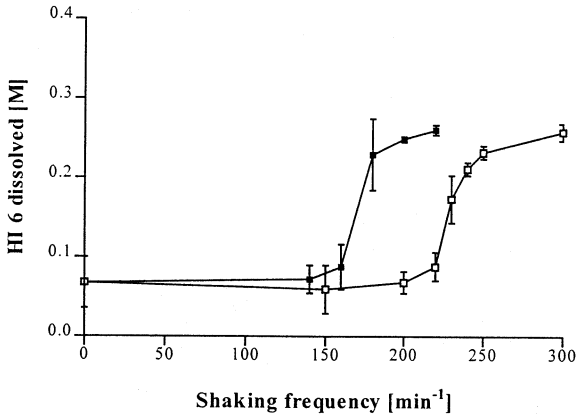

Fig. 5. Influence of shaking frequency and height of stroke on the extent of dissolution of HI 6 dichloride in STI mockups. The experiments were carried out with 0.4 M at 5°C. Vertical shaking was performed for 5 s (means ± S.D., $n = 3$). ■, height of stroke 21 cm; □, Height of stroke 12 cm.

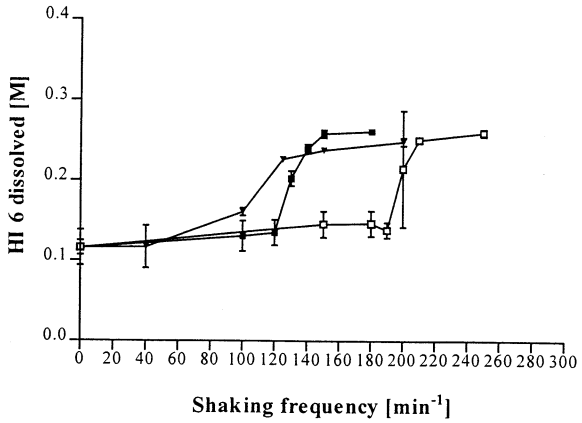

Fig. 6. Influence of shaking frequency and inclination of the device on the extent of dissolution of HI 6 dichloride in the Astra mockup. The experiments were carried out with 0.4 M at 5°C. Shaking time 5 s, height of stroke 12 cm (means ± S.D., $n = 3$). □, Inclination 0°; ■, 45°; ▼, 90°.

6 dichloride exceeded 2/3 of the possible value (0.4 M).

In contrast, dissolution of HI 6 dimethanesulphonate was complete within 5 s. Again, this goal was reached more easily at increased stroke height or with the shaking axis inclined (Figs. 8 and 9).

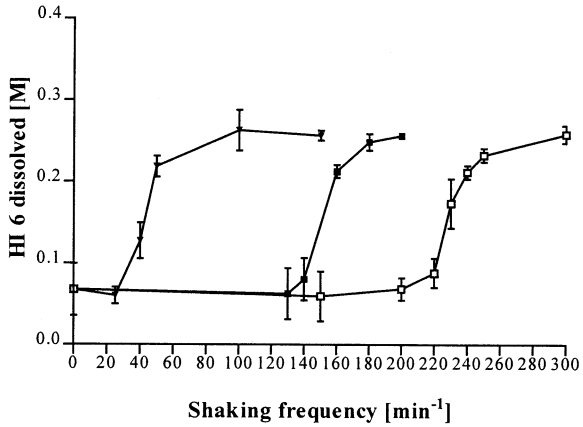

Fig. 7. Influence of shaking frequency and inclination of the device on the extent of dissolution of HI 6 dichloride in the STI mockup. The experiments were carried out with 0.4 M at 5°C. Shaking time 5 s, height of stroke 12 cm (means ± S.D., $n = 3$). □, Inclination 0°; ■, 45°; ▼, 90°.

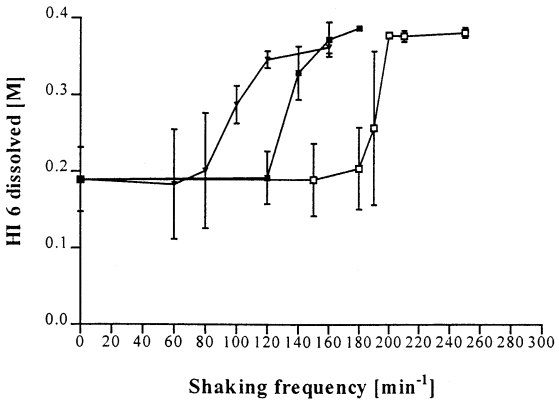

Fig. 8. Influence of shaking frequency and inclination of the device on the extent of dissolution of HI 6 dimethanesulphonate in the Astra mockup. The experiments were carried out with 0.4 M at 5°C. Shaking time 5 s, height of stroke 12 cm (means ± S.D., $n = 3$). □, Inclination 0°; ■, 45°; ▼, 90°.

4. Discussion

The evaluation of the natural shaking behaviour of untrained subjects revealed some unexpected facts. The shaking motion was principally periodical and symmetric and could be roughly described as a motion on an orbit, thus allowing reasonable approximation to a sine wave ($r^2 = 0.92$). The mean shaking frequency of 217 ± 51 per minute was lower than 325 ± 54 per minute as found by Kwon (1996), who requested healthy

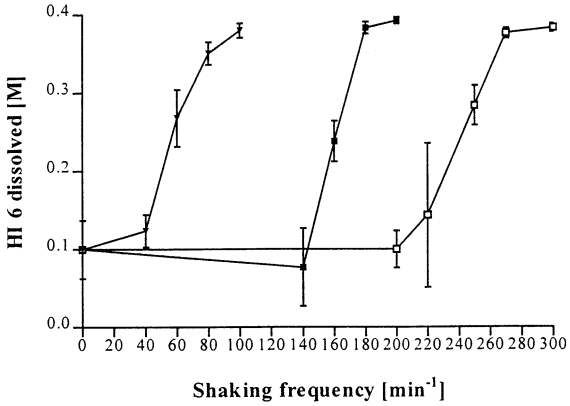

Fig. 9. Influence of shaking frequency and inclination of the device on the extent of dissolution of HI 6 dimethanesulphonate in the STI mockup. The experiments were carried out with 0.4 M at 5°C. Shaking time 5 s, height of stroke 12 cm (means ± S.D., $n = 3$). □, Inclination 0°; ■, 45°; ▼, 90°

persons and patients to shake eye-drop bottles (3 cm diam. × 5.5 cm, 50 g). Unfortunately, there are no data describing the type of shaking. It may be argued that a small-sized bottle, probably fixed between thumb and index, is shaken at a higher frequency than a larger autoinjector dummy held in the fist.

Since the stroke height was rather small (13 ± 5 cm) compared to the radius (31 ± 3 cm), the track of the autoinjector on the orbit did not markedly differ from a straight line, thus facilitating the design of a shaking apparatus. Mechanical shaking under defined conditions was desirable to minimise the otherwise considerable variations inevitably occurring during manual shaking. Pneumatically controlled start and stop of the dissolution process should even further enhance the reproducibility. In fact, experimental data of dissolution kinetics with paracetamol (data not shown) fitted one-phase exponential functions quite well ($r^2 = 0.99$) with a coefficient of variation of the triplicates below 10%.

It must be admitted, however, that our device did not contain a membrane separating the powder from the solvent. For convenience, the liquid was injected into the mixing chamber. Although care was taken not to swirl the solids it cannot be ruled out that such a design may have some impact on the very early dissolution phase. Looking at the influence of the various shaking parameters on the dissolution kinetics of solids, we considered those aspects to be less important.

An increase in shaking frequency regularly resulted in an abrupt rise in dissolution rate, giving fairly steep sigmoidal curves, particularly upon vertical shaking (Fig. 5). The inflexion point was shifted to lower frequency by 30% when the height of stroke was increased. Interestingly, the dissolution of HI 6 dichloride did not reach its maximal value (0.4 M), but revealed a ceiling phenomenon. Any further increase in shaking frequency did not markedly enlarge the amount dissolved. Obviously, agitation cannot totally remove the stagnant layer around the crystals and more time is needed for diffusion (Stricker et al., 1987). In fact, more than 30 s were required for complete dissolution (Fig. 4).

The threshold phenomenon deserves separate comment. Conceivably, straight vertical lowering and lifting of the fluid does hardly agitate the suspension as long as accelerating forces do not surpass gravitation. Above this threshold, the fluid and solids are hurled to the top of the chamber, resulting in intense swirling. Calculation predicts such an effect for 122 and 92 min^{-1} at a stroke height of 12 and 21 cm, respectively. In the experiments, however, the threshold frequencies exceeded the calculated ones by about 60%. Obviously, further forces such as cohesion and adhesion must be surmounted.

Shaking efficiency could be markedly improved when the shaking axis was inclined. This effect was particularly pronounced with the STI mockup (Fig. 7). Thus, a shaking frequency of 80 per minute hardly increased the dissolution of HI 6 in the Astra mockup but had a considerable effect in the STI model (Figs. 6 and 7). Since the crest of the wave runs a longer way in the STI (70 mm) compared to the Astra model (23 mm), dispersing forces may be correspondingly higher. At any rate, shaking in an oblique direction enhances dissolution efficiency.

In contrast, HI 6 dimethanesulphonate which was already superior to the dichloride upon stirring at 5°C (Thiermann et al., 1996) met the requirements. Dissolution was complete within 5 s (Fig. 4) upon sufficient agitation. The shaking parameters used in the experiments shown in Fig. 4 were found to be representative for natural shaking of untrained subjects. More than 3/4 of the volunteers displayed shaking frequencies of greater than or equal to 180 per minute.

These results indicate that HI 6 dichloride may be a critical substance when used in autoinjectors at low ambient temperatures. Although a special design in the commercial autoinjectors may increase the initial dissolution process, it is hard to imagine that complete dissolution of this salt is feasible in view of physico-chemical boundaries. At any rate, a special training for efficient shaking would be mandatory if this salt was used.

References

Apt, L., Henrick, A., Silverman, L.M., 1979. Patient compliance with use of topical ophthalmic corticosteroid suspensions. Am. J. Ophthalmol. 87, 210–214.

Diestelhorst, M., Kwon, K.A., Süverkrüp, R., 1995. Dose Uniformity of Ophthalmic Suspensions. ACRCS Symposium on Cataract, IOL and Refractive Surgery, Best Papers of Sessions, San Diego.

Eyer, P., Hell, W., 1985. Chemical stability of the Hagedorn oximes HGG-12 and HI 6. Arch. Pharm. 318, 938–946.

Eyer, P., Hell, W., Kawan, A., Klehr, H., 1986. Studies on the decomposition of the oxime HI 6 in aqueous solution. Arch. Toxicol. 59, 266–271.

Eyer, P., Hagedorn, I., Ladstetter, B., 1988. Study on the stability of the oxime HI 6 in aqueous solution. Arch. Toxicol. 59, 224–226.

Fyhr, P., Nicklasson, M., Gunnvald, K., Brodin, A., 1987. A preformulation study on the kinetics of HI-6 in concentrated solution. Int. J. Pharm. 40, 193–200.

Kwon, K.A., 1996. Schüttelintensität und Gleichförmigkeit der Dosierung von Suspensions-Augentropfen. Thesis, Bonn.

Kwon, K.A., Süverkrüp, R., Diestelhorst, M., 1996. Dosierungsprobleme bei Suspensions-Augentropfen. Klin. Monatsbl. Augenheilkd. 209, 144–149.

Sachs, L., 1978. Angewandte Statistik. Springer, Berlin.

Stricker, H., Martin, A.N., Swarbrick, J., Cammarata, A., 1987. Physikalische Pharmazie. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart.

Strobel, J., 1991. Zur lokalen applikation von indomethacin zur prostaglandinsynthesehemmung am auge. Ophthalmologica 202, 43–47.

Thiermann, H., Seidl, S., Eyer, P., 1996. HI 6 dimethanesulphonate has better dissolution properties than HI 6 dichloride for application in dry/wet autoinjectors. Int. J. Pharm. 137, 167–176.