J Incl Phenom Macrocycl Chem (2007) 59:105–113
DOI 10.1007/s10847-007-9302-7

ORIGINAL ARTICLE

Preparation and investigation of mixtures containing lidocaine base and β-cyclodextrin

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Received: 21 August 2006 / Accepted: 7 February 2007 / Published online: 21 March 2007

Abstract The effects of β-cyclodextrin (β-CD) on the solubility properties of lidocaine base were studied. Products were prepared by physical mixing, kneading, spray-drying and precipitation methods in drug : β-CD ratios of 3:1, 2:1, 1:1, 1:2 and 1:3. Some auxiliary materials (hydroxy acids, etc.) were also used. The solubility and the rate of dissolution both in distilled water and in artificial gastric juice, the in vitro diffusion, the thermoanalytical properties (TG, DTG, DSC and DTA) and the surface tension were determined, and the measured results were compared with the corresponding data for lidocaine hydrochloride.

Keywords β-Cyclodextrin · Inclusion complexation · In vitro diffusion · Lidocaine base · Rate of dissolution · Thermoanalytical investigations

Introduction

Lidocaine (LID) is a local anaesthetic and cardiac depressant (antiarrhythmic); it was developed as a drug in 1948 [1]. In consequence of its advantageous chemical structure, its low relative molecular weight (234.35), its apolar properties and the small dose required, it is a good candidate for inclusion complexation. It is practically insoluble in water, and it has a melting point of 67–70 °C. Its hydrochloride derivative (LID·HCl), in contrast, is very soluble in water, which furnishes an ideal chance to compare it with inclusion complexes of LID base containing β-cyclodextrin (β-CD), if such inclusion complexes can be prepared.

LID·HCl is indeed an ideal drug in respect of both its solubility and its stability. We should like to study and to compare how CD complexation influences these parameters. This study demonstrates that the CDs are sometimes not able to improve these conditions.

Both compounds are official in the 5th edition of the European Pharmacopoeia [2]. Information on the slope of the solubility isotherm of LID was reported by Szejtli [3]. In 1981, Schubert et al. investigated the transfer of LID through aqueous layers, mediated by CD derivatives [4], and Ferenczy et al. described the pharmacological effects of the inclusion complex LID + DIMEB (dimethyl-β-CD) [5]. In a comparative study, Szemán et al. dealt with the complexation of LID [6]. Fredro-Kumbaradzi et al. reported on the physical stability of a topical liposomal formulation containing LID·HCl [7]. Másson et al. investigated fish skin as a model membrane for the absorption of LID [8]. Morales et al. established that complexation slows down the rate of LID release, suggesting a potential therapeutic use for the complex LID-CD [9]. Ten years ago, Dollo et al. reported conditions of complexation of bupivacaine with CDs [10]. The advantageous parameters of inclusion complexes with CDs are well known for the readers of this journal [11].

The aims of the present work were to study the complexation of LID with CD derivatives (primarily β-CD), to examine their effects on the physicochemical properties of LID, and to investigate the interactions between LID and CDs by thermal analysis. The results will reveal whether LID·HCl or LID base + CD inclusion complexes have the better solubility properties.

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Experimental

Materials

LID base, 2-(diethylamino)-N-(2,6-dimethylphenyl) acetamide (Fig. 1) (EGIS Pharmaceuticals, Budapest, Hungary); *α-CD*, *β-CD*, *γ-CD*, *hydroxyethyl-β-CD* (HE-β-CD) and *randomly methylated β-CD* (RAMEB), (Cyclolab R & D Laboratory Ltd., Budapest, Hungary); *hydroxypropyl-β-CD* (HP-β-CD) (DS: 5.5, Cerestar Inc., Hammon, IN, USA); *citric acid* (CA) and *tartaric acid* (TA) pharmacopoeial grade; *malic acid* (MA) (Reanal Ltd., Budapest, Hungary); *Poloxamer 188* (Pol, BASF, Ludwigshafen, Germany); and *pentaerythritol* (PE) (LOBA Chemie, Vienna, Austria). The solvents (methanol, ethanol, etc.) used are official in Pharmacopoeia Hungarica VIII [12].

Apparatus

A USP modified dissolution (paddle) apparatus, type DT (Heusenstamm Kr. Offenbach, Main, Germany); a Unicam UV/Vis spectrometer with Vision software V3.40 (Unicam Ltd., Cambridge, UK); a Krüss tensiometer (Hamburg, Germany); a NIRO atomizer (Copenhagen, Denmark); a Mettler Toledo type STAR^e Thermal Analysis System, version 6.0 (Schwerzenbach, Switzerland); a Stricker's Sartorius membrane apparatus (Sartorius-Membranfilter GmbH, Germany); and a Derivatograph-C (MOM, Budapest, Hungary).

Preliminary experiments

The effects of the different CD derivatives and hydroxy acids on the solubility properties of LID were determined. For this purpose, mixtures of 0.05 g LID and 0.45 g of one or other CD were diluted to 50.0 mL with distilled water and then stirred for 2 h with a magnetic stirrer. The suspension systems were filtered through filter papers and the UV spectra were recorded (Unicam UV/Vis); LID without CD was used as a control.

On the basis of these investigations, it was established that α-CD, *β*-CD, HP-*β*-CD, *γ*-CD, HE-*β*-CD and RAMEB barely influence the solubility of LID in distilled water.

β-CD was the best of these CD derivatives (Fig. 2).

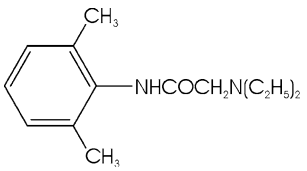

Fig. 1 Chemical structure of LID

Preparation of mixtures

Products were prepared in different molar ratios (drug: *β*-CD molar ratio = 3:1, 2:1, 1:1, 1:2 and 1:3).

Physical mixtures (PMs)

The components were mixed in a mortar and sieved through a 100 μm sieve (Feinstkornprüfsieb).

Kneaded products (KPs)

PMs of LID and *β*-CD were mixed in the same quantity of a water + methanol (1:1, v/v) mixture. They were kneaded until the bulk of the solvent mixture had evaporated. After this, they were dried at room temperature and then at 105 °C, pulverized and sieved (100 μm).

Spray-dried products (SDs)

LID/methanol and *β*-CD/warm distilled water solutions were mixed and heated to obtain clear solutions (60 °C). The SDs were obtained by using a NIRO atomizer at 110 °C inlet temperature with gas heating and a rotation rate of 25,000 rpm. Both chamber and cyclone products were collected. In another experiment, preparations were made containing 10% LID, Lut and PE as auxiliary materials.

Precipitated products (PPs)

LID/methanol and *β*-CD/warm distilled water solutions (55 °C) were mixed and heated to 75 °C, and the resulting clear solutions were cooled, first spontaneously, and next

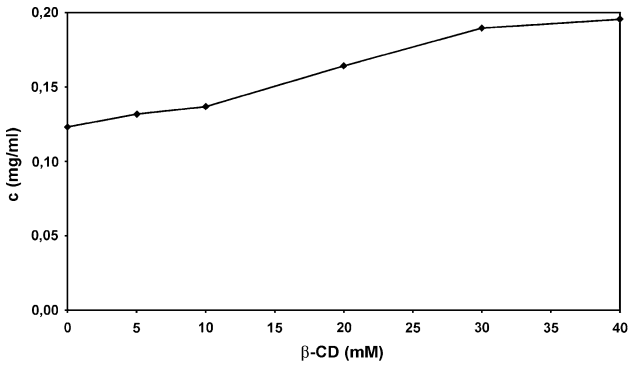

Fig. 2 Solubility of LID with *β*-CD

with ice to 4 °C with continuous stirring. The precipitated products were filtered off under vacuum, then dried, ground, sieved (100 μm) and homogenized. In comparison with other CD derivatives, β-CD is less soluble in water, and is therefore well usable to prepare PPs.

All products were stored under normal conditions (45 ± 5% relative humidity) at room temperature (20 ± 2 °C) in closed glass containers.

Studies in the liquid phase

Effects of hydroxy acids on aqueous solubility of LID

Auxiliary materials were sometimes also used. In connection with the use of hydroxy acids, two important publications should be mentioned. Szente and Szejtli [13, 14] reported that the multicomponent complex formation of base-type drugs with CDs in the presence of acids at an appropriate molar ratio results in a solubility enhancement for sparingly soluble drugs. They used citric, malic and tartaric acids, etc. From a consideration of the specific capacities of the carboxylic groups, 0.11 g of MA or 0.13 g of TA or 0.18 g of CA was dissolved in 25 mL of distilled water in which 0.20 g of LID was suspended. After magnetic stirring for 2 h and filtration, the absorbances were determined spectrophotometrically; the reference contained only the hydroxy acid.

CA contains three carboxylic groups, and therefore 0.06 g, 0.12 g and 0.18 g quantities of CA were also investigated together with 0.20 g of suspended LID in 25 mL of distilled water in the previous manner.

Phase solubility studies

Solubility diagrams were obtained according to Higuchi and Connors with β-CD in distilled water [15]. Excess LID was added to aqueous solutions containing various concentrations of β-CD (0–40 mM). The suspensions were stirred at room temperature (20 ± 2 °C) until equilibrium had been reached (7 days). Next, the suspensions were filtered and the concentrations of the solubilized LID were measured spectrophotometrically at 264 nm.

The apparent stability constants of the LID + β-CD complexes were calculated from the initial straight portion of the phase solubility diagram.

Partition coefficients and surface tension measurements

The partition coefficient (K_p) measurements were carried out in two separate solutions: *n*-octanol saturated with distilled water, and distilled water saturated with *n*-octanol. 0.10 g of LID and products containing 0.10 g of LID were suspended in 5 mL of each solvent. The suspensions were stirred at 25 ± 2 °C until equilibrium had been reached (7 days) and then filtered, and the concentrations of the solubilized LID were determined spectrophotometrically. K_p values were calculated according to the Nernst distribution law [16].

For the determination of surface tension, 0.10 g of LID and β-CD or products containing 0.10 g of LID were dissolved or suspended in 30 mL of distilled water and the suspensions were stirred for 2 h. After filtration, the surface tensions of the solutions were determined by a modified tensiometric ring method, with a Krüss tensiometer [17].

Determination of heat of dissolution in different temperature intervals

0.10 g of LID or the LID:β-CD (1:2) KP containing 0.10 g of LID was suspended in 50 mL of distilled water. The suspensions were placed in water-baths at 20, 40 or 60 °C and stirred for approximately 6 h, samples being taken after 3 and 6 h. After filtration and suitable dilution, the absorbances were examined spectrophotometrically. The energies of dissolution in the temperature intervals 20–60 °C and 40–60 °C were calculated via the Clausius–Clapeyron equation [18].

In vitro dissolution studies

The dissolution studies were carried out on the products by using the USP dissolution apparatus with a modified paddle method in distilled water and in artificial gastric juice (AGJ) at 37 ± 1 °C during 90 min. Sampling was performed after 5, 10, 15, 30, 60 and 90 min. The LID contents were determined spectrophotometrically at 264 nm (Unicam UV/Vis spectrometer). All of the determinations were carried out at least in triplicate.

In vitro membrane diffusion experiments

Stricker's Sartorius instrument was used [19, 20]. Measurements were performed from 100 mL of AGJ into artificial plasma (Table 1). About 100 mg of LID or product containing 100 mg of LID was in the donor phase in all cases. The temperature was 37.5 ± 1.5 °C. About 5.0 mL sample aliquots were taken five times (after 30, 60, 90, 120 and 150 min) and their active agent contents were determined

Table 1 Compositions of artificial juices

	Gastric juice	Plasma
pH (±0.1)	1.1	7.5
1 N HCl	94.0 g	–
NaCl	0.35 g	–
Glycine	0.50 g	–
$Na_2HPO_4 \cdot 2H_2O$	–	20.5
KH_2PO_4	–	2.8
Distilled water	to 1000 mL	to 1000 mL

spectrophotometrically after filtration and suitable dilution. The amount of diffused LID and the diffusion constant K_d were calculated:

$$K_d = \frac{c_{II2} - c_{II1}}{T_2 - T_1} \cdot \frac{1}{c_{I0}} \cdot \frac{V_{II0}}{F} \text{ [cm min}^{-1}\text{]}$$

where c_{IIx} is the corrected LID concentration in phase II at time T_x (mg mL^{-1}); V_{IIo} is the volume of aqueous phase II at time T_0 (100 mL); F is the surface area of the membrane (cm^2); T_x is the time (min); and C_{I0} is the theoretical initial drug concentration in phase I (mg mL^{-1}) [19, 20].

Studies in the solid phase

Particle size distribution study

The particle size and particle size distribution were determined for LID, SD LID and SD LID:β-CD with a molar ratio of 1:2, by means of a Leica Q500 MC image processing and analysis system (Leica, Cambridge, UK).

Thermoanalytical studies

The thermal behaviour of LID, β-CD and each inclusion complex was examined by using a Derivatograph-C and a Mettler Toledo STAR Thermal Analysis System DSC 821^e. Argon was used as carrier gas and the DSC analysis was performed at a heating rate of 5 °C min^{-1} and an argon flow rate of 10 L h^{-1}. The sample size was in the range 3–5 mg and examinations were made in the temperature interval 25–300 °C.

TG and DTG studies were carried out with a Derivatograph-C apparatus. A normal air flow was used and the heating rate was 5 °C min^{-1}. About 50 mg samples of materials and products were examined, the inert material being 50 mg of aluminium oxide.

Results

Results of studies in the liquid phase

Improvement of aqueous solubility

Studies were performed both in liquid and solid phase. In preliminary experiments, it was established that β-CD was the best of the eight CD derivatives, which is not usual, and that stoichiometric quantities of different weak solid organic acids influence the aqueous solubility of LID to very various degrees, which is in harmony with the results of earlier experiments. The effect of TA was best. The different quantities of CA affected the solubility of LID only very moderately (Table 2).

Phase solubility studies

The intrinsic solubility of LID is S_o = 0.1231 mg mL^{-1}. In the presence of 5, 10, 20, 30 or 40 mM β-CD, the solubilities of LID were 0.1317, 0.1367, 0.1642, 0.1896 and 0.1954 mg mL^{-1}, which means that LID gave an A_N-type diagram, with a slope of 0.17196.

Partition coefficients and surface tension measurements

These results reveal that, although LID is very well soluble in *n*-octanol, LID·HCl is much better soluble in distilled water. Consequently, the K_p of LID is far the highest, while the K_p values of LID·HCl and all the products containing LID and β-CD are relatively very small.

The surface tension of the solution containing β-CD is the largest, while it is the smallest in the case of LID base. With the exceptions of LID + β-CD (1:1) PP and LID + β-CD + TA (1:1:1) PM, the surface tensions of all the products lie in the interval 60–71 mN m^{-1}. The surface tension of a solution influences the membrane diffusion results (Table 3) [21].

In vitro dissolution studies

From the PMs with ratios of 1:1 and 1:2, the *rate of dissolution* of LID *in distilled water* was 50–60% more

Table 2 Aqueous solubility enhancement of LID with weak solid organic acids

LID, alone	100%
LID + 0.11 g MA	235%
LID + 0.13 g TA	468%
LID + 0.06 g CA	216%
LID + 0.12 g CA	235%
LID + 0.18 g CA	239%

Table 3 Solubilities, partition coefficients and surface tensions of materials and mixtures

Materials and products	$C_{n\text{-octanol}}$ (mg mL^{-1})	C_{water} (mg mL^{-1})	Partition coefficient K_p $C_{n\text{-octanol}}/C_{water}$	Surface tension (mN m^{-1})
LID base	14.606	0.118	123.780	51.2
LID·HCl	2.831	166.435	0.017	61.6
LID + β-CD (1:1) PM	0.079	0.185	0.427	60.5
LID + β-CD (1:2) PM	0.024	0.149	0.161	60.8
LID + β-CD (1:1) KP	0.065	0.183	0.355	61.2
LID + β-CD (1:2) KP	0.029	0.146	0.199	60.5
LID + β-CD (1:1) PP	0.010	0.005	2.000	73.2
LID + β-CD (1:2) PP	0.043	0.004	10.75	70.8
LID + β-CD (3:1) SD	0.051	0.064	0.796	62.7
LID + β-CD (2:1) SD	0.052	0.123	0.422	64.3
LID + β-CD (1:1) SD	0.008	0.064	0.125	63.3
LID + β-CD (1:2) SD	0.016	0.041	0.390	62.8
LID + β-CD (1:3) SD	0.019	0.062	0.306	60.5
LID + β-CD + TA (1:1:1) PM	0.040	0.289	0.138	73.7
β-CD	0.016	0.185	0.086	79.1

after 5, 10 and 15 min; later, these values were only between 10% and 30% (Fig. 3). In the case of the PMs, complexes are not formed during the dissolution experiments, because the rate of dissolution did not increase appreciably.

As concerns the PPs, LID alone dissolves better than from its products. This result is in harmony with the results of Morales et al.: inclusion complex formation in the crystals decreases the rate of dissolution (Fig. 4). As the duration of dissolution increased, the standard deviations became smaller.

As regards the rate of dissolution *in AGJ*, after 15 min the quantity of LID dissolved was uniformly between 14.5 mg and 15.5 mg for all PMs and KPs. The rates of dissolution were in agreement with the earlier results for the 1:1:1 PMs of LID + β-CD + TA or CA or MA.

Membrane diffusion experiments

These results may be seen in Table 4. Similarly to the results of the in vitro dissolution studies, first it was surprising that the rate of diffusion of LID was the largest. This is connected with its good solubility in lipids, its large K_p value and its low surface tension. Accordingly, it has a relatively high concentration in a membrane lipid mixture, which facilitates its diffusion into the artificial plasma. In contrast, the products well soluble in water have comparatively low K_d values [22, 23].

Determination of heat of dissolution in different temperature intervals

Heats of dissolution are determined by using the Clausius–Clapeyron equation [18]:

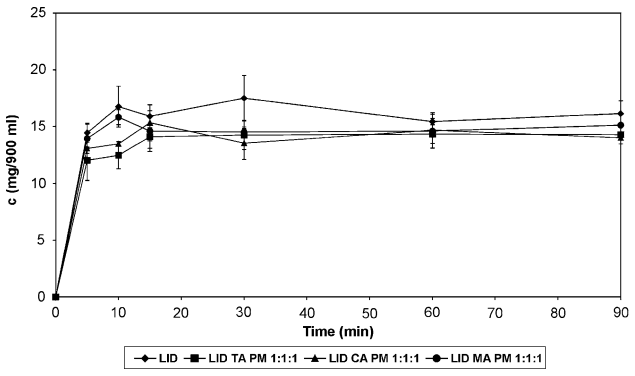

Fig. 3 Dissolution results on products containing LID, β-CD and different hydroxy acids and distilled water

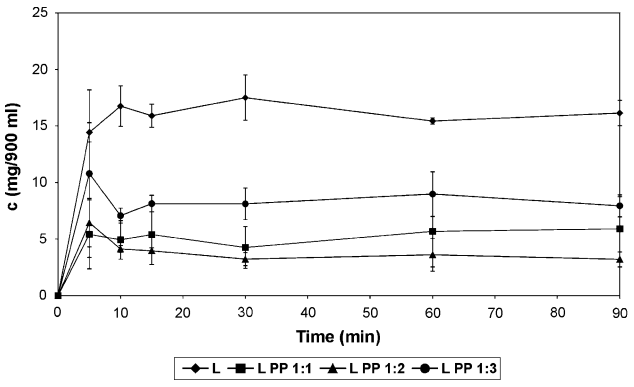

Fig. 4 Dissolution results on PP products containing LID and β-CD in distilled water

Table 4 In vitro membrane diffusion examinations of LID·HCl, LID and their products (SD ± = standard deviation)

Materials	K_d (10^{-4}) (cm min^{-1})	SD (±)	Diffused (%)
LID	3.74	6.11	2.49
LID, SD	1.09	1.55	1.55
LID·HCl	0.72	0.52	0.48
LID + β-CD, PM 1:1	1.09	0.79	0.73
LID + β-CD, PM 1:2	0.76	0.74	0.50
LID + β-CD, KP 1:1	0.62	0.45	0.41
LID + β-CD, KP 1:2	0.97	1.08	0.65
LID + β-CD, PP 1:1	0.42	0.42	0.28
LID + β-CD, PP 1:2	0.54	0.95	0.36
LID + β-CD, PP 1:3	0.44	0.38	0.30
LID + β-CD, SD 3:1	1.08	2.25	1.06
LID + β-CD, SD 2:1	0.35	0.34	0.23
LID + β-CD, SD 1:1	0.67	1.01	0.50
LID + β-CD, SD 1:2	0.64	1.05	0.45
LID + β-CD, SD 1:3	0.28	0.43	0.19
LID + β-CD + Lut + PE, SD	1.31	1.81	0.87
LID + β-CD + CA, PM 1:1:1	0.52	0.45	0.34
LID + β-CD + MA, PM 1:1:1	0.31	0.26	0.21
LID + β-CD + TA, PM 1:1:1	0.71	0.70	0.47

$$\log\frac{c_1}{c_2} = \frac{\delta Q_{sol}}{4.573}\cdot\frac{T_1 - T_2}{T_1 \cdot T_2}$$

where δQ_{sol} = heat of dissolution; and c_1 and c_2 = solubilities at temperatures T_1 and T_2 (absolute temperatures, K).

The energy needed to dissolve different materials (or for a change of phase) is dependent on the conditions of the dissolution process. From the solubility results at 20 °C, 40 °C and 60 °C, we can calculate the values of heat of dissolution (δH_{sol}) by using the Clausius–Clapeyron equation. During inclusion complex formation, we have to take into consideration at least three part-processes.

(1) Cessation of the crystal structure of the drug or cyclodextrin, etc. which is an endothermic process.
(2) The dissolved molecules may interact with the molecules of the solvent, which in contrast is generally an exothermic process.
(3) The interaction of the earlier two phenomena with the auxiliary materials used in pharmaceutical technology, e.g. surfactants, CDs, wetting and complexing agents, etc.

For example, in the case of iomeglamic acid and sorbitan laurate (=Tween 20) [2], which is a surfactant or β-CD, the values of δH_{sol} are smaller at 20–40 °C than for iomeglamic acid alone, while they are higher at 40–60 °C. The plots of the log solubility values as a function of $1/T$ usually consist of two intersecting straight lines (Table 5).

Similar results were obtained with furosemide, diazepam and nitrazepam.

The experimentally determined energies for LID and LID + β-CD (1:2) KP, e.g. the heats of dissolution in the intervals 20–60 °C and 40–60 °C, are presented in Table 6.

These results indicate that the energy needed for LID to dissolve is less in the higher temperature interval; it may be noted that the melting point of LID is 67–70 °C. The energy needed for the product to dissolve is more than that for LID; this phenomenon suggests only weak complex formation between LID and β-CD.

Results of studies in the solid phase

Particle size distribution study

About 38–42% of the particles of LID, SD LID and the SD product of LID + β-CD (1:2) measure 10–20 μm. The SD particles are spherical, of course, while the crystals of LID frequently have a prismatic form (Fig. 5).

Thermoanalytical studies

The DSC spectra of LID and LID·HCl demonstrate that they have practically the same melting point range: 66.97–69.78 °C for LID and 67.00–69.98 °C for LID·HCl (Fig. 6). This fact is important in investigations of the products with β-CD. TG, DTG and DTA curves of LID can be seen in Fig. 7. The curves for LID·HCl are analogous.

Table 5 δH_{sol} values of iomeglamic acid alone and with auxiliary materials (kJ/mol)

Material(s)	20–40 °C	40–60 °C	20–60 °C
Iomeglamic acid	18.72	22.79	20.63
Iomeglamic acid + Tween 20	5.80	32.94	18.50
Iomeglamic acid + β-CD 1:1	6.80	19.27	12.64
β-Cyclodextrin	25.26	41.76	32.99

Table 6 Heats of dissolution in different temperature intervals

Temperature intervals	Lidocaine base (kJ mol^{-1})	LID + β-CD (1:2) KP (kJ mol^{-1})
20–60 °C	6.328	9.363
40–60 °C	2.676	6.319

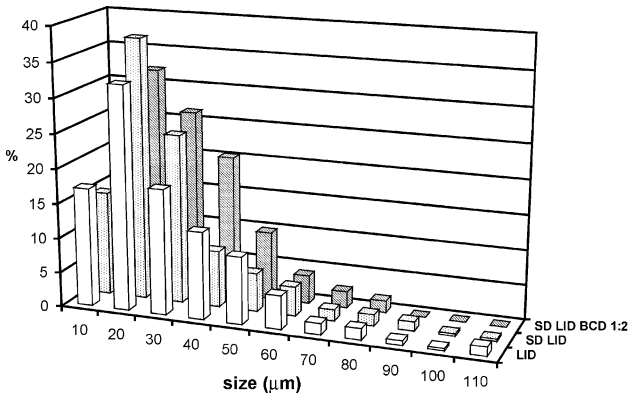

Fig. 5 Particle size distributions of LID and some SD products

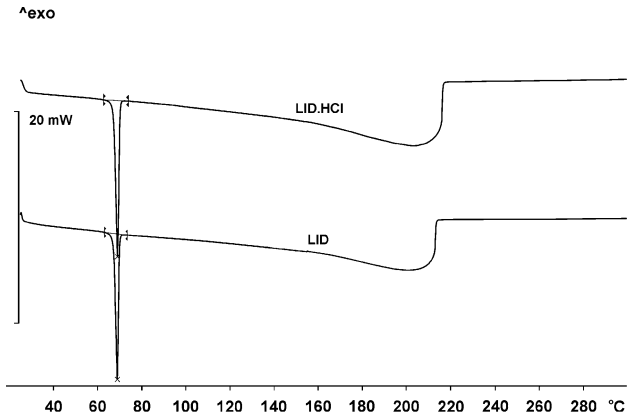

Fig. 6 DSC curves of LID and LID HCl

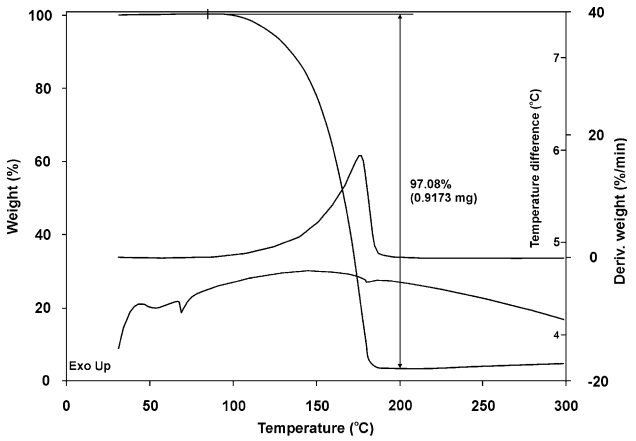

Fig. 7 TG, DTG and DTA curves of LID

The general findings are presented in Table 7. Naturally, in the products containing relatively more LID (in ratio 1:1), the thermoanalytical changes are larger than in the 1:2 and 1:3 products. LID and

Table 7 Weight losses of samples and products

Sample or product	Weight loss (%)	Temperature interval (°C)
LID	97.08	25–200
LID·HCl	0.6345	25–75
	95.89	75–200
LID + βCD 1:1 PM	11.50	25–95
	14.46	95–195
LID + βCD 1:2 PM	12.70	25–90
	8.147	90–190
LID + βCD 1:1 KP	10.08	25–90
	16.03	90–190
LID + βCD 1:2 KP	11.62	25–90
	8.508	90–190
LID + βCD 1:1 SD	8.654	25–125
LID + βCD 2:1 SD	8.151	25–105
	1.032	105–150
LID + βCD 3:1 SD	6.420	25–100
	7.922	100–180
LID + βCD 1:1 PP	7.655	25–125
LID + βCD 1:2 PP	8.403	25–125
LID + βCD + CA 1:1:1 PM	10.43	25–110
	9.325	110–180
	10.28	180–260
LID + βCD + MA 1:1:1 PM	11.23	25–110
	8.896	110–200
	3.527	200–250
LID + βCD + TA 1:1:1 PM	11.03	25–100
	6.766	100–180
	4.279	180–250

LID·HCl contain moisture or crystal water which evaporates up to 100 °C (this means 1 step).

Both LID and LID · HCl have low melting points (67–70 °C), and consequently LID and LID · HCl alone evaporate to extents of 86.54% and 97.08%, respectively. They also evaporate from all PM and KP products which do not form complexes (exhibiting a 2nd step, too).

The SDs and PPs of the 1:1 products form 1 step only (the 2nd step does not appear), which means that LID is presumably situated in the cavity of CD, and thus complex formation is probable. The 2:1 and 3:1 SD products contain more LID, and therefore their weight losses are 1.03% and 7.92%, respectively, in the 2nd step.

The 1:1 and 1:2 PP products exhibit only 1 step, because the LID is probably present as a weak complex in these cases.

In the DSC investigations, the TA begins to evaporate when the LID has already practically totally evaporated.

As concerns the influence of these three acids, the 1:1:1 products evaporate in three steps: up to 100–110 °C, they lose their water and LID content; between 100 °C and 180–200 °C, they lose the acids

(CA, MA and TA); and finally, between 200 °C and 260 °C, they lose their CD derivatives.

Discussion

LID base is an important local anaesthetic and cardiac depressant which has disadvantageous solubility properties. At the same time, it may be an excellent candidate for inclusion complexation. As a derivative well soluble in water, LID·HCl affords a good possibility for comparison of the physicochemical and pharmaceutical properties of LID + β-CD complexes with those of its LID·HCl derivative. Studies were performed in both the liquid and the solid phase. The preliminary experiments revealed that in this case β-CD was the best of the eight CD derivatives, which is not usual.

In the phase solubility studies, it was found that LID gives an A_N-type diagram with a slope of 0.17196 (*N* means a deviation in the negative direction).

The effects of different auxiliary materials, such as hydroxy acids, on the aqueous solubility of LID were investigated. Stoichiometric quantities of weak solid organic acids proved to influence the aqueous solubility of LID, which is in harmony with the results of earlier experiments. The best results were obtained with TA.

The products were prepared in LID:β-CD molecular ratios of 3:1, 2:1, 1:1, 1:2 and 1:3 by using physical mixing, kneading, spray-drying and precipitation methods.

The dissolution rate was measured by using a modified USP rotating basket method. β-CD increased the rate of dissolution of LID by 46–80% during 5–15 min. Later, the value was generally only between 10% and 30%.

Why is the rate of dissolution of LID in water higher in the first 15 min? This phenomenon may have at least two causes. (1) In the case of very well-soluble drugs and products, it may happen that a metastable solution is formed by supersaturation, which will later be stabilized. (2) Sampling occured at the height of the rotating basket and 15 min is not enough to achieve a homogeneous solution. This was caused by the inhomogeneity of the system. The local concentration at the sampling site was higher, so the calculated concentration was also higher than the average. The difference between the local and the average concentrations decreased as a result of mixing. This is a general phenomenon (e.g. iomeglamic acid, fenofibrate, etc.).

The solubility and penetration of drugs are the two most important parameters in the process of absorption of biologically active materials, and thus in connection with the partition coefficients and surface tension measurements. As we hoped, we observed dramatic changes in the solubility of LID in both *n*-octanol and water, and the values of the partition coefficients are therefore of significance. The changes in the surface tension of the investigated basic materials (LID, LID · HCl and β-CD) and their mixtures were also considerable. Since both the partition coefficient and the surface tension depend on the components and the methods of preparation of the mixtures, these results are noteworkly. As the solubility in water increased, the partition coefficient and surface tension of the products changed considerably.

From the solubility and penetration parameters of the basic materials and their mixtures, we obtained useful results which are in good consonance with the data of membrane diffusion examinations. The best K_p value was for LID (3.74×10^{-4} cm min^{-1}), which goes without saying as we know that LID has a relatively high concentration in the lipid mixture in the membrane. In consequence of the low solubility of LID in water, which means that the LID molecules dissolved into the lipid mixture, they have to penetrate only into the acceptor phase. The rate of diffusion of LID proved to be the highest; at first sight, this was surprising, but it is nevertheless very logical if we consider that the in vitro diffusion depends sensitively on the solubility of LID in the membrane lipid mixture.

The experimentally determined energies of LID and its complex with β-CD suggest only weak complex formation between LID and β-CD.

In thermoanalytical experiments, the TGA and DTA curves of LID and its PMs and KPs of ratio 1:1 point to water contents of 10.08–12.70%. For the molecular ratio 1:2, the mixtures naturally contain a little more water. A relatively high water content disturbed the signs of melting of LID and LID · HCl.

Conclusions

The behaviour of LID with CDs is exceptional. Overall, it may be stated that β-CD appreciably influenced the physicochemical and pharmaceutical properties of LID in its products, possibly via weak inclusion complexation. This influence is generally smaller than for the same properties of LID·HCl.

From a therapeutical aspect, it is better to use LID · HCl than LID complexed with CDs for systemic purposes (orally in tablets or capsules), because LID·HCl has better biopharmaceutical properties. On the other hand, it is advantageous to apply LID + CD

complexes locally, e.g. in ointments, where there is no chance for the transformation of LID to LID·HCl, as in the stomach. Therefore, LID + CD complexes may be advantageously used primarily in topical dosage forms.

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