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ORIGINAL ARTICLE

Hepatic and renal toxicities of indomethacin acid, salt form and complexed forms with hydroxypropyl-β-cyclodextrin on Wistar rats after oral administration

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ABSTRACT

Indomethacin (IM), a non-steroidal anti-inflammatory drug, has the capacity to induce hepatic and renal injuries when administrated systemically. The aim of this study is to assess the IM absorption from complexed forms when orally administered to rats, by means of a comparative evaluation of its capacity to induce hepatic and renal injury in different forms, namely IM acid, IM sodium salt or IM complexed with hydroxypropyl-β-cyclodextrin (HP-β-CD), using freeze- and spray-drying methods.

A total of 135 Wistar rats weighing 224.4 ± 62.5 g were put into 10 groups. They were allowed free access to water but were maintained on fast for 18 h before the first administration until the end of the experiment. Water and HP-β-CD (control groups) and IM acid form, IM trihydrated-sodium-salt and IM-HP-β-CD spray- and freeze-dried, at normal and toxic doses (test groups), were orally administered once/day for 3 days. Seventy-two hours after the first administration, the animals were sacrificed and a fragment of the liver and one kidney were collected and prepared for histopathological evaluation. Lesion indexes (rated 0/4 for liver and 0/3 for kidney) were developed and the type of injury scored according to the severity of damage. A statistical analysis of the severity and incidence of lesions was carried out.

Animals administered with IM complexed forms showed similar hepatic and renal lesions, both in toxic and therapeutic doses, when compared with those observed in animals administered with IM acid or salt forms. This suggests that under the present experimental conditions, IM is equally absorbed from the gastrointestinal tract, independently of the administered IM form.

INTRODUCTION

Indomethacin (IM) is a non-steroidal anti-inflammatory drug (NSAID) used for the treatment of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and for the closure of patent ductus arteriosus in newborns. IM can be administered by injection, tablet, capsule or suppository. Independently of the administration route used, IM can produce gastrointestinal side effects like irritancy because of its mechanism of action, which involves the inhibition of the synthesis of prostaglandins. IM can also cause ulceration of the stomach and intestine, this effect being more severe following oral administration [1–3].

Patent ductus arteriosus is the persistence of a normal foetal structure between the left pulmonary artery and the descending aorta. Persistence of this foetal structure beyond 10 days of life is considered abnormal. Intravenously administered IM is the drug of choice for closure of the ductus [4–6].

To overcome the difficulty of using the intravenous route in newborns as well as the impossibility of using the oral route to administer IM to this kind of patient (because of characteristic of newborns that the hydrolysis of IM that occurs at gastric basic pH (6–8) and because of the gastrointestinal toxicity to which it is associated), we investigated the possibility of using an inclusion complexed form of IM to treat patent ductus arteriosus by oral administration.

For this purpose, we first prepared IM hydroxypropyl-β-cyclodextrin (HP-β-CD) complexes by enclosure of either the *p*-chlorobenzoic part or the ring of the indol unit of the molecule in the cyclodextrin channel, either by freeze-dried (FD) or spray-dried (SD) methods [7–10]. Our previous studies of dissolution and partition coefficient showed that complexation enhances dissolution capacities of lipophilic drugs without changing the characteristics that make them suitable for membrane diffusion [11]. These inclusion complexes have the capacity to enhance IM's solubility and stability in aqueous solution [10] and were expected to reduce the gastrointestinal adverse effects [7,12]. To test this hypothesis, we performed experimental procedures on Wistar rats to evaluate the gastric damage induced by IM inclusion complexes, compared with indomethacin sodium salt (IMss) and indomethacin acid form (IMaf). The results showed that IM inclusion complexation protects against gastric injury, reducing the incidence and the maximum degree of severity of the gastric lesion index from 4 to 1, with a better performance of the SD complex [13].

The mechanism of action of IM includes the capacity to induce hepatic and renal lesions when administrated systemically [14–24].

In the liver, the mechanism by which the medicines or their metabolites cause cellular death may function in two ways: (i) the reactive metabolites break the balance of the factors that support survival, leading to a direct loss of viability; (ii) the reactive substances modify this balance to make the hepatic cells susceptible to the lethal effects of the inherent immunity system, that is, cytosines, such as the tumoral necrosis factor, produced by the activation of the resident inflammatory cells in the liver. The result may vary between the maintenance of the viability and the apoptosis or necrosis, depending on the drug, on the degree of exposition to the reactive metabolites and on a variety of genetic and environment factors that modulate the drugs' metabolism, the transport, defence and regeneration's metabolism, as well as on the presence of cytosines and genes leading to the survival or death [25,26]. IM can be associated to reversible cholestatic lesion, transitory changes of the hepatic enzymes and fatal cases of acute hepatocellular necrosis and steatosis. The lesion's incidence is low, and the information is insufficient to explain the induction mechanism of cytolytic lesion and steatosis. The lesion's registers are mainly hepatocellular, massive or central necrosis, accompanied in some cases by microvascular steatosis, relevant cholestasis and biliverdin [14,23, 24,26,27]. In a recent study to assay molecular indicators of acute hepatic injury associated with the administration of IM, the authors concluded that even brief exposure to IM altered serum enzymatic activities and that high levels of IM significantly altered gene expression in the liver and hepatic histology and the regulation of basal metabolism [28].

In the kidneys, renal blood flow is regulated through processes that involve prostaglandins, vasodilator substances that protect renal blood flow and glomerular filtration rate, with an opposite function of that of catecholamine, angiotensin II, vasopressin and endothelin vasoconstrictors. The inhibition of prostaglandins by NSAIDs induces renal injury, leading to acute renal insufficiency with or without oliguria, chronic insufficiency, clinically relevant proteinuria, fluid metabolism changes or hyperkaliemia. An increase in vascular resistance, a reduction in blood flow and a reduction in the glomerular filtration rate can also be observed. In addition, a vasopressin rise leads to water retention and hyponatremia, with the common consequences of oliguria, hypercreatinaemia, hyperazotaemia, decrease in free water excretion and an increase in the quantity of sodium and potassium eliminated fractions as well as consequent development of renal insufficiency. Nephrotoxic effects of NSAIDs are related with the inhibition of cyclo-oxygenases (COXs), which are essential enzymes in the morphogenesis and natural renal maturation: COX-1 is a constitutive enzyme present in many tissues, including the kidneys, and COX-2 has recently been identified as another constitutive enzyme of these organs. IM rarely induces nephrotoxicity on patients with normal renal function but can aggravate pre-existing situations of renal dysfunction [15–18,20–22,29,30]. In a study developed to determine the type of renal changes found in light and electron microscopy following admin-

istration of IM, ibuprofen and gentamicin in a neonatal rat model, the authors found that light microscopy examination in all IM- and ibuprofen-treated pups, both antenatal and postnatal, showed vacuolization of the epithelial proximal tubules, interstitial oedema, intratubular protein deposition but no significant glomerular changes. Electron microscopy examination showed pleomorphic mitochondria and loss of microvilli in the tubules [31]. In another recent study, the authors concluded that IM caused renal epithelial cell injury independently of COX inhibition and that IM treatment was associated with the disruption of mitochondrial transmembrane potential, release of cytochrome c, downregulation of Bcl-2 and Mcl-1, upregulation of Bax and elevation of caspases' activity [32].

Based on these facts, the aim of this study is to evaluate in Wistar rats the capacity of IM of inducing hepatic and renal injuries by comparing its oral administration as IMaf, IMss or IM HP-β-CD FD/SD complexes. The following hypothesis will be tested: if IM is well absorbed from the gastrointestinal tract and its capacity of hepatic and renal lesion induction will be similar among all the formulations used, either in the therapeutic dose (TD) or in the toxic dose (TxD).

MATERIALS AND METHODS

Drug products

Indomethacin acid form (IMaf) was kindly provided by Merck Sharp & Dohme (Lisboa, Portugal); IMss tri-hydrated was purchased under the name of Indocid® (Coimbra, Portugal); HP-β-CD, molecular weight of 1300 and medium molar substitution degree of 0.39, was obtained from Jassen Biotech (Beerse, Belgium); IM complexes with HP-β-CD were prepared using FD and SD methods.

Dose selection

Two different doses of the testing products were administered: a TD, defined as the dose equivalent to the one used to treat newborns with patent ductus arteriosus – 0.2 mg/kg – and a TxD, defined as the dose referred in the literature as having the capacity to induce lesions without causing mortality – 10 mg/kg [33,34]. The calculation of the dose equivalent to the TD was based on the application of the conversion factor recommended by the Food and Drug Administration when the animal under study is the rat (available at: http://www.fda.gov/cder/cancer/animalframe.htm). The IM dose present in the complexes obtained by each of the complexing methods was calculated from the percentage of IM included in the HP-β-CD, based on the results of the technological study performed – the freeze-dried complex (CFD) contained 17.3% of IM and the spray-dried complex (CSD) contained 24.3% of IM [10]. HP-β-CD dose, used as control, was the same amount of HP-β-CD contained in the TxD sample, corresponding therefore to the higher percentage. It was assumed that the dose of IMss to be administered for the TxD would be double the quantity of the TD, because this dose is already considered as having a toxic capacity.

Product solutions were prepared as follows: TxD (IMaf and IMss) = 2 mg/mL (30 mg IM/15 mL water); TD (IMaf and IMss) = 46.28 μg/mL (1 mg IM/21.6 mL water); TxD (CSD) = 8.24 mg/mL (123.6 mg CSD/15 mL water); TD (CSD) = 190.46 μg/mL (4 mg CSD/21 mL water); TxD(CFD) = 11.56 mg/mL (173.4 mg CFD/15 mL water); TD (CFD) = 267.5 μg/mL (5.35 mg CFD/20 mL water); TxD (HP-β-CD) = 9.56 mg/mL (95.6 mg CD/10 mL water); Water = 5 μL/g animal.

Animals

This study was carried out on 2-month-old male and female Wistar rats weighing 224.4 ± 62.5 g (Harlan Iberica, Barcelona, Spain). The rats were housed in a local *bioterium* under standard laboratory conditions, which include a temperature of 20–24 °C, relative humidity about 50–60% and a controlled 12-h light cycle beginning early in the morning. Animals were allowed free access to water but the food was withdrawn from them 18 h before the beginning of the first administration. Animal experimentation in this study was conducted in accordance with the European guidelines for the care and use of laboratory animals (86/609/EEC), and the project was approved by the Portuguese Veterinary General Division.

Experimental design

Hepatic and renal toxicity studies in animals

After oral administration of IM to rats in doses between 2.9 and 20 mg/kg, the plasmatic peak is attained at 3 h. After the absorption and distribution phases, IM is submitted to hepatic metabolization and reveals linear elimination kinetics, being excreted through the urine either in the unaltered form or under the form of metabolites conjugated with glucuronic acid [35–37]. Accordingly, IM has the capacity to induce hepatic and renal lesions when administrated systemically.

Experimental procedures

The experimental design was previously described [13]. Briefly, a total of 135 animals were randomly distributed

into 10 groups. Ten rats per group were used for the TxD of IMaf, complexed IM forms and negative control group (water), and 20 rats per group were used for the TD of IMaf, complexed IM forms and for the cyclodextrin group used as control. The number of animals used for the IMss form was a minor sample because of limitation of the available product: eight rats for the TD of IMss group and seven rats for the TxD of IMss group.

The product solutions were orally administered every 24 h over 3 consecutive days by resorting to a cannula [38], to a volume of 0.005 mL/g of body weight, by analogy with the frequency of administration of the IM for the pharmacological treatment of the patent ductus arteriosus [34]. The food was withdrawn from the animals 18 h before the beginning of the first administration, having been allowed free access to water during the entire experiment [34,39,40]. Twenty-four hours after the last administration the animals were sacrificed. A fragment of the liver and of the right kidney was collected for histopathological study procedures.

Histopathological studies

Liver fragment preparation

Once collected, the liver fragment was washed with isotonic sodium chloride, photographed and prepared for the histopathological study. Transversal fragments of the liver were placed in proper boxes and fixed in neutral formaldehyde plugged with phosphates (pH = 7.2). The tissues were preserved in paraffin and shears with haematoxylin/eosin colouration were prepared. Five serial 5-μm sections of each block were evaluated for severity of damage by light microscopy and photographed [41,42].

Kidney preparation

Once collected, the right kidney was washed with isotonic sodium chloride, longitudinally opened, fixed on a dissection tray, photographed and prepared for the histopathological study. Transversal fragments of the kidney were placed in proper boxes and fixed in neutral formaldehyde plugged with phosphates (pH = 7.2). The tissues were preserved in paraffin and shears with haematoxylin/eosin colouration were prepared. Five serial 5-μm sections of each block were evaluated for severity of damage by light microscopy and photographed [41,42].

Hepatic index lesion evaluation

The calculation of the hepatic index lesion in the morphological study was made according to a developed lesion level of severity scale, microscopically visible, developed by us, with the attribution of the following degrees: 0 – normal morphological aspect; 1 – inflammatory and/or circulatory lesions; 2 – degenerative or tinctural changes, without fibrosis or necrosis; 3 – fibrosis without the formation of nodules, or necrosis focuses, or formation of evident pre-neoplastic formation; 4 – cirrhosis or extended necrosis or neoplastic. The study of the morphological lesion was performed in each animal and when more than one type of lesion was observed in the same animal, the more serious lesion was considered for index classification.

Renal index lesion evaluation

The calculation of the renal index lesion in the morphological study was made according to a developed lesion level of severity scale, microscopically visible, developed by us, with the attribution of the following degrees: 0 – normal morphological aspect; 1 – only tubular or circulatory lesions; 2 – glomerular lesions attaining few glomerulus; 3 – glomerulus destruction or lesions that attain many glomerulus. The study of the morphological lesion was performed in each animal and when more than one type of lesion was observed in the same animal, the more serious lesion was considered for index classification.

Statistical analysis

The SPSS 11.0 (Statistical Package for the Social Sciences) for Windows was used in the present data processing.

Lesion assessment

For the lesion's index studies, the Kruskal–Wallis test was used. Every time that a significant difference was observed for an H value, it was followed by the application of the Mann–Whitney U test. The statistically significant difference was considered for $P < 0.05$.

The evaluation of the incidence's statistical meaning and the lesion's severity was made between the intervention groups in relation to the comparative one (TD of IMaf), either for TD or TxD, and between complexes in the TD.

RESULTS

Hepatic lesion assessment

Hepatic morphologic changes

All the animals that received IM presented one or several types of morphological changes that comprised of stasis, inflammatory infiltrated and necrosis focuses (*Figure 1*)

and steatosis (*Figure 2*). The animals from the groups that were given distilled water or HP-β-CD showed no evidence of lesion (*Figure 3*).

Hepatic index lesions

The hepatic lesion incidence and degree of severity, either in the TD or in the TxD, for all groups, are shown in *Table I*. Similar results were achieved when comparing the data obtained with IMaf and IM complexes, both for the TD and the TxD. With IMss, the ratio between animals with maximal index lesion change and total number of animals of each group (PR = AIL M/At) is lower when compared to IMaf and CFD (0.125).

Comparative analysis of hepatic lesion's index between products

The Kruskal–Wallis test originated a value of $H = 4.011$ for TD, with a non-significant difference between the groups ($P = 0.260$), and $H = 8.462$ for TxD and with a significant difference between the groups ($P = 0.037$). The application of the Mann–Whitney U test for TxD originated the values of P shown in *Table II*, revealing significant differences between the IM complexed forms and the IMss and between the IMaf and the IMss.

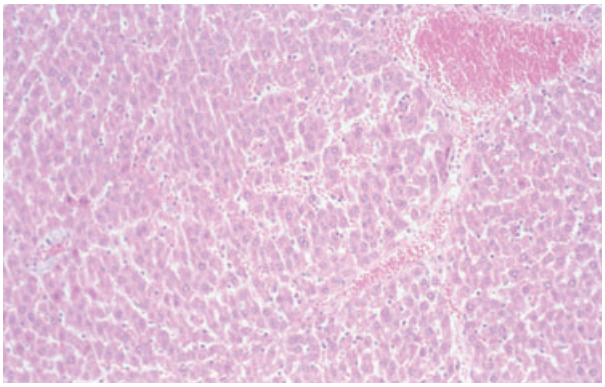

Figure 1 Histological section of the liver. Necrosis focuses in one animal submitted to the administration of indomethacin sodium salt in the therapeutic dose (H&E, original magnification ×50).

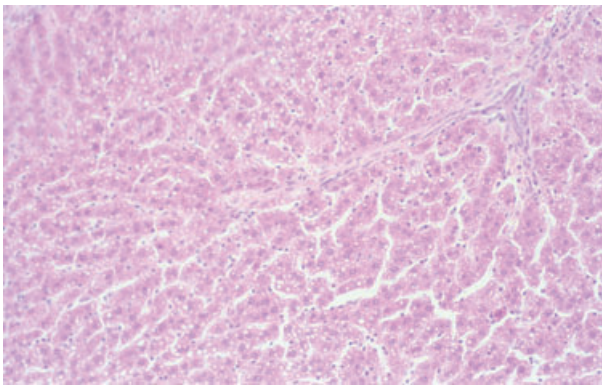

Figure 2 Histological section of the liver. Steatosis in one animal submitted to the administration of indomethacin complexed by freeze-dried, in the toxic dose (H&E, original magnification ×50).

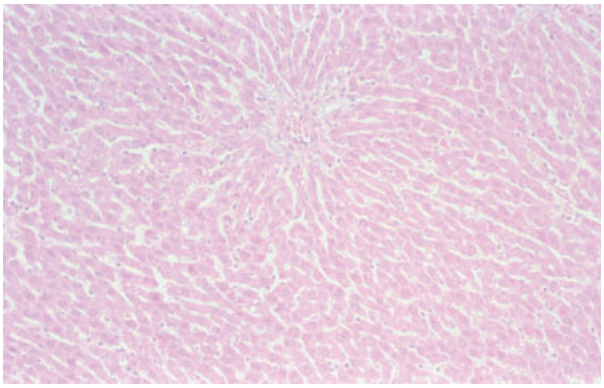

Figure 3 Histological section of the liver. No evidence of morphologic changes in one animal submitted to the administration of hydroxypropyl-β-cyclodextrin (H&E, original magnification ×50).

Renal lesion assessment

Renal morphologic changes

All animals that received IM presented one or several types of morphological changes, like vacuolization of the tubules (*Figure 4*), and a retraction of the glomerular tuff and small hubs of stasis (*Figure 5*). The animals from the groups that were given distilled water or HP-β-CD showed no evidence of lesion (*Figure 6*).

Renal index lesions

The renal lesion incidence and degree of severity, either in the TD or in the TxD, for all groups, are shown in *Table III*. Similar results were achieved when comparing the data obtained with IMaf and IM complexes, both for the TD and the TxD. With IMss, the ratio between animals with maximal index lesion change and total number of animals of each group (PR = AIL M/At) is greater when compared to the values of all the other products.

Comparative analysis of renal lesion's index between products

The Kruskal–Wallis test originated a value of $H = 8.288$ for TD and $H = 21.000$ for TxD, both presenting a significant difference. This statistical test was followed by the application of the Mann–Whitney U test, whose P values showed significant differences between the IMaf

Table I Proportion of animals that showed hepatic morphologic modifications.

Product	Dose	Presence (PR = Am/At)	LLS	HIL (PR = AIL M/At)	LLS	HIL (PR = AIL m/At)
IMaf	TD	11/20 (0.55)	3	05/20 (0.25)	1	03/20 (0.15)
	TxD	10/10 (1.00)	3	05/10 (0.50)	1	01/10 (0.10)
IMss	TD	02/08 (0.25)	3	01/08 (0.125)	1	01/08 (0.125)
	TxD	05/07 (0.71)	2	03/07 (0.43)	1	02/07 (0.28)
CFD	TD	15/20 (0.75)	3	03/20 (0.15)	1	07/20 (0.35)
	TxD	09/10 (0.90)	3	06/10 (0.60)	2	03/10 (0.30)
CSD	TD	12/20 (0.60)	3	02/20 (0.10)	1	06/20 (0.30)
	TxD	08/10 (0.80)	3	06/10 (0.60)	2	02/10 (0.20)
Water	0.005 mL/kg	00/10 (0.00)	–	–	–	–
HP-β-CD	TxD	00/20 (0.00)	–	–	–	–

HIL, hepatic index lesion; PR = Am/At, ratio between animals with presence of morphologic change and total number of animals of each group; PR = AIL M/At, ratio between animals with maximal index lesion change and total number of animals of each group; PR = AIL m/At, ratio between animals with minimal index lesion change and total number of animals of each group; CFD, freeze-dried complex; CSD, spray-dried complex; HP-β-CD, hydroxypropyl-β-cyclodextrin; IMaf, indomethacin acid form; IMss, indomethacin sodium salt; LLS, level of lesion severity; TD, therapeutic dose; TxD, toxic dose.

Table II Comparative analysis of hepatic lesion between pairs of products (Mann–Whitney *U* test).

Pairs of products (TxD)	IMaf IMss	IMaf CFD	IMaf CSD	IMss CFD	IMss CSD	CFD CSD
Level of significance (*P*)	0.010*	0.933	0.734	0.042*	0.012*	0.863

CFD, freeze-dried complex; CSD, spray-dried complex; IMaf, indomethacin acid form; IMss, indomethacin sodium salt; TxD, toxic dose.
*$P < 0.05$.

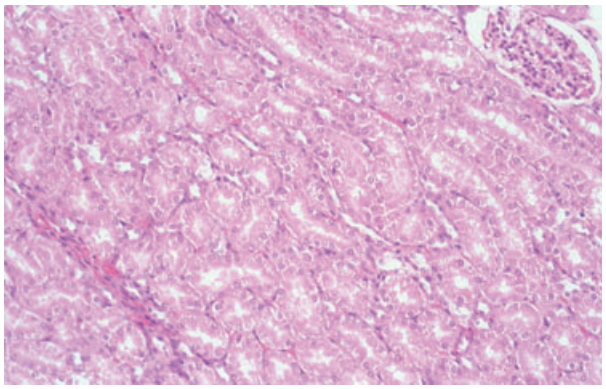

Figure 4 Histological section of the kidney. Vacuolization of the tubules in one animal submitted to the administration of indomethacin sodium salt in the therapeutic dose (H&E, original magnification ×50).

and IMss either in the TD or in the TxD (*Table IV*). No significant difference was detected in the lesion index provoked by IM complexes towards the IMaf except with the TxD of CFD. When complexed forms are compared

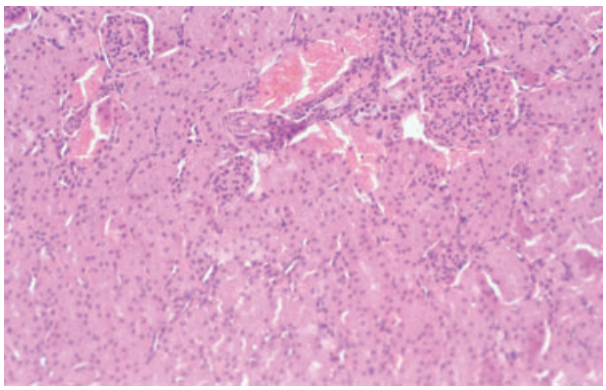

Figure 5 Histological section of the kidney. Small hubs of stasis in one animal submitted to the administration of indomethacin complexed by freeze-dried, in the toxic dose (H&E, original magnification ×50).

with IMss, *P* values show a significant difference either in the TD or in the TxD. Between complexed forms, there are no significant differences.

DISCUSSION

The hepatic and renal lesion incidence and degree of severity, either in the TD or in the TxD, for all animal groups, are similar, when comparing the results obtained with IMaf and IM complexes. These results confirm that IM is absorbed independently of the IM form orally administered, because these effects are described in the bibliography as being characteristics of the drug when administrated by intravenous route.

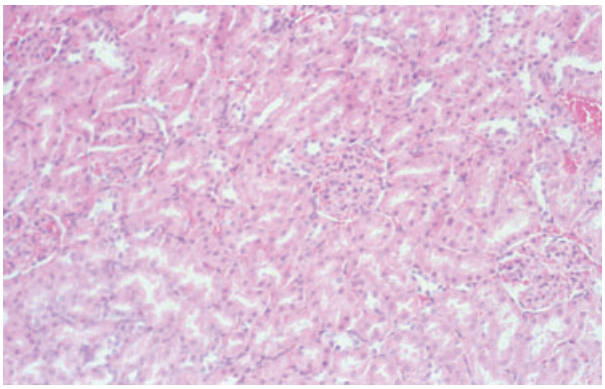

Figure 6 Histological section of the kidney. No evidence of morphologic changes in one animal submitted to the administration of hydroxypropyl-β-cyclodextrin (H&E, original magnification ×50).

The kind of hepatic lesions obtained – inflammatory lesions, necrosis and steatosis – are in accordance with that described in the literature [14,23,24,26,27]. The results we have had with the administration of one dose on three consecutive days support recent studies, showing that acute hepatic injury can be associated with only brief exposure to IM, leading to altered serum enzymatic activities, gene expression and hepatic histology [28].

The renal morphologic lesions observed can be explained by the capacity of IM to inhibit the synthesis of prostaglandins that regulate renal flow and glomerular filtration rate [15–18,20–22,29,30]. This inhibition is known to induce renal histological injuries like those obtained in the present study – vacuolization of the tubules, retraction of the glomerular tuff and stasis [31,32].

Table IV Comparative analysis of renal lesion between pairs of products (Mann–Whitney *U* test).

	IMaf IMss	IMaf CFD	IMaf CSD	IMss CFD	IMss CSD	CFD CSD
Pairs of products (TD)						
Level of significance (*P*)	0.007*	0.739	0.333	0.014*	0.044*	0.524
Pairs of products (TxD)						
Level of significance (*P*)	0.000*	0.001*	0.342	0.000*	0.000*	0.170

CFD, freeze-dried complex; CSD, spray-dried complex; IMaf, indomethacin acid form; IMss, indomethacin sodium salt; TD, therapeutic dose; TxD, toxic dose.
*$P < 0.05$.

The scales developed to evaluate the incidence and degree of severity, either for hepatic or renal histological injury, are relevant when the intention is to compare different products, allowing a quantitative and a qualitative evaluation. The analysis of this data reveals the existence of a lower degree of hepatic lesion for the IMss in view of the IMaf either with TD or TxD, with similar results when complexed forms of IMfa are compared with IMss. This result might serve as a base to decide, in future studies, to complex the IM under the sodium salt form in alternative to the acid form. However, one has to bear in mind that in the case of the renal lesion, the IMss does not offer advantages of the IMaf. In fact, the IMaf complex will have more advantages, considering that the incidence and the renal lesion degree are superior for the IMss.

CONCLUSION

The results obtained revealed that the severity and the incidence of the lesions induced by IM complexes, both at

Table III Proportion of animals that showed renal morphologic modifications.

Product	Dose	Presence (PR = Am/At)	LLS	RIL (PR = AIL M/At)	LLS	RIL (PR = AIL m/At)
IMaf	TD	06/20 (0.30)	1	06/20 (0.30)	–	–
	TxD	10/10 (1.00)	3	04/10 (0.40)	2	06/10 (0.60)
IMss	TD	07/08 (0.67)	1	07/08 (0.875)	–	—
	TxD	07/07 (1.00)	1	07/07 (1.00)	–	–
CFD	TD	09/20 (0.45)	1	09/20 (0.45)	–	–
	TxD	10/10 (1.00)	3	02/10 (0.20)	2	08/10 (0.80)
CSD	TD	07/20 (0.35)	1	07/20 (0.35)	–	–
	TxD	10/10 (1.00)	3	05/10 (0.50)	2	05/10 (0.50)
Water	0.005 mL/kg	00/10 (0.00)	–	–	–	–
HP-β-CD	TxD	00/20 (0.00)	–	–	–	–

RIL, renal index lesion; PR = Am/At, ratio between animals with presence of morphologic change and total number of animals of each group; PR = AIL M/At, ratio between animals with maximal index lesion change and total number of animals of each group; PR = AIL m/At, ratio between animals with minimal index lesion change and total number of animals of each group; CFD, freeze-dried complex; CSD, spray-dried complex; HP-β-CD, hydroxypropyl-β-cyclodextrin; IMaf, indomethacin acid form; IMss, indomethacin sodium salt; LLS, level of lesion severity; TD, therapeutic dose; TxD, toxic dose.

hepatic and renal levels, are equivalent, either in the TD or in TxD, to those provoked by IMaf when administrated by the oral route. When compared to IMaf, IMss showed a lower degree of hepatic lesion but a greater degree of renal lesion. Considering the hypothesis we have formulated, we can conclude that under the present experimental conditions, IM is equally absorbed from the gastrointestinal tract, independently of the dose and the IM form administered.

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CONFLICT OF INTERESTS

The authors have no conflict of interests to disclosure.

ABBREVIATIONS LIST

CFD – freeze-dried complex
COX – cyclo-oxygenase
CSD – spray-dried complex
FD – freeze-dried
HP-**β**-CD – hydroxypropyl-**β**-cyclodextrin
IM – indomethacin
IMaf – indomethacin acid form
IMss – indomethacin sodium salt
NSAID – non-steroidal anti-inflammatory drug
SD – spray-dried
TD – therapeutic dose
TxD – toxic dose.

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