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ARTICLE

ORAL ADMINISTRATION OF ZOLPIDEM TARTRATE IN AN ABUSE-DETERRENT FORMULATION VERSUS AN IMMEDIATE RELEASE FORMULATION IN BEAGLE DOGS

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Objective: The continuing rise of prescription drug abuse has greatly necessitated the development of an abuse-deterrent formulation. Geopolymers are a promising base for drug design as they allow for tuneable drug release and possess superior physical and chemical properties compared with conventional pharmaceutical excipients.

Methods: Geopolymer pellets containing zolpidem tartrate were administrated orally to beagle dogs as a controlled-release formulation with the commercial immediate-release product, Stilnoct® tablets, as the control.

Results: The administration of zolpidem tartrate as immediate-release tablets demonstrated an elevated immediate release plasma profile and the zolpidem tartrate in the geopolymers demonstrated a controlled-release plasma profile. The pharmacokinetic analysis demonstrated that immediate-release tablet administration generated much higher plasma concentration when compared with geopolymer pellets administration for zolpidem tartrate. On the other hand, the geopolymer formulation prolonged the time of drug release.

Conclusion: Oral administration of zolpidem tartrate in geopolymer pellets demonstrated a controlled-release plasma profile.

Key words: In vivo; zolpidem; abuse-deterrent formulation; HPLC.

LAY ABSTRACT

The increase of abuse of prescription drugs has shown the necessity for an abuse-deterrent formulation (ADF). Geopolymers have been designed as an ADF by adding physical and chemical barriers making them more difficult to abuse. In this study, we studied the oral administration of zolpidem tartrate in geopolymer pellets in dogs. The control group was a commercial product (Stilnoct® tablets), which give an immediate release compared with the geopolymer, which is a controlled-release drug, i.e. longer time to release the drug. The results showed a controlled-release of the geopolymer, while Stilnoct® demonstrated an elevated immediate release. However, the amount of drug detected in the plasma was significantly lower for the geopolymer formulation when compared with the control group. Finally, no adverse signs were seen in the dogs after oral administration of the two different test items.

Opioids are narcotic analgesics that bind to the receptors in the central and peripheral nervous systems and are frequently used for the treatment of chronic pain – and as pain relief in cancer conditions (1). With the increase in opioid consumption, concern has been expressed on the escalating misuse and non-medical use of prescription opioids, which has resulted in increased deaths by overdose. The Center for Behavioural Health reported, in their 2015 National Survey on Drug Use and Health, that approximately 2 million people are misusing opioids and it is now considered a public health issue in the USA (2). In the USA, 63,632 persons died of an overdose in 2016 and 66.4% of the cases involved an opioid, while in 2017, the number increased to 70,237 where 67.8% involved opioids (3, 4). The Food and Drug Administration (FDA) strongly recommended an assessment regarding the abuse potential to all opioid products (5). Controlled-release drug products are particularly attractive targets for abuse as they contain larger drug doses than their corresponding immediate-release counterparts.

The addition of physical and chemical barriers is the most efficient and useful method to prevent drug abuse in abuse-deterrent formulations (6). Physical destruction of the matrix and extraction with a solvent are two common ways of obtaining higher doses from opioid oral tablets, which has led to the development of rigid structures and insoluble coatings (5). Currently, eight commercial abuse-deterrent formulations are approved by the FDA (7). These formulations are polymer-based tablets and new efforts are now focused on how to make the matrix rigid against extraction, crushing and gelling (6, 7).

Compared with the polymer-based matrix, a ceramic-based matrix provides a stronger physical barrier. Medications, from small molecule drugs to biopharmaceuticals, have been loaded into ceramic matrices for treating different diseases

(8, 9). Geopolymers have been developed as a ceramic-based matrix for an abuse-deterrent formulation with controlled drug release and low abuse ability, as shown in our previous studies (10). In those studies, the geopolymer showed high mechanical strength when subjected to crushing, and low amounts of drug were extracted with solvents such as 40% ethanol (10). Geopolymers are often referred to as inorganic polymers with the basic unit of polysialates, containing SiO_4 and AlO_4 tetrahedra. Depending on the different compositions and synthesis conditions, geopolymers can exhibit various physical and chemical properties, such as high mechanical strength, low porosity and low solubility (11).

The leach out of aluminium from the geopolymer matrix could potentially be harmful in the long-term, since exposure to a high level of aluminium can cause damage to the reproductive and nervous system (12). The release of aluminium from a geopolymer has previously been assessed, where the release of aluminium has been collected up to 24 h in both pH 1 and pH 6.8 (13). The findings showed that the aluminium leached after 24 h but was still significantly lower than the non-observed-adverse-effect levels (1 mg aluminium/kg bw/week) issued by the European Food Safety Authority (14).

To the best of the authors' knowledge, geopolymers have not previously been tested ***in vivo*** as an oral formulation. However, geopolymers containing tricalcium phosphate and hydroxyapatite have previously been evaluated in vivo as a bone filling material showing that geopolymers are highly biocompatible and no significant leakage of aluminium was detected after 1 month of implantation (15, 16).

Drug release of fentanyl and zolpidem from a geopolymer has been compared in a previous study (17), which showed that the two drugs had similar physicochemical properties (**Table I**). Due to safety reasons, in this study, zolpidem was used as a model substance for Fentanyl, since it is less potent. The aim of this study was to evaluate the plasma profiles and the pharmacokinetic parameters following oral administration of zolpidem tartrate in geopolymer pellets aiming for controlled-release, in comparison to a commercial immediate-release tablet formulations in dogs. The immediate-release formulation was chosen according to FDA guidelines, which state that immediate-release formulations are a valid comparator to controlled release formulations (6). In addition, abuse-deterrent properties of both geopolymer and Stilnoct® were investigated according to the FDA's guidelines in three common media; 70°C, 40% ethanol and pH 1.

MATERIALS AND METHODS

Materials

Kaolin, fumed silica, sodium hydroxide, monopotassium phosphate and 37% fuming hydrochloric acid was purchased from Sigma Aldrich (Sweden). Zolpidem tartrate from Cambrex AB (USA). Eudragit L100-55 was purchased from Evonik (Germany). Stilnoct® tablets were purchased from Sanofi AB (Stockholm, Sweden). Capsules (Coni-shaped, size 0) were purchased from Capsugel (Sweden).

Pellets Manufacture/Geopolymer Synthesis

By thermally treating Kaolin at 800°C for 2 h, 'metakaolin' was formed. A waterglass was made by mixing fumed silica and sodium hydroxide with water, into a homogenous and clear fluid. The waterglass was then mixed with metakaolin, Eudragit L100-55 (1 g per 6.5 g of metakaolin) and zolpidem (1 w/w%) to form a geopolymer paste. Eudragit L100-55 is a copolymer that starts dissolving above a pH of 5.5, i.e. it protects the geopolymer under acidic conditions. The geopolymer paste was moulded by hand into 1.5 mm × 1.5 mm Teflon moulds. After curing the pellets (48 h, 100% RH) were packed into capsules **(Fig. 1)**. The manufactured pellets consisted of the following molar ratios: Si/Al:1.94, H_2O/Al_2O_3:12.24 and Na_2O/Al_2O_3:1.23.

The final assay analysis demonstrated a total amount of 6 mg of zolpidem per manufactured capsule after packaging.

Preparation of Stilnoct® Tablets

Each Stilnoct® tablet was packed into a capsule to match those of the pellets.

Characterization of the Geopolymer

The morphology of the geopolymer was studied with Scanning Electron Microscopy (SEM; Zeiss Leo 1550, operated at 3 kV). The pellets were attached to carbon tape and coated with Pt–Au to avoid charging. The phase composition was determined by X-ray diffraction (XRD; Bruker, D8 Advanced) by using CuKα (λ=1.5418 Å).

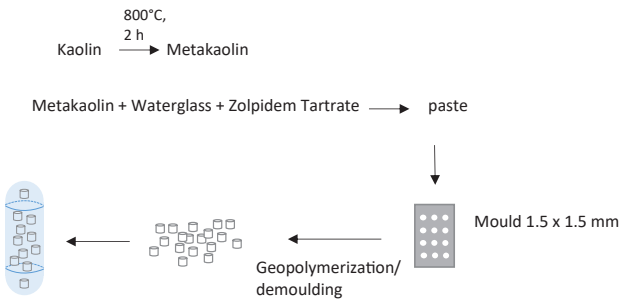

Fig. 1. Illustration of procedure for manufacturing and packing geopolymer pellets.

Table I. Physicochemical properties for fentanyl citrate and zolpidem tartrate (18, 19)

	Zolpidem tartrate	Fentanyl citrate
Molecular weight (g/mol)	457.483	528.602
Solubility in water	23 mg/mL	25 mg/mL
pKa	6.2	8.4
Log P	1.2	2.98
Topological polar surface area (Å²)	153	156

Abuse-deterrent Properties of the Test Items

Both Stilnoct® tablets and geopolymer pellets were investigated for abuse-deterrent properties according to FDA guidelines in three household solvents in non-sink conditions; pH 1, 40% ethanol and 70°C water (5). The three different media were chosen to mimic commonly used abuse methods; pH 1 for cleaning supplies, 40% ethanol for alcoholic beverages and 70°C water for tea. The same method was applied to pH 1 and 40% ethanol; 500 mg of pellets was added to 10 mL of media with a stirring rate of about 50 rpm. Samples (1 mL) were taken out after 5, 30 and 60 min. Due to the fast evaporation of water at 70°C, 500 mg of pellets were added to a larger volume (50 mL) of 70°C water with a stirring rate of about 50 rpm. Samples were taken out after 5 min and 30 min. All geopolymer samples were filtered with 0.2 µm millipore and analysed with a UV-spectrophotometer at 241 nm, while the Stilnoct® tablets were analysed with HPLC due to high background noise from the tablet matrix.

In Vitro Drug Release of Zolpidem from Test Items

An *in vitro* characterization was done prior to the start of the *in vivo* test to simulate gastric and intestinal pH. The characterization was done in sink conditions by using a USP II dissolution bath to measure drug release f rom both Stilnoct® tablets in capsules and geopolymer pellets in capsules, over time in two different media: a phosphate buffer (pH 6.8) and 0.1 M HCl (pH 1), which simulated the condition in the intestine tract and stomach, respectively. The volume of the dissolution bath was 400 mL, the temperature was set to 37°C and the paddle rate at 50 rpm. Samples were collected up to 24 h; each sample (*n*=3) was filtered with 0.2 µm millipore and analysed using a UV-spectrophotometer at 241 nm.

In Vivo Study – Plasma Profile of Zolpidem after Oral Administration to Dogs

The *in vivo* study was performed on beagle dogs by the test facility SPM Biocameltec (Sidi Bou Othmane, Morocco) and was approved by the local Animal Care Veterinary Procedure in accordance with animal care guidelines. The study was also based on the OECD principles of Good Laboratory Practice ENV/MC/CHEM(98)17. The study consisted of two groups with four animals in each **(Table II)**. The dogs were fasted for 12 h prior to dosing. One group were given a Stilnoct® tablet in a capsule (5 mg of zolpidem tartrate) and the other group were given the encapsulated pellets (6 mg zolpidem tartrate). The difference in the administered doses was not compensated for in the plasma release profiles due to the low *in vitro* drug release from the geopolymer pellets. Body weight was measured before dosing and 24 h after the first dosing. the administration of the capsules was done by a veterinarian who put the capsule in the back of each dog's throat. Blood samples were collected at the following time points after administration: *t*=0, 0.5, 1, 2, 3, 4, 6, 9, 12 and 24 h. Daily clinical observations were made to detect sedative effects, mortality and morbidity.

Analytical Method and Statistics

Blood samples were centrifuged for plasma separation. A total of 50µL of the plasma was added to 450 µL of CH_3CN + Internal standard (zopiclone, 200 nM). The mixture was vortexed and centrifuged. The supernatant was analysed on an LC/MS-MS system and Acquity BEH C18 column (2.1 mm ID × 50 mm, 1.7 µm).

The statistics were performed by calculating the average for each parameter and the standard deviation.

RESULTS

Characterization of the Geopolymer

The morphology of the geopolymer was studied with both SEM and XRD. The analysis with SEM showed a dense surface **(Fig. 2)**. Furthermore, small cracks were formed when the sample was exposed to the vacuum in the microscope.

After hardening, the geopolymer showed an amorphous structure **(Fig. 3)**. The two peaks (*) at 21.1 and 27.1 degrees indicate that there is still some unreacted Metakaolin present in the geopolymer.

Abuse Deterrent Properties of the Test Items

The geopolymer pellets demonstrated similar levels of extraction at pH 1 and in 40% ethanol **(Fig. 4)**. After 1 h, 8–10% of zolpidem was released in pH 1 and 40% ethanol, while almost 50% was released after 30 min in 70°C water. All pellets were intact after the tests were terminated.

All of the drug was released from Stilnoct® tablets within 1 h in pH 1 and within 30 min in 70°C water **(Fig. 5)**. The tablets were completely dissolved within 30 min in both pH 1 and 70°C water. In 40% ethanol, the tablets were intact in the first 10 min, which

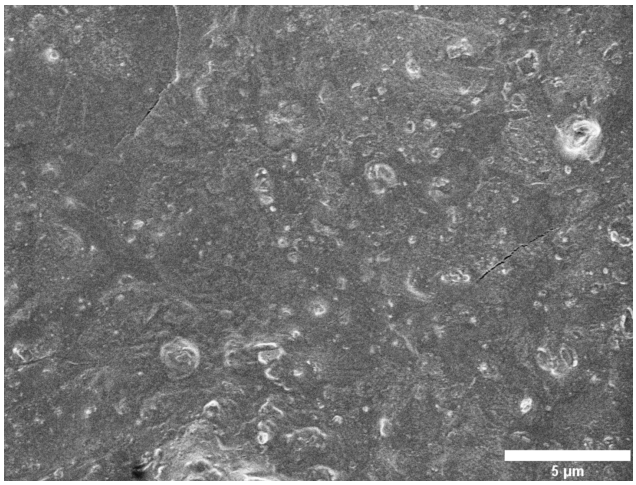

Fig. 2. Scanning electron microscope (SEM) image of the geopolymer surface.

Table II. Groups tested in the *in vivo* study

Group no.	*n*	Treatment	Dose per dog (mg)
1	4	Dose A: Stilnoct® tablets in a capsule containing 5 mg zolpidem	5
2	4	Dose B: Geopolymer pellets in a capsule containing 6 mg zolpidem	6

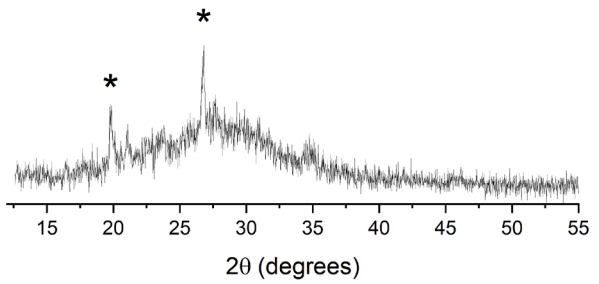

Fig. 3. Diffraction pattern of geopolymer with two peaks (*) indicating unreacted metakaolin.

can explain the low release in 5 min. The slow disintegration of the tablet led to the slower release of zolpidem, which resulted in 80% release after 1 h.

In Vitro Release of Zolpidem from Stilnoct® Tablets and Geopolymer Pellets

The *in vitro* release of the drug from Stilnoct® tablets showed an immediate release profile. Almost all of the drug was released in both gastric pH 1 and intestinal pH 6.8 within 30 min **(Fig. 6**A**)**. After 24 h, 75% of the zolpidem in geopolymer pellets was released in pH 1 and 50% in pH 6.8 **(Fig. 6**B**)**.

In Vivo Plasma Profile of Zolpidem after Oral Administration of the Test Items to Dogs

In group 1, one of the four tested dogs in the immediate release formulation had zero levels throughout the study **(Fig. 7**A**)**. The zolpidem concentration in plasma reached the top (C_{max} = 17.4 ng/mL) and went back to the lower limit of quantitation (LLOQ) after 12 h. In group 2, only two of the four dogs had zolpidem levels above LLOQ in plasma following acute pellet administration **(Fig. 7**B**)**. The other two exhibited low concentrations in plasma.

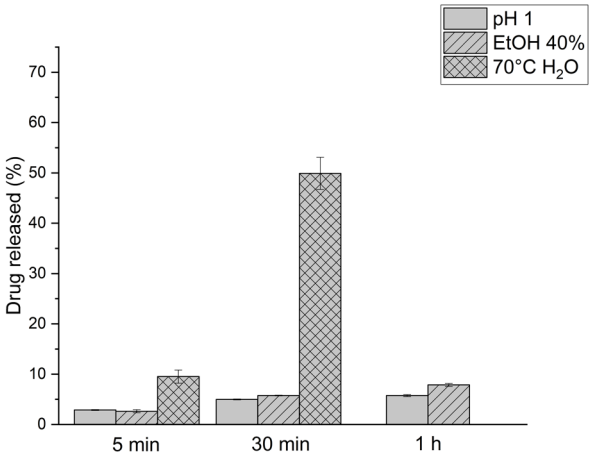

Fig. 4. Abuse deterrent properties for geopolymer in three different media, *n*=3.

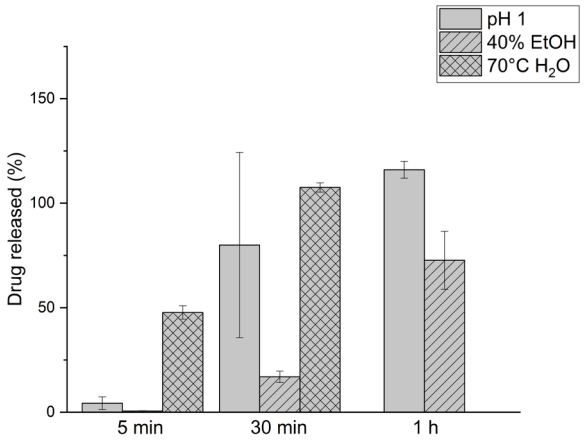

Fig. 5. Abuse deterrent properties for Stilnoct® tablets in three different media, *n*=3.

Pharmacokinetic analysis of the collected data demonstrated that immediate-release tablet administration (group 1) generated much higher values for C_{max} and AUC compared with geopolymer pellets administration (group 2) **(Table III)**. On the other hand, the geopolymer pellet formulation prolonged the time of drug release.

Clinical signs were normal for all dogs at all time points investigated. However, dog 2 (geopolymer pellets, group 2) vomited 30 min after administration. The number of vomited pellets was 12 compared with 64 pellets in each capsule, which is 20% of the administered dose. Since the dog was already administered with the majority of the dose, the decision of the veterinarian responsible and the study director was not to administer the dog with an additional capsule.

DISCUSSION

The abuse-deterrent properties were investigated in non-sink conditions in order to mimic some extraction methods which are available to abusers (6). After termination of the tests, approximately 10% zolpidem was released from the geopolymer pellets in both pH 1 and 40% ethanol, while almost 50% zolpidem was released when 70°C water was used as the solvent (Fig. 4). Eudragit starts dissolving above pH 5.5, which can explain the higher release of zolpidem in water compared with acidic conditions. All geopolymer pellets were intact after the tests. Stilnoct® tablets completely disintegrated within 30 min in 70°C water and after 1 h in pH 1. A variation in the 30-min samples at pH 1 could be observed. This might be due to the fast disintegration of the tablets in a small volume resulting in a higher risk of uneven sampling. Overall the geopolymer pellets showed better abuse-deterrent properties than the immediate-release tablet.

Table III. Pharmacokinetic parameters for both groups, including average with standard deviations.

	Group 1, zolpidem IR tablets					Group 2, zolpidem pellets				
	D1	D2	D3	D4	Average	D1	D2	D3	D4	Average
C_{max} (ng/mL)	23.7	16.7	ND	22.9	21.1±3.8	1.5	0.1	ND	1.0	0.9±0.7
T_{max} (h)	0.5	1	ND	0.5	0.7±0.3	6.0	1	ND	1.0	2.5±3.0
$t_{1/2\ elimination}$ (h)	0.2	0.4	ND	0.4	0.3±0.1	0.1	NC	NC	0.5	0.3±0.3
$AUC_{24\ h}$ (h*ng/mL)	43.7	30.4	ND	26.5	33.5±9.0	13.1	0.1	0.0	2.9	4.0±6.2

D: dog; IR: immediate release; NC: not calculated; ND: not detected.

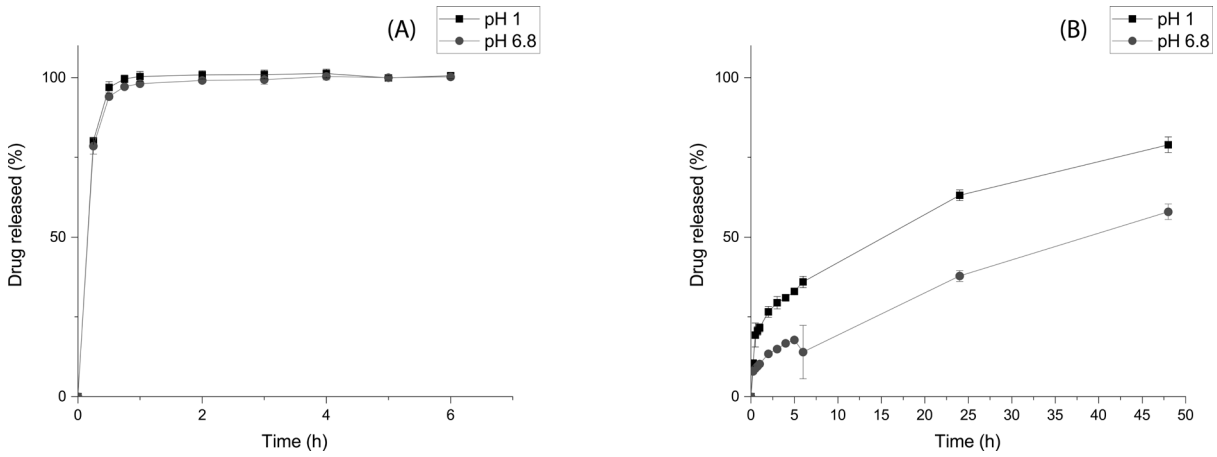

Fig. 6. Zolpidem tartrate release from: (A) Stilnoct® tablets and (B) geopolymer pellets, n=3. The dissolution test was performed under 24 h in pH 1 (□) and pH 6.8 (●). The error bars represent the standard deviation at each time point.

In vitro data for the geopolymer pellets predicted a prolonged release for 24 h (Fig. 6B) but ***in vivo*** data showed that the plasma concentration started to decrease after 1 h for dog 4 and 6 h for dog 1 (group 2) (Fig. 7B). This difference in T_{max} for dogs 1 and 4 can be explained by the transit time. The gastrointestinal tract in beagle dogs has been investigated in a previous study, showing that there is significant variability in pH profiles and transit times (20). For example, the median gastric transit time is 1 h, but with a standard deviation (SD) of 6 h; and the median total transit time is 18 h with an SD of 10 h. The drug release profile in Fig. 6 demonstrates that the drug release is somewhat faster at gastric pH 1 than intestinal pH 6.8. Dog 4 may have had a longer gastric transit time but a shorter total transit time than dog 1, causing the shorter T_{max} for dog 4 compared with dog 1. Thus, the low uptake of zolpidem from geopolymer pellets, still demonstrates a controlled-release profile compared with the instant release tablets.

As mentioned previously, dog 2 (geopolymer pellets, group 2) vomited 20% of the dose after administration. The lack of 20% of the dose may have contributed to the low uptake shown for dog 2, with low plasma values below the LLOQ. For the dogs in group 2 (geopolymer pellets), the lack of detection suggests that the drug release was most likely low as a consequence of the controlled-release properties of the geopolymer pellets, but for the dog in group 1 (Stilnoct® immediate-release tablets), the lack of absorption has no rational explanation.

To the best of the authors' knowledge, this is the first time a geopolymer has been tested as an oral formulation ***in vivo***. In this study, we present preliminary ***in vivo*** data for geopolymer as an oral formulation showing the feasibility of delivering zolpidem by prolonged release from an abuse-deterrent formulation. Furthermore, previous studies have shown that no significant amount of aluminium leakage occurs after dissolution at pH 1 and pH 6.8 (13).

CONCLUSIONS

Abuse-deterrent properties were investigated for both Stilnoct® tablets and geopolymer pellets, where geopolymer pellets showed significantly lower drug release. The pharmacokinetics of zolpidem tartrate were examined in dogs after a single administration of tablets or pellets. Oral administration of zolpidem tartrate in geopolymer pellets demonstrated a controlled-release plasma profile opposite to the immediate-release tablets. However, the geopolymer pellet exhibited low plasma levels and exposure, which can be explained by the prolonged drug release, as demonstrated in ***in vitro*** studies. Both groups show the same half-life ($t_{1/2}$=0.3 h). No significant adverse clinical signs were seen in the dogs after oral administration of

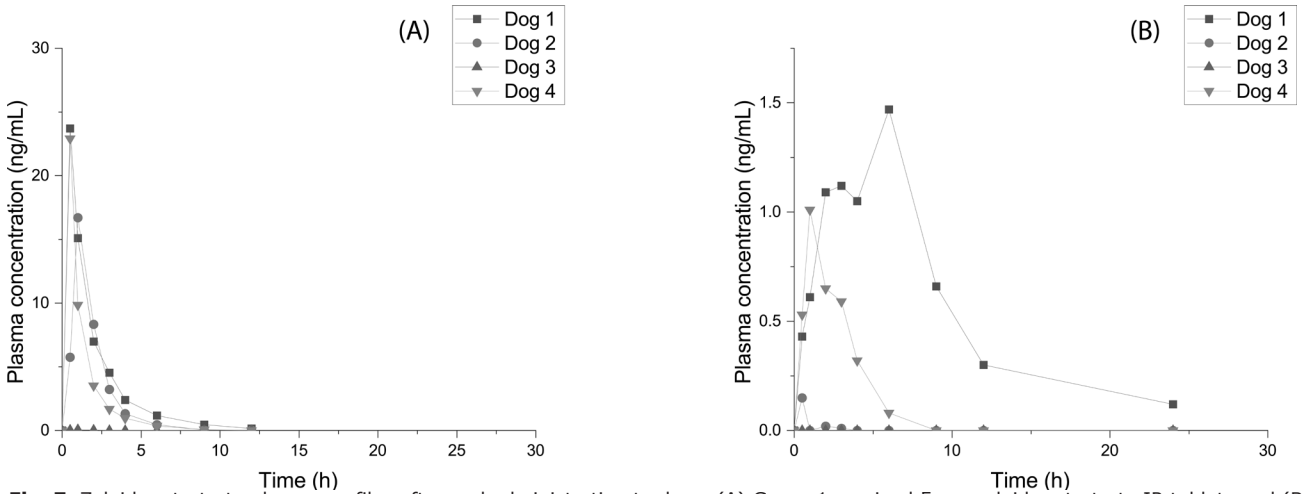

Fig. 7. Zolpidem tartrate plasma profiles after oral administration to dogs. (A) Group 1 received 5 mg zolpidem tartrate IR tablets and (B) Group 2 received 6 mg zolpidem tartrate geopolymer pellets

the two test items. To conclude, it was possible to safely deliver zolpidem from a geopolymer abuse-deterrent formulation.

Conflicts of interest

Engqvist is a board member and shareholder in Emplicure AB – a drug delivery company.

Acknowledgement

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