Research Article

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Development of memantine orodispersible tablets and their *in vitro* description and biopharmaceutical performance

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Aim: New approaches are required to improve compliance in older patients with problems in swallowing traditional formulations. A novel memantine orodispersible tablet (ODT) was formulated, and its bioavailability and taste acceptability were evaluated. **Materials & methods:** *In vitro* characterization of ODT comprised dispersion in simulated saliva prior to dissolution assay in a limited volume of biorelevant media. A single oral dose of 20-mg memantine ODT exhibits similar bioavailability to that of an immediate release 20-mg tablet in a healthy population under fasting conditions. **Results:** 90% confidence interval for C_{max} was of 96.78–106.52% and 98.27–104.78% for $AUC_{0–72}$. An applied palatability survey showed exceptional acceptance of the formulation. **Conclusion:** Memantine microspheres prepared by a solid-dispersion technique results in ODT with adequate biopharmaceutical performance.

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Keywords: aging • Alzheimer's disease • bioavailability • memantine orodispersible tablets • palatability

According to the WHO, the aging of a population "*should be considered a success of public health policies and socioeconomic development, but it also constitutes a challenge for its society, which must be adapted in order to maximize the health and functional capacities of older citizens*". It has been predicted by the Mexican Population Council that by the year 2050, women older than 60 years will comprise 23.3% of the total female population and males with similar ages will make up 19.5% of the total male population. Aging is accompanied by multimorbidity, including mental illness such as depression (17.6%), cognitive impairment (7.3%) and several types of dementia (7.9%) [1].

During the therapeutics of the geriatric population, several problems become evident, such as correct understanding of instructions, difficulties in opening containers, breaking tablets manually and swallowing oral solid formulations. In this context, the EMA has worked on a paper entitled 'Quality aspects in the pharmaceutical development of medicines for older people'. This reflective paper reports on three key aspects concerned with the practical use of medicines for geriatric population including the following: storage conditions, easy-to-open containers and novel pharmaceutical formulations, such as minitablets and orodispersible tablets (ODTs) [2].

Under these premises, declaring dementia as the first cause of impairment in older people, the WHO has considered the treatment of dementia as a public health priority for social assistance. Recent efforts to formulate novel transdermal systems for memantine have been published [3]. Memantine (3,5-dimethyladamantan-1-amine; CAS no. 19982-08-2) is a noncompetitive N-methyl-D-aspartate-receptor antagonist effective in the treatment of moderate-to-severe dementia, including the symptoms of Alzheimer's disease, with several advantages over other antidementia drugs [4] and it has recently been implicated in the therapeutics of obsessive compulsive disorders [5].

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The development of memantine hydrochloride ODTs is a recent therapeutic strategy [6]. ODT has become a technology for easy administration and swallowing, with taste acceptability for geriatric patients, which results in better treatment compliance [7]. Memantine HCl is a highly soluble (35 mg/ml in water at 20°C) and highly permeable molecule (corresponding to biopharmaceutical class I; logP = 3.28; pKa = 10). It is recognized by several regulatory agencies that bioequivalence can be biowaived by proper dissolution assays. However, the Mexican Regulatory Agency establishes that for novel formulations not previously commercialized in Mexico, it is essential to demonstrate bioequivalence with respect to a reference formulation available on the Mexican market.

Thus, the aims of present work were to describe the strategies in the development of *in vitro* assays to evaluate the dissolution performance of a novel memantine ODT formulation, as well as its biopharmaceutical behavior during a comparative bioavailability trial in Mexican healthy volunteers, and the acceptability of the ODT during an organoleptic survey.

Materials & methods

Chemicals & reagents

Memantine (Olainfarm; Riga, Latvia) and amantadine (Sigma-Aldrich; Toluca, Mexico) standards were kindly supplied by Productos Científicos SA de CV (Mexico City, Mexico). HPLC-grade acetonitrile, in addition to hydrochloric acid, sodium chloride, phosphoric acid, monobasic and dibasic potassium phosphate and amylamide analytical grades, as well as Triton™ X-100 and Tween™ 80, were purchased from JT Baker (Mexico City, Mexico), while formic acid was obtained from Sigma-Aldrich-Fluka (Toluca, Mexico). Ultrapure water was obtained from a Milli-Q™ system (Millipore, MA, USA).

Akatinol® 20 mg immediate release tablets (Merz Pharma; Mexico City, Mexico) were used as reference product, while memantine 20 mg ODTs (Productos Científicos SA de CV, Carnot Laboratorios; Mexico City, Mexico) were the test products.

Formulation of orodispersible tablets

Memantine ODTs were formulated employing common excipients for this technology (crospovidone and starch sodium glycolate as disintegrants, microcrystalline cellulose and mannitol as diluents, talcum powder as lubricant, sucralose and a strawberry/mint flavor). Memantine microspheres were prepared by a solid-dispersion technique with stearyl alcohol, using Eudragit™ E PO (Evonik Health Care; IN, USA) as taste masker. 20-mg memantine ODTs were round, flat, slotted tablets with a hardness of 30.4 N, an average weight of 400 mg, a diameter of 9 mm and a thickness of 3 mm.

Dissolution tests

Pharmacopeic conditions

Akatinol and first evaluations of ODT were performed by using US Pharmacopeia conditions for solid forms of memantine [8]. Briefly, the method consists of assay having six units of each formulation in 900 ml of dissolution media (HCl 0.1 N and 2 g/l of NaCl), by using apparatus I at 100 r.p.m., 37°C, sampling 10 ml without reposition at 10, 20, 30 and 45 min. Dissolution instruments employed were Distek 2500 (NJ, USA).

Discriminative media

In order to establish a more discriminative assay, the following conditions were proposed that emulate the physiological environment inside the bowel in terms of small volumes, pH, osmolality and surface tension. Methodology previously reported [9,10] was adapted as follows: apparatus II at 25 r.p.m., 250 ml dissolution media, sampling 3 ml without reposition at 1, 3, 5, 10, 20 and 30 min. Dissolution media were as follows: HCl 0.1 N, Triton X-100 (0.1%), NaCl 2 g/l, pH = 1.2, or HCl 0.1 N, Tween 80 (0.1%), NaCl 2 g/ml, pH = 1.2.

Simulated saliva

At last, to resemble the whole bucal dispersion and dissolution process, a dispersion step in simulated saliva was included only for ODT prior to the dissolution assay. ODTs were placed in 1 ml of simulated saliva (NaCl 8 g, monobasic potassium phosphate 0.19 g and dibasic potassium phosphate 2.38 g, all in 1 l of ultrapure water, and adjusted to pH = 6.8) for 1 min; after that, both dispersed ODT and Akatinol were added to discriminative media to continue with dissolution tests [11].

Quantification of memantine in dissolution samples

HPLC (Waters 2695; MA, USA) coupled with a refractive index detector (Waters 2414RI) was employed, interfaced by Empower® software (MA, USA). Memantine separation was carried out by means of a Hypersil Gold C18 column (4.6 × 150 mm, 5 µm particle size; Thermo Fisher Scientific, MA, USA). Flow rate was maintained at 1.0 ml/min under isocratic conditions, with a mobile phase of aqueous buffer (1 ml of phosphoric acid plus 1 ml of amylamine in 1 l of ultrapure water)/acetonitrile (80:20 *v*/*v*). Column was maintained at 40°C and autosampler temperature was set at 10°C. Volume of sample injection was 5 µl, having a complete run of 3 min. Memantine was quantified by using calibration curves validated for each dissolution medium, in a range of 40–120% dissolution [12].

Comparative bioavailability trial

18 healthy Mexican volunteers participated in this study: 7 women and 13 men. Inclusion criteria were BMI between 18 and 27 kg/m^2, age between 18 and 55 years, normal electrocardiogram and clinical history, laboratory values within normal ranges (hematology, blood biochemistry, urine analysis and liver function), nonsmokers and negative for AIDS, hepatitis B and C, and in women, for pregnancy tests. Exclusion conditions comprise allergic history to any component of the formulations assayed, pregnancy, active alcoholism, positive results for the rapid urine assay of cocaine, barbiturates, benzodiazepines, methamphetamines and tetrahydrocannabinol, and any serious health condition that would affect the evolution of the study. Withdrawal situations throughout the study considers any kind of hypersensitivity reactions, loss of two or more samples around C_{max}, vomiting between administration time and twofold T_{max} or any diet transgression [13].

All volunteers granted their signed informed consent forms, and were medically monitored closely throughout the entire study. Current protocol was reviewed and authorized by the Global Bioanalytical Consulting Ethics Committee, registered in the Mexican Regulatory Agency (COFEPRIS registration trial no. 163300410B0263/2016) and conducted with full compliance with the latest Declaration of Helsinki and in agreement with the Good Clinical Practice defined by the International Conference on Harmonization.

The clinical study was controlled, randomized, simple-blinded to the analytical investigator, cross-over, two periods (sampling truncated up to 72 h per period, with 18 days of washout period in between), two treatments (20-mg memantine ODT or Akatinol 20 mg immediate release tablet), under fasting conditions. Experimental groups had the same number of volunteers randomly assigned to each treatment sequence.

Volunteers presented the day prior to drug administration. They received dinner at 8:00 pm and fasted overnight (12 h). An intravein catheter was set in a forearm area the next morning. At 8:00 am in the case of volunteers receiving Akatinol, a single dose was taken with 250 ml of water; in the case of volunteers receiving ODT, they washed their mouths briefly with 20 ml of tap water, swallowed this and placed one ODT on the tongue, making gentle motions to disperse the tablets within the closed mouth – no chewing. Then, the particles were completely swallowed and 230 ml of water was drunk in order to compare the bioavailability of both formulations under the same conditions.

Approximately 6 ml of blood was drawn from each study participant for each sample through the catheter at 0 h (before administration) and at 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 12, 24, 48 and 72 h after memantine administration. Samples were taken in vacuum heparinized tubes and centrifuged at 4000 r.p.m. for 5 min at 20°C for plasma separation. Plasma was collected in identified cryovials and stored at -70°C until memantine quantitation.

Determination of memantine in human plasma

Sample extraction, chromatography and spectrometer settings were adjustments of previously reported articles [14,15]. Shortly, 100 µl of plasma was fortified with 20 µl of amantadine solution (internal standard: 200 ng/ml in 60% methanol), alkalinized with 20 µl of a 10% solution of ammonium hydroxide, proteins were precipitated with 300 µl of acetonitrile (4°C) and centrifuged; supernatant was mixed with water in the ratio 1:1 and 2 µl was introduced into the ultraperformance liquid chromatograph (UPLC).

UPLC (Acquity™ Class-I/, Waters Co, MA, USA) coupled with a tandem mass spectrometer (Xevo™ TQ-S, Waters Micromass, Manchester, UK) was employed, interfaced by MassLynx™ version 4.1 software. Memantine and amantadine were separated from possible endogenous interferences employing a BEH C18 column (2.1 × 50 mm, 1.7 µm particle size, acquity UPLC, Waters; Dublin, Ireland). Flow rate was fixed at 0.45 ml/min under isocratic conditions, and the mobile phase was optimized as 0.1% aqueous formic acid/0.1% formic acid in acetonitrile

(85:15 *v*/*v*). Column was maintained at 40°C and autosampler temperature was set at 10°C. Under these conditions, a complete run took 5 min.

Quantitation was done by positive electrospray, selecting the ion transitions of m/z^{+1} 180.20 >163.15 and 152.20 >135.15 for memantine and amantadine, respectively.

Method was fully validated according to Mexican guidelines [13] and proved to be linear, precise and accurate between 0.8 and 80 ng/ml of memantine.

Palatability survey

A memantine ODT palatability and acceptability survey (based on Nilausen *et al.*, 2011) was applied to the 18 volunteers who participated in the bioequivalence trial, during the period of test-product intake [16]. The survey comprised 35 questions grouped in five items, with the intention of evaluating the following: physical properties (size of tablet, texture, velocity of disintegration and amount of lumps); perception of taste (initial and residual taste); comfort of use (compared with other solid presentations); ease of use (ease of opening and handling); and treatment compliance (compared with other formulations).

Survey responses were obtained through an analog-visual-validated linear scale of 10 cm, where possible responses could fall between opposite values (completely disagree–fully agree) that were transformed into a numerical scale ranging from 0 to 10. Arithmetic mean and %CV were calculated for each question in order to establish the value of the item, and %CV values were used to describe agreement between questions and items. Values of <35 %CV were assigned as high agreement, 35% < %CV < 70% were assigned as moderate agreement and >70% were assigned as poor agreement.

Statistical analysis

For dissolution profiles, an independent time series approach was employed to compare assays when differences were not evident.

Pharmacokinetic parameters were calculated from analyzed plasma obtained from single dose-receiving volunteers, utilizing Phoenix WinNonlin version 6.4 software (Certara LP, NJ, USA), considering a noncompartmental model. Plasma elimination half-life ($t_{1/2}$), AUC until 72 h ($AUC_{0–72}$) and elimination constant (k_e) were software outputs. C_{max} and T_{max} were obtained experimentally.

To evaluate fixed effects such as period, sequence and formulation, we utilized analysis of variance (ANOVA) for a standard 2 × 2 crossover design. Pharmacokinetic differences were assayed based on a bioequivalence approach, building 90% CI of log-transformed relationships for C_{max} and $AUC_{0–72}$ between both formulations. Statistical analyses were carried out using Phoenix WinNonlin and Minitab TM version 16 software (Minitab, State College, PA, USA).

Concerning palatability survey, measurement of consistency inside items was validated by the use of Cronbach's alpha [17]. Possible differences between sequences of administration were assayed by the Student's *t*-test for independent samples.

Results & discussion

Dissolution assays

The different results obtained during dissolution assays are depicted in Figure 1. As can be observed, pharmacopeic media were not able to discriminate solubility differences between the formulations (Figure 1A), confirming that such conditions are adequate for quality-control purposes, but that they do not resemble physiological conditions.

These results compelled the development of teamwork in order to assay more discriminative media. The new media adopted, attempted to simulate closer conditions that reflected with dissolution microenvironment in which the tablets would be dissolved, such as small volume of media, acidic pH, osmolality, surface tension of bowel fluids, which were formulations that would disintegrate and deliver the memantine. First results with the medium containing Triton X-100 did not correspond to the expected behavior for both the formulations because the reference product exhibited faster delivery compared with ODT (Figure 1B).

Thus, it was decided to change Triton X-100 (surface tension of 42.5 mN/m) for Tween 80 (surface tension of 41 mN/m), the latter closely simulating the tension produced by endogenous surfactants. In addition to this, noncompressed powders for ODT were assayed in order to determine whether lack of delivery was due to certain excipients, or caused by the compression process (Figure 1C). It was evidenced that slow delivery of memantine was related with a limited disintegration step of the ODT, which was not observed with the powder.

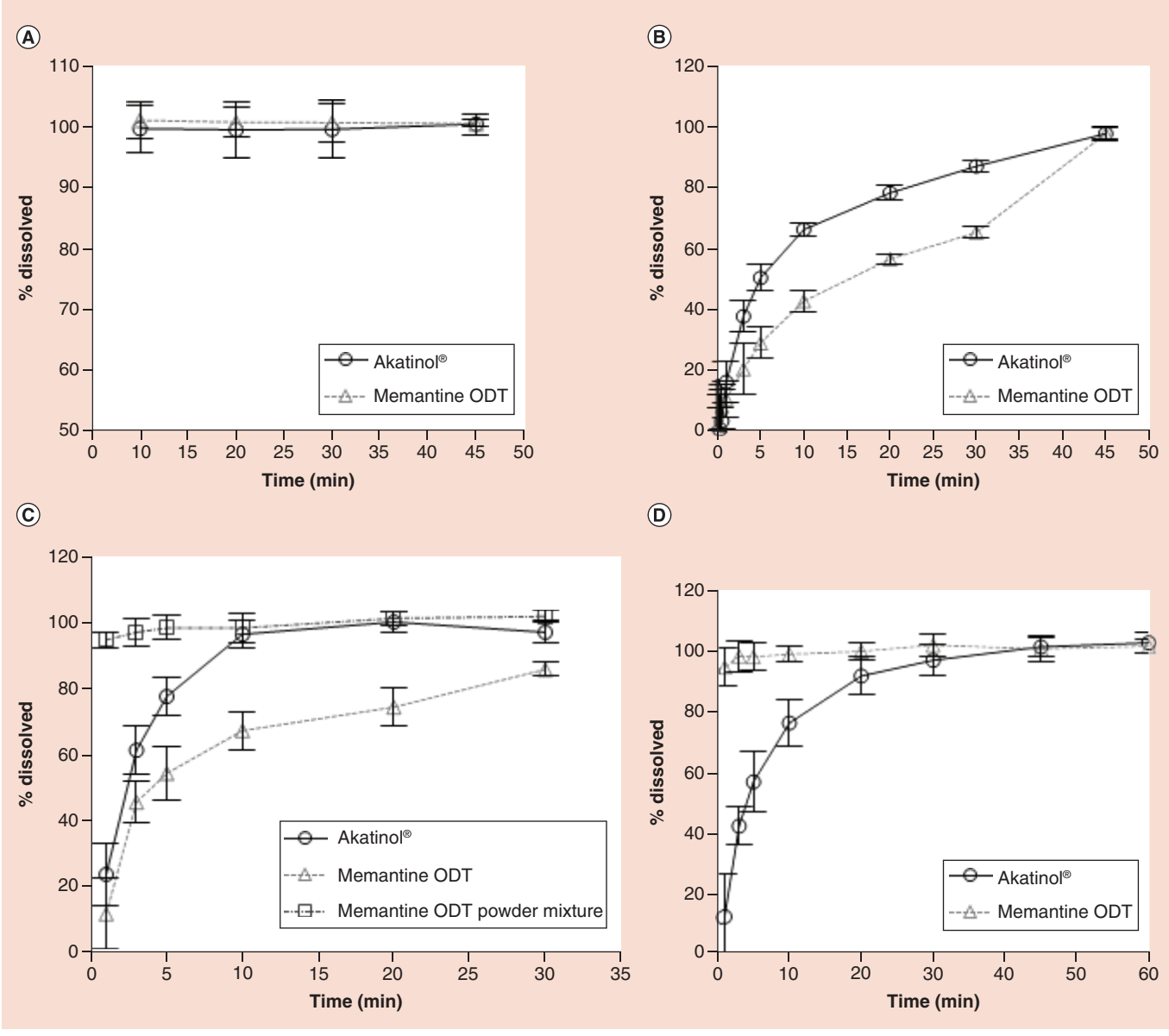

Figure 1. Dissolution profiles of memantine 20 mg orodispersible tablets and Akatinol® immediate release 20-mg tablets. (A) In 0.1 M HCl United States Pharmacopeia medium, having apparent similarities despite different mechanisms of delivery; **(B)** In 0.1 M HCl, NaCl and 0.1% Triton™ X-100 (pH = 1.2) as first 'physiological medium' approach; **(C)** In HCl 0.1 M, NaCl and 0.1% Tween™ 80 (pH = 1.2), including ODT powder mixture, in order to discriminate the influence of excipients or ODT compression on dissolution; **(D)** In simulated saliva as a disintegration step prior to the dissolution in 'C' conditions.
ODT: Orodispersible tablet.

In order to mimic the normal conditions for ODT administration, we proposed to previously disintegrate the ODT in 1 ml of simulated saliva for 1 min, and then add the dispersed material into the Tween 80 dissolution media. It is noteworthy (Figure 1D) that dissolution profiles agree with the pharmaceutical formulations. While ODT possesses rapid and complete dissolution during the first times, the reference product demonstrates a humectation-disintegration period with gradual dissolution that at around 30 min is quite similar at the different ODT levels, due to which the memantine is considered a highly soluble molecule. It would be expected that such differences would not be relevant during the *in vivo* assay.

Comparative bioavailability trial

The concentration–time profiles of the 18 volunteers for memantine up to 72 h are presented in Figure 2. All

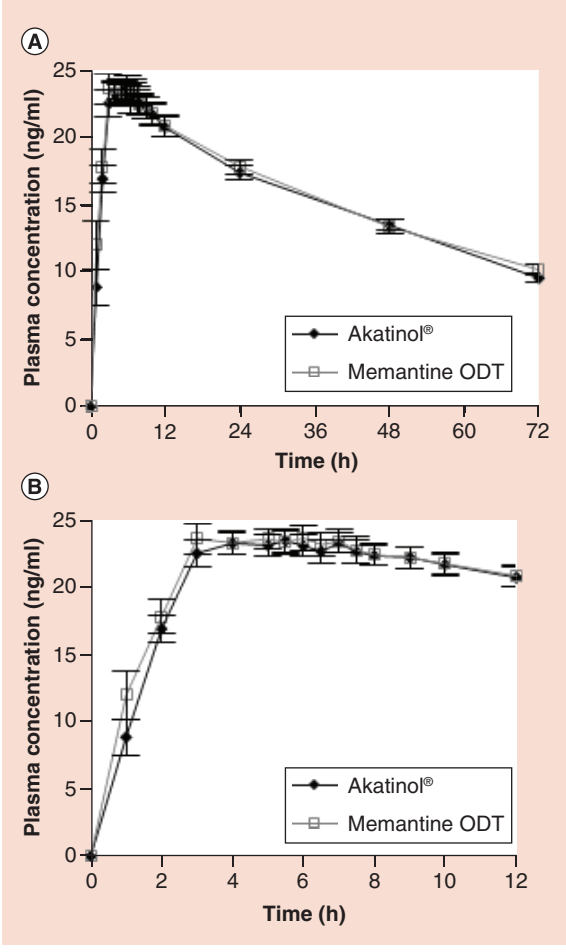

Figure 2. Memantine plasma concentration–time profile of 18 healthy Mexican volunteers, after an oral, single-dose administration of one 20 mg immediate release tablet of Akatinol® (reference product in Mexican market) or memantine orodispersible tablet (test product), under fasting conditions. (A) Full sampling truncated up to 72 h; **(B)** Pharmacokinetic profiles of the first 12 h.
ODT: Orodispersible tablet.

Table 1. Memantine pharmacokinetic data after administration of a single oral dose of one 20-mg tablet to healthy Mexican volunteers under fasting conditions.

	Mean	SD	%CV	Minimal	Maximal
Memantine ODT					
T_{max} (h)	4.97	2.018	40.587	1	7.5
C_{max} (ng/ml)	25.491	4.655	12.261	17.226	34.638
k_e (h^{-1})	0.013	0.003	21.995	0.009	0.018
$t_{\frac{1}{2}}$ (h)	58.578	12.824	21.893	38.885	80.818
AUC_{0-72} (ng.h/ml)	1134.092	168.428	14.851	825.306	1446.796
Akatinol®					
T_{max} (h)	5	1.871	27.417	2	7.5
C_{max} (ng/ml)	24.931	3.346	13.421	17.384	29.808
k_e (h^{-1})	0.013	0.003	19.503	0.009	0.019
$t_{\frac{1}{2}}$ (h)	55.871	10.064	18.014	36.118	77.509
AUC_{0-72} (ng.h/ml)	1113.515	135.005	12.124	915.021	1378.009

ODT: Orodispersible tablet; SD: Standard deviation.

calculated pharmacokinetic (PK) parameters are summarized in Table 1. As can be noted, no significant differences were observed in terms of velocity of absorption and total amount absorbed (Table 2), respectively. Thus, during ODT formulation, it appears that oral disintegration and rapid dissolution in the bowel did not to exert any influence on the bioavailability of memantine.

Table 2. Statistics bioequivalence of memantine 20 mg orodispersible tablets and Akatinol® 20-mg immediate release tablets.

Parameter	(%) Intrasubject CV	90% Confidence intervals		Statistic power
		Lower	Upper	
C_{max} (ng/ml)	8.250	95.992	108.284	1.000
$AUC_{0-72\,h}$ (ng*h/ml)	5.510	100.232	111.015	1.000

Concerning pharmacokinetic data obtained in Mexican population, it is interesting to note differences with previously published information. In a healthy Indian population [14], the study participants were administered with a single oral dose of 10 mg under fasting conditions, reaching a mean C_{max} of 14.39 ng/ml, (approximately 44% less with the half dose used in this work), while T_{max} was 7.5 h with an elimination half-life of 49 h. Moreover, in a Brazilian study conducted under the same conditions, with a 10-mg oral dose, the C_{max} reported was 21.6 ng/ml (86.4% of C_{max} acquired in Mexican, but using one half of the dose), with a delayed T_{max} of 8 h and a shorter $t_{\frac{1}{2}}$ of 43 h [18]. At last, the present data appear quite to those obtained in a Chinese trial [19], where the authors reported a C_{max} of 25.34 ng/ml, with a T_{max} of 6.8 h and a $t_{\frac{1}{2}}$ of 62 h with a single oral dose of 20 mg.

Although it is known that memantine is not metabolized, all of these apparent demographic differences in bioavailability should be explored more thoroughly, and its clinical relevance must be discussed in the face of the new findings on its cellular mechanisms associated with the prevention of the expression of cell-adhesion molecules induced by proinflammatory signals in the endothelium of human brain microvasculature, which is linked to cognitive impairment and dementia during aging [20].

Palatability survey

The survey was fully validated employing placebo ODT with volunteer personnel of Pharmometrica, and no statistical effect of the sequence-of-administration in the responses was demonstrated.

The most concordant answers in terms of mean values in the analog-visual scale were (detected in decreasing order):

- ODTs have a nice flavor;
- ODTs did not leave an unpleasant aftertaste or sensation in the mouth;
- ODTs would be preferred over common tablets and other pharmaceutical forms, with higher compliance for prolonged treatments;
- ODTs are easily handled and did not break into the blister or in the fingers.

Conclusion

It might be considered that pharmacopeic dissolution conditions have quality-control purposes, and that in many of the cases, they do not have a discriminative capacity to distinguish differences in the delivery of the active pharmaceutical ingredients from the pharmaceutical formulation that could impact the bioavailability of the drugs. The development and adoption of the discriminative dissolution assay must resemble the physiological conditions, such as small volumes, slower agitation speeds, similar surface tension, pH and temperature, as well as consider a previous disintegration step in the case of ODT.

In the case of the ODT developed, they exhibited adequate palatability characteristics and were well accepted in a sample of healthy volunteers. Memantine ODTs were bioequivalent with the reference product and the pharmacokinetics of memantine in Mexican population exhibits slight differences with those previously reported in other populations.

With this biopharmaceutical development and human pharmacokinetic and palatability characterization, memantine ODT has established a new approach to be used as a dosage form with value proposition in concordance with EMA 'Quality aspects in the pharmaceutical development of medicines for older people'. Further research should be conducted in order to assess patient preference.

Future perspective

Considering the aging of global population, we must observe a trend in the development and commercialization of pharmaceutical formulations such as ODT, minipills, transdermic patches and so on for geriatric population.

During those developments, researchers must create *in vitro* assay that resembles as close as possible the physiological conditions during drug delivery. Such assays should include not only media (pH, salinity, osmolality, tensoactive presence and limitaintg volume), but also new apparatus that can simulate disintegration, bowel empting, peristaltic motion and gastroenteric reabsorption. Adoption of these technologies will be able to generate stronger *in vitro–in vivo* correlations.

At last and concerning new insights in the cellular therapeutic mechanism of memantine, it is promissory that it could be used not only in the treatment of Alzheimer's disease, but also in other kinds of dementia and cognitive disorders.

Summary points

- Aging of global population has been accomplished by an increase in several kinds of dementia, including Alzheimer's disease.
- Modern public health policies must consider the design of pharmaceutical formulations suitable for older patients.
- Developed memantine orodispersible tablet complies with the quality aspects in the pharmaceutical development of medicines for older people.
- During formulation characterization, it is very convenient to develop biorelevant conditions during dissolution assays that mimic the physiological environment of the drug delivery, instead of pharmacopeic methodology.
- Memantine orodispersible tablet was bioequivalent to 20-mg immediate release tablet, having advantages in flavor and handling that may result in a better treatment compliance.

Financial & competing interests disclosure

This study was partially funded by Productos Científicos, SA de CV. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that the clinical protocol was reviewed and approved by an independent Ethics Committee. In addition, the authors obtained COFEPRIS approval for the conduction of present study. Volunteers signed informed consent, which was formulated according to the latest version of the Declaration of Helsinki (64th General Meeting, Fortaleza, Brazil; October 2013).

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