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The effect of oil as a dietary component on *in vitro* dissolution of an acid-labile drug

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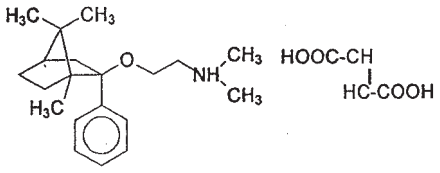
The non-benzodiazepine-like anxiolytic agent deramiclane fumarate (EGIA-3886) was used to demonstrate that the presence of high oil/fat content in dissolution media serves as a barrier against accelerated drug degradation in acidic media.

1. Introduction

Drug absorption from the gastro-intestinal tract and, consequently, bioavailability is greatly influenced by simultaneous food intake [1]. Meals may modify the pharmacokinetics of drugs and thereby elicit clinically significant food-drug interactions [2]. Oral administration of acid-labile drugs, e.g. digoxin [3], didanosine [4] is affected by stomach pH. Administration in a special pharmaceutical form might even be unavoidable, such in the case of omeprazole [5] or lansoprazole [6]. For this class of drugs, determination of active ingredient stability under the condition set during the dissolution process is essential. Using animal models for food-interaction studies of some acid-labile drugs has been dismissed as a substitute for humans due to major biological differences regarding basic gastric pH [7]. On the other hand, a limited number of work exists regarding the use of i*n vitro* modells for the evaluation of food effects on drug dissolution [8, 9].

2. Investigations, results and discussion

To demonstrate an example, a new non-benzodiazepine-like anxiolytic agent, deramciclane fumarate (EGIS-3886; (1*R*,2*S*,4*R*)-(−)-*N*,*N*-dimethyl-2-{(1,7,7-trimethyl-2-phenyl-bicyclo-[2,2,1]-hept-2-yl)oxy}-ethamine-2-(*E*)-butendioate (1 : 1)) **1**) was used. The drug was synthesised by EGIS Pharmaceuticals Ltd. (Budapest, Hungary). It is a 5-HT receptor antagonist with no muscle relaxant or sedative effects [10]. Extensive pharmacokinetic studies of **1** have been conducted after oral administration in several animal species and human beings [11]. Clinical pharmacokinetic studies in healthy volunteers showed that the compound was well absorbed, safe and well tolerated after the administration of both single and multiple oral doses [12, 13].



Regarding its physico-chemical properties, **1** is very slightly soluble in water (0.0088 g/100 ml, at 25 °C). The aqueous pK_a value of deramciclane fumarate is 9.61. Octanol/water partition coefficient (Log*P*) values for deramciclane and the deramciclane salt are 5.9 and 1.41, respectively. Deramciclane is an acid-labile drug, with *in vitro* studies revealing this nature to be most prominent over a pH range of 1.2–2.1 [7]. The use of different formulations of deramciclane-containing preparations in man and dog (i.e. conventional capsules and enteric coated tablets) has yielded different drug pharmacokinetic profiles, allowing the assumption of a possible pH-effect involvement. Low pH of a fasting stomach in man might have caused degradation of deramciclane, resulting in a decreased total amount of drug available for absorption from the intestinal tract [7]. With animal models being ruled out, *in vitro* modelling of *in vivo* conditions provides an alternative approach for drug release studies.

The aim of our work was to compare the *in vitro* dissolution behaviour of deramciclane under physiologically simulated gastric environment, i.e. during fasting and fed conditions. Taking into account the emphasis on high fat content of test meals included in food-interaction studies [14], this dietary component was studied in detail.

In vitro dissolution profiles of deramciclane-containing film-coated tablets, both in simulated fasting conditions (artificial gastric juice, pH 1.2) and simulated fed state (pH 6.8 buffer; pH 1.2 buffer with oil added) are shown in the Fig. For each point plotted, the average reading of three tablets is shown expressed as percentage of released deramciclane base to the total amount of drug available for dissolution. In simulated fasting state, the deramciclane release reached a maximum of 66.5% and started decreasing afterwards in accordance with its acid labile characteristic. In pH 6.8 buffer, the dissolution was completed within 10 min with release values close to 100%. Although the amount of drug dissolved in the presence of oil reached the maximum within 10 min, these values started to decrease afterwards. This observation is due to the effect of acidic medium, since oil lacks acid buffering capacity compared to other dietary components [15]. Considering the hydrophobic character of deramciclane, a par-

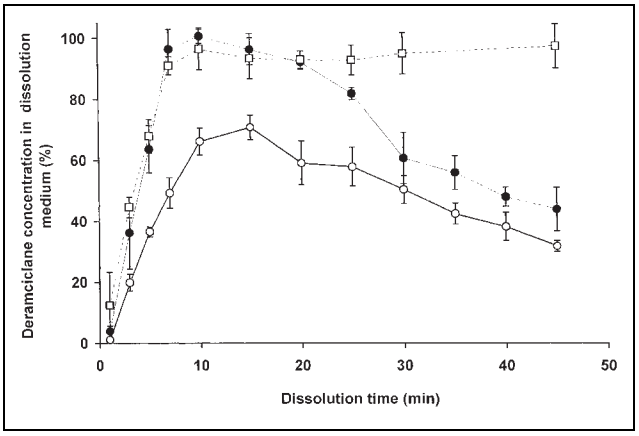


Fig.: Deramciclane release as a function of time after *in vitro* dissolution of film-coated tablets containing 30 mg drug base, studied with the USP dissolution apparatus II (paddle method). —○— fasting state simulated with pH 1.2 buffer, —□— fed state simulated with pH 6.8 buffer, —●— fed state simulated with pH 1.2 buffer + oil

titioning between the water and oil (lipophilic) phase of the emulsion could possibly have taken place. Such a phenomenon remains to be investigated.

Based on our results, and regarding this particular drug, it can be concluded that the presence of high oil/fat content in dissolution media serves as a barrier against accelerated drug degradation in the acidic medium. This protection, however, is limited as it does not affect the pH of the dissolution medium itself. Nevertheless, these findings support intensive investigation to refine *in vitro* modelling of the *in vivo* environment.

3. Experimental

3.1. Chemicals, standards and dietary components

Film-coated tablets each contained 30 mg deramciclane base, bencyclane fumarate (internal standard for the analytical work) both synthesised by EGIS Pharmaceuticals Ltd. (Budapest, Hungary). Methanol, ethylacetate and *n*-hexane (obtained from E. Merck, Darmstadt, Germany) were of chromatographic purity. Ammonium hydroxide (approx. 25 (m/m)%) was of analytical purity (Fluka). Double distilled water was further purified using a Milli-Q equipment (Millipore, Milford, USA). For the preparation of the oil emulsion, 50 ml of sunflower oil (Ph. Hg. VII) was emulged in 450 ml of distilled water containing 1% methylcellulose (Ph. Hg. VII) as stabilizer (giving a result of 10% oil emulsion used to simulate dietary fat).

3.2. Instrumental

For *in vitro* dissolution testing of deramciclane film-coated tablets, the USP dissolution apparatus II/paddle method (USP 24; Pharmatest PTWSII, Pharma Test GmbH, Hainburg, Germany) was used. A HP 5890 gas chromatograph (Hewlett-Packard, Palo Alto, USA) equipped with a HP 7673 autosampler and nitrogen-phosphorous selective detector (NPD) was used for analytical work. Data acquisition, instrument control and evaluation of results were performed by a Hewlett-Packard Chemstation software (version A 03.02.) running on HP Vectra VE computer.

3.3. In vitro simulation of in vivo conditions

Experimental test conditions, dissolution media preparation and procedure specifications followed those already validated and published [16]. To simulate *in vivo* conditions, the dissolution apparatus contained 500 ml of test media maintained at 37 °C. Oil emulsion was added to the test media and examined. Aliquots of dissolution media (5 ml) were collected 1, 3, 5, 7, 10, 15, 20, 25, 30, 35, 40 and 45 min after initiation of the test, diluted with equal volumes of 0.25 M ammonium hydroxide and analysed by gas chromatography – nitrogen phosphorous selective detection.

3.4. Analytical methods

Deramciclane was extracted from the dissolution media by liquid-liquid extraction at alkaline pH as described before [17]. The extraction solvent was prepared by mixing 100 ml ethylacetate and 900 ml hexane (1 : 9 (v/v) ethylacetate-hexane). Stock solutions of deramciclane and internal standard (bencyclane fumarate) were prepared by dissolving 10 mg deramciclane and bencyclane in 10 ml methanol-water (9 : 1 v/v), respectively. A calibration curve was constructed between 50 ng/ml and 100 μg/ml.

All extractions were performed in duplicates. 1 ml of calibration solution or dissolution sample was mixed with 1 ml of 0.25 M ammonium hydroxide solution and 50 μl internal standard were added. The sample was extracted for 30 s with 2 ml extraction solvent by vortexing. The two phases were separated by centrifugation (2000 min^{-1}, 15 min), the organic phase was evaporated to dryness in a nitrogen stream at 50 °C. The evaporation residue was dissolved in 200 μl propanol and injected into the gas chromatographic system. The column used was a Supelco SPB-1 (30 m × 0.25 mm × 0.25 μm) fitted with an HP retention gap (5 m × 0.25 mm) and helium as carrier gas with a flow rate of 1.95 ml/min. Temperatures of the injector and detector were 240 and 300 °C, respectively. Separation was performed using the following temperature program: 100 °C for 0.05 min, then heated at 35 °C/min to 195 °C and kept isothermally for 8 min; then heated at 50 °C/min to 280 °C for 2 min. 2 μl aliquots of the extracted samples were injected in split mode.

References

1 Davis, S. S.: Controlled-release formulations in hard gelatine capsules, p. 7, Capsugel, Basel 1989
2 Drabant, S.; Klebovich, I.; Gachályi, B.; Renczes, G.; Farsang, Cs.: Acta Pharm. Hung. **68**, 294 (1998)
3 Sonobe, T.; Hasumi, S.; Yoshino, T.; Kobayashi, Y.; Kawata, H.; Nagai, T.: J. Pharm. Sci. **69**, 410 (1980)
4 Li, R. C.; Narang, P. K.; Sahai, J.; Cameron, W.; Bianchine, J. R.: Antimicrob. Agents Chemother. **41**, 1566 (1997)
5 Sharma, V. K.; Heinzelmann, E. J.; Steinberg, E. N.; Vasudeva, R.; Howden, C. W.: Am. J. Gastroenterol. **92**, 848 (1997)
6 Sharma, V. K.; Ugheoke, E. A.; Vasudeva, R.; Howden, C. W.: Aliment. Pharmacol. Ther. **12**, 1171 (1998)
7 Kanerva, H.; Klebovich, I.; Drabant, S.; Urtti, A.; Nevalainen, T.: J. Pharm. Pharmacol. **50**,1087 (1998)
8 Maturu, P. K.; Prasad, V. K.; Worsley, W. N.; Shiu, G. K.; Skelly, J. P.: J. Pharm. Sci. **75**, 1205 (1986)
9 Williams, R. O.; Sriwongjanya, M.; Liu. J.: Pharmaceutical Dev. Tech. **2**, 1 (1997)
10 Gacsályi, I.; Schmidt, E.; Gyertyán, I.; Vasar, E.; Lang, A.; Haapalinna, A.; Fekete, M.; Hietala, J.; Syvälahti, E.; Tuomainen, P.; Mannistö, P.: Drug Dev. Res. **40**, 333 (1977)
11 Klebovich, I.; Kanerva, H.; Bojti, E.; Urtti, A.; Drabant, S.: Pharm. Pharmacol. Commun. **4**, 129 (1998)
12 Kanerva, H.; Kilkku, O.; Heinonen, E.; Helminen, A.; Rouro, J.; Tarpila, S.; Scheinin, M.; Huuponen, R.; Klebovich, I.; Drabant, S.; Urtti, A.: Biopharm. Drug Dispos. **20**, 327 (1999)
13 Kanerva, H.; Kilkku, O.; Helminen, A.; Rouro, J.; Scheinin, M.; Huuponen, R.; Klebovich, I.; Drabant, S.; Urtti, A.: Int. J. Clin. Pharm. Ther. **37**, 589 (1999)
14 Food and Drug Administration (FDA) Guidance for Industry Food-effect bioavailability and bioequivalence studies. Office of Generic Drugs, Rockville, MD, USA 1997
15 Al-Behaisi, S.; Antal, I.; Drabant, S.; Plachy, J.; Marton, S.; Klebovich, I.: Symposium of Pharmacokinetics and Drug Metabolism, Mátraháza, Hungary. April 28–29, 2000. Abstr. p. 35 (2000)
16 Kristensen, H. G.: Pharmeuropa. **8**, 386 (1996)
17 Al-Behaisi, S.; Antal, I.; Morovján, Gy.; Szúnyog, J.; Drabant, S.; Marton, S.; Klebovich, I.: Eur. J. Pharm. Sci. *In press*