

## COMMENTARY

# Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Amitriptyline Hydrochloride

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**ABSTRACT:** Literature data relevant to the decision to allow a waiver of *in vivo* bioequivalence (BE) testing for the approval of immediate release (IR) solid oral dosage forms containing amitriptyline hydrochloride are reviewed. Its therapeutic uses, its pharmacokinetic properties, the possibility of excipient interactions and reported BE/bioavailability (BA) problems are also taken into consideration. Literature data indicates that amitriptyline hydrochloride is a highly permeable active pharmaceutical ingredient (API). Data on the solubility according to the current Biopharmaceutics Classification System (BCS) were not fully available and consequently amitriptyline hydrochloride could not be definitively assigned to either BCS Class I or BCS Class II. But all evidence taken together, a biowaiver can currently be recommended provided that IR tablets are formulated with excipients used in existing approved products and that the dissolution meets the criteria defined in the Guidances. © 2006 Wiley-Liss, Inc. and the American Pharmacists Association *J Pharm Sci* 95:966–973, 2006

**Keywords:** amitriptyline hydrochloride; Biopharmaceutics Classification System (BCS); permeability; solubility; absorption; biowaiver

## INTRODUCTION

A monograph based on literature data is presented on amitriptyline hydrochloride, with respect to its biopharmaceutical properties and the risk of waiving *in vivo* bioequivalence (BE) testing in the approval of new immediate release (IR) solid oral dosage forms containing this active pharma-

ceutical ingredient (API), including both reformulated products and new, multisource drug products. The purpose and scope of this series of monographs were discussed previously.<sup>1</sup> Briefly, the aims of the present study are to evaluate all pertinent data available from literature sources to assess the appropriateness of such a biowaiver from the biopharmaceutical point of view and also from the perspective of public health. The progress in this series can be followed at the FIP Website.<sup>2</sup> Up to now, monographs have been published on acetaminophen (paracetamol),<sup>3</sup> atenolol,<sup>1</sup> chloroquine,<sup>4</sup> ibuprofen,<sup>5</sup> propranolol,<sup>1</sup> ranitidine,<sup>6</sup> and verapamil.<sup>1</sup>

This paper reflects the scientific opinion of the authors and not the policies of regulating agencies.

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## EXPERIMENTAL

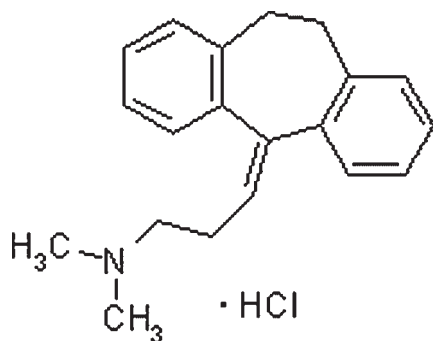
A search in the PubMed Central and Scirus was conducted using the keyword amitriptyline combined with: absolute, absorption, aqueous, bioavailability, permeability, pharmacokinetics, oral, and solubility. Whenever possible, original literature was consulted; data from secondary sources were included for completeness or when original literature could not be located.

## GENERAL CHARACTERISTICS

Amitriptyline is an INN name. Its chemical name is 3-(10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5-ylidene)-propyldimethylamine. The molecular weight and melting point of amitriptyline hydrochloride are 313.9<sup>7</sup> and 196–197°C<sup>8</sup>, respectively. Its structure is shown in Figure 1.

### Therapeutic Indication and Therapeutic Index

The major therapeutic indication for amitriptyline is for the treatment of depression, although is also indicated for a number of nervous system related disorders.<sup>9</sup> In the treatment of depression, amitriptyline hydrochloride is given by mouth initially in a daily dose of 75 mg. Thereafter, the dose may be gradually increased, if necessary, to 150 mg daily. Therapy may also be begun with a single dose of 50–100 mg, increased by 25 or 50 mg as necessary to a total of 150 mg daily. Doses of up to 200 mg daily and, occasionally, up to 300 mg daily have been used in severely depressed patients.<sup>10</sup> Severe symptoms of overdosage have been described, including unconsciousness, convulsions and myoclonus, hyperreflexia, hypothermia, hypotension, metabolic acidosis, and respiratory and



**Figure 1.** Structure of amitriptyline hydrochloride.

cardiac depression, with life-threatening cardiac arrhythmias that may recur some days after apparent recovery.<sup>10</sup> No data are available on the dose that gave rise to these symptoms.

## CHEMICAL PROPERTIES

### Salts, Isomers, and Polymorphs

In therapeutic use are an ester: amitriptyline embonate and the hydrochloride salt. This monograph will refer exclusively to amitriptyline hydrochloride. Polymorphic forms have not been reported, nor are there stereoisomers.

### Solubility

Amitriptyline hydrochloride is soluble 1:1 in water.<sup>11</sup> The USP<sup>12</sup> and the Ph. Eur.<sup>7</sup> report this API to be “freely soluble in water”. Amitriptyline free base is practically insoluble in water and its solubility in 0.1 M sodium hydroxide at  $24 \pm 1^\circ$  was recorded as  $1.1 \times 10^{-2}$  mg/mL.<sup>13</sup> More recently, its solubility at 25°C was measured, using both the acid-base titration method and the shake-flask method.<sup>14</sup> Both methods gave  $2.0 \times 10^{-3}$  mg/mL.

Experimental measured values of the solubility at 37°C in different physiologically relevant pHs, as required by the different Guidances,<sup>15–17</sup> were not found, but solubilities at 25°C were estimated from the solubility and pKa. Taking the lowest reported solubility at that temperature, that is,  $2.0 \times 10^{-3}$  mg/mL, and the pKa value at 25°C reported, that is, 9.45 (see below), the values of Table 1 were calculated, whereas the solubility in pH 1.2 was estimated from the solubility of 1:1, reported for amitriptyline hydrochloride.<sup>11</sup>

Several reports indicate the protonated form of amitriptyline to self-aggregate with a critical micelle concentration of  $3.6 \times 10^{-2}$  mol/L and an aggregation number of 7.<sup>18–20</sup>

### Partition Coefficient

Amitriptyline is a highly lipophilic molecule having a log *P* (octanol/water, pH 7.4) of 3.0,<sup>11</sup> while the intrinsic log *P* of the free base was reported as 5.04.<sup>21</sup> Calculations using fragmentation methods based on atomic contributions to lipophilicity gave values of 4.42 and 4.85, respectively.<sup>22</sup> Other workers reported a *C* log *P* of 4.85.<sup>23</sup>

**Table 1.** Calculated Solubilities of Amitriptyline Hydrochloride at 25°C at Critical pH Values and Dose/Solubility Ratios for Different Tablet Strengths

pH	Calculated Solubility <sub>pH</sub> (mg/mL)	Dose/Solubility Ratio (mL) for Different Tablet Strengths					
		10 mg	25 mg <sup>a</sup>	50 mg	75 mg	100 mg	150 mg
7.5	0.18	55	139	277 <sup>b</sup>	416 <sup>b</sup>	555 <sup>b</sup>	832 <sup>b</sup>
6.8	0.90	11	28	56	84	112	168
4.5	178	0.06	0.14	0.28	0.42	0.56	0.84
1.2	1000	0.01	0.025	0.05	0.075	0.10	0.15

Solubilities at pH 7.5, pH 6.8, and pH 4.5 were calculated from the Henderson–Hasselbalch equation.<sup>43</sup>

$$\text{Solubility}_{\text{pH}} = 2.10^{-3} \cdot (1 + (10^{-\text{pH}}/10^{-9.45}))$$

in which  $2.10^{-3}$  and 9.45 are the solubility<sup>14</sup> and the pKa of amitriptyline base,<sup>14</sup> respectively, both at 25°. The solubility at pH 1.2 was estimated from the reported solubility of 1:1.<sup>11</sup>

<sup>a</sup>WHO recommended dose.

<sup>b</sup>Dose/solubility ratios higher than the critical value of 250 mL<sup>15–17</sup> are indicated.

## pKa

The pKa of amitriptyline has been reported as: 9.4<sup>24</sup>; 9.4 (24°C ± 1),<sup>13</sup> 9.45 (25°C),<sup>14</sup> and 9.31 (37°C).<sup>11</sup>

## Available Strengths

The WHO recommended dose is 25 mg.<sup>25</sup> IR solid dosage forms with marketing authorization (MA) in Argentina<sup>26</sup> and in Germany (DE)<sup>27</sup> have strengths of 10 mg up to 75 mg; in the USA, MAs have been given to tablet strengths up to 150 mg.<sup>28</sup>

## PHARMACOKINETIC PROPERTIES

### Absorption and BA

Amitriptyline is passively absorbed<sup>29</sup> and undergoes extensive hepatic metabolism; it is metabolized in the liver to nortriptyline, an active metabolite that is also marketed separately. Amitriptyline and nortriptyline are distributed into the lungs, heart, brain, and liver. Both undergo enterohepatic circulation. Half-life values range from 10–50 h for amitriptyline and 20–100 h for nortriptyline. Pharmacokinetic determinations of both amitriptyline and nortriptyline show that the fraction absorbed from IR amitriptyline tablets is 0.90.<sup>30,31</sup> Although amitriptyline is well absorbed the oral BA is only 48% ± 11,<sup>32</sup> as a result of the extensive first-pass metabolism. The oral BA of an IR tablet versus an oral solution, expressed as AUC<sub>∞</sub> was reported to be 112%.<sup>33</sup>

## Permeability

The permeability in Caco-2 cell monolayers was measured at a high and a low concentration, in two directions.<sup>23</sup> Apparent Caco-2 permeability for apical to basolateral transport values reported for two concentrations were  $2.10 \times 10^{-5}$  cm/s and  $1.73 \times 10^{-5}$  cm/s, respectively. In the same study, the permeability of other APIs with a high fraction absorbed were also measured; all these APIs showed a permeability of approximately  $10^{-5}$  cm/s or higher, indicating that amitriptyline is a high permeable API also.

## DOSAGE FORM PERFORMANCE

### Excipients

Excipients present in IR amitriptyline hydrochloride tablets with a MA in DE, Finland (FI), and The Netherlands (NL) are summarized in Table 2. *In vivo* comparisons of different formulations were not reported. Therapeutic inequivalence between brand-name drug products and FDA-approved generic drug products has not been reported<sup>34</sup> and there have been no reports of bioequivalence of IR tablets with a MA in Argentina.<sup>26</sup>

### Dissolution

The USP 28 specification for Amitriptyline Hydrochloride Tablets is not less than 75% (Q) dissolved

**Table 2.** Excipients<sup>a</sup> Present in Amitriptyline Hydrochloride<sup>b</sup> IR Solid Oral Drug Products<sup>c</sup> with a Marketing Authorization (MA) in Germany (DE), Finland (FI), and The Netherlands (NL)

Acacia	DE (1)
Aluminium hydroxide	DE (2)
Beeswax	DE (1); NL (3, 4)
Calcium carbonate	DE (1); FI (5, 6)
Calcium hydrogen phosphate	DE (2, 7–10); NL (11)
Calcium phosphate	NL (3, 4)
Calcium stearate	DE (12)
Carmellose sodium	DE (13)
Carnauba wax	DE (1); FI (5, 6); NL (3, 4, 11)
Cellulose	DE (8, 10, 13–16); FI (17); NL (3, 4, 11, 18)
Copovidone	FI (17); NL (18)
Croscarmellose	DE (15)
Croscarmellose sodium	FI (17); NL (18)
Crospovidone	DE (16)
Dibutyl phthalate	NL (19)
Diethyl phthalate	NL (20)
Disodium edetate	NL (20)
Ethylcellulose	NL (20)
Gelatin	DE (12)
Glucose, liquid	DE (1)
Glycerol palmitostearate	NL (3, 4, 19)
Hydroxypropylcellulose	NL (3, 4, 11)
Hypromellose	DE (2, 7–9, 14, 15); NL (3, 4, 11, 19)
Lactose	DE (1, 2, 7–9, 12–16); FI (5, 6, 17); NL (3, 11, 18–20)
Macrogol	DE (2, 7–9, 12–15); FI (5, 6, 17); NL (3, 4, 18, 19)
Magnesium stearate	DE (1, 2, 7–10, 13–16); FI (5, 6, 17); NL (3, 4, 11, 18–20)
Maize starch	DE (1, 2, 7–10, 12, 14); FI (5, 6, 17); NL (3, 4, 11, 18, 19)
Maize starch, pregelatinised	DE (13)
Methylcellulose	NL (20)
Polymethacrylate	DE (1, 13); NL (19)
Povidone	DE (1, 8, 10, 13); FI (5, 6); NL (3, 4, 19)
Shellac	DE (1); NL (3, 4)
Silica	DE (2, 7–9, 12, 13); FI (17); NL (11, 18, 20)
Sodium benzoate	FI (6)
Sodium starch glycolate	DE (1, 2, 7–9, 14); NL (3, 4, 19)
Starch	NL (20)
Starch, pregelatinised	NL (20)
Stearic acid	NL (11)
Sucrose	DE (1); FI (5, 6)
Talc	DE (1, 12–14); NL (3, 4, 11, 19)

1. Amitriptylin-neuraxpharm<sup>®</sup> 10/-25/-50 Dragees.
2. Amitriptylin beta<sup>®</sup> 10 Filmtabletten.
3. Amitriptylinehydrochloride 10 mg, tabletten (MA holder: Katwijk Farma).
4. Amitriptylinehydrochloride 25 mg, tabletten (MA holder: Katwijk Farma).
5. Triptyl<sup>®</sup> 10 mg tabletti.
6. Triptyl<sup>®</sup> 25/50 mg tabletti.
7. Amineurin<sup>®</sup> 10/-25 Filmtabletten.
8. Amineurin<sup>®</sup> 50 Filmtabletten.
9. Amitriptylin beta<sup>®</sup> 25 Filmtabletten.
10. Amitriptylin—CT 25/-75 mg Tabletten.
11. Tryptizol, tabletten 10/25/50/75 mg.
12. Amitriptylin-RPh<sup>®</sup> 25 mg Filmtabletten.
13. Amitriptylin-neuraxpharm<sup>®</sup> 75/-100 Filmtabletten.
14. Novoprotect<sup>®</sup> 10/-25 mg Filmtabletten.
15. Saroten<sup>®</sup> Tabs 50 mg Filmtabletten.
16. Syneudon<sup>®</sup> 50 Tabletten.
17. Saroten 10/25/50 mg tabletti, kalvopäällysteinen.
18. Sarotex 10/25, omhulde tabletten 10/25 mg.
19. Amitriptyline HCl Gf 25 mg, omhulde tabletten.
20. Amitriptyline HCl, tabletten 10 mg (MA holder: Pharmethica).

Sources of data: DE: www.rote-liste.de; FI: www.nam.fi; NL: www.cb-g-meb.nl.

<sup>a</sup>Colourants are not included.

<sup>b</sup>Drug products containing other APIs than Amitriptyline Hydrochloride are excluded.

<sup>c</sup>Excluded are dosage forms that are swallowed by the patient in liquid form, such as oral solution.

in 45 min in 900 mL 0.1 N HCl using the basket at 100 rpm.<sup>12</sup> Results of comparative studies *in vitro* of different formulations were not reported.

## DISCUSSION

### Solubility

The FDA defines “highly soluble” over the pH range 1–7.5,<sup>15</sup> while the EU<sup>16</sup> and the recently revised WHO Guidelines<sup>17</sup> limit the requirements to the pH range 1–6.8. It was recently suggested that the FDA should also redefine the solubility boundaries for BCS Class I to pH 1.2–6.8.<sup>35</sup> At 25°C, all tablet strengths conform to the criterion of 250 mL for the dose/solubility ratio at pH 6.8 and below, see Table 1. At pH 7.5, the WHO recommended dose complies with this dose/solubility ratio criterion but higher tablet strengths do not. However, these data refer to 25°C, not at 37°C, as required by the Guidances.<sup>15–17</sup> If amitriptyline hydrochloride, like most drug substances, has an endothermic heat of solution it is reasonable to assume that amitriptyline hydrochloride will exhibit higher solubility at 37°C. On the other hand, calculating solubilities, using the Henderson–Hasselbalch equation, are highly inaccurate and differences between the calculated solubility and the experimental value of up to a factor of 776 have been reported.<sup>36</sup> In summary, experimental solubility data at the conditions specified by the BCS Guidances are lacking and no concrete conclusion can be drawn as to whether amitriptyline hydrochloride meets either the FDA<sup>15</sup> or EU/WHO<sup>16,17</sup> definition of “highly soluble.”

### Permeability

According to the present FDA and EU BCS Guidances, an API is classified as “highly permeable” if the fraction absorbed is 90% or higher<sup>15,16</sup> whereas the recently revised WHO Guidelines<sup>17</sup> sets a lower limit of 85% absorbed. Amitriptyline hydrochloride fulfills both criteria. Both log *P* and Caco-2 permeability data support the classification of this API as “highly permeable.”

### Surrogate Techniques for *In Vivo* BE Testing

For amitriptyline hydrochloride, it is unlikely that bioequivalence between two IR solid oral dosage forms would arise from differences in permeability produced by formulation differences, in

view of its high and hence non-critical permeability.<sup>37</sup>

Bioequivalence between formulations, if any exists, would most probably be caused by differences in *in vivo* dissolution, which is expected to be the most critical parameter in the absorption process, at least in the neutral pH range. Consequently, for amitriptyline hydrochloride IR solid oral dosage forms, comparative *in vitro* dissolution testing as per BCS Guidances<sup>15–17</sup> is an appropriate surrogate technique for *in vivo* BE testing.

The dissolution test USP 28 for amitriptyline hydrochloride Tablets uses dilute hydrochloric acid as test medium. In view of the solubility characteristics of amitriptyline hydrochloride, this dissolution medium is likely to be less discriminating than testing at a pH of about 6.8.

### Risks with Respect to Excipient and/or Manufacturing Variations

Table 2 shows that a wide variety of well-known excipients used in IR amitriptyline hydrochloride formulations with MAs in a number of countries. In contrast to some previously discussed APIs<sup>3,5,6</sup> the “bioavailability committee” of the regulatory authorities of DE classified amitriptyline hydrochloride in 1998 as an API for which *in vivo* BE testing was required.<sup>38</sup> So, at least for the MA’s granted in DE, it can be assumed that these drug products successfully passed an *in vivo* BE study versus the innovator’s drug product.

The lack of reports of BA/BE problems supports the view that these common excipients will have no effect on the BE of a test drug product, as long as they are incorporated in amounts currently used in IR tablet formulations.

An indication of the amounts usually present in dosage forms for drug products with a MA in the USA can be obtained from the FDA Inactive Ingredients Database.<sup>39</sup>

### Risk of Bioequivalence in Terms of Therapeutic Outcome

The Argentine Health Authority classified amitriptyline hydrochloride as an intermediate health-risk drug,<sup>40</sup> which means that eventual complications of the sickness and/or adverse reactions arising from plasma concentrations outside the therapeutic window of the drug are not necessarily serious, and are unlikely to compromise the integrity of the individuals or be life-threatening.

## BCS Classification and Biowaiving

Amitriptyline hydrochloride is “highly permeable,” but, as solid solubility data are lacking, no definitive conclusion can be drawn as to whether amitriptyline hydrochloride is “highly soluble.” Until appropriate experimental data are available, amitriptyline hydrochloride must be regarded as lying at the interface of BCS Class I/II. Other workers reached the same conclusion.<sup>41</sup> Still other workers classified amitriptyline hydrochloride as BCS Class I, but this classification was reached on the basis of calculated log *P* data, and took only the 25 mg tablet strength into account.<sup>22,29,42</sup> Nevertheless, all available data suggest that, even if a limited solubility of this API at pH 7.5 at 37°C should exist, this will not be problematic *in vivo* because, owing to its high permeability, the major absorption occurs in the first portion of the small intestine where pH is below 7. Moreover, comparative *in vitro* dissolution testing at pH 6.8, as requested in the BCS Guidances,<sup>15–17</sup> can be expected to detect any bioequivalence caused by differences in *in vivo* dissolution.

## CONCLUSION

Despite the relative uncertainty of the BCS classification for amitriptyline hydrochloride, a biowaiver is scientifically justifiable for this API, provided that the test product is formulated with the excipients shown in Table 2, in amounts currently used in IR tablet formulations<sup>39</sup> and shows rapid *in vitro* dissolution, according to the criteria as defined in the BCS Guidances.<sup>15–17</sup>

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