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Letter to the Editor

# Dobupride—What exactly is its degradation behavior?

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Dear Sir,

Recently, Segarra et al. [1] have reported the degradation profile and identification of the major degradation products of dobupride, 4-amino-2-butoxy-5-chloro-*N*-[1-(1,3-dioxolan-2-ylmethyl)-piperid-4-yl]benzamide (**1**, Fig. 1), under several conditions by GC/MS and HPLC-particle beam/MS. The authors have identified two reaction pathways and have proposed the formation of 4-amino-2-butoxy-*N*-[1-(1,3-dioxolan-2-ylmethyl)-piperid-4-yl]benzamide (**4**)[1], 4-amino-2-butoxy-5-chlorobenzamide (**2**), 4-amino-5-chloro-2-hydroxybenzamide (**5**) and 4-amino-2-butoxybenzamide (**6**) as the major degradation products. The products are postulated to be formed on loss of chlorine and/or cleavage of the drug molecule at the benzamide–piperidine bond.

Dobupride, as may be seen from the structure, is an amide and, like all other amido compounds, the drug is likely to undergo amide hydrolysis in solution as a result of which 4-amino-2-butoxy-5-chlorobenzoic acid (**2a**) and 1,3-dioxolan-2-ylmethyl-4-piperidylamine (**5a**) ought to be formed as the degradation products. In a similar manner, the dechlorinated product observed by the authors to be formed on photodecomposition, i.e. 4-amino-2-butoxy-*N*-[1-(1,3-dioxolan-2-ylmethyl)-piperid-4-yl]benzamide (**4**), also ought to undergo further amide hydrolysis to produce 4-amino-2-butoxybenzoic acid (**6a**) and **5a** (Fig. 1). The authors have not mentioned the presence of **2a**, **5a** and **6a** in the degradation pathways outlined by them for decomposition of the drug in either the solid state or in solution, on exposure to light or in darkness. The apparent implausibility that cleavage of dobupride occurs at the benzamide–piperidine bond, with an immediately adjoining more facile amide bond remaining intact, led us to a literature search on degradation behaviour of related compounds, and calculation of molecular weights of compounds **2**–**6** and **2a**, **5a** and **6a**.

The literature survey reveals that metoclopramide, 4-amino-5-chloro-*N*-(2-diethylaminoethyl)-2-methoxybenzamide (Fig. 2), a drug with a close structure and similar pharmacological activities to dobupride, cleaves to 4-amino-5-chloro-2-methoxybenzoic acid [2] and *N*,*N*-diethyl ethylene diamine [3]. As both these are products of amide hydrolysis, it lends support to the postulation that dobupride undergoes hydrolysis at the amide bond.

Incidentally, the proposed products of amide hydrolysis, viz., **2a**, **5a** and **6a**, also carry the same

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[1] The numbers 1, 2, ,3,..., 7 pertain to the compounds discussed by Segarra et al. [1]. For structures, refer to their paper.


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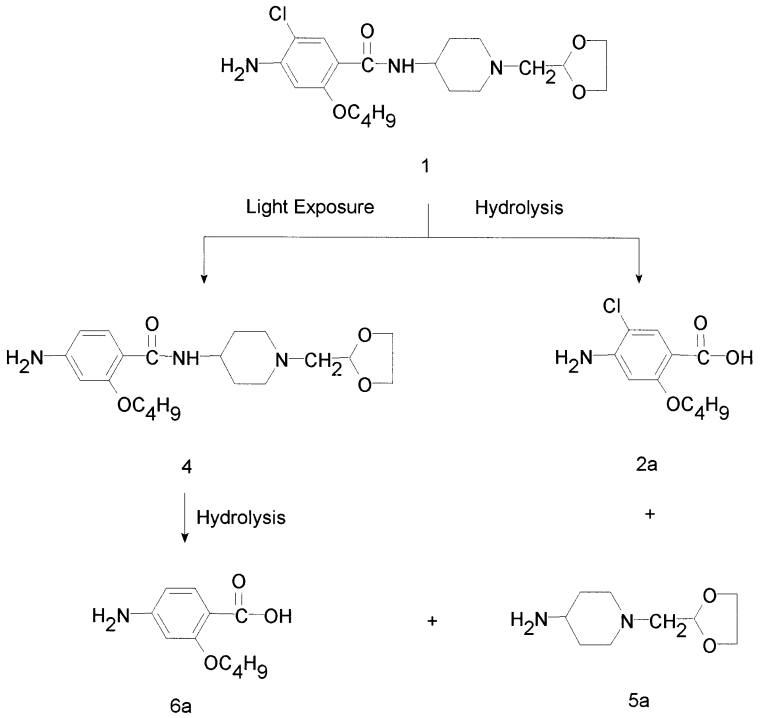


Fig. 1. Postulated reaction schemes involving cleavage of dobupride at the amide bond.

molecular weights as the products **2**, **5** and **6**, respectively (Table 1). An interesting aspect is the parity in molecular weights of **5** and **5a**, which possess entirely different structures. A comparison of molecular weights to $M^+$ values reported by Segarra et al. [1] (Table 1) indicates that there exists a remote possibility of misinterpretation by the authors. The same might also be so because their inference is solely based on mass spectral and fragmental analysis, without resorting to the commonly employed and recommended practice during drug degradation studies of comparison with the standards and/or separation of the products and subsequent confirmation of structure by IR, NMR, CHN, MS, etc. [4,5].

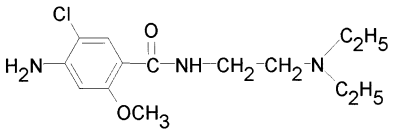


Fig. 2. Structure of metoclopramide.

There are some other unanswered aspects in the degradation pattern reported by Segarra et al. [1]. Firstly, while the authors have discussed and described the structures of compounds **2**, **5** and **6**, the detection and characterization of the remnants of the molecules are not discussed. Secondly, compound **7**, which was identified in all types of chromatograms, whether obtained by HPLC/UV, HPLC/PB-El-MS or GC-MS, has not been characterised and also has not been included in the reaction schemes. Another intriguing aspect is that if **4** can convert directly to **6**, why cannot **1** similarly convert to **2** without 4-amino-2-butoxy-5-chloro-*N*-[4-piperidyl]-benzamide (**3**) being an intermediate? Similarly, product **3** which is said to be formed, though in minor quantities, under suntest conditions from **1**, ought to lose chlorine analogous to **1** on exposure to light, resulting in the formation of 4-amino-2-butoxy-*N*-[4-piperidyl]benzamide, which gives scope for further decomposition to **6** on the lines of conversion of **4** to **6**. Taking into account these aspects, the degra-

Table 1
Molecular weights and $M^+$ values of various postulated degradation products of dobupride

| Compound number as per Segarra et al. [1][a] | M. wt[b] | $M^+$[c] | Compound number of suggested alternate | M. wt[b] |
|---|---|---|---|---|
| **1** | 411.93 | 411 | — | — |
| **2** | 242.70 | 242 | **2a** | 243.80 |
| **3** | 324.83 | 325 | — | — |
| **4** | 376.48 | 377 | — | — |
| **5** | 185.27 | 186 | **5a** | 186.25 |
| **6** | 207.25 | 208 | **6a** | 208.24 |
| **7** | — | 244 | — | — |

[a] For structures refer to their paper.
[b] Calculated from atomic weights.
[c] From PCl/El spectra, as reported by Segarra et al. [1].

dation scheme of dobupride should present an entirely different look.

It, therefore, calls for a further in-depth study on the degradation behavior of dobupride both in solution and in the solid state. The reaction schemes proposed by Segarra et al. [1] will find better acceptance if the authors carry out and report additional exploratory and confirmatory work.

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