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# D E C I S I O N
## of 20 February 2001

**Case Number:** T 0748/96 - 3.3.4

**Application Number:** 87310772.6

**Publication Number:** 0279986

**IPC:** A61K 47/00

**Language of the proceedings:** EN

**Title of invention:**
Skin permeation enhancer compositions using glycerol monolaurate

**Patentee:**
ALZA CORPORATION

**Opponents:**
Henkel Kommanditgesellschaft auf Aktien
UNILEVER N.V. / UNILEVER PLC
Minnesota Mining & Manufacturing Company of 3M Centre

**Headword:**
Skin penetration enhancers/ALZA CORPORATION

**Relevant legal provisions:**
EPC Art. 123(2), 56

**Keyword:**
"Main request: inventive step (no)"
"First auxiliary request: inventive step (no)"

**Decisions cited:**
-

**Catchword:**
-

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**Case Number:** T 0748/96 - 3.3.4

# D E C I S I O N
## of the Technical Board of Appeal 3.3.4
## of 20 February 2001

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**Decision under appeal:**

**Decision of the Opposition Division of the European Patent Office posted 25 June 1996 revoking European patent No. 0 279 986 pursuant to Article 102(1) EPC.**

**Composition of the Board:**

**Chairman:** U. M. Kinkeldey
**Members:** R. E. Gramaglia
S. C. Perryman

## Summary of Facts and Submissions

I. The appeal lies against the decision of the opposition division revoking European patent No. 0 279 986 (application No. 87 310 772.6) which was granted on the basis of 10 claims, of which claim 1 read as follows:

"1. A composition of matter for application to a body surface or membrane to deliver a biologically active agent by permeation through said body surface or membrane; the said composition comprising a biologically active agent and a permeation enhancer therefor, characterized in that said permeation enhancer is substantially urea-free and non-alcoholic and comprises glycerol monolaurate in an amount sufficient to enhance permeation of said biologically active agent through the said body surface or membrane."

Claims 2 to 4 depended directly or indirectly on claim 1 and specified respectively, that said agent and permeation enhancer are dispersed within a carrier (2) therefor, that said agent is present in an amount in excess of its saturation concentration in the carrier (2), and that the composition is adapted for application to intact skin.

Claim 5 was directed to a transdermal biologically active agent delivery device comprising a composition of any of claims 2, 3, or 4 characterised by an occlusive backing (3) behind the skin distal surface of said carrier; and means (4) for maintaining said carrier in agent and permeation enhancer transferring relationship to intact skin.

Claims 6 to 9 were device claims directly or indirectly dependent on claim 5, while claim 10 was in the form of a use claim.

II. The following documents are cited in the present decision:

(1) Franz J. M. et al., Arch. Dermatol. Res., Vol. 271, pages 275-282 (1981);

(2) WO-A-86/06281;

(9) US-A-4 568 343.

III. Oral proceedings were held on 20 February 2001, during which the appellant submitted a new main request with two claims, and a new auxiliary request with a single claim, in replacement of all preceding claim requests. The claims of the main request read as follows:

"1. A transdermal delivery device for application to the skin to deliver therapeutically active amounts of systemically active agent to the bloodstream, the device comprising: a systemically active agent and a skin penetration enhancer therefor dispersed within a carrier therefor (2;12,14); in-line adhesive means for maintaining the agent and enhancer in contact with the skin, said adhesive means forming the skin proximal surface of the device; and an occlusive backing (3;15) forming the skin distal surface of the device; characterized in that said systemically active agent is one or more of estradiol, estradiol valerate, estradiol diacetate, hydrocortisone, progesterone, testosterone and norgestrel; in that said permeation enhancer is substantially urea-free and non-alcoholic and comprises glycerol monolaurate in an amount sufficient to enhance

permeation of said systemically active agent through the skin; and in that the agent is present in the device at a concentration below saturation.

2. The device of claim 1 characterized by the glycerol monolaurate being the sole permeation enhancing component."

The sole claim of the auxiliary request differed from claim 1 of the main request in that the wording "comprises glycerol monolaurate" in the latter had been replaced with "consists of glycerol monolaurate".

IV. The submissions by the appellant, insofar as they are relevant to the requests still on file, can be summarized as follows:

(i) With respect to the main request

*Inventive step*

- There was little expectation of achieving enhanced systemic permeation by combining glycerol monolaurate (GML) with the steroids listed in claim 1, known to have a low permeability through the skin. In particular, the 23-fold skin permeation enhancement shown by Table I of the patent in suit would not be expected by the skilled person since permeation enhancers were highly drug specific.

- While claim 1 at issue related to the **systemic** transdermal delivery of drugs, document (1) was merely concerned with the **topical** transdermal delivery of proquazone and griseofulvin. This document indeed disclosed very high penetration of these drugs through the stratum corneum (horny

layer) but low penetration in the epidermis, upper and lower corium and subcutis (see Table 2). Therefore, document (1) taught that the flux rates and penetration of drugs through these layers was not affected by GML combined with glycerinformal.

- Also the presence of bile or urine radioactivity upon administration of proquazone and griseofulvin labelled with $^{3}H$ was no proof of systemic penetration of the drug. This experimental finding indicated nothing more than that topical administration of the drug eventually resulted in the degradation of the drug to labelled metabolites that were successively excreted in these biological fluids. The document did not report any concentration measurement of the drug as such in the bile or urine, nor was it possible to derive therefrom information about the drug's site of action or metabolisation.

- There was no teaching in documents (1) and (2) to use GML in combination with the steroids listed in claim 1. Enhancement with one drug did not indicate that a skin permeation enhancer was likely to work for another drug.

(ii) With respect to the first auxiliary request

*Inventive step*

- The arguments as under the main request were still valid for this request, with the additional submissions below in relation to the feature that the permeation enhancer consists of GML (ie that GML was the sole skin permeation enhancer present):

- The effect of skin penetration enhancement noted in the experiments disclosed in document (1) was due to the combined action of GML with the solvent glycerinformal (see page 281, last line: "combined action") rather than to GML alone. Therefore no teaching could be derived from this document that skin penetration by drugs would be improved by GML alone.

- The effect of skin penetration enhancement for nitroglycerin noted in the experiments (Example 3 and Table II) disclosed in document (2) was due to the combined action of GML with the fatty acid ester ethyl oleate rather than to GML alone. Therefore the skilled person was not taught by document (2) considered in its entirety that skin penetration by drugs would be enhanced by GML alone.

- It was true that Table II of document (2) showed an increase in flux between GML as skin penetration enhancer and no such enhancer, however, reproducibility of skin permeability was highly variable (± 40%) so that the skilled person would not have derived from Table II that skin penetration by drugs would be enhanced by GML alone.

V. The submissions by the respondents, insofar as they are relevant to the requests still on file, can be summarized as follows:

(i) With respect to the main request

*Inventive step*

- Document (9) (see column 3, lines 16-21 and Examples I to III) related to the systemic administration through the skin of the same steroids as listed in claim 1. The only difference lay in that polyethylene glycol monolaurate (hereinafter: PEGML) instead of GML was used as skin penetration enhancer. It would have been obvious, in the light of documents (1) and (2), showing the skin permeation enhancing properties of GML, to replace PEGML with GML.

- It was true that the skin penetration enhancer disclosed in document (1) was a combination of GML with a solvent (glycerinformal), while the one disclosed in document (2) was a combination of GML with ethyl oleate. However, the broad formulation of claim 1 ("comprises glycerol monolaurate"), interpreted in the light of page 4, lines 26-27 of the description ("may also contain other materials") did not exclude these combinations.

- The experiment disclosed in document (1), according to which radioactivity was present in the rat's bile or urine upon topical administration of proquazone and griseofulvin labelled with $^{3}H$ was a proof of **systemic** penetration of the drug.

- In any case, the transdermal nitroglycerin systems disclosed by document (2), comprising GML and a fatty acid ester, were useful for the **systemic** treatment of angina pectoris.

(ii) With respect to the auxiliary request

*Article 123(2) EPC*

- The feature in the sole claim of this request according to which GML had to be the sole skin penetration enhancer ("characterized in that said permeation enhancer... consists of glycerol monolaurate") found no basis in the application as filed. In the Examples of the application as filed, GML was used in combination with Staybelite® Ester and EVA.

*Inventive step*

- It could be deduced from documents (1) and (2) that GML alone was a skin penetration enhancer.

VI. The Appellants (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the amended main request or the amended auxiliary request, both filed at the oral proceedings on 20 February 2001.

The Respondents (opponents) requested that the appeal be dismissed.

## Reasons for the Decision

1. The appeal is admissible.

*Main request*
*Formal admissibility (Articles 84, 123(2)(3) EPC)*

2. The formal admissibility of the claims of this request is not disputed by the respondents and the board also sees no objections, so that there is no need for detailed discussion of these points.

*Inventive step*
*Closest prior art*

3. It is established jurisprudence of the boards of appeal that the assessment of inventive step has to be preceded by the determination of the technical problem which the invention addresses and solves, and that the technical problem is to be formulated in the light of the closest state of the art. In order to apply this approach, it is essential to start by establishing the closest prior art. In the present case, this requires that the claimed invention should be compared with the prior art relating to a similar device which requires the minimum of structural and functional modifications.

4. In the board's view, document (9) must be treated as the closest prior art in this sense, as in relation to Figures 1 and 2 thereof there is described a transdermal delivery device having all the features of the precharacterizing clause of the claim 1 now put forward. Further document (9) in column 3, lines 16-21 and Examples I, II and III thereof, discloses the very same steroids as those listed in claim 1 as "systematically active agents" (estradiol, estradiol diacetate, hydrocortisone, progesterone, testosterone

and norgestrel). The transdermal delivery device according to claim 1 at issue thus differs from this prior art in that the permeation enhancer comprises GML instead of PEGML (compare page 4, lines 24-28 of the patent in suit with column 4, lines 37-42 of document (9)).

The permeation enhancer PEGML in document (9) was also substantially urea-free and non-alcoholic. These features were introduced into the claim during examination to distinguish over two citations, FR-A-2 276 832 and EP-A-152 281 where one or other of these components was essential, but do not serve to provide any additional distinction of claim 1 over document (9).

*Problem to be solved*

5. The appellant emphasizes the enhanced skin permeation effect achieved by combining GML with the steroids listed in claim 1. This advantageous effect is demonstrated, according the appellant, by the 23-fold skin permeation enhancement shown by Table I of the patent in suit. However, in the board's opinion, the multiplier 23-fold has been obtained by comparing a composition comprising 25.2% GML and 10% progesterone, (skin flux = 3.19) with a composition containing 10% progesterone but **no** GML (skin flux = 0.14). The latter composition represents a state of the art far more distant from the one now claimed than is the composition disclosed in document (9). Further the board notes that Table I shows a similar skin flux increase when compositions comprising progesterone and other skin permeation enhancers such as glycerol monooleate (GMO) or sucrose monococoate (SMC) are compared with this composition devoid of the permeation enhancer.

As to whether the composition present in the claimed device exhibits an enhanced skin permeation effect when compared with those disclosed by document (9), no evidence is before the board that this is the case. This is because the blood level of a percutaneously administrated drug depends on many factors, such as, to only mention a few, the patch's surface, the concentrations of both the permeation enhancer and the drug and the time of application. As a consequence, it is not possible to compare, for instance, the progesterone level in blood reached by following the protocol of Example 1 of the patent in suit (a 80 $cm^2$ patch impregnated with a composition comprising 10% progesterone and GML with no indication of the concentration is applied to a human subject and an increase of 70 ng/dl of plasma progesterone level is measured after 24 hrs) with that of Example III of document (9)(a 45 $cm^2$ patch impregnated with a composition comprising 5% progesterone and 20% PEGML is applied to a human subject and a blood progesterone level of 20-60 pg/ml is measured after 5 hrs). Too many factors which can affect the result differ between the two Examples for the comparison to say anything meaningful about the effect of any single factor.

6. Nor can an alleged "systemic" as opposed to "topical" effect be taken into account by the board. There is indeed no clear boundary between topical and systemic bearing in mind all the factors upon which the concentration in the blood of a percutaneously administered medicament depends: the patch's surface, the skin penetration enhancer's and drug's concentrations, the excipients, the solvent, the time of application. It also depends on what is a useful level of drug in blood in the sense that eg achieving useful blood levels of picograms/dl of steroids may be easier than achieving useful blood levels of micrograms/dl of antibiotics. Especially the duration

of application seems to play a critical role since a topical medicament is likely to become a systemic one if allowed a sufficient time to permeate the horny layer (stratum corneum), which is the limiting layer (see document (1), page 276, first full paragraph). Vice-versa, if eg the patch disclosed in Example 1 of the patent in suit were applied to the skin for 5 min only, the composition would probably act topically in the sense that the steroid would be confined to outer skin layers.

7. For all these reasons, the board cannot recognise, for the formulation of the technical problem solved by the claimed device, that the latter achieves an enhanced systemic skin permeation effect. Consequently, the objective technical problem solved by the claimed subject-matter vis-à-vis the closest prior art represented by the device disclosed by document (9) has to be restated to meet a less ambitious objective which can be regarded as solved, namely the provision of an alternative skin penetration enhancer to PEGML in the device of document (9).

8. Table I of the patent in suit shows that the skin flux of a preparation comprising progesterone and GML is 23-fold (3.19/0.14 ~ 23) greater than that of a composition comprising progesterone alone. Example I (ibidem) shows that an increase of 70 ng/dl progesterone and 4.7 ng/dl estradiol in blood can be achieved by application to a patient of the claimed device. The board is thus satisfied that the above problem has been solved.

9. Documents (1) and (2), specifically disclosing examples of the skin permeation enhancing properties of GML in combination with glycerinformal or ethyl oleate, and also containing indications that GML alone would enhance skin penetration of drugs, it would have been

obvious, in the board's judgement, for the skilled person looking for an alternative skin penetration enhancer to PEGML in the device of document (9), to turn to documents (1) and (2) and as a result select GML either by itself or with other components as a skin permeation enhancer for the drugs suggested in document (9).

10. The appellant's argument that skin permeation enhancers are highly drug specific and that permeation enhancement with a drug does not indicate that the enhancer is likely to work for another drug, is not supported by any statements in the prior art. The suggestion is rather that a permeation enhancer has broad spectrum utility (see eg document (2), page 2, lines 22 to 24). It may be that the degree of enhancement for a combination of a particular penetration enhancer and a particular drug cannot be precisely predicted, but some enhancement making GML worth testing as an alternative to PEGML of document (9) can be expected from the teaching of documents (1) and (2).

11. Since for the reasons given in this decision it was obvious for the skilled person to arrive at the claimed device, the appellant's main request must be refused for lack of inventive step in the sense of Article 56 EPC.

*Auxiliary request*
*Formal admissibility (Articles 84, 123(2)(3) EPC)*

12. The respondents argue that claim 1 finds no basis in the application as filed because in the Examples of the application as filed, GML is never used alone but always in combination with Staybelite® Ester and EVA. However, the board has to dismiss this objection since page 3, lines 12-14 of the published application as

filed prescribes the combination of the drug with GML alone. Moreover, Staybelite® Ester is a tackifier (see document (9), column 5, line 56) while EVA is the polymer ethylene vinylacetate (see page 4, line 19 of the patent in suit). These components do not belong to the "permeation enhancer" but rather to the "carrier therefor (2;12,14)" (see claim 1).

*Inventive step*

13. The sole claim of the auxiliary request differs from claim 1 of the main request in that the wording "comprises glycerol monolaurate" in the latter had been replaced with "consists of glycerol monolaurate", ie the claim of this request states that GML has to be the sole skin permeation enhancer.

14. The board agrees with the appellant that the teaching of documents (1) and (2) as a whole highlights the combined action of GML with other ingredients, namely glycerinformal or ethyl oleate. Nevertheless, it is stated in the summary of document (1) that "monoglycerides of medium chain length enhance significantly the permeability of the stratum corneum for solutes". Under point (h) on page 277 of this document, concrete examples of these monoglycerides of medium chain length are mentioned expressis verbis, namely GML (C12) and glycerolmonocaprinate (C8), although in combination with other ingredients. According to the second full paragraph on page 276, the authors of document (1) were looking for a skin penetration enhancer, other than the unacceptable dimethylacetamide and dimethylformamide, to be used in combination with the solvent glycerinformal. Their choice fell on "monoglycerides of medium chain" because of the "observation" that these mild surface active agents "promote the percutaneous absorption of drugs". The skilled person will thus derive from document (1)

that though the experiments described used also other substances, GML and glycerolmonocaprinate could be expected to act as skin penetration enhancers on their own.

Moreover, according to document (2), page 2, lines 22-24, "the use of glyceryl monolaurate as a penetration enhancer for transdermal administration of medicaments has been suggested previously". Finally, Table II (C) of this document experimentally demonstrates that the 5, 12 and 24 hr flux rate of a composition comprising nitroglycerin (NTG) and GML is higher than that of a composition devoid of GML.

In view of this, the conclusion must be drawn that the technical information that GML alone was a skin permeation enhancer, would be derived by the skilled person from reading these documents.

15. Since it would have been obvious, for the skilled person looking for an alternative skin penetration enhancer to PEGML to turn to documents (1) and (2), disclosing the skin permeation enhancing properties of GML alone, the negative conclusion under point 11 above arrived at by the board also applies to the first auxiliary request.

## Order

**For these reasons it is decided that:**

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona U. M. Kinkeldey