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(54) **STABILISED OVERSATURATED TRANSDERMAL THERAPEUTICAL MATRIX SYSTEMS**

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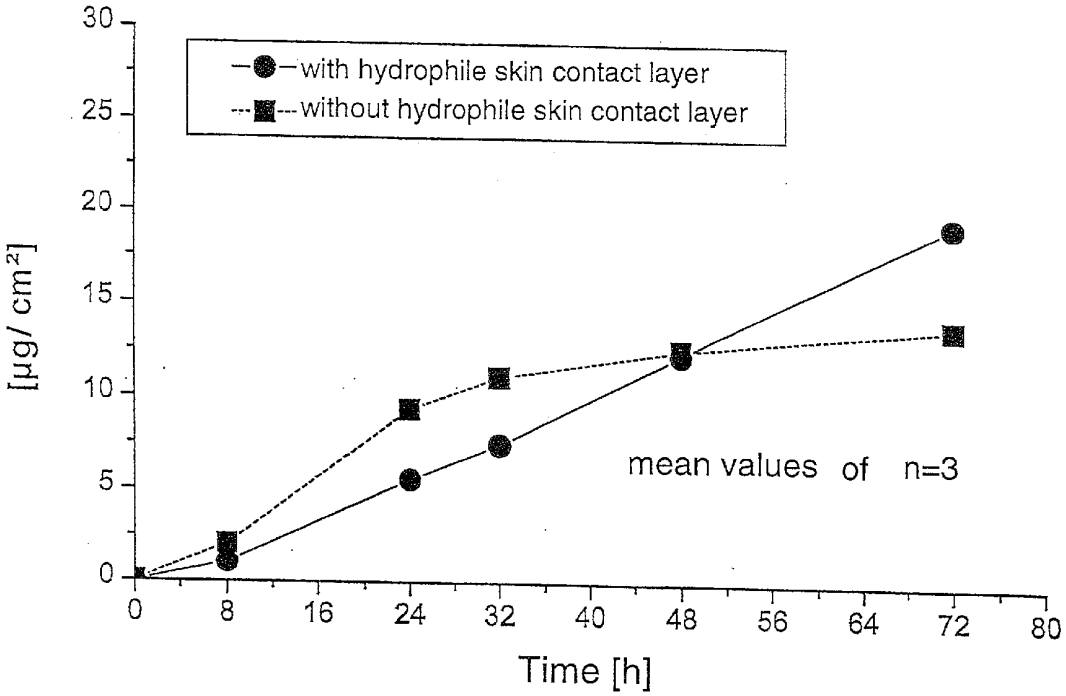
(57) **ABSTRACT**

A transdermal therapeutic system of the matrix type, comprising an active substance-impermeable backing layer, a detachable protective layer and an active substance-containing matrix based on hydrophobic polymers, the active substance having a melting point above room temperature and being present at least during part of the application time of the TTS in a concentration exceeding the saturation solubility, is characterized in that a polyacrylate polymer is admixed to the hydrophobic base polymers of the active substance matrix, or/and in that the matrix layer containing the hydrophobic polymers is provided with a self-adhesive skin-contact layer based on polyacrylates.



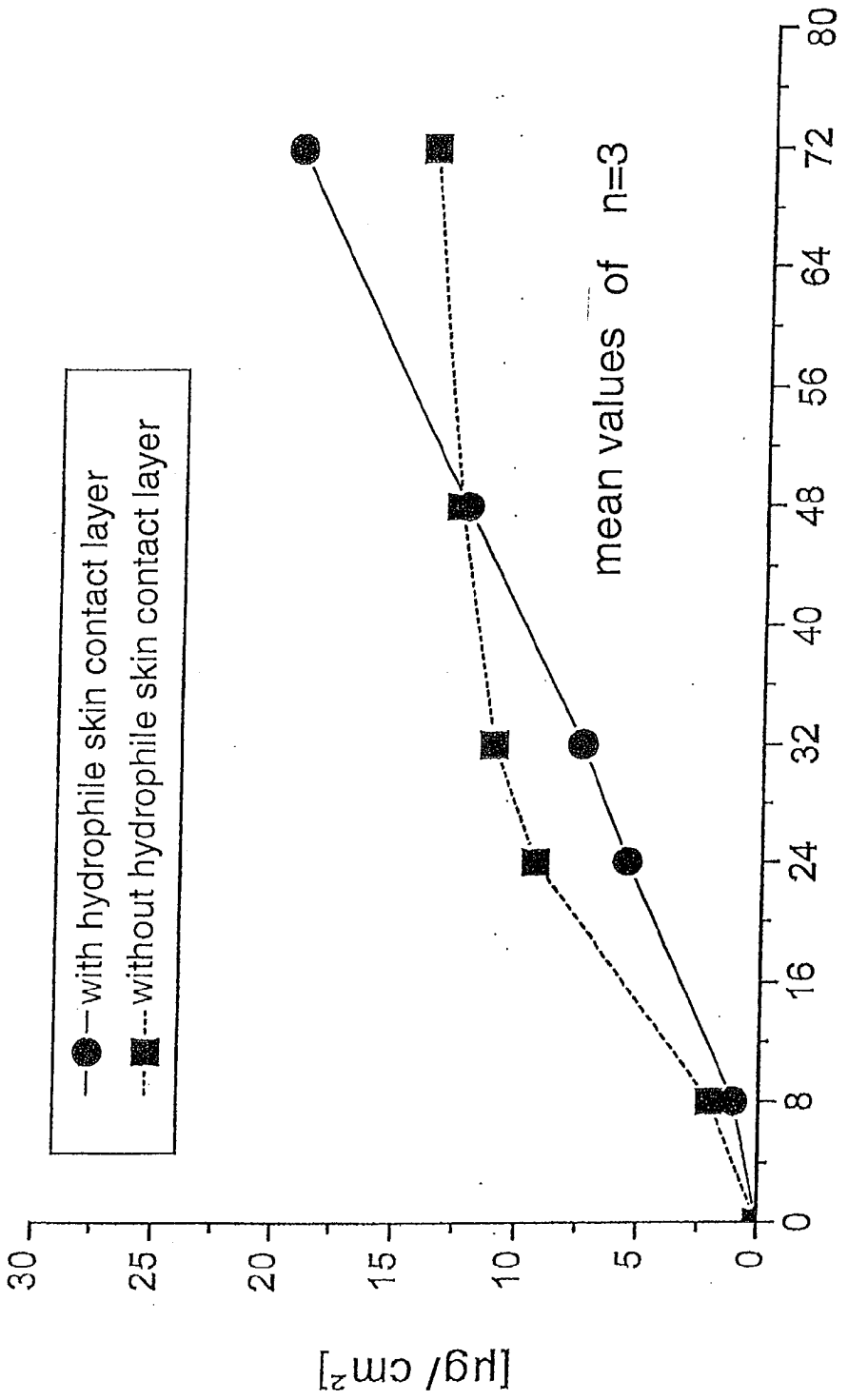


FIG. 1

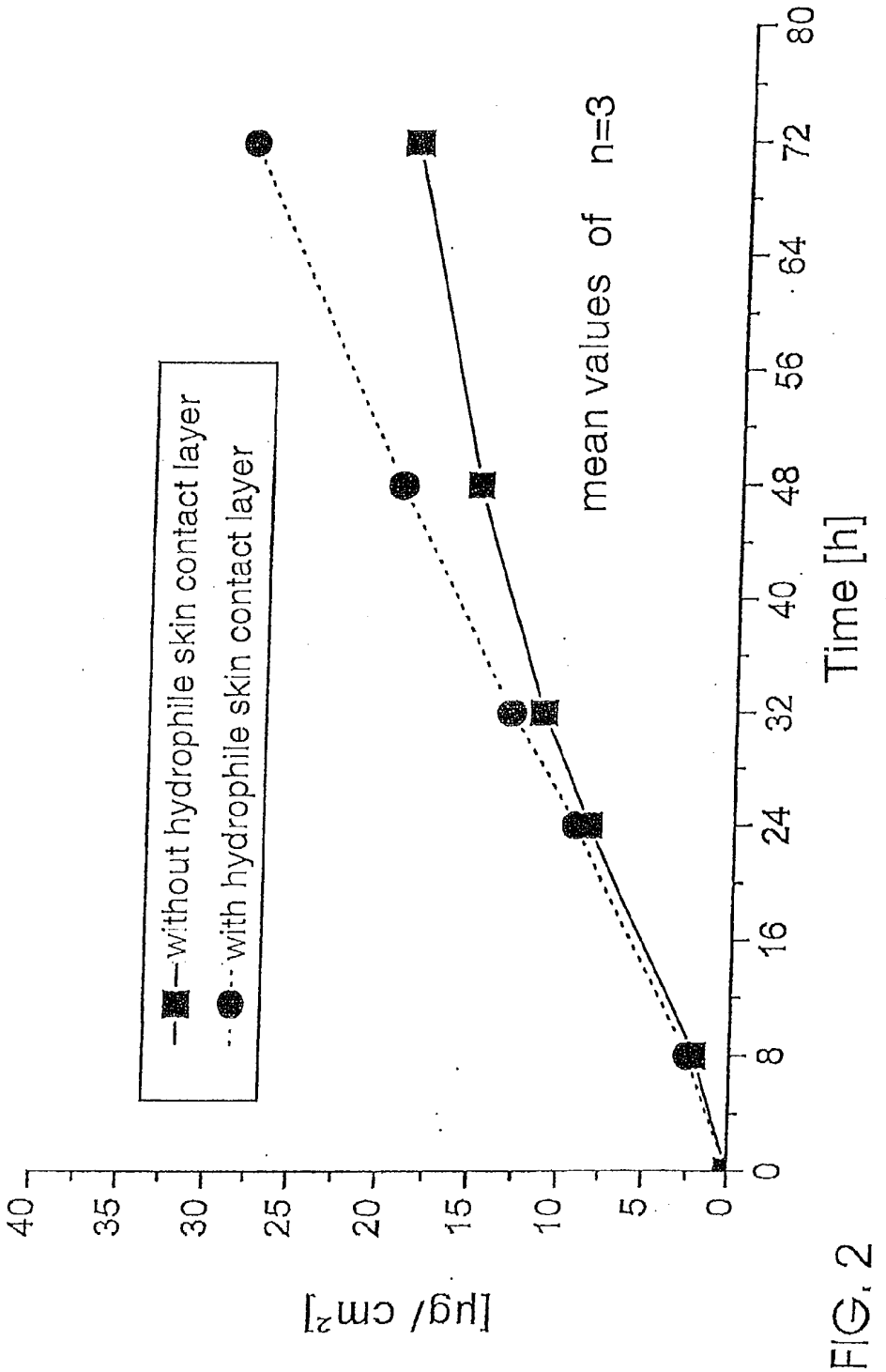


FIG. 2

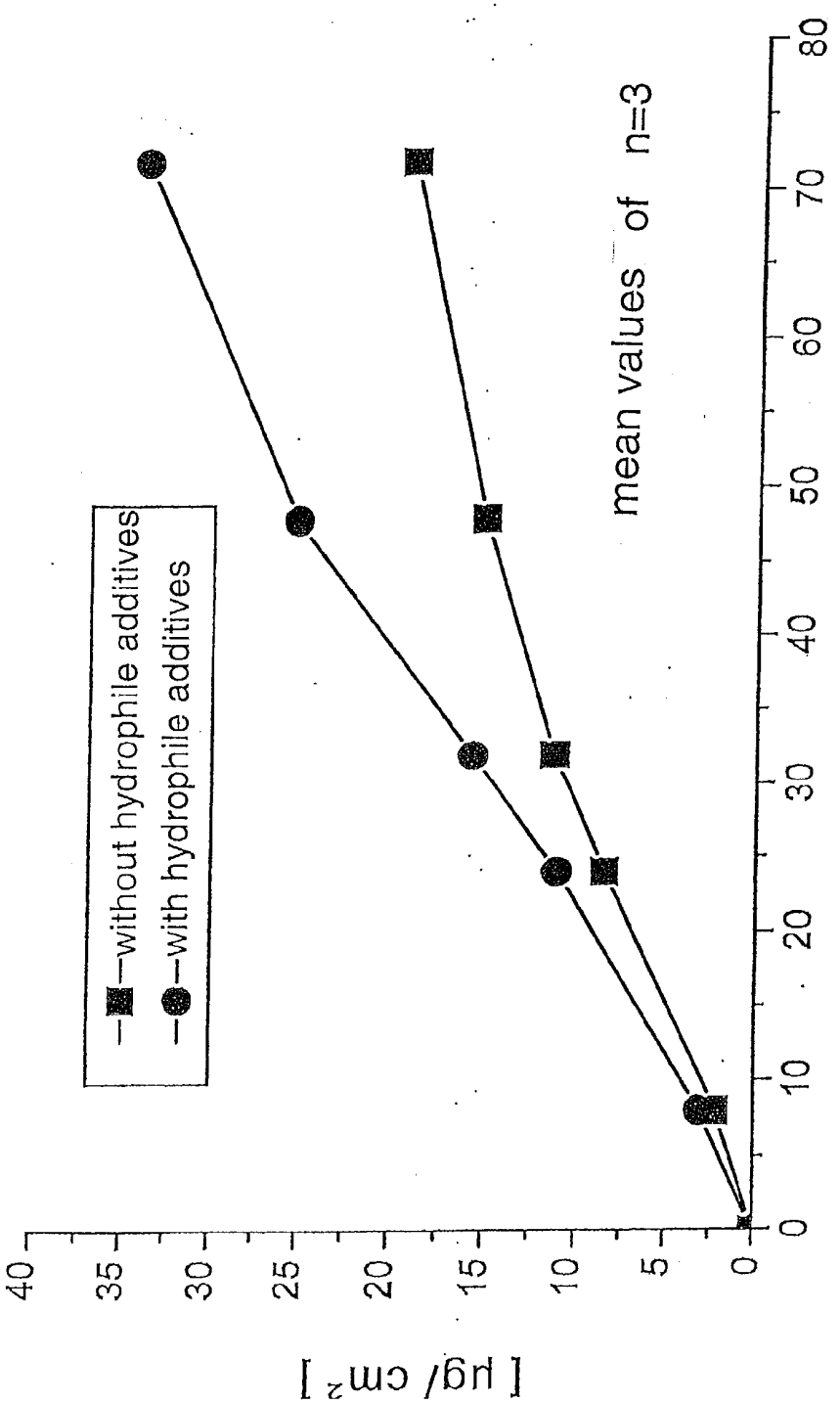


FIG. 3

STABILISED OVERSATURATED TRANSDERMAL THERAPEUTICAL MATRIX SYSTEMS

[0001] The invention relates to transdermal therapeutic systems (TTSs) of the matrix type comprising an active substance-containing matrix based on hydrophobic polymers. More particularly, the invention relates to TTSs of the type mentioned which are at least temporarily oversaturated with active substance and wherein measures have been taken to prevent the recrystallization of an active substance which is solid at room temperature.

[0002] The invention furthermore relates to processes for the production of transdermal therapeutic systems of the type mentioned.

[0003] Transdermal therapeutic systems (TTSs) are relatively new medicinal forms but meanwhile have become quite established in a variety of application fields. Their general advantages lie in preventing the so-called first-pass effect and in maintaining therapeutically useful plasma levels over a period of up to 7 days. The application possibilities of a transdermal system are, however, frequently restricted by the fact that they are mainly suitable for administering drugs which are very potent and are already effective in very small doses. The reason for this lies in the barrier properties of the stratum corneum of the skin, which limit or prevent the absorption of drugs via the skin.

[0004] For this reason, a considerable effort has been made to at least partially by-pass this obstacle. This can be achieved, for example, by employing permeation enhancers (also called penetration enhancers), which weaken the skin's barrier action. Furthermore, a sufficient active substance flow through the skin can also be attained by actively transporting the active substance by means of electric current. A further measure through which the absorption of active substances through the skin can be promoted consists in aiming at a thermodynamic activity of the active substance in the transdermal therapeutic system which is as high as possible.

[0005] Permeation enhancers are substances which affect the stratum corneum in such a way that its diffusion resistance is reduced, thus increasing the transdermally administerable amount of active substance. A large number of substances are suitable as permeation enhancers, for example, fatty acids, fatty alcohols, dimethyl sulfoxide, partial glycerides and propylene glycol.

[0006] Transdermal systems enabling an active transport of the active substance are known as so-called electrophoresis or iontophoresis systems. Such systems have so far been employed first of all for transdermal application of predominantly topically active drugs. Recently, efforts are being made, however, which focus on minimizing the size of those systems for practical use so as to render them suitable for application of systemically active drugs too.

[0007] With the exception of the electrophoresis or iontophoresis systems described above, the active substance release of transdermal therapeutic systems is in principle based on the principle of passive diffusion of the active agent from the patch into and through the stratum corneum of the skin, and subsequent systemic absorption of the active substance.

[0008] The third above-mentioned possibility of improving the active substance uptake via the skin consists in rendering the thermodynamic activity of the active substance in the transdermal therapeutic system as high as possible. In this way it is possible to increase the flow of active substance. A very high thermodynamic activity is achieved if the active substance concentration of the active substance dissolved in the active substance-containing components of the TTS corresponds to the saturation concentration of the active substance concerned. Such TTSs, in addition, possess good storage stability.

[0009] A further increase of the thermodynamic activity of the active substance can be attained by raising the concentration of the active substance above its saturation concentration. However, the advantage of higher thermodynamic activity is linked to the disadvantage of such TTSs being physically unstable, i.e. the storage stability of such oversaturated systems is reduced.

[0010] The adverse effect on the storage stability is based on the fact that active substances which at room temperature are present in a solid state have a tendency to recrystallize in such oversaturated TTSs. Owing to the crystal growth or formation of crystals, the concentration of dissolved active substance decreases, with the consequence that the thermodynamic activity of the active substance is reduced and the release rate of the active substance lowered. It is for this reason that it is not possible to produce oversaturated TTSs containing partially undissolved active substance, as in such cases, due to the crystal growth, the concentration of the dissolved active substance will correspond to the saturation concentration already after a very short time.

[0011] There are, however, special TTS formulations where the state of oversaturation occurs only after application of the TTS to the skin, so that, prior to application, the storage stability is not adversely affected. Such systems reach the state of oversaturation by the fact that a solubilizer contained in the patch is likewise released from the system to the skin, respectively by the fact that the uptake of moisture from the skin reduces the saturation solubility of the active substance in the TTS. The advantage of such systems is their storage stability with respect to recrystallization. However, in these cases, too, the active substance must be prevented from quickly recrystallizing to a considerable extent during the application time of the TTS. This would make it impossible to achieve a sufficient active substance release during the intended duration of application.

[0012] The simplest way to produce TTSs that reach an oversaturated state during the application period is to base them on polysiloxanes. Polysiloxanes have only a very poor solubility for most active substances. To be able to load the polysyloxane matrices of such TTSs with sufficient amounts of dissolved active substance, it is necessary to add solvents to the polysiloxanes. Here, those solvents are used with preference which possess only restricted miscibility with the polysiloxanes and are present in the matrix in dispersed form, as droplets. In this way it is possible to largely prevent an adverse effect on the physical properties of the active substance matrix. The dispersed solvent droplets at the same time contain the predominant portion of the pharmaceutical active agent, which is why they can be regarded as microreservoirs for active substances.

[0013] Suitable and physiologically safe solvents are, for instance, propylene glycol, 1,3-butanediol, dipropylene gly-

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