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Drug Release from Lipogels According to Gelling Conditions and Mechanical Treatment

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ABSTRACT

The release rate of a drug dissolved in the liquid phase of lipogels may be greatly affected by the type and concentration of gelling agent and by processing conditions and mechanical treatment of the ointment. These differences in release rate are reduced after application of mechanical stress comparable with the strain exerted on the ointment during application to the skin. Therefore, changes in the concentration of gelling agents used to achieve suitable consistency and manufacturing and packing processes that meet industrial and marketing requirements do not appear to exert a practical influence on drug availability after application to the skin.

INTRODUCTION

Ointments are gel-like preparations and their characteristics, such as consistency, physical stability, and spreadability, are closely related to their network structure, which depends on the type and concentration of gelling agent (3–5). The processing conditions in which the gel-like system is formed may even markedly affect the network structure and consequently the rheological parameters of the various types of ointment (4,6–11). The structure shape of the gel system may also influence the release rate of the drug (4,12–15).

In the present study, a series of lipogels were prepared using a vegetable oil (peanut) and several gelling agents at various concentrations. The influence that the kind and concentration of the gelling agent and processing conditions exert on rheological behavior and on the release rate of a test drug such as benzocaine, dissolved in the liquid phase of the gel system, was investigated.

This study was also aimed at evaluating the effect on drug availability produced by mechanical stress comparable to the strain usually exerted on the ointment during its application to the skin.

MATERIALS

Peanut oil of food quality from a single batch (Unil-It, Milano, Italy) was used to prepare oily gels. The following gelling agents were tested:

White beeswax (Croda, Mortara, Italy)
A mixture of partial glycerides and esters of long-chain fatty acids (Cutina BW®)
Glyceryl monostearate (Cutina GMS®)
A mixture of mono- and diglycerides of palmitic and stearic acids (Cutina MD®) (all the above kindly provided by Henkel Chimica, Lomazzo, Italy)
Polysiloxane polyalkylene copolymer (Abil Wax 9810®) (kindly supplied by Th Goldschmidt, Essen, Germany)

Hoechst benzocaine (Istituto Behring, Scoppito, Italy) was used as the test drug.

EXPERIMENT

Preparation of Lipogels

The calculated amount of gelling agent (10%, 15%, 20%, 25%, 30% w/w) was heated to 70°C with peanut oil over a water bath and the appropriate amount of benzocaine (3% w/w) was dissolved into the melted mass. The ointments were then gelled in two different conditions: (a) cooling to room temperature (20 ± 2°C), at rest; (b) cooling to 35°C under continuous stirring (60 rpm) and maintaining the preparations undisturbed at room temperature.

Portions of the ointments gelled at rest were milled in a three-roller mill (Erweka, Guarniero & Mantelli, Milano, Italy).

Rheological Evaluation

A Rotovisco RV12 viscosimeter (Haake, Karlsruhe, Germany) with a M500 sensor system and PKI-1° measurement equipment was used. Determinations were performed at 20°C.

Determination of Oil Number

Ointment samples were placed inside glass rings 12 mm in diameter and 5 mm high. The resulting cylindrical samples were supported in the middle of Perfecte 2 filter paper discs (Superfiltro, Milano, Italy) 10 cm in diameter. The discs were thermostated at 20°C for 24 h. The "oil number" was expressed as the mean value from three determinations of the area (cm^2) of the outward spread produced by the oily phase diffused, after subtracting the area originally covered by the sample.

Evaluation of Release Rate

Ointment samples were placed in wells 35 mm in diameter and 2 mm deep in the center of Perspex discs 70 mm in diameter and 10 mm thick. The surface of the ointment was leveled by a spatula. A Millipore membrane (HA type, pore size 0.45 μm, 47 mm in diameter) was laid over the surface of the ointment, a rubber O-ring (40 mm in diameter) was placed on top, and the membrane was fixed by a Perspex ring (external diameter 70 mm, internal diameter 35 mm) by three stainless steel screws. The cells were then placed, with the membrane upward, in 400 ml beakers with an internal diameter of 75 mm, containing 200 ml of purified water thermostated at 37°C and kept constantly stirred at 60 rpm by a blade stirrer. Every 15 minutes 1 ml of the diffusion fluid was withdrawn and replaced with the same amount of water at 37°C.

After suitable dilution, the amount of benzocaine was spectrophotometrically determined at 283 nm. Results were expressed as mg of drug released by the ointment per cm^2 of surface.

RESULTS

In gel systems such as ointment vehicles (1,2), consistency depends on the ratio of solid fraction, which produces the structure, to liquid fraction. Thus, as the concentration of gelling agent increases, a more and more compact and close structure occurs, giving the rheological parameters of the mass increasing higher values (3–5).

Differences in processing conditions may change the consistency, concentrations of gelling agents being equal (4,6–9,11). These variations are due to the shape and dimension of the crystallites of the solid fraction and their ordering in the three-dimensional structure; within the resulting network, the liquid phase is held by mechanisms such as adsorption, capillarity, and molecular interaction. Mechanical strain on the gelled system causes a breakdown in structure and consequently a fall in viscosity (7,16–22).

The rheological behavior of thixotropic pseudoplastic systems, generally typical of the lipogels studied here, showed marked changes as a consequence of the kind and content of gelling agent, gelling process, and mechanical treatment. So, in lipogels gelled at rest, the increase in consistency with the increase in solid components, due to their ordering in a thicker and thicker structure, is shown in the rheograms by the yield point

and by the more and more marked "spur" shape of the curve. The apparent viscosity values and the extent of the hysteresis loop area, which increases with increasing amount of gelling agent, were used as measures of lipogel consistency. Solid contents being equal, these values appeared even markedly lower in the lipogels gelled under continuous stirring, thus revealing changes in the network structure.

The marked fall of these rheological parameters confirmed the structural breakdown that occurs after application of strong mechanical stress such as that produced by milling.

The "oil number" was used to evaluate the texture compactness of the lipogels and the capacity of the solid fraction to hold the liquid phase within its network, mainly by adsorption and capillarity (22,27–33). This parameter was determined by the extent to which the liquid components "bled" from the lipogel and spread in a porous material such as filter paper.

Differences in structure, due both to gelling agent concentration and to processing conditions and mechanical treatment, may influence drug release rate (4,12–15,21). In any case, drug release is recognized to be inversely related to ointment viscosity (23–25). Thus, gels gelled at rest, having a compact and close structure, may have a slower release rate than gels prepared under continuous stirring, as the latter are characterized by a less well-ordered structure, in which the solid particles are aligned in the flow direction produced by stirring.

A still higher release rate is attributed to masses gelled and then subjected to shear stress high enough to destroy most of the structure. In any case, the extent of ordering in the solid components and the size of the network mesh may influence the release rate of a drug dissolved in the liquid fraction (14,15) by mechanically hindering the free diffusion of drug molecules (4,33).

The amount of drug released from the lipogels studied here showed a linear relationship with the square root of time (correlation coefficient ≥0.998). The release rate (V) of the test drug, benzocaine, was therefore expressed following the theoretical model by W. I. Higuchi (26):

$$Q = 2c/\sqrt{Dt/\pi}$$

and the rearrangement:

$$V = Q/\sqrt{t}$$

where Q is the amount of drug released per unit area of ointment sample at time t (4).

Beeswax

Natural beeswax is one of the most common gelling agents for oily liquid phases. In peanut oil it produced lipogels that were excessively fluid and poorly homogeneous at concentrations below 10%. Above 10%, increasing amounts of solid phase produced a progressive and remarkable increase in ointment consistency. As Figure 1 shows, with increasing percentages of beeswax, the rheological parameters, particularly hysteresis areas, also markedly increased.

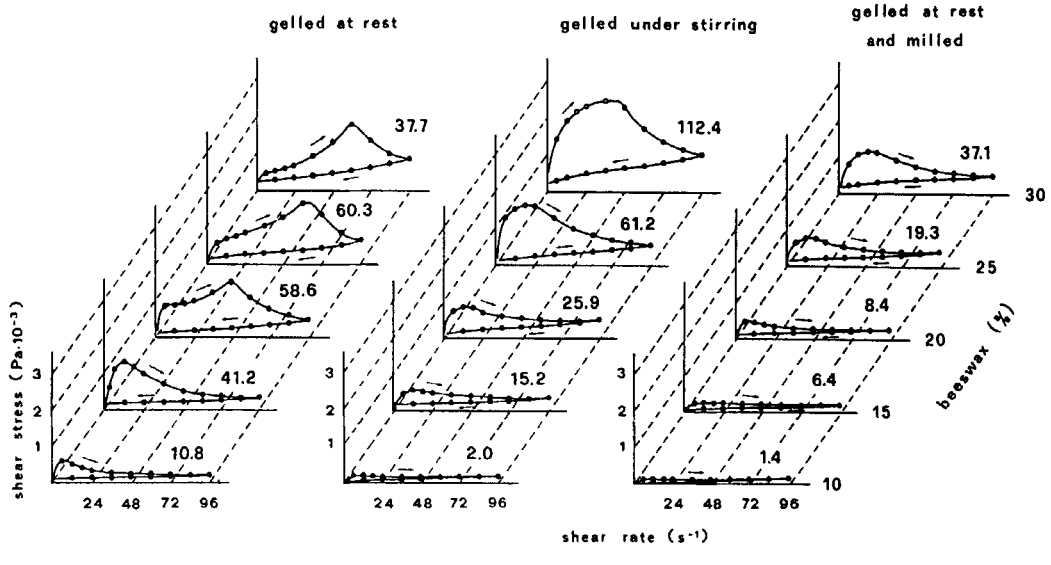

Figure 1. Rheograms of lipogels prepared with peanut oil and increasing concentrations of beeswax in three different conditions of gelling and mechanical treatment. Numbers near each rheogram: hysteresis loop areas.

The masses gelled at rest at room temperature showed higher rheological parameters and therefore higher consistency than those gelled under stirring, the concentration of the gelling agent being equal. Only in the presence of the highest beeswax concentration (30%) did the mass gelled at rest show a more fragile structure than under stirring.

The masses gelled at rest and then subjected to the high shear strain of a three-roller mill had lower values of shear stress and hysteresis area, revealing that the structure of the system had broken down.

The release rate of benzocaine from lipogels prepared in various conditions is compared in Figure 2 to the course of apparent viscosity and oil number according to beeswax concentration. In the ointments prepared at rest, the oil numbers were low, proving the texture compactness and strong immobilization of the liquid phase even at low gelling agent concentrations; the release rate was closely related to gelling agent concentration and to the consequent viscosity of the ointments.

The masses gelled under stirring, although showing higher viscosity and oil number than those gelled at rest, had clearly higher release rates, in any case still inversely related to viscosity. These differences in release rate are to be attributed to differences in gel structure (4,14,15,34), as proved by the rheogram shapes (Figure 1). The breakdown in the structure of the milled lipogels is shown not only by the rheograms, but also by the viscosity values (halved) and the oil numbers (slightly higher). The release rate was faster than in the previous two series of lipogels, but showed only slight differences with the increase in gelling agent content. Obstructions normally encountered in the diffusion path of drug molecules were reduced by structural breakdown, thus allowing fast release, in spite of the increase in solid components in the gels.

Mixture of Glycerides and Esters as Substitutes of Beeswax (Cutina BW®)

The lipogels exhibited rheological behavior similar to that of gels containing natural beeswax, but showed a lower consistency at equal concentrations, as can be seen by the rheogram shapes (Figure 3). The masses gelled at rest showed a relatively weak structure, as proved by the fast drop in shear stress with increasing shear rate. Gelling under stirring produced masses with a much lower consistency. The shape of the rheograms indicates that these lipogels are easier to apply than lipogels containing natural beeswax. The strain produced by milling on the masses gelled at rest caused extensive breakdown in the structure and consequent fall in viscosity.

In comparison to lipogels containing beeswax, the less compact texture of these ointments yields a smaller capability to hold the liquid phase inside the network, as shown by the markedly higher oil numbers (Figure 4), inversely related to viscosity. The course of oil numbers appeared interesting in the masses mechanically treated by milling. Even at the lowest concentrations of gelling agent, oil numbers were unusually low and fell to zero at the two highest concentrations. This suggests

Figure 2. Comparison between courses of release rate, apparent viscosity (D = 96 s^{-1}), and oil numbers of lipogels prepared with increasing concentrations of beeswax in three different conditions of gelling and mechanical treatment.

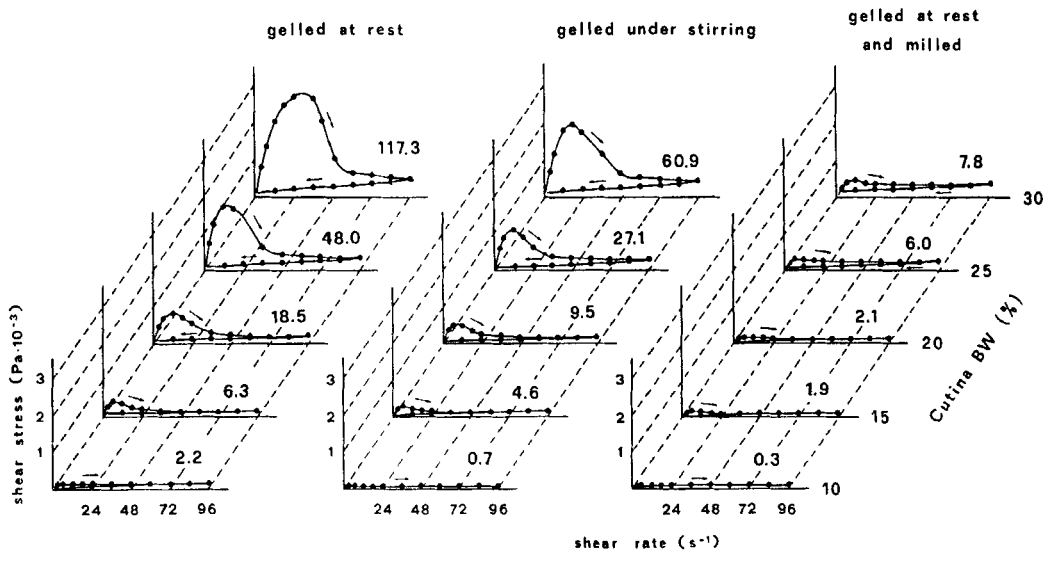

Figure 3. Rheograms of lipogels prepared with peanut oil and increasing concentrations of Cutina BW® in three different conditions of gelling and mechanical treatment. Numbers near each rheogram: hysteresis loop areas.

that the gelling crystallites, no longer ordered in a structure, but now uniformly dispersed in the liquid phase, produced a new random structure, capable of hindering bleeding.

Drug release rates showed a similar course according to gelling agent concentration. Masses gelled at rest had a markedly decreasing release rate with increasing solid phase content and therefore viscosity. In the masses gelled under stirring, the release rate was much faster and less affected by gelling agent concentration, as a consequence of the different network structure and therefore of the fewer obstacles in the diffusion path of drug molecules. The lipogels, whose structure was destroyed by milling, showed similar release rates, although with slight differences related to the solid phase content.

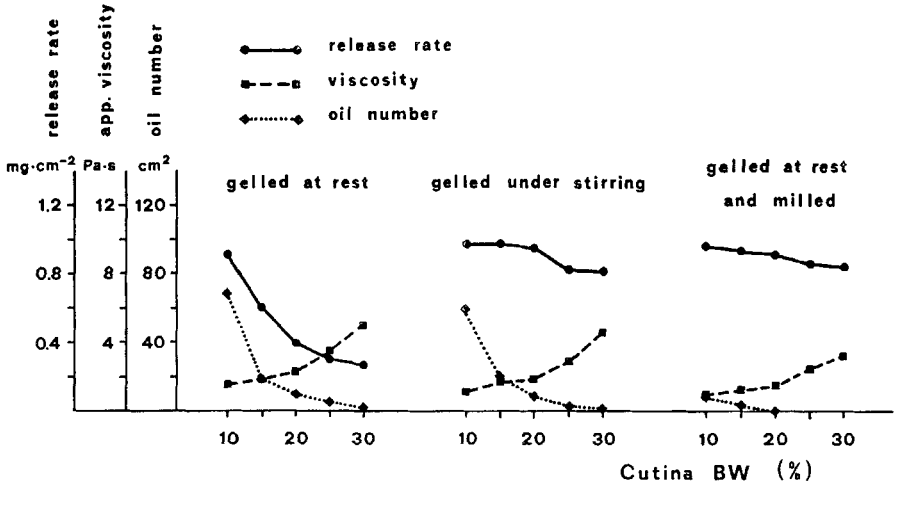

Figure 4. Comparison between courses of release rate, apparent viscosity (D = 96 s^{-1}), and oil numbers of lipogels prepared with increasing concentrations of Cutina BW® in three different conditions of gelling and mechanical treatment.

Glyceryl Monostearate (Cutina GMS®)

Glyceryl monostearate produced lipogels with remarkable viscosity, characterized by a well-ordered and close structure, both if gelled at rest and under stirring (Figure 5). In both these conditions the shape of the rheograms indicates difficult spreading, requiring high shear stress. The rheograms after milling also suggest difficult application and indicate that, in spite of the large strain exerted, the crystallites do retain some structure.

The high oil numbers of the three series of lipogels treated in different conditions associated with high viscosity (Figure 6) denote that the structure produced by the gelling agent is well ordered and stable, although its meshes do allow quite free flow of the liquid phase. This may also explain the high release rate, although affected by the amount of solid components.

Although some structure was preserved, its shape did not hinder drug diffusion, which was fast and practically uncorrelated with gelling agent content and mass viscosity.

Mixture of Palmitic and Stearic Mono-Diglycerides (Cutina MD®)

Using the same chemical kind of gelling agent but changing the ratio of mono- to diglycerides, masses were obtained showing similar rheological behavior but with lower consistency and therefore lower spreadability (see rheograms of Figure 7). Lower compactness may be deduced not only from the lower viscosity but also from the high oil numbers (Figure 8).

The course of release rate according to amount of gelling agent was similar to those of the previous series of lipogels in different conditions of processing and mechanical treatment. A progressive decrease in release rate was observed with increasing solid components in the ointments gelled at rest, and proportionally higher values were observed in those gelled under stirring. In the milled lipogels, drug release was confirmed to be practically uncorrelated to gelling agent content, in spite of the progressive increase in viscosity.

Polysiloxane Polyalkylene Copolymer (Abil Wax 9810®)

This high-MW silicon wax is reported to be a good viscogenic agent in paraffin oil. At a concentration of 10% w/w in peanut oil, it produced a lipogel with high consistency after gelling at rest. Concentrations higher than 20% produced brittle waxy masses. Only three concentrations—10%, 15%, and 20%—of this gelling agent were therefore tested.

As the rheograms of Figure 9 show, the gels cooled at rest had a well-ordered structure, but it was easy to destroy. Under stirring, a realizable lipogel was obtained only at the highest gelling agent concentration. Under

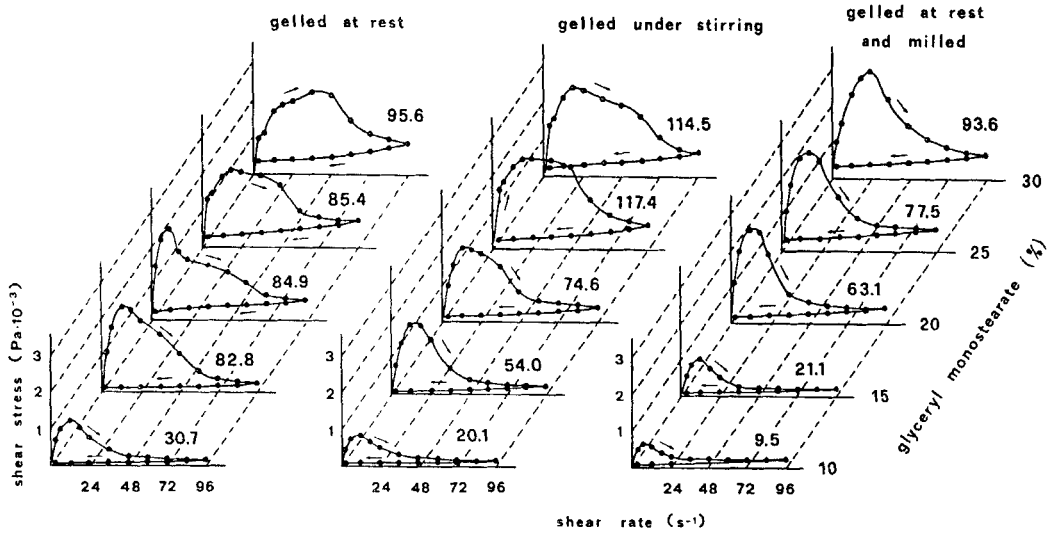

Figure 5. Rheograms of lipogels prepared with peanut oil and increasing concentrations of Cutina GMS® in three different conditions of gelling and mechanical treatment. Numbers near each rheogram: hysteresis loop areas.

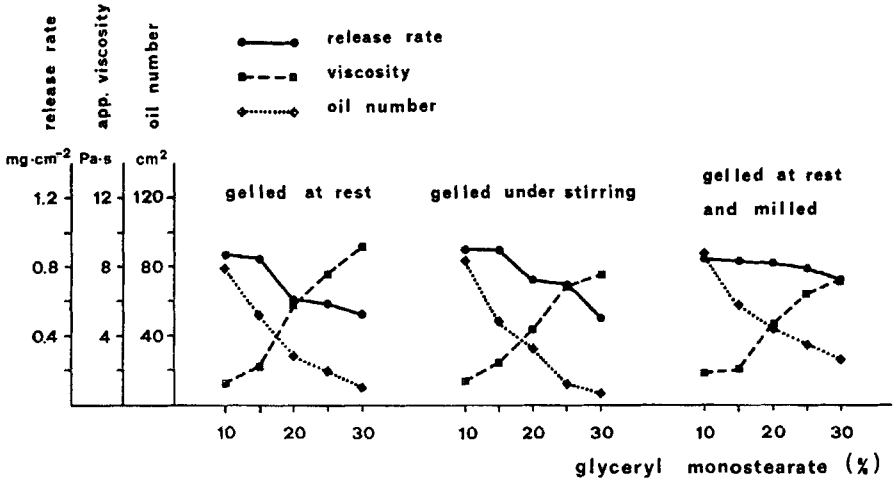

Figure 6. Comparison between courses of release rate, apparent viscosity (D = 96 s^{-1}), and oil numbers of lipogels prepared with increasing concentrations of Cutina GMS® in three different conditions of gelling and mechanical treatment.

the strain of milling, the structure was completely destroyed and the resulting masses had persistently low viscosity.

The oil numbers confirmed the different structures in the three treatment conditions (Figure 10): they were low in the masses gelled at rest and high in the remaining two series of gels, in any case inversely related to the amount of solid phase and resulting viscosity.

Release rates decreased with the increase of the solid components in the gels structured at rest; conversely, they were fast and practically uncorrelated to gelling agent concentration when the ordering of solid components was hindered by stirring or destroyed by mechanical strain.

DISCUSSION

Testing of lipogels of various qualitative and quantitative compositions confirmed that drug release may be

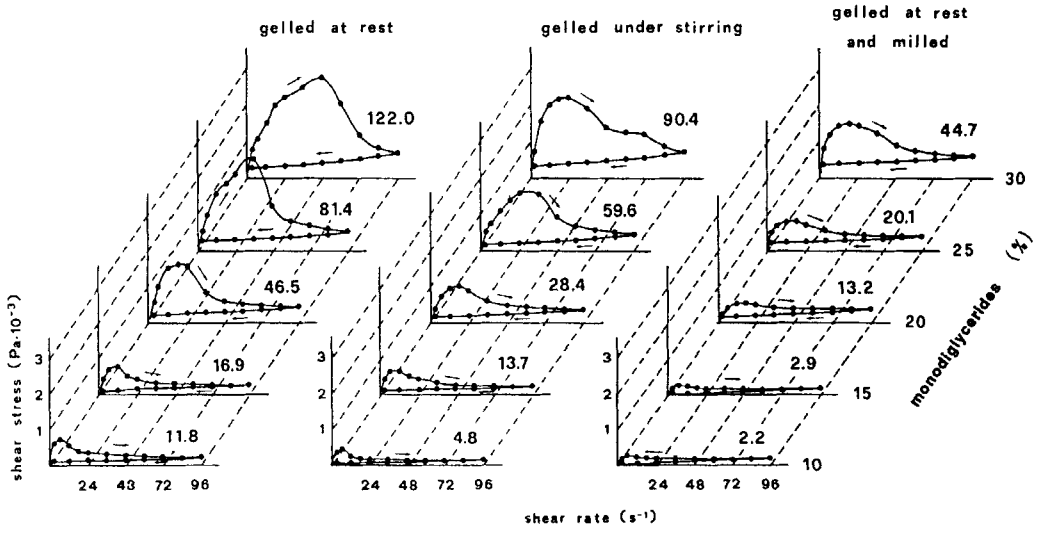

Figure 7. Rheograms of lipogels prepared with peanut oil and increasing concentrations of Cutina MD® in three different conditions of gelling and mechanical treatment. Numbers near each rheogram: hysteresis loop areas.

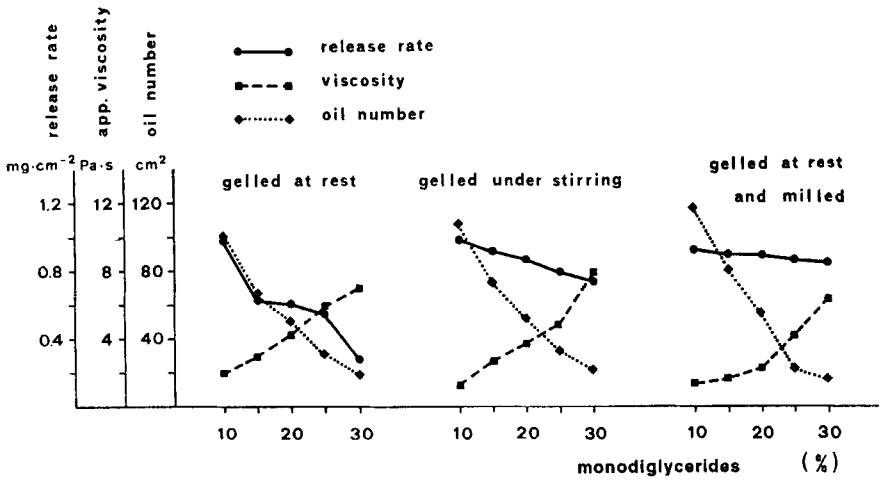

Figure 8. Comparison between courses of release rate, apparent viscosity (D = 96 s^{-1}), and oil numbers of lipogels prepared with increasing concentrations of Cutina MD® in three different conditions of gelling and mechanical treatment.

greatly affected by variations in the type and concentration of gelling agent and by variations in the thermal and mechanical processing conditions. These conditions may influence the network structures and, in turn, the physical characteristics of the resulting lipogels, particularly as regards rheological behavior.

Qualitative and quantitative compositions being equal, slow gelling at rest always produced gels of higher viscosity than those obtained under stirring. Under shear stress capable of destroying the structure, masses were of markedly lower viscosity. Independently of gelling agent, release rates were lower from masses gelled at rest than from the other two series.

In practice, processing conditions are dictated by industrial manufacturing and packing requirements. The lower the viscosity, the easier the mixing and volume partitioning of ointments, and the easier it is to pack melted masses and let them gel directly in their containers rather than work with semisolid masses gelled under stirring. In the former case, the masses are thicker and more compactly structured, thus producing slower release rates than in the latter case.

In any case, the various mechanical strains to which ointments are subjected during application must also be considered. First, a mechanical stress capable of destroying some of the structure is already produced when

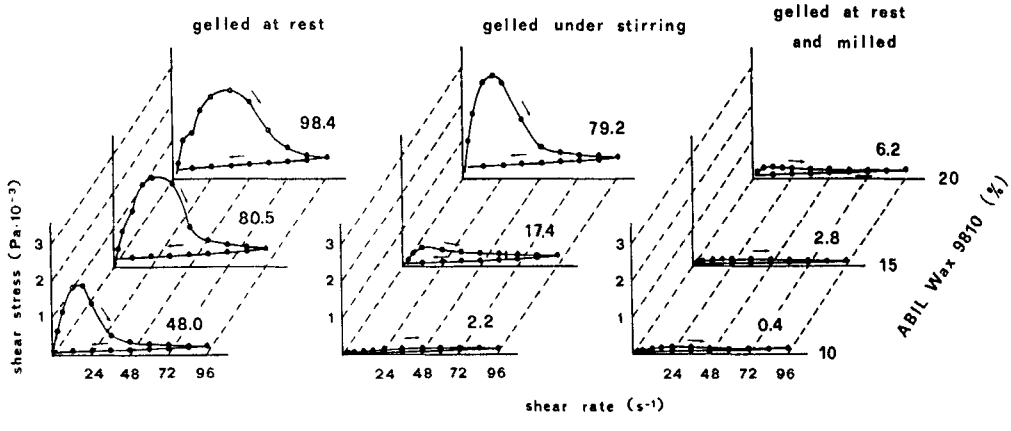

Figure 9. Rheograms of lipogels prepared with peanut oil and increasing concentrations of Abil Wax 9810® in three different conditions of gelling and mechanical treatment. Numbers near each rheogram: hysteresis loop areas.

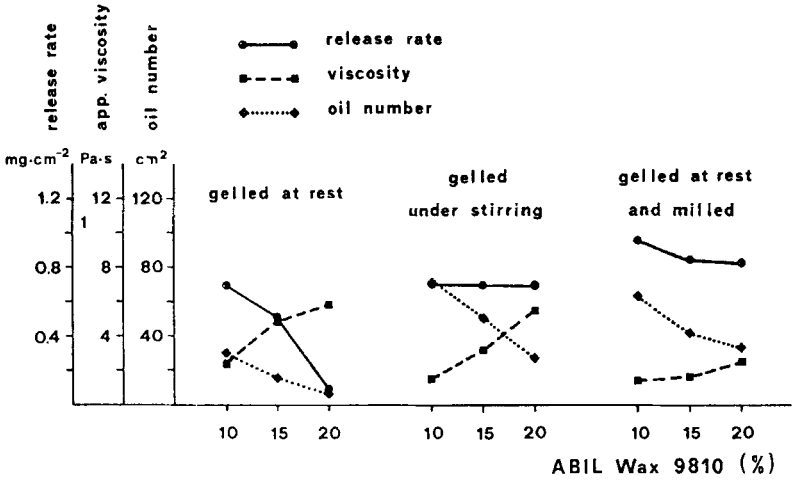

Figure 10. Comparison between courses of release rate, apparent viscosity (D = 96 s^{-1}), and oil numbers of lipogels prepared with increasing concentrations of Abil Wax 9810® in three different conditions of gelling and mechanical treatment.

the user dips her/his finger into the pot of ointment or presses the tube to extrude the right amount. The ointment is then subjected to strong shear stress during its application onto the surface of the skin, particularly if it is rubbed in. Ointment on the skin appears to have undergone severe breakdown in the structure of its gel system. Thus, it is as if the ointment were subjected to milling. As observed in these series of lipogels, release rates were fast and poorly affected by amount of gelling agent or mass viscosity.

Composition of the liquid phase being equal, the type of gelling agent did not appear to exert a practical influence on release rate, although it did affect the viscosity of masses subjected to milling. This is clear in the histograms of Figure 11, where the amount of benzocaine released per cm^2 of surface from the milled gels containing 20% of gelling agent is compared to the markedly different viscosity values.

In conclusion, therefore, whatever the manufacturing and packing processes used to meet industrial and marketing requirements (whether the melted mass is poured into its end-use containers or gelled in a mixer and then extruded into final containers), the availability of the drug is ensured to be unchanged when it is applied to the skin. Moreover, during formulation, gelling agent concentrations may be varied in order to achieve the suitable consistency, so that drug availability differences have little or no practical importance after application to the skin.

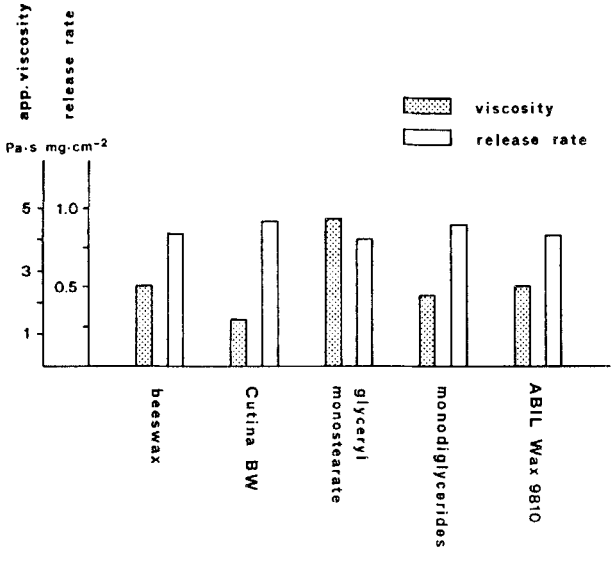

Figure 11. Release rate of benzocaine after milling from lipogels prepared with peanut oil and 20% of gelling agent compared with apparent viscosity (D = 96 s^{-1}).

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