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Release of a drug from homogeneous ointments containing the drug in solution

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The rate of release of resorcinol (5%) from hydrogels (Carbopol, sodium carboxymethylcellulose, starch), lipogels (alcoholic-base, esteric-bases containing different amounts of beeswax with and without a spreading additive, respectively) and Labrafils has been examined. For the experimental design adopted the release of the drug is linear between 10 and 70% of the amount of drug released. The results agree well with the mathematical model postulated by Higuchi (1962) for the release of a drug from homogeneous ointments containing the drug in solution.

A theoretical equation describing the release of drugs from homogeneous ointments containing the drug in solution was proposed by Higuchi (1962). Another equation postulated by Higuchi may be used for most practical applications for drug release in these conditions:

$$Q = 2\,C_o \cdot \sqrt{\frac{D}{\pi}} \cdot \sqrt{t} \qquad .. \quad .. \quad .. \quad (1)$$

The diffusion coefficient of the drug in the ointment may be found by rearranging equation 1 to:

$$D = \left(\frac{Q}{\sqrt{t}} \cdot \frac{\sqrt{\pi}}{2\,C_o}\right)^2 \qquad .. \quad .. \quad .. \quad (2)$$

By replacing $Q/\sqrt{t}$ by tg α (calculated slope of the line of the release) equation 3 is obtained:

$$D = \left(\mathrm{tg}\,\alpha \cdot \frac{\sqrt{\pi}}{2\,C_o}\right)^2 \qquad .. \quad .. \quad .. \quad (3)$$

On the introduction of a releasing surface area the diffusion coefficient of the drug becomes independent of the apparatus:

$$D = \left(\frac{\mathrm{tg}\,\alpha}{A} \cdot \frac{\sqrt{\pi}}{2\,C_o}\right)^2 \qquad .. \quad .. \quad .. \quad (4)$$

Q = amount of drug released per unit area at time t (g cm^{-2}); C_o = initial concentration of dissolved drug in the ointment (g cm^{-3}); D = diffusion coefficient of drug in the ointment (cm^2 s^{-1}); t = time (s); A = releasing surface area.

Equation 4 shows that, if the releasing surface area (A) and the initial concentration of drug in the ointment (C_o) are kept constant, the diffusion coefficient (D) is depen-

dent only on the slope of the releasing line (tg α). Therefore the diffusion coefficient of a drug in an ointment-base can be calculated from the slope of the function of the release rate of the drug and from equation 4.

We have found this theory to apply over a wide range of preparations.

MATERIALS AND METHODS

The apparatus used to determine the release of a drug from homogeneous ointments containing the drug in solution was that described by Brunner & Speiser (1970). This allows calculation of the diffusion coefficient of the drug in the ointment. The 'inlay' of the apparatus has an effective exposed surface area of 12·12 cm^2 (after subtraction of the strap). The amount of ointment poured into the 'inlay' is about 650 mg.

Phosphate buffer (pH 5·4, ionic strength $\mu = 0{\cdot}16$, 250 ml) was used as the receptor phase. Its temperature was kept at 30 $\pm$ 0·1°, since this was the mean skin temperatured measured intraepidermally at various sites of the body (upper arm, back, neck, palm, back of the hand and thigh) on healthy volunteers by means of microthermoelements. The receptor phase was agitated by a magnetic stirrer at 205 rev min^{-1} to prevent the formation of too thick a diffusion layer.

Separation of the ointment from the receptor phase was achieved with a membrane of cellulose esters of mean pore diameter 5 μm. This membrane did not interfere with the release of the drug and was no hindrance for the diffusion of resorcinol. The membrane was immersed in the receptor phase for 24 h before use. A membrane was essential for the hydrogel and Labrafil preparations, but not for experiments with lipogels. An ointment layer of 0·6 mm thickness was selected to prevent deformation of the surface of the membrane during the experiments due to osmotic pressure.

Sampling was done at equal $\sqrt{}$time intervals to allow a quantitative analysis of variance by means of orthogonal polynomials. Sample size was limited to 1 ml, in order to maintain the volume of the receptor phase practically constant. The samples were diluted with 0·1 N HCl and the absorbance of the solutions was measured at 273 nm in an ultraviolet spectrophotometer against a reference solution. Beer–Lambert's law was found to be valid within the concentration range used.

As the slopes of the releasing lines (see Table 2) are calculated in mg min^{-1} but not in g s^{-1} the following two factors $(10^{-3})^2$ and 1/60 must be taken into consideration for calculating the diffusion coefficients using equation 4.

Resorcinol was of Ph. Helv. VI grade. Polyacrylate was Carbopol 941 (B. F. Goodrich Chem. Comp.), sodium carboxymethylcellulose was CMC 7 MP (N.V. Hercules Powder Comp.). PCL liquidum (a mixture of synthetic alkyl-branched fatty acid esters prepared to simulate the preening oil of water fowl) was supplied by Dragoco and Labrafils by Gattefossé. Wool alcohols were of B.P. grade (Hartolan, Croda). Cetylalcohol and hydrogenated arachis oil were of Ph. Helv. V grade. Maize starch, castor oil, arachis oil, white beeswax were of Ph. Helv. VI grade. Disodium hydrogenphosphate, potassium dihydrogenphosphate and sodium hydroxide were of 'pro analysi' grade.

Hydrogels

Three types of hydrogels were examined: polyacrylate gels (Carbopol 941), sodium carboxymethylcellulose gels (CMC 7 MP) and starch gels (maize starch). To evaluate the influence of the viscosity of the ointment on the release rate of the drug

from the ointment, gels containing different amounts of gel-forming agents were examined. Resorcinol was present at 5% in all preparations.

Aqueous solutions of Carbopol 941 were prepared to give final concentrations of 0·5, 1·0, 1·5 and 2·0% containing 2·0, 4·0, 6·0 and 8·0% NaOH respectively. CMC 7MP was used at concentrations of 3·0, 4·0 and 5·0% in water. Maize starch was used at concentrations of 7·0, 8·0 and 9·0% in water.

Resorcinol was always dissolved in water. The polyacrylate and sodium CMC gels were prepared by the flotation method. The starch gels were prepared by hydrolysing the maize starch by adding water at 90°. The gels were evacuated in a vacuum desiccator, because air inclusions influenced the reproducibility of the release rate of the drug from the gels. The post-evacuation water content of the gels was kept constant by adding water in amounts previously determined experimentally.

Table 1. *Experimental values of the release of resorcinol from alcoholic-base.*

Time ($\sqrt{}$min)	Amount of drug released (mg) 1	2	3	4	Σ1
5	1·25	1·10	1·49	1·86	5·70
10	4·39	4·01	4·55	4·55	17·50
15	7·46	7·23	6·57	7·40	28·66
20	10·68	9·93	10·80	10·20	41·61
Σ2	23·78	22·27	23·41	24·01	93·47

Lipogels

Three types of lipogels were examined: alcoholic-base and esteric-base with and without a spreading additive. The viscosity of the esteric-base was modified by adding different amounts of white beeswax. The influence of a spreading additive (PCL liquidum) on the release rate from the esteric-bases was also examined. Resorcinol was present at 5% in all preparations.

The alcoholic-base contains cetylalcohol 29·0%, wool alcohols 18·5%, castor oil 47·5%.

For the 'esteric-bases without a spreading additive' white beeswax was used at concentrations of 3·0, 5·0 and 7·0%, containing arachis oil at concentrations of 18·0, 17·0, 16·0% respectively, and diluted with hydrogenated arachis oil.

For the 'esteric-bases with a spreading additive' PCL liquidum at 18·0, 17·0, 16·0% replaced the arachis oil in the previous formulation.

All excipients were liquified together in a water bath and the resorcinol was then dissolved in the base and the ointments were poured into the 'inlays' in a manner to avoid air inclusions (see above).

Labrafils

Labrafils are hydrogenated palmoil esters containing mixtures of mono-, di- and tri-glycerides with mono- and di-glycides of palmitic-, stearic- and lauric-acids. They are transitions between hydrogels and lipogels. Three types of Labrafils (M 2130 BS, M 2130 CS and M 2273 CS) were used at 95% and the resorcinol content was 5% in all cases. Labrafil M 2130 BS is the most hydrophilic and Labrafil M 2273 CS is the most lipophilic. Resorcinol was dissolved in the melted Labrafils and the ointments poured into the 'inlays', avoiding air inclusions.

RESULTS AND DISCUSSION

Hydrogels

Initially samples were taken at 1, 2, 3, 4 $\sqrt{}$min for the determination of the release of resorcinol from sodium CMC gel (4%). Statistical analysis revealed a non-linear pattern of drug release. This suggested the drug release to be linear only in a certain range. To confirm this, further series with different sampling times were examined. Sampling was done at 1·0, 1·5, 2·0, 2·5, 3·0, 3·5, 4·0 $\sqrt{}$min and the following amounts of drug released were found: 0·00, 5·44, 9·85, 14·12, 18·76, 22·88, 26·25 mg respectively.

The analysis of variance showed that the square term of time is significant at the level $P < 0{\cdot}025$. The following square function of the release rate is obtained:

$$y = -5{\cdot}2275 + 6{\cdot}1314\,x + 0{\cdot}5240\,x^2$$

Thus the pattern of drug release is non-linear if all the sample time data are used. But if the 1·0 and 4·0 $\sqrt{}$min data points (<10% >70%) are ignored the analysis of variance showed that only the linear term of the time is significant and the following function for the release rate results:

$$y = -7{\cdot}6850 + 8{\cdot}7580\,x$$

A linear release of resorcinol was found for the samples times representing 10–70% drug released. Sampling at 1 $\sqrt{}$min is critical because 1 min is approximately the time required to mix the receptor phase.

The functions for the release rate and the resulting diffusion coefficients of resorcinol in the hydrogels were obtained by identical interpretation of the experimental data and they are shown in Table 2.

Lipogels

When the sampling times used to determine the release rate of resorcinol from alcoholic-base were: 5, 10, 15, 20 $\sqrt{}$min, analysis of variance of the experimental data (Table 1) showed, that only the linear term of time is significant and therefore a linear function for the release rate is obtained:

$$y = -1{\cdot}5881 + 0{\cdot}5944\,x$$

Examination of the time intervals between zero and 5 $\sqrt{}$min revealed a non-linear pattern of the release rate. This phenomenon, an initial non-linear release pattern which becomes linear only after a certain time, has been described by Jost & Hauffe (1972). A lag time is necessary to establish a steady state for the diffusion process. Then the release rate is linear and the mathematical model becomes valid. The lag time may be calculated as the time between zero and the point of intersection of the extrapolated linear part of the curve with the time axis. For this reason the calculated liner curves do not necessarily pass through the origin.

If the release rate of resorcinol from the esteric-base containing 5% of white beeswax and a spreading additive is determined at the same sampling times as for alcoholic-base, a non-linear result is obtained. The curve of the release rate flattens out, when more than 70% of the drug is released. This phenomenon is probably due to the diminished content of drug in the releasing system. The system is thus no longer in a steady state by the time >70% of the drug have been released.

Table 2. *Functions for the release rate of resorcinol from hydrogels, lipogels and Labrafils and the resulting diffusion coefficients.*

Ointment	Function for the release rate	Diffusion coefficient ($cm^2\ s^{-1}$)
Polyacrylate gels		
0·5%	$y = -7{\cdot}53 + 8{\cdot}44\,x$	$2{\cdot}54.10^{-6}$
1·0%	$y = -10{\cdot}43 + 10{\cdot}78\,x$	$4{\cdot}14.10^{-6}$
1·5%	$y = -6{\cdot}80 + 10{\cdot}01\,x$	$3{\cdot}57.10^{-6}$
2·0%	$y = -7{\cdot}47 + 9{\cdot}58\,x$	$3{\cdot}27.10^{-6}$
Sodium carboxymethyl cellulose gels		
3·0%	$y = -8{\cdot}50 + 8{\cdot}24\,x$	$2{\cdot}42.10^{-6}$
4·0%	$y = -8{\cdot}85 + 8{\cdot}23\,x$	$2{\cdot}41.10^{-6}$
5·0%	$y = -8{\cdot}50 + 7{\cdot}99\,x$	$2{\cdot}28.10^{-6}$
Starch gels		
7·0%	$y = -7{\cdot}28 + 8{\cdot}23\,x$	$2{\cdot}41.10^{-6}$
8·0%	$y = -8{\cdot}27 + 9{\cdot}06\,x$	$2{\cdot}93.10^{-6}$
9·0%	$y = -8{\cdot}64 + 8{\cdot}91\,x$	$2{\cdot}83.10^{-6}$
Alcoholic-base	$y = -1{\cdot}59 + 0{\cdot}59\,x$	$1{\cdot}52.10^{-8}$
Esteric-bases without spreading additive		
3·0% beeswax	$y = -0{\cdot}20 + 0{\cdot}99\,x$	$4{\cdot}25.10^{-8}$
5·0% beeswax	$y = -0{\cdot}45 + 0{\cdot}96\,x$	$3{\cdot}96.10^{-8}$
7·0% beeswax	$y = -0{\cdot}89 + 0{\cdot}66\,x$	$1{\cdot}85.10^{-8}$
Esteric-bases with spreading additive		
3·0% beeswax	$y = -0{\cdot}82 + 1{\cdot}34\,x$	$7{\cdot}76.10^{-8}$
5·0% beeswax	$y = -2{\cdot}14 + 1{\cdot}40\,x$	$8{\cdot}46.10^{-8}$
7·0% beeswax	$y = -1{\cdot}00 + 0{\cdot}88\,x$	$3{\cdot}31.10^{-8}$
Labralfils		
M2130 BS	$y = -4{\cdot}19 + 1{\cdot}67\,x$	$1{\cdot}09.10^{-7}$
M2130 CS	$y = -5{\cdot}29 + 1{\cdot}84\,x$	$1{\cdot}33.10^{-7}$
M2273 CS	$y = -2{\cdot}25 + 1{\cdot}04\,x$	$0{\cdot}42.10^{-7}$

By omitting the 20 $\sqrt{}$min-value (>70% amount of drug released) the analysis of variance for the time shows that only the linear term is significant. Therefore a linear function for the release rate is obtained for the other three sampling times:

$$y = -2{\cdot}1400 + 1{\cdot}4010\,x$$

The functions for the release rate of resorcinol from the lipogels and the resulting diffusion coefficients are shown in Table 2.

Labrafils

By arrangement and calculation of the experimental data as previously described the functions for the release rate and the resulting diffusion coefficients given in Table 2 were obtained.

CONCLUSION

In most of the ointments studied it was evident with the initially chosen sampling times, that a non-linear pattern of the release rate curves was obtained. But by the

use of more sampling times and by means of analysis of variance a linear release rate of resorcinol from the ointments examined was found. Our results showed, that the release rate of resorcinol is linear in the range between 10 and 70% of drug released which supports the mathematical model postulated by Higuchi (1962).

The calculated diffusion coefficients of resorcinol in the types of ointments examined (e.g. homogeneous ointments containing the drug in solution) are an indication of the drug's release rate from these ointments.

The release from hydrogels is about 20–30 times faster than that from Labrafils and about 50–300 times faster than that from lipogels.

In hydrogels the diffusion coefficient of resorcinol ranges from $2{\cdot}3 \times 10^{-6}$ to $4{\cdot}1 \times 10^{-6}$ ($cm^2\ s^{-1}$). There is only a slight variation of the diffusion coefficient in the same type of gel at different concentrations of gel-forming agent and between different types of gels.

In lipogels the diffusion coefficient of resorcinol ranges from $1{\cdot}5 \times 10^{-8}$ to $8{\cdot}5 \times 10^{-8}$ ($cm^2\ s^{-1}$). In esteric-bases the diffusion coefficient of resorcinol decreases with increasing concentration of beeswax. The use of a spreading additive (PCL liquidum) approximately doubles the diffusion coefficient of resorcinol in the esteric ointments. That is, the resorcinol is released from esteric-bases containing the spreading additive approximately 1·4 times as fast as without this additive.

In Labrafils the diffusion coefficient of resorcinol ranges from $1{\cdot}3 \times 10^{-7}$ to $4{\cdot}2 \times 10^{-8}$ ($cm^2\ s^{-1}$). Labrafil M 2273 CS, the most lipophilic of the Labrafils examined, can be considered as behaving like the lipogels in its release characteristics while the two other Labrafils are transitional between hydrogels and lipogels.

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