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Study of Some Factors Affecting the Speed of Release of Lidocaine from Externally Applied Preparations

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ABSTRACT

This study aimed to find out the mechanism of release of active medicinal substances from ointments, creams, and gels, and the effect of changing the properties and texture of these preparations through the excipients that form them on the release because there is no longer any doubt in our time about the effect shown by the cofactors (excipients). There is an observation that the decrease in the amount of lidocaine HCL released is due to the lidocaine base, which is transported through the membrane by absorption on the surface of the oily droplets. Too large, which contributes to the transport of large quantities of lidocaine ready-to-transport basis. When the external phase is oily, the contact surface area is less and the movement of the oily phase is limited. Thus, oil/water creams release lidocaine better than water/oil creams.

INTRODUCTION:

This study aimed to find out the mechanism of release of active medicinal substances from ointments, creams, and gels, and the effect of changing the properties and texture of these preparations through the excipients that form them on the release because there is no longer any doubt in our time about the effect shown by the cofactors (excipients). In the release of active substances in general, and this is what the researchers take into account when choosing a formulation of a compound that is used through the skin and finalizing the ointment basis which should suit the prescribed ointment, which gives new life to the medicinally active substances, the nature of the carrier excipients, the method of manufacture used, the concentration of the active substances within the excipients of the carrier, and thus the thermodynamic effect of the drug in the excipients, all affect the pharmacodynamics efficacy of the dermal preparation.

Hence, the research plan was based on a study of the release of Lidocaine hydrochloride, from microemulsions and gels, by studying a large change of constants such as oils, emulsifiers, and other auxiliary materials that could give other changes.

The change of texture and the ability of excipients to dissolve pharmaceutical substances and to change the value of the water-oily balance of these excipients, as well as changes to the chemical structure to place esterian or other functions next to hydrogen coals and the presence or absence of hydroxyl groups in the excipient structure, all factors can change the release of the drug substance from ointments that are applied objectively On the surface of the skin.

To study the aforementioned factors, we selected Lidocaine Hydrochloride as an active medicinal substance that can help us to better understand the effects of these factors.

MATERIALS AND METHODS

The device used to study the release of medicinal substances from externally applied preparations:

In this paper, a released cell similar to an ainsworth has been used with properties that allow us to better compare results in glass *(In-vitro*) as well as upon completion of the work *in-vitro*, (as it has been shown through theoretical studies the ability of this cell to give

converging results when studying the release of medicinal substances in glass and organic as mentioned above.

Device Sections:

The device consists of three main sections: (As shown in Figure No. 1).

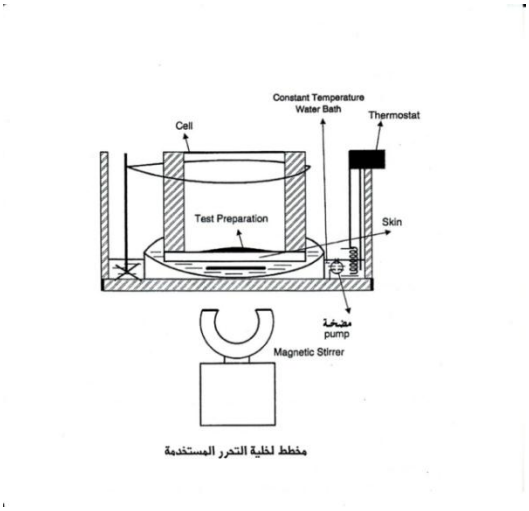


Figure No. 1: Device used to study the release of medicinal substances

A - Release cell:

It is an open-ended container, cylindrical in shape, with a diameter of 157 mm, installed using a holder placed within the receiving liquid. A membrane is attached to the bottom, which is a deerskin. The suede leather was selected after numerous experiments and comparisons with different types of leather, including sheep, cow, and fish skin. And in the end and within our next study, we selected suede for its satisfactory and good results to study the release of medicinal substances and their transfer from their excipients to the recipient fluid, and every time and for every active substance we used the same suede skin at work.

As for the upper end of the cylinder, it is closed with its cover after placing the studied product inside the cylindrical container and certainly on the upper face of the membrane part of the cylinder after its installation is immersed in the receiving fluid.

B-Reception basin:

It is a glass basin in which we place the receiving medium according to its type, oily or aqueous, in which the cell is immersed, and the medium is moved by a magnetic stirrer at a movement of 50 revolutions / d. The glass basin is placed in a suitable water bath.

C-Water Bath:

It is a large glass basin in which the receiver is placed, and the temperature of the basin is adjusted by a thermostat to set the temperature of the receiving basin to 37 ° C ± 0.5 ° C. As for this basin, it is moved by a pump or a magnetic stirrer to ensure the uniformity of its temperature distribution.

How to work and how to take samples:

The temperature of the water bath is adjusted, so that we obtain a temperature of 37 ° C and 0.5 ° C for the receiving medium, which is distilled water acidified with hydrochloric acid with a value of pH = 1 (pH = 1) or normal distilled water or paraffin oil.

The volume of the recipient phase in all experiments and for all media was 600 ml, and when preparing the cell and the membrane used, they were left for half an hour in the water bath to stabilize the temperature. After that, the studied dermal preparation is placed on the upper face of the membrane with a weight of 60 g, to be stretched evenly on the surface of the membrane, and then the cell is fixed in the receiving phase so that the membrane is submerged to a depth of approximately 2 cm. This is considered to be the start of work "time zero" The cell cylinder closes with a special cover and lets the magnetic motor in the receiving phase rotate at 50 revolutions/minute.

As for taking samples from the receiving medium, it was only at a rate of 10 ml of the receiving medium every 30 minutes for three or four hours each time. We used to replace that quantity with a similar amount and at the same temperature from a liquid that was incubated at a temperature of 37 ° C, and sometimes we had to take a sample for release after 24 hours.

As for the method of titration of active medicinal substances, we have mentioned it when studying the properties and what are the active substances in each phase whether they are calibrated directly or after extraction.

Lidocaine Hydrochloride

Its content shall not be less than 97.5% and not more than 102.5% of Cl_4 $H_{22}N_{22}$ HCl (8) calculated to the non-aqueous basis. Note that we used the anhydrous form in all our experiments. Lidocaine hydrochloride is a white crystalline powder, odorless, with a slightly bitter taste with tongue numbness. It is a relatively stable compound that does not hydrate

easily to place the amide function between the two metal groups, which impedes hydration and this is called steric obstruction.

It pickles at 20 ° C in water, alcohol, and chloroform and does not dissolve with ether. (8) (23)

It melts between 74-79 ° C, and the water content in it ranges by weight between 5-7%. Its aqueous solution at a concentration of 0.5% has a pH between 4-5.5.

As for heavy metals, the permissible is not more than 0.002% (18). 1- Identification: (1995 INF.P. S. U) - (1)

1- Its solutions respond to tests conducted on chlorinated compounds.

2- Approximately 300 mg of Lidocaine hydrochloride was dissolved in 10 ml of water and transferred to a gate cell separator, then 4 ml of regular 6 ammonium hydroxide was added, and it is extracted with 15 ml of chloroform four times, the chloroform extracts were combined and then evaporated on hot water vapor The remainder was dried by vacuum with silica gel for 24 hours, and the self-crystallized precipitate must match the Lidocaine self-base, and for testing it we did the following:

1 - Dissolve 100 ml of it in 1 ml of alcohol and add 10 drops of freshly prepared cobalt chlorine to it and stir the mixture for two minutes, showing a bright green color with the formation of fine sediment.

2- The melting point of this crystalline precipitate (Lidocaine base) is between 66 - 69 ° C.

3- The residue after incineration or incineration: not more than 0.1%

4-chloride:

Dissolve 1 g in a mixture of 3 ml of systemic nitric acid 2 and 12 ml of water, and add 1 ml of silver nitrate to it. The turbidity obtained is not more than the turbidity caused by 50 µl of hydrochloric acid 0.02 systemic (0.0035).

3- Sulfate: 200 mg of Lidocaine hydrochloride or Lidocaine base are dissolved in 20 mL of water, and 2 mL of 3-systemic chlorine acid (Lidocaine hydrochloride) or 2 ml of a systemic nitrogen acid (Lidocaine base) are added and filtered if needed. Then this solution is divided into two parts, 1 ml of barium chloride solution is added to the first section, so the turbidity

obtained does not exceed the turbidity in the second section, to which nothing has been added.

2- Carelease assay: (1)

A standard series of Lidocaine hydrochloride works and the degree of absorption of this series is read by a spectrophotometer with a wavelength of 254 nm "ultraviolet ray". The reading of a standard solution of Lidocaine hydrochloride with a concentration of 500 mcg/ml gave an absorption value of 0.669, which is the average of the absorption readings for this concentration.

Thus, the following law can be formulated:

$$(AU / AS)\ Q = C.$$

According to the following:

$$Q = 500\ (AU / 0.669)$$

Where Q is the amount of Lidocaine hydrochloride in mg/ml

The standard concentration or quantity is in mg / mL

AU reading in a kind

0.669 standard reading

As for the release of the samples, they were done as follows:

1. The sample is in the process of an aqueous receptor:

The sample is taken and its absorption value is measured by a Spectrophotometer with a wavelength of 254 nm "the field of ultraviolet rays", then according to the concentration of the substance in mg/ml after applying the previous law. The answer is multiplied by 600 and divided by 1000, so we get the total amount released in milligrams during the specified time.

2. The sample is from an oily receptor stage

After taking the sample, the Lidocaine is extracted with acidified water with hydrochloric acid with a pH value 1 and in several batches, with a total quantity of 100 ml. Then we read

the aqueous extract containing Lidocaine hydrochloride with a spectrophotometer at a wavelength of 254 nm. Apply the following law:

$$Q = 500 (AU / 0.669)$$

So we get the amount present in ml (mcg/ml), then we multiply this value by 100 because we extracted by 100 ml, so we get the quantity in mg/100 ml, and this amount is the same as that in 10 ml of oil (the initial take).

To obtain the liberated quantity and in a given time, we multiply the previous product by 60 and divide by 1000, so we get the liberated amount in milligrams, which is contained within 600 ml of the "recipient phase" oil.

3- USE: (2) Lidocaine Hydrochloride is a local anesthetic that is widely used in injection and topical applications on the skin and muscles because at the same doses it is stronger and faster than procaine, but it is more toxic. Do not use Lidocaine solutions that contain adrenaline to neutralize sensation in the fingers, as this can lead to deep local anemia (temporary anemia) that can lead to gangrene.

2-3-4-: Lidocaine Hydrochloride is released from micro-emulsions, "clear gels":

When studying the release of Lidocaine hydrochloride from micro-emulsions, we adopted seven different formulas with varying degrees of pH with a difference in the receiving phase.

First formula:

A transparent gel containing cetostearyl alcohol bound with 30 molecules of ethylene oxide "emo-lignin B3" as an emulsifying and non-displacing agent with high aqueous polarity. The oil phase consists of polar oils and large quantities of seraphim oil and cetiol he oil. The aqueous phase is glycerine, distilled water, and a buffer (citric acid/sodium lemonade) with a pH of 5.

Table No. 1 Percent drug release

Time of sampling (Minute)	Amount released (µg/ml)	Total Amount released (mg)	% of release	% of release difference
0	0	0	0	0
30	58	34.8	2.9	0
60	102.4	61.44	5.12	57
90	110	66	5.5	93.1
120	118.1	70.9	5.9	93.2
150	126	75.6	6.3	93.7
180	127.1	76.23	6.4	98

We notice from the previous table that Lidocaine was rapid during the first hour compared to what happened after that, where we notice a slowing of release up to 180 minutes.

The second formula: a transparent gel containing stearyl alcohol with the number of ethylene oxide molecules not specified by the manufacturer and commercially named "genapol 200", which is a non-displacement emulsifying agent with high water polarization, has a relatively high water balance and can form a gelatinous aqueous solution in proportions Not more than 10-15%, and it is useful to mention that these concentrations are always higher than the critical concentration for the formation of "CMC" micelles, so that the emulsifying agent can give a high viscosity by forming colloidal micelles in water.

It is noted that these formed gels have a high viscosity with a sticky greasy texture due to the oily electrode, making their application to the skin similar to that seen in the case of polyethylene glycol compounds.

The oily phase is seraphim oil, and the aqueous phase is the same as that used in the first formula. The results in Table (2) illustrate the release of Lidocaine hydrochloride from this transparent gel.

Table No. 2: Lidocaine Hydrochloride was released from a clear gel containing Genopol emulsifying agent and Cerafil oil.

Time of sampling (Minute)	Amount released (µg/ml)	Total Amount released (mg)	% of release	% of release difference
0	0	0	0	0
30	46	27.6	2.3	0
60	93.3	56	4.7	49
90	104	62.4	5.2	90.4
120	113.3	68	5.7	91.2
150	136	81.6	6.8	82
180	153.3	92	7.7	88.3
240	192.8	115.3	9.61	80
1440	192.08	115.3	9.61	1

We note from the previous table that the hydrophilicity of the genopolyside retained the remainder of the quantity of the drug after releasing some of it for only four hours.

The third formula: a transparent gel containing polyethylene oxide and polypropylene, commercially called pluronic f 127. The aqueous phase is a defect of citric acid and sodium lemons with a variety of pH 5 or 7.2, with or without glycerine, using distilled water with a pH = 1 (Hydrophilic acid has been used for this purpose) or paraffin oil as a receptor phase and the distribution was as follows:

1- A transparent gel with a value of pH = 5 by previous protection with glycerine and distilled water as a future phase.

2- A transparent gel of pH = 7.2 with glycerine and acidified water as the acceptor phase.

3- A transparent gel with a value of pH = 5 without adding glycerine and the receiving phase is paraffin oil.

4- A transparent gel with a value of pH = 5 with the addition of glycerine and the receiving phase is paraffin oil.

5- A transparent gel with a pH value of = 7.2 without adding glycerine and the receiving phase is paraffin oil.

Noting that all the previous gels take the gel consistency with the normal temperature (laboratory temperature), while the temperature drops to 8 ° C, it gives a transparent liquid solution.

RESULTS AND DISCUSSION

As for the results of the release of Lidocaine hydrochloride from these transparent gels, they are indicated in Table No. 3, 4, 5, 6 and 7.

Table No. 3: Lidocaine Hydrochloride was released from a transparent gel containing Peluronic f127 and a citric acid/sodium lemonade with a degree of pH = 5 and using glycerin, and the receiving medium is acidified water.

Time of sampling (Minute)	Amount released (µg/ml)	Total Amount released (mg)	% of release	% of release difference
0	0	0	0	0
30	120	72	6	0
60	180	108	9	67
90	190	114	9.5	95
120	201.8	121	10.1	94.1
150	224	134.4	11.2	90.2
180	245.0	147.0	12.25	91.4

Table No. 4: Lidocaine Hydrochloride was released from a transparent gel containing Peluronic f127 and a citric acid/sodium lemonade with a pH = 7.2 and using glycerin, and the receiving medium is acidified water.

Time of sampling (Minute)	Amount released (µg/ml)	Total Amount released (mg)	% of release	% of release difference
0	0	0	0	0
30	110	60	5.5	0
60	165	99	8.25	67
90	224	134.4	11.2	74
120	285	171	14.25	79
150	324	194.4	16.2	88
180	363.3	218.0	18.2	89
1440	500.8	300.45	25.1	73

Table No. 5: Lidocaine Hydrochloride was released from a transparent gel containing Pluronic F127 and a citric acid/sodium lemonade at a degree of pH = 5 without adding glycerin, and the receiving medium is paraffin oil.

Time of sampling (Minute)	Amount released (µg/ml)	Total Amount released (mg)	% of release	% of release difference
0	0	0	0	0
30	180	108	9	0
60	285	171	14.25	63.2
90	358	214.8	17.9	80
120	433.3	260	21.7	82.4
150	770	462	38.5	56.4
180	1091.7	655	54.6	56.4
240	1405.0	843	70.25	78

Table No. 6: Lidocaine Hydrochloride was released from a transparent gel containing Peluronic f127 and a citric acid/sodium lemonade with a degree of pH = 5 using glycerin, and the receiving medium is paraffin oil.

Time of sampling (Minute)	Amount released (µg/ml)	Total Amount released (mg)	% of release	% of release difference
0	0	0	0	0
30	280	168	14	0
60	463.3	278.0	23.2	60.3
90	526	315.6	26.5	88
120	596.7	358.0	29.83	73
150	920	552	46	65
180	1256.7	754	62.83	73
240	1473.3	884	73.7	86

Table No. 7: Lidocaine Hydrochloride was released from a transparent gel containing Peluronic f127 and a citric acid/sodium lemonade at a pH = 7.2 without adding glycerin, and the receiving medium was paraffin oil.

Time of sampling (Minute)	Amount released (µg/ml)	Total Amount released (mg)	% of release	% of release difference
0	0	0	0	0
30	280	168	14	0
60	463.3	278.0	23.2	60.3
90	526	315.6	26.5	88
120	596.7	358.0	29.83	73
150	920	552	46	65
180	1256.7	754	62.83	73
240	1473.3	884	73.7	86

Through the results recorded in the previous five tables, we note that the best amount of release of Lidocaine hydrochloride was with a degree of pH = 7.2 and with the presence of glycerine, and this is explained by the pH value of Lidocaine hydrochloride directly related to the changes in the pH of the mean, the higher the pH value of the medium, the greater The proportion of the base Lidocaine that can more freely pass the used starch.

Through Table No. 5 and Table No. 6, we note that there was an increase in the amount of liberated Lidocaine associated with the presence of glycerine in the gel, but with the use of paraffin oil as a receptor phase, the amount of Lidocaine liberated increased because the oily phase had attracted Lidocaine mainly. It contributed to the increase in the level of Lidocaine released compared to acidified water.

On the other hand, it should be noted that when taking the sample from the oily receptor phase, the Lidocaine must be extracted with acidified water with hydrochloric acid with a value of (pH = 1). (See Lidocaine Hydrochloride Titration Methods)

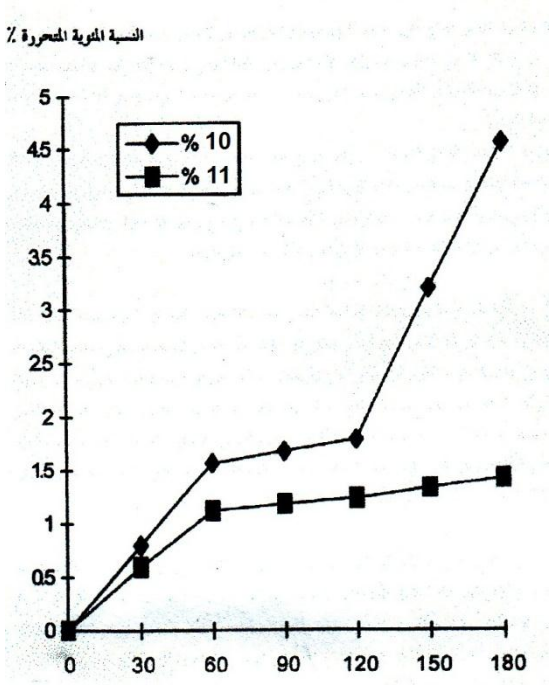
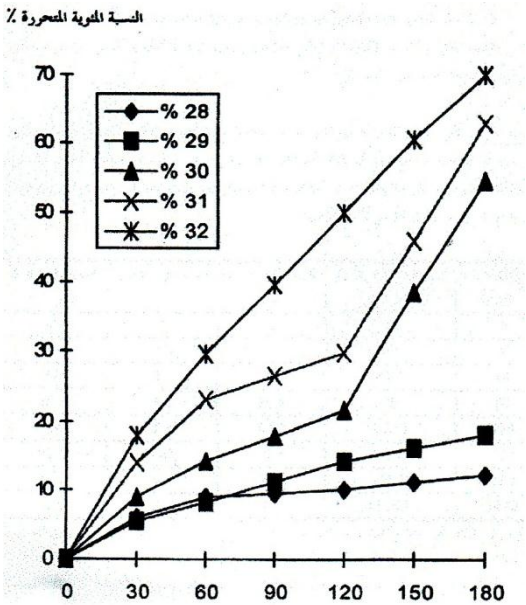


Figure No. 2: Percentage of Lidocaine HCl released over time from micro-emulsions (clear gels)



Lidocaine hydrochloride is released from hydrogels

In the composition of hydrogels, we adopted two main materials, which are carboxymethylcellulose soda and sodium alginate, as follows:

The first formula: lidocaine hydrochloride is released from an aqueous gel, containing carboxymethylcellulose soda with a medium viscosity at a concentration of 6%, while the aqueous medium is a defect of citric acid and sodium citrate with a degree of pH = 5, and the receiving medium is acidified water and Table No. 8 shows the results The active substance is released from this gel:

Table No. 8: Lidocaine Hydrochloride was released from an aqueous gel containing carboxymethylcellulose soda at a concentration of 6%.

Time of sampling (Minute)	Amount released (µg/ml)	Total Amount released (mg)	% of release	% of release difference
0	0	0	0	0
30	20	12	1.0	0
60	41.7	25	2.1	48
90	76	45.6	3.8	55.3
120	112.0	67.2	5.6	68
150	121	72.6	6.05	92.6
180	130.0	78.0	6.5	93.1
1440	1118.3	671.3	5	11.6

Note from the previous table that the release of lidocaine hydrochloride from the aqueous gel remained linear.

The second formula: lidocaine hydrochloride is released from an aqueous gel containing sodium alginate at a concentration of 2% while retaining the aqueous medium and the degree of pH as in the first formula.

Table No. 9: Lidocaine Hydrochloride was released from an aqueous gel containing sodium alginate at a concentration of 2%.

Time of sampling (Minute)	Amount released (µg/ml)	Total Amount released (mg)	% of release	% of release difference
0	0	0	0	0
30	72	43.2	3.6	0
60	157.7	94.6	7.9	46
90	228	136.8	11.4	70
120	294.5	176.7	14.7	77.4
150	334	200.4	16.7	88.2
180	379.7	227.8	18.8	89
1440	522.3	331.4	27.6	68.1

We notice from the previous table the increase in the proportion of Lidocaine "almost three times" due to the hydrogel structure formed from the sodium gene (see Figure No. 3).

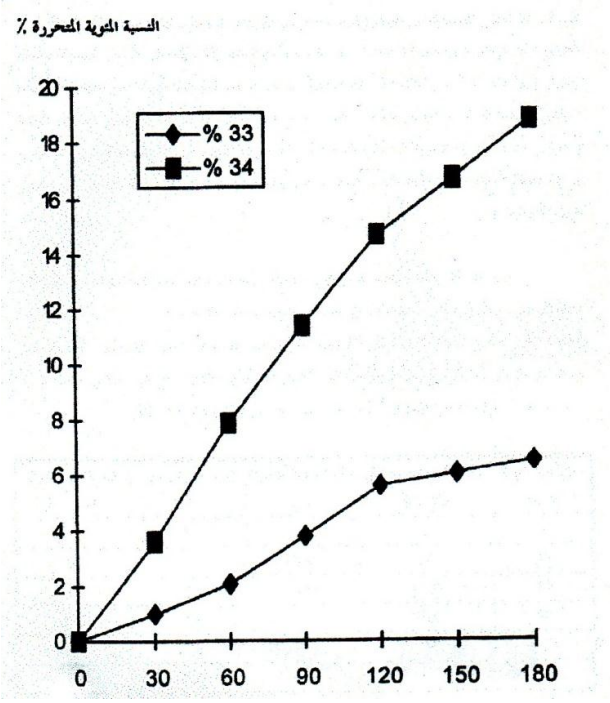


Figure No. 3: Percentage of lidocaine hydrochloride released over time from hydrogels

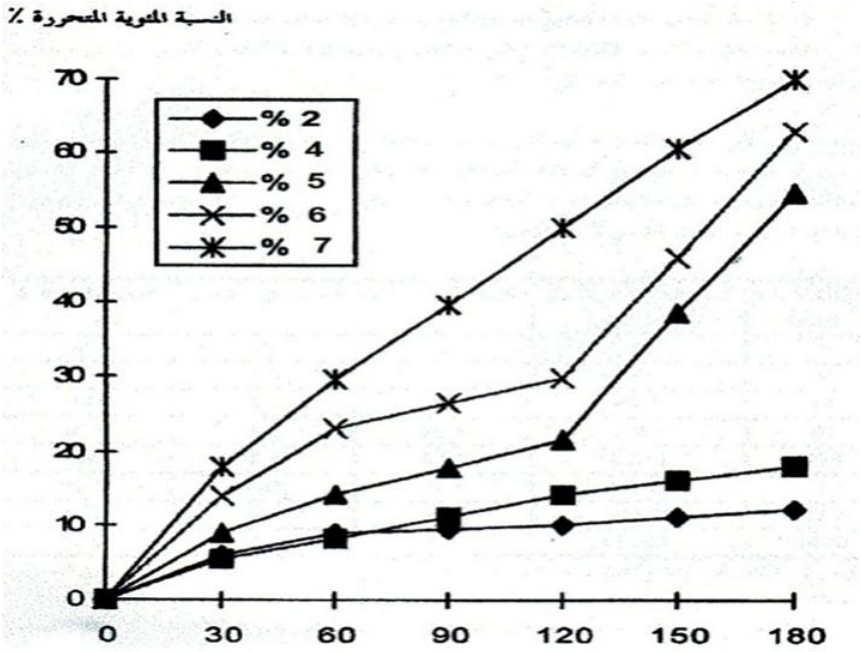


Figure No. 4: % Lidocaine HCl released over time from microemulsions (clear gels)

Lidocaine hydrochloride released from water-dissolved ointments (P.E.G ointments).

These ointments contain only water-soluble components. They can be washed with water as in washed bases and usually referred to as "greaseless" due to the absence of fatty substances. Physical and chemical pharmacokinetics, because the speed of absorption is not related only to the type of base, but rather the nature of the drug and the condition of the skin on which the ointment is applied plays an effective role in the process of absorption and the release of drug substances.

In addition to this, the ointments absorb water very quickly, which leads to the drying of the patient's skin and thus can be used in cases of Congestive dermatitis.

The first formula: Lidocaine Hydrochloride is released from a polyethylene glycol ointment consisting of polyethylene glycol (6000) polyethylene glycol (1540) with a 12% aqueous phase, which is a buffer of citric acid/sodium citrate with a pH value = pH = 5.

Table No. 10: Lidocaine Hydrochloride was released from polyethylene glycol 6000 and 1540 ointments.

Time of sampling (Minute)	Amount released (µg/ml)	Total Amount released (mg)	% of release	% of release difference
0	0	0	0	0
30	16	9.6	0.8	0
60	31.39	18.86	1.57	51
90	33.6	20.16	1.68	93.5
120	35.87	21.53	1.79	94
150	64	38.3	3.2	56
180	91.181	54.71	4.56	70.2
1440	790.73	474.44	39.54	11.5

The second formula: lidocaine is liberated from polyethylene glycol, consisting of polyethylene glycol (6000) and polyethylene (400), and an aqueous phase as in the first formula, but the water content in it is 30%.

Table No. 11: Lidocaine Hydrochloride was released from polyethylene glycol 6000 and 4000 ointments.

Time of sampling (Minute)	Amount released (µg/ml)	Total Amount released (mg)	% of release	% of release difference
0	0	0	0	0
30	12	7.2	0.6	0
60	22.0	13.45	1.12	54
90	23.6	14.16	1.18	95
120	24.67	14.79	1.23	96
150	26.6	15.96	1.33	92.5
180	28.3	17.04	1.42	94
1440	106.1	63.68	5.31	27

We note from the previous table a decrease in the amount of lidocaine hydrochloride released compared to the first formulation, and this is evidence that the more water in the "P.E.G" ointment, the less lidocaine release, noting that the lidocaine hydrochloride is completely soluble with water.

% Lidocaine HCl released over time from microemulsions (clear gels).

3.2.5-Interpretation of the results of the release of lidocaine hydrochloride:

We note that replacing the mineral paraffin oil with another half-potent oil, isopropyl myristate contributed to the increase of the release rate.

There is an observation that the decrease in the amount of lidocaine HCL released is due to the lidocaine base, which is transported through the membrane by absorption on the surface of the oily droplets. Too large, which contributes to the transport of large quantities of lidocaine ready-to-transport basis. When the external phase is oily, the contact surface area is less and the movement of the oily phase is limited. Thus, oil/water creams release lidocaine better than water/oil creams.

As for table (1-2-3-4-5-6-7) and chart No. (1), we note that when emulsifying B3 is used as an emulsifying agent and it is important for making transparent gel emulsions, the percentage of lidocaine hydrochloride is released.

This is due to the formation of soluble micelles in the preparation and thus the blocking of the release of lidocaine hydrochloride, with an increase in the dissolution of the drug substance.

As for the transparent gel Genopolymer 200S, the release is similar to what happened with the emolgen gel, with a decrease in the percentage of release that lasted for only four hours, then the gel kept the rest of the drug.

With the use of biluronic 127F, we notice a clear increase in the rate of release of lidocaine hydrochloride, which is due to the chemical structure of the biluronic and the length of the oxyatylene and oxybropylene chain, and this corresponds with the scientist Merrox and his colleagues (3), noting that an increase in the percentage of biluronics 127F leads to a decrease in the percentage of lidocaine hydrochloride and this is the congruent release. Scientist Snack and his colleagues (4) As for using glycerin (as a dissolving agent), we notice an increase in the rate of release, which is due to the polarity of excipients and its increase in dissolution.

As for the increase in the mean pH value according to PKA of lidocaine hydrochloride: we notice an increase in the percentage of lidocaine hydrochloride liberated and this is due to the increase in the base ratio of lidocaine hydrochloride, which is the preferred form of transfusion across the membrane.

Log + pka basis = pH

However, when using the oil as a future phase, the increased release is due to the attraction of lidocaine mainly for absorption by the oil and its dissolution.

Noting that the release here occurs according to Higuchi's plan to release hydrogels.

As for Tables (7-11) and from Figure (2), we notice a severe decrease in the percentage of lidocaine hydrochloride release, and this is due to the structure of the ointment polyethylene glycol, which formed complexes with the medicinal substance and did not release it (this corresponds to what was mentioned in reference (9), noting that An increase in the percentage of water in the PEG ointment, a decrease in the proportion of Lidocaine released, which is normal and due to the increased dissolution of Lidocaine hydrochloride.

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