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Study of local anaesthetics. Part 172*
Comparison of the influence of auxilliary substances on physicochemical parameters of two phenylcarbamic acid derivatives

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Abstract

It this work was studied the influence of polyols (propylene glycol, glycerol and sorbitol) on the physicochemical parameters (partition coefficient and surface tension) and liberation from aqueous solutions with propylene glycol of two derivatives of phenylcarbamic acid. Studied parameters and liberation were influenced by the structure of the studied derivatives and with the type and concentration of polyols.

Keywords

Partition coefficient, surface tension, derivative of phenylcarbamic acids, in vitro liberation

Introduction

The partition coefficient and the surface tension are physicochemical parameters that considerably influence absorption and effect of the drug. The determination of partition coefficient was studied in many papers. Beside classical

shake-flask method of determination, which is in actual practice still used, were developed some new experimental methods [1,2,3,4,5,6,7].

The physicochemical properties and relationship between structure, physicochemical properties and biological activity of potential local anaesthetics drugs from the group of phenylcarbamic acid derivatives were the matter of many studies published in several papers [8,9,10,11,12,13,14,15,16,17,18].

The dosage forms in which the local anaesthetics are often applied are hydrogels. They are used as lubricants e.g. for insertion of catheters. Because the necessary components of hydrogels are humectants, the physicochemical properties were determined in water solution of humectants: propylene glycol (PG), glycerol (GL) and sorbitol (SO) in concentration 5,10,15 a 20%.

Results and Discussion

The two derivatives of phenylcarbamic acid with local anaesthetic effect, with the operative names – substance XXIII Z and XIV were compared. The substance XXIII Z, N-[2-(3-oktyloxyfenylkarbamoyloxy) -ethyl] –pyrrolidiniumchloride, is 16 times more effective in surface anesthesia in comparison with cocaine and 7 times more effective in infiltration anaesthesia in comparison with procaine as standard [19]. The substance XIV, N-[2-(3-penthyloxyfenylkarbamoyloxy) -ethyl] – piperidiniumchloride is 80 times more effective in surface anesthesia in comparison with cocaine as standard and 135 times more effective in infiltration anaesthesia in comparison with procaine as standard [20]. The both substances differ with the structure of molecule, i.e. with substitution of aromatic ring and with the length of alkoxy substituent whereby lipophility is affected. It has been assumed that different structure of substances under investigation can affect the examined physicochemical parameters. Partition coefficient (P) and surface tension (γ) were determined, because both parameters can influence liberation, absorption and drugs action.

From the results (Table 1) appears that the structure of potential drug and used auxilliaries and their concentration influence both physicochemical

parameters. The influence of physicochemical parameters on the partition coefficient is bigger than on the surface tension.

Experimental determined values partition coefficients of substance XXIII Z were about 13 – 15 times bigger than of substance XIV and confirm higher lipophility of substance XXIII Z.

	Substance XIV			Substance XXIII Z		
Vehicle	**P**	**log P**	**γ** (mNm^{-1})	**P**	**log P**	**γ** (mNm^{-1})
0	4,22	0,6249	63,63	55,36	1,7432	38,33
5% PG	3,05	0,4841	63,88	46,72	1,6695	42,19
10% PG	2,85	0,4554	60,31	41,44	1,6174	46,93
15% PG	2,24	0,3508	58,83	32,12	1,5067	48,57
20% PG	2,22	0,3458	56,34	26,23	1,4187	51,89
5% GL	3,39	0,5305	62,98	48,58	1,6865	39,53
10% GL	3,31	0,5192	62,57	47,83	1,6797	40,29
15% GL	3,22	0,5076	60,52	42,99	1,6334	40,02
20% GL	2,91	0,4638	62,27	40,84	1,6111	40,54
5% SO	3,84	0,5845	64,51	49,75	1,6968	39,82
15%SO	4,09	0,6116	64,67	51,80	1,7143	39,51
15%SO	3,68	0,5661	62,34	55,83	1,7469	39,29
20% SO	4,15	0,6183	61,41	57,29	1,7581	40,38

Tab. 1. Partition coefficients (P), surface tension (γ) of substance XIV and XXIII Z
PG : propylene glycol, Gl : glycerol, SO : sorbitol

The differences between surface tensions of compared substances were smaller. The γ of XXIII Z substance was about 1.3 times lower in comparison with XIV substance.

Generally humectants with the XXIII Z substance reduce P and increase the γ, and with the XIV substance reduce both P and γ.

The influence of polyols and their concentrations on the determined parameters were different. With increased concentration of PG and GL is decreased value of P of XXIII substance. On the contrary SO increases the value of P. With increased concentration of PG is the γ value increased. The influence of GL and SO is

insignificant. With increased concentration of polyols is P of the XIV substance insignificantly decreased. The γ value is decreased with PG and SO, but only in 15-20% concentration of PG and SO. The GL is without any influence.

From the results it can be concluded that from the humectants the biggest influence on the studied parameters has PG, therefore it was used on the study of in vitro liberation of potential drugs from the solutions. The results of liberation indicate that it was liberated 3 to 5 times less of the substance XXIII Z in comparison with substance XIV (Table 2 and 3). The presence of PG in the sample increased the liberation of substance XXIII and decreased the liberation of substance XIV in comparison with the sample without the humectant.

Vehicle	K		k_E (h^{-1})	r^2
	mg	%		
0	11,3517	56,76	0,4765	0,999
5% PG	11,0018	55,01	0,2905	0,9997
10 % PG	11,0224	55,11	0,2604	0,9990
15 % PG	9,9051	49,53	0,1708	0,9996
20 % PG	9,3569	46,78	0,1073	0,9981

Tab. 2. Cumulative liberated amount K of substance XIV (mg, %) after 3,0 h, liberation rate constant (k_E), correlation coefficient (r^2)

Vehicle	K		k_E (h^{-1})	r^2
	mg	%		
0	2,1921	10,96	0,3294	0,9988
5% PG	2,6564	13,28	0,2647	0,9999
10 % PG	2,6245	13,12	0,2179	0,9990
15 % PG	3,0456	15,23	0,2209	0,9997
20 % PG	3,4069	17,03	0,0814	0,9945

Tab. 3. Cumulative liberated amount K of substance XXIII Z (mg, %) after 3,0 h, liberation rate constant (k_E), correlation coefficient (r^2)

The work confirmed the influence of molecule of potential drugs on the partition coefficient and surface tension and the effect of the type and concentration of auxilliary substances on the physicochemical parameters and the liberation of potential drugs from aqueous solution of PG.

Experimental

Materials

The substance XXIII Z, chemically N-[2-(3-oktyloxyfenylkarbamoyloxy)-ethyl]-pyrrolidinium chloride [19], the substance XIV, chemically N-[2-(3-pentyloxyfenylkarbamoyloxy)-ethyl]–piperidiniumchloride [20] were prepared at the Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Comenius University, Bratislava, Slovakia. Sorbitol, glycerol 85 % and propylene glycol (PENTA, Czech republic), n-oktylalkohol pure (Lachema a.s., Czech republic).

Determination of partition coefficient

Partition coefficient values (P) were determined in the system consisting of n-octanol/aqueous phase at 37°C [11]. The aqueous phase comprised either pure water or water with 5 , 10, 15 and 20 wt. % of polyol added. The potential drug was determined in the aqueous phase by UV spectrophotometry (XXIII Z at λ = 235 nm, XIV at λ = 236 nm) against similarly prepared reference containing no drugs.

Determination of surface tension

Surface tension (γ) was evaluated 24 h after preparation of the solution at a temperature of 20°C in stalagmometer by weighing the drops. It was used 0.1 wt. % water solutions of potential drug with or without 5 , 10, 15 and 20 wt. % of polyol added.

Determination of liberation

Potential drug was left to permeate at 37 °C through a hydrophilic membrane (19.6 cm^2) (Nephrophan, Filmfabrik Wolfen, Germany) into isotonic NaCl solution. Released drug amounts were determined by spectrophotometry (Philips Pye UV VIS, Unicam Ltd., UK) in the respective intervals [21].

*Part 171: Die Pharmazie in press

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References

[1] Remko M. editor
Fyzikálnochemické vlastnosti liečiv.
In: Základy medicínskej a farmaceutickej chémie. Bratislava:SAP, 2005:227-313.

[2] Schräder W., Anderson J.T.
Fast and Direct Method for Measuring 1-Octanol-Water Partition Coefficients Exemplified for Six Local Anesthetics.
J. Pharm.Sci. 2001;90:1948-1954.

[3] Østergaard J., Hansen S.H., Larsen C., Schou CH., Heegaard N.H.H.
Determination of octanol-water partition coefficients for carbonate esters and other small organic molecules by microemulsion electrokinetic chromatography.
Electrophor. 2003;24:1038-1046.

[4] Grouls R.J.E., Ackerman E.W., Korsten H.H.M., Hellebrekers L.J., Breimer D.D. Partition coefficients (n-octanol/water) of N-butyl-p-aminobenzoate and other local anesthetics measured by reversed.phase high-performance liquid chromatography. J. Chromatogr. B 1997;694:421-425.

[5] Omran A.A., Kitamura K., Takegami S., El-Sayed A-A.Y., Abdel-Mottaleb M.
Determination of partition coefficients of diazepam and flurazepam between phosphatidylcholine bilayer vesicles and water by second derivative spectrophotometric method.
J. Pharm. and Biomed. Anal. 2001;25:319-324.

[6] Poole S.K., Poole C.F.
Separation methods for estimating octanol-water partition coefficients.
J. Chromat. B 2003;797:3-19.

[7] Hartmann T., Schmitt J.
Lipofilicity – beyond octanol/water: a short comparison of modern technologies
Drug Discovery Today: Technologies/Drug development 2004;1:431-439.

[8] Andriamainty F., Čižmárik J., Uhríková D., Balgavý P.
Phospholipid liposomes-aqueous phase partition coefficient of alkyloxy homologs of local anesthetic heptacaine estimated by a surfactant ion sensitive electrode.
Adv. Med. Phys. Biophys. and Biomat. 1997;32-35.

[9] Andriamainty F., Čižmárik J.
Štúdium micelizácie homológov heptakaíniumchloridu.
Čes. a Slov. Farm. 2001;50:153-155.

[10] Andriamainty F., Čižmárik J., Mariščáková Z.
Štúdium lokálnych anestetík CLX. Stanovenie kritickej micelovej koncentrácie (c.m.c) série piperidínoetylesterov 3-alkoxyfenylkarbámovej kyseliny.
Čes. a Slov. Farm. 2002;51 : 154-156.
[11] Gardavská K., Vitková Z., Čižmárik J.
Study of the influence of auxiliary substances on the partition coefficient of some substituted phenylcarbamic acid derivatives.
Acta Pharm. Hung. 1994;64:79-81.
[12] Gardavská K., Vitková Z., Čižmárik J., Rak J.
Štúdium lokálnych anestetík CXLII. Porovnanie vplyvu pomocných látok na rozdeľovací koeficient potenciálnych liečiv zo skupiny derivátov kyseliny fenylkarbámovej.
Čes. a slov. Farm. 1998;47:124-127.
[13] Gyürösiová L., Sedlárová E., Čižmárik J.
Study of local anaesthetics, part 156: Some physicochemical and lipophilic properties of pyrrolidinoethyl esters of o-, m-, p-alkoxy-substituted phenylcarbamic acid.
Chem. Pap. 2002;56:340-344.
[14] Gyürösiová L., Laitinen L., Raiman J., Čižmárik J., Sedlárová E., Hirvonen J.
Permeability profiles of m-alkoxysubstituted pyrrolidinoethylesters of phenylcarbamic acid across Caco-2 monolayers and human skin
Pharm. Res. 2002;19:162-168.
[15] Malík I., Sedlárová E., Čižmárik J., Andriamainty F., Csöllei J.
Štúdium fyzikálno-chemických vlastností derivátov kyseliny 2-, 3-, 4-alkoxyfenylkarbámovej s bázickou časťou tvorenou substituovaným N-fenylpiperazínom
Farm. Obzor 2005;74:211-215.
[16] Malík I., Sedlárová E., Čižmárik J., Andriamainty F., Csöllei J.
Štúdium fyzikálno-chemických vlastností derivátov kyseliny 2-, 3-, 4-alkoxyfenylkarbámovej s bázickou časťou tvorenou substituovaným N-fenylpiperazínom
Čes. a slov. Farm. 2005;54:235-239.
[17] Sedlárová E, Čižmárik J, Búčiová L.
Štúdium fyzikálno-chemických vlastností látok zo skupiny 1-(4-fenyl-1-piperazinyl)-3-metoxy-2-propyl-esterov kyselín 2-,3-alkoxyfenylkarbámových.
Čes. a slov. Farm. 1999;48:170-174.
[18] Sedlárová E, Čižmárik J
Štúdium lokálnych anestetík 153. Vzťah medzi chemickou štruktúrou, fyzikálno-chemickými vlastnosťami a biologickou aktivitou v sérii piperidíopropyesterov alkoxysubstituovaných kyselín fenylkarbámových.
Čes. a slov. Farm. 2000;49:306-311.

[19] Čižmárik J., Polášek E., Račanská E., Švec P.
Štúdium lokálnych anastetík. CX. Príprava, aktivita a rozdeľovacie koeficienty pyrolidínoetylesterov 2-, 3-, 4-alkoxysubstituovaných kyselín fenylkarbámových..
Čes. a slov. Farm. 1993;42:88-91.
[20] Čižmárik J., Borovanský A., Švec P.
Study of local Anesthetics. LII. Piperidinoethyl Esters of Alkoxyphenylcarbamic Acids.
Acta Fac. Pharm. Univ. Comenianae 1976;29:53-80.
[21] Gardavská K., Gruntová Z., Hanzelová H., Račanský V., Mandák M.
Formulačné štúdie topických prípravkov s obsahom pentakaínu a heptakaínu.
Farm. Obzor 1991;60:97-104.

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