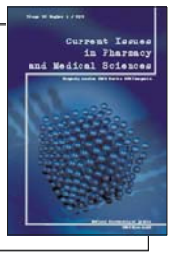
2012 © Curr. Issues Pharm. Med. Sci. Vol. 25, No. 4, Pages 381-383

Current Issues in Pharmacy and Medical Sciences

Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA
on-line: www.umlub.pl/pharmacy



The release of phenobarbital from parenteral emulsions

DOROTA DWORNICKA*, MARIA ZUŃ, KATARZYNA ŚWIĄDER, EWA POLESZAK

* Chair and Department of Applied Pharmacy, Medical University of Lublin, Poland

ABSTRACT

Five nonisotonised emulsions with different degree of compaction containing 1% solution of phenobarbital in soybean oil, lecithin, human albumin and four concentrated emulsions with the same composition containing the addition of isotonic agents such as: glucose, sodium chloride, Ringer salt, glycerin were prepared. The release of phenobarbital was examined by dialysis through the semipermeable membrane using the modified Franz diffusion cell. The studies show that the release is a diffuse. Phenobarbital releases with a lag time and the process is biphasic; first faster, in the second stage slower. The release of phenobarbital depends on the amount of external phase (water) in nonisotonised emulsions and on the kind of using isotonic agent in concentrated emulsions.

Keywords: parenteral emulsions, phenobarbital, releasing

INTRODUCTION

Parenteral emulsions are used as a vehicle of many drugs, especially those, which are weakly soluble in the water. Fat emulsions such as: Intralipid, Liposyn and Lipofundin have lipohydrophylic character [2,9]. They enable the transport of the active, poorly watersoluble ingredients in the lipid phase. The compositions of emulsions have been developed containing substances such as: anesthetics, tranquilizers, anti-inflammatory, anticancer, liposoluble vitamins and others like: amphotericin, nitroglycerin, physostigmine [1,5,6], and many lipophylic benzodiazepines such as: alprazolam, clonazepam, diazepam, lorazepam, tetrazepam [3,4,7,10].

The possibility of introducing a drug into the circulatory system, protection of the active substances from degradation processes and quick release into the blood – these are the factors which ensure more bioavailability in comparison with the conventional water forms. Furthermore, a logical consequence of introducing a drug to fat emulsions is to enhance the comfort of patients by avoiding the need to connect the additional veins lines, increase the efficacy thanks to the possibility of maintaining the constant therapeutic concentration, increase the safety of treatment and reduce its costs.

Corresponding author
* Chair and Department of Applied Pharmacy,
Medical University of Lublin, 1 Chodzki Str., 20-097 Lublin, Poland
e-mail: dor.dwor@wp.pl

The current state of knowledge about using the parenteral emulsions as a vehicle of phenobarbital is poor. That is why, the aim of the study was to investigate the release of phenobarbital from the nonisotonised emulsions with different degrees of compaction, depending on the volume of water used and from the concentrated isotonic emulsions. These studies were to answer the question whether the quantity of the released substance depends on the water content in the emulsion and what is the influence of isotonic substances on release parameters.

MATERIALS AND METHODS

Emulsion preparation. Five emulsions (A, B, C, D, E) without the addition of isotonic agents, with different degrees of compaction were prepared (Tab. 1). Lecithin was dissolved in 1% solution of phenobarbital in soybean oil and human albumin was dissolved in the water. Then, the oil solution was emulsified with continuous stirring in the water solution of human albumin. The preparation was homogenized for five minutes by ultrasounds. Moreover, four concentrated isotonic emulsions (K_a, K_b, K_c, K_d) with four different isotonic agents (glucose, sodium chloride, Ringer salt, glycerin) were prepared (Tab. 2). Lecithin was dissolved in 1% oil solution of phenobarbital, albumin and one of the isotonic agent – in water. The oil phase was emulsified with continuous stirring in water phase. The final preparation was homogenized for five minutes by ultrasounds.

Table. 1. Composition of the nonisotonised emulsions A,B,C,D,E

Emulsion	Pheno-barbital (g)	Soybean oil (g)	Lecithin (g)	Human albumin (g)	Water (g)
A	0.10	9.90	1.20	2.50	86.30
B	0.10	9.90	1.20	2.50	64.95
C	0.10	9.90	1.20	2.50	43.60
D	0.10	9.90	1.20	2.50	22.25
E	0.10	9.90	1.20	2.50	9.44

Table 2. Composition of the concentrated emulsions K_a, K_b, K_c, K_d

Emulsion	Ka	Kb	Kc	Kd
Phenobarbital (g)	0.100	0.100	0.100	0.100
Soybean oil (g)	9.900	9.900	9.900	9.900
Lecithin (g)	1.200	1.200	1.200	1.200
Human albumin (g)	2.500	2.500	2.500	2.500
Glucose (g)	4.315			
Sodium chloride (g)		0.777		
Ringer's salt (g)			0.770	
Glyceride (g)				2.158
Water (g)	5.125	8.663	8.663	7.283

The study of phenobarbital release. The release of phenobarbital was examined by dialysis through the cellulose semipermeable membrane. The modified Franz diffusion cell was used [8]. A portion of 5 ml of each emulsion was placed in the 5 glass tubes closed at the bottom with the membrane. The tubes were placed in 100 ml of phosphate buffer (pH=7.35) and incubated at 37°C. At specified time intervals, i.e. after 1, 2, 4, 6, 8 h, the 5 samples of each emulsion were taken. In this way the diffusion of phenobarbital from the buffer solution R (containing 5mg of phenobarbital in 5ml of solution) to phosphate buffer was examined as well.

Determination of phenobarbital released. The absorbance at λ=240 nm and in the presence of phosphate buffer (pH=7.35) was measured in spectrophotometer Spektromom 195 D. The concentration of phenobarbital in determined sample was read from calibration curve and the quantity of released substance in 5 ml of emulsion was calculated.

RESULTS

The results of the phenobarbital diffusion from buffer solution (R) and release of phenobarbital from emulsions with the different amount of water (A-E) are presented in Table 3.

The results of releasing phenobarbital from concentrated emulsions with isotonic agents (K_a-K_d) are presented in Table 4.

The percentage correlation between the quantity of released phenobarbital and the time of dialysis is showed on Fig. 1, 2.

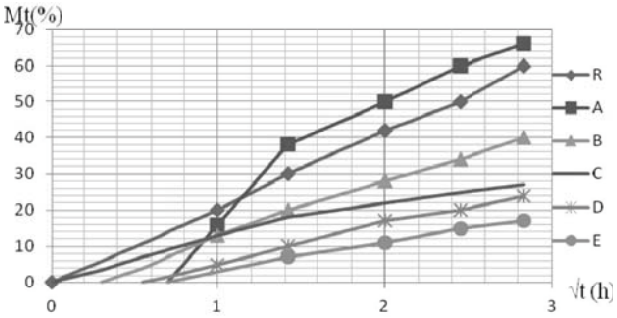


Fig. 1. The releasing of phenobarbital from the buffer solution and emulsions A,B,C,D,E

DISCUSSION

The data presented in Table 3 show that after 8 h, from the nonisotonised emulsions A, B, C, D, E the following amounts of phenobarbital are released: 66.2% (A), 42.0%

Table 3. Diffusion of phenobarbital from the buffer solution R and emulsions A,B,C,D,E

Time (h)	Amount of the released substance																	
	Solution R			A			B			C			D			E		
	Mt %	SD %	K $\%h^{-0.5}$	Mt %	SD %	K $\%h^{-0.5}$	Mt %	SD %	K $\%h^{-0.5}$	Mt %	SD %	K $\%h^{-0.5}$	Mt %	SD %	K $\%h^{-0.5}$	Mt %	SD %	K $\%h^{-0.5}$
1	20.0	7.2	20.0	15.4	8.1	30.2	13.2	5.4	14.5	11.6	7.0	11.7	5.6	6.2	8.8	3.2	4.8	2.7
2	32.4	3.2	23.0	38.0	7.8	41.3	20.2	6.8	15.3	18.2	6.8	13.0	10.8	3.4	10.3	7.8	4.9	6.9
4	44.4	4.5	22.2	43.0	10.2	28.5	28.0	3.9	14.7	22.6	6.9	11.4	17.4	7.8	10.6	12.2	2.7	8.1
6	51.8	2.7	21.1	59.2	7.4	30.2	35.6	7.1	15.1	25.0	9.2	10.2	21.4	5.4	10.2	15.2	5.2	7.8
8	58.7	3.5	20.7	66.2	6.2	28.3	42.0	6.4	15.3	27.8	8.0	9.9	24.8	3.8	10.0	17.8	3.3	7.6
T lag (h)	0			0.49			0.09			0.01			0.36			0.49		
K*($\%h^{-0.5}$)	21.4			31.2			15.0			11.2			10.0			6.6		

T lag – the release lag time; K – the release rate constant; K* – the mean for five measurements

Table 4. Diffusion of phenobarbital from the emulsions Ka, Kb, Kc, Kd

Time (h)	Amount of the released substance											
	Ka			Kb			Kc			Kd		
	Mt %	SD %	K $\%h^{-0.5}$	Mt %	SD %	K $\%h^{-0.5}$	Mt %	SD %	K $\%h^{-0.5}$	Mt %	SD %	K $\%h^{-0.5}$
1	9.4	4.5	14.7	14.8	5.2	23.1	12.3	3.6	19.2	16.0	5.2	25.0
2	20.7	3.1	19.7	30.4	4.2	28.6	23.5	3.0	22.4	29.6	2.8	28.2
4	26.3	2.8	16.0	41.2	7.0	25.1	33.0	3.5	20.1	39.2	2.9	23.9
6	29.3	4.1	14.0	54.7	3.2	26.2	42.1	3.1	20.1	47.6	3.4	23.2
8	33.2	2.8	13.4	63.4	3.1	25.7	47.1	3.5	19.1	53.2	3.6	21.5
T lag (h)	0.36			0.36			0.36			0.36		
K*($\%h^{-0.5}$)	15.6			25.7			20.2			24.4		

T lag –the release lag time; K – the release rate constant; K* – the mean for five measurements

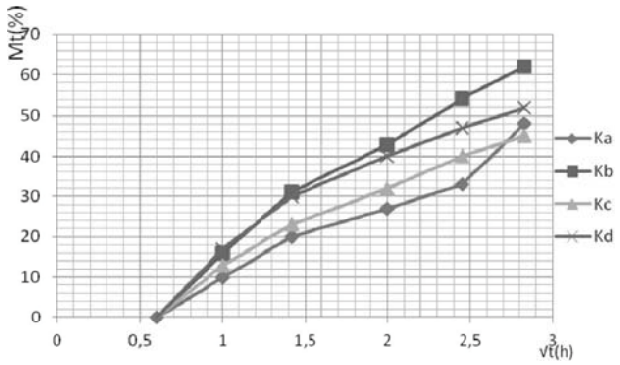


Fig. 2. The releasing of phenobarbital from the emulsions Ka,Kb,Kc,Kd

(B), 27.8% (C), 24.8% (D), 17.8% (E) and they were proportional to the amount of water in the external phase. The quantity of released substance from emulsion A was slightly higher than solution R (58.7%).

Table 4 shows that the release of phenobarbital from concentrated emulsions is as follows: 33.2% (K_a – glucose), 47.1% (K_c – Ringer salt), 53.2% (K_d – glycerin), 63.4% (K_b – sodium chloride).

Figure 1, 2 show, that the releasing can be based on simplified Higuchi's equation:

$$M_t = K_H \cdot t^{1/2}$$

where: M_t – the amount of released substance after the time t,
K_H – the release rate constant.

The correlation between released substance M_t (%) and the square root of releasing time $\sqrt{t}$, presented on Figure 1, 2 shows that the release is a diffusion which starts with a lag time (T_{lag}) and at the beginning the rate release is higher and then (after 2 h) it decreases.

The T_{lag} (h) values can be read from the intersection of the line with the axis of $\sqrt{t}$, and the values of constant K can be calculated:

$$K = \frac{Mt}{\sqrt{t} - \sqrt{T}lag} \ (\%h^{-0.5})$$

where: M_t – percentage amount of released substance after the time t.

The results also show that the decrease of substance release is proportional to the decrease of the water amount in emulsions A-E.

The changes of releasing of phenobarbital in the concentrated emulsions depend on the isotonic agent. The addition of sodium chloride is the best.

We can conclude, comparing the release from the concentrate E (17.8% of water) and from the concentrated emulsions K_a-K_d, that the presence of isotonic agents in the external water phase significantly increases the amount of released substance (about 2-3.5 times).

CONCLUSIONS

1. The release of phenobarbital from all examined emulsions is a diffusion based on simplified Higuchi model.
2. The substance releases with a lag time, at first the rate release is higher and then (after 2 hours) the process of releasing decreases.
3. The releasing of the substance from nonisotonised emulsions decreases with the decrease of the water content in the external phase.
4. The presence of isotonic agents in concentrated emulsions increases (2-3.5 times) the releasing of phenobarbital.
5. The addition of sodium chloride has the best influence on the process of releasing.

REFERENCES

1. Benita S., Levy M.Y.: Submicron emulsions as colloidal drug carriers for intravenous administration: comprehensive physicochemical characterization. *J. Pharm. Sci.,* 82, 1069, 1993.
2. Ishii F., Sasiki J., Ogata H.: Effect of phospholipid emulsifiers on physicochemical properties of intravenous fat emulsions and/or drug carrier emulsions. *J. Pharm. Pharmacol.*, 42, 513, 1990.
3. Jumaa M, Muller B.W.: Development of a novel parenteral formulation for tetrazepam using a lipid emulsion. *Drug Dev. Ind. Pharm*., 27, 1115, 2001.
4. Jumaa M., Muller B.W.: Formulation and stability of benzodiazepines in a new lipid emulsion formulation. *Pharmazie*, 57, 740, 2002.
5. Kleinstern J., Markovitz E., Benita S.: The effect oil nature in o/w submicron emulsion on the oral absorption profile on physostigmine salicylate in rats. *S.T.P. Pharma Sci*., 3, 163, 1993.
6. Mbela T.K.M.N., Ludwig A.: Physical properties and stability evaluations of submicron mefloquine emulsions. *S.T.P. Pharma Sci.*, 5, 225, 1995.
7. Medina J., Salvado A., Del Pozo A.: Use of ultrasound to prepare lipid emulsions of lorazepam for intravenous injection. *Int. J. Pharm*., 216, 1, 2001.
8. Owczarek A., Pluta J., Kogut J.: Ocena właściwości żeli hydrofilowych z simwastatyną sporządzonych na bazie Carbapolu 2020. *Polimery w medycynie,* 40, 57, 2010.
9. Peterkiewicz M.: *Preparaty stosowane w żywieniu pozajelitowym*. PZWL, Warszawa, 1994.
10. Sila-on W. at al.: Influence of incorporation methods on partitioning behavior of lipophilic drugs into various phases of a parenteral lipid emulsions. *AAPS Pharm. Sci. Tech.*, 9, 684, 2008.