Bull. Pharm. Sci. Assiut University
Vol. 6, PP. 81 - 88

THE PROLONGED RELEASE OF SODIUM PHENOBARBITONE FROM SOLID DISPERSION SYSTEM

A. T. Nouh and M. S. Mesiha

Department of Pharmaceutics, Mansoura and Department of Industrial Pharmacy, Faculty of Pharmacy, University of Assiut, Assiut, Egypt.

Stearic acid was used for the preparation of solid dispersion systems containing sodium Phanobarbitone in ratios of 1:2. 1:1, 2:1 drug: carrier respectively. The dispersion prepared by melting and sudden cooling was passed through a set of standard sieves and tested for in vitro release rate. The release was slow for large particle size fractions and for systems containing high stearic acid content

A diffusional model was assessed for the drug release from the solid dispersion by a linear correlation observed between the percent release of the drug and the square root of time.

The prolonged release of sodium Phenobarbitione was previously prescribed using the technique of polymer separation to form microcapsules. The technique is time consuming and a slight change in the procedure produces marked variation in the final product[1].

The *in vitro* release pattern of phenobarbitone from various waxy matrices was used in preparing formulations by the congealing method[2] stearic acid proved to retard the release of Phenobarbitone in dissolution media.

In this research, the effect of drug carrier ratio and particle size of the particles on sodium phenobarbitone release in simulated gastric juice(B.P. 1980) was studied.

EXPERIMENTAL

Materials and Methods:

Materials:

Sodium Phenobarbitone B.P.: Evans Medical Ltd, Stearic acid (Prolabo), Sodium Hydroxide (BDH).

Apparatus: Dissolution Tester (Erweka, DT-D6)
Spectrophotomer (Pye- Unicam, SP_6 - 400).

Methods:

1- Preparation of Dispersion Systems:

The dispersion system was prepared by fusion. A suitable amount of the stearic acid-sodium Phenobarbitone mixtures (1:2, 1:1, and 2:1 w/w) was put in a porcelain dish (Ca. 10 Cm diameter), which was placed on a thermostatically controlled water bath at 80^{o} for complete melting over 10 min. Then the mixture was allowed to congeal by placing the dish in an ice bath subjected to vigorous stirring during the melting and congealing stages. The solid dispersion produced was desiccated over calcium chloride for at least 12 hours, pulverized using a sieve No 16 (B.P) and the final granules were kept in an oven at 33^{o} overnight.

2- Screening of Granules:

The whole granules were separated into suitable fractions by sieving on a mechanical shaker for 10 minutes at a maximum vibration. (Erweka-Apparatebau G.P.b.H, West Germany), using a standard sieve set ranging from 200 µm to 800 µm

3- Assay of Sodium Phenobarbitone:

A dissolution tester (Erweka. Type DT-D6) was used. Sodium Phenobarbitone (50 mg) or the equivalent weight of solid dispersion was introduced into 500 ml of simulated gastric fluid (B.P. 1980). A stirring speed of 100 rpm, and a temperature of $37^{o} \pm 0.1^{o}$ were maintained constant throughout the course of dissolution experiments. Over 7 hours and at a selected intervals, a 2 ml of the dissolution medium was sampled out, rendered alkaline with 3 ml sodium hydroxide solution 0.5 N, and the released sodium phenobarbitone was assayed spectrophotometrically at 255 nm. An equivalent amount of simulated gastric fluid was added at each withdrawn sample with adequate corrections. Two runs were made for each size fraction, and the average was calculated.

RESULTS AND DISCUSSION

The use of stearic acid as a matrix for retardation of drug release was previously described for some drugs such as Phenobarbitone[2] and potassium chloride[3]. The release of the water-soluble sodium phenobarbitone from stearic acid dispersion is now discussed. The particle size distribution of the crushed mass obtained is given in Table 1. No significant difference in particle size distribution for different drug: carrier ratios.

The study of dissolution rate of the different size fractions of the solid dispersion was carried out to assess the possible use of these fractions as delayed release form. Tables 2-4 show the release of sodium phenobarbitone from solid dispersion fractions with different drug: carrier ratios of different paticle size. The effect of particle size at different ratios follows a similar pattern. At a constant

drug; carrier ratio, the smaller particles released their sodium phenobarbitone content more rapidly. This is not true for particles less than 200 μ in diameter. The unexpected relative delay in drug release is due to the aggregation of the fine particles with subsequent formation of apparently larger particles with less surface available for release of the drug.

Greater delay in the release rate was obtained when increase in the stearic acid content of the solid dispersion. While, the release of the drug was complete within 45 min for the largest size fraction of the sodium phenobarbitone stearic acid 2:1 system, the corresponding complete release for the 1:1 ratio was reached after nine hours and for the 1:2 ratio it was very much slower as shown in Table 3.

The particles of the studied solid dispersion did not disintegrate during the dissolution experiments. The percent release from these dispersions was found to show a linear dependence on the square root of time which is an evidence that a diffusion process is responsible for the release of the drug. The linear correlation is best evidenced by the values of regression coefficient (r) given in Table 5 for different size fractions, these values were deduced by the least square equation when the percent release of the drug was correlated with square root of time . From this correlation, the time of 50% release (t_{50}) was calculated for each size fraction and shown in Table 5. It is of greate value in comparison of the ability of different dispersions in prolonging the rate of release. The t_{50} ranged between 2.4 min up to 369 min. for the largest granules of drug:carrier ratio 1:2.

Table 1: Size Distribution of the Granules for the Prepared sodium Phenobarbitone-Stearic Acid solid Dispersion

Size µm	*Mean Size* µm	*% Fraction for a given drug: carrier ratio* 2:1	1:1	1:2
< 200	< 200	6.73	7.71	12.50
200 - 315	258	12.27	15.43	15.83
315 - 400	358	14.36	16.58	16.08
400 - 630	515	17.18	18.29	17.67
630 - 800	715	24.36	19.14	17.92
800 - 1000	900	24.73	22.85	20.00

Table 2: Rate of Release of sodium Phenobarbitone from the Solid Dispersion as a function of Particle Size (Drug:carrier 2:1)

Mean Size µ	*Cumulative Percent Release* after time (min)* 5	15	30	45
< 200	87.4	87.7	96.2	100.0
258	95.5	99.9	100.0	
358	92.7	96.5	99.3	
515	89.1	99.4	100.0	
715	92.0	97.0	98.3	100.0
900	48.8	73.7	94.0	100.0

* Mean of three determinations

Table 3: Rate of Release of sodium Phenobarbitone from solid Dispersion as a function of Particle Size (Drug: carrier 1:1)

Mean Size µ	*Cumulative Percent Release* after time (hr)* 0.25	0.5	1	2	3	4	5	6	7
< 200	100								
258	85.7	88.9	90.9	97.2	100				
358	60.4	79.5	80.4	93.9	99.2	100			
515	54.4	64.1	72.5	95.1	100				
715	41.3	52.8	55.6	70.8	81.0	85.5	95.4	100	
900	27.8	35.1	40.1	55.5	65.5	69.0	77.9	85.0	89.7

* Mean of three determinations

Table 4: Rate of release of sodium phenobarbitone from solid dispersion as a function of particle size (Drug : carrier 1:2)

Mean Size μ	Cumulative Percent Release* after time (hours) 0.25	0.5	1	2	3	4	5	6	7
< 200	32.7	48.0	54.8	71.8	72.2	75.4	79.4	88.9	93.8
358	26.0	33.5	41.8	68.4	77.1	78.2	89.7	100	
515	25.4	13.3	38.1	58.1	59.6	67.9	79.1	83.9	88.6
715	15.8	20.5	25.6	39.2	43.6	54.2	56.8	65.3	70.0
900	9.7	16.5	18.0	26.8	31.0	41.5	44.5	50.1	54.7

* Mean of three determinations

Table 5: Linear regression Data for the release of sodium phenobarbitone as a function of square root of time

Drug:carrier	Mean size μ	Regression coefficient	Calculated t_{50} (min)	t_{100} (hr)
1:1	258	0.9953	< 5	3
	358	0.9866	2.4	3
	515	0.9925	8.5	3
	715	0.9942	36.5	6
	900	0.9980	96.3	9
1:2	200	0.9736	47.1	8
	358	0.9879	77.6	6
	515	0.9941	104.7	9
	715	0.9961	212.7	15
	900	0.9922	369.0	45

REFERENCES

1) *I. Jalsenjak, C.F. Micolaidou and J.R. Nixon, J. Pharm. Pharmacol.,* 28, *912 (1976).*

2) *S.A. Khalil., S.S. El-Gamal and M.M Abdel-Khalek , Acta Pharm. Suec.,* 8, *311 (1971).*

3) *A.A. Kassem, A.M. Sakr, A.A. Kassem. (Jr) and H. Abdou, Manuf. Chem. Aeros. News, 4. 23-29 (1973).*

الأتاحة الممتدة لفينوباربيتون صوديوم من المشتتات الصلبة

أحمد طلعت نوح و منير صبحى مسيحة

قسم الصيدلانيات - جامعة المنصورة - وقسم الصيدلة الصناعية

جامعة أسيوط

تم أستخدام حمض الشمعيك لتحضير أنظمة مشتتات صلبة تحوى الصوديوم فينوباربيتون بنسب ١:٢ ، ١:١ ، ٢:١ للدواء: الحامل على التوالى. وقد حضر المشتت بالانصهار والتبريد الفجائى ثم تمرير الحبيبات خلال مناخل قياسية وعين معدل الانطلاق بجهاز الدستور الامريكى للادوية.

وقد تبين من النتائج أن الانطلاق يكون ابطأ للحبيبات الكبيرة وفى الحبيبات المحتوية على نسبة أكبر من حمض الشمعيك ويتبع الأنطلاق النموذج الأنتشارى .

recieved in 25/3/1982 & accepted in 1/4/1982