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Effect of Aromatic Hydrotropes on the Solubility of Carbamazepine. Part II: Effect of Nicotinamide, Sodium Salts of Benzoic, Naphthoic and Nicotinic Acids

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THE EFFECT of nicotinamide and sodium benzoate, naphthoate and nicotinate on the solubility of carbamazepine in water was studied. The investigated hydrotropes were found to increase the solubility of carbamazepine. The solubilizing power of these hydrotropes was shown to be highly dependent on their chemical structure. The replacement of benzene ring by a naphthalene or pyridine ring enhances solubilization. Molecular interaction of carbamazepine with the investigated solubilizers were depicted via differential ultraviolet spectrophotometric measurements. Applying the continuous variation method revealed formation of 1:1 complex with sodium nicotinate, 2:1 complex with nicotinamide and sodium naphthoate and a mixture of 2:1 and 1:2 complexes with sodium benzoate. An apparent correlation seems to exist between the solubilizing power of these hydrotropic agents and the stability constant of their respective complexes. Calculating the amount of drug solubilized in free as well as complexed forms revealed that complex-formation as well as the decrease in activity coefficient of the drug are the two factors governing the hydrotropic behaviour of these compounds towards carbamazepine.

In the preceding communication, sodium salts of hydroxy and amino derivatives of benzoic acid have been shown to exhibit solubilizing properties towards carbamazepine which have been attributed to both complex-formation as well as to the decrease in the activity coefficient of the

drug. This motivated investigating the influence of other hydrotropes towards the solubility of carbamazepine in water. Thus, the present contribution deals with evaluating and elucidating both the solubilizing behaviour as well as the mechanism of solubilization of nicotinamide, sodium salts of benzoic, naphthoic and nicotinic acids towards carbamazepine.

Experimental

Materials

Carbamazepine (Egyptian International Pharmaceutical Industries Co.). Pharmaceutical grade of benzoic acid, naphthoic acid, nicotinic acid, nicotinamide and sodium biocarbonate.

Solubility Measurements

Solubility measurements were carried out according to the method of Higuchi and Zuck ⁽¹⁾ as previously described ⁽²⁾.

Results and Discussion

Figures 1-3 reveal that the apparent water solubility of carbamazepine is increased in presence of sodium benzoate, naphthoate, nicotinate and nicotinamide as a function of their concentrations. A linear relationship exists between the maximum additive concentration of the drug and sodium nicotinate concentration.

The solubilizing power of these hydrotropic agents towards carbamazepine calculated as mole drug solubilized by one mole of hydrotrope seems to be highly dependent on their concentration, with the exception of sodium nicotinate, whereby its solubilizing power is more or less independent of its concentration (Table 1). On the other hand, the solubilizing power of sodium benzoate, naphthoate or nicotinamide increases with increasing their concentration. It is also evident from the table that the solubilizing power of sodium naphthoate is higher than that of sodium benzoate. Thus, expansion of ring system from benzenoid to the naphthoate structure leads to augmenting the solubilizing efficiency. This result agrees with the results previously reported regarding the higher solubilizing power of sodium naphthoate towards chlorothiazide, hydrochlorothiazide and allopurinol compared to sodium benzoate ^(3,4).

Egypt. J. Pharm. Sci. 35, No. 1-6 (1994)

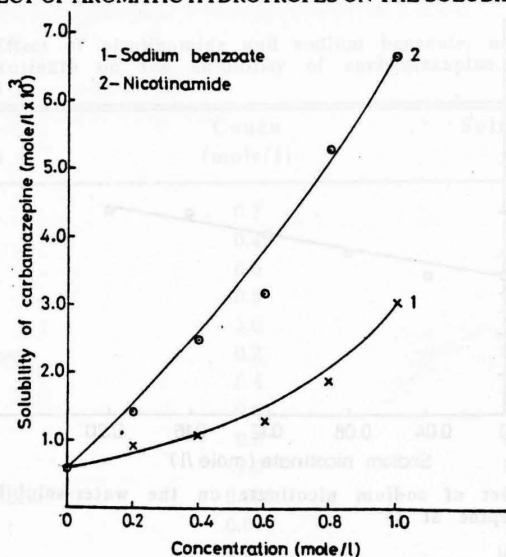


Fig. 1: Effect of sodium benzoate and nicotinamide on the water-solubility of carbamazepine at 25°

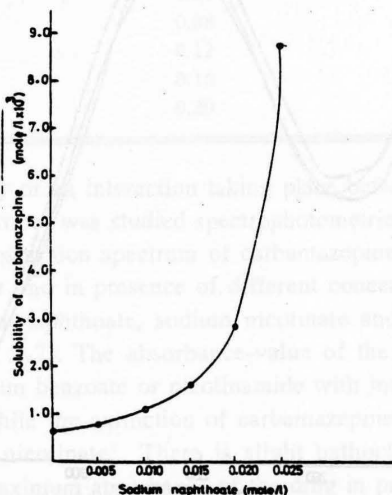


Fig. 2: Effect of sodium naphthoate on the water-solubility of carbamazepine at 25°

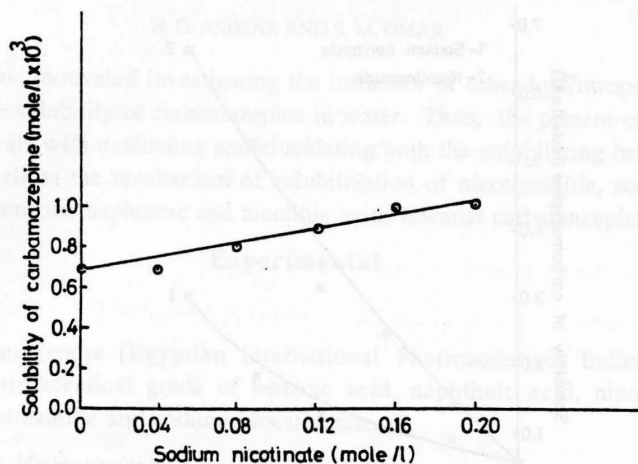


Fig. 3: Effect of sodium nicotinate on the water-solubility of carbamazepine at 25°

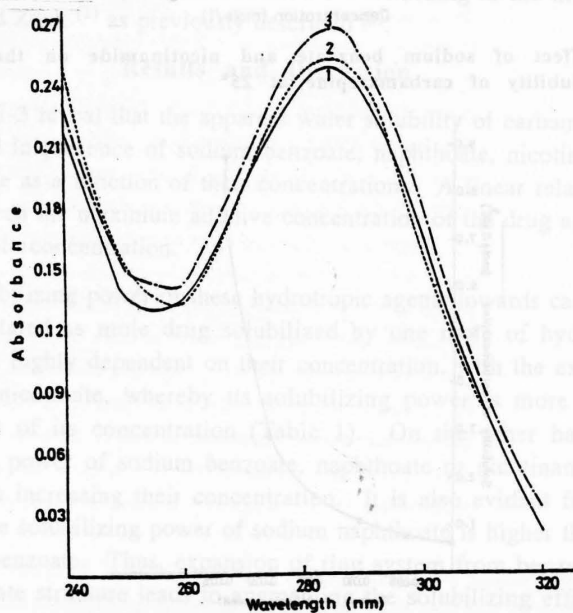


Fig. 4: Differential ultraviolet absorption spectrum of carbamazepine in presence of sodium benzoate (mmole/l) 1:0, 2:0.1, 3:0.4

Egypt. J. Pharm. Sci. 35, No. 1-6 (1994)

TABLE 1. Effect of nicotinamide and sodium benzoate, naphthoate and nicotinate on the solubility of carbamazepine in water at 25°.

Hydrotrope	Concn (mole/l)	Solubilizing power
Nicotinamide	0.2	0.0036
	0.4	0.0044
	0.6	0.0044
	0.8	0.0058
	1.0	0.0060
Sodium benzoate	0.2	0.0011
	0.4	0.0010
	0.6	0.0014
	0.8	0.0015
	1.0	0.0025
Sodium naphthoate	0.005	0.0134
	0.010	0.0388
	0.015	0.0613
	0.020	0.1051
	0.025	0.3200
Sodium nicotinate	0.04	-
	0.08	0.0014
	0.12	0.0017
	0.16	0.0018
	0.20	0.0018

The possibility of an interaction taking place between carbamazepine and these hydrotropes was studied spectrophotometrically. The differential ultraviolet absorption spectrum of carbamazepine solution (2×10^{-5} mole/l.) in water and in presence of different concentrations of sodium benzoate, sodium naphthoate, sodium nicotinate and nicotinamide was determined (Fig. 4-7). The absorbance-value of the drug increases in presence of sodium benzoate or nicotinamide with increasing hydrotrope concentration, while the extinction of carbamazepine decreases in presence of sodium nicotinate. There is slight bathochromic shift in the wavelength of maximum absorbance of the drug in presence of nicotinamide from 285 to 286 nm. On the other hand, the ultraviolet absorption spectrum of the drug in presence of different concentrations of sodium

Egypt. J. Pharm. Sci. 35, No. 1-6 (1994)

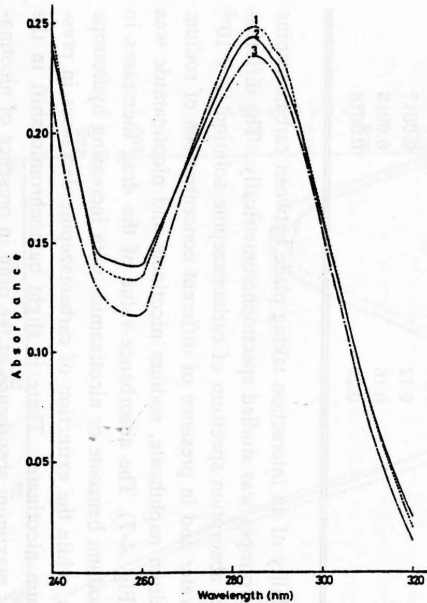


Fig. 5: Differential ultraviolet absorption spectrum of carbamazepine in presence of sodium naphthoate (m mole/ l) 1:0.0, 2:0.06 3:0.08

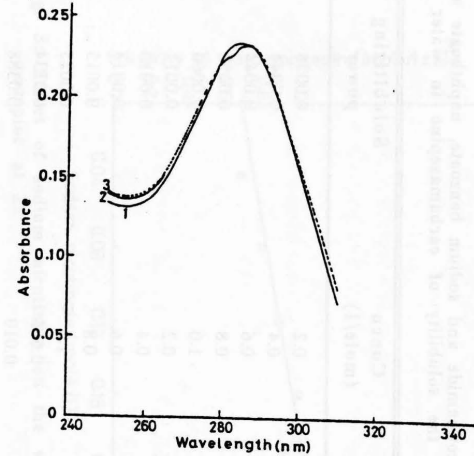
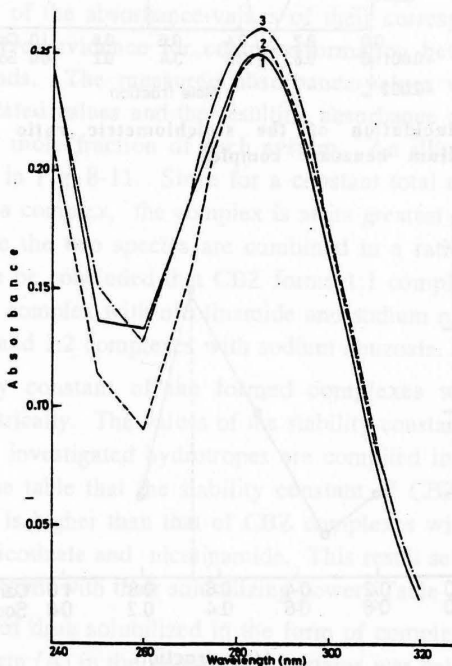


Fig. 6: Differential ultraviolet absorption spectrum of carbamazepine in presence of sodium nicotinate (m mole/l) 1:0.0, 2:0.05, 3:0.3

TABLE 2. Stability constant (K) of carbamazepine-hydrotrope complexes at 25°.

Hydrotrope	Stoichiometric ratio of complex	K (mole ⁻¹)
Nicotinamide	2: 1	1.225
Sodium benzoate	2: 1	0.454
	1: 2	1.143
Sodium naphthoate	2: 1	42.364
Sodium nicotinate	1: 1	1.549

**Fig. 7:** Differential ultraviolet absorption spectrum of carbamazepine in presence of nicotinamide (m mole/l) 1:0.0, 2:0.4, 3:0.5*Egypt. J. Pharm. Sci.* 35, No. 1-6 (1994)

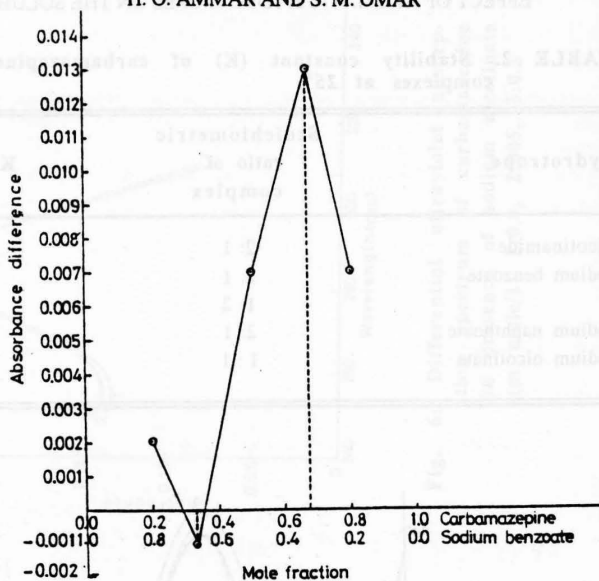


Fig. 8: Elucidation of the stoichiometric ratio of carbamazepine-sodium benzoate complex

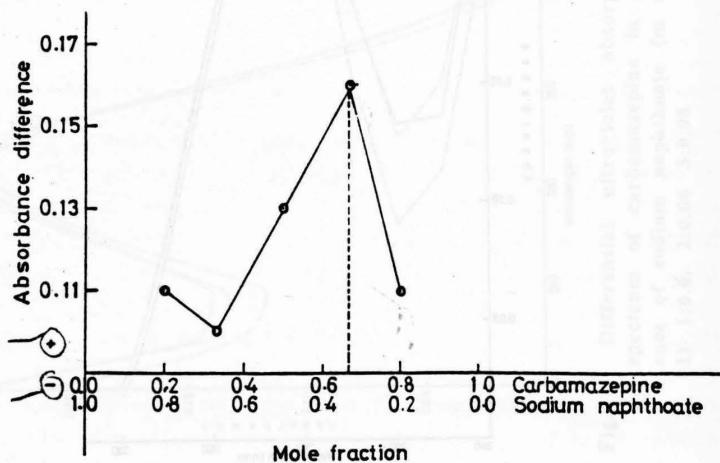


Fig. 9: Elucidation of the stoichiometric ratio of carbamazepine-sodium naphthoate.

Egypt. J. Pharm. Sci. 35, No. 1-6 (1994)

naphthoate exhibits two isosbestic points at wavelengths of 280 and 288 nm (Fig. 5). The spectral changes taking place in presence of all the investigated hydrotropes may give an indication of a sort of molecular interaction taking place between carbamazepine and these compounds. Also, the existence of isosbestic points in the spectrum of the drug in presence of sodium naphthoate might indicate the formation of a single species of complexes in this system. These interactions were further investigated through other spectral measurements utilizing the continuous variation method. The absorbance of solutions containing different mole fractions of the drug and each of the investigated hydrotropes was measured at 285 nm. The total concentration of CBZ and hydrotropes in each solution was fixed at a concentration of 0.06 mmole/l. The absorbance-values of all the investigated solutions were found to differ from the summation of the absorbance-values of their corresponding components. This gives evidence for complex-formation between CBZ and these compounds. The measured absorbance-values were subtracted from the calculated values and the resulting absorbance differences were plotted against mole fraction of each system. An illustration of such plots is shown in Fig. 8-11. Since for a constant total concentration of two species of a complex, the complex is at its greatest concentration at the point where the two species are combined in a ratio they occur in complex. It can be concluded that CBZ forms 1:1 complex with sodium nicotinate, 2:1 complex with nicotinamide and sodium naphthoate and a mixture of 2:1 and 1:2 complexes with sodium benzoate.

The stability constant of the formed complexes was determined spectrophotometrically. The values of the stability constant of CBZ complexes with the investigated hydrotropes are compiled in Table 2. It is evident from the table that the stability constant of CBZ-sodium naphthoate complex is higher than that of CBZ complexes with sodium benzoate, sodium nicotinate and nicotinamide, This result seems to run parallel to a great extent with their solubilizing power (Table 1).

The amount of drug solubilized in the form of complex (AB) as well as in the free form (A) in the investigated systems was calculated according to the equation of Benesi and Hildebrand (5) (Table 3). It can be seen from the table that the percentage concentration of complex formed

Egypt. J. Pharm. Sci. 35, No. 1-6 (1994)

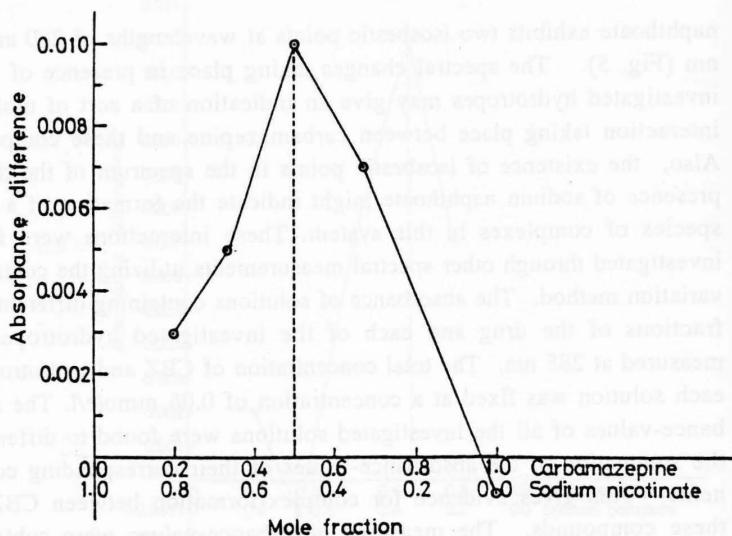


Fig. 10: Elucidation of the stoichiometric ratio of carbamazepine-sodium nicotinate complex.

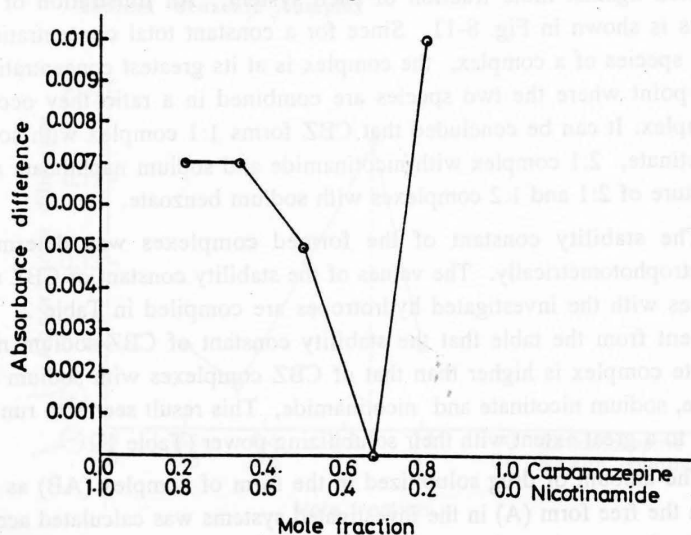


Fig. 11: Elucidation of the stoichiometric ratio of carbamazepine nicotinamide complex

Egypt. J. Pharm. Sci. 35, No. 1-6 (1994)

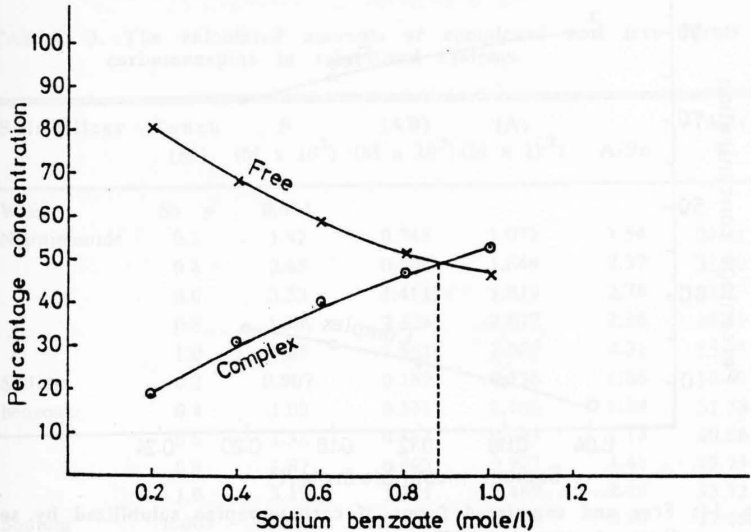


Fig. 12: Free and complexed forms of carbamazepine solubilized by sodium benzoate at 25°

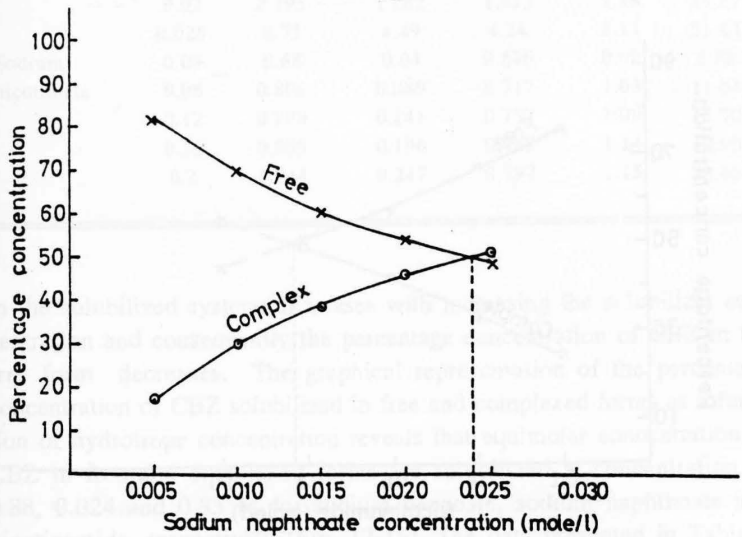


Fig. 13: Free and complexed forms of carbamazepine solubilized by sodium naphthoate at 25°

Egypt. J. Pharm. Sci. 35, No. 1-6 (1994)

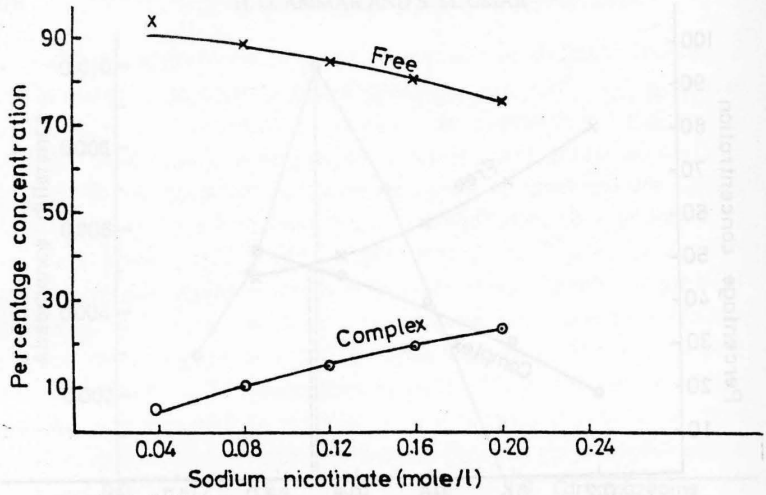


Fig. 14: Free and complexed forms of carbamazepine solubilized by sodium nicotinate at 25°

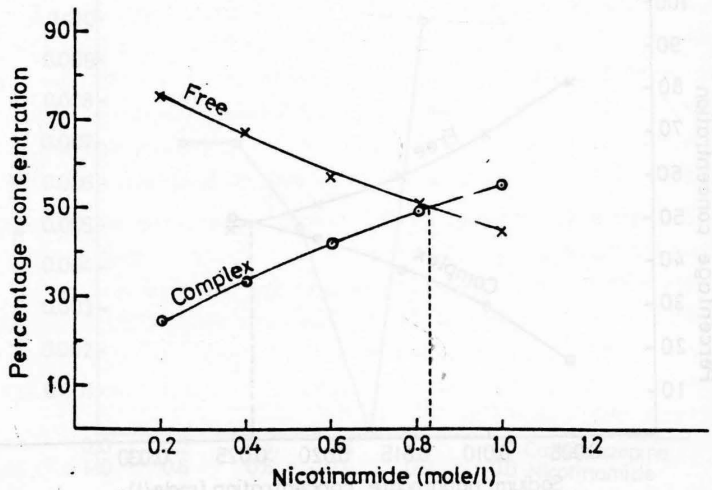


Fig. 15: Free and complexed forms of carbamazepine solubilized by nicotinamide at 25°

Egypt. J. Pharm. Sci. 35, No. 1-6 (1994)

TABLE 3. The calculated amounts of complexed and free forms of carbamazepine in solubilized systems.

Solubilizer	Concn (M)	S (M x 10 ³)	(AB) (M x 10 ³)	(A) (M x 10 ³)	A/So	(AB) %
Water	So =	0.694				
Nicotinamide	0.2	1.42	0.348	1.072	1.54	24.51
	0.4	2.45	0.806	1.644	2.37	32.90
	0.6	3.33	1.411	1.919	2.76	42.37
	0.8	5.30	2.623	2.677	3.86	49.49
	1.0	6.65	3.661	2.989	4.31	55.05
Sodium benzoate	0.2	0.907	0.169	0.738	1.06	18.63
	0.4	1.09	0.342	0.748	1.08	31.38
	0.6	1.32	0.537	0.783	1.13	40.68
	0.8	1.87	0.893	0.977	1.41	47.75
	1.0	3.19	1.701	1.489	2.15	53.32
Sodium naphthoate	0.005	0.761	0.133	0.628	0.90	17.48
	0.01	1.082	0.322	0.76	1.09	29.76
	0.015	1.614	0.627	0.987	1.42	38.85
	0.02	2.795	1.282	1.513	2.18	45.87
	0.025	8.73	4.49	4.24	6.11	51.43
Sodium nicotinate	0.04	0.68	0.04	0.640	0.92	5.88
	0.08	0.806	0.089	0.717	1.03	11.04
	0.12	0.898	0.141	0.757	1.09	15.70
	0.16	0.985	0.196	0.789	1.14	19.90
	0.2	1.044	0.247	0.797	1.15	23.66

in the solubilized systems increases with increasing the solubilizer concentration and consequently the percentage concentration of CBZ in the free form decreases. The graphical representation of the percentage concentration of CBZ solubilized in free and complexed forms as a function of hydrotrope concentration reveals that equimolar concentration of CBZ in free and complexed forms are solubilized at concentration of 0.88, 0.024 and 0.83 M for sodium benzoate, sodium naphthoate and nicotinamide, respectively (Fig. 12-15). The data presented in Table 3 show that the increased solubility of CBZ by sodium nicotinate is more

Egypt. J. Pharm. Sci. 35, No. 1-6 (1994)

or less entirely due to complex-formation between the drug and the hydrotrope, since the ratio of $(A)/S_0$ is about unity. On the other hand, there seems to exist another factor beside complex-formation promoting solubilization of the drug in presence of the other hydrotropes, since the ratio of the drug solubilized in free form to the solubility of the drug in water in these systems is higher than unity. This factor is most probably related to the decrease in the activity coefficient of the drug in presence of these hydrotropes (6). On the other hand, the data presented in Table 3 may explain to a great extent the lower solubilizing power of sodium nicotinate towards the drug relative to the other investigated compounds, since its solubilizing effect is only due to complex-formation.

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تأثير المواد الأيدروتروبية على ذوبان الكارابامازبين. الجزء الثانى : تأثير النيكوتيناميد واملاح الصوديوم لأحماض البنزويك والنافثويك والنيكوتينيك .

حسين عثمان عمار ، سناء محمد مصطفى عمر

قسم العلوم الصيدلية - المركز القومى للبحوث - الدقى - القاهرة

- مصر

يتناول البحث دراسة تأثير النيكوتيناميد واملاح الصوديوم
لأحماض البنزويك - النافثويك والنيكوتينيك على ذوبان
الكارابامازبين فى الماء . وقد وجد ان هذه المواد جميعا تزيد من ذوبان
الكارابامازبين وبحساب قوة الاذابة لهذه المواد وجد انها تعتمد
اعتماداً كبيراً على شكلها الكيميائى بمعنى ان استبدال حلقة
البنزين بالنفتالين او البردين يزيد من قوة اذابة المادة
الايدروتروبية.

وقد تم ايضا دراسة التفاعلات الجزيئية بين هذه المذيبات
والكارابامازبين بواسطة الامتصاص الضوئى فى المجال فوق
البنفسجى . كما تم دراسة تراكبات هذه المواد مع الكارابامازبين وقد
وجد ان الكارابامازبين يتراكب بنسبة ٢ : ١ مع النيكوتيناميد او
نافثوينات الصوديوم وكذلك بنسبة ١ : ١ مع نيكوتينات الصوديوم
ومن جهة اخرى هناك نوعين من التراكبات تتكون بين
الكارابامازبين وبنزوات الصوديوم بنسبة ١ : ٢ وايضا بنسبة ٢ : ١
وقد تم تعيين عامل الثبات لهذه التراكبات بطريقة الامتصاص
الضوئى وقد ظهر علاقة وثيقة بين قوة الاذابة لهذه المواد وعامل
الثبات لتراكباتها مع الكارابامازبين .

وقد تبين ان الزيادة فى ذوبان العقار فى وجود هذه المواد يرجع
الى عاملين اساسيين وهما تكوين متراكبات مع هذه المواد
الايدروتروبية بالاضافة الى نقصان معامل النشاط للدواء فى وجود
هذه المركبات.