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Solubility study of tolbutamide in monocomponent and dicomponent solutions of water

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Abstract

Solubility of tolbutamide was studied in different monocomponent (aqueous solutions of surfactant or β-cyclodextrin) and dicomponent solutions (aqueous solutions of surfactant with β-cyclodextrin). Surfactants used were Tween 20 (Polysorbate 20), Brij 35 (Poloxyl 23 lauryl ether) and sodium lauryl sulphate. In dicomponent solutions, surfactant/β-cyclodextrin ratios were 1:1, 1:2, 1:3 mol/mol. Results of drug solubility from demineralised water and monocomponent solutions containing different surfactants in various concentrations were almost the same, even though most of the used concentrations were above the critical micelle concentrations of some of the surface active agents. Although tolbutamide/β-cyclodextrin inclusion compound was formed in the monocomponent solutions of β-cyclodextrin, however, the formation of an inclusion compound was impeded in the Brij 35/β-cyclodextrin and sodium lauryl sulphate/β-cyclodextrin dicomponent solutions. Data indicate that surfactants compete with drug molecules to form inclusion compounds with β-cyclodextrin and eventually modify the drug solubility. Results also demonstrate that the resultant competitive binding depends on the chemistry of surface active agents. © 1998 Elsevier Science B.V.

Keywords: Tolbutamide/β-CD inclusion compound; Tween 20; Brij 35; Sodium lauryl sulphate; Solubility; Surfactant/β-CD interaction

1. Introduction

In the last few decades a tremendous number of studies have been carried out on cyclodextrins and on their inclusion compounds with pharmacologically active substances. Most of these were attempts to enhance the dissolution of poorly water-soluble drugs (Johnson et al., 1994), to improve the drug stability (Oh et al., 1994) and bioavailability (Kedzierewicz et al., 1993). Few have studied the complexation between cyclodex-

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trins and pharmaceutical excipients and their subsequent influence on pharmaceutical formulations. Tolbutamide is a very poorly water-soluble drug and its structural geometry allows it to form an inclusion compound with β-cyclodextrin (Gandhi and Karara, 1988; Kedzierewicz et al., 1990). The bioavailability studies show that the drug is absorbed rapidly from the complex; the t_{max} value obtained from tolbutamide/β-cyclodextrin inclusion compound (5 h) was shorter than that obtained from 5% aqueous solution of tolbutamide (7 h) (Kedzierewicz et al., 1993).

Serajuddin et al. (1988) showed that dissolution from drug polymer solid dispersion containing a surfactant was higher than that obtained from the same without the amphiphile. In pharmaceutical formulations, use of surfactants to improve the drug dissolution is a classical method. Sodium lauryl sulphate, polysorbate 20 and poloxyl 23 lauryl ether are well established pharmaceutical excipients used as surfactants. In commercial oral solid dosage forms, some surfactants are used extensively to optimise the dissolution of very poorly water soluble drugs. So, it is noted that polysorbate 80 is used in the formulation of nifedipine tablets and the use of sodium lauryl sulphate is also very common in different tablet formulations such as lidoflazine, griseofulvin and albendazole (Vidal Dictionaire, 1991). In recent years, use of surfactant in the dissolution media for in vitro dissolution testing of water-insoluble drug has increased because of its mechanistic similarity to in vivo dissolution (Crisen et al., 1997). Official compendia sometimes recommend carrying out dissolution tests of certain drugs like griseofulvin, estradiol, megestrol acetate and norethindrone acetate with a low concentration of sodium lauryl sulphate in the dissolution medium (US Pharmacopoeia, 1995). It can be assumed that the presence of surface active agents in the dissolution media or in the formulation of tolbutamide, may affect the release behaviour of this oral hypoglycaemic agent.

On the other hand, it is well documented that the formation of inclusion compounds between β-cyclodextrin and a chemical entity depends on the proper fitting of the substrate into the cavity of cyclodextrin. Some surfactants with adequate chemical features are found to form inclusion compound with β-cyclodextrin (Dharmawardana et al., 1993). So, the simultaneous presence of a drug like tolbutamide and a surface active agent with proper chemical geometry in a formulation containing β-cyclodextrin, may lead to competition between drug and the amphiphile molecules to form inclusion compound with β-cyclodextrin in aqueous solution. This competition may cause a modification of the release pattern of the drug from the formulation.

The aim of this paper was to determine the consequences of the simultaneous presence of a surfactant and β-cyclodextrin in pharmaceutical formulations. With this objective, tolbutamide solubility was studied in different monocomponent solutions of surfactants or β-cyclodextrin and dicomponent solution of surfactants and β-cyclodextrin. Three very different surface active agents i.e. sodium lauryl sulphate (ionic surfactant with linear structure), Tween 20 (polysorbate 20: non-ionic surfactant with non linear structure) and Brij 35 (poloxyl 23 lauryl ether: non-ionic surfactant having linear structure) were chosen in order to study the influence of the nature of surfactants over the competitive binding between drug molecules and surfactants.

2. Materials and methods

2.1. Materials

Tolbutamide, Tween 20 and Brij 35 were purchased from Sigma Chemical (St. Louis, MO, USA). Sodium lauryl sulphate and β-cyclodextrin (β-CD) were supplied by Panreac (Barcelona, Spain) and Janssen (Olen, Belgium) respectively.

2.2. Methods

2.2.1. Solubility study

Monocomponent solutions were prepared by adding either surfactants or β-CD into 1 l of demineralised water. The quantities of different amphiphiles used are shown in the Tables 1–3. Dicomponent solutions were prepared by adding surfactant and β-CD in different ratios. For this

purpose, the quantities of β-CD were chosen in order to have the following surfactant/β-CD molecular ratios: 1:1, 1:2, 1:3 mol/mol (Tables 1–3). The amounts of the β-CD used in the monocomponent solutions were the same as that of dicomponent solutions. A volume of 30 ml solution was taken in a series of test tubes where 50 mg of tolbutamide was added. After closing the tubes, they were shaken at room temperature in an oscillating water bath (15 opm). To make sure that an equilibrium was established, samples (4 ml) were withdrawn after seven days. Every sample was filtered by Millipore filter (HA 0.45 μm) and after suitable dilution with water, the quantity of dissolved tolbutamide was assayed at a wavelength of 228 nm in a Beckman DU-6 Spectrophotometer. Three replicates of the study were made. To nullify the absorbance due to excipients, every time the instrument was calibrated by the corresponding blank (monocomponent or dicomponent aqueous solution of surfactant and β-CD). It was tested previously that there was no change in λ_{max} of tolbutamide due to the presence of β-CD, Tween 20, Brij 35 and sodium lauryl sulphate in the solution or due to the dilution of samples with water.

Table 1
Tolbutamide solubility obtained from Tween 20/β-CD dicomponent solutions and corresponding monocomponent solutions of Tween 20 and β-CD

Tween 20[a]	β-CD[b]	Solubility[c]	Solubility[d]	Solubility[e]
0.044	0.044	0.327	0.312	0.313
0.044	0.088		0.299	0.340
0.044	0.132		0.333	0.319
0.222	0.222	0.311	0.341	0.352
0.222	0.444		0.371	0.331
0.222	0.666		0.353	0.379
0.444	0.444	0.325	0.371	0.345
0.444	0.888		0.412	0.380
0.444	1.332		0.457	0.407
0.666	0.666	0.316	0.353	0.362
0.666	1.332		0.457	0.384
0.666	1.998		0.459	0.444
0.888	0.888	0.372	0.412	0.394
0.888	1.776		0.462	0.406
0.888	2.664		0.511	0.497
1.332	1.332	0.411	0.457	0.385
1.332	2.664		0.511	0.466
1.332	3.996		0.665	0.406

[a] Concentration of Tween 20 in the solution (10^{-3} M).
[b] Concentration of β-CD in the solution (10^{-3} M).
[c] Tolbutamide solubility from monocomponent solutions of Tween 20 (10^{-3}M).
[d] Tolbutamide solubility from corresponding monocomponent solutions of β-CD (10^{-3}M).
[e] Tolbutamide solubility from dicomponent solutions of Tween 20 and β-CD (10^{-3}M).

Table 2
Tolbutamide solubility obtained from Brij 35/β-CD dicomponent solutions and corresponding monocomponent solutions of Brij 35 and β-CD

Brij 35[a]	β-CD[b]	Solubility[c]	Solubility[d]	Solubility[e]
0.042	0.042	0.268	0.334	0.291
0.042	0.084		0.323	0.307
0.042	0.126		0.336	0.305
0.208	0.208	0.301	0.329	0.274
0.208	0.416		0.343	0.265
0.208	0.624		0.338	0.289
0.417	0.417	0.301	0.343	0.288
0.417	0.834		0.372	0.303
0.417	1.251		0.388	0.338
0.626	0.626	0.301	0.338	0.276
0.626	1.252		0.388	0.303
0.626	1.878		0.427	0.320
0.835	0.835	0.322	0.371	0.296
0.835	1.670		0.441	0.379
0.835	2.505		0.486	0.405
1.252	1.252	0.306	0.388	0.285
1.252	2.504		0.486	0.343
1.252	3.756		0.653	0.418

[a] Concentration of Brij 35 in the solution (10^{-3} M).
[b] Concentration of β-CD in the solution (10^{-3} M).
[c] Tolbutamide solubility from monocomponent solutions of Brij 35 (10^{-3}M).
[d] Tolbutamide solubility from corresponding monocomponent solutions of β-CD (10^{-3}M).
[e] Tolbutamide solubility from dicomponent solutions of Brij 35 and β-CD (10^{-3}M).

3. Results and discussion

Drug solubility was controlled by the nature of the ingredient(s) present in the solutions. Solubility data using demineralised water (0.276×10^{-3} M) and monocomponent solutions having different surfactants were almost the same (Tables 1–3), even though most of the used concentrations

of two surfactants (Tween 20 and Brij 35) were above the critical micelle concentrations (CMC) of the surface active agents (CMCs of Tween 20, Brij 35 and sodium lauryl sulphate are 0.053×10^{-3}, 0.108×10^{-3} and 7.987×10^{-3} M respectively); (Wan and Lee, 1974; Reiger, 1988; Handbook of Pharmaceutical Excipients, 1994). Slopes (b) of the tolbutamide solubility versus surfactant concentration curve and correlation coefficient value (r) were calculated (Table 4). From the r and b values it is observed that the amount of surfactant added practically had no influence over drug solubility.

From aqueous solutions of β-CD, a characteristic solubility pattern was observed due to the formation of tolbutamide/β-CD inclusion compound and the phase solubility diagram (Fig. 1) was of Bs type (Higuchi and Connors, 1965). The increase in the initial ascending portion of the curve was due to the interaction with β-CD and the formation of soluble inclusion complex which has higher solubility than the drug alone. When the solubility limit of the formed complex is exceeded, the ascending linear portion of the curve flattens out and the further addition of β-CD results in the precipitation of a complex. The complex continues to form and precipitates from the saturated solution as the concentration of β-CD increased. These results are in agreement with the results obtained by Gandhi and Karara (1988), Kedzierewicz et al. (1990).

Tables 1–3 and Figs. 2–4 show comparative data of tolbutamide solubility obtained from different monocomponent solutions of β-CD and dicomponent solutions of β-CD and surfactant.

Table 3
Tolbutamide solubility obtained from sodium lauryl sulphate/β-CD dicomponent solutions and corresponding monocomponent solutions of sodium lauryl sulphate and β-CD

SLS[a]	β-CD[b]	Solubility[c]	Solubility[d]	Solubility[e]
0.174	0.174	0.309	0.387	0.333
0.174	0.348		0.363	0.335
0.174	0.522		0.382	0.351
0.868	0.868	0.309	0.417	0.389
0.868	1.736		0.494	0.418
0.868	2.604		0.557	0.487
1.736	1.736	0.329	0.494	0.359
1.736	3.472		0.614	0.461
1.736	5.208		0.729	0.597
2.604	2.604	0.345	0.557	0.367
2.604	5.208		0.729	0.501
2.604	7.812		0.731	0.705
3.472	3.472	0.347	0.614	0.399
3.472	6.944		0.742	0.671
3.472	10.416		0.664	0.919
5.208	5.208	0.502	0.729	0.345
5.208	10.416		0.664	0.755
5.208	15.624		0.555	0.912

[a] Concentration of sodium lauryl sulphate in the solution (10^{-3} M).
[b] Concentration of β-CD in the solution (10^{-3} M).
[c] Tolbutamide solubility from monocomponent solutions of sodium lauryl sulphate (10^{-3}M).
[d] Tolbutamide solubility from corresponding monocomponent solutions of β-CD (10^{-3}M).
[e] Tolbutamide solubility from dicomponent solutions of sodium lauryl sulphate and β-CD (10^{-3}M).

Table 4
Linear regression for tolbutamide solubility (M) versus concentration of surfactant (M) curve

Surfactant	r	Intercept (a)	Slope (b)
Tween 20	0.865	0.00031	0.0728
Brij 35	0.679	0.00028	0.0278
SLS[a]	0.886	0.00027	0.0353

[a] Sodium lauryl sulphate.

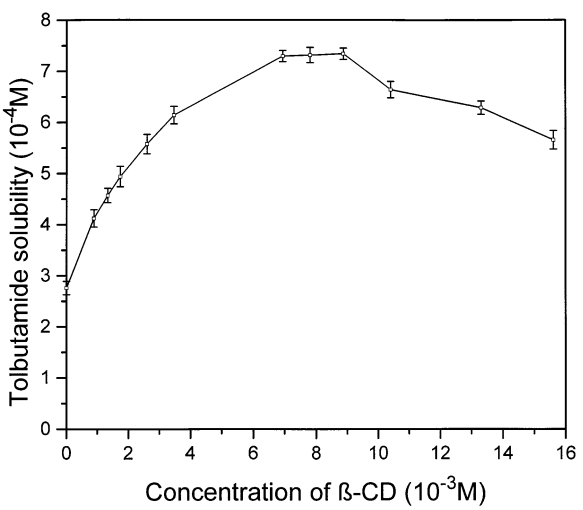

Fig. 1. Tolbutamide phase solubility diagram obtained from monocomponent solutions of β-CD.

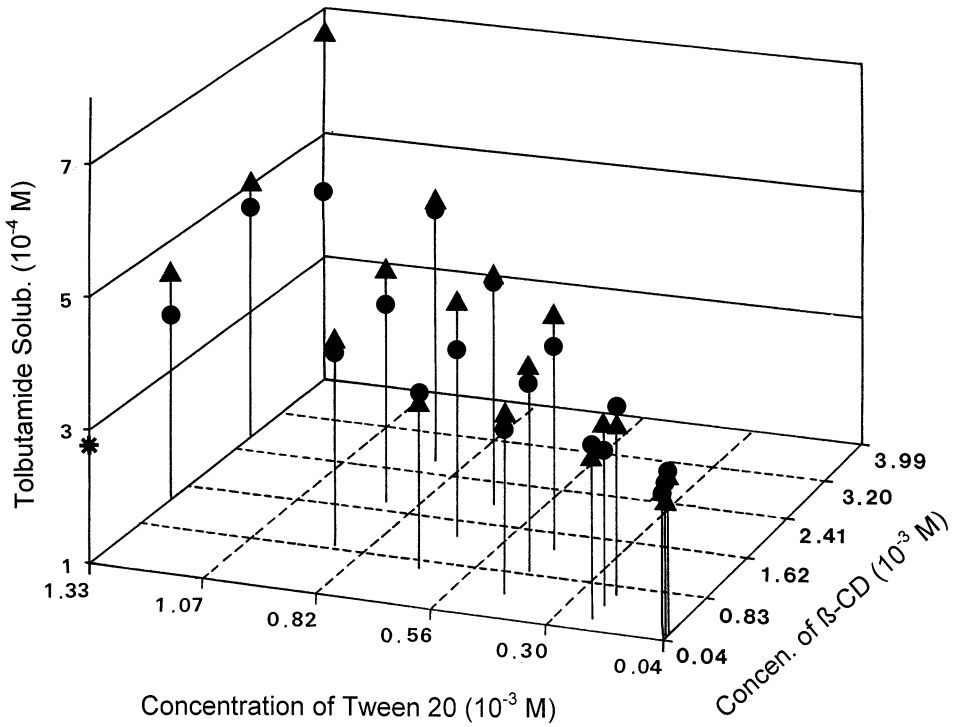

Fig. 2. Tolbutamide solubility data obtained from different monocomponent solutions of β-CD (▲), dicomponent solutions of Tween 20 and β-CD (●) and from demineralised water (*).

In these three dimensional diagrams, each vertical line represents two solubility values: tolbutamide solubility obtained from monocomponent solutions of β-CD and solubility obtained from dicomponent solutions of surfactant and β-CD. The asterisk mark in the vertical axis represents the solubility from demineralised water.

Fig. 2 exhibits the influence of the addition Tween 20 over tolbutamide/β-CD inclusion phenomenon. From the result, it can be speculated that the presence of Tween 20 does not modify tolbutamide solubility obtained from monocomponent solutions of β-CD. Only a significant difference in solubility was obtained when the amount of β-CD and Tween 20 was maximum (3.99×10^{-3} M of β-CD and 1.33×10^{-3} M of Tween 20). In these cases, the presence of Tween 20 causes a decrement in solubility by displacing tolbutamide molecules from β-CD. The results indicate that incorporation of Tween 20 up to a certain amount in the formulation of tolbutamide with β-CD will not affect the formation of tolbutamide/β-CD inclusion compound. In this case a competitive binding was not produced due to the bulky nature of the surfactant. In the higher concentrations, micelles of Tween 20 could have interacted with β-CD resulting a decrement in drug solubility.

Solubility data from dicomponent solutions of β-CD and Brij 35 and from monocomponent solutions of β-CD are displayed in Fig. 3. By comparing tolbutamide solubility obtained from different solutions, it is observed that solubility was lower in all dicomponent solutions than that of the monocomponent solutions containing the same amount of β-CD. This lowering in solubility was higher at higher concentrations of β-CD and Brij 35. These results indicate that Brij 35 competes with tolbutamide for binding with β-CD and incorporation of this surfactant in a formulation of tolbutamide with β-CD will cause a decrement in the drug solubility.

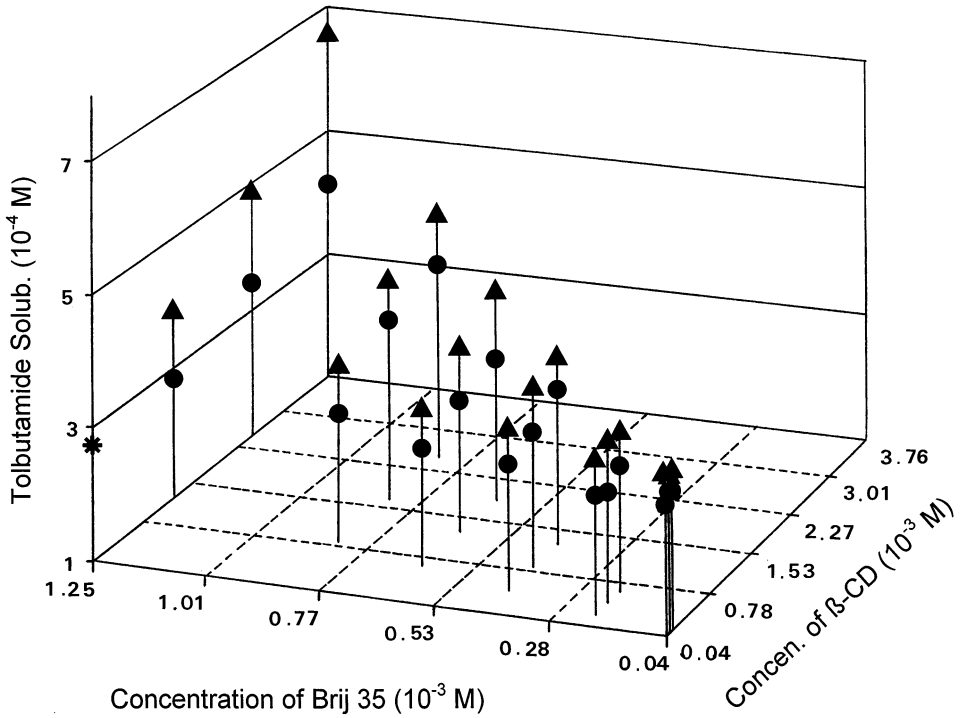

Fig. 3. Tolbutamide solubility data obtained from different monocomponent solutions of β-CD (▲), dicomponent solutions of Brij 35 and β-CD (●) and from demineralised water (*).

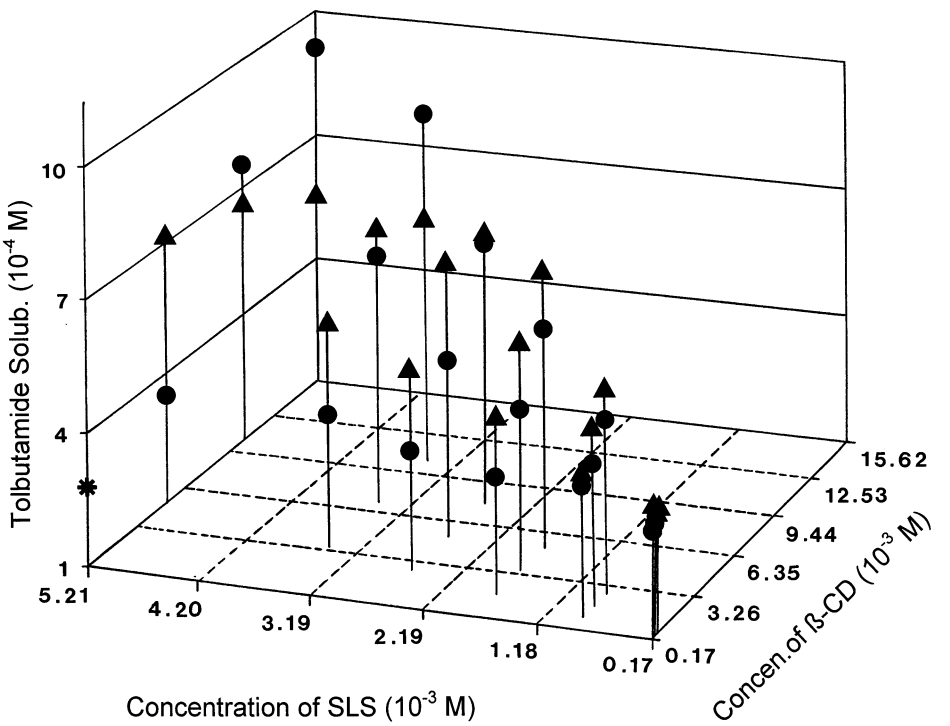

Fig. 4. Tolbutamide solubility data obtained from different monocomponent solutions of β-CD (▲), dicomponent solutions of sodium lauryl sulphate (SLS) and β-CD (●) and from demineralised water (*).

Like Brij 35, presence of sodium lauryl sulphate in the solution with β-CD gives rise to a competition between surfactant molecules and tolbutamide to enter into the apolar cavity of β-CD (Fig. 4). As a result of this competitive binding, in most of the cases solubility from dicomponent solutions was lower than that of the monocomponent solutions having the same amount of β-CD alone. However, in three cases, tolbutamide solubility was increased due to the addition of sodium lauryl sulphate to the solution of β-CD. In these three exceptional cases, an insoluble tolbutamide/β-CD inclusion compound was formed (Fig. 1; Gandhi and Karara, 1988; Kedzierewicz et al., 1990) in the corresponding monocomponent solutions containing β-CD (10.41×10^{-3} and 15.61×10^{-3} M). The presence of sodium lauryl sulphate in these three dicomponent solutions sequesters the excess amount of β-CD molecules and, in consequence, a soluble tolbutamide/β-CD inclusion compound is formed that eventually leads to an increment in drug solubility.

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