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COMMUNICATION

Study of Surfactants/β-Cyclodextrin Interactions over Mequitazine Dissolution

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ABSTRACT

Surfactant/β-cyclodextrin interactions were investigated by studying the dissolution of mequitazine in different binary (aqueous solutions of β-CD or surfactants) and ternary (aqueous solution of β-CD and surfactants) dissolution media. Results were compared with those obtained from binary media with 50, 250, and 500 mg of surfactants (preceding paper). Results show that there is an interaction between β-cyclodextrin and surface-active agent, and that the type and extent of interaction are controlled by the nature and the amount of the surface-active agent. A decrement in drug dissolution rate was obtained from all of the ternary media containing β-cyclodextrin and sodium lauryl sulfate as surfactant in the ratio of 1:1 mol/mol. These facts suggest that sodium lauryl sulfate and β-cyclodextrin form an inclusion compound in the molecular ratio of 1:1.

INTRODUCTION

Cyclodextrins have attracted growing interest in pharmaceutical technology due to their ability to form inclusion compounds with a number of guest molecules by incorporating them into their central cavities. This phenomenon can be utilized to enhance the dissolution of poorly water-soluble drugs (1) and to improve stability (2) and drug bioavailability (3).

The ability of a guest molecule to enter into the cavity of a cyclodextrin depends on its size, shape, and stereochemical features. It is possible that a surfactant molecule with proper size and structural geometry can form inclusion compounds with cyclodextrins. If a poorly water-soluble drug and a surfactant are added in an aqueous solution of a cyclodextrin, there may be a competition between drug and surfactant molecules in forming the inclusion compound with cyclodextrin.

With this objective, in our previous paper (4) we studied the influence of surfactants over the dissolution of mequitazine. Here, an attempt has been made to study the interaction between β-cyclodextrin and different sur-

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factants owing to simultaneous presence of both substances in the dissolution media of the drug.

MATERIALS

Mequitazine (M) was a gift from Rhône Poulenc Rorer (Madrid, Spain). β-cyclodextrin (β-CD) was purchased from Janssen (Olen, Belgium). Sodium lauryl sulfate (SLS) was supplied by Panreac (Barcelona, Spain), and Brij 35 (B-35) was purchased from Sigma (St. Louis, MO, USA).

METHODS

The dissolution process of M was studied by using different media. The quantities of β-CD in binary dissolution media were chosen in order to have the following molecular ratios of M/β-CD in the dissolution media: 1:1, 1:10, and 1:100 mol/mol. In all ternary dissolution media, the molecular ratio of surfactant/β-CD was 1:1, 1:2, or 1:3 (Table 1). All of the conditions of the dissolution tests were similar to those of the preceding study (4) and quantity of M was assayed as before.

RESULTS AND DISCUSSIONS

The influence of β-CD on dissolution of M is shown in Fig. 1. In these binary media, drug dissolution rate increases in accordance with the quantity of β-CD added. This enhancement may be due to the formation of a soluble inclusion compound between β-CD and M.

The dissolution behavior of mequitazine in ternary dissolution media with β-CD and a surface-active agent depends on the nature and the amount of surface-active agent and the proportion of β-CD added. The results obtained from ternary media with 50 mg of B-35 and β-CD (Fig. 2) indicate that when β-CD was added to the dissolution medium containing an amount of B-35 below its critical micelle concentration (CMC), no change in drug dissolution was observed in respect to the data obtained from the equivalent binary medium. It seems that in these ternary media, there is no interaction between β-CD molecules and B-35, or β-CD and drug molecules. Hence, the addition of β-CD does not affect the wettability and dissolution of drug.

The presence of β-CD in ternary dissolution media containing 250 mg of B-35 (concentration above its CMC) decreases drug dissolution rate with regard to the

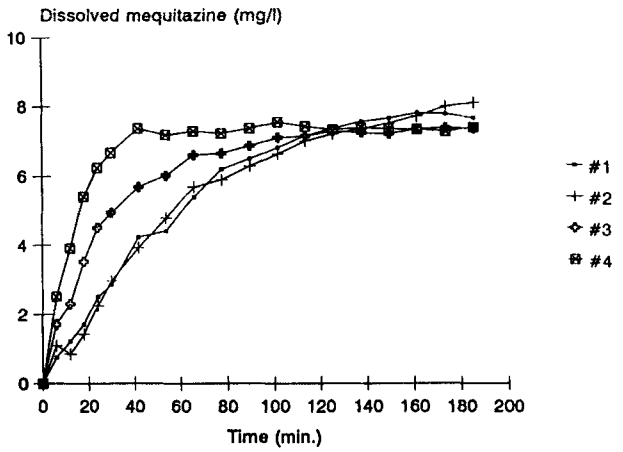

Figure 1. Dissolution profiles of M obtained from distilled water and binary dissolution media with β-CD. Numbers shown are the numbers of corresponding dissolution media.

results obtained from the corresponding binary medium (Fig. 3). The dissolution patterns obtained from ternary media with 500 mg B-35 and β-CD (Fig. 4) are similar to that obtained from ternary media with 250 mg of B-35. That is, the extent of drug dissolution from these media was greater than that obtained from distilled water but lower than that from the binary media with the same amount of B-35.

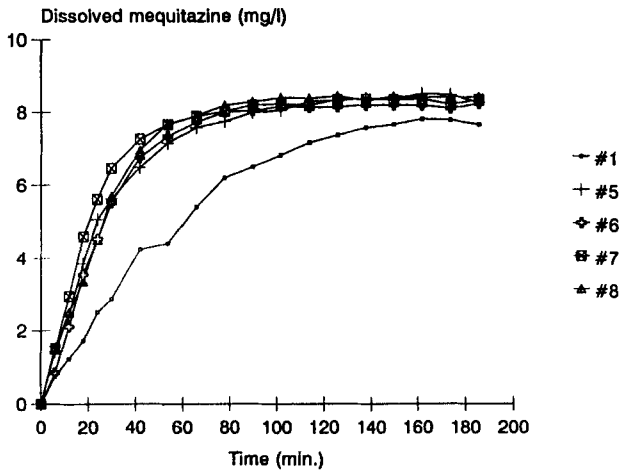

Figure 2. Dissolution profiles of M obtained from distilled water, binary dissolution medium with 50 mg of B-35, and ternary dissolution media with β-CD and 50 mg of B-35. Numbers shown are the numbers of corresponding dissolution media.

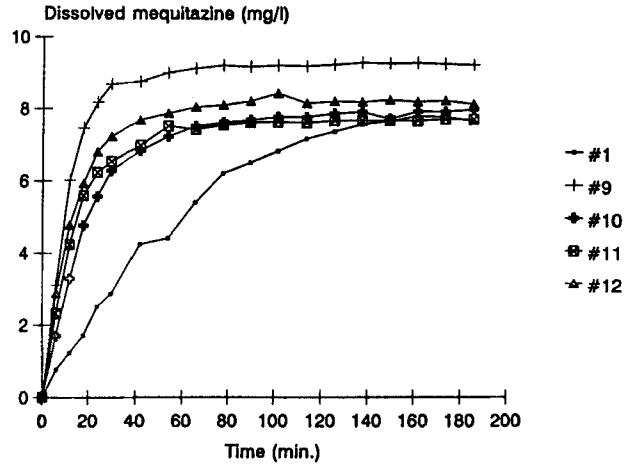

Figure 3. Dissolution profiles of M obtained from distilled water, binary dissolution medium with 250 mg of B-35, and ternary dissolution media with β-CD and 250 mg of B-35. Numbers shown are the numbers of corresponding dissolution media.

From the results displayed in Figs. 3 and 4, it can be thought that there is an interaction between β-CD molecules and micelles of B-35. The values of drug dissolution efficiency obtained from the study of all the ternary media containing β-CD and surfactant are similar and independent of the amount of β-CD added (Table 1). This indicates that simultaneous addition of β-CD and surfactant above a certain concentration does not improve the dissolution rate because of an interaction between molecules of β-CD and micelles of B-35. Only free molecules of both substances can enhance drug dissolution.

From the results of ternary media with SLS, it is observed that the addition of β-CD increases the drug dissolution in comparison to the respective binary medium when the SLS/β-CD ratios were 1:2 and 1:3, and the drug dissolution rate was minimum when SLS/β-CD ratio was 1:1 (Figs. 5–7). With an increase in the amount of β-CD added, an elevation in drug dissolution was observed, and maximum amount of drug was dissolved when the ratio was 1:3. A decrement was noticed in the values of drug dissolution efficiency obtained from ternary media in comparison to the corresponding binary media when SLS/β-CD ratio was 1:1 (Table 1). From these data, it is very clear that in the media containing SLS and β-CD, the interaction between β-CD and SLS was maximum, and this interaction might be due to the formation of an inclusion compound (1:1) between β-CD and SLS molecules.

CONCLUSIONS

At the concentrations studied, β-CD increases drug dissolution, and this may account for the formation of a soluble inclusion compound of M/β-CD.

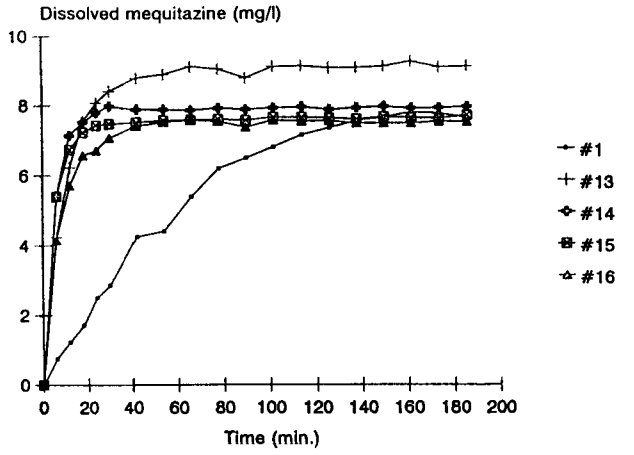

Figure 4. Dissolution profiles of M obtained from distilled water, binary dissolution medium with 500 mg of B-35, and ternary dissolution media with β-CD and 500 mg of B-35. Numbers shown are the numbers of corresponding dissolution media.

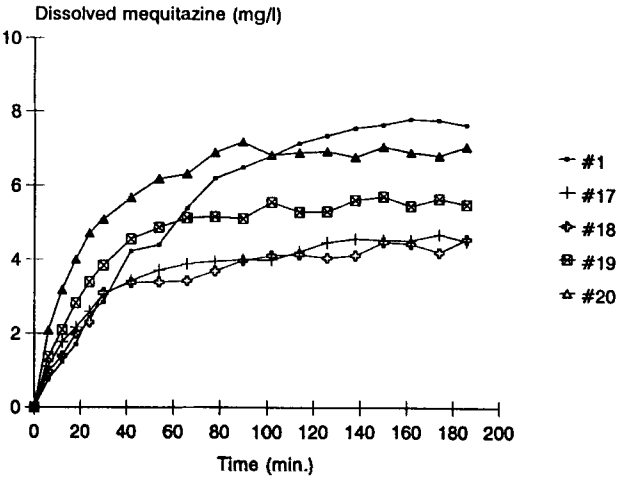

Figure 5. Dissolution profiles of M obtained from distilled water, binary dissolution medium with 50 mg of SLS, and ternary dissolution media with β-CD and 50 mg of SLS. Numbers shown are the numbers of corresponding dissolution media.

Table 1

Composition and Dissolution Efficiency Values of Various Media

Medium	B-35[a]	SLS[a]	β-CD[a]	Ratio	*DE* (%)
1	—	—	—	—	56.76
2	—	—	40.97	—	55.97
3	—	—	409.7	—	61.87
4	—	—	4097	—	68.26
5	50	—	—	—	70.98
6	50	—	55.16	1:1	70.12
7	50	—	110.32	1:2	73.14
8	50	—	165.48	1:3	72.39
9	250	—	—	—	86.05
10	250	—	275.8	1:1	69.64
11	250	—	551.60	1:2	70.07
12	250	—	827.4	1:3	75.60
13	500	—	—	—	85.4
14	500	—	551.60	1:1	76.69
15	500	—	1103.2	1:2	73.71
16	500	—	1654.8	1:3	71.47
17	—	50	—	—	37.68
18	—	50	229.3	1:1	35.73
19	—	50	458.7	1:2	47.71
20	—	50	688.1	1:3	61.22
21	—	250	—	—	65.60
22	—	250	1147	1:1	55.98
23	—	250	2294	1:2	68.73
24	—	250	3442	1:3	86.72
25	—	500	—	—	80.40
26	—	500	2294	1:1	59.65
27	—	500	4587	1:2	80.12
28	—	500	6880	1:3	92.88

[a]Amount (mg) added in 1 liter of water.

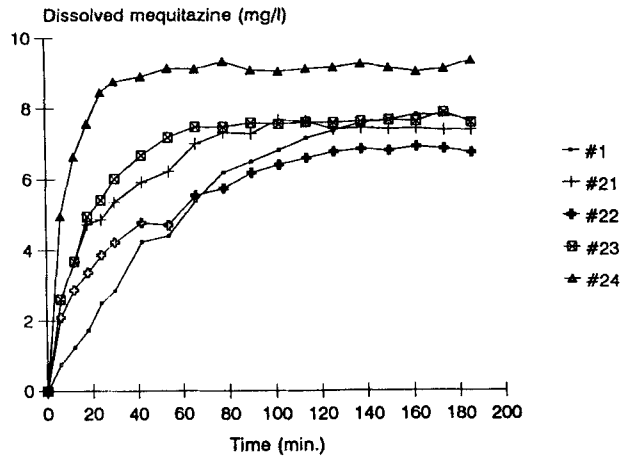

Figure 6. Dissolution profiles of M obtained from distilled water, binary dissolution medium with 250 mg of SLS, and ternary dissolution media with β-CD and 250 mg of SLS. Numbers shown are the numbers of corresponding dissolution media.

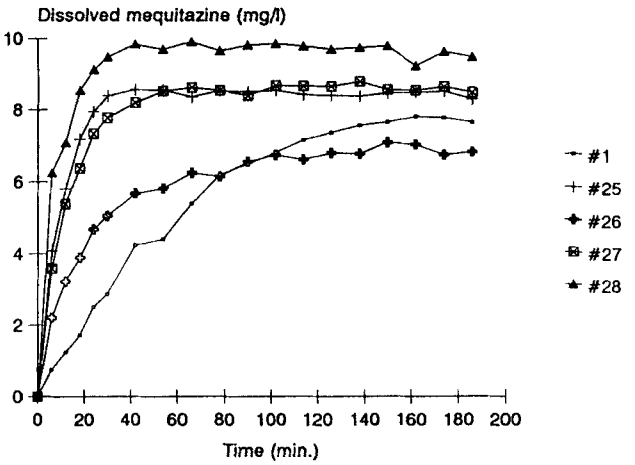

Figure 7. Dissolution profiles of M obtained from distilled water, binary dissolution medium with 500 mg of SLS, and ternary dissolution media with β-CD and 500 mg of SLS. Numbers shown are the numbers of corresponding dissolution media.

The simultaneous presence of β-CD and a surface-active agent in dissolution media causes a decrease in drug dissolution due to the interaction between cyclodextrin and the amphiphile.

β-CD interacts with B-35 only if there are micelles of the amphiphile in the medium. Due to steric hindrance, β-CD cannot form inclusion compound with molecules of B-35.

A remarkable decrease in mequitazine dissolution was obtained in ternary media with SLS and β-CD in a ratio of 1:1 mol/mol due to the formation of an inclusion compound among themselves.

The dissolution study of a poorly water-soluble drug in the ternary dissolution media with cyclodextrin and a surface-active agent has proven to be a useful method in knowing the interactions that may be produced among the components present in the dissolution media.

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