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Solubilization and dissolution of famotidine from solid glass dispersions of xylitol

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Summary

The aqueous solubility and dissolution of famotidine from solid glass dispersions of xylitol, prepared by the fusion method, were investigated. Both famotidine and xylitol exhibited minimal degradation during the fusion process. Famotidine alone and in the presence of xylitol was found to be relatively stable in water at 37 ± 0.5°C for at least 3 days: less than 4% degradation was observed at the end of 72 h. Solubility of famotidine from solid glass dispersions and physical mixtures containing varying proportions of famotidine and xylitol at 37 ± 0.5°C was found to be higher than that of famotidine alone in water. However, the solid glass dispersions were more effective in enhancing the solubility of famotidine. A 1:40 famotidine:xylitol dispersion produced greatest solubility enhancement (31%). The solubility of famotidine from physical mixtures increased linearly with the increase in xylitol concentration, but the relationship was not linear for glass dispersions. Dissolution studies on glass dispersions with famotidine:xylitol ratios of 1:1, 1:10 and 1:20 in water at 37 ± 0.5°C revealed a marked increase in the dissolution rate of famotidine from solid glass dispersions when compared to the dissolution rate of famotidine powder alone. The increase in the dissolution rate was greatest at the lowest drug level (1:20) with 100% of the drug dissolving within one minute. Thermograms of the solid glass dispersions obtained by differential scanning calorimetry showed no evidence of chemical interaction between famotidine and xylitol. The phase diagram of the dispersion system by the capillary tube method suggested the formation of a eutectic mixture of famotidine and xylitol at a drug:carrier ratio approaching 1:40.

Introduction

Famotidine (3-[[[2-[(aminoiminomethyl)amino]-4-thiazolyl]methyl]thio]-*N*-(aminosulfonyl) propionamide) is a relatively new and potent histamine-2 receptor antagonist (Campoli-Richards and Clissold, 1986). It is structurally related to cimetidine and ranitidine, but differs principally in having a nucleus which is a thiazole rather than an imidazole (cimetidine) or a furan (ranitidine) ring (Fig. 1). It has been found to be effective for acute treatment of duodenal ulcer (dose: 20 or 40 mg per day), maintenance therapy in duodenal ulcer and treatment of pathological hypersecretory conditions like Zollinger Ellison syndrome. Famotidine is incompletely absorbed, its oral bioavailability being 37–45%. It has an aqueous solubility of 0.1% w/v at 20°C (Vincek et al., 1985). It is possible to change the physicochemical properties of such poorly soluble drugs in order to improve their solubility. One such approach to increasing the solubility is the incorporation of the poorly soluble drug into a highly water-soluble carrier such as urea to form a solid dispersion (Sekiguchi and Obi, 1961). Chiou and Riegelman (1969) pro-

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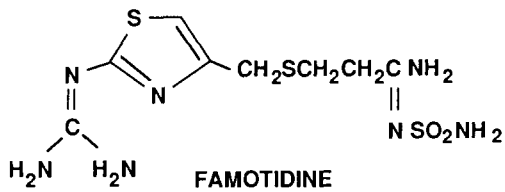

Fig. 1. Chemical structure of famotidine.

posed the use of organic glass-forming compounds as carriers for preparing binary glass systems with water-insoluble drugs. Besides achieving an extremely fine state of subdivision of ingredients, such formulations provide for an intimate contact between the drug and the carrier molecules or molecular aggregates thereby contributing to increased wettability and dispersibility of the hydrophobic drug. In this study, the solubility and dissolution of famotidine from xylitol glass dispersions were investigated. Xylitol, a pentahydric sugar alcohol, was used as the carrier because of its high water solubility, low melting point (93–94.5°C) and stability up to 180°C (Sirenius et al., 1979).

Materials and Methods

Materials

Famotidine powder (125–200 μm), used as received, was supplied by Merck Sharp and Dohme Laboratories (Rahway, NJ, U.S.A.). Xylitol was purchased from Sigma (St. Louis, MO, U.S.A.). All other chemicals/solvents were of reagent/HPLC grade and were obtained commercially. For the preparation of aqueous solutions, deionized water was filtered by a NANOpure Water Purification System (Barnstead, Division of Sybron, Boston, MA, U.S.A.).

Drug analysis

A reverse-phase high-performance liquid chromatographic method (Biffar and Mazzo, 1986) was used to quantitate the drug in aqueous solutions during stability studies. The HPLC system was equipped with a U6K injector, 6000A pump, model 450 variable wavelength detector and 730 data module (Waters Associates, Milford, MA, U.S.A.). The concentration of famotidine in the samples during solubility and dissolution studies was determined at a wavelength of 267 nm using a UV/Vis spectrophotometer (Model 25, Beckman Instruments Inc., Fullerton, CA, U.S.A.).

TABLE 1

Composition of solid-glass dispersions

Drug:carrier ratio	Ingredients (% w/w)	
	Famotidine	Xylitol
1:40	2.40	97.60
1:20	4.80	95.20
1:10	9.10	90.90
1:4	20.00	80.00
1:2	33.33	66.66
1:1	50.00	50.00
2:1	66.66	33.33
4:1	80.00	20.00

Preparation of solid-glass dispersions

A series of solid-glass dispersions of famotidine in xylitol were prepared (Table 1). Accurately weighed quantities of famotidine and xylitol in the required ratios were blended thoroughly using a glass pestle and mortar and transferred to small glass petri dishes (5 cm diameter). The drug-carrier physical mixtures were heated carefully to about 100°C with constant stirring until clear homogeneous melts (dispersions) were obtained. The melts were placed immediately in a desiccator over anhydrous calcium chloride at room temperature and stored for at least 3 days prior to pulverization and use in order to ensure complete solidification.

Stability studies

Stability studies were carried out to ensure that famotidine would remain stable during the subsequent equilibrium solubility determinations. The stability of famotidine alone in water and in an aqueous solution of the solid-glass dispersion (famotidine:xylitol ratio of 1:10) was studied. 1 ml aliquot samples of famotidine solution (0.65 mg/ml) or the solution of the solid-glass dispersion (equivalent to 0.62 mg/ml drug) were pipetted into a series of 100-ml volumetric flasks and placed in a constant temperature room at 37 ± 0.5°C. The flasks were withdrawn in triplicate at appropriate time intervals up to 72 h, volume made up to 100

ml with the mobile phase solvent and assayed for drug content by HPLC.

Solubility studies

Solubility studies (duplicate) were carried out on famotidine and famotidine-xylitol physical mixtures and glass dispersions by adding a known excess of the samples to 5 ml water in 20-ml screw-capped glass vials mounted on a shaker. The equilibration (4 h), and subsequent filtration through 0.22 μm filter (Swinex-25, Millipore Filter Corp., Bedford, MA, U.S.A.) and sampling were carried out in a constant-temperature room at 37 ± 0.5°C. Drug concentration in each of the samples was determined spectrophotometrically as stated under 'Drug analysis' after appropriate dilution with water.

Dissolution studies

Dissolution studies (triplicate) were carried out on famotidine and famotidine-xylitol glass dispersions using the USP/NF dissolution assembly (Hanson Research Corp., Northridge, CA, U.S.A.) at 37 ± 0.5°C in water. An accurately weighed quantity of the powdered sample (150–180 micron) equivalent to 20 mg of drug was added to 400 ml of water (dissolution medium) under constant agitation (50 rpm). 10-ml samples were withdrawn, with replacement, at regular time intervals over a 1 h period using a 10 ml syringe, filtered through 0.22 μm filter paper and assayed for drug content after appropriate dilution with water.

Thermal analysis of the solid glass dispersions

Thermal analysis was performed on the glass dispersions using a Perkin-Elmer differential scanning calorimeter (model DSC-2, Perkin-Elmer Corp., Norwalk, CT, U.S.A.). Samples (5–10 mg) were scanned at 10°C/min over the range of 40–170°C in a static air atmosphere using an empty aluminum pan as the reference. The collection and integration of the thermogram was computerized and recording was done with the help of a chart recorder (model 7470 A plotter, Hewlett-Packard, San Diego, CA, U.S.A.). Cooling was carried out at a rate of 160°C/min after each sample analysis.

The melting onset and complete fusion temperatures of the solid glass dispersions were visually determined with a magnifying glass using the conventional capillary tube melting-point apparatus (Arthur H. Thomas Co., Philadelphia, PA, U.S.A.).

Results and Discussion

Solid glass dispersion formation

Famotidine appeared to be wetted well by fused xylitol and was easily dispersible in the fused mixture. At a low drug content (<10%), the molten mixture was less viscous and its solidification was slow (4–6 days). When the drug content was increased, the melt was highly viscous and solidified faster (1–2 days). The glass dispersions with drug content of less than 50% were harder, more brittle, and more glassy than those with a higher drug content. No discoloration was observed in any of the dispersions.

Stability studies

Famotidine alone and in the presence of xylitol was found to be relatively stable in water at 37 ± 0.5°C for at least 3 days. Greater than 97.4 and 96.5%, respectively, of the drug could be accounted for at the end of 72 h (Table 2). The mass balance on the drug in the 0 h dispersion samples accounted for the drug used to prepare the glass dispersion. The potential famotidine degradate peaks were not detected in any of the chromatograms taken over the course of 72 h study at the wavelength studied possibly because of low levels and dilution of samples required for the assay.

TABLE 2

Stability of famotidine in water at 37 ± 0.5°C

Time (h)	Amount left (mg) ± S.D. (%)[a]	
	Famotidine powder	1:10 xylitol dispersion
0	16.250 ± 0.575 (100.0)	15.672 ± 0.566 (100.0)
12	16.372 ± 1.602 (100.8)	15.752 ± 0.902 (100.5)
24	16.272 ± 0.437 (100.1)	15.698 ± 0.928 (100.2)
36	15.902 ± 0.168 (97.9)	15.241 ± 1.514 (97.2)
48	15.820 ± 2.485 (97.4)	15.602 ± 0.356 (99.6)
60	16.790 ± 0.642 (103.3)	--
72	16.206 ± 0.320 (99.7)	15.130 ± 0.261 (96.5)

[a]Indicates mean of three determinations.

The pH of the aqueous solutions of the various physical mixtures or dispersions of famotidine and xylitol on the one hand and that of famotidine alone on the other was monitored and found to be 7.6 and 7.8 ± 0.1, respectively, over a period of 5 days under experimental conditions. No adjustments were made during stability, solubility or dissolution studies.

Solubility studies

The aqueous solubility of famotidine from physical mixtures and solid glass dispersions is shown in Table 3. Equilibrium was attained within 4 h in each case. The solubility of famotidine in water has been reported to be 0.1% w/v at 20°C (Vincek et al., 1985). In the present study, at 37°C, the solubility was found to be 1.353 ± 0.010 mg/ml (0.14% w/v), approx. 40% higher.

The solubility of famotidine from physical mixtures was higher than that of famotidine alone in water (Table 3 and Fig. 2).

As shown in Fig. 2, the presence of dissolved xylitol in water caused a linear increase in the solubility of famotidine analogous to the previously reported effect of xylitol on the aqueous solubility of hydrochlorothiazide (Bloch et al., 1982). The solubility of famotidine (S_f) could be related to the concentration of xylitol (C_x) by the equation:

TABLE 3

Solubility of famotidine from physical mixtures and solid glass dispersions in water at 37 ± 0.5°C

	Xylitol concentration (mg/ml)	Solubility (mg/ml)[a]
Famotidine	0	1.353 ± 0.010
1:1 mixture	3	1.371 ± 0.000
1:20 mixture	60	1.434 ± 0.019
1:40 mixture	120	1.548 ± 0.019
1:1 dispersion	3	1.442 ± 0.004
1:20 dispersion	60	1.474 ± 0.009
1:25 dispersion	75	1.475 ± 0.004
1:30 dispersion	90	1.471 ± 0.008
1:35 dispersion	105	1.714 ± 0.083
1:40 dispersion	120	1.782 ± 0.000

[a]Indicates mean ± S.D. of concentrations measured after 2 and 4 h.

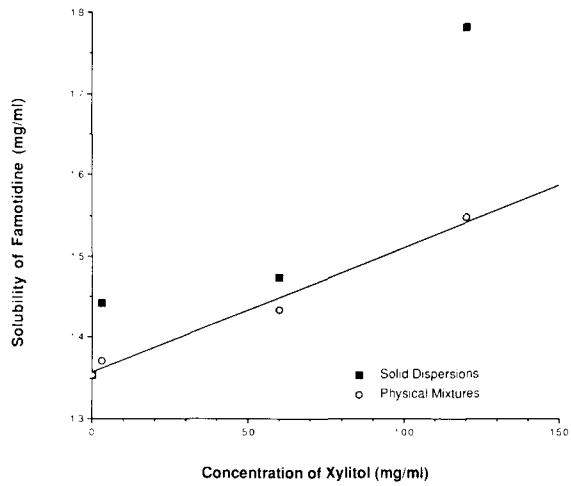

Fig. 2. Effect of xylitol on the aqueous solubility of famotidine from physical mixtures and solid glass dispersions at 37 ± 0.5°C.

$$S_f = 0.00154(\pm 0.000038)\,(C_x) \pm 1.3559(\pm 0.0096) \quad (1)$$

The glass dispersions were even more effective than physical mixtures of corresponding drug:carrier ratios in improving the aqueous solubility of famotidine (Table 3, Fig. 3). The 1:40 famotidine:xylitol dispersion showed 31.7% enhancement of famotidine solubility when compared to famotidine alone in water and 15% enhancement relative to the corresponding physical mixture. While this is noteworthy, it may not be as useful in formulating a dosage form, since even a 20 mg dose would require 800 mg of xylitol. The observed solubility enhancement could be partly due to the possible solubilization effect by the carrier, as observed with physical mixtures, in the diffusion layer surrounding the particles of the drug resulting in saturation or supersaturation of this layer prior to diffusion of drug molecules in the bulk fluid. In addition, when a glass dispersion is exposed to water, the drug may be released in a fine crystalline form (Chiou and Riegelman, 1969). For very fine particulate systems, the magnitude of solubility increases with decreasing particle size (May and Kolthoff, 1948). It may be possible that, at a drug:carrier ratio of 1:40, a eutectic mixture of famotidine and xylitol is formed. The composition of a eutectic has a significant effect on the crystallite size. If it is made up of a low weight fraction of the drug,

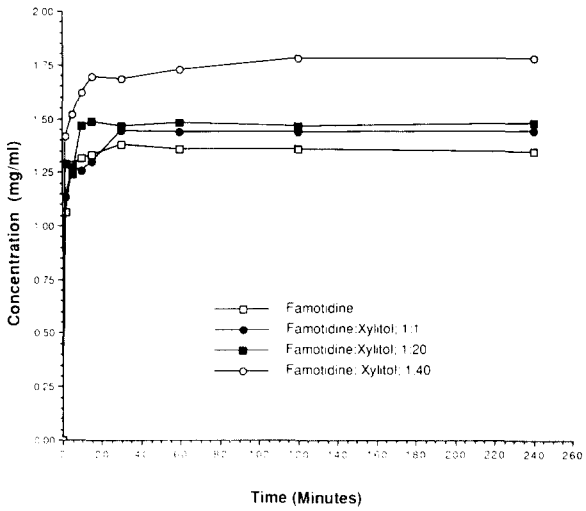

Fig. 3. Aqueous solubility of famotidine from solid glass dispersions at 37 ± 0.5°C.

an ultrafine crystallization of the drug will be obtained i.e. the higher the dilution, the finer the crystallite size (Chiou and Riegelman, 1971). This would then account for the increase in drug solubility. Also, some solid-state solubility can be expected for most two component systems. Therefore, it can be argued that the 1:40 famotidine-xylitol glass dispersion is quite possibly a solid glass solution instead of a eutectic mixture. In a solid solution, the particle size of the drug is reduced to its minimum state, the molecular size, which might in turn be responsible for the formation of a saturated or supersaturated solution of the drug in water. The phase diagram (Fig. 6) supports eutectic formation. Additionally, even at 1:40 ratio, famotidine-xylitol melt was a dispersion, suggesting little or no solid solution formation.

It is often difficult to disperse a fine powder in water because the particles are surrounded by nonpolar air that is hard to penetrate or displace by water, especially if the affinity between the solid drug and water is weak or nonexistent. During the preparation of this dispersion system, each single crystallite of the drug (125–200 μm) was very intimately encircled by the highly soluble carrier, xylitol. The high temperatures involved in preparation of the dispersions by the fusion method helped in removing the entrapped air as well as leading to improved wettability and reduced aggregation and agglomeration of famotidine particles. However, these factors would account for only modest increases in solubility of slightly soluble drugs and possibly adequately explain slightly greater efficacy of solid dispersion in general over corresponding physical mixtures, in the absence of other interactions, in dissolving and solubilizing the drug. The significantly higher solubility of famotidine from 1:40 dispersion as observed in our study (Table 3) cannot be thus fully explained.

Dissolution studies

From Fig. 4, it is evident that about 92% of famotidine was dissolved in about 15 minutes and within 30 minutes, all of the drug was in solution. The dissolution rate of famotidine was markedly increased when formulated as glass dispersions. A 1:20 dispersion resulted in the fastest dissolution rate with 100% of the drug dissolving within one minute. Therefore, 1:40 dispersion was not tested. The Noyes-Whitney equation (Eqn. 2) predicts that the dissolution rate of a drug (dC/dt) is proportional to the surface area of the dissolving solid, S, and the gradient ($C_s - C$), and can be described by

$$dC/dt = KS(C_s - C) \quad (2)$$

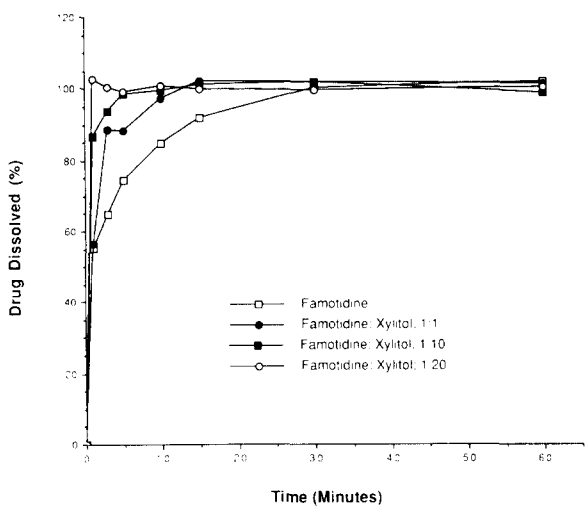

Fig. 4. Dissolution profile of famotidine from solid glass dispersions in water at 37 ± 0.5°C.

where C_s is the solubility of the drug in the dissolution media, C is the concentration of the drug in the solution and K is the apparent dissolution rate constant describing the diffusion of the drug in the media. The enhancement in dissolution rate is probably mainly due to an increase in the surface area of the famotidine due to the smaller particle size for famotidine in glass dispersions. The solubility data would suggest that the contribution of drug solubility, C_s, was relatively minor. Undoubtedly, other factors such as wettability and reduced aggregation, discussed earlier, also have contributed to the enhancement of dissolution to some extent.

Dissolution behavior of famotidine from physical mixtures was not studied. The physical mixture may also show an increase in dissolution rate, although less dramatic, since rapid dissolution of xylitol would allow water molecules to surround and dissolve famotidine. Solubility studies have already shown that even at high xylitol to drug ratio of 40 to 1, the increase in the drug solubility from physical mixture is only 14%.

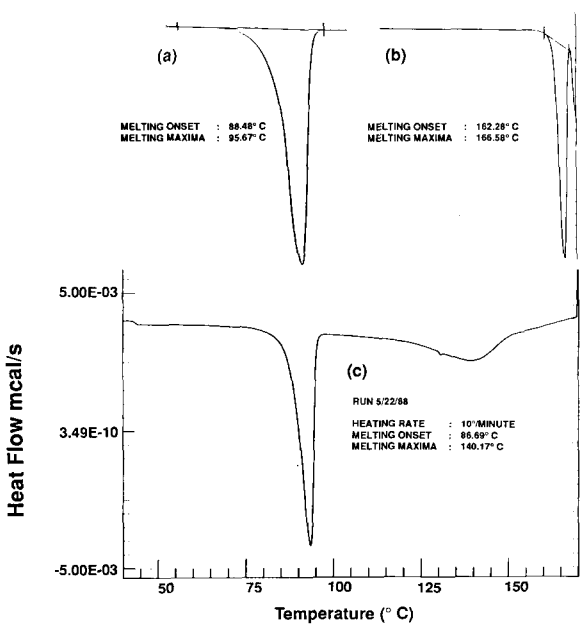

Fig. 5. Thermograms. (a) Xylitol glass, (b) famotidine powder, (c) 1:1 famotidine:xylitol solid glass dispersion.

Thermal analysis of solid glass dispersions

Xylitol and famotidine, when subjected to differential scanning calorimetry, each gave an endothermic peak corresponding to fusion. The second incomplete endothermic peak in the thermogram of famotidine might have been due to boiling or vaporization probably followed by decomposition of the drug. The solid glass dispersions (1:1) exhibited two transitions corresponding to the fusion of the carrier and the drug respectively (Fig. 5). The thermogram showed no evidence of the formation of solid complexes or solutions. The calorimeter was unable to detect transition for a drug content of less than 20% w/w and hence a complete phase equilibrium diagram could not be obtained by this method. Fig. 6 shows the phase diagram for the famotidine-xylitol glass dispersion system constructed from the melting temperatures determined by the capillary tube method. The slight depression in the curve suggests the formation of a eutectic mixture of famotidine and xylitol at a drug:carrier ratio approaching 1:40. The absence of chemical interactions between famotidine and xylitol upon fusion indicates that xylitol probably influenced the solubility and dissolution rate of famotidine by altering only its surface properties such as particle size and affinity between solid drug and water.

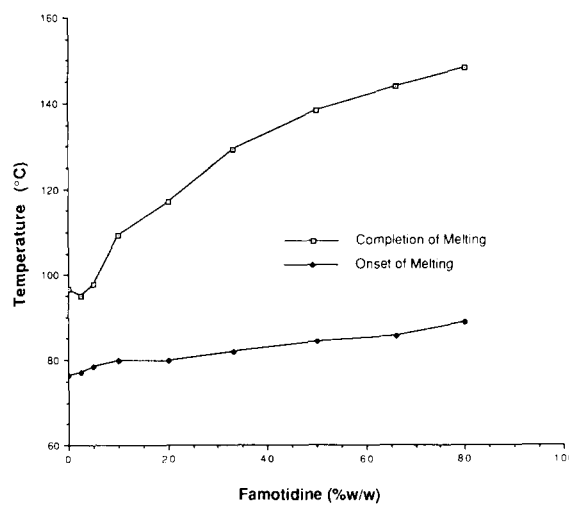

Fig. 6. Phase diagram for famotidine:xylitol solid glass dispersions by the capillary tube method.

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