DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(7), 939-952 (1988)



# ADSORPTION OF SOME 1.4-BENZODIAZEPINES ON INSOLUBLE TABLET EXCIPIENTS AND CHARCOAL

Mounir S. Mesiha* and Sozan Shawky

Departments of Industrial Pharmacy and Pharmaceutics,
Faculty of Pharmacy, University of Assiut, Assiut
(Egypt)

## ABSTRACT

The adsorption of five widely used 1.4-benzodiazepines on talc, calcium phosphate, magnesium stearate, microcrystalline celluloses, ethyl cellulose and starch was studied. Adsorption of these compounds on charcoal was also investigated for comparison. Diazepam was found not to be adsorbed on talc, calcium phosphate and magnesium stearate. A relatively low adsorption of the drug by cellulose and starch was measured. The amount of diazepam adsorbed per unit weight of ethyl cellulose was high in water and in phosphate buffer, while no adsorption could be measured in 0.1 N HCL. The drug interact with ethyl cellulose at higher concentrations (100-180 mcg/ml). The UV and IR of the reactants and products were studied.

The adsorption of nordiazepam, nitrazepam, flunitrazepam and chlordiazepoxide onto ethyl cellulose and charcoal from their

* Present address: College of Pharmacy, University of Puerto Rico, San Juan, Puerto Rico 00936

aqueous solutions was also studied. Diazepam and nordiazepam showed the highest adsorption on ethyl cellulose. The desorption of benzodiazepines from ethyl cellulose in 0.1 N HCl was at the following decreasing rate: flunitrazepam, chlordiazepoxide, nitrazepam, diazepam, nordiazepam.



## INTRODUCTION

Benzodiazepines are widely used low dose psychotherapeutic agents [1]. The pharmaceutical and clinical evaluation of some benzodiazepines showed great differences in their absorption due to subjective and objective parameters[2-5]. The possible effect of adsorption on the impaired absorption of some benzodiazepines was discussed by some authors [6,7]. They restricted their studies on antacids and very few pharmaceutical excipients [6-8].

The adsorption of some drugs onto insoluble tablet excipients was previously reported [9,10].

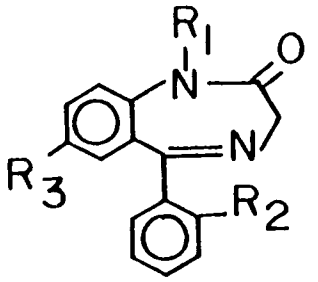
The available literature lack quantitative approach to the absorbability of low dose drugs on tablet excipients as a parameter which may affect their rate or extent of dissolution [9,10], or even their rate of degradation during shelf life [11, 12].

In this article the adsorption of five widely used 1, 4-benzodiazepines on talc, calcium phosphate, magnesium stearate, microcrystalline celluloses, ethyl cellulose and starch was studied. The adsorption of these compounds on the classical adsorbent charcoal was also investigated for comparison.

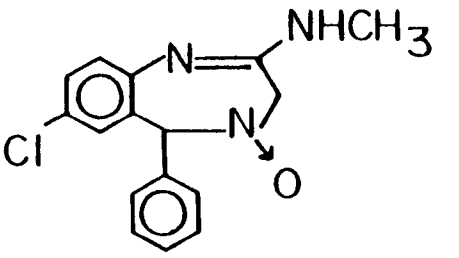
TABLE 1

STRUCTURE, ABSORPTION MAXIMA AND Rf VALUES OF THE STUDIED 1,4-BENZODIAZEPINES

| | Benzodiazenine | $R_1$ | $R_2$ | $R_3$ | $\lambda$ max water | $\lambda$ max in HCl | $R_f$ |
|---|---|---|---|---|---|---|---|
| 1 | Diazepam | $CH_3$ | H | Cl | 230 | 239 | 0.52 |
| 2 | Nordiazepam | H | H | Cl | 228 | 239 | 0.26 |
| 3 | Nitrazepam | H | H | $NO_2$ | 216 | 278 | 0.24 |
| 4 | Flunitrazepam | $CH_3$ | F | $NO_2$ | 218 | 268 | 0.51 |
| 5 | Chlordiazepoxide | | | | 260 | 248 | 0.97 |




Compounds 1-4




Chlordiazepoxide

$R_f$ values were determined on TLC (Schutz, 1982) using chloroform: acetone 9:1 as the developing solvent.

## EXPERIMENTAL

### Materials:

The five 1,4-benzodiazepines shown in Table 1 were kindly donated by Professor P. De Moerloose; checked for purity by TLC, melting points and IR spectra [13] immediately before study. Activated charcoal (E. Merck, Darmstadt), dibasic calcium phosphate

dihydrate (Emcompress lot 90138X, courtesy of E. Mendell, Carmel, N.Y,), microcrystalline cellulose (Avicel PH101, FMC, Philadelphia), microfine (P 100) and granular(G 250) celluloses (Elcema, Degussa, Frankfurt), ethyl cellulose (Searle, HW, Essex), compressible starch (STA-Rx 1500, Staley, Illinois), talc, magnesium stearate and buffer components were pharmaceutical or analytically pure chemicals. All chemicals were used as received.

Apparatus:

UV-visible spectrophotometer, Pye Unicam SP 400, a recording Unicam SP 1750 spectrophotometer and Unicam 1025 IR spectrophotometer were used for measuring the absorbances, scanning the UV spectra and the IR spectra respectively.

A rotating bottle constant temperature water bath was used for equilibrium of the adsorbents with drug solutions and also for the desorption studies.

Adsorption:

The benzodiazepines under investigation were dissolved in ethanol (1 mg. $ml^{-1}$) then diluted with water to a series of concentration raging between 10-70 mcg/ml, keeping the final ethanol content (7% v/v) in all solutions constant. The solution (5 ml), was equilibrated with an accurately weighed 200 mg samples of the tablet excipient in a 15 ml stoppered amber-coloured glass bottles rotating in a constant temperature water bath at 37°C. Diazepam adsorption was studied on talc, calcium phosphate, magnesium stearate, celluloses, starch, ethyl cellulose and charcoal in water. Its adsorption on the last two solids was also studied both in

hydrochloric acid buffer of pH 1.2 (USP) and in phosphate buffer of pH 8.0 (USP).

The adsorption of nordiazepam, nitrazepam, flunitrazepam and chlordiazepoxide on ethyl cellulose and on charcoal was studied in water. In all cases charcoal was used in 100-mg samples only. After equilibrium was attained (3 hours) the suspensions were filtered through sintered glass G3 filters. The filtrates were assayed for benzodiazepine content. Ethyl cellulose was also equilibrated with 5-ml samples of diazepam solutions containing higher concentrations (100-180 mcg. $ml^{-1}$) of diazepam in water prepared by dilution of the stock alcoholic solution (1 mg. $ml^{-1}$) with water.

Rate of benzodiazepine desorption:

Dry samples of adsorbate-containing ethyl cellulose and charcoal were obtained by filtration of the equilibrated systems with benzodiazepine solutions in water (70 mcg. $ml^{-1}$). The samples 50 mg, were suspended in 10 ml of 0.1 N HCl in 20-ml amber coloured bottles rotating in a constant temperature water bath at 37°C and 50 rpm, After 5, 10, 15, 30 and 60 min. 5-ml samples were withdrawn and replaced by 5 ml 0.1 N HCl previously wormed to 37°C. The samples taken were assayed for benzodiazepine content.

Assay for benzodiazepines:

Suitable dilutions of the samples taken after adsorption were made with distilled water and the absorbances were measured at the corresponding wave lengths of maximum absorbances shown in table 1. Th absorbances of samples taken from the desorption studies in 0.1 N

HCl were similarly measured at the appropriate wave lengths shown in table 1. Concentrations were calculated from the linear regression equations (r= 0.9996). No interferences from the solid additives with the assay were noticed except when high concentrations of diazepam (100-180 mcg. $ml^{-1}$) were equilibriated with ethyl cellulose as will be discussed below.

Diazepam-ethyl cellulose interaction:

The interaction of diazepam with ethyl cellulose was elucidated by UV and IR spectroscopy. The systems containing equilibrated diazepam at concentrations 100-180 mcg. $ml^{-1}$ with ethyl cellulose were filtered. The filtrates were divided into two portions: The first was diluted with water and scanned spectrophotometrically between 190-400 nm. The second portions were evaporated to dryness in a discicator, mixed with solid potassium bromide, compressed into discs and studied for IR spectra.

## RESULTS AND DISCUSSION

Adsorption:

Equilibrium was achieved during the first one hour, however all the systems were allowed to agitate for 3 hours to ensure equilibrium. During this time no measurable adsorption of the benzodiazepines onto glassware and no degradation of the drugs was detected.

The limited solubilities of benzodiazepines in water[14] required solubilization of these drugs in a limited amount of alcohol with subsequent high dilution with water. The final

concentrations (10-70 mcg. $ml^{-1}$) are chosen to be near the expected dilutions of 2 - 10 mg doses of benzodiazepines in normal volumes of gastro intestinal fluids ranging from 40 - 50 ml residual volumes for adults [15].

At these concentrations diazepam was found not to be adsorbed on talc, calcium phosphate or magnesium stearate, when the medium was water. A limited adsorption of diazepam on magnesium stearate and calcium phosphate was previously reported but only at higher concentrations of diazepam reached 250 mcg. $ml^{-1}$ [8]. In our study no change in concentrations could be measured before and after equilibrium over 3 hours.

The adsorption data of diazepam on celluloses, starch and ethyl cellulose are shown in Table 2. A relatively low adsorption of the drug by cellulose and starch was measured. Linearity according to the Langmuirian equation $C_e/(x/m) = 1/ab + C_e/b$ (through ref. 16) was not completely followed. No linearity was observed in case of starch. The amount of diazepam adsorbed per unit weight of ethyl cellulose was considerably high in water and in phosphate buffer of pH8. This is evident from the high limiting adsorption coefficient values (Table 2). No adsorption could be measured when diazepam was equilibrated at similar concentration range with ethyl cellulose in hydrochloric acid medium. Thus the unprotonated species of diazepam being hydrophobic was more preferably adsorbed onto the ethylated cellulose than the ionized protonated molecule.

Equilibration of diazepam at higher concentrations (100-180 mcg. $ml^{-1}$) in water with ethyl cellulose resulted in solubilization

TABLE 2

ADSORPTION OF DIAZEPAM ON DIFFERELNT CELLULOSES, STARCH AND ETHYL CELLULOSE

| Excipient | $C_e$ | x/m | $C_e/(x/m)$ |
|---|---|---|---|
| Avicel | 8.75 | 31.25 | 0.280 |
| | 17.55 | 61.25 | 0.287 |
| r=0.8743 | 37.58 | 60.50 | 0.621 |
| b=21.94 | 48.52 | 37.00 | 1.311 |
| | 59.18 | 20.50 | 2.887 |
| Elcema P100 | 8.48 | 38.50 | 0.220 |
| | 17.13 | 71.75 | 0.239 |
| r=0.9591 | 27.64 | 59.00 | 0.469 |
| b=52.57 | 38.01 | 49.75 | 0.764 |
| Elcema G250 | 16.84 | 79.00 | 0.213 |
| | 26.65 | 83.75 | 0.318 |
| r=0.9684 | 36.59 | 85.25 | 0.429 |
| b=61.20 | 47.39 | 65.25 | 0.726 |
| STA-Rx | 19.69 | 15.50 | 1.270 |
| | 29.35 | 32.50 | 0.903 |
| no linearity | 37.30 | 135.00 | 0.276 |
| | 48.38 | 81.00 | 0.597 |
| | 59.32 | 34.00 | 1.744 |
| Ethyl cellulose | 4.06 | 148.5 | 0.027 |
| (in water) | 6.76 | 331.0 | 0.020 |
| r=0.9873 | 11.87 | 435.3 | 0.036 |
| b=730.46 | 17.70 | 557.5 | 0.036 |
| | 23.66 | 658.5 | 0.036 |
| | 33.75 | 656.3 | 0.057 |
| Ethyl cellulose | 3.46 | 163.5 | 0.021 |
| (in phosphate buffer) | 8.33 | 291.8 | 0.029 |
| r=0.8430 | 12.30 | 442.5 | 0.028 |
| b=1642.31 | 16.72 | 383.28 | 0.030 |

$C_e$ , is the equilibrium concentration of diazepam ($mcg.ml^{-1}$);

x/m , is the microgram of the drug adsorbed per gram of the excipient

r , is the regression coefficient when plotting $C_e/(x/m)$ versus $C_e$ according to Langmuir

b , is the limiting adsorption coefficient, which represents the reciprocal of the slope.

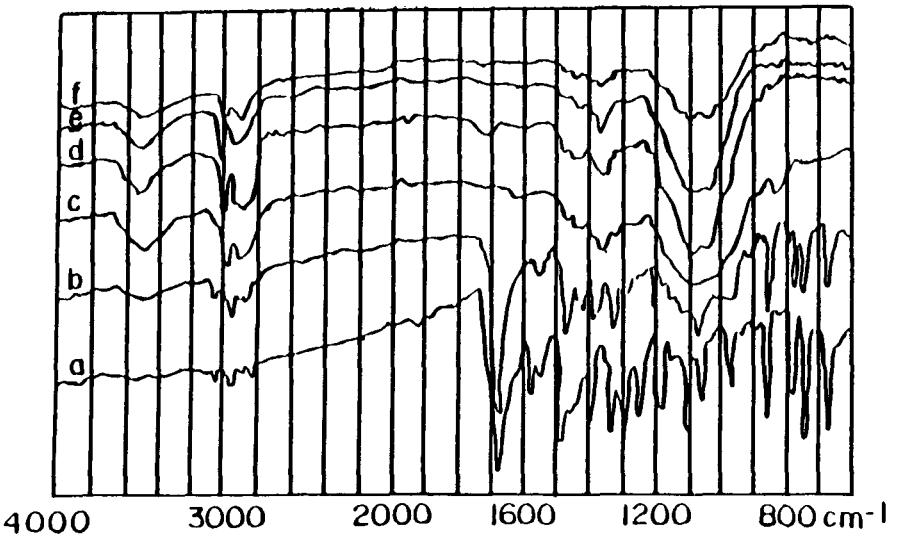



**Fig.1 Infrared spectra of a, diazepam; b, physical mixture of diazepam and ethyl cellulose; c, d, e and f, diazepam (120, 140, 160 and 180 mcg/ml) complex with ethyl cellulose.**

of ethyl cellulose i.e. apparent disappearance of the adsorbent from the bottles. A shift in the wavelength of maximum absorption from 230 to 270 nm was observed when dilute samples of the liquid phase were scanned by UV-spectrophotometer. Samples of different concentrations of diazepam were dried after equilibrium with constant weight of ethyl cellulose (200 mg). Their KBr discs showed the IR spectra illustrated in Fig. 1. Diazepam and ethyl cellulose singly and in physical mixture were also studied for comparison. The interpretation of IR spectra were done according to the tables given by Parikh (17). The weak absorption bands at 3360, 3100 $cm^{-1}$ in diazepam spectrum could be due to N-C stretching in the amide

stretching band at 1680 $cm^{-1}$ and other bands at 1600, 1580, 1570 $cm^{-1}$ which are characteristics of the amide group. The disappearance of these bands from the complex spectrum as well as the hypsochromic shift strongly suggests cleavage of the seven membered ring of diazepam at the amide link. The formation of 2-methylamino-5-chlorobenzophenone is excluded as the IR spectrum of the product does not correspond to the spectrum of this benzophenone derivative found in the literature [13].

Adsorption of nordiazepam, nitrazepam, flunitrazepam, and chlordiazepoxide onto ethyl cellulose from their aqueous solutions was also studied (Table 3). Diazepam and Nordiazepam showed the highest adsorption if the values of x/m were compared for similar equilibrium concentrations. This may be attributed to steric hinderence caused by side chains in nitrazepam, flunitrazepam and chlordiazepoxide, preventing free access of the molecule on the adsorption sites.

Adsorption on charcoal was very high. The equilibrium concentrations were more or less constant for a given system with consequent increase of the amount adsorbed by increasing the initial concentrations. The limiting values of equilibrium concentration is the solubility of the drug in the aqueous medium. These values differed for the different benzodiazepines. It seems that at these low concentrations available sites for adsorption are still unoccupied and permit more molecules to be absorbed.

Desorption:

The desorption studies were done when diazepam showed no adsorption in HCL medium while high adsorption in other aqueous media was clear. Adsorbates were taken from systems of ethyl cellulose or charcoal equilibrated with aqueous benzodiazepine solutions. The rate of desorption of the drug was faster from systems of less adsorption power (Table 4 and 5). Thus benzodiazepines were desorbed form ethyl cellulose to 0.1 N HCl at the following decreasing rate: Flunitrazepam, chlordiazepoxide, nitrazepam, diazepam and

TABLE 3

ADSORPTION DATA OF BENZODIAZEPINES OF ETHYL CELLULOSE AND CHARCOAL IN WATER

| Benzodiazepine | $C_o$ | Etheyl cellulose | | Charcoal | |
|---|---|---|---|---|---|
| | | $C_e$ | x/m | $C_e$ | x/m |
| Diazepam | 10 | 4.06 | 148 | 1.49 | 425 |
| | 20 | 6.76 | 331 | 1.38 | 931 |
| | 30 | 11.87 | 435 | 1.86 | 1407 |
| | 40 | 17.70 | 557 | 1.86 | 1907 |
| | 50 | 23.66 | 658 | 2.37 | 2387 |
| | 60 | 33.75 | 656 | 4.14 | 2793 |
| Diazepam in HCl buffer | 10 | No adsorption at all concentrations | | 3.14 | 343 |
| | 20 | | | 3.53 | 823 |
| | 30 | | | 3.47 | 1326 |
| | 40 | | | 3.47 | 1826 |
| | 50 | | | 3.59 | 2320 |
| | 60 | | | 3.56 | 2822 |
| | 70 | | | 3.73 | 3313 |
| Diazepam in phospate buffer | 10 | 3.46 | 164 | 4.65 | 267 |
| | 20 | 8.33 | 292 | 4.56 | 772 |
| | 30 | 12.30 | 443 | 5.61 | 1219 |
| | 40 | 16.72 | 383 | 4.97 | 1751 |
| Nordiazepam | 10 | 5.77 | 106 | 1.50 | 425 |
| | 20 | 10.41 | 240 | 1.52 | 925 |
| | 30 | 12.14 | 446 | 2.04 | 1398 |
| | 40 | 15.49 | 613 | 2.41 | 1879 |
| | 50 | 20.24 | 744 | 1.78 | 2411 |
| | 60 | 24.99 | 875 | 1.97 | 2901 |
| | 70 | 32.23 | 944 | 2.23 | 3388 |
| Nitrazepam | 10 | 8.24 | 44 | 6.47 | 176 |
| | 20 | 20.00 | 0 | 6.68 | 666 |
| | 30 | 20.14 | 246 | 7.45 | 1127 |
| | 40 | 24.87 | 378 | 7.72 | 1614 |
| | 50 | 20.06 | 498 | 9.86 | 2007 |
| | 60 | 36.93 | 576 | 15.72 | 2214 |
| | 70 | 41.81 | 705 | 16.30 | 2685 |
| Flunitrazepam | 10 | 8.74 | 31 | 6.51 | 174 |
| | 20 | 16.46 | 88 | 7.19 | 640 |
| | 30 | 23.18 | 170 | 7.44 | 1128 |
| | 40 | 28.06 | 299 | 11.40 | 1430 |
| | 60 | 39.99 | 500 | 9.79 | 2510 |
| | 70 | 45.87 | 603 | 9.02 | 3049 |
| Chlordiazepoxide | 10 | 10.13 | 0 | 0.53 | 473 |
| | 20 | 18.87 | 28 | 0.76 | 962 |
| | 30 | 27.53 | 62 | 0.82 | 1159 |
| | 50 | 40.43 | 239 | 0.55 | 2472 |
| | 60 | 44.97 | 376 | 0.45 | 2977 |
| | 70 | 51.16 | 471 | 0.78 | 3461 |

TABLE 4

THE RATE OF BENZODIAZEPINES DESORPTION FROM ETHYL CELLULOSE IN 0.1 N HCl

| Benzodiazepine | Cumulative percent drug desorbed Time, min | | | | |
|---|---|---|---|---|---|
| | 5 | 10 | 15 | 30 | 60 |
| Diazepam | 5.69 | 11.82 | 13.02 | 17.66 | 22.90 |
| Nordiazepam | 5.38 | 7.95 | 9.78 | 12.58 | 14.99 |
| Nitrazepam | 24.13 | 36.19 | 44.78 | 53.09 | 61.53 |
| Flunitrazepam | 30.03 | 43.28 | 59.17 | 75.36 | 96.24 |
| Chlordiazepoxide | 35.80 | 43.52 | 52.82 | 65.63 | 79.31 |

TABLE 5

THE RATE OF BENZODIAZEPINES DESORPTION FROM CHARCOAL IN 0.1 N HCl

| Benzodiazepine | Cumulative percent drug desorbed Time, min | | | | |
|---|---|---|---|---|---|
| | 5 | 10 | 15 | 30 | 60 |
| Diazepam | 1.05 | 1.58 | 2.23 | 1.76 | 3.92 |
| Nordiazepam | 12.08 | 15.63 | 17.86 | 19.39 | 21.21 |
| Nitrazepam | 15.69 | 19.11 | 20.09 | 26.78 | 36.84 |
| Flunitrazepam | 14.90 | 20.96 | 28.18 | 37.48 | 60.03 |
| Chlordiazepoxide | 12.80 | 15.38 | 19.58 | 24.02 | 33.38 |

group. There is very strong absorption C=O nordiazepam (Table 4). The desorption from charcoal was slower than that from ethyl cellulose (Table 5).

## REFERENCES


1. Lader, M., New perspective in benzodiazepine therapy. Drug Res., 30 (1980) 851-915.

2. Bliding, A., Effect of different rates of absorption of two benzodiazepines on subjective and objective parameters. Eur. J. Clin Pharmacol. 7 (1974) 201-211.

3. Gamble, J.A.S., Factors influencing the absorption of diazempam Proc. Roy. Soc. Med. 68 (1975) 22.

4. Kangas, L., Pekkarinen, A., Sourander, G., Raijola, E., A comparative gas chromatography study on absorption of diazepam tablets in man. Ann. Clin. Res. 6 (1974) 12-20.

5. Kugler, V.J., Der Wirkungsunterschied zweir glenisch verschiedener Oxazepam - zubereituneen in EEG, Forsch, Drug Res. 33 (11) (1983) 1310-1313.

6. Greenblatt, D.J., Allen, M.D., Maclaugulin, D.S., Harmaty, J.S., Shader, R.I., Diazepam absorption - effect of antacid and food, Clin. Pharm. 5 (1978) 600 - 9.

7. Shader, R.I., Georgota, A., Greenblatt, D.J., Harmatz, J.S., Allen, M.D., Impaired absorption of desmethyldiazepam from chlorazepam by magnesium aluminium hydroxide, Clin. Pharm. 24 (1978) 308 - 15.

8. Naggar, V.F., An in vitro study of the interaction between Diazepam and some antacids or excipients, Pharmazie. 36 (1981) 114 - 117.

9. Mesiha, M.S., Shawky, S., Adsorption of isoniazid on insoluble tablet excipients and charcoal, Bull. Pharm. Sci., Assiut Univ. 7 (1984) 173-189.

10. Odeala, O.K. and Aly, S.A., The adsorption of chloroquine phospate and base by some pharmaceutical clays and tablet excipients., 3rd International Conference on Pharmaceutical Technology, Paris (1983).

11. Loewe, W., Soliva, M. and Speiser, P.P., Decomposition of nitrazepam in tablets in presence of silica and $CaHPO_4$, Drugs made in Germany 26 (1983) 158-164.

12. Perrier, P.R., and Kesslring, U.W., Quantitative Assessment of the effect of some excipients on nitrazepam stability in binary powder mixtures, J. Pharm. Sci. 72 (1983) 1072-1074.

13. Schutz, H., Benzodiazepines, Springer - Verlag, Berlin (1982).

14. Uekama, K., Narisawa, S., Hirayama, F. and Otagiri, M., Improvement of dissolution and adsorption characteristics of benzodiazepines by cyclodextrin complexation. Int. J. Pham. 16 (1983) 327-338.

15. Diem, K., ed., Scientific tables, 6th ed., Geigy Pharm. Co., Machester, (1962) 520.

16. Blaug, S.A. and Gross, M.R., In Vitro adsorption of some anticholinergic drugs bya various antacids., J. Pharm. Sci. 54 (1965) 289 - 294.

17. Parikh, V.M., Adsorption spectroscopy of organic molecules, Addison Wesley Publish., Reading MS (1974) 247-252).