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# EFFECT OF SODIUM CARBOXYMETHYLCELLULOSES ON THE DISINTEGRATION, DISSOLUTION AND BIOAVAILABILITY OF LORAZEPAM FROM TABLETS

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## ABSTRACT

A new range of sodium carboxymethylcelluloses (i.e. Nymcel$^{R}$ types ZSB-10, ZSB-16 and ZSD-16) were included into lorazepam tablet formulations to improve the disintegration, dissolution and bioavailability of the drug. Tablets of the batch G containing 5% Nymcel ZSB-16 exhibited quicker disintegration, faster dissolution, and higher rate and extent of bioavailability in mongrel dog in comparison to tablets of the other batches.

## INTRODUCTION

Lorazepam (Wy-4036) is a potent trianquillizer with dedative, hypnotic and anticonvulsant properties. The chemistry[1] and pharmacology[2] of the drug has been reported. It is almost insoluble in water and the usual adult oral dose is 1 to 10 mg daily[3].

It has been shown that the dissolution rate, and often the bioavailability, of a drug from oral tablets can be increased by decreasing the disintegration time[4-8]. The purpose of this study was to evaluate the influence of a new range of sodium carboxymethylcelluloses on the disintegration, dissolution and bioavailability of the drug. It has been reported that the addition of these disintegrants in small amounts ensures the rapid breakdown of even the hardest tablets[9]. Sodium carboxymethylcellulose, a white, tasteless, odourless powder, is available in three forms which are Nymcel ZSB-10, Nymcel ZSB-16, Nymcel ZSD-16. The effect of different percentages of these three types of sodium carboxymethylcelluloses on the disintegration, dissolution and bioavailability of lorazepam from tablet formulations was investigated.

## MATERIALS

Lorazepam was obtained from CIPLA, Bombay, Emcompress, talc and magnesium steate were received from Edward

Mendell Co., Inc., U.S.A.; Hansa Chemical, Bombay, and Chemilon Laboratory, Bombay, respectively. Nymcel ZSB-10, Nymcel ZSB-16 and Nymcel ZSD-16 were procured from Nyma, v.b. Holland.



## METHODS

**Preparation of Tablets** - Batches of tablets were prepared containing Lorazepam (2 mg), Emcompress (90 mg), sodium carboxymethylcelluloses (1 or 3 or 5 mg), talc (2 mg), magnesium stearate (1 mg) in each tablet. Sufficient quantities of each ingredient to prepare 200 tablets were weighed and then mixed by geometric dilution for 2 h on a Labaid Vortex Mixer. A Manesty E-2 type single punch tablet machine fitted with a 7/32 inch die and punch set was used to directly compress the mixture into tablets at compression pressure of 13 tons/in$^2$.

**In vitro Disintegration and Dissolution** - The disintegra- time (D.T.) of each batch of tablets was determined with Thermonik Tablet Disintegration Machine of B.P. standard.

In vitro dissolution rate measurements were made using a Thermonik Dissolution Rate Test Equipment USP XVIII. Each tablet was placed in a stainless steel rotating basket and agitated at 100 rpm in 900 ml of simulated gastric fluid USP (excluding pepsin), pH 1.2, at a temperature of 37±1°C. 10 ml aliquots were withdrawn at different intervals,

filtered through Whatman no. 44 filter paper and the absorbance of the drug was measured at 232 nm in a Ultra Violet spectrophotometer. An equal volume of fresh dissolution fluid maintained at $37 \pm 1^{o}C$ was added to replace the sample used for analysis. Dissolution data was corrected for this dilution effect. Seven tablets of each batch were subjected to in vitro dissolution.

**Bioavailability Study** - Healthy male and female mongrel dogs 10 kg in body weight were fasted for 24 h. Each dog was anaesthetized with an intravenous injection of aqueous solution of Pentobarbital sidium equivalent to a dose of 50 mg/kg body weight. One Lorazepam tablet or Lorazepam solution was administered to each dog. 2 ml blood samples were withdrawn before administration and subsequently at 1, 2, 3, 4, 8 and 24 h time intervals. All samples were frozen until analyzed. The amount of free drug in serum and bioavailability parameters were evaluated as previously reported[10]. Seven dogs for such batch were subjected to bioavailability study.

All the results are expresed as mean $\pm$ S.D. of seven determinations.

## RESULTS AND DISCUSSION

In vitro disintegration and dissolution rates for each batch of tablets are shown in Table 1. Tablets of all the

**TABLE 1**

*In vitro* Disintegration and Dissolution (mean ± S.D., n = 7) of Tablets

| Batch | Disintegrants | | D.T. | Cumulative and release | | | | |
|---|---|---|---|---|---|---|---|---|
| | Name | mg/tablet | sec. | 10 min | 20 min | 30 min | 40 min | 60 min |
| A | Potato starch | 5 | 120.00 ±10.00 | 25.21 ±1.55 | 34.23 ±2.94 | 37.13 ±3.56 | 41.85 ±1.42 | 47.50 ±2.19 |
| B | Nymcel ZSB-10 | 1 | 25.67 ±0.58 | 26.37 ±1.23 | 35.51 ±1.85 | 40.75 ±3.10 | 47.14 ±3.85 | 57.33 ±5.44 |
| C | Nymcel ZSB-10 | 3 | 12.33 ±0.58 | 37.78 ±3.39 | 46.82 ±2.29 | 51.20 ±0.84 | 54.50 ±3.26 | 59.82 ±2.80 |
| D | Nymcel ZSB-10 | 5 | 8.67 ±0.58 | 40.44 ±5.34 | 47.33 ±3.06 | 54.50 ±2.06 | 58.50 ±3.33 | 63.50 ±2.45 |
| E | Nymcel ZSB-16 | 1 | 26.00 ±1.00 | 45.56 ±2.11 | 55.98 ±2.20 | 62.85 ±2.29 | 63.31 ±5.52 | 70.39 ±6.74 |
| F | Nymcel ZSB-16 | 3 | 9.33 ±0.58 | 50.37 ±2.33 | 58.50 ±2.80 | 63.85 ±3.01 | 66.13 ±3.56 | 73.50 ±3.26 |
| G | Nymcel ZSB-16 | 5 | 8.50 ±0.50 | 53.05 ±2.67 | 60.63 ±2.66 | 66.86 ±3.01 | 69.38 ±4.62 | 76.25 ±2.19 |
| H | Nymcel ZSD-16 | 1 | 12.00 ±0.63 | 45.50 ±1.85 | 60.45 ±2.65 | 65.45 ±2.30 | 68.07 ±2.31 | 70.92 ±3.50 |
| I | Nymcel ZSD-16 | 3 | 12.33 ±0.58 | 49.65 ±2.05 | 62.02 ±2.11 | 66.16 ±1.95 | 68.50 ±3.15 | 71.00 ±2.85 |
| J | Nymcel ZSD-16 | 5 | 12.67 ±1.01 | 53.00 ±0.56 | 63.25 ±1.58 | 67.79 ±2.44 | 69.22 ±1.53 | 72.33 ±1.40 |

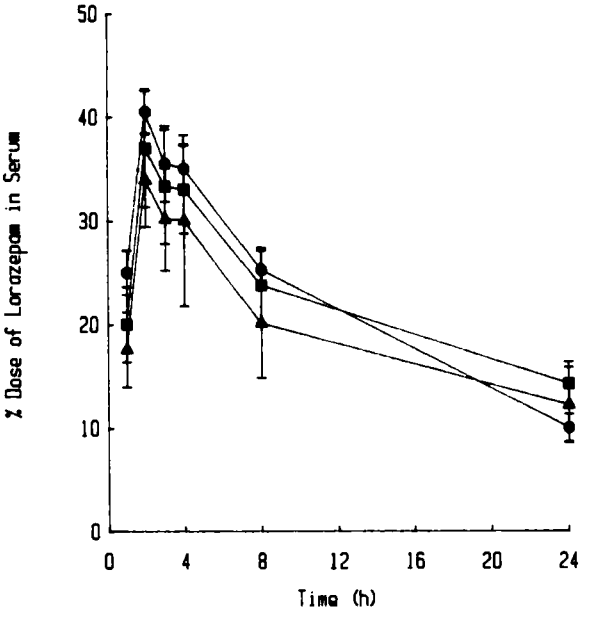


FIGURE 1

Serum concentration of lorazepam after oral administration in dogs.

●. solution : ▲. A tablets: ■. G tablets.

batches containing sodium carboxymethylcelluloses rapidly disintegrated within 30 sec. An increase in the concentration of disintegrants caused the decrease in disintegration time except tablets containing Nymcel ZSD-16. However, the fastest disintegration time of 8.50 sec was observed in tablets of the batch G. Similarly, an increase of the concentration of sodium carboxymethylcelluloses produced correspondingly higher dissolution rates. The highest dissolution of 76.25% within 1 h was exhibited by tablets

**TABLE 2**

Bioavailability Parameters (Mean ± S.D., n = 7) of Lorazepam from Tablet Formulations in Dogs

| Batch | $AUC_o^{24}$ (% dose-h) | $C_{max}$ (% dose) | $t_{max}$ (h) | F (%) |
|---|---|---|---|---|
| Solution | 522.39 ±37.64 | 40.50 ±2.05 | 2.00 ±0.02 | 100.00 ±7.21 |
| A | 459.80 ±109.46 | 33.91 ±4.51 | 2.00 ±0.02 | 88.02 ±20.95 |
| G | 510.47 ±68.12 | 37.00 ±5.69 | 2.00 ±0.06 | 98.67 ±13.04 |

of the batch G. Thus, there is a large decrease in disintegration time and increase in dissolution rate of tablets containing 5% Nymcel ZSB-16 relative to the tablets containing 5% potato starch as a disintegrant.

Using the in-vitro disintegration and dissolution data, tablets of the batch G were selected for a comparative bioavailability study with tablets containing potato starch, batch A, and the drug solution containing 2 mg of the drug dissolved in 10 ml of a solvent mixture consisting of ethanol 2 ml, propylene glycol 6 ml, and glycerol 2 ml. The results are shown in Fig. 1 and Table 2. The rate and extent of bioavailability of the drug from tablets containing Nymcel ZSB-16 were found to be greater than the tablets containing 5% potato starch. However, the rate of bioavailability from tablets of the batch G was lower but the extent was almost equal to the oral solution of the drug.

In conclusion, tablets containing 5% Nymcel ZSB-16 exhibited quicker disintegration, faster dissolution and higher rate and extent of bioavailability among tablets of all the batches studied.

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