DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 17(3), 463-468 (1991)

COMMUNICATION

ENHANCED DISSOLUTION AND ABSORPTION OF TRIMETHOPRIM FROM COPRECIPITATES WITH POLYETHYLENE GLYCOLS AND POLYVINYLPYRROLIDONE

R.L. Gupta*, R. Kumar and A.K. Singla
Department of Pharmaceutical Sciences,
Panjab University, Chandigarh - 160 014 (India)

ABSTRACT

Coprecipitates of trimethoprim have been prepared by solvent method using polyethylene glycols 4000, 6000 and 9000, and polyvinylpyrrolidone (M.W. 40,000) as water soluble carriers. A marked increase in the dissolution rate of trimethoprim in the coprecipitates was observed compared with that of the drug alone. Coprecipitates with polyethylene glycol 6000 (1:2) showed faster release as well as bioavailability of the drug in human volunteers.

INTRODUCTION

The mechanism of increasing solubility of insoluble or slightly soluble drugs via solid dispersion technique has been extensively reviewed by Chiou and Riegelman (1). To optimize the bioavailability and absorption rates of these, both the carrier and the method employed to prepare dispersions should be properly selected. Recently, Meshali et al. (2) used the glass dispersion technique to enhance the dissolution rate and bioavailability of trimethoprim (TMP). Singla and Vijan (3) reported that coprecipitates with polyvinylpyrrolidone, PVP, (M.W. 40,000) were superior to other carriers in releasing sulphamethoxazole into solution. Since TMP is widely used in combination with sulphamethoxazole in various systemic infections (4), it was of interest to study the effect of polyethylene glycols (PEG) and PVP (M.W. 40,000) in different levels, incorporated by solvent technique in dispersion, on the dissolution characteristics and bioavailability of TMP.

*Correspondence

EXPERIMENTAL

Materials : These include trimethoprim (Ranbaxy Labs.Ltd.New Delhi); PEG 4000 (BDH), 6000 and 9000 (Sisco); PVP, M.W. 40,000 (Loba Chem.,India). All other chemicals used were analytical or reagent grade.

Solubility Determination : An excess of TMP (200 mg) was added to 6 ml water or solutions of varying levels of carriers in 10 ml ampoules which, after sealing, were shaken longitudinally at 120 strokes per min (stroke length = 7 cm) at 37±1° for 36 hr. The contents were centrifuged and the supernatant liquid (1 ml) was diluted to 10 ml with 0.1 N HCl and mixed for 2 min, and analysed by reference to standard solution of TMP at 271 nm. Each measurement is the mean of duplicate determinations.

Preparation of Solid Dispersions : PEG (different Mol. Wt.) and PVP-drug dispersions (1:1 and 1:2, w/w) were prepared by dissolving the required amount of the drug and the polymer in minimum volume of chloroform. The solvent was then removed under vacuum, and sieved through # 120 screen.

Dissolution Rate Studies: The dissolution rates of the drug from the dispersions were determined using 500 ml water as dissolution medium at 37±1°C and rotating basket (USP XXI) dissolution apparatus I(5). The stirrer speed was 60 rpm. At suitable time intervals, 2 ml sample was withdrawn, filtered, and replaced with 2 ml of fresh dissolution medium. The drug content was determined spectrophotometrically (Perkin Elmer, Model Lambda 3) at 271 nm.

Bioavailability Trials : Six healthy male adults (age range 24-27 yr and body weight range 47-65 kg) were selected for the study and were divided into two groups of three each. No history of sensitivity or allergy to any drug was the condition for joining the study. The volunteers were instructed to abstain from any kind of medication at least one week earlier and during the course of study. The purpose of this study was explained to them and written consent obtaiined.

In the first phase, group A had self administered orally, on fasted stomach, a single dose of 160 mg of trimethoprim and the second group (B) received its coprecipitates with PEG 6000 (1:2) equivalent to 160 mg TMP in capsule form with 200 ml water in the morning, after collecting a blank urine by fully voiding the bladder. They were asked not to eat anything for at least 3 hr following the ingestion of the dose but to drink for the next 4 hr, post application, 200 ml water each at hourly interval. In the second phase, the formulations were crossed over with a wash over period of one week. Urine samples collected at regular intervals were measured and a portion of each was frozen till analyzed, in duplicate. Concentration of TMP in urine was measured according to method reported by Bushby and Hitchings (6).

Data Analysis: Optimal calibration lines were calculated by least square regression analysis. Cumulatiive excreted amounts in urine and urinary excretion rates were calculated for all subjects. Elimination and absorption rate constants, elimination and absorption half-life were determined by Sigma-minus method (7).

RESULTS AND DISCUSSION

Coprecipitates of PEG (4000, 6000, 9000) and PVP (40,000): The dissolution rate profiles for these are shown in Fig.1. At each time interval, marked differences exist between the amount of drug in solution from the coprecipitates and the drug alone. For the drug alone, the release rate was slow ($t_{90\%} > 90$ min). However, the maximum release attained depends upon the weight fraction of the polymer (Fig.1). Coprecipitates with PEG 6000 and 9000 (1:2) showed the fastest and almost identical release ($t_{50\%}$, 5 and 6 min, $t_{90\%}$ 25 and 26 min, respectively). The dissolution might be attributed to the TMP present in a state of subdivision and partly by molecular dispersion, and the second phase could account for the release of particles of the drug dispersed in the coprecipitates. Since PEG and PVP are hydrophilic, they would increase the wettability of dispersed particles.

Chromatographic Behaviour: TLC in $CHCl_3$:CH_3OH (1:9) mixture revealed the presence of only one spot with R_f (0.76) value not greater in intensity exhibited by the drug alone and indicated the complexation between TMP and PEG or PVP.

Infra-red Spectra: No significant differences were observed on comparing IR (KBr) spectra of coprecipitates and corresponding physical mixture.

Solubility : The estimated water solubility of TMP (Sw_A = 407.05+ 4.18 µg/ml) is in reasonable agreement with the literature value (4) of 400 µg/ml, suggesting that the first part of the curve (Fig.2) is due to solubility of the drug in water containing PEG or PVP. The inflection point in the solubility curve is perhaps due to non-availability of free water in solubilizing system. Figure 2 indicates an increase in solubility with increase in the water-soluble carrier concentration and that too in the order as PEG 6000 > PVP > PEG 9000 > PEG 4000.

Bioavailability in Human Volunteers: Coprecipitates of TMP with PEG 6000 (1:2) was chosen for *in vivo* study as this represented better release characteristics *in vitro*. The drug from the coprecipitates is absorbed faster and the rate of absorption of TMP is increased significantly ($p < 0.01$). The time of maximum excretion rate is also significantly lower than that of the standard formulation (Table 1). This phenomenon can prove to be useful in improving the bioavailability of trimethoprim in tablet dosage forms

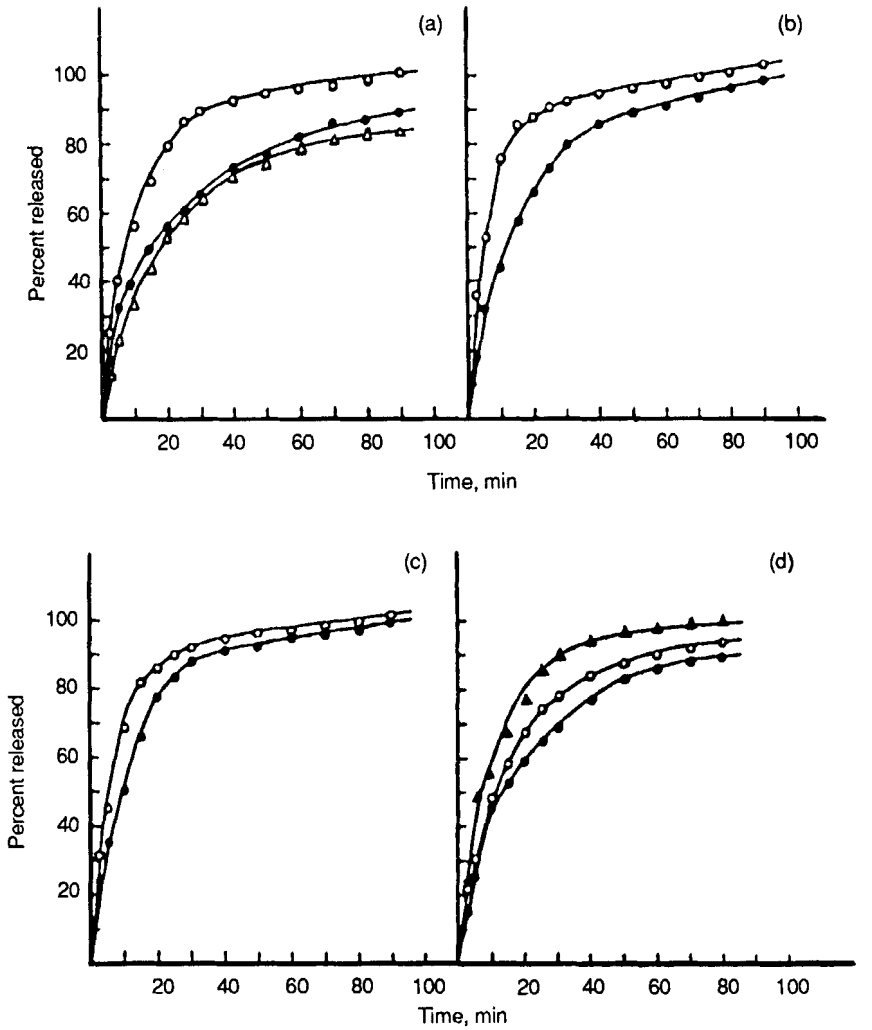

FIGURE 1

Dissolution rate of trimethoprim from coprecipitates with (a) PEG 4000, (b) PEG 6000, (c) PEG 9000, and (d) PVP.

Key: ●, 1:1; ○, 1:2; ▲, 1:3 (drug:carrier ratio), and △, trimethoprim.

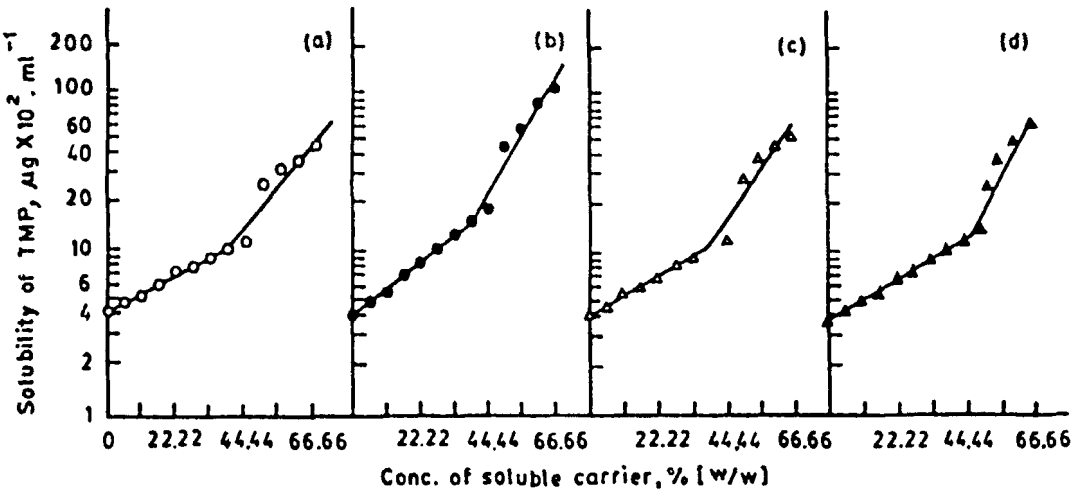

FIGURE 2

Solubility profile of trimethoprim vs concentration soluble carriers (a) PEG 4000, (b) PEG 6000, (c) PEG 9000, and (d) PVP

TABLE 1

Pharmacokinetic parameters of trimethoprim (I) and its coprecipitate with PEG 6000 (1:2) (II) after oral administration of a dose equivalent to 160 mg trimethoprim

Parameters	I	II
Comulative excreted amount of unchanged drug in t_∞, A_e^∞, (mg)	93.72 ± 12.712	111.62 ± 12.22
Peak urinary excretion rate, ($mg.h^{-1}$)	3.925 ± 0.81	3.86 ± 0.85
Time of peak urinary excretion rate, t_{max},(h)	6.05 ± 3.89	4.08 ± 3.346
Elimination rate constant, k_e,(h^{-1})	0.0610±0.04 (0.0532±0.007)*	0.0577±0.006 (0.0523±0.007)*
Absorption rate constant, k_a,(h^{-1})	0.1308±0.0.03 (0.1219±0.01)	0.1999±0.352 (0.160±0.023)
Elimination half-life, $t_{\frac{1}{2}}$,(h)	11.412±0.862 (13.2±1.858)	12.135±1.257 (13.52±1.97)
Absorption half-life, $t_{\frac{1}{2}}$,(h)	5.55±1.123 (5.737±0.509)	3.58±0.67 (4.43±0.7)

*Data in parentheses are according to elimination rate method

with PEG dispersions. However, the extent of absorption was not significantly attained. Maximum excretion rate constant, biological half-life remained unaffected. Using Westlake confidence intervals (8) with 90% confidence the mean total urinary excretion of the drug for the formulation containing TMP alone is within 18.4% (i.e. 20.52/111.62) of the mean for the coprecipitates. Hence, the latter is essentially equivalent to the former even though their difference is significant at the 0.1 level.

REFERENCES

1. W.L. Chiou and S. Riegelman, J. Pharm. Sci., 60, 1281 (1971).
2. M. Meshali, A. Ghanem and Y. Ibraheem, Pharm. Acta Helv., 58, 62 (1963).
3. A.K. Singla and Tarun Vijan, Drug Develop. Ind. Pharm. (accepted).
4. E.F. Reynolds (Ed.), "The extra Pharmacopoeia, 28th ed., The Pharmaceutical Press, London, 1982, p. 1484.
5. United States Pharmacopoeia, 21st revision, United States Pharmacopoeial Convention, Inc., Rockville, Md. 20852, 1985, p. 1243.
6. S.R.M. Bushby and G.H. Hitchings, Br. J. Pharmacol. Chemother., 32, 72 (1968).
7. B.K. Martin, Br. J. Pharmacol. Chemother., 29, 181 (1967).
8. W.J. Westlake, J. Pharm. Sci., 61, 1340 (1972).