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DRUG RELEASE FROM PEG SUPPOSITORY BASES AND FROM THEIR COMBINATION WITH POLYMERS

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SUMMARY

In vitro investigation was conducted to evaluate the drug (Metronidazole) release from the formulation containing "PEG SUPPOSITORIES BASES" and its combination with CMC and PVP. The experiments were conducted at various temperatures and at rectal pH.

When the percentage of the drug release was upto 65%, the rate of release vs time was linear but with combinations (with PVP and CMC) the rate was only linear upto 50% drug release at 37 °C.

Linear relationship was also observed between average molecular weight of the bases upto 50% release rate at temperatures 37 °C, 40 °C, and 45 °C.

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Different drug release was not only dependant on the average molecular weight but also the proportions of various PEG bases.

Key words: Ethylene glycol, Diethylene glycol, Tragacanth, Metronidazole, Suppository bases.

INTRODUCTION

Physicians, pharmacists and patients generally do not appreciate the use of suppositories although this dosage form has many clinical advantages, similarly the drug release from the suppositories bases and factors influencing the drug release have not been fully established.

PEGs, water soluble polymers of ethylene glycol, are used as suppository bases. These are tolerant to cations, to insoluble drugs and are relatively unaffected by the variations in pH. They are chemically inert and do not cause physiolgical side effects (1, 2). In contrast to PEG, other water soluble polymers have been reported to retard the drug release from the suppository (3). So, the combination of both these classes of polymer can modify the release characteristics (4, 5).

Metronidazole was selected as a model drug as it is not properly absorbed by other dosage forms resulting in therapeutic failure against *Trichomonas vaginalis* (6).

EXPERIMENTAL

Materials

PEG 1000, PEG 1500, PEG 6000, CMC, PVP 25000 tragacanth (Merck) PEG 4000 (BDH) ethylene glycol, Diethylene glycol (Merck) metronidazole (China).

Formulations

Twelve blends of PEGs with and without the additives (Table 1) were formulated with similar and different average molecular weight. One hundred gram of each blend was refrigerated in stainless steel moulds which were first calibrated.

The displacement values of each blend was calculated to determine the required base for the preparation of 400 mg metronidazole suppositories. The drug was added to the melted bases. Mixture was poured just above the congealing point into the moulds to minimize the cavity formation at the apex of the suppositories.

CMC and PVP were levigated with a small portion of the base on a tile with spatula and then incorporated with the remaining of the melted base. Suppositories were recovered after 25-30 minutes and were stored in a well closed container at 15 °C.

Table 1: Composition of various blends.

Ingredients	BLENDS											
	1	2	3	4	5	6	7	8	9	10	11	12
PEG 1000	25		30	10	40					40	40	30
PEG 1500	35	65			25		94	93	64	25	24	50
PEG 4000	30	10	60	90	25	70	4	4	4	23	22	
PEG 6000	10	25	10		10	24				10		
Tragacanth						3			2		2	
PVP						3		2		2	2	
CMC							2	1				
Ethylene Glycol												10
Diethylene Glycol												10
	100	100	100	100	100	100	100	100	100	100	100	100

Determinantion of Drug Release from Formulations

The release rate of metronidazole was found in rotating bottle apparatus (1). Distilled water was selected as dissolution medium, the pH of which was adjusted to 6.5 as that of rectal fluids. Buffer solution was not employed since the rectal fluids lack buffering capacity. Release was determined at 37 °C, 40 °C, and 45 °C in the dissolution medium.

The rotating bottle apparatus was operated at 40 rpm. The bottle was rotated end over end in the water bath after attaining the equilibrium at test temperature. A quantity of 10 ml samples were withdrawn from the dissolution medium at approperiate intervals.

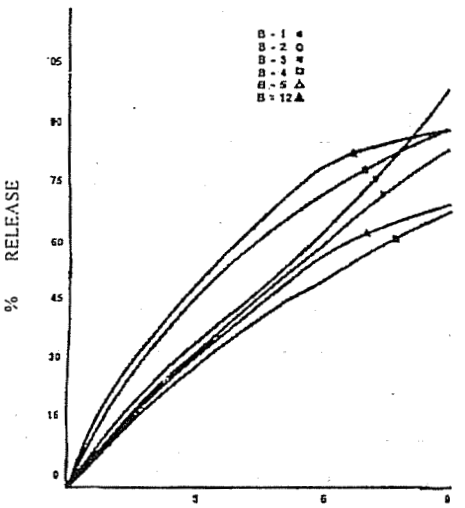
The samples collected were subjected to spectrophotometric analysis in ultraviolet range having the maximum absorbance at 277 nm for metronidazole. After suitable dilution, the blank for each one of the base was prepared by dissolving the suppository made without metronidazole with the respective base formulation. Standard curve for metronidazole was plotted and the absorbances of the samples collected were converted to concentration µg/ml from the metronidazole standard curve.

RESULTS AND DISCUSSION

1. Drug Release from PEG Formulations

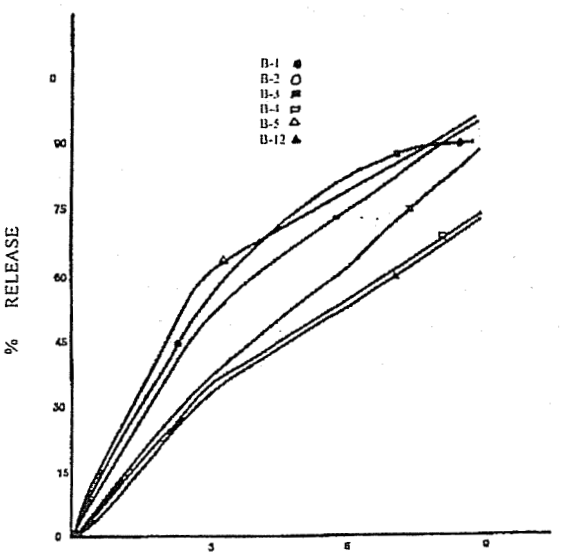
Rate of percentage release in PEG formulation at 37 °C was linear upto 65%. Initially the release was quicker but it slowed later on. It did not follow this

pattern at higher temperature nad the release slowed a short time ago. This may be due to the larger surface area of the suppository exposed first to the surrounding dissolution medium (Fig 1-3).



DRUG RELEASE PROFILE AT 37°C

Figure 1



DRUG RELEASE PROFILE AT 40°C

Figure 2

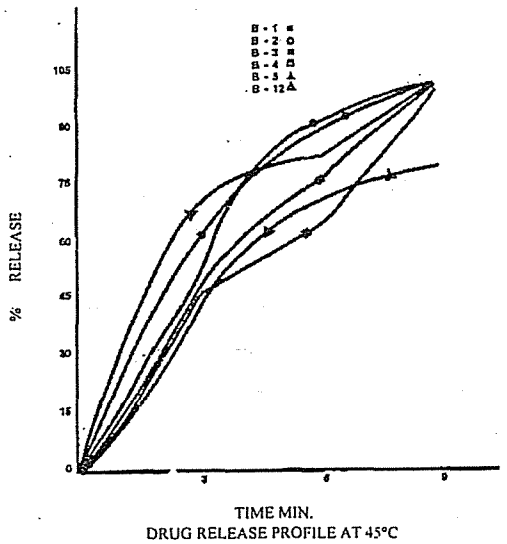


Figure 3

2. Effect of Molecular Weight

Average molecular weights of the blends of formulation bases were calculated as a weight average using the following equation:

$$MV_{(base)} = \frac{N_1 M_1^2 + N_2 M_2^2}{N_1 M_1 + N_2 M_2}$$

Where M_1 and M_2 are molecular weights of the two PEGs and N_1 and N_2 are the number of moles of each in the base. The average molecular weight of the twelve bases formulated are tabulated in Table 2.

Relationship between 50% rate of release and the average molecular weight was studied (Fig. 4, 5, 6). This was linear at 37 °C. 50% release time increased for bases B5, B2, B3, B4 with the increase in average molecular weight of PEG blends in the order listed. Addition of ethylene glycol and diethylene glycol reduced the 50% release time.

Formulation B1 and B10 have almost similar average molecular weights but their release behaviour is different (Fig 4, 5), 50% release time is similar at 40 °C, but it varies at 37 °C (Fig 4, 5). This may be due to the proportion of high molecular weight PEG in formulation B1 as compared to B10, thus required high temperature for initial release.

Table 2: Average molecular weights of the formulated bases.

Base Formulation Number	Average Molecular Weight
01	2566 or 2.56 X 10^3
02	2869 or 2.86 X 10^3
03	3289 or 3.28 X 10^3
04	3645 or 3.64 X 10^3
05	2358 or 2.35 X 10^3
06	4617 or 4.61 X 10^3
07	1603 or 1.60 X 10^3
08	1603 or 1.60 X 10^3
09	1603 or 1.60 X 10^3
10	2318 or 2.31 X 10^3
11	2318 or 2.31 X 10^3
12	5248 or 5.24 X 10^3

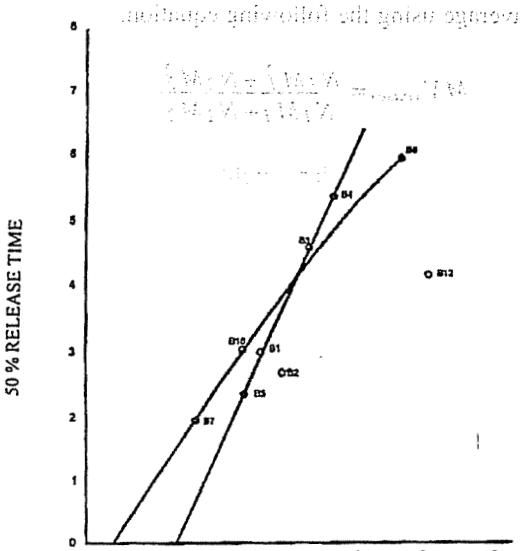


Figure 4

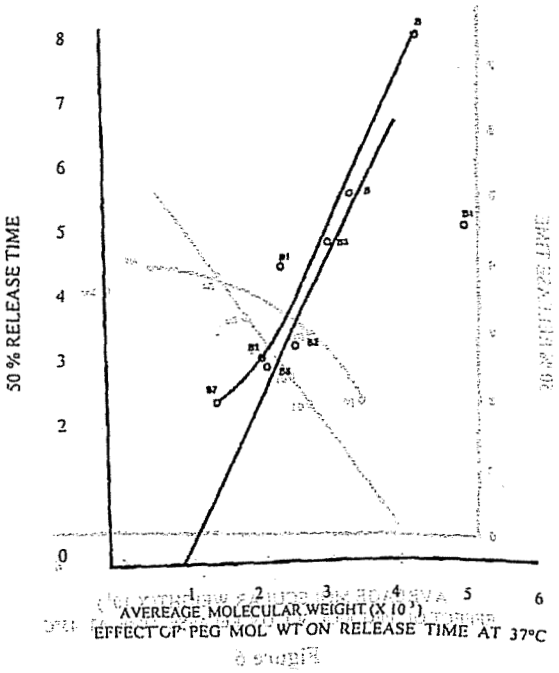


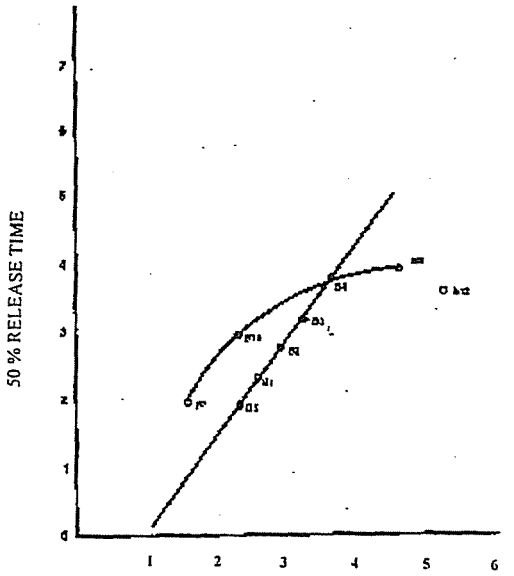
Figure 5

3. Effect of Additives

The different additives along with their percentages formulated in the PEG bases and their 50% release time at different temperatures are tabulated in Table 3. Increase in the amount of additive increases 50% release time at 37 °C (Fig 6, Table 3). Formulations B7 and B8 have similar average molecular weights but only 1% increase in the amount of additive (PVP) increased the release time. Addition of tragacanth further increased the release time. Addition of CMC reduced the release rate at 37 °C but increased significantly at higher temperatures. Thus the addition of additive to PEG changes the rate and is dependent upon the temperature and the blend.

Addition of PVP reduces the release rate at higher temperatures. Thus, PVP and CMC behaves opposite to each other. Any combinations can have the required release rate.

In most formulations, both PEG and PEG with additives show linear relationship at 37 °C (i.e., body temperature). Thus the blood levels can be effectively maintained. The investigation is relevant to the drug used i.e., Metronidazole. The following investigations are in agreement with the present study.



EFFECT OF PEG MOL WT ON RELAESE TIME AT 45°C

Figure 6

Table 3: Percentages of additives in bases formulations and drug release profile at various temperatures.

Formulation	Av. Mol. Wt.	CMC%	PVP%	Tragacanth%	Total%	50% Release Time		
						37 °C	40 °C	45 °C
B6	4.61 X 10^3		3	3	6	7.85	6.00	3.90
B7	1.60 X 10^3	2			2	2.40	1.97	1.55
B8	1.60 X 10^3	1	2		3	2.70	2.63	2.10
B9	1.60 X 10^3			2	2	2.55	1.85	1.88
B10	2.31 X 10^3		2		2	2.25	3.03	3.00
B11	2.31 X 10^3	2	2		4	3.53	3.45	2.36

In vitro release and in vivo absorption studies of ketoprofen suppository dosage forms in rabbits was conducted by Babar et al. (7) using the USP dissolution method. The release of ketoprofen was observed to be greater from polyethylene glycol 1000 Nair & Bhargava (8) compared in vitro dissolution and permeation of fluconazole prepared in hydrophilic, lipophilic, and amphiphilic bases using USP dissolution apparatus. Results suggest that in vitro release of fluconazole is greater from a hydrophilic base (PEG).

Utility of a rectal suppository containing the antiepileptic drug zonisamide was studied by Nagatomi et al. (9). Two types of zonisamide suppositories were prepared. One used Witepsol (H-15:S-55 = 3:1) as a lipophilic base and the other polyethylene glycol (PEG, 4000:1500 = 4:1) as a hydrophilic base. The in vitro release rate of zonisamide from the PEG suppository was significantly rapid compared with that of zonisamide from Witepsol.

The in vitro release characteristics of four suppository formulations of morphine (15 mg) were investigated by Morgan et al. (10) using the USP rotating basket dissolution apparatus. Morphine hydrochloride in polyethylene glycol (PEG), a hydrophilic suppository base, morphine alkaloid in PEG and morphine hydrochloride in Novata BBC (a lipophilic suppository base) completely released the drug within 25 min whereas, morphine alkaloid in Novata BBC (MAN) released the drug over 10 h.

CONCLUSIONS

1. PEG blends are effective vehicles for the drug release by means of suppositories for the drug metronidazole.
2. The percentage release of drug from PEG blends can be controlled at various temperatures by the addition of additives showing positive or negative response depending upon the type and concentration of the additive added. Thus, effective drug level for the drug can be maintained.
3. Release rate for drugs can be predicted from the knowledge of molecular weights of PEG blends and is effected by the presence of high and low molecular weight PEG.
4. Addition of ethylene glycol and diethylene glycol increases the dissolution of PEG in PEG bases.

5. CMC and PVP imparts controlling influence on dissolution of PEG bases.

6. Addition of additives line CMC at low concentration does not prolong drug release but increases the stability due to enhanced viscosity.

7. These bases should be practically useful clinically for drug delivery by means of suppositories.

These facts indicates the necessity to choose the base carefully if water soluble polymer as thickening agents are to be employed.

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