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RESEARCH PAPER

Solutol and Cremophor Products as New Additives in Suppository Formulation

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ABSTRACT

Our research has a double purpose. On the one hand, doctors have expressed the need to formulate a rectal suppository dosage form from diuretic ethacrynic acid, which would add to the choice of treatment methods and thereby increase the possibilities of individual cure. On the other hand, the liberation and thereby the bioavailability of poorly-soluble ethacrynic acid needs to be enhanced, and for this purpose solubility-increasing additives new to rectal therapy were used. Solutol HS 15, Cremophor RH 40, and Cremophor RH 60 were used as additives in concentrations of 1, 3, 5, and 10%. The quantity of drug released changed as a function of additive concentration. Depending on the acceptor phase, the best results were achieved with an additive concentration of 1–3%, which is related to the optimal additive quantity accumulated on the boundary surface.

Key Words: *Cremophor RH 40; Cremophor RH 60; Ethacrynic acid; Solutol HS 15; Suppository*

INTRODUCTION

One of the tasks of drug formulation is to develop an already-existing dosage form in such a way that drug release is the best possible under the given circumstances, so increasing the bioavailability. Another important aim is to make a given drug available in as many dosage forms as possible (1–5), which is also confirmed by the concrete therapeutic need expressed by doctors for the formulation of a rectal preparation containing furosemide (6), followed—after favorable human trials—by the formulation of further diuretic rectal suppositories.

The rectal administration of drugs may have definite advantages in certain cases: the drugs enter the organism bypassing the primary metabolism of the liver. Therefore, despite its disadvantages compared with oral administration, rectal application may be the optimal solution, especially in hepatic patients

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for whom this route of administration may offer special therapeutic advantages (7,8).

Diuretic ethacrynic acid belongs to the group of loop diuretics, since its effect is exerted on the ascending loop of Henle (9).

The aim of this research was to formulate a rectal suppository dosage form from a well-known drug, which would add to the choice of existing treatment methods and thus improve the possibilities of individual cure. However, it is a well-known fact that the release of drugs which are easily water-soluble is better from lipophilic suppository bases, so various solubility-increasing additives were used to enhance drug release (10–12).

MATERIALS

Ethacrynic acid was from EGIS (Hungary); Suppocire AML and Suppocire AP were from GATTEFOSSÉ (France); Witepsol H 15, Witepsol W 35, Witepsol S 58, and Massa Estarinum BC were from CONDEA Chemie GmbH (previously HÜLS AG) (Germany); Solutol HS 15, Cremophor RH 40, and Cremophor RH 60 were from BASF (Germany).

METHODS

In Vitro Dissolution Study

The drug content of the rectal suppositories prepared by molding was 2.5%, which corresponded to the therapeutic dose, that is an adult suppository of 2.00 g contained 50 mg of drug. The method of dynamic membrane diffusion (13) was used to determine the extent of drug liberation and diffusion through the membrane, both from the powder without a suppository base and from drug suppositories of various composition. Distilled water and phosphate buffer of pH 7.5 were used as the acceptor phase. The suppositories packed in membrane (VISKING®, Germany) were placed one by one into 20 mL of dissolution medium at body temperature ($37 \pm 0.5^{\circ}$C). The samples were exposed to slight horizontal shaking and the entire acceptor phase was changed after 30, 60, 120, and 240 min. The quantity of ethacrynic acid contained in the samples was determined spectrophotometrically at a wavelength of $\lambda = 278$ nm from the results of five parallel measurements.

Mathematical Evaluation

Linear regression was used to find a relationship between the process of dissolution and time. The calculations revealed that the process of dissolution could be characterized by a power function, which is also confirmed by the fact that lines were obtained when the logarithm of the quantity of the dissolved drug was plotted against the logarithm of time. The formulae of the lines giving the mathematical description of the relationship and the values of the correlation coefficient are shown in Table 1.

Table 1

Formulae of the Lines Describing the Process of Dissolution Mathematically and the Values of the Correlation Coefficient (R^2)

	Dissolving Medium: Distilled Water		Dissolving Medium: Phosphate Buffer	
Base	Line Equation	R^2	Line Equation	R^2
Powder	$y = 0.0272x + 1.2517$	0.9945	$y = 0.313x + 6.6322$	0.9886
Suppocire AML	$y = 0.0284x + 0.6852$	0.9968	$y = 0.2902x + 7.553$	0.9699
Suppocire AP	$y = 0.0071x + 0.493$	0.9882	$y = 0.2126x + 7.157$	0.9775
Massa Estarinum BC	$y = 0.0245x + 0.59$	0.999	$y = 0.2195x + 5.853$	0.9986
Witepsol H 15	$y = 0.0251x + 1.1526$	0.9866	$y = 0.2328x + 9.8609$	0.9294
Witepsol W 35	$y = 0.0201x + 0.6765$	0.9877	$y = 0.1201x + 13.191$	0.9448
Witepsol S 58	$y = 0.0168x + 0.4609$	0.9992	$y = 0.2368x + 8.213$	0.9702

x = log time (min).
y = log diffused drug (%).

RESULTS

The evaluation of the results shows that the changing of the acceptor phase led to about a 10-fold increase in drug release, which can be explained by better drug solubility in a phosphate buffer of pH 7.5 (Figs. 1 and 2).

Compared with the diffusion values of the ethacrynic acid powder without a suppository base, considered as standard, Suppocire AML proved to be the best in both dissolving media. The quantity of ethacrynic acid released was approximately the same as in the case of the Witepsol H 15 base, probably due to the relatively low hydroxyl number of both bases. This is also confirmed by the fact that the worst result was obtained with the Suppocire AP base, the hydroxyl number of which is considerably higher than those of the other bases. The amount of drug released from this base was much smaller than the membrane diffusion of the powder without a suppository base. The relationship between the hydroxyl number and the release of ethacrynic acid is also confirmed by the fact that the hydroxyl numbers of Witepsol S 58 and Witepsol W 35 are similarly high, and the quantity of drug diffused from them is also much less than from other CONDEA (HÜLS) products (Table 2).

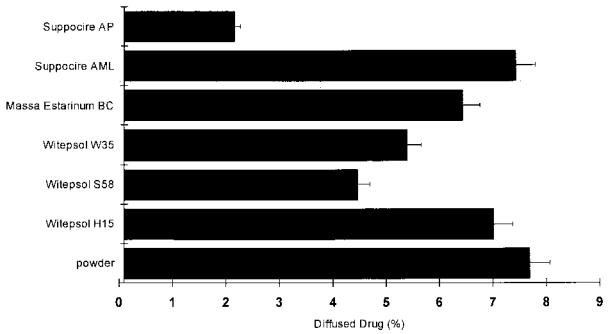

Figure 1. Release of ethacrynic acid from various suppository bases after 240 min. Acceptor phase: distilled water.

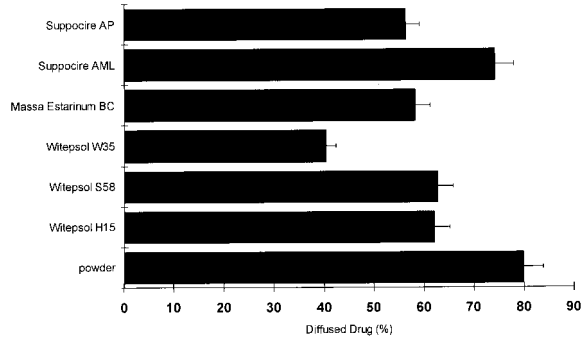

Figure 2. Release of ethacrynic acid from various suppository bases after 240 min. Acceptor phase: phosphate buffer.

Three solubility-increasing additives were tested for enhancing the liberation of poorly water-soluble ethacrynic acid. Solutol HS 15, Cremophor RH 40, and Cremophor RH 60 non-ionic surfactants were added to Witepsol H 15, which had previously proved to be one of the best suppository bases. These are all well-known additives, which had not been used in the dosage form of rectal suppositories before.

These surfactants have good physiological tolerance and considerable efficiency as regards solubilization. Solutol HS 15 is recommended as a non-ionic solubilizing agent to be added to injection solutions, while the use of Cremophor products is proposed to make fat-soluble vitamins, essential oils, hydrophobic drugs, and cosmetics water-soluble (14–16).

When surfactants were used in a concentration of 1, 3, 5, and 10%, the diffusion of the drug was found to vary with their concentration. When distilled water was used as the acceptor phase, a concentration of 3% yielded the best results for all three surfactants. This led to about a twofold increase in liberation. Their use in a concentration of 1–5–10% either did not change or decreased drug liberation (Fig. 3), which can probably be explained by the concentration of surfactants accumulated on the boundary surface as the quantity of the diffused drug is increased by proper saturation. In contrast, a too small or too large amount of surfactant may lead to its decrease.

Table 2

Hydroxyl Number of Bases

Bases	Hydroxyl Number
Suppocire AML	Max. 6
Suppocire AP	30–50
Massa Estarinum BC	30–40
Witepsol H 15	5–15
Witepsol W 35	40–50
Witepsol S 58	60–70

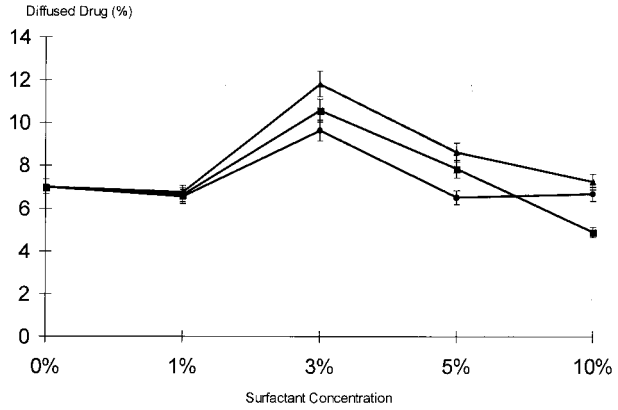

Figure 3. Drug release as a function of additive concentration after 240 min. Acceptor phase: distilled water. ■ Solutol HS 15, ● Cremophor RH 40, ▲ Cremophor RH 60.

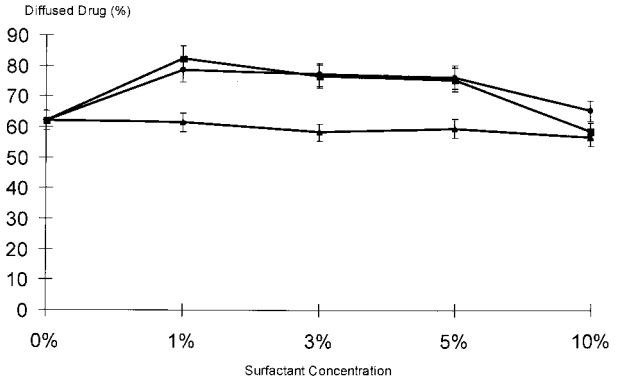

Figure 4. Drug release as a function of additive concentration after 240 min. Acceptor phase: phosphate buffer. ■ Solutol HS 15, ● Cremophor RH 40, ▲ Cremophor RH 60.

When the same examinations were performed in a buffer medium, 1% of Solutol HS 15 and Cremophor RH 40 led to a slight increase in diffusion, while the use of Cremopor RH 60 did not bring about a change in the extent of drug release. Therefore the pH increase is accompanied by a decreasing influence exerted by solubility-increasing additives on the liberation of ethacrynic acid, which is related to the dissolution property of the drug, namely that the solubility of ethacrynic acid increases in phosphate buffer of pH 7.5 (Fig. 4).

CONCLUSION

As a summary, it can be concluded that the use of additives enhanced the release of poorly water-soluble ethacrynic acid in the medium of distilled water. The increase of liberation was the greatest in a concentration of 3% for all three surfactants. When the pH of the acceptor phase was increased, a surfactant concentration of 1% was found to increase drug release to a slight extent, so the importance of the use of surfactants decreased. This can be explained by the fact that the solubility of ethacrynic acid is better in phosphate buffer of pH 7.5, thus it is released from lipophilic suppository bases more readily. Based on these results, a composition of Witepsol H 15 + 1% Solutol HS 15 is recommended for the formulation of rectal suppositories containing ethacrynic acid, as this composition increased drug release in both dissolving media.

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