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Invited Review

# Recent research on bioavailability of drugs from suppositories

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**Abstract**

The most interesting publications which have appeared within the last decade on the bioavailability of drugs from suppositories are taken into consideration. The topics concern the factors affecting bioavailability, the avoidance of first-pass effects, the role of absorption promoters, a sustained-release effect and selected therapeutic indications for the application of suppositories. The publications were mainly searched by means of 'Casonline' and 'Medline®' computer library programs.

*Keywords:* Suppository; Bioavailability; First-pass effect; Promoter; Sustained release

## 1. Introduction

During the last approx. 10 years, several publications on the rectal absorption of drugs have also appeared in the US and Japan where suppositories had not been previously well accepted from the cultural or emotional points of view. For a long period of time the rectal route was used only for the administration of local anaesthetics, anti-haemorrhoidal, vermifugal and laxative agents. Now the majority of natural and synthetic drugs are also formulated in the form of suppositories to produce a systemic effect. The elimination of drugs subject to the first-pass effect in liver and/or in the gastrointestinal tract may be partially avoided by rectal administration (Jonsson et al., 1988; Ogiso et al., 1991; Babul et al., 1992; Kato et al., 1992; Kurosawa et al., 1993).

Many researchers have concentrated their efforts in rectal drug absorption on those drugs which currently must be injected parenterally to provide effective therapy. Those drugs may be divided into two categories: antibiotics and polypeptides (Caldwell et al., 1984; Muranishi, 1984; Ritschel and Ritschel, 1984; Davis et al., 1985; Beskid et al., 1988; Bahia and Guedes, 1991; Mizuno et al., 1992; De Muynck et al., 1994). Unfortunately, many of these antibiotics and polypeptides are not absorbed from the rectum any more efficiently than from the small intestine, and require the coadministration of some absorption-promoting agents or adjuvants.

The suppository may be useful as a sustained-release formulation for the long-term treatment of chronic diseases like essential hypertension,

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asthma, diabetes, AIDS, anaemia, etc. (Kurosawa et al., 1985; Kawaguchi et al., 1991; Morgan et al., 1992; Reynolds, 1993; Hsyu et al., 1994).

Furthermore, there is a growing interest in the possibility of rectal administration in the treatment of post-operative pain or malignant pain (Moolenaar et al., 1984; Leow et al., 1992; Saruki et al., 1992; Koja et al., 1994).

## 2. Factors affecting bioavailability of drugs from suppositories

There are several therapeutic reasons mentioned above why a drug should be administered rectally rather than orally. One of these is that it is possible to avoid partly hepatic first-pass elimination following rectal administration. The rectal venous drainage is such that the upper part (superior rectal vein and middle rectal vein) is connected with the portal system and the lower part (inferior rectal vein) directly with the systemic circulation. However, there is no sharp distinction between these venous drainages, since the rectal veins are linked by an extensive anastomoses network (De Boer et al., 1984). It has been accepted that at least 50–70% of a drug suitable for rectal administration is absorbed via the above direct pathway (Jaminet, 1973).

The absorption surface of the rectum ranges between 0.02 and 0.05 $m^2$ and a viscous rectal fluid which is spread over the surface is evaluated to be equal to from 0.5 to 1.25 ml of pH approx. 7.9 with very low buffer capacity (Ziegler, 1986).

It is well recognized that drug absorption after rectal administration is in agreement to a considerable extent with the pH partition theory (Muranishi, 1984). Thus, colorectal absorption is a simple diffusion process through the lipoidal membrane in which carrier-mediated mechanisms play no role. Subtle differences in the properties of mucous membranes have been found between the colorectal and upper gastrointestinal area. The high sensitivity of the colorectal mucous membrane to membrane-active adjuvants is most attractive for the formulation design of poorly absorbed drugs (Muranishi, 1984).

In many suppositories the drug substance is in suspension in the vehicle. This means that drug absorption by the rectal route is governed by particle size, solubility in water and interfacial tension. However, there are some systems in which the drug dissolves either fully or in part in the base. In these cases other factors such as solubility in base and water, distribution coefficient and relative phase volume will play a role (Armstrong and James, 1984). Kakemi (cited by Armstrong and James, 1984) suggested that when a drug is administered rectally as an oily solution, direct absorption from the oil is of little consequence. A necessary preliminary is the release of the solute into the aqueous rectal fluid, and only then can absorption occur. If Kakemi's suggestion is correct, the factors of drug amount in oil ($M_o$), volume of oil and partition coefficient ($K$), represented in the following equation, must play a role in drug absorption from a rectally administered oily solution:

$$M_w = M_o/(K\emptyset) \quad (1)$$

where $M_w$ is the amount of a drug in the aqueous phase and $\emptyset$ represents the volume ratio of oil to water (Armstrong and James, 1984). Furthermore, the above equation describes equilibrium conditions. If the rate at which partitioning of the drug is achieved is slow in comparison with absorption from the aqueous phase, then equilibrium may never be reached and transfer from oil to water becomes the rate-determining process.

Hence, the condition of sink is important in cells designed for the testing of drug release from suppositories in vitro. Therefore, the above conditions favor the flow-through method with open supply of fresh fluid. Transport of the dissolved drug out of the molten mass and into the aqueous receiver requires a large and/or agitated area of contact between two phases in order to make the release kinetics similar to those in vivo (Langenbucher, 1984).

Active substances which are highly soluble in the excipient in fact diffuse much less rapidly out of the excipient than those active principles which are insoluble or have low excipient solubility, and hence the former substances are not so readily absorbed. As in all passive absorption processes it is necessary for a drug to reach rapidly a high

concentration at the rectal mucous membrane compartment. This is perhaps one reason why certain salts of organic acids which are fairly soluble in water (barbiturates, salicylates, etc.) are absorbed faster than their undissociated free acids. It is reasonable to use a fat-like base for a water-soluble drug and a hydrophilic base for an insoluble drug in water. Furthermore, the diffusion rate of a drug suspended in a fat base of both low hydroxyl number and viscosity is increased (Jaminet, 1973).

Small particles of a drug do not always result in higher blood levels. An explanation for this phenomenon can be provided on the basis of the release processes: melting, spreading, sedimentation, wetting and dissolution. Apparently, the rate-limiting step for the release of an insoluble drug from the vehicle could be its transport rate through the molten suppository, which would favor the larger particles of a drug that is readily soluble in the rectal fluid. However, the dissolution rate of drugs that are slightly soluble in that fluid usually will be limited and thus smaller particles ($< 50$ $\mu$m) should be preferred. The spreading of a suppository base with a suspended drug in the rectocolon is dependent on the pressure exerted through the rectal wall by abdominal organs and/or by rectal wall muscles. The final spreading area decreases with increasing apparent viscosity of the spreading system (De Blaey and Tukker, 1982).

The bioavailability of chemically stable rectal drugs is also influenced by the physical stability of suppositories during storage (Müller, 1984; Thoma, 1984). The so-called hardening effect occurs during storage of suppositories. It results in an increase in the melting time of suppositories. Considerable changes in melting times arise only with bases of higher melting ranges (Witepsol H 37, 36–38° C). Bases with the lowest melting points (e.g., Witepsol H 32, 31–32° C) are subject only to minor changes. This hardening effect can be almost completely inhibited, for example, by the addition of 2% soya lecithin. Three hypotheses for an explanation of the hardening effect of suppositories have been postulated: polymorphic phase transitions, increase in crystallinity, and transesterification (Thoma, 1984).

The blending of triglycerides with mono- and diglycerides or suppository bases with surface-active agents prevents the crystallization of polymorphs with higher melting points and promotes the spreading of the molten base over the whole rectal region. However, higher surface-active agent concentrations produce retardant and/or irritative effects. Thermal behavior, hardening effects and brittleness are a question not only of polymorphism, but also of lattice defects due to the thermal treatment of suppositories during the manufacturing process (Müller, 1984).

## 3. Avoidance of the first-pass effect

Morphine (Jonsson et al., 1988; Babul et al., 1992), 6-mercaptopurine (Kato et al., 1992) and salbutamol (Kurosawa et al., 1993) are examples of drugs which have recently been studied with the aim of avoiding hepatic and/or alimentary canal first-pass effects and the results are relatively positive without any use of absorption promoters.

A high-clearance drug such as morphine is subject to substantial first-pass metabolism, when administered orally. Plasma concentrations of morphine were followed for 24 h in eight postoperative patients after intravenous and rectal (hydrogenated fat) administration of 10 mg morphine hydrochloride. The bioavailability of morphine after rectal administration was found to be $53 \pm 18\%$. In a study in seven cancer patients, the mean oral bioavailability of morphine was found to be 37% (Jonsson et al., 1988).

The bioavailability of 30 mg morphine sulfate controlled-release suppository formulations (high and low viscosity) was compared with that of 30 mg oral controlled-release morphine sulfate tablets in a study of 14 subjects. Compared with oral controlled-release morphine, the high- and low-viscosity suppositories had significantly greater relative bioavalability ($73 \pm 13\%$ for the oral preparation vs $99 \pm 36$ and $106 \pm 37\%$ for the suppositories) (Babul et al., 1992). The above studies indicate that the first-pass elimination of morphine may be partially avoided by rectal administration.

6-Mercaptopurine is one of the major drugs used in maintenance therapy of children with acute lymphoblastic leukaemia. The poor bioavailability of oral 6-mercaptopurine is thought to be due to its extensive presystemic elimination in the alimentary canal and/or liver. The low and variable bioavailability of this drug has been suggested as one of the possible causes of relapse in some children with leukaemia. The relative bioavailability of the Macrogol suppositories compared to the oral powder was approx. 439% in five children with acute lymphoblastic leukaemia (Table 1). These results indicate that rectal administration of 6-mercaptopurine could avoid the first-pass effect, resulting in a large AUC of 6-mercaptopurine and could be more effective than empirical oral dosing (Kato et al., 1992).

In order to evaluate rectal administration of salbutamol, five healthy volunteers were dosed orally and rectally with racemic salbutamol. The $C_{max}$ following rectal administration was 17.9 ng/ml (17.0 ng/ml for oral administration), $t_{max}$ = 0.67 h (1.5 h for oral administration) and the AUC = 98.2 ng $ml^{-1}$ h (100 ng $ml^{-1}$ h for oral administration). Heart rate also rose more rapidly after rectal dosing. The concentration vs response curve indicated that rectal salbutamol was more effective than oral. A plausible explanation for this phenomenon might be a difference in the stereo-selective first-pass metabolism of the two enantiomers. The rectal dose of salbutamol administered as a suppository for prophylactic treatment of asthma should be lower than that used orally (Kurosawa et al., 1993).

## 4. Coadministration of absorption promoting agents or adjuvants

A rectal route of administration or sophisticated drug delivery systems have been greatly desired for poorly absorbed drugs such as antibiotics and high molecular weight drugs. Ionic surfactants, sodium lauryl sulfate and the chelating agent EDTA, for example, are rather harmful to the mucosal membrane. Therefore, the nutrient-like lipids were used as safe adjuvants. As these lipids are generally insoluble in water, unharmful surfactants were utilized for solubilizing or dispersing the lipids. Streptomycin and cefazolin were chosen as poorly absorbed drugs with water-soluble small molecules, and heparin, bleomycin, and interferon as typical water-soluble large molecules (Muranishi, 1984). The monoolein-taurocholate mixed micelle concentration required to potentiate the absorption of heparin from the large intestine appears to be one-fourth of that needed in the small intestine. Lipids such as monoolein are considered to play an important role in the induction of absorption. Among the fatty acids, the unsaturated fatty acids with lower melting point showed greater promotion of streptomycin absorption. It appears that unsaturated fatty acids and their monoglycerides are membrane-active compounds useful for dosage design of rectal delivery systems. The micellar state may facilitate the incorporation of the polar lipid component of mixed micelle into the mucosal membrane. The fusogenic lipid interacts with the polar region of the membrane phospholipids and disturbs the membrane lipids interior. The interaction of fusogenic lipid may enhance the fluidity of the membrane, initiate a formation of transient lipid complex and destabilize the bilayer configuration. Consequently, such a transient change in membrane lipid configuration can contribute to the permeation of less permeable drugs (Muranishi, 1984). Monoolein-taurocholate mixed micelles increased the bleomycin concentration in plasma and lymph about 10-fold. Neither linoleic acid nor the polyoxyethyl derivative of hydrogenated castor oil promoted the absorption of human interferon-$\beta$ via the colorectal route. However, the administration of a mixed micellar system combined with the above components gave a high concentration of the interferon in the lymph, but only a minimal level in the serum. The extremely strong lymphotropic property of interferon might be attributed to such factors as the shape and configuration of the molecule, in addition to its molecular size (Muranishi, 1984).

Sodium 5-methoxysalicylate, when administered together with a water-soluble form of an antibiotic (sodium cefmetazole, sodium cefoxitin, potassium penicillin) can dramatically improve

rectal bioavailability. In some cases equivalence to the i.v. route was observed. The lymphatic pathway allows drugs to circumvent first-pass liver exposure. There is currently some evidence accumulating that 5-methoxysalicylate may augment the lymphatic transport of coabsorbed drug after rectal administration. Pretreatment of rectal mucosa with ouabain, a specific inhibitor of active sodium transport, reduced in a concentration-dependent fashion the adjuvant effects of a number of active agents, including salicylates, thereby implicating the transmucosal sodium gradient in the adjuvant process. It was demonstrated that phlorizin (an inhibitor of glucose transport) and 2,4-dinitrophenol (a metabolic inhibitor) decreased the adjuvant effects of sodium salicylate and sodium 5-methoxysalicylate (Caldwell et al., 1984).

It was shown that insulin is not absorbed rectally by the blood vessels nor via the lymphatics. In the presence of 5-methoxysalicylate, approx. 68% of the total insulin uptake was found in lymph collected from the thoracic duct. About 30% of rectally absorbed insulin enters the portal vein and consequently the liver. Although the liver is the major place of insulin degradation, it is also the site of greatest insulin utilization. The authors believe insulin is the first drug where the presence of the first-pass effect is essential in eliciting the pharmaceutical response. Assuming the liver as the target organ, the pharmacological response to insulin may be greater upon rectal administration than would be anticipated from the insulin concentration measured in systemic circulation because part of the insulin reaches the plasma compartment, which can be sampled only after it has passed through the target organ (Ritschel and Ritschel, 1984).

If the surface-active agent accumulates in the rectal fluid to a concentration above the CMC, the absorption rate of a drug will be reduced mainly due to entrapment in micelles. A surface-active agent lowers the surface tension, thus improving the wetting and contact with the epithelium, and distribution of the drug. Furthermore, the action of fatty acids, fatty alcohols and esters of fatty acids (oils, oleates, lactates, etc.) may be due to their good solvent properties for various drugs, and their miscibility with phospholipids (Ritschel and Ritschel, 1984).

The bioavailability of cefoxitin administered in the form of suppositories was examined in six human subjects. The presence of sodium salicylate and a nonionic surfactant Brij 35 enhance the bioavailability to 20% which was as low as 3% for a system without adjuvants (Davis et al., 1985).

Ceftriaxone sodium salt formulated in mono- and diglyceride extracts of coconut oil as a suspension developed the bioavailability to 42% (Beskid et al., 1988).

The suppositories of cefatoxime, ceftazidime and cefoxitin in the presence of sodium lauryl sulfate appear to be applicable to humans (Bahia and Guedes, 1991).

The low bioavailability of oral propranolol dosage forms and its variation have been attributed to extensive drug metabolism in the liver. In fact, the hepatic first-pass effect of propranolol can be avoided by rectal administration. Medium chain fatty acids significantly enhance the in vitro rectal absorption of propranolol. A portion of propranolol, by forming a 1:1 complex with lauric acid, would penetrate across the rectal mucosa more readily than propranolol itself. The higher molar ratio (1:3) of lauric acid decreased

Table 1
Mean (SD) pharmacokinetic parameters of 6-mercaptopurine after oral and rectal administration to five children with acute lymphoblastic leukemia (Kato et al., 1992)

| Route of administration | Dose (mg $m^{-2}$) | $C_{max}$ (ng $ml^{-1}$) | $t_{max}$ (h) | AUC (ng h $ml^{-1}$) | $F_{rel}$ [a] |
|---|---|---|---|---|---|
| Oral | 87.5 | 280 (183) | 1.2 (0.4) | 366 (118) | 1.0 |
| Suppository | 30.0 | 125 (99.6) | 1.4 (0.9) | 539 (116) [b] | 4.39 (0.44) |

[a] Relative bioavailability was estimated using the following equation: $F_{rel} = (AUC_{rectal}/AUC_{oral}) \cdot (dose_{oral}/dose_{rectal})$.
[b] Significantly different from oral administration ($p < 0.05$) according to ANOVA.

Table 2
Pharmacokinetic parameters in rats following rectal administration of propranolol formulated without (1,3) and with lauric acid (2,4) in either Witepsol H-15 (1,2) or in Macrogol 1500 and 4000 suppository base (3,4) (Ogiso et al., 1991)

| No. | $C_{max}$ (ng ml$^{-1}$) | AUC (ng h ml$^{-1}$) | Bioavailability (%) | MRT (h) |
|---|---|---|---|---|
| 1 | 453.8 ± 100.0 | 757.5 ± 123.5 | 22.7 ± 4.3 | 2.25 ± 0.52 |
| 2 | 984.2 ± 177.7 [a] | 2641.3 ± 440.0 [a] | 79.0 ± 13.2 [a] | 2.34 ± 0.33 |
| 3 | 298.9 ± 55.9 | 288.7 ± 71.7 | 17.3 ± 4.3 | 0.97 ± 0.11 |
| 4 | 400.6 ± 90.5 [b] | 612.2 ± 113.6 [a] | 36.6 ± 6.8 [a] | 0.97 ± 0.58 |

Each value represents the mean ± SD ($n$ = 3–8).
[a] $p < 0.01$ and [b] $p < 0.05$, respectively, compared with the suppository without lauric acid.

the release rate markedly compared with that at the 1:1 molar ratio, probably due to the retention of the drug in excess fatty acid. De Boer et al. (1984) showed that the mean oral and rectal bioavailabilities of propranolol in rats are 3.1 and 101.1%, respectively. Ogiso et al. (1991) calculated that the bioavailability of propranolol without lauric acid was increased rectally in rats by a factor of 6–7 if compared with the oral route. The addition of lauric acid at 1:1 molar ratio to propranolol further increased the bioavailability of propranolol Macrogol suppositories by a factor of 12 (Ogiso et al., 1991) (Table 2).

Currently, polypeptide hormones such as human erythropoietin are administered by injection because of their poor membrane permeability. Without a promoter recombinant human erythropoietin was not absorbed in the rectum from a solution or a suppository. Sodium glycocholate, sodium caprate, and sodium salicylate increased the absorption of erythropoietin. The bioavailability of erythropoietin from a suppository containing 5% sodium salicylate was 1.2% when compared to an i.v. injection. The erythropoietin given in a suppository containing sodium salicylate and inserted once a day for six consecutive days increased erythropoiesis in rat peripheral blood. $AUC_{0\rightarrow 2h}$ was the greatest with sodium salicylate and the smallest with sodium glycocholate. Bile salts such as sodium glycocholate seem to bind with calcium ions and sodium caprate changes the pore size in the tight junctions of membranes. These promoters probably increase the permeability of membranes to hydrophilic macromolecules via the paracellular route. Sodium salicylate seems to increase transport through both paracellular and transcellular routes (Mizuno et al., 1992).

Triglycerides as well as PEG have been shown to induce rectal irritation when used repetitively. The degree of rectal irritation was reduced by coadministration of monoglycerides or a blend of fatty acids and fatty acid methyl esters with triglycerides. Adding monoglycerides to the triglycerides apparently enhanced the bioavailability. Linoleic acid based monoglycerides have been shown to be absorbed from the rectum. In the epithelial cell, these *cis*-unsaturated fatty acid

Table 3
Area under the curve (AUC) and area under the first moment curve (AUMC) for ibuprofen (IBP) and ibuprofen lysinate (IBPL) in rats calculated from Eq. 3 and 4, respectively, taking into consideration either the lag time ($t_{C=0}$) observed (2) or neglecting it (1) (Hermann et al., 1993)

| Suppositories | | IBP | | IBPL | | | | |
|---|---|---|---|---|---|---|---|---|
| | | IBP Polfa | I | Imbun 500 | II | IV | II′ | III |
| AUC ($\mu$g ml$^{-1}$ h) | 1 | 541.8 | 167.4 | 699.8 | 188.1 | 387.8 | 191.9 | 144.5 |
| | 2 | 543.1 | 167.9 | 699.8 | 189.5 | 389.7 | 192.8 | 152.8 |
| AUMC ($\mu$g ml$^{-1}$ h$^2$) | 1 | 1296.4 | 176.8 | 1314.9 | 140.9 | 477.7 | 132.4 | 151.2 |
| | 2 | 1296.4 | 176.8 | 1315.0 | 140.9 | 477.8 | 132.4 | 151.5 |
| $t_{C=0}$, lag time (h) | | 0.0783 | 0.0383 | 0.0048 | 0.0383 | 0.0517 | 0.033 | 0.1283 |

monoglycerides disorder the hydrophobic region of the membrane's interior and interact with the polar head groups of phospholipids inducing an increase in permeability of these cells. Monoglycerides can also solubilize cholesterol, a membrane stabilizer, which could result in facilitated transcellular transport (De Muynck et al., 1994).

## 5. Sustained-release effect

The so-called lag time is quite often observed in absorption and/or release of drugs from suppositories (Kurosawa et al., 1985; Hermann et al., 1993). However, it is not often considered for calculation of the area under the curve (AUC) and area under the first moment curve (AUMC) (Table 3). Plasma concentration ($C$)-time ($t$) plots of many drugs from suppositories are characterized by the difference in two exponentials (Hermann et al., 1993):

$$C = Be^{-\lambda_2 t} - Ae^{-\lambda_1 t} \quad (2)$$

In Eq. 2, $A$ and $B$ are the corresponding zero time intercepts, $\lambda_1$ and $\lambda_2$ denote the apparent first-order fast and slow disposition rate constants, respectively, and $t$ is time. It should be taken into consideration that $A$ exceeds $B$ because there is a lag time ($t_{C=0}$). Calculations of AUC on integration of Eq. 2 lead to erroneous results until it is integrated between $t_{C=0}$ and $t_\infty$. Therefore, the correct calculations of $AUC_{calc}^{true}$ should be as follows:

$$AUC_{calc}^{true} = \left(Be^{-\lambda_2 t_{C=0}}/\lambda_2\right) - \left(Ae^{-\lambda_1 t_{C=0}}/\lambda_1\right) \quad (3)$$

Also, the corrected AUMC from $t_{C=0}$ to infinity ($t_\infty$) is as follows:

$$AUMC_{corr}^{A \neq B} = \left(1/\lambda_2^2\right)\left(Be^{-\lambda_2 t_{C=0}}\right)\left(1 + \lambda_2 t_{C=0}\right) - \left(1/\lambda_1^2\right)\left(Ae^{-\lambda_1 t_{C=0}}\right)\left(1 + \lambda_1 t_{C=0}\right) \quad (4)$$

A variety of approaches have been investigated for producing controlled-release suppository formulations of different drugs. These include modification of the suppository base, use of additives and polymer-coated drug particles.

The potential advantage of morphine base suppository formulated in a lipophilic base Novata BBC has led to its approval for human use. This suppository releases morphine slowly but completely and produces sustained plasma concentrations for at least a 7 h period (Morgan et al., 1992).

Nifedipine rectal suppositories were prepared in polyethylene glycol base as a treatment of hypertensive emergency subjects. The mean nifedipine plasma concentration curve following rectal administration showed slightly delayed absorption as compared to oral administration. However, both dosage forms are characterized by the same extent of bioavailability. A hypotensive effect of nifedipine suppository in the subjects was observed 30 min after administration and the effect was more definite and sustained compared to the oral capsule (Kurosawa et al., 1985).

A new type of double-phase suppository with two different drug release mechanisms (fast-release and sustained-release) was developed. The fast-release phase was prepared using Witepsol H 15 as a hollow-type suppository, whereas the sustained-release phase was made from an oily semisolid matrix consisting of soybean oil and stearyl alcohol. Diclofenac sodium was selected as a model drug. An in vivo rectal absorption study in rabbits showed that the relative bioavailability of diclofenac from the double phase suppository, compared to a reference Witepsol H 15 mono-phase suppository, was approx. 100%. However, the double-phase suppository showed approx. 2-fold enhancement of the mean residence time (Shibata et al., 1992).

3′-Azido-3′-deoxythymidine (AZT or zidovudine) has been shown to provide clinical benefit mostly by oral administration in the management of syndromes (AIDS and ARC) associated with HIV infection. Although orally administered AZT is rapidly absorbed, a considerable first-pass effect (> 40%) and rapid elimination (half-life of 1 h) necessitate a high daily dose and frequent administration (5–10 mg/kg, every 4 h). The usefulness of sustained-release suppositories for reducing the frequency of drug administration has been reported. A sustained-release suppository was prepared by direct compression of hy-

doxypropylcellulose with AZT. A glyceride base (Witepsol H 15) was used for preparation of a conventional suppository. The suppository formed by the direct compression of hydroxypropylcellulose has demonstrated sustained and relatively constant release of the drug. While AZT was absorbed rapidly from the conventional suppository and eliminated within 3 h, the plasma levels following the hydroxypropylcellulose suppository remained high, greater than the supposed minimum level for antiviral effect of 1 $\mu$M, being maintained over 6 h (Kawaguchi et al., 1991).

Ondansteron, an antagonist of the serotonin type 3 receptor (5-$HT_3$), is indicated for the treatment of chemotherapy-induced emesis in cancer patients. The absolute bioavailability after oral dosing, colonic infusion and rectal administration averaged 71 ± 14, 74 ± 26 and 58 ± 18%, respectively. These values were not significantly different. It has been suggested that compounds transported transcellularly by passive diffusion tend to have similar rates of absorption in different segments of intestine. The recommended oral dosing regimen of ondansteron for ematogenic neoplastic agents is 8 mg three times a day. Sustained-release formulations such as suppositories may reduce the dosing frequency of ondansteron and, therefore, increase patients' compliance (Hsyu et al., 1994).

## 6. Suppositories selected on therapeutic indications

Rectal dosing with metronidazole has been shown to be effective for prophylaxis and therapy of anaerobic infections in patients undergoing abdominal and gynaecological surgery. Of all rectal dosage forms, the polyethylene glycol suppositories gave the highest peak plasma levels and the highest relative bioavailability (80% compared with oral administration) (Vromans et al., 1984) (Table 4).

Methadone is a narcotic analgesic that possesses attractive pharmacokinetic and pharmacodynamic properties for the relief of moderate to severe pain of an acute character as well as malignant pain. Compared with oral dosing, the extent of rectal absorption from an aqueous solution was almost 80%. Rectal absorption conditions of methadone from fatty suppositories were found to be less favourable (33–58%). This rate-limiting absorption pattern may be due to the critical solubility properties of methadone hydrochloride at physiological pH. A factor which may contribute to the less favourable driving force for absorption is the relatively high $pK_a$ value of methadone (9.2) when compared to codeine (8.1) and morphine (7.9). The free base of methadone precipitates out presumably partially in the rectum (pH 7.5–8.0). It is interesting to note that the rectal absorption profile for codeine phosphate and morphine hydrochloride was identical compared with the oral absorption profile of these drugs and did not vary significantly. It should be mentioned that the solubility of codeine and morphine is much greater than that of methadone itself in an aqueous medium (Moolenaar et al., 1984).

The pharmacokinetics of oxycodone have been determined in 48 patients undergoing minor surgery. The amount of oxycodone reaching the

Table 4
Absorption characteristics of metronidazole (mean ± SD) from various dosage forms after rectal and oral administration of metronidazole (500 mg) to seven healthy volunteers (Vromans et al., 1984)

| Parameters | Oral solution | Rectal suspension | Fatty suppositories | PEG 1000 + 6000 suppositories |
|---|---|---|---|---|
| $C_{max}$ ($\mu$g ml$^{-1}$) | 10.7 ± 1.7 | 4.8 ± 1.6 | 4.5 ± 1.2 | 6.8 ± 1.4 |
| $t_{max}$ (min) | 40 ± 20 | 80 ± 25 | 270 ± 100 | 170 ± 50 |
| $AUC_{0-24\,h}$ ($\mu$g ml$^{-1}$ h) | 114.1 ± 17.1 | 62.6 ± 12.1 | 63.1 ± 11.8 | 89.1 ± 14.5 |
| $F_{rel}$ (0–24 h) (%) | 100 | 55 ± 20 | 55 ± 7 | 78 ± 13 |

systemic circulation after extravascular routes of administration (oral and rectal) was < 50% of that obtained after intravenous dosing (Leow et al., 1992).

The dose and route of administration of a corticosteroid given for the treatment of patients with ulcerative colitis are determined according to the range of the diseased area and its severity. The spread of the drugs after intrarectal administration and their therapeutic effect were determined. A therapeutic effect on the colitis induced in rats by acetic acid was noted in the area up to 10 cm from the anus in the case of the hydrophilic suppository, while the effect of the hydrophobic suppository was seen only in the area up to 2.5 cm from the anus. In patients with ulcerative colitis, the hydrophilic suppository showed retrograde spread to a site $34.4 \pm 5.3$ cm from the anus, while the hydrophobic suppository spread to a site $19.0 \pm 2.4$ cm from the anus. These results suggest that a hydrophobic suppository should be used for patients in whom inflammation is confined to the rectum, and a hydrophilic suppository for those in whom inflammation reaches the rectum and the middle part of the sigmoid colon (Sadahiro et al., 1992).

Both rectal mesalamine and oral olsalazine (5-aminosalicylic acid products) provide clinicians with an effective therapeutic option for the treatment of inflammatory bowel diseases in patients unresponsive to or intolerant of the effects of sulfasalazine or corticosteroids (Segars and Gales, 1992).

Buprenorphine hydrochloride suppository was given immediately postoperatively to patients who had undergone surgery under general anaesthesia. Post-operative pain has been observed after $782 \pm 41$ min in the patients with suppository and $127 \pm 18$ min in the control group (Saruki et al., 1992).

50 patients with head and neck cancer were treated with tegafur – a prodrug of 5-fluorouracil – preoperatively. It was revealed that high 5-fluorouracil concentrations were seen in cancer tissues of the nasal-paranasal cavity, tongue and mesopharynx and then metastatic lymph nodes. The tegafur suppositories were useful because of the high concentrations reached in the target organs without any obvious side effects in the head and neck region (Koja et al., 1994).

## 7. Conclusion

There is no doubt that suppositories are used in the treatment of many diseases in contemporary medicine. A remarkable number of drugs is formulated in the form of suppositories to produce either local or systemic effects. The former effect is developed by local anaesthetics, antihaemorrhoidal, vermifugal and laxative agents. The latter effect is produced mainly by analgesic, antipyretic, antihypertensive, anti-asthmatic, antimicrobial, anti-inflammatory and antineoplastic drugs administered per rectum. The elimination of drugs subject to the first-pass effects in liver and/or in the gastrointestinal tract may be partially avoided by rectal administration. Many researchers have concentrated their efforts in rectal drug absorption on those drugs which currently must be injected parenterally, e.g., antibiotics and polypeptides. The suppository may be useful as a sustained-release formulation for the long-term treatment of chronic diseases like essential hypertension, asthma, diabetes, AIDS, anaemia, etc. It is also administered in unconscious and paediatric patients as well as for the treatment of pregnancy-, chemotherapy- and allergy-induced emesis.

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