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# PHYSIOLOGICALLY BASED NOVEL PERORAL MODIFIED RELEASE DRUG DELIVERY SYSTEM: SELF-DESTRUCTING HYDROGEL PISTON-PUMP

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## ABSTRACT

Peroral modified drug delivery systems on the market release the drug by either O-order, 1 st-order, square root of time or mixed rate. This means that the drug is released into the gastrointestinal lumen in amounts being either constant per unit of time or decreasing with time. However, physiologically absorption from the GI lumen gets slower and more difficult past the small intestine. A novel drug delivery system is described for 24 hours drug delivery which follows approximate 0-orden release throughout the small intestine, but releases increasing amounts of drug once in the colon to compensate for increasingly more difficult absorption. Nearly constant steady state drug plasma concentrations are achieved. The novel drug delivery system is a two layered dosage form with an immediate release layer and a modified release layer. The latter one is a hydrogel piston pump comprised of a drug core layer and a hydrogel swelling layer, embedded into a semipermeable shell by compression coating. The upper site of the shell has a release channel in the center.

## INTRODUCTION

Peroral delivery systems for prolonged, now-called modified release are on the market since more than 50 years. In the 1950 empirical trial and error release prolongation was achieved by using embedment of drug substances into waxes and fats. In the 1960´s coating with polymers and other materials by spraying and congealing was used. In the 1970´s various mathematical models were developed to describe release patterns of drugs from the different kinds of mechanical delivery systems. In the 1980´s a flood of sophisticated and «exotic» modified drug delivery systems appeared in the literature.

Parallel with the growth of biopharmaceutics and pharmacokinetics the modified drug delivery systems were designed on pharmacokinetic principles to achieve a plateaulike steady state therapeutic drug concentration in blood or plasma during the entire dosing intervel.

## BACKGROUND

The «gold standard» for drug release from modifield drug delivery systems became a zero-order release, where a constant amount of drug is liberated per unit of time. If O-orden release was not achieved, at least a first-orden release or square root of time release was desirable. Fig. N.° 1 shows schematically these time release patterns, where the ordinate shows the % of drug remaining in the dosage form versus the time on the abscissa (1-3).

Some of the mathematical models to describe drug release are listed in Table N.° 1.

Figure 1 and Table 1 represent the drug release from peroral dosage forms in vitro into a specified aqueous medium, such as plain water, buffer solutions, artificial gastro intestinal fluids without or with enzymes, with various modes of agitation or motion, usually at 37 °C.

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## A SECOND LOOK

The desired 0-order «gold standard», 1st-order, «t and all other liberation profiles obtained *in vitro* assume that *in vivo* the human alimentary tract behaves as a one-compartment system. Such an over-simplification reduces the complicated alimentary tract to a water-filled beaker.

Let us consider the individual physiologic, histologic and anatomic aspects for the travel of a peroral drug delivery system through the alimentary tract from the moment, of ingestion through the mouth cavity, esophagus, stomach, small intestine, large intestine, rectum to the fecal excretion (4-7). The figures 2 to 8 show the individual parameters (on ordinate) as they vary from anatomic segment to segment (on abscissa) (8). The segments mouth cavity and esophagus were omitted since this type of delivery system is swallowed intact and the transit time through the two segments lasts only a few seconds or not more than about half a minute.

Fig. N.° 2 shows the transit time through the major segments stomach, small intestine, large intestine and rectum. The transit time in the segments vary from 0.5 to 16 hours. Each of the following parameters needs to be considered in context with the corresponding transit time in each segment.

Fig. N.° 3 shows the luminal surface areas which vary from 0.015 to 200 $m^2$.

Macro- and microvilli greatly increase the luminal surface. The larger the surface area the faster is the absorption.

Fig. N.° 4 gives the pH ranges varying from 7,5 pH to pH8. this is of importance for drugs which form ions. Usually the nonionized moiety is more lipophilic and is preferentially absorbed by passive diffusion. For organic compounds the drug´s pKa determines the degree of ionization at a given pH.

Fig. N.° 5 shows the viscosity or consistency of the luminal content. The lower the viscosity the more watery or liquid is the content. Hence, the faster will a drug molecule, released from the delivery system, reach the absorbing mucosal surface, aided by mixing and kneading action in the gastro-intestinal tract, diffusion and Brown´s movement.

Fig. N.° 6 shows the number of microorganisms per g of luminal content for gram positive, coliform and anaerobic microorganisms. This is of importance regarding intraluminal metabolism of drugs and chemical breakdown of polymeric coating, and matrix material.

Fig. N.° 7 shows peptidase activity which is of importance regarding degradation of peptides.

Fig. N.° 8 gives a localization of Peyer´s patches, particularly of interest for uptake of peptides and for lymphatic absorption.

It becomes clear that the further down the drug delivery system travels the gastrointestinal tract past the small intestine, the more the viscosity of content increases. Hence, the slower will a released drug molecule be able to diffuse to the absorbing surface. At the same time the absorbing surface decreases. Even for 0-orden release the absorption process decreases. This is even more pronounced in the case of 1st-order and other release profiles because less drug is released with increasing time.

## A MECHANISTIC SOLUTION TO PHYSIOLOGIC CHALLENGE

Since the human alimentary tract is not a single compartment model we developed a peroral modified drug delivery system which mechanistically has three sequential release profiles:

I. An **INSTANT RELEASE** phase which is activated within about half a minute after swallowing of the dosage form and brings pharmacokinetically the blood/plasma drug concentration to the desired therapeutic level.
II. An approximate **ZERO-ORDER RELEASE** phase over a period of about 8 hr for a 12 h to 24 effect, depending on the drug's elimination half-life. This time period is based on the transit time through stomach and small intestine.
III. An Approximate **EXPONENTIAL INCREASE RELEASE** phase which begins when the drug delivery system reaches the large intestine past the cecum. Physiologically, water reabsorption occurs in the cecum to the extent of about 3.5L per day resulting in quick rise of consistency (viscosity) of intraluminal content, making diffusion of released drug molecules increasingly difficult, paired with decreasing absorbing mucosal surface area. To compensate for the decrease in absorption increasingly more drug must be released.

Fig. N.° 9 gives a schematic drug release profile for the three phases.

## NOVEL SELF-DESTRUCTING HYDROGEL PISTON PUMP SDHPP

The SDHPP (9,10) consists of a two-layered tablet. ON top is a compression-coated «hydrogel-piston-pump» for modified release and on the bottom is a fast dissolving layer for immediate release, acting as initial phase. In Fig. 10 a schematic diagram is given of the novel Self-Destructing Hydrogel Piston Pump (9). Background information on the systematic development of this novel delivery system can be found elsewhere (11-15).

The initial phase (13 mm diameter, 100 mg) carries the drug, microcrystalline cellulose and Cab-O-Sil. The hydrogel piston pump is composed out of an inner sandwich core and a shell. The inner core is composed out of a drug core layer (7 mm diameter, 10% drug in microcrystalline cellulose and Cab-O-Sil) and a push-driving layer (7 mm diameter, 1 mm thick), composed out of 5% hydroxypropyl methylcellulose and lactose. In case of high affinity of the drug for the HPMC, a diaphragm (nylon film) may be placed between the two core layers. The shell is a semipermeable matrix (375 mg) of cellulose ester, or cellulose ether or cellulose ester ether, acrylic acid-methacrylate copolymer, containing 25% of destruction bodies. Compression-coating (14 Kp hardness) is used to form the shell around the core layers. On the upper side of the shell a channel along the axis through the thickness of the shell apex serves as release orifice (350 mm diameter). The channel may be created by a special stylus protruding from the center of the surface of the upper punch, or by laser technique. The destruction bodies are microcrystalline cellulose particles either coated or granulated with methacrylic acid/methacrylate copolymers (125 mg lacquer/g ) to dissolve at pH 6.5 (the environment in the ileum).

The amount data, measurements, and compositions listed above were the ones used for the delivery systems tested in humans (chlorpheniramine ; promethazine) and may vary according to drug and dose and desired release time.

## PROGRAMED RELEASE MECHANISMS

Upon peroral administration by swallowing the delivery system intact, within 30 seconds the initial phase disintegrates and liberates the drug independent of pH. Gastrointestinal fluids are imbibed across the shell, regardless of pH, reaching both the drug core layer and the push driving layer. The former one, with the help of the «wick» effect of Cab-O-Sil, forms a concentrated drug solution. Imbibed fluid enters the push driving layer from the side and bottom and starts swelling of the layer, thus acting like a plunger of a syringe, forcing the drug solution from the chamber above the push-driving compartment via the release orifice to the outside. We used a diaphragm between the two compartments to prevent migration of drug solution into the upper side of the push-driving layer. Gastrointestinal fluid continues to de imbibed across the shell and drug solution continues to be expelled via the orifice at a desired rate. After 6 to 7 hours post administration the destruction bodies will be activated by dissolving the coating / embedding material, and the microcrystalline cellulose will start damaging the wall by forming fissures and cracks. By this time the delivery system will have reached the large intestine. With time the delivery system is self-destructing until total disintegration at the end of the desired release or delivery time, $t_{del}$.

## CALCULATION OF DESIRED RELEASE DATA (16)

Prerequisites for a drug to be a viable candidate for the SDHPP are:

I. The drug must be absorbable from all segments of the GI-tract, predominantly by passive diffusion.
II. The drug must be highly water soluble.
III. The therapeutic dose must not exceed 100 mg. per dosage form.

The desired drug release data are based on:

1. **PHYSICO-CHEMICAL** parameters of **DRUG**
II. **PHARMACOKINETIC** parameters of **DRUG**
III. **THERAPEUTIC RANGE** of **DRUG**

The equations (16) to calculate the release parameters are listed in table N.° 2.

$t_{elim}$ is the time it takes to reduce the drug plasma level from the desired steady state peak concentration $C_{ss\ max\ des}$ to the desired steady state trough concentration $C_{ss\ min\ des.}$ $l_z$ is the drug's terminal elimination rate constant. $t_{del}$ is the time over which the drug should be released from the drug delivery system, where is T (tao) the chosen dosing interval. $DM_{test}$ is the «preliminary» test dose for

modeling purpose where $DM_{conv}$ is the usual, not modified release conventional dose size. $R°_{prelim}$ is the «preliminary» O-order drug release rate, where F is the drug's bioavailability and P is the % of drug released from the delivery system. C(t) is the expected plasma level of the test dose at various times, namely at 1/3 of $t_{del,}$ 2/3 of $t_{del}$ of $t_{del}$ and t. The C(t) data are used for modeling. $DM_{final}$ is then the required dose for the modified release part of the delivery system, i.e. the drug amount in the core layer. $R°_{final}$ is the required release rate from the hydrogel piston pump.

For the example of promethazine the following data were used:

Pharmacokinetic Parameters

$Vz = 3\ L\ kg^{-1}$
$lz = 0.158\ h^{-1}$
$t_{1/2} = 4.4\ h$
$F = 0.25$
$P = 0.95$
$DM_{conv} = 25\ mg$
$t_{conv} = 6\ h$
$C_{ss\ max\ des} = 0.02\ mg\ L^{-1}$
$C_{xx\ min\ des} = 0.01\ mg\ L^{-1}$
$t = 24\ h$

Data for DSHPP design were:

$t_{elim} = 4.4\ h$
$t_{des} = 19.6\ h$
$DM_{final} = 55\ mg$
$R°_{delivery\ orifice} = 0.7\ mg\ h^{-1}$
$DI_{initial} = 10\ mg$

Fig. N.° 11 gives an example of comparison of the promethazine Self-Destructing Hydrogel Piston Pump (65 mg) versus Phenergan™, 25 mg in a crossover desing in the P.J. (10).

**Table N.° 2:** Equations to calculate release parameters from the Hydrogel Piston Pump.

$$t_{elim} = (\ln C_{ss\ max\ des} - \ln C_{ss\ min\ des}) / \lambda z$$

$$t_{del} = \tau - t_{elim}$$

$$DM_{test} = (DM_{conv} \cdot 0.693 \cdot \tau) / t_{1/2}$$

$$R°_{prelim} = (DM_{test} \cdot F \cdot P) / t_{del}$$

$$C(t) = [R°_{prelim} \cdot (1-e^{\lambda Z \cdot t})] / (V_Z \cdot \lambda z)$$

$$DM_{final} = (C_{ss\ max\ des} / C_{ss\ min\ des}) / DM_{test}$$

$$R°_{final}\ (DM_{final} / DM_{test}) \cdot R°_{test}$$

$$DL = (C_{ss\ min\ des} \cdot V_Z) / F$$

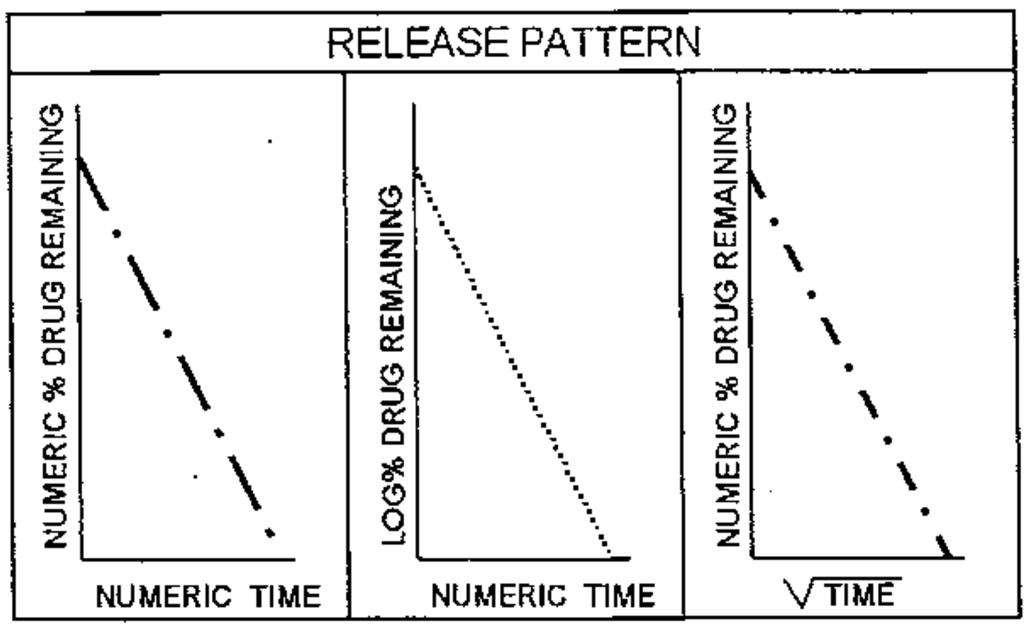


Fig. **N.° 1:** Schematic diagram for thee most widely used drug release patterns from modified release peroral drug delivery systems.

**Table N.° 1**: Data characteristics for liberation profiles for different methods of evaluation (3)

| METHOD | INDIVIDUAL DATA IN SEQUENCE OF TIME IN HOURS |
|---|---|
| Drug Amount Dissolved | % of drug in dissolution medium at time t relative to potency |
| Drug Amount Remaining in Dosage Form | % of drug remaining in dosage form at time t relative to potency |
| Sigma Minus, numeric | $(M_o - M_t)$ vs t |
| Sigma Minus, logarithmic | [in $(M_o - M_t)$ vs t |
| Hixon-Crowell | $(W_o^{1/3} - W_t^{1/3})$ vs t |
| Higuchi | % dissolved vs $\sqrt{t}$ |
| Kitizawa, numeric | $C\infty / (C\infty - C_t)$ ] vs t |
| Kitizawa, logarithmic | ln $C\infty / (C\infty - C_t)$ ] vs t |
| RRSW | log [ - ln $(1 - M_t / M_o)$ ] vs t |
| Schering | 1/M vs 1/t |

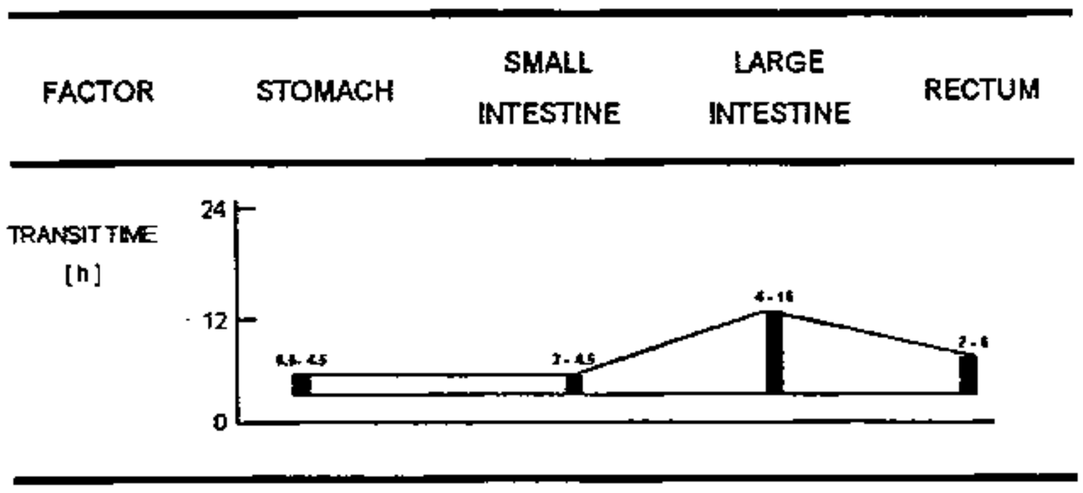


**Fig. N.° 2:** Physiologic factors influencing gastrointestinal absorption: transit time.

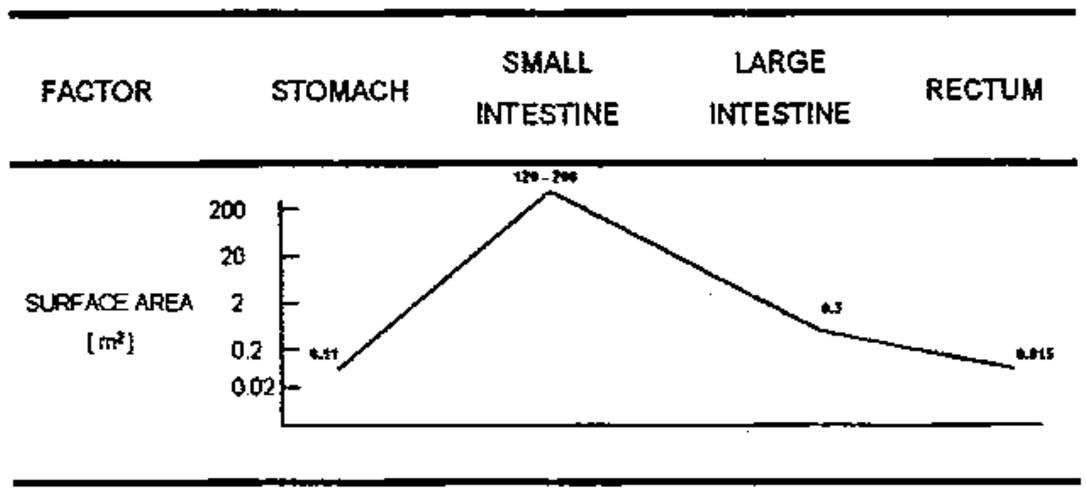


**Fig. N.° 3:** Physiologic factors influencing gastrointestinal absorption: Surface area.

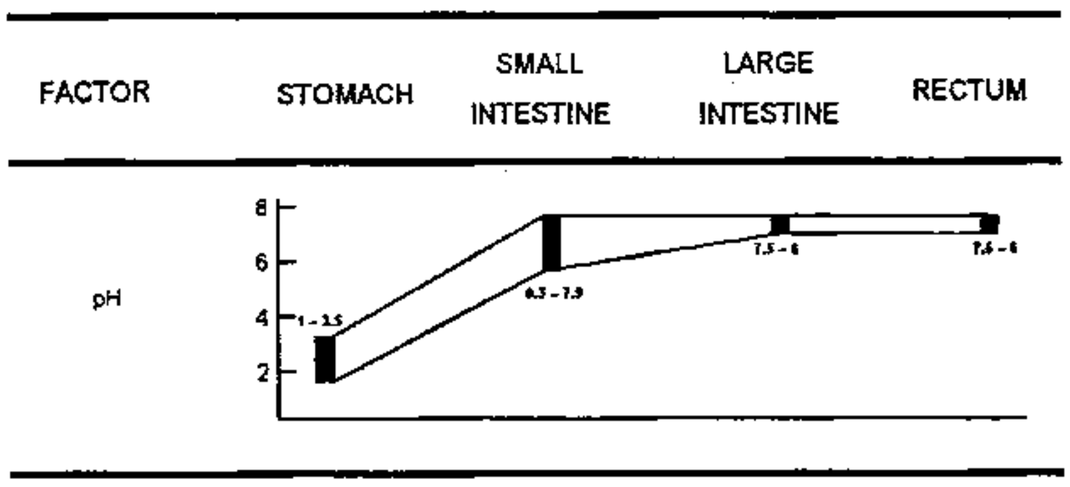


**Fig. N.° 4:** Physiologic factors influencing gastrointestinal absorption: pH.

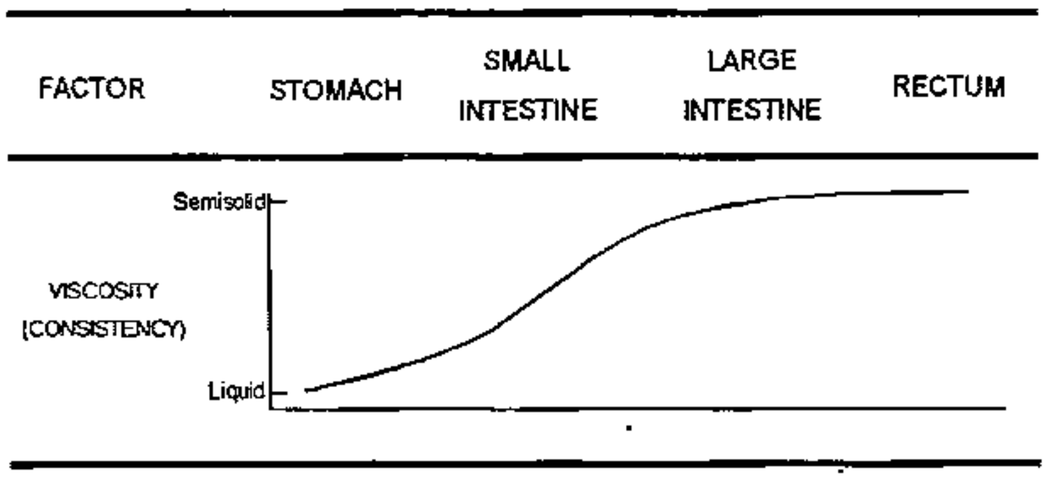


**Fig. N.° 5:** Physiologic factors influencing gastrointestinal absorption: Viscosity.

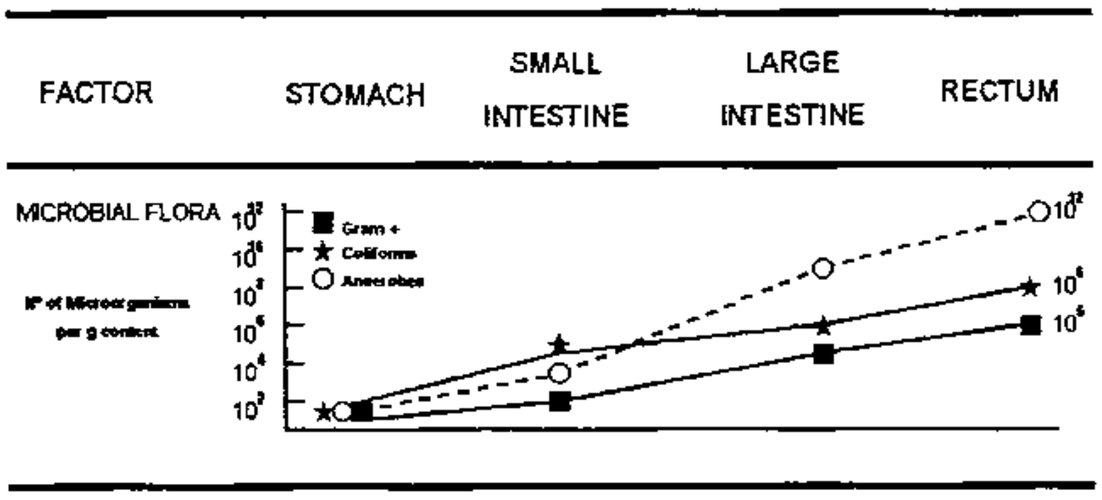


**Fig. N.° 6:** Physiologic factors influencing gastrointestinal absorption: Microbial flora.

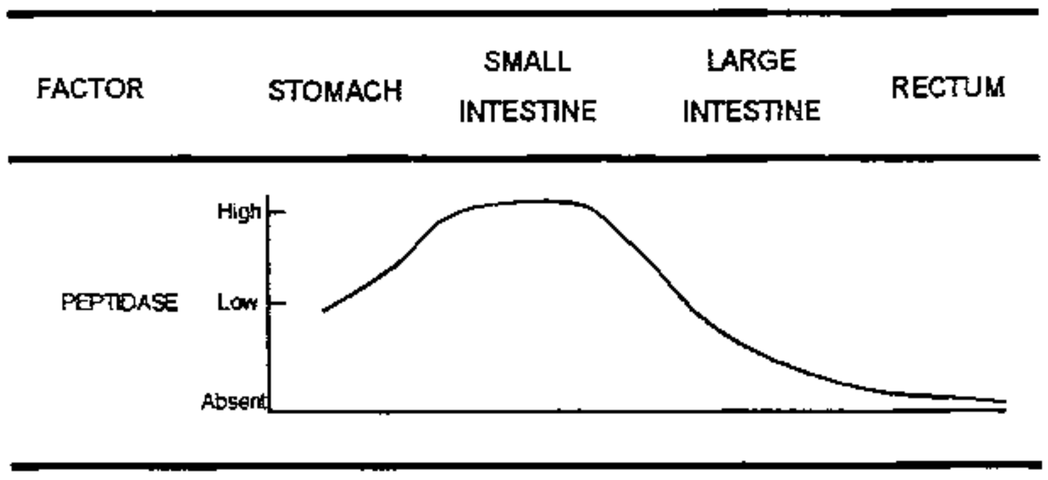


**Fig. N.° 7:** Physiologic factors influencing gastrointestinal absorption: Peptidase.

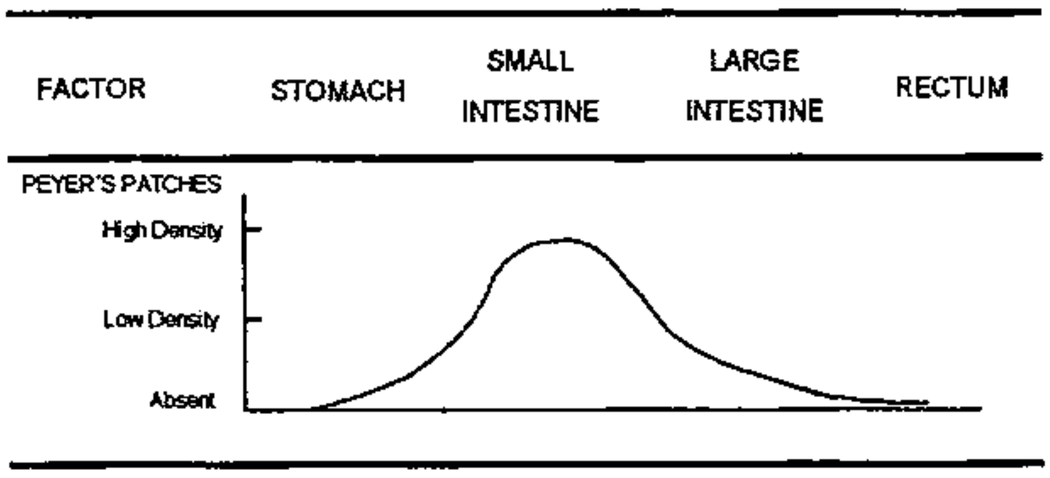


**Fig. N.° 8:** Physiologic factors influencing gastrointestinal absorption: Peyer's patches

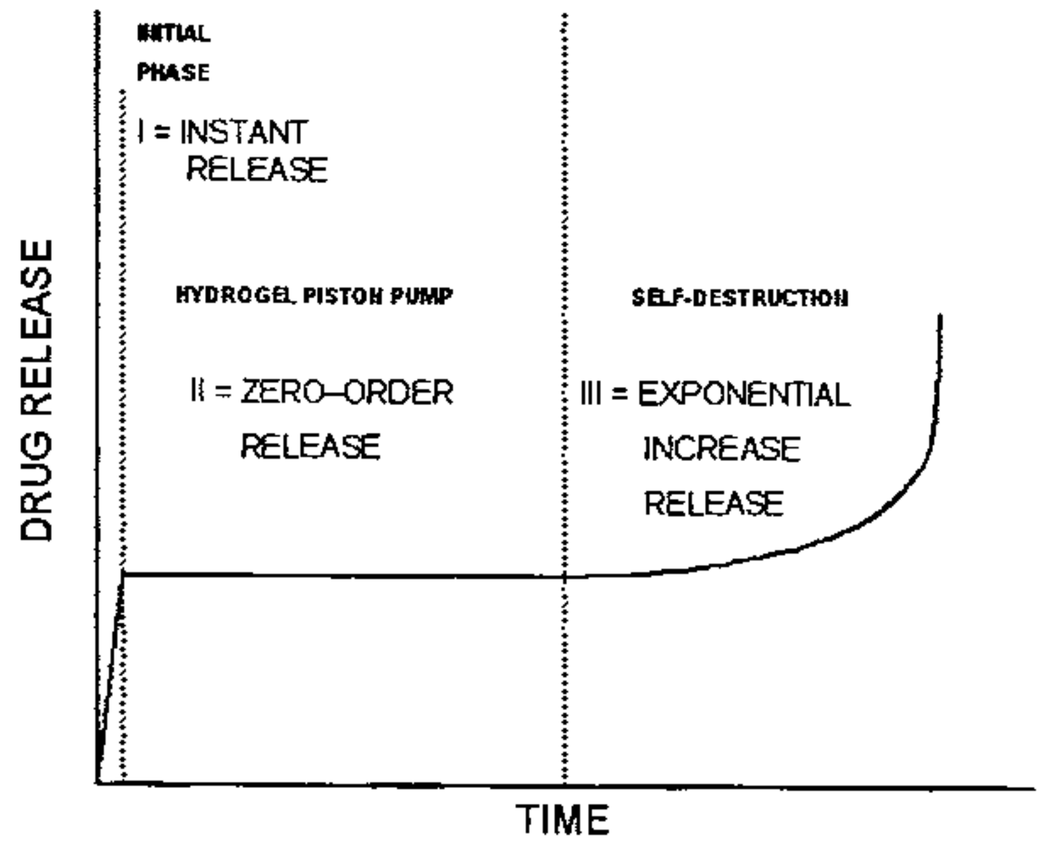


Fig. N.° 9: Drug release profile from novel self-destructing hydrogel piston pump p.o. drug delivery system.

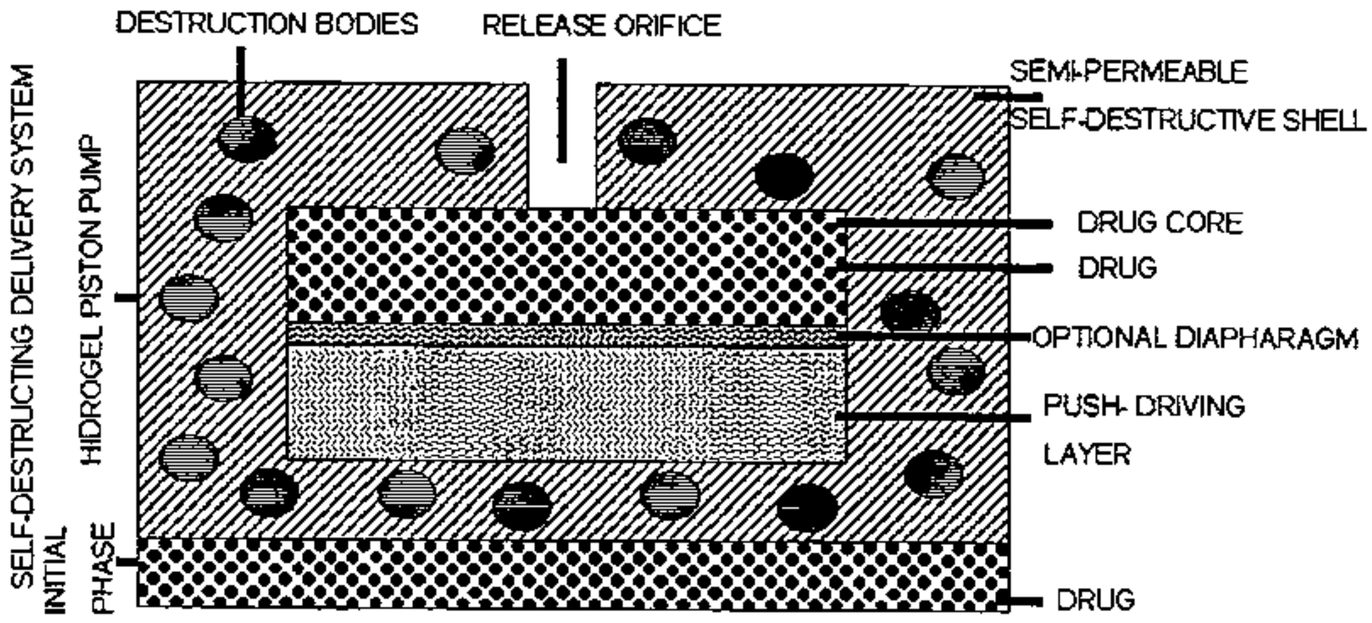


Fig. N.° 10: Schematic diagram of cross-section of novel self-destructing hydrogel piston pump p.o. drug delivery system (9).

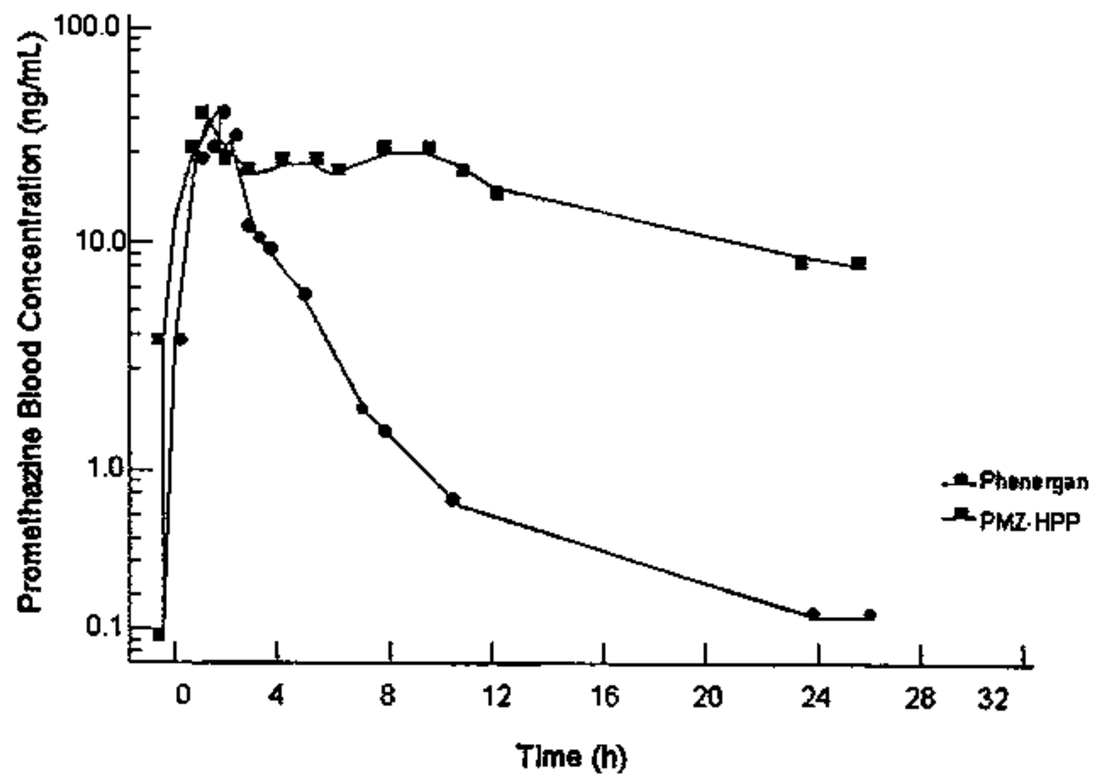


Fig. N.° 11: Promethazine blood concentration-time profiles after p.o. administration of PhenerganTM, 25 mg and SDHPP, 65 mg, in crossover, study in man, subject PJ.(10).