Development of a Novel Controlled-Release System for Gastric Retention

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Purpose. We report on the development of a novel controlled-release gastric retention system, which consists of a matrix tablet, coated with a permeable membrane. When immersed in simulated gastric fluid, the tablet expands. The tablet remains expanded for eighteen to twenty hours, during which time the drug is released. The tablet then either disintegrates into fragments or loses its integrity.

Methods. Tablets containing a soluble drug (chlorpheniramine maleate, i.e., CPM) and a poorly soluble drug (riboflavin 5′ phosphate, i.e., R5′P) were compressed. They were coated with a permeable and elastic polymer (Eudragit®). Dissolution profiles of these tablets were studied. The changes in the pH, viscosity, and deformation characteristics as a function of time were measured.

Results. Carbopol® provided a firm structure to the swollen tablet. Polyvinyl pyrrolidone XL (PVP XL) contributed to the swelling of the tablet. Carbonates provided the initial alkaline micro-environment for Carbopol® to gel and conferred buoyancy to the tablet. Coating provided the support needed for the core to remain intact during drug release and, at the same time, it allowed drug release due to its permeable nature. During release, the gelling properties of Carbopol® lessened, resulting in a decrease in the firmness of the core. This was evident from the decrease in the viscosity of the core. The energy required at 50% strain also decreased as the drug release progressed.

Conclusions. When this tablet is ingested, the chances of its elimination through the pylorus should be greatly reduced due to tablet's expansion, and due to its disintegration or loss in integrity it should then be expelled out of the stomach at the end of the drug release.

KEY WORDS: controlled-release; gastric retention; floating; swelling; matrix.

INTRODUCTION

Today more than fifty percent of the drug delivery systems available on the market are administered orally. The inability to restrain and confine these systems to selected regions of gastrointestinal tract has been the principal obstacle to the development of oral controlled-release systems. Various approaches have been tried to overcome such an obstacle. They include the development of swelling and expanding systems, floating systems and bioadhesive systems. There are various patents describing swelling systems (1,2,3). Researchers have used various polymers to develop such systems. They have developed swelling devices having different shapes, such as a ring, a disk, a string and many others (4,5,6,7). Various approaches have been used to develop floating systems. Some scientists developed shells of polymers with lower density than that of the gastrointestinal fluid, to enable them to float (8). Some scientists developed a drug and hydrocolloid mixture (9) whereas others developed a gel type matrix (10), a hydrodynamically balanced capsule (11), or a bilayer capsule (12). In order to develop a bioadhesive system, researchers have studied a broad range of polymers for their bioadhesive properties (13). Some of these polymers have been used to prepare bioadhesive systems (14,15). A matrix tablet has also been evaluated as a bioadhesive gastrointestinal retention system (16). It has been suggested that all these different kinds of devices improve bioavailability of those drugs which exhibit a site specific absorption and that they prolong the transit time sufficiently to achieve controlled release allowing a once a day administration. Unfortunately, most of these devices have many drawbacks. For instance, floating systems require the presence of food to delay their gastric emptying. They do not always release the drug at the intended site. For example, when Mazer *et al.* studied an isradipine floating device, they found that the maximum release of the drug took place in the colon and not in the stomach, as desired (17). Bioadhesive systems adhere to the mucus. This adhesion is a result of electrostatic and hydrogen bond formation at the mucus-polymer boundary. The bond formation is prevented by the acidic environment and thick mucus present in the stomach. High turnover of mucus adds to the difficulty of retaining the bioadhesive systems at the site. A gastric retention system overcoming such drawbacks of floating and bioadhesive systems can have significant advantages and could have a strong impact upon improving the therapeutic effect of the drugs.

This paper reports on the development of a novel drug delivery system with a prolonged gastric residence time. A tablet coated with a membrane was designed which, during *in vitro* studies, expanded to two to four times its original volume. The tablet swelled in about ten to fifteen minutes and drug release occurred for at least fifteen to eighteen hours. At the end of the release, the tablet either burst into small fragments due to continuous expansion or lost its integrity. A schematic representation of such a delivery system is shown in Figure 1.

MATERIALS AND METHODS

The drug delivery system investigated here consisted of (I) a core that swelled and of (II) a permeable coating that provided a shell for the swollen core and allowed drug release to occur.

Materials

The core consisted of soluble or poorly soluble drugs. Chlorpheniramine maleate, i.e., CPM (Interchem Corp., CA, USA) was used as an examplary soluble drug and riboflavin 5′ phosphate, i.e., R5′P (Hoffman-La Roche Inc., NJ, USA) was used as an examplary poorly soluble drug. Carbopol® 934P (B.F. Goodrich, OH, USA) was used as a pH sensitive polymer. Polyvinyl pyrrolidone XL (PVP XL from ISP, USA) was used as a swelling agent. A base such as calcium carbonate (Pharmacarb® from Crompton and Knowles, NJ, USA) or sodium bicarbonate (Mallinckrodt-Baker Inc., MO, USA) was used to

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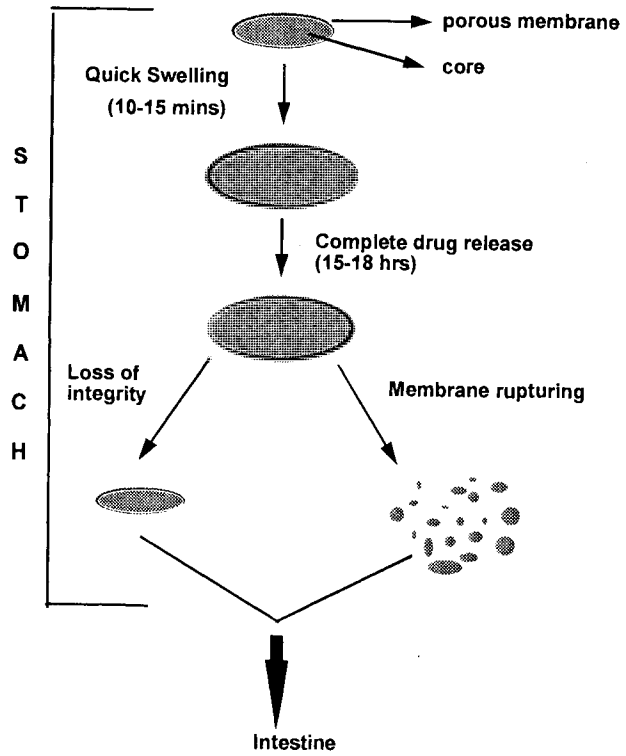

Fig. 1. Schematic representation of a novel gastric retention system.

provide an initial alkaline micro-environment and confer buoyancy to the tablet. Magnesium stearate (Hoffman-La Roche Inc., NJ, USA) was added as a lubricant for easy compression of the tablets.

The membrane consisted of methacrylate co-polymers (Eudragits® from Röhm Pharma Tech Inc., MA, USA), a plasticizer such as triethyl citrate (TEC) from Morflex Inc., NC, USA, an anti-tacking agent such as talc (Ashland Chemical Distr., OH, USA), and of the anti-foaming agent simethicone (OSI Specialities Inc., WV, USA). Methacrylate co-polymers were used because of their permeability and elasticity. Plasticizer was added to avoid breaking of the tablet after swelling. An anti-tacking agent was added to avoid tablets' sticking to one another during and after coating.

Methods

Preparation of Tablets

In the first step, the drug was mixed with the swelling agent in geometric proportion. In the second step, other ingredients were incorporated by blending in a V blender for 30 mins. The tablets were compressed on a manually operated tablet press (from Fred S. Carver Inc., WI, USA) at a suitable compression force, using 5/16 * 3/4 inch capsule-shaped punches to obtain tablets which were about 0.75 in length and 0.25 in width. Tablet hardness was between 22–25 scu.

Coating of Tablets

A laboratory coater (Glatt Air Techniques Inc., NJ, USA, Model # GC 300) was used to coat these tablets. The coating preparation was a dispersion. It was stirred continuosly in order to ensure uniform dispersion during coating. The coating preparation was sprayed at the rate of 3 ml/min on a batch of about 1.5 kg of tablets. The coating pan was rotated at the speed of 8 rpm. The temperature was maintained around 30°C during coating, to avoid any sticking of the tablets. After coating the tablets were dried in an oven at 30°C for one day and then stored under vacuum. The tablets were coated to different 'coating levels'. Coating levels indicate the increase in weight of the tablets after coating (e.g., 10% coating level means tablet weight increased by 10% after coating compared to its original weight).

In Vitro Studies

The tablets containing CPM were evaluated for the following criteria:

1. Swelling of tablets
2. Dissolution profile
3. Changes in viscosity of swollen cores over time
4. Changes in pH of swollen cores over time
5. Deformability of the tablets as a function of time
6. Thermo-mechanical properties of the tablets

Swelling of Tablets. Tablets were immersed in a simulated gastric fluid at 37°C. Swelling of tablets was monitored by measuring the weight gain as well as the increase in the thickness and the length of the tablets. It was measured at equilibrium as well as at various time intervals.

Dissolution. USP XXII/NF XVII dissolution method with apparatus II was used to study drug release. Simulated gastric fluid (900 ml, pH 1.2) prepared according to the procedure given in USP XXII at 37°C was used as a dissolution medium. The paddles were rotated at the speed of 50 rpm. The amount of drug dissolved was measured at various time intervals by using a spectrophotometer with ultraviolet light source. The amount of CPM dissolved was measured at the wavelength of 274 nm and the amount of R5'P dissolved was measured at the wavelength of 282 nm. Dissolution studies were conducted on twelve tablets from each formulation. The first order dissolution rate constants were calculated for the comparison of the data.

Viscosity of the Tablet Core. Tablets were immersed in simulated gastric fluid at 37°C for various time intervals such as two, four, eight, twelve and twenty hours. The tablets were removed from simulated gastric fluid and the tablet membranes were separated from the cores. Viscosity of the cores from three tablets was determined using CSL Controlled Stress rheometer (TA Instruments, DE, USA). A parallel plate assembly was used. The diameter of the plate was two cm. The temperature was maintained at 37°C. A stress of 12000 dyne/cm^2 was applied. The starting and ending angular frequencies were 0.6283 rad/sec and 62.83 rad/sec respectively.

pH of the Tablet Core. Tablets were immersed in simulated gastric fluid at 37°C for various time intervals, such as, two, four, eight and twenty hours. After removing the tablets from simulated gastric fluid, the tablet membranes were separated from the cores and the pH of the cores from three tablets were measured. A digital pH/millivolt meter 611 from Orion Research Inc., MA, USA was used to measure the pH.

Deformability. Tablets were immersed in simulated gastric fluid at 37°C for various time intervals, such as, two, four,

eight, twelve and twenty hours. The hardness of tablets was measured immediately after removing them from the simulated gastric fluid. Hardness, in terms of energy at 50% strain, was measured on three tablets using compression mode on a tensiometer (Instron Corp., Ma, USA, model # 4301). The tablet was placed on the platform. The upper platform was lowered on the tablet at a speed of 0.5 in/min. The instrument was not equipped to maintain the temperature constant. Thus, all the measurements were made at room temperature.

Thermo Mechanical Analysis (TMA). These studies were conducted using a thermo-mechanical analyzer (Seiko Instruments Inc., CA, USA, Model # 120C). A penetration probe was used. Coated tablets were heated from −45°C to +150°C at a rate of 10°C/min. Glass transition temperature (Tg) of three tablets with different coating levels and different coating preparations was measured.

RESULTS AND DISCUSSION

Core Formulation

In case of tablets containing CPM, the principal ingredients for the core consisted of Carbopol®, polyvinyl pyrrolidone XL (PVP XL) and calcium carbonate. The effect of Carbopol® and PVP XL on the swelling time was studied by compressing tablets with different combinations of these ingredients. When compressing the tablets, the concentration of one ingredient was kept constant and the concentration of the other was varied.

Carbopol® provided a firm structure for the swollen tablet due to its adhesive, binding, and gelling properties. It was desirable for the delivery system to swell in ten to fifteen minutes in the gastric fluid to prevent premature gastric emptying. The effect of the concentration of Carbopol® on the swelling time of the tablet is shown in Figure 2. High concentrations of Carbopol® provided slower diffusion of gastric fluid into the matrix which resulted in an increase in the swelling time, e.g., Carbopol® concentrations of 10% resulted in swelling time of one hour or more. It was necessary to use a concentration of Carbopol® that would not hinder the swelling and at the same time would confer adequate gelling properties for imparting the required firmness to the tablet. Even a small concentration (such as 2.0%) of Carbopol® was enough to obtain this effect.

The concentration of PVP XL also affected the swelling time. A high concentration of PVP XL was used to enhance swelling (not for its disintegrating properties). Figure 2 shows the effect of PVP XL concentration on the swelling time. Based on this data, PVP XL was used at concentrations of 25 to 35% in the final formulation.

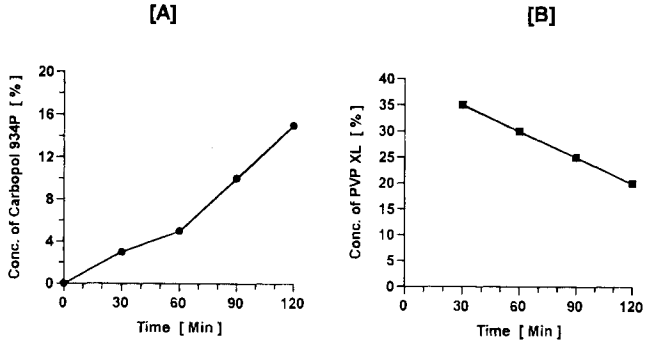

Fig. 2. Effect of Carbopol® and PVP XL on swelling time of tablets after immersing them in simulated gastric fluid at 37°C; [A] = Concentration of PVP XL held constant at 2.0%.

Calcium carbonate provided a faster rate of expansion for the core and initial alkaline micro-environment for Carbopol® to gel. It also provided buoyancy to the tablet in simulated gastric fluid. It was observed that the particle size, method of precipitation, and concentration of other ingredients such as starch or maltodextrin present in the calcium carbonate used, affected the time taken by tablets to swell significantly. In this experiment, the primary purpose was to minimize the time taken by the tablets to swell after they were immersed in simulated gastric fluid. It was required that the tablets swell in about fifteen minutes. Calcium carbonate (Pharma-Carb®) satisfied these requirements and hence was used for further studies. Pharma-Carb® is a natural calcium carbonate which meets all USP XXII specifications. According to the data sheet provided with the sample, the mean particle size of calcium carbonate was 12 μ.

Coating Formulation

The coating provided the support needed by the core to remain intact during the release. It also provided a permeable membrane for the release of the drug. Tensile strength and elongation properties of the membrane were very important in ensuring this behavior. Eudragit® RL 30 D was used for its permeability. However, its elongation properties were insufficient in withstanding the pressure of expansion. TEC was added to increase the elasticity. It improved the elasticity, but did not prevent disintegration. Eudragit® NE 30 D was added to the Eudragit® RL 30 D and TEC combination, to improve the elasticity and firmness of the membrane. When Eudragit® RL 30 D was alone, the drug was released quickly due to the high permeability of Eudragit® RL 30 D. The addition of Eudragit® NE 30 D contributed in slowing down the release, as it is less permeable than Eudragit® RL 30 D. The selection of the final formulation of the coating solution was based on the time taken by the tablets to swell, the release characteristics of the drug during dissolution, and the ability of the film to prevent disintegration of the tablet until complete drug release had occurred. Three ratios of Eudragit® RL 30 D and Eudragit® NE 30 D were investigated. They were 80:20, 70:30 and 60:40 (Eudragit® RL 30 D:Eudragit® NE 30 D). The ratio of 80:20 (Eudragit® RL 30 D:Eudragit® NE 30 D) resulted in a brittle film whereas the ratio of 60:40 (Eudragit® RL 30 D:Eudragit® NE 30 D) resulted in a film that was too elastic. The ratio of 70:30 (Eudragit® RL 30 D:Eudragit® NE 30 D) was optimum for the drug release as well as for imparting the elasticity to the film needed to withstand the swelling pressure of the core.

In Vitro Studies

When tablets were immersed in simulated gastric fluid at 37°C, they swelled two to three times their original volume.

Dissolution studies were conducted in simulated gastric fluid at 37°C. The effects of three ratios of Eudragit® RL 30 D and Eudragit® NE 30 D in membranes at different coating levels are shown in Table I and Figure 3. The rate of release of the drug followed first order reaction kinetics, since the release depended on the concentration of the drug. According

Table I. Effect of Coating Level on Release of CPM tablets

Ratio of Eudragit® RL 30 D to Eudragit® NE 30 D	Coating level (%)	Dissolution rate constant (min^{-1})
50:40	10.0	$0.004 \pm 5.0*10^{4}$
	15.0	$0.004 \pm 5.5*10^{4}$
70:30	10.0	$0.003 \pm 8.0*10^{4}$
	15.0	$0.005 \pm 5.5*10^{4}$
80:20	10.0	$0.005 \pm 6.0*10^{4}$
	15.0	$0.006 \pm 6.0*10^{4}$

to student t test at 95% confidence level, the rate of release increased significantly with the increase in the coating level when Eudragit® RL 30 D and Eudragit® NE 30 D were used in the ratio of 70:30 and 80:20. However, the rate of drug release showed no change with changes in the coating level when Eudragit® RL 30 D and Eudragit® NE 30 D were used in the ratio of 60:40. Such an unusual increase in the rate of release was contrary to the general behavior of a drug when it diffuses from tablets coated with a membrane.

To elucidate the possible mechanism associated with this behaviour, two studies were conducted:

1. Thermo Mechanical Analysis (TMA) on the tablets,
2. Time taken by the cores to form a gel

TMA results of the three coating preparations are shown in Figure 4. These studies were not very helpful in explaining the unusual drug release from the tablets. The TMA studies showed that when Eudragit® RL 30 D and Eudragit® NE 30 D were used in the ratio of 70:30 and 80:20, the Tg decreased in a statistically significant manner (student t test at 95% confidence level) as coating level increased but not when Eudragit® RL 30 D and Eudragit® NE 30 D were used in the ratio of 60:40. The study did not provide any indication as to the reasons behind this behaviour. It is known that Tg influences many physical properties such as elasticity, viscosity, solvent release and permeability of coating polymers. Lower Tg results in

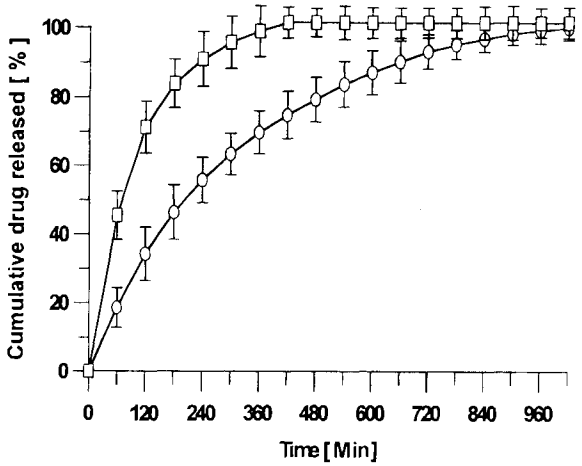

Fig. 3. Effect of coating level on cumulative in vitro release of CPM (5% w/w) from coated tablets in 900 ml of simulated gastric fluid at pH 1.2 at 37°C, n = 12, Eudragit® RL 30 D: Eudragit® NE 30 D = 70:30. (○) 10% coating level; (□) 15% coating level.

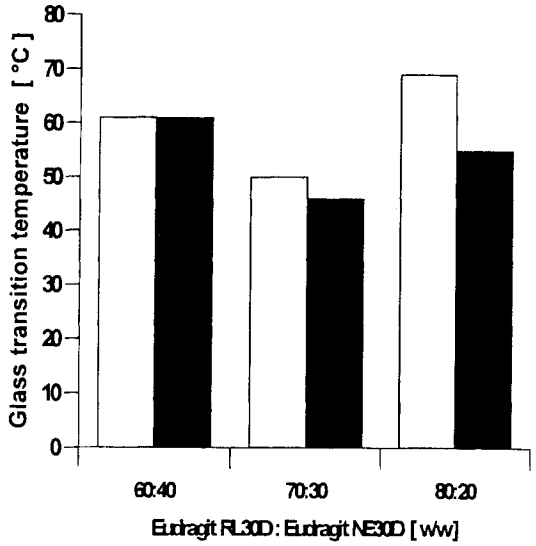

Fig. 4. Glass transition temperature of coated tablets containing CPM; n = 6. (□) 10% coating level,; (■) 15% coating level.

increased permeability and increased release rate. As the membrane at a higher coating level attained its Tg point at a lower temperature than that of a lower coating level, the drug was released faster.

Another possibility, that of relating drug release rate to the gel formation time of the core, was explored. Tablets coated with Eudragit® RL 30 D and NE 30 D (70:30) were selected. Gel formation time of the core at 10% and 15% coating level was found to be two hours and four hours, respectively. This indicates a correlation between shorter gel formation time and slower drug release, and vice versa. Hence the following mechanism can be deduced. As the core of the tablet absorbs gastric fluid, gel formation occurs. The faster the gel formation, the faster the drug entrapment and slower the release.

Dissolution studies were also conducted in dissolution media with pH 2.0 and 3.0 in order to account for individual variations in stomach pH. The data indicated that the swelling occurred in less than fifteen minutes. The data showed that the release rate was somewhat slower with an increase in pH. This could be due to the differing solubility of CPM at various pH values.

To illustrate that this tablet can also be used for the delivery of poorly soluble drugs, R5'P was selected as a model drug. Dissolution studies were conducted on these tablets using the same method as in case of tablets containing CPM as a model drug.

Initially, the composition of the core and that of the membrane were kept the same as in the case of tablets containing CPM and CPM alone was replaced with R5'P. When dissolution studies were conducted on these tablets, the membrane and the core used for CPM tablets were not adequate and resulted in an incomplete release of R5'P. To overcome this problem, it was necessary to change either the core or the membrane, or both. First, attempts were made to modify the membrane in order to achieve complete drug release. Since the drug was poorly soluble, it was necessary to use a highly permeable membrane. However, at the same time, the membrane was required to be elastic enough to withstand the pressure of swelling. The core was modified in order to achieve quick swelling

of tablets. Calcium carbonate in the core was replaced with sodium bicarbonate which ensured a faster swelling. Thus, by changing both the core and the membrane, fast swelling as well as complete drug release were achieved for the tablets containing R5'P as a model drug of poorly soluble drugs.

VALIDITY OF THE HYPOTHESIS

In order to fully verify the validity of the concept of a gastric retention system that can swell in ten to fifteen minutes, allow the drug release to occur in fifteen to eighteen hours, and, at the end of the release, either disintegrate or loose its integrity in order to be expelled from the stomach, the change in the pH, viscosity, and deformation characteristics as a function of time were measured. It was observed that during the release, the gelling properties of Carbopol® were reduced due to penetration of gastric fluid into the tablet, resulting in a decrease in the firmness of the core during the release. This was evident from the decrease in the viscosity of the core. Figures 5 shows the change in pH and viscosity of the swollen core as a function of time. They show that a decrease in the pH of the core resulted in a reduction in the viscosity of the core. The reduction in the core viscosity was due to the decrease in the viscosity of Carbopol® with the decrease in the pH. In addition, deformation studies of the tablets indicated that energy required at 50% strain decreased as the release of the drug progressed (Figure 6). Strain energy is a measure of the energy absorption characteristics of a material under load up to fracture. It is a measure of the toughness of a material. This decrease in the required energy at 50% strain will result in the loss of firmness and integrity of the core matrix. This reduction in the firmness due to the decrease in the viscosity will enable the tablet to be squeezed out of the stomach at the end of the release if it remained intact at the end of the release. This satisfies one of the major criteria that this delivery system should disintegrate or be squeezed out at the end of the release period.

CONCLUSIONS

This study has shown that there is the potential to develop a tablet dosage form which remains in the stomach for a long time. This tablet will release the drug in the desired time and then either disintegrate into small fragments or will lose its integrity so that it can be expelled from the stomach. This study has also shown that such a tablet can be used for soluble as well as for poorly soluble drugs. Coating solution and core formulation can be modified to achieve the release rate required by the nature of the drug. This tablet provides ideal attributes of gastric retention system and overcomes some of the drawbacks associated with presently available systems.

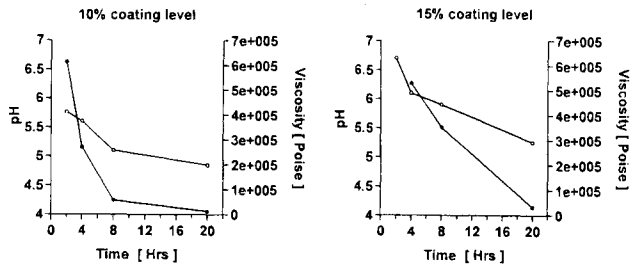

Fig. 5. Changes in pH and viscosity of cores separated from membranes after immersing in simulated gastric fluid at 37°C for different time intervals. Eudragit® RL 30 D: Eudragit® NE 30 D = 70:30, n = 6, (○) pH; (●) viscosity.

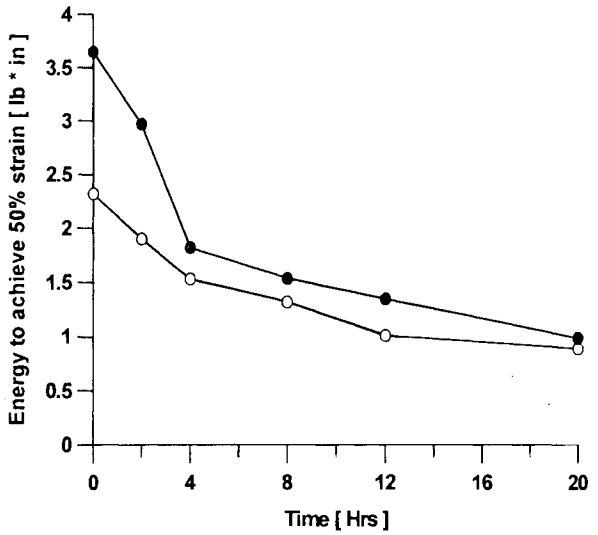

Fig. 6. Changes in energy required to achieve 50% strain on coated tablets with CPM after immersing in simulated gastric fluid at 37°C for various time intervals, n = 6 (○) 10% coating level; (●) 15% coating level.

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