DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(18), 2085-2096 (1995)

EFFECT OF EUDRAGIT TYPE POLYMERS ON THE DRUG RELEASE FROM MAGNESIUM OXIDE GRANULES PRODUCED BY LABORATORY FLUIDIZATION

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ABSTRACT

The differences in the bioavailability of different drug products are most frequently caused by differences in the dissolution rates of the active ingredient. In case of magnesium oxide the drug release can be directly determined by reaction kinetics method based on acid neutralization.

For a more precise study of the factors influencing the kinetical characteristics of the neutralization rates it is advisable to use homogeneous granule fractions. Before the granulation the substance was pretreated with silicone oil. The granulation of the obtained grains having hydrophobe surface was carried out in an AEROMATIC STREA-1 type laboratory fluidization equipment with Eudragit polymer solved in isopropyl alcohol.

For determining the acid neutralization kinetics of the granules the "constant pH" method and the Rossett-Rice test were used.

As a result of the granulation the neutralization rate decreased. The granules can be considered as an Eudragit matrix which contains the pretreated magnesium oxide in embedded form. During the chemical reaction the resulted salt (magnesium chloride) leaves the surface of the unreacted magnesium oxide unless having a chemical reaction with the polymer. Meanwhile the residual matrix forms a mesh which increases the viscosity of the solution and the thickness of the diffusion layer. The dissolution rate decreases in both cases.

Under the same conditions the kinetic values of the neutralization change by several magnitudes depending on the utilized methods. In this way

different systems of medicine, which alter their reaction capacity according to the expected physiological purposes, can be created.

INTRODUCTION

The dissolution rate of the drug - a determining factor of the bioavailability - greatly depends on the composition of the product, on the characteristics of the active and auxiliary ingredients as well as on the applied technology (1).

In case of products of well-defined therapeutic effect based on simple chemical reaction (e.g. antacides) the time dependence and the reaction kinetics can be studied directly.

In such cases there is a close connection between the in vivo pharmacokinetic parameter of the curative effect and the kinetic parameters of the in vitro investigated process (2, 3).

It is reasonable to use homogeneous granule fractions for a more precise study of the factors influencing the pharmacokinetic parameters. These fractions can be produced most favourably by fluidization granulation. The fluidized bed granulation method provides well-rolling, fine, more homogeneous and porous granules than the traditional granulation methods (4-8).

The purpose of this study is to determine the neutralization kinetic parameters of the magnesium oxide granules produced by laboratory fluidization and to study the relationship between the Eudragit type polymer used as binder and the drug release. The kinetic parameters were investigated as a function of the quality of the granulating liquid, of the proportion of the binder to magnesium oxide and of the applied technologies.

MATERIALS AND METHODS

Magnesium oxide

The magnesium oxide - the basic substance of the granulation - is of Ph. Hg.VII. grade, white , loose powder with high volume. It consists of grains, 95% of which are smaller than 40μm - according to the air-flow screen analysis. Since the substance adheres onto the wall of the plastic fluidization column, it could not be fluidized without pretreatment.

Hydrophobized magnesium oxide

2,5 g of silicone oil (FERAX Laborat. GmbH, Berlin) was blended in 300 g isopropyl alcohol (Reanal, Budapest). In the obtained composite 100 g of magnesium oxide was suspended for 30 min. using paddle stirrer (VEB MR25). As soon as the solvent had been evaporated the substance was

strained through a sieve of 250 μm. The obtained material was fractionated. Only fractions of (100-250) μm were used for further investigation.

Morphological characterisation of the substances with scanning electron microscope

In order to characterise the surface morphology of the basic substance and to evaluate the morphological effect of the hydrophob treatment, the samples were studied with scanning electron microscope (Opton DSM 940, Carl Zeiss GmbH, Germany, D-7082 Oberkochen).

The specimens were mounted to aluminium stubs with double adhesive tape. To reduce the charging, the specimens were vacuum coated with gold by a Jeol JEE 4B vacuum evaporator. Examination was carried out at 3 kV, 5 kV or 30 kV accelerating voltage and 500-10 000 times magnifications were used.

Laboratory fluidized bed granulation

Base materials

Hydrophobized magnesium oxide

Copolymers of methacrylic acid ester (Eudragit L100, Eudragit L100-55, Eudragit S100 from Rohm Pharma, Germany

Granulation method

The granules were prepared in AEROMATIC STREA-1 laboratory fluidization equipment (filling quantity: 0,25-2 kg).

The process parameters were the following:

The quantity of the base material (hydrophobized magnesium oxide): 200 g

Granulating liquid: 5% (w/w) of Eudragit polymer solved in isopropyl alcohol

Inlet air temperature: 40°C

Outlet air temperature: 25°C

Feeding rate of the granulating liquid: 15 rpm

Atomising pressure: 2 bar

Drying time: 2 minutes after each atomising periods

Drying temperature: 40°C

The granulating liquid was increased so that the proportion of the binder to magnesium oxide would be 10%, 20%, 30% (w/w).

Controlling the antacides with constant pH method and with the Rossett-Rice test

Equipment

Universal pH measuring equipment (Radelkis 211/1 model)

Combined electrode (Radelkis OP-0808P model)

Magnetic stirrer (Radelkis OP-912/3 model)

Semi-automatic burette
Thermostable glass beaker with double wall
Ultrathermostat (Stuers)
Chronograph

Materials
Testing solution pH=3
1N hydrochloric acid solution
0,1N hydrochloric acid solution

Constant pH method
200 cm^3 of testing solution (pH=3) was poured into a glass beaker of double wall. The reaction chamber was thermostated at a temperature of 37,5± 0,2 °C by means of an ultrathermostate.
The solution was stirred with a Radelkis-type magnetic stirrer (revolution number: 250-300 rpm). The sample weighed - with an accuracy of 0,1 mg - was poured into the liquid with a sudden movement and simultaneously the chronometer was started.
The release of the magnesium oxide from the granules causes pH-increase. When pH-increase was observed, 1N hydrochloric acid was added to the system from a burette to keep the pH at a constant value (pH=3). The difference between the pH value of the digital pH-meter and the selected value (pH=3) was not more than 0,3 pH. Hydrochloric acid consumption was recorded as a function of time.

Rossett-Rice test
30 ml distilled water was added to 70 ml 0,1N hydrochloric acid then the granules containing antacid were put into the liquid. From that moment 4,00 ml / min. 0,1N hydrochloric acid was added to the mixture under constant stirring and the pH values were recorded as a function of time (9).

RESULTS AND DISCUSSION

The neutralization-kinetic parameters of antacids were determined by the following equation:

$$\ln \ln \frac{C_s}{C_s - C} = \ln K + \alpha \ln t \qquad (1)$$

where C - concentration of the solution after time (t)
C_S - concentration of the saturated solution
K - rate constant of the dissolution

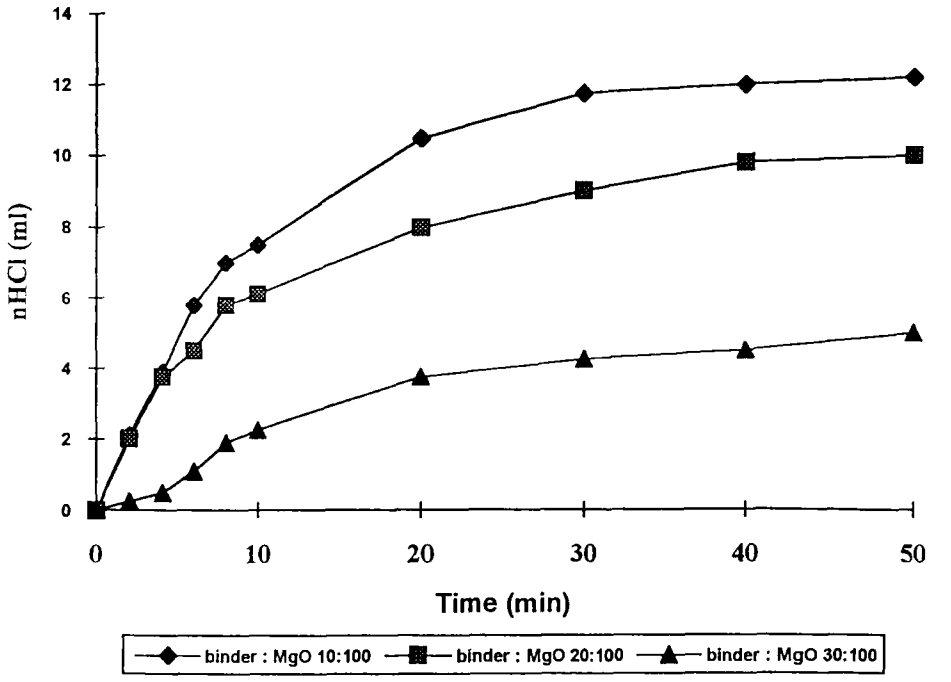

FIGURE 1.

Time dependence of the neutralization reaction of granules produced from hydrophobized magnesium oxide with Eudragit L100-55 solved in isopropanol

Equation (1) can be applied for graphical evaluation. The above determines linear equation $y = a + bx$ where $y = \ln \ln \frac{C_s}{C_s - C}$ and $x = \ln t$. The slope of the straight line- that is the constant of the kinetic relationship - is "b" and the intercept "a" is the natural logarithm of the "K" rate constant of dissolution.

Considering that the measured acid consumption values correspond to "C" and the acid consumption values measured for sufficiently long time (theoretically at infinity) correspond to "C_S", thus "t" and "V" values can be substituted, "y" can be represented as a function of "x".

Figure 1. indicates the time function of the acid neutralization reaction of the granules consisting of magnesium oxide and Eudragit L100-55 polymer while Figure 2. the acid consumption curves of the same granules linearized

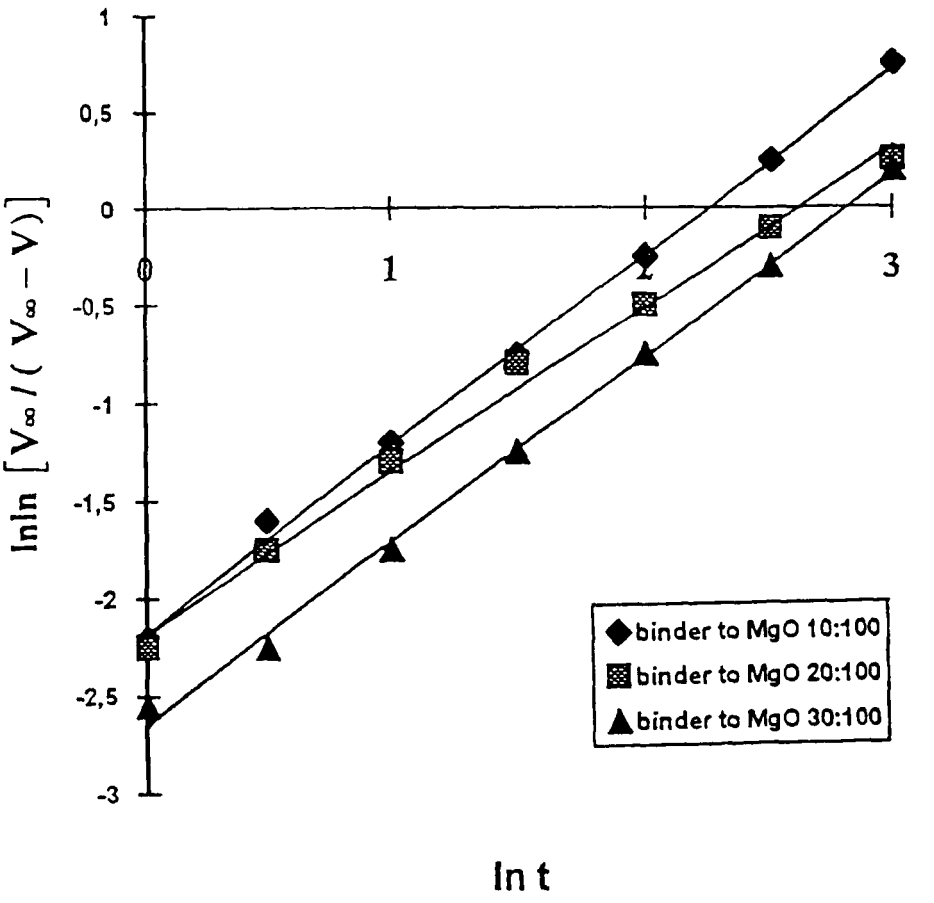

FIGURE 2.
Dissolution rate according to the equation (1) relating for granules prepared from hydrophobized magnesium oxide with Eudragit L100-55 solved in isopropanol

independently of the sampling time by Eq. (1). "α" and "K" values can be determined from the slope and the intercept of the straight lines. The following conclusions can be drawn from the results (Table 1.).

The neutralization rate of the pretreated magnesium oxide samples decreases as a result of the granulation. The granules can be considered as an Eudragit matrix which is insoluble in the reaction medium and contains the pretreated magnesium oxide in embedded form. During the chemical reaction the resulted salt leaves the surface of the magnesium oxide and the residual

TABLE 1.
α and K values of the various neutralization processes

Sample	α	K
Untreated MgO	**1,0256** (0,0205)	**0,5541** (0,0111)
Hydrophobized MgO	**0,5101** (0,0102)	**0,3327** (0,0067)
Granulated with Eudragit L100-55		
A	**0,8386** (0,0167)	**0,1149** (0,0023)
B	**0,8856** (0,0177)	**0,1058** (0,0021)
C	**0,9006** (0,0180)	**0,0770** (0,0015)
Granulated with Eudragit L100		
A	**0,8253** (0,0165)	**0,1088** (0,0022)
B	**0,8851** (0,0177)	**0,1003** (0,0020)
C	**0,9105** (0,0182)	**0,0801** (0,0016)
Granulated with Eudragit S100		
A	**0,8359** (0,0165)	**0,1092** (0,0022)
B	**0,8832** (0,0176)	**0,0998** (0,0019)
C	**0,9069** (0,0181)	**0,0755** (0,0015)

A = 10:100 binder:MgO in the granules
B = 20:100 binder:MgO in the granules
C = 30:100 binder:MgO in the granules
* Standard deviations in parenthesis

matrix forms a mesh which on the one hand increases the viscosity of the solution and on the other increases the thickness of the diffusion layer. The dissolution rate decreases in both cases.

The more granulating liquid - consequently bigger amount of binder - is used, the slower the neutralization reaction of the examined granules becomes.

The neutralization reaction of the hydrophobized magnesium oxide is slower than that of the untreated magnesium oxide (Figure 3.) therefore the

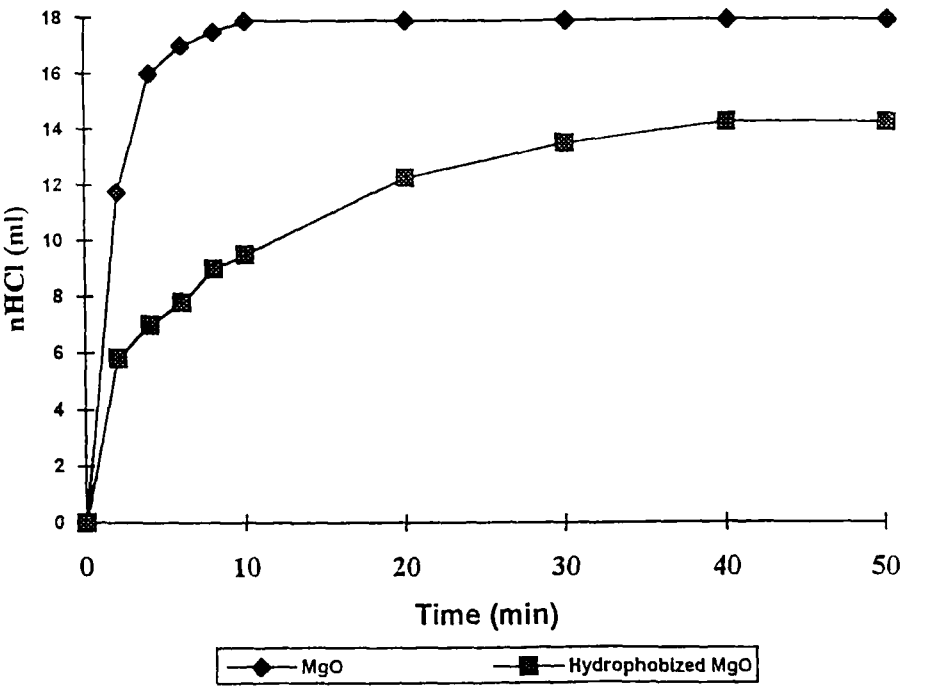

FIGURE 3.
Time dependence of the neutralization of magnesium oxide and hydrophobized magnesium oxide

hydrophobization decreases the wettability of the magnesium oxide. The silicone oil increases the contact angle of the water on the compressed tablet.

Between the structural moisture absorption of the developed system and the width of the diffusion layer developed during the reaction, there exists a correlation - that is to say with certain components of the acid neutralization constant. The reaction rate is not governed by the very fast neutralization reaction, but it is controlled by the acid concentration and the diffusion of the end-product, which is highly characteristic of the system.

Figure 4. shows the changes in the results of the Rossett-Rice test caused by hydrophobization. The scanning electron micrographs (Figure 5.,6.) demonstrate the morphological changes on the surface of the magnesium oxide caused by hydrophobization.

The surface of the hydrophobized magnesium oxide is much more even than that of the untreated magnesium oxide. The neutralization kinetics of the

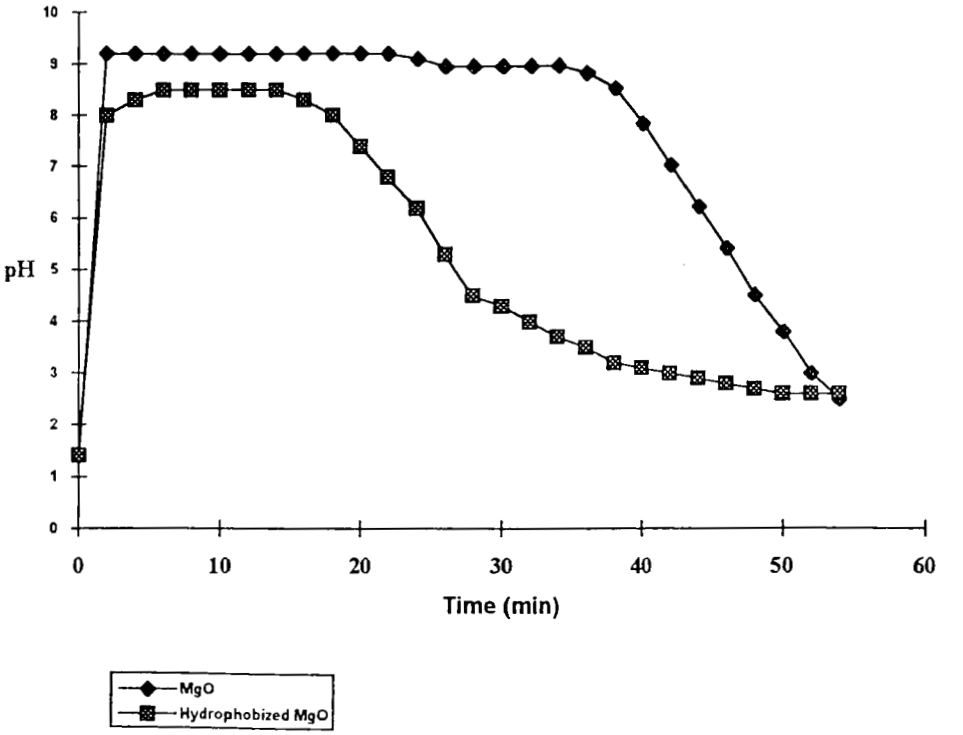

FIGURE 4.
Investigation of the neutralization kinetics of the untreated and hydrophobized magnesium oxide by means of Rossett-Rice test

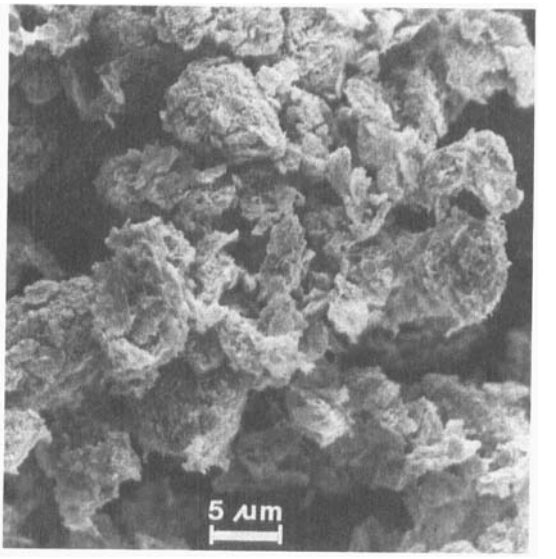

FIGURE 5.
Scanning Electron Micrograph of the magnesium oxide
Magnification 2000 x

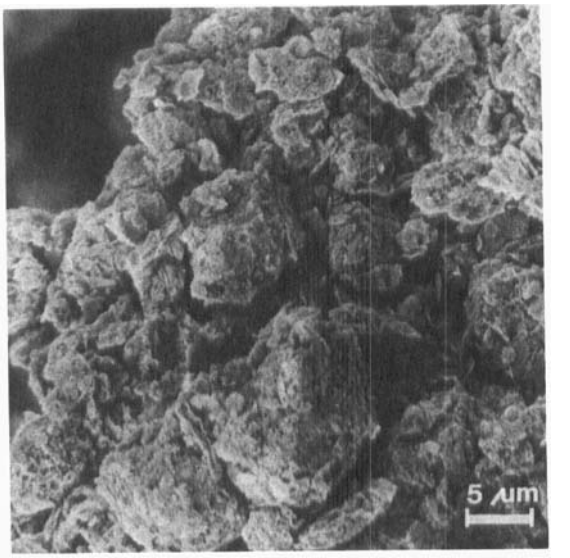

FIGURE 6.
Scanning Electron Micrograph of the hydrophobized magnesium oxide
Magnification 2000 x

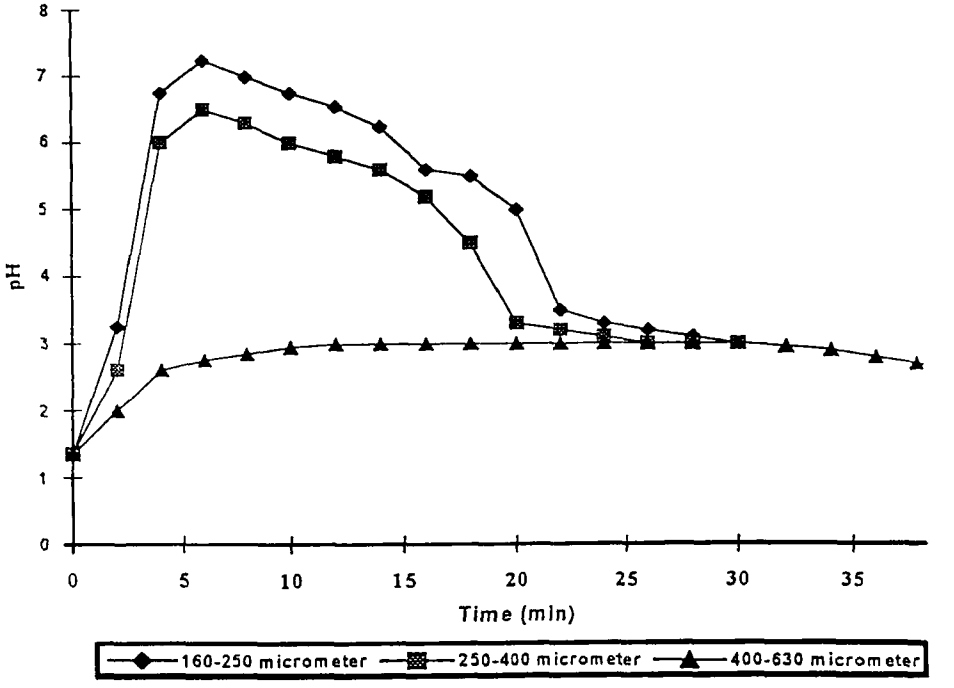

FIGURE 7.
Investigation of the neutralization kinetics of the magnesium oxide granules by means of Rossett-Rice test
Binder: 20% Eudragit S100

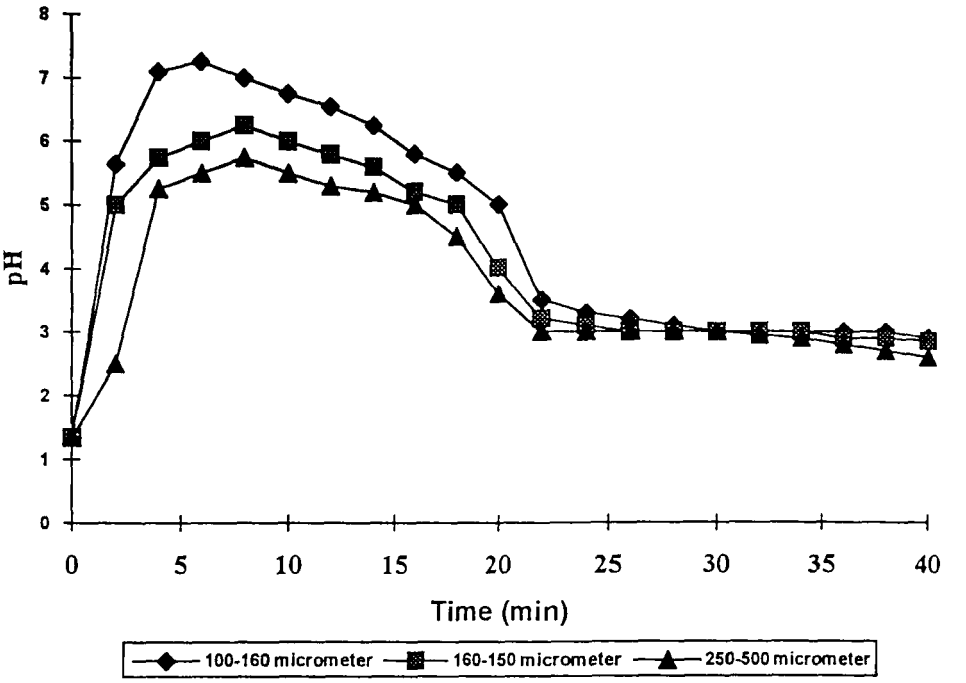

FIGURE 8.

Investigation of the neutralization kinetics of the magnesium oxide granules by means of Rossett-Rice test
Binder: 20% Eudragit L100-55

granules containing Eudragit in various proportion is influenced by the particle size of the granules.

Figure 7., 8. show the neutralization curves measured by Rossett-Rice test in case of various granules containing Eudragit S100 and L100-55 polymers.

Granules those of bigger grain size produce OH^--flux at a lower pH value. It has a great significance as regards therapy. In the opposite case, due to the quick OH^--release, the pilorus opens in neutral pH-range, consequently the content of the stomach is excreted and the unreacted magnesium oxide granules pass by. The grain size of the granules effects the neutralization reaction kinetics because of the difference in the binder distribution within the granules. In case of granules of bigger grain size the binder (Eudragit) forms a layer on the surface of the granules, which functions as a diffusion barrier. The polymer swells above pH=5 - thus hindering the drug release.

CONCLUSIONS

It can be concluded from the results that the hydrophobization decreases the rate constant of neutralization.

If the proportion of the binder (insoluble in the neutralization medium) in the granules increases, the neutralization reaction slows down.

The distribution of the binder in the granules which is determined by the grain size significantly changes the neutralization reaction.

By changing the above parameters the time dependence of the neutralization reaction can be planned in advance.

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