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SUCRALFATE AS A BIOADHESIVE GASTRIC INTESTINAL RETENTION SYSTEM: PRELIMINARY EVALUATION

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ABSTRACT

A prototype formulation of a gastric intestinal retention system was successfully developed. A matrix tablet containing sucralfate, Methocel E4M and the appropriate type of drug powder, granules or pellets was prepared using the Carver Press. Three different formulations were evaluated using three different drug entities, namely; theophylline sustained release pellets, aspirin granules and antacid powder. Tablets of these three different formulations showed remarkable adhesive characteristics onto the glass vessel in acidic medium up to at least eight hours. In addition, all three different formulations exhibited sustained release in-vitro dissolution profiles. These data

imply that this gastric intestinal retention system can be used to prepare sustained release formulations.

INTRODUCTION

Sucralfate, an aluminum salt of sulfated disaccharide, is effective in healing duodenal and gastric ulcers[1]. It has been distributed commercially in Japan and other countries for treatment of peptic ulcer since 1968 under the approval by the respective health authorities[2]. Sucralfate has been shown to be very safe. Acute oral toxicity studies in animals using doses up to 12 g per kg body weight (144 times the human dose), could not find a lethal dose[3]. In addition, sucralfate is only minimally absorbed from the gastrointestional tract. The small amounts of the sulfated disaccharide that were absorbed were excreted primarily in the urine. The side effects of sucralfate were minor. Only 4.7% of patients out of 2500 patients in clinical trials reported side effects. The most frequent complaint was constipation (12.2%). This might be the result of the high content of aluminum in the formulation[3]. Data indicate that sucralfate has an exceptional safety margin as a drug substance.

The mechanism of sucralfate's ability to accelerate healing of duodenal ulcer remains to be fully defined. It is known that it exerts its effect through a local, rather than systemic, action. It is thought that sucralfate forms an ulcer-adherent complex with proteinaceous exudate at the ulcer site. This complex covers the ulcer site and protects it against further attack by acid, pepsin, and bile salts[4].

Sucralfate has negligible acid neutralizing properties. Therefore, its anti-ulcer effect cannot be attributed to the neutralization of gastric acid[3].

Sucralfate, currently is marketed in the U.S. as a prescription item under the trade name of Carafate® by Marion Laboratories, Inc. The daily dosage is one tablet (1 g of sucralfate) four times daily[3].

During early experimental work in this study with sucralfate, it was observed that sucralfate powder could react with 0.1 N HCL solution (equivalent to pH of the gastric fluid) to form a tacky gel. This tacky sucralfate gel exhibited a remarkable adhesive characteristic onto the glass vessel. However, sucralfate powder did not form a tacky gel when exposed to aqueous medium. This interesting observation implied that sucralfate may be a good candidate to be used as an adhesive polymer to yield a gastric intestinal retention drug delivery system.

The unique adhesive characteristic of sucralfate in acidic medium plus its safety status make sucralfate an ideal material to be used as an inactive polymer for the development of a gastric intestinal retention system.

The hypothesis of how the gastric intestinal retention system works is given as follows: As the matrix formulation containing drug and sucralfate is ingested, the sucralfate mixture will react with gastric fluid in the stomach to form a tacky matrix gel. This matrix gel may preferably adhere to the stomach mucosa. The ideal matrix tablet should be able to attach onto the stomach mucosa for eight hours or more. In addition, the tablet should also be able to remain intact for the same length of time. Consequently, the drug would then diffuse out of the matrix tablet at a controlled rate over an extended period of time. The use of sucralfate as the adhesive

polymer in developing a gastric intestinal retention system is examined in this study.

EXPERIMENTAL

MATERIALS

One lot of sucralfate (Rorer, Japan, Inc., Tokyo, Japan) was used. Guar gum (Aqualon Company, Wilmington, DE), Methocel E4M (Dow Chemical Company, Midland, MI), Ac-Di-Sol® (FMC Corporation, Philadelphia, PA), aspirin granulation (Rhone-Poulenc Basic Chemicals CO., Shelton, CT) and magnesium hydroxide powder (Barcroft CO., Lewes, DE) were used as received. Theophylline sustained release pellets (Rhône-Poulence Rorer Pharmaceutical, Inc., Collegeville, PA) were used. All reagents were analytical grade or better.

EQUIPMENT

Carver press (Model C, Fred S. Carver Inc., Menomonee Falls, WI) equipped with an one-half inch flat faced punch was used to compress tablets.

DISSOLUTION TEST

The dissolution tests were conducted using USP XXI/NF XVI apparatus 2. The dissolution medium (900 ml) for theophylline and magnesium hydroxide formulations was 0.1 N simulated gastric fluid without enzymes. The aspirin formulation utilized 900 ml pH 3.0 phosphate buffer. The agitation speed was 50 rpm. Samples were removed at suitable time intervals. The collected samples were assayed either at 271 nm for theophylline or at 265 nm for aspirin using a

TABLE 1

Composition of Theophylline Sustained Release Matrix Tablet

Material Used	mg/Tablet	% w/w
Theophylline S.R. Pellets (contains 300mg of theophylline)	500	50
Sucralfate	400	40
Methocel E4M or Guar gum	100	10
	1000	100

spectrophotometer (Model DU-6, Beckman Instrument, Inc., Fullerton, CA) to determine drug content. The in-vitro dissolution profile of the magnesium hydroxide formulation was determined by measuring total magnesium ions in the dissolution medium via atomic absorption spectroscopy at 285 nm wavelength.

Preparation of Gastric Intestinal Matrix Tablet

The appropriate amount of theophylline sustained release pellets, sucralfate and other suitable additives (such as Methocel E4M or guar gum) were admixed. The mixture was compressed with the appropriate compression force using the Carver press. The formulation for the theophylline sustained release matrix tablet is given in Table 1.

The formulations for bilayer matrix tablet containing either aspirin or magnesium hydroxide are given in Tables 2 and 3. Figure 1 is the graphic presentations for the above three different formulations. The adhesive-layer mixture containing the appropriate amounts of sucralfate and Methocel E4M

TABLE 2

Composition of Aspirin Sustained Release Bilayer Matrix Tablet

Material Used	mg/Tablet	% w/w
Matrix Layer		
Aspirin Granulation (contains 90% aspirin)	500	52.7
Methocel E4M	100	10.5
Ac-Di-Sol®	100	10.5
Adhesive Layer		
Sucralfate	187.5	19.7
Methocel E4M	62.5	6.6
	950.0	100.0

TABLE 3

Composition of Antacid Sustained Release Bilayer Matrix Tablet

Material Used	mg/Tablet	% w/w
Matrix Layer		
Magnesium Hydroxide (contains 500 mg of magnesium hydroxide)	481	45.5
Methocel E4M	175	16.6
Sucralfate	75	7.1
Ac-Di-Sol®	75	7.1
Adhesive Layer		
Sucralfate	187.5	17.8
Methocel E4M	62.5	5.9
	1056.0	100.0

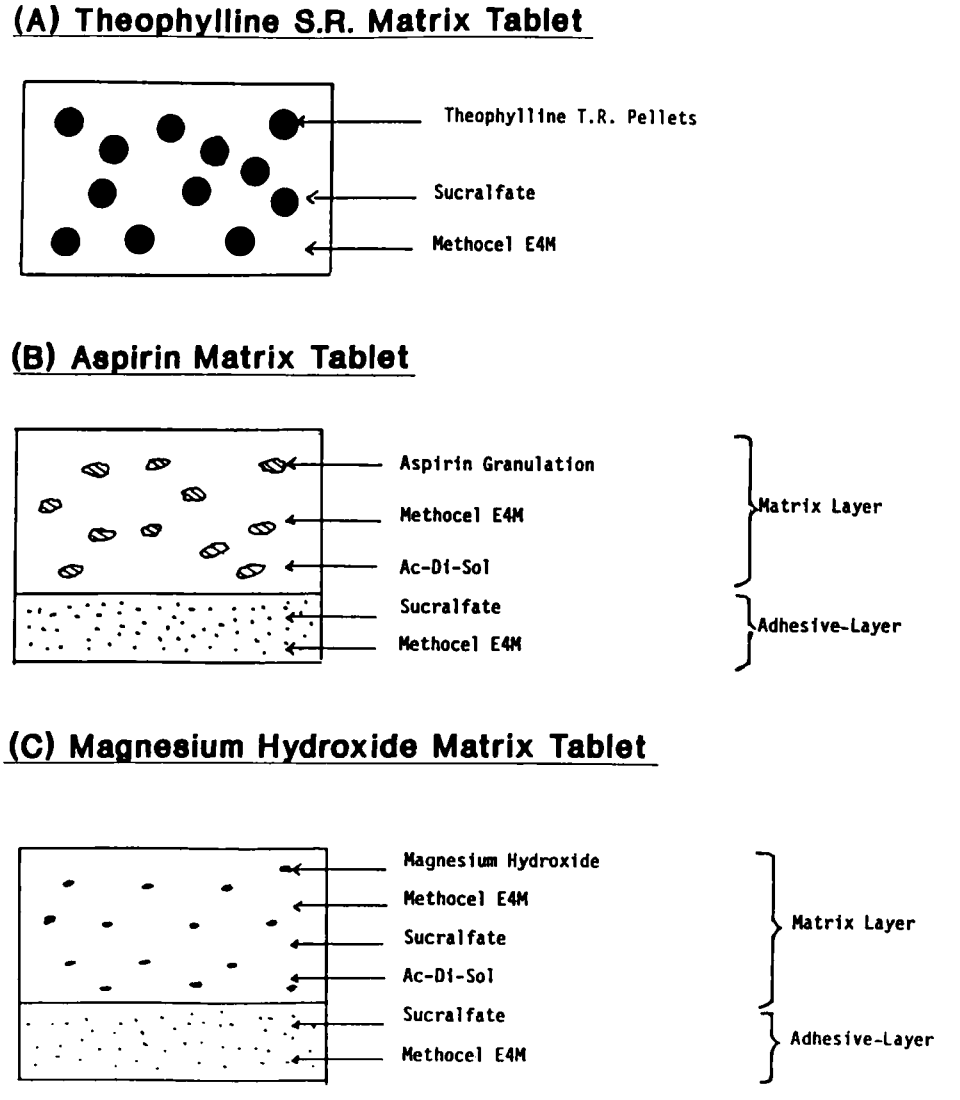

Figure 1. Composition of Three Different Matrix Tablet Formulations.

blend were admixed, then added to the die of the Carver press. The appropriate amount of drug entities (aspirin granulation or magnesium hydroxide), Methocel E4M, Ac-Di-Sol® were admixed with or without sucralfate and added into the die containing the adhesive-layer mixture. The bilayer mixtures were then compressed with the appropriate compression force. The composition of each of the three different formulations were designed to contain 500 mg of active ingredient. The amount of inactive materials were varied depending on the formulation requirements.

In order to evaluate the utility of the bioadhesive system, three different model types of drug entities with three different particle size distributions were selected for the study.

RESULTS AND DISCUSSIONS

It should be pointed out that the scope of this paper is to investigate whether sucralfate is a suitable bioadhesive material for gastric intestinal controlled release application. All preliminary work presented in this article is focused to develop a matrix system which can demonstrate in vitro bioadhesive characteristics. A simple, in vitro method was adapted as a screening tool to provide a quick guideline. Visual observation and monitoring of the overall swelling and gelling tendency of the matrix tablet in the acidic medium were used to screen for an appropriate formulation for further in-depth testing. The desirable matrix system should demonstrate adhesive characteristics onto the dissolution glass vessel during the dissolution test up to eight hours or more. In addition, this desirable matrix system should retain its geometrical physical dimension up to eight hours or

more in the dissolution vessel. This arbitrary design can simplify and quicken the screening test to evaluate prototype formulations. In vivo performance of the desirable bioadhesive formulation will be evaluated in future experiments, but it was not the scope of this work.

Formulation Development of the Prototype Gastric Intestinal Matrix Tablet

In the initial stage of developmental work, sucralfate, guar gum and either the theophylline sustained release pellets or aspirin granulation were mixed and compressed into a matrix tablet. Visual observations of these two types of tablets in 0.1 N HCL solution indicated that the mixture of drug, sucralfate and guar gum did form a tacky gel and attached onto the glass vessel. However, it was also observed that this formulation approach did not provide a constant rate and shape of gel formation (in vitro), which in turn could affect the release rate profile of the finished product. This data seemed to imply that the guar gum may not be suitable as either a binder or diluent for this matrix tablet.

Further experimental work identified that the incorporation of Methocel E4M or K4M into the drug/sucralfate matrix could improve the gel formation of the matrix tablet. Tablets containing appropriate amount of Methocel E4M, sucralfate and theophylline sustained release pellets showed an exceptional adhesive characteristic in contact with 0.1 N HCL solution in the glass vessel. The tablet remained intact and attached to the glass vessel for an extended period of time. After eight hours in the acidic medium, tablets could only be removed from the glass

TABLE 4

Physical Properties of Three Different Type Matrix Tablets

Type of Matrix Tablet	Hardness (kp)	Thickness (Inch)	Compression Force Used (lb)
Theophylline	6.2	0.252	1000
Aspirin	8.2	0.240	1500
Magnesium Hydroxide	9.5	0.277	1500

vessel by using an excessive mechanical force with the aid of a spatula. A tablet formulation (used as a control) was prepared using only theophylline sustained release pellets and Methocel E4M and was subjected to the same screening test. The tablet (control) only showed a slight sticking tendency to the glass vessel after soaking in the acidic medium for 30 minutes. At the end of the eighth hour, the control tablet swelled and floated in the acidic medium. This experiment indicated that Methocel E4M alone did not contribute to the sticking tendency of the resultant tablet and that sucralfate was the material primarily responsible for the adhesive characteristic of the matrix tablet. Data seemed to indicate that Methocel E4M could provide a strong gelling network to prevent the tablet from disintegrating, whereas the tacky characteristic of sucralfate in contact with 0.1 N HCL allowed the matrix tablet to adhere to the glass vessel.

The initial physical characteristics of the three different types of matrix tablets are given in Table 4.

Effect of Particle Size of Drug Entity on the Formulation Composition of the Matrix Tablets

A prototype formulation for a theophylline sustained release tablet was successfully developed using the theophylline sustained release pellets (average pellet diameter of 1250 microns), sucralfate and Methocel E4M. The composition of the tablet is given in Table 1. The ratio of Methocel E4M to sucralfate (4:1) in this formulation gave the best balance of gelling and adhesive characteristics of the matrix tablet.

The matrix tablet remained intact and adhered onto the glass vessel up to at least 8 hours. The

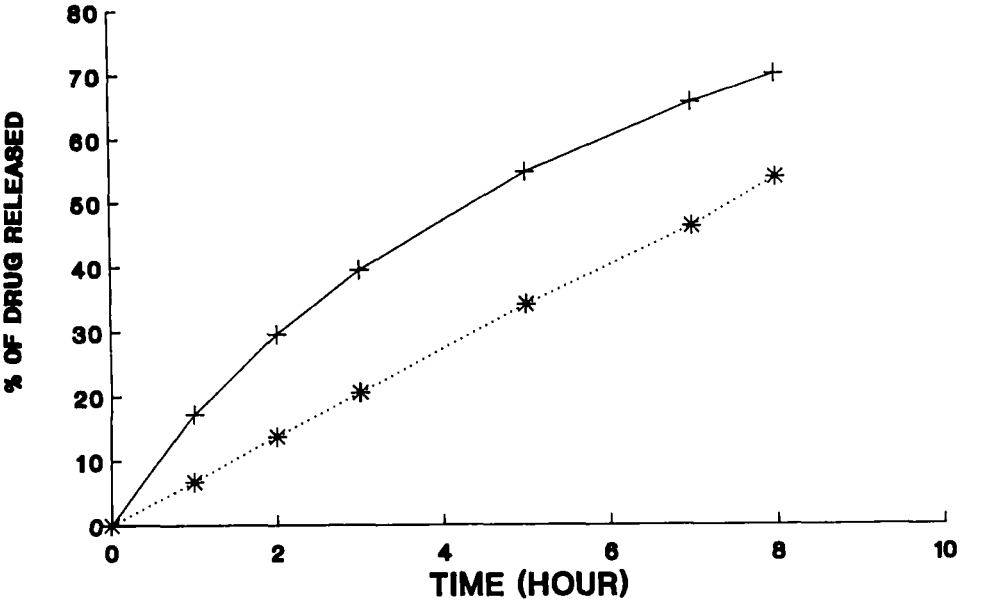

Figure 2. In Vitro Dissolution of Theophylline from Theophylline Matrix Tablet and Theophylline Sustained Release Capsule in 0.1 N HCL. Key: * - Matrix Tablet; + - Capsule.

in vitro dissolution result of this tablet formulation exhibited a slower in vitro release rate profile as compared to the intact theophylline sustained release capsule (Figure 2). The same batch of theophylline sustained release pellets was used to prepare the tablet and the capsule. In pH 1.2 simulated gastric fluid (without any enzymes), the tablet exhibited zero order release kinetics (R^2= 0.9997) up to at least eight hours; whereas the theophylline sustained release capsule exhibited a release pattern with square root of time dependence. This indicated release from a typical matrix formulation described by T. Higuchi (R^2 = 0.9994)[5]. The incorporation of 10% of Methocel E4M

into the matrix tablet contributed to the sustained release profile of the resultant tablet. It retarded the release rate of theophylline sustained release pellets and subsequently yielded a matrix tablet with zero order release kinetics. A 100% recovery of theophylline at the end of the 24 hour dissolution study indicated that the matrix tablet was capable to deliver the full dose of drug following a zero order release profile.

Data indicated that this formulation approach can potentially be used as a gastric retention system to deliver sustained release pellets medication.

As the particle size of active ingredient in the matrix tablet decreased from 1250 microns to 700 microns (aspirin granulation), it was found that the same matrix tablet formulation used for theophylline sustained release pellets could not be used for the aspirin granulation. The aspirin matrix tablet did not show the same adhesive characteristics as the theophylline matrix tablet. The aspirin granulation, having significantly larger surface area than the theophylline sustained release pellets, may interfere with the swelling rate and gel formation of the matrix tablet. Consequently, it delayed the onset of adhesive characteristic in the resultant tablet onto the glass vessel.

In order to maximize the effectiveness of sucralfate as a bioadhesive agent, a bilayer formulation approach was evaluated for the aspirin granulation. After a series of optimization experiments, a prototype formulation was developed (refer to Table 2 for the formula). An adhesive-layer of sucralfate and Methocel E4M (3:1 ratio) provided the anchor to attach to the glass vessel, whereas the matrix layer containing the aspirin granulation,

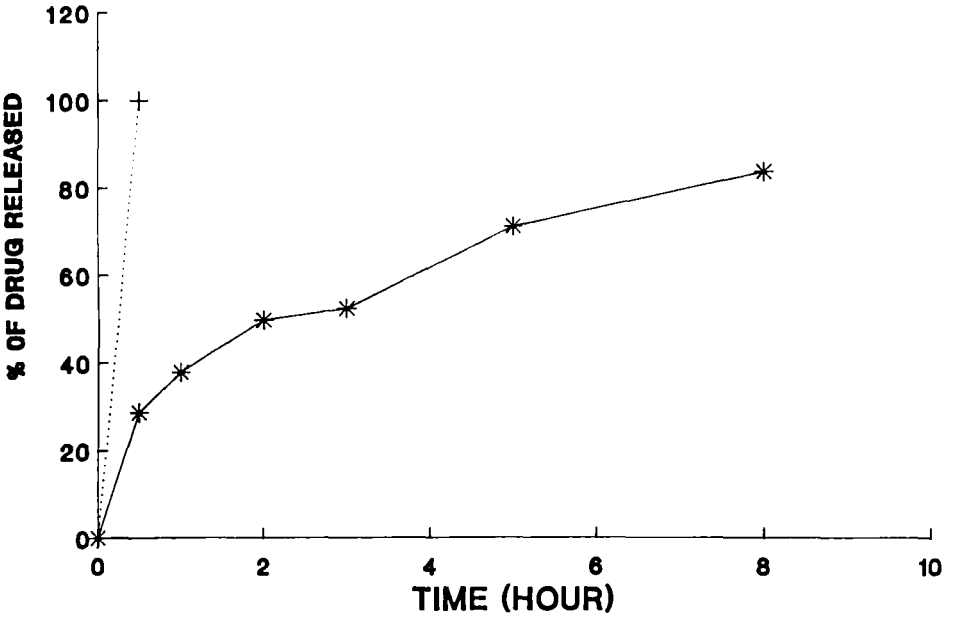

Figure 3. In Vitro Dissolution of Aspirin from Aspirin Matrix Tablet and Aspirin Granulation in pH 3.0 Phosphate Buffer.
Key: * - Matrix Tablet; + - Granulation.

Methocel E4M and Ac-Di-Sol® (croscarmellose sodium) provided the matrix mass to control the release rate characteristics of the resultant tablet. Based on the visual observation of the swelling tendency of the tablet in the acidic medium, it was determined that croscarmellose sodium (super disintegrant) was needed to balance the proper degree of swelling and maintain the appropriate release profile of the resultant tablet. By varying the ratio of Methocel E4M and Ac-Di-Sol® in the matrix layer containing aspirin, the swelling tendency of the tablet was controlled and subsequently used as a means to regulate the release profile of the tablet.

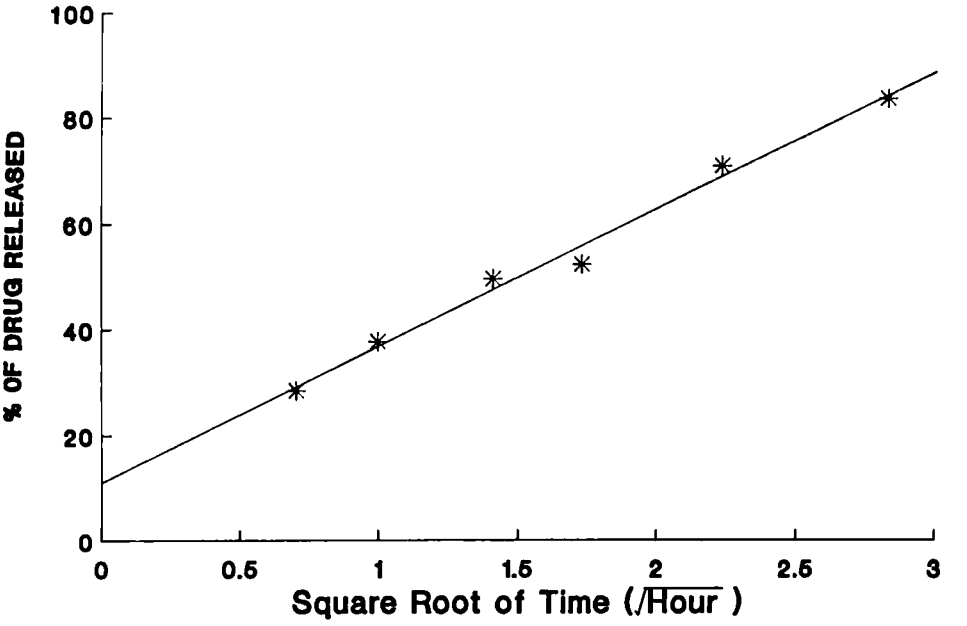

Figure 4. Release Profile of Aspirin from Matrix Tablet in pH 3.0 Phosphate Buffer Plotted Assuming Higuchi Matrix Equation (R^2 = 0.9947).

During the dissolution study (in pH 3.0 phosphate buffer), the aspirin bilayer matrix tablet exhibited a remarkable adhesive characteristic onto the glass vessel. The matrix tablet remained intact up to at least eight hours and showed a sustained release profile (Figure 3). At the end of the 24^{th} hour, the matrix tablet still adhered to the glass vessel and required mechanical force to remove it from the glass vessel. The release kinetics of this formulation apparently followed the Higuchi matrix release kinetics (R^2 = 0.9947)(Figure 4). It should be pointed out that the dissolution study was conducted using pH 3.0 phosphate buffer instead of the 0.1 N simulated gastric fluid because of the poor solubility of aspirin at pH

1.2 dissolution medium. A pH 3.0 phosphate buffer, which represents the upper pH limit of the gastric fluid, was utilized for the study.

As can be seen from Figure 3, Methocel E4M was a major contributor to the sustained release profile of this bilayer matrix tablet. The use of Methocel E4M in the matrix layer provided a matrix environment to retard the release rate of the aspirin granulation from the matrix tablet. The resultant matrix tablet showed a sustained release profile as compared to the aspirin granulation which was completely solubilized within 15 minutes in the same dissolution medium.

As the particle size of the active ingredient further decreased from aspirin granulation (700 microns) to magnesium hydroxide powder (100 microns), it was found that a similar aspirin bilayer matrix tablet formulation approach with a minor formulation adjustment was suitable to prepare matrix tablets of magnesium hydroxide. This formulation utilized the same adhesive-layer as the aspirin matrix tablet which contained sucralfate and Methocel E4M (3:1 ratio). The composition of ingredients in the matrix layer were readjusted to accommodate the effect of dramatic increase in surface area of the magnesium hydroxide powder (Table 3). Incorporation of a small percentage of sucralfate into the matrix layer was needed to improve the overall compressibility and the binding of the two functional layers. The ratio between the Methocel E4M (gelling agent) and Ac-Di-Sol® (disintegrant) in the matrix layer was found to be critical in controlling the integrity of the matrix tablet in the acidic medium. This formulation required a higher amount of Methocel E4M (21.7%) and a smaller amount of Ac-Di-Sol® (9.3%) in the matrix layer as

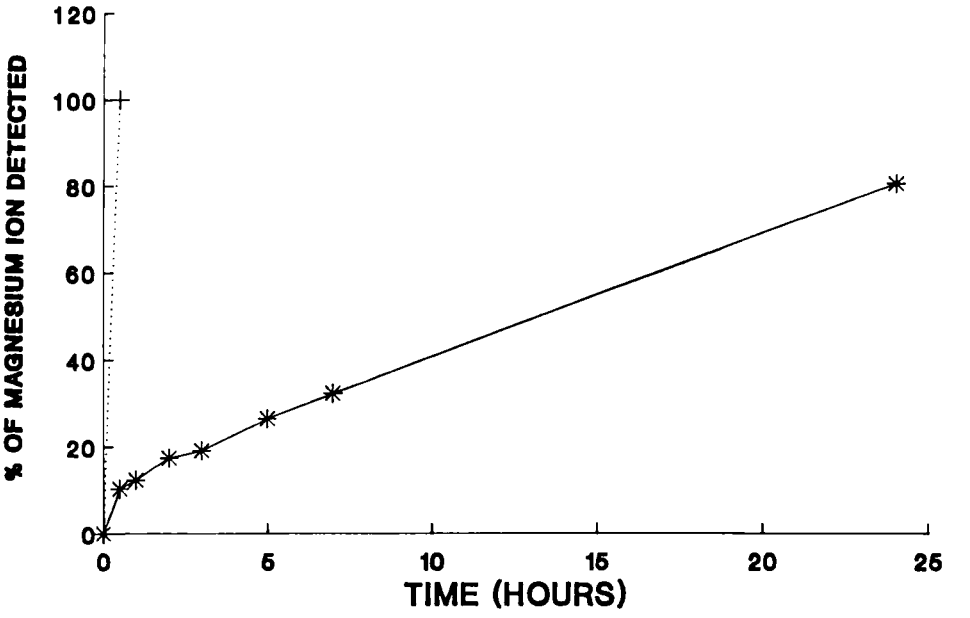

Figure 5. In Vitro Dissolution of Magnesium Hydroxide from Magnesium Hydroxide Matrix Tablet and Magnesium Hydroxide powder in 0.1 N HCL. Key: * - Matrix Tablet; + - Powder.

compared to the aspirin matrix tablet (containing 14.2% of Methocel E4M and 14.2% of Ac-Di-Sol®). This phenomenon can be attributed to the effect of particle size of active ingredient. As the particle size of the active ingredient becomes smaller, a higher amount of gelling agent is needed to ensure the proper gel formation in the acidic medium.

During in vitro dissolution testing in simulated gastric fluid (without any enzymes, pH 1.2), the matrix tablet demonstrated a remarkable adhesive characteristic onto the glass vessel and remained intact up to at least 24 hours. The in vitro release rate profile of the tablet showed a biphasic

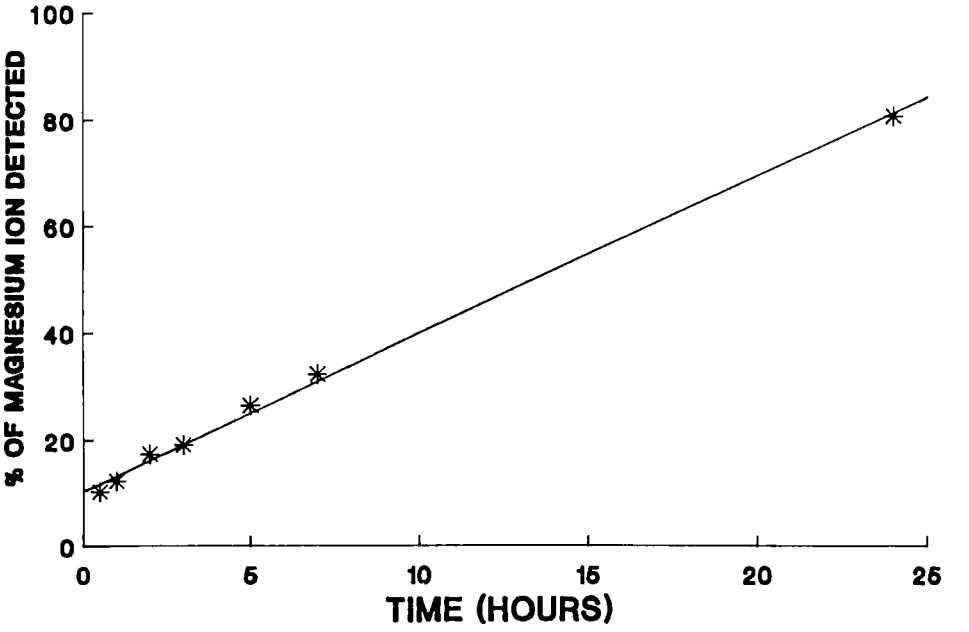

Figure 6. Release Profile of Magnesium Hydroxide from Matrix Tablet in 0.1 N HCL Plotted Assuming Zero Order Release Kinetics (R^2 = 0.9989).

dissolution profile. After initial bursting of drug released from the surface of the tablet during the first 30 minutes, the release rate of the tablet seems to follow a zero order rate (R^2 = 0.9989) up to 24 hours (Figures 5 and 6). This antacid matrix tablet demonstrated a typical celluose ether matrix tablet release profile as compared to a similar Methocel E4M formulation in the literature[6].

CONCLUSION

Preliminary development work and in vitro dissolution data of three different formulations indicated that the combination of sucralfate and

Methocel E4M in a matrix tablet approach showed potential as a good means to yield a long acting gastric intestinal retention delivery system. All three formulations showed remarkable adhesive characteristics onto the glass vessel in acidic medium up to at least eight hours and demonstrated acceptable in vitro sustained release rate profiles. The diffusion rate of drug through the matrix gel can be regulated by adjusting the amount of Methocel E4M and Ac-Di-Sol® in the matrix tablet. However, it will require extensive in vitro analytical development work and in vivo studies to verify whether this system can work effectively in vivo.

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