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A programmable drug delivery system for oral administration☆

Farouk M. Sakr

Department of Pharmaceutics, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt

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Abstract

A programmable, controlled release drug delivery system has been developed. The device in the form of a non-digestible oral capsule (containing drug in a slowly eroding matrix for controlled release) was designed to utilize an automatically operated geometric obstruction that keeps the device floating in the stomach and prevents it from passing through the remainder of the GIT. Different viscosity grades of hydroxypropyl-methyl-cellulose were employed as model eroding matrices. The duration during which the device could maintain its geometric obstruction (caused by a built-in triggering ballooning system) was dependent on the erosion rates of the incorporated polymers (the capsule in-hosed core matrix). After complete core matrix erosion, the ballooning system is automatically flattened off so that the device retains its normal capsule size to be eliminated by passing through the GIT. In vitro long-term drug delivery from a prototype model was studied using levonorgestril as a model drug. Zero-order release could be maintained for periods ranging between 5 and 20 days before the geometric obstruction is triggered off. The rate of drug release was dependent on the nature, viscosity and ratios of polymer employed. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Controlled release; Drug delivery systems; Drug targeting; Eroding matrix; Floating systems; Hydroxypropylmethylcellulose; Levonorgestril; Oral administration; Zero-order release

1. Introduction

The pharmaceutical industry and the medical profession are today prepared to accept, and to introduce broadly into human and animal health care, controlled-release drug dosage form for gastrointestinal delivery via oral administration. Although significant advances have been made in controlled drug delivery (Langer and Wise, 1984a,b; Peppas et al., 1987; Robinson and Lee, 1987), the application of controlled release technology to oral administration has been limited. This mainly due to the fact that the extent of drug absorption from the gastrointestinal (GI) tract is determined by the GI transit time of the dosage irrespective of the controlled release properties of the device. In general, the transit time from

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mouth to cecum can vary from 3 to 16 h (Davis et al., 1987; Feely and Davis, 1989; Khosla and Davis, 1989; Khosla et al., 1989). The transit time in the small intestine ranged from 3 to 4 h under both fasted and fed conditions (Wellman, 1984; Davis et al., 1987; Khosla et al., 1989). Thus the time for absorption from the GI tract is limited for most drugs.

While numerous alternatives exist for controlled-release oral dosage forms (osmotic tablets, controlled dissolved coatings, biodegradable and bioerodible polymer matrices, etc.), none can circumvent the inherent limitation of the passive oral dosage form namely, the limits in delivery program imposed by the transit time in the gut. This limitation could be obviated and the utility of GI controlled administration greatly broadened if means for immobilizing an ingested device within the stomach or on the intestinal wall for an extended (and predictable) time period could be developed. With such a device, long duration systemic (or, for that matter, local gastrointestinal) therapies could be instituted.

Many attempts were made to control gastric retention time by altering the size (Meyer et al., 1985; Itoh et al., 1986; Park et al., 1987; Khosla et al., 1989; Khosla and Davis, 1990; Sirois et al., 1990), shape (Meyer et al., 1985; Park et al., 1987), density (Bechgaard et al., 1985; Meyer et al., 1985; Davis et al., 1986; Inganni et al., 1987; Sirois et al., 1990), and surface properties (Ch'ng et al., 1985; Harris et al., 1990a,b) of oral devices. These attempts, however, have resulted in only limited success. Cargill et al. (1988, 1989) showed for the first time that objects could be retained in the stomach for 24 h under fasted conditions if they possess certain tetrahedral or ring-like geometries. Their work demonstrated that the combined effects of size, shape and flexibility were important in gastric retention. The mechanisms of gastric retention of those devices, however, are not understood.

In the present investigation, a new oral delivery system was designed to control drug release rate for several days according to the required duration and purpose of treatment. In vitro long-term drug delivery from a prototype model was studied using levonorgestril as a model drug.

2. Materials and methods

Levonorgestril, different viscosity grades of HPMC (H8384, H9262 and H7509) with respective viscosities of 50, 100 and 4000 cps (2% aqueous solutions) were from Sigma (St. Louis, MO, USA), Polyethylene glycol 6000 was from Aldrich (St. Louis, MO, USA). All other chemicals were HPLC and analytical grade materials.

2.1. Construction of the device

Prototype models of the new device (3 cm long and 0.9 cm internal diameter were made to comprise the following structures:

1. A Cylindrical shell in the form of an oral capsule made from a special non-digestible acid resistant high density polymer (Figs. 1 and 2 No.1).
2. One end of the shell has a controlled diameter circular hole for maintaining drug release (Figs. 1 and 2 No. 2).
3. The drug is housed in the device in the form of a cylindrical disc (Figs. 1 and 2 No. 3) after being mixed with the slowly eroding polymer and compressed to nearly zero porosity.
4. A flexible rubber disc with a vertical-horizontal by pass orifice (Figs. 1 and 2 No. 4) is placed above the drug-polymer compact. The rubber disc separates the drug-polymer compact at the lower part of the device and the spring chamber in the upper part.
5. A compressible acid resistant spring with a suitable expanding force (Figs. 1 and 2 No. 5) is placed on the top of the flexible rubber disc to exert pressure over both the disc and the drug-polymer compact. The spring is fixed inside the device (Figs. 1 and 2 No. 11) so that it pushes both the rubber disc and the drug-polymer compact down as the drug-polymer compact erodes.
6. The upper space above the rubber disc containing the spring (Figs. 1 and 2 No. 6) is filled with an acid (hydrochloric acid or a solution of citric acid in water) through a rubber non-returning valve (Figs. 1 and 2 No. 7).
7. A special acid resistant, impervious, non-permeable expanding rubber ballooning system

(Fig. 1, No. 8) containing entrapped bicarbonate granules is fixed at the upper end of the device, tightened with a water soluble tape and sealed with a gelatin cap (Fig. 1 No. 9), to prevent mixing of the bicarbonate with the acid before use.

2.2. Preparation of the plain polymer compacts

Each grade of the plain HPMC polymer was individually compressed into 1 g cylindrical compacts with flat-faced round (8-mm diameter) tooling to nearly zero porosity. The lateral surfaces of the compacts were lightly greased with soft paraffin before being inserted inside the device (Figs. 1 and 2 No. 3). This was to protect the lateral surface from the moisture of the release medium and also to facilitate the downward movement of the compact during erosion. The plain compacts were used to test for the effect of the different viscosity grades of the HPMC on the operational mechanism and duration of the device.

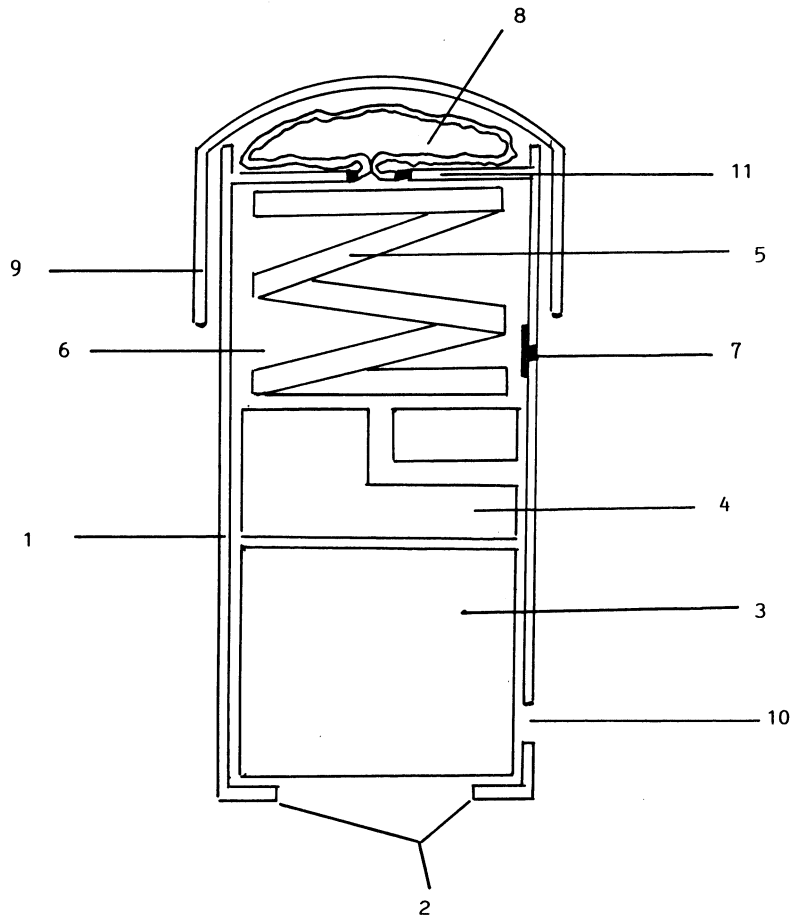

Fig. 1. Diagrammatic sketch of the intact device before the release study. Key: 1, a cylindrical non-digestible polymer shell; 2, circular hole for maintaining drug release; 3, drug–polymer (Levonorgestril-HPMC) compact; 4, a flexible rubber disc with a vertical–horizontal orifice; 5, compressible spring; 6, hydrochloric acid (or suitable acid solution); 7, non-returning rubber valve; 8, flexible impermeable rubber balloon containing bicarbonate granules; 9, hard gelatin cap; 10, small side orifice; and 11, water soluble tape fixing the balloon.

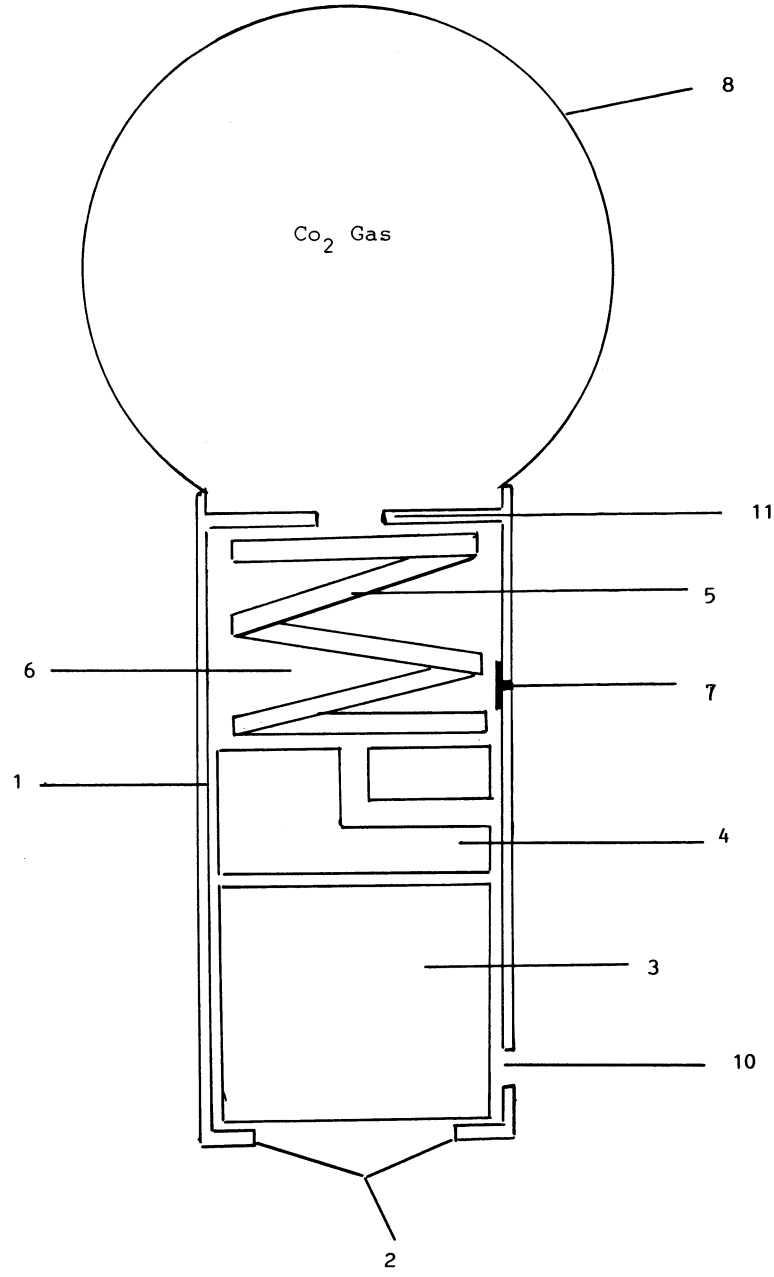

Fig. 2. Diagrammatic sketch of the device during the release study. Key as in Fig. 1.

2.3. Preparation of levonorgestril–polymer compacts

Each grade of HPMC (9.75 g) was dispersed in 50 ml chloroform containing the dissolved levonorgestril together with 0.5% of PEG. The amount of levonorgestril incorporated in each polymer matrix was decided according to its required daily dose and depended on the duration taken for complete drug release from each grade

of polymer. Preliminary experiments showed that the maximum time taken for complete drug-polymer erosion and full device operation was about 18 days for devices containing the highest viscosity grade HPMC (4000 cps). The organic solvent was evaporated in a rotary evaporator in order to deposit the drug on the substrate polymers. Each drug-polymer mixture was individually compressed into 1 g cylindrical compacts with flat-faced round (8-mm diameter) tooling as mentioned previously. The drug content in each compact was 6 mg (equivalent to 20 days supply of the oral contraceptive where the normal daily dose of levonorgestril is 300 μg). The lateral surfaces of the drug-polymer compacts were treated like those of the plain compacts before being inserted inside the device. The levonorgestril–polymer compacts were used to study the possible application of the device as a long-term delivery system for the incorporated contraceptive.

2.4. Percentage overall erosion of the plain polymer compacts

The percentages overall erosion from the different viscosity grades of the plain compacts were determined by placing each compact without the device (initial weight W_I) in a basket equipped with a USPI basket model dissolution tester. The basket was immersed at 37°C in 800 ml of distilled water and rotated at 50 rpm. The compacts were lifted from the medium at designated time intervals and their dry weight (W_d) were determined using an infrared moisture meter. During the drying period, the temperature was 120 ± 0.5°C. The end of the drying point was considered after two consecutive constant weights in 5 min. The percentage overall erosion of each compact was calculated using Eq. (1):

$$E_p = [(W_i - W_d)/W_i] \times 100 \quad (1)$$

The obtained values represent the erosion from the total surface area of each compact. Three compacts from each individual polymer were used for each determination.

2.5. Operation mechanism and drug-release study

The operational mechanism of the device containing the different viscosity grades of the plain HPMC, and the release profile of levonorgestril from the HPMC compacts were examined in 800 ml distilled water containing 5 ppm of polysorbate 80. As the constructed device was designed to float in the release media, The experiments were therefore performed in 1 l flat bottomed beakers equipped with synchronized magnetic heads and stirring bars at rotational speed of 50 rpm. The release media were maintained at 37°C by immersing the beakers in a thermostated glass water bath underneath which the magnetic heads were mounted to rotate the bar magnets in the bottoms of the beakers. The times required for complete erosion of the plain compacts and the device to perform its full operation cycle (Fig. 3(A–D)) were recorded. In the drug release study, samples (15 ml) were withdrawn every 12 or 24 h until the drug-core matrices were completely eroded and all drug contents have been released. The obtained samples were filtered through 0.22 μm Millipore filters. The first 10 ml of the filtrate was discarded and the remaining volume used for the assay. The devices containing the drug-polymer compact were transferred into fresh release medium every 12 or 24 h in order to maintain sink conditions.

2.6. Drug assay

Levonorgestril (LN) was assayed using HPLC (Shimadzu LC-6A, Shimadzu Corp. Tokyo, Japan), using a 4.6-mm × 25-cm, 10 μm, Whatman ODS-3 Partisil C-18 column. The LN was measured with a mobile phase of acetonitrile–water (50–50 v/v) at a flow rate of 2.0 ml/min with absorbance monitoring at 243 nm. The retention time of LN was 6.0 min. A comparison reference standard was made by dissolving accurately known concentrations of LN (300 μg) in 800 ml of the release medium. A volume of alcohol not exceeding 2% of the final volume of the reference solution was used to aid in dissolving the reference standard (USP XXII).

3. Results and discussion

3.1. Operation mechanism of the device

Fig. 3(A–D) is representative of the different steps showing how the device is functioning. The duration of release was about 4, 8 and 18 days, respectively, for devices containing 50, 100 and 4000 cps of the plain HPMC. The degree of polymer erosion was dependent on the viscosity of the selected polymers. The results were in agreement with the E_p values represented in Fig. 4. When the E_p values were plotted as a function of time, delayed overall erosion rates were observed as the polymer viscosity was increased. Detailed explanation, of the effect of polymer viscosity on compact erosion and consequent duration for full device operation will be discussed in Section 3.2. The mechanism can be explained as follows:

1. When the device was immersed in the release medium (in vitro testing) or after being swallowed (not tested) the gelatin cap and the water soluble tape fixing the ballooning system dissolve (Fig. 3(A)).
2. The bicarbonate content inside the balloon mixes with the acid in the compartment above the rubber disc (where the spring is mounted). The evolution of carbon dioxide gas allows the balloon to expand as desired. The expanding balloon acts as a geometric obstruction that allows the device to float in the dissolution medium (Fig. 3(B)), consequently prevents it from passing through the lower lumen of the stomach into the small intestine if taken orally (not tested). The balloon also helps the device to float in the stomach.
3. The exposed surface of the polymer compact at the lower part of the device starts to swell and erode slowly through the controlled diameter circular hole (Fig. 3(B)).
4. As part of the polymer compact erodes (Fig. 3(C)), the spring and the entrapped gas pressure above the rubber disc push it down to expose new polymer surface for erosion.
5. After complete compact erosion (Fig. 3(D)), the flexible rubber disc is pushed further to the lower end of the device where the vertically-

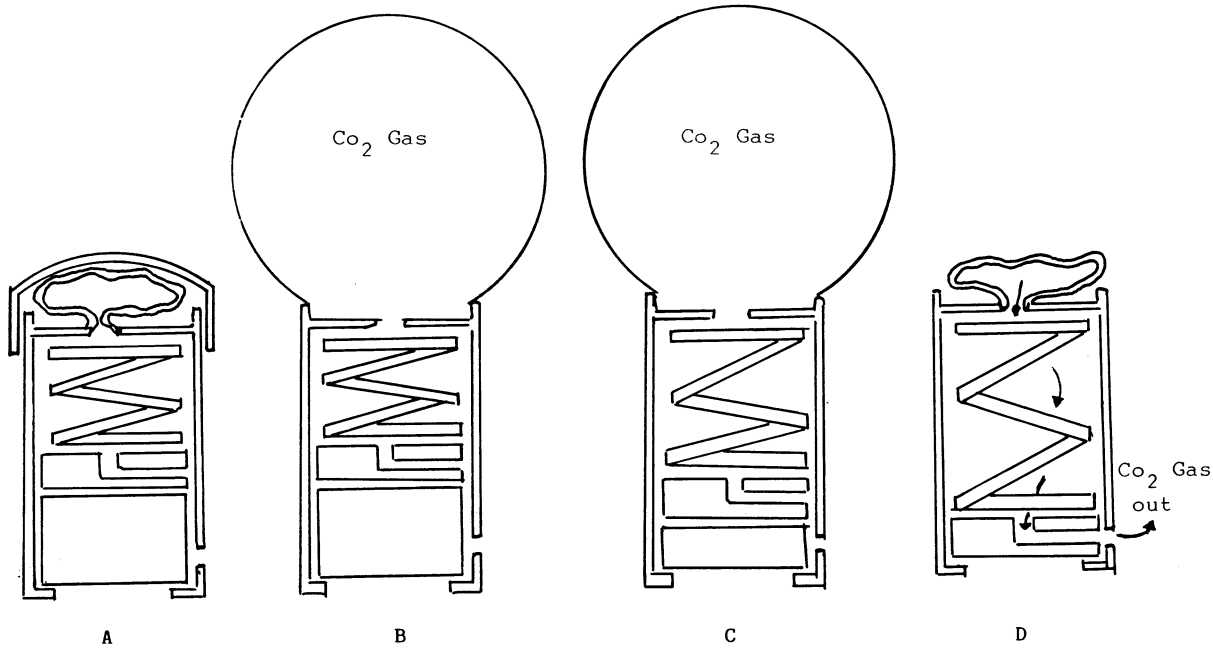

Fig. 3. (A, B, C, D) Diagrammatic sketch of the device representing its operation mechanism. (A) intact device; (B) device at the beginning of drug release; (C) device with half drug-polymer compact eroded; and (D) device after complete drug–polymer erosion and evacuation of entrapped carbon dioxide (inflated balloon).

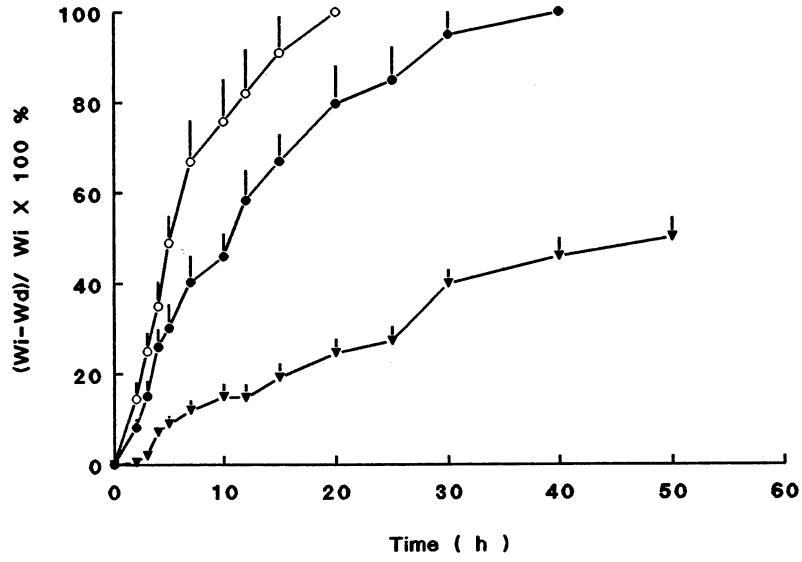

Fig. 4. The erosion profiles of the different viscosity grades of HPMC compacts without the device as function of time. / 50 cps HPMC compacts; * 100 cps HPMC compacts; and ▼ the 4000 cps compact.

traversed orifice in the rubber disc (Fig. 1 No. 4) faces the lower side orifice in the housing polymer shell of the device (Figs. 1 and 2 No. 10). The entrapped air above the rubber disc eventually escapes from the side orifice near the lower end of the device so that the balloon is flatted and loses its obstruction properties (Fig. 3(D)). The device returns to its normal capsule size, which is small enough to be eliminated through the GI tract when taken orally.

3.2. Levonorgestril release

The release profiles of levonorgestril from the different viscosity grade polymer compacts after being housed inside the device are shown in Fig. 5. The release kinetics of the drug from all types of compacts were linear with regression values of 0.98 (indicating apparent zero-order release). The upper graph in Fig. 5 represents the release rate of levonorgestril from the 50 cps viscosity grade HPMC compacts. The duration for 100% release from these compacts was prolonged for up to 5 days before the geometric obstruction of the constructed device was triggered. The middle graph illustrates the drug release from the 100 cps viscosity grade compacts with an extended duration of 9 days for 100% release. The lower graph represents the longest release duration (up to 20 days) from the 4000 cps viscosity grade polymer. HPMC used in the present study has been classified as swelling controlled release system. Generally, in swelling control matrix systems there are two major factors which control the rate of drug release from the matrix. One is the rate of aqueous medium infiltration into the matrix followed by a relaxation process (hydration, gelation or swelling) and the other is the rate of erosion of the matrix. As a result of these simultaneous processes, two fronts are evident, a swelling front (glassy polymer/gel interface) and an eroding front (gel/medium interface). The distance between the two fronts (diffusion layer thickness) depends on the relative rates at which the swelling and eroding fronts move in relation to each other. In the present study, levonorgestril was incorporated in different viscosity grade HPMC polymer and compressed to nearly zero porosity; in addition, the drug-polymer compacts were allowed to be wetted from only one surface (Fig. 1, No. 2). These factors markedly reduced the ability of the release medium from penetrating inside the bulk

of the drug-polymer compact and hence reduced the thickness of the gel/medium interface. The effect was more pronounced with the higher viscosity grade HPMC. As a result, the rate of polymer erosion was reduced (Fig. 4) and prolonged drug release could be obtained (Fig. 5) as the polymer viscosity was increased. These results are in agreement with those reported previously on the effect of different grades polymers on the release of drugs from swelling and erosion controlled polymeric matrices (Dahl et al., 1990; Rao et al., 1990; Malamataris and Ganderton, 1991). In the present study, the use of high viscosity grade polymer, such as HPMC (4000 cps) has therefore resulted in much reduced compact erosion and more prolonged duration for the device to maintain its geometric obstruction. Thus the selection of the viscosity grade polymer is an important consideration in the formulation of the device.

4. Conclusions

A new programmable long-term drug delivery system for oral administration was developed. Laboratory prototype models were examined. The duration of action was dependent on the erosion rate of the incorporated polymers. In vitro release rate of Levonorgestril (used as a model contraceptive drug) from the constructed device could be maintained for up to 20 days. The possible use of the new system for oral obesity control was discussed. In general, this new system in the form of an ordinary oral capsule was designed to utilize the following advantages:

1. Reasonable cost of production;
2. Self-administered by the patient;
3. No tools or medical intervention are required for administration;
4. Automatically fixes itself in the stomach where it releases all drug content;
5. Programmable to operate for any specified period of time up to weeks;
6. Programmable to release its drug content at a zero-order kinetic patterns (constant rate of release);
7. Automatically eliminated via the GI tract after the specified period of action;
8. No tools or surgical intervention are required for elimination;
9. Can be universally employed as a delivery system for a wide range of drugs, hormones, trace elements, etc.; and

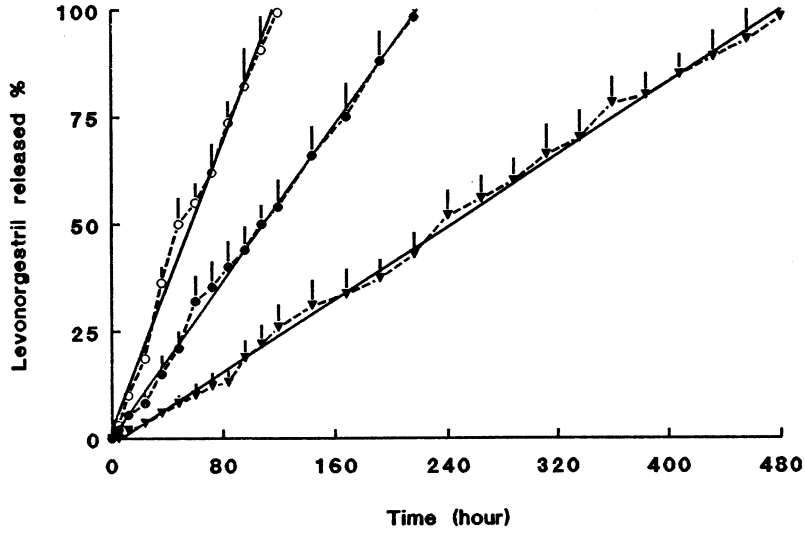

Fig. 5. Long-term release profile of Levonorgestril from different viscosity grade HPMC compacts. / 50 cps HPMC compacts; * 100 cps HPMC compacts; and ▼ the 4000 cps compact. (-----) experimental results, (—) linear regression.

10. Can be used as a targeting device for drugs acting locally on the stomach and duodenum.

References

Bechgaard, H., Christensen, F., Davis, S.S., Hardy, J., Taylor, M., Whalley, D., Wilson, C., 1985. Gastrointestinal transit of pellet systems in ileostomy subjects and the effect of density. J. Pharm. Pharmacol. 37, 718–721.

Cargill, R., Caldwell, L., Engle, K., Fix, J., Porter, P., Gardner, C., 1988. Controlled gastric emptying. I. Effects of physical properties on gastric residence times of non-disintegrating geometric shapes in beagle dogs. Pharm. Res. 5, 533–536.

Cargill, R., Engle, K., Gardner, C., Porter, P., Sparer, R., Fix, J., 1989. Controlled gastric emptying II. In-vitro erosion and gastric residence times of an erodible device in beagle dogs. Pharm. Res. 6, 506–509.

Ch'ng, H.S., Park, H., Kelly, P., Robinson, R., 1985. Bioadhesive polymers as platforms for oral controlled drug delivery II: synthesis and evaluation of some swelling water-insoluble bioadhesive polymers. J. Pharm. Sci. 74, 399–405.

Dahl, T.C., Calderwood, T., Bormeth, A., Trimble, K., Piepmeier, E., 1990. Influence of physico-chemical properties of hydroxypropylmethylcellulose on naproxen release from sustained release tablets. J. Control. Release 14, 1–10.

Davis, S.S., Stockwell, A., Taylor, M., Hardy, J., Whalley, D., Wilson, C., Bechgaard, H., Christensen, F., 1986. The effect of density on the gastric emptying of single-multiple-unit dosage forms. Pharm. Res. 3, 208–213.

Davis, S.S., Khosla, R., Wilson, C.G., Washington, N., 1987. Gastrointestinal transit of controlled-release pellet formulation of tiaprofenic acid and the effect of food. Int. J. Pharm. 35, 253–258.

Feely, L.C., Davis, S.S., 1989. Correlation of phenylpropanolamine bioavailability with GI transit by scintigraphic monitoring of III in-labeled hydroxypropylmethylcellulose matrices. Pharm. Res. 6, 274–278.

Harris, D., Fell, J., Sharma, H., Taylor, D., 1990a. GI transit of potential bioadhesive formulations in man: a scintigraphic study. J. Control. Release 12, 45–53.

Harris, D., Fell, J., Taylor, D., Lynch, J., Sharma, H., 1990b. GI transit of potential bioadhesive system in rate. J. Control. Release 12, 55–65.

Inganni, H., Timmermans, J., Moes, A., 1987. Conception and in vivo investigation of peroral sustained release floating dosage forms with enhanced gastrointestinal transit. Int. J. Pharm. 35, 157–164.

Itoh, T., Higuchi, T., Gardener, C., Caldwell, L., 1986. Effect of particle size and food on gastric residence time of non-disintegrating solids in beagle dogs. J. Pharm. Pharmacol. 38, 801–806.

Khosla, R., Davis, S.S., 1989. Gastric emptying and small and large bowel transit of non-disintegrating tablets in fasted subjects. Int. J. Pharm. 52, 1–10.

Khosla, R., Davis, S.S., 1990. The effect of tablet size on the gastric emptying of non-disintegrating tablets. Int. J. Pharm. 62, R9–R11.

Khosla, R., Feely, L.C., Davis, S.S., 1989. Gastrointestinal transit on non-disintegrating tablets in fed subjects. Int. J. Pharm. 53, 107–117.

Langer, R.S., Wise, D.L., 1984a. Medical Applications of Controlled Release, vol. I. CRC Press, Boca Raton, FL.

Langer, R.S., Wise, D.L., 1984b. Medical Applications of Controlled Release, vol. II. CRC Press, Boca Raton, FL.

Malamataris, S., Ganderton, D., 1991. Sustained release from matrix system comprising hydrophobic and hydrophilic (gel-forming) parts. Int. J. Pharm. 70, 69–75.

Meyer, J., Dressman, J., Fink, A., Amidon, G., 1985. Effect of size and density on canine gastric emptying of non-digestible solids. Gastroentrology 89, 805–813.

Park, H.M., Chrnish, S.M., Rosenek, B., Brunelle, R., Hagrove, B., Peppas, N.A., 1987. Hydrogels in Medicine and Pharmacy, vol. III. CRC Press, Boca Raton, FL.

Peppas, N.A., Ponchel, G., Duchene, D., 1987, Bioadhesive analysis of controlled release systems, Part 2. Time dependent bioadhesive stress of poly(acrylic acid) containing systems, J. Controlled Release, 5, 143–149.

Rao, K.V.R., Devi, K.P., Buri, P., 1990. Influence of molecular size and water solubility of the solute on its release from swelling and erosion controlled polymeric matrices. J. Control. Release 12, 133–141.

Robinson, J.R., Lee, V.H.L., 1987. Controlled Drug Delivery: Fundamentals and Applications, 2nd ed. Marcel Dekker, New York.

Sirois, P., Amidon, G., Meyer, J., Doty, J., Dressman, J., 1990. Gastric emptying of nondigestible solids in dogs: a hydrodynamic correlation. Am. J. Physiol. 258, G65–G72.

Wellman, H., 1984. Gastric emptying of enteric-coated tablets. Dig. Dis. Sci. 29, 207–212.