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Development and *in vitro* evaluation of expandable gastroretentive dosage forms based on compressed collagen sponges

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The objective of this study was to develop and evaluate new collagen gastroretentive dosage forms (GRDFs) which expand in the stomach after contact with gastric fluids. The GRDFs should remain in the stomach for a prolonged period of time due to their size. The dosage forms were prepared from collagen sponges. The sponges were manufactured by freeze-drying a riboflavin-containing collagen solution. A computer controlled material supply was constructed to transport precompressed collagen into a tablet machine. A second type of tablet was manufactured by combining compressed collagen sponges with hydrophilic matrix layers of hydroxypropylmethylcellulose. Matrix layers containing captopril or aciclovir were developed. *In vitro* experiments were performed with both types of dosage forms. The collagen tablets expand within a few minutes after contact with artificial gastric juice and form a drug delivery system with a size of 8 mm × 18 mm × 60 mm. Riboflavin is released over 16 h. If two layer tablets are used, the release of aciclovir or captopril can be controlled by the composition of the sustained release layer.

1. Introduction

Besides drug substances like theophylline, metoprolol and rivastigmine, which are completely absorbed from the distal segments of the gastrointestinal (GI) tract (Abrahamsson et al. 1996; Lee et al. 2004; Marathe et al. 1995; Staib et al. 1986; Vidon et al. 1986; Vila et al. 1992), many substances like aciclovir, captopril or riboflavin are only absorbed in the upper part of the small intestine (Hu and Amidon 1988; Levy and Jusko 1966; Lewis et al. 1986; Schroeder et al. 2004). If controlled release formulations of such drugs reach distal regions of the gastrointestinal tract, no further absorption takes place (Gröning 1981; Gröning 1984). To enhance bioavailability, gastric residence forms have been developed which remain in the stomach for a prolonged period of time. The drug is released into the stomach. The dissolved drug is transported through the pylorus to the absorbing areas of the small intestine. As a result of the gastric retention, a more complete and prolonged absorption of drugs from sustained release dosage forms can be achieved. Several approaches to extend the gastric residence time of drug delivery systems have been described (Klausner et al. 2003): buoyant drug delivery systems release the drug from the surface of the stomach contents over a prolonged period of time (Singh and Kim 2000), bioadhesive systems adhere to the mucosa to delay the transit (Akiyama et al. 1998), furthermore control of gastric residence time of magnetic tablets is controlled by extracorporal magnets (Gröning et al. 1998). Drug delivery systems can release transit delaying excipients which influence the motility of the GI-tract (Gröning and Heun 1989; Möes 1993). Expandable dosage forms (Chen et al. 2000; Deshpande et al. 1997; Klausner et al. 2002) will be retained in the stomach because their size exceeds the diameter of the pylorus in the fed state. The expandable dosage forms must be small enough for ingestion and transport through the esophagus. They expand in the stomach and should be stable for a defined period of time. Optimal expanding GRDFs should degrade, disintegrate or collapse in the stomach a plausible time after ingestion to allow gastric emptying during the peristaltic contractions in phase 3 of the interdigestive myoelectric motor complex.

In the present investigations gastroretentive dosage forms based on compressed collagen sponges were developed. Collagen is a major structural component of animal tissues such as skin, bone, cartilage, tendon and basement membranes (Friess 1998). Collagen for pharmaceutical purposes is a material which is derived from animal collagen by a decomposition process. In our studies pharmaceutical collagen produced from the skin of the neck of young bulls was used**.** Collagen is a protein biomaterial which is slowly digestible in the stomach. If collagen is placed in artificial gastric juice of pH 1, a loss of structural integrity is observed after 3.5 h (Cloer 1999). The sponges were produced by lyophilisation followed by thermal denaturation of the protein at 90 °C (Eckmayer 1983). In the present investigations new peroral drug delivery systems were developed from collagen sponges. The studies were part of a cooperation with a manufacturer of medical devices.

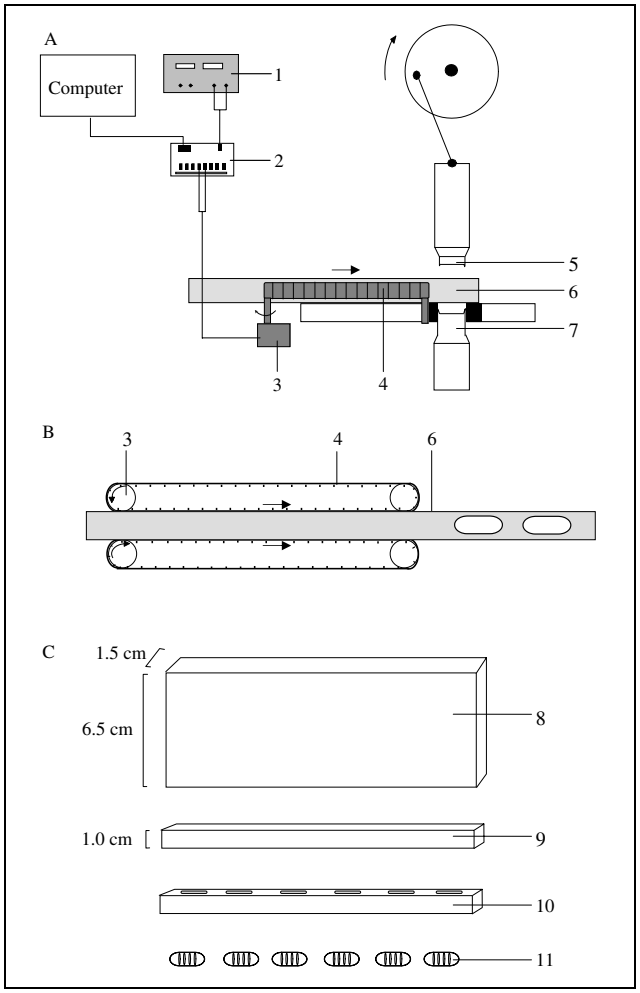

Fig. 1: A, B: Tablet machine with computer-controlled material supply C: Schematic figure of the production steps of oblong tablets from collagen sponges
(1) power supply
(2) interface
(3) stepping motor
(4) conveyor belt
(5) upper punch
(6) pre-compressed collagen strip
(7) lower punch
(8) strip of collagen sponge
(9) pre-compressed collagen strip
(10) residual collagen strip after tabletting
(11) oblong collagen tablets

2. Investigations and results

2.1. Production of collagen oblong-tablets

GRDFs based on compressed collagen sponges have not yet been described in the literature. Thus a method to manufacture oblong collagen tablets was developed. The oblong tablets (19 mm × 8 mm) were manufactured by a single punch tablet press. To compress the tablets, special punches normally used for tablets with four breaking notches were chosen. In the case of collagen tablets the notches are not intended as areas for predetermined breaking, but for stabilising the compressed collagen against expansion. In the area of the notches the material is compressed more intensively.

A computer-controlled material handling apparatus was constructed to feed precompressed pieces of collagen to the tablet machine (Fig. 1A). The freeze-dried collagen was cut into pieces 30 cm long, 6.5 cm wide and 1.5 cm thick (Fig. 1C-8) by the manufacturer. Using a pneumatic press the collagen pieces were precompressed from a width of 6.5 cm to 1.0 cm. The surface of the collagen was covered with a thin layer of magnesium stearate as lubricant using a small brush. The precompressed collagen pieces (Fig. 1C-9) were transported to the compression zone of the single punch tablet machine using computer controlled stepping motors and two transport chains which were moved by the motors (Fig. 1B). The transport mechanism is activated by a microswitch. This microswitch gives a signal to the computer when the punch is in the upper position. This results in synchronised transport of the material. The collagen is transported step-by-step to the compressing zone of the machine. A rubber plug around the upper punch prevents the remaining collagen material from adhering at the punch. The oblong tablets (Fig. 1C-11) are ejected from the tablet machine supported by a constant air stream. During the whole manufacturing process the collagen sponge is compressed from 6.5 cm to a flat tablet with a thickness of 3.5 mm. The remaining collagen strips (Fig. 1C-10) show the typical holes formed during compression.

The collagen tablets can be ingested like normal tablets. They can be swallowed without problems. In contact with saliva they are stable for some minutes without expanding. In vitro tests with artificial gastric or intestinal juices show that in contact with aqueous fluids the tablets expand to a size of about 6 cm. In Fig. 2 collagen tablets are shown before and after fluid contact. A hard gelatine capsule (No. 1) is shown for comparison.

Collagen can be impregnated with active ingredients during the manufacturing process. In the present investigation riboflavin-containing sponges (10%) were produced in cooperation with the collagen manufacturer. Each oblong tablet contains 25 mg riboflavin. Riboflavin, which is only absorbed in the upper part of the GI tract, was added to the tablets as a marker to determine the gastric residence time of the expanded collagen sponges (Jusko and Levy 1967; Stripp 1965).

In vitro release experiments were carried out with the riboflavin-containing tablets. 0.01 N hydrochloric acid was used. The collagen sponges released 90% of the riboflavin in 12 h (Fig. 3).

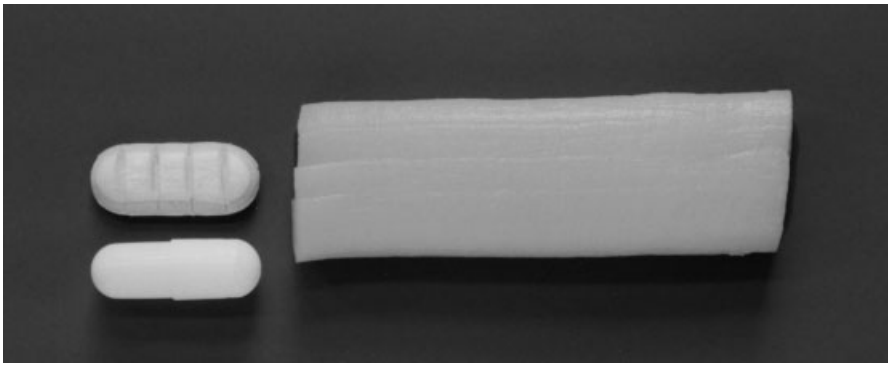

Fig. 2:
Collagen dosage form before and after expansion in water (white opaque No. 1 hard gelatine capsule as scale).

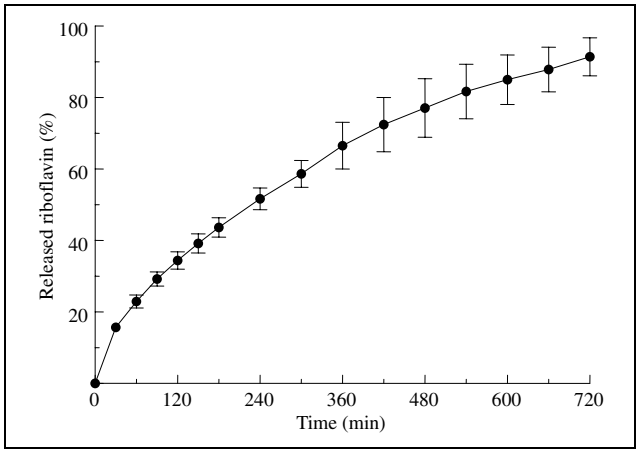

Fig. 3: Riboflavin release (dose 25 mg) from collagen tablets (●) (0.01 N hydrochloric acid; 37 °C; paddle method; n = 6, mean ± SD)

2.2. *Two-layer tablets*

If controlled release delivery systems are manufactured by compressing drug-impregnated collagen, the release profiles of the systems depend mainly on the solubility of the substances incorporated. To vary the release profile, two-layer tablets were developed. The tablets consist of a collagen layer in combination with a conventional depot layer based on hydrophilic cellulose derivatives (Fig. 4). The function of the collagen layer is to expand and control the gastric residence time, while the HPMC layer is the drug carrier system. The two layers were stuck together by stearic acid. This fatty acid is a component of the depot layer (Fig. 4–2). To enhance the bond between the two layers, the surface of the collagen was coated with a thin layer of powdered stearic acid. The fatty acid was melted using an IR lamp to fix it to the collagen surface. The collagen and HPMC depot layers were bonded by compression in a tablet machine. After expansion the two layers stick together for more than 8 h.

Tablets with a sustained release layer containing aciclovir or captopril were developed. Different release patterns were obtained by varying the amounts of HPMC, stearic acid and drug substance (Table). Three different formulations of each drug were chosen to vary the drug release rate. Dissolution results are given in Figs. 5 and 6. An increase in the amount of HPMC led to a sustained release of aciclovir and captopril. Stable drug release over a period of 8 h was achieved with both drugs. During the release experiments the bond between the depot layer and the expanded collagen layer remained unchanged. Fig. 7 shows the two-layer dosage form before and after contact with fluid.

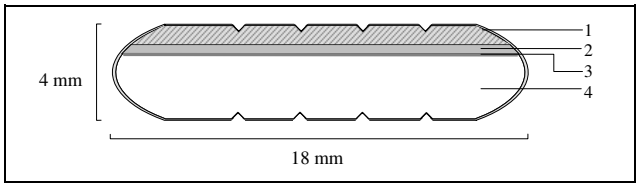

Fig. 4: Schematic figure of two-layer tablets consisting of a
(1) depot layer containing a drug and HPMC
(2) bonding layer consisting of HPMC and stearic acid
(3) bonding layer: stearic acid melted to fix it to the collagen
(4) compressed collagen

Table: Contents of HPMC depot layer

Formulation	Contents (mg)			
	Aciclovir	Captopril	HPMC	Stearic acid
F1	100	–	55	50
F2	100	–	61	50
F3	100	–	75	50
F4	–	50	55	50
F5	–	50	100	50
F6	–	50	150	50

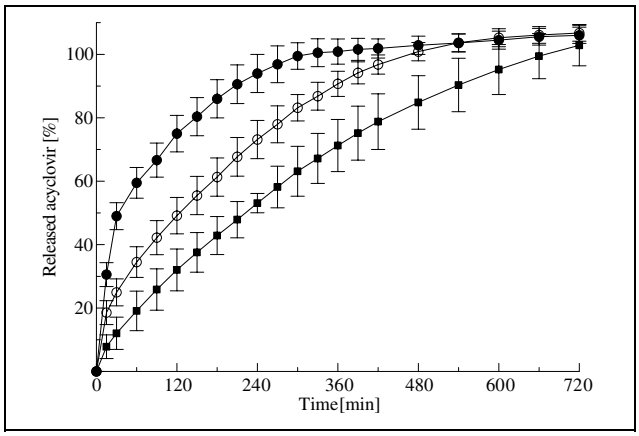

Fig. 5: *In vitro* aciclovir release from two-layer formulations with different amounts of HPMC: F1 (●), F2 (○) and F3 (■) (0.01 N hydrochloric acid; 37 °C; paddle method; n = 6, mean ± S.D.)

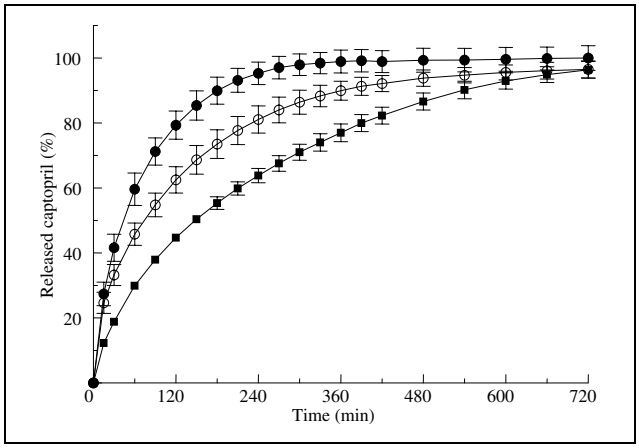

Fig. 6: *In vitro* captopril release from two-layer formulations with different amounts of HPMC: F4 (●), F5 (○) and F6 (■) (0.01 N hydrochloric acid; 37 °C; paddle method; n = 6, mean ± S.D.)

3. Discussion

The peroral route is the most important route for absorption of drugs in humans. GRDFs will become more and more important to optimise the absorption of drugs which are only absorbed from the upper part of the gastrointestinal tract. In the present study the development of collagen GRDFs is described. The compressed collagen dosage form, which was developed in our laboratories, is now on the market in Europe as a gastroretentive system which expands in the stomach and which induces satiety in the treatment of obesity. Collagen with 10% riboflavin is used. The urinary excretion of riboflavin is an indicator for the gastric residence time of the preparation (Levy and Gilbaldi 1972; Levy and Rao 1972). Riboflavin is ab-

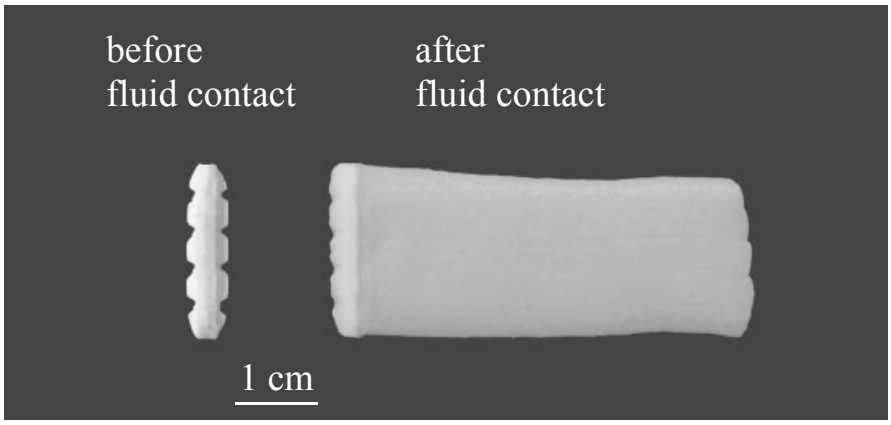

Fig. 7:
Two-layer tablet with a drug-containing depot layer (white) and an expandable collagen layer before and after contact with fluid

sorbed in the upper part of the small intestine (Jusko and Levy 1967; Stripp 1965). Therefore, absorption and renal excretion only occur when the dosage form is in the upper gastrointestinal tract.

It cannot be excluded that certain swelling materials, which can be used to manufacture gastroretentive dosage forms, could cause obstruction of the lumen of intestinal segments under certain circumstances (Ireson and Leslie 1971; Suttmann et al. 2002). Compared with other material like cellulose, the advantage of collagen is the disintegration of the material in the presence of gastrointestinal enzymes (Cloer 1999). Hence there is no risk that the material remains in the stomach too long. Further, ileus caused by indigestible materials is impossible.

In drug therapy with gastroretentive drug delivery systems it is necessary that nearly all patients show reproducible and similar gastric residence times. Normally, there are great differences between subjects. The gastric residence time of particles depends on many factors (Gupta and Robinson 1995; Mojaverian 1996; Naslund et al. 1998). Antral contractions and pyloric opening play an important role in the gastric emptying of particles of different sizes (Brown et al. 1993). In the fed state only small particles in the range of 1 to 3 mm pass the pylorus (Lin et al. 1994). The size of the expanded collagen sponge is 8 mm × 18 mm × 60 mm (Cloer 1999). It may be expected that the system will remain in the stomach during phase 1 and phase 2 of the interdigestive myoelectric motor complex (Collard and Romagnoli 2001; Demol et al. 1984; Naslund et al. 1998). In phase 3, which is characterised by high amplitude contractions ("housekeeper waves"), large particles, e.g. 5 × 7 mm tablets, can pass the opened pylorus (Coupe et al. 1991; Mojaverian 1996). In some cases transport of collagen sponges out of the stomach may occur during this phase because collagen sponges are compressible systems. It is unknown if contractions of the stomach may not only contribute to moving and retaining the collagen sponges, but also to breaking up the systems (Brown et al. 1993; Schulze-Delrieu et al. 1998). To get more information about the gastric residence time of the systems, *in vivo* studies in man are necessary.

4. Experimental

4.1. Materials

Drug-free collagen sponges and riboflavin-containing collagen sponges were kindly provided by Dr. Suwelack Skin & Health Care AG (Billerbeck, Germany). They were manufactured from skin from the neck of young bulls. Aciclovir was supplied by Fährhaus Pharma (Hamburg, Germany) and captopril by Sigma (Steinheim, Germany). The analytical procedures were based on USP reference standards for captopril, aciclovir and riboflavin (USPC, Rockville MD, USA). Hydroxypropylmethylcellulose (HPMC) (4000 mPas) was from Colorcon (Orpington, UK), stearic acid was purchased from Merck (Darmstadt, Germany) and Eudragit® NE30D from Röhm Pharma (Darmstadt, Germany). All other chemicals and solvents were of analytical grade.

4.2. Preparation of collagen tablets

A single punch tablet machine (Korsch, Berlin, Germany) was combined with a computer controlled material feeder (Fig. 1). A computer, a relay interface and two stepping motors controlled conveyer belts which transported the pre-compressed collagen strips stepwise to the compressing zone of the tablet machine.

4.3. Preparation of two-layer tablets

For tablet preparation the active ingredients, aciclovir and captopril, and the excipients HPMC and stearic acid were mixed in different ratios (Table). The collagen was covered with a thin layer of stearic acid so that each tablet contained 9 mg. An IR lamp was used to melt the fatty acid. The depot layer and the pre-compressed collagen strips (described in 3.1.) with the molten stearic acid layer were stuck together during the compression process in the single punch tablet machine.

4.4. Drug release studies

Drug release studies were performed using USP XXIII paddle apparatus at 37 °C and 50 rev/min. Hydrochloric acid (0.01 N) was used as the dissolution medium. All substances were measured in a 1 cm flow-through cell of a Hitachi 100–40 (Tokyo, Japan). Riboflavin was measured at 267 nm, aciclovir at 226 nm and captopril at 212 nm. The measured values were continuously recorded on a computer disk over a period of 12 h.

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