

## **Polymer-coated gelatin capsules as oral delivery devices and their gastrointestinal tract behaviour in humans**

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**Abstract**—In oral delivery of protein and peptide drugs there is a great need for suitable devices for delivering the therapeutic agent-incorporated microspheres selectively in the intestine. It is essential that the drug-loaded multiple unit carrier system should be protected from the harsh environment of the stomach and deliver the carrier system in the large intestine where drug action or absorption is desired. Gelatin capsules were coated with various concentrations of sodium alginate and cross-linked with appropriate concentrations of calcium chloride and tested *in vitro* for resistance to gastric and intestinal medium. Gelatin capsules coated with 20% w/v of the polymer which gave the most promising result *in vitro* were evaluated in human volunteers for their *in vivo* gastro intestinal tract behaviour. The radiographical studies show that while the uncoated gelatin capsules disintegrated in the stomach within 15 min of ingestion, the alginate coated gelatin capsules remained intact as long as they were retained in the stomach (up to 3 h) and then migrated to the ileocecal region of the intestine and disintegrated.

*Key words:* Gelatin capsules; intestine; microspheres; polymer coat; sodium alginate.

### **INTRODUCTION**

Microencapsulation of drugs for oral administration has been employed to disguise the unpleasant taste of drugs, eliminate gastrointestinal irritation, and sustain drug release [1, 2]. System design for oral delivery of drugs has undergone major metamorphosis from enteric coated single unit systems such as tablets to zero order multiple unit delivery systems like pellets, granules, and microspheres. Over the last few years instances of the therapeutic failure of enteric coated single unit systems has been reported [3, 4, 5]. The microparticulate dosage forms are becoming an increasingly popular method for providing controlled drug release in the gastrointestinal (GI) tract because they possess certain advantages over the corresponding single unit preparations. They spread out more uniformly in the GI tract and have relatively reproducible upper GI transit times, minimize the risk of local irritation, and dose dumping when compared to tablets and pellets in chronic therapy [6–8].

Even though microspheres with favourable controlled release properties may be developed, the extent of absorption of the released drug is dependent on the GI transit time of the dosage form. It has been reported that gastric emptying is a controlling factor in GI transit of the oral dosage forms [9]. In fasted subjects, single unit formulations and pellets have been reported to have gastric residence times of about 1 h, whereas in the fed state the gastric residence time for single unit preparations increased from 10 to 12 h and in case of multiple unit dosage forms from 3 to 4 h [10]. The transit time generally varies from 3 to 6 h from mouth to cecum. The gastric emptying time of drug delivery systems is usually within 1–2 h in the fasted

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state. However in the fed state, the rate of gastric emptying is dependent on the properties of the meal and will vary with different meals. The enteric coated multiple unit delivery system such as microspheres may be administered enclosed in a gelatin capsule. However, the gelatin capsule will rapidly disintegrate in the gastric environment releasing the numerous multiparticulate delivery systems containing the active substance in the stomach. It was recently reported that the gastric emptying of most of the granules released from a compressed matrix occurred 3–4 h following administration [11]. This would lead to widespread dispersion and slow accumulation of the multiparticulate units in the stomach.

The exposure of multiparticulate systems such as microspheres containing the bioactive substance, especially acid and protease sensitive protein-based drugs to the gastric environment, will result in the inactivation and proteolytic degradation of the therapeutic agent. Hence the administration of drug-loaded gelatin microspheres enclosed in gelatin capsules is of little or no use in therapies where the drug should transit to the stomach and reach the intestine for therapeutic action or absorption.

The present study was directed towards the development of enteric capsules for dumping microspheres containing therapeutically active proteins and peptides (for example, insulin) or other drugs, that are well absorbed in the intestine but need protection against degradation, selectively in the intestine. Sodium alginate which is a natural, biodegradable polysaccharide was chosen for coating the gelatin capsules. The gelatin capsules coated with this pH-sensitive biopolymer will pass through the stomach unaffected by the acidity of the gastric juice and disintegrate in the intestinal fluid where it can dump the microspheres. The microspheres will then provide controlled release of the drug in the intestine. The viability of the polymer-coated gelatin capsules for the oral delivery has been demonstrated using human volunteers.

#### MATERIALS AND METHODS

Barium sulphate (Ranbaxy, India), sodium alginate (Riedel, Germany), calcium chloride (BDH, England), and gelatin capsules ('0' size, hard) (Shibi Capsules Ltd., India) were used as received. All other reagents used were of analytical grade.

##### *Polymeric coating of gelatin capsules*

The gelatin capsules were coated with sodium alginate and cross-linked by dropping in a solution of calcium chloride (contact time 3 min). The coated capsules were quickly air dried. They were then coated and cross-linked with various concentrations of sodium alginate and calcium chloride. After *in vitro* disintegration tests were performed on the gelatin capsules coated with various concentrations of the polymer, the most promising was selected for evaluation in humans.

##### *In vitro disintegration test of uncoated and coated gelatin capsules*

Disintegration tests were carried out to determine the behaviour of sodium alginate-coated and -uncoated gelatin capsules in simulated gastric fluid (0.1 N HCl, pH 1.2) and simulated intestinal fluid (0.01 M phosphate buffer, pH 7.4) at 37°C. The disintegration times were evaluated as the time taken to rupture the coating. The behaviour of uncoated and coated gelatin capsules in simulated gastric and intestinal media was also studied by taking optical photographs at stipulated time intervals.

*In vivo radiographical study of uncoated and coated gelatin capsules*

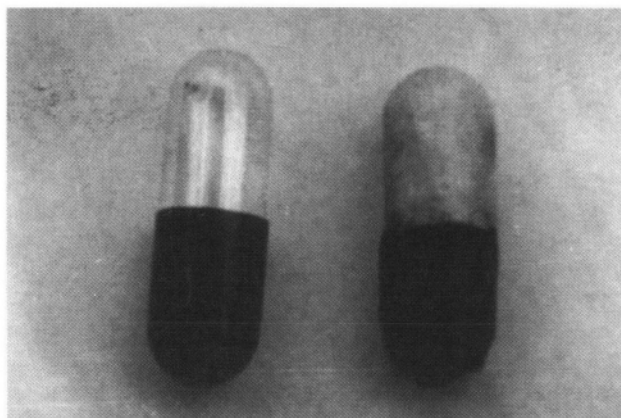
The gelatin capsules were packed with about 250 mg of barium sulphate and then coated with sodium alginate for *in vivo* tests. Uncoated gelatin capsules packed with the same amount of barium sulphate served as controls. The study was carried out in healthy male volunteers (age group 30–35 years) and free from any detectable gastrointestinal disorders. The subjects having fasted overnight were administered three coated capsules along with 100 ml water. Similarly three uncoated gelatin capsules were administered to another subject. X-rays were taken after regular time intervals to study the behaviour of uncoated and coated capsules in the GI tract of the human subjects.

**RESULTS AND DISCUSSION***In vitro disintegration studies*

For the purpose of dumping multiple unit delivery system of gelatin microspheres selectively in the intestine, the gelatin capsules were coated and cross-linked with various concentrations of sodium alginate and calcium chloride. Even though some investigations have been carried out in the preparation of microspheres using sodium alginate for drug delivery, this biopolymer has not been used as a pH-sensitive polymer for coating capsules for targeted drug delivery, when compared to synthetic polymers such as Eudragit [12]. In an attempt to use this natural biocompatible and biodegradable polymer, sodium alginate was selected for coating the gelatin capsules. The ultimate aim of the study was to utilize the system for loading them with drug-containing microspheres for colon-targeted delivery.

*In vitro disintegration of uncoated and coated gelatin capsules*

Figure 1 shows the uncoated and alginate-coated gelatin capsules. The results of the disintegration tests of capsules coated and cross-linked with various concentrations of sodium alginate and calcium chloride are presented in Fig. 2. The data given are the average of the disintegration times of six capsules evaluated at pHs 1.2 and 7.4. The optical photographs show that the uncoated gelatin capsules disintegrated



**Figure 1.** Optical photograph of uncoated and polymer coated gelatin capsules.

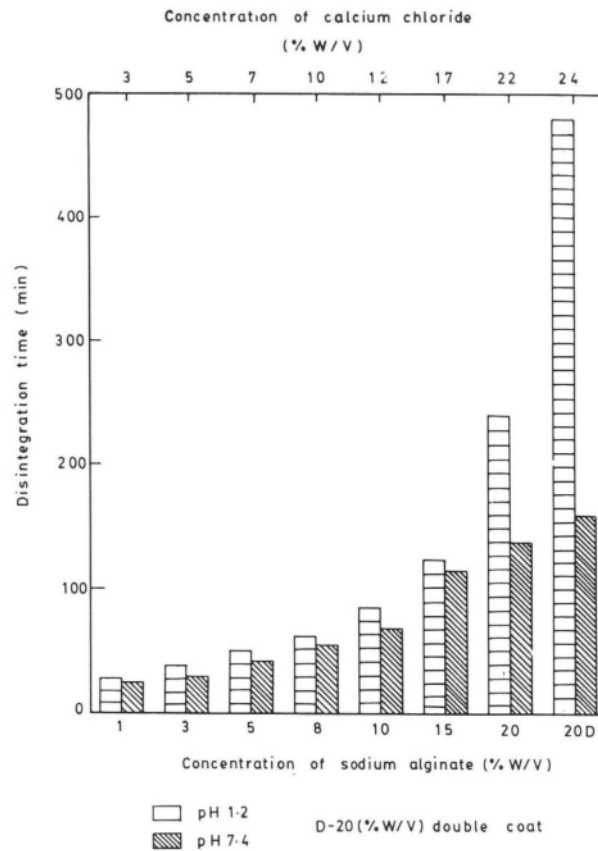


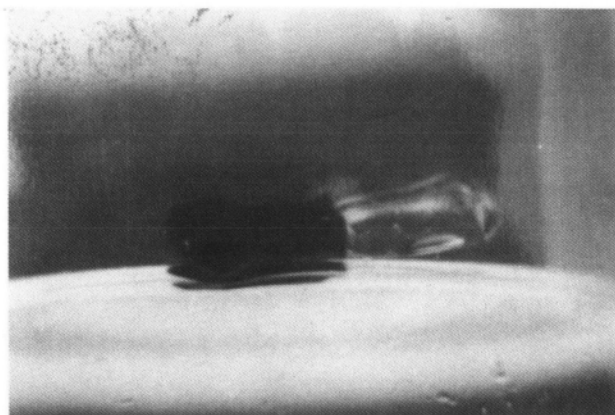
Figure 2. Effect of sodium alginate polymeric coating on the *in vitro* disintegration of gelatin capsules.

within 10 min in simulated gastric fluid and within 20 min in simulated intestinal fluid (Figs 3 and 4). Whereas coating of gelatin capsules with alginate increased their resistance to gastric medium, the data of the *in vitro* disintegration study indicated that the resistance of the capsules to gastric medium increased with an increasing concentration of alginate (Fig. 2). Gelatin capsules coated with 20% alginate (double coat) were intact in 0.1 N HCl for up to 8 h, and following a change to 0.01 M phosphate buffer, pH 7.4, the disintegration of the same capsule occurred after 15 min (Figs 5 and 6).

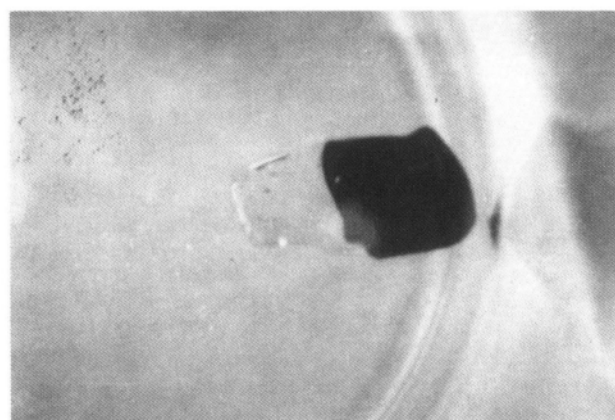
#### *In vivo radiographical studies of uncoated- and coated-gelatin capsules in humans*

The behaviour of uncoated and polymer coated gelatin capsules in the GI tract was studied by administering the coated capsules to human volunteers and taking X-rays at stipulated time intervals. Figure 7 illustrates the behaviour of uncoated- and coated-gelatin capsules in the human GI tract.

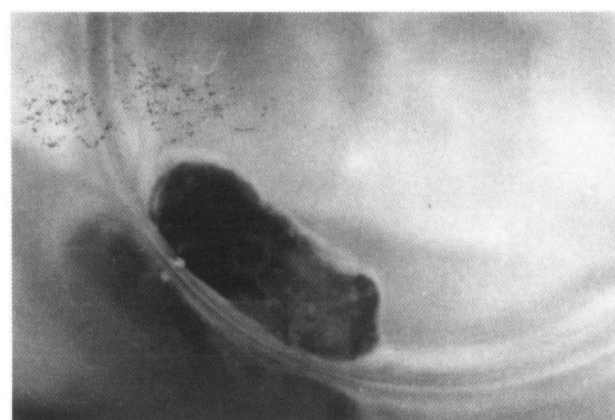
Figure 8 a-c illustrates the gastrointestinal behaviour of uncoated gelatin capsules in human subjects. Figure 8a shows that all the three capsules were intact in the stomach of the subject after 5 min of ingestion. Figure 8b, c show the X-ray



**Figure 3.** Photograph of the disintegration of uncoated gelatin capsule in simulated gastric fluid (0.1 N HCl, pH 1.2) after 10 min.



**Figure 4.** Photograph of uncoated gelatin capsule in simulated intestinal fluid (0.01 M phosphate buffer, pH 7.4) after 20 min.



**Figure 5.** Photograph of alginate-coated gelatin capsule (20% w/v) in simulated gastric fluid (0.01 N HCl, pH 1.2) after 8 h.

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