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• BASIC RESEARCH •

Study on of bioadhesive property of carbomer934 by a gamma camera *in vivo*

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Abstract

AIM: **To study the bioadhesive property of carbomer934 in dog alimentary tract.**

METHODS: **Carbomer934 and ethylcellulose were radiolabelled with technetium-99m; and Gastrointestinal emptying rate of materials was measured using the technique of gamma scintigraphy.**

RESULTS: **After oral administration, the maximum intestinal radioactivity of non-bioadhesive granules and bioadhesive granules were observed in the second hour and the sixth hour respectively. Constants of stomach emptying rate of nonadhesive granules, bioadhesive granulesI and bioadhesive granulesII were $0.774h^{-1}$,$0.265h^{-1}$ and $0.321h^{-1}$ respectively on the base of gastric residual amount. Compared to nonadhesive material (ethylcellulose), the migration rate of adhesive material(carbomer934) was remarkably slower in dog alimentary canal.**

CONCLUSION: **It is concluded that, in the dog, interactions between gastrointestinal mucus layer and adhesive material or nonadhesive material were significantly different. Carbomer934 had stronger *in vivo* bioadhesive property than ethylcellulose.**

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INTRODUCTION

A problem frequently encountered with controlled release dosage forms is the inability to increase residence time of the dosage form in the stomach and proximal portion of the small intestine. Under fast condition, gastric residence of a dosage form is typically short, which is not more them an hour and it is also common for dosage forms to transit rapidly through the small intestine for not more than 3h[1]. Rapid GI transit phenomena may consequently diminish the extent of absorption of many drugs. Since many drug compounds are absorbed exclusively in the small intestine or in a limited segment of the intestine, it would therefore be beneficial to develop sustained release dosage forms, which remain in the stomach for an extended period of time. Several approaches have been tried to prolong gastric residence, one of which is the use of oral bioadhesive formulation[2,3]. A number of charged and neutral polymers have been classified as bio/mucoadhesives, since they are known to bind very strongly to mucus via non-covalent bonds.[4,5] Carbomer is a polyacrylic acid polymer, crosslinked with allyl sucrose. As a mucoadhesive polymer, carbomer has been investigated extensively by the pharmaceutical researchers because of its high viscosity at low concentration and low toxicity.[6-15] *In vitro* experiment has proved that carbomer934 have good bioadhesion with the gastrointestinal mucus[16-19]. Our research strategy is to investigate the *in vivo* bioadhesion of carbomer934 through measuring the migration rate of radioactive carbomer934 granules in dog alimentary tract by a gamma camera. Gamma scintigraphy is an elegant imaging technique which allows the intestinal performance of pharmaceutical formulations to be visualized.[20] Over the past 20 years the approach has become the technique of choice for probing the complex interaction of drug preparation/formulations with the heterogeneous environment of the gut.[21-29]

MATERIALS AND METHODS

Materials and apparatus

Ethylcelluose200cps (EC, imported from Roth Co. Ltd., obtained from Shanghai Chemical Agents Distributing Factory); Stearic acid(AP, supplied by Shanghai Stock and Accommodate Station of Chemical Agents); Carbomer934 (Cb934, purchased from Shanghai Shenxing Pharmacy Co. Ltd); ^{99}m TcO_4(China Institute for A-energy and Isotope); γ-ray camera(Orbiter, Semens Co. Ltd, Germany); and Dog (provided by Laboratory Animal Center, Sicuan University).

Methods

Radiolabeling of Cb934 and ethylcellulose Procedures of Cb934 and ethylcellulose radiolabelled were described in brief as follows: In vacuum bottle, 1ml of 0.1mol·L^{-1} hydrochloric acid containing 1mg $SnCl_2$ and 1mg vitamin C was added to 2mL of 15g·L^{-1}Cb934(or 30g·L^{-1}EC) of ethanol solution, then with incorporation of Tc $^{99}mO_4$. The mixture was warmed at 90℃ for 10 minutes. Radioactivity chemical purity of radiolabelled materials measured by TLC was beyond 95%.

Preparation of radioactive granules According to the materials proportion of granules listed in Table 1, the mixed materials were solved in ethanol and dried in a rotated vaporizing apparatus. The product was crushed, then manually sieved. The collecting fraction have a size range of 20-40 mesh. An amount of the final blend was filled into hard gelatin capsules (size No.0). Each capsule has an activity of about 111MBq technetium99m at the time of administration.

Table 1 Component proportion of radioactive granules

granules	Percentage/%		
	EC	Cb934	Stearic acid
Non-bioadhesive	100	0	0
Bioadheive I	0	100	0
Bioadheive II	0	50	50

Measurement of migration rate of granules in dog alimentary tract

The study was an open-labeled, three-period, three treatment crossover study in three dogs (15-20kg). Each subject received the

following treatment in a randomized order: Treatment A: control nonbioadhesive granules, 2×111MBq radioactivity following 24 h fast. Treatment B: bioadhesive granulesI, 2×111MBq radioactivity following 24 h fast. Treatment C: bioadhesive granulesII2×111MBq radioactivity following 24 h fast. Percentage of granules in different segments of dog alimentary canal could be determined according to radioactivity by a γ-ray camera.

RESULTS

Migration rate of three kinds of granules

The dog alimentary tract was divided into three segments of stomach, intestine and colon(including colon,rectum and anus). Radioactivity was measured respectively in different segments (Tables). The gastric emptying rate of granules containing Cb934 (bioadhesive granules Iand bioadhesive granulesII) was significantly slower than the control non-bioadhesive granules. After 4h, percentage of non-bioadhesive granules in stomach was only 7.63%, while bioadhesive granulesI 45.92% and bioadhesive granulesII 37.52%. In the sixth hour, percentage of non-bioadhesive granules,bioadhesive granulesI and bioadhesive granulesIIin dog stomach was 0, 23.2%and 15% respectively.

Table 2 Non-bioadhesive granules in alimentary tract of dog (*n*=3)

Sites	Granules in different segment of alimentary tract(%)					
	1h	2h	4h	6h	8h	12h
Stomach	83.7	26.9	7.6	0	0	0
Intestine	16.3	73.2	59.7	0	0	0
Colon	0	0	32.6	43.2	10.6	0

Table 3 Bioadhesive granulesI in alimentary tract of dog (*n*=3)

Sites	Granules in different segment of alimentary tract(%)					
	1h	2h	4h	6h	8h	12h
Stomach	100	79.6	45.4	23.3	7.5	0
Intestine	20.4	54.7	59.7	55.1	30.9	0
Colon	0	0	0	21.8	61.6	54.3

Table 4 Bioadhesive granules IIin alimentary tract of dog (*n*=3)

Sites	Granules in different segment of alimentary tract(%)					
	1h	2h	4h	6h	8h	12h
Stomach	100	67.1	37.5	15	0	0
Intestine	0	32.8	51.6	57.9	29.6	0
Colon	0	0	10.9	29.7	70.4	64.8

Non-bioadhesive granules were emptied to intestine in the first hour and the maximum intestinal radioactivity was observed in the second hour, then intestinal radioactivity was completely eliminated in the sixth hour, bioadhesive granulesI and bioadhesive granulesII began to intestine migrated to in the second hour, and the maximum intestinal radioactivity was observed in the sixth hour. Furthermore considerable intestinal radioactivity could been inspected in the eighth hour. Compared with the non-bioadhesive granules, the bioadhesive granules had delayed onset of emptying to intestine and the maximum radioactivity in intestine. This result indicated that bioadhesion of Cb934 granules on the intestinal mucus was stronger than nonbioadhesive granules. In the fourth hour, a considerable non-bioadhesive pellets have entered the colon and were completely discharged out of anus in the eighth hour. Meanwhile, only very small parts of bioadhesive granules migrated into colon, and as long as the twelfth hour a great deal of granules were still in the dog alimentary tract.

Emptying half life of three kinds of granules in dog stomach

Emptying rate of stomach is fit to the first order kinetics[30]. $LogV_t=LogV_0-Kemt/2.303$ V_t:Gastric residual amount at the time of t V_0:Gastric residual amount at the time of 0 in stomach Kem: Constant of stomach emptying rate.

Constants of stomach emptying rate of nonadhesive granules, bioadhesive granulesI and bioadhesive granulesII can been calculated as $0.774h^{-1}$, $0.265h^{-1}$, $0.321h^{-1}$ respectively on the base of gastric residual amount. According to gastric residual amount of the first three points of time, constant of gastric emptying rate of bioadhesiveIgranules can be calculated as $0.265h^{-1}$, while according to the latter three points of time, constant can be calculated as $0.449h^{-1}$.

Pictures of γ-ray camera

A majority of nonadhesive granules have been emptied into intestine in the second hour (Figure 1B), then reached colon in the fourth hour (Figure 1C) and a great deal collected at anus in the seventh hour (Figure 1D). In the fourth hour, most bioadhesiveIgranules still mustered in the stomach(Figure 2C) and reached colon in the twelfth hour(Figure 2D). In the fifth hour, most bioadhesiveIIgranules were still in the intestine (Figure 3C) and reached colon in the seventh hour.

DISCUSSION

According to radioactivity measured by a gamma camera, migration rate of granules containing Cb934 was significantly slower than nonbioadhesive granules. It can be concluded that Cb934 has good bioadhesive properties *in vivo* and is a possible candidate material for oral bioadhesive preparation.

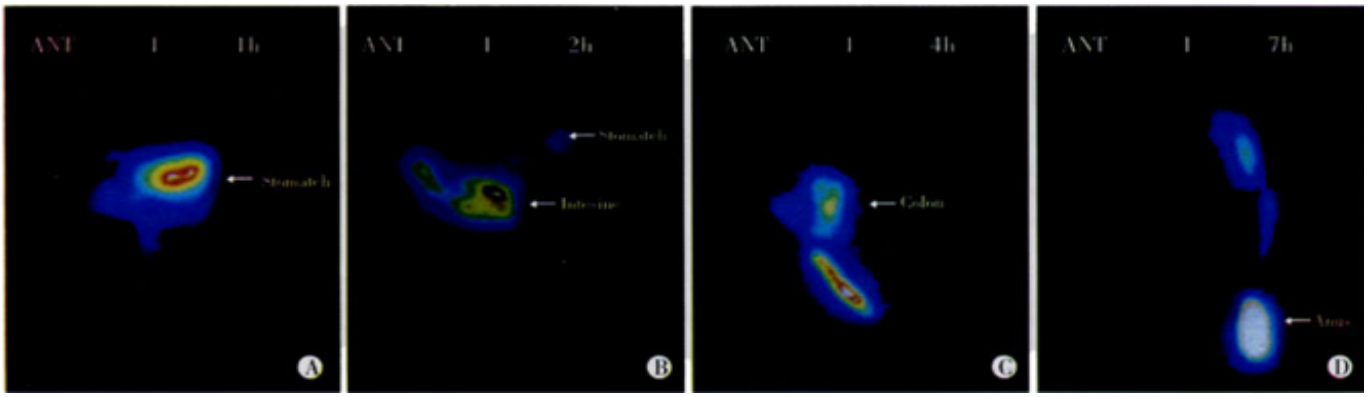

Figure 1 Radioactivity in alimentary tract of dog swallowing nonadhesive granules.
A, B, C, D: radioactivity at 1, 2, 4 and 7h.

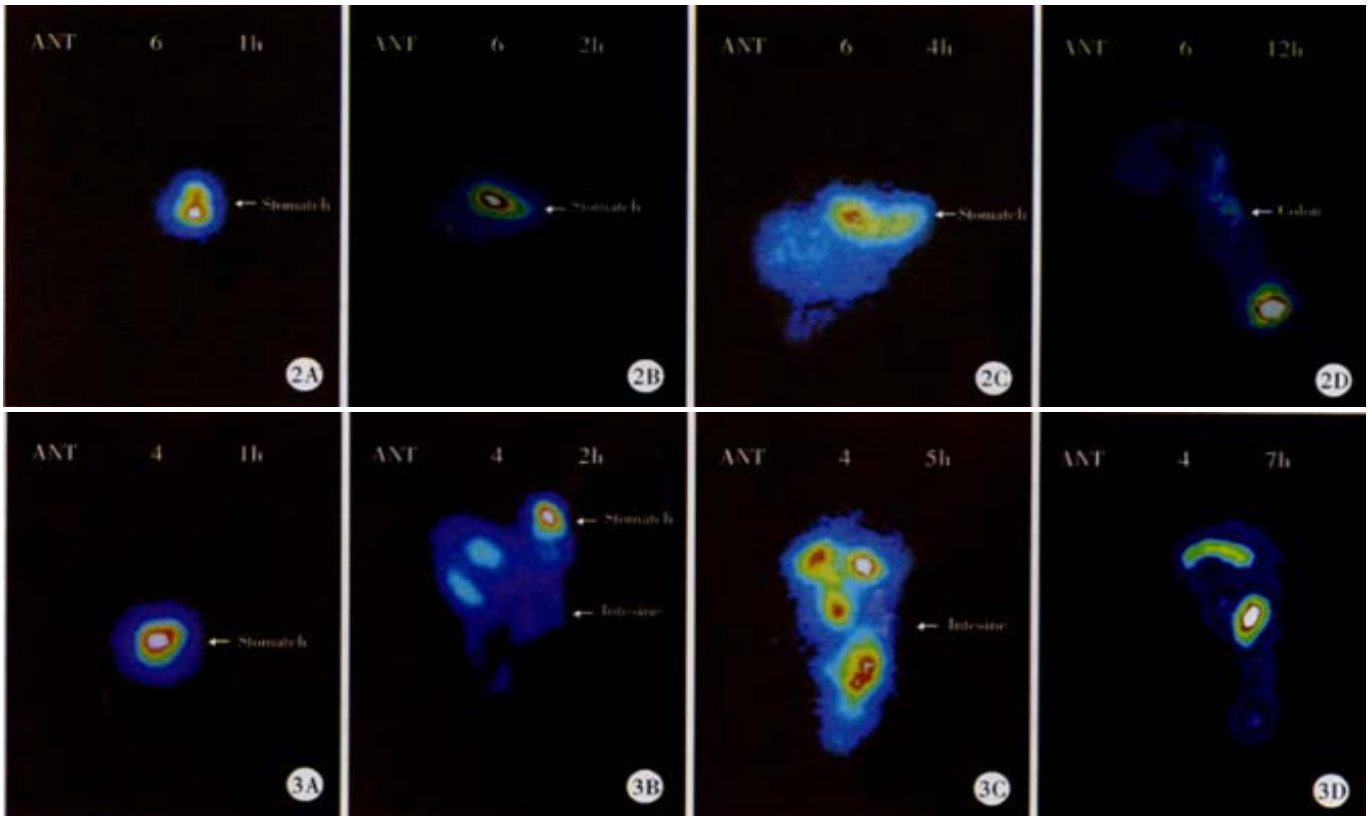

Figure 2 Radioactivity in alimentary tract of dog swallowing bioadhesiveIgranules.
A, B, C, D: radioactivity at 1, 2, 4 and 12h.

Figure 3 Radioactivity in alimentary tract of dog swallowing bioadhesiveIIgranules.
A, B, C, D: radioactivity at 1, 2, 4 and 7h.

Compared with the rate constant ($0.265h^{-1}$) at gastric prophase emptying, gastric anaphase emptying rate constant ($0.449h^{-1}$) of bioadhesive granulesIbecame larger. This result showed that gastric emptying rate of Cb934 granules became faster as time went along. It can be inferred that Cb934 was excessively hydrated and caused a lubricative effect, which quickened the gastric emptying of granules. This implied that materials, which not only have good bioadhesive properties and but also can maintain gel status to avoid excessive hydrating, should be preferably considered in oral bioadhesive preparation design.

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