Digestive Endoscopy 2014; **26**: 63–68 doi: 10.1111/den.12054

Original Article

Polysaccharide hemostatic system for hemostasis management in colorectal endoscopic mucosal resection

Rui Huang,† Yanglin Pan,† Na Hui,† Xuegang Guo,† Linhui Zhang, Xiangping Wang, Rongchun Zhang, Hui Luo, Xiong Zhou, Qin Tao, Zhiguo Liu and Kaichun Wu

Department of Gastroenterology, Xijing Hospital, Fourth Military Medical University, Xi'an, China

Background: A new polysaccharide hemostatic system (EndoClot™) was recently developed for bleeding control in gastrointestinal tract endoscopy; however, its efficacy and safety is not yet well established in colorectal endoscopic mucosal resection (EMR). The aim of the present study was to observe the bleeding control effect after EMR in the colorectum.

Patients and Methods: EndoClot™ was applied immediately to mucosal defects after resection whether or not there was post-resection bleeding. Bleeding was monitored post-procedurally by clinical findings including positive stool occult blood test and by second-look endoscopy. Hemostasis, rebleeding rates and treatment-related complications were observed.

Results: In total, 82 patients were enrolled, totaling 181 lesions. Among them, 20 lesions in 18 cases showed bleeding immediately after the procedure. Among them, two lesions were treated by combined hot biopsy forceps, and complete hemostasis was achieved in all cases without surgery. It took 1.1 min (0.4–2.1) to carry out hemostasis treatment. Rebleeding with positive stool test and colonoscopy recurred in three of 18 patients with immediate post-procedural bleeding. In patients without immediate post-procedural bleeding, three patients were confirmed with delayed bleeding. No major adverse events of treatment or procedure-related serious adverse events were reported during a 30-day follow up. Colonoscopy was done in selected patients at 30 days and full recovery of mucosal defect was achieved in all cases.

Conclusion: Polysaccharide hemostatic system effectively achieves hemostasis in controlling and preventing EMR-related bleeding with the advantage of simple application; thus it might be a useful alternative in treating bleeding endoscopically.

Key words: colonic polyp, colonoscopy, endoscopic hemostasis, endoscopic mucosal resection (EMR), polysaccharide hemostatic system

INTRODUCTION

ENDOSCOPIC MUCOSAL RESECTION (EMR) was developed from polypectomy. By injecting solution into the submucosal space, a lesion can be lifted and a safe cushion forms to ensure complete and safe lesion removal with reduced risk of perforation.[1] It has the advantages of simplicity, minimal invasiveness, and reliable resection results.[2] However, due to the enlarged mucosal defect created by EMR, the risk of intra-procedure and post-procedure bleeding remains problematic.[3] Various techniques have been used to treat EMR-related bleeding including drug injection, spraying, electrocoagulation and metallic hemoclips.[4]

Corresponding: Zhiguo Liu, Department of Gastroenterology, Xijing Hospital, Fourth Military Medical University, 127 West Changle Road, Xi'an 710032, China. Email: liuzhiguo@fmmu.edu.cn

Received 23 November 2012; accepted 23 January 2013.

†These authors contributed equally to this paper.

In the past few years, absorbable polysaccharide hemostat has been shown to have reliable hemostatic efficacy in surgical applications as a new hemostasis method.[5,6] Among the hemostasis methods, Absorbable Modified Polymers (AMP®) particles (Ref# Y2007090722; Starch Medical Inc., San Jose, CA, USA) is a biocompatible powder derived from purified plant starch.[7] Recently EndoClot™ Polysaccharide Hemostatic System (EndoClot™ PHS) has been developed (EndoClot Plus, Inc., Santa Clara, CA, USA). However, there is no related research to evaluate the efficacy and safety of such hemostat in endoscopic applications. The present study has been carried out to observe hemostatic efficacy and related safety to control and/or prevent procedure-related bleeding of EMR.

METHODS

Patients

CONSECUTIVE CASES OF colorectal mucosal and submucosal lesions >0.5 cm with intended EMR treatment were enrolled in Division 6, Xijing Hospital of

Digestive Diseases, Xi'an, China. Patients were eligible if they were >18 years and the lesions were manageable by EMR. Exclusion criteria were severe cardiovascular disease, liver and kidney dysfunction, hematological disorders, platelet and coagulation dysfunction (PLT < 50×10^9/L, INR > 2), taking anticoagulant drugs or non-steroidal anti-inflammatory drugs (NSAIDs) within 1 month of surgery, pregnancy or lactation, or unavailability for follow up. Patients with positive fecal occult blood test (gFOBT, Hemoccult II; Beckman-Coulter, Fullerton, CA, USA) were also excluded to rule out the possible influence of gastrointestinal bleeding from sites other than the colorectum. The study protocol was approved by the human ethics review committee of Fourth Military Medical University, and informed consent was obtained from all patients before the start of this study.

Endoscopic procedure

Endoscopic mucosal resection was carried out using an Olympus H260-AI colonoscope (Olympus Optical Co., Tokyo, Japan). A mixed solution of normal saline, epinephrine and indigocarmine dye was used for submucosal injection. After injection, a 25-mm or 35-mm oval snare was used to resect the lesions according to lesion size. After lesion removal, AMP® particles (Ref# Y2007090722; Starch Medical Inc.) were sprayed onto the mucosal defect created by EMR through the EndoClot™ applicator (Ref# EPA230; EndoClot Plus, Inc., Fig. 1) whether or not there was post-resection bleeding. Generally, a bottle (3 g) of AMP® particles was sprayed and the mucosal defect was observed for 5 min under endoscopy. If bleeding recurred during observation, the hemostat would be reapplied. If bleeding recurred a second time, this was considered to be a treatment failure. Endoscopic combined hemostasis or emergency surgery would then be applied.

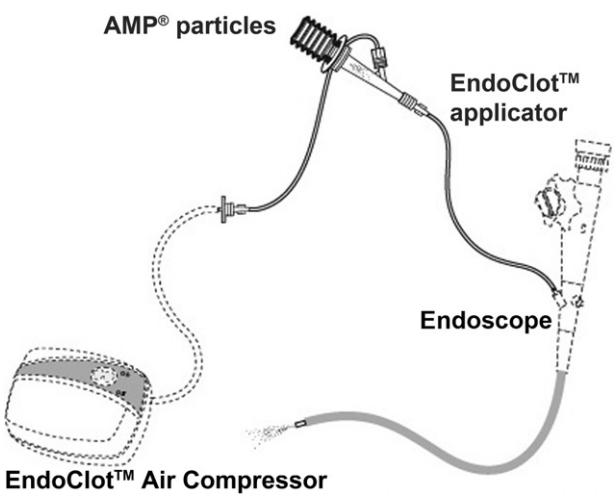

Figure 1 Schematic diagram of EndoClot™ Polysaccharide Hemostatic System (EndoClot™ PHS). EndoClot™ PHS includes AMP® particles and an applicator consisting of a powder-gas mixing chamber and a delivery catheter that is inserted into the working channel of the endoscope. EndoClot™ Air Compressor is used to propel the AMP® particles out of the catheter.

Clinical outcomes

Primary outcome measures were: (i) hemostasis rate in the proportion of patients with bleeding; and (ii) rebleeding rate of patients within 30 days after treatment. Secondary outcome measures were: (i) post-procedure bleeding prevention rate; that is, the bleeding rate in the proportion of patients without immediate bleeding after procedure; and (ii) safety outcome; that is, the incidence of procedure- and treatment-related severe adverse events. The time to achieve hemostasis was defined by the time between putting the accessory into the endoscope channel and achieving hemostasis endoscopically. No hemostatic medicine was given after the procedure.

Patients were monitored for signs of bleeding for up to 30 days. Bleeding and/or rebleeding rate was obtained by clinical manifestations such as hematochezia, hemodynamic instability, fresh bleeding from the wound under emergency endoscopy and/or positive fecal occult blood test. For patients with positive fecal occult blood test only, colonoscopy was repeated to confirm rebleeding or delayed bleeding. Colonoscopic examination was repeated 30 days after to ensure healing of the mucosal defect in patients with lesions >1 cm. Three experienced endoscopists (Y.P., Z.L., L.Z.) carried out treatment and follow up without preference.

Data were expressed as mean ± standard deviation. Hemostasis time showed a skew distribution, thus was expressed as median (interquartile range) and compared by Mann–Whitney *U*-test. Results were considered statistically significant if $P < 0.05$.

RESULTS

Preprocedure data for enrolled patients

FROM APRIL 2010 to July 2011, 94 cases were admitted for EMR treatment, but 12 cases were excluded due to conditions that met the exclusion criteria (Fig. 2). Therefore, 82 cases were enrolled according to the protocol requirements. During endoscopic treatment, a total of 181 lesions were resected by EMR. Lesion size ranged from 0.5 cm to 4.0 cm. Clinical and lesion features of cases are shown in Table 1. All lesions were removed en bloc by EMR and EndoClot™ PHS was applied. It took 1.1 min (0.4–2.1) to

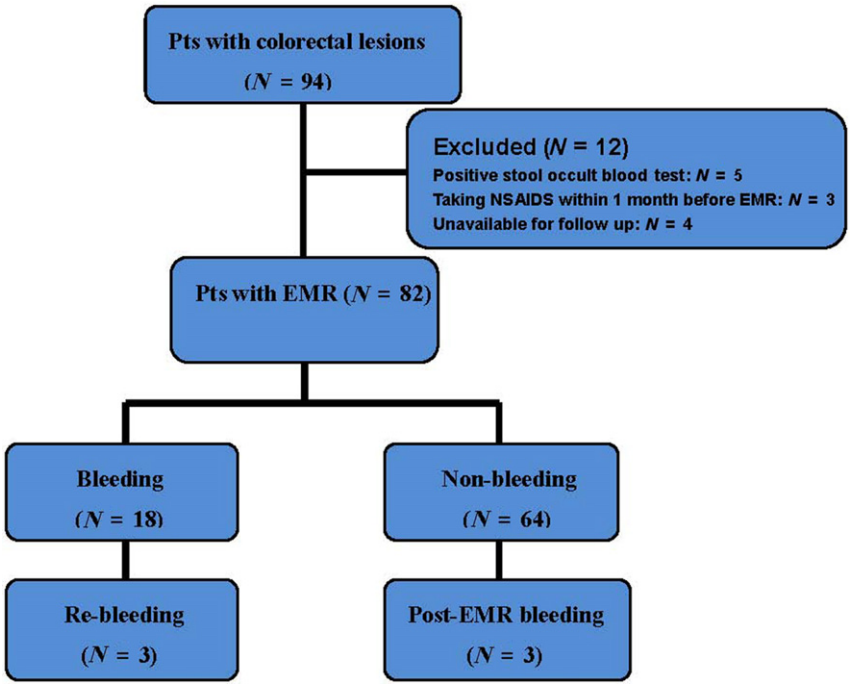

Figure 2 Schematic figure showing patient screening and outcomes. EMR, endoscopic mucosal resection; NSAIDS, non-steroidal anti-inflammatory drugs; Pts, patients.

Table 1 Clinical and lesion features of patients observed for bleeding control after EMR in the colorectum

	Patients (n = 82)
Age (years ± SD)	57.1 ± 13.6
Sex (male : female)	48:34
Hemoglobin level (g/L ± SD)	132.4 ± 17.1
PTA (% ± SD)	99.0 ± 15.3
Location (n)	
Proximal colon	84
Distal colon	90
Rectum	7
Mucosal/submucosal lesion (n)	
Mucosal	180
Submucosal	1
Size (cm ± SD)	
Lesion	0.8 ± 0.4
Mucosal defect	0.9 ± 0.5
EMR procedure time (min/lesion ± SD)	6.1 ± 3.9
Proximal colon	5.7 ± 3.2
Distal colon	6.7 ± 4.9
Rectum	5.5 ± 2.9
Hemostasis treatment time (min/lesion)†	1.1 (0.4–2.1)
Proximal colon	1.1 (0.5–2.1)
Distal colon	1.0 (0.6–2.1)
Rectum	1.1 (0.4–1.9)

†Hemostasis treatment time is expressed as median (interquartile range) due to skew distribution.
EMR, endoscopic mucosal resection; PTA, prothrombin activity.

carry out hemostasis treatment per lesion, with no differences among rectum, left colon and right colon (P = 0.699). Pathological findings revealed tubular adenoma (n = 112), tubulovillous adenoma (n = 13), hyperplastic polyp (n = 43), inflammatory fibroid polyp (n = 1), inflammatory retention polyp (n = 2), juvenile polyp (n = 3), serrated adenoma (n = 5), Peutz-Jeghers-type polyp (n = 1) and lipoma (n = 1).

Primary outcome

Twenty lesions in 18 cases showed bleeding after EMR. Among them, five lesions showed spurting bleeding. Hemostasis was successfully achieved in 18 lesions (90.0%) with a single round of spray. Two cases were treated by combined hot biopsy forceps due to minimal bleeding after two rounds of spray, and satisfactory hemostasis was finally achieved in all cases. In all patients, no severe bleeding requiring emergency surgery or other endoscopic therapy occurred. EndoClot™ PHS showed rapid bleeding control even in relatively large lesions and severe bleeding (Fig. 3). Upon contact with liquid, it soon formed a gel-like coating layer to cover the mucosal defect, therefore stopping bleeding. It took 1.7 min (1.0–1.9) to achieve hemostasis in these cases.

Signs of bleeding or rebleeding were carefully observed after procedures. No hematochezia, hemodynamic instability or fresh bleeding was observed. Fecal occult blood test

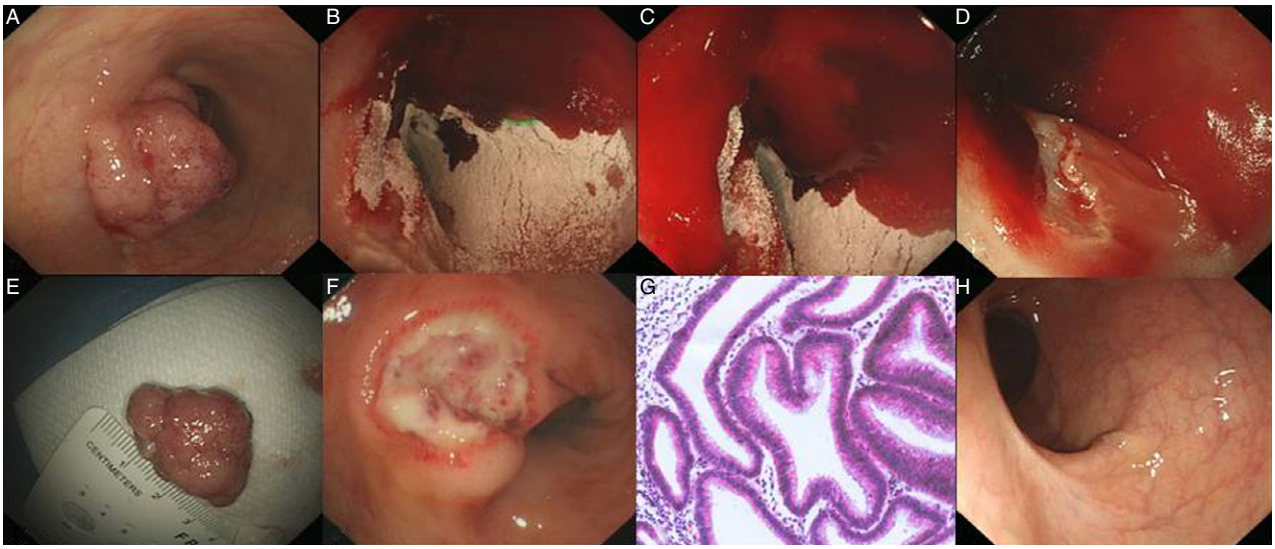

Figure 3 Rectal adenoma case treated by EndoClot™ Polysaccharide Hemostatic System (EndoClot™ PHS). (a) A large rectal sessile adenoma was resected by endoscopic mucosal resection. (b–d) After resection, massive bleeding occurred, and EndoClot™ PHS was applied. Five min later, hemostasis was achieved after water flushing the coating. (e) Size of resected adenoma was approximately 3 cm. (f) Colonoscopy revealed no bleeding at 72 h re-check-up. (g) Pathological analysis revealed tubular adenoma with high-grade intraepithelial neoplasia (h) Complete healing was observed at 1-month follow up.

was re-examined on the third and 30th days after EMR to detect possible post-procedure bleeding. Among the five patients with positive fecal occult blood test, minimum rebleeding was confirmed in 16.7% (3/18) of patients. No additional therapy was needed. In five patients with severe bleeding, a second-look endoscopy on the third day post-procedure was carried out without additional therapy performed. AMP® particles were found to have been eliminated from the colon and clean-based ulcers were observed (Fig. 3F).

Secondary outcome

For cases without intra-procedure bleeding, 4.7% (3/64) showed post-procedure bleeding with positive fecal occult blood test and colonoscopic findings, without severe bleeding requiring emergency surgery or endoscopic therapy. All patients were stable after the procedure and were discharged uneventfully. In the present study, there were no reported procedure-related serious adverse events, including perforation. No hemostasis-related severe adverse events occurred, including vascular embolization, bowel obstruction or allergic reaction. Follow-up colonoscopy was carried out 1 month after EMR in patients with lesions >1 cm and complete healing of the ulcer was demonstrated in all cases.

DISCUSSION

ALONG WITH THE continuous development of endoscopy, EMR and endoscopic submucosal dissection (ESD) have been widely used in clinical settings to remove gastrointestinal mucosal lesions with the expectation of achieving curative resection for early cancer, precancerous lesions or submucosal tumors. These methods have the advantages of simplicity and minimal invasiveness, but intra-procedure and post-procedure bleeding is still a common complication. Many hemostasis methods can be used to stop bleeding, including injection therapy, thermal ablation (electrocoagulation and argon plasma coagulation) and mechanical devices such as hemoclips.[8] Although bleeding can generally be treated by any of these methods, there are cases in which successful hemostasis is difficult to achieve because of the lesion features.

For example, hemoclips are currently regarded as one of the most reliable hemostasis methods and are commonly used clinically.[4,9–12] However, in certain circumstances, such as a difficult approach position, hemoclips could be difficult to apply. Sometimes, the bleeding sites might be obscured, so there is difficulty in applying the hemoclip to the correct position which often leads to failed hemostasis. The use of hemostasis clips requires expertise. As a result, new devices have emerged to further improve our standard of hemostasis

treatment or to simplify the procedure.[13] When using the EndoClot™ PHS, the applicator does not contact the wound directly, so the operator can maintain a good field of vision to observe the wound. Thus, it might provide an easy alternative to stop bleeding. However, precautions should be taken not to block the catheter delivery system as introduction of any fluid into the catheter might result in clogging.

AMP® particles have a molecular structure that rapidly absorbs water from blood, causing a high concentration of platelets, red blood cells and coagulation proteins at the bleeding site that accelerates the physiological clotting cascade. The interaction of AMP® particles with blood rapidly produces a gelled matrix that adheres to and seals the bleeding tissue.[5,14–18] Theoretically, however, when a high flow of arterial blood spurts out, the hemostat would be of limited use as it would be hard to form the layer due to the high bleeding pressure.[19] However, in our study, even relatively severe bleeding caused by removing a large adenoma could still be safely managed. Previous animal experiments have also demonstrated that arterial bleeding can be successfully managed.[20] The sprayed hemostat generally falls from the wound within 3 days according to observation, which leaves a clean wound base and no residual blood scab. AMP® particles are readily removed by saline irrigation; therefore re-application would be possible if unsatisfactory hemostasis is achieved.

A similar product, Hemospray (Cook Endoscopy, Winston Salem, NC, USA), has previously been reported to control peptic ulcer bleeding, indicating the broad application of this type of hemostat.[20,21] Although hemostat has the potential advantage of simple application, little is known about potential risks such as allergic reactions, embolism, and bowel obstruction.[22] AMP® particles are derived from plant starch which contains no protein components of animal or human origin. Although not characterized in the mucosa, apart from its hemostatic property, it has been reported to improve skin wound healing by activating fibroblasts and transforming growth factor (TGF)-β1 release.[7] It can be rapidly degraded *in vivo* and has good compatibility with the human body. Possible formation of emboli leading to embolism has been a concern, although the possibility is very low.[20] Our follow up showed that no embolism occurred in patients after hemostat application, possibly because the lesion vessels were not large enough to allow significant amount of hemostat to get into the bloodstream. There is also a potential risk that a large amount of hemostat falling off from the intestinal wall may cause intestinal blockage. Unlike Hemospray which required 21–150 g hemostat,[21] usually 3 g AMP® particles is sufficient to stop bleeding; furthermore, it degrades rapidly in the gastrointestinal tract, therefore the chance of causing intestinal blockage is small. In the present study, the 1-month follow up showed that no intestinal blockage occurred in patients, and also no allergy reaction or other severe adverse events occurred.

One limitation in the current study is that there were only a few severe bleeding occurrences due to the limited case number. Furthermore, it was only a pilot study from a single center. However, our data showed that EndoClot™ PHS might also be effective to control severe bleeding and has the potential advantage of a simple application. A large-scale, randomized multicenter study with proper control would be needed to further establish the role of EndoClot™ PHS in hemostasis. In conclusion, this pilot study indicates that EndoClot™ PHS is safe and effective in endoscopic hemostasis. Our results indicate that as a new treatment option in endoscopic hemostasis, EndoClot™ PHS can be a new complementary and alternative hemostatic technique for endoscopic minimally invasive surgery.

CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflict of interests for this article.

REFERENCES

1 Rembacken BJ, Gotoda T, Fujii T, Axon AT. Endoscopic mucosal resection. *Endoscopy* 2001; **33**: 709–18.
2 Ahmad NA, Kochman ML, Long WB, Furth EE, Ginsberg GG. Efficacy, safety, and clinical outcomes of endoscopic mucosal resection: A study of 101 cases. *Gastrointest. Endosc.* 2002; **55**: 390–6.
3 Okano A, Hajiro K, Takakuwa H, Nishio A, Matsushita M. Predictors of bleeding after endoscopic mucosal resection of gastric tumors. *Gastrointest. Endosc.* 2003; **57**: 687–90.
4 Sung JJ, Tsoi KK, Lai LH, Wu JC, Lau JY. Endoscopic clipping versus injection and thermo-coagulation in the treatment of non-variceal upper gastrointestinal bleeding: A meta-analysis. *Gut* 2007; **56**: 1364–73.
5 Humphreys MR, Castle EP, Andrews PE, Gettman MT, Ereth MH. Microporous polysaccharide hemospheres for management of laparoscopic trocar injury to the spleen. *Am. J. Surg.* 2008; **195**: 99–103.
6 Pozza M, Millner RW. Celox (chitosan) for haemostasis in massive traumatic bleeding: Experience in Afghanistan. *Eur. J. Emerg. Med.* 2011; **18**: 31–3.
7 Wang Y, Xu M, Dong H *et al*. Effects of PerClot((R)) on the healing of full-thickness skin wounds in rats. *Acta Histochem.* 2012; **114**: 311–7.
8 Conway JD, Adler DG, Diehl DL *et al*. Endoscopic hemostatic devices. *Gastrointest. Endosc.* 2009; **69**: 987–96.
9 Gevers AM, De Goede E, Simoens M, Hiele M, Rutgeerts P. A randomized trial comparing injection therapy with hemoclip and with injection combined with hemoclip for bleeding ulcers. *Gastrointest. Endosc.* 2002; **55**: 466–9.

10 Katsinelos P, Paroutoglou G, Beltsis A *et al*. Endoscopic hemoclip application in the treatment of nonvariceal gastrointestinal bleeding: Short-term and long-term benefits. *Surg. Laparosc. Endosc. Percutan. Tech.* 2005; **15**: 187–90.
11 Parra-Blanco A, Kaminaga N, Kojima T *et al*. Hemoclipping for postpolypectomy and postbiopsy colonic bleeding. *Gastrointest. Endosc.* 2000; **51**: 37–41.
12 Raju GS, Gajula L. Endoclips for GI endoscopy. *Gastrointest. Endosc.* 2004; **59**: 267–79.
13 Wong Kee Song LM, Banerjee S, Barth BA *et al*. Emerging technologies for endoscopic hemostasis. *Gastrointest. Endosc.* 2012; **75**: 933–7.
14 Murat FJ, Ereth MH, Dong Y, Piedra MP, Gettman MT. Evaluation of microporous polysaccharide hemospheres as a novel hemostatic agent in open partial nephrectomy: Favorable experimental results in the porcine model. *J. Urol.* 2004; **172**: 1119–22.
15 Hamdi G, Ponchel G. Enzymatic degradation of epichlorohydrin crosslinked starch microspheres by alpha-amylase. *Pharm. Res.* 1999; **16**: 867–75.
16 Hamdi G, Ponchel G, Duchene D. An original method for studying in vitro the enzymatic degradation of cross-linked starch microspheres. *J. Control. Release* 1998; **55**: 193–201.
17 Tan SR, Tope WD. Effectiveness of microporous polysaccharide hemospheres for achieving hemostasis in mohs micrographic surgery. *Dermatol. Surg.* 2004; **30**: 908–14.
18 Yadav AV, Mote HH. Development of biodegradable starch microspheres for intranasal delivery. *Indian J. Pharm. Sci.* 2008; **70**: 170–4.
19 Bjorses K, Holst J. Various local hemostatic agents with different modes of action; an in vivo comparative randomized vascular surgical experimental study. *Eur. J. Vasc. Endovasc. Surg.* 2007; **33**: 363–70.
20 Giday SA, Kim Y, Krishnamurty DM *et al*. Long-term randomized controlled trial of a novel nanopowder hemostatic agent (TC-325) for control of severe arterial upper gastrointestinal bleeding in a porcine model. *Endoscopy* 2011; **43**: 296–9.
21 Sung JJ, Luo D, Wu JC *et al*. Early clinical experience of the safety and effectiveness of Hemospray in achieving hemostasis in patients with acute peptic ulcer bleeding. *Endoscopy* 2011; **43**: 291–5.
22 Weusten B, Bergman JJ. A hemostatic spray: The easy way out for upper gastrointestinal bleeding? *Endoscopy* 2011; **43**: 343–4.