PHARMACY

Gas-Generating Floating Mucoadhesive Microspheres of Vonoprazan: A Quality-by-Design Review

Mohd Jalaluddin Jyoti Patel*, Sanjay Chaurasia

Department of Pharmaceutics, Apex Institute of Pharmacy, Samaspur, Chunar, Mirzapur, Uttar Pradesh, India (affiliated to Dr. A. P. J. Abdul Kalam Technical University, Lucknow)

Published November 2026

Abstract

Vonoprazan is a potassium-competitive acid blocker that holds gastric pH above 4 for longer than lansoprazole in published trials. We found no published vonoprazan formulation designed to stay in the stomach. This review asks whether a pH-responsive, gas-generating, floating and mucoadhesive microsphere of vonoprazan is a reasonable subject for development, and how it could be optimised by Quality by Design (QbD). We read the abstracts of 47 papers on the drug, on gastric retention, on floating and mucoadhesive microspheres, on pH-dependent polymers and on designed experiments. Each element of the concept has been used separately for other drugs: carbonates as gas formers, Eudragit-type polymers, mucoadhesive polymers, and factorial or Box-Behnken designs. We found no gastroretentive, floating or extended-release vonoprazan formulation and no measured solubility or pH-stability study of the drug. Forced-degradation reports describe degradation products under acidic conditions. We propose a conceptual QbD pathway, a set of critical quality attributes and an in-vitro test plan. The design is conceptual and no experimental data are reported.

Keywords: Box-Behnken design; floating microspheres; gas-generating; gastroretentive; mucoadhesion; pH-responsive polymers; Quality by Design; vonoprazan

1 Introduction

Vonoprazan is a potassium-competitive acid blocker (P-CAB). It binds selectively to the H+,K+-ATPase of the parietal cell, and it does so whether or not the cell is secreting acid [1]. It has been sold in Japan since February 2015, and it inhibits the enzyme about 350 times more potently than lansoprazole [2]. In the United States it is approved for healing and maintaining healing of erosive oesophagitis and for heartburn relief, with once-daily dosing that does not depend on meal timing [3].

The clinical literature is large, but we found no study of any other dosage form. Whether a form that stays in the stomach and releases the drug slowly would add anything is therefore an open question. Floating microspheres are one way to test the idea, because as multiple-unit systems they spread through the stomach and are said to give more reproducible absorption and less local irritation than single-unit forms [4]. The system in the title is gas-generating (a carbonate reacts with gastric acid to give carbon dioxide, CO2, which lowers particle density), mucoadhesive (a polymer holds it to the gastric mucus) and pH-responsive (gas formation and polymer behaviour depend on the acidity of the medium).

We searched online sources for the drug, the case for prolonged gastric exposure, floating and mucoadhesive microspheres, pH-dependent polymers and designed experiments, and read the ab-

stracts of the papers cited. Most microsphere papers concern other drugs. No experimental work of our own is reported, and the design outlined is a proposal.

2 Vonoprazan: properties and clinical profile

Vonoprazan is described as a base with a pKa of 9.6 that concentrates in the acidic canaliculi of parietal cells [2]. Another paper gives the pKa as 9.37 [1]. After an oral dose the time to peak concentration is 1.5 to 2.0 h, food has a minimal effect, protein binding is 80%, the apparent volume of distribution is 1050 L, and the mean apparent terminal half-life is about 7.7 h; the drug is metabolised mainly by CYP3A4 [2]. In healthy men the peak came within 2 h and the half-life reached up to 9 h [5].

Acid suppression is quick and long. Intragastric pH above 4 was reached as early as 4 h after 20 mg and kept to 24 h, and the 24-h holding-time ratio for pH above 4 was 63% on day 1 and 83% on day 7 [2]. With 40 mg for seven days the ratio was 100% in a Japanese study and 93.2% in a UK study [5]. In US subjects, vonoprazan kept pH above 4 for 62.4% of day 1 and 87.8% of day 7, against 22.6% and 42.3% for lansoprazole, and the pH curves began to separate about 2.5 h after the first dose [6]. Serum gastrin was 2 to 3 times higher than with lansoprazole [2].

In erosive oesophagitis, healing at week 4 was 92.3%, 92.5%, 94.4% and 97.0% with vonoprazan 5, 10, 20 and 40 mg, against 93.2% with lansoprazole 30 mg [7]. A later trial found healing in 92.9% with vonoprazan 20 mg against 84.6% with lansoprazole 30 mg, and vonoprazan was also superior for maintaining healing [8]. For *Helicobacter pylori*, first-line eradication was 92.6% with a vonoprazan triple regimen and 75.9% with a lansoprazole regimen [9]. Meta-analyses report higher first-line eradication, 87.9% against 72.8% in one and 85.1% against 68.0% in another, although the second-line advantage was not shown in the latter (83.4% against 82.0%) [10], [11]. A vonoprazan and amoxicillin dual regimen gave an intention-to-treat cure rate of 85.6% in a pooled analysis [12]. In erosive oesophagitis resistant to PPIs, vonoprazan 20 mg healed 91.7% at week 4 [13]. One review ties eradication success to control of intragastric pH over 24 h, which matters for acid-labile antibiotics [14].

A meta-analysis of 77 studies gave pooled rates of 20% for any adverse event, 7% for drug-related events, 1% for serious events and 1% for discontinuation, with no significant difference from PPIs [15]. In a three-year interim analysis, parietal, foveolar and G-cell hyperplasia were more frequent with vonoprazan than with lansoprazole, with no neoplastic changes and no new safety issues [16]. Table 1 summarises these findings.

Table 1. Key findings on vonoprazan from the abstracts reviewed.

Area	Finding	Ref.
Mechanism	Binds selectively to parietal-cell H+,K+-ATPase; slow dissociation attributed by modelling to an electrostatic barrier	[1]
Physicochemical	Base; pKa 9.6 in one source and 9.37 in another; no measured solubility or solubility-pH profile found	[1], [2]
Pharmacokinetics	Tmax 1.5-2.0 h; half-life about 7.7 h (up to 9 h in another study); protein binding 80%; minimal food effect	[2], [5]
Acid control	24-h pH>4 holding-time ratio 83% on day 7; 87.8% in US subjects against 42.3% for lansoprazole	[2], [6]

Area	Finding	Ref.
Oesophagitis	Week-4 healing 92.3-97.0% (5-40 mg); superior to lansoprazole for maintenance of healing	[7], [8]
H. pylori	First-line eradication 92.6% against 75.9%; pooled advantage in first line, not shown in second line in one meta-analysis	[9]–[11]
PPI-resistant disease	Healing 91.7% at week 4 (20 mg); gastric acid exposure time 23.8% against 41.1% on a PPI (13 patients)	[13], [17]
Safety	Pooled adverse events similar to PPIs; hyperplasia more frequent over three years, no neoplastic change	[15], [16]
Chemical stability	Six process-related impurities; nine degradation products from forced degradation, including acidic hydrolysis	[18], [19]

Values are as reported by the authors. A dash means that the abstract gives no value.

The stability data are thin. A forced-degradation study with LC-QTOF-MS/MS found nine degradation products, of which DP-1, DP-2 and DP-4 formed under acidic hydrolysis; three products shared the protonated mass of the parent drug [19]. Another stability-indicating HPLC paper reports degradation under acidic, alkaline and oxidative stress and stability under photolytic and thermal stress, so the two reports differ about light [20]. Neither abstract gives the acid strength or the time, so the rate of loss in gastric fluid cannot be judged. Six process-related impurities of the fumarate have been quantified by a validated HPLC method [18], and a green UHPLC impurity method was built with analytical QbD [21].

3 Prolonged gastric exposure and the case for retention

The best-known argument for longer acid control comes from PPIs. Nocturnal acid breakthrough, defined as intragastric pH below 4 for over an hour, was found on PPIs in 70% of 61 patients with reflux disease, 80% of 15 with Barrett's oesophagus and 67% of normal controls, with no significant difference between groups; oesophageal acid exposure was present in 33%, 50% and 8%, respectively [22]. In 52 patients with persistent symptoms on PPIs, 71% had nocturnal and 69% daytime breakthrough, yet symptom scores did not differ with or without it, so breakthrough alone did not explain refractory symptoms [23]. In 13 PPI-refractory patients monitored by impedance-pH, median gastric acid exposure time was 23.8% on vonoprazan against 41.1% on a PPI [17]. A review of food and dosing suggested that poor adherence is a major cause of inadequate response to standard-dose PPIs in reflux disease [24].

These data support strong, steady acid control, but they were gathered with PPIs and with the marketed tablet. A once-daily vonoprazan tablet already gives strong control without regard to meals [3], so the adherence argument for a prolonged-release form is weaker than for a short-acting drug. Gastroretentive systems keep a dosage form in the upper gut long enough for dissolution in gastric fluid and absorption in the stomach or proximal small intestine, which suits drugs with a narrow absorption window, and combining retention with controlled release may improve efficacy and adherence by cutting the dosing frequency [25]. They are also proposed for drugs that are unstable at alkaline pH, soluble mainly in acid, or active locally in the stomach [26], and bioavailability is said to depend on gastric residence time [27].

None of the vonoprazan abstracts we read states where in the gut the drug is absorbed or that its absorption window is narrow. The case for a retained form is therefore a hypothesis, namely that a depot in the stomach could smooth drug exposure through the night. It has not been tested.

4 Floating and mucoadhesive microspheres

Floating (hydrodynamically controlled) systems are meant to offset the variability of gastric emptying and intestinal transit [4]. Retention approaches in the literature include effervescent agents, mucoadhesive polymers, magnetic materials, buoyancy-enhancing excipients and plug-like devices [27], and a review of polymers describes low-density systems as the most promising approach [28]. Figure 1 shows how the mechanisms discussed below could combine in one particle, and Table 2 lists examples from the literature.

Hollow microballoons are made by emulsion solvent diffusion or evaporation. Ethyl cellulose microballoons of theophylline floated for over 12 h in simulated gastric medium [29], and in propranolol microballoons the preparation temperature controlled cavity formation and thus buoyancy [30]. Nizatidine microballoons of Eudragit S-100 and HPMC sustained release over 12 h [31].

Gas-generating particles use a carbonate that reacts with acid. In nevirapine beads, calcium carbonate dispersed in an alginate and HPMC solution was dripped into acidified calcium chloride, and CO2 was trapped in the gelled membrane. More carbonate gave immediate and complete floating for 24 h and increased release without changing the time to float, while a thicker gas-entrapping coat lengthened the time to float and slightly slowed release [32]. Sodium bicarbonate has been used in the same way in alginate microspheres [33] and in effervescent pellets [34].

Mucoadhesion is added with polymers such as Carbopol or chitosan. In Carbopol-934P and ethyl cellulose microspheres the polymer ratio had the larger effect on the responses, and the best batch showed 82% mucoadhesion after 1 h [35]. Alginate-chitosan microspheres showed *in vitro* gastric retention of 82.63% [36], and a float-adhesive famotidine system combined *Mimosa pudica* mucilage with alginate and chitosan [37]. In a pig model, a micro-in-macro design gave controlled ciprofloxacin release over 24 h and greater bioavailability than a marketed immediate-release product [38].

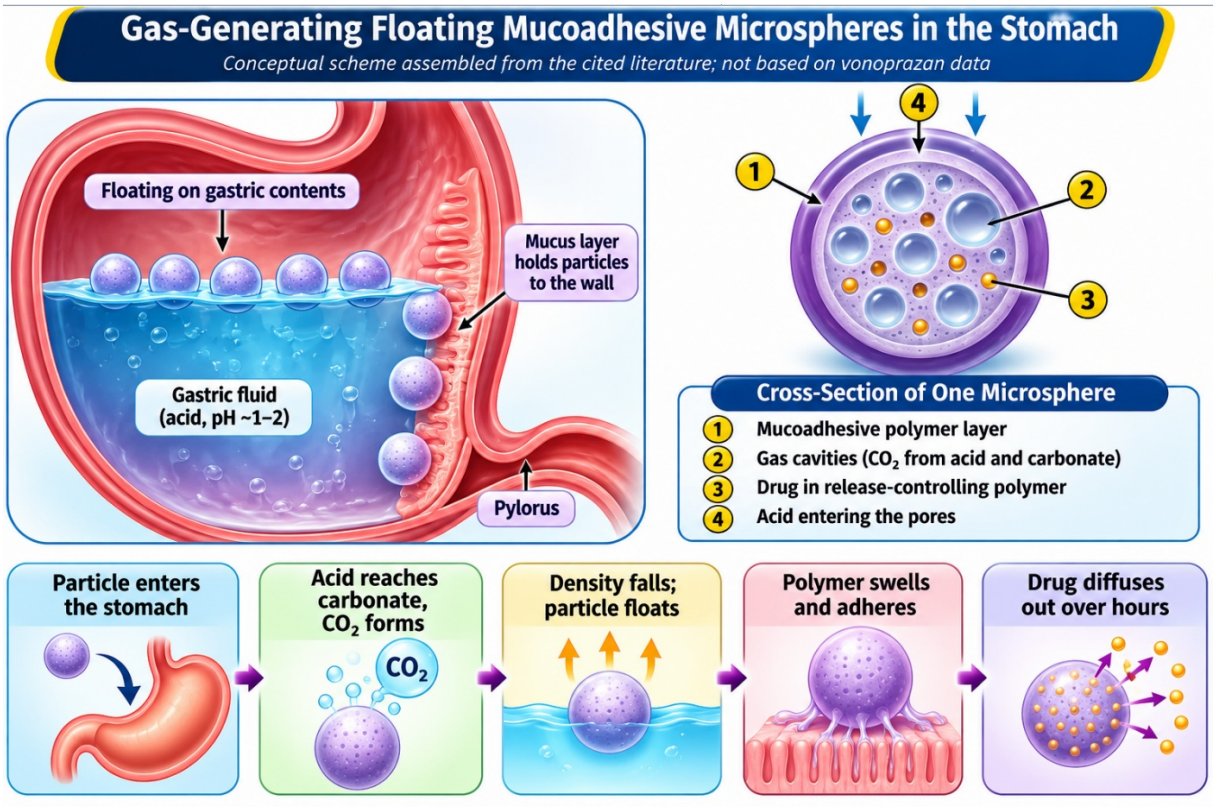


Figure 1. Conceptual scheme of a gas-generating, floating, mucoadhesive microsphere in the stomach. Left, particles floating on gastric contents and adhering to the mucus layer. Right, a cross-section of one particle. The scheme combines mechanisms described in the cited literature and is not based on data for vonoprazan.

Table 2. Examples of floating, gas-generating and mucoadhesive approaches in the literature.

Approach	Example (drug; main materials)	Reported finding	Ref.
Hollow microballoon	Theophylline; ethyl cellulose	Floated over 12 h in simulated gastric medium; stirring speed set size and release rate	[29]
Hollow microballoon	Propranolol HCl; Eudragit RSPO	Temperature controlled cavity formation and buoyancy; burst then sustained release	[30]
Hollow microballoon	Nizatidine; Eudragit S-100, HPMC	Release sustained over 12 h; greater ulcer protection than free drug	[31]
Carbonate gas former	Nevirapine; CaCO3, alginate, HPMC	CO2 trapped in the gelled membrane; more carbonate gave immediate floating	[32]
Bicarbonate gas former	Enalapril maleate; alginate, iota-carrageenan	Eleven formulations; yield, entrapment, buoyancy and release characterised	[33]
Effervescent pellets	Norfloxacin; NaHCO3, HPMC K15M, Eudragit RL 100	Lag time below 10 min in best batch; thicker coat reduced release	[34]
pH modifier	Ranitidine HCl; ethyl cellulose, Eudragit RS100	Fumaric acid (15% w/w), citric and tartaric acid (20% w/w) increased release	[39]
Mucoadhesive polymer	Propranolol HCl; Carbopol-934P, ethyl cellulose	82% mucoadhesion after 1 h in best batch; release beyond 12 h	[35]
Mucoadhesive polymer	Zuojin Pill alkaloids; alginate, chitosan	In vitro gastric retention 82.63%; tracer retained within 12 h	[36]
Float-adhesive	Famotidine; mucilage, alginate, chitosan	Mucilage with chitosan beat chitosan alone for mucoadhesion and buoyancy	[37]

Approach	Example (drug; main materials)	Reported finding	Ref.
Micro-in-macro	Ciprofloxacin; alginate, pectin, PLGA	Controlled release and greater bioavailability than marketed product in pigs	[38]

Findings are as stated in the abstracts and are limited to the points listed.

5 pH-responsive polymers, preparation and stabilisation

The pH-dependent polymers in the abstracts we read were mostly used to protect a drug from acid. Spray-dried lansoprazole particles showed the highest gastric resistance with Eudragit S 100, compared with Eudragit L 100-55 and L 100, which the authors attribute to its higher pH threshold, while triethyl citrate lowered resistance [40]. Pantoprazole microspheres of Eudragit S 100 and HPMCP were made to stabilise the drug in acid [41]. Anionic papain particles aggregated at pH 1.2 and dispersed again above pH 5.0 [42], and naproxen microspheres of Eudragit L100 and HPMC E5 released under 5% in the first 120 min at pH 1.2 and over 85% at pH 6.8 [43].

This is the opposite of what a gastric-retentive vonoprazan particle needs. An enteric shell would hold the drug back in the stomach, so a gastric design needs polymers that stay permeable at pH 1 to 3 or whose permeability is tuned by blending. Organic acids raised release from ethyl cellulose and Eudragit RS100 microspheres [39], and acid-triggered gas formation [32] is another tool. Whether vonoprazan needs shielding from acid is not known. The forced-degradation abstracts report acid-hydrolysis products [19], [20] without conditions, so a form that holds the drug in acid for hours must be tested for chemical stability as well as release.

Preparation methods in the literature are emulsion solvent diffusion or evaporation [4], [31], ionotropic gelation [32], [37], extrusion-spheronisation [34] and spray drying [40]. Stirring speed [29], temperature [30], drug:polymer ratio, emulsifier concentration and stirring time [31] all affected the product. Residual solvent has to be checked, and GC/MS found none in dipyridamole microspheres [44]. Spray-dried lansoprazole microparticles were stable for three months under ICH Q1A(R2) conditions [40].

6 Quality by Design and design of experiments

QbD starts from a quality target product profile (QTPP) and lists the critical quality attributes (CQAs) that the product must meet. Risk assessment links the CQAs to critical material attributes (CMAs) and critical process parameters (CPPs), designed experiments quantify the links, and the result is a design space with a control strategy (Figure 2). It replaces testing at the end of production with quality built into the process.

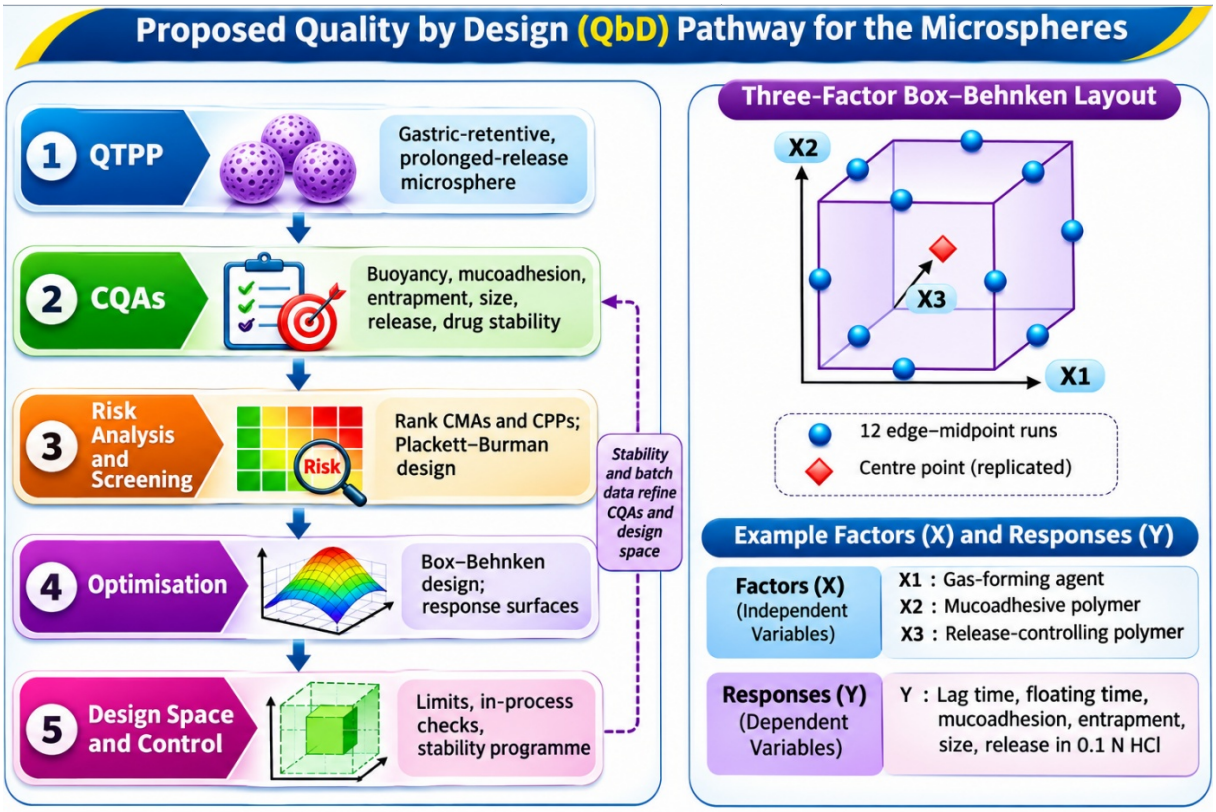


Figure 2. Proposed Quality by Design pathway for the vonoprazan microspheres (left) and a three-factor Box-Behnken layout (right). Factors and responses are examples chosen from the literature reviewed, not results. QTPP, quality target product profile; CQA, critical quality attribute; CMA, critical material attribute; CPP, critical process parameter.

Designed experiments are common in the microsphere papers. A 3^2 full factorial design on drug:polymer ratio and stirring speed used mucoadhesion, entrapment, particle size and t80 as responses [35]. Similar 3^2 designs were used for dipyridamole microspheres [44] and gabapentin floating microspheres [45]. A central composite design optimised chitosan and methylcellulose microspheres, with an optimum close to model predictions [46]. For glipizide microsponges, Plackett-Burman screening picked polymer concentration, stirring speed and temperature as significant before a Box-Behnken design was run [47], and a 17-run Box-Behnken design was used for floating norfloxacin pellets [34].

We propose the same two-stage path. A screening design would test the gas-forming carbonate level, the mucoadhesive polymer level, the ratio of release-controlling polymer to drug, the stirring speed and the temperature. A three-factor Box-Behnken design would then optimise the three most active factors; it has 12 edge-midpoint runs plus replicated centre points and avoids extreme corner combinations. Responses would be floating lag time and duration, mucoadhesion, entrapment, particle size and release at set times in 0.1 N HCl. Factor ranges would come from the screening work, and nothing in Figure 2 or Table 3 is an experimental result.

7 Characterisation and in-vitro evaluation

Standard characterisation covers yield, entrapment, particle size, SEM morphology, buoyancy, *in vitro* mucoadhesion and release. The microsphere papers measured floating lag time and duration [32], [34], mucoadhesion on gastric tissue [35], [37] and release in 0.1 N HCl over 12 h [37], and fitted release data to Higuchi and Korsmeyer-Peppas models [37], [46]. Retention *in vivo* was shown by gamma scintigraphy in rabbits [44], by radiography [47] and by fluorescent tracer [36].

A vonoprazan study adds one requirement: the drug assay must separate the drug from its degradation products. Stability-indicating HPLC and UHPLC methods exist [20], [21], and the forced-degradation work identifies the degradants to look for [19]. Release samples taken in acid should be analysed by such a method, so that a low drug peak caused by degradation is not mistaken for retention in the particle. Table 3 lists the proposed tests; acceptance limits would be set from the target profile.

Table 3. Proposed CQAs and in-vitro tests for the vonoprazan microspheres.

CQA or test	Proposed approach and purpose	Basis in the literature	Ref.
Particle size and shape	Sieving and SEM; confirm spherical, porous, hollow structure	Size depended on stirring speed; hollow porous particles seen by SEM	[29], [31]
Entrapment and drug content	Stability-indicating HPLC assay of drug in particles	Validated stability-indicating methods exist	[20], [21]
Buoyancy	Floating lag time and total floating time in 0.1 N HCl, target 12 h	Lag time and floating duration reported for gas-forming systems	[32], [34]
Mucoadhesion	In vitro adhesion to gastric tissue	Used for Carbopol and mucilage systems	[35], [37]
Drug release	0.1 N HCl, 12 h; Higuchi and Korsmeyer-Peppas fitting	Release in acid over 12 h; model fitting	[37], [46]
Drug stability in medium	Assay of drug and degradants in release samples	Acidic hydrolysis products reported	[19], [20]
Residual solvent	GC for solvents from emulsion methods	GC/MS found none in another system	[44]
Storage stability	ICH Q1A(R2) accelerated study	Three-month stability reported for a microparticle	[40]
Retention *in vivo* (later stage)	Scintigraphy or radiography in animals	Used in rabbits for other drugs	[44], [47]

These are proposals based on methods in the cited literature, and no results are reported.

8 Gaps and conclusion

Seven gaps limit what can be said today. First, we found no gastroretentive, floating or extended-release vonoprazan formulation. Second, we found no paper reporting a measured solubility or pH-stability profile of vonoprazan, and the two pKa values we found differ [1], [2]. Third, the forced-degradation abstracts give no acid strength or time, and two reports differ on photolysis [19], [20]. Fourth, no abstract says that vonoprazan has a narrow absorption window or benefits from retention, and the nocturnal breakthrough data come from PPIs, where breakthrough alone did not explain symptoms [22], [23]. Fifth, among the abstracts we read, no microsphere study combined gas generation, mucoadhesion and a pH-dependent polymer in one particle; the nearest examples are a float-adhesive system and polymer-blend systems with pH modifiers [37], [39]. Sixth, most microsphere evidence comes from other drugs, often in small animal or *in vitro* studies. Seventh, we read abstracts only, and a full evaluation would need the full texts.

A gas-generating, floating, mucoadhesive microsphere of vonoprazan is a reasonable subject for development, but the case for it is a hypothesis and not an established need. The drug has strong, well-documented acid control, the carriers and designed-experiment tools are well described for

other drugs, and stability-indicating assays are available. The proposed design is conceptual. The next steps would be a stability study of the drug in acidic media, a screening design, a Box-Behnken optimisation and in-vitro testing with a stability-indicating assay. Only then could the idea be weighed against the marketed tablet.

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