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DEVELOPMENT OF A FLOATING GASTRORETENTIVE TABLET OF METFORMIN HYDROCHLORIDE USING NATURAL GUMS

THERESA PICHLER[1]*, AGNIESZKA JABLONSKI[2], BRAM HOEKSTRA[3]

Affiliation

[1]Department of Pharmaceutics, Styrian Institute of Pharmacology, Leoben, Austria
[2]Department of Pharmaceutics, Warmia Institute of Pharmaceutical Sciences, Olsztyn, Poland
[3]Department of Pharmaceutics, Twente Institute of Pharmaceutical Technology, Hengelo, Netherlands

*Corresponding author: Theresa Pichler, t.pichler@sip-leoben.at
ORCID iD: Theresa Pichler 0000-0001-4172-0539; Agnieszka Jablonski 0000-0001-3194-3069; Bram Hoekstra 0000-0001-0064-6985

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Abstract

Metformin hydrochloride is absorbed mainly from the upper small intestine, has a short half-life and often causes gastrointestinal upset, which makes it a frequent model drug for gastroretentive delivery. This narrative review summarises published work on floating tablets of metformin that use natural gums such as xanthan, guar, locust bean gum and alginate as release-controlling matrices. It covers gastric physiology, drug properties, gum behaviour, formulation and processing variables, evaluation methods, release kinetics and in vivo evidence. The literature shows that buoyancy with sustained release is readily achieved in vitro, but gum variability, limited in vivo data and uneven reporting restrict translation. The article presents no new experimental data.

1. INTRODUCTION

Most oral tablets spend a modest part of their working life in the stomach. For drugs absorbed throughout the gut that causes no difficulty, but for drugs absorbed in a narrow region of the upper small intestine, quick transit past that region means incomplete absorption and a short duration of effect. Gastroretentive systems try to solve this by keeping the dosage form in the stomach for several hours, releasing drug slowly into the gastric contents so that it reaches the absorption window continuously [1, 2]. Several strategies have been tried, including floating or low-density systems, swelling and expanding systems, mucoadhesive systems and high-density systems [3, 4]. Floating

systems remain the most widely studied because they need no unusual excipients or equipment.

Metformin hydrochloride illustrates the problem well. It is the first-choice oral drug for type 2 diabetes in most guidelines, yet conventional tablets must be taken two or three times a day at gram-level total doses, and many patients report diarrhoea, nausea and abdominal discomfort [5, 6, 7]. Extended-release products reduce dosing frequency and have been shown to maintain glycaemic control with better gastrointestinal tolerability for some patients [8, 9]. Among the matrices used, natural gums attract steady interest because they are inexpensive, widely available, biocompatible and approved as food additives, and because they swell in water to form viscous gel layers that control diffusion [10, 11].

This review looks at the published literature on floating gastroretentive tablets of metformin hydrochloride made with natural gums. It describes the physiological basis of gastric retention, the properties of the drug and of the commonly used gums, the formulation variables reported to matter, the tests used to assess floating and release, and the clinical evidence available. It does not report new experiments, and where an article describes a development study, only its general findings are used.

A note on terminology is useful. 'Floating' in the strict sense means that the tablet's bulk density is lower than that of gastric fluid, about 1.0 g/mL, so that it stays on top of the contents. Many papers use the word loosely for any tablet that rises to the surface in a beaker of dilute acid, which is a necessary but not sufficient test of behaviour in a real stomach where motility, food and fluid volume vary [3, 12]. Readers should keep this distinction in mind when reading claims of gastric retention.

2. GASTRIC PHYSIOLOGY AND GASTRORETENTION

In the fasted state the stomach shows a cyclic pattern of motility, the migrating motor complex, whose strong phase III contractions sweep undigested material through the pylorus. Small tablets and pellets are emptied within an hour or two in this phase, while large indigestible solids can be retained until the next housekeeper wave [13, 14]. After a meal the pattern changes: the stomach grinds and meters food into the duodenum at a rate of a few kilocalories per minute, and dosage forms larger than about a centimetre are held back with the food [14, 15]. Gastric residence of a floating system is therefore strongly linked to feeding, which is why most reports of success refer to the fed state.

Density and size are the two physical variables on which designers can act. Work with single- and multiple-unit forms in healthy volunteers showed that buoyant units had longer gastric residence in the fed state than non-buoyant ones, whereas the effect of density differences vanished in the fasted state [15]. Posture, age and sex influence the residence time of an indigestible solid, with supine posture shortening it [14]. A floating tablet lying on its side on a stomach wall, or in a stomach with little fluid, may not float at all. Small volumes of fasting-state gastric fluid, often only a few tens of millilitres, impose a harsher test than a 900 mL dissolution vessel [3, 16].

Absorption site matters as much as retention. Many drugs are absorbed preferentially in the duodenum and jejunum, and a dosage form that releases slowly in the stomach delivers drug continuously to that region as the stomach empties its contents [16]. This is the rationale for metformin. There is, however, a limitation: if gastric emptying of the dosage form is delayed but the drug dissolved in the stomach empties normally, the benefit depends on release rate being matched to transit [1, 4]. Expandable systems and bioadhesive systems were developed in part to avoid dependence on food and posture, with mixed success and with safety questions such as obstruction for large expandable devices [17].

Interindividual variability in gastric emptying is large, and it is exaggerated in people with diabetes. Delayed gastric emptying, gastroparesis, is a recognised complication of long-standing diabetes, and a product that relies on prolonged gastric stay may behave unpredictably in these patients [4]. This issue is rarely mentioned in formulation papers,

even though the target population is precisely people with diabetes. Mean values from healthy volunteers should be interpreted cautiously for this group, and trials in patients are needed to see whether retention is shorter or longer than expected.

3. METFORMIN HYDROCHLORIDE AS A MODEL DRUG

Metformin is a hydrophilic biguanide, freely soluble in water, with a high pKa, so it exists as a cation across the physiological pH range [18, 19]. Its absolute oral bioavailability is roughly half, absorption is saturable and incomplete, and the fraction absorbed falls as dose rises, a pattern consistent with a limited absorption window and transporter involvement [18, 20]. It is not metabolised, binds hardly at all to plasma proteins and leaves the body in urine by tubular secretion. Plasma half-life is only a few hours. For regulatory purposes it is usually treated under the Biopharmaceutics Classification System (BCS) as a low-permeability compound, and its aqueous solubility removes dissolution as a barrier to absorption [19].

The pharmacology explains why modified release has been attractive. The antihyperglycaemic effect of metformin comes mainly from reduced hepatic glucose output, with improved peripheral insulin sensitivity and effects on the gut, and it has long been associated with a low risk of hypoglycaemia and weight gain [5]. Doses range from a few hundred milligrams to over two grams per day. Activation of AMP-activated protein kinase (AMPK) in the liver is one accepted mechanism [21]. Large single doses cause high local concentrations in the intestine, which probably contribute to gastrointestinal intolerance; one explanation is accumulation of drug in enterocytes and effects on bile acid and serotonin handling [7]. Slow, steady delivery to the upper gut may reduce those peaks.

Safety restrictions are strict where renal function is concerned. Clearance of metformin falls in parallel with glomerular filtration, and accumulation increases the risk of lactic acidosis, a rare but serious complication; the dose is reduced in moderate renal impairment and the drug is withheld in severe impairment [18, 20, 22]. Population data suggest that the incidence of lactic acidosis in metformin users is very low and not clearly higher than with other agents [22]. Any gastroretentive product would have to respect these limits, and a design that prolongs systemic exposure must be shown not to raise peak concentrations in patients with reduced clearance.

Existing extended-release metformin products offer a benchmark. Osmotic pump and gel-forming matrix tablets taken once daily with the evening meal have shown steady-state pharmacokinetics and glycaemic control comparable to immediate-release dosing in trials in type 2 diabetes [8, 9]. Some are designed to swell in the stomach so as to lengthen retention. A new gum-based floating tablet will be judged against these, and evidence of equivalent exposure with simpler, cheaper manufacture would be the most convincing argument for it [8, 9].

4. NATURAL GUMS AS RELEASE-CONTROLLING MATRICES

Natural gums are high molecular weight polysaccharides obtained from plant exudates, seeds, algae or microbial fermentation. On contact with water they hydrate and swell, building a viscous gel layer that slows ingress of fluid and outward diffusion of drug, and in time the layer erodes, so release is controlled by a combination of diffusion and erosion [10, 23]. They are attractive to the pharmaceutical industry for reasons of cost, safety and renewable supply, and many are listed excipients [11, 24]. Their drawbacks are equally well known: batch-to-batch variation in molecular weight and composition, susceptibility to microbial contamination, and changes in viscosity with time, pH and ionic strength [10, 11].

Xanthan gum, produced by fermentation with *Xanthomonas campestris*, is probably the most popular choice for floating matrices. It is an anionic polysaccharide with a cellulose backbone and trisaccharide side chains, and it gives high viscosity at low concentrations that is stable over a wide range of pH and salt concentration [25]. Matrix tablets of xanthan form a strong gel quickly, which helps to trap

gas and sustain buoyancy. It often shows synergy with galactomannans: mixtures of xanthan with locust bean gum or guar gum form firmer gels than either alone, a property taken advantage of in many designs [10, 25, 26].

Microbial and chemical stability of hydrated gums needs a mention. Polysaccharide gels are nutrient-rich, and microbial growth can occur during granulation with water or during storage in humid climates, which explains the preservative limits set for gum excipients [11, 24]. Gamma irradiation or other sterilisation can depolymerise some gums and lower viscosity, so control of bioburden is best achieved through supplier qualification and dry processing [10, 11]. Such details are routine in the manufacturing world but are rarely discussed in the academic formulation papers on which this review draws.

Guar gum and locust bean gum are galactomannans extracted from the seeds of *Cyamopsis tetragonoloba* and *Ceratonia siliqua*. They are non-ionic, so their behaviour is less affected by pH and electrolytes, and they hydrate rapidly to give highly viscous dispersions [26, 27]. Guar gum, with a higher proportion of galactose side chains, is more water soluble and swells faster, which can produce quick initial release or even disintegration at low polymer level. Locust bean gum has fewer galactose units and hydrates more slowly. Both have a history of use as colon-targeting carriers because the gut flora ferment them, but this is of little importance for a system that is designed to work in the stomach [26, 27].

Sodium alginate, extracted from brown seaweed, behaves in a different way. In acid it forms alginic acid gel, and in the presence of calcium it forms cross-linked 'egg-box' structures, so alginate can create a gel barrier in the stomach that entraps gas bubbles and floats; this principle is used in antireflux raft preparations as well as in floating tablets [28]. Release from alginate matrices can therefore depend on the calcium content of the formulation and on the acidity of the medium. Alginates with high guluronic acid content form stronger gels, and the grade chosen can alter the rate of release substantially [28]. Specification of the grade is another detail missing from many reports.

Characterisation of the gum itself is the step most often skipped. Viscosity of a defined concentration under defined shear, swelling index, moisture content, particle size and microbial count all affect tablet behaviour, and monograph tests in compendia exist for several of the common gums [11, 24]. Rheology is informative: gums that show strong shear-thinning flow are easier to compress and hydrate evenly, while those with high yield stress form gels that resist erosion in the gastric environment [10, 25]. Because tablet performance tracks gum viscosity so closely, a formulation that works with one lot of xanthan may fail with another from a different supplier, and reporting the viscosity grade would make results easier to repeat.

Other gums, including karaya, tragacanth, gellan and acacia, have also been tested alone or in combination, although with less frequency [10, 11]. The practical lesson from this body of work is that blends of gums are usually more successful than single gums, because the weaknesses of one are offset by another: a fast-hydrating gum provides a rapid gel layer for early buoyancy, while a slower, stronger gum sustains the barrier through the remainder of the release period [10, 26]. Combination with a small amount of a cellulose ether such as hydroxypropyl methylcellulose (HPMC) is also common and adds robustness [24, 29].

Safety and regulatory status vary. Xanthan, guar, locust bean gum and alginate are all accepted food additives, and exposure through tablets is small by comparison with dietary intake. Guar gum in large doses caused oesophageal obstruction when taken as a dry swelling tablet in the past, which is a reminder that high-swelling materials in a solid form need attention to dose and fluid [11, 27]. For metformin, which must be taken at high dose, tablet size is a real concern, since a gum-rich matrix of 1000 mg drug can be too large to swallow comfortably.

5. FORMULATION DESIGN AND PROCESSING

Buoyancy in a tablet is produced either by entrapped air within a low-density matrix or

by gas generated in situ. The commonest gas-generating pair is sodium bicarbonate with an acid, usually citric acid, or sometimes bicarbonate alone reacting with gastric hydrochloric acid to release carbon dioxide, which is trapped by the gelling matrix and lowers the apparent density [1, 3]. Gas formation depends on the gel layer closing around the bubbles quickly enough, which is why viscosity and hydration speed of the gum control floating lag time and duration [12, 30]. Effervescent excipient levels in published tablets are generally in the range of a few per cent to a quarter of tablet weight, higher levels shortening lag time but increasing friability and weakening the matrix.

The ratio of drug to gum is the dominant factor for release rate. With a hydrophilic and highly soluble drug such as metformin, a matrix with low polymer content releases most of the dose within an hour or two, because drug dissolves quickly and escapes through water-filled channels, whereas higher polymer content gives a thicker gel layer and slower release [10, 29]. Because of the high dose, though, there is a limit on how much gum can be added without making the tablet too large. Papers commonly report a compromise in which gum makes up 20 to 40 per cent of the tablet, with drug contributing the rest of the weight, and release lasting from eight to twelve hours [12, 30].

Drug-gum interaction is a further point. Metformin is cationic, while xanthan and alginate are anionic polysaccharides, so electrostatic binding between drug and polymer is plausible and could slow release beyond what diffusion alone would predict [25, 28]. Compatibility screening by infrared spectroscopy and differential scanning calorimetry is reported in many studies to show no interaction, but the sensitivity of these techniques to weak ionic association is limited [24, 31]. Ionic strength of the medium also changes gum hydration, and release in acid with dissolved salts may differ from release in water, which is one reason why the dissolution medium should be chosen with care [10, 32].

Other excipients matter too. Lactose or microcrystalline cellulose as diluents change the porosity and wettability of the matrix, magnesium stearate, a hydrophobic lubricant, can slow wetting if over-mixed, and talc or colloidal silica improve flow [24]. Fats and waxes, for instance hydrogenated vegetable oil or glyceryl behenate, lower density and delay hydration, and several floating designs combine a gum with a lipid to prolong buoyancy [30, 33]. In each case the effect on lag time, tablet hardness and release has to be tested, since interactions between components are frequent and rarely linear [31].

Manufacturing process also affects behaviour. Direct compression is simple and suits moisture-sensitive effervescent mixtures, but metformin has poor flow and compressibility, and gum particle size influences hydration speed. Wet granulation with a binder improves flow and compactability of metformin yet can prematurely react the effervescent components if water is used, so non-aqueous granulation liquids or separate granulation of drug and gas-generating agents are used [24, 34]. Compression force changes tablet porosity and therefore both density and initial hydration, with higher forces generally increasing density and floating lag time [12, 30]. Flow is assessed through angle of repose and compressibility indices [34].

Quality by design (QbD) thinking is becoming more common in this work. Statistical designs such as factorial and central composite designs allow the effects of gum level, effervescent level and compression force on lag time, buoyancy duration and release to be modelled together, and a design space can then be defined [31]. The approach brings discipline that one-factor-at-a-time studies lack. Its value depends on a sound choice of factors and ranges and on the reliability of the responses, and optimisation based on in vitro results alone remains an optimisation for the beaker.

6. EVALUATION OF FLOATING TABLETS

Evaluation follows the usual pharmacopoeial scheme for tablets, with additional tests for floating behaviour. Weight variation, thickness, hardness, friability and drug content are measured first. Hardness must be sufficient to withstand handling, but in a

floating tablet a very hard compact has higher density and takes longer to float. Friability of effervescent matrices is often higher than for conventional tablets, and the pharmacopoeial limit of about one per cent is not always reached without optimising binder level [24, 32]. Published formulations and their reported behaviour are summarised in table 1, which lists also the corresponding method standards and the main findings reported.

Table 1: Published evidence on floating and gum-based matrix design relevant to metformin hydrochloride

Topic or material	Reported finding or role	Ref.
Fed-state gastric emptying	Dosage forms larger than about a centimetre are retained with food; fasted retention is short	[14, 15]
Metformin absorption	Incomplete, saturable absorption points to a narrow upper-gut window	[18, 20]
Extended-release metformin	Once-daily products give steady exposure and comparable glycaemic control	[8, 9]
Xanthan gum	Rapid strong gel with viscosity stable across pH and salt levels	[25]
Guar and locust bean gum	Non-ionic galactomannans that hydrate quickly and gel with xanthan	[26, 27]
Sodium alginate	Forms gas-entrapping gel in acid and cross-links with calcium	[28]
Gum blends	Mixtures outperform single gums for buoyancy and sustained release	[10, 11]
Effervescent agents	Bicarbonate with acid generates carbon dioxide that lowers density	[1, 3]
Floating assessment	Resultant weight measures buoyancy over time better than visual lag time	[35, 36]
Dissolution conditions	Paddle apparatus in 0.1 N acid is standard but does not mimic fasting stomach	[32]
Release modelling	Korsmeyer-Peppas exponent suggests anomalous transport in swelling matrices	[37, 38]

Floating lag time, the time taken for the tablet to rise to the surface, and total floating time are recorded visually in 0.1 N hydrochloric acid or simulated gastric fluid at 37 °C. Acceptable lag times in the literature are under a minute or so, with floating lasting at least eight to twelve hours [12, 36]. A weighing-based approach measures the force required to keep a dosage form submerged, giving a resultant weight that quantifies buoyancy as a function of time and shows how gas loss and fluid uptake change the balance [35]. This is a richer measure than a stopwatch and shows when floating is about to fail.

Dissolution testing most often uses the paddle apparatus at 50 or 75 rpm in 900 mL of 0.1 N hydrochloric acid, as described in the United States Pharmacopeia (USP) general chapter, with samples taken hourly and assayed by ultraviolet (UV) spectrophotometry at about 233 nm [32]. These conditions are standard, but they do not reproduce the stomach, with its small volumes, intermittent motility and food. Several authors use media of different pH, or test in fed-state simulated media, to check robustness. The paddle can also push a floating tablet against the vessel wall, and sinkers or alternative apparatus alter the result, so the arrangement used must be stated [32, 36]. Reference to a marketed extended-release product is helpful when the similarity factor is used to compare profiles [39].

Drug content and uniformity need special care in a high-dose tablet. Because metformin makes up half or more of the tablet weight, small differences in blend segregation translate into measurable content variation, and the high proportion of gum can make drug extraction incomplete if the assay procedure does not allow full hydration and sonication [24, 32]. Content uniformity should be demonstrated for both the tablet and, if used, any coated or layered variant. Method validation for the assay, covering linearity, accuracy, precision and specificity against the gum extractives, is expected under ICH principles and is seldom described in full [31, 40].

Swelling and erosion studies, in which tablets are removed from medium at intervals, weighed wet and then dried, give a measure of gel layer growth and loss and help explain

release behaviour [10, 29]. Imaging by texture analysis of the gel strength, or by microscopy and, in research settings, magnetic resonance imaging (MRI), offers more detail. Stability studies follow International Council for Harmonisation (ICH) guidance, usually storage at 40 °C and 75 per cent relative humidity for six months with periodic assessment of buoyancy and release, since effervescent components are moisture-sensitive and gums can change viscosity on storage [40]. Reports of such studies on gum-based floating metformin tablets are less numerous than the initial development reports.

A convenient way to see where the evidence lies is to count the entries by theme (fig. 1). Most are about formulation and in vitro buoyancy, a smaller group concerns release modelling, and clinical or in vivo evidence is a minority. This imbalance matches what the general gastroretentive literature shows, where many designs have been proposed and few have been tested in humans [1, 4]. It also points to the principal gap this review identifies, namely the distance between in vitro floating and demonstrated gastric retention in people.

Palatability and swallowability deserve a brief comment. A single tablet containing 500 mg metformin together with 30 per cent gum and effervescent agents can weigh well over a gram and a half, which is large by the standards of oral dosage forms. Tablet shape also influences floating: an oblong tablet has a larger surface-to-volume ratio and floats more readily than a round one. Patient acceptance data on size are not usually collected, but they matter for a drug taken for life by older adults [4].

7. RELEASE KINETICS

Release profiles from floating matrices are usually fitted to several mathematical models to infer the mechanism. The zero-order model describes constant release and is rarely achieved with swelling matrices. The Higuchi model relates cumulative release to the square root of time and was derived for diffusion from a planar matrix [41]. The Korsmeyer-Peppas power law, in which fractional release is proportional to time raised to an exponent n, is the most popular for polymer systems, and for cylindrical tablets n of about 0.45 is read as Fickian diffusion, values between 0.45 and 0.89 as anomalous transport combining diffusion and relaxation, and values near 0.89 or higher as relaxation- or erosion-controlled release [37, 38].

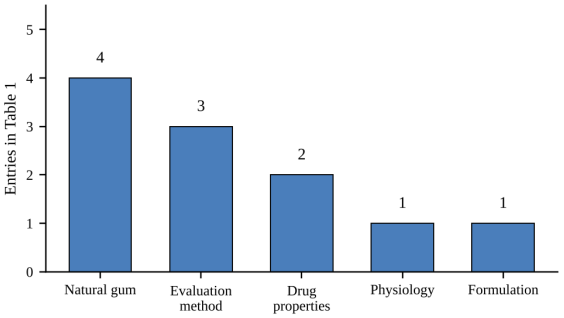


Fig. 1: Number of entries in table 1 by evidence theme

These interpretations should be treated with some caution. The power law applies strictly to the first 60 per cent of release, the geometry assumed in the derivation is not that of a swelling, eroding tablet, and an n value cannot prove a mechanism on its own [37, 38, 39]. Reports of gum-based metformin tablets commonly find anomalous transport, which accords with the visual picture of a swelling gel layer through which drug diffuses while the layer erodes at its surface [10, 29]. Model-independent comparisons, such as difference and similarity factors, are safer when the aim is to compare two products, and the number of time points and the variability must satisfy the conditions for those factors [39].

8. IN VIVO PERFORMANCE

Evidence on gastric retention in people comes mostly from gamma scintigraphy and, in a few cases, imaging by X-ray or magnetic resonance of radio-opaque or labelled dosage forms. Buoyant systems in the fed state have been reported to remain in the stomach for several hours longer than non-buoyant controls, whereas in the fasted state the benefit is smaller and less predictable [14, 15, 35]. For metformin specifically, studies of extended-release and gastroretentive designs show prolonged absorption and a delayed time to peak concentration, but whether this converts into improved clinical outcomes is

not so clear [8, 9]. For gum-based floating tablets, the data in animals or humans are few and mostly preliminary. Radiolabelled or radio-opaque markers, though, show only where the dosage form is, not how much drug it has released, which is a further reason for pairing imaging with plasma sampling [9, 35].

Study design determines how useful in vivo data are. Relevant questions include dose proportionality, food effect, intersubject variability and the relationship between in vitro release and plasma levels, which is investigated through in vitro in vivo correlation [31, 39]. Because metformin absorption saturates and the drug is distributed to the gut wall, plasma concentration is an imperfect index of gut exposure, and clinical endpoints such as glycaemic control and gastrointestinal tolerability are needed alongside pharmacokinetics [7, 18]. A comparison with a marketed extended-release tablet in the fed state, in a crossover design, is the standard that most investigators could achieve and the one regulators would expect.

9. LIMITATIONS AND FUTURE DIRECTIONS

The principal limitations of the evidence are fairly consistent. Gum quality is variable and incompletely specified, with source, grade and viscosity seldom reported. Most studies are in vitro and small, and the dissolution conditions used do not represent the fasting stomach. Floating is assessed by visual observation in acid, without consideration of food, posture or gastric volume. Lack of data in patients with delayed gastric emptying is conspicuous. Few reports address manufacturing scale-up or long-term stability, and statistical treatment of results is often thin [10, 11, 40]. Publication bias towards successful formulations is likely. Taken singly none of these is fatal, but together they explain why so few gum-based floating metformin tablets have progressed beyond the bench.

Progress would require several things. Gums should be characterised by viscosity, molecular weight, moisture and microbial limits, and sourced from defined suppliers [10, 11]. Floating should be quantified by resultant weight measurements and tested in small-volume and fed-state media [35, 36]. Candidate formulations should move to imaging studies in volunteers and then to pharmacokinetic comparison with a marketed extended-release product [8, 9]. Quality by design should be used to define robust operating ranges [31]. If these steps confirm benefit, natural gum based floating metformin tablets could be an inexpensive option for settings where branded extended-release products are costly.

10. CONCLUSION

Published work shows that natural gums, alone or in blends, can be used to make floating metformin tablets that rise within a short time, stay buoyant for many hours and release drug over eight to twelve hours in vitro [10, 12]. Xanthan and galactomannan combinations are the most successful, alginate offers a gas-entrapping alternative, and effervescent agents supply the necessary low density [1, 25, 26, 28]. Release usually follows anomalous transport, consistent with swelling and erosion [37, 38].

What remains uncertain is performance in people. Gum variability, simplified dissolution conditions and the near absence of in vivo and patient data limit confidence, particularly for people with diabetes who may have slowed gastric emptying [4, 15]. Characterised gums, fed-state and small-volume testing, imaging studies and comparison with a marketed extended-release product are the practical next steps [8, 9, 35].

11. ABBREVIATIONS

BCS-Biopharmaceutics Classification System, ICH-International Council for Harmonisation, USP-United States Pharmacopeia, HPMC-Hydroxypropyl methylcellulose, UV-Ultraviolet, MRI-Magnetic resonance imaging, AMPK-AMP-activated protein kinase, QbD-Quality by design

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13. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

14. CONFLICT OF INTERESTS

Declared none

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