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ADVANCED ORAL DRUG DELIVERY PLATFORMS FOR TYPE 2 DIABETES MELLITUS: BRIDGING PHARMACOKINETIC CHALLENGES AND GLYCAEMIC OUTCOMES

Bidgar Saraswati M.*[1], Tambade Yogesh B.[1], Kolekar Mahesh D.[2]

[1]Department of Pharmaceutics, Vidya Niketan Institute of Pharmacy and Research Center, Bota, Sangamner.
[2]Dr. Ithape Institute of Pharmacy, Sangamner, Ahilyanagar.

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***Corresponding Author: Bidgar Saraswati M.**
Department of Pharmaceutics, Vidya Niketan Institute of Pharmacy and Research Center, Bota, Sangamner.
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ABSTRACT
Type 2 diabetes mellitus imposes a pharmacological management challenge that extends beyond drug discovery to the fundamental question of how orally administered antidiabetic agents are delivered to their absorptive sites. Conventional formulations systematically underperform for a pharmacologically diverse drug class whose members include BCS Class II compounds with dissolution-limited bioavailability, agents with saturable proximal intestinal transport, and short-acting secretagogues requiring postprandial concentration peaks that standard tablet technology cannot reliably sustain. This review examines the gastrointestinal physiological basis for these failures, analyses how the T2DM disease state further distorts the absorptive environment through gastroparesis and GLP-1 receptor agonist-mediated motility changes, and critically evaluates the advanced oral delivery platforms developed to address them. Gastroretentive floating systems effervescent and non-effervescent, single-layer and bilayer are analysed mechanistically with evidence from published in vivo pharmacokinetic studies demonstrating up to 3.17-fold bioavailability improvements for narrow absorption window antidiabetics. Nanocarrier platforms including PLGA nanoparticles, solid lipid nanoparticles, and chitosan-coated nanoemulsions are evaluated against BCS-based selection logic, while mucoadhesive thiomers, stimuli-responsive systems, and phenylboronic acid-based glucose-responsive architectures are examined as next-generation concepts. Quality by Design frameworks, physiologically based pharmacokinetic modelling, and translational barriers spanning IVIVC limitations and regulatory ambiguity are addressed. The synthesis reveals that matching delivery platform to the dominant pharmacokinetic barrier of each drug class is the central organizing principle for next-generation oral antidiabetic formulation.

KEYWORDS: Biopharmaceutics classification system, gastroretentive drug delivery, glucose-responsive nanoparticles, mucoadhesive polymers, oral bioavailability enhancement, type 2 diabetes mellitus.

1: INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) is growing to the extent that it is time to consider a paradigm shift for pharmacological management delivery in T2DM. The 11th edition of the International Diabetes Federation Diabetes Atlas found that in 2024, 11.1% of all adults (20-79 year) had diabetes, a figure that is projected to increase to 853 million by 2050.[1] T2DM constitutes about 90-95% of all diabetes cases, and the cost of T2DM-related health expenditure alone amounted to USD 1 trillion in 2024. The stress this puts on healthcare systems is directly related to the clinical challenge at its heart: to achieve sustainable and stable A1C control in patients who must take oral pharmacotherapy for life.[2] The oral route is still the most popular method of drug delivery in managing T2DM, not only for its convenience, but also for its advantages. There are five classes of oral hypoglycemic agents with different mechanisms of action, including biguanides, sulfonylureas, meglitinides, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, alpha-glucosidase

inhibitors and the thiazolidinediones.[3] However, even with this therapeutic depth, many of these drugs have a significant, but often overlooked problem if they are prepared in conventional formulations their pharmacokinetic weaknesses. Bioavailability is not only dependent on the chemical structure of the molecule but also on the dynamic interaction of the molecule with the gastrointestinal environment that it must navigate, which is more complicated and variable than traditional tablet technology can cover.[4]

There are several oral antidiabetic drugs that have properties that are fundamentally incompatible with the simple immediate-release formulation.[5] The most important therapeutic agent for T2DM is metformin hydrochloride, which has low oral bioavailability (50–60%), and in which absorption is mainly seen in the upper gastrointestinal tract and higher doses have reduced systemic exposure.[6] Repaglinide belongs to the meglitinide class and has a short plasma half-life (1 hr) and extensive first pass metabolism, mainly via CYP3A4 and CYP2C8, which generates multiple daily doses of repaglinide, resulting in peaks in plasma concentration immediately after meals. Poor aqueous solubility and gastric pH dependent absorption, like seen with gliclazide and glibenclamide, are known BCS Class II drugs where the bioavailability is limited by dissolution rate.[7] These are not peculiarities of single drugs, but a trend that can be observed throughout the class of oral antidiabetic drugs. The formulation science community has been addressing these limitations with a growing repertoire of advanced oral delivery platforms that each overcome one or more pharmacokinetic limitations, such as gastroretentive systems, nanocarrier-based strategies, mucoadhesive dosage forms and stimuli-responsive architectures.[8] However, the information on these platforms is still siloed, scattered among the individual studies on formulations and lacking in the integrative pharmacokinetic view needed to facilitate linking platform design decisions to glycemic outcome expectations by both clinicians and formulation scientists.[9]

This review adds to that landscape. It does not summarize the individual drug formulations but provides a pharmacokinetic rationale for each of the platforms, maps the choices of delivery strategies to the biopharmaceutical properties of oral antidiabetic drug classes, and critically investigates the evidence from clinical and preclinical trials of the glycemic effects of these drugs beyond dissolution and release data. The objectives are to offer a mechanistically coherent framework to lead to rational selection of platforms for developing next-generation oral antidiabetic formulations.

2: PATHOPHYSIOLOGY OF T2DM AND THE PHARMACOLOGICAL RATIONALE FOR ADVANCED ORAL DELIVERY

T2DM does not occur as a simple biochemical event, but as a gradual accumulation of various metabolic abnormalities. Two key mechanisms of the disease are the peripheral insulin resistance (mainly in skeletal muscle, adipose tissue, and liver) and the inability of the pancreatic beta cells to provide adequate compensatory insulin secretion to overcome the peripheral insulin resistance.[10] This adaptive response is initially characterized by upregulation of insulin production by the beta cells, but is eventually lost over time as glucotoxicity, lipotoxicity, endoplasmic reticulum stress, and chronic low-grade inflammation further stress beta cell mass and function.[11] Before the onset of the clinical manifestation of T2DM many beta cells are lost and the detectable beta cell markers are reduced under chronic metabolic stress, which contributes to functional dedifferentiation, not only to apoptosis. At the same time, there is abnormal overproduction of glucagon by the pancreatic α cells, especially after eating, leading to increased hepatic glucose production and post meal hyperglycaemia.[12] This glucagon dysregulation has been proposed, at least in part, to be caused by a defect in incretins (deficient production of or beta cell unresponsiveness to GLP-1 and GIP, the gut-derived peptide hormones that potentiate glucose stimulated insulin secretion and inhibit the release of glucagon after feeding).[13]

Knowing these overlapping mechanisms will not only help with the choice of a drug target for bioassays but also help to understand how the dosage of a drug at the site of absorption affects the therapeutic response depending on the time and consistency of its exposure.

Any drug that is designed to act on insulin secretion after a meal (postprandial insulin) needs to be optimized for peak plasma level to match the peak postprandial glucose.[14] To achieve the desired effect, a drug that inhibits hepatic glucose production (such as metformin) should maintain sufficient concentrations in the plasma during fasting and post-prandial periods.[15] The therapeutic efficacy of an agent that inhibits glucose absorption from the gut or in the kidney will depend on the amount of drug in the lumen or systemically that is always present to keep the glucose absorption and reabsorption process suppressed. All these pharmacodynamic requirements pose their own pharmacokinetic demand on the delivery system.[16] The biopharmaceutical properties of the different classes of oral antidiabetic drugs are mapped and show a systematic lack of conventional drug formulations.

Although the safety and efficacy profile of metformin is good, its gastrointestinal absorption is mainly in the proximal small intestine by organic cation transporter–mediated mechanisms, and absolute bioavailability is decreased at higher doses, which is a saturable

phenomenon that makes dose escalation pharmacokinetically inefficient. Repaglinide is a BCS Class II drug with a log P of 3.97 and aqueous solubility of 34 μg/mL at 37°C and is rapidly absorbed from the gastrointestinal tract but has a very short plasma half-life of about 1 h, due to extensive hepatic first-pass metabolism by CYP2C8 and CYP3A4. This requires the pre-prandial dosing before every meal, which is both clinically inconvenient and pharmacokinetically suboptimal since the concentration-time profile leaves gaps in-between, where there is no glycaemic coverage.[17] Sulfonylureas, such as glibenclamide and gliclazide, are highly bioavailable (both orally and in plasma) and plasma protein bound (>95%) but are also pH dependent in the gastrointestinal system and can have bioavailability altered significantly by the pH in the gastrointestinal system which can be influenced by other medications taken concurrently and is common in T2DM patients. By contrast, DPP-4 inhibitors and SGLT-2 inhibitors typically have a favourable pharmacokinetic profile and the latter group (dapagliflozin, empagliflozin, ertugliflozin) have a high systemic bioavailability and rapid absorption and are metabolized primarily via metabolic pathways.[18]

These differences illustrate that the improved oral delivery is not a shared goal of all antidiabetic drugs. It is most seriously indicated for agents in which a pharmacokinetic insufficiency is directly correlated to glycaemic under-performance and as outlined in Table 1, this distinction is between agents most likely to benefit from platform engineering and those that can be formulated conventionally. The pharmacokinetic susceptibility of the first group is the major reason for the formulation strategies discussed in this review.[19]

Table 1: Pharmacokinetic Profiles and Key Biopharmaceutical Challenges of Major Oral Antidiabetic Drug Classes.[20–23]

Drug Class	Representative Agent(s)	BCS Class	Primary Absorption Site	Oral Bioavailability (%)	Plasma Half-Life	Predominant PK Limitation	Preferred Delivery Strategy
Biguanides	Metformin HCl	III	Proximal small intestine	50–60	4–8.7 h	Saturable intestinal absorption; upper GI window	Gastroretentive sustained release
Meglitinides	Repaglinide	II	Upper GI tract	~56	~1 h	Extensive hepatic first-pass (CYP2C8/3A4); poor aqueous solubility	Gastroretentive or nanocarrier-based prolonged release
Sulfonyl-ureas	Glibenclamide, Gliclazide	II	Proximal GI	>90	5–12 h	pH-dependent dissolution; poor solubility (glibenclamide)	Solid dispersion; nanosuspension
DPP-4 Inhibitors	Sitagliptin, Linagliptin	I	Small intestine	80–100	8–24 h	Minimal — favourable PK	Conventional IR tablet suitable
SGLT-2 Inhibitors	Dapagliflozin, Empagliflozin	I/II	Proximal small intestine	>60–78	10–14 h	Minimal — generally well-absorbed	Conventional tablet; targeted colon delivery explored
Thiazolidinediones	Pioglitazone	III	Small intestine	~83	3–7 h (active metabolites longer)	Extensive CYP2C8/3A4 metabolism	Modified release under investigation
Alpha-glucosidase inhibitors	Acarbose, Voglibose	—	Minimal systemic (local action)	<2%	—	Intended luminal action; not systemically absorbed	Localized intestinal delivery
GLP-1 Receptor Agonists (oral)	Semaglutide (oral)	—	Gastric mucosa (SNAC-facilitated)	~1%	~7 days	Extreme proteolytic degradation; absorption enhancer required	Absorption enhancer co-formulation (SNAC)

3: GASTROINTESTINAL PHYSIOLOGY AS THE FORMULATION DESIGN LANDSCAPE

The gastrointestinal tract does not present a uniform absorptive surface. The physicochemical environment undergoes striking changes in its length (with its pH, fluid volume, surface area, transit time, enzymatic activity and motility pattern), each of which has a measurable effect on the dissolution, stability and permeability of drugs.[24] In the fasted state, the stomach has a very low pH (1.5-2), which increases to 5.5-6 after food is ingested because of buffering, and then returns to the fasted state within 2-3 hours after feeding.[25] As the food moves from the stomach into the duodenum, the pH of the food bolus rises rapidly to about 6, and further, as pancreatic bicarbonate neutralizes the gastric acid. This pH gradient is not only a chemical background, but it also determines the ionization of weakly acidic and basic drugs which affects the solubility and permeability of the membrane of all orally administered molecules passing through it. BCS Class II antidiabetic drugs with pH-dependent solubility profiles are not physiologic events but rather are critical to the formulation process.[26]

Gastric transit time is also variable and physiologically important. The emptying process in the fasted state is controlled by the migrating motor complex (MMC) and can cause dosage forms to pass from the stomach to the duodenum in less than 5 minutes, depending on the MMC phase at which the dosage form was taken.[27] In the fed state, gastric emptying is significantly delayed, solid dosage forms can take up to 4-6 hours to move to the upper small intestine, and the low amplitude contractions and pyloric resistance are combined to meteredly empty stomach contents into the duodenum.[28]

The gastrointestinal tract may be viewed as a continuous absorptive terrain in which the regional pH, transit time, fluid volume and absorptive surface area collectively define the absorptive window in which a drug can be dissolved and absorbed.[29] This window is narrow for drugs which can only be absorbed effectively in the proximal small intestine as the result of saturable uptake mechanisms and differences in permeability between the intestine and other organs, such as metformin and repaglinide. The window cannot be addressed with formulation strategies that only release the drug into the stomach and rely on passive gastric emptying to ensure delivery to the absorptive window, if it can be depended upon at all or if it can be duplicated for all patients and dosing conditions.[30]

The small intestine, although the largest absorptive area in the GI tract (estimated to be approximately 200 m2 when microvilli are considered), has a relatively predictable transit time of approximately 3 – 4 hours, which is still a very short period of time for drug products that require continuous systemic drug levels during a dosing interval. Outside the small intestine, the amount of time a drug takes to pass through the colon is variable, between 6 and 70 hours, and the absorption in the colon is generally poor for most of the conventional anti-diabetic drugs. This physiological approach is different from an empirical approach to gastroretentive drug delivery, the point being that there is spatial heterogeneity which is why a gastroretentive drug delivery approach is physiologically important.[31] This formulation design landscape is complicated even more in the T2DM patient population because the disease itself has clinically relevant effects on GI physiology. In about 30-50% of patients with long-standing T2DM, gastric emptying is abnormally delayed, due to autonomic neuropathy either to the vagal nerves to the stomach or to the function of the interstitial cells of Cajal (pacemaker cells) that are found in the antral walls and lead to antral deconstructivity. Acute hyperglycaemia, unrelated to neuropathy, also inhibits gastric emptying by slowing antral motility; insulin-induced hypoglycaemia can have the opposite effect, as insulin is a counterregulatory substance.[32] The effects of gastroparesis in T2DM are significant: narrow window of absorbable antidiabetic medications in the gut have delayed and variable absorption, and, in gastroparetic patients, taking sulfonylureas before meals may lead to hypoglycaemia if the food reaches the gut after the drug. Furthermore, the widespread adoption of GLP-1 receptor agonists in the treatment of T2DM brings an added dimension of GI motility modulation GI motility is dose-dependently modulated by these drugs, with the time to maximum plasma concentration of co-administered oral agents being dose-dependent and varying significantly between acute and chronic administration of these drugs.[33]

All of this makes it clear that the GI physiological environment in T2DM is not a fixed backdrop of how things turn out and will be unpredictable for the formulation, it is a variable that is dynamic and has been modified by the disease and should be specifically considered when choosing the platform. However, the formulation scientist working on the formulation of an oral antidiabetic delivery system is not only tasked with considering the physicochemical characteristics of the drug, but the absorptive geometry that T2DM has altered and this is a major reason for the sophistication of the advanced platforms.[34]

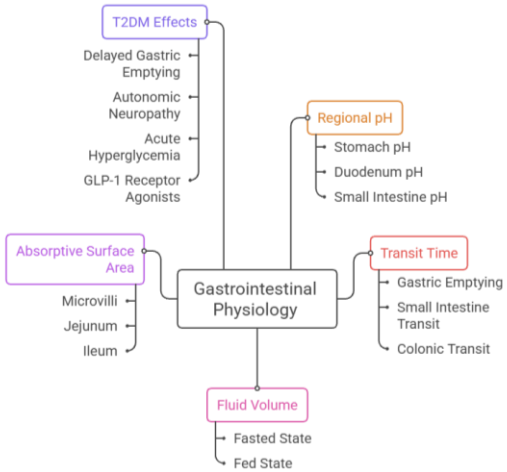

Figure 1: Gastrointestinal Physiology in Oral Antidiabetic Drug Delivery.

4: GASTRORETENTIVE DRUG DELIVERY SYSTEMS: MECHANISTIC DIVERSITY AND FORMULATION ENGINEERING

One of the most thoroughly analysed platforms for oral antidiabetic drug delivery is the gastroretentive drug delivery system (GRDDS) whose absorption must be mechanistically dependent on extended upper GI contact.

The rationale for their therapeutic use is simple: the systems delay the release of the drug from the dosage form from the stomach into the region where the drug is physiologically available for absorption, which provides a plasma therapeutic concentration without inter-dose troughs experienced with short acting conventional dosage forms.[35] The mechanisms of GRDDS include low-density floating systems, swellable/expandable systems, mucoadhesive platforms and hybrid systems that combine two or more mechanisms of retention, each with unique engineering properties depending on the drug and clinical target. The most widely studied class of GRDDS are floating systems which can remain buoyant in the stomach by having a lower bulk density than the stomach fluid (approx. 1.004g/cm^3) and release the drug in a controlled way.[36] There are two types: effervescent and non-effervescent, depending on how buoyancy is achieved.

Effervescent systems contain gas generating agents usually sodium bicarbonate, and citric or tartaric acid (as proton donors) that react with gastric acid in the stomach to release CO_2, which is trapped by a swelling hydrophilic polymer matrix, and so the overall density of the system is lower than the gastric fluid. Hydroxypropyl methylcellulose (HPMC) grades are the most popular hydrophilic polymers in this application; the viscosity grade is related to the rate of gel layer formation and the rate of drug release.[37] HPMC acts as a buoyancy generating swelling matrix and as a diffusion barrier: water absorption by the outer HPMC layer is retained in the form of a gel boundary to slow down the drug diffusion, while the CO_2-entrained inner matrix ensures flotation. An important performance parameter is the floating lag-time which is the time between the dosage form coming into contact with gastric fluid and it achieving sustained buoyancy which is typically less than 60 seconds in effervescent systems with optimized sodium bicarbonate concentration, and can be 8–12 hours, depending on the polymer load and concentration.[38]

The non-effervescent floating systems are based on low density properties of polymers like polyethylene oxide (PEO) and contain the air inside porous or matrix architecture. In non-effervescent gastroretentive tablets, HPMC-PEO combinations have been used with the aim of developing low-density matrix to ensure low-density matrix formation in conjunction with the immediate buoyancy ensured by HPMC in fasted state simulated gastric fluid, which was achieved with a total floating time of more than 24 hours.[39] Cetyl alcohol has also been incorporated in non-effervescent metformin floating system as a low-density hydrophobic component which acts as a structural density modifier and also acts as a water-insoluble matrix forming component to provide sustained drug delivery. Several factors are practically determining the choice between effervescent and non-effervescent systems: drug-acid instability at the gastric pH (which would make gas-generating systems unsuitable); available compression technology and the need for a rapid floating onset in drugs with immediate postprandial dose requirements.[40]

Although most of the evidence base is still preclinical, there is compelling pharmacokinetic justification for using GRDDS for oral anti-diabetic therapy. The preparation of repaglinide in the form of calcium silicate-based gastroretentive floating microspheres with Eudragit S polymer and emulsion solvent diffusion method showed high and prolonged gastric residence time of more than 6 hours in albino rabbits on gamma scintigraphy and showed 3.17-fold higher relative bioavailability than the marketed repaglinide tablet formulation, which was directly attributed to the extended gastric residence time at the upper GI absorption site of the drug.[41] In the same manner, repaglinide microspheres were prepared using emulsion

solvent diffusion technique with the ratio of HPMC:EC as 1:2 and their buoyancy was confirmed by radiological imaging which lasted for more than 6 hours and showed statistically significant decrease in blood glucose level in alloxan induced diabetic rats when compared to plain drug.[42] The entrapment efficiency of the sodium alginate-HPMC floating microspheres of repaglinide optimized by Box Behnken design and the drug release profile were found to be dependent on polymer concentrations and sustained drug release for 12 h, respectively, thus highlighting the potential of the ionic gelation-based matrix design as an alternative route to the emulsion diffusion method. Metformin:HPMC:PEO = 1:4:4 with effervescent agent sodium bicarbonate was found to be an optimized formulation to overcome the limitation of floating lag time < 60 seconds and sustained release > 12 hours in HPMC-PEO combination effervescent floating tablets. Glumetza® (metformin hydrochloride extended-release) is a commercially available version of this platform that uses a non-effervescent gastroretentive technology and has been found to have superior dose-proportionality and a lower gastrointestinal adverse effect profile as compared to the traditional metformin formulations.[43]

In addition to single polymer matrices, there has been a development of bilayer gastroretentive tablets containing both hydrophilic and hydrophobic polymers, which seemed to be a solution to combine immediate buoyancy and long-term controlled release. A well-designed non-effervescent bilayer approach exhibited a floating lag time of just 1.5 seconds and total floating duration > 24 h in fasted state simulated gastric fluid (FSSGF) and sustained plasma concentrations above the minimum effective concentration (MEC) at the 24-hour timepoint in Beagle dogs, representing the clinical translatability of non-effervescent bilayer systems. Published gastroretentive data for the formulation of these comparative products are summarized to illustrate the data for the different antidiabetic products that would be referenced by formulation scientists looking for new platforms in this therapeutic arena.[44,45]

TABLE 2: Comparative Summary of Gastroretentive Drug Delivery Platforms for Oral Antidiabetic Agents: Polymer Systems, Buoyancy Parameters, and In Vivo Pharmacokinetic Outcomes.[46,47]

Drug	Formulation Type	Key Polymers/Materials	Floating Lag Time	Total Floating Duration	Drug Release Duration	In Vivo Model	Key PK/PD Outcome
Repaglinide	Floating microspheres (effervescent)	Calcium silicate (porous carrier), Eudragit S	Not reported	>6 h (scintigraphy confirmed)	>12 h	Albino rabbits	3.17-fold increase in relative bioavailability vs marketed tablet
Repaglinide	Floating microspheres (solvent diffusion)	Ethylcellulose: HPMC (1:2, 5 cps)	<60 s	>6 h (X-ray confirmed)	>12 h (zero-order)	Alloxan-diabetic rats	Significant blood glucose reduction ($p<0.01$) vs. pure drug
Repaglinide	Floating microspheres (ionic gelation)	Sodium alginate, HPMC, $CaCl_2$ (crosslinker)	Not reported	>12 h	12 h	In vitro only	Optimized by Box-Behnken; entrapment efficiency dependent on polymer concentration
Metformin HCl	Effervescent floating matrix tablet	HPMC K15M:PEO (1:4), $NaHCO_3$, SSG	<60 s	12 h	12 h	In vitro	Optimized by Box-Behnken; biopharmaceutically superior release profile
Metformin HCl	Non-effervescent floating tablet	Cetyl alcohol, HPMC K15M	~1.5 s	>24 h	24 h	In vitro	Direct compression; similarity factor ≥ 69 to reference XR product
Bilayer investigational drug	Bilayer gastroretentive tablet	PEO, Kollidon® SR (hydrophobic)	1.5 s	>24 h	24 h	Beagle dogs	Plasma conc. > MEC at 24 h; confirms clinical gastroretentive utility
Gliclazide	Floating microspheres	HPMC K100, EC	<2 min	8–12 h	8–10 h	Wistar rats	3.35-fold higher Cmax; 1.9-fold higher AUC vs plain drug

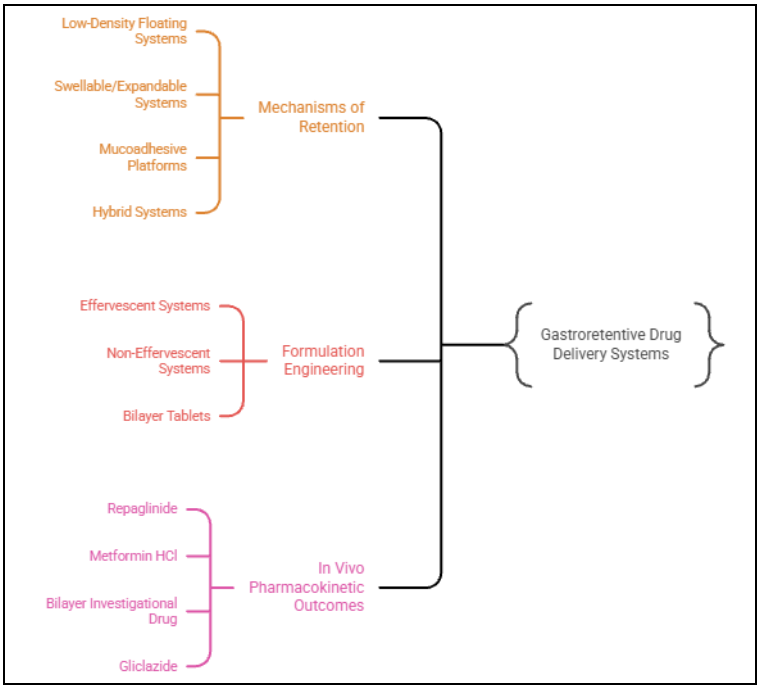

Figure 2: Gastroretentive Drug Delivery Systems: Mechanisms and Formulations.

5: NANOCARRIER-BASED PLATFORMS FOR ENHANCING ORAL ANTIDIABETIC BIOAVAILABILITY

A complementary, but parallel engineering challenge for drugs for which the bioavailability problem is not that of access to the site of absorption, but due to the fundamental physicochemical barriers to dissolution and membrane permeation, is that of residence time.

Nanocarrier-based delivery platforms provide mechanistically different and clinically relevant solutions for BCS Class II antidiabetic drugs (aqueous solubility is rate limiting) and for agents that are highly metabolized in the first-pass or highly transported by efflux transporters.[48] The variety of nanocarrier architecture available today is a reflection of the diversity in absorption barriers these are able to overcome, which includes polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanoemulsions and self-emulsifying drug delivery systems (SEDDS) and cyclodextrin inclusion complexes.[49]

The most well characterized nanocarrier platform for poorly soluble antidiabetic drugs are polymeric nanoparticles, specifically produced using the poly(lactic-co-glycolic acid) (PLGA) polymer. It is FDA approved, biodegradable, and biocompatible, and the molecular weight and lactide-to-glycolide ratio can be precisely controlled for the desired drug release profile (fast burst to sustained release over 24 hours or longer).

In vitro dissolution studies revealed the second-generation nanocrystals of gliclazide (Glicclazide-2nd-Gen Nanocrystals) prepared with the combination of emulsion diffusion and high-pressure homogenization technique with the optimization criteria- Taguchi design-using Poloxamer-188 as a stabilizer exhibited superior dissolution profiles in comparison with conventional gliclazide formulations. In diabetic rats induced with streptozotocin, the second-generation nanocrystals of gliclazide exhibited significantly better antidiabetic effect than gliclazide conventional formulations. PLGA-based systems have also been investigated for delivery of metformin and GLP-1 analogs; in this case, the sustained release of the encapsulated drug is intended to reduce the exposure of the drug to the enzymes of the gastrointestinal tract and to provide an appropriate exposure to the plasma that is consistent with the pharmacodynamics of each drug.[50]

Solid lipid nanoparticles take advantage of the solid-state lipid matrix to allow for high drug encapsulation efficiency, protect from chemical degradation, and increase the drug absorption through both transcellular and lymphatic pathway, which is especially important for lipophilic BCS Class II molecules. Optimized by a 3^2 factorial design, GLG-SLNs fabricated by high-speed homogenization technique has mean diameter of ~125 nm, entrapment efficiency of 88.93% and drug release for 24 h. The in vivo study in alloxan diabetic rats revealed significant improvement in its antidiabetic activity in comparison to the plain drug and marketed formulation. This increase in therapeutic efficiency was linked to the long-lasting drug release, to increased lymphatic uptake via Peyer's patches and to the anti-absorption effect of the lipid matrix on intestinal efflux transporters which would otherwise limit glibenclamide absorption.

Both nanoemulsions and SEDDS give an almost unique benefit for BCS Class II antidiabetics in question:

extremely small oil-in-water droplets (typically 20-200 nm) are formed upon aqueous dilution which gives rise to an enormously large surface area for dissolution of the drug, while the lipid environment in the emulsion is maintained at the absorptive site where the drug remains soluble, and is also presented to the absorptive membrane in an optimally permeable form. The mean droplet size of the chitosan-coated nanoemulsions (internal phase: olive oil, emulsifiers: Span 80, Tween 80 and Poloxamer 188) were 86.5 nm for uncoated and 149.3 nm for chitosan-coated formulations, respectively, with entrapment efficiency > 96%. In vivo study in rats showed that the repaglinide nanoemulsion exhibited 3.51 fold and 1.78 fold higher $AUC_{0–12}h$ and Cmax, respectively, than the free drug, whereas coating of the nanoemulsions with chitosan also resulted in a higher elimination half-life and overall bioavailability due to mucoadhesive interaction with the intestinal epithelium.

The individual delivery of nanotransporters of metformin and repaglinide, which were developed for combination therapy for T2DM, resulted in droplet sizes of 110–120 nm and showed statistically significant reductions in blood glucose levels in diabetic rats induced by streptozotocin and nicotinamide, with improvements in oxidative stress markers and histopathological profiles, indicating that the nanotransporter co-delivery of mechanistically complementary agents may provide additive glycaemic benefit beyond individual drug bioavailability improvement.[51]

The BCS Class II solubility limitation is overcome by the cyclodextrin inclusion complexation which involves the encapsulating of the hydrophobic drug molecule in the hydrophobic cavity of cyclodextrin ring in its aqueous soluble complex form without undergoing the modification of the drug molecule itself. The repaglinide–hydroxypropyl-β-cyclodextrin (HP-β-CD) inclusion complex, which was confirmed by DSC, XRD and ^{1}H-NMR spectroscopy (1:15 molar ratio) prepared by lyophilization technique, exhibited a 2.5-fold increase in Cmax and a 2-fold increase in $AUC_{0–t}$ compared to the physical mixture in beagle dogs (a clinically relevant species for pharmacokinetic correlation).

Based on the structural analysis, it was concluded that the A-ring of the drug fits better in the narrow rim of the CD cavity and thus disturbs the crystalline lattice of the drug and causes a transition from the crystalline to the amorphous state, which results in an apparent increase in the aqueous solubility of the drug.[52]

The choice of nanocarrier platform for the application of antidiabetic is not random but is dictated by a set of biopharmaceutical parameters. For drugs of BCS class II are those with low solubility and high permeability and require dissolution to enhance the apparent solubility; nanosuspensions, PLGA nanoparticles, SLNs and cyclodextrin complexes are the most promising products.

Drugs that are poorly soluble and poorly permeable (BCS Class IV) can be most effectively used on platforms that enhance the absorption of the drug, such as platforms that contain absorption-enhancing excipients, which are best suited for drugs that are prone to first-pass metabolism, including those that can be absorbed via the lymphatics, such as those best accommodated by nanocarriers, with the lipid-based systems (SLNs, NLCs, and nanoemulsions) most mechanistically appropriate. If the hierarchy is understood, it ensures that the design effort of any nanocarrier is focussed on the most important pharmacokinetic barrier and not targeted in a random manner to all poorly bioavailable drugs.[53]

6: MUCOADHESIVE AND STIMULI-RESPONSIVE SYSTEMS: TAILORING RESIDENCE AND RELEASE TO GLYCEMIC FLUCTUATIONS

Bioadhesive drug delivery takes advantage of the bio-adhesive effect of the polymers of the dosage form and the mucin glycoprotein film that covers the gastrointestinal tract, thereby increasing the contact time between the absorptive epithelium and the dosage form and hence the window of effective absorption above that allowed by passive transit kinetics. The most used polymers include both natural and synthetic polymers.

The interaction between the negatively charged sialic acid and sulfonic acid substructures of mucus glycoproteins and the positively charged chitosan is a result of electrostatic forces, with the latter being especially effective in the acidic gastric environment where it becomes protonated and positive. Carbopol (polyacrylic acid) and its crosslinked forms interact with mucin through hydrogen bonding and physical chain entanglement, and the high molecular weight of the networks creates strong binding forces to the mucus because of a long contact period. Pectin and sodium alginate provide gel-forming properties that form a viscous boundary layer which prevents washout by gastric fluid, and thus further extends retention.[54]

The potential for mucoadhesive systems for oral antidiabetic drugs is significantly improved by the development of polymers beyond the first generation of bioadhesive polymers to thiomers, which are polymers containing covalently attached thiol groups capable of binding to the cysteine-rich subdomains of the glycoprotein in mucus. The covalent mucoadhesion mechanism results in adhesion significantly greater and longer than non-covalent interactions of unmodified polymers. Thiolated chitosan, which is chitosan modified by the attachment of thiolating agents (e.g., thioglycolic acid, 6-mercaptonicotinic acid, 2-imminothiolane HCl) to the primary amine groups of chitosan, has been shown to display a mucoadhesion greater than threefold more potent than that of unmodified chitosan in the porcine intestinal adhesion model.[55] Thiomers have also been shown to be permeation enhancers by transiently

disrupting tight junctions in the intestinal epithelium, and efflux pump inhibitors that inhibit the expulsion of drugs from enterocytes by P-glycoprotein thus, they not only enhance permeation but also increase the residence time in the intestine. Mechanistically relevant in the field of oral antidiabetic drug delivery, drugs like repaglinide, which are substrates for the efflux transporters, can benefit from thiolated chitosan coatings which can help to keep the dosage form at the surface of the absorptive surface and reduce the activity of efflux transporters at the surface of the mucosal membrane, while poorly permeable drugs such as metformin can benefit from coating with thiolated chitosan which will keep the dosage form at the absorptive surface. One of the most important practical limitations is the pH-dependent reactivity of the thiolate anion; the reactive form is characterized by a pKa of 8–10, and thus, the thiomers are more reactive at a higher pH and less reactive at a lower pH, which is important for designing them to be either gastric or small intestinal.[56]

The most physiologically complete system for the retention in the upper GI is the combined floating-mucoadhesive system that combines buoyancy with bioadhesion in one dosage form. For such hybrid systems, chitosan is the polymer of choice because its floating and mucoadhesive properties are activated simultaneously, which results in a reduction of the formulation density caused by the hydration and expansion of the gel layer and an increased adhesive anchorage to the gastric mucosa. The combination is particularly beneficial because it overcomes the basic drawback of floating-only systems, which is that the peristaltic force of housekeeper waves on interdigestive phase can break free even from a floating dosage form, whereas this is prevented by the tissue-anchoring mechanism. The comparative data obtained from practical application of the mucoadhesive and stimuli-responsive systems for T2DM agents are summarized in Table 3.[57]

The frontier of stimuli-responsive delivery for T2DM marks a paradigm shift from all sustained-release passive delivery platforms: the systems deliver the drug at a time-programmed rate, which is dependent on the glycemic state of the patient, rather than the drug being delivered in a time-programmed manner independent of the glycemic state of the patient. PBA chemistry is the most scientifically advanced glucose-sensing mechanism used in this context. As glucose concentration increases, PBA and its derivatives reversibly form boronate esters with cis-diol compounds, such as glucose, leading to a shift in the equilibrium and triggering structural changes that disrupt nanoparticle assemblies and release of encapsulated drug. Hyperglycemic concentrations (>200 mg/dL) cause the glucose to bind to the PBA-functionalized nanoparticles, which causes swelling or dissociation of the polymer matrix that results in accelerated insulin release; as glucose levels return to the normoglycemic range, the PBA becomes closed in the trigonal ester conformation and insulin release slows, thereby automatically providing a feedback loop that models the responses of the pancreatic islets, without the need for electronic glucose monitoring.[58] The dual-sensitive nanoparticle system comprised poly(2-hydroxyethyl methacrylate) and poly(carboxybetaine) with glucose oxidase (GOx) and insulin co-encapsulated, which showed glucose-responsive oral insulin release in vivo, with the co-encapsulated GOx oxidizing glucose to gluconic acid and H_2O_2, which together caused the disassembly of the nanoparticles and insulin release at the site of insulin absorption in the intestine. The use of modified PBA with electron donating groups or with amino groups in close proximity to the boronic acid functionality, which lowers the effective pKa to allow for formation of boronic esters in the physiological pH range 6.5–7.4, is an ongoing area of synthetic chemistry optimization to make these more sensitive to glucose.[59]

TABLE 3: Mucoadhesive and Stimuli-Responsive Systems for Oral Antidiabetic Drug Delivery: Materials, Triggering Mechanisms, and Key Outcomes.[60,61]

System Type	Drug/Agent	Key Material/Trigger	Mechanism	Model	Key PK/PD Outcome	Translational Status
Mucoadhesive (chitosan)	Repaglinide	Chitosan-coated nanoemulsion	Electrostatic mucoadhesion; mucus residence prolongation	In vivo (rats)	Extended t½; higher $AUC_{0-\infty}$ vs uncoated NEs	Preclinical
Thiomer (thiolated chitosan)	Insulin (model peptide)	Chitosan-thioglycolic acid	Disulfide bond to mucin; tight junction opening; efflux inhibition	In vitro/porcine intestine	>3-fold increase in mucoadhesion vs unmodified chitosan	Preclinical/ex vivo
Floating-mucoadhesive combined	Metformin, repaglinide	Chitosan + HPMC (buoyancy + adhesion)	Hybrid buoyancy-adhesion retention	In vitro	Extended drug release; floating >8 h; mucin adhesion confirmed	Preclinical

pH-sensitive	Insulin	Eudragit L100-55 enteric coating	pH-triggered dissolution at intestinal pH >5.5	In vivo (diabetic rats)	Blood glucose reduction; improved AUC vs oral suspension	Preclinical
Glucose-responsive (PBA)	Insulin	PBA-functionalized polymer nanoparticles	Boronate ester formation with glucose; glucose-concentration-dependent swelling/release	In vivo (diabetic mice)	Autonomous blood glucose regulation; response proportional to glucose level	Preclinical
Dual-responsive (pH/H_2O_2)	Insulin	PBE-PHEMA-PCB nanoparticles + GOx	GOx oxidizes glucose to H_2O_2 and gluconic acid; dual trigger releases insulin at intestinal site	In vivo (2024, diabetic mice)	Glucose-responsive insulin release; blood glucose control with reduced hypoglycemia risk	Preclinical (2024)

7: QUALITY BY DESIGN AND COMPUTATIONAL APPROACHES IN ORAL ANTIDIABETIC FORMULATION DEVELOPMENT

The paradigm of evolution of oral antidiabetic drug delivery from trial and error to systematic approach based on scientific principles is represented by Quality by Design (QbD) formalized in regulatory guidelines published by ICH (Q8, Q9, Q10 and Q11). In essence, QbD is about having a proactive approach to product development and building quality into the product by understanding how critical material attributes (CMAs) and critical process parameters (CPPs) interact to create critical quality attributes (CQAs). This framework is the only rigorously defensible and regulatorily acceptable design path for oral antidiabetic formulations, especially those that involve floating lag time and/or nanocarrier-based formulations, where several formulation parameters are simultaneously affecting the floating lag time, drug release rate, particle size, encapsulation efficiency, and in vivo absorption.

The most important experimental tool of QbD, Design of Experiments (DoE), allows the evaluation of several factors and factor interactions simultaneously using a statistically efficient experimental plan which would be too costly to investigate one factor at a time. In the field of advanced oral antidiabetic product formulation, the Box-Behnken Design (BBD) and Central Composite Design (CCD) are the most popular response surface methodology (RSM) designs. An optimized formulation was obtained in the Box-Behnken design, with only 17 experimental runs for three factors (A, B, and C), while a full 3^3 factorial design requires 27 runs and was found to be quantitatively unreliable, with an accuracy of validation <97% for the three responses (R1, R2, and R3). Floating lag time and 12-hour drug release profile for metformin effervescent floating tablets were modeled by Box–Behnken design, with HPMC:PEO ratio, sodium bicarbonate content and sodium starch glycolate as independent variables, and the factors' influence and quadratic interactions on these responses were statistically evaluated. These outputs directly defined the range of operation and boundaries of the design space.

In order to translate this formulation-level QbD evidence to clinical relevance, it is necessary to develop an in vitro to in vivo correlation (IVIVC) as per the ICH framework which establishes the correlation between the dissolution of the drug product and the clinical pharmacokinetic behavior. If a gastroretentive metformin system is demonstrated to retain for 5 or more hours in the gastric environment of human volunteers by gamma scintigraphy, then the establishment of Level A IVIVC where a fraction of the formulation absorbed in vivo is directly proportional to the fraction dissolved in vitro provides regulatory backing for good in vitro dissolution conditions and the ability to defend the approved design space without additional clinical studies for post-approval formulation changes. The significance of IVIVC is especially important for gastroretentive antidiabetic dosage forms as the biorelevant dissolution medium should simulate the fed-state gastric environment (pH, buffer capacity, and surfactant concentration) to avoid getting overly positive results in vitro that are not predictive of the in vivo performance.[62]

Experimental IVIVC development is complemented by physiologically based pharmacokinetic (PBPK) modelling.

PBPK models can be used to simulate plasma concentration-time profiles from in vitro dissolution data through the use of software platforms such as GastroPlus™ and Simcyp®, with the inclusion of regional GI physiology (pH gradients, transit times, fluid volumes, membrane permeability) and drug specific ADME parameters, under both fasted and fed state

conditions. For antidiabetic drugs with known absorption windows and saturable transport mechanisms, such as metformin, this approach is especially useful, as the PBPK model can predict the impact of changes in the release rate of the drug on the AUC and postprandial glucose suppression without the need for additional clinical studies. The application of artificial neural networks (ANNs) to a RSM-based DoE for formulation optimization in the case of rivaroxaban extended-release osmotic tablets, ANN-based formulations were validated with CCD-based, optimized formulations, and PBPK modeling of the optimized formulations demonstrated improved fasting state bioavailability represents a trend that is emerging, and one that is likely to continue to shape next-generation oral antidiabetic formulation development: the convergence of machine learning and physiologically based simulation.[63]

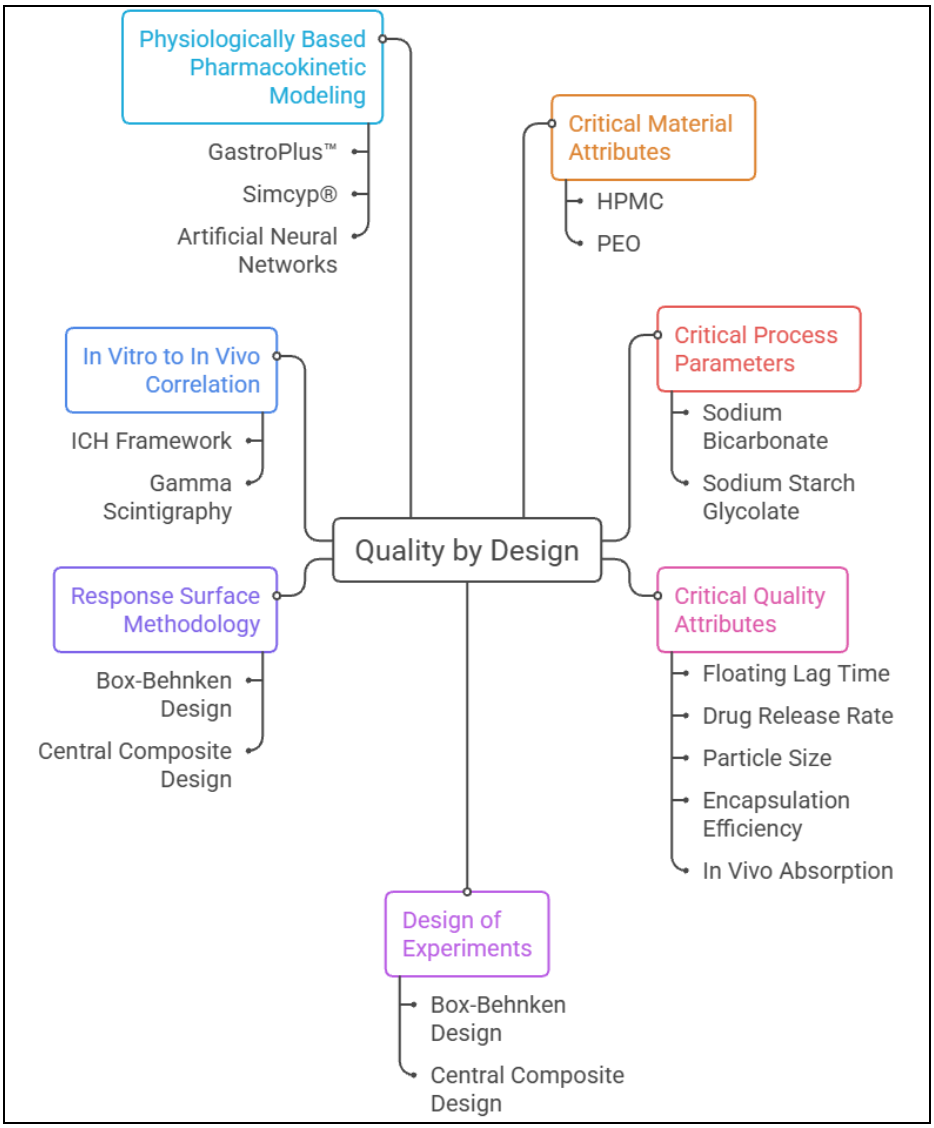

Figure 3: Quality by Design in Oral Antidiabetic Formulation Development.

8: LIMITATIONS, TRANSLATIONAL BARRIERS, AND REGULATORY CONSIDERATIONS

The paradox of the exciting preclinical promise of progressive oral antidiabetic delivery systems and their lack of clinical availability is a suite of closely linked translational hurdles that warrant candid discussion. One of the basic problems in gastroretentive systems is the very high physiological variance of gastric residence time between and within subjects. The performance landscape is characterized by variation in gastric emptying, which is regulated by such factors as meal composition, posture, disease state, co-administered drugs and the presence of the interdigestive migrating motor complex at the time of administration, and this may result in the removal of the buoyant system from the stomach prior to the release of the desired drug dose.[64]

T2DM patients are a very variable population on this score: gastroparesis occurs in 30–50% of longstanding patients, but the type of gastric motility disorder is not uniform in some it is fast, in others it is slow and the nature of the gastric motility abnormalities are not necessarily predictable just from the level of glycemic control. Clinically optimized floating systems can

therefore behave very differently in the clinical patient population they aim to treat, which is not well managed in most preclinical programs. Moreover, in vitro dissolution testing of gastroretentive formulations is not standardized and the dynamic in vivo conditions (fluids in the stomach, mechanical agitation, and surfactant composition) are not fully simulated in standard compendial media (hydrochloric acid pH 1.2) and therefore the drug release data may overestimate the in vivo performance.[65]

The challenge of translation for nanocarrier-based systems is multidimensional and perhaps more deeply rooted. When scaling-up from laboratory batch production to a pharmaceutical manufacturing scale, there are risks that the particle size distribution, zeta potential, and drug encapsulation efficiency would differ from batch to batch all of which affect the pharmacokinetic behavior of the product, and are extremely sensitive to a range of process variables. The protein corona problem, the spontaneous adsorption of plasma proteins on the surface of nanoparticles in contact with biological fluids, which changes the surface properties of the nanoparticles, disrupts the function of the targeting ligands and modifies the cellular uptake pathways, is one of the factors responsible for the discrepancy between nanoparticle performance in vitro and in vivo. However, the IVIVC of nanoformulations is still a challenging research goal, and existing IVIVC models are mostly not suitable to capture the in vivo complexity of nanomaterial pharmacokinetics, such as particle disaggregation, protein corona dynamics and interactions with the mucus layer, which cannot be replicated in dissolution bath experiments.[66]

These delivery systems are not fully understood and have not been fully accommodated by regulatory structures.

Guidance by FDA on modified-release oral dosage forms and nanomedicine is evolving but lacks nanoparticle-specific IVIVC requirements and there is no FDA guidance on a uniform bioequivalence requirement for nanoformulations.

Development of novel excipients in advanced antidiabetic formulations, such as second-generation thiomers, PBA-functionalized polymers and stimulus-responsive copolymers, is a lengthy process for first in-human approval, as these excipients do not currently have a safety database for use in pharmaceutical formulations, so require specific toxicology studies that extend the development timelines and cost. Co-administering co-formulations with T2DM therapies that act on the GLP-1 receptor, which is now commonly prescribed to treat T2DM, adds another level of complexity: This receptor is associated with a dose-dependent and drug-specific slowing of gastric emptying, which may either enhance or impair the performance of gastroretentive co-formulations an effect that has yet to be evaluated with any marketed gastroretentive antidiabetic drug. The potential solution to these translational challenges do not only include formulation innovation, but the creation of increasingly physiologically realistic in vitro models, consensus IVIVC frameworks that can be applied to more complex dosage forms, and early-stage regulatory interaction where biopharmaceutic risk assessment is part of the development program, instead of being a late documentation exercise.[67]

9. CONCLUSION

The pharmacokinetic characteristics that limit the use of oral antidiabetic drugs are not a consequence of individual drug structures, but rather of the fact that the drugs in this class have been developed based on the specificity of the receptor to which they bind and the efficacy in achieving glycemic levels in a clinical patient cohort without sufficiently considering the biopharmaceutical characteristics that determine whether the drug is actually delivered to the patient. The knowledge gathered from the gathered evidence from gastroretentive systems, nanocarrier platforms, mucoadhesive architectures and stimuli-responsive technologies is clear that there is no one single platform that solves the pharmacokinetic heterogeneity of this class of drugs. The question is not which one is better, it is which one is the rate limiting step for a particular drug, as this will determine the delivery strategy in a mechanistic sense. This concept has been proven time and time again in published pharmacokinetic studies: gastroretentive platforms achieve extended bioavailability for drugs with upper GI absorption windows, nanocarriers overcome dissolution bottlenecks for BCS Class II agents, and thiomers have the added benefit of increasing the residence time, while also lowering the efflux of permeability-limited drugs. But the record of translation is scanty. The majority of the pharmacokinetic evidence is generated in the standardized rodent model, which may not reflect the unique gastroparesis risk profile, GLP-1 co-medication, and postprandial GI fluid dynamics of a T2DM patient population that will determine performance on the clinical population.

The biggest need in the field is not just continuation of in vitro drug release and/or Cmax improvement in healthy rats, but the development of biorelevant dissolution models that better simulate the fed-state diabetic stomach, the construction of PBPK frameworks that can incorporate disease-modified GI physiology, and clinical pharmacokinetic studies evaluating advanced antidiabetic formulations in patients with documented gastroparesis or with concurrent GLP-1 agonist therapy.

The development of 3D printed gastroretentive dosage forms with individualized release geometry, and the use of artificial neural network in the formulation optimization as part of QbD, makes personalized pharmacokinetic engineering of the geometry, polymer identity and release rate of the dosage form to the

absorptive profile of the patient technically possible. “To unleash that potential, the gap between formulation design science and clinical pharmacology needs to be closed a convergence that will be the final key to translating the promise of a therapeutic advance in oral antidiabetic delivery to sustained glycemic results.

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