Natural Pore Formers in a Glipizide Osmotic Pump: A QbD Review

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***Abstract*—Glipizide is a widely used second-generation sulfonylurea with a short half-life and poor water solubility, which makes it a sensible candidate for once-daily osmotic delivery. This review asks whether a controlled-porosity osmotic pump (CPOP) tablet of glipizide, built with a natural pore-forming system and developed by Quality by Design (QbD), is a reasonable idea to test. We read the abstracts of 35 papers on glipizide and on osmotic pumps. Glipizide has been released at near zero-order rates from elementary osmotic pumps, and two CPOP studies of glipizide used polyvinylpyrrolidone (PVP) or sorbitol as pore formers. Other osmotic tablets have been optimised with factorial, central composite and Box-Behnken designs, usually with release independent of pH and agitation. Natural materials appear in osmotic systems only as swelling or push agents. We found no study of a glipizide CPOP with a natural pore former, so the proposed system is an idea to be tested and not an established result. We outline a conceptual QbD pathway, candidate factors and in-vitro tests. The review is based on published abstracts and reports no experimental data.**

***Index Terms*—Glipizide; controlled-porosity osmotic pump; natural pore former; Quality by Design; zero-order release; Box-Behnken design**

I. INTRODUCTION

Glipizide is a second-generation sulfonylurea used in type 2 diabetes [1,2]. Its biological half-life is short, at 2 to 4 h [3], and it is poorly water-soluble [4]. Both facts favour an extended-release tablet that gives a steady supply of drug through the day. Osmotic pump tablets release drug by osmotic pressure, and the release is largely independent of gastric fluids [5].

A classical osmotic tablet needs a laser-drilled orifice. A controlled-porosity osmotic pump (CPOP) avoids this, because water-soluble additives in the membrane dissolve on contact with water and leave a microporous membrane in situ [6]. In the two CPOP studies of glipizide that we found, the pore-forming additives were PVP and sorbitol [7,8]. Whether a natural water-soluble material could take that role is an open question.

This review therefore examines a proposed glipizide CPOP tablet with a natural pore-forming system, developed by QbD, for zero-order release. We searched online sources and read the abstracts of the papers cited. The paper is a literature review. It reports no experimental data, and the design it describes is conceptual. Where the literature is silent, we say so.

II. GLIPIZIDE AND THE CASE FOR CONTROLLED RELEASE

Glipizide was introduced as a second-generation sulfonylurea whose chemical substitutions raised its hypoglycaemic activity about 100-fold by weight over first-generation agents [1]. Sulfonylureas stimulate pancreatic insulin release and also act outside the pancreas, for example by lowering glucagon secretion and improving peripheral insulin sensitivity. Hypoglycaemia, weight gain and cardiovascular risk are the main concerns, though the authors of one review state that safety can be maintained with reasonable use [2]. In older people, the adjusted relative risk of serious hypoglycaemia was 1.9 for glyburide against glipizide in a Medicaid cohort [9]. Metabolism by CYP2C9 matters too: carriers of the *3

and *13 alleles had 44.8% and 58.2% higher AUC after a single 5 mg dose, although glucose and insulin responses did not differ between genotype groups [10].

The case for a controlled-release product rests on pharmacokinetics and on adherence. In a claims analysis of newly treated patients, users of immediate-release glipizide and of glibenclamide were less adherent than users of the gastrointestinal therapeutic system (GITS) tablet, and the authors suggested that dosing frequency may explain this [11]. Two randomised, placebo-controlled trials of glipizide GITS tested several doses and found improved glycaemic control with few withdrawals for hypoglycaemia [12]. These data support the clinical value of a steady-release product, but they concern the marketed GITS and not a CPOP.

Formulation is harder than the pharmacology suggests. Glipizide belongs to BCS class II, and a co-amorphous blend with arginine raised its solubility from 300.89 to 3876.8 µg/mL [4]. Particle size also matters. In dissolution tests and in dogs, a glipizide product made from larger drug particles dissolved more slowly than the reference and was not bioequivalent, whereas smaller particles matched it [13]. Matrix tablets have been tried as an alternative to osmotic systems, with HPMC the better release retardant in one study [3]. Table 1 collects these findings.

Table 1. Evidence on glipizide, as reported in the abstracts reviewed.

Topic	Finding as reported	Ref.
Pharmacology	Second-generation sulfonylurea; about 100-fold more active by weight than first-generation agents	[1]
Metabolism	CYP2C9*3 and *13 carriers had AUC 44.8% and 58.2% higher after 5 mg; glucose and insulin responses similar	[10]
Hypoglycaemia	Adjusted relative risk 1.9 for glyburide against glipizide in people aged 65 or over	[9]
Adherence	Immediate-release glipizide and glibenclamide users less adherent than GITS users	[11]
Solubility	BCS class II; 1:2 arginine co-amorphous blend gave 3876.8 against 300.89 µg/mL for pure drug	[4]
Particle size	Larger drug particles dissolved slower and were not bioequivalent; 2-5 µm suggested as an inert size range	[13]
Half-life	Short biological half-life of 2-4 h	[3]

III. OSMOTIC PUMP SYSTEMS

Osmotic pumps are regarded as among the most reliable controlled-release systems, because they release the active agent by osmotic pressure [5]. Reviews describe a zero-order rate that does not depend on the starting drug concentration or on gastrointestinal conditions, and they suggest the systems suit drugs with limited solubility or permeability [14]. The typical device has a core of drug and osmogens inside a semipermeable membrane. Water enters the core, and the resulting pressure pushes drug solution out through delivery ports [15]. The principle was worked out first for implantable pumps, which delivered at a constant rate once water activated them [16].

The nifedipine GITS shows what a well-built oral osmotic tablet can do. Its release rates were 1.7, 3.4 and 5.1 mg/h for the 30, 60 and 90 mg strengths, release did not change between pH 1.2 and 7.5, and in humans the amount absorbed over 24 h was proportional to the amount released in vitro [17]. Core variables matter in such push-pull tablets: the viscosity grade of polyethylene oxide and the amount and location of the osmogen affected performance, while changes in granulating liquid or drying method did not alter release at the scale tested [18].

Glipizide has been formulated in elementary osmotic pumps. A combined metformin and glipizide pump used sodium carbonate to adjust glipizide solubility in the core and released both drugs at near zero-order rates for up to 10 h at pH 6.8, whatever the medium [19]. In a comparison with bilayer hydrophilic matrix tablets, the osmotic pump was insensitive to pH and hydrodynamics, whereas glipizide release from the matrix depended on stirring rate. Only the pump gave

linear in-vitro to in-vivo correlations for both drugs in dogs [20]. Figure 1 shows how a controlled-porosity version of such a pump works.

IV. CONTROLLED-POROSITY MEMBRANES AND PORE FORMERS

In a CPOP the membrane carries water-soluble additives, and release is governed by drug solubility, the osmotic pressure of the core, and the membrane, with release generally following zero order and not depending on pH [6]. Several drugs show how the pore former and the membrane are tuned. For diltiazem, a sorbitol level of 25% w/w with 6% weight gain gave release over 12 h independent of pH and agitation [21]. For gliclazide, a hot-melt-extruded solid dispersion was built into a CPOP designed for 16 h, and release was independent of pH and agitation but dependent on the osmotic pressure of the medium [22]. A lamotrigine tablet used an Acryl-EZE and HPMC E5 coating and avoided laser drilling [23], and a nifedipine tablet used an asymmetric cellulose acetate membrane with the same advantage [24]. For tapentadol, release rose with NaCl and PEG 400 and fell with more coats of Eudragit-based membrane [25]. Table 2 lists these examples and the glipizide studies discussed below.

Membrane ageing is a practical risk. In isosorbide mononitrate tablets, release through membranes with PEG 4000 fell on storage, while a membrane with PVP K30 changed little [26]. The choice of pore former therefore affects stability as well as release, and a new pore former will need its own storage data.

Table 2. Osmotic tablets with pore formers, and natural materials in osmotic systems, from the abstracts reviewed.

Drug	Pore former or natural material	Main finding	Ref.
Glipizide	Sorbitol (pore former), wicking and solubilising agents in core	Release rose with pore former, fell with weight gain; independent of pH and agitation	[7]
Glipizide	PVP and sorbitol (pore formers)	Pores seen on SEM; stable 3 months; zero order in vitro	[8]
Glipizide	Sterculia seed matrix as propellant	Typical osmotic-pump release; matrix tablet area 20.1 times the start after 600 s of swelling	[27]
Diltiazem HCl	Sorbitol	25% w/w sorbitol with 6% weight gain gave 12 h release	[21]
Gliclazide	Pore former type and amount optimised	Zero order up to 16 h; depends on osmotic pressure	[22]
Tapentadol	NaCl and PEG 400	Release rose with both and fell with more coats	[25]
Metoprolol succinate	Water-soluble pore former instead of laser drilling; level optimised by Box-Behnken design	Zero order for up to 20 h; later Tmax and lower Cmax than marketed tablet in dogs	[28]
Lamotrigine	Acryl-EZE and HPMC E5 coating blend	No laser drilling; optimum showed zero-order release	[23]
Nifedipine	Asymmetric cellulose acetate membrane (dry phase inversion)	No drilled orifice; release independent of agitation and pH	[24]
Isosorbide mononitrate	PEG 4000 or PVP K30	PEG 4000 membranes slowed on storage; PVP K30 changed little	[26]
Felodipine	Chitosan and poly (acrylic acid) complex (push layer)	Zero order for 12 or 24 h; two-step release	[29]

For glipizide itself, the studies are few. One used a wicking agent and a solubilising agent in the core, and release rose with sorbitol and fell with greater membrane weight gain [7]. Another made PVP solid dispersions by physical mixing and spray drying, found release dependent on solubility-modifier level in the core, and reported SEM-confirmed pores and stability over 3 months of accelerated testing [8]. A third loaded a poloxamer 188 solid dispersion into an osmotic tablet and reported zero-order release comparable to the marketed push-pull tablet [30].

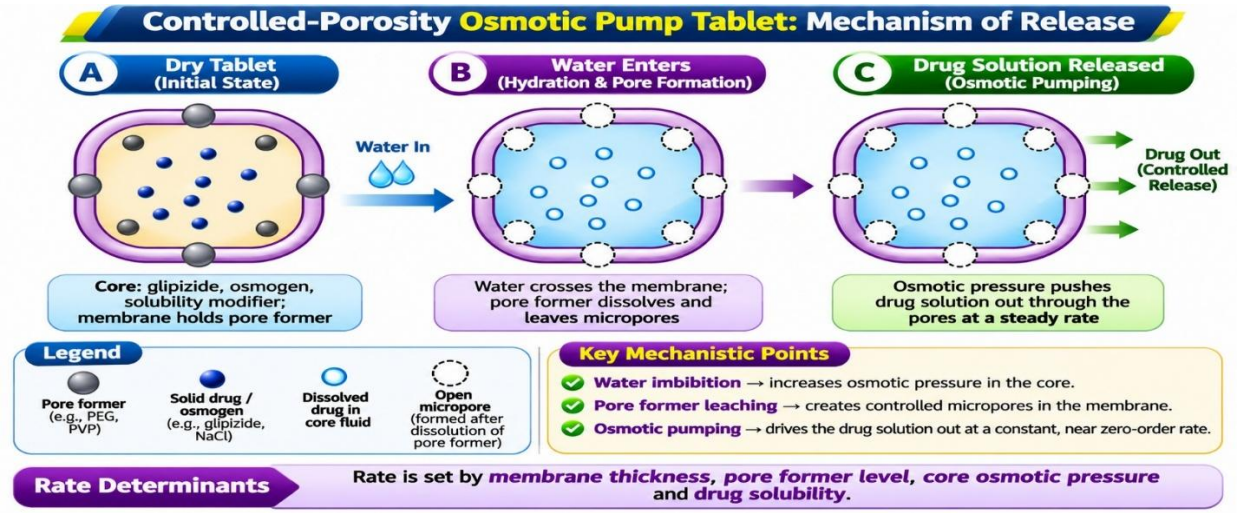


Figure 1. Mechanism of a controlled-porosity osmotic pump tablet. Water-soluble pore former in the membrane dissolves, leaving micropores through which osmotic pressure drives drug solution out. The scheme is conceptual and contains no measured values.

Natural materials have entered osmotic tablets, but not as pore formers. A chitosan and poly (acrylic acid) complex served as the push layer of felodipine tablets, with zero-order release for up to 12 or 24 h depending on plasticiser [29]. A natural swelling matrix from a sterculia seed acted as osmotically active agent and propellant in glipizide bilayer tablets, which showed typical osmotic-pump release [27].

V. ZERO-ORDER RELEASE: WHAT THE EVIDENCE SHOWS

Zero-order release means a constant amount of drug leaves per unit time. For osmotic systems it is expected while the core stays saturated and the membrane properties stay constant. Several glipizide studies report this behaviour. The metformin and glipizide pump released both drugs at near zero-order rates for up to 10 h [19]. In the poloxamer solid dispersion tablet, release rose with the hydrophilic polymer and fell with osmogen level, in line with an osmotic mechanism, and the profile was comparable to a marketed push-pull product [30]. The glipizide CPOP studies report zero-order release in vitro, but their abstracts give no numerical fit [7,8].

A good fit alone does not prove an osmotic mechanism. A hydrophilic matrix of glipizide fitted zero order with r^2 of 0.9959, yet SEM suggested release by diffusion and erosion [31]. Matrix release also depended on stirring rate in a head-to-head study, while the pump did not [20]. Mechanistic tests are therefore needed: independence of pH and agitation, and a fall in release as the osmolarity of the medium rises. These tests were reported for gliclazide, tapentadol and glipizide CPOP tablets [8,22,25].

Other osmotic tablets give a sense of how fits are quantified. The optimum of a metoclopramide pump followed zero order with r^2 of 0.9703 [32], and the optimised lamotrigine tablet gave R^2 of 0.9912 [23]. A flurbiprofen pump was fitted to zero-order, first-order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell models [33]. In-vitro to in-vivo correlation then tests whether the in-vitro profile predicts absorption. A level A correlation has been reported for extended-release glipizide [34], and in-vitro release predicted absorption for isosorbide mononitrate osmotic tablets [26].

VI. QUALITY BY DESIGN AND EXPERIMENTAL DESIGN IN OSMOTIC TABLETS

QbD starts from a quality target product profile (QTPP) and identifies the critical quality attributes (CQAs), critical material attributes (CMAs) and critical process parameters (CPPs). Designed experiments then map their effects, and the results define a design space within which quality is assured. Osmotic tablets have been developed with many such designs. A central composite design was applied to a metoclopramide pump, with NaCl level, orifice size

and coating weight gain as factors. Numerical optimisation predicted more than 90% release at 13.30% NaCl, a 0.6 mm orifice and 7.96% weight gain, checkpoint batches agreed, and the calculated shelf life was 2.8 years [32].

Box-Behnken designs have been used with pore-former membranes. For metoprolol, membrane level and pore-former level were optimised, giving zero-order release for up to 20 h and a later Tmax and lower Cmax than the marketed tablet in dogs [28]. For tapentadol, batches ranged from 29.87 to 56.92% released at 12 h and from 59.64 to 99.96% at 24 h across the design, and the CPOP gave a 2.35-fold relative bioavailability in rabbits [25]. A sandwiched metoprolol tablet went further: a modified Ishikawa diagram identified critical parameters and a Plackett-Burman design screened them before the Box-Behnken optimisation, aiming at 80% release or more over 20 h [35]. Factorial designs have also been used for glipizide and flurbiprofen osmotic tablets [30,33].

For glipizide, designed experiments have been used in other dosage forms, such as a central composite design for pellets of a co-amorphous mixture [4]. We did not find a paper that applies a full QbD sequence of QTPP, risk assessment and design space to a glipizide osmotic tablet. Figure 2 gives a conceptual pathway, and Table 3 lists the factors and tests we would propose.

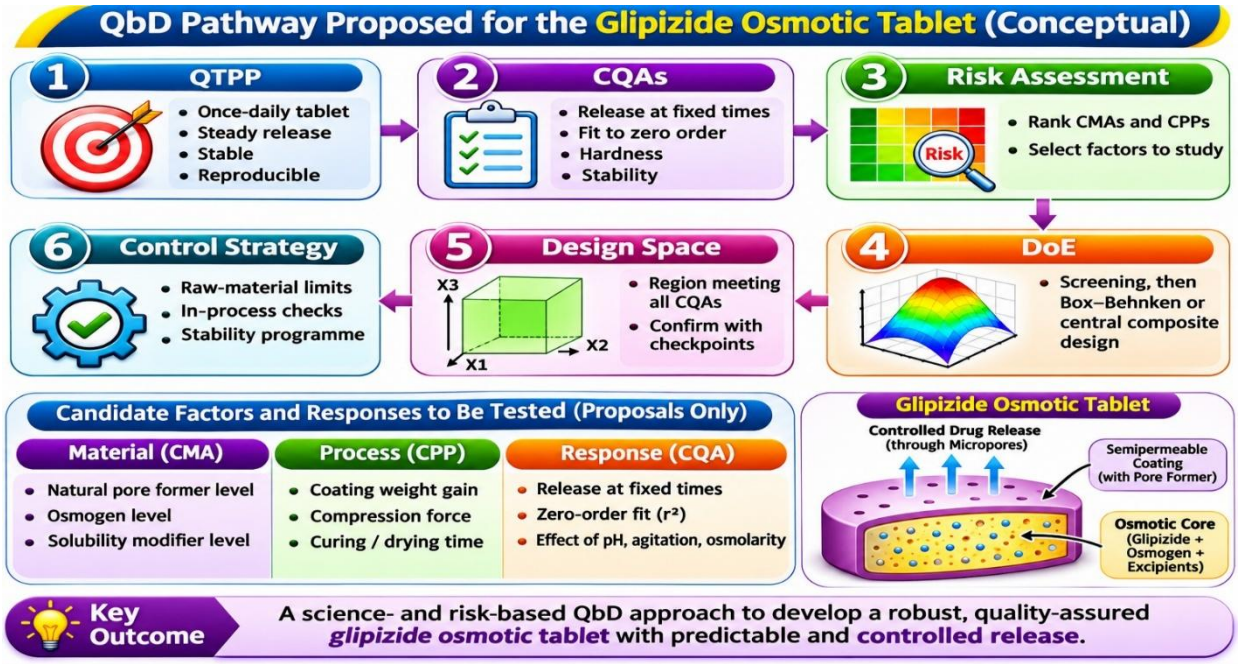


Figure 2. Conceptual QbD pathway proposed for the glipizide CPOP tablet, with candidate factors and responses. The entries are proposals drawn from the literature reviewed and are not results. QTPP, quality target product profile; CQA, critical quality attribute; CMA, critical material attribute; CPP, critical process parameter; DoE, design of experiments.

Table 3. Proposed QbD elements and tests for the glipizide CPOP tablet. All entries are proposals and not reported results.

Element	Proposed content	Literature basis	Ref.
QTPP	Once-daily oral tablet with steady release, free of laser drilling, stable on storage	Short half-life; CPOP avoids orifice	[3,6]
CQAs	Release at fixed times; fit to zero order; independence of pH and agitation; dependence on osmolarity	Mechanism tests in CPOP studies	[22,25]
CMAs	Natural pore former level; osmogen level; solubility modifier; glipizide particle size	Pore former and solubility effects; particle size	[7,13]

CPPs	Coating weight gain; membrane composition; compression force	Weight gain controls release	[18,21]
Screening and optimisation	Ishikawa diagram and Plackett-Burman screening, then Box-Behnken or central composite design	Used for other osmotic tablets	[28,32,35]
Design space and checks	Region meeting all CQAs; checkpoint batches; 3-month accelerated stability	Checkpoints and stability reported	[8,32]
In-vitro tests	USP II dissolution; SEM of pores; membrane ageing on storage	Discriminating method; pores; ageing	[8,26,34]

VII. PROPOSED NATURAL PORE-FORMING SYSTEM AND ITS EVALUATION

The proposal is to replace the synthetic or sugar-alcohol pore former of earlier glipizide CPOP tablets [7,8] with a natural water-soluble material, or a blend of such materials, and to test whether it gives the same pore formation and zero-order release. This is an idea to test and not a result. The natural material would have to dissolve readily in water, be compatible with the film former, and leave a membrane that is strong enough to resist the internal pressure. Its effect on membrane stability would need study, since the pore former changed ageing behaviour in the isosorbide mononitrate tablets [26]. A natural swelling material could also serve as the osmotic agent, as the sterculia matrix did for glipizide [27], but that is a separate question from pore formation.

Evaluation would start from the design in Table 3. Dissolution by USP apparatus II in pH 6.8 buffer at 100 rpm was the most discriminating method for extended-release glipizide in one study [34], and it is a reasonable starting point, to be checked for osmotic tablets. The core would need a solubility modifier, as sodium carbonate was used in the glipizide pump [19], and the glipizide particle size would be fixed because it affects dissolution [13]. Release would then be tested at different pH values, stirring rates and osmolarities, membranes would be examined by SEM, and accelerated stability would be run [8,25]. In-vivo work and correlation would follow only for a candidate that passes these steps [26,34].

VIII. GAPS AND CONCLUSION

Several gaps limit what can be said. First, we found no glipizide CPOP paper that uses a natural pore former; the two on-topic CPOP papers used PVP or sorbitol [7,8], and the nearest natural-material items are a chitosan push agent for felodipine and a sterculia seed propellant with glipizide as the model drug [27,29]. Second, we did not find a full QbD study of a glipizide osmotic tablet; the QbD example we found concerns metoclopramide [32]. Third, the clinical evidence for osmotic glipizide rests on the marketed GITS [11,12] and not on a CPOP. Fourth, this review draws only on abstracts, several of the journals are of limited indexing, and numbers should be checked against the full papers before they are used.

A QbD-based glipizide CPOP tablet with a natural pore-forming system is a reasonable proposal for experimental work. Glipizide has a clear need for steady release, osmotic delivery of glipizide has worked, CPOP tablets with other pore formers give zero-order release, and the QbD tools are well described. Whether a natural pore former can match the synthetic ones is untested. The design in this review is conceptual, and the next step is laboratory screening of candidate materials.

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