EXPERT OPINION

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Newer insights into the drug delivery approaches of α-glucosidase inhibitors

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Introduction: α-Glucosidase inhibitors (AGIs) are an important category of oral antidiabetic agents being extensively exploited for the effective management of type 2 diabetes and associated disorders. These drugs significantly reduce the postprandial rise in glycemic and plasma insulin levels both in non-diabetics and in type 2 diabetic patients. Currently only three drugs belonging to this category, *viz,* acarbose, miglitol and voglibose are in the market. The major limitations associated with the administration of AGIs are the stringent repetitive dosing schedule at specified time intervals, along with a high incidence of gastrointestinal disturbances that mainly include flatulence, abdominal distension, borborygmus and diarrhea. All these factors tend to decrease patient compliance.
Areas covered: This review focuses on the various formulation approaches being targeted for the effective delivery of AGIs, *viz,* unit matrix systems, bioadhesive pellets, hydrogels and lipid-based granules.
Expert opinion: It is concluded that development of a successful controlled-release delivery system for these drugs will obviate the need of repeated administration, which in turn will improve patient compliance.

Keywords: α-glucosidase inhibitors, controlled release, granules and hydrogels, pellets, side effects, tablets

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1. Introduction

Diabetes is the fifth leading cause of death in the world (4 million deaths annually), outnumbering the global deaths due to HIV/AIDS. Recently, the International Diabetic Federation has reported that approximately 285 million people are suffering from this *silent epidemic* [1]. Type 2 diabetes is a global pandemic accounting for more than 90% of all the reported cases of diabetes. The major reasons responsible for this drastic increase in the prevalence of this disorder are a burst in population growth, aging, urbanization and increasing incidence of obesity and physical inactivity [2]. Data from several studies have indicated that postprandial hyperglycemia (PPHG) is a key indicator of the actual therapeutic standing of the diabetic individual as it alone can precipitate many macrovascular and microvascular complications [3]. The major elements affecting the disproportionate rise in PPHG are the nature of the ingested food, fraction of polysaccharides in it and rate of gastric emptying. Gastric emptying rate further alters the secretion of insulin and glucagon by modulating the release of gut hormones, such as gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), and the peripheral uptake of glucose. Acute episodes of PPHG affect many vital parts in the human body, due to a variety of glucose-mediated cellular and tissue defects that are generated due to corresponding increase in the oxidative stress, glycation and advanced glycation end product (AGE) formation [4,5]. Thus, the elevations in postprandial blood glucose (PPBG) levels beyond 140 mg/dl are an early indicator of the precipitation of various

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Article highlights.

- α-Glucosidase inhibitors (AGIs) significantly reduce the postprandial rise in glycemic and plasma insulin levels both in nondiabetics and in type 2 diabetic patients.
- The major side effects associated with the AGIs are the poor adherence to the stringent repetitive treatment regime and the higher incidence of bothersome gastrointestinal side effects.
- There is an unmet need of a successful pharmaceutical formulation, which not only obviates the need of multiple dosing of these drugs but also reduces the incidence of the gastrointestinal side effects closely associated with these drugs.
- A suitable controlled-release composition is a suitable mode of effective delivery of AGIs, *viz*, acarbose and miglitol.

This box summarizes key points contained in the article.

macrovascular and microvascular complications in diabetic individuals. As a result, the measurement of PPBG is a more accurate measure of the metabolic state of the diabetic patient [6]. de Veciana and coworkers have demonstrated the benefits of tailoring treatment regimens for females with gestational diabetes based on their postprandial glucose monitoring. In their study, they have given insulin therapy to the diabetic females at the 30th week of gestation based on the measurement of both preprandial and postprandial glucose levels. The results clearly demonstrate the relevance of measuring PPBG levels as the infants born to the females being given a treatment based on the measurement of the postprandial glucose showed a lower incidence of neonatal hypoglycemia and macrosomia [7].

Nowadays a great deal of emphasis is being laid on the effective treatment of PPHG. The World Health Organisation is continuously promoting the adoption of a proper treatment regime for the effective control of this disorder. Hence there is a considerable scope for developing effective therapeutic strategies for the treatment of PPHG. Correspondingly, there is an exponential increase in the demand of a successful dosage form that aids in achieving near-normoglycemic (blood glucose 70 – 120 mg/dl) levels by eliminating short-term episodes of PPHG (90 – 120 min) leading to a reduction in the higher rate of morbidity and mortality associated with the disease and improves the living standards of diabetic individuals. Oral hypoglycemics are generally employed in the patients in order to achieve a suitable control after about 3 months of dietary modification and exercise. Among the oral hypoglycemics, the sulfonylureas and biguanides are the two major category of drugs prescribed until recently in major parts of the world, but both of them function only in the presence of endogenous insulin and thus have a potential to produce severe hypoglycemia. They also possess very weak control over postprandial glucose levels [8]. Meglitinides mimic the physiological secretion of insulin and also have a marked tendency to produce hypoglycemia because of their long duration of action especially in elderly patients. Thiazolidinones are also prescribed to a limited extent as they tend to produce undesirable cardiovascular side effects [9]. The α-glucosidase inhibitors (AGIs) are a more recently developed class of oral hypoglycemic, which remarkably control the PPBG levels by delaying the absorption of glucose in the gastrointestinal tract of the diabetic individuals [10-12]. Thus, this category of drugs provide an edge over the other agents such as insulin, sulfonylureas and meglitinides by providing an overall control of postprandial increase in blood glucose without causing any hypoglycemia along with a significant effect on the weight control [13,14]. This article summarizes the research conducted till date for the development of successful drug delivery systems for the optimal delivery of the AGIs.

AGI is an important category of oral antidiabetic agents being exploited extensively these days for the effective therapy of type 2 diabetes (non-insulin-dependent diabetes, NIDDM) and associated disorders. These enzyme inhibitors significantly reduce the postprandial rise in glycemic and plasma insulin levels both in nondiabetics and in type 2 diabetic patients. These drugs lower the plasma insulin levels by lowering the activity of the pancreatic beta cells and hence also assist in reducing the risk of ischemic heart diseases [15,16]. Nowadays there are three major drugs in the market belonging to this category, that is, acarbose, miglitol and voglibose. All these drugs also have a marked effect on the glycosylated hemoglobin (HbA1C) levels in the following order acarbose (0.77%) > miglitol (0.68%) > voglibose (0.47%) in comparison with placebo [17]. Acarbose (BAY g 5421) was the first AGI, launched in Switzerland in 1989 by Bayer and is disclosed in US 4062950 for the treatment of type 2 diabetes. It is used for the treatment of common diabetic complications, including retinopathy and neuropathy [18]. It is also approved by FDA for use in combination therapy for the treatment of NIDDM. Miglitol was a follow-up compound to acarbose, which was launched by Bayer in 1998 and marketed by Sanofi-Aventis, Pfizer and Sanwa Kagaku world over. However, voglibose is developed by Takeda in September 1994. Recently, in October 2009, it has been approved in Japan for the prevention of the onset of type 2 diabetes in patients with impaired glucose tolerance (IGT). In the US market, this category of drugs made entry with acarbose, which was launched in January 1996 by Bayer, followed by miglitol in January 1998 by Pfizer; however, voglibose has been recently discontinued from the US market. International Phase III clinical trials of all the three drugs have been conducted as an individual therapy as well as an adjuvant to insulin therapy in patients with type 1–2 diabetes. At present, various formulations of drugs belonging to this category are listed in the *Orange Book*, *viz,* Precose®, Bayer Healthcare (Acarbose tablets, 25, 50, 100 mg) and Glyset® (Miglitol tablets, 25, 50, 100 mg) Pharmacia and Upjohn (**Table 1**).

Table 1. Formulations available for the treatment of type 2 diabetes (Orange Book, Electronic Medicines Compendia.

S No.	Drugs	Dose	Doses/day	Approved by FDA	Innovator	Major marketed formulations	Marketing status	Remarks
1	Acarbose	25 – 100 mg	t.i.d.	Sep 6, 1995	BAYER	PRECOSE	Prescription	Due to repeated administration, occurrence of side effects, *viz*, flatulence. abdominal distension, diarrhea due to fullness of stomach, this category has sufficient potential for design as CR systems for better therapeutic efficacy
2	Miglitol	25 – 100 mg	t.i.d.	Dec 18,1996	PHARMACIA AND UPJOHN	GLYSET	Prescription	
3	Voglibose	0.2 mg	t.i.d.	Not approved	TAKEDA	BASEN	Prescription	

2. Mechanism of action

This category of drugs basically acts by reducing the intraluminal generation of glucose in the intestine and thereby restricting the systemic entry of the sugars in the blood stream. **Figure 1** depicts a schematic representation of the mechanism of action of these drugs. The critical site of action of these drugs for delaying the rate of absorption of the glucose derived from dietary carbohydrates is the brush border membranes of the intestinal absorptive cells of proximal small intestine. These drugs inhibit the α-glucosidase enzymes (maltase, isomaltase, glucoamylase and sucrase) present in the intestinal brush border epithelium. Hence, the overall production of simpler sugars is reduced, which in turn reduces the consequent absorption of these units and help in preventing the occurrence of PPHG. Due to the significant reduction in glucose production, the levels of HbA1C (0.4%) are also significantly reduced in the diabetic individuals receiving AGIs [2,19].

3. Chemistry

The AGIs have a common pharmacophore consisting of a substituted cyclohexane ring and a 4,6-dideoxy-4-amino-D-glucose unit. The secondary amino group present in the structure is commonly thought to have the inhibitory effect on the α-glucosidase enzymes. It interacts with the carboxyl group of the enzymes and thus prevents the protonation of the glycosidic oxygen bonds of the substrate resulting in inhibition of the production of monosaccharides. Although chemically all the three drugs have distinct structures, the newer agents, *viz,* miglitol and voglibose are simple amino sugars [19]. **Figure 2** and **Table 2** highlight few important parameters, *viz,* chemical structure and chemical properties (molecular weight and solubility) of these candidates respectively.

US 4062950 assigned to Bayer Aktiengesellschaft (DT) discloses acarbose *per se* and its property of inhibiting glycoside hydrolases of the digestive tract, which aids in reducing alimentary hyperglycemia substantially in turn reducing the PPBG peak [18]. Acarbose is a complex oligosaccharide that delays the digestion of ingested carbohydrates. It delays the production of monosaccharides mainly glucose, by inhibiting the α-glucosidases associated with the brush border membrane of the small intestine [20]. A linear correlation has been established between the enzyme inhibitory potential of the molecule and its dose in both *in vitro* and *in vivo* studies [21]. It produces its inhibitory activity in the following order glucoamylase > sucrase > maltase > isomaltase [22]. It is metabolized extensively within the bowel, principally by intestinal bacteria and partially by digestive enzymes. The metabolites have limited inhibitory activity on the oligosaccharide digestion [23]. Ruppin *et al.*, 1988, performed ileal intubation studies and indicated that acarbose induced significant carbohydrate malabsorption of up to 50% of the ingested carbohydrates [24]. The drug also inhibits pancreatic islet glucan-1,4-α-glucosidase activity in mouse in parallel with a suppressive action on glucose-induced insulin release [25]. Various clinical trials conducted in patients with non-insulin dependent diabetes mellitus indicate that acarbose is a potential drug, which reduces PPBG levels significantly along with a marked effect on the hypertriglyceridemia, which is closely linked to carbohydrate and insulin metabolism [26,27]. Dosing recommendations for acarbose include the administration of the drug with the first mouthful of food to achieve its best hypoglycemic effect [28]. The major side effects associated with this drug are the occurrence of a high incidence of bothersome gastrointestinal side effects, which include flatulence, abdominal distension, borborygmus and diarrhea [29]. Diarrhea is predominantly caused due to an increase in the carbohydrate spilling in the colonic segment of the gastrointestinal tract. This spillage is due to the reduced absorption of the carbohydrates in the earlier segment of the tract due to the inhibitory effect of the drug on α-glucosidase enzymes in the small intestine. The bacteria present in the colonic segment in turn acts on the carbohydrate content and produces a higher amount of gases causing flatulence and improper

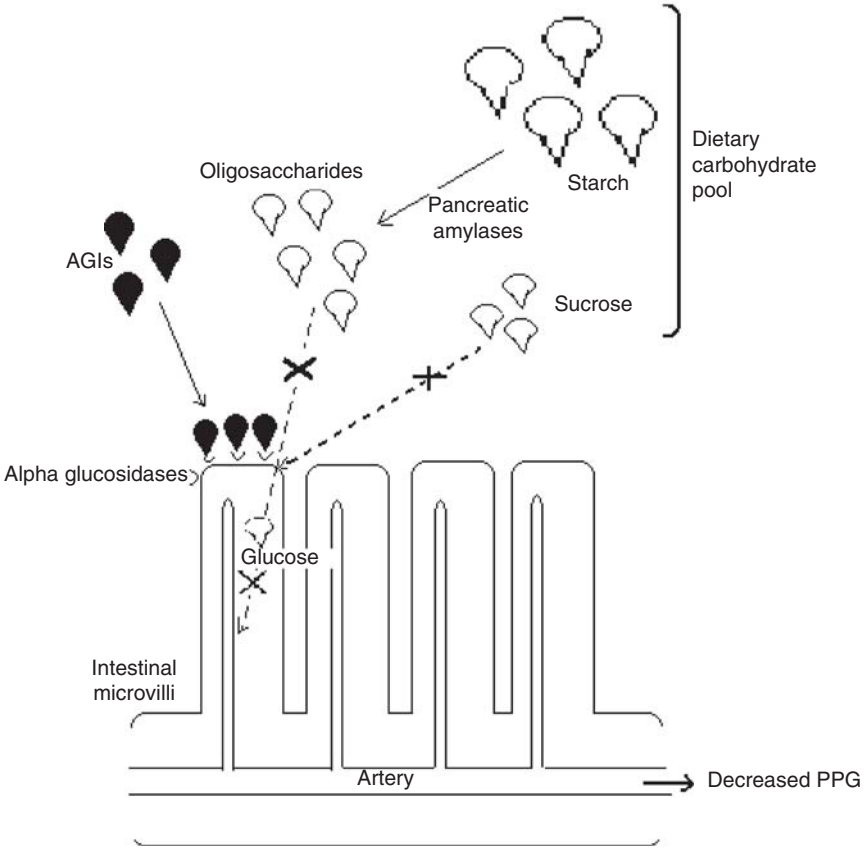
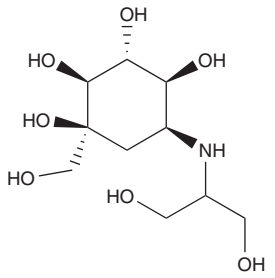


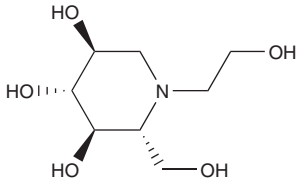
Figure 1. Schematic representation of the competitive inhibition of the brush border α-glucosidases by acarbose resulting in a decrease in postprandial glucose levels.

bowel movement [30]. A dose-dependent effect was recorded on the occurrence of these gastrointestinal side effects [17]. Treatment with various doses of acarbose in patients with type 2 diabetes is associated with a marked reduction in glycosylated hemoglobin levels (HbA1C) of 0.76%. It has also shown significant lipid (apolipoprotein, cholesterol and LDL)-lowering effects in patients with suboptimally controlled type 2 diabetes along with improvement in near-glycemic levels [31]. It also lowers the fasting insulin levels and body weight in comparison with sulfonylureas [17]. Furthermore, it also has a preventive effect on cataract development and has also reported to reverse abnormal retinal hemodynamics as reported via a pharmacodynamic study in sand rats due to its inhibitory effect on the aldolase enzyme [32,33].

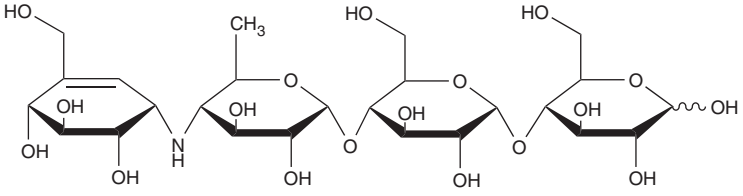
Miglitol is also a competitive inhibitor of α-glucosidases, which reduces tendency to PPBG, a condition that complicates maintenance of normoglycemic levels in patients with IDDM. US 4639436 assigned to Bayer discloses the compound *per se* [34]. The term of this patent was extended till January 2009 under the provisions of the Hatch-Waxman Act. This drug acts in a similar fashion as acarbose by inhibiting brush border disaccharidases, thus delaying the absorption of complex carbohydrates and lowering the levels of glucose available in the blood stream [35]. However, it does not have any effect on the active transport of L-leucine or methyl α-D glucoside and plasma triglycerides like the other counterparts of this category [36]. Kingma and coworkers conducted a double-blind randomized trial in diabetic individuals and reported that miglitol reduces the PPBG levels independent of the starch content of the meal. It was also concluded that miglitol exerts certain extraintestinal effects like on the disposition of glucose or anti-insulin counter-regulatory factors [37]. Ladas *et al.*, in 1992, conducted a complete study to evaluate the effect of acarbose and miglitol on the transit time of food from the mouth to cecum (MCTT) using the breath hydrogen analysis in healthy individuals. MCTT was defined as the interval between finishing the meal and the first of two sequential increases in breath hydrogen concentration ≥ 20 ppm over the base line, which is an indicator of arrival of lactulose and/or malabsorbed carbohydrate into the cecum. Hydrogen excretion was maximum in the humans fed on acarbose (122.56 ppm) followed by miglitol (112.67 ppm), with the lowest levels (74 ppm) in case of animals fed on placebo. However, fermentation of the carbohydrates in the colonic segment results in generation of short-chain fatty acids, which provide 90 – 240 kcal/day in normal subjects [38]. A dose of 50 mg miglitol had been recommended as being



(1S,2S,3R,4S,5S)-5-(1,3-dihydroxypropan-2-ylamino)-1-(hydroxymethyl) cyclohexane-1,2,3,4-tetraol



(2R,3R,4R,5S)-1-(2-hydroxyethyl)-2-(hydroxymethyl) piperidine-3,4,5-triol



(2*R*,3*S*,4*S*,5*S*)-5-((2*R*,3*S*,4*S*,5*S*)-5-((2*R*,3*S*,4*R*,5*S*)-3,4-dihydroxy-6-methyl-5-((1*S*,4*R*,5*R*,6*R*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enylamino) -tetrahydro-2*H*-pyran-2-yloxy)-3,4-dihydroxy-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yloxy)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-2,3,4-triol

Figure 2. Chemical structure of A) voglibose, **B)** miglitol and **C)** acarbose.

both clinically tolerable and effective [39]. Furthermore, the incidence of gastrointestinal disturbances with miglitol is relatively lower than those associated with acarbose treatment. Recently, Aoki and coworkers conducted a randomized open-label crossover design trial in which 22 healthy men were administered 75 mg of miglitol or 100 mg of acarbose per every meal for 3 days. The results of the study indicated that the flatulence and abdominal bloating scores were likely to be higher after acarbose administration than after miglitol, which was attributed to the additional inhibition of pancreatic and salivary α-amylase by acarbose relative to miglitol [40]. On the other hand, miglitol administration increases unabsorbed disaccharides, rather than polysaccharides, in the intestine, which further led to the higher incidence of softening of stool in patients being treated with miglitol. The study results clearly indicate that the patient's clinical state should be thoroughly evaluated before prescribing either of these drugs for better compliance [41]. Among the various causes for lack of adherence to treatment with various AGIs, another major concern behind the lack of adherence to treatment with the AGIs is the stringent dosage regime. Both acarbose and miglitol are prescribed to be taken before meals to achieve better results. However, of late, there are studies that clearly indicate that administration of miglitol after a meal was equally effective as when administered just before a meal. Aoki *et al.*, 2007, examined four different schedules of miglitol administration in 15 healthy men to identify a suitable dosing regime for the drug. Pharmacokinetic parameter, *viz,* area under the curve of plasma glucose, was calculated for all the treatment groups. The study results showed that administration of miglitol in two divided doses appeared to be more suitable for obtaining effective regulation of postprandial glucose excursions relative to administration of the same amount of the drug in a single dose just before the start of the meal or

Table 2. Chemistry of α-glucosidase inhibitors.

Name	Molecular weight (g/mol)	Solubility	Official in
Acarbose	645.61	Highly soluble in water	IP, BP, JP
Miglitol	207.224	Soluble in water	-
Voglibose	267.28	Very slightly soluble in water and ethanol	JP

15 min after the start of the meal [42]. Similar results were concluded in a subsequent trial conducted by Masuda *et al.*, in 2011 [43]. However, in a subsequent trial conducted by this group in 2008, it was concluded that if patients have difficulty remembering to take miglitol just before meal, they should be instructed to take the medicine together with other medicine (s) after the meal; this instruction may improve the treatment compliance of diabetic patients. Although the most appropriate time of administration of miglitol to the patient still remains uncertain, pre-meal administration of miglitol induced better plasma GLP-1 response rather than post-meal administration of the same [44]. Miglitol has shown beneficial effects in diabetic individuals in both single and combination therapy [45,46].

Voglibose is a relatively newer drug of this category. A few clinical trials conducted in both diabetic and nondiabetic individuals indicate that the drug is effective in delaying the absorption of glucose, which in turn reduces the risk of macrovascular complications [47]. Voglibose is an orally active α-D-glucosidase inhibitor marketed in Japan, South Korea, Thailand and the Philippines for the management of PPHG in diabetic patients. Voglibose was disclosed in US 4701559 assigned to Takeda Pharma in October 2009 [48]. It has also been approved by the Japanese Ministry of Health, Labor and Welfare for the prevention of onset of type 2 diabetes in patients with IGT. The approval was based on data showing that the agent had preventive effects against the onset of type 2 diabetes in Japanese patients with IGT [49]. In this study, it was observed that the administration of 0.2 mg voglibose three times a day reduced the risk of patients with IGT developing type 2 diabetes by 40.5% and increased the proportion who achieved normoglycemia by 53.9% in comparison with those treated with placebo. Many other studies have aided in establishing the efficacy of voglibose in the treatment of IGT [50,51]. The drug also lowers mean HbA1C levels significantly ($p<0.005$) in diabetic individuals [52]. Various studies indicate that voglibose is 20- to 30-fold more potent competitive inhibitor of intestinal α-glucosidase than acarbose [53]. A randomized crossover open study conducted by Vichayanrat and group in 30 patients with type 2 diabetes indicated that relative to acarbose, voglibose was found to be associated with a lesser incidence of gastrointestinal side effects [54]. Therefore, there is an unmet need of reducing the incidence of gastrointestinal side effects associated with the AGIs especially acarbose and miglitol in order to achieve full potential of their therapy.

4. Pharmacokinetic–pharmacodynamic behavior of AGIs

On oral administration, acarbose is poorly absorbed from the gastrointestinal tract and has a very low mean systemic bioavailability of approximately 0.5 – 1.6% only (Putter 1980). It is extensively degraded by the digestive enzymes or microorganisms present in the intestinal tract. As a result, only 2% of orally administered dose is absorbed in intact form [22]. Therefore, it is difficult to measure the concentration of the drug in the plasma, hence no well-defined pharmacokinetic method for estimation of the drug is available till date. Pharmacodynamic assessments are most commonly performed to evaluate the bioavailability and the efficacy of the drug *in vivo* [55]. On the other hand, miglitol is significantly absorbed systemically with a bioavailability of 100%. Thus, miglitol is extensively absorbed after oral administration but the absorption is found to be saturable and decreases with the increase in dose [56]. Elimination half-life of both acarbose and miglitol is approximately 2 h making them potential candidates for controlled-release delivery systems. On administration through the i.v. route, 89% of the dose of acarbose is excreted in intact form in the urine within 48 h. C_{max} is attained within 1 – 3 h for both acarbose and miglitol. The low mean distribution half-life of both acarbose and miglitol calls for the repetitive dosing schedule of the drug throughout the day. Similar to acarbose, voglibose is also very poorly absorbed and excreted mainly in the feces in intact form [10].

5. Estimation of the glucosidase inhibitors

All the three AGIs do not have any common structural feature in all the drugs enlisted in it. However, a significant feature noted in all the three drugs is that they lack a chromophore, which limits the ease of identification of these drugs by normal spectrophotometric techniques. As a result, the derivatization methods are normally exploited for the sensitive and accurate estimation of these drugs by spectrophotometry. The derivatized products thus formed have an ease of detection using normal spectrophotometric methods. Ibrahim *et al.*, 2007, fabricated a kinetic method for determination of both acarbose and miglitol after oxidative treatment with alkaline potassium permanganate. The basic reaction mechanistics involved the generation of free manganate ions on the reaction of the drugs with potassium permanganate in presence of sodium hydroxide. The concentration of the manganate ions produced was found to be proportional to the concentration of the drug. Thus the absorbance of the colored manganate ions was recorded at 610 nm as an indicator of the corresponding concentration of the drug both in bulk and in pharmaceutical dosage forms. The reaction kinetics was studied by both the fixed concentration method and the fixed time

method. The results obtained indicated that the optimum reaction conditions included oxidation at room temperature for a fixed time of 15 min for acarbose and 25 min for miglitol with 1×10^{-2} M potassium permanganate and 0.5 M sodium hydroxide. Limit of detection of the method was calculated to be 0.081 and 0.179 µg/ml for acarbose and miglitol respectively [57].

Similarly, Rao *et al.* (2010) have developed a spectrophotometric method for estimation of voglibose by derivatizing it with taurine and sodium periodate in water and methanol. The following reaction leads to the imination of the carbonyl group of voglibose, which is produced by oxidation of the hydroxy methyl group by sodium periodate, with the primary amino group of taurine. The resultant compound showed an absorbance λ_{max} at 282 nm., which is safely detected. The developed method was found to be precise, accurate, reproducible and linear in the concentration range of 10 – 80 µg/ml with a high correlation coefficient of the order of 0.9976 [58].

Thus, the aforementioned methods can successfully be used for determination of the drugs spectrophotometrically and involve a lower cost of analysis. However, many other sophisticated methods involving various chromatographic techniques have also been explored. **Table 3** includes the details of various chromatographic techniques available till date for estimation of the drugs. These methods are more sensitive and assist in accurate determination of the enlisted drugs in pharmaceutical compositions as well as plasma samples. As a result, these methods can be exploited for the pharmacokinetic studies. Furthermore, chromatographic techniques for evaluation of these drugs are official; the Indian Pharmacopoeia and the British Pharmacopoeia prescribe a chromatographic method for the estimation of acarbose. Similarly an HPLC technique for the estimation of voglibose is elaborated in the Japanese Pharmacopoeia.

6. Drug delivery systems

Historically, the oral route has by far been the most versatile route of delivery for both conventional and novel drug delivery systems. The total market share of oral medications adapted to delivery systems is predicted to reach $56.7 billion in 2012, that is, up 7.1% annually from 2007 for the US alone. Oral products represent about 70% of the value of pharmaceutical sales and, among drug delivery systems, some 60% of the market. The major driving force behind this robust increase in the market share is the increase in the development of proprietary medicines in new oral controlled-release forms. Many studies indicate that the poor adherence to the medication has a significant impact on the management of glycemic levels in diabetic individuals. Many researchers world over have conducted exhaustive retrospective and prospective studies indicating the eminent role of adhering to the proper dosing regimen in attaining the proper results of the desired oral hypoglycemic medication. Melikian *et al.* conducted a retrospective study in 2002 in diabetic individuals grouped on the basis of the medication use patterns. The patients received monotherapy (metformin or glyburide), combination therapy (metformin and glyburide) or fixed-dose combination therapy (glyburide/metformin) during the course of the study. The overall results of the study indicated a significant improvement of approximately 16% in the adherence rate in the patients receiving the fixed-dose combination relative to those receiving the combination therapy [59]. Thus, it has been observed that the pill count is a key factor affecting the patient's compliance to the diabetic medication and in turn its therapeutic outcome. Current regimes in market for the AGIs include simple immediate-release unit systems, which have a dosing schedule that indicates intake of the medication three times a day. This schedule is prone to lower patient compliance due to the repetitive dosing and many times the dose gets missed. Thus, a more compliant regimen of the inhibitors is desirable to achieve maximal therapeutic efficacy.

6.1 Strategic approach

In the recent years, a lot of attention has been laid on the development of novel drug delivery systems due to innumerable reasons. The prime benefit being the feasibility of re-patenting successful drugs by applying newer concepts and techniques of sustained-release drug delivery systems coupled with the benefit of bypassing the huge amount of expenses involved in getting a new chemical entity to the market. Oral sustained-release dosage forms (SRDF) offer many benefits over conventional dosage forms such as convenient use, narrow fluctuation of drug concentrations in plasma, less frequency of administration, less toxicity and higher patient compliance. Currently, all the AGIs are marketed as unit immediate-release dosage forms. However, the lower half-life ($t_{1/2}$ ~ 2 – 3 h), repetitive administration schedule and frequent occurrence of gastrointestinal disturbances due to fullness of the stomach necessitate the design and development of controlled-release delivery systems for this category of drugs. The development of such systems will not only obviate the need of repetitive administration of the drug, but it will also assist in significant lowering of the gastrointestinal disturbances and hence improve patient compliance.

Some researchers have started exploring the possibilities in the direction of developing a successful modified release system for acarbose. It has been observed that approximately 60% of the diabetic neuropathy patients suffer from chronic constipation while following treatment of diabetes. Acarbose is found to be therapeutically effective in the treatment of such chronic constipation in elderly patients with diabetes mellitus [60].

Acarbose has the tendency to get discolored in the presence of moisture; to overcome this problem, it is stored in amber-colored tightly closed moisture-resistant containers. Another approach includes the adsorption of the medicament on porous absorbents. Tablets containing acarbose adsorbed

Table 3. HPLC methods for the determination of α-glucosidase inhibitors.

Drug (s)	In	Column	Mobile phase	Detection	Ref.
Acarbose	Pure form and pharmaceutical dosage forms	C18	65% acetonitrile and 35% phosphate buffer pH 7	UV, 210 nm	I.P 2007
Miglitol	Pharmaceutical dosage forms and rabbit plasma	Lichrospher, ODS, (4.6 mm × 250 mm, 5 μm)	0.05 M ammonium acetate	UV, 216 nm	[85]
	Human plasma	Nucleosil C_{18} column (5 μm, 50 × 4.6 mm i.d.)	10 mmol/l ammonium acetate at 1.0 ml/min	Tandem mass spectrometry	[86]
		C18 inertsil column (5 μm, 50 × 4.6 mm i.d.)	Acetonitrile 2 mM and ammonium acetate (pH 3.5) with formic acid	Electrospray ionization tandem mass spectrometry	[87]
		Phenyl column		Tandem mass spectrometry	[88]
		Macherey-Nagel CN column (4.6 mm × 250 mm, 5 μm)	Acetonitrile, methanol and 0.02% hydrochloric acid	Electrospray mass spectrometry	[89]
Voglibose	Pharmaceutical dosage forms	Cosmosil® 5NH_2-MS column (150 mm × 4.6 mm, 5 μm)	Acetonitrile and 30 mM NaH2PO4 (pH 6.5) (2:1, v/v)	Post-column derivatization using taurine and sodium periodate and fluorescence detector	[90]
		RP-18e, Hibar RT column (250 × 4.6 mm)	0.025M potassium dihydrogen phosphate pH 2.5: acetonitrile: methanol (40 : 55 : 5 % v/v/v)	282 nm	[91]
		Supelcosil LC-NH_2 (25 cm × 4.6 mm, 5 μm)	Acetonitrile–water (0.05 mol/l ammonium acetate)(80:20)	Evaporative light scattering detector	[92]
		Novapak C18 (300 x 3.9 mm, 4 μ)	0.01 M mixture of sodium dihydrogen orthophosphate and disodium hydrogen orthophosphate, pH 6.0 and acetonitrile in 35:65 v/v ratio	Pre-column derivatization and detection at 667 nm	[93]

on various absorbents, *viz*, magnesium aluminometasilicate, light anhydrous silicic acid and water-containing silicon dioxide having a specific surface area of ≥ 50 m^2/g have also been developed. The tablets obtained were found to be more resistant to high humid conditions [61].

6.2 Unit systems

AGIs aid in the significant reduction in weight due to decrease in the absorption of sugars systemically from the carbohydrate pool [62]. Earlier in 2001, Morrison disclosed that development of a sustained-release formulation of acarbose will have unexpected benefits of ameliorating the limitations of improper supply of the drug in the intestine through other delivery systems. Hydrophilic matrices comprising 100 – 300 mg of acarbose and 20 – 40% hydroxypropylmethylcellulose (HPMC K100M) were formulated. These systems were further coated with approximately 0.54% w/w of Opadry. A clinical study of the designed formulation was performed in nondiabetic, healthy, obese patients over a period of 16 weeks. An average weight loss of 7.4 pounds was recorded in 11 out of 13 subjects being treated with the sustained-release acarbose [63]. Hence, the designed systems also provided the edge over the older systems as they were also able to control the body weight of the diabetic patients more effectively. Furthermore, it is proposed that such systems may also assist in a significant reduction in the occurrence of varied gastrointestinal disturbances commonly encountered with the repeated administration of the medicine.

Blume *et al.*, 2009, developed a novel retard formulation of acarbose consisting mainly of a gas-forming agent. They observed that inclusion of gas-forming agents, *viz,* sodium bicarbonate, citric acid, tartaric acid and so on, aided in the reduction of sudden burst release of the drug resulting in its undesirable high plasma levels upon oral administration together with or after a meal. As a result, the drug release is prolonged for a relatively longer duration assisting in better therapeutic efficacy of the delivery system. *In vivo* pharmacodynamic studies were also performed in healthy volunteers for 8 h. Mean plasma glucose levels were recorded in both the

modified- and immediate-release formulation (Glucobay®)-treated groups. A significant lowering in the glucose levels in the retard formulation-treated group was observed within 1 h of administration of the delivery system [64].

Devane also developed simple matrix and coated unit systems for delayed release of acarbose in the distal part of the small intestine for the treatment of constipation. Simple hydrophilic matrix-based systems containing varying ratios (20 – 40%) of methocel as the release retardant and PVP as the binder were prepared. *In vitro* studies were performed in USP type II apparatus at 37°C. The study results indicated that the designed formulations controlled the release to less than 10% initially for 2 h in the acidic medium, that is, 0.01 N HCl. However, approximately > 30, 50 and 75% of the drug was released after 2, 4 and 8 h of the study in pH 6.8 buffer. In the other approach, a dual coated unit system containing Eudragit L 100 in the first coat and Eudragit S 12.5 in the subsequent coat on immediate-release core were also tested. The retardation observed was similar to that of the simple matrices. Although a slight improvement in the retardation (approximately 10%) was observed in case, the dual coating system was applied onto the methocel matrices. A clinical study was also performed in 60 – 120 patients to establish the pharmacokinetics of the optimized delivery system. The *in vivo* results indicated a significant improvement in the bowel movement of the patients following treatment with the developed system [65].

A novel acarbose-loaded ultra-deformable liposome gel has recently been developed by Kumar and coworkers for effective transdermal delivery of the drug (2010) to reduce the occurrence of gastrointestinal side effects frequently associated with oral delivery of the drug. Discrete spherical systems were designed with an entrapment efficiency of nearly 33 – 46%. The prepared systems achieved the desired control release profile in the *in vitro* studies [66].

Hydrophilic matrices of acarbose composed of HPMC, sodium carboxymethylcellulose, sodium alginate and/or triglycerides were developed and evaluated by Sun and Wu in 2009. The designed system aided in sustaining drug release of 20 – 40% in 2 h, 40 – 65% in 4 h followed by almost complete release within 8 h of the dissolution studies [67]. Similar hydrophilic matrices were also prepared using varying proportions of HPMC and guar gum individually, using wet granulation technique. Granulation was performed using 4% w/v starch paste. Batches containing approximately 40% of either of the polymers depicted a sufficient retardation of drug release with a release of 55 – 60% and 70% in 6 h respectively. However, both batches showed a release of approximately 80% within 12 h. The drug release was observed to follow zero-order kinetics with a diffusion-controlled mechanism of release [68]. The same group has also developed directly compressed monolithic controlled-release matrices for acarbose with different proportions of Eudragit S 100 both individually and in combination with HPMC K 100M. The incorporation of Eudragit was observed to significantly affect the release of acarbose from the developed matrices based directly on the proportion of the said polymer in the system [69].

Recently, our research group also explored the therapeutic potential of a novel combination of a galactomannan with acarbose (100 mg) in attaining a desired hypoglycemic effect over a prolonged period of time. Three major antidiabetic galactomannans, *viz,* fenugreek gum, boswellia gum and locust bean gum were selected in this study in order to achieve a synergistic effect of both the drug and the gums in treatment along with retardation in drug release. Batches containing varying percentages of the galactomannans, *viz*, fenugreek gum (AF40-60), boswellia gum (AB40, 50) and locust bean gum (ALBG30, 50), were developed for comparison with respect to the conventional immediate-release formulations. *In vitro* studies indicated that batches containing various proportions of fenugreek gum (AF40-60) were able to control drug release for a longer duration of approximately 10 – 12 h. By contrast, the matrices prepared using boswellia and locust bean gum were able to sustain the release for relatively shorter durations. Drug release mainly followed first-order release kinetics owing to the highly soluble nature of the drug. *In vivo* study results depicted a significant reduction ($p < 0.001$) in the PPBG and triglyceride levels in the diabetic rats on treatment with the optimal formulation AF40. The developed system provided a much better control of the postprandial glycemic levels relative to the immediate-release tablets (AF0). The study results clearly indicated the presence of synergism between the antidiabetic drug and the galactomannan in controlling the postprandial glucose, triglycerides and cholesterol levels. The optimized formulation also resulted in a marked reduction in the incidence of gastrointestinal side effects such as diarrhea, fullness of stomach and flatulence along with a noticeable increase in the food intake. Thus, it was concluded that such novel synergistic approaches can be beneficially exploited for the designing of an efficacious delivery system for the sustained release of the drug along with the therapeutic benefits of release rate-controlling polymer [70].

In the past few years, a lot of emphasis was being diverted to the development of rapidly disintegrable delivery systems for better patient compliance. The major benefit achieved through this mode of delivery is the ease of drug administration without water especially in the case of geriatric patients. It also improves the availability of the drug immediately for action. In 2004, voglibose rapidly disintegrable tablet (VODT) was launched in Japan. Koh and coworkers performed a post-marketing survey to evaluate the efficacy of the VODT in everyday clinical practice. The study was performed in a large cohort of Japanese patients with diabetes. They were treated with 0.6 or 0.9 mg/day VODT for 12 weeks. Of those patients, 53.1% reported an ease in intake of VODT in comparison with the conventional voglibose tablets. It also led to a corresponding significant reduction in the HbA1C levels [71]. Recently, a rapidly disintegrable

tablet formulation containing voglibose has been developed. The designed tablet formulation possessed the benefit of rapid dissolution in the oral cavity in the presence of saliva, obviating the need of intake of large quantity of water during administration along with rapid availability of the drug. Granulation was performed with purified water in a fluidized bed granulator: 0.4 – 0.6 g of voglibose, 410.4 – 470.6 g of erythritol, 120.0 g of low-substituted hydroxypropylcellulose LH-33 (for faster disintegration), 6.0 g of anhydrous citric acid and 1.2 g of aspartame were charged into the granulator. The effect of addition of superdisintegrant was also studied by addition of crosspovidone in some of the batches. After drying, the granules were lubricated with magnesium stearate and compressed on a beveled edged (10 mm) punch using a rotary type tabletting machine. The hardness and oral disintegration time of each batch were recorded and were found to be a function of the concentration of the superdisintegrant added. All the prepared formulations had a rapid disintegration, that is, within approximately 26 s. The invention proposes the use of this formulation for the treatment and prevention of obesity, adiposis, lipemia and diabetes mellitus [72].

6.3 Multiparticulate systems

Currently, with an exponential increase in the availability of a huge variety of drug delivery technologies, the development of multiparticulate delivery systems is emerging as a new era in the development of controlled-release delivery systems. These systems offer many advantages, *viz*, a higher degree of flexibility in the design and development of oral dosage forms, ability to deliver the incompatible agents simultaneously, homogeneous distribution throughout the gastrointestinal tract, augmented absorption of the drug, minimal local irritation, reduced risk of dose dumping, attainment of stable drug plasma levels and reduced inter- and intra-patient variability [73-75]. These properties are mainly attributable to the inclusion of a larger number of pharmaceutical variables such as the nature of the core of the pellet, the amount of the drug loaded, the nature and the percent coat weight of the polymer used to coat these systems [76]. Extended-release dosage forms containing varying doses of acarbose (75 – 300 mg) were recently developed in order to achieve a desired therapeutic activity of the dosage form over 12 and even 24 h in the gastrointestinal tract after single administration. Both unit and multiparticulate systems were developed. Initially, the drug was mixed with silicon dioxide in a high shear mixture. The mixture thus obtained was further discharged into a v-blender to which microcrystalline cellulose and magnesium stearate were added and further mixed in order to obtain a uniform mixture. The mixture in the v-blender was discharged after blending and compressed into tablets or pellets or beads. The pellets or beads were manufactured by extrusion spheronization in which a wet mass of the composition is extruded alone or with the aid of extruding aids and spheronized. The non-encased tablets or pellets or beads were further charged into a perforated coating pan in a pan coater and coated with different grades of methacrylic acid copolymers (alone or in combination) at various levels. Subsequently *in vitro* studies were performed that clearly indicated that the non-encased formulations released more than 80% of the drug within 1 h in the simulated gastric fluid. On the other hand, the final coated extended-release formulations controlled the initial drug release sufficiently, that is, less than 10% in the initial 1 h followed by almost complete drug release in the simulated intestinal fluid [77]. Similarly, multiparticulate controlled-release formulations of miglitol were prepared by Deshpande and coworkers. Drug-layering approach comprising layering of the polymer and drug on inert celpheres (grade CP 305) was employed for preparing bioadhesive beads of miglitol. The inert particles were initially coated with drug and hydroxypropyl methyl cellulose (HPMC, 5 cps, 2.47%, w/w), in water in a fluid bed dryer. Furthermore, a layer of ethylcellulose followed by 30% HPMC was applied onto the beads to impart bioadhesive character to the beads. Finally, an enteric coat comprising 30% w/w of Eudragit L 100-55 was applied on the coated pellets. Four different batches (CR1, CR2, CR3 and CR4) were prepared using varying proportions of coat weight with different grades of ethyl cellulose (10 cps, 20 cps). *In vitro* study results indicated that batch CR4 containing 30% w/w of 20 cps of ethyl cellulose as release retardant showed slower release of the drug in comparison with the other formulations. *ex vivo* bioadhesive results indicated a variable adherence profile with maximal adherence of the particles in jejunum region (approximately 61%). PPBG were lowered significantly and maintained in the range of 105 – 109 mg/dl for both the CR formulations until the time interval of 7 h in comparison with 117 – 119 mg/dl after placebo administration [78].

6.4 Topical preparations

Surprisingly, this category of drugs is found to be useful in the treatment of some skin ailments such as atopic eczema, inflammatory skin conditions and pigment disorders, which actively counteract skin dehydration sustained by establishing the barrier properties of the skin. Therefore, currently newer avenues for the topical delivery of the AGIs are also being explored. These drugs act topically by a similar mechanism as in the case of diabetics, that is, they reduce the production of simpler sugars on the surface of the skin. These drugs basically prevent the metabolism of carbohydrates, disaccharides and 1,4 polysaccharides on the skin surface into their constituent sugars. This lack of generation of free sugars further prevents the cascade of reactions, which result in an irreversible cross-linking of collagen and the production of AGEs. The AGEs are a heterogeneous and complex mixture of compounds that have been found to play a key role in skin aging. Hence, reduction in the production of AGEs via topical administration of the AGIs ameliorates the adverse effects of aging or sun damage on the keratinous surfaces. Accordingly, Maes and coworkers are exploring all the possible approaches

used for the optimal topical delivery of these drugs via semi-solid formulations. They are also trying to establish a suitable dosing regime for the same. AGIs from either the botanical sources, *viz,* extracts of Salacia, Connarus, Donella, Sapium, Zanthophyllum, Dimocarpus, Erythroxylon and so on, or chemical compounds *per se, viz,* acarbose, miglitol and voglibose, are under investigation for this purpose [79]. Similarly, acarbose-containing topical formulations for the prevention and treatment of degenerative skin conditions, *viz,* dry or inflamed skin, atopic eczema and neurodermatitis, have also been formulated based on the same rationale. Emulsion-containing components, *viz,* glycerin monostearate, polyethylene(30)cetylstearyl ether, cetyl alcohol, diethylhexyl-butamidotriazone, ethylhexyl triazone, phenylbenzimidazole sulfonic acid, titanium dioxide, zinc oxide, butylene glycol dicaprylate/dicaprate, phenylmethylpolysiloxane, PVP–hexadecene copolymer, glycerine, tocopherol acetate, acarbose, α-glucosylrutin, preservative, perfume, ethanol and water, have been successfully developed. Furthermore, topical delivery of acarbose via a solution, an emulsion, a dispersion or a gel is also being explored. These novel topical compositions tend to provide the barrier properties to the skin, counteracting skin drying out efficiently [80].

7. Combination therapy

Combination therapy as well as fixed-dose therapy is a mainstay in the treatment of diabetic disorders. All the drugs of this category are being actively exploited both *per se* and in combination therapy for the treatment of type 2 diabetes mellitus. These drugs mainly contribute synergistically in lowering the blood glucose levels along with the other drug used in combination and additionally provide the benefit by lowering the risk of hypoglycemia, which is very commonly associated with other combination regimens. Rosak *et al.*, 2002, conducted a study in which 84 patients with type 2 diabetes were treated with a combination of acarbose with glibenclamide. The treatment regimen was administered before breakfast, fasting and in postprandial state, and a significant reduction in PPBG levels (23.7 ± 17.3 mg/dl) was recorded in comparison with 58.4 ± 31.6 mg/dl with acarbose monotherapy. A marked reduction in the serum insulin levels was also observed in the combination-treated group, which indicated that acarbose modified the insulin release induced by glibenclamide along with a lower incidence of hypoglycemia [81]. Tablets containing a mixture of acetylsalicylic acid 100 mg and acarbose 50 mg have been developed by Wagener *et al.*, 2004, for the treatment of cardiovascular disorders associated with diabetes. Similarly, a combination of the AGIs with nitric oxide scavengers is also reported for the treatment of cardiovascular disorders [82]. As discussed earlier, the effect of the AGIs on GLP-1 and GIP levels has recently opened up newer avenues for combination therapy in the treatment of type 2 diabetes. Various drugs, *viz,* (GLP-1) receptor agonists, such as exenatide and liraglutide, or dipeptidyl peptidase 4 (DPP-4) inhibitors, such as sitagliptin, saxagliptin, alogliptin and vildagliptin are successfully being studied for use in combination with AGIs for achieving better therapeutic goals [83,84].

8. Expert opinion

The primary aim of effective diabetes care is to reduce the long-term complications by following an effective dosing schedule. Proper dosing regime and schedule is a key milestone in the effective management of diabetes. Thus, the main objective of optimum drug therapy is to achieve a constant level of the drug in the plasma or the site of action to obtain desired therapeutic response. AGIs have a short half-life, repetitive dosing regime and are frequently associated with a number of gastrointestinal side effects. Recent trends clearly indicate that limited research work has been done to address these problems. Therefore, there is an unmet need of a successful pharmaceutical formulation, which not only obviates the need of multiple dosing of these drugs but also reduces the incidence of the gastrointestinal side effects closely associated with these drugs. The current review provides a deeper insight into the various formulation strategies that can be explored for the efficacious treatment with the AGIs. A comprehensive compilation of the studies done by pharmaceutical technologists all over the world till now have been summarized for ease of understanding of the topic. Through the intensive investigation based on the available literature and experimental data generated by the authors, it can be concluded that a suitable controlled-release composition is a suitable mode of effective delivery of AGIs, *viz,* acarbose and miglitol. On the other hand, as voglibose is associated with a lesser incidence of side effects, conventional immediate-release dosage forms are beneficial for its optimal delivery. Furthermore, newer arenas for the topical delivery of these drugs can also be explored for the optimal treatment of newer therapeutic indications.

Declaration of interest

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