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Sitagliptin and its formulations: a comprehensive review

Asmaa Abdelaziz Mohamed [1]*, **Firas Aziz Rahi**[2]

[1] College of Pharmacy, Al-Zahraa University for Women, Karbala, Iraq
[2] Department of pharmaceutics, Al Mansour University College, Baghdad, Iraq
* asmaa.abdelaziz@alzahraa.edu.iq

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ABSTRACT

Sitagliptin (SIT), an oral dipeptidyl peptidase-4 (DPP-4) inhibitor used in the management of type 2 diabetes, has been formulated in various ways to optimize its delivery and improve patient outcomes. The conventional dosage form is immediate-release tablets, which allow for quick absorption. However, researchers have explored advanced formulations, including extended-release matrix tablets, such as those created with xanthan gum matrices, which can yield approximately 99.6% drug release over a period of 10 hours. Additionally, polymeric micro/nanoparticles have been developed, offering sustained release profiles ranging from 12 to 24 hours. These innovative approaches aim to enhance the therapeutic efficacy of Sitagliptin while minimizing peaks and troughs in drug levels, ultimately leading to better glycemic control and improved patient adherence to treatment regimens. Fixed-dose combination tablets (notably SIT+metformin) such as Janumet (immediate-release) and Janumet XR (extended-release) have been introduced to simplify therapy. Emerging carriers – including SIT-loaded nanoparticles, transdermal patches, and mucoadhesive buccal films – have shown promise in bypassing first-pass metabolism and sustaining drug release. These formulation innovations aim to enhance SIT's bioavailability, extend its action, and improve patient adherence.

Keywords: Sitagliptin, Polymers, Excipients, Solubility

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Introduction

The commercially available oral SIT is taken alone or in combination at 100 mg once a day [1]. SIT manages blood glucose by boosting insulin secretion [2-4]. SIT has satisfactory solubility and permeability as its biopharmaceutics classification system (BCS) is Class 1. Moreover, SIT has a 1 to 4 h Tmax and rapid absorption [5]. Sitagliptin tablets a is the first-approved orally active (FDA 2006) for type 2 diabetes. In clinical use, SIT effectively lowers both fasting and postprandial glucose and has a favorable safety profile (minimal hypoglycemia or weight gain). It is prescribed alone or often in combination with metformin (MET). However, SIT has limitations: it is rapidly absorbed (T_max ~1–4 h) but has a relatively short half-life (~8–14 h), and a large fraction is excreted unchanged (≈80–87%). Such pharmacokinetics necessitate daily dosing and can limit efficacy. Indeed, one report notes that only 38% of SIT is protein-bound and 79% of an oral dose is excreted unchanged, implying suboptimal utilization. These factors – plus the need for combination therapies – motivate novel formulation strategies. By developing sustained-release and alternative-route formulations, researchers aim to prolong SIT action, enhance bioavailability, and improve patient compliance [6,7]. This review discusses sitagliptin pharmacological, physicochemical characteristics and its formulations such as tablets, buccal delivery system, Transdermal patches, and self-nanoemulsifying.

Formulation Strategies

Tablets

The standard form of sitagliptin is an immediate-release (IR) oral tablet (25–100 mg once daily). These are typically prepared by direct compression with disintegrants. Formulation studies have shown that superdisintegrants can yield very rapid release: for example, an optimized SIT phosphate IR tablet (50 mg) containing crospovidone and sodium starch glycolate disintegrated in ~14 s and released ~99% of the drug within 15 min. Such IR tablets provide rapid bioavailability but require frequent dosing to maintain glycemic control [6, 8]. To extend SIT release, various controlled-release systems have been used. Hydrophilic matrix tablets using swellable polymers (e.g. xanthan gum, HPMC) have been developed. In one study, a SIT phosphate matrix tablet with 27.5% xanthan gum achieved nearly 99.6% release over 10 h.

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Likewise, SIT has been encapsulated in polymeric microspheres or beads to slow release. Biodegradable polymers like PLGA, chitosan, and Eudragit have been used: resulting microspheres exhibited diffusion-controlled release with drug release spanning 12–24 h. These formulations often impart mucoadhesive or floating properties to prolong gastric residence. For instance, SIT-loaded mucoadhesive microspheres increased gastrointestinal retention, thereby extending systemic exposure. Multilayer or gastroretentive tablets have also been reported – e.g. bilayer tablets combining SIT with simvastatin or trilayer systems with metformin – and floating tablet designs to retain SIT in the stomach [9]. Tablets remain the most popular because of their many advantages, such as ease of intake and adaptability. However, variations in the drug's plasma concentration may induce forgotten doses. Therefore, sustained-release formulations have been produced to resolve this problem and achieve enhanced patient convenience and compliance, lesser side effects [10]. The evaluation of SIT should be carried out regarding the parameters required as in table 1.

Table 1. Evaluation Parameters of Tablets.

Parameter	Description
Pre-compression parameters	Flow properties such as angle of repose, bulk density, tapped density, and Carr's index determine compressibility [11].
Post-compression parameters	Hardness, friability (<1%), thickness, weight variation, and content uniformity (85–115%) ensure tablet quality [12].
Disintegration time	IR tablets should disintegrate within 1–2 min; optimized SIT tablets showed 14 s [12].
In vitro dissolution	Carried out using USP Type II (paddle) apparatus in phosphate buffer (pH 6.8). IR tablets release >85% within 15 min, while matrix tablets release up to 12 h following zero-order or Higuchi models [13].
Kinetic modeling	Drug release data fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to understand the mechanism [14].
Stability studies	Conducted under ICH conditions (40 °C/75% RH) for 3–6 months to evaluate changes in drug content, hardness, and release [15].

Buccal Delivery System

Buccal delivery system (BDS) was used to skip first pass metabolism as it absorbed through the buccal mucosal membrane [16]. BDS comprised polymers that retain excellent mucoadhesive parcels such as PVP (Poly vinyl pyrrolidine), MC (Methyl cellulose), SCMC (Sodium carboxyl methyl cellulose), HPC (Hydroxyl propyl cellulose), carbopol, chitosan and eudragit analogues.

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Shakir et al[17] in (2022) designed a mucoadhesive BDS for the extended action of MET and SIT against diabetes with enhanced bioavailability. In formulations, blend of Carbopol® 940 (CP), agarose, or PVP as mucoadhesive agents was employed. Tablets were assessed for physicochemical, and in vivo mucoadhesive characteristics. The formulation R4 demonstrated drug loading, with total drug release for six h and ex vivo mucoadhesive power [18]. SIT can be absorbed directly into the bloodstream. For example, a mucoadhesive buccal *patch* containing SIT (formulated with HPMC E5 and Eudragit RL100) was reported to detach within 6.5 h and release ~99.7% of the drug in vitro. Such a patch formulation "overcomes the limitations of current routes" by providing rapid onset via the oral mucosa. Similarly, mucoadhesive buccal *tablets* co-formulating sitagliptin with metformin have been developed. One optimized Carbopol®/PVP buccal tablet (with high "exorbitant" drug loading) achieved complete release of both SIT and metformin in ~6 h. These buccal formulations offer prolonged exposure and reduce first-pass loss, potentially improving bioavailability. [19, 20]. The foremost advantage of Buccal drug delivery is the getaway of first pass metabolism, enhancing compliance and rapid drug action.[21, 22]. The evaluation of SIT buccal tablets should be carried out regarding the parameters required as in table 2.

Table 2. Evaluation of SIT Buccal Formulations.

Parameter	Description and Significance
Physical appearance and thickness	Uniformity ensures proper dosing and patient comfort [22].
Surface pH	Maintained between 6.0–7.0 to avoid mucosal irritation [23].
Folding endurance	Indicates mechanical strength; should exceed 200 folds [23].
Mucoadhesive strength/time	Measured using texture analyzer or modified balance; reflects polymer–mucosa interaction (optimal >30 g/cm²) [23].
Swelling index	Determines hydration and mucoadhesion potential [24].
Drug content uniformity	Ensures consistent drug distribution; acceptable range 95–105% [24].
In vitro dissolution	Conducted in artificial saliva or phosphate buffer (pH 6.8). SIT release typically sustained up to 6 h [25].
Ex vivo permeation	Using goat/bovine buccal mucosa in Franz diffusion cells to assess permeability and flux [25].
In vivo bioavailability	Evaluated in animal models or humans to compare plasma concentration vs. oral administration [26].

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Transdermal patches

Transdermal drug delivery techniques are a possible treatment choice for diabetes. The skin is a barrier that can be manipulated for drugs to permeate the body; therefore, a transdermal patch is likely to treat diabetes. Ng et al [27] developed SIT transdermal patches used a solvent-casting method to produce SIT patches from ethylcellulose and HPMC polymer blends. These patches were uniform (~0.21–0.26 mm thick) with high SIT loading (95.6–99.4% of target dose). In vitro skin diffusion (Franz cell) showed Higuchi kinetics and sustained SIT release; notably, an ethylcellulose/HPMC patch gave faster release than an Eudragit/HPMC one. All formulations remained physically stable under storage. Such patches can deliver SIT continuously through skin, potentially enabling once- or twice-daily dosing without gastrointestinal passage. Transdermal SIT patches were manufactured by the solvent casting evaporation employing ethyl cellulose: HPMC, and Eudragit. The physicochemical characteristics, such as flexibility, thickness, weight variation, moisture content, hardness, and folding endurance, were assessed. The formulation exhibited flexibility, uniform thickness and weight, smoothness, and drug content (>95%). The stability investigations demonstrated that all the patches preserved acceptable physicochemical characteristics and drug content after being kept in various storage conditions [28]. Transdermal patches induce skin reactions. These reactions usually generate pain or discomfort for the patient. Signs and symptoms of irritant contact dermatitis may be minimized by rotating the application site, careful discarding of the patch, and proper usage of moisturizers and topical corticosteroids [29, 30]. The evaluation of SIT transdermal patches is revealed in Table 3.

Table 3. Evaluation of SIT Transdermal Patches

Parameter	Purpose and Observation
Thickness & weight variation	Ensures uniformity in dosing [31].
Moisture content & uptake	Affects patch flexibility and stability [31].
Folding endurance	Confirms mechanical strength; >200 folds acceptable [31].
Tensile strength & elongation	Evaluates patch elasticity [31].
Drug content uniformity	Should be within 95–105% of the label claim [32].
In vitro drug release	Conducted using Franz diffusion cells and phosphate buffer (pH 7.4). SIT release sustained up to 24 h [32].
Permeation studies	Using excised rat/human skin; data fitted to diffusion models (Higuchi or Korsmeyer–Peppas) [32].
Skin irritation test	Performed on animal models to evaluate erythema and

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Parameter	Purpose and Observation
	edema [33].
Stability studies	Patches remain stable under ambient and accelerated storage conditions [32].

Self-nanoemulsifying (SNEDDS)

SNEDDS is one of the favorable procedures to overcome the formulation complications of diverse hydrophobic/lipophilic drugs and to enhance the oral bioavailability of poorly absorbed drugs [3, 4]. SNEDDS is isotropic mixture of natural or synthetic oil, surfactants, and co-surfactants that have a unique ability to form fine oil-in-water (O/W) nano-emulsions [34]. Kazi et al. [35] in 2020 developed SIT and dapagliflozin using SNEDDS employing triglyceride oil, mixed glycerides, and surfactants. The *in vivo* bioavailability and anti-diabetic influence were investigated to compare the SNEDDS with the marketed product Dapazin®. The SNEDDS comprised black seed oil, which exhibited excellent self-emulsification. SNEDDS were characterized, delivering droplets of ranged from 50nm to 66.57 nm. The investigations demonstrated the substantial inhibition of glucose in diabetic mice. SNEDDS enhance drug solubility, permeability, and bioavailability after oral administration [36]. However, the main disadvantage of SNEDDS are instabilities, high Surfactant percent, cost and incompatibility and reduced stability [37]. The evaluation of SIT SNEDDS is illustrated in table 4.

Table 4. Evaluation of SIT SNEDDS

Evaluation Parameter	Purpose and Results
Self-emulsification time	Time for emulsion formation upon dilution; <1 min preferred [38].
Visual assessment	Clarity and absence of phase separation confirm good emulsification [39].
Droplet size & PDI	Measured by dynamic light scattering; 50–100 nm with PDI < 0.3 desirable [39].
Zeta potential	Indicates physical stability; values ±20–30 mV signify stable nanoemulsion [39].
Drug loading & entrapment efficiency	Assesses how much drug is solubilized; >95% ideal [39].
Thermodynamic stability	Freeze–thaw and centrifugation tests ensure physical stability [40].
In vitro dissolution	Compared with pure drug or tablet; SIT-SNEDDS shows faster and complete release within 15–30 min [40].
In vivo bioavailability	Animal studies reveal higher C_max and AUC values compared to marketed formulations [41,42].

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All formulations strategies are demonstrated in Table 5 and Figure 1 regarding excipients, advantages, mechanism and limitation

Table 5. Summarize the formulation of SIT.

Formulation	Key Components/Polymers	Mechanism	Advantages	Limitations
Immediate-release tablets	Crospovidone, sodium starch glycolate	Rapid disintegration	Fast onset, simple manufacture	Frequent dosing
Controlled-release tablets	HPMC, xanthan gum, PLGA	Diffusion/erosion control	Prolonged effect	Variable release rate
Buccal systems	Carbopol, PVP, HPMC, chitosan	Mucoadhesion	Avoids first pass, sustained action	Limited drug load
Transdermal patches	Ethylcellulose, HPMC, Eudragit	Skin permeation	Non-invasive, steady levels	Possible irritation
SNEDDS	Oils, surfactant/co-surfactant	Nanoemulsion formation	Enhances solubility and bioavailability	Instability, high surfactant load

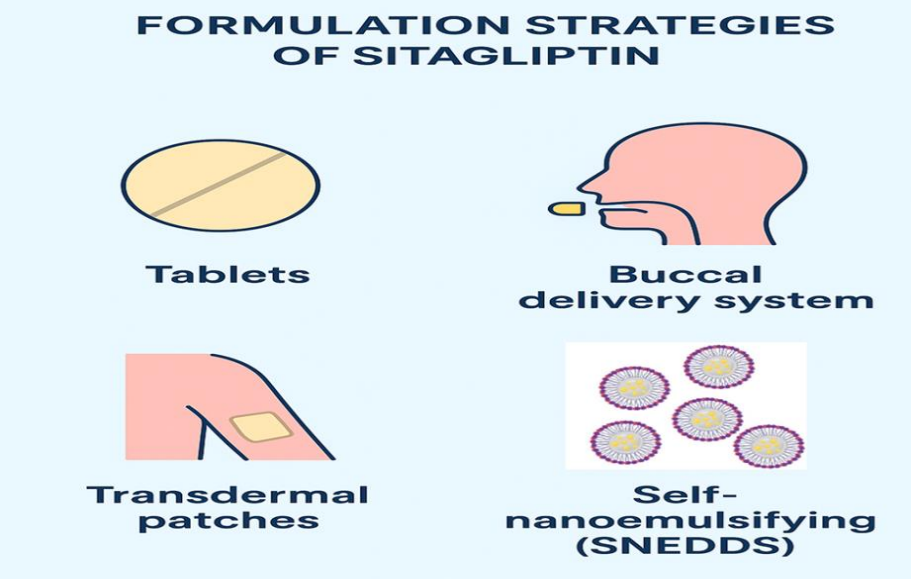

Figure 1. SIT formulations strategies.

Conclusion

Sitagliptin (SIT) continues to receive significant formulation attention due to its short half-life, moderate bioavailability, and the clinical need for flexible, patient-friendly delivery systems. A wide spectrum of formulation strategies ranging from conventional immediate-release tablets to advanced buccal, transdermal, and lipid-based systems demonstrates the versatility of SIT and

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highlights ongoing efforts to optimize its therapeutic performance. Immediate-release tablets remain the simplest and most commonly used dosage form, providing rapid onset but requiring strict adherence to avoid fluctuations in plasma levels. Controlled-release matrix tablets, microspheres, and gastroretentive designs successfully prolong SIT release for 12–24 hours, improving convenience and steady glycemic control. Buccal delivery systems further enhance bioavailability by bypassing first-pass metabolism, offering sustained release with strong mucoadhesion. Transdermal patches provide an alternative non-invasive approach, enabling extended and controlled drug delivery while avoiding gastrointestinal barriers, though skin irritation remains a potential limitation. Lipid-based SNEDDS formulations show significant promise for enhancing solubility, permeability, and systemic exposure, especially for combination therapies. Overall, these formulation strategies collectively demonstrate that SIT can be tailored for rapid, sustained, targeted, or enhanced delivery depending on clinical need. Future research should focus on integrating patient-centric design, minimizing excipient-related limitations, and validating in vivo performance to support the translation of these advanced systems into commercial products.

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