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Comparative In-Vitro Dissolution and HPLC Analysis of Metformin-Sitagliptin Combination: A Study of the Iraqi Pharmaceutical Market

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Abstract

The study aimed to evaluate in vitro dissolution profiles and bioequivalence of three metformin-sitagliptin combination drug products Janumet (Reference Product), SITAVIA PLUS and Sitaglamet products available in the Iraqi pharmaceutical market. A dissolution profile was running using a validated HPLC method in 0.025 M NaCl media following the Dissolution Test at 37°C. HPLC used an LC-20AD Shimadzu binary pump, an SPD-20A detector operating under isocratic conditions at a flow rate of 1 mL/min and detection wavelength was set up at 208 nm. difference factor (f1) values of metformin 0.48 and 0.89 with sitagliptin for SITAVIA PLUS, and 2.79 and 1.10 for Sitaglamet were obtained, indicating minimal differences compared with Janumet. Furthermore, similarity factor (f2) of 89.82, 85.01 with metformin and sitagliptin for SITAVIA PLUS, and 67.75, 70.86 for Sitaglamet was obtained indicating equivalence. The study concluded that all products released over 90% of their products within 30 minutes with Sitaglamet demonstrating faster initial release. The results of this study emphasize the importance of utilizing HPLC to accomplish accurate quantification of in-vitro drug release, allowing the substitution of Sitaglamet or SITAVIA PLUS for Janumet. Additionally, rigorous quality control testing is critical in guaranteeing patient safety and treatment.

Introduction

The number of people living with type-2 (non-insulin dependent) diabetes has surged dramatically, from 108 million in 1980 to 422 million in 2014, with low- and middle-income countries have seen particularly rapid increases [1]. This chronic blood glucose-regulating condition goes hand in hand with severe health complications like blindness, kidney failure, heart attack, stroke, and lower limb amputation [2]. Between 2000 and 2019, diabetes mortality rates modestly increased by 3% per age group resulting in nearly 2 million deaths due to diabetes and diabetes-related kidney disease in 2019 [3,4].

Oral antidiabetic drugs, which are tablets used to manage type 2 diabetes, mainly act by one or more mechanisms which help in regulating blood glucose levels. Biguanides are a category of oral antidiabetic drugs primarily used in type 2 diabetes management with metformin being the most commonly used drug in this category [5,6]. They are known for their glucose-lowering efficacy without causing significant hypoglycemia. Metformin (1,1-Dimethylbiguanide) lowers blood glucose through multiple pathways. They mainly stop glucose production in liver by inhibiting hepatic gluconeogenesis. In addition, they increase sensitivity to insulin in both muscle and fat tissues leading to increased glucose uptake, and glucose utilization. Metformin also inhibits intestinal glucose absorption, which decreases blood sugar after meals. By activating AMPK (AMP-activated protein kinase), metformin alters the energetic balance in the body, reducing glucose and fat production. Given its mechanism and low risk of hypoglycemia metformin is recommended for all patients newly diagnosed with type 2 diabetes [6-8].

Sitagliptin ((3*R*)-3-amino-1-[3-(trifluoromethyl)-6,8-dihydro-5*H*-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl) butan-1-one), like other oral antidiabetic agents, plays a crucial role in managing type 2 diabetes. Sitagliptin works by inhibiting the dipeptidyl peptidase-4 inhibitors (DPP-4) enzyme, which is responsible for degrading incretin hormones, particularly glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). [9] By blocking this enzyme, sitagliptin enhances the levels of active incretin hormones in the bloodstream, leading to increased insulin secretion and decreased glucagon levels, which help control blood glucose without a significant risk of hypoglycemia. This makes it comparable to other oral agents like metformin, which primarily reduces glucose production in the liver, or sulfonylureas, which directly stimulates insulin release [10,11].

The global pharmaceutical market plays a crucial role in healthcare, with drugs accounting for approximately 10% of total market share, a figure expected to rise to 25% in developing countries and up to 50% in poorer regions. However, counterfeit and substandard drugs are a growing concern, especially in low-income countries, where the FDA reports that nearly 25% of available medications fall below quality standards [12]. The World Health Organization (WHO) estimates that the global trade in fake medicines amounts to around 75 billion euros annually [13]. Ensuring the quality of pharmaceutical products is essential for patient safety and efficacy, particularly with generic medications, which are widely used to reduce healthcare costs. Quality assessments of generic drugs, including tests for weight variation, and dissolution, are critical in ensuring bioequivalence with innovator drugs. Pharmaceutical products must meet stringent standards to be classified as quality drugs. Ensuring the quality of generic medications involves examining various parameters during manufacturing and throughout their shelf-life. Additionally, the drug release profile from tablet dosage forms is assessed through disintegration and dissolution studies. It is crucial for a drug to be in solution before absorption into systemic circulation; thus, effective release in the gastrointestinal tract is vital for therapeutic efficacy [14,15].

In vitro dissolution testing plays a pivotal role in understanding the rate and extent of drug release within the body. WHO advocates for substituting innovator products with generics when sufficient evidence supports their bioequivalence and quality. Comparative in vitro bioequivalence studies between innovator and generic products are necessary for marketing authorization. Failure to ensure bioequivalence may lead to altered pharmacokinetic profiles, resulting in subtherapeutic drug concentrations and diminished therapeutic effects. Dissolution testing serves as an important indicator for identifying bioavailability issues. Recently, the use of in vitro dissolution testing has expanded significantly, as it can sometimes replace in vivo bioequivalence studies for certain active pharmaceutical ingredients (APIs). The need for the selection of such technical medicine testing in healthcare to keep its efficiency intact with quality maintenance in minimum resources has now been on a rise due to this shift [14,16].

The Aim of the study employed High-performance liquid chromatography HPLC chromatographic technique for the assessment of in-vitro release profiles of tablets (50 mg Sitagliptin and 500 mg Metformin) in 0.025 M NaCl aqueous solution (FDA Dissolution Methods Database). It is a very accurate method for control comparisons between the test and reference product in drug release data.

Materials and Methods

Chemicals and Reagents

The quantification study, of Janumet (MSD, Germany), SITAVIA PLUS (Pioneer, Iraq) and Sitaglamet (Maddox, Netherland) tablets (50/500 mg sitagliptin and metformin) were sourced from a local Pharmacy, Sodium Chloride (NaCl), pure form BDH (UK). The active pharmaceutical ingredients (APIs) analyzed included Metformin Hydrochloride (Sohan Healthcare, India, and Sitagliptin Phosphate (Indexim International, Gujarat, India), Monopotassium phosphate (A-Z Chem, 95-100.5% purity) with all APIs exhibiting purity levels exceeding 99.9%. HPLC-grade Acetonitrile and Methanol (99.95% purity) were acquired from Merck, Germany.

Apparatus and Chromatographic System Conditions

The simultaneous quantification of Metformin Hydrochloride, and Sitagliptin Phosphate, was conducted on a Shimadzu HPLC system (Shimadzu, Japan), featuring an LC-20AD binary pump, a DGU-20A5 degasser, and a manual injector with a 100 µL loop (USA). The separation was achieved on a CN column (250 mm), utilized in reverse-phase mode with a stationary phase. The detection was performed using an SPD-20A UV/VIS detector at a wavelength of 208 nm. The column temperature was maintained at 30°C under isocratic conditions, with 1 mL/min flow rate. Dissolution tester apparatus Test eight vessels (PHARMATEST, Germany).

Data acquisition and processing: were managed using the LC Solution software (Shimadzu, Japan), interfaced with a CBM-20A communication bus module. Microsoft Office 2019 and Excel 2019 were utilized to determine the following parameters: area under the dissolution curve (AUP), mean dissolution time, dissolution efficiency (DE), difference factor (f1), similarity factor (f2), and linearity curve.

Solutions Preparation

Mobile phase: To prepare the mobile phase, whight 2.721gm of monopotassium phosphate KH_2PO_4 was dissolved in 1L of deionized water to create a 20 mM phosphate buffer. The pH was initially adjusted to 2.35 using 10 mM of phosphoric acid. Subsequently, methanol (30% v/v) and acetonitrile (5% v/v) were added to the buffer. A final pH adjustment to 2.9 was made to ensure optimal conditions if necessary. The mobile phase was carefully filtered and degassed, a crucial step to enhance the ruggedness and reliability of the analytical method used.

Dissolution medium: A 0.025 M sodium chloride (NaCl) dissolution medium was prepared by dissolving 8.766 g of NaCl in 6 Liter of distilled water, providing a controlled and stable environment for accurate drug dissolution testing (see FDA Dissolution Methods Database). [17,18] To evaluate the linearity of the method, calibration curves for metformin hydrochloride and sitagliptin phosphate were established through systematic preparation of stock and working solutions using separate volumetric flasks for accuracy.

Stock Solution Preparation: 100 ml volumetric flask was taken for the preparation of stock solution of 1 mg/ml of each analyte. For metformin weighing about 100mg of metformin was taken in the flask followed with filling off the flask up to 100 mL mark with mobile phase turning it to the aspired concentration.

The flask was rinsed and dried after every use prior to sitagliptin stock solution preparation and in the same manner for sitagliptin 100mg of sitagliptin phosphate was weighed and dissolved and diluted to get a 1 mg/mL solution in 100 ml volumetric flask.

Standard Curve Solution Preparation: For the linearity study, working solutions were prepared by diluting the stock solutions in 50 mL volumetric flasks. Nine metformin solutions with concentrations ranging from (0.01 mg/mL to 0.1 mg/mL) were prepared by appropriate dilutions from the metformin stock. Similarly, for sitagliptin, eight solutions with concentrations ranging from (0.002 mg/mL to 0.01 mg/mL) were prepared by diluting the stock solution in 50 mL volumetric flasks.

Dissolution Profile Test

The dissolution test was conducted to compare the generic product with the brand (innovator) product using three independent runs on a USP Apparatus 2 (paddle) system, with each run comprising eight vessels. For each product (generic and brand), a total of twelve tablets were tested across these runs, allowing for a statistically robust comparison. [16] In each run, the eight vessels were filled with 900 mL of 0.025 M NaCl dissolution medium, maintained at 37 ± 2 °C. The paddle apparatus was set to operate at 75 rpm. Samples of 5 mL were withdrawn from each vessel at intervals of 10, 15, 20, and 30 minutes. [17,18] After each withdrawal, the volume was immediately compensated with fresh dissolution medium to maintain consistent conditions across all vessels. Following sample withdrawal, each sample was filtered through a Filter paper to ensure clarity and purity. From each filtered sample, 1 mL was diluted to 10 mL using the mobile phase as a diluent to achieve the appropriate concentration for HPLC analysis. Subsequently, the diluted samples were injected into the HPLC system for accurate quantification of drug release at every time point. Under these conditions, metformin showed a retention time of 3.0 min while sitagliptin at 6.1 min.

The method validation was performed and chromatographic conditions were established as per the International Council for Harmonization (ICH) guidelines and USP (United States Pharmacopeia) method validation requirements, that assure accuracy, precision, specificity reproducibility. [19-21] The percentage of drug released over time as analyzed after plotting dissolution profiles of generic and brand products. Bio-equivalence was determined by using a difference factor (f1) and similarity factor (f2). A generic product with f1 value between 0 to 15, and f2 value between 50 to 100 could be regarded as having similar dissolution profile concerning the brand product indicating potential bioequivalence. [16,22]

The f1 and f2 values were calculated by the following formulas:

$$f1 = \left(\frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right) \times 100$$

$$f2 = 50 \times \log \left(\frac{1}{1 + \left(\frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right)} \right) \times 100$$

Rt and Tt indicate respectively the cumulative percentage dissolved each sampling time for the reference (brand) and test (generic) products and of course n stand for number of sampling points. This design of three batches with 12 units per bath was suitable to get a dependable comparison of dissolution profiles that would serve as warrant for bioequivalence determination between the generic and brand products. [16,22].

Results and Discussion

Standard curve and Linearity

Linearity of this method for metformin and sitagliptin assessed standard solutions covering specific concentration ranges were prepared and each concentration level was replicated three times to ensure precision. For metformin, solutions ranged from 60% to 140% (nine levels) of the target concentration, corresponding to concentrations from 0.011 to 0.11 mg/mL Fig. 1 and Fig.2a, while for sitagliptin, the range was 70% to 140% (eight levels) of the target concentration, corresponding to concentrations from 0.0022 to 0.011 mg/mL, Fig. 1 and Fig.2b. These target concentrations represent the drug content of a fully dissolved tablet in 900 mL of medium, further diluted by 1:10 with mobile phase.

The relationship between peak area and concentration was evaluated for each compound. Results demonstrated excellent linearity over the specified ranges, with correlation coefficients (R^2) of 0.9992 for metformin and 0.998 for sitagliptin. Additionally, the relative standard deviation coefficients were calculated as 1.54% for metformin and 1.97% for sitagliptin. These values confirm the method's robustness and accuracy across the tested concentration ranges. The LOD, LOQ, linearity equations, and other parameters are detailed in Table 1, reflecting the method's sensitivity and fit:

Table 1: Parameter data results of Linearity curve.

Parameter	Metformin	Sitagliptin
Concentration Range (mg/mL)	0.011-0.11	0.0022-0.011
Correlation Coefficient (R^2)	0.999	0.998
Relative Standard Deviation Coefficient%	1.54	1.97
Limit of Detection (LOD, mg/mL)	0.00649	0.00118
Limit of Quantitation (LOQ, mg/mL)	0.01967	0.00357
Slope	432,785,442.44	216,309,445.16

Intercept	113,091.57	-31,763.91
Area under the peak (AUP) Mean	24132683.63	1288805
Recovery Mean %	99.80	100.22
Linearity Equation	y = 432,785,442.442x + 113,091.574	y = 216,309,445.159x - 31,763.913

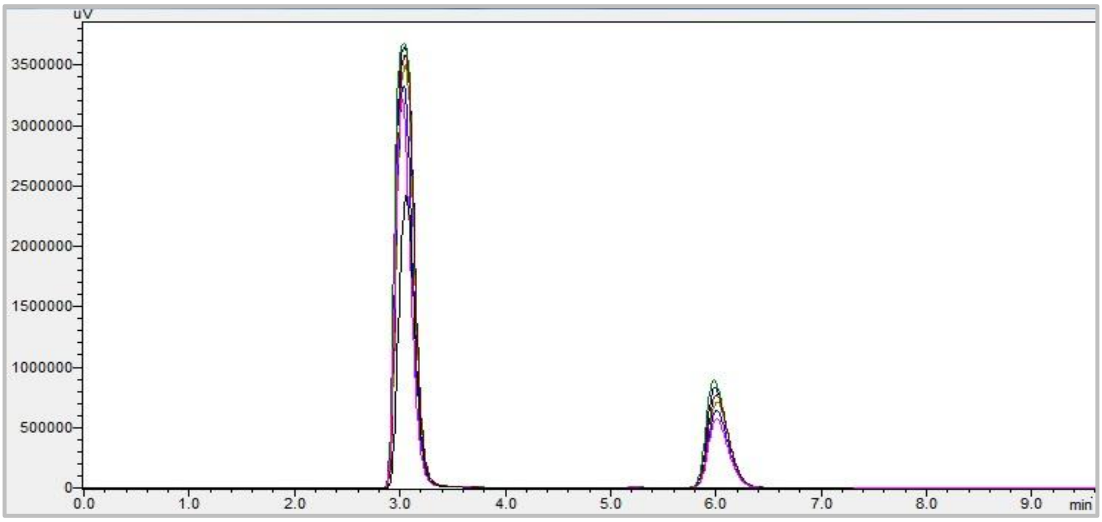
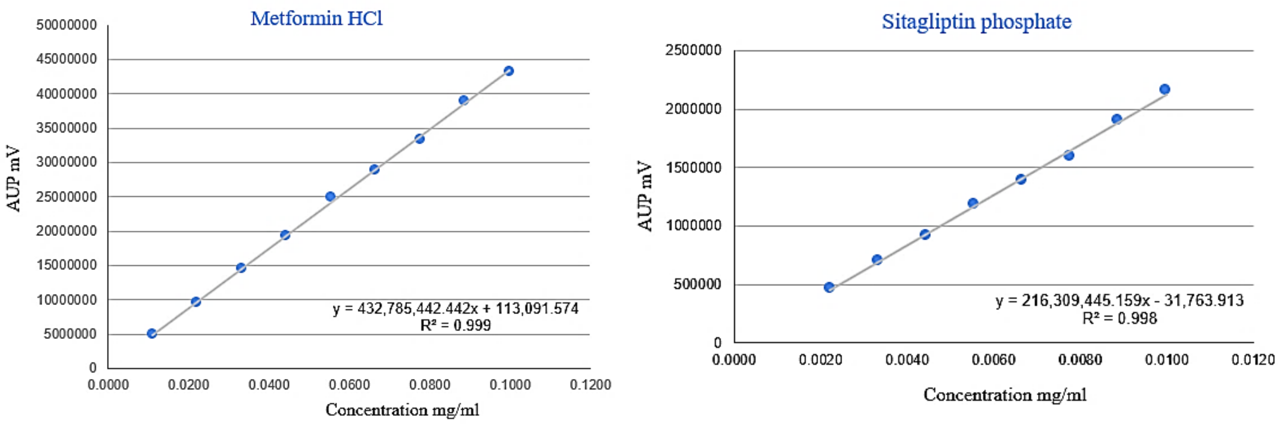


Fig. 1: *HPLC Chromatogram of Metformin HCl was 0.011-0.110 mg/mL, Sitagliptin Phosphate 0.0022-0.011 mg/mL in all levels.*



a *b*

Fig. 2: *Linearity and equation of (a) Metformin HCl was 0.011-0.110 mg/mL, (b) Sitagliptin Phosphate 0.0022-0.011 mg/mL. AUP: Area under the peak.*

Dissolution Profile

The tables present data on the release profiles of metformin and sitagliptin from three drug formulations—Janumet, SITAVIA PLUS, and Sitaglamet. The first table details the percentage of drugs released over time (10, 15, 20, and 30 minutes) and corresponding (AUP) release percentages, comparing these with the reference, Janumet. For metformin, the release percentages show that while all three drugs reach a similar release plateau around 30 minutes, there is a distinction at the earlier time points. Sitaglamet exhibits a slightly faster release rate, reaching 85.4% at 10 minutes compared to 77.1% for Janumet and 78.2% for SITAVIA PLUS. By 30 minutes, all three drugs demonstrate comparable metformin release, around 91-92%, indicating a convergence in their release profiles (Table 2).

Similarly, for sitagliptin, the initial release rates vary more distinctly, with Sitaglamet again showing a higher release (80.2%) at 10 minutes versus Janumet's 73.4%. As time progresses, the release percentages for sitagliptin align closely across the three formulations, approaching 94-95% by 30 minutes (Table 2). These patterns are supported graphically, showing the release curves for each formulation that converge as time progresses, especially after 20 minutes (Fig. 3).

Similarity factors, f1 and f2, which quantify the differences and similarities in drug release between the reference product (Janumet) and the other formulations. The f1 factor measures the difference in release, with values under 15 indicating minor differences. Both SITAVIA PLUS (0.48 for metformin and 0.89 for sitagliptin) and Sitaglamet (2.79 for metformin and 1.10 for sitagliptin) have low f1 values, suggesting minimal divergence from Janumet. The f2 factor reflects the similarity, with values above 50 confirming close similarity. SITAVIA PLUS displays higher f2 values (89.82 for metformin and 85.01 for sitagliptin), indicating a near-identical release profile to Janumet, while Sitaglamet, with slightly lower f2 values (67.75 for metformin and 70.86 for sitagliptin), still demonstrates similarity but with a slightly faster release in the initial stages (Table 3).

The data suggest (Table 2,3) that all formulations offer comparable drug release profiles with SITAVIA PLUS closely matching Janumet's release pattern and Sitaglamet achieving faster initial release, particularly for metformin, yet converging over time. The graph illustrates (Fig. 3) these trends clearly, highlighting the similarity in the release kinetics over time and validating both SITAVIA PLUS and Sitaglamet as potential alternatives to Janumet, with minor variances at earlier time points.

Table 2: The in vitro drug release study of sitagliptin and metformin hydrochloride was compared with the release profile of the reference product, Janumet ® 50/500 mg.

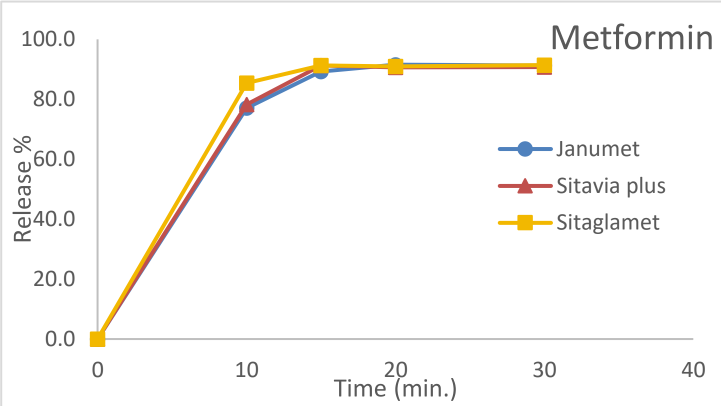
Drug	Time (min.)	Drug release (mean for n*)					
		Janumet®		SITAVIA PLUS®		Sitaglamet®	
		AUP (mV)	Release %	AUP (mV)	Release %	AUP (mV)	Release %
Metformin	10	37144774	77.1	37692125	78.2	41146245	85.4
	15	43005800	89.3	42821514	88.9	43949261	91.3
	20	44092156	91.5	43608570	90.7	43790265	90.9
	30	43980344	91.3	43724157	90.8	44024267	91.4
Sitagliptin	10	2232783	73.4	2334258	76.7	2443786	80.2
	15	2742391	89.8	2765859	90.7	2767700	90.7
	20	2865389	93.8	2859457	93.7	2809622	92.1
	30	2899109	94.9	2877354	94.3	2841039	93.0

*Drug release was evaluated for each brand with **n = 12** replicates. Janumet is the reference product.

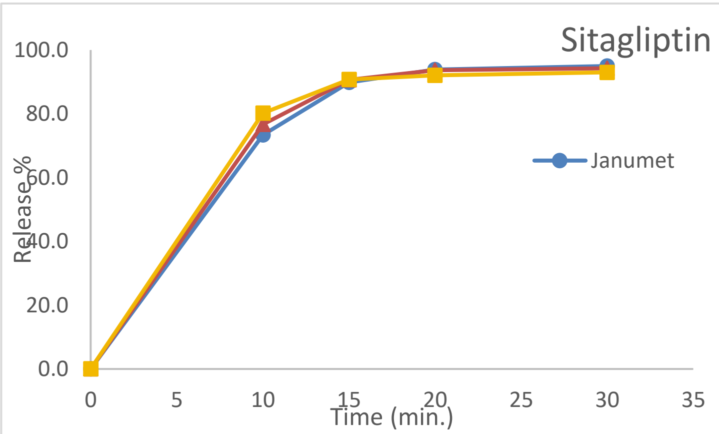
Table 3: Comparative Similarity Factors (f1 and f2) for Metformin and Sitagliptin Release

Drug	Comparison	SITAVIA PLUS®	Sitaglamet®
Metformin	**f1**	0.48	2.79
	f2	89.82	67.75
Sitagliptin	**f1**	0.89	1.10
	f2	85.01	70.86

Fig.3: In Vitro Release Profiles of (a) Metformin and Sitagliptin from Tablet (SITAVIA PLUS and Sitaglamet) Compared to Janumet ® 50/500 mg.



a



b

Conclusions

The optimized mobile phase preparation and dissolution test setup provided a robust basis for comparing the in vitro release profiles of metformin and sitagliptin from Janumet, SITAVIA PLUS, and Sitaglamet. The mobile phase, a carefully adjusted 20 mM phosphate buffer at pH 2.9 with added methanol and acetonitrile, ensured stability and reliability in HPLC analysis, contributing to the precision of drug quantification at each interval. Using the USP Apparatus 2 (paddle) with a standardized 900 mL NaCl dissolution medium at 37 ± 2 °C and a sampling protocol designed to maintain consistent vessel conditions, the study achieved a statistically sound comparison of the release profiles between the test and reference formulations. Results indicate that SITAVIA PLUS shows a nearly identical release pattern to Janumet, while

Sitaglamet exhibits a slightly faster initial release, though all formulations converge in release behavior by 30 minutes. The similarity factors further reinforce the close alignment of SITAVIA PLUS with Janumet, supporting its potential as a highly similar alternative. Sitaglamet also demonstrates comparable release behavior, making it a viable option with slightly distinct initial release kinetics. This analysis underscores the potential interchangeability of these formulations, with SITAVIA PLUS particularly well-suited as an alternative based on its close match to Janumet's therapeutic release profile, thus meeting essential bioequivalence criteria while accommodating therapeutic needs and release timing preferences.

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التحليل المقارن للذوبانية خارج الجسم الحي والتحليل الكروماتوغرافي السائل عالي الأداء لمزيج الميتفورمين-سيتاكلبتين: دراسة عن سوق الأدوية العراقي

محمود شاكر السامرائي، ايمان ذياب احمد

قسم الكيمياء، كلية التربية، جامعة سامراء

البحث مستل من اطروحة دكتوراه الباحث الاول

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تاريخ القبـــول: 2025/03/05
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الكلمات المفتاحية:

ازالة الكادميوم، التخثر الكهربائي، مياه الصرف الصحي

معلومات المؤلف

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الموبايل:

الخلاصة:

هدفت الدراسة إلى تقييم سلوك انحلال الأدوية ومدى التكافؤ الحيوي لثلاثة منتجات دوائية تجمع بين الميتفورمين والسيتاجليبتين، وهي Janumet :(المنتج المرجعي)، وSITAVIA PLUS، وSitaglamet، المتوفرة في السوق الدوائي العراقي. تم إجراء اختبار الانحلال باستخدام طريقة HPLC معتمدة في وسط من كلوريد الصوديوم بتركيز 0.025 M، وتم تنفيذ الاختبار عند درجة حرارة 37 °C.استخدمت تقنية HPLCمضخة ثنائية من طراز LC-20AD Shimadzu، وكاشف من نوع SPD-20Aيعمل بمعدل تدفق 1 مل/دقيقة، وتم ضبط طول الموجة الكاشفة على 208 نانومتر. أظهرت النتائج أن عوامل الاختلاف (f1) للميتفورمين كانت 0.48 و0.89 للسيتاجليبتين في منتج SITAVIA PLUS، بينما كانت 2.79 و1.10 في منتج Sitaglamet، مما يشير إلى وجود اختلافات طفيفة مقارنة بالمنتج المرجعي Janumet. كما أظهرت عوامل التشابه (f2) قيمًا بلغت 89.82 و85.01 للميتفورمين والسيتاجليبتين في SITAVIA PLUS، و67.75 و70.86 في Sitaglamet، مما يؤكد التكافؤ بين المنتجات. خلصت الدراسة إلى أن جميع المنتجات أطلقت أكثر من 90% من المادة الفعالة خلال 30 دقيقة، مع ملاحظة أن Sitaglamet أظهر سرعة أعلى في الإطلاق الأولي. تؤكد هذه النتائج أهمية استخدام تقنية HPLC للحصول على قياسات دقيقة لانحلال الأدوية في المختبر، مما يسمح باستبدال Janumet بمنتجات مثل Sitaglamet أو SITAVIA PLUS. بالإضافة إلى ذلك، تُبرز الدراسة ضرورة إجراء اختبارات مراقبة جودة صارمة لضمان سلامة المرضى وفعالية العلاج.