

RESEARCH ARTICLE

Development and Validation of New Discriminative Dissolution Method for Dapagliflozin Tablets

Sandip Badadhe¹, Hanumant Bhusnar², Avinash Birajdar³, Jayadeep Yadav^{3*}, Bhagwat Chavan⁴

¹Abasaheb Kakade College of B Pharmacy Bodhegaon, Dist-Ahmednagar, Maharashtra, India.

²Endo India Par Formulation Mumbai, Maharashtra, India.

³Dinesh Bembade College of Pharmacy, Mahalangra, Chakur, Latur, Maharashtra, India.

⁴JSPM's Jayawantrao Sawant College of Pharmacy and Research, Hadapsar, Pune, Maharashtra, India.

Received: 05th January, 2024; Revised: 29th January, 2024; Accepted: 25th February, 2024; Available Online: 25th March, 2024

ABSTRACT

In this study, we aimed to find out how well dapagliflozin worked by creating and testing a new way to dissolve the pills. We considered a great many factors, including the quantity of dissolved liquid, the liquid's composition, and the rotational speed of the paddle. Apparatus II, or the paddle, was employed to get the perfect *in-vitro* breakdown profile. The dissolving media consisted of 900 mL of phosphate buffer with a pH of 6.8, and the machine was spun at a speed of 50 revolutions per minute. For the purpose of assessing the drug release method's properties, high-performance liquid chromatography (HPLC) was used. Regarding the dissolving procedure, which was found to be in compliance with regulations, all applicable laws were followed, including those of the Food and Drug Administration (FDA). Extensive evaluation of several attributes, including precision, sensitivity, accuracy, and stability, led to the conclusion that the outcomes were satisfactory. We examined the patterns of breakdown for many entities using a range of methodologies, including model-dependent methodology, model-independent methodology, and analysis of variance (ANOVA). According to the results, there was a great deal of overlap between the two things. Dapagliflozin tablet production and quality control could benefit from the melting test that was given and shown. This is because it can distinguish among the examined commodities according to their unique release characteristics.

Keywords: Dapagliflozin, Dissimilarity factor, Discriminative dissolution, Similarity factor.

International Journal of Drug Delivery Technology (2024); DOI: 10.25258/ijddt.14.1.58

How to cite this article: Badadhe S, Bhusnar H, Birajdar A, Yadav J, Chavan B. Development and Validation of New Discriminative Dissolution Method for Dapagliflozin Tablets. International Journal of Drug Delivery Technology. 2024;14(1):396-404.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

After oral administration, the absorption of pharmacological molecules is influenced by a number of different circumstances. All of these factors should be taken into account, including the gastrointestinal permeability, solubility, and release manner of the prescription. Given the amount of focus that is placed on the first two steps, it is possible that *in-vitro* dissolution processes may cause *in-vivo* performance estimations to be inaccurate. Disintegration is an extremely important factor to consider when evaluating the quality of solid oral medication delivery devices such as tablets and capsules. *In-vitro* dissolution testing, a valuable quality control tool, guarantees the constancy of solid dosage forms throughout the research and manufacturing processes. Multiple studies have shown this.^{1,2}

Tablets and capsules are also included in this package. Testing for dissolution may be used in a variety of contexts, including the pharmaceutical business. It is possible that these technologies will first evaluate the crystal structure of the active pharmaceutical ingredient (API), as well as the

particle size and other significant features. It is possible that, upon examination, this data may give insights that might lead to innovations in formulation. They could come in handy while selecting the optimal mix and enhancing output. It is possible that the approach will need careful equipment and compressive pressure selection in order to achieve the highest possible dosage form quality and efficiency. The fourth part of the process involves dissolving tests, which are used to check the quality consistency of a pharmaceutical product among samples. Additionally, the comparison of innovative or generic formulations to medications already on the market might be sped up with these methodologies.^{3,4}

These tests may be used to evaluate the stability of a pharmaceutical product and assist in determining the date on which it will expire. Last but not least, dissolution tests are very important for ensuring the quality of a product after it has been approved and at certain expansion levels (SUPAC). Changes can be required to be made to the minimum number of units, the manufacturing facility, and the size of the unit.

*Author for Correspondence: drjayadeepyadav@gmail.com

These modifications could be required in the future. In order to conduct an analysis of biopharmaceutical classification system (BCS) class II pharmacological compounds that have moderate to poor solubility, dissolution tests are required. The rate at which a chemical dissolved in water influences the rate at which the digestive system absorbs it. When developing a dissolving technique for this category of drugs, it is necessary to take into consideration a number of additional concerns. The ability to differentiate between different formulations of active components is referred to as “discriminatory capacity” in dissolving procedures. Even if there is a possibility that the method has certain problems, it is necessary to evaluate the selectivity of the dissolving approach, especially when assessing the formulation of the API. In order to achieve the greatest possible efficacy with a medication that has a low solubility, it is necessary to provide this information. There may be a lot of difficulty in finding a solvent that is capable of dissolving insoluble pharmaceutical compounds in water while also satisfying criteria for volume, concentration, selectivity, and other factors.⁵

For the purpose of determining the chemical’s solubility, tests must be conducted in three different pH-ranged dissolving solutions. Given that the disintegration test procedure is not defined in the dosage form monograph, it is possible that problems such as these might arise. It is necessary to have a medium that is capable of identifying and distinguishing between significant industrial components in light of the existing state of things. When it comes to the behavior of disintegration mediums, the USP is responsible for establishing “sink conditions” guidelines. If the ratio of a material’s concentration to its solubility at saturation is higher than or equal to three, then the substance is said to match the sink criteria.^{6,7}

The amount of medicine that dissolves in the dissolving medium during a certain amount of time is the quantity that must be determined to evaluate the solubility of both the reference formulation and the test formulation. The objective is to compare the dissolving characteristics of the two different formulations. The solubility of different pharmaceutical formulations may be evaluated by comparing the disintegration patterns of these formulations over time. The Food and Drug Administration (FDA) encourages conducting robust and long-term data studies for drugs that have delayed dissolving characteristics or reduced water solubility. When disintegration patterns are compared across a number of different time periods, it is possible to uncover flaws that are not immediately apparent when looking at patterns at a single moment. Recent studies have shown a number of approaches to evaluating and describing the characteristics of temporal dissolution⁷. Techniques such as ANOVA, model-dependent techniques, and model-independent approaches are examples of opportunities.^{8,9}

Dapagliflozin

Among the enzymes functioning in the human body during the glucose reabsorption process is sodium-glucose co-transporter

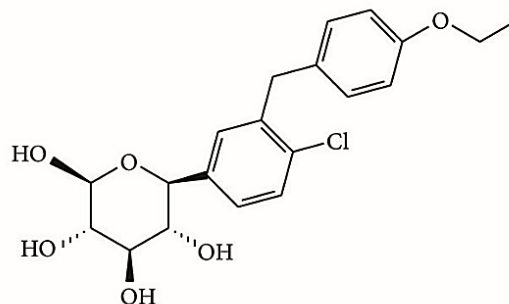


Figure 1: Structure of dapagliflozin

2 (SGLT2). With remarkable specificity, dapagliflozin, an oral medication, inhibits this enzyme. Should the need arise, it is possible to revoke this effect. By leveraging the kidneys’ direct and insulin-independent clearance of glucose—a critical component in the management of diabetes—this prescription differs in its mechanism of action from other presently available options. The results of the research indicate that dapagliflozin exhibits a greater degree of efficacy in inhibiting SGLT2 compared to SGLT1. Scientists employ the symbol phenyl (s) -1, 5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl) methyl] phenyl to designate glutamate phosphate. The chemical compound dapagliflozin is depicted in Figure 1.

Based on the severity of the sickness, the Biopharmaceutics Classification System (BCS) suggests that the dosage be increased to class II. It is customary to provide two doses of 25 mg of dapagliflozin throughout therapy. According to the findings of the study, even 3.125 mg could be beneficial. Considering that it is digested in the first pass, this medication has a plasma half-life of six hours and an absolute bioavailability of 25%. Pure dapagliflozin producers are permitted to offer their products entirely thanks to the European Pharmacopoeia. The Food and Drug Administration mandates that dapagliflozin tablets be evaluated in simulated gastric fluid (SGF) that does not include enzyme. There is a possibility that differential disintegration tests, which are the most trustworthy method for evaluating this technology, might not apply to all dosage formulations. Research is being conducted to find ways to improve the effectiveness of dapagliflozin capsules and improve their breakdown. This approach is intended to improve both the product creation and quality control process. Before beginning the inquiry, choosing the appropriate settings for the dissolving test is essential. Take into consideration the capacity of the medium as well as the paddle speed. Therefore, additional solvents such as product-A, which may be purchased and is used by the FDA, are required. The next thing that must be done is research the dissolving patterns of two different APIs with different particle sizes. Analysis of variance (ANOVA), non-parametric, and parametric methods are applied for the purpose of conducting extra evaluations of three items. A verification and improvement of the disintegration reaction parameters is also included in this work.^{10,11}

MATERIALS AND METHODS

Two samples of API-I (micronized dapagliflozin) were donated by Sai Lifesciences, a pharmaceutical company situated in Hyderabad. When examining the samples, it was seen that there was a significant range of d90 values, beginning at 35.3 μm . According to the information provided by Sun Pharma Advanced Research Company, located in Vadodara, India, the SPARC sample had a d90 value range of 9.5 μm . I went to a local pharmacy and purchased two tablets of the brand-name medication dapagliflozin. The pills of SPARC Product A, which are manufactured in India, contain ten milligrams of the active component, among the things offered by the organization. Products B tablets are manufactured by VHB Life Sciences Limited, which has its headquarters in Mumbai, India. There are ten milligrams of the active substance included inside each pill. In addition to that, the manufacturing number 010708 is significant. Those individuals were selected for recruiting purposes: Each chemical component used in this investigation came from reputable sources. The most environmentally friendly sodium hydroxide, hydrochloric acid, potassium dihydrogen orthophosphate, and glacial acetic acid were all that Qualigens of Mumbai had to offer for sale. The Merck company in Mumbai was the source of our HPLC-pure acetonitrile and methanol purchases. Millipore Corporation provided us with a hypodermic filter receptacle made of polypropylene measuring 25 mm in diameter and a membrane filter receptacle measuring 0.45 μm . One acetate buffer, one phosphate buffer, one 0.1N hydrochloric acid (HCl) solution with a pH of 4.5, and one simulated gastric fluid (SGF) solution were all prepared in accordance with the standards established by USP 29. Every single solution was developed in accordance with the specifications. Origin Pro 8 and GraphPad Prism 5, both of which were developed by GraphPad Software, Inc. in the United States, were used in the calculations. There are a number of inactive components included into product-C tablets. Crospovidone (Polyplasdone XL), colloidal silicon dioxide (Aerosil 200), and microcrystalline cellulose are all components that are included in this compound. There are 25 mg of the active component included in each pill. Analytic chemicals were used in the synthesis of each component.

Determination of Saturation Solubility

A study was conducted to examine the solubility of dapagliflozin (API-II) at different pH settings of the buffer. This was carried out in order to determine the chemical's saturation solubility characteristic. The substances that were able to meet the requirements were hydrochloric acid (0.1N), phosphate (6.7), acetate (4.5), and clean water. Each experiment may be divided into three separate iterations. A vial with a screw-capped cover had 10 mL of the medication, which was used to make sure the dapagliflozin was distributed evenly throughout the medium. It is essential to shake the vials often during the day to keep the temperature at 37°F. This was absolutely required to maintain a steady temperature. The solutions reached equilibrium at the surrounding environment's temperature six hours after that. A Millipore 0.45 μm membrane was used to filter the

material as soon as the acclimatization process was complete. Methanol was added to the filtrate in order to achieve the desired concentration. The examination of the 20 μL sample was carried out using HPLC.¹²

Dissolution Test

The first test was conducted at 37°C with a 0.5°C standard deviation using the United States Pharmacopoeia Apparatus II. Using this test, the dissolution capacity of product-A was assessed. For every sample, three different dissolvability tests were performed. Paddle speeds of 50 and 75 rotations per minute were utilized in the dissolving experiment. Regardless of the pace, the RPM remained constant. Throughout the experiment, a number of different dissolving solutions were utilized. Many solutions were used, such as SGF, phosphate buffer with a pH of 6.8, acetate buffer with a pH of 4.5, pure water, and 0.1N hydrochloric acid. Most of the time, dissolved media in sizes ranging from 500 to 900 mL were employed. The sample collection took a total of 135, 10, 15, 30, 45, 60 minutes, and 50 mL. Additionally, it was necessary to gather samples. A fresh medium was added to these components in order to maintain the previously established temperatures and volume levels. After every test was finished, the sample pieces were put through a membrane filter with a 0.45-millimeter aperture to remove any substances that were considered undesirable. In order to perform the tests, the materials under examination required a significant amount of dilution with an appropriate dissolving solvent. To do a more thorough component analysis, an HPLC analysis was performed.^{13,14}

Estimation of Dapagliflozin in the Dissolution Samples

Based on dissolution samples, it has been established that high-performance liquid chromatography (HPLC) using a Shimadzu liquid chromatograph (LC) has been used to quantify the concentration of dapagliflozin. An LC-10ATVP binary pump and an SPD-M10AVP PDA detector were required to complete the HPLC system. Every component was put to use. A breakthrough was found in the German manufacturer Merck's LiChrospher® 100 RP-18 octadecyl silane columns. Five-meter-long particles were present in these columns. Chromatographic analysis was chosen as the method, and LC Solution Version 1.23 SP1 was the software utilized to do the analysis. The following ingredients were mixed together to create a mobile phase buffer: potassium dihydrogen orthophosphate (0.03M, pH 4.8), methanol (58:32:10), and acetonitrile (10:2). The mobile phase production method consisted of sonication, low-pressure degassing, and daily output, each of which was carried out in a different sequence. The mixture was filtered through a membrane filter with a 0.45-millimeter aperture as soon as the preparation was finished. The device was operated for ten minutes for each sample after the flow rate was adjusted to 1.2 mL per minute. About 20 liters of the chemical were recommended as the dose. The temperature was at the typical ambient temperature of 25°C, yet the molecules' 242 nm sizes were discernible to the researchers. While the temperature was at room temperature, this was completed.¹⁵

Preparation of Standard Stock Solutions

Methanol A volumetric flask with a 50 mL capacity was filled with methanol containing 25 mg of dapagliflozin in order to contain the drug. As a consequence, the stock solution was shown sooner. Our target was accomplished at a concentration of 500 micrograms per milliliter. Seven standard solutions were prepared using the following ingredients: Sterile water, 0.1N hydrochloric acid, synthetic stomach juice, a pH 4.5 acetate buffer, a pH 6.8 phosphate buffer, and sterile water. These solutions were produced based on the stock solution that was developed. The working standard solution is available in a wide variety of concentrations for the participants to choose from. There was a range of 0.5 to 10 micrograms per milliliter in the amounts. A membrane filter was used to filter the fluid prior to its introduction into the column. The average size of a filter's pores is 0.45 μm .¹⁶

Validation of the Dissolution Method

A thorough assessment was conducted to make sure that the chosen dissolution test condition complied with the guidelines set out by the International Council for Harmonisation (ICH) and the Food and Drug Administration (FDA) of the United States of America.¹⁷⁻¹⁹

Specificity

Our goal was to ascertain how specific the dissolving medium is in relation to the medication, placebo, and dissolving medium peak interference levels that we were investigating. This was accomplished by first evaluating the dissolving medium's effectiveness in the absence of the medication. This information was known ahead of time, and it is known that the medicine has a certain concentration in the liquid that is dissolving. It was decided to dissolve a sugar tablet into the beverage being considered in order to create a placebo effect. It was thought that adding an industrial tablet to the solvent would help achieve the intended result of generating product A. It spun for thirty minutes at a speed of 100 revolutions per minute to ensure the samples were well mixed. Subsequently, the specimens were run through a membrane filter with a 0.45 micrometre pore size. This was the next action that was done. That was followed by this specific phase. In conclusion, the filtered materials were examined using high-performance liquid chromatography (HPLC) equipment.

Accuracy

This particular experiment's design calls for mixing a reference substance containing dapagliflozin in predetermined proportions with a placebo. Methanol was used to create a stock solution of dapagliflozin at a concentration of 10 mg/mL. The previously mentioned solution was divided into three equal parts at the end of the process: 1, 10, and 15 mL. This produced a total volume of 1000 mL. The next stage included transferring the elements to receptacles that held chemicals that were soluble. The containers were kept at $37 \pm 0.5^\circ\text{C}$ for the whole procedure while the technique was carried out. This allowed the confined liquids to reach their maximum concentrations of 10, 100, and 150 mg/mL, respectively, inside

the tubes. After being kept in storage for an hour, the samples were agitated for a further hour at a speed of 150 revolutions per minute. The next step was examining specific portions of each sample using HPLC.

Precision

The precision of the strategy was found by comparing the method's performance on many distinct days and evaluating its ability to repeat the findings on the same day. This was done in order to assess the procedure's degree of accuracy. We computed the measurements' relative standard deviation (RSD) in order to do this analysis. We were able to ascertain the technique's degree of precision by looking at the accuracy test replies.

Stability

Samples of purified dapagliflozin and product-A were gathered once the dissolving process was finished to assess whether the solutions could be used in real-world settings. The samples were then carefully placed within a light-sensitive chamber and let to remain at room temperature for a maximum of seven days. For the duration of that time, the temperature was maintained within a constant range of 2 to 8°C. Five-millilitre samples of the extracted material were subjected to a HPLC examination every day. This was really done after the chemical had been diluted appropriately. Three distinct incidents happened over the course of this inquiry. The standard and formulation medication concentrations might be determined thanks to daily sample collection. The samples under comparison were those that had been kept in storage at temperatures between 2 and 8°C. The concentrations of the drugs were the main consideration in this comparison.

Methods Used to Compare Dissolution Profiles

It is possible to compare dissolution profiles by using the following techniques

One of the several techniques that were used to evaluate the data related to the dissolution was the analysis of variance (ANOVA). Methods that are independent of the model include the f_1 and f_2 factors, among others. However, the Hixson-Crowell, Weibull, and Higuchi and Korsmeyer-Peppas approach rely on the model. Three distinct pharmaceutical products—designated as A, B, and C—were compared and contrasted using the analysis of variance (ANOVA) approach throughout the inquiry. We began by comparing the proportion of medication that was dissolved at each time point using a one-way analysis of variance (ANOVA). The results of the two distinct approaches were then compared using a Tukey test. Extensive research was conducted to identify the critical components accountable for the observed demographic variances. The statistical software packages OriginPro 8 and GraphPad Prism 5 were used concurrently to do these calculations. Throughout the investigation, a significance criterion of $p < 0.05$ was used to determine the presence of statistical significance. A multitude of approaches that relied on the model were used to compare the kinetic properties of the dapagliflozin release. The

amount of drug delivered throughout a time interval of 0 to 120 minutes was ascertained using the appropriate methodological procedures. The similarity factor (f_2) and the difference factor 1 are the two elements of the model-free technique that are thought to be the most important. Additionally, these two halves are referred to by names that are different from one other. We may conclude that greater disparities are more noticeable throughout all time periods since the F_2 measure is negatively correlated with the mean squared difference between the two profiles. Despite this, there is a considerable association between the average difference and the F_1 measure, as seen by their high correlation. The FDA's new business guidelines have included more information for comparing dissolution profiles. By using the previously provided signals, this guideline was successfully introduced. The reference and test dissolution profiles are reflected in R_t and T_t , which may be expressed as averages or percentages of dissolution at each time point t . R_t and T_t may be expressed as percentages of dissolution, and equations 1 and 2 provide precise information on the fractions. It's conceivable that the following statement contains both of these equations. An alternative way to characterise the fractions would be as a percentage of the total dissolution. The total number of collected samples, which finally included samples obtained by dissolution, is represented by the value of the variable "n". When the dissolving profiles lie between 0 and 15 for f_1 and 50 and 100 for f_2 , they are considered comparable. This complies with FDA regulations that have previously been established.²⁰⁻²²

RESULTS AND DISCUSSION

Some have raised concerns about the current disintegration approach, which has FDA approval, not being able to reasonably predict the reactions that dapagliflozin causes. This is mostly because dapagliflozin dissolves more readily in the particular dissolving fluid being utilized, necessitating more agitation throughout the process. These ingredients make it difficult to assess the formulation's true dissolving abilities, and any changes made to increase its efficacy could go undetected. Due to this regrettable situation, we cannot examine the dissolving properties. The aim of this research was to assess the efficacy of dapagliflozin derived from three different commodities using USP type II authorized equipment. To achieve the study's main goal, the researchers contrasted their results with those of an approach called SGF, which the Food and Drug Administration has approved.²³

Determination of Saturation Solubility

When it comes to the dissolution of solid dosage forms, the solubility of the medication is a crucial factor to consider. Experiments have shown a relationship between the intrinsic solubility of several pharmacological compounds and their rate of solubility in particular solvents. It has been shown that this relationship does in fact exist. An investigation was carried out to observe the behavior of dapagliflozin and how different washbasin settings affected its solubility. This data

is listed in Table 1, which displays the experiment's results. This allows for a complete summary of the statistics. An observation was made that the medicine's solubility varied over the complete physiological pH range. The only solution that was demonstrated to have a higher solubility for dapagliflozin than any other solution was the one that included 0.1N hydrochloric acid, simulated gastric fluid (SGF), and an acetate buffer with a pH of 4.5. It was found that placing the compound in a phosphate buffer solution with 6.8% phosphate decreased its solubility. This was specifically caused by the molecule being analysed in an acidic environment. It was discovered during the experimental assessment that dapagliflozin was 2.89 $\mu\text{g/mL}$ soluble in distilled water. This determines dapagliflozin's solubility. One statistic that may be used to assess how similar the circumstances under consideration are to sinks is the solubility to drug concentration ratio, or D_s/D_d . To achieve sink conditions, the drug must be dissolved in the dissolving medium three times as much as it is meant to be dissolved. This entails letting the medication dissolve in the media. It is necessary to take this action to ensure that the washbasin requirements are fulfilled. There must be conditions that do not sink to the surface if the ratio of D_s to D_d is low. It is expected that the medication's solubility in the medium will be impeded, leading to a slower rate of dissolution in the medium. The current examination concluded that there were no sinking situations since the water's D_s/D_d ratio was less than 3. We have reached this judgement in light of the investigation's results.

The notation " D_s " indicates dapagliflozin saturation solubility in 900 mL of dissolving fluid, whereas " D_d " indicates tablet dose.

Dissolution Test

Preliminary study helped researchers adjust the product-A tablet dissolving test. Two stirring speeds were tested with USP equipment II. The rpm was 50 to 75. As shown in Figure 2, the tablets were immersed in various liquids for a complete analysis. The sequence of constituents for hydrochloric acid (HCl) solutions was distilled water, acetate buffer, and phosphate buffer. Both 500 and 900 mL hydrochloric acid solutions had 0.1N concentrations. Product-A tablets dissolved similarly in simulated gastric juice, an acetate buffer with a pH of 4.5, paddle speeds (50 and 75 rpm), and volumes (500 and 900 mL). In just 15 minutes, 95% of the drug was extracted from the pills. The previously mentioned dissolving test settings showed no bias. The medicine is released continuously

Table 1: Saturation solubility of dapagliflozin as well as the relative sink conditions in a range of dissolving mediums ($n = 3$)

| <i>Dissolution medium</i> | <i>Sink condition (D_s/D_d) (10 mg tablet)</i> | <i>Solubility ($\mu\text{g/mL}$) (mean \pm SD)</i> |
|---------------------------|---|--|
| 0.1N HCl | 9.42 | 261.54 \pm 15.27 |
| Distilled water | 0.10 | 2.89 \pm 0.46 |
| pH 4.5 Acetate buffer | 13.54 | 376.01 \pm 14.37 |
| SGF | 10.31 | 286.41 \pm 13.28 |
| pH 6.8 Phosphate buffer | 3.32 | 92.13 \pm 1.53 |

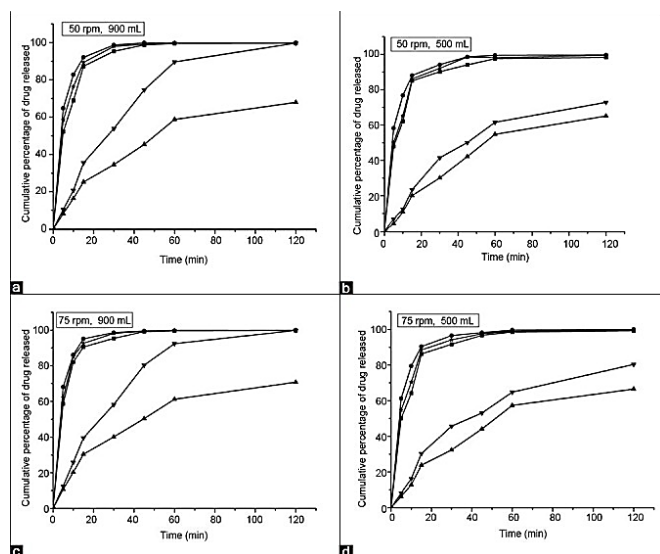


Figure 2: Determine product A's solubility in different dissolving fluids

at 50 and 75 rpm in 500 and 900 mL volumes. This was the case since 0.1N HCl, SGF, and pH 4.5 acetate buffer dissolve the medication efficiently. Product-A discharged less than 60% of its medicament in 500 mL of distilled water at 50 or 75 rpm. Increasing paddle speed revealed this. However, the washbasin's poor conditions may explain the partial disintegration. The result was valid since the D_s/D_d ratio was more than three. Distilled water is not advised for dissolving experiments because to its low buffer capacity.

Estimation of Dapagliflozin in the Dissolution Samples

According to the analysis, product A released over 85% of its medication in just 60 minutes. A 900-cc phosphate buffer solution was spun at 50 to 75 rpm to get the same result. The fluid pH was 6.8, according to the study. An attentive supervision environment was used for the experiment. Drug release % was evaluated in a 500 mL phosphate buffer with a pH of 6.8. It rotated at 50 or 75 rpm. No paddle speed could achieve the specified drug release concentration in a 500 mL phosphate buffer solution with a pH of 6.8. A D_s/D_d ratio below 3 may explain this phenomenon. Because certain dissolving circumstances don't need a washbasin. Therefore, this will happen. The research found that dapagliflozin dissolution rate is closely proportional to dissolving fluid volume. Product A released more medication than a 500 mL suspension in 900 mL phosphate buffer at pH 6.8. Both velocities demonstrated this. The consistent sink conditions during dissolving cause this effect. The medication will be delivered more swiftly and significantly if you use the minimum calibrated paddle speed of 50 rpm. This improves the capacity to distinguish treatment settings and pharmaceutical compositions. Thus, 50 rpm was chosen for the paddle speed. Dissolving was done using USP apparatus II. The device contained 900 cc of pH 6.8 phosphate buffer and spun at 50 rpm. The anticipated dissolving test results were analyzed to verify whether the drug release profile was correct.

Particle size distribution

After discovering that API-I and API-II had different particle size distributions, this study examined their disintegration characteristics. API-I tests revealed particle sizes of 3.3, 9.6 and 25.3 μm at d10, d50, and d90. Data analysis yielded these values. API-II particle sizes varied from 1.2 μm at d10, 5.2 μm at d50, and 8.5 μm at d90. To simulate stomach fluid, 900 cc of phosphate buffer with a pH of 6.8 was mixed with 50 RPM paddles during dissolving experiments.

Drug release study

Both APIs released about 50% of their drug content into simulated gastric fluid (SGF) during 60 minutes. When evaluated with a pH 6.8 phosphate buffer, both APIs produced 23 to 35% medication. The two APIs in the 6.8-pH phosphate buffer release dapagliflozin similarly, but particle size differences allow them to be distinguished. API-II distributes drugs more effectively than API-I due to its higher concentration of minute particles. The drug was rendered useless to distinguish APIs by particle size since it dissolves in SGF. A horrific chain of events occurred.

Dissolution profiles

The disintegration properties of product A, product B, and product C dapagliflozin tablets and their similarities and differences were reported. Synthetic stomach fluid (SGF), 900 cc of pH 6.8 phosphate buffer, and 50 RPM paddle speed were used for dissolving investigations. Using a pH of 6.8 phosphate buffer resulted in a significant difference ($p < 0.05$) in drug release across the three dapagliflozin tablet forms. Each of the three combinations showed this variance. After 60 minutes, product A and B released more than 85% of their medicines, whereas product C released more than 65%. All three solutions released over 95% of the medication during the 60 minutes test. The dissolving medium was simulated gastric fluid (SGF). This followed FDA guidelines. An in-depth study found that the commodities' disintegration rates were not statistically different ($p > 0.05$). The investigation showed that the pH 6.8 phosphate buffer, one of the dissolving conditions, had unusual properties. The fact that they can distinguish between items with various medicinal capabilities and manufacturing and formulation changes may help explain this phenomenon. According to the data, the above properties may distinguish micronized APIs from non-micronized ones. These traits may help identify generics and other commodities. Dissolve test parameters from drug release percentage analysis might replace the FDA's dapagliflozin tablet dissolving test. Items A, B, and C had different outcomes when the USP-II dissolving device was utilized in its entirety. About 900 mL of phosphate buffer and 37°C were employed throughout the experiment. The buffer pH was 6.5. The paddle spun the apparatus at 50 rpm. According to the research, dapagliflozin dissolving test conditions were most effective and recognizable at 900 cc of phosphate buffer solution with a pH of 6.8 and 50 revolutions per minute of paddle speed. Trial findings supported this claim. The correctness of this assessment is debatable.

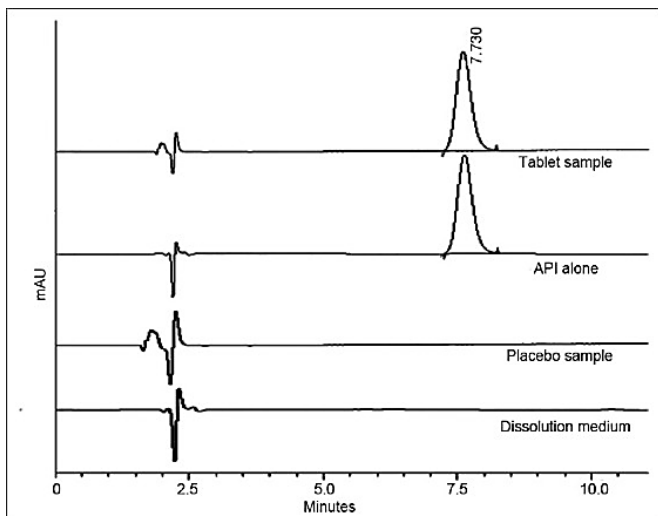


Figure 3: Dissolving media chromatograms on a tablet, API, placebo, and overlay.

Validation of the Dissolution Method

Figure 3 compares product A, placebo, and active medicinal component dissolving mediums. This investigation uses HPLC chromatograms. A comparison was done between previously reported chromatograms and those from the dissolving medium after adding saline solution showed no extra peak during retention. Dapagliflozin elutes in 7.7 minutes. The sample’s purity was determined using LC Solution Version 1.23 SP1 Software’s chromatographic peak purity tool. The gadget examines the highest value on a 0–1 scale to determine purity as part of its function. Given the predicted value of 0.9999, the observed peak could not have been caused by any other chemicals.

Accuracy

A recovery test assessed technique accuracy during the assessment. Accuracy testing recoveries between 95.0 and 105.0% S must be carefully considered. The study found a 99.5 to 102.9% dapagliflozin recovery rate. The recovery results in Table 2 suggest that the study project’s dissolving process was exact.

Precision

Table 3 shows single-day and multi-day measurements. The table shows the results. An RSD below 2% indicates a precise dissolving procedure. The stability of dapagliflozin in a pH 6.8 phosphate buffer was tested using standards and samples. The medication concentrations in the samples were constant for seven days at 98 to 102% of the original value. No degradation products were found in the chromatograms. Dapagliflozin demonstrated stability in the dissolving medium both on its own and in combination with the excipients.

ANOVA test to compare dissolution profiles

Our analysis of variance (ANOVA) examined whether the three products differed significantly in the proportion of medication provided at each time point. Then, a Tukey post hoc test with

Table 2: Dapagliflozin accuracy (Recovery Percentage)

| Spike Level | Amount found (mg) | %Recovery | Mean | SD | %RSD |
|-----------------|-------------------|-----------|-------|------|------|
| 10%_1 | 0.49 | 101.6 | | | |
| 10%_2 | 0.49 | 100.6 | 98.6 | 0.78 | 0.8 |
| 10%_3 | 0.49 | 100.2 | | | |
| 50%_1 | 4.94 | 103.6 | | | |
| 50%_2 | 4.94 | 101.5 | 101.2 | 2.99 | 3.0 |
| 50%_3 | 4.94 | 102.5 | | | |
| 100%_1 | 9.89 | 100.5 | | | |
| 100%_2 | 9.89 | 100.5 | 100.3 | 1.94 | 1.9 |
| 100%_3 | 9.89 | 100.5 | | | |
| 150%_1 | 14.83 | 100.2 | | | |
| 150%_2 | 14.83 | 101.0 | 100.1 | 2.14 | 2.1 |
| 150%_3 | 14.83 | 102.4 | | | |
| Overall Average | | 100.1 | | | |
| Overall SD | | 2.06 | | | |
| Overall % RSD | | 2.1 | | | |

RSD indicates relative standard deviation

Table 3: Intra- and inter-day precision for dapagliflozin

| | Concentration (%) | RSD (%) | |
|-------|-------------------|-----------|-----------|
| | | Intra-day | Inter-day |
| Day 1 | 10 | 1.12 | 1.28 |
| Day 2 | 10 | 1.47 | |
| Day 1 | 100 | 0.74 | 0.68 |
| Day 2 | 100 | 0.60 | |
| Day 1 | 150 | 0.48 | 0.64 |
| Day 2 | 150 | 0.60 | |

RSD indicates relative standard deviation

Table 4: Tukey’s multiple comparison test for products findings

| Comparison | Q | 95% LCL | P | Mean Diff | 95% UCL | Significant p < 0.05 |
|------------|-------|---------|--------|-----------|---------|----------------------|
| A vs B | 2.96 | -1.08 | 0.133 | 3.97 | 9.02 | No |
| A vs C | 10.54 | 9.06 | <0.001 | 14.12 | 19.17 | Yes |
| B vs C | 7.58 | 5.09 | <0.001 | 10.15 | 15.20 | Yes |

multiple comparisons was performed. The Tukey test, with a significance level of $p < 0.05$, shows a significant difference between products A, B, and C. A statistically significant difference. However, Table 4 shows that commodities A and B are not statistically different.

The letters LCL and UCL stand for lower and upper control limits, respectively. Matrix representations are typically employed to parametrically model dissolution data. Several models were utilized for dissolving data analysis. The research used the model with the highest coefficient of determination to determine which model best represented product dissolving

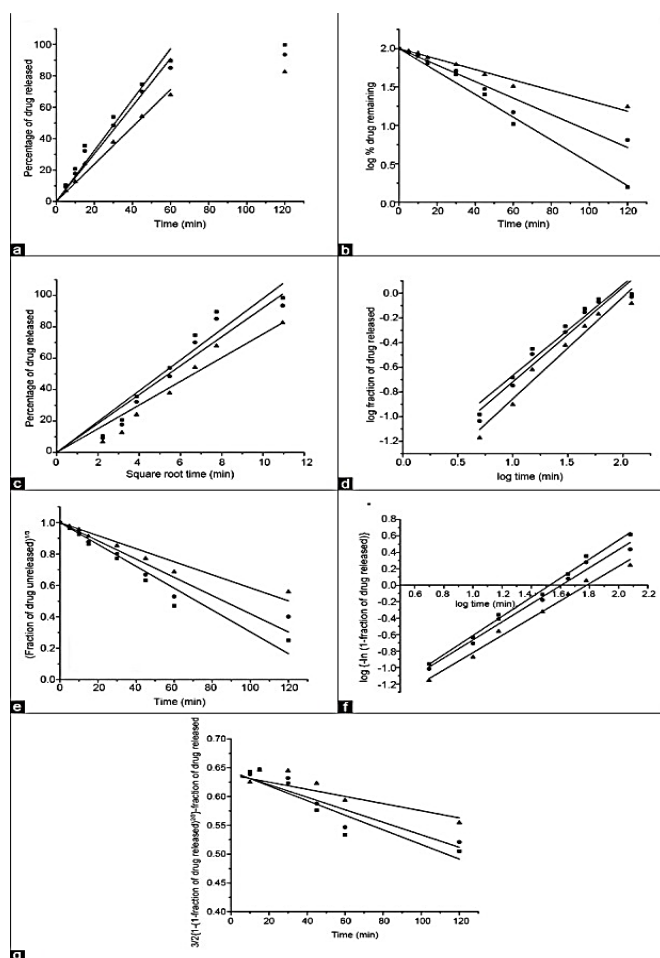


Figure 4: Model-dependent plots for products-A, B and C Zero-order, first-order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell, Weibull, and Baker Lonsdale models are discussed. You may pick from goods A, B, and C.

Table 5: Lists the F1 and F2 variables for each product dissolution profile comparison in phosphate buffer at pH 6.8.

| Comparison | f_1^a | f_2 | Dissolution profile |
|------------|---------|-------|---------------------|
| A vs B | 7.22 | 67.94 | Similar |
| A vs C | 25.70 | 40.59 | Dissimilar |
| B vs C | 19.92 | 47.28 | Dissimilar |

^aThe first f_1 value is obtained when the first formulation on the left column is set as reference.

data. Several substances with varying dissolving characteristics were studied for drug release kinetics. Investigations included this action. We created this to simplify evaluating each device's multiple medication release models. Several mathematical models were employed to analyze dapagliflozin tablet dissolving data (Figure 4). This group featured zero-order, first-order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell, Weibull, and Baker-Lonsdale models. The Weibull model outperforms all other product analysis models. First-order, zero-order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell, and Baker-Lonsdale models were used to demonstrate goodness of fit. Sequentially presented models are below. The Weibull

distribution model was most relevant for all dissolution data and had the highest coefficient of determination (R^2). Data study revealed this. A t-test was performed on Td (the time interval needed for 63.2% drug release) and ρ (form factor) to compare model parameters across three items. The t-test results showed a significant difference ($p < 0.05$) between the parameters. The average medicine release % for each time point was calculated using Equations 1 and 2. To calculate f_1 and f_2 , equations A, B, and C were employed. Table 5 shows the effects of the variables indicated before. F-criteria analysis showed that A/C and B/C had unique characteristics despite having similar dissolving profiles.

CONCLUSION

Finally, dissolving the dapagliflozin pill was thorough and accurate. We conducted a pilot study to test how well product A dissolves. This study examined and analyzed the impacts of dissolving fluid quantities and paddle stirring speeds. Using 900 cc of a pH 6.8 phosphate buffer in the experiment worked well. During 50 RPM buffer solution spinning, temperatures were maintained at 37°C with a 0.5°C variability. We did this constantly. A pH 6.8 phosphate buffer solution was used to assess the solubility profiles of products A, B, and C and APIs I and II. The FDA advised using a dissolving medium. We created and tested a novel technology for dissolving test determination that meets the latest FDA and ICH criteria. Our main goal in choosing this strategy was to reduce formulation time. The analysis of variance method improved commodity A, B, and C differentiation. These three commodities differed statistically. The Weibull model best describes drug distribution patterns for items A, B, and C. Location and similarity allow for relevant comparisons (release profile). We used factors f_1 and f_2 to investigate dissolution profiles. The investigation indicated that product-A and product-B had comparable dissolving profiles, whereas product-C had a drastically different profile. Every approach employed to compare dissolution profiles in this study appears realistic and beneficial. This study presents a novel dissolving method that might improve manufacturing and formulation, evaluate tablet batches, and reduce bio-equivalent product exposure.

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