Novel microdialysis method for complex generic products

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KEYWORDS

In Vitro Study, Micro dialysis, Suspension, Dialysis Membrane, Drug Release.

ABSTRACT

A novel microdialysis method was utilised to evaluate the degree and range of drug dispersion from different formulations, including suspensions, emulsions, liposomes, and drug-protein complexes. The particles were sorted according to size using a microdialysis technique and then released, and the remaining medicines were examined simultaneously. To calculate the compound's initial flow, buffer solutions containing the drug (donor side) and drug-free buffer solutions (receiver side) were dialysed. The drug presence velocity on the receiver side was monitored. By using the micro dialysis approach, discriminatory drug release profiles were obtained for both the medication in solution and small-size suspension. This study examines the use of dialysis cartridges in developing in vitro evaluation methods for complex formulations.

1. Introduction

In vitro release studies were utilised for evaluating the quality and efficacy of complex medications, such as emulsions, suspensions, liposomes, and microspheres, for product development and regulatory purposes [1]. To assure batch-to-batch consistency, evaluate changes, support product comparability, and confirm bioequivalence, an in vitro release study should directly correlate changes in the drug's critical quality attributes (CQAs) to its release characteristics.

Developing an accurate and consistent in vitro release study for complex medicinal formulations has proven challenging [2-5]. In vitro release studies are helpful as a standard screening procedure for complex healthcare products [6]. The in vitro release studies suggest that achieving bioequivalence with the reference-listed drug (RLD) could be challenging. In vitro drug release studies, such as those using reverse dialysis, micro dialysis, and USP 4 apparatus, focus on determining the quantity and rate of release [7, 8].

According to the dosage type, in situ or in vitro testing may be utilised to validate efficacy and purity [9]. Drug dissolution kinetics are crucial for evaluating product efficacy and effectiveness, providing essential information regarding dose response. In vitro release is a cost-effective, time-saving, and non-invasive method for measuring drug dissolution pharmacokinetics in laboratory conditions, making it a popular option for product evaluations. In vitro diffusion monitoring is frequently utilised to estimate in-vivo activity. In execution, in

vitro release testing is frequently used to calculate in vivo behaviour. This has historically been true for traditional dosage forms such as pills and capsules (which disintegrate) and more recently developed dosage forms such as implants and injected degradable nanoparticles [10-12]. In vitro dissolution studies are typically conducted at 37°C; however, higher temperatures have been investigated to describe drug release from various dose forms [13, 14]. In vitro distribution evaluation aims to achieve a few of the following goals: (a) evaluating the way manufacturing processes and formulation factors affect the drug product; (b) frequently assessing quality assurance to promote batch distribution; (c) determining claims provided on product labels; (d) developing an in vitro in vivo correlation/relationship (IVIVC/R); (e) ensuring product sameness by SUPAC guidelines; and (f) demonstrating comprehensive necessity [15, 16].

Furthermore, these commonly used in vitro release assays typically focus on the diffusion route, such as across a dialysis membrane, to distinguish between "released" and "remaining" drugs, which has significant limitations. Using a dialysis membrane requires maintaining adequate sink conditions across the membrane, allowing users to focus on analysing the "released" drug. The amount of drug needed for sinking conditions to develop inhibits the capacity of the individual to identify remaining medicines and preserve an equilibrium in pharmacological transmission. A dialysis approach was established to understand better the parameters of complicated medication products (such as ophthalmic suspension) and significant variables that may impact the drug release mechanism (17-19).

These studies provided knowledge and insight that eventually led to the creation of the dialysis process. The need for a better release strategy was also generated by the product, which could: a) do away with the time-consuming sample-and-separate approach to isolate the drug that was "released"; b) provide setup flexibility; c) Eliminate rate-limiting elements like diffusion and dialysis; d) modify drug transfer control to dosage form types and replicate in-vivo circulation parameters.

The absence of standardised in vitro release mechanisms for suspension and other colloidal dosage forms is a difficulty that the current study attempts to address. A unique micro dialysis approach that utilises the dialysis membrane was developed, optimised, and demonstrated. This method allows colloidal dose forms like suspensions, liposomes, and emulsions to be examined for release in vitro. Optimisation and assessment tests with solution and suspension dose forms of dexamethasone and ciprofloxacin were carried out to test the validity of this novel dialysis procedure. This study exhibits the creation of fluid formulations for the hydrophobic medication dexamethasone with various release rates. These different formulations assessed the innovative dialysis-based method's generalizability [20].

Two main techniques were used to assess the in vitro distribution of dexamethasone from different suspension formulations: fraction recovery and drug release studies. A dialysis-based technique was adopted because deformable formulations, such as suspension, respond better to it. The micro dialysis method was used to separate the particles based on their size and evaluate the released and remaining drugs at the same time. By analysing dialysis buffer solutions with compound (donor side) to buffer solutions without compound (receiver side), researchers could determine the compound starting flow and track the compound growth rate on the recipient side. The micro dialysis approach successfully produced different drug release profiles for solution and small-size suspensions.

The requirement for an in vitro dissolution method for complicated dosage forms will significantly contribute to pharmaceutical dosage form design and analysis. Microdialysis is a particularly valuable technique because it continuously monitors drug concentrations in

extracellular spaces. It has been extensively employed in pharmacokinetics and pharmacodynamics research [21-23]. The in vitro micro dialysis sampling technique has also been used to measure a drug's protein binding, partition coefficient, and dissolution testing of pharmaceutical formulations [24, 25]. This research aims to create an in vitro dissolution method that employs a micro dialysis sample methodology to investigate the release characteristics of drugs from complex dosage forms [26].

Materials and Methods

2.1 Materials

Ciprofloxacin and Dexamethasone USP was provided as a gift samples from OCIM Pharmaceuticals LLC, USA. Hydroxyethyl cellulose, benzalkonium chloride, and tyloxapol were supplied by SRL in Mumbai, India. Fisher Scientific in Waltham, MA, provided glycerin, sodium acetate, boric acid, and edetate disodium. Sodium dihydrogen phosphate and sodium hydroxide were obtained from Sigma Aldrich in St. Louis, MO. Acetonitrile was acquired from Fisher Scientific, Waltham, MA, and ethanol from Decon Labs in King of Prussia, PA. The water used in the study was purified with a Milli-Q system from Millipore in Burlington, MA, and had a specific resistivity of 18.2 MΩ cm. All chemicals were of analytical grade and used without any further processing. Hollow fibers membrane (Dialysis Cartridge membrane) made up of modified polyether sulfone 100 kDa & 300 kD molecular weight cutoff (MWCO), 0.5 mm diameter, 20 cm effective length, 20 cm2 surface area).

2.2 Qualitative and Quantitative Chromatographic Method for Drugs

The concentration of Ciprofloxacin and Dexamethasone sodium was measured using high-performance liquid chromatography (HPLC) (Jasco HPLC-LC-2000 with the Ultraviolet detector, Tokyo, Japan) with a Thermo Accucore C18 column (2.6mm particle size & 4.6mm dimension) for separation and a detection wavelength of 254nm. For Dexamethasone sodium, the mobile phase contained 60% 1.0 M Formate buffer with 40% acetonitrile, and for Ciprofloxacin, 52% Methanol and 48% of 6.5 M Formate buffer. This was pushed through the column at a velocity of 1 mL per minute while keeping the temperature at 25.0 °C. The calibration curves were plotted for Dexamethasone and Ciprofloxacin standards, weighing 180mg and 100 mg, respectively. Both standard solutions were prepared using acetonitrile for Dexamethasone and methanol for Ciprofloxacin in separate 100 mL volumetric flasks. The Drug release % was obtained according to:

$$\boldsymbol{Drug\ Release}\ (\%) = \frac{\mathbf{Dt}}{\mathbf{Do}} \times \mathbf{100}\% \qquad \text{..... (1)}$$

Dt and Do represent the drug dose in suspension and total, respectively.

2.3 Preparation of Suspension

Suspensions are complex structures composed of two phases. The external stage (sometimes called the continuous phase or dispersion media) is soluble. However, the interior or dispersed phase consists of particulate materials that do not dissolve in the external phase. Most pharmaceutical suspensions are made with an aqueous dispersion media. The aqueous phase A (containing hydroxyethyl cellulose, benzalkonium chloride, edetate disodium dehydrate, sodium chloride, sodium acetate, acetic acid, and boric acid dissolved in 50% purified water) was mixed at high shear with a magnetic stirrer to create a clear solution before adding the drug ciprofloxacin. The aqueous phase II comprised tyloxapol and dexamethasone medicines dissolved in deionised water using sonication and was subsequently combined with phase A through an overhead stirrer. The pH was then adjusted to 4.5 at room temperature using 1 M sodium hydroxide.

2.4 Micro dialysis methods

2.4.1. Dialysis cartridge based In-vitro Drug Release method

Micro dialysis has been a common in vitro test method for separating soluble drugs from their dosage forms in the pharmaceutical industry. Still, due to some physical limitations of the membrane property, such as a lower surface area and thickness of the membrane, which controls the diffusion of soluble drugs, there is a delay in analysing the drug release in real-time from the dosage form dispersed in the donor system. The development of single hollow fibre dialysis overcame this physical limitation related to conventional dialysis. The drug can diffuse through it more quickly than it would through an average dialysis tube or the membrane used to separate soluble from dispersed medications since it has a larger surface area and thinner membrane. This is because the single hollow fibre was first used to analyse biological tissue in an in-vitro study [26].
Due to the smaller membrane thickness and internal diameter, the drug's diffusion from the disperse system was monitored in real-time because it does not have a long path to the cross. Retro dialysis or standard dialysis setup with sample collection and chromatographic system analysis is possible with hollow fibre dialysis [20].

This method utilises a dialysis membrane to separate dosage kinds and facilitates sample collection at regular intervals. Other options include reverse and side-by-side dialysis [27-29]. A side-by-side dialysis setup divides the donor and recipient cells, with a magnetic stirrer agitating equal amounts of fluid in the recipient cell [27, 31, 32].

The dialysis membrane is a fundamental technique for measuring drug release from various nano-sized administration forms, including nanospheres, liposomes, emulsions, and nanosuspension. It is easy to set up and sample [28-30]. However, issues with the standard dialysis method have been recognised. If the dialysis membrane setup is not correctly sealed, media and dose forms may leak from both sides. If there are no sink conditions or long equilibration intervals, partial release data may be observed [33]. In contrast, the difference in equilibration times can be used to distinguish between the release characteristics of rapid and slow-releasing dosage forms [34]. Another important consideration is that medications that connect to the dialysing membrane can be utilised while working with it. Before using a dialysing membrane, it is recommended to establish its compatibility [16, 35].

A new experimental dialysis setup using a dialysis cartridge that contains multiple single hollow fibre probes and has a higher fill volume capacity was designed to overcome the limitation of single-probe retro dialysis. This system also overcomes the limitations of the chromatographic system [26].

In addition to concentrating solutions and several biotechnology applications, dialysis cartridges have been used to replicate the function of the kidney to forecast the drug reduction process. The in vitro release of pharmaceuticals from solutions or dispersed systems, which must go through the dissolution and separation process, has not previously been tested using these techniques; however, this needs mathematical modelling to determine. This experimental setup will help solve most of the technical issues the single hollow fibre probe faces, dilution.

2.4.2. Setup and Procedure

The micro dialysis setup (depicted in Figure 1) consists of a new medium reservoir, a device for filtering particles, two peristaltic pumps (one for the donor and one for the receiver), a hollow fibre dialysis cartridge, and a magnetic stirrer, a stir plate to blend the sample and the medium, and tubing to connect it all.

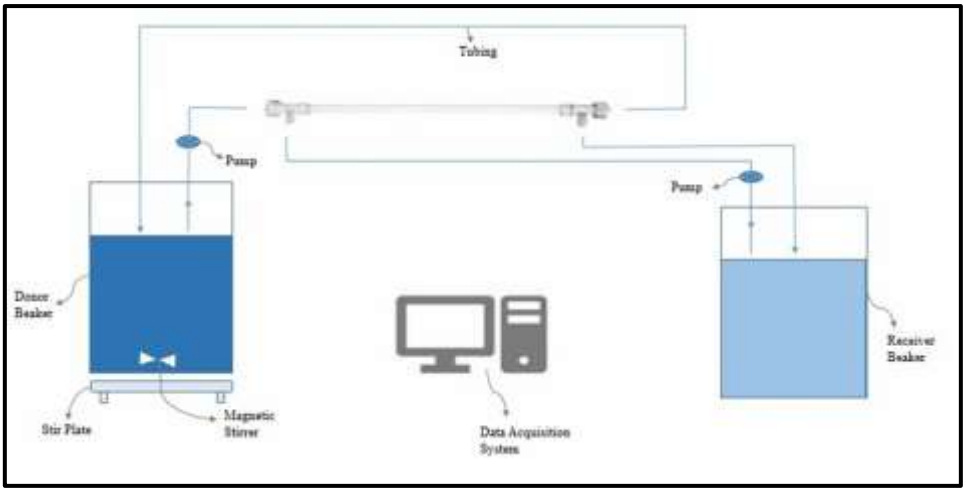

Figure 1: A diagram of the dialysis process using a dialysis cartridge.

The micro dialysis experiment comprises three phases: pre-conditioning, run-time, and re-conditioning. The cartridge was connected to the inlet and outlet tubing during each stage using a partial-open loop design (refer to Figure 1). The liquid was pushed from the donor side (inlet) to the dialysis membrane and then circulated through tubing from the receiver side (outlet) back to the dialysis membrane.

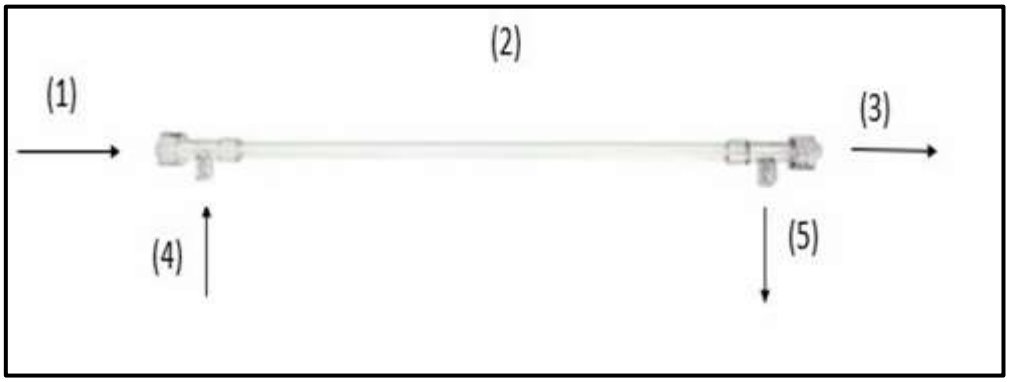

Figure 2: A diagram of the tube connection to the dialysis cartridge.

Before use, the dialysis cartridge was prepared by flushing it with deionised water and an organic solvent, such as ethanol. This process removed the manufacturer's storage media, like glycerin. To remove the organic solvent, the cartridge was rinsed with deionised water. The cartridge was then conditioned using a deionised water solution containing 0.01% w/v tween-80. During the pre-conditioning stage, the dialysis cartridge was connected to tubing in a partial open-loop configuration.

The cartridge was flushed with deionised water and released media during the run-time stage. Both inlet and output tubings were emptied to eliminate any residual liquid that could dilute the sample further. All the components were put together, as shown in Figure 1. A predefined volume of the drug solution or suspension was mixed with a set volume of media solution in the feed reservoir. A magnetic stirrer was used to stir the mix at 200-400 rpm constantly. After mixing the sample with the media for 10 seconds, an aliquot was obtained to measure the drug concentration before turning on the sample feeding pump. The sample was passed through the filter at a flow rate of 50 mL/min in an open-loop mode using the sample feed pump.

The period between the first dilution of the sample with media and the commencement of the sample feed pump was unchanging during the trials. The fresh media promptly restored the volume of the sample on the receiver side to its original value to adjust for the decrease in

volume on the receiver side caused by the dead volume of the tubing. The experiment began when the liquid emerged from the tubing at time zero. The rate of fresh medium supply was continuously modified based on the actual flow rate to compensate for the decrease in volume caused by permeating flow while keeping the volume on the receiver side constant. Samples were taken from the donor side at specific intervals, and the tube was used to check the remaining drug content. The permeate was collected at the same time on the receiver side. At the end of the experiment, a sample was taken from the receiver side, and the total volume was measured to determine the cumulative drug release.

In the final reconditioning stage, the media supply was replaced with deionised water and an organic solvent (such as ethanol), which flowed through the cartridge in a partially open-loop configuration. After cleaning, the resulting fluid was disposed of in a trash can. Then, the cartridge was reconditioned in a partially open-loop configuration using the conditioning solution. After reconditioning, the cartridge was stored in the refrigerator until the next test.

2.4.3. Development and optimisation of microdialysis method

The microdialysis method relies on concentration gradients and flow separation. We studied and optimised several essential elements for dialysis procedures.

2.4.3.1. Different dialysis method variables

(1) **Type of Membrane**

(A) The cartridge used as a dialysis membrane (membrane A) is disposable and goes by the Synthetic hollow fiber dialyser. It is composed of a mixture of polysulfone, polycarbonate, and polyurethane. The membrane of the cartridge is made of glycerin-free polysulfone, with an effective surface area of 1.7 m2 and a thickness of 40 µm. The priming volume of the membrane is 108 ml, and the effective length is 271mm, with an inner diameter of 200 µm. The maximum TMP of this membrane is 500 mmHg.

(B) The cartridge used as a dialysis membrane (membrane B) is a reusable hollow fiber module. It comprises polysulfone, polyurethane, and modified polyethersulfone (100 KD and 300KD), with a process volume of 20-200 ml and a surface area of 0.002 m2. It is intended for single use within three years for gamma-irradiated and five years for non-irradiated from the date of manufacture.

(2) Membrane dimension and molecular weight cut-off (MWCO)

The MWCO of the membrane B is crucial for controlling drug release as it determines the size range of particles that can flow through. Dexamethasone, a medication, was utilized to analyze the hollow fiber module MWCO of membrane A, 100 kDa, and 300 kDa at constant RPM and time intervals to determine the optimal MWCO. Figure 3 demonstrates that the membrane A released 30% of the dexamethasone medicine in 3 hours, 50% less than the other two membranes. Slow and low drug dispersion (as in the membrane A) is undesirable for solutions that spend only a few minutes in the ear or eye [36,37]. Thus, dispersion can be a rate-limiting step in medication release. More than half of the medication was released, and no change was seen between 100kDa and 300kDa membranes 3 hours after the dexamethasone injection, as shown in Fig. The 100kDa membrane was one of two MWCO that were least prone to membrane fouling, or particle deposition on the membrane surface. As a consequence, a 100 kDa membrane was selected for further testing of other formulations.

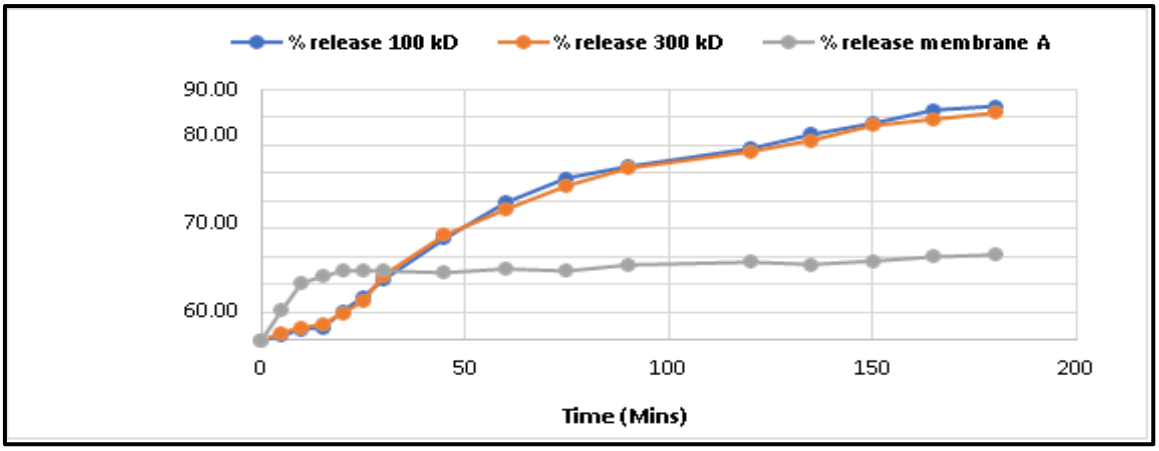

Figure 3: The impact of three different MWCO hollow fiber membranes on drug release

(3) Optimization of feed flow rate

The maximum flow on the receiver side was preferred when studying drug release media solutions. Simple membrane flux enhances drug removal and accelerates transfer from the donor to the receiver. Feed flow rate and RPM were critical dialysis processes influencing permeate flux. The figure shows an increase in flow rate at different time intervals while maintaining constant RPM. Increasing RPM enhances both feed flow rate and volume flow. The link between feed flow velocity, RPM, and time points is crucial for optimisation [38]. The flow rate was changed by adjusting the RPM of the peristaltic pump, as seen in the figure; a lower value indicated a greater applied RPM. Under all experimental conditions, the membrane inlet pressure stayed within the filter manufacturer's specified range. Figure 4 represents how maximum flow was obtained as RPM increased.

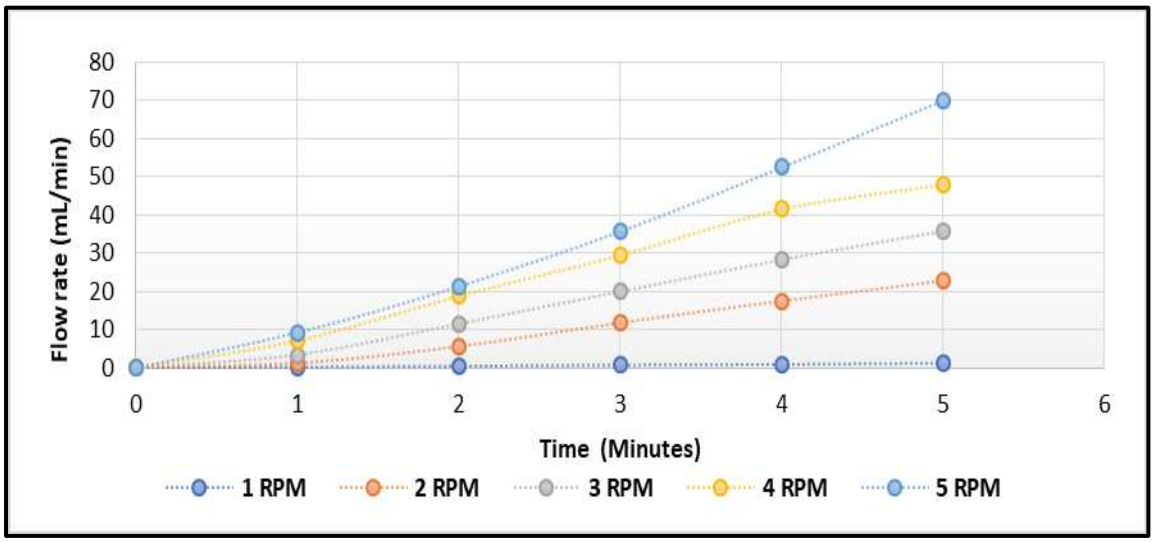

Figure 4: Effect of changing RPM on flux at different feed flow rates

(4) Sample Concentration

As previously mentioned, the feed flow rate and various time intervals were tuned using an Otic suspension sample with a 10 ug/ml medium concentration. Despite the membrane's continued operation, fouling became more severe with increased input flow rates and backpressures. This was evident from the flux's peak at higher RPM, followed by its decline (as shown in Fig. 4). To enhance overall dialysis efficiency and minimise membrane fouling, the sample concentration was increased to 100 ug/ml.

(5) Membrane Conditioning

Dialysis cartridges often result in membrane variability, which is a common issue. A significant concern that has limited the adoption of cartridge processes is membrane fouling, which reduces filtration efficacy and increases filtering run times. Although the issue of membrane fouling has already been addressed in some studies [39-41], it remains a substantial challenge. To improve membrane performance and reproducibility, membrane conditioning is a critical step. Tween-80 was utilised to condition the dialysis cartridge as it is a frequent excipient in suspension, improving compatibility with the formulation. The conditioning solution used was Tween-80 at a concentration of 0.02% w/v. The configuration of the conditioning process played an important part as well. Conditioning with a partial-open loop layout (Figure 5) improves membrane-to-membrane consistency and data repeatability compared to an open-loop design. Therefore, a partial-open loop arrangement was used to condition the dialysis cartridges [1].

2.4.4. Fraction recovery study of the drug:

It is crucial to assess a compound's unbound fraction (fu) to understand its distribution, effectiveness, interactions with other drugs, and toxicity. The two-compartment kinetic model (as shown in Figure 5) demonstrates how compound donor and receiver concentrations change throughout dialysis. When sink conditions are initially present, the rate of compound appearance on the receiver side (flux) is proportional to the donor matrix's unbound fraction (fu, donor). Mathematical relationships exist between the fu values in donor and receiver matrices, the permeability of the compound unbound dialysis membrane (P mem), the area of the dialysis membrane (A), the ratio of receiver/donor compound concentration (C), and the volume of the compartment (V) [42].

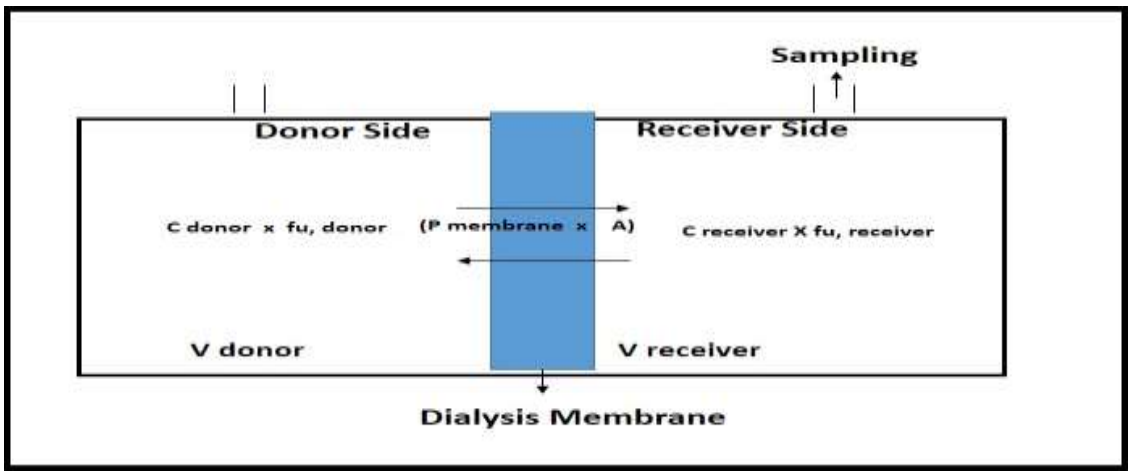

Figure 5. Demonstrates a two-compartment kinetic model [19].

A method was used to test the release of dexamethasone from a complex suspension by creating a formulation with different particle sizes and using water containing 0.1% Sodium Lauryl Sulphate (SLS). However, before conducting the drug release, each dialysis cartridge must be calibrated for its membrane property, which can affect the dispersion of soluble drugs. The membrane of the dialysis cartridge was characterised using the same setup as that used to measure drug release from the scattered system, but with 1% SLS in water to maintain the sink condition for the drug since the fraction recovery experiment needs to be performed on a solubilised drug. A sample was added while continuously stirring with a magnetic stirrer. The first sample was taken at 0 minutes on the donor side to determine the actual concentration of the solution. A sample was taken from both the donor and receiver sides at five-minute intervals for 30 minutes. Media solution was added to the collected sample's 1 mL volume to prevent

sinking. After 30 minutes, the samples were collected at 15-minute intervals. Sampling was carried out at predetermined intervals, and the solution in the receiver compartment was refreshed before the drug's quantitative analysis using High-Performance Liquid Chromatography (HPLC). The retentate aliquots were appropriately diluted (1 mL sample solution + 1 mL acetonitrile) using acetonitrile before HPLC analysis at room temperature (23.5 ± 1.5 ◦ C ap).

2.4.5. Drug release study using dexamethasone drug:

A cartridge for dialysis (membrane B) was utilised to measure the transfer of dexamethasone across the membrane in the dialysis setup. The drug transfer process used in the dialysis method and the setup were similar to those described in section 2.4.2. The pure dexamethasone drug [1, 52] was employed in the partial open-loop configuration. Solid lines represented the tube attachments, and arrows depicted the liquid flow direction (ap). Dexamethasone pure medication (10 ug/ml) was utilised in this technique with water comprising 0.1% Sodium Lauryl Sulphate (SLS) (1,2p) to determine drug release. Ethanol was added as a co-solvent to prevent the precipitation of SLS in the media solution. The sample was added while being continuously stirred with a magnetic stirrer. The first sample was taken at 0 minutes to determine the actual concentration of the solution. A sample was collected from the receiver side at five-minute intervals for 30 minutes. Media solution was added to the collected sample's 1 mL volume to prevent the samples from sinking. After 30 minutes, the samples were collected in 15-minute intervals. Sampling was conducted at predetermined intervals, and the solution in the receiver compartment was refreshed before the drug's quantitative analysis using High-Performance Liquid Chromatography (HPLC) [43, 44]. The retentate aliquots were appropriately diluted (1 mL sample solution + 1 mL acetonitrile) using acetonitrile before HPLC analysis at room temperature (23.5 ± 1.5 ◦ C ap).

2.4.6. In-Vitro Release Study using Suspension:

In vitro release testing for suspensions with small particle sizes was carried out using a dialysis cartridge to show the discriminatory ability of the microdialysis method. The setting and method used to carry out the release investigations utilising the dialysis method were the same as those previously detailed in section 2.4.2. Before starting the dialysis procedure, spike 0.6 mL of the suspension into 60 mL of the media solution (0.1% SLS solution in deionised water). The starting concentration of dexamethasone was 10 ug/ml. To measure the concentration of dexamethasone, aliquots of the donor and receiver were periodically taken from the permeate tube and the receiver side, respectively. Before HPLC analysis, the retentate aliquots were appropriately diluted using acetonitrile. The study was conducted at room temperature (23.5 ± 1.5 ◦C ap).

3. Results and Discussion.

3.1. Invitro drug release studies using micro dialysis:

3.1.1. Fraction recovery study of drug

An investigation was carried out using micro dialysis to study the release of dexamethasone from pure drug solutions. Fraction recovery was thoroughly examined. Fraction recovery studies were performed using a dialysis configuration to maintain the sink state. This ensured that the concentration of free medication (not in globules) remained low in the local area of the solution. It can be achieved by diluting in a higher intermediate volume. Throughout the test, the drug concentration gradient remained consistent, leading to the increased release of drugs from emulsion globules [42].

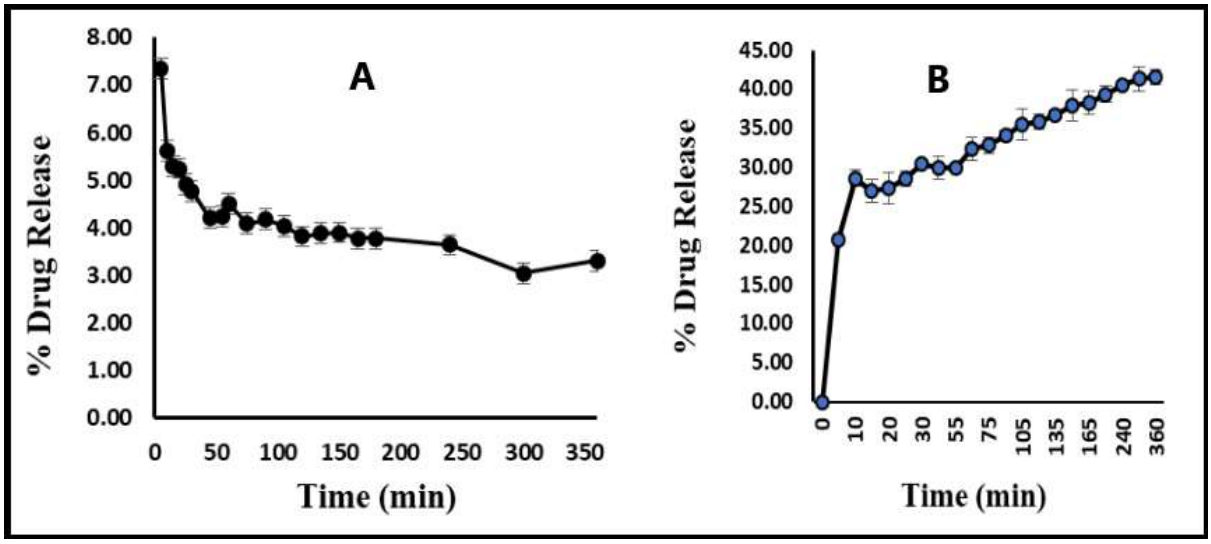

Figure 6: Drug release from dialysis membrane at different time intervals Donor side and (B) Receiver side

Figure 6 demonstrates that 50% of the dexamethasone (membrane A) took over 3 hours to diffuse over the dialysis membrane, and the concentration remained after approximately 8 hours. Dexamethasone's lipophilicity and probable interactions with the dialysis membrane were thought to cause delayed membrane diffusion, leading to a slow drug release rate. Additionally, after 3 hours, the concentration of dexamethasone on the donor side decreased, which was confirmed to be the result of the drug's breakdown in an alkaline medium. The data from the reference sample, which included a direct examination of dexamethasone in solution, clearly indicated that the medicine was decomposing. After three hours, only 30% of the pure medication was released, leaving approximately 50% in the bulk medium.

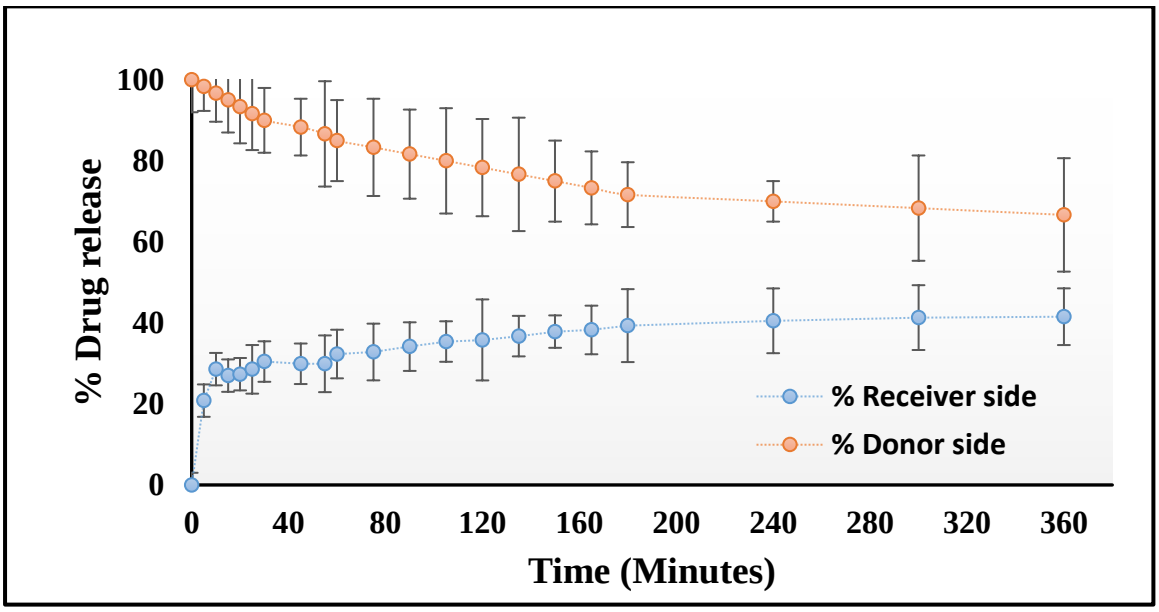

Figure 7: Comparison of % drug release study (donor and receiver side both)

The leftover drug began to break down after extended contact with an alkaline media. Despite high dilution ratios (100 dilution by release media), immediate shaking (50 rpm), and elevated temperatures (34 °C), drug release was delayed and incomplete. The dialysis membrane a procedure could not distinguish between different drug dissolution profiles in the solution. We utilized the Spectrum Midikros (100kDa) cartridge for drug release experiments to solve this issue.

3.1.2. Drug release study from pure drug (Dexamethasone) solution and suspension using dialysis method.

The newly developed dialysis method assessed the drug transfer from pure dexamethasone solution to a spectrum midikros dialysis membrane B (100kDA). According to the graph, more than 90% of the dexamethasone in the pure solution passed across the membrane (in the permeate) in 3 hours.

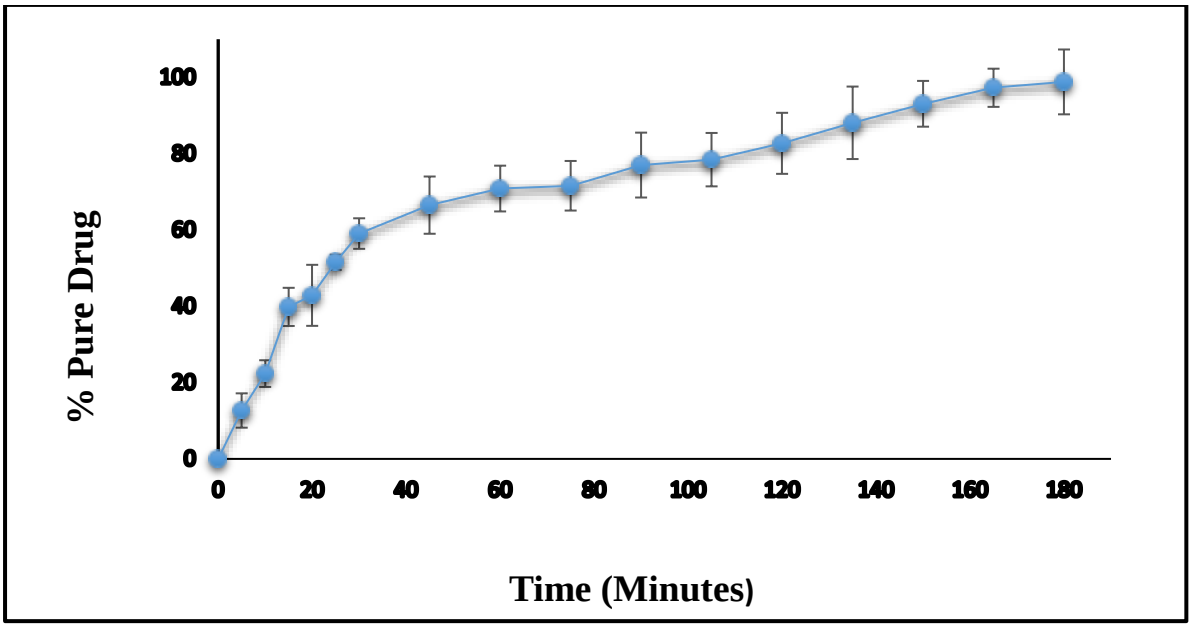

Figure 8: % Drug release study of Pure drug (Dexamethasone)

Pure dexamethasone solutions were tested using a release medium containing 20% ethanol for two reasons: first, to compare the process to medium dialysis, and second, to avoid drug precipitation caused by the enhanced rate of drug transfer attained with the dialysis method. The filtration procedure in the dialysis technique managed the overall rate of medication transfer across the cartridge [1].

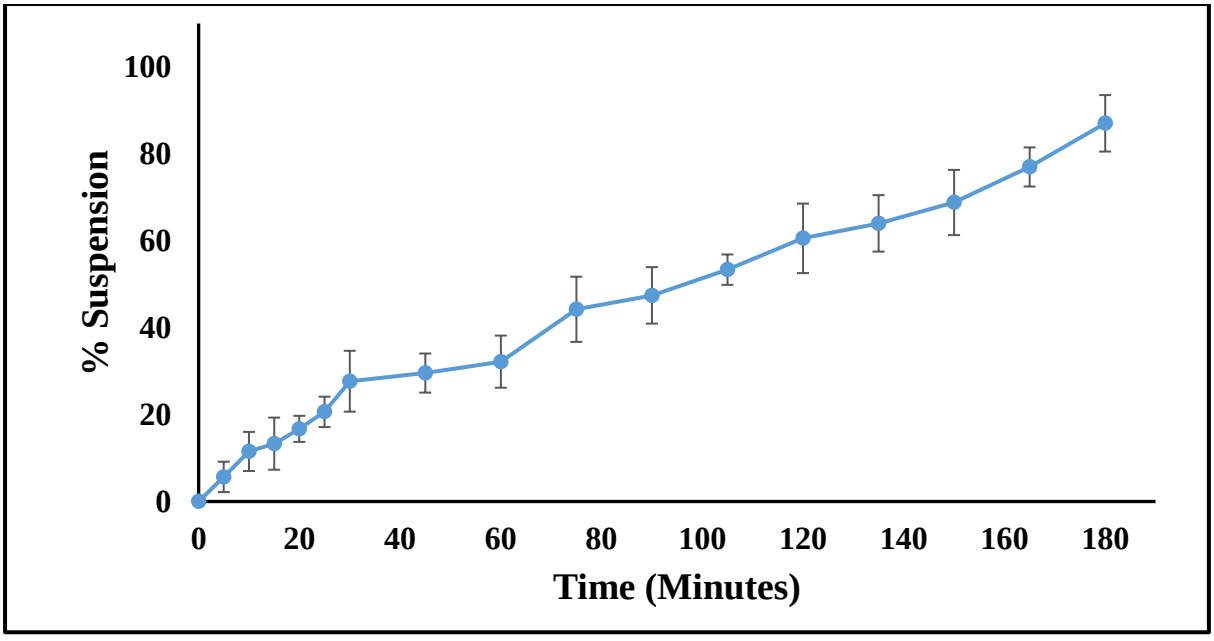

Figure 9: % Drug release study of Suspension

Using the dialysis procedure, around 80% of the medication was released from suspension. According to the results indicated in the figure, drug release from suspension was slower than drug diffusion from pure dexamethasone solution, with 90% release happening within three hours. The benefit of this technique is distinguishing between differences in the release rates of free drugs and medication in suspension [1].

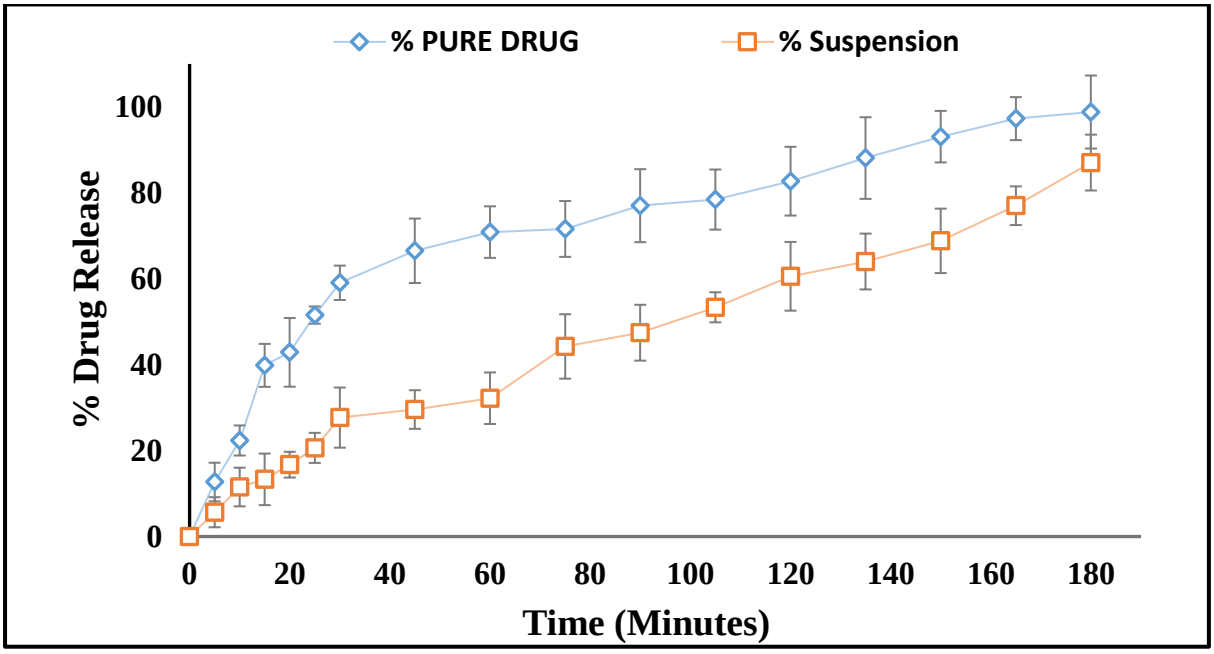

Figure 10: Comparison % Drug release study of both pure drug and suspension.

Furthermore, employing the membrane B (100kD) Cartridge rather than the membrane A Cartridge resulted in a higher degree of medication release. Using a 100kDa dialysis cartridge, around 90% of the medication was released from pure dexamethasone solution and 80% from dexamethasone suspension; however, only 30% of the drug was released when a membrane a cartridge was utilised. These studies demonstrated that the dialysis approach was practicable and valuable for determining the in vitro release of medicines containing particles.

3.2 Other factors that control drug release from suspension.

The current dialysis technique is based on two factors to assess medicine release from nanoemulsions: 1) Surfactant dispersion in suspension and 2) flow during dialysis [18]. Larger globules with lower surface areas require less surfactant to stabilise the interface, leading to a higher surfactant concentration in the bulk aqueous phase during suspension formation. The flux during dialysis determined the amount of medication transported from the filter to the receiver beaker.

3.3 Regarding an IVRT method's capacity for discrimination

An IVRT-based approach that can identify formulations based on changes in critical quality traits could be helpful in new product development, quality control, and evaluating a product's performance after adjustments made during approval. The findings of this study show that the micro dialysis technique can successfully differentiate between formulations by analysing in vitro drug release. Changes in critical quality characteristics are likely to influence drug release, affecting product efficiency. While the traditional dialysis process did not reach the same level of selectivity, the micro dialysis technique described in this study enables in vitro release testing of various complex dosage forms [45-48].

Because of the configurable drug removal and dilution rate, the proposed dialysis methodology outperforms traditional IVRT approaches such as micro dialysis and the USP 4 apparatus. The

micro dialysis approach also allows for the adjustment of feed flow and fresh medium supply rates, which determines how quickly the drug is diluted and how long the in vitro release test takes [49-51]. Finally, the micro dialysis approach opens up new avenues for using dialysis cartridge techniques to analyse in vitro release from complex dosage forms. Each of these applications uses the cartridge approach to retrieve finished goods. In this study, we use a cartridge in the micro dialysis method to suspend a complicated dosage form.

4. Conclusion

Micro dialysis is an innovative way to assess drug release from complex formulations in vitro. It can also investigate manufacturing-induced variables that affect dexamethasone's distribution and release kinetics from suspension formulations.. The dialysis method also better represents different drug release profiles in various dosage forms (such as suspensions, solutions, micelles, and nanoemulsions). The GSD (a critical product quality factor) was strongly linked to drug release features, which are performance attributes. The drug distribution throughout each suspension was calculated using filtration-derived aqueous medium concentrations and release phase data. The study also explored the effects of exposing the formulation to a rapid change in temperature and RPM on drug release. One of the potential advantages of using dialysis as an IVRT technique is the ability to gather and disseminate data quickly, especially during rapid temperature changes, as otic suspensions have short ocular residence times, and the temperature of the injected formulation can vary quickly. Microdialysis could be a good tool for increasing bioequivalence with the brand product while acting as a quality control test to assure consistency between batches. Such approaches can also help to speed up the development of new pharmaceutical products by improving understanding of drug release, especially in complicated formulations.

5. Funding

None

6. Conflicts of Interest

No conflict of interest to declare.

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