In Vitro Drug Release Methods for Drug-Eluting Stents

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The drug release profile of drug-eluting stents (DESs) is affected by a number of factors, including the formulation, design, and physicochemical properties of the utilized material. DES has been around for twenty years and despite its widespread clinical use, and efficacy in lowering the rate of target lesion restenosis, it still requires additional development to reduce side effects and provide long-term clinical stability. Unfortunately, for analyzing these implants, there is still no globally accepted in vitro test method. This is owing to the stent's complexity as well as the dynamic arterial compartments of the blood and vascular wall. The former is the source of numerous biological, chemical, and physical mechanisms that are more commonly observed in tissue, lumen, and DES. As a result, universalizing bio-relevant apparatus, suitable for liberation testing of such complex implants is difficult.

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1. Evolution of Cardiovascular Stents

There has been a global increase in the number of patients being treated each year for Cardio Vascular Disease (CVD). It is increasing, due to risk factors such as smoking, diabetes, obesity and lifestyle changes. According to the World Health Organization (WHO), in 2016, 17.9 million people died from CVDs, accounting for 31% of all deaths worldwide. Following this issue, the first developed technology, balloon angioplasty, was introduced. The very first angioplasties, based on balloon expansion in the artery, faced the problems of elastic recoil and neointimal hyperplasia and were the reason for 40–60% of restenosis in the years 1977–1990 [1][2].

It is noteworthy that there are second generations of balloons coated with drugs, commonly paclitaxel, to overcome in-stent restenosis. In this case, the drug should be transferred rapidly during the contact of the balloon with the vessel wall, which lasts approximately one minute. Some researchers are interested in this technique as this method decreases the risk of bleeding, avoids the risky presence of a foreign object in the body and limits the side effects [3]. However, this method was not completely developed for various reasons, mainly due to the promising results of stents.

Furthermore, due to the restenosis of the treated artery after deflecting the balloon, Bare Metal Stents (BMS) were introduced in the 1990s to overcome to this deficiency in the ballooning, and line the artery wall, wherein the

incidence of restenosis decreased to 20–30% due to the elimination of elastic recoil between 1991 and 2003. Meanwhile, as a disadvantage, BMS acted as a foreign object for the immune system and this may respond to this intrusive object in a variety of ways: macrophages (white blood cells) accumulate around the stent, and nearby Smooth Muscle Cells (SMC) proliferate, disrupting the process of endothelialization; migration and proliferation of vascular SMC from the media to the intima, generating an extra cellular matrix layer in the intima (intimal hyperplasia) followed by a narrowing of the luminal area [4][5]. It is likely that the phenomenon of thickened intima is due to the leukocytes that adhere to the activated endothelium and disrupt its recovery [6][7][8][9][10][11][12].

Therefore, the incorporation of the stents in the body was achieved by combining the drugs to avoid these serious effects. Thereafter, the treatment of the restenosis in the artery has been revolutionized by new generation of the stents, named drug eluting stents (DES) in 2003 [13]. This generation carries restorative drugs with them in order to treat the stenting area. These stents were coated by a polymer layer containing an active substance used to reduce neointimal hyperplasia. The incidence of restenosis decreased to about 3–20%. Although the use of DES rather solved the problem of restenosis, the issues of denuded intima and the related inflammation and thrombosis still persist and open a wide range of research [7][14][15][16].

It is reported in 2010 that annually about 0.3–0.6% of stenting with DES is followed by stent thrombosis (ST) followed by increased human mortality by 10–30% [17]. Stent malapposition, late or incomplete re-endothelialization and polymer induced inflammation are the main reasons for the inflammation and late thrombosis [4][7][15][18][19][20][21].

To overcome this problem, scientific advances are being made. They started about 40 years ago and the techniques continue to improve today: balloon angioplasty, bare stent, drug-eluting stent, bioresorbable stent.

The feasible way to decrease the ST is to prevent the risk of bleeding after stenting using anticoagulants and antiplatelet agents (the healthy endothelium also affords the anti-inflammatory support due to natural anticoagulant protein C [7]. Maintaining the dose of drug during the therapy can minimize the risk of thrombosis [22].

2. Release Compartment

As previously mentioned, the complexity of designing a universal test apparatus for stents is due to the stent's complexity, as well as the dynamic arterial compartments of the blood and vascular wall. These are the source of numerous biological, chemical, and physical mechanisms that are more commonly observed in tissue, polymer, and lumen mediums.

2.1. Artificial Blood

One of the important parameters, which has a key role in achieving the accurate drug release results from the drug-eluting stents in the in vitro condition, is the flow medium. As blood consists of plasma, red blood cells, white blood cells, and platelets, therefore seem not very easy to replace with a real representative of blood. Moreover,

using real blood in the in vitro experimental is not very applicable. However, the aim of the experiment defines all the needed parameters. As the portion of the white blood cells (less than 1% of blood) and platelets (less than 1% of blood), the red blood cells (40–45% of blood) are not very high compared to the plasma, which makes up 55% of the blood, but their reaction to the drug and implanted material, and more importantly, their real impact on the purpose of the experiment should be considered.

Ignoring the probable effect of the blood cells in the therapy experiments, plasma is the essential liquid determining the blood properties. It consists of 91% water, 7% proteins, 2% nutrients, hormones, electrolytes such as sugar, lipids, insulin, sodium, potassium, and calcium. Efforts have been made to simulate the components in this order, and different types of media are considered for the substitution with biological flow. Not all the essential parameters are mimicked by these artificial solutions, but the reason for the choice is dependent on the aim of the experiment. The water, phosphate buffered saline (PBS), organic component/PBS, and inorganic component/PBS are such common solutions that have been used as a medium. In particular, the pH and viscosity of the medium are important parameters that are impacting the drug release kinetics.

In general, PBS with a pH of 7.4 has been considered in many studies as a medium for studying the drug release [23][24][25][26][27][28]. Due to the ability of PBS to keep the pH constant and the proximity of its ions to the ions of the body, it has shown a good choice in analyzing the release of the drug. However, using this medium to evaluate the release of some drugs such as sirolimus has been challenging. Studies showed that sirolimus showed very low stability in the buffer solution with pH 7.4 [29]. Where hydrolyses of sirolimus to form newer compounds with opened lactam ring at alkaline pH and buffer salts was a problem that led to its instability in these environments. Thereafter, Naseerali et al. [30], studied the influence of various media on the release profile of sirolimus from a drug-eluting stent. Their results suggested that the medium consisted of 9:1 (*v*/*v*) of normal saline and isopropanol can be considered a suitable medium for the investigation of the in vitro release kinetics of sirolimus. According to their study, obtaining a medium with the least degradation of the drug, and also an environment that provides a slower release kinetic, was considered to be an essential parameter in order to achieve the suitable environment.

Pruessmann et al. [31], studied the impact of deionized water, PBS and phosphate-buffered saline without sodium chloride (PB) as a medium on the kinetic release of triamterene from coated stents. According to their study, deionized water showed the greatest release compared to PBS and PB. This increase was justified due to the higher solubility of the triamterene in deionized water and PB compared to PBS. This shows the important effect of increasing the soluble polarity by sodium chloride on organic compounds in aqueous solutions, which in turn leads to a decrease in the solubility of non-polar solutes such as triamterene. It is worth noting that according to the results of the study, the properties of the drug should always be considered as an important parameter in order to select the medium as it clearly has an effect on the kinetics of drug release, and besides, the common properties of the artificial media and real media in the body should be preserved.

As mentioned, the type of drug should be considered as an effective parameter in choosing the media. In particular, the solving of problems such as solubility and stability of non-polar drugs that have shown low solubility in an aqueous medium has attracted the attention of many studies. In fact, the ‘-olimus’ groups of drugs are not

stable at alkaline or neutral pH. So, lowering the pH to less than 7.4 could be a way to reduce the degradation of these drugs in the media. Furthermore, improving the solubility of the poorly water-soluble drugs in the aqueous media by using suitable solvents, such as surfactants, have been one of the suitable approaches that have been used in this field. If sirolimus (SRL) release from DES was taken as an example in this regard, Raval et al. [32], worked on optimization of media for the release of SRL from drug-eluting stents. They buffered the media at pH 4 for minimizing the degradation of SRL. In order to increase the solubility of the drug, a special amount of surfactant was used. Their results proposed that a release medium consisting of 0.1% P123 (kind of PEO–PPO–PEO block copolymers) in phosphate buffer pH 4.0 was most suitable for in vitro release of it from DES. In another study by Jelonek et al. [33], they have used acetonitrile and methylene chloride as a media for analyzing the SRL loaded in PLLA and PDLA. It is worth noting that the solutions, which were used as media, were the solvent for solving both the drug and the polymeric carrier. This solution is used, rather, to extract and quantify the entrapped drug (SRL) in the DES.

It should be noted that the use of solvents and surfactants could increase the kinetics of drug release from stents. As in most cases the drug released from the stent is loaded on the stent by being trapped in the polymer coating, the use of solvents and surfactants can increase the rate of degradation of the polymer coating. On the other hand, the use of surfactants can affect the separation and quantification of SRL by HPLC, which can lead to erroneous results.

In another study by Pruessmann et al. [31], they have analyzed the effect of different release medium, PBS and deionized water, on the release of the triamterene from the DES. The results indicated that triamterene has been released about two times higher in deionized water compared to PBS.

In another study for analyzing the effect of the struts and also distribution of the drug in the two media (artificial blood and artificial tissue) the viscosity of the medium was amongst the important parameters to be considered, therefore a mixture of glycerol-water (40/60 vol%, 0.01% surfactant) with the $\mu = 0.0044$ Pa.s, and $\rho = 1101$ kg/m^3 resulting in a kinematic viscosity of 0.04 cm^2 was used, which is similar to that of blood [34][35].

Merciadez and his colleagues [36] have used a new medium containing an organic solvent prepared using 2% ultra-pure sodium dodecyl sulfate (SDS), in high purity water with 10% gradient-grade acetonitrile (ACN), and buffered to pH 4.5 with phosphate. The mobile phase was a mixture of 55:45:0.02 water/tetrahydrofuran (THF)/formic acid (*v*/*v*). This allowed them to correlate in vitro release profile with the in vivo one from the porcine.

Moreover in a study by Chabi et al. [37] where the hemodynamic of the flow with the presence of stent was under consideration a mixture of 87% of glycerol and 13% of water was used.

2.2. Artificial Tissue

The release of drug from DES is only one part of the story. On the other side the amount of the drug diffused to the artery is the main clinical goal and certainly more difficult to investigate. Clinicians advise that a uniform drug concentration should be attained across the arterial wall, and the concentration should be maintained within some

therapeutic window [38]. In this regard, studies are trying to measure the amount of drug that has penetrated the vessel by using different gels that can simulate the vessel artery.

Neubert et al. [39] applied the calcium alginate hydrogel for simulation of the vessel artery. The water content of the gel was approximately 96%. Stability at 37 °C, the feasibility to adapt gel strength and elasticity and the mild gelling conditions, which allow for the incorporation of diverse substances such as proteins or living cells, were the reasons for choosing the calcium alginate hydrogel matrix. The gelling time can also be adapted by variation in concentrations and the gelling mechanism, which can directly affect the drug diffusion in the gel. Furthermore, the results of the study showed that the presence of another compartment (hydrogel) changed the kinetic of the release from the samples, which was accompanied by a decrease in the amount of drug released into the flow medium. In addition, according to the results, the current composition of the medium and the hydrogel was not representative of the in vivo condition, and it needs more adaptations of the hydrogel compartment or periodic medium replenishment.

Depending on the environmental conditions of setup for analyzing drug released from the stents, some properties of hydrogels such as rheological properties, degradation and swelling are among the factors that will affect their selection. In a study by Semmling et al. [40] the hydrogels of 2 wt.% agar, 2 wt.% agarose, 10 wt.% PAA and 15 wt.% PVA were selected. In order to find a measure for the long-term stability of the gels, the mechanical properties of the prepared gels were determined by texture analysis. In this regard, stress–strain curves of native gels, as well as gels that had been perfused with phosphate-buffered saline (PBS) pH 7.4 in their setup for 28 days were studied. Their results showed that agarose gel seems to be the most suitable candidate for long-term dissolution testing since the target gel parameters are relevant for their use as a tissue simulating compartment in their setup.

It should be noted that in addition to the desired physical and rheological properties, in order to select a hydrogel as a vessel wall, the drug penetration coefficient in the hydrogel has great importance and should be considered as a parameter with high status. In a study by Semmling et al. [31], the penetration coefficient of triamterene was under 3 wt.% alginate, 2 wt.% agar, 2 wt.% agarose, 10 wt.% PAA and 15 wt.% PVA hydrogels were examined. According to their results, the penetration coefficients of these gels were in the range of 2×10^{-4} mm^2/s (PVA) to 8×10^{-4} mm^2/s (Agaros). The results of these studies showed that the hydrogel with the lowest diffusion coefficient had 4% of drug penetration. This is where the penetration coefficient of sirolimus in the human coronary arteries is reported as $1.5–2.5 \times 10^{-4}$ mm^2/s [41], which is near to the penetration coefficient of triamterene in hydrogels used in these experiments.

Bandomir et al. [42] studied the amount of paclitaxel diffused in the calcium alginate, polyacrylamide (PAAm) and poly(vinylethylimidazolium bromide) hydrogels from a drug-coated balloon. Certain properties such as permeability, flexibility and long-term stability of synthetic hydrogel, were the properties which are considered for introducing a good candidate as the vessel wall. The dissolution of the network by monovalent cations such as Na^+, as well as its susceptibility to microbial contamination, were among the disadvantages mentioned for calcium alginate hydrogel.

In order to select the type of hydrogel and to obtain and select the suitable cross-linkers used to make the hydrogel, it is important to know the mechanism of drug transport to the hydrogel. Studies have shown that drug delivery from drug-impregnated stents is controlled by both penetration and convection mechanisms. Given that the penetration mechanism will occur based on the concentration gradient, firstly, the drug must be dissolved in the matrix and subsequently, the drug can penetrate to the gel or media [43]. For this purpose, the solubility of the drug in the matrix, and then the penetration of the hydrogel, should be considered as the important parameters. For example, a study of a balloon impregnated with paclitaxel in a hydrogel showed that due to the low solubility of the paclitaxel in the aqueous medium, the amount of drug transferred to the hydrogel was by mechanical forces during balloon expansion [42]. In addition, the research has shown that biological reactions, such as binding the drug particles with the receptors in the tissue, affects the drug penetration in the tissue for simulating in vivo reactions, and some proteins were added to the hydrogel. The presence of proteins can cause the drug to deposit in the vessel wall, which after a while can allow the drug to penetrate into the tissue [44]. Therefore, it is worth noting that when the drug has low solubility, after opening the stent by balloon, part of the drug can be transferred into the gel by mechanical force, but after that, the remaining amount of the drug, due to the inability to penetrate into the gel, will only wash-off from the stent and this can cause an error in calculating the amount of drug that has penetrated into the gel.

Semmling et al. [45] examined the effect of using different hydrophobic additives to the vessel wall simulating the hydrogel compartment on release and distribution from model substance-coated stents. In this regard, four alginate-based gel formulations containing reversed-phase column microparticles LiChroprep® RP-18 or medium-chain triglycerides in the form of preprocessed oil-in-water emulsions Lipofundin® MCT with different concentrations were chosen. In general, use of additives was applied for improving the media contact with the hydrogels used. It is worth mentioning that in the study, fluorescein and triamterene were studied as hydrophilic and hydrophobic drug models, respectively. The results showed that the effect of gel improvement had no significant effect on the penetration of the hydrophilic drug into the hydrogel, while the improved gels were a more suitable substrate for the transfer of hydrophobic drug into the hydrogel.

Another important and effective factor with hydrogels for the penetration of drugs through them, is the suitable choice of the base agent within the hydrogel. Pruessmann et al. [31] investigated the effect of deionized water, PBS and PB as the base for preparing hydrogels for the diffusion of triamterene in them. Their study showed that more drug was transferred to deionized water-based hydrogels than PBS and PB-based hydrogels. This effect was due to the absence of salt in deionized water, which was discussed in the previous section.

3. Release Test Methods

Analysis of the kinetics and amount of drug released from the drug-eluting stents play the most important role in evaluating a drug-impregnated stent. Due to the cost and time-consuming in vivo tests, examination by in vitro tests has been the center of attention in many studies. Studies have always been trying to increase the accuracy of the in vitro tests in order to provide a good estimate of the results in comparison to in vivo tests. In general, the methods used for this purpose are divided into two static and dynamic conditions. The main difference between the

two tests was the use of media flow. However, the temperature used in these two methods is 37 °C and has been accepted by researchers.

3.1. Static Condition

The static method has been used as a common method in measuring drug release from drug-impregnated stents and other drug delivery systems. In general, in this method, the stent is immersed in a certain amount of media, and then the sampling of the media will be completed in certain periods of time. The drug release mechanisms in this method occur mainly through the concentration gradient between the DES and the media. The test temperature will be constant during the drug release test.

One of the important points for testing the drug release in the static state is media sampling. In this way, at the time of sampling, what volume of media should be replaced with fresh media [46]. In the study by Khan et al. [47] the rapamycin release from drug-eluting stents was evaluated under static conditions. The sample was immersed in 2 mL of medium. In order to evaluate the amount of drug released, 1.5 mL of medium was replaced with fresh medium at each time point. The sampling time for the experiments was six hours, one day, three days, five days, ten days, and then weekly up to seventy-five days.

As mentioned, the evaluation of drug release from stents is very important to determine the effectiveness of stents, and studies have always tried to bring the test conditions closer to the body environment. Abbasnezhad et al. [48] showed that there is a significant difference between the drug release under the static and dynamic conditions (the next section will discuss more on the effect of flow on drug release). One of the drawbacks of the static method is the absence of circulating flow. Moreover, since the release of the drug in the static state will have slower kinetics than in the dynamic state [49], and more experimental time will be needed. However, due to the availability of this method, it seems that useful basic information can be obtained from this test.

3.2. Dynamic Condition

Several drug release mechanisms contribute to the drug release from the drug-eluting stents. The most important mechanisms consists of the diffusion-controlled drug release, dissolution/degradation-controlled drug release, and osmosis-based controlled release [50]. It is worth noting that each mechanism provides a different kinetic of the release from the stents. A study by Abbasnezhad et al. [51] has showed the effect of the flow rate on the kinetic of the release by considering the associated mechanisms.

The use of shakers has been amongst the common methods of measuring the amount of drug release at the dynamic condition. For this purpose, a certain number of stents (usually one stent) to media are placed in the screwed-glass vials [52], tubes [53], or flasks [54], and then the test is performed at a certain agitation of the shaker. In most studies, the temperature intended for the experiment was kept constant at 37 °C by an incubator [51][55] or a water bath [52][56]. The agitation speed of shaker in studies considered in the range of 50 [57][58], 75 [59][60], 80 [54], 100 [52][55], 120 [56], 130 [61], 175 [53], 250 and 300 [62] rpm. Sampling in this method to check the amount of drug

released has been one of the variable parameters, which consist of several methods. Generally, the methods of sampling are as follows:

- Changing the special volume of media with fresh media (fresh media is added to keep the test volume constant and avoid the saturation) [62];
- The media is completely replaced with new media at specific times [52][54][55];
- A specific portion of the media is removed to analyze and returned to the test environment after analysis [60].

To the best of knowledge, the effect of shaker agitation on drug release has not been studied by simulation. In addition, in the studies, the reason for choosing a special agitation to evaluate drug release was not specifically mentioned, and this value was in the range of 50 to 300 rpm. In general, it can be said that the conditions created by using shakers, due to the importance of the presence of flow on the drug release, cannot give an accurate estimate of drug release of the in vivo tests, but this method will accelerate the drug release from the stent and can reduce the time required to perform the test.

Apart from the shakers there is another method for the dynamic condition, which is the circulation of the flow at the continuous state, and this condition may have more similarities to the real case comparing to the shakers. The same can be said for agitation for the continuous state, which also has different values for the flow rate that has been chosen in different studies.

As an example in a study by Bandomir et al. [42], a flow rate of 35 mL/min was chosen for studying the drug delivery from the drug-coated balloon, whereas, in a study by Zheng et al. [63] the flow rates of 3, 10, 30 mL/s were chosen for the Sirolimus release from DES.

Another study for the release of Sirolimus from DES has been conducted by Merciadez et al. [36], where in this method a medium with the flow rate of 25 mL/min was used. This value was chosen due to the optimum pump performance with respect to priming and flow characteristics of the Sotax apparatus media pump.

Another study [64] has considered the laminar flow rates of 6.8, 10, 11.6, 12.3 and 17.3 L/min where they have selected the different laminar flow rates of an oscillated heart pulse.

In an investigation by Seidlitz et al. [65] they have used the flow rate of 35 mL/min, where they have referenced the flow rate in the coronary vessels, as well as the flow rate of 4 mL/s for two different types of drugs. Their analysis indicated that the variation in the flow rate had not a distinct effect on release and distribution. Therefore, they have concluded that the effect of the flow rate should be analyzed by case-by-case examinations through individual assessments of their sensitivity to such changes.

In another study by Bernard et al. [66] they have considered two flow rates of 60 and 140 mL/min as the minimum and maximum values of the right coronary artery. They have stated that an increase in the flow rate emphasizes

fluid perturbations, and generates a wall shear stress rise except for inter-strut area.

Moreover, to the continuous flow in the case of dynamic condition, pulsatile flow and especially systolic-diastolic flow pattern are in the interest of studies, which can simulate the real flow pattern of the blood circulation in the body.

In another study [67] the comparison of the continuous flow and pulsatile flow, experiments have shown that the pulsatile flow shows a different character of flow, especially at the bifurcations, where the steady flow shows a fixed separation of the flow, without any turbulence and wall shear stress, which is rather constant during the time. However, the pulsatile flow does not have the constant region of separation, with the possible turbulence at the end of the systole and the wall shear stress that varies in magnitude and direction and, moreover, increases the time of the resistance of the bubbles.

4. Apparatus for Release Testing

In vitro drug release from the DES is a big challenge for researchers. In this regard for designing an apparatus, which can be specialized to contain the similar condition of the in vivo condition such as treatment of the vessel wall in the vicinity of the DES and the lumen side, providing a systalic-diastolic flow pattern also improvising a system for filtering the drug released in the medium are amongst the new plans for improving the release test setups. In the following the most famous apparatus, which are commonly used, will be discussed.

In the static state generally, laboratory vials are used. However, in the dynamic state shakers, basket apparatus USP 1 (United States Pharmacopeia), or paddle apparatus USP 2, which are normally destined for capsules and tablets, have only one difference between them, which is the replacement of the paddle to the basket for drug carriers that float or drop at the bottom of the vessel. Reciprocating Cylinder USP 3, which was developed to mimic gastrointestinal test, flow-through cell apparatus (USP 4), which has a continuous flow circulation it is designed for low soluble drugs, implants and suppositories. They can be used in two types of open type or closed-loop system, where the pump delivery in this case is about 240–960 mL/h. Compendial Apparatus 5 (paddle over disc) is similar to the paddle system (USP 2) but with an additional disc mounted on it.

Cylinder type or USP 6, resembles the basket type but the basket and shaft are replaced with a cylinder stirring element. USP 5 and USP 6 are normally destined for drug release from the transdermal patches.

Reciprocating holder apparatus with agitation (USP 7), this type is the most recent apparatus destined for different types of drug carriers such as tablets, capsules, transdermals, osmotic pumps, and arterial stents, with different agitation speeds.

Generally in the case of stenting, these devices are not sophisticated enough [48][68]. The importance of the systolic-diastolic flow and the inherent pressure variation is indicated in in silico models, which are parameters that are not really respected in the experimental tests [69]. The presence of a simulating arterial tissue is another

important element affecting the release, where the efforts in this regard lead to the development of the Vftc (vessel-simulating flow-through cell) method [70]. However, so far, the simulating tissue is not accurately reproducing the characteristics of the real one [71][72][73]. The apparatus USP 2, USP 4, USP 7 and vFTC in the closed-loop mode, are amongst those that have taken attention away from the DESs in the field of drug delivery.

For comparing the effect of the different test setups on the release profile, a study by Medina et al. [74] has compared the release profile of the ibuprofen obtained by two methods of USP 2 and USP 4 with the reference by model-independent, model-dependent, and analysis of variance (ANOVA). Their results have indicated that the release profile obtained by the method of USP 4 was similar to the profile of the reference.

In another study Pruessmann et al. [40] have studied the release of triamterene as a model substance from the DES at three different test setups: USP apparatus 7, USP apparatus 4 (FTC) and vessel-simulating flow-through cell (vFTC). According to the results obtained in in vitro experimentation, they have stated that dissolution vessel geometry and medium volume had no influence on the release behaviour, whereas the flow through cell method had a lower release rate than the incubation methods.

The same method of vFTC was used by Seidlitz et al. [65] for the comparison of the dissolution and release results of fluorescein sodium and triamterene from stent coatings by the methods of the vessel-simulating flow-through cell with a standard paddle (USP 2) and flow-through cell (USP 4) apparatus. The results showed that release from the coating was decelerated by embedding in the hydrogel in the adapted apparatus. However, in another study by Pruessmann et al. [31] triamterene showed a higher release in the medium at the first stage by vFTC method, then it is underneath of the profile of the release obtained by FTC method.

The studies in this regard show that to achieve an apparatus, highly adapted for studying the drug release from drug-eluting stents, there is already much to be done. Moreover, in vitro/in vivo correlations, by considering the different parameters, in order to personalize the therapy and thus increase the efficiency of the therapy, remain a challenging topic.

5. Analytical Tools to Determine Drug Release

The first step to determine the efficiency of a drug delivery carrier is to evaluate the amount of drug released from the carrier at different times. The main technologies used in this aim are: High-performance liquid chromatography, UV-Vis spectroscopy and Raman spectroscopy.

5.1. High-Performance Liquid Chromatography

Liquid chromatography is a classical technique used to separate a sample into its individual parts. This separation occurs based on the chemical or physical interactions of the sample with the mobile and stationary phases. There are many different types of chromatography techniques and systems available for a wide range of applications, all of which are defined as High Performance Liquid Chromatography (HPLC). HPLC analysis focuses on

macromolecule isolation through chemical interaction, affinity or hydrodynamic volume. As the molecules present in the mobile liquid phase interact differently with the stationary phase, they produce different signals on the detectors. This technique is generally associated with other analytical techniques (optical detectors), such as UV detectors or fluorescence detectors.

5.2. UV-Vis-Detector

Ultraviolet-visible (UV-Vis) spectrophotometry is a technique based on the absorption of photons belonging to the UV, visible or near IR regions of the electromagnetic spectrum. Substances exposed to such radiations are prone to electronic transitions. The signal consists in a series of peaks in an absorbance versus wavelength spectrum. Compared to HPLC, UV-spectrophotometry method is much faster and less expansive.

By this approach, aromatic structures, unsaturated (conjugated) compounds, or carbonyl groups inside the molecule are detectable. Compared to HPLC, UV-spectrophotometry method is much faster. Determining of solution using HPLC-UV needs organic solvent (HPLC grad) as flushing and mobile phase. Moreover, HPLC is more expensive than the UV-spectrophotometer.

In a study by Dhole et al. [75] they have compared the two methods of HPLC and UV for the detection of Repaglinide drug in the tablets. They have stated that two methods have enough accuracy, however, HPLC is prone to being more precise. The approach of UV compared to HPLC has the benefit of not requiring the time-consuming treatment and processes associated with chromatographic methods.

5.3. Fluorescence Detector

Fluorescence detectors are probably the most sensitive among the existing modern HPLC detectors. It is possible to detect even a presence of a single analyte molecule in the flow cell. Typically, fluorescence sensitivity is 10–1000 times higher than that of the UV detector for strong UV absorbing materials. Fluorescence detectors are very specific and selective among the other optical detectors.

Compounds having specific functional groups are excited by shorter wavelength energy and emit higher wavelength radiation, which is called fluorescence.

Fluorescence detector is a method where the compounds often contain conjugated aromatic ring systems, can be detected via it. Due to a missing chromophore, the study of amino acids can be very difficult, so neither UV-Vis nor fluorescence detection can be used for detection.

5.4. Raman Spectroscopy

This technique consists in illuminating the sample with monochromatic light (usually from a laser in the visible, near infrared, or near ultraviolet range, although X-rays can also be used). The interaction of this light with the molecules of the sample depends on their vibrations (this phenomenon is called inelastic diffusion or Raman

scattering) and a shift in the energy spectrum of the diffused photons is observed. This method is more advanced compared to UV and HPLC. One of its advantages is the ability to use it in situ during the experimentation, therefore it decreases the use of disposables, it is fast, precise and has less risk due to less transportation of test substances [76][77]. In a study by Bourget et al. [77] on the detection of an anti-cancer drug, the researchers have pointed out that both approaches offer sufficient precision and accuracy. Raman spectroscopy, on the other hand, is beneficial for ensuring the analytical quality of this drug and helps to safeguard careers and their working environment.

6. In Vitro–In Vivo Correlations

The importance and evaluation of in vitro tests are further emphasized when they are representative of an in vivo test or are used to predict the in vivo performance of the active substances. Therefore, the attempts are for developing a correlation between in vitro and in vivo tests, which presents the major challenge of the coming decades. IVIVC is described by the US FDA as a predictive mathematical model that describes the relationship between an in vitro property of an extended release profile (usually the rate or extent of in vitro drug release) and a related in vivo response, for example, plasma drug concentration or amount of drug absorbed [78].

This relationship may be qualitative or semi-quantitative, such as the correlation of the mechanism of release. This method is more developed and used for the oral administration, where it permits the development of drug administration and controls the dosage between the therapy window.

In this case important parameter between the in vitro and in vivo test methods is the difference of the physiological properties of the plasma with in vitro medium and the absorption of the drug in the biological environment. A mathematical model for the correlation between the release mechanisms and also a correlation between the entire release time of the in vitro and in vivo methods would be most helpful and most effective IVIV correlation [79].

Therefore, a validated predictive IVIVC will have a substantial positive effect on the consistency of the commodity, the productivity of production and decreased compliance costs.

For developing the IVIVC model, both in vitro and in vivo results are requested, where the results could be different for a certain logic with a certain difference in the release rate.

According to the statement of Qiu and Duan [80] for developing the IVIVC mathematical model, relating the entire release of the drug in vitro and predicting the drug absorbed or the concentration of the drug in plasma, the mathematical correlation is applied in a two-stage procedure.

Developing an IVIVC model needs in vitro drug release data at different release rates (e.g., fast, medium, and slow) and a discriminating in vitro test methodology [80].

Indeed, several failures in attempts to achieve IVIVC for drug administration can typically be due to the absence of an in vitro predictive test, or to a discrepancy between the formulations of the in vitro, and in vitro tests. It is therefore important to consider how in vitro and in vivo results can be influenced by the physicochemical and biopharmaceutical properties of the drug, administration technology, and formulation of a drug and its interactions with the in vivo and in vitro environment. The typical efforts in this regard were for the oral administration by changing the release media, hydrodynamics and generating shear force, which was almost at a static state that cannot totally be representative of in vivo conditions [80].

In this regard, a qualitative and quantitative relationship should be established between the drug release profiles, considering different parameters of in vitro tests. The latter will help to better choose the in vitro experimental methods and conditions in order to better correlate with the kinetic and the mechanisms of the in vivo release.

In another study by Ma et al. [60] they have investigated the release profile of the combinations of two drugs of paclitaxel/sirolimus in vitro (measuring the drug content in PBS) and for the in vivo a rat aorta model was utilized. The results from these experiments showed that both drugs at both conditions of in vitro and in vivo had two-phase release profiles.

On the condition that the in vitro results are not correlative with in vivo results, the in vitro conditions should be improved to get closer to the in vivo condition, and therefore to the in vivo results.

In this regard, a study by Merciadez et al. [36] has tried different parameters of the in vitro release tests from DES in order to bring the in vitro release profile close to the in vivo release profile. In this regard, they have obtained a release profile of in vitro from USP apparatus 4 in 24 h, which corresponds to the release profile of 30 days in vivo in porcine.

The parameters chosen for the in vitro test were as follows: test apparatus (USP 4); elution medium was an organic solvent; flow circulation of 25 mL/min; pH about 4.5; and temperature of 37 °C.

In another study by Sako et al. [81] they have evaluated the release of acetaminophen from the different compositions of a hydrophilic matrix, where the in vitro tests showed the same profile of the release for different agitation, however, it was not corresponding with the in vivo tests, thereafter by modifying the in vitro test conditions, the results were consistent with the in vivo results.

Some other variables are formulation design, dosage, drug properties, release environment. It is notable that different formulation of the drug carriers may have different sensitivity to each of these variables [82][83]. Therefore, it is essential to examine its sensibilities to different variables in the in vitro case before defining the IVIVC model.

One of the difficulties in this method is that each IVIVC is valid just for a specific type of dosage and drug delivery system, therefore by changing the type of the drug delivery system (DDS) or even with the same dosage and DDS, just with or without excipients can have different release mechanisms (e.g., diffusion, degradation, osmosis) where it is necessary to develop a new IVIVC [84][85].

The state of the art has indicated that there is not a universal method of in vitro test that can mimic the complexity of the test conditions of the in vivo case, for better predicting the in vivo release profile. Therefore developing an IVIVC should be studied case by case, referring to the different types of the DDS and considering different effective parameters, and their adaptability to the in vitro conditions.

For example in a study by Kim et al. [86], they have studied the durability of a polyurethane-covered stent for the biliary endoprosthesis, destined for patients with biliary stricture, and in this regard they have used the bile juice as the circulating medium. Whereas it is not applicable when the in vitro medium is used for simulating the plasma and blood components.

As mentioned depending on the type of DDS, adaptability of the in vitro conditions to the in vivo would be more or less complicated. In the case of drug eluting stents, there is high enough parameters for adaptation. In this regard, some researchers focus on one parameter, such as the strut thickness, dosage, type of the drug or type of the material, etc., whereas some others focus on multiple parameters. In a study by McGinty et al. [87] they have coated the stents with low and high dose of the Sirolimus/polymer (25/75 and 75/25) and in the in vitro case they have immersed the stents in the release medium of PBS. For the case of in vivo, they have used the porcine arterial tissue and the release profile was cumulative of the drug transport by the mechanisms of diffusion, advection and binding. Their investigation showed that the discrepancy for the results of high dose DES was notable, whereas the results for low dose DES were more consistent.

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