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Review

In vitro dissolution/release methods for mucosal delivery systems

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Abstract

In vitro dissolution/release tests are an indispensable tool in the drug product development, its quality control and the regulatory approval process. Mucosal drug delivery systems are designed to provide both local and systemic drug action following ocular, nasal, oromucosal, vaginal or rectal administration. They exhibit significant differences in formulation design, physicochemical characteristics and drug release properties. Therefore it is not possible to devise a single method which would be suitable for release testing of such versatile and complex dosage forms. Different apparatuses and techniques for in vitro release testing for mucosal delivery systems considering the specific conditions at the administration site are described. In general, compendial apparatuses and methods should be used as a first approach in method development when applicable. However, to assure adequate simulation of conditions in vivo, novel biorelevant in vitro dissolution/release methods should be developed. Equipment set up, the selection of dissolution media and volume, membrane type, agitation speed, temperature, and assay analysis technique need to be carefully defined based on mucosal drug delivery system characteristics. All those parameters depend on the delivery system and physiological conditions at the site of application and may vary in a wide range, which will be discussed in details.

Keywords

In vitro dissolution/release test; nasal drug delivery; ocular drug delivery; oromucosal drug delivery; rectal drug delivery; vaginal drug delivery

Introduction

The drug dissolution/release test is a key test of dosage form performance both during formulation development as well as for quality control purposes. For majority of mucosal drug delivery systems (i.e. formulations aimed to provide local and/or systemic drug action via nasal, ocular, oral, rectal and vaginal mucosa) the methods and apparatuses for dissolution/release testing are not standardized and described in pharmacopoeial monographs, indicating the need for further development and systematisation of the currently used methods [1].

It should be noted that the terms *drug dissolution* and *drug release* are often not appropriately distinguished in the literature and even in regulatory documents. The drug dissolution process refers to all formulations in which the drug is initially present in the solid state and encompasses 5 major mass transport steps: (i) the wetting of the particle surface with water; (ii) breakdown of solid state bonds in drug particle; (iii) solvation of the individualized species such as ions or molecules; (iv) their diffusion through the liquid unstirred boundary layer and (v) convection within the well-stirred bulk fluid. If drug dissolution process is the rate-limiting step in the overall release process, than the terms drug dissolution and drug release can be considered as synonyms. In all other cases, drug release is the more appropriate term. In fact, the drug release is a more complex phenomenon, where drug dissolution is just one of its steps. Upon the contact with the aqueous dissolution medium, water penetrates into the matrix of the delivery system and dissolves the drug. The dissolved drug species subsequently diffuse out of the matrix of the delivery system due to concentration gradient. Additionally, the matrix of the delivery system might also undergo several changes such as swelling and consequent dissolution in the aqueous medium, all contributing to the overall drug release process [2,3]. Considering the complexity of mucosal delivery systems, often containing nanoparticulate carriers included in soluble or insoluble matrices, *in vitro drug release* seems to be the appropriate term when describing the liberation process of the drug from such formulations.

In methods listed in USP and Ph. Eur. monographs, USP Dissolution Database and FDA Dissolution Database (Table 1), the apparatuses traditionally used for oral formulations are also often applied for mucosal delivery systems. However, many noncompendial methods have been developed with intention to take into account the specific physiochemical properties of the formulation and the physiological environment at which the drug should be released. The goal is to develop a test able to provide predictive estimation of *in vivo* drug product performance, with preferably level A of *in vitro-in vivo* correlation (IVIVC) [4]. Development of noncompendial methodologies requires standardization of test parameters and procedures in order to ensure reproducible and reliable results. Besides the equipment set up, selection of the dissolution media and volume, membrane type, agitation speed, temperature, and assay analysis technique need to be carefully defined based on mucosal drug delivery system characteristics and physiological conditions at the site of application [5]. This article is aimed to provide useful guidelines and recommendations in this regard.

The dissolution medium selection

As shown in Table 1, apparatuses traditionally used for oral formulations are often applied for mucosal delivery systems. Generally, the relatively high volume of the dissolution medium used (500-1000 ml) and the hydrodynamics provided by such apparatuses is not in line with the *in vivo* conditions at the mucosal administration sites. To mimic the physiological conditions at mucosal administration sites, a low volume of aqueous dissolution medium in the physiological pH range should be used. Some of the commonly used dissolution media for mucosal delivery systems are listed in Table 2. On the other hand, sink conditions should be maintained. In order to achieve sink conditions for a water-insoluble active compound it may be necessary to add surfactants (such as Tween 80 or sodium lauryl sulphate), complexing agents (such as cyclodextrins) or organic solvents (ethanol, methanol etc.) into the dissolution medium [14]. If organic solvents need to be included in dissolution medium, they have to be compatible with the formulation, and their concentration needs to be adjusted not to disrupt the formulation. In addition, in case of membrane diffusion methods, the selected solvent should also be compatible with the membrane used [15]. The most commonly applied temperature for oromucosal, rectal and vaginal formulations testing is 37 °C, while in

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case of ocular and nasal formulations, temperature may wary between 32-34 and 33-37 °C, respectively [3].

Table 1. Apparatuses used/recommended for in vitro release testing of mucosal formulations according to monographs and methods published by USP, Ph. Eur. and FDA. Reprinted from ref. [3] with permission of Elsevier.

Formulation type	Apparatus	Reference
Semisolid dosage forms (creams, gels, ointments, lotions)	Vertical diffusion cell	[6]
	Immersion cell	[6]
	Flow through cell with adapter for semisolid dosage forms	[6]
	Paddle apparatus	[7]
Oral, buccal and sublingual films	Paddle over disk apparatus	[7–10]
	Basket apparatus (small-volume configuration)	[7,8]
Sublingual and buccal tablets	Paddle apparatus (standard or small-volume configuration)	[7,8,11]
	Basket apparatus (standard or small-volume configuration)	[7,8]
Lozenges	Basket apparatus	[7,8]
	Paddle apparatus	[7,8,11]
	Reciprocating cylinder	[7,8]
Medicated chewing gums	Dissolution apparatus for chewing gums	[7,8,12]
Suppositories (hydrophilic)	Paddle apparatus	[7,8,11]
	Basket apparatus (standard or Palmieri type basket)	[7,8]
	Flow-through cell	[8]
Suppositories (lipophilic)	Dual chamber flow-through cell	[8,13]
Vaginal tablets and vaginal inserts	Paddle apparatus	[7,8]
	Basket apparatus	[7,8,11]
Vaginal rings	Incubator shaker	[7]
Mucosal suspensions	Paddle apparatus (standard or small-volume configuration)	[7,8]
Mucosal emulsions	Paddle apparatus	[8]
	Vertical diffusion cell	[8]
Ocular systems	Reciprocating shaker	[11]
Periodontal systems	Tube rotator	[11]

Table 2. Some frequently used dissolution media for in vitro drug release testing of mucosal drug delivery systems. Reprinted from ref. [3] with permission of Elsevier.

Medium	Composition	pH	Reference
Simulated tear fluid	2.18 g $NaHCO_3$, 6.78 g NaCl, 0.063 g $CaCl_2$, 1.38 g KCl and distilled water up to 1000 ml	7.4	[16]
Simulated nasal fluid	8.77 g NaCl, 2.98g KCl, 0.59 g $CaCl_2$ and distilled water up to 1000 ml	5.5	[17]
Simulated nasal electrolyte solution	7.45 g NaCl, 1.29 g KCl, 0.32 $CaCl_2x2H_2O$ and distilled water up to 1000 ml	5.5-6.5	[18]
Artificial nasal electrolyte	0.8 g NaCl, 3.0 g KCl, 0.45 g $CaCl_2$ and distilled water up to 1000 ml	6.8	[19]
Nasal fluid simulant	7.13 g NaCl, 2.98 g KCl, 2.14 g $NaH_2PO_4xH_20$, 1.21 g $Na_2HPO_4x7H_2O$ and distilled water up to 1000 ml	7.4	[20]
Simulated saliva	2.38 g Na_2HPO_4, 0.19 g KH_2PO_4, 8 g NaCl and distilled water up to 1000 ml	6.8	[21]
Modified simulated saliva	1.63 g KH_2PO_4, 2.32 g NaCl, 0.22 g $CaCl_2$ and distilled water up to 1000 ml	6.2	[22]
Vaginal fluid simulant	3.51 g NaCl, 1.4 g KOH, 0.222 g $Ca(OH)_2$, 0.018 g bovine serum albumin, 2 g lactic acid, 1 g acetic acid, 0.16 g glycerol, 0.4 g urea, 5 g glucose and distilled water up to 1000 ml	4.2	[23]

Selection of the apparatus type and setup

Basket apparatus

Basket apparatus (Apparatus 1; Figure 1) has been applied for the *in vitro* release testing of different mucosal delivery systems, such as nasal microparticles [24] and inserts [25] using relatively large volume (200-400 ml) of the dissolution medium and moderate stirring rate (50 rpm). Similar apparatus, operating with 250 ml of the simulated saliva and 50 or 100 rpm stirring rate were used to investigate the release of tizanidine hydrochloride [26] and buspirone hydrochloride [27] from freeze-dried buccal sponges/wafers. Those drugs are classified as Class I drugs (high solubility and permeability) according to the Biopharmaceutical Classification Systems (BCS) and in both cases, level A of IVIVC was obtained by such instrumental setup [26,27]. Basket apparatus has been also applied for the *in vitro* drug release testing of both solid and *in situ* gelling rectal suppositories. In latter case, the formulation was first thermostated at 37 °C in suppository moulds to achieve solidification of the formulation prior its placing into basket [28]. Another approach, where a liquid suppository formulation was directly introduced into the basket covered with gauze, was also described [29]. Compendial monographs, USP Dissolution Database and FDA Dissolution Database also recommend the use of basket apparatus, both in standard and the small-volume configuration, for the *in vitro* testing of mucosal delivery systems (Table 1).

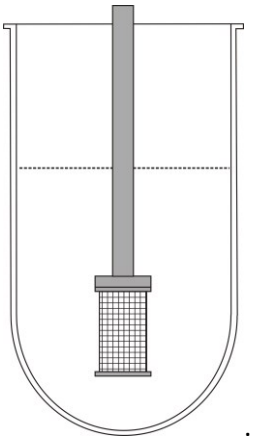

Figure 1. Schematic representation of the basket apparatus (Apparatus 1). Reprinted from ref. [3] with permission of Elsevier.

Paddle apparatus and modifications

Conventional paddle apparatus (Apparatus 2; Figure 2a) with 900 ml of the dissolution media stirred at 50 rpm has been occasionally used for the *in vitro* release testing from buccal tablets [30], sublingual formulations [31], vaginal tablets [32] and self-microemulsifying rectal suppositories [33]. According to the monographs and methods published by USP, Ph. Eur. and FDA (Table 1), the paddle apparatus is used for a variety of mucosal drug delivery systems. However, the general intention of the researchers in the field is to reduce the volume of the dissolution medium applied [34,35]. In cases where the volume is significantly reduced to only 10-25 mL, the agitation is performed by the use of shaking incubators. Using such apparatus, level A IVIVC with correlation coefficient of 0.909 was obtained for carbamazepine release from buccal multi-composite constructs [34]. The same level of IVIVC was obtained in the case of vaginal NuvaRing®, using similar approach [36]. While analysing the *in vitro* release of buccal and sublingual films by paddle apparatus, a formulation is commonly attached to a glass slide with cyanoacrylate glue [37] or two sided adhesive tape [38] and then immersed into dissolution vessel or glued onto the inner side of the dissolution vessel [37]. Considering the porosity and the thickness of the formulation, the permeation of

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the glue into the formulation could be presumed with consequent modification of the drug release process. In this regard, the use of metal clamps, supports with wire mesh or compendial Apparatus 5 (paddle over disc, Figure 2b) is preferred. Furthermore, the position of the formulation (bottom or the side of the dissolution vessel) influences greatly on the observed *in vitro* drug release kinetic, due to differences in hydrodynamics inside the dissolution vessel [37].

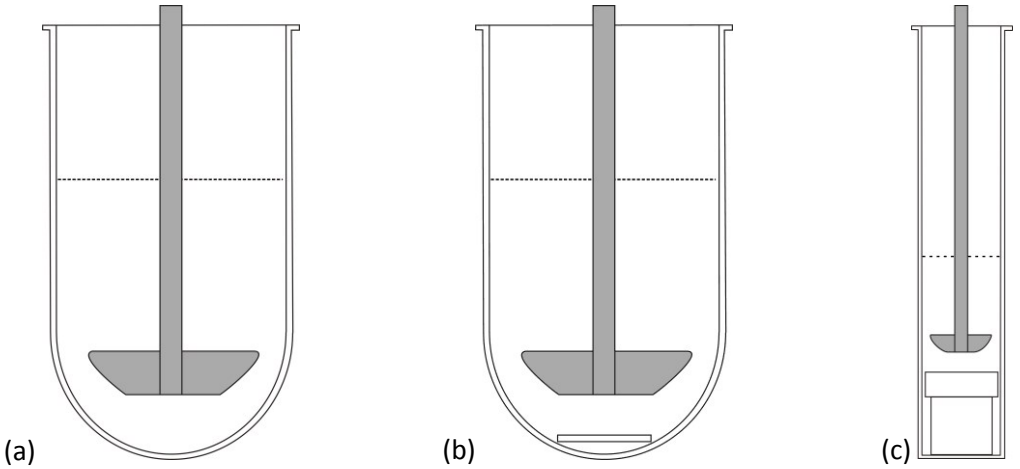

Figure 2. Schematic representation of the paddle apparatus (a), paddle over disc apparatus (b) and immersion cell in combination with the small-volume paddle apparatus (c). Reprinted from ref. [3] with permission of Elsevier.

Membrane diffusion methods

Membrane diffusion (i.e. dialysis) method is considered as one of the most convenient techniques for determining the drug release profiles of nano-sized drug delivery systems like nanoparticles, liposomes, nanosuspensions and emulsions [3,39]. The most commonly used setups are dialysis bag, flow-through apparatus (with a membrane-containing adapter), Franz-diffusion cell and immersion cell. The advantages of dialysis over other methods are in the ease of sampling and replacement of receptor media due to the physical separation of the formulation (by semipermeable dialysis membrane) from the receptor media. However, it is important to emphasize that non-critical interpretation of the obtained results can lead to flawed conclusions about the kinetics of drug release from the colloidal carriers [40,41] and other formulation types [42–46]. The presence of the drug in the receptor medium is the result of drug release from the carrier to the continuous phase in the donor compartment and diffusion of the drug through the membrane from the donor to the receptor compartment. Each of these two processes can limit the overall drug release rate. If diffusion through the dialysis membrane is the limiting factor, then the results obtained do not say much about the kinetics of the drug release from the carrier. Therefore, to account for the resistance of the dialysis membrane to drug diffusion and its influence on the overall drug release rate, an *in vitro* release study has to be performed with the drug solution too. Furthermore, the possibility of reversible binding of the released drug onto a carrier in the donor compartment must be considered, which may reduce the thermodynamic activity of the drug in the donor compartment and thus the diffusion rate. This may lead to the wrong conclusions about the extended release of the drug. Finally, it is very important to consider that as drug diffuses through the diffusion membrane, the ions diffuse from one compartment to another as well. This is of the most importance for ion activated *in situ* gelling systems for which the gelation as well as gel strength is related to the concentration of crosslinking ion such as Ca^{2+} [3].

Dialysis bag with molecular weight cut-off in range from 8 to 14 kDa is the most frequently used non-compendial setup among membrane diffusion methods. The volume of receptor media is usually between 20 and 100 ml and stirring conditions are ranging from 50 to 150 rpm. Using dialysis method, a good IVIVC

was found for gatifloxacin release from ocular inserts [47]. Level A IVIVC was also achieved for paracetamol release from suppository formulation using similar apparatus setup [48]. Dialysis bag is also widely used to study the *in vitro* release properties of semisolid and nanoparticulate formulations aimed for ocular, nasal and vaginal drug delivery [3]. In some cases, the dialysis bag is introduced to the basket of Apparatus 1 or attached onto the paddle of the Apparatus 2. Another setup includes the use of a glass cylinder containing the formulation, sealed at the bottom with the semipermeable membrane and vertically immersed into the dissolution medium. Such apparatus is used for *in vitro* release testing of rectal suppositories [49].

The compendial flow through apparatus (Apparatus 4; Figure 3) can be used in combination with a membrane containing adapter. This setup is widely employed for *in vitro* drug release testing from ocular inserts [50] and contact lenses [51]. Sometimes is also used in case of semisolid dosage forms [6], microparticles for nasal application [52] and thermosensitive gels for buccal application [53]. This apparatus allows the drug release testing under physiological flow rate of the dissolution medium and offers ability to maintain the sink conditions while operating in an open system setup. Besides compendial, some self-made flow through apparatuses were also used [54]. However, the flow through method shows some disadvantages, including instrument cost and set-up, filter clogging, drug adsorption to the apparatus, problems to maintain a constant flow rate and consequent high variability in the results [39].

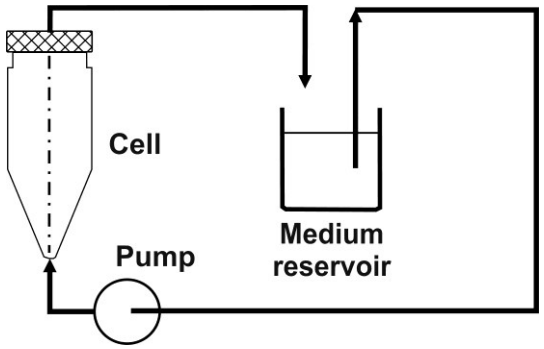

Figure 3. Schematic representation of the flow through cell. Reprinted from ref. [3] with permission of Elsevier.

Franz-diffusion cell (i.e. vertical diffusion cell, Figure 4) was originally developed for *in vitro* drug release testing from dermal creams, ointments and gels, but nowadays is widely used to test *in vitro* drug release from various mucosal delivery systems. The formulation loaded into upper donor compartment is separated from the receptor medium present in the lower compartment by a semipermeable membrane. Franz-diffusion cell was used to assess the drug release properties from numerous formulations aimed for nasal application, such as thermoresponsive soluble gels [55], ion activated *in situ* gels [56], microparticles [57], nanostructured lipid carriers [58], gel containing microspheres [59], lipidic emulsomes [60], *in situ* gelling microemulsions [61] and solid lipid nanoparticles [62]. This method is advantageous over other compendial and non-compendial membrane diffusion methods particularly in case of dry powders as it allows them to hydrate slowly, and gel eventually, in humid environment conditions designed to be similar to those encountered in the nasal cavity [63]. It has been also used in case of nano sized and gelling ophthalmic formulations [64,65] as well as for films [66], wafers [67] and tablets [68] aimed for oromucosal administration. Also, in majority of the *in vitro* drug release studies from nanosystem-in-hydrogel type vaginal formulations Franz diffusion-cell method was applied [69]. The restricted volume of acceptor compartment is a drawback of the Franz diffusion apparatus, which might impair significantly the observed drug release profile, especially in the case of poorly soluble drugs.

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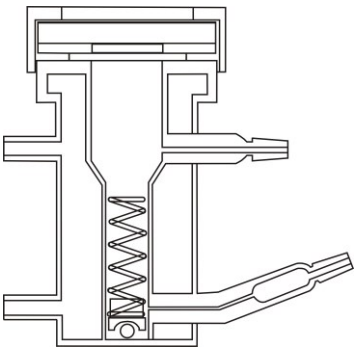

Figure 4. Schematic representation of the Franz-diffusion cell. Reprinted from ref. [3] with permission of Elsevier.

The immersion cell (Figure 2c), another compendial membrane diffusion method mostly used for semisolid preparations, was successfully applied to study the drug release kinetic from microparticles aimed both for nasal and dermal application [70].

Recently, some membrane-less diffusion methods have been reported to study the drug release from ocular inserts [64] and nasal *in situ* forming gels [20], providing the direct contact of the formulation with the dissolution medium. Agarose method is another membrane-less diffusion model which allows to monitor the release of both the released drug and liposomally associated drug in environment simulating the conditions presented at the vaginal site [71].

Sample and separate method

Sample and separate method is simple and provides a direct approach to determine the drug release. Dosage form is introduced into the release medium maintained at a constant temperature and the drug release is assessed by sampling of the release medium at defined time, separated by filtration [72] or centrifugation [73] and quantified by a suitable analytical technique [3]. The volume of the receptor medium should be adjusted to maintain sink conditions. This approach is applicable if the drug release lasts much longer (in hours) than the particle separation (in minutes) process and is often used to test *in vitro* drug release from nasal micro- and nano-sized delivery systems [72,74]. As the particle size decreases, the difficulties of separation increase. Complete separation of nanoparticles requires ultracentrifugation or ultrafiltration. The application of such a strong force for particle separation may impair their integrity and thus affect the drug release profile. Therefore, the conditions of separation procedure should be clearly stated in the published results. In (ultra)filtration the adsorption of the released drug to the filter should be considered. Also, the particles may clog the filter pores resulting in slow filtration and limited volume of filtered sample. Another disadvantage of this method is the loss of drug-loaded particles due to sampling, thereby resulting in an incomplete drug release profile. Another important obstacle is aggregation of particles which may decrease the release rate. Loss in volume because of filtration during sampling and buffer replacement is a concern when the amount of release media is small [75].

Conclusions

Mucosal drug delivery systems differ significantly in formulation design and their physicochemical and release characteristics. Therefore versatile *in vitro* release methods are currently used for their characterisation, considering the specific conditions at the administration site. Compendial methods are used as a first approach in method development whenever applicable. Further progress in this field is focused towards the development of novel biorelevant methods, which would be able to predict more

closely the *in vivo* performance of the formulation.

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