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Review

Current perspectives in dissolution testing of conventional and novel dosage forms

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Abstract

The purpose of this article is to review USP and non-pharmacopeial dissolution testing methods for conventional and novel pharmaceutical dosage forms and give an insight to possible alternatives in drug dissolution study design and appropriate choices for dissolution media. For each dosage form first the USP method(s) for dissolution testing are reviewed followed by alternative methods used in research and development.
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1. Introduction

Dissolution testing is an official test used by Pharmacopeias for evaluating drug release of solid and semisolid dosage forms. Dissolution tests were first developed to quantify the amount and extent of drug release from solid oral dosage forms including immediate/sustained release tablets and capsules (Siewert et al., 2003). More recently, dissolution has become important in testing drug release of dosage forms such as powders, chewable tablets, buccal and sublingual tablets, chewing gums, soft gelatin capsules, suppositories, transdermal patches, aerosols and semisolids (Siewert et al., 2003). Novel dosage forms

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present unique problems in the development of *in vitro* release technologies simply because of the physicochemical properties of the formulations and the unique physiological environment in which they should release their content (Siewert et al., 2003). Currently, the USP is working to increase the prevalence of USP performance testing, moving beyond solid oral dosage forms. The goal is to have a fully functional set of USP performance tests for all kinds of dosage forms. USP apparatus 4 and apparatus 7 and modifications of the official apparatuses have shown great potential and value for *in vitro* release for novel dosage forms (Williams and Foster, 2004).

Dissolution testing is routinely used in Quality Control (QC) and Research & Development (R&D). The focus of dissolution testing in QC is batch to batch consistency and detection of manufacturing deviations. For QC purposes, the test should be designed to demonstrate that the dosage forms were manufactured according to specifications and all critical manufacturing steps result in a consistent product. In R&D the focus of dissolution testing is shifted to provide some predictive estimates of the drug release in respect to the *in vivo* performance of a drug product.

In most cases the goals of QC versus R&D approaches make it necessary to design two different dissolution protocols. An over-discriminatory test might be suitable for QC purposes to detect even small production deviations. However, such a test is not desirable for the prediction of the *in vivo* performance of drug product. Here dissolution testing should be a sensitive and a reliable predictor of bioavailability (Siewert et al., 2003). Dissolution testing is used here as a predictive tool for the *in vivo* performance of a drug product. This requires that the *in vitro* and *in vivo* dissolution behavior of a dosage form be either similar or have a scalable relationship to each other (Siewert et al., 2003).

The differences in QC and R&D approaches bring up the question of the most appropriate dissolution media for the intended purpose. Typical dissolution media listed in the USP are: dilute hydrochloric acid, buffers in the physiologic pH range of 1.2–7.5, simulated gastric fluid (with or without enzymes), simulated intestinal fluid (with or without enzymes), water, and surfactants solutions such as polysorbate 80, and sodium lauryl sulfate (General Chapter ⟨1092⟩, USP 29, Suppl. 2).

However, these kinds of media only simulate pH effects and osmolarity on the drug release or in the case of the surfactant solutions increase the solubility of drugs in aqueous media (Jinno et al., 2000). Such media are well characterized and easily reproducible and routinely used in QC protocols. However, more physiologically adapted media are needed if the dissolution test is intended as a predictive tool (Löbenberg and Amidon, 2000). The International Pharmaceutical Federation (FIP) guidelines published two biorelevant media, Fasted State Simulated Intestinal Fluid (FaSSIF) and Fed State Simulated Intestinal Fluid (FeSSIF), which can be used to simulate fasted and fed states for oral dosage forms (Aiache et al., 1997). There are several examples of using these biorelevant dissolution media in research studies (Galia et al., 1998; Nicolaides et al., 1999; Löbenberg et al., 2000; Schulte-Lobbert et al., 2003; Dinora et al., 2005; Wei and Löbenberg, ~~in press~~).

The purpose of this article is to review USP and non-conventional dissolution testing methods for conventional and novel pharmaceutical dosage forms. The review gives an insight to possible alternatives in drug dissolution study design and the choices of dissolution media for such tests.

2. Immediate release tablets

Immediate release dosage forms are intended for rapid delivery of a drug into the blood circulation. However, drug absorption into systemic circulation may be limited by the dissolution rate. Studies of dissolution in immediate release drugs are typically done with USP apparatuses 1–4, those being the rotating basket, paddle, reciprocating cylinder and flow-through cell, respectively. Examples of using apparatus 1 in the USP are aspirin, brompheniramine maleate and ethambutol hydrochloride tablets. Bethanecol chloride, betaxolol and cefadroxil tablets are examples of using apparatus 2 for USP dissolution tests.

Currently there is no example for the use of apparatuses 3 and 4 for immediate release tablets in the USP. Only one example of the use of apparatus 3 exists for chewable tablets. There are several examples of using apparatuses 3 and 4 in literature (Ribeiro et al., 2005; Young et al., 2005; Mu et al., 2003; Hurtado y de la Pena et al., 2003; Perng et al., 2003). Ribeiro et al. (2005), and Young et al. (2005) evaluated the *in vitro* release profiles of vinpocetine and theophylline, respectively, using USP apparatus 3 and applying a pH gradient method. Hurtado y de la Pena et al. (2003), studied the dissolution of albendazole from different commercially available products using apparatus 4 in 0.1N HCl as dissolution medium. Perng et al. (2003) used USP apparatus 4 as a screening technique to evaluate the drug release of several proprietary (SB-247083) formulations using a pH gradient method.

A dissolution study by Wei and Löbenberg (~~in press~~) demonstrated how the application of a dynamic dissolution protocol can be used to simulate the *in vivo* dissolution of glyburide, a Biopharmaceutical Classification System (BCS) class II drug. In this study SIF and biorelevant dissolution media were used in apparatus 2 to investigate the dissolution of different immediate release glyburide tablets. The pH of the dissolution medium was changed from pH 6.5 gradually to pH 7.5 and back to pH 5.0. These changes simulate the physiological pH change in the small and large intestine. The study showed that the micelle solubilization of the biorelevant media was able to keep the drug in solution when the pH drops from pH 7.5 to 5.0. If the same pH gradient was applied to SIF the drug precipitated. This kind of dissolution protocol may be used instead of apparatus 4. Galia et al. (1998) showed further examples for the use of biorelevant media to assess immediate release tablets. The study concludes that biorelevant media are preferable for BCS class II drugs, but do not improve the dissolution of BCS class I drugs.

Schamp et al. (2006) showed that the addition of surfactant (Triton X-100) can improve the dissolution of DME 50733 in simulated gastric fluid.

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Table 1
Typical [illegible]es of different USP dissolution media used for dissolution testing of tablets and capsules

Dissolution medium	Example
Water	Ampicillin capsule, butabarbital sodium tablet
Buffers	Azithromycin capsule, cefixime tablet
HCl solution	Cimetidine tablet, bethanecol chloride tablet
Simulated gastric fluid	Astemizole tablet, piroxicam capsule
Simulated intestinal fluid	Valproic acid capsule, glipizide tablet
Surfactant solution	Clofibrate capsule, danazol capsule

3. Powders

The USP does not state any official method for dissolution testing of powders. The only application of powder dissolution in the USP is the evaluation of the intrinsic dissolution of powders in General Chapter ⟨1087⟩ of the USP 29. However, in this method the powder is pressed into a tablet like a disk with a defined surface. The dissolution from the surface is evaluated.

Dissolution testing of finely divided particles can be performed using apparatus 2 (Chauhan et al., 2005; Williams et al., 2005; Shimpi et al., 2005) or may be conducted using the flow-through cell apparatus (Aiache et al., 1997; Siewert et al., 2003).

However, it has to be noted that in the standard USP apparatuses, the dispersal of the powders may have an impact on the dissolution behavior (Jun et al., 2005; Chauhan et al., 2005; Shimpi et al., 2005). In an attempt to keep both drug and excipients together, a modified basket method was developed to better simulate the environment in which powder is exposed to when ingested (Shay et al., 2002). By keeping drugs in longer contact with excipients, a closer approximation can be made as to their true *in vivo* dissolution behavior. The basket used in this setup was dipped into molten wax in order to seal the bottom. In this modified apparatus, researchers noted that excipients were able to interact with the drug for a longer period of time. Thus, such excipients can enhance drug dissolution to a greater extent. This is in accordance with the results of Valizadeh et al. (2004) who showed that a microenvironment surrounding powder particles can influence the dissolution rate of the indomethacin. However the opposite is true for dissolution inhibiting excipients like Mg-stearate due to shielding the powder from the solvent, which reduces the effective surface area of the drug (Von Orelli and Leuenberger, 2004; Rao et al., 2005) ~~(Table 1)~~.

4. Extended-release tablets

Apparatuses 1, 2 and 7 are mentioned in the USP for the dissolution testing of extended-release tablets. Table 2 shows some USP examples of using different dissolution apparatuses for extended-release tablets. New modified dissolution apparatus has been stated in USP for felodipine, nifedipine and metformin hydrochloride extended-release tablets. This new apparatus contains a stationary stainless steel tablet basket located 1 cm above the paddle in which tablet is placed. Different researchers used flow-through cell (Missel et al., 2004; Tugcu-Demiroz et al., 2004) or reciprocating cylinder (Wong et al., 1997; Rohrs et al., 1995) for the dissolution testing of the extended-release tablets. Different buffers, SGF, SIF, simulated colonic fluid (SCF) and normal saline were used as the dissolution medium in these researches.

Table 2
Examples of using different dissolution apparatuses for extended-release tablets in USP and the media used

Dissolution apparatus	Example
Apparatus ~~1~~	Cefaclor extended-release tablets (0.1N hydrochloric acid), lithium carbonate extended-release tablets (dilute hydrochloride acid 7 in 1000), phenylpropanolamine hydrochloride extended-release tablets (water)
Apparatus ~~2~~	Acetaminophen extended-release tablets (pH 5.8 phophate buffer), aspirin extended-release tablets (0.1N hydrochloric acid), bupropion hydrochloride extended-release tablets (water)
Apparatus ~~7~~	Nifedipine extended-release tablets (water), pseudoephedrine hydrochloride extended-release tablets (0.9% sodium chloride in water)

5. Dosage forms for the oral cavity

Dosage forms for the oral cavity such as sublingual tablets, buccal tablets, chewing gums and chewable tablets are solid dosage forms that are placed in the mouth, allowing the active ingredient to dissolve in the saliva and then absorb either via the oral route or by the buccal/sublingual mucosa within the mouth (Abdelbary et al., 2005; Hao and Heng, 2003). However, there are challenges regarding the extent of drug delivery in the mouth as opposed to the oral route, namely due to a short residence time in the mouth, and the small volume of liquid available to dissolve the medication (Hao and Heng, 2003). As a result, modifications in the standard USP test apparatuses (as well as the development of novel apparatuses) are required in order to mimic *in vivo* conditions for accurate analysis of these dosage forms.

5.1. Chewable tablets

Rapidly disintegrating chewable tablets are used primarily for the oral route of administration, and are designed to increase compliance among individuals who are unable to swallow traditional tablets. But the extent to which each tablet will be chewed may vary from individual to individual, ranging from being completely chewed to swallowing the tablet in chunks. The USP has stated the need to use apparatus 2 for chewable tablets, the same as for traditional tablets with the exception of ampicillin chewable tablets, here the USP 29 requires use of apparatus 1, and carbamazepine chewable tablets, the USP 29, uses apparatuses 2 and 3 as two different tests. Furthermore, Siewert et al. (2003) has recommended the use of USP apparatus 3, a reciprocating cylinder, along with glass beads in order to create a large amount of agitation within the dissolution medium. They also recommend mechanical breakage of the tablet prior to per-

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220 forming the dissolution test. Using this apparatus along with
221 mechanical forces to break the tablet might mimic the effect of
222 chewing on the tablets.

223 5.2. Buccal/sublingual tablets

224 Rapid orally disintegrating tablets may be used to achieve a
225 fast onset of action. Alternatively, the buccal/sublingual route is
226 also suitable for medications that cannot or shall not be taken
227 by the oral route due to instability of the drug at the low pH of
228 the stomach, or their susceptibility to the hepatic first pass effect
229 (Senel et al., 2001). Much like the previous dosage form, these
230 tablets are also advantageous for patients who are unable to swal-
231 low whole tablets. USP 29 states the use of disintegration test
232 for ergoloid mesylate and ergotamine tartrate sublingual tablets
233 and apparatus 2 with water as dissolution medium for isosorbide
234 dinitrate sublingual tablet. However, *in vivo* dissolution is lim-
235 ited for these tablets by the amount of saliva present within the
236 mouth. As a result, dissolution tests using standard USP appara-
237 tuses and large volumes of liquids might not produce results that
238 reflect the *in vivo* dissolution. Furthermore, since such medica-
239 tions are designed to dissolve the drug in a short time period, it
240 is obvious that disintegration and not necessarily dissolution is
241 the true rate-limiting step for drug release of these dosage forms
242 (Abdelbary et al., 2005). However, this assumes that the drug
243 dissolution is not limited which can be assumed for BCS class I
244 and III drugs only.

245 Therefore, several studies have been performed to investigate
246 drug dissolution in smaller volumes or using different appara-
247 tuses. Fabregas and Garcia (1995) used USP apparatus 3 at a
248 rate of 20 strokes/min for conducting *in vitro* dissolution studies
249 of hydrcortisone hemisuccinate mucoadhesive tablets.

250 Another system, which has been introduced recently, com-
251 prises a single stirred; continuous flow-though filtration cell with
252 a dip tube to remove finely divided solid particles (Hughes,
253 2003). The volume of liquid in the cell is small (10 ml) and
254 the fluid is pumped through to give a short residence time with
255 almost complete removal in about 8 min. The cell is filled and
256 flow rates are set up and allowed to reach steady state before the
257 dosage form (solid, liquid, suspension or powder) is introduced.
258 The filtered sample is analyzed in-line (e.g. by UV flow-through
259 cell) or samples are collected in a fraction collector for later anal-
260 ysis. Fig. 1 shows a schematic drawing of this apparatus. The
261 dissolution fluid used in this system was simulated saliva for-
262 mulated from published data, as there is no USP recommended
263 simulated saliva. Table 3 shows the composition of two different
264 proposed simulated salvias by Tavss et al. (1984) and Davis et
265 al. (1971).

266 Dor and Fix (2000) developed a special disintegration test
267 using a Texture Analyzer Instrument to accurately determine
268 the rate of drug release from sublingual/buccal medications. In
269 this method, the tablet is attached to a cylindrical probe and
270 placed under a constant force to promote disintegration. The
271 tablet is then submerged into a defined volume of medium and
272 the time for complete tablet disintegration versus distance trav-
273 eled is determined. According to Abdelbary et al. (2005), there
274 are a few downsides to this method, namely due to the adhesive

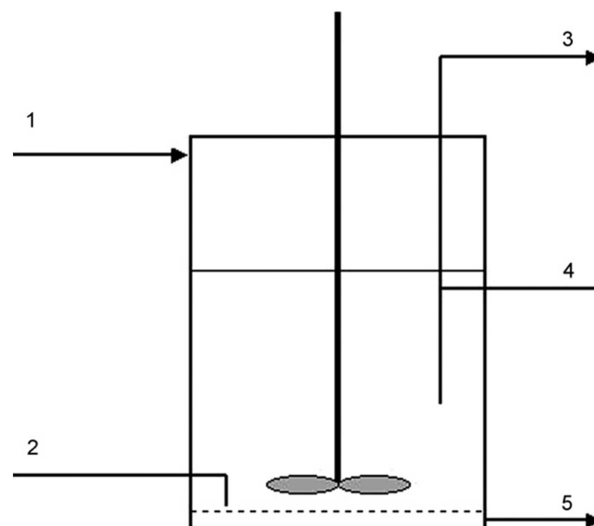

Fig. 1. Schematic of dissolution apparatus for buccal/sublingual tablets: (1) inlet, (2) filter membrane, (3) outlet, (4) dip tube, (5) outlet to flow through UV cell (adopted from Hughes, 2003).

that attaches the tablet to the probe one side of the tablet cannot 275
interact with the immersion medium, whereas in the oral cavity 276
the tablet will be moistened on all sides and this will enhance 277
disintegration. To compensate for this, authors placed the tablet 278
in a perforated grid, and then allowed the probe to be lowered 279
onto the tablet until the desired pressure was created (Abdelbary 280
et al., 2005). The force created by the probe was 50 g and suffi- 281
cient to push the tablet and grid into the disintegration medium. 282
In order to imitate oral disintegration as much as possible they 283
used simulated saliva (pH 5.8). 284

Drug release studies for buccal tablets are normally per- 285
formed using USP apparatus 2 (Rambali et al., 2001; Ceschel et 286
al., 2001; Jain et al., 2002; Jug and BecirevicLacan, 2004). How- 287
ever some authors wanted to mimic the intended drug release in 288
one direction only (buccal mucosa) and proposed to use an intrin- 289
sic dissolution apparatus to analyze the drug release from one 290
surface only (Cilurzo et al., 2003; Akbari et al., 2004; Parodi et 291
al., 1996; ElGindy, 2004). In order to expose a single face with 292
constant area to the medium, they coated all surfaces except one 293
using a water impermeable coating. 294

Table 3
Formulas for simulated saliva

Formula 1*		Formula 2§	
Component	Weight (g/l)	Component	Weight (g/l)
$CaCl_2{\cdot}2H_2O$	0.228	Mucin gastric	1.000
$MgCl_2{\cdot}6H_2O$	0.061	α-Amylase	2.000
NaCl	1.017	NaCl	0.117
$K_2CO_3{\cdot}1.5H_2O$	0.603	KCl	0.149
$Na_2HPO_4{\cdot}7H_2O$	0.204	$NaHCO_3$	2.100
$NaH_2PO_4{\cdot}H_2O$	0.273		
Submaxillary mucin	1.000		
α-Amylase	2.000		

* Tavss et al. (1984).
§ Davis et al. (1971).

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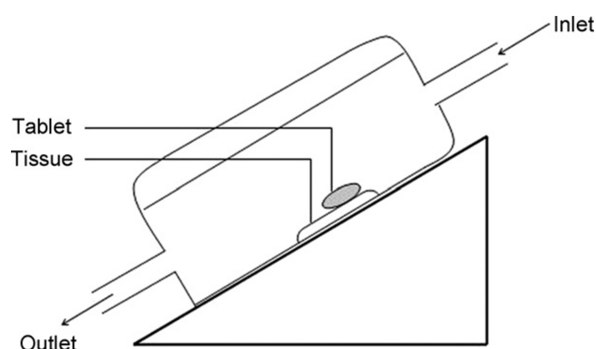

Fig. 2. Schematic drawing of the dissolution apparatus used by Mumtaz and Ch'ng (1995) for studying the dissolution of buccal tablets.

Ikinci et al. (2004) used an alternative method to study the release of nicotine from buccal tablets. They used modified Franz diffusion cells for this purpose. The dissolution medium was 22 ml phosphate buffer saline (PBS) (pH 7.4) at 37 °C. Uniform mixing of the medium was provided by magnetic stirring at 300 rpm. To provide unidirectional release, each bioadhesive tablet was embedded into paraffin wax which was placed on top of a bovine buccal mucosa as membrane.

Another group used an easier method to perform the *in vitro* drug release study (Mohammed and Khedr, 2003). They introduced single tablets in separate beakers containing 10 ml of phosphate buffer (pH 6.8). The beakers were shaken horizontally at 50 rpm in a water bath, which maintained at 37 °C. Samples were withdrawn at predetermined time intervals over 7 h and replaced with fresh medium.

Mumtaz and Ch'ng (1995) introduced another method for studying the dissolution of buccal tablets. The device that they introduced is based on the circulation of pre-warmed dissolution medium through a cell as shown in Fig. 2. Here the buccal tablet was attached on chicken pouches. Samples were removed at different time intervals for drug content analysis. They stated "the results obtained by using this apparatus for the release of drug from bioadhesive tablets concurred with the predicted patterns".

5.3. *Chewing gums*

For the unique case of chewing gums, USP has not yet created an apparatus to test the release of medication. Today drugs are more and more delivered by convenient dosage forms like gums or lately by strips. The European Pharmacopoeia has developed a 3-piston apparatus, which in essence "chews" the gum at a rate of 60 cycles/min in a test medium with pH of 6.0 at 37 °C (Ph. Eur. 2.9.25). One study claims that there are several obvious disadvantages using this method, for instance, the chewing gum may adhere to the equipment, thus affecting its ability to imitate *in vivo* condition (Maggin et al., 2005). As a result, these researchers have attempted to develop alternative way, with one notable and rather unorthodox method that was recently published. In this study, the researchers selected volunteers to chew the medicated gum for a specific period of time (i.e. 10, 20, 30, or 40 min); followed by analyzing the residual quantity for the amount of active ingredient remaining in the gum (Maggin et al., 2005). This method definitely warrants some scrutiny in methodology but is a prime example, which demonstrates the need of developing an appropriate *in vitro* test apparatus to analyze the release of medication from chewing gums.

6. Soft gelatin capsules

Soft gelatin capsules can be composed of either hydrophilic or hydrophobic components. In the case of hydrophilic capsules, dissolution tests can be performed quite easily using USP apparatus 2, but this becomes more difficult for hydrophobic medications.

For soft gelatin capsules which are dietary supplements and are not considered as drugs the USP has added a rupture test (General Chapter ⟨2040⟩). This test is based on the time needed for capsule shell to rupture in 500 ml water. The capsule shell must rupture within 15 min but no drug release is measured.

In vitro dissolution tests of lipophilic drugs from oil-containing soft gelatin capsules have up to now been performed in the USP paddle or basket apparatus or in a specially developed flow-through cell (Moller, 1983).

Because of the unfavorable oil–water partition coefficient of lipophilic drugs and their solvents, surface-active compounds have been added to the aqueous dissolution media in order to avoid long dissolution times. Alternatives to this are larger dissolution volumes (Sheen et al., 1991; Shah et al., 1992–1993; Crison et al., 1997; USP 28, 2005) or the use of water alcohol mixtures (Neisingh et al., 1986; Sheen et al., 1991; Shah et al., 1992–1993; Crison et al., 1997; Serajuddin et al., 1998; USP 28, 2005). However, it is speculated that exposure of the gelatin shell to such media may induce physical and/or chemical changes of the drug, arising either through complex formation or cross-linking reactions (Rades et al., 1993; Gautam and Schott, 1994; Maulik et al., 1998; Chatterjee et al., 2002).

The official methods have the serious disadvantage that the dissolution conditions for lipophilic floating materials are poorly defined and sample taking might be difficult.

One way to solve such problems is to use a flow-through cell in which the site of dissolution is smaller and the flow conditions are better defined; sample taking is simple because the drug is removed from the excipient by continuous extraction with an aqueous perfusion medium and automatically filtered. But the standard flow-through cell is only suitable for sustained-release formulations and ordinary solid tablet or capsule formulations. It is not suitable for lipid-filled soft gelatin capsules, because after capsule rupture, the oil phase is quickly drawn into the filter on the top of the cell, which can clog the filter, or the oil is forced through the filter.

To solve this problem Hu et al. (2005) introduced a new flow-through cell for lipid-filled soft gelatin capsules. Fig. 3 shows the schematic view of this device. This special flow-through cell works differently from the standard flow-through cells. The dissolution medium enters through the medium inlet, on the right-hand side of the cell, going over to the left side of the cell, the medium pushes the air out through a capillary, and then the medium flows through the center channel to the filter. After the capsule ruptures in the right-side of the cell, the lipid content

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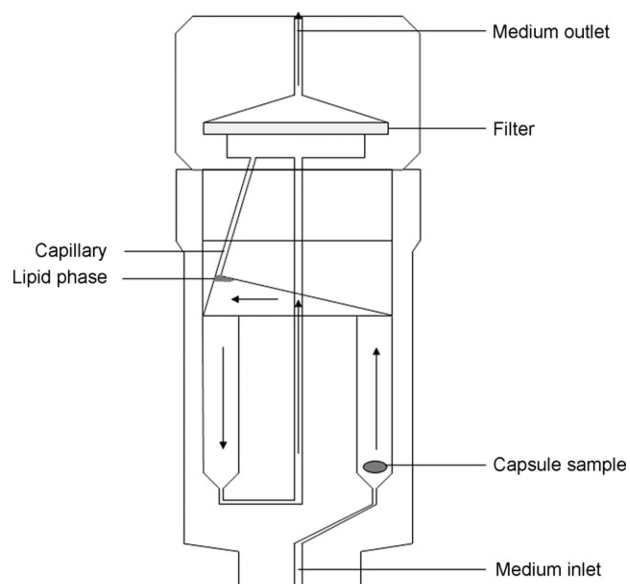

Fig. 3. Schematic view of flow-through cell designed for lipid-filled soft gelatin capsules (adopted from Hu et al., 2005).

rises up, due to its lower density. When the lipid phase reaches the triangular area top of the left side cell, it stays there. Thus the dissolution medium continuously extracts the drug from the lipid layer as it flows through the cell. The dissolved drug can

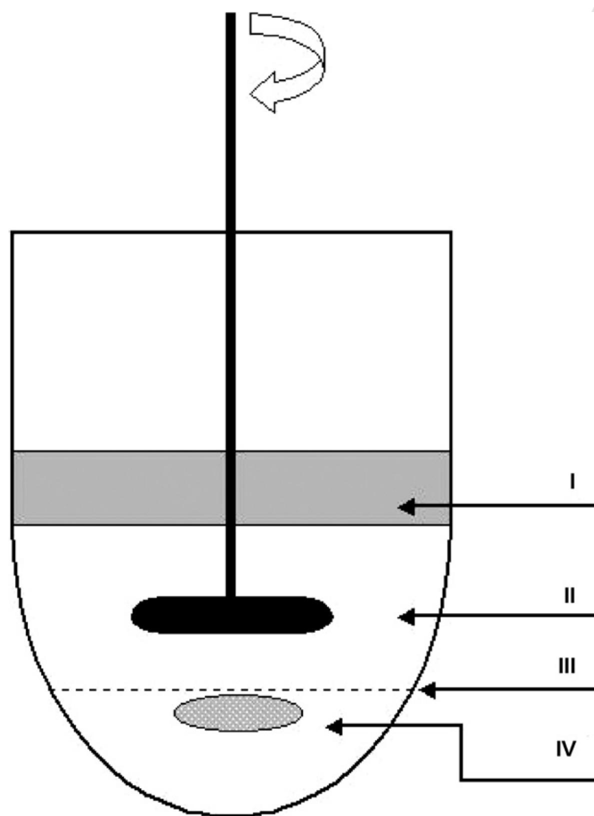

Fig. 4. Schematic illustration of apparatus for the dissolution testing of lipid-filled soft gelatin capsules. I = organic phase, i.e., 100 ml, II = aqueous phase, III = ring/mesh assembly and IV = position of capsule (adopted from Pillay and Fassihi, 1999).

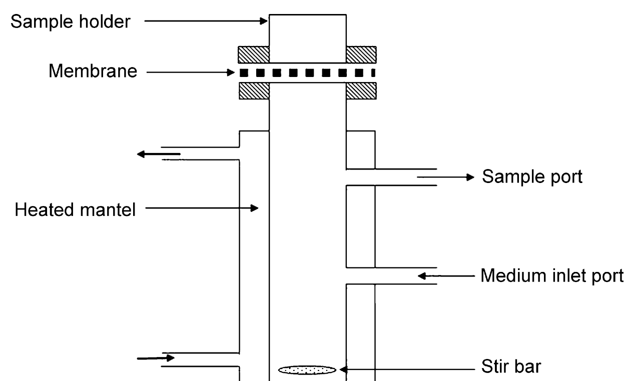

Fig. 5. Schematic picture of Franz diffusion cell.

now be determined using a conventional fraction collector and be analyzed in the medium.

Takahashi et al. (1994) introduced a rotating dialysis cell method to investigate the dissolution of tocopherol nicotinate from soft gelatin capsules. Here the inside of the cell was regarded as the digestive tract and the outside of the cell as the tissue. An aqueous solution was used in the internal phase and *n*-octanol was used in the external phase as a model organic solvent to simulate drug absorption inside the body.

Pillay and Fassihi (1999) introduced a two-phase dissolution medium (organic and aqueous) for conducting dissolution in lipid-filled soft gelatin capsules (Fig. 4). They used either the rotating basket or paddle or a modified paddle method. The results of their study showed that, after 6 h of dissolution, most of the viscous oily vehicle still remained entrapped within the basket; hence failure to release drug into the aqueous phase. It appears that the standard dissolution basket pores (40 mesh) and lack of appropriate hydrodynamic conditions within the basket had a significant limiting effect on drug release from the oleaginous formulation. The study showed that the most reproducible results can be obtained when the paddle is positioned in aqueous medium and the capsule is below the mesh assembly (Fig. 5).

7. Suppositories

Similar to lipid-filled soft gelatin capsules, it is challenging to find a standard method to test *in vitro* drug release from lipophilic suppositories. This is due to the melting and deformation of the suppository in the dissolution medium. USP 29 states apparatus 2 for conducting dissolution tests of indomethacin suppositories.

Lipophilic suppositories release the drug after melting in the rectal cavity. Therefore, rectal temperature greatly affects drug release. In the rectum, the drug partitions between the lipophilic base and the present fluid. Distribution equilibrium between the base and fluid can occur rather than complete dissolution (Siewert et al., 2003). For *in vitro* release testing, one requires knowledge of the melting point range of the suppository base, and testing temperature should be similar with physiological conditions. However, some studies allow higher temperatures to account for patients using the suppository to treat fever; this was suggested for, acetaminophen suppositories used in pediatrics (Siewert et al., 2003).

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A modified basket or paddle method with a wired screen and a sinker or a modified flow-through cell with a specific dual chamber suppository cell have all been recommended for lipophilic suppositories (Siewert et al., 2003; Janicki et al., 2001). Hydrophilic suppositories release the drug by dissolving, as opposed to melting, in rectal fluids. Conventional basket, paddle, or flow-through cell seem to be suitable to be used for hydrophilic suppositories (Siewert et al., 2003). However, no simulated rectal fluid exists at the moment to simulate the *in vivo* dissolution of suppositories.

8. Transdermal patches

For transdermal delivery systems, many variables may alter the release of the drug into the skin. Large changes in the rate and extent of drug delivery may occur caused by the slightest change of the formulation (Van Buskirk et al., 1997). These parameters include adhesives, solvents, semipermeable films and microporous layers which all play a role in the rate and extent of release and consequently impact the absorption (Van Buskirk et al., 1997). Due to these factors, a strict manufacturing process has to be applied and the finished products have to be tested *in vitro* to assure the quality of the product and reproducibility of the systems.

The USP has published three different *in vitro* drug release tests for dissolution testing of patches. These include paddle over disk, cylinder method, and reciprocating disk method, apparatuses 5, 6, 7, respectively (USP 29). The paddle over disk method is the most widely used method because it is simple and easy to reproduce (Shah et al., 1989). The testing conditions should be ideally adjusted to pH 5–6, reflecting physiological skin condition (Siewert et al., 2003). The temperature should also be set to 32 °C, even though skin temperatures may increase when it is covered by the transdermal delivery system. The agitation speed rate should be set at 100 rpm. Nicotine transdermal patch is an official monograph in the USP. The mentioned three different apparatuses are recommended for drug release testing of this patch. However, there are numerous examples of using Franz diffusion cell for release studies of transdermal systems in literature (Gupta and Jain, 2004; Tirnaksiz and Yuce, 2005; Babu and Pandit, 2005; Csoka et al., 2005). They used phosphate buffered saline (PBS) pH 4.5 containing 20% PEG 400, water, PBS at pH 7.4 and PBS at 5.4 as the dissolution medium in the receiver chamber, respectively.

9. Semisolid dosage forms

Semisolid dosage forms include creams, ointments and gels. Currently no monograph exists in the USP which uses dissolution testing of semisolid bases. In research the drug release test is normally performed using the Franz cell diffusion system (Siewert et al., 2003). Critical components of the *in vitro* release test for semisolid products include selection of an assay method, diffusion cell volume, selection of an appropriate membrane, nature of receiving medium, equipment related parameters, e.g. stirring speed and temperature and validation of the method (Van Amerongen et al., 1992; Thakker Kailas and Chern Wendy, 2003). The membrane must be an inert material that does not interact chemically or physically with the drug. The membrane should not contain leachables that may interfere with the assay. Common membranes are Tuffryn®, Supor®, Cellulosic, Acetate Plus®, Nylon, Teflon, and polycarbonate. The receiving medium must be similar to physiological conditions of the skin. Thakker Kailas and Chern Wendy (2003) assert that no more than 30% of the total amount of the dose applied should be released into the medium at the end of the experiment. To achieve sink condition, the receptor medium must have a high capacity to dissolve or carry away the drug, and the receptor medium should not exceed 10% of Cs (drug solubility) at the end of the test (Ueda et al., 2006). Selection of pH of the aqueous component should be based on the pH of the formulation, pH-solubility of the drug and the pH of the target membrane (Van Amerongen et al., 1992; Thakker Kailas and Chern Wendy, 2003). The selection of equipment related parameters includes number of diffusion cells (commonly 6 to account for individual dosage form variability), temperature, e.g. 32 °C to mimic the skin temperature, sampling intervals (0.5, 1, 2, 4, and 6 h) and sampling volume (Thakker Kailas and Chern Wendy, 2003).

Enhancer cell, designed by Vankel Technology Group, is another device, which is used for dissolution testing of semisolid products (Vankel Buyer's Guide, 2005). This device is a Teflon cell with adjustable volume and a screw cap to retain the skin or artificial membrane (Sanghvi and Collins, 1993; Mafune et al., 1998). The semisolid product is put into the cell and a membrane is used to provide a defined surface to determine the drug release. The assembly can be used with any dissolution tester and is available with 4.0, 2.0, or 0.5 cm^2 surface area. Using the Paddle-Over-Enhancer-Cell method provides release rates comparable to Franz Cell technology (Vankel Buyer's Guide, 2005).

10. Aerosols

To date no single *in vitro* test system has yet emerged as the ideal choice for performing dissolution measurements as a tool to estimate *in vivo* solubility in the lung fluids. The only method, which has been used to study the dissolution of aerosols, was introduced by Davies and Feddah (2003). They used a custom made flow through dissolution apparatus to study the dissolution of inhaled glucocorticoid particles. In this method the aerosol particles, obtained using impaction, were collected onto a glass pre-filter for dissolution studies. The dissolution medium, which was equilibrated at 37 °C, was pumped upward through the dissolution cell by means of an HPLC pump calibrated to give a constant flow of 0.7 ml/min. The dissolution medium was pumped to flow through the aerosol particles previously collected and immobilized on the glass fiber filter between 0.45 μm membrane filters. The dissolved fraction of the dose, which passed the upper filter, was collected separately for individual analysis at predetermined intervals. As dissolution medium they used water, simulated lung fluid (SLF) and modified SLF (MSLF) with L-phosphatidylcholine (DPPC). They showed that MSLF significantly increased the dissolution rate compared with SLF alone.

So far four different lung fluids were published to approximate the composition of extracellular fluid in the lungs. These

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Table 4
Compositions of biological fluid simulants

Salt	Molar concentration[a]		
	SUF[b]	SLF[c]	Gamble[d]
KCl	–	0.004	–
NaCl	0.116	0.145	0.116
$MgCl_2$	–	0.001	–
NH_4Cl	0.010	–	0.010
$NaHCO_3$	0.027	0.024	0.027
Glycine	0.005	–	0.006
L-Cysteine	0.001	–	0.001
Na_3 citrate	0.0002	0.0003	0.0002
Na acetate	–	0.007	–
$CaCl_2$	0.0002	0.0025	0.0002
H_2SO_4	0.0005	–	–
Na_2SO_4	–	0.0005	–
Na_2HPO_4	–	0.002	–
NaH_2PO_4	0.0012	–	0.0012
DTPA[e]	0.0002	–	
ABDC[e] (ppm)	50	–	

[a] Aqueous solution.
[b] Eidson and Mehinney (1981).
[c] Eidson (1982), Dennis et al. (1982).
[d] Gamble (1967).
[e] DTPA = diethylenetriaminepentaacetic acid, a chelating agent not present in serum; ABDC = alkylbenzyldimethyl ammonium chloride, and antibacterial agent not present in blood serum.

are serum ultra-filtrate simulant (SUF), ~~serum~~ lung fluid (SLF), Gabmle's or Ringer's solutions (Ansoborlo et al., 1999) and modified SLF with DPPC (Davies and Feddah, 2003). Their composition is given in Table 4.

11. Conclusion

There are different dissolution media and apparatuses for dissolution testing of both conventional and novel dosage forms. However, some of these methods and dissolution media which are reviewed in this article are intended to be used in research and development only and might not be suitable for routine quality control. However, despite the fact that they are not pharmacopeial standard methods, they have the potential to provide valuable information of the expected *in vivo* drug release. Therefore, it is necessary to further develop *in vitro* assays for novel dosage forms and to establish standard protocols for their drug release tests including the use of biorelevant dissolution media. This will ensure that *in vitro/in vivo* correlations can be established. For quality control purposes of certain dosage forms like gums and liquid filled capsules, new pharmacopeial apparatuses or assay methods are needed. However, for most dosage forms slight modifications of the existing apparatuses might be sufficient to ensure batch to batch consistency even if the assay method might be over discriminating and not reflect the *in vivo* environment.

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