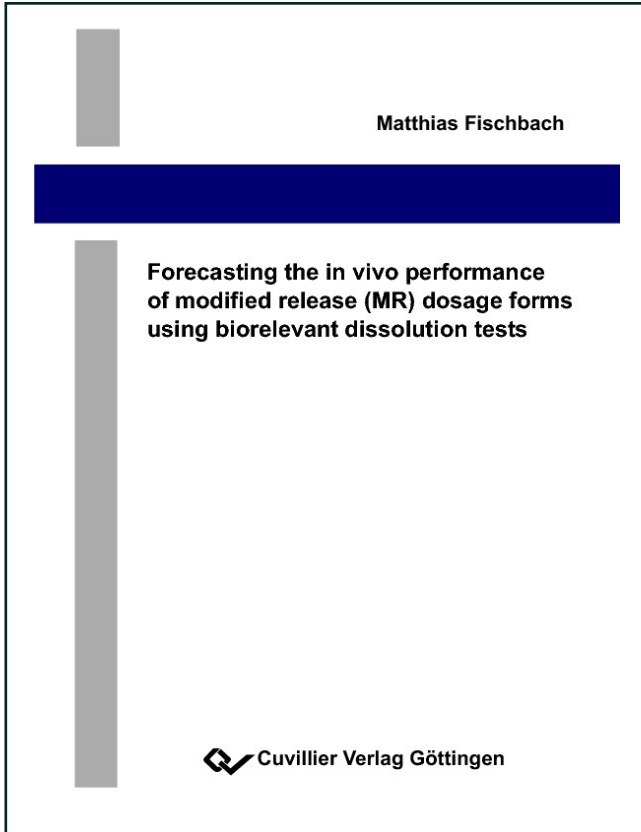




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**Forecasting the in vivo performance of modified release (MR)  
dosage forms using biorelevant dissolution tests**



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# 1. Introduction

## 1.1. Concept of dissolution

For most drug substances systemic availability is the key factor to efficacy. For oral administration, in particular, two aspects regulate the systemic availability of a drug substance:

- a) Dissolution of the drug substance from the dosage form
- b) Permeation of the drug substance through the mucosa

Before a drug reaches the systemic circulation it has to be dissolved in the gastro-intestinal (GI) fluids, because only a dissolved drug is able to permeate the mucosa. Hence, dissolution is of primary importance to the bioavailability of orally administered drugs. The drug, presented as a solid dosage form, undergoes several steps before reaching blood, fluids and tissues of the human body. A short overview is given in Figure 1.1.1

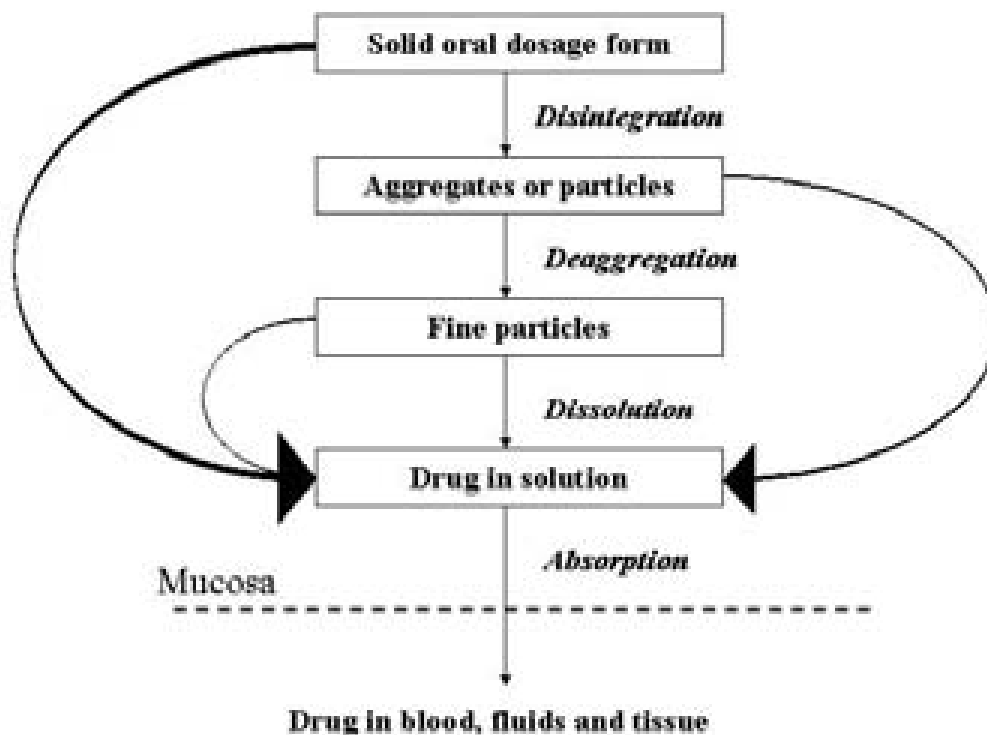


Figure 1.1.1 Scheme of the dissolution process in vivo

The first step that a solid oral dosage form undergoes in the gastro-intestinal tract (GI tract), usually the stomach, is disintegration. Only in rare cases there is substantial dissolution direct from the dosage form. Furthermore, the aggregates and larger particles disaggregate or disintegrate into fine particles from which the drug dissolves and can then be absorbed through the intestinal mucosa and reach the systemic circulation.

In 1897 Noyes and Whitney described first theories of the dissolution process (Noyes and Whitney 1897). Nernst extended these theories in 1904 (Nernst 1904). The modified version of the Noyes-Whitney equation clearly shows the factors influencing the rate of dissolution:

$$v = \frac{dx}{dt} = \frac{A \cdot D}{h} \cdot \left[ C_s - \frac{X_d}{V} \right] \quad (1.1)$$

- V: rate of dissolution
- A: available surface area for dissolution
- D: diffusion coefficient of the drug substance
- h: thickness of the diffusion layer
- C<sub>s</sub>: solubility of the drug substance in the respective medium
- X<sub>d</sub>: amount drug dissolved
- V: volume of dissolution medium

The only variables that can be modified to enhance the rate of dissolution in vivo are the solubility of the drug substance in the respective medium and the surface area available for dissolution, as it is not possible to increase the diffusion coefficient of the drug substance or decrease the thickness of the dissolution layer.

The only way to increase the volume of available dissolution medium in the GI tract is to administer the oral dosage form with food, triggering secretions and so achieving a higher available volume.

To enhance the solubility of poorly soluble compounds and thereby their bioavailability, salt formation (Randinitis and Kinkel 1995), co-compressing with highly soluble excipients (Supabphol and Stewart 1996), manufacturing of solid dispersions (Goldberg, Gibaldi et al. 1966; Ford 1986; Jachowicz 1997; Taylor and Zografi 1997; Leuner 2004) or complexation with cyclodextrine (Ammar, Ghorab et al. 1996; Fawaz, Bonini et al. 1996), can be attempted.

Another approach is to minimize the particle size of the drug substance, mainly by micronisation (Johanson and Bye 1978; Liversidge and Cundy 1995). Unfortunately this approach does not guarantee an improvement in the dissolution (Solvang and Finholt 1970). The milling process can result in development of an electronic charge, which can lead to aggregation of the small particles as large or even larger than the unmilled drug (Lin, Menig et al. 1968).

Another scientist tactic is the addition of surfactants to the formulation to increase the rate of dissolution by aiding the wetting and/or solubilization process of the drug. This process was shown to be effective in the case of prednisolone by Schott et. al. (Schott, Kwan et al. 1982).

The influence of varying each single factor of the modified Noyes-Whitney equation (1.1) on the dissolution rate is described in detail in several reviews by Abdou et al. and Hörter et al. (Abdou 1989; Hörter and Dressman 1997).

The second important issue regarding the absorption of a drug substance into the blood, fluids and tissues is the permeability of the drug substance through the mucosa. Only a few mechanisms will be mentioned here. A detailed explanation is given by Karlson et al. (Karlson, Doenecke et al. 1994). Important mechanisms of permeation through the membrane are:

- Passive diffusion
- Passive co-transport
- Carrier transport (uniport, antiport, symport, ionophore)

- Active transport mechanisms (channels, receptors)

### **1.2. History of in vitro dissolution tests of MR dosage forms**

Although the concept of dissolution was investigated at the end of the 19<sup>th</sup> century by Noyes and Whitney (Noyes and Whitney 1897), it took more than fifty years until the first standardized dissolution apparatus and procedures were established. In the 1950s and 1960s disintegration testing was used as surrogate for the dissolution of solid oral dosage forms, since it was recognized that the disintegration into small particles is essential for the absorption by the body. The disintegration apparatus became the first apparatus connected to the theory of dissolution that reached official status in the United States Pharmacopoeia (USPXV 1950). To ensure reproducibility of test results with the same dosage form between laboratories, the configuration and dimensions of this apparatus were explained in detail. This approach of testing the disintegration time for predicting the dissolution behavior of a drug is successful only for high soluble drugs, where a correlation of absorption with disintegration time might be possible, since only for these drugs can the rate limiting step to dissolution be the disintegration of the dosage form (Bhagavan and Wolkoff 1993). Unlike highly soluble drugs, dissolution rather than disintegration is the rate-limiting factor for poorly soluble drugs. This was mentioned by Galia who investigated the disintegration behavior of various albendazol generic solid dosage forms and could not achieve a correlation between disintegration time and rate of dissolution (Galia, Horton et al. 1999). Although disintegration is one of the requirements for the absorption of a drug, it does not guarantee drug absorption because dissolution rather than disintegration might be the rate-limiting factor (see Figure 1.1.1). Over the last decades a lot of work has been conducted on this matter. A summary of these works has been published by Wagner and Pernarowski (Wagner and Pernarowski 1971). The USP (USP 1981) was the first pharmacopoeia to recommend use of dissolution rather than disintegration tests. With this new recommendation disintegration tests seemed to be dispensable. Nevertheless, disintegration tests are still widely used to date as an important tool in quality control, because it is an easy way to

examine impacts on changing formulation compositions or manufacturing processes, in particular changes in the tableting procedure.

A complete description of the early devices for dissolution testing can be found in the review of Banakar (Banakar 1992). In the early 1930s many different devices emerged from individual research efforts. One of the earliest dissolution testing devices was the “tumbling apparatus” developed by Wruble (Wruble 1930). This device includes test tubes containing the dosage form, which were clamped to a rotating barrel, revolving from six to twelve rpm (rounds per minute).

Another apparatus of this period was the Klein solvometer (Klein 1932). In this apparatus the dosage form is placed on a little vessel and the scale moves downwards. As soon as the dosage form dissolves the scale gradually rises.

A further apparatus was developed by Broadbent et al. (Broadbent, Mitchell et al. 1966). It was known as the oscillating tube and was a modification of the disintegration apparatus of the British Pharmacopoeia.

These apparatus can be seen as forerunners of the current dissolution test apparatus. Since each of the early apparatus had limitations, none was widely adopted. In the 1960s and 1970s many different approaches to dissolution apparatus design were developed. With their different designs and operating conditions, the dissolution curves obtained were often not comparable. To address the lack of missing standardized methods, the National Formulary (NF) XIV and USP XVII and XIX standardized the apparatus design and the conditions of operation for given products (Carstensen, Lai et al. 1978). Using these standardized apparatus and conditions led to comparable dissolution profiles, even if the apparatus was produced by different manufacturers. The first dissolution apparatus for *in vitro* testing of solid oral dosage forms which appeared in a pharmacopoeia was the USP I apparatus, the rotating basket. With this apparatus it was possible to enable inter-laboratory comparisons. In the 1970s, it became apparent that dissolution testing could be extremely useful for predicting the bioequivalence (or lack thereof) of immediate release (IR) oral dosage products. One major factor for the dramatic increase in interest in dissolution testing was work performed to investigate problems associated

with generic digoxin IR products. A series of collaborative studies was carried out by the government and some industry laboratories (Johnson, Greer et al. 1973; Lindenbaum, Butler et al. 1973; Shaw, Carless et al. 1973; Shaw, Raymond et al. 1973). It was ascertained that for the digoxin products, the mean dissolution time could be related to pharmacokinetic parameters such as the rate and extent of drug absorption, thus resulting in successful correlation between the *in vivo* and *in vitro* performance. This achievement of correlating *in vitro* dissolution results with *in vivo* data supported the incorporation of dissolution tests and specifications into the USP.

In the following years the importance of dissolution testing, in particular for quality control continued to rise. It became a well-established and indispensable tool in quality control and formulation research. The increased number of monographs in the USP reflects the increasing importance of dissolution testing. In 1968 (USP, 1968) only twelve monographs described the application of dissolution tests, today there are more than 600 (USPXXVII 2002). Furthermore, several new dissolution testing devices have been admitted to the pharmacopoeia in recent years.

Over the last 30 years an appropriate dissolution procedure has become a simple and economical method to assure acceptable drug product quality and performance (Shah and Williams 1999). Dissolution testing finds application as a tool in drug development, in providing control of manufacturing process, for batch release, as a means of identifying potential bioavailability problems and to assess the need for further bioequivalence studies relative to scale-up and post-approval changes (SUPAC) and to signal possible bioinequivalence of formulations. Dissolution profile comparison has additionally been used extensively in assessing product sameness, especially when post approval changes are made. It is clear to see that dissolution testing has moved from a traditional quality control test to an *in vitro* surrogate of bioequivalence test (Shah 2001), which is generally referred as a biowaiver.

A further improvement of the conventional dissolution testing was made by the research group of Dressman, who introduced the concept of using more biorelevant dissolution media, mainly FaSSIF (fasted state simulating intestinal fluid) and FeSSIF (fed state simulating intestinal fluid). By using compendial

devices Dressman et al. succeeded in more closely predicting the behavior of oral dosage forms in the GI tract, in particular with respect to concomitant intake of food.

### 1.3. Devices for dissolution testing of MR dosage forms

Today the following seven apparatus can be found in the USP (USPXXVII 2002)

- Apparatus I (rotating basket)
- Apparatus II (Paddle)
- Apparatus III (reciprocating cylinder, BioDis)
- Apparatus IV (flow-through cell)
- Apparatus V (transdermal cylinder)
- Apparatus VI (Paddle over disk)
- Apparatus VII (reciprocating cylinder over disk)

The choice of an appropriate dissolution apparatus should be considered during the development of the dissolution methods, since it can affect the results and the duration of the test. The type of dosage form under investigation is the primary consideration in apparatus selection.

The European Pharmacopoeia (Ph. Eur. 4 Ed. 2004) has also adopted some of the apparatus design described in the USP, with some minor modifications in the specifications.

Of all these types, the apparatus I (rotating basket) and II (Paddle) are the most widely used around the world, mainly because they are cheap, simple, robust and adequately standardized. Due to these facts, they are usually the first choice for *in vitro* dissolution testing of solid oral dosage forms (immediate as well as extended/controlled/modified release products). However, the apparatus I and II are not appropriate for investigating the dissolution behavior of all dosage forms. Because of the increasing variety of medical formulations (chewing gum, transdermal patches, implants etc.) there is a need for more



types of dissolution apparatus. As a result, the application of other apparatus, such as the apparatus III (reciprocating cylinder, BioDis) and IV (flow-through cell) is increasing.

In the following pages the appearance of the USP apparatus II (Paddle), the USP apparatus III (BioDis) and the USP apparatus IV (flow-through cell) are described in detail. In this thesis the dissolution investigations were performed using the USP II and III apparatus.

### 1.3.1. The USP apparatus II (Paddle)

The assembly consists of a covered vessel (glass or inert transparent material), a motor and a paddle formed from a blade and a shaft. The metallic shaft and blade comprise a single entity that may be coated with a suitable inert coating. The vessel is partially immersed in a suitable water bath and the temperature is kept at  $37 \pm 0.5^\circ\text{C}$ . The vessel is cylindrical, with a hemispherical bottom. It is 160 to 175 mm high and its inside diameter is 98 to 106 mm. Its normal capacity is 1000 ml. Usually, experiments are performed with volumes ranging from 500 to 1000 ml. The dosage unit is allowed to sink near to the bottom of the vessel before rotation of the blade is started.

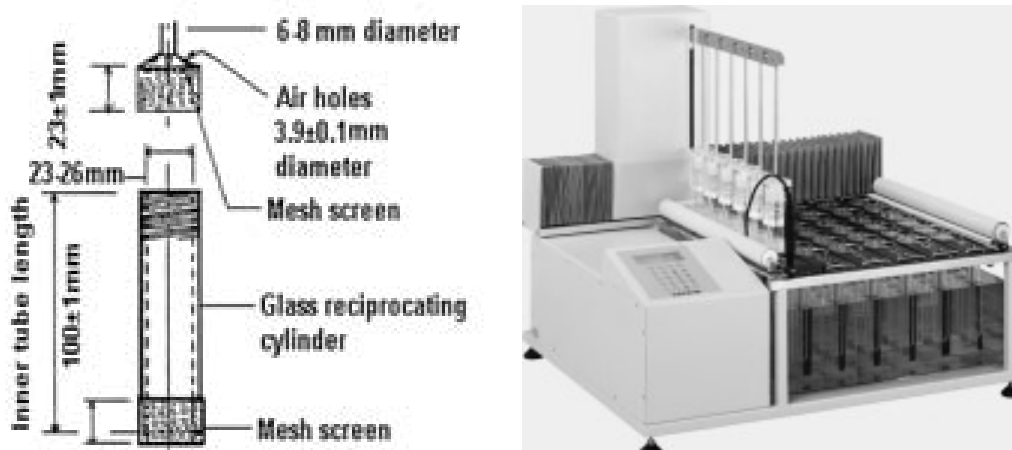
Figure 1.3.1 shows the set-up of a commercial available USP apparatus II (Paddle).



**Figure 1.3.1 USP apparatus II (Paddle)**

As mentioned before the USP apparatus II is the most widely used apparatus worldwide. One benefit of this apparatus is the possibility of automation, which is important for routine investigations (Carrie and Sanders 1983; Dunkle, Gleason et al. 1992; Lamparter and Lunkenheimer 1992). Nevertheless, some problems may arise when a pH- or media change during the investigation is desired or when poorly soluble drugs are investigated. Furthermore, the hydrodynamics are of major importance. Diebold et al. and Scholz et al. showed that the hydrodynamics in the Paddle apparatus are very complex and vary with site in the vessel (Diebold 2000; Scholz, Abrahamsson et al. 2002). These variations may have a great impact on drug dissolution if the position of the dosage form in the vessel varies due to floating or sticking. (Qureshi and Shabnam 2001; Healy, McCarthy et al. 2002; McCarthy, Kosiol et al. 2003). To avoid these effects “sinkers” are often employed for tablets or capsules, which tend to float. However, the use of a sinker may also have an impact on the hydrodynamics.

### 1.3.2. The USP apparatus III (reciprocating cylinder, BioDis)



**Figure 1.3.2 USP apparatus III, reciprocating cylinder, BioDis**

Figure 1.3.2 presents the UPS apparatus III (reciprocating cylinder, BioDis).

The USP III apparatus (reciprocating cylinder, BioDis) was proposed by Beckett (Beckett, Borst et al. 1987) and its incorporation into the USP followed in 1991. Primarily the “BioDis” apparatus was developed for purpose of dissolution