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STRUCTURE OF CHEMICAL COMPOUNDS, METHODS OF ANALYSIS AND PROCESS CONTROL

DISSOLUTION TEST: CAUSES OF UNDERSTATED RESULTS AND THEIR ELIMINATION (REVIEW)

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Understated results of the pharmacopoeial Dissolution test are often encountered in practice. Elimination of this problem is not an easy task. This review considers possible causes of obtaining underestimated data during the development, validation, and use of drug Dissolution test methods. Four groups of factors that can potentially lead to understates results of the Dissolution test are discussed in detail, including (1) factors related to the analytical method, dissolution tester performance, and data collection; (2) factors associated with the dissolution medium; (3) factors related to the properties of the drug substance; and (4) technological factors. Recommendations for eliminating understated results of the Dissolution test are given.

Keywords: Dissolution test, understated results, reasons, factors, recommendations.

Understated results of the Dissolution test are often encountered in practice mainly during drug development and stability studies. Sometimes, incomplete drug release can be observed during quality control of the product. In all such instances, the cause of the incomplete drug release comes into question. Experience shows that determination and elimination of this cause is not an easy problem. Certain knowledge, including that discussed in this article, is needed to solve it. The goals of the present article were to examine the main causes (factors) that can lead to understated results of the Dissolution test and to give recommendations for eliminating these causes.

Several publications on problems with the Dissolution test have appeared [1 – 17]. The causes that can lead to understated or overstated Dissolution test results are usually listed in them or the effects of individual factors on the Dissolution test results are examined.

Let us examine in greater detail the causes (factors) that can lead to understated Dissolution test results. We will do this with an emphasis on the possibility for practical application of the derived information and recommendations.

All factors that could potentially lead to understated results are conveniently divided into four groups to establish the causes of understated results from the Dissolution test. Let us examine each of them in succession.

1. Factors related to the method, Dissolution tester performance, and generation of results

A negative result must be confirmed or rejected if an understated result of the Dissolution test is obtained. For this, the Dissolution test is repeated with samples of the same batch, preferably by another chemist. If the repeated test also gives understated results, then the reliability of the analytical method or Dissolution tester should first be questioned, as shown by practice. Therefore, visual evaluation of the dissolution of the dosage form in the tester vessel is recommended after completion of the repeated test. The cause of the understated result may be visually explained by this. For example, film-coated tablets can be sticky in the dissolution medium and stick to the bottom or wall of the vessel [3]. Tablets and granules from capsules may not be fully disintegrated upon completion of the Dissolution test. Incomplete dissolution

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could be due to floating of capsules or tablet particles; formation of a cone on the bottom of the dissolution vessel; formation of a swollen or rubbery mass; a thin pellicle coating the capsule contents, etc. [1, 16].

If a visual inspection does not explain the cause of the understated results, then the drug recovery at a concentration corresponding to the nominal one and the expected minimal drug concentration in the dissolution vessel should be checked. For this, the dissolution test is simulated by dissolving accurate weights of the drug and a placebo under the conditions of the Dissolution test. This is important because the aim of the Dissolution test is to determine the content of released drug in the solution in the presence of placebo components regardless of the degree of drug release. The problem could be poor solubility or poor wettability of the drug. This can be overcome by dissolving an exact weight of drug in a small amount of suitable organic solvent, usually ≤1 mL. Then, the drug solution is quantitatively transferred into the vessel with the dissolution medium (containing placebo) using the same dissolution medium for this. The drug recovery should be checked in at least three vessels. In practice, a drug recovery of 97.0 – 103.0% is acceptable. It is noteworthy that the small amount of solvent (≤0.1%) has practically no effect on the properties of the dissolution medium and on the correctness of the obtained data.

Sometimes, an understated dissolution result can be caused by partial sorption of a drug on a filter during filtration of a drug suspension with a placebo.

Note 1. Objections arise in practice that a check of the recovery for poorly soluble compounds is inadequate to conclude that the method is not affecting understated results of the Dissolution test. This is justified because the poor solubility of the drug in the dissolution medium could be the cause of the understated results despite a high recovery. However, this is in fact a technological problem that is not related to the method and is solved by selecting excipients required to ensure rather good dissolution of the drug. Let us emphasize that the correctness of the Dissolution test depends on whether the method determines correctly or insufficiently correctly the amount of drug in the dissolution medium as it is, regardless of the degree of drug release from the dosage form.

Note 2. If understated release occurs during development of an original drug, then the following steps are taken. The dissolution test is performed with the original drug using the existing method. If positive results for drug release are obtained, then a problem with the method can be excluded with high probability. Conversely, if negative results are obtained with the original drug, then the method must certainly be checked (evaluate the drug recovery, as described above) and, if necessary, the performance of the Dissolution tester must be checked.

If it is confirmed that the understated results are not related to the method and the performance of the Dissolution tester, then the effects of the factors examined below should be assessed.

If a problem is found with drug recovery, then a procedure for handling out-of-specification (OOS) results is used. For this, the calculations, the correctness of preparing the dissolution medium, the reagents, the level at which samples are collected, the position of the sample relative to the vessel bottom and walls, the possibility of sorption of the drug on the filters, the stirring rate, etc. are checked [3, 7, 17]. If the OOS procedure does not reveal the causes of obtaining understated results, then the need to revise the analytical method of the Dissolution test is questioned. For this, the stirring rate and/or duration of the Dissolution test can be increased; a test with a basket can be switched to a test with a stirrer; or, conversely, the pH and composition of the dissolution medium can be changed.

2. Factors related to the dissolution medium

pH, buffer type and concentration. The pH of the dissolution medium can have a strong influence on drug release. Therefore, the accuracy of the pH-meter readings should be checked if a buffer solution is used as the dissolution medium.

Drug release from a dosage form can depend on the type of buffer. Therefore, one buffer can be replaced by another with the same pH, e.g., acetate by phosphate (pH 4.5) or *vice versa*, during development of the Dissolution test method. This is especially important for obtaining a suitable dissolution profile. It should also be considered if buffer solutions are used that a high buffer concentration can reduce drug release because of a salting-out effect.

Insufficient degassing. As a rule, drug release decreases if the dissolution medium is inadequately degassed. The use of water left in contact with a gas phase (air) for more than a day should be treated carefully.

During determination of a dissolution profile, an understated dissolution may be obtained if the selected amount of drug solution is not considered. Therefore, the following formula should be used for a chromatographic method during determination of dissolution profile points without compensation for the volume of dissolution medium:

$$X_i = \frac{S_i a_0 [V - (i-1)V_p] P \cdot 100}{S_0 D L \cdot 100} + \sum_1^i \frac{V p X_{i-1}}{[V - (i-1)V_p]}, \quad (1)$$

where X is the amount of dissolved drug in percent of the declared amount; S_i, drug peak area on the chromatogram of the test solution; S_0, drug peak area on the chromatogram of the standard solution; a_0, weight of reference standard (RS) drug (mg); D, dilution of the standard solution; L, declared drug content in a tablet (capsule) (mg); P, content of main ingredient in the drug RS (%); V, initial volume of dissolution medium (mL); V_p, volume of selected sample (mL); i, ordinal number of the sample collection point; and $X_0 = 0$. Opti-

cal densities D_i and D_0 instead of S_i and S_0, respectively, are used in Eq. (1) for spectrophotometric methods.

3. Factors related to drug properties

Solubility in the dissolution medium. The nominal drug concentration in the Dissolution test vessel should not exceed one third of the saturation concentration. The solubility of ionizable drugs should be considered to decrease if the drug molecule is neutral and not ionized. The database at the website https://chemicalize.com can be used to assess the presence of molecular or ionic drug species as a function of solution pH. If the particular compound is not in this database, then its structure can be drawn to obtain dependences of the contents of ionic and neutral species on pH.

Crystalline or amorphous drug modifications; particle size. A problem with understated release of a drug from a dosage form can be caused by a different fractional composition of the substance. This can especially affect a transition from the substance of one manufacturer to that of another. The drug dissolution rate depends on the crystal size, i.e., the greater the crystal size, the slower the dissolution rate (drug release from the dosage form) [3]. This is related to the decreased specific surface area and, as a result, the slower dissolution rate upon increasing the crystal (particle) size.

Polymorphism can significantly affect drug release in the Dissolution test. Amorphous drugs usually have the fastest dissolution rate [3] because an amorphous compound does not require energy to be spent on destroying the crystal lattice, in contrast with crystals. Drugs that exhibit polymorphism can exist in different (polymorphic) crystalline states. Stable forms are usually less soluble than metastable forms. On the other hand, the more soluble metastable forms can gradually transform into more stable forms during storage of the drug substance or preparation. Consequently, the results of the Dissolution test will be more variable.

Sometimes, crystals of poorly soluble compounds are micronized to ensure adequate solubility [9]. However, micronization does not always guarantee that drug release from the dosage form will improve. Aggregation of particles and flotation after micronization can have negative effects [13]. Furthermore, crystals can transform from a less stable to a more stable and less soluble form during micronization [18]. The energy released during micronization can cause partial destruction of the drug and increase the impurity content. Therefore, micronization of drugs should be used only in extreme cases.

Formation of a poorly soluble complex of a drug with an excipient. For example, poly(ethylene glycol) PEG-4000 can form a poorly soluble complex with phenobarbital [19].

Partial decomposition of a drug in the dissolution medium or test solution. These situations can occur during development of the Dissolution test method. Moreover, we have encountered partial decomposition of a drug in the Dissolution test upon transfer of a method from an outside organization.

4. Technological factors

a. Negative factors related to excipient properties

An incorrect choice or suboptimal amount of a disintegrator, solubilizer, binder, powdering, filler (diluent), or lubricant excipient.

Excipients can have the following effects in general [5, 13]:

– *Solvents (diluents)*. Hydrophilic diluents usually increase the drug release rate. For example, starch particulates can form a hydrophilic surface layer on particulates of a hydrophobic drug and thereby increase its dissolution rate. On the other hand, certain diluents can hinder drug release. For example, ethyl cellulose, because of hydrophobicity; K_2HPO_4, especially in combination with MCC; Sta-Rx-1500 gelatinized starch granules, because of the formation of a viscous matrix in contact with the dilution medium.

– *Disintegrants* usually but not always increase the drug release rate. For example, Copagel (low viscosity sodium carboxymethyl cellulose) added before granulation decreases the drug dissolution rate. It does not affect the drug dissolution rate if added after granulation.

– *Binders and granulating agents* have different effects on the dissolution rate. Hydrophilic binders increase the dissolution rate of poorly wetted drugs. Nonaqueous binders, e.g., ethyl cellulose, slow drug release.

– *Lubricants.* Hydrophobic lubricants form a hydrophobic layer around granules and; therefore, decrease drug dissolution. For example, we know of a situation where drug release was ?65% with a magnesium stearate content of 1.0% and increased to 85% if the magnesium stearate content was decreased to 0.5%. The possibility of negative effects of magnesium stearate on drug release was reported [20]. In general, prolonged stirring with a lubricant has a negative effect on drug release from a dosage form [13].

– *Surfactants (SAs)* increase the rate and magnitude of dissolution of poorly soluble drugs. Therefore, an SA (e.g., sodium dodecyl sulfate) is usually added to the dissolution medium for poorly soluble drugs to improve the drug dissolution. The action of SAs is based on reducing the surface tension and thereby facilitating penetration of H_2O into the dosage form. Furthermore, SAs like sodium dodecyl sulfate form micelles at concentrations above the critical micelle-forming concentration. Molecules of poorly soluble drugs accumulate within such micelles, which enhances their solubility in aqueous media.

Cyclodextrins, which form clathrates with drug molecules, can be used to increase solubility.

The method of addition of an SA can strongly influence the dissolution rate of a drug. For example, the drug dissolution rate was observed to increase more when polysorbate 80 (PS 80) was sprayed onto phenacetin granules than when PS 80 was added in the granulating agent [13].

Cross-linking gelatin molecules in a capsule shell. So-called cross-linking of gelatin molecules can occur during improper storage of gelatin capsule shells and during

long-term storage of drug capsules. A three-dimensional network that hinders release of the drug from the capsules forms [3, 12, 14]. The basic processes and chemical compounds that cause cross-linking of gelatin molecules were discussed before [2]. The cross-linking characteristically occurs irregularly and often does not appear in all capsules [14]. This can lead to highly understated and highly variable results for drug release from individual capsules. Enzymes should be used to overcome this negative situation. Those recommended for use are [12, 21]:

– pepsin at pH ≤ 4.0 (activity at least 750,000 U per L of dissolution medium);

– papain or bromelain at 4.0 < pH ≤ 6.8 (papain activity at least 550,000 U; bromelain activity at least 30 gelatin-digesting units (GDU) per L of dissolution medium);

– pancreatin at pH > 6.8 (pancreatin activity at least 2000 U per L of dissolution medium).

Interaction of excipients (EX) between themselves and with the drug can lead to understated results of the Dissolution test [19]. Let us give several examples.

Polyvinylpyrrolidone (PVP). A characteristic example is the interaction of povidone and stearic acid. It leads to slow release of drugs from granules. The slowdown of drug release was explained by the formation of a glass-like substance that reduced the granule porosity and, as a result, decreased the drug release rate after storage of the capsules with granules for several months [6]. Complexation of povidone with aromatic compounds is known [22].

Croscarmellose sodium can bind drugs with basic properties, e.g., atenolol, diphenhydramine, lidocaine, and propranolol [23]. This was shown to occur via interaction of drug cations with croscarmellose sodium –COO– carboxylate ions. This could result in incomplete recovery of a drug from the test solution (a problem of the analytical method) [24, 25]. On the other hand, croscarmellose sodium can interact with EX with basic properties (technological problem) [26]. The drug release rate from tablets is significantly decreased because of this. This was proposed to occur because of hydrolysis of croscarmellose sodium at ether bonds. The resulting product created a viscous barrier that prevented ingress of H_2O into the tablet [26].

Hydrophilic matrices of swelling polymers incorporated into tablet shells can form a viscous gel upon contact of tablets with H_2O. For example, hydroxypropyl cellulose (HPMC), hydroxymethylpropyl cellulose (HMPC), hydroxymethyl cellulose (HMC), methyl methacrylate, etc. can form a viscous gel on tablet surfaces that slows drug release [4]. The drug release rate for cellulose derivatives increased with increasing medium pH and in the presence of PVPK 30 [4]. It is noteworthy that the above negative property of HPMC could be neutralized by adding polyvinylpyrrolidone (PVP) and using wet granulation [27].

b. Negative factors related to technological conditions for preparing a dosage form

Excessive compression pressure can degrade drug release from tablets [8, 15].

Increased granulation time during wet granulation can lead to compaction of granules and, as a result, poorer drug release.

A change from wet granulation to direct pressing could in several instances lead to poorer drug release [10, 15].

Suboptimal residual moisture after drying and can cause cementation of tablets during storage and hindered drug release because of this.

Exceeding the powdering time by lubricants can hinder drug release.

Use of classical wet granulation technology instead of moist granulation in a pseudo-liquefied layer increases the variability of Dissolution test results.

An increased temperature of technological operations, especially during tablet coating, can accelerate negative effects leading to understated Dissolution test results.

Note. If understated results are obtained for film-coated tablets, drug release from the tablet core (without the coating) should be checked. If the release meets the standard, then the cause of the understated result was due with high probability to the coating.

The information and recommendations given in the article are useful for determining and eliminating the causes for obtaining understated Dissolution test results.

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