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Generic Solid Oral Immediate Release Products in the EU – Regulatory Perspectives of Dissolution Specification

Abstract
Development of a dissolution method with suitable specifications is a key part of any oral drug product control strategy. Dissolution testing is an *in vitro* technique of great importance in the formulation and development of pharmaceutical dosage forms, as it can be used as a substitute for *in vivo* studies under strictly defined and specified conditions. The main objective of the present study is to know that the drug release rate is identical batch to batch, and the same as those batches proven to be bioavailable and clinically effective. Results from IVIVC studies have been used to select the appropriate excipients and optimise the manufacturing process for quality control purposes and for characterising the release patterns of newly formulated IR products relative to the references. To facilitate generic drug manufacturers in the arranging of dissolution limits for IR solid oral dosage form for *in vitro* purposes, the European agency had revealed some guidelines through a reflection paper on August 17, 2017. The limits relate to solid immediate release drug products with systemic action, characterised as having at least 75% dissolution within 45 minutes. The principle is to derive the specification of the drug product on the basis of the quality characteristics of the biobatch.

Key words: EMA, dissolution specifications, *in vivo* behaviour, batch–to-batch consistency

Dissolution

Academic Definition

The solid substance, when placed in a solvent, dissolves and forms a solution; this entire process is called dissolution.

Pharmaceutical Definition

To know the amount of drug substance released from the dosage form, a test called dissolution is used in the entire life cycle of a pharmaceutical drug product.

The ultimate test which is used to distinguish the performance characteristics for a solid dosage form is the dissolution test. As dissolution tests have become the unique and more commonly used test for the past 50 years, the apparatus of dissolution has needed non-stop upgrading and changes in order to supply favourable conditions with more variety of products for testing performance. Anyway, on new tablets and capsules, almost ninety-nine per cent of dissolution testing was performed.

These are evolved for instantaneous launch (IR) dosage forms and are supposed to offer:

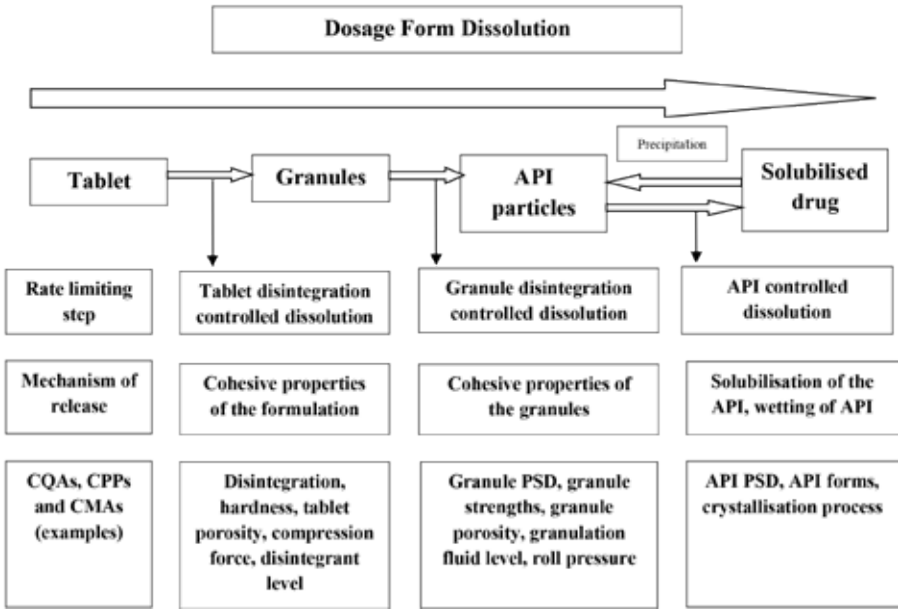
1. Trendy suggestions for testing of dissolution method.
2. Various routes for arranging dissolution limits relevant to the biopharmaceutical traits of a drug substance.
3. Methods used statistically for CDP; and
4. The method which helps to check testing of the dissolution method is enough to release a waiver for an *in vivo* BE study.

Discussion

To know the complete dissolution method of a finished product, and also to know which components of the preparation and manufacturing process have the greatest effect on *in vitro* launch charge, are essential in evolving a dissolution method. The below flow chart explains the procedure in steps worried when a normal tablet or capsule shape dissolves. The dissolution procedure may be categorised into three levels: pill erosion/breakdown into granule particles, granule breakdown into initial drug particles, and active pharmaceutical ingredient dissolution. Potential CQAs, potential critical process parameters (CPPs), and potential crucial material attributes (CMAs) are indexed to every three-level procedure.

In early drug product improvement, wherein exceptional preparations and techniques are taken, modifications of each volume and method will affect each of these dissolution methods variously. Experimentation inclusive breakdown of drug particles, essential active pharmaceutical ingredients dissolution, and granule dissolution will assist in the knowledge of the relevant contribution of every step to the entire dissolution rate.

As a part of choosing a quality control dissolution approach to the product, one frequently suffered with the value of challenging and evaluating the discriminatory power of the process. In order to come up with this, it is easy to perhaps know the effect of the aforementioned critical



process parameters and/or critical material attributes in clinical studies or he may agree to strict limits and mitigate capability biopharmaceutical risk by arranging strict controls during manufacturing.

Development of Immediate Release Solid Oral Dosage Form: Method of Dissolution and Exploring Factors

In fasting conditions, the gastric emptying time, i.e. mean T50%, is within fifteen to twenty minutes. According to this data, the final conclusion is that a drug with eighty-five per cent dissolution within fifteen minutes under low dissolution test conditions in 0.1N HCl shows the characters of solution and commonly it shouldn't have problems like bioavailability. In the case of slow dissolution when compared to GI emptying time, multiple time points of dissolution profile are suggested in various media.

Apparatus Classification in European Pharmacopoeia for different dosage forms:

For solid dosage forms	Paddle apparatus
	Basket apparatus
	Flow – through apparatus
For transdermal patches	Disk assembly method
	Cell method
	Rotating cylinder method
For special dosage forms	Chewing apparatus (medicated chewing gums)
	Flow – through apparatus.

Biopharmaceutics Classification System:

Depending on the solubility and permeability of the drug, the BCS has suggested the below four cases:

- Case 1: High Solubility – High Permeability Drugs
- Case 2: Low Solubility – High Permeability Drugs
- Case 3: High Solubility – Low Permeability Drugs
- Case 4: Low Solubility – Low Permeability Drugs

The biopharmaceutical classification system is used as base for the purpose of arranging dissolution specification limits for *in vitro* purpose and in the same way it helps as a base for knowing the chances of IVIVC successful dissolution. The dissolution of a drug is known by converting a solid substance into a solution, maximum drug of one unit dose with 1.0 and 8.0 pH in 250ml of buffer solution. If the dose volume or the solubility composition of a particular solution is ≤ 250 ml, then the drug substance is taken as more soluble. If the increase of absorption was > 90% in the lack of known instability in the GI tract or if the permeability is known experimentally then the drugs are commonly highly permeable. In some cases the rate limiting step for absorption of the drug is GI, i.e. the biopharmaceutical classification system for two cases. Dissolution up to 85% in 0.1N HCl within fifteen minutes will guarantee dissolution cannot limit drug bioavailability.

In the same way the case 2 expectations will be like a rate-limiting step in absorption of the drug, and *in vivo* and *in vitro* correlation will be the drug dissolution. In this group for the drug product, various media dissolution profiles are suggested. In case 4 of the BCS, the rate-controlling step is the permeability and restricted *in vivo* – *in vitro* correlation might be possible, depending on comparable rates in dissolution and intestinal transit. In case 4, the drug causes major problem for oral drug delivery.

1. Methods of Dissolution Test

Dissolution Technique Development:

This process is meant for use as a regular control test. A look at instant release drug products must be strong, reproducible and discriminatory so that you can guarantee a regular product is great and to find out quality attributes of a product, which, if changed, might also affect the *in vivo* performance. To make improvements in this sort of dissolution method, subsequent elements are specifically to be considered:

1. The physico-chemical qualities of the active substance depend entirely on the dissolution medium (volume, composition) which is going to be selected and the drug products mean dose range and the method to be examined. Sink conditions may or may not be followed.
2. In common, primarily pH should be maintained within the physiological pH range and an aqueous medium should be used. The surfactants are not used. If used to attain good enough release of active substances which are low soluble, the known surfactants should be used. The concentration of the surfactant must be maintained very low and it was checked by relevant solubility and dissolution statistics and associated scientific discussion.
3. Dissolution equipment has to be selected by an applicant according to his own needs and should be known about exactly. The starting stage of the dissolution method was done with the paddle apparatus and the speed limit should be adjusted to 50rpm, and in the same way the basket apparatus should start with a speed limit of 100rpm. The known various mesh sizes or different speed limits are used in the method. The higher rotations per minute was known by seeing high changes in the outcome results at low speed rates due to hydrodynamic effects, or possibly because of other factors.
4. Already it was identified that techniques with more rotating limits may be low discriminatory. A rise in rotating limits at the expense of discriminatory power just to minimise the changes of outcome results or to finish the entire dissolution process in less time ought to be averted. A rise in the stirring speed may be accepted in case of over-discriminatory conditions near to *in vivo* performance. Anyway, in all cases of dissolution profiles, raising the rotation limits ought to bring enough discriminatory power to the finished product QC.

When the dissolution process is developed, the inputs of process parameters to the various outcomes must be investigated and minimised.

Suitable Conditions and Discriminatory Power:

QC Test Conditions Selection:

To permit increased outcomes of BE study from biobatch to commercial batch, it is essential to have an exact amount of active substance released at a given time point. Test conditions ought to allow discrimination among batches prepared by various CPP and/or CMA

which might also have an effect on the bioavailability. The other batches which are not bioequivalent have been perfected.

The dissolution outcomes, beneath various conditions at some point of development, need to be compared with pharmacokinetic data prepared to pick the most appropriate testing conditions in regular testing. The low *in vivo* data which is obtained for most generic applications was not possible to know mathematical correlations, but all the related *in vivo* information has to be considered in deciding on the appropriate *in vitro* dissolution conditions.

Discriminatory Power Demonstration:

Appropriateness of test conditions to a common batch test ought to explain utilizing batches with various quality attributes. To accomplish this, batches with correct variations compared with the applied drug product ought to be prepared. Such variations might be relevant to the quantitative formulation and material specifications, and additionally utilise somewhat altered process parameters. Present information which is available on both BCS and the drug product should be considered when selecting the quality attributes to slight variations. For example, for a drug product in which the *in vivo* absorption is known to have restricted the solubility/intrinsic dissolution of the active substance, for example BCS II and IV, reasonable quality attributes might be the molecule size of an active substance or different attributes that would affect the *in vivo* dissolution.

For drug product in which *in vivo* absorption is thought to be restricted with gastric discharging or intestinal permeability, for example, BCS I or III class active substance by fast / extremely quick dissolution appropriate quality attributes might be factors in the formulation, as well as preparation methods that will affect the breaking down of the drug product and essentially influence the *in vitro* dissolution rate.

Modifications to the drug composition to make a "bad batch" ought to be enclosed by released qualitative batch formula, and the extent of engaged excipients might be a variant. Total release with one or more than one excipient from formulation (for example binder, disintegrant) is not supported. The conditions for the testing of the dissolution method ought to have the option to distinguish these modifications by setting appropriate specifications.

Ideally, the test for the *in vitro* dissolution method ought to expect the *in vivo* result; however, occasionally the tests for *in vitro* dissolution are not expected due to over-discrimination. This is additionally accepted due to dissolution profiles being changed, leading to *in vivo* equivalence being accepted. As a rule, *in vivo* information to the batches with various quality attributes is not present. The conditions setting for the dissolution test are totally based on their ability to identify variations within batches with various quality attributes, and as given modifications are not known to be *in vivo* related, it is impossible to claim that these conditions for the dissolution test are *in vivo* discriminative.

The finished products, which are BCS class I or III active substances by more excessive solubility towards a physiological pH range and by fast or faster dissolution, may now be impossible to identify any variations with dissolution behaviour after relative modifications by appropriate formulation, material specifications and/or preparation parameters have been made. Within those situations, techniques can be taken as good enough without any more clarifications, or get changed by means of a dissolution test.

Batch by Various *In Vivo* Behaviour Inside Pharmaceutical Improvement:

In some situations where more batches of finished product have been tested in *in vivo* development, leading to batches by suitable pharmacokinetic parameters and those which are not by proper pharmacokinetic parameters, the dissolution takes a look at conditions which must be selected which permit discrimination between applicable and non-ideal batches via putting in place an appropriate specification. The first choice should be given to *in vivo* discrimination when compared with other influencing factors to the selected method.

Batches with Suited *In Vivo* Behaviour Present in Pharmaceutical Improvement: Approaching Side-batch

Batches showing various *in vitro* dissolution profiles originated from described manufacturing methods through the way of process parameters below the limit of maximum changes predicted by process validation studies, which are known as “side-batches”. This method profile of side-batch might be helpful in setting appropriate dissolution specified, while BE with the brand product was explained. In case the batches with an intense variety of *in vitro* dissolution profiles (i.e., fast & slow) are shown to be BE to the reference product, then future dissolution profile batches inside this range are also estimated to be the same.

Test Conditions Selection vs *In Vivo* Trend:

For MAA of a test product, BE study between representative batches of test product series versus reference product available on the market must do. Approval standards for BE arrange for the pharmacokinetic parameters area under the curve and Cmax. The latter is warning of rotation speed *in vivo* in case of a similar area under the curve, and Cmax suggests quicker *in vivo* dissolution. Corresponding to a bioequivalence, have a look at an assessment of dissolution profiles (n=twelve) of generic and brand batches used in BE study which is necessary for the use of planned test situations of the test drug product.

For the examination of *in vivo* data of the bioequivalence study, it is helpful to know the discriminatory power of the dissolution test. Because of acceptance criteria for BE, the point known for Cmax + the respective 90% confidence interval of the test product should be in limit, i.e. eighty per cent and one-twenty-five per cent (according to the Guideline on Investigation of BE) of the Cmax of the branded product. By following the equivalence rules (contrary to a superiority test, with the goal of discovering statistical significant variations) minor variations not including clinical relevance will accept these criteria as long as confidence intervals are fulfilled by ninety per cent.

For these types of cases, the comparison of *in vivo* and *in vitro* results must be done for rank order. If a test

product with large Cmax indicates faster *in vitro* dissolution than the branded product, for suitability of selected test situations, this may be used as an indicator. The more the difference and the less the changes in *in vivo* point estimates, the greater the option that this variation may also be opposite to *in vitro*. If possible, in case of a reverse rank order, i.e. a test product with appreciably more Cmax suggests less *in vitro* dissolution behaviour or vice versa, test situations need to be similarly optimised additionally to replicate the *in vivo* trend.

Batches Without *In Vivo* Behaviour Incorporated in Pharmaceutical Improvement

In some cases, the requirement for BE study was waived depending totally on satisfying criteria, referred to as a biopharmaceutical classification system-based biowaiver. In that case, there was no batch utilised in BA/BE studies or in clinical testing (biobatch) and by analogy, the batch, which has been proven to be the same as the brand product primarily depends on reasonable in vitro dissolution data in a batch of not less than three various pH media taken to be tested.

2. Specifications Setting for Dissolution

If the dissolution conditions for testing are chosen, an appropriate dissolution specification should be arranged to obtain the perfect dissolution outcomes. The limit for the dissolution arrangement is described via the Q value, called mean value, at a known point in time, which allows bias among batches which are acceptable and non-acceptable. Batch results displaying compliance by means of stage S1, S2 and S3 are acceptable. The specification ought to be set in one of these ways so that in routine manufacture and testing, it would be predicted that compliance with S2 was attained.

Prior to setting Q value, the time ranges are permitted with discrimination needing to be considered from the dissolution profile of the biobatch. Sampling time points need to be enough to attain a significant dissolution profile.

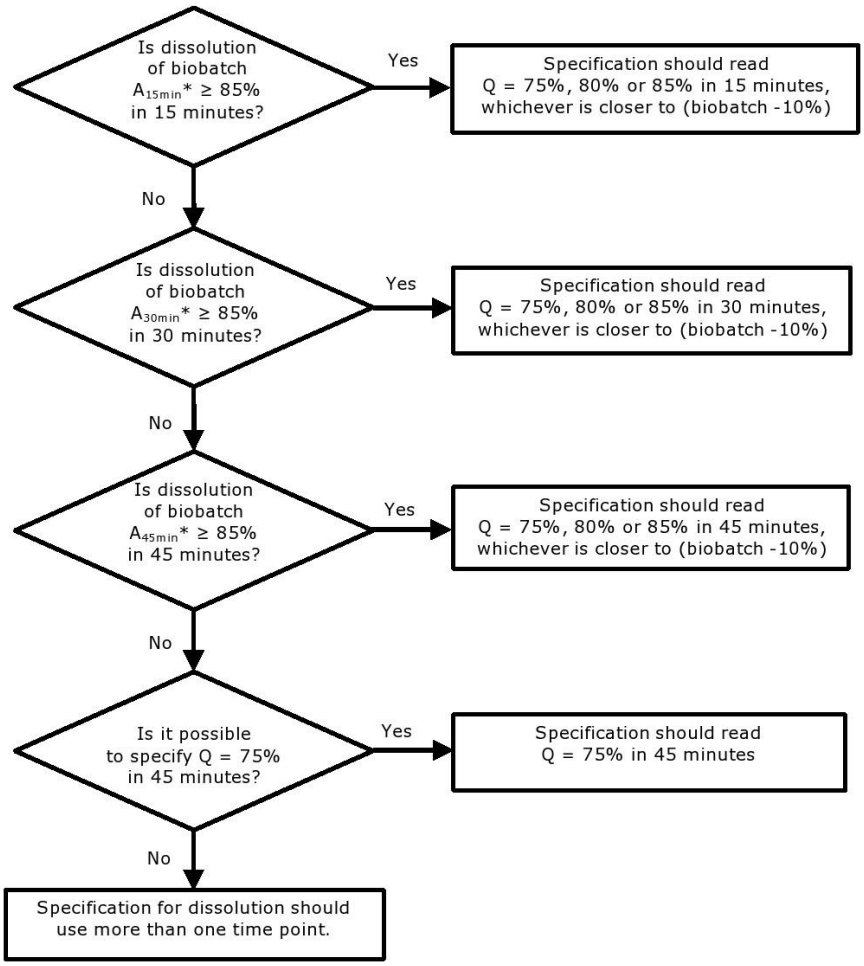
To make sure that the results of the BE study may be extrapolated to the drug product administered to the patient, the entire commercial batches ought to display related behaviour in comparison to the biobatch. The dissolution profile of biobatch, using test conditions supplying discriminatory power, has to be used to set an appropriate arrangement. Relative dissolution of two batches might be expected in case of variations of <10% of the label claim of their mean consequences. Therefore, Q value was recommended to be set on the basis of biobatch dissolution result (mean price of 12 units) minus 10%.

The recognition criterion, Q value is normally set in the range 75-85% (5% intervals) to illustrate discriminatory and satisfactory dissolution. A maximum value >85% is not related. Usually the time points 15, 30 or 45 mins would be sufficient, but different time points may be used if justified. It does not always take into consideration the relevance of selecting a time factor before 15 minutes.

Way to Read the Suggestions in the Annex:

The suggestions in the Annex are intended as guidance in arranging the dissolution specification. Discriminatory power was strongly related to the point of time and the Q value selected. If point of time / Q value differs from that proposed in the flow chart, this may lead to discriminatory power which is also satisfactory.

- In case the dissolution process of biobatch is >=ninety-five per cent in fifteen minutes, the limit can be set to Q value equal to eighty-five per cent after fifteen minutes.
- In case the dissolution process of biobatch is much <ninety-five per cent, but >= eighty-five per cent in fifteen minutes, the limits (Q value) can be arranged to seventy-five per cent, eighty per cent or eighty-five per cent which value is near to Q and equal to biobatch end result of ten per cent at fifteen minutes.
- In case the dissolution process of biobatch is >= eighty-five per cent a half-hour later, the limits (Q value) might be arranged to seventy-five per cent, eighty per cent or eighty-five per cent, which value is near to Q and equal to biobatch outcomes, i.e. ten per cent in half an hour.
- In case the dissolution process of



biobatch is >= eighty-five per cent only 30 mins later, the limits can be arranged to seventy-five per cent, eighty per cent or eighty-five per cent forty-five minutes later.

In case dissolution of biobatch is much <or = 85% after 45 mins, not less than 75% at 45 mins ought to be specified if possible. Otherwise, if dissolution specification (Q) is much < 75% after forty-five minutes, the dissolution specification must be primarily based on > 1 time point.

Suggestions in Case of Biopharmaceutical Classification System Biowaiver

If there was no biobatch, the limit for the specification with standard Q value within fifteen minutes or half an hour should be released. The given value of Q has to be minimum eighty per cent using conditions of a discriminatory test, regardless of the outcomes of test batch dissolution found in a study which was helpful for the biopharmaceutical classification system biowaiver. The dissolution test conditions within the specification ought to be selected as mainly discriminatory among those used in the CDP.

Conclusion

Dissolution specification settings by giving similar choices for *in vitro* purposes of generic drug products with the aim of IR traits. It can be concluded that developing the specification limits of finished products is based on the quality characteristics of biobatch. Relative standards can be taken into consideration in deriving the specification limits for brand products.

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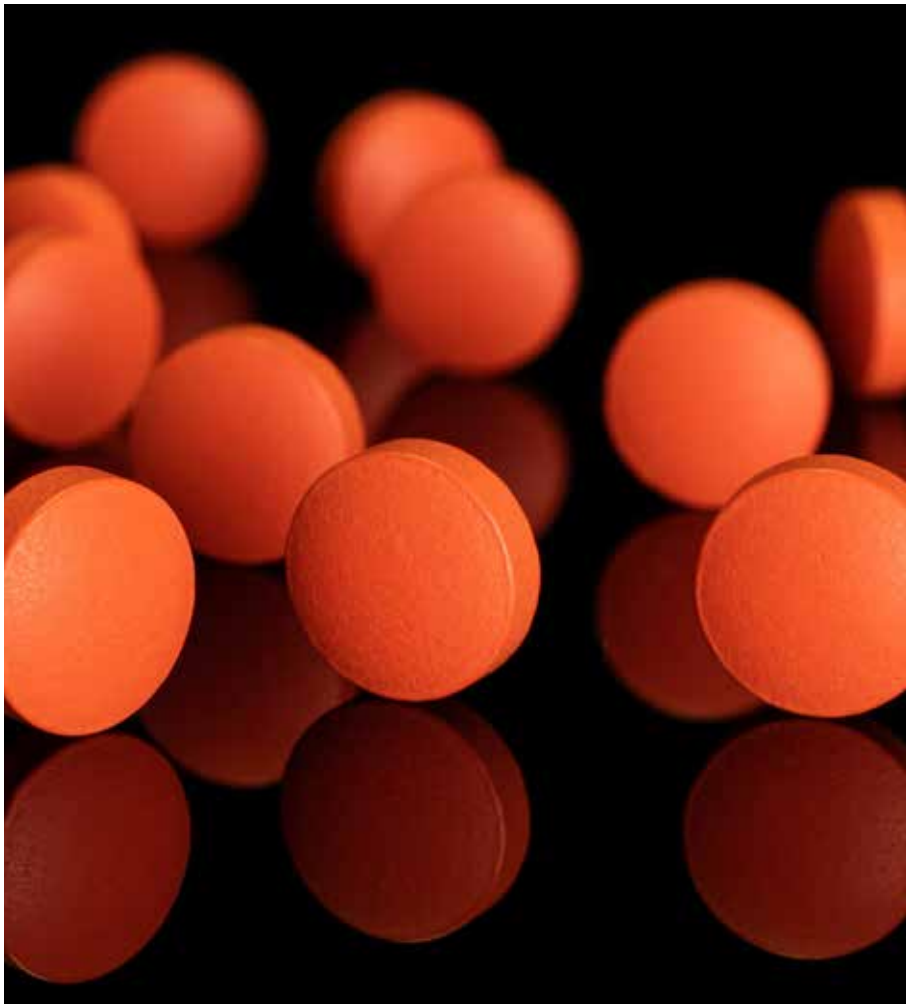

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