# Chapter - 3

Chapter - 3. THEORETICAL ANALYSIS

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3. THEORETICAL ANALYSIS

It is necessary to demonstrate the release nature of a drug from solid dispersions and fast dissolving tablet by both \textit{in vitro} and \textit{in vivo} methods. Formulators of fast dissolving tablets are needed to develop reproducible and sensitive \textit{in vitro} methods to characterize the drug release from fast dissolving tablets. The \textit{in vitro} test developed should be utilized to access the bioavailability of the fast dissolving tablets by possible lot-to-lot \textit{in vivo} performance differences.

3.1 BIOPHARMACEUTIC CONSIDERATIONS

While it is generally accepted that the present state of technology does not permit meaningful \textit{in vitro} versus \textit{in vivo} correlations for fast dissolving tablets, adequately validated \textit{in vitro} and dissolution testing can be developed to facilitate process control and to enable the determination of some of the final product specifications. The fast dissolving tablet studies recommended that to determine the suitability of this \textit{in vitro} test, the relationship of the results obtained with this test to the actual \textit{in vivo} absorption characteristics of the test products should be established in a small group of human or animal subjects.

3.1.1 \textit{In Vitro} Dissolution Rate Testing

It is recommended that the \textit{in vitro} test was desirable for the purposes of providing necessary process control and stability determinations of the relevant characteristics and facilitating certain regulatory
determinations and judgements, concerning minor formulation changes, site of manufacturing changes, etc. The *in vitro* drug release kinetics of the dosage form intended to be marketed should be characterized as a function of pH of the medium, rate of agitation and possibly medium composition also (such as surfactants and bile salts).

The key elements for dissolution are:

1. Reproducibility of the method
2. Proper choice of media
3. Maintenance of sink conditions
4. Control of solution hydrodynamics
5. Dissolution rate as a function of pH ranging from pH 1 to pH 8, including several intermediate values, preferably as topographic dissolution characterization.
6. Selection of the most discriminating variables (media, pH, rotation speed, etc) as the basis for the dissolution test and specification.
7. The dissolution procedure should establish:
8. Fast release characteristics- indicated by releasing the complete drug with in 20 minutes.
9. Complete drug release- indicated by almost 100% release specification at last sampling interval.
10. Dosage form pH dependence- indicated by dissolution in 6.8 pH phosphate buffer.
The United State Pharmacopoeia provides for continued testing through three stages. If the results do not conform to the requirements at stage $S_1$ given in the table, continue testing with additional dosage units through stages $S_2$ and $S_3$ unless the results conform at stage $S_2$. This requirement is an important step forward in providing assurance for batch to batch reproducibility.

**Table 3.1 USP Dissolution Acceptance Criteria**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number of Dosage Units Tested</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_1$</td>
<td>6</td>
<td>No dosage unit is less than Q+5%</td>
</tr>
<tr>
<td>$S_2$</td>
<td>6</td>
<td>Average of twelve dosage units $(S_1 + S_2)$ and no dosage unit is less than Q+5%</td>
</tr>
<tr>
<td>$S_3$</td>
<td>12</td>
<td>Average of twenty four dosage units $(S_1 + S_2 + S_3) \geq Q%$ and not more than two dosage units are less than Q-15% and no dosage unit is less than Q-25%</td>
</tr>
</tbody>
</table>

**3.1.2 Specific Types of In Vivo Studies**

1. **Fasted single-dose studies:**

For a fast dissolving tablets the major concern is that fraction of dose absorbed.
The Wagner-Nelson or Loo-Reigelman equation needs to be applied to single dose study data, so as to obtain the fraction of the amount absorbed per unit time.

2. Postprandial Study:

The conditions of the postprandial study should be same as for the fasted study except for drug dosing. In this instance, the drug product should be administered immediately after the ingestion of a standard breakfast.

3. Multiple-dose Steady-state Studies:

It is not really possible for a drug product to be properly evaluated by single dose administration alone. For prescription products there is a need to determine whether the drug product can achieve well defined therapeutic plasma levels or that the plasma levels obtained are comparable to those generated by a reference drug product administered to healthy volunteers or patients as labelled.

It should be emphasized that bioequivalence employing exact superimposition or plasma levels need not be demonstrated for the purposes of product approval; for by definition, the rate of absorption for a drug product will differ appreciably relative to reference drug product.
The following criteria should be met:

a) Satisfactory steady state plasma levels should be obtained with the test and reference drug product in sufficient patients or volunteers to warrant a comparability determination.

b) Determination of steady-state should be established by comparison of $C_{\text{min}}$ (trough values) on three or more consecutive days. Fluctuation greater than 15% should be closely examined for food effect, diurnal variation, achievement of steady-state, etc.

c) Failure to achieve satisfactory steady-state in a large percentage of subjects tested may indicate possible lack of patient compliance, failure of dosage form performance.

d) Comparison of pharmacokinetic parameters, e.g., $C_{\text{min}}$, AUC values, etc., should be limited only to subjects who achieve steady-state conditions.

e) Comparison of AUC during a dosing interval is only proper if both the test drug and reference drug are at steady-state.

3.2 DEMONSTRATION OF SAFETY AND EFFICACY OF FAST DISSOLVING TABLETS

1. For drugs that have been approved by the FDA as safe and effective in conventional forms, the Food and Drug Administration has taken the position that clinical studies may be required to demonstrate the safety and efficacy of the drugs in fast dissolving tablets.
2. For drugs that have been previously approved as safe and effective in fast dissolving dosage forms data are required to establish bioavailability comparability to an approved fast dissolving drug product.

3. Single dose bioavailability studies are acceptable for determining the fraction of the amount absorbed, lack of dose dumping, lack of food effects, etc. Pharmacokinetic studies performed under steady-state conditions are acceptable, to demonstrate comparability to an approved drug product, occupancy time within a therapeutic window, percentage fluctuation, etc., and are acceptable for supporting dosage administration labelling.

4. The optimum single dose study would be a three way cross over comparing a rapidly available dosage form (i.v. solution, oral solution or a well characterised FDA approved conventional dosage form) and the fast dissolving dosage form under fasting conditions, with the fast dissolving dosage form administered immediately after ingestion of a high fat meal. If there are no significant differences in AUC and Peak concentrations as a function of the meal, no further food effect studies are necessary.

3.2.1 Submitted Data:

Submitted data should provide assurance that

1. The drug product meets the fast dissolving release claims for it.
2. The bioavailability profile established for the drug product rules out the occurrence of dose dumping.

3. The drug product performance is equivalent to a currently marketed conventional release or a specified fast dissolving drug product containing the same active ingredient or therapeutic moiety, which is subject to an approved new drug application.

4. The drug product formulation provides consistent pharmacokinetic parameters between individual dosage units.

### 3.2.1 Recommended Reference Standard for Comparative Studies:

1. Either an intravenous solution or an oral solution or suspension of the same active drug ingredient or therapeutic moiety. If a suspension is used, care must be taken that the suspension itself has adequate bioavailability.

2. A currently marketed, approved, conventional release drug product with defined bioavailability and reproducibility, containing the same active ingredient or therapeutic moiety.

3. A specified currently marketed fast dissolving drug product with defined reproducible bioavailability, subject to an approved new drug application containing the same active ingredient or therapeutic moiety.

4. In some instances (1) or (2) or (3) may be required.

5. In order to avoid selection of an inappropriate reference, the Director, Division of Biopharmaceutics (or in case of generic
drugs, Director, Division of Bioequivalence), should be consulted before initiating studies.

### 3.3 STABILITY TESTING

The term pharmaceutical stability encompasses several concepts. First it is applied to the chemical stability of a drug substance in a dosage form and this the most common interpretation. However, the performance of a drug when given as a tablet, capsule, syrup or injection is not only dependent upon the content of drug substance but also on its pharmaceutical properties (hardness, disintegration and dissolution, etc.,). All of these aspects must therefore be part of the stability program.

The ICH (International Conference on Harmonization) had some impact on the way the stability is viewed in the U.S. An accelerated test (40°C, 75% RH) is included and failure at three months (outside product limits or 2% loss for bulk drug) will be sequential to a (30°C, 60% RH) back-up test.

**Table 3.2 ICH Guidelines for Stability Testing**

<table>
<thead>
<tr>
<th>Product</th>
<th>Conditions</th>
<th>Minimum Time Period of Submission</th>
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<tr>
<td><strong>Bulk Drug</strong></td>
<td>25°C ± 2°C, 60% ± 5%RH</td>
<td>12 Months</td>
</tr>
<tr>
<td></td>
<td>40°C ± 2°C, 75% ± 5%RH</td>
<td>06 Months</td>
</tr>
<tr>
<td><strong>Drug Product</strong></td>
<td>25°C ± 2°C, 60% ± 5%RH</td>
<td>12 Months</td>
</tr>
<tr>
<td></td>
<td>40°C ± 2°C, 75% ± 5%RH</td>
<td>06 Months</td>
</tr>
<tr>
<td><strong>If Fails</strong></td>
<td>40°C ± 2°C, 75% ± 5%RH</td>
<td>12 Months</td>
</tr>
</tbody>
</table>
3. 4 LIST OF MATERIALS USED IN THE PRESENT STUDY

The following is the list of materials used in the present study:

1. Atorvastatin Calcium
   (Gift sample from M/S. MATRIX Laboratories Ltd, Hyderabad.)

2. Rosuvastatin Calcium
   (Gift sample from M/S. MATRIX Laboratories Ltd, Hyderabad.)

3. Gemfibrozil
   (Gift sample from M/S. MATRIX Laboratories Ltd, Hyderabad.)

4. Polytethylene glycol-6000
   (Gift sample from M/s. NATCO Pharma Ltd, Hyderabad.)

5. Croscarmellose sodium
   (Gift sample from M/s. NATCO Pharma Ltd, Hyderabad.)

6. Crospovidone
   (Gift sample from M/s. NATCO Pharma Ltd, Hyderabad.)

7. Pregelatinized starch
   (Gift sample from M/s. NATCO Pharma Ltd, Hyderabad.)

8. Sodium starch glycolate
   (Gift sample from M/s. NATCO Pharma Ltd, Hyderabad.)


10. Sodium hydroxide (S.D Fine Chem Ltd., Mumbai)

11. Talc (S.D Fine Chem Ltd., Mumbai)


13. Hydrochloric acid (S.D Fine Chem Ltd., Mumbai)


15. Aspartame (Gift sample from M/s. NATCO Pharma Ltd, Hyderabad.)


17. Acetonitrile (S.D Fine Chem Ltd., Mumbai)
3. 5 LIST OF INSTRUMENTS/EQUIPMENTS USED IN THE PRESENT STUDY

The following is the list of instruments/equipments used in the present study

1. UV Visible Spectrophotometer (Elico)
2. High Performance Liquid Chromatography (Agilent)
3. Incubator shaker (Remi)
4. Rotary Flash Evaporator (Cyber lab)
5. Lyophiliser (Ilshin)
6. Differential Scanning Calorimeter (Schimadzu)
7. X-Ray Diffractometer (Bruker)
8. Fourier Transform Infra Red Spectrophotometer (Bruker)
10. Hardness Tester (Monsanto)
11. Friabilator (Remi)
12. Disintegration Rate Testing Apparatus (Lab India)
13. Eight Stage Dissolution Rate Testing Apparatus (Lab India)