Ex. 2010

Arthur Kibbe Lecture Notes

Dosage form Evaluation - Dissolution, Disintegration and Bioequivalence.

Disintegration
Tablet disintegration testing is used as a quality-assurance measure. It is not a true predicter of how well the dosage form will release its active ingredient *in vivo*. The United States Pharmacopea (USP) sets standards for tablet disintegration testing. The apparatus is relatively simple. It consists of a basket rack holding six plastic tubes open at the top and bottom. The bottom is covered with a 10 mesh screen. The rack is immersed in a suitable liquid at 37 degrees C. It moves up and down at a specified rate. One tablet is placed into each tube and the time to disintegrate and fall through the screen is noted.(see Ansel page 192)

Dissolution
Like the disintegration test the dissolution test does not prove that the dosage form will release the drug in vivo in a specific manner but it is one step closer to the absorption process. Again the USP sets standards for the dissolution but often those suggested procedures are modified by the manufacturer to meet the specific needs of the product. This test is most often performed on products that have known absorption problems or known poor solubility. It is also performed on sustained or delayed release products such as enteric coated products.(See Ansel page 193) Dissolution testing can be carried out on either capsules or tablets. This test requires the solution to be tested for concentration of active ingredient over the time. A dissolution profile is then constructed (Time vs Amount Dissolved) and this is compared to the reference compound or standard for the dosage form in being dissolved.

Bioequivalency

Our goal is to give the patient a consistent therapy. This requires that the dosage forms release the active ingredients in a consistent and reproducable manner. The real test is therapeutic outcome but as a close second we use the levels of active ingredient in the blood supply. (please read pages 67 to 79 in Ansel) Remember the definitions of Bioavailability and bioequivalence from earlier?? Please re-read those now.

The Food and Drug Administration has established standards which apply to changes in the dosage form or to the comparison of dosage forms of different manufacturers. These rules take into account our understanding of the process and the types of data that must be provided to the FDA before it will approve a change in dosage form design or a generic equivalent of the innovator product.
This information is published by the FDA in a book called "Approved Drug Products - with therapeutic equivalence evaluations". It is published yearly. It is often referred to as the Orange book because of the color of the cover. There is a good story about the cover color. Ask me in class.
For our purposes the introduction (pages vii to xvii in the 1995 edition) is of the most interest to us.
The FDA uses some specific definition of terms which are listed on pages vii & viii. It goes on to define or discuss other important concepts.

- **Pharmaceutical Equivalents** - Drug products are considered pharmaceutical equivalents if they contain the same active ingredient in the same dosage form and are identical in strength or concentration.
- **Pharmaceutical Alternatives** - Drug products that contain the same therapeutic moiety, but are

have the same clinical effect and safety profile when administered to patients under conditions specified in the labeling.

To establish the therapeutic equivalence of different formulations of the same active moiety (whether manufactured by the same company or two different companies) the agency evaluates both the nature of the dosage form and the Bioavailability or Bioequivalence of the active moiety from the dosage form.

- **Bioavailability**. This term means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.
- **Bioequivalent Drug Products** This term describes pharmaceutically equivalent products that display comparable bioavailability when studied under similar experimental conditions.

The FDA Equivalency Codes

FDA Code	Type of Product	Reason for or explanation of code
AA	Oral Dosage forms	These do not present either an actual or potential bioequivalence problem
AB	Solid oral dosage forms	Considered bioequivalent because of the results of a bioequivalence study
AN	Solutions and Powders for Aerosolization	If the product can be used in any of a number of delivery systems
AO	Injectable oil Solutions	Considered equivalent only if the oil used as the vehicle is the same
AP	Injectable aqueous solution	IV solutions are always considered equivalent if the concentrations of the active moiety are the same.
AT	Topical Products	Ointments and creams which contain the same active ingredient and can be shown to have the same therapeutic effect locally
B	all	Product which have actual or potential therapeutic differencies
BC	Extended release tablets or capsules	If a bioequivalence study has been performed they can be reclassed AB
BD	Active ingredients with known bioequivalence problems	
BE	Delayed Release	Not equivalent. Will be reclassed as AB if bio study done.
BN	Aerosol	Product that has a unique method of administration
etc.	other classes	Any B- code is considered not equivalent because it has not been proven to be equivalent by study.

Page 67 in your text book is a classic example of a traditional bioavailability curve. Any products which are administered to a patient and are expected to have the same therapeutic effect must have the same general shape to thier individual bioavailability curves. The three parameters that are most important to us are area under the curve, peak height and time to peak height. The FDA requires that the two products

of the parameters be the same. In class we will discuss a typical bioequivalence study. Be prepared to discuss the issues that might surround this type of approval process.

AUC Calculations

The three important measurements of bioequivalency are AUC, Tmax and Cmax. An examination of the drug concentration versus time curve allows us to estimate both Cmax and Tmax directly from the curve. As an example the curve on page 67 has a Cmax of 4.0 mcg/ml and a Tmax of 2 hours. To determine the AUCt and AUCinf you must do some simple calaculations. The most common method is the Trapazoidal Rule. This assumes that the curve can be divided into triangles or trapazoids. We then calculate the area within each geometric shape and add them together. This will give us the AUC from time of dosing to the last measurable value for the concentration of drug in the blood. To get the remaining AUC from t to inf. we take the last value and divide it by the elimination rate constant. We can then add that amount to our total AUC. As an example I have done this analysis to the curve on page 67 of your text. We use the equation $\{(C_1 + C_2)/2\}X(t_2 - t_1)$ = AUC between t_1 and t_2

In this example the Kel can be determined by selecting any two points on the terminal phase of the curve. $K_{el} = \ln(2/0.5)/(10 - 6)$. Therefore K_{el} is $0.346hr^{-1}$

Time (hours)	Concentration (mcg/ml)	Segment	Calculation	AUC(Hours X mcg/ml)
0.0	0.0			0.0
0.5	1.0	0 to 0.5	(0+1)/2 times (0.5 -0.0)	0.25
1	2	.5 to 1	(1 + 2)/2 times (1 - 0.5)	0.375
2	4	1 to 2	(2 + 4)/2 times (2 - 1)	3.0
3	3.8	2 to 3	(4 + 3.8)/2 times (3 - 2)	3.9
4	3	3 to 4	(3.8 + 3)/2 times (4 - 3)	3.4
6	2	4 to 6	(3 + 2)/2 times (6 - 4)	5
8	1.25	6 to 8	(2 + 1.25)/2 times (8 - 6)	3.25
10	0.5	8 to 10	(1.25 + 0.5)/2 times(10-8)	1.75
12	0.25	10 to 12	(0.5 + 0.25)/2 times(12-10)	.75
		12 to Inf.	.25/.346	0.72

The total AUC from dose to the last sample is ?? the value of AUCinf is ???