Setting clinically relevant tolerances for dissolution testing: A simple and practical alternative

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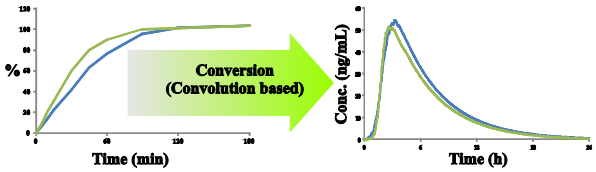
The in vitro drug dissolution tests, or simply dissolution tests, are conducted to evaluate potential drug release characteristics of a product in vivo or in the GI (gastrointestinal) tract. This in vivo dissolution is indirectly measured based on the observed plasma drug levels or profiles in humans. The drug levels in plasma provide the therapeutic (or toxic) effects thus representing the clinical outcome. Equal or similar drug levels in plasma are considered to provide equal or similar therapeutic effects and vice versa. Therefore, to have clinically relevant dissolution tolerances, dissolution results are to be linked to plasma drug levels.

A methodology based on convolution method to convert dissolution results into plasma drug profiles has been reported in the literature (link). With the suggested method, in reality, there is no specific need for setting dissolution tolerances because these dissolution results can easily be converted to plasma drug levels (clinical response) which can be evaluated using standard industry practices using C_{max} and AUC parameters.

The following summarizes the steps in this regard: (1) conduct a dissolution test using product independent dissolution method or experimental conditions (link); (2) convert the dissolution results to plasma drug concentration-time (C-t) profiles using convolution method (link); (3) determine the values of bioavailability parameters (C_{max} and AUC) and compare these values to those reported in literature to assess on average bioavailability characteristics of the product; (4) transfer the profile into multiple profiles by incorporating variability in stomach emptying time and hepatic (liver) metabolism (link). These multiple profiles would represent inter-subject variability and provide expected variabilities in C_{max} and AUC values from a human study; (4) repeat the steps for every test product, calculate the C_{max} and AUC values, along with variabilities (SD) and compare to establish similarity (such as bioequivalent) or differences (different release) in product characteristics.

Example:



The dissolution profiles (left profiles in the above figure) represent dissolution characteristics of two 60 mg IR diltiazem products. The blue (or lower) line represents actual data from a test, while the green (or upper) line represents a simulated faster dissolution profile. Drug experiments were conducted using water as a dissolution medium (900 mL) maintained at 37 °C while stirring at 25 rpm with the crescent shape spindle. Table 1 summarizes the calculated C_{max} and AUC parameters. Note non-linearity of the conversion of the dissolution results to C-t profiles where slower dissolution profiles may provide slightly higher C_{max} and AUC values. This is because of the randomness of the bioavailability of the drug in different subjects (volunteers). However, overall both products show similar values of pharmacokinetic parameters ($p < 0.05$). Therefore, a direct comparison to C-t profiles from dissolution results should be avoided.

Table 1: Mean (±SD) bioavailability parameter values calculated from C-t profiles for two products with normal and faster dissolution profiles of a 60-mg diltiazem IR product.

	C_{max} (ng/mL)	**AUC (ng.h/mL)**	**T_{max} (h)**
Normal (Reference)	59.5±17.3	346±101	2.7±0.5
Faster	54.5±13.0	314±75	2.7±0.4