

Unit 5: Consolidation Parameters, Dissolution Models and Pharmaceutical Statistics

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5.1 Consolidation parameters: the study framework

Consolidation parameters are the measured quantities that describe how a powder responds to pressure and how the resulting compact performs. Unit 4 described the mechanisms; this unit covers the numbers: parameters that describe the compacting process itself (transmitted force, ejection force, work of compression, elastic recovery), parameters that describe release from the compact or dosage form (diffusion and dissolution parameters), pharmacokinetic parameters that link the profile in the test tube to the profile in the body, and the model plots (Heckel, Higuchi, Peppas) and comparison factors (f_1 and f_2) built from them. The statistics at the end of the unit are the tools used to decide whether observed differences are real.

5.2 Diffusion parameters

Diffusion is the movement of molecules from a region of high concentration to one of low concentration under a concentration gradient. Fick's first law states that the flux (amount crossing unit area per unit time) is proportional to the concentration gradient: $J = -D \frac{dC}{dx}$, where D is the diffusion coefficient. Fick's second law describes how concentration changes with time at any point. In dosage forms, diffusion controls release through polymer membranes and matrices, and permeation across biological membranes.

The practical diffusion parameters are the diffusion coefficient D (which falls as viscosity rises and as molecule size grows), the permeability coefficient of a membrane (which combines D with the partition coefficient and membrane thickness), the lag time before steady state flux is reached, and the steady state flux itself. For a reservoir system with a rate controlling membrane, flux is nearly constant, giving zero order release; for a matrix, the diffusing front moves and the release follows the Higuchi square root pattern of section 5.7.

5.3 Dissolution parameters

Dissolution is the process by which a solid drug enters solution; for most oral products it must happen before absorption. The Noyes-Whitney equation describes the rate: $\frac{dC}{dt} = \frac{D A}{h} (C_s - C)$, where D is the diffusion coefficient, A the surface area of the solid, h the thickness of the stagnant diffusion layer around each particle, C_s the saturation solubility and C the concentration already in solution. The equation explains every common way of speeding dissolution: reduce particle size (A rises), stir better (h falls), choose a more soluble form (C_s rises), and keep sink conditions (C stays low).

Dissolution parameters reported for a product include the percentage released at specified times (for example Q at 30 or 45 minutes), the dissolution efficiency (area under the dissolution curve up to a time, expressed as a percentage of the rectangle for complete release), the mean dissolution time, and t_{50} percent, the time for half the drug to dissolve. Whole profiles, not single points, are compared when formulations change, using the similarity approach of section 5.6.

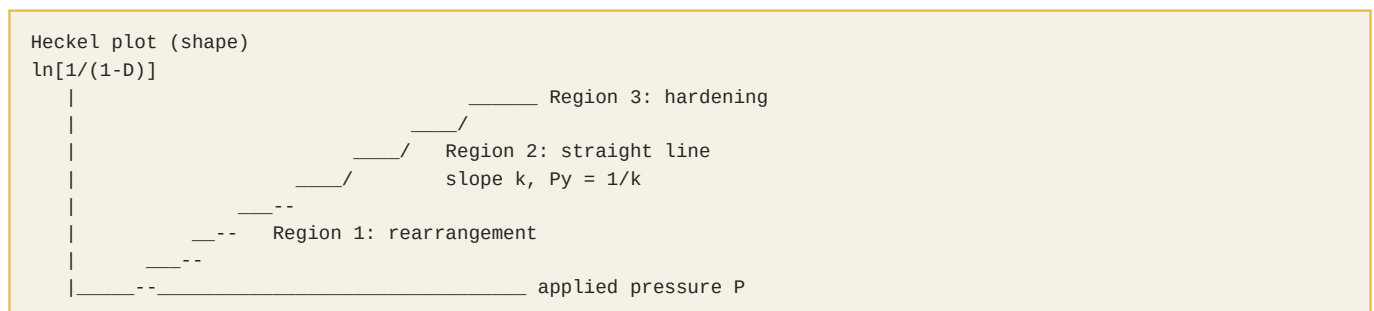
5.4 Pharmacokinetic parameters in profile comparison

Pharmacokinetic parameters translate the in vitro profile into the expected behaviour in the body. The standard parameters are C_{max} (the peak plasma concentration), T_{max} (the time to reach the peak) and AUC, the area under the plasma concentration time curve, which measures the total extent of absorption. When a modified release product is developed or a formulation changes, these parameters from bioequivalence studies are compared with the reference product: the rate of absorption is judged by C_{max} and T_{max}, the extent by AUC. The pharmacokinetic parameters are the end point that the diffusion and dissolution parameters of the earlier sections are trying to predict, and correlations between dissolution and absorption (in vitro in vivo correlations) are built on exactly this chain.

5.5 Heckel plots

The Heckel plot is the standard analysis of compaction data. As pressure P increases, the relative density D of the compact rises towards 1. Heckel proposed the relation: $\ln [1 / (1 - D)] = k P + A$, where k is a constant related to the plasticity of the material and A is an intercept reflecting the initial rearrangement and packing. A plot of $\ln [1/(1-D)]$ against P typically has three regions:

- **Region 1, initial curve:** at low pressure the line curves upward; particles rearrange and fragment, and density rises faster than the straight line predicts.
- **Region 2, straight line portion:** plastic deformation dominates. The slope k is inversely related to the yield pressure of the material: the reciprocal 1/k is the mean yield pressure, P_y. A low P_y (steep slope) means a soft, plastic material that consolidates easily; a high P_y means a hard, resistant material.
- **Region 3, upper curve:** at high pressure the line bends again as the compact approaches its limiting density, work hardens, and elastic effects grow.



Heckel analysis compares materials and the effect of lubricants, moisture and press speed on P_y, and it quantifies the difference between plastic and fragmenting behaviour. Deviations of a plot from the usual shape warn of problems such as over lubrication or capping tendency.

Heckel Plot of a Compaction

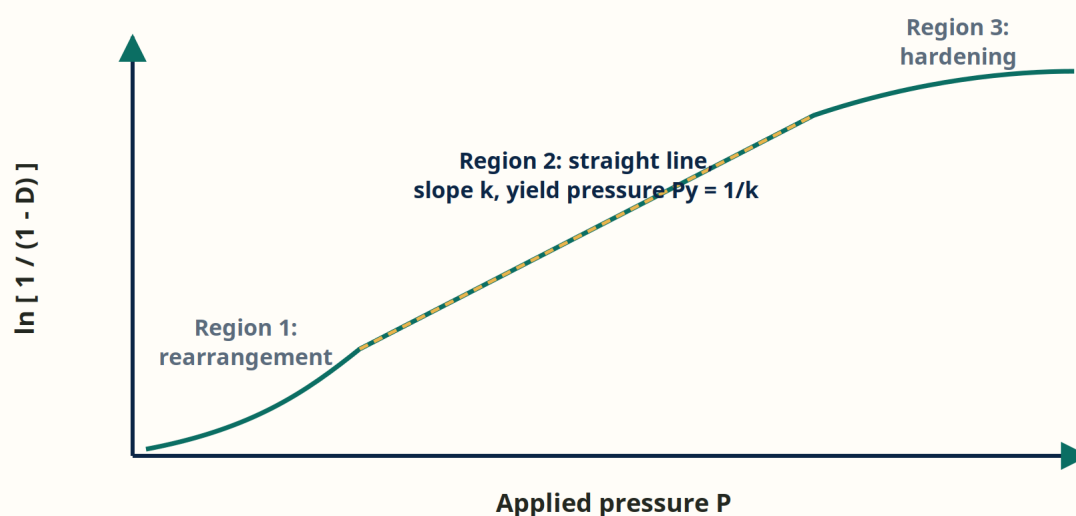


Figure: The Heckel plot. The straight line region gives the slope k , and the mean yield pressure is P_y equals 1 over k .

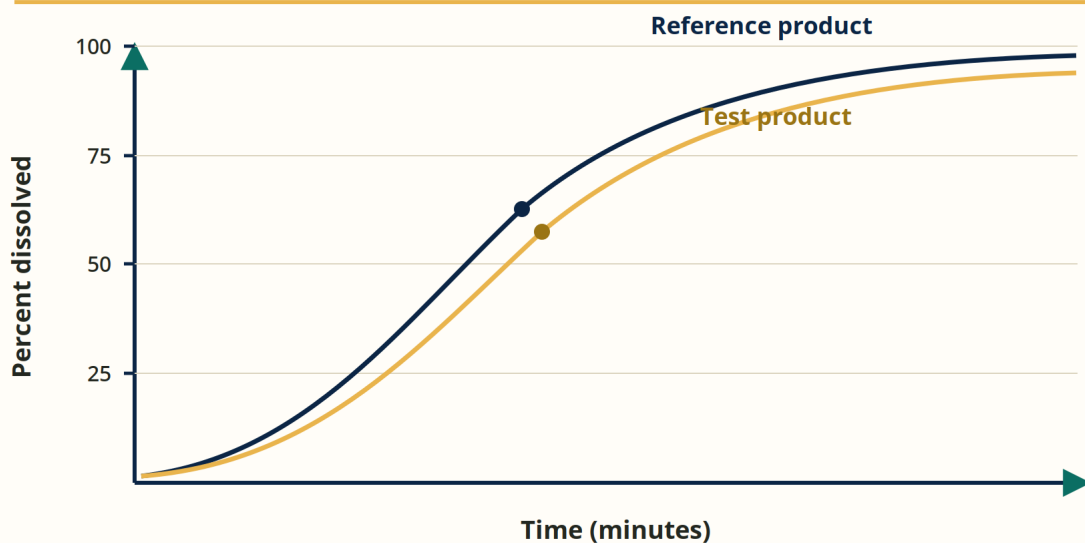
5.6 Similarity factors f_1 and f_2

When a formulation, process or site changes, regulators ask whether the new dissolution profile matches the reference. The similarity approach answers with two numbers calculated from the mean percentage dissolved of reference (R) and test (T) products at the same time points:

- **Difference factor f_1 :** the average percentage difference between the two profiles. $f_1 = [\text{sum of } |R_t \text{ minus } T_t| \text{ divided by sum of } R_t] \text{ times } 100$. Profiles are considered similar when f_1 lies between 0 and 15.
- **Similarity factor f_2 :** a logarithmic measure of closeness: $f_2 = 50 \text{ times log of } \{ [1 + (1/n) \text{ sum } (R_t \text{ minus } T_t) \text{ squared}] \text{ raised to minus } 0.5, \text{ times } 100 \}$. Profiles are considered similar when f_2 lies between 50 and 100; $f_2 = 100$ means identical profiles.

Conditions for a valid comparison include: the same dissolution conditions and time points for both products, at least 3 to 4 time points, 12 units of each product, only one time point after both products have reached 85 percent dissolved, and limited variability (coefficient of variation not more than 20 percent at the early points and 10 percent later). The f_2 approach is preferred worldwide because it judges the whole profile rather than single points.

Comparing Dissolution Profiles: f1 and f2



Profiles are similar when f1 is 0 to 15 and f2 is 50 to 100

Figure: Reference and test dissolution profiles compared point by point; the pair is similar when f1 is 0 to 15 and f2 is 50 to 100.

5.7 Higuchi and Peppas plots

The Higuchi model describes drug release from an insoluble matrix in which the drug is dispersed. Its central result is that the amount of drug released is proportional to the square root of time: $Q = kH$ times the square root of t . A plot of cumulative release against the square root of time (the Higuchi plot) is a straight line when release is controlled by diffusion through the matrix as the depletion zone moves inward. Higuchi release is expected from matrix tablets, ointments and transdermal systems in which a solid drug reservoir is dispersed in the vehicle.

The Korsmeyer-Peppas (power law) model is a general equation for the first 60 percent of release: $M_t/M_\infty = k t$ raised to the power n . Taking logarithms gives a straight line plot of log fraction released against log time, whose slope is the release exponent n . The value of n identifies the mechanism:

Geometry	n for Fickian diffusion	n for anomalous (mixed) transport	n for Case II (relaxation controlled)
Thin film (slab)	0.5	0.5 to 1.0	1.0
Cylinder	0.45	0.45 to 0.89	0.89
Sphere	0.43	0.43 to 0.85	0.85

An exponent at the Fickian value means release is diffusion controlled; an intermediate value means diffusion and polymer relaxation or erosion both contribute; the upper value means constant rate, relaxation or erosion controlled release. Fitting the Higuchi and Peppas models to the same data set is a routine part of release mechanism work.

5.8 Linearity, standard deviation and the concept of significance

Before any test of significance, the quality of the measurement itself is described.

Linearity is the ability of an analytical method to give results directly proportional to the concentration of the analyte over a stated range; it is shown by the calibration plot and its correlation. In statistics generally, linearity also refers to whether a relationship between two variables follows a straight line, which decides which model may be fitted (as in the Heckel and Peppas plots above).

Standard deviation (SD) measures the spread of results around their mean. A small SD means tight, reproducible data; a large SD means scatter. The variance is the square of the SD, and the coefficient of variation (SD divided by the mean, times 100) expresses spread as a percentage, allowing comparison between measurements of different size.

Concept of significance: a difference between two sets of results is statistically significant when it is larger than could reasonably arise from random variation alone. The judgement is made by choosing a significance level, most commonly 5 percent (p less than 0.05): if the probability of seeing a difference at least this large, when there is really no difference, is below 5 percent, the difference is declared significant. Significance is not importance: with enough data, a trivially small difference becomes significant, so statistical results are always read together with their practical size.

5.9 Chi square test, Student's t test and ANOVA

These three tests answer the three most common questions in pharmaceutical data work:

Test	Question it answers	Typical pharmaceutical use
Chi square test	Do observed frequencies differ from expected frequencies?	Goodness of fit; association in categorical data, for example pass and fail counts between two processes
Student's t test	Do the means of two groups differ significantly?	Comparing mean assay or hardness of two formulations; paired t test for before and after on the same units
ANOVA (analysis of variance)	Do the means of three or more groups differ, and which factors matter?	Comparing several formulations at once; analysing factorial design experiments of Unit 1, separating the effects of factors and their interactions

Chi square test compares counts in categories. The statistic sums, over all categories, (observed minus expected) squared divided by expected. A large chi square value means the observed counts stray too far from expectation to be chance. Conditions: data must be counts, categories independent, and expected frequencies should not be too small.

Student's t test compares means using the t statistic, the difference of means divided by the standard error of the difference. It exists in unpaired form (two independent groups) and paired form (the same units measured twice, tested on the differences). Assumptions are approximately normal data and, for the simple form, similar variances.

ANOVA extends the t test to many groups and many factors at once, without the error inflation that repeated t tests cause. It divides the total variation in the data into parts due to each factor, due to interactions, and due to random error (the residual). An F test on each factor compares its mean square with the error mean square: a large F with a small p value means the factor genuinely affects the response. ANOVA is the analysis engine behind the factorial and response surface designs used for optimization, closing the loop of this subject: experiments are designed statistically, products are made under validated, GMP controlled conditions, and the results are judged with these tests.

Frequently Asked Questions

Q: What is the aim of preformulation studies? Preformulation characterises the physicochemical properties of a drug, alone and with excipients, before a dosage form is designed. It covers solubility, stability, crystal form, particle properties and excipient compatibility, and its results decide the dosage form, the excipients, the process and the packaging, saving far greater cost if problems appear later.

Q: How are drug excipient interactions detected? A combination of methods is used. DSC gives a rapid thermal screen (shifts or loss of the drug melting peak suggest interaction), infrared spectroscopy checks for changes in characteristic peaks, isothermal stress testing of mixtures imitates storage and shows physical change, and HPLC gives the final proof by quantifying actual degradation products.

Q: What is t_{90} and how is it calculated for a first order reaction? t_{90} is the shelf life time at which the drug concentration falls to 90 percent of its initial value, the usual acceptable potency limit. For a first order reaction, t_{90} equals 0.105 divided by the rate constant k . The related half life is $t_{1/2}$ equals 0.693 divided by k , independent of the starting concentration for first order reactions.

Q: What are the stability study conditions under ICH guidelines? Long term studies run at the zone condition (for Zone IV countries such as India, 30 degrees Celsius at 65 or 75 percent relative humidity) over the full shelf life, and accelerated studies run at 40 degrees Celsius and 75 percent relative humidity for 6 months. Stress testing exposes the drug substance to severe heat, light, oxidation and hydrolysis to reveal degradation pathways.

Q: What is the difference between a flocculated and a deflocculated suspension? In a deflocculated suspension the particles are separate, settle slowly, but pack into a hard cake that cannot be redispersed. In a flocculated suspension the particles form loose flocs that settle quickly to a loose, voluminous sediment which redisperses easily on shaking. Controlled flocculation is preferred for most pharmaceutical suspensions.

Q: What is the difference between validation and qualification? Qualification applies to facilities and equipment: it proves through URS, DQ, IQ, OQ and PQ that the equipment is designed, installed and works as intended. Validation applies to processes and methods: it proves with documented evidence that the whole process consistently produces product meeting its specifications.

Q: What do IQ, OQ and PQ mean? Installation qualification checks that equipment is delivered and installed as specified. Operational qualification tests that it operates correctly across its working ranges. Performance qualification shows that, in the real process with real materials, it consistently gives the required result, after which the equipment can be released for process validation and routine production.

Q: What is a factorial design and why is it better than changing one factor at a time? A factorial design studies two or more factors at two or more levels in all combinations, in a planned set of experiments. Unlike the one factor at a time approach, it detects interactions between factors, where the effect of one factor depends on the level of another, and it reaches the optimum with fewer, better organised experiments.

Q: What is a Heckel plot and what does the slope tell us? A Heckel plot graphs $\ln$ of 1 over (1 minus relative density) against applied pressure. Its straight line region reflects plastic deformation; the slope k is inversely related to the mean yield pressure, P_y equals 1 over k . A low yield pressure indicates a soft, easily consolidated plastic material, while a high yield pressure indicates a hard material that resists consolidation.

Q: When are two dissolution profiles considered similar? Profiles are similar when the difference factor f_1 lies between 0 and 15 and the similarity factor f_2 lies between 50 and 100, calculated from mean percentage dissolved values of 12 units of each product at the same time points under the same conditions, with only one time point included after both products pass 85 percent dissolved.