Application of Percolation Theory in Pharmaceutical Solid Dosage Forms: A Case Study of Compression and Consolidation of Pharmaceutical Materials
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Purpose
According to the QbD concept, identification of critical quality attributes of product by risk assessment and design of experiments tools or other scientific approach are crucial steps to identify critical process parameters and material attributes that influence quality attributes of the product. However, pharmaceutical solid dosage forms are complex, heterogeneous and disordered particulate systems, often showing non-linear and non-monotonous behavior. To predict the behavior of these disordered systems demonstrating significant difference in their attributes, percolation theory, a topological/statistical and scientific tool was applied.

Methods
Percolation theory deals with the formation of finite and infinite clusters or existence of site and bond percolation phenomena beyond a critical concentration of components in a formulation. Site percolation involves increasing occupation of lattice sites, and once all these lattice sites are occupied and there is little or no possibility of particle rearrangement, bond percolation takes place. The present study is based on the assumption that site and bond percolation phenomena can play a critical role in the compression and consolidation of powder masses. In the present study, carbamazepine, a poorly compactable and brittle drug with two classes of superdisintegrants (namely, Kollidon® CL-SF and Ac-di-Sol® that are well compactable materials), was studied. Studies were performed on single components as well as binary mixtures of carbamazepine with each disintegrant in varying proportions. Heckel plots, tabletability profile and compressibility profile of superdisintegrants were generated; also tensile strength and disintegration time of compacts consisting of binary mixtures of carbamzepine with each disintegrant in varying proportions were determined. Percolation model was used to fit the data in fundamental power law equation \( X = S (\rho - \rho_c)^q \), where \( X \) is the property of compacted tablets, \( S \) is the scaling factor, \( \rho_c \) is the site occupation or bond formation probability, and \( q \) is the critical exponent.

Results
The power law describes the change in tablet properties with change in the relative density of the compacted mass. Heckel analysis conducted on compacts of superdisintegrants yielded two linear sections with increasing compression load possibly due to initial plastic deformation followed by elastic recovery with increasing compression pressure. The intercept of the linear portions of loose compacts and dense compacts in Heckel plot was considered as percolation threshold of superdisintegrants. Compressibility profile (relative density vs. compression pressure) of superdisintegrants yielded critical relative density (\( \rho_c \)) of Kollidon® CL-SF (0.877) and Ac-Di-Sol® (0.868). At or below critical relative density of Kollidon® CL-SF and Ac-Di-Sol®, the tablets remained well compactable with tensile strength of 8.11 MPa and 7.86 MPa, respectively. The result of phase transition of single component system of superdisintegrants at critical relative density (\( \rho_c \)) was further applied to formulate fast disintegrating tablets of carbamazepine. It was observed that at lower concentration of superdisintegrants (10%) and higher concentration of drug (90%), structural failure of tablets occurred. But with increasing concentration of superdisintegrants, geometrical phase transition of binary system was observed with superdisintegrants spanning the lattice of poorly compactable carbamazepine thereby forming well compactable tablets with acceptable tensile strength of 2.61 MPa and 3.13 MPa with Kollidon® CL-SF and Ac-Di-Sol®, respectively at 50% w/w composition.

Conclusion
From the results of present investigations, it can be concluded that percolation theory is a powerful concept and can be applied to understand the compression and consolidation of pharmaceutical materials.