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The SeDeM Expert Diagram System: Its performance and predictability in direct compressible formulations containing novel excipients and different types of active ingredients

Jacques C. Scholtz, Jan H. Steenekamp *, Josias H. Hamman, Louwrens R. Tiedt

North-West University, Centre of Excellence for Pharmaceutical Sciences, Private Bag X6001, Potchefstroom, 2520, South Africa

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ABSTRACT

The SeDeM Expert Diagram System is a galenic pre-formulation system, which evaluates the suitability of excipients and active pharmaceutical ingredients (API's) for direct compression into tablets as well as predicting possible formulations (i.e. ratios of API:excipient) to obtain acceptable direct compressible tablets. In this study, the prediction ability of the SeDeM Expert Diagram System with a special focus on testing the limits of the system was investigated. Three different active pharmaceutical ingredients (API's) in combination with a mix of classic and novel excipients which are currently in use in the wider pharmaceutical community were utilized. The API's and seven excipients were selected based on their physicochemical properties in order to determine the system's ability to predict ratios of API:excipient for acceptable direct compression tablets (e.g. acceptable weight variation as well as sufficient strength to withstand handling). Predicted formulations were tableted and evaluated according to the set criteria. If a tablet formulation failed to meet the criteria, the ratio of excipient to API was increased in 5% increments until a successful formulation was obtained, while the reverse was applied if a formulation was successful. The SeDeM Expert Diagram System proved to be proficient at predicting acceptable tablet formulations, with a few exceptions. The SeDeM system gave successful predictions for only two excipients (FlowLac® 100 and StarLac®) in the case of paracetamol as API. Contrary to predictions by SeDeM for paracetamol, drug loads between 15 and 30% were prepared depending on the excipient. This may be attributed to the ability of the novel excipients to compensate for the elastic properties of paracetamol. With regard to furosemide, none of the predicted formulations rendered acceptable tablets. This could be attributed to the cohesive properties of furosemide forming interactive mixtures with the excipient particles being coated by the relatively small furosemide particles (86.77% < 50 μm) imparting poor flow to the powder particles. In the case of pyridoxine, most of the formulations were predicted acceptable. This work indicates that in cases where the predicted formulation proved to be unsuccessful, by following an increment wise step-up in excipient:API ratio as formulation approach, it is possible to identify an acceptable formulation saving valuable time spent on formulation by a trial and error approach.

1. Introduction

Tablets are popular dosage forms for the administration of active pharmaceutical ingredients (API's), because of relatively low production costs, excellent patient compliance and simplicity of production. Different manufacturing techniques such as wet-granulation, dry-granulation and direct compression of dry powders can be used for tablet manufacturing. Wet granulation remains the most employed technique in spite of it being more time-consuming and therefore more expensive. However, direct compression has recently become popular because it offers the advantage of requiring a smaller number of production steps which is more cost-efficient. Furthermore, direct compression can be applied to thermo-sensitive and moisture-sensitive API's and often produces tablets with faster dissolution times because primary drug particles are released when disintegration takes place [1].

Unfortunately, direct compression as tablet production technique has some disadvantages. The excipients that are used for direct compression have to be able to compensate for poor flow and compression properties, which are often inherent to API's. These challenges often limit the amount of active ingredient to 30% of the tablet formulation [2]. Other problems associated with direct compression include the

Abbreviations: % < 50, Particle size; %H, Hygroscopicity; %HR, Loss on drying; API, Active pharmaceutical ingredient; Carr, Carr's index; Coh, Cohesion index; Da, Bulk density; Dc, Tapped density; Haus, Hausner ratio; Ie, Inter-particle porosity; Iθ, Homogeneity index; t, Powder flow; θ, Angle of repose; MCC, Microcrystalline cellulose; PI, Parameter index; PPI, Parameter profile index; GCI, Good compressibility index; f, Reliability factor; ESEM, Environmental scanning electron microscope; σ_x, Tensile strength; USP, United States Pharmacopoeia.

* Corresponding author.
E-mail address: jan.steenekamp@nwu.ac.za (J.H. Steenekamp).

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time and cost of experimenting and testing excipient and API combinations. A new system was therefore needed to help decrease both the number of experiments required as well as the time required to render an optimised direct compression tablet formulation. The SeDeM Diagram Expert System was developed to address this need. This system indicates which of the powder properties need to be adjusted in order to facilitate the successful formulation and manufacturing of tablets by direct compression [3–7].

By applying powder assessment techniques which are widely used and accepted within the pharmaceutical industry, SeDeM creates a unique profile for each excipient and API. These profiles can then be used to determine and predict appropriate combinations and ratios of excipient to API for direct compression tablets. This system not only points out specific weaknesses inherent to each API or excipient, but can also indicate if variation between batches occurs [3]. The SeDeM method combines quantitative and experimental results from 12 tests or parameters to determine the specific properties of each pharmaceutical powder. The properties or parameters include bulk density (Da), tapped density (Dc), inter-particle porosity (Ie), Carr's index (Carr), cohesion index (Coh), Hausner ratio (Haus), angle of repose (θ), powder flow (t), loss on drying (%HR), hygroscopicity (%H), particle size (% < 50), and homogeneity index (Iθ). The results of these powder tests are then processed using the equations as presented in Table 1.

The results of tests provide parameters which are converted to radius values to create an irregular shaped polygon with maximum radius values of 10. This graphic representation gives a quick and complete graphical representation of the advantages as well as the shortcomings of each different pharmaceutical ingredient. Overlaying different proposed pharmaceutical powders can show shared weaknesses or indicate areas where an excipient can compensate for an API. The basic shape of a twelve sided polygon as used in this study can be seen in Fig. 1.

Besides creating profiles of the different pharmaceutical ingredients, the SeDeM Systems' goal, is to give an indication of whether a specific pharmaceutical ingredient is suitable for direct compression or not, with each radius value of less than five showing an inadequacy in that area. SeDeM also gives an indication of the overall suitability of the main components, i.e. API and fillers for direct-compression. The SeDeM Expert System can theoretically use the obtained data to predict the amount of required excipient to compensate for API inadequacies. Or stated in another way, SeDeM can shorten pre-formulation times, as a starting formulation can be predicted without preparing numerous different concentration and excipient combinations for a given API by just applying the SeDeM methodologies.

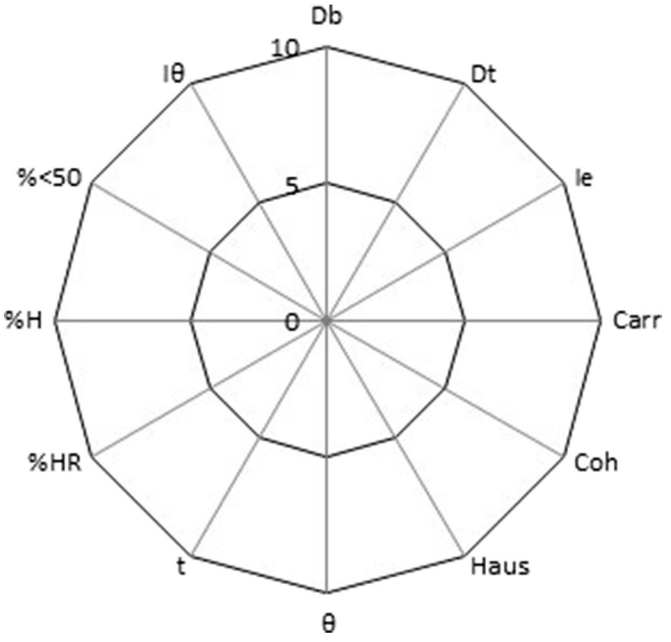

Fig. 1. SeDeM diagram consisting of twelve parameters.

The purpose of this study was to determine if the SeDeM Diagram Expert System is able to identify deficiencies inherent to different pharmaceutical tablet ingredients when applied to a variety of excipients and model API's. The study then continued on to test the ability of the SeDeM Diagram Expert System to predict concentration combinations between API's and excipients, which will deliver an acceptable direct compression tablet formulation. This was done in an effort to identify possible shortcomings and successes of the SeDeM Diagram Expert System. In the event that a formulation did not produce an acceptable tablet, the percentage of API was decreased and the percentage of excipient was increased until an acceptable tablet was compressed. If the SeDeM Expert System predicted an acceptable direct compressible formulation, the percentage API was increased with a corresponding decrease in the percentage of excipients, until the formulation failed to produce acceptable tablets, in order to determine the upper and lower limits of prediction for the SeDeM Expert Diagram System. Furthermore, in the case of unexpected formulation failure an attempt was made to identify a probable cause.

Table 1
Summary of the incidences, parameters and equations used in the SeDeM Diagram Expert System, as well as acceptable ranges of parameter values and equations for converting values into radius values according to the SeDeM Diagram Expert System [3].

Incidence	Parameter	Symbol	Unit	Equation	Acceptable ranges	Equation to convert values to SeDeM radius values
Dimension	Bulk density	Da	g/ml	$Da = m / V_a$	0–1 g/ml	Value × 10
	Tapped density	Dc	g/ml	$Dc = m / V_c$	0–1 g/ml	Value × 10
Compressibility	Inter-particle porosity	Ie	–	$Ie = Dc - Da / Dc \times Da$	0–1.2	(Value × 10) ÷ 1.2
	Carr's index	Carr	%			$Carr = ((Dc - Da) / Dc) \times 100$
	0–50 (%)			Value ÷ 5		
Cohesion index	Coh	N	Determined by	experiment	0–200 N	Value ÷ 20
Flowability	Hausner ratio	Haus	–	$Haus = Dc / Da$	3–1	(30 − (10 × Value)) ÷ 2
	Angle of repose	θ	°	Determined by experiment	50–0 (°)	10 − (Value ÷ 5)
	Powder flow	t	*sec*	Determined by experiment	20–0 (s)	10 − (Value ÷ 2)
Lubricity/Stability	Loss on drying	%HR	%	Determined by experiment	20–0 (%)	10 − Value
	Hygroscopicity	%H	%	Determined by experiment	0–50 (%)	10 − (Value ÷ 2)
Lubricity/Dosage	Particles <50 μm	% < 50	%	Determined by experiment	50–0	10 − (Value ÷ 5)
	Homogeneity index	Iθ	–	$I\theta = F_m / (100 + \Delta F^a_{mn})$	$0–2 \times 10^{-2}$	Value × 500