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Study of MCC, Mannitol and SiO_2 Based Co-processed Excipient for Improving the Direct Compression Properties of Paracetamol using SeDeM/SeDeM-ODT Expert System

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Abstract

Co-processed excipients have enhanced functionality attributes required for developing tablet dosage forms by direct compression technology. In the present study, mannitol, microcrystalline cellulose, and silicon dioxide were developed by dry granulation and proposed as a viable solution for correcting the flowability and compressibility issues commonly encountered in developing paracetamol tablets. SeDeM (12 parameter based) and SeDeM ODT (15 parameter based) expert systems were employed as tools for developing orally disintegrating tablets of paracetamol. SeDeM diagram of paracetamol, mannitol, microcrystalline cellulose and co-processed excipients were prepared and parametric index values of 3.9 and 2.01 indicated poor flowability and compressibility properties of paracetamol. The percentage of corrective excipient required to correct the flowability and compressibility of paracetamol was then calculated followed by preparation of SeDeM ODT expert system diagrams. An increase in concentration of silicon dioxide from 1% to 5% in the co-processed excipient resulted in a decrease in dissolution rate due to increased apparent viscosity/ gel-like structure at higher concentrations of silicon dioxide. The study revealed that co-processed excipient sample with 2.5% of silicon dioxide showed the highest IGCB value of 6.39, implying its suitability for the direct compression of tablets.

Keywords**:** *SeDeM, SeDeM-ODT expert system, co-processed excipient, direct compression, paracetamol*

1. Introduction

In recent times, nearly half of the total drugs approved by the Center for Drug Evaluation and Research (CDER) of the United State Food and Drug Administration (USFDA) have been in solid dosage form (Trisopon et al., 2021). Such an increased demand for tablets has highlighted the need for advancement in tablet formulation. Researchers across the world are devising new techniques that could support the pharmaceutical industry in developing advanced tablet formulations. One such technique is co-processed excipient (CpE), which is a combination of several excipients (Shende, & Jain, 2019; Garg et al., 2015). This technique enhances the properties of individual excipients when used as a CpE and provides a single CpE that possesses multiple characteristics (Jain et al., 2023; Kanojia et al., 2013). It eliminates the need for addition of individual (or additional) excipients during tablet manufacturing, thereby decreasing the cost of the overall project. CpE offers improved flowability, compressibility, tabletability, stability, disintegration & dissolution rate of the formulation (Bhatia et al., 2022; Bin et al., 2019). They are also advantageous

for pharmaceutical manufacturers as they are economical, non-toxic, compatible, cost-effective, exhibit high flexibility, and are physically and chemically inert (Garg et al., 2013; Puri et al., 2016). Commonly used methods for co-processing of excipients are granulation, spray drying, hot melt extrusion, solvent evaporation, milling and roller compaction (Patil et al., 2021). CpE enhances content uniformity as it is a single excipient, leading to reduced segregation challenges (Dominik et al., 2021). Considering these factors, a CpE serves multiple roles in the formulation. Direct compression (DC) is the most prevalent tablet manufacturing method owing to its cost-effectiveness, high stability and process technique that it provides to manufacturers (Dziemidowicz et al., 2018). However, like other formulation processes, researchers have to perform various tests to understand the right concentration of excipients to be used in the formulation. An innovative computational tool known as the Sediment Delivery Model (SeDeM) expert system, is centered on the idea of pharmaceutical quality by design (QbD) (Singh et al., 2021). It is a unique galenic approach being used during the tablet pre-formulation and formulation studies, specifically for DC method. It is used to evaluate the powder characteristics of the API and the excipients leading to the selection of appropriate excipients. SeDeM expert system is an advanced tool that aims to improve the compatibility of powder materials for DC. It is based on 12 parameters that account for 5 factors responsible for powder characterization, such as dimension, compressibility, flowability, stability, and dosage (Pérez et al., 2006; Limpongsa et al., 2022). The Sediment Delivery Model for orally disintegrating tablets (SeDeM-ODT), on the other hand includes an additional 3 parameters, making a total of 15 parameters that accounts for 6 factors (Khan et al., 2022). The additional 3 parameters in SeDeM-ODT are responsible for the tablet characterization prepared through DC. It is a reproducible tool for characterizing and classifying excipients, as well as helpful in selecting the best excipient to overcome API deficiencies (Sipos et al., 2017). Research on the SeDeM ODT system has highlighted its value as a robust tool for enhancing the direct compression of challenging drug substances. Multiple studies have applied the SeDeM methodology to a wide range of active pharmaceutical ingredients (APIs) and excipients, demonstrating its capability to predict and improve the compressibility and flowability of powder blends. This technique involves experimental as well as quantitative study of the powder and tablet characteristics. SeDeM-ODT expert system recognizes the API properties that are required to be improved in order to optimize DC of ODT tablets (Kotsur, & Flisjuk, 2021).

Paracetamol was selected as a model drug because of its unfavorable powder characteristics responsible for its poor compression behavior (Hamman et al., 2019). Paracetamol is known for its poor compressibility, which present challenges for developing tablet formulation, particularly through direct compression. The poor compressibility of paracetamol can be attributed to its crystalline structure, particle size, and shape, elastic recovery and moisture sensitivity (Garekani et al., 2001).

The SeDeM expert system was used to select the best excipient or CpE for the DC of paracetamol. Then, the SeDeM-ODT expert system was applied to the selected excipient or CpE to validate excipient-API compatibility after tablet formation. Scholtz et al., (2017) demonstrated that the SeDeM expert system is an effective tool for predicting the direct compression of paracetamol, furosemide, and pyridoxine using Flowlac and Starlac as co-processed excipients. Salim et al., (2021) integrated SeDeM expert system employing starch: microcrystalline cellulose based co-processed excipient for predicting direct compression manufacturability of solid drug delivery systems. Trisopan et al., (2021) proposed rice starch-based co-processed excipient as all-in-one excipient for developing paracetamol tablets using the SeDeM ODT expert system. Trisopon et al., (2023) used crosslinked carboxymethyl rice starch co-processed with sodium silicate for enhancing direct compression suitability of paracetamol employing SeDeM expert system.

In the present study, MCC, Mannitol, MCC: Mannitol and MCC:Mannitol:Silicon dioxide (SiO_2) (in different concentrations) were employed as excipients/ CpE for evaluating the direct compression suitability of Paracetamol using SeDeM-ODT expert system. Initially, values for 12 parameters of SeDeM expert system were calculated to design SeDeM diagram for excipient, CpE and paracetamol. When computed, incidence factors indicated the poor compressibility and flowability of paracetamol. Incidence factors with excipient or CpE value greater than 5 were selected for correcting compressibility or flowability issue of paracetamol. As suggested by the SeDeM expert system, the percentage of corrective excipient required for developing ODTs of paracetamol was computed. SeDeM-ODT expert

system was developed for the prepared ODT, followed quality evaluation (in vitro dissolution testing) of tablets.

2. Objectives

The objectives of the study are to develop a co-processed excipient (CpE) consisting of microcrystalline cellulose (MCC), mannitol, and silicon dioxide (SiO_2) that enhance the direct compression properties of paracetamol using the SeDeM-ODT expert system.

3. Materials and methods

3.1 Materials

Paracetamol was supplied as a gift sample by Helios Pharmaceutical Ltd., Baddi, India. Microcrystalline cellulose and Silicon Dioxide were procured from Loba Chemie, India., while mannitol was gifted by Signet Chemical Corporation Pvt. Ltd. Mumbai, India.

3.2 Preparation of MCC, Mannitol and SiO_2 based co-processed excipient using dry granulation technique

Co-processed excipients were prepared using the dry granulation technique (Canadell et al., 2022). Different samples were prepared using MCC, mannitol, and SiO_2, as shown in Table 1.

Table 1 Experimental samples employed in the research

Samples	Excipient(s)
Sample 1 (S1)	MCC
Sample 2 (S2)	Mannitol
Sample 3 (S3)	MCC + Mannitol
Sample 4 (S4)	MCC + Mannitol + SiO_2 (1%)
Sample 5 (S5)	MCC + Mannitol + SiO_2 (2.5%)
Sample 6 (S6)	MCC + Mannitol + SiO_2 (5%)
Sample 7 (S7)	Paracetamol

3.3 Optimization of powder characteristics using SeDeM-ODT expert system

SeDeM-ODT expert system was based on 6 factors that were derived from 15 different parameters (Aguilar-Díaz et al., 2012). These parameters were evaluated to study the feasibility of the powder for direct compression and tablet properties (Singh et al., 2019). This technique was explained using mathematical and graphical representation with the 15 parameters listed in Table 2. The final value of each parameter obtained from the equations mentioned in column 4, was denoted by 'v', the value of 'v' should lie within the limit provided for each parameter. The 'v' value was then used to calculate the radius(r) value, to populate the polygon graph. Each excipient and API were tested on 12 parameters of SeDeM expert system and then selected excipients on 15 parameters of SeDeM-ODT expert system classified in Table 2, to get the best excipient – API combination (Flórez Borges et al., 2018; Khan, 2019).

Dimension, compressibility, flowability, stability, and dosage were the selected incidence factors for preparing the SeDeM diagram. For this purpose, various characteristics of the powder materials were experimentally evaluated, and the 12 SeDeM parameter values (bulk and tapped density, inter-particle porosity, Carr's index, cohesion index, Hausner's ratio, angle of repose, powder flow, loss on drying, hygroscopicity, particle size below 50 µm and homogeneity index) were calculated (Aguilar-Díaz et al., 2009; Aguilar-Díaz et al., 2014) (see Table 2). For preparing SeDeM ODT expert system diagram, disgregability (effervescence, disintegration time with disc, disintegration time without disc) was included as an additional incidence factor, apart from the factors considered in the SeDeM expert system. For the experimental methodology, various compendial methods as described in the United States pharmacopeia were employed with slight modifications where needed. All tests were performed in triplicate to reduce the chances of variation.

3.4 Index calculation using SeDeM diagram

The Index Parameter (IP) was calculated by counting the number of parameters (n^o P>5) with radius >5 and is divided by the total number of studied parameters (n^oPt) i.e., 12 parameters. The acceptable limit of IP should correspond to >0.5 (Campiñez et al., 2016).

$$IP = n^o P>5 / n^oPt$$

The Index Profile Parametric (IPP) was measured as the arithmetic average of the radius values of all the 12 parameters. The acceptable limit of IPP should correspond to ≥ 5 (Wan et al., 2019).

Table 2 SeDeM-ODT evaluation parameters

Incidence Factor	Parameter	Symbols	Equation (v)	Limit for v	Radius (r)	Limit for r
Dimension	Bulk Density (g/ml)	Da	Da=M/Va	0-1	10v	0-10
	Tap Density (g/ml)	Dc	Dc=M/Vc	0-1	10v	0-10
Compressibility	Inter-particle porosity	Ie	Ie=(Dc-Da)/(Dc*Da)	0-1.2	10v/1.2	0-10
	Carr Index (%)	IC	%IC=(Dc-Da/Dc)*100	0-50	v/5	0-10
	Cohesive Index (N)	Icd	Experimental	0-200	v/20	0-10
Flowability	Hausner Ratio	IH	IH=Dc/Da	1-3	(30-10v)/2	0-10
	Angle of Repose (°)	α	α =tan-1 (h/r)	0-50	10-(v/5)	0-10
	Powder Flow (S)	t”	Experimental	0-20	10-(v/2)	0-10
Stability	Loss on Drying (%)	%HR	Experimental	0-10	10-v	0-10
	Hygroscopicity (%)	%H	Experimental	0-20	10-(v/2)	0-10
Dosage	Particle (%)	%PF	Experimental	0-50	10-(v/5)	0-10
	Homogeneity Index	Iθ	Iθ =Fm/(100+Δ) fmn	$0.2*10^{-2}$	500v	0-10
Disgregability	Effervescence (min)	DE	Experimental	0-5	(5-v)2	0-10
	Disintegration time with Disk (min)	DCD	Experimental	0-3	(3-v)3.33	0-10
	Disintegration time without Disk (min)	DSD	Experimental	0-3	(3-v)3.33	0-10

IPP = Avg. r value of all 12 parameters

The Index of Good Compressibility (IGC) and Index of Good Compressibility and Bucodispersibility (IGCB) were calculated with the following equation (Suñé et al., 2014).

IGC or IGCB = IPP x (Pa/ Ca);

Pa and Ca are polygon area and circle area respectively.

The acceptable limit of IGC and IGCB should correspond to ≥5. IP, IPP, IGC and IGCB are calculated to study the characteristics of powder for direct compression and tablet.

3.5 Mathematical calculation of the quantity of corrective excipient required to compensate for the deficit API

The API had a major deficit in its compressibility and flowability characteristics, which was addressed by combining it with a suitable amount of excipient. The amount of corrective excipient (CE) required was calculated using the equation below (Suñé et al., 2008; Nofrerias et al., 2020).

%CE= 100 - [((RE – R)/(RE – RP))*100]

Here,

%CE= percentage of the CE

RE= average radius value of CE

R= required average radius value of API, thus 5 is the minimum value to correct API

RP= average radius value of the deficit API

3.6 Preparation and evaluation of paracetamol tablets

Tablets of paracetamol were prepared using a direct compression method. Paracetamol powder was homogeneously blended with corrective excipient, as calculated by the SeDeM expert system. The powder mixture was compressed into tablets using a multi-punch tableting machine (AK Industries, Nakodar, Punjab, India) equipped with an 8.5 mm round, flat-face punch.

The paracetamol tablets, formulated using corrective excipient as suggested by SeDeM expert system, were evaluated for weight, breaking force, friability, disintegration time, and in vitro dissolution testing as per the guidelines of the United States Pharmacopoeia (USP 43) (United State Pharmacopeia, USP 43, 2020a-d).

4. Results

Direct compression is the most desirable technique for tablet manufacturing. Extensive research has been conducted on the development of smart excipients, for the advancement of commercially applicable methods. In the current study, various excipients and co-processed excipient were tested to evaluate their suitability for preparing DC tablets using standard pharmacopeial methods. API and excipients were evaluated on 12 parameters

of the SeDeM expert system to analyze paracetamol deficiency and corrective excipient. After selecting the percentage of the corrective excipient, the SeDeM-ODT expert system was employed to cross-check excipient-API compatibility for DC tablet characterization. These parameters guided us through the suitability of the excipients to enhance the overall properties of the API for direct compression (Mamidi et al., 2021).

4.1 Radius (r) Value

The samples were tested based on the 12 parameters for powder characterization. The values obtained were then used to calculate the r value of all the seven samples, as showcased in Table 3. The higher the value of r, the better the characteristics of the excipient for direct compression. Therefore, samples with optimum characteristics will compensate for the deficiency of the API in the final formulation (Singh, & Kumar, 2012).

The radius values projected in Table 3 were then used to generate the web-based SeDeM diagram that graphically represents the area covered by each sample. As the limit of the radius value was between 1-10, the graphs that were plotted had the range of 0 and 10, 0 being the centermost value of the graph and 10 being outer highest value of the graph. Figure 1 shows the graphical representation of the seven samples in different polygon shapes. The larger the polygonal area of the sample, the more suitable it is for selection. Paracetamol, i.e., S7 had the smallest polygonal area in the SeDeM diagram, indicating that most of the parameters were below the required limit and needed improvement for direct compression. SeDeM diagrams obtained for other samples were significantly different from one another. Samples with different percentages of SiO_2 i.e., S4, S5 and S6, also projected different polygonal charts. S5 showed the largest shaded area, indicating that the majority of the parameters had r value more than 5. Its IGC value was also higher than other samples, as shown in Table 4.

4.2 Dimension Incidence Factor

Free-flowing powders have less significant inter-particulate interactions, which is appropriate for poorly flowing powders. The dimension factor is the average radius value of bulk and tap density, as shown in Table 4. The dimension values of S2, S3, S4 and S5 were more than 5, which was the acceptable limit of the factor. S2 showed the highest dimension value among the seven samples followed by S3, S4 and S5 respectively. On the other hand, S1 and S6 showed the least dimension value as they had low bulk and tap density. S7, which represents paracetamol also had a dimension value lower than 5, signifying it might need a densification process before tableting. The dimension factor directly impacts the flowability and compressibility of the formulation, as its value was used to calculate parameters like inter-particular porosity, Carr index, and Hausner's ratio.

Table 3 Radius value of excipients, CpE and Paracetamol

Parameters	S1	S2	S3	S4	S5	S6	S7
Da	3.63	5.82	5.32	5.30	4.59	3.63	3.50
Dc	4.50	7.30	6.90	6.89	5.90	5.26	4.90
Ie	4.43	2.90	3.58	3.62	4.03	7.11	6.80
Ic	6.13	5.94	5.42	5.38	5.55	3.80	4.28
ICD	10.00	3.95	5.62	5.69	7.85	4.50	0.80
IH	5.86	5.81	5.67	5.66	5.71	5.16	5.33
α	4.59	2.50	3.41	4.72	4.90	5.28	0.70
t”	5.68	4.36	4.86	7.32	8.20	7.90	0.00
%HR	5.01	9.35	7.26	6.69	5.32	4.60	9.40
%H	9.80	9.50	9.78	9.03	6.12	6.52	9.90
%Pf	8.20	4.59	7.85	7.53	5.37	3.80	4.10
Iθ	1.90	5.00	2.20	2.47	2.95	3.50	5.15

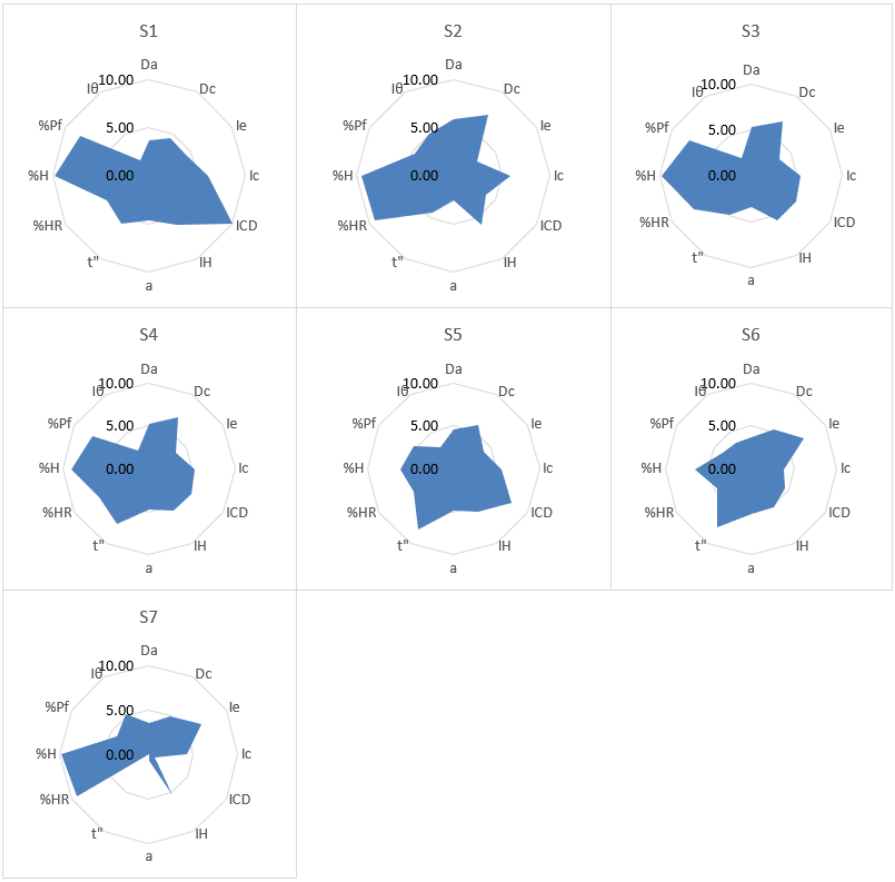

Figure 1 SeDeM diagram of S1 and S2 excipient, S3, S4, S5 and S6 CpE, and S7 paracetamol

Table 4 Incidence factor and parametric index values of different samples as per SeDeM expert system

Samples	Incidence Factors					SeDeM Diagram		
	Dimension	Compressibility	Flowability	Stability	Dosage	IP	IPP	IGC
S1	4.06	6.85	5.37	7.40	5.05	0.58	5.81	5.45
S2	6.56	4.26	4.22	9.42	4.79	0.58	5.58	5.23
S3	6.11	4.87	4.64	8.52	5.02	0.66	5.65	5.39
S4	6.09	4.90	5.90	7.86	5.00	0.83	5.86	5.24
S5	5.24	5.81	6.27	5.72	4.16	0.66	5.54	5.18
S6	4.44	5.13	6.11	5.56	3.65	0.50	5.09	4.76
S7	4.20	3.96	2.01	9.65	4.62	0.41	4.57	4.32

Table 5 Percentage of corrective excipient/ CpE required to correct paracetamol characteristics for DC

Excipients	Compressibility			Flowability			
	S1	S5	S6	S1	S4	S5	S6
RE	6.85	5.81	5.13	5.37	5.90	6.27	6.11
RP	3.96	3.96	3.96	2.01	2.01	2.01	2.01
R	5	5	5	5	5	5	5
%CE	35.89	56.12	88.28	88.98	76.85	70.18	72.92

4.3 Compressibility Incidence Factor

Particles with greater porosity and non-free-flowing properties may result from small size, sticky nature or extreme shape. The compressibility factor is the average of 3 parameters i.e. inter-particle porosity, Carr index and cohesive index as shown in Table 4.

S1 showed the highest compressibility among all other samples, this was because MCC had the highest plasticity leading to high values of the Carr index and Cohesive index. S5 and S6 also showed compressibility values more than 5, which was the acceptable limit. This can possibly be due to the presence of MCC in the co-processed excipient. S2, S3, S4 and S7 showed compressibility values lower than 5, depicting poor compressibility. Paracetamol, i.e., S7, showed the least compressibility value, making it a desired factor for improvement.

4.4 Flowability Incidence Factor

The flowability value of most samples was within the acceptable limit (>5). S2, S3 and S7 had the least value as shown in Table 4, making them unfit for direct compression. The flowability radius value of S7 was least among all other factors, making it a major factor to be corrected for paracetamol. Powder flow was primarily evaluated under gravity loading conditions, and the angle of repose depends on particle movement or inter-particulate friction.

4.5 Stability Incidence Factor

The stability factor of all samples were greater than 5, as shown in Table 4, indicating suitability for all direct-compressed formulations. Hygroscopicity and Loss on drying represents moisture content of the powder. All the samples showed acceptable limits to these parameters.

4.6 Dosage Incidence Factor

Dosage is the final incidence factor for SeDeM analysis. It is responsible for the uniformity of power material in the final formulation. Table 4 shows a few samples with dosage values within acceptable limits, i.e., greater than 5. S6 showed the least dosage value because of low particle size and homogeneity index.

4.7 Index Value

IP, IPP and IGC are the index parameters for determining the comprehensive indices of excipient and API for direct compression. The values were calculated based on the SeDeM diagram shown (Fig. 1). As per the analysis, IP, IPP, and IGC values of paracetamol were below the acceptable limits, making it incompatible for tablet formation.

The majority of incidence parameters of paracetamol were below 5, with only a stability factor (9.65) within the acceptable limit. Comprehensive indices of paracetamol also had undesired values, making it unacceptable for manufacturing through the direct compression method and would require the support of other excipients for tablet formation (Scholtz et al., 2017).

4.8 Percentage of Corrective Excipient (%CE) for API

SeDeM expert system is based on five factors that are used for powder characterization. Flowability and compressibility however are the most desired factors for the success of tablet formation. Therefore, these two factors were selected to correct the deficit of paracetamol powder, as these also had the lowest radius values of the incidence factors. Samples (S1, S5 and S6) for compressibility and samples (S1, S4, S5 and S6) for flowability were further selected for %CE calculation, as they had radius values greater than 5. The %CE value is the amount of corrective excipient required to adjust paracetamol compressibility and flowability. %CE value was calculated with the help of radius value of the corrective excipient (RE), radius value of the API to be corrected (RP) and the desired average radius value (R) which was set to 5 to attain an acceptable API characteristic (Table 5).

Samples with the lowest %CE value were considered suitable to compensate for the paracetamol deficit. Compressibility and flowability, being the key parameters, showed significant differences in the %CE values of the excipients. S1 required 35.89% to compensate for paracetamol compressibility, followed by S5 and S6. S6 projected the worst compressibility value of 88.28%. Flowability, on the other hand was also required the suitable DC formulation. The %CE value showed that 70.18% of S5 would be required to correct paracetamol flowability, followed by S6 (72.92%), S4 (76.85%), and S1 (88.98%). It was concluded that %CE value would be selected based on the flowability parameter of SeDeM, as a greater number of excipients are required to enhance the flowability of paracetamol. S5 was identified as the most suitable CpE to enhance the flowability and compressibility of paracetamol.

To validate the practical enhancement of flowability and compressibility of paracetamol, it was then formulated with excipients as per their %CE values. The powder blend thus prepared was renamed (S1a, S4a, S5a and S6a) and analysed using the SeDeM-ODT expert system. All four samples were subjected to 15 parameters of SeDeM-ODT to calculate the r value and SeDeM-ODT diagram was analysed as shown in Figure 2. S1a, S4a, S5a and S6a samples comprised of MCC,

MCC/Mannitol/SiO_2(1%), MCC/Mannitol/SiO_2 (2.5%) and MCC/Mannitol/SiO_2 (5%) respectively as the corrective excipients with paracetamol in all the samples. Respective percentages of paracetamol and the corrective excipient are depicted in Table 6.

Incidence factors of four formulations were calculated along with their parametric index values (IP, IPP, IGC, and IGCB) as shown in Table 6. The SeDeM-ODT index projected values of all four samples, some of which were above the minimum acceptable limit, making them suitable for DC. Among the incidence factors, dimension had a major setback with no value within the acceptable limit. The compressibility results revealed that all samples had factors higher than 5, with no significant difference, implying good compressibility characteristics for paracetamol. On the other hand, flowability being the major factor for improvement showed S5a and S6a values within the acceptable limit, except for the S1a and S4a formulation. SeDeM-ODT diagrams also revealed that S1a and S4a did not project satisfactory IPP and IGCB values, leading to their incompetence for DC.

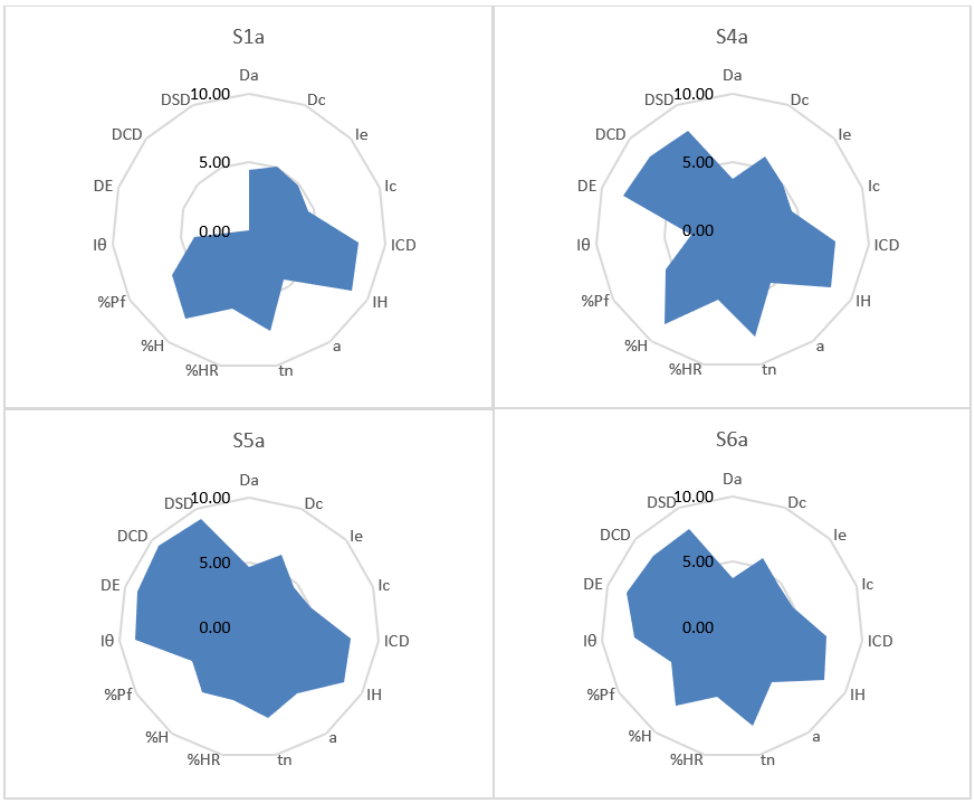

Figure 2 SeDeM-ODT diagram of S1a, S4a, S5a and S6a

Table 6 Incidence factor and parametric index values of different samples as per SeDeM-ODT expert system

Samples	Excipient (%)	Paracetamol(%)	Incidence Factors						SeDeM Index			SeDeM-ODT Index		
			Dimension	Compressibility	Flowability	Stability	Dosage	Disgregability	IP	IPP	IGC	IP	IPP	IGCB
S1a	89	11	4.78	5.03	3.95	5.92	7.15	1.58	0.59	5.4	5.14	0.54	4.73	4.6
S4a	77	23	4.84	5.13	4.46	5.96	7.02	5.54	0.58	5.6	5.33	0.46	4.65	4.25
S5a	70	30	4.95	5.62	5.55	6.74	8.06	8.76	0.66	5.9	5.62	0.68	6.58	6.39
S6a	73	27	4.73	5.36	5.15	6.3	7.84	7.99	0.58	5.65	5.38	0.45	5.23	5.38

Different quality attributes of paracetamol tablets prepared using the SeDeM ODT expert system are depicted in Table 7. The breaking force of the prepared paracetamol tablets using the SeDeM ODT expert system was found to range between 2.92±0.51 and 4.28±0.66 kg/cm^2 indicating significant strength for bearing the wear and tear pressures. The friability of the prepared tablets was found to range between 0.62±0.09 and 1.29±0.25 percent. The addition of a suitable binder may be considered in the final formulation for further enhancement of breaking strength or reducing the friability as required. Disintegration time of the tablets was found to be 18.51±3.85 to 65.10±2.23 seconds. The increase in the concentration of silicon dioxide from 1 to 5 percent in formulations S4a-S6a could be held responsible for the reduction in disintegration time from 34.15±3.64 to 18.51±3.85 seconds due to the wicking action and disintegrant property of silicon dioxide (Sangnim et al., 2022).

Paracetamol is predominantly absorbed in the gastrointestinal tract with minimal absorption in the stomach. An in vitro drug release study was conducted to examine the effect of increasing concentration of SiO_2 in the co-processed excipient on the release of paracetamol in pH 1.2 dissolution media (Zhang et al., 2019). Tablets were prepared to evaluate the cumulative drug release profiles of the samples. Dissolution study was conducted with tablets of S1a, S4a, S5a and S6a samples as shown (Figure 3).

The tablets formulated using MCC (S1a) exhibited 94% drug release in 15 minutes. However, tablet batches S4a, S5a, S6a, containing 1%, 2.5%, 5% respective concentration of SiO_2, showed 82%, 58%, and 53% release of paracetamol in 15 minutes. S6a showed the slowest release among all the samples, followed by S5a, S4a and S1a, respectively. An increasing concentration of SiO_2 exhibited a significant reduction in the drug release from the tablet formulation. At higher concentrations, silicon dioxide can act as a barrier that slows down the penetration of the dissolution medium into the tablet matrix (Monton et al., 2023). This can reduce the rate at which the drug is released from the tablet. Additionally, it can create a more compact and denser tablet structure, further hindering the dissolution process (Sangnim et al., 2022). S5a showed optimum dissolution rate, flowability and compressibility index, making it a good fit for tablet formulation. Similar results were reported by Sultana et al. where increased concentration of silicon dioxide showed reduced drug release behavior in gel formulation (Sultana et al., 2013). Hence, careful optimization of the concentration of silicon dioxide in pharmaceutical formulations is required to achieve the desired drug release profile.

5. Discussion

Tablets are the most preferred form of pharmaceutical dosage form, because of their stability and ease of manufacturing. The selection of the right quality and quantity of excipients plays a major role in the development of tablets. Industry experts face major concerns in maintaining their uniformity. To overcome such impediments, various quality by design tools have been developed by researchers, one of which is SeDeM expert system. The tool was used to calculate the accurate amount and type of excipient required to overcome API deficiency. Paracetamol which was selected as the API to be corrected, lacks majorly in its flowability and compressibility properties, properties that are crucial for the development of ODT. SeDeM-ODT technique was used to analyze the efficiency of CpE in different concentrations and to select the best CpE for API enhancement. The CpE used in this research were prepared using the dry granulation technique. Initially there were 7 samples selected for analysis, which included excipients, CpE and paracetamol. These 7 samples were then tested on 12 parameters of SeDeM expert system, to calculate the radius value of each test which was useful for creating the web graph. S7, i.e., paracetamol had the smallest polygonal graph, indicating that it had the lowest radius values. Critical parameters for DC, such as flowability and compressibility had the lowest radius value in S7, indicating parameters that needed to be corrected. Samples with radius value more than 5 in flowability (S1, S4, S5& S6) and compressibility (S1, S5 & S6) were selected to further calculate the percentage of excipient required to overcome paracetamol deficiency. Furthermore, to validate the enhanced properties of S7, all the 4 samples (S1, S4, S5, and S6) were reformulated using the %CE value and paracetamol. These 4 samples (S1a, S4a, S5a & S6a) were again subjected to 12 parameters of SeDeM and additional 3 parameters for tablet characterization, making a total of 15 parameters of SeDeM-ODT. IP, IPP and IGCB are parameters that confirm the suitability of formulation for direct compression. Post analysis, S1a and S4a projected unsatisfactory results for compressibility, flowability, IP, IPP and IGCB values, whereas S5a and S6a projected promising results for all the parameters. In-vitro dissolution

studies were also conducted to practically experience the release of the tablets (Sultana et al., 2013). CpE S5a with 2.5% silicon dioxide projected the best results and showcased optimum properties to overcome flowability and compressibility issues related to paracetamol. SeDeM Expert System can be applied to guide the design and development of novel co-processed excipients, particularly focusing on their particle characteristics and how these influence the final dosage form.

6. Conclusion

The study of co-processed excipients of MCC/Mannitol/SiO_2 was designed to elucidate the application of SeDeM and SeDeM ODT expert system for correcting the direct compression suitability issues of paracetamol. The SeDeM diagram, comprising of 12 parameters, was prepared for paracetamol, excipients, and CpEs to compute various incidence factors (dimension, compressibility, flowability, stability, dosage) and parametric index values (IP, IPP, IGC). Paracetamol depicted poor compressibility and flowability in SeDeM expert system with 4.57 and 4.32 values of IPP and IGC. Percentage of corrective excipient required to correct the flowability and compressibility issues of paracetamol was then calculated. SeDeM ODT expert system diagrams were then prepared employing S1, S4, S5 and S6 excipients for preparing paracetamol tablets. The tablets formulated using MCC (S1a) exhibited 94% drug release in 15 minutes. However, tablet batches S4a, S5a, S6a containing 1%, 2.5%, 5% respective concentration of SiO_2 in CpEs of MCC/Mannitol/SiO_2 showed 82%, 58% and 53% release of paracetamol in 15 minutes. An increasing concentration of SiO_2 exhibited a significant reduction in the drug release from the tablet formulation. Owing to the potential advantages of CpE, advanced CpE would be gaining attraction for pharmaceutical industry as effective, economical and sustainable option over conventional excipients. Co-processed pharmaceutical excipients offer significant advantages in terms of performance and efficiency, their scalability and cost-effectiveness depend on various factors, including manufacturing technology, supply chain robustness, and market dynamics. In conclusion, SeDeM expert system is an effective tool for predicting the direct compression suitability of the developed CpE. SeDeM may be a useful development tool for assisting process development, products development, preformulation and for process optimization.

Table 7 Properties of paracetamol tablets formulated using the SeDeM ODT expert system

Formulation Code	Corrective Excipient (%)	Paracetamol (%)	Tablet Weight (mg)	Breaking Force (kg/cm^2)	Friability (%)	Disintegration Time (sec)
S1a	89	11	524.45±1.56	2.92±0.51	1.29±0.25	65.10±2.23
S4a	77	23	523.17±3.27	3.16±0.32	1.01±0.13	34.15±3.64
S5a	70	30	522.51±2.11	4.28±0.66	0.62±0.09	22.68±1.92
S6a	73	27	526.82±1.84	3.95±0.85	0.91±0.20	18.51±3.85

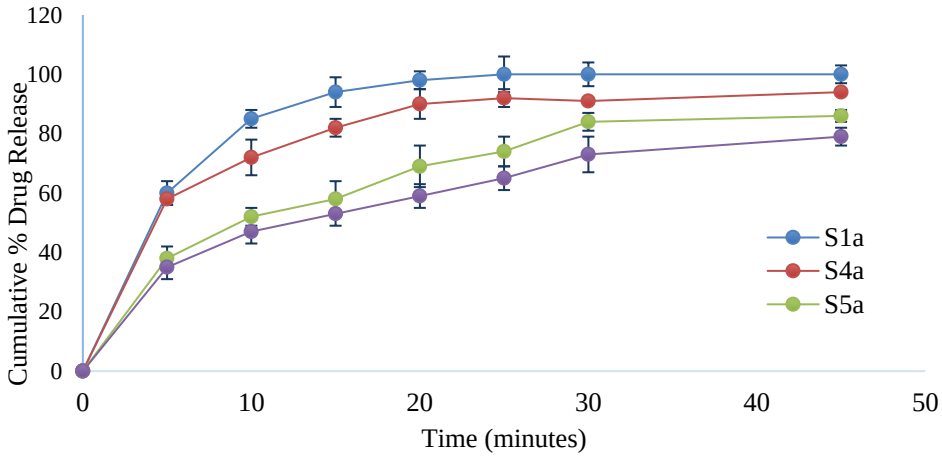

Figure 3 In-vitro dissolution study results of tablets formulated using S1a, S4a, S5a and S6a

6. Abbreviations

CDER: Center for Drug Evaluation and Research

USFDA: United State Food and Drug Administration

CpE: Co-processed excipient

DC: Direct compression

SeDeM: Sediment delivery model

QbD: Quality by design

CMAs: Critical material attributes

US: United States

Da: Bulk density

Dc: Tapped density

Ie: Inter-particle porosity

IC: Carr index

Icd: Cohesive Index

IH: Hausner's ratio

α: Angle of repose

t": Powder flow

%HR: Loss on drying

% H: Hygroscopicity

%Pf: Particle Size

Iθ: Homogeneity index

DE: Effervescence Test

ODT: Orally Disintegrating Tablets

DCD: Disintegration time with disk

DSD: Disintegration time without disk

IP: Index Parameter

IPP: Index Profile Parametric

IGC: Index of Good Compressibility

IGCB: Index of Good Compressibility and Bucodispersibility

CE: Corrective Excipient

RE: Average radius value of CE

R: Required average radius value of API, thus 5 is the minimum value to correct API

RP: Average radius value of the deficit API

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