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Composites of Chitin as Excipient for Pharmaceutical Solid.

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Abstract

Chitin, the second most abundant biopolymer after cellulose, can function as an excipient for pharmaceutical solid dosage forms. Chitin, due to its chemical inertness, is useful in extending the shelf life of many drugs. Binary composites of chitin and another suitable excipient can be formed to improve the compressibility and compatibility of chitin. Composites composed of chitin/CaCO2, chitin/CaHPO4, and chitin/MCC were prepared by slugging the powders using a single punch machine, ground, and screened over mish#22. Characterization of the composites was performed by measuring the density, particle size, and flowability of the powder composites. The compression behavior of the composites was performed utilizing Kawakita analysis. Characterization of the compacts (tablets) formed was undertaken by measuring the hardness (crushing strength), disintegration time, and friability of the tablets. Modeling and optimization of the performance of the various composites and the correlation between the input factors (compression force, chitin content, and additive type) and the responses (powder volume reduction and tablet hardness) were achieved by Response Surface Method (RSM) analysis. The tablet hardness was modeled by a linear model with both the compression force and the composite composition. The powder volume reduction was best modeled by a quadratic model with compression force and composite composition. One of the major conclusions from this work is the effect of synergy between different modes of deformation of binary excipients. In this regard, there is an impact of brittle excipients added to a plastically deforming excipient in improving the compressibility of a composite of chitin-CaHPO4 and chitin-CaCO3. The RSM models were in agreement with the compression analysis results using the Kawakita method.

Paper type: Research paper

Keywords: Chitin composites; compression analysis; tablet hardness; Kawakita analysis; RSM modeling.

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Introduction

Chitin is a naturally occurring polysaccharide and ranks among the most prevalent biopolymers found in nature. It is primarily located in the exoskeletons of crustaceans, including shrimps, crabs, and lobsters, as well as in the internal structures of various invertebrates. The remarkable properties of chitin, including its biocompatibility, biodegradability, and non-toxic characteristics, render it suitable for a diverse array of pharmaceutical applications, particularly in drug delivery systems. As the pharmaceutical sector increasingly prioritizes materials that are safe, effective, and environmentally sustainable, the adaptability of chitin positions it as a promising candidate for the development of innovative excipients, especially in solid dosage forms like tablets and capsules. (Abu Fara, 2024, Badwan, et al., 2015, Zargar, et al., 2015, Daraghmeh, et al., 2011, Rinaudo, 2006, Rowe, et al., 2009).

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Despite its advantages, pure chitin faces certain limitations, such as low solubility in water and common organic solvents, low bulk density, and suboptimal mechanical properties, that constrain its direct application as a single multifunctional excipient in solid dosage forms (Abu Fara et al., 2020, Badwan, et al., 2015). These limitations indicate the need for chitin modifications or combinations with other materials to fully realize its potential as a pharmaceutical excipient. To address these challenges, researchers have begun to explore chitin composites by combining it with various polymers or inorganic fillers. These composites allow for the modification and improvement of chitin's mechanical, physical, and chemical properties, enhancing its properties and performance as an excipient (Singha and Deb, 2022, Aranaz and Acosta, 2021, Daraghmeh, et al., 2011).
Two primary methods are employed in creating chitin-based composites: wet co-precipitation and dry processing, such as roller compaction and slugging. The co-precipitation method involves dissolving chitin with additional materials, mainly silicon dioxide or metal silicates (e.g., magnesium, calcium, or aluminum) in solution and then precipitating them to form a composite. This process often yields homogenous composites with improved powder compactibility, flowability, and stability, and can incorporate various additives, but it has limitations. It requires high solvent use, extensive stirring, potential environmental concerns (careful pH control), and cost implications due to the need for solvent recovery and processing (Assaf, et al., 2019, Chaheen, et al., 2018, Al-Nimry and Alkhamis, 2018, Gana, et al., 2012, Hamid, et al., 2010, Rashid, et al., 2009, Rashid. Et al., 2008, El-Barghouthi et al., 2008).

Alternatively, the dry processing method, which typically involves physical blending and compressing chitin with other excipients or polymers, offers significant advantages. This method eliminates the need for solvents, resulting in fewer environmental concerns and lower production costs. It also simplifies regulatory compliance, as there are no residual solvents to manage. Dry processing can yield powder with sufficient structural integrity, increased powder bulk density, enhanced flowability, and increased tensile strength, making it particularly suitable for creating tablets and capsules where controlled release and stability are required (Al-Hmoud, et al., 2020, Abu Fara et al., 2020, Badwan, et al., 2015, Rojas, et al., 2014, Mir, et al., 2011, Rojas, et al., 2014).

Powder roller compaction and tablet slugging have been also applied to other single excipients to enhance their physical characteristics. For example, α-lactose monohydrate demonstrates increased compactibility comparable to spray-dried lactose when subjected to pressures exceeding 15 kPa, while repeated compaction cycles on microcrystalline cellulose (MCC) reinforce granule strength (Abu Fara, et al., 2020, Abu Fara, et al., 2018, Bultmann, 2002). However, despite these benefits, research on dry-processed chitin composites, particularly those that include chitin and co-excipients such as calcium carbonate, calcium hydrogen phosphate, and MCC, remains limited (Assaf, et al., 2019, Chaheen, et al., 2018, Daraghmeh, et al., 2010), with most studies favoring co-precipitation due to its established methodologies and ease of initial formulation in lab settings (Zargar, et al., 2015). Studies on binary mixtures could clarify how the physical properties of these powders—such as bulk density, Carr's index, tensile strength, and compression behavior—evolve under processing conditions.
In their comprehensive review, Burand et al. (Burand, et al., 2024) investigated the limitations associated with existing excipients and underscored the advantages of co-processed excipients. It can be concluded that the emergence of innovative combinations of excipients and advanced co-processing methods will undoubtedly facilitate the creation and utilization of standalone multifunctional excipients, serving as a viable alternative to the reliance on multiple excipients in pharmaceutical formulations. Ren et al. (Ren et al., 2024) provided a thorough review summarizing the mechanisms involved in the compression processes of pharmaceutical powders, along with the commonly employed methods for assessing their compression properties. Furthermore, the review emphasized the modeling and optimization of the powder compression process. Strategies to enhance the compression characteristics of active pharmaceutical ingredients (APIs) and excipients were also discussed. Haider et al. (Haider et al., 2024) provided a comprehensive review of the latest advancements in chitosan-based drug delivery, concentrating on different formulations, techniques, and practical applications. Their findings illustrate how films, hydrogels, microparticles, and chitosan nanoparticles facilitate the delivery of drugs, proteins, peptides, and nucleic acids. Rana et al. (Rana et al., 2024) published a review article that outlines the latest advancements in the utilization of chitin-MXene composites across various interdisciplinary fields, including the removal of contaminants from water, applications in biomedicine, and the detection of various contaminants in food and water. Pathak et al. (2023) provided a comprehensive review of the latest progress in the creation of chitosan-based nanocomposites, emphasizing their role as biocompatible carriers for drug delivery applications, particularly in the areas of gene delivery, wound healing, microbial treatment, and the delivery of anticancer drugs. Berkenkemper et al. (Berkenkemper et al., 2023) conducted a study examining various compressibility descriptors to assess their effectiveness in predicting the tableting behavior of binary mixtures. Their analysis, which included compressibility evaluation, the Walker equation, and the rearrangement index from Kawakita analysis, yielded encouraging outcomes. They identified a linear correlation between the compression parameter and the composition of the binary mixture, which may serve as a basis for understanding more complex mixtures. Ambaye et al. (Ambaye et al., 2022) examined the enhancement of chitin and chitosan properties through the

development of composite materials combining chitosan and cellulose, highlighting their applications across various industrial sectors, including food packaging, wastewater treatment, protective coatings, and drug delivery systems.

To mitigate the shortcomings of chitin as a pharmaceutical excipient, Patil et al. (Patil et al., 2021) formulated a novel tri-component excipient system consisting of chitosan, mannitol, and crospovidone, using the spray drying technique. The central composite response surface model (RSM) was applied to determine the optimum combination of these ingredients. The resulting co-processed excipient exhibited notable improvements in density and flowability. Additionally, assessments based on Heckel and Kawakita analyses suggested that the developed excipient has enhanced compression properties, making it well-suited for tableting applications. Kostag and El Seoud (Kostag and El Seoud, 2021) conducted an extensive review focusing on the preparation, characteristics, and applications of cellulose/chitin/chitosan biocomposites in various physical forms, including (nano)fibers, films, membranes, and hydrogels. They elucidated the molecular structures of cellulose, chitin, and chitosan, demonstrating how their structural attributes facilitate the dissolution of these biopolymers in common solvents, such as ionic liquids. The use of mutual solvents for cellulose, chitin, and chitosan enables the preparation of composites through solution mixing, which offers advantages in terms of processing complexity and cost efficiency. Despite the profound work carried out on compaction/slugging of single excipients, there is still a lack of understanding of how powders behave when compacted/slugged as binary excipient mixtures.

The current study will investigate the compression behavior of chitin-based composites: chitin-calcium carbonate (chitin-$CaCO_2$), chitin-calcium hydrogen phosphate (chitin-$CaHPO_4$), and chitin-microcrystalline cellulose (chitin-MCC). The designed product is intended to be used in formulations of solid dosage forms. The study includes the following tasks:

1. Preparation of the composites: chitin/calcium carbonate, chitin/calcium hydrogen phosphate, and chitin/microcrystalline cellulose.
2. Characterization of the composites: powder properties and compression analysis.
3. Characterization of the compact (tablet): hardness (crushing strength), disintegration time, and tablet friability.
4. Modeling of the compression behavior of the composites.

1 Materials and Methods

1.1 Materials

Chitin powder extracted from shrimp was obtained from G.T.C. Bio Corporation (Qingdao, China). A highly pure calcite comprising 99.95% w/w calcium carbonate (PC-20 grade) was purchased from Petra Carbonate Factory (Al-Jeeza, Jordan). The natural calcium carbonate used complies with pharmaceutical-grade requirements (current US Pharmacopeia). MCC (Avicel® PH-101) tested according to Ph Eur., (FMC BioPolymer, Philadelphia, PA, USA) as per the material specification data sheet supplied by the manufacturer was used. Calcium Hydrogen Phosphate and anhydrous was obtained from Budenheim, Germany. All the powder samples were sieved and the portion of particle size less than 90 μm was used for further analysis, characterization, and testing.

1.2 Composite Preparation

Powder samples were prepared according to the composition given in **Table 1**. 50g of each combination (chitin-CaCO3), (chitin-CaHPO4), and (chitin-MCC 101) were subjected to slugging at 50 kN using a single punch tableting machine (Holand Tableting Science, Holand Limited, Meadow Lane, Long Eaton, UK). The produced tablets were ground over sieve# 22.

Table 1: Composition of Chitin-based Composites

Composite	Chitin (wt %)	$CaHPO_4$ (wt) %	$CaCO_2$ (wt %)	MCC (wt %)
1	90	10	-	-
	70	30		-
	50	50	-	-
2	90	-	10	-
	70	-	30	-
	50	-	50	-
3	90	-		10
	70	-		30
	50	-		50

1.3 Experimental Design

Response Surface Method (RSM) was adopted to design the experimental work based on statistical analysis and the inputs and outputs in **Table 2.** The coded experimental design sets are depicted in **Table 3.**

Table 2: Inputs and output for the experimental design

Inputs	Outputs
Composite composition (chitin %)	Volume reduction
Compression Force	Tablet hardness (Crushing strength)
Additive	Tablet disintegration time
	Tablet friability

Table 3: Coded Experimental Design Combinations

Run		Factors Coding		
		A	B	C
	Run Description	Comp. Force	Chitin wt %	Additive Type
1	30kN-50%Ch - $CaHPO_4$	-1	-1	0
2	50kN-50%Ch - $CaHPO_4$	+1	-1	0
3	30kN-90%Ch - $CaHPO_4$	-1	+1	0
4	50kN-90%Ch - $CaHPO_4$	+1	+1	0
5	30kN-70%Ch - MCC	-1	0	-1
6	50kN-70%Ch - MCC	+1	0	-1
7	30kN-70%Ch - $CaCO_2$	-1	0	+1
8	50kN-70%Ch - $CaCO_2$	+1	0	+1
9	40kN-50%Ch - MCC	0	-1	-1
10	40kN-90%Ch - MCC	0	+1	-1
11	40kN-50%Ch - $CaCO_2$	0	-1	+1
12	40kN-90%Ch - $CaCO_2$	0	+1	+1
13	40kN-70%Ch - $CaHPO_4$	0	0	0

Level	+1	0	-1
Compression Force (kN)	50	40	30
Chitin Content (wt%)	90	70	50
Additive	$CaCO_2$	$CaHPO_4$	MCC

1.4 Composite Powder and Tablet Characterization
1.4.1 Bulk Density

The bulk density of the powder was assessed by carefully introducing the powder into a 100 mL graduated cylinder until the desired volume was reached. The mass of the powder within the 100 mL cylinder was measured using a precise digital balance. Subsequently, the bulk density was computed by dividing the recorded mass of the powder by 100mL.

1.4.2. Tablet Preparation

Compression using a rotary tablet press. The sample weight subjected to compression was fixed around 250 mg. A flat circular punch size of 8 mm was used. Compression was carried out at compression force equal to 30, 40, and 50 kN.
Powder volume reduction (C) is calculated from the ratio between powder bulk density (ρ_b) and the density of the compressed tablet (ρ_c) according to the formula:
$C = 1 - (\rho_b / \rho_c)$.

1.4.3. Tablet Crushing strength measurement

The analysis of powder compression was conducted utilizing a single punch tablet press (Manesty, County Durham, UK). This type of tablet press offers an accurate simulation of the industrial compression processes applied to powders. Approximately 250 mg of each chitin composite sample was subjected to compression using an 8 mm die. The compression was performed at forces of 30, 40, and 50 kN, with a total of 10 tablets compressed at each specified force. The crushing strength of the resulting compacts was evaluated using a crushing strength tester (Copley, Nottm Ltd, Therwil, Switzerland).

1.4.4. Compression Analysis

The compression process was examined using the Kawakita method to assess the compression properties of the chitin composites, as outlined in Table 1. This method reformulates the non-linear pressure-porosity correlation presented by the Heckel model (Heckel, 1961; Krycer et al., 1982) into a linear relation between pressure and volume reduction. As a result, the Kawakita equation **(Equation1)** is based on the initial bulk density of the powder, in contrast to the true density emphasized by the Heckel equation. The Kawakita equation is articulated as follows.:

$$C = \left[\frac{V_o - V}{V_o}\right] = \frac{abP}{1+bP} \qquad (1)$$

where, C represents the degree of volume reduction of the powder column under the applied pressure, P. The constant (a) indicates the minimum porosity of the material before compression, while the constant (b) is associated with the material's plasticity. The reciprocal of b, or P_K, signifies the pressure necessary to achieve a 50% reduction in the powder bed (Shivanand and Sprockel, 1992, Lin and Cham, 1995). Furthermore, Equation (1) can be rearranged into a linear format as follows:

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab} \qquad (2)$$

2. Results and Discussion

The current study aims to investigate the physical and mechanical properties of binary composites formed from chitin with other fillers, namely calcium carbonate ($CaCO_2$), calcium hydrogen phosphate ($CaHPO_4$), and microcrystalline cellulose (MCC). Composite powder characteristics were assessed. The compression process of chitin and its composites was investigated and analyzed through Kawakita analysis. Interaction between parameters affecting the compression process was examined and modeled using the Response Surface

Methodology (RSM). In addition, the compacts (tablets) formed using these composites were characterized by disintegration, hardness, and friability perspective.

2.1. Powder Characterization

Figure 1 shows the bulk density of the various chitin-based composites. It can be seen that there is a noticeable increase in bulk density of chitin powder when adding $CaHPO_4$, while slight increase when adding $CaCO_2$. On the other hand, there is a slight decrease in bulk density when adding MCC with marginal variation with the content of chitin. The results indicate an improvement in the powder flowability of the composites.

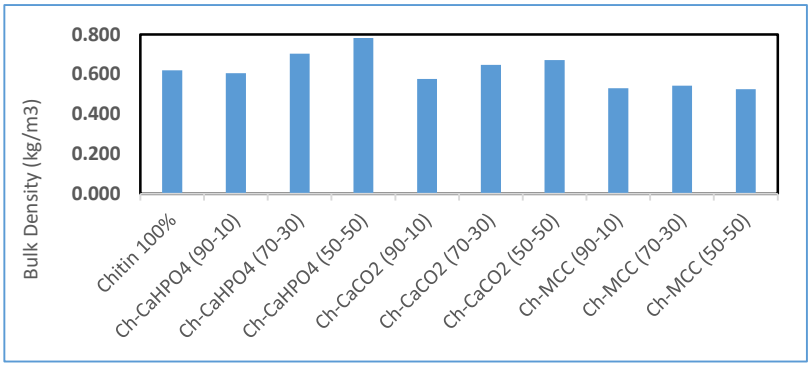

Fig. 1 Bulk density of chitin and its composites**.**

The remarkable increase in bulk density in the case of chitin-$CaHPO_4$ and chitin-$CaCO_2$ could be attributed to the formation of densely aggregated particles caused by the fragmentation of the brittle inorganic components, $CaHPO_4$ and $CaCO_2$, under the slugging force of 50 kN used in the preparation of the composites (sec. 2.2). On the other hand, MCC has been reported to deform in a plastic behavior (Mohyluk, et al., 2024, Abu Fara, et al., 2020).

2.2. Compact (Tablet) Characterization

Table 4 shows the characteristics of compacts **(tablets)** of chitin and its various composites compressed at different compression forces. It can be noticed that most binary mixtures have disintegration times of less than 15 minutes representing the pharmacopeial limit for immediate-release tablets. However, the two composites recorded slightly higher than that by a maximum of 5 minutes margin. Such a margin cannot be considered significant to investigate. Similarly, all friability data were below the maximum acceptable limit of 1.0. Therefore, tablet disintegration time and friability were not considered in the modeling investigation.

The powder volume reduction is an important factor since it is a reflection of the powder compressibility (Abu Fara, et al., 2020). As presented in **Figure 2**, the chitin composites showed an increase in volume reduction more than chitin alone at the different compression forces. It can be seen that there is a noticeable variation in powder volume reduction in the case of chitin-$CaHPO_4$ and chitin-$CaCO_2$ composites. However, such variation is marginal in the case of chitin-MCC composite. The results show an agreement between the trends of the calculated powder volume reduction and the experimentally measured bulk density. Again, the chitin-MCC composite produced a trend in powder volume reduction different than both chitin-$CaCO_2$ and chitin-$CaHPO_4$ composites.

Table 4: Characteristics of compacts (Tablets) of chitin and its composites at the different compression forces

Composite	Compression Force (kN)	Volume Reduction	Tablet Hardness (kN)	Tablet Disintegration Time (min)	Tablet Friability
Chitin 100%	30	0.559	132	4.75	0.37
	40	0.556	133	4.25	0.37
	50	0.554	135	4.72	0.5
Ch-$CaHPO_4$ (90-10)	30	0.593	155	4.3	0.32
	40	0.594	163	4.58	0.51
	50	0.595	180	4.58	0.63
Ch-$CaHPO_4$ (70-30)	30	0.560	160	6.5	0.33
	40	0.562	172	7	0.53

	50	0.561	174	7.5	0.48
Ch-$CaHPO_4$ (50-50)	30	0.559	160	17	0.38
	40	0.566	173	19	0.48
	50	0.567	176	20	0.4
Ch-$CaCO_2$ (90-10)	30	0.612	179	4.1	0.3
	40	0.614	185	3.8	0.46
	50	0.615	192	3.3	0.55
Ch-$CaCO_2$ (70-30)	30	0.585	156	7.5	0.27
	40	0.588	165	6.5	0.37
	50	0.589	178	6.5	0.46
Ch-$CaCO_2$ (50-50)	30	0.627	180	14.8	0.31
	40	0.632	184	14	0.34
	50	0.632	200	14.6	0.37
Ch-MCC (90-10)	30	0.622	136	5	0.25
	40	0.623	153	6	0.22
	50	0.624	175	4.75	0.25
Ch-MCC (70-30)	30	0.614	135	12.75	0.2
	40	0.615	168	10.5	0.22
	50	0.614	173	12	0.2
Ch-MCC (50-50)	30	0.628	158	18	0.22
	40	0.627	175	20	0.15
	50	0.626	182	16	0.17

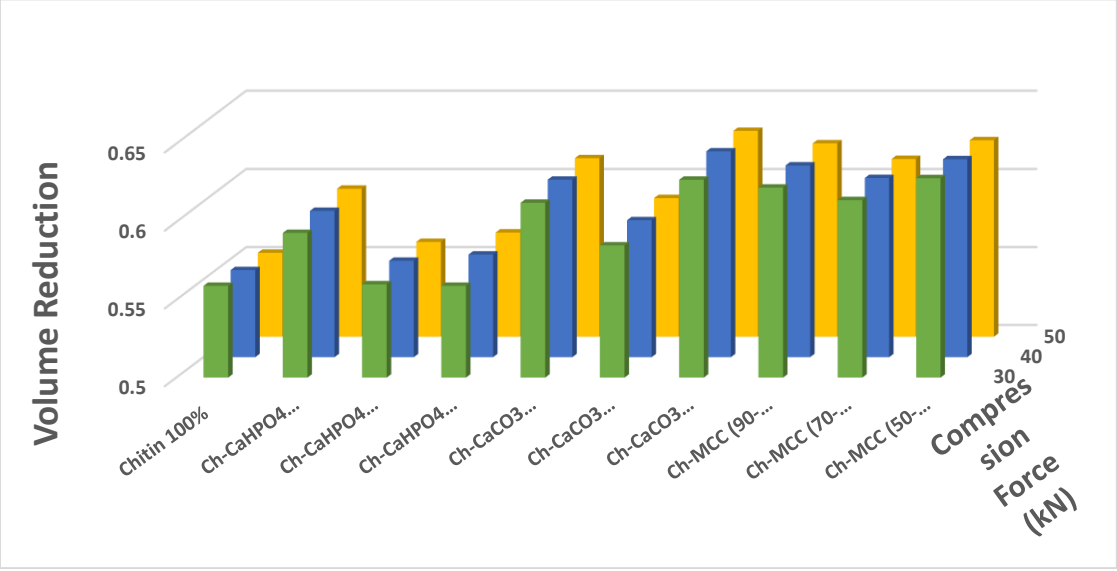

Fig. 2 : Powder volume reduction for the different chitin composites compressed at three compression forces.

Generally, an increase or a decrease in powder volume reduction is correlated to the physical status of the granules or how weak or strong these granules are. Such a statement depends on the nature of the excipient powder added to chitin before compaction (slugging) in terms of plastic/elastic or brittle character. For example, $CaHPO_4$ deforms by brittle fracture into smaller fragments that hinder the movement of the powder bed when compression force is applied (Mohylyuk, et al., 2024). In Other words, volume reduction in the chitin-$CaHPO_4$ and chitin-$CaCO_2$ case is mostly dominated by the presence of plastically deforming chitin and the movement of the small $CaHPO_4$ and $CaCO_2$ fragments. In the case of chitin-MCC composite, the two components undergo plastic deformation of the powder particles, thus exhibiting a different behavior upon compression and showing different powder volume reduction.

The tablet hardness results presented in **Figure 3** reveal a remarkable dependency of tablet hardness on the composition of the chitin composites. The results show the following hardness-value pattern per binary mixture type; Chitin < Chitin-MCC < Chitin- $CaHPO_4$< Chitin-$CaCO_2$.

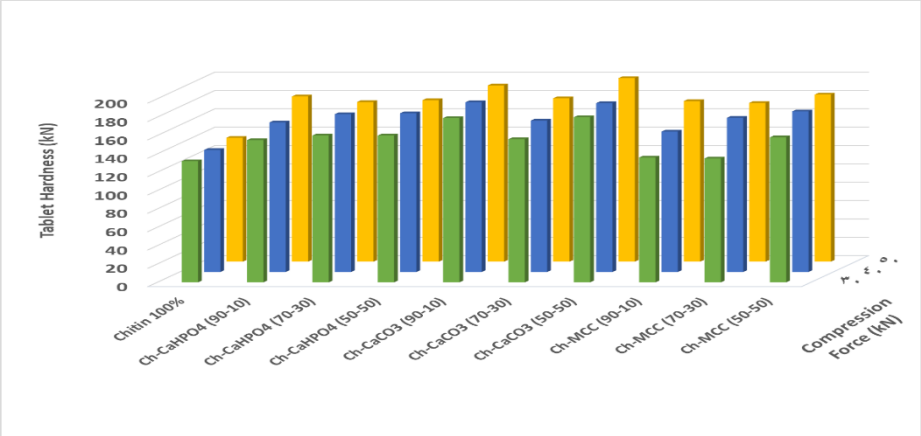

Fig. 3 : Hardness of tablets produced from the different chitin composites at three compression forces.

It can be seen that $CaHPO_4$ and $CaCO_2$ provided a remarkable increase in tablet crushing strength when processed (compacted/slugged) with chitin. This increase can be theoretically correlated to the synergetic effect taking place when a plastic/elastic material is mixed/or processed with a brittle material (Mohyluk, et al., 2024, Abu Fara, et al., 2020).
In all composites the tablet hardness increases with increasing the compression force. This can be attributed to the more compact structure of the tablets at the higher compression forces.

2.3. Compression Analysis

The analysis of the compression process was conducted using the Kawakita method to evaluate the compression characteristics of the chitin composites as detailed in Table 1. The Kawakita parameters (given in Equation 2); (a), ($1/b$; P_K), (ab), and (1-a) were used to describe the behavior of the powders when they were subjected to compression. Table 5 presents the calculated Kawakita parameters for Chitin and its various composites.

Table 5: Calculated Kawakita Parameters for Chitin and its various Composites.

Composite	*a*	*ab*	*b*	*1/b (P_K)*	*1 - a*
Chitin 100%	0.561	0.050	0.089	11.217	0.439
Ch-$CaHPO_4$ (90-10)	0.597	0.177	0.297	3.366	0.403
Ch-$CaHPO_4$ (70-30)	0.564	0.131	0.232	4.306	0.436
Ch-$CaHPO_4$ (50-50)	0.558	0.058	0.103	9.667	0.442
Ch-$CaCO_2$ (90-10)	0.593	0.123	0.208	4.808	0.407

Ch-$CaCO_2$ (70-30)	0.618	0.080	0.129	7.755	0.382
Ch-$CaCO_2$ (50-50)	0.643	0.051	0.079	12.594	0.357
Ch-MCC (90-10)	0.627	0.130	0.208	4.810	0.373
Ch-MCC (70-30)	0.618	0.136	0.221	4.529	0.382
Ch-MCC (50-50)	0.627	0.188	0.299	3.346	0.373

The Kawakita parameter (*a*) illustrated in **Figure 4** indicates the compressibility of the powder during compression. Fig 4 demonstrates that the composite of chitin and MCC exhibits a high value of (*a*), signifying considerable compressibility with minimal variation across the MCC content range of 10-50%. This finding may be advantageous from a compressibility standpoint, as it allows for a broad range of MCC content within the composite. Conversely, the chitin-$CaHPO_4$ composite displays a slight increase in compressibility only at lower levels of $CaHPO_4$. Beyond a 10% concentration of $CaHPO_4$, there is no observable impact on the compressibility of the composite. In the case of the chitin-$CaCO_2$ composite, the degree of compressibility rises as the content of $CaCO_2$ increases.

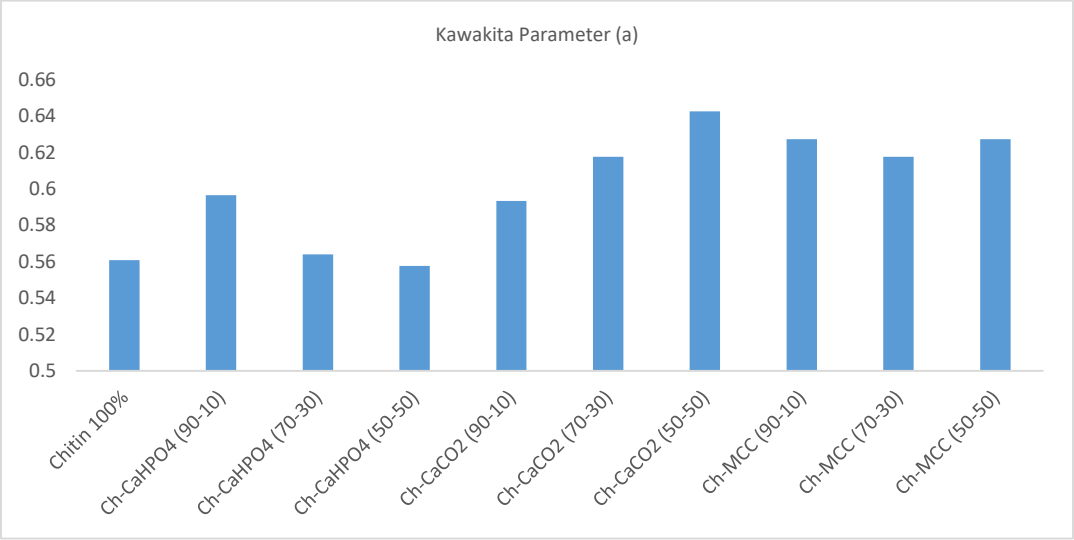

Fig. 4 : Kawakika parameter (*a*) for Chitin and its composites with $CaHPO_4$, $CaCO_2$, and MCC

Figure 5 shows the Kawakita parameter (*1/b*) or (P_K) which represents the pressure required to decrease the powder bed by 1/2 of its initial height. It can be seen from the figure that composites of chitin-$CaHPO_4$ and chitin-$CaCO_2$ show a similar trend in which P_K was reduced drastically at small content of $CaHPO_4$ and $CaCO_2$ and it increased by increasing their content in the composite. On the other hand, the composite of chitin-MCC shows an opposite trend. The trends depicted in Figure 5 regarding (P_K) indicate that the inclusion of organic plastic MCC or a low concentration of the inorganic brittle powders $CaCO_2$ and $CaHPO_4$ within the chitin composite improves its compression characteristics. Conversely, an elevated concentration of $CaCO_2$ or $CaHPO_4$ necessitates a greater compression pressure. This phenomenon can be attributed to the fact that a higher concentration of these materials results in increased fragmentation, thereby consuming a portion of the applied compression pressure (energy) in the fragmentation process.

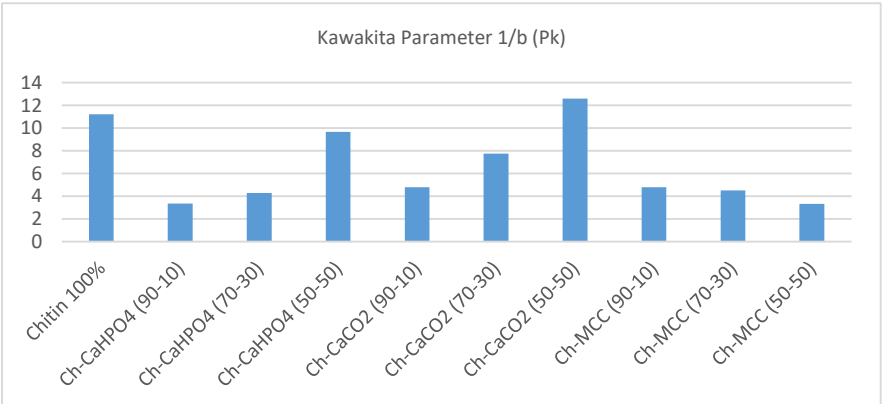

Fig. 5 : Kawakika parameter P_K ($_{1/b}$) for Chitin and its composites with $CaHPO_4$, $CaCO_2$, and MCC

The Kawakita parameter (*ab*) which is correlated to powder particle rearrangement is shown in **Figure 6.** Again, it can be noticed that composites of chitin-$CaHPO_4$ and chitin-$CaCO_2$ show similar trends and are opposite to that of the composite of chitin-MCC. These phenomena can be explained in the light of particle deformation mode.

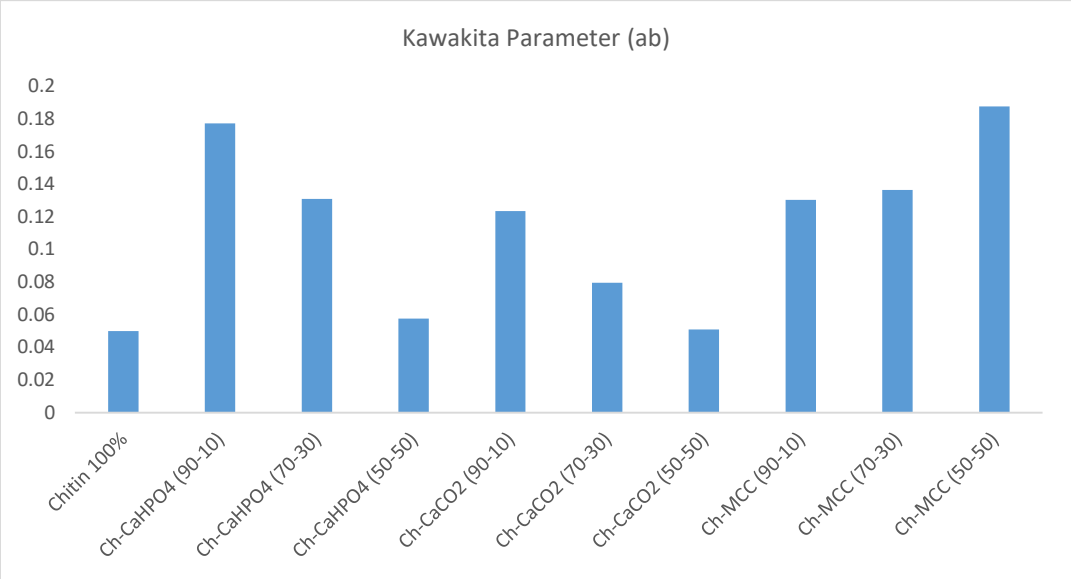

Fig. 6 : Kawakika parameter (*ab*) for Chitin and its composites with $CaHPO_4$, $CaCO_2$, and MCC

2.4. Modeling of the Composite Systems using RSM Technique

As stated earlier, examining the results data given in Table 4 showed that changes in tablet disintegration time and friability were not critical in response to changes in the input parameters. Therefore, they were not considered in the modeling analysis. Table 6 presents the data for the RSM modeling runs.

The experimental responses and the 3-dimensional fitted response surface plots obtained using Box-Behnken method are shown in Figures 7 & 8. The variation in powder volume reduction in response to changes in the input factors (Compression force, Composite composition, and Composite type) was best modeled as a quadratic model with the coefficients and statistics given in Table 7. The relation of the tablet hardness and the above-mentioned input factors was modeled with a linear model with the coefficients and statistics given in Table 8.

Table 6: The RSM Experimental Design and Results

Run	Factors				Responses	
	X1	X2	X3		Y1	Y2
	Compression Force	Chitin wt %	Additive Type	Run Description	Volume Reduction (C)	Tablet Hardness
1	-1	-1	0	30kN-50% -$CaHPO_4$	0.559	160
2	+1	-1	0	50kN-50% - $CaHPO_4$	0.566	176
3	-1	+1	0	30kN-90% -$CaHPO_4$	0.593	155
4	+1	+1	0	50kN-90%-$CaHPO_4$	0.595	180
5	-1	0	-1	30kN-70%-MCC	0.614	135

6	+1	0	-1	50kN-70%-MCC	0.614	173
7	-1	0	+1	30kN-70%-$CaCO_2$	0.585	156
8	+1	0	+1	50kN-70%-$CaCO_2$	0.589	178
9	0	-1	-1	40kN-50%-MCC	0.627	175
10	0	+1	-1	40kN-90%-MCC	0.623	153
11	0	-1	+1	40kN-50%-$CaCO_2$	0.632	184
12	0	+1	+1	40kN-90%-$CaCO_2$	0.614	185
13	0	0	0	40kN-70%-$CaHPO_4$	0.562	172

Level	**+1**	**0**	**-1**
Compression Force (kN)	50	40	30
Chitin Content (wt%)	90	70	50
Additive	$CaCO_2$	$CaHPO_4$	MCC

Examining the results shown in **Figure 7** reveals that the powder volume reduction follows the expected behavior and increases with increasing the compression force. On the other hand, an optimum value of the composite composition has to be identified for a desired powder volume reduction. In addition, the results show that the variation in the powder volume reduction is highly dependent on the composite type and its composition.

Regarding the tablet hardness, **Figure 8** shows that there is a linear relation between the hardness of the tablet and both the compression force and the chitin content in the composite. The results also reveal that the dependency of tablet hardness on the compression force is much higher than on the composite composition or type. Thus, the compression force is the dominant processing factor affecting the tablet's hardness. The chitin content might have more influence on the volume reduction. Finally, the predictions of RSM models were in agreement with the compression analysis results using Kawakita method.

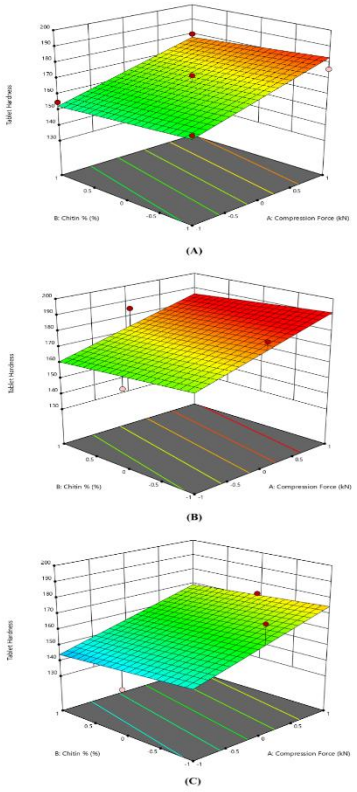

Fig. 8: Tablet hardness as a function of chitin content and compression force for Chitin-$CaHPO_4$ (A), Chitin-$CaCO_2$ (B), and Chitin-MCC (C).

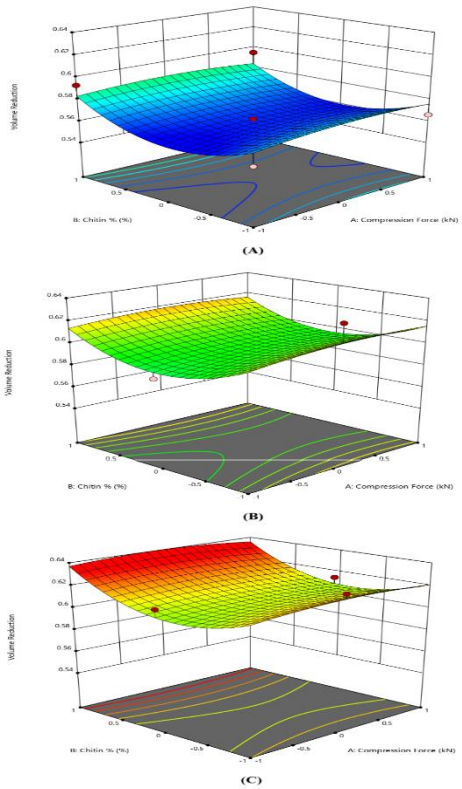

Fig. 7: a function of chitin content and compression force for Chitin-$CaHPO_4$ (A), Chitin-$CaCO_2$ (B), and Chitin-MCC (C).

Table 7: Coefficients and statistics for the model relating powder volume reduction to the inputs: compression force (A), Chitin content (B), and additive type (C)

Factor	Coefficient Estimate	Standard Error	95% CI Low	95% CI High	VIF
Intercept	0.5620	0.0218	0.4927	0.6313	
A-Compression Force	0.0072	0.0077	-0.0173	0.0318	1.00
B-Chitin %	0.0075	0.0077	-0.0170	0.0320	1.00
C-Additive Type	-0.0040	0.0077	-0.0285	0.0205	1.00
AB	-0.0065	0.0109	-0.0417	0.0282	1.00
AC	0.0070	0.0109	-0.0277	0.0417	1.00
BC	-0.0040	0.0109	-0.0387	0.0307	1.00
A^2	-0.0030	0.0144	-0.0489	0.0427	1.35
B^2	0.0145	0.0144	-0.0314	0.0604	1.35
C^2	0.0480	0.0144	0.0021	0.0939	1.35

Table 8: Coefficients and statistics for the model relating tablet hardness to the inputs: compression force (A), Chitin content (B), and additive type (C)

Factor	Coefficient Estimate	Standard Error	95% CI Low	95% CI High	VIF
Intercept	168.00	2.47	162.40	173.60	
A-Compression Force	8.12	3.15	0.9926	15.26	1.00
B-Chitin %	-2.00	3.15	-9.13	5.13	1.00
C-Additive Type	9.13	3.15	1.99	16.26	1.00

Conclusions

The characteristics of the solid dosage forms are functions of the excipient powder properties and the compression process. To achieve the desired tablet properties, an optimum combination of compression and powder parameters should be established. In the current study, different chitin-based composites were used as binary excipients. The Kawakita method was utilized to analyze the compression process and the Response Surface Methodology (RSM) was used to investigate the combination of the powder and compression process parameters. It has been found that the compression force has a dominant effect on the final tablet properties (hardness and volume reduction). The composite composition and type have a remarkable effect on the powder volume reduction. This effect could be attributed to the synergy effect between different modes of deformation of binary excipients. In this regard, there is a great impact of brittle excipients added to a plastically deforming excipient in improving the tabletability of a compacted mixture of Chitin-$CaHPO_4$ and Chitin-$CaCO_2$. The predictions of RSM models were in good agreement with the compression analysis results using Kawakita method.

Nomenclature

V_0 = Initial volume of the powder [m^3]

V = final volume of the compressed powder [m^3]

C =Powder volume reduction [fraction]

ρb =Bulk density [kg/m3]

ρc =Compact density [kg/m3]

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