RESEARCH ARTICLE

Processing and Evaluation of Dicalcium Phosphate and Lipid Comprised Co-Processed Excipient

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Received: 20th Dec, 2024; Revised: 23rd Jan, 2025; Accepted: 12th Feb, 2025; Available Online: 25th March, 2025

ABSTRACT

The adaptability of co-processed excipients significantly supports the direct compression process in pharmaceutical formulations. This research aimed at developing and assessing a co-processed excipient, made from dicalcium phosphate and lipid excipients, using hot melt granulation to improve drug delivery. Four lipids—glyceryl monostearate, stearic acid, cetyl alcohol, and palmitic acid—were investigated to process raw dicalcium phosphate. Key parameters such as powder flow properties and density were analyzed to select the optimal lipid combination and concentration. Advanced analytical techniques, including DSC, X-ray diffraction, FT-IR, and SEM, were used to assess the compatibility and stability of the co-processed excipients. The DSC analysis of the caffeine tablet formulation (CA 90:10) showed a melting point of 275.74 ºC, while FT-IR spectra indicated no interaction between caffeine, cetyl alcohol, and other excipients. X-ray diffraction analysis confirmed the drug's crystalline structure, showing distinct peaks in the formulation's diffractogram. SEM images displayed a porous and rough surface morphology with microcapillaries, contributing to rapid water absorption and wicking. The performance of the developed dicalcium phosphate co-processed excipient was tested by formulating caffeine immediate-release tablets. The lipid-based excipient demonstrated enhanced drug solubility, dissolution, and bioavailability. The study concluded that lipid co-processed excipients, particularly cetyl alcohol, play a vital role in improving drug delivery systems. This research lays the groundwork for future developments in optimized drug formulations using co-processed excipients.

Key words: Dicalcium Phosphate, Co-Processed excipient, Melt granulation, Caffeine, Immediate Release Tablet

How to cite this article: Shravasti Mane, Nishikant Shinde, Dhanyakumar Chougule, Santosh Gejage. Processing and Evaluation of Dicalcium Phosphate and Lipid Comprised Co-Processed Excipient. International Journal of Drug Delivery Technology. 2025;15(1):27-35. doi: 10.25258/ijddt.15.1.4

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Tablets and capsules stand out as widely embraced dosage forms, prized for their multitude of advantages. These benefits encompass patient compatibility, precise dosing, streamlined large-scale manufacturing, cost efficiency. Integral role of excipients in bolstering manufacturability, enhancing stability, ensuring safety, and optimizing product performance is universally acknowledged. According to the "International Pharmaceutical Excipients Council (IPEC)," excipients that are co-processed as are blends of two or more pharmacopeial or non-pharmacopeial excipients, carefully designed to create physical modifications that go beyond simple physical mixing, all while avoiding significant chemical alterations.[1] Many active pharmaceutical ingredients (APIs) used in various pharmaceutical formulations such as powders, granules, tablets, and capsules exhibit poor flow properties, which can complicate manufacturing processes and product consistency. This challenge drives the ongoing search for innovative excipients that are not only cost-effective but also specifically engineered to improve particle size control and distribution. By optimizing micromeritics and compressibility, co-processing can enhance flowability, making handling and processing of the material smoother. Additionally, it increases the potential for dilution, allowing higher proportions of excipients to be incorporated without compromising tablet integrity. Furthermore, co-processed excipients reduce the formulation's sensitivity to lubricants, improving the performance of the final product.[2] The advantages of co-processing are numerous: it significantly enhances the flow characteristics of materials, making manufacturing more efficient. It also improves compressibility, allowing for better tablet formation under pressure. The approach elevates the dilution potential, enabling formulators to incorporate larger volumes of APIs and excipients. Moreover, co-processing streamlines the manufacturing process by reducing steps and improving consistency, making it a cost-effective and efficient solution for pharmaceutical development.The principle of co-processing involves the careful selection and modification of excipients to enhance their functional performance in pharmaceutical formulations. The process begins with an initial screening of excipients based on their material attributes and functional requirements. A critical step is the selection of suitable excipients for co-processing, which must be done with precision to ensure compatibility and

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Table 1: Three comparative batches of Co-processed excipients with different ratios of Lipid Excipients

Batches				Ratio in (w/w%)	Weight (gms)
DCP + GMS	DCP + SA	DCP + CA	DCP + PA		
Batch No. A1	Batch No. B1	Batch No. C1	Batch No. D1	100 gms	
Dicalcium-phosphate	Dicalcium-phosphate	Dicalcium-phosphate	Dicalcium-phosphate	95	95
Glyceryl Monostearate	Stearic Acid	Cetyl Alcohol	Palmitic Acid	5	5
Batch No. A2	Batch No. B2	Batch No. C2	Batch No. D2	100 gms	
Dicalcium-phosphate	Dicalcium-phosphate	Dicalcium-phosphate	Dicalcium-phosphate	90	90
Glyceryl Monostearate	Stearic Acid	Cetyl Alcohol	Palmitic Acid	10	10
Batch No. A3	Batch No. B3	Batch No. C3	Batch No. D3	100 gms	
Dicalcium-phosphate	Dicalcium-phosphate	Dicalcium-phosphate	Dicalcium-phosphate	85	85
Glyceryl Monostearate	Stearic Acid	Cetyl Alcohol	Palmitic Acid	15	15

Table 2: Working Formula using Caffeine as a model drug

Sr. No.	Content	Specification	Role in Tablet	Amount (mg/tab).
1.	Caffeine	IP	Model API	150
2.	Co-processed excipient BATCH C2	IH	Buking agent	35.5
3.	Sodium starch glycolate	IH	Super Disintegrating agent	10
4.	Silicon dioxide	Tech	Glidant	1.50
5.	Starch	Food	Disintegrating agent	1
6.	Magnesium stearate	Tech	Lubricant	1
7.	Talc	Tech	Lubricant	1

performance. Determining the optimal proportions of various excipients is key to achieving the desired results. Additionally, choosing the appropriate particle size and other physicochemical traits, such as solubility and flowability, plays an important role. Adjustments may be made to the particle size and physical properties of the excipients to meet specific formulation needs. Finally, choosing a suitable process formulation is critical for ensuring the efficiency and efficacy of co-processed excipients.[3]

PCA which broadly knowns as Principal Component Analysis which is a very important statistical method routinely utilised in the pharmaceutical industry to simplify and interpret complex datasets by reducing their dimensionality while retaining the most critical variations in the data. This method proves highly valuable in various applications. In formulation development, PCA helps identify key factors that influence product performance, enabling more efficient optimization. In quality control, it aids in detecting subtle variations that could affect product quality. PCA is also employed in process optimization to streamline manufacturing by identifying important process parameters. It supports multivariate analysis, offering insights into the relationships between multiple variables. By analysing batch-to-batch variability, PCA helps ensure consistency in production.

In dissolution and bioequivalence studies, it assists in evaluating the performance of drug products. Furthermore, PCA finds application in biopharmaceutical analysis, providing insights into complex biological data.[4] Lastly, its ability to transform large datasets into easily interpretable visualizations makes PCA an invaluable tool for data exploration and decision-making in pharmaceutical research and development. Overall, PCA is a valuable tool in pharmaceutical research and development, helping scientists and researchers make sense of intricate datasets and uncover meaningful insights that can influence formulation, manufacturing, quality control, and regulatory compliance. Present research work highlights the utilisation of lipids as potential meltable binder for making of co-processed excipients and its assessment of process parameters using caffeine as model drug for development and evaluation of tablets.

MATERIALS AND METHODS

Materials

Caffeine anhydrous drug was sourced from Research Lab Fine Chem Industries Islampur, Sangli. Rest remaining other chemicals as Dicalcium Phosphate, Glyceryl Monostearate, Stearic Acid, Cetyl Alcohol, Palmitic Acid used were of AR grade.

Rationale for selection of excipients

Excipient was selected based on its characteristics, such as particle size, moisture content, shape, flow behaviour, etc. The excipients were chosen based on prior knowledge and experience about excipients, including the Co-processed excipients that are already available for purchase and their suitability for use with particular model pharmaceuticals. The excipients GRAS listing should have served as the basis for the excipients level.

Formulation of Co-processed excipients by Hot Melt Granulation (HMG)

Dicalcium phosphate with varying amounts of lipid excipients such as glyceryl monostearate, stearic acid, cetyl

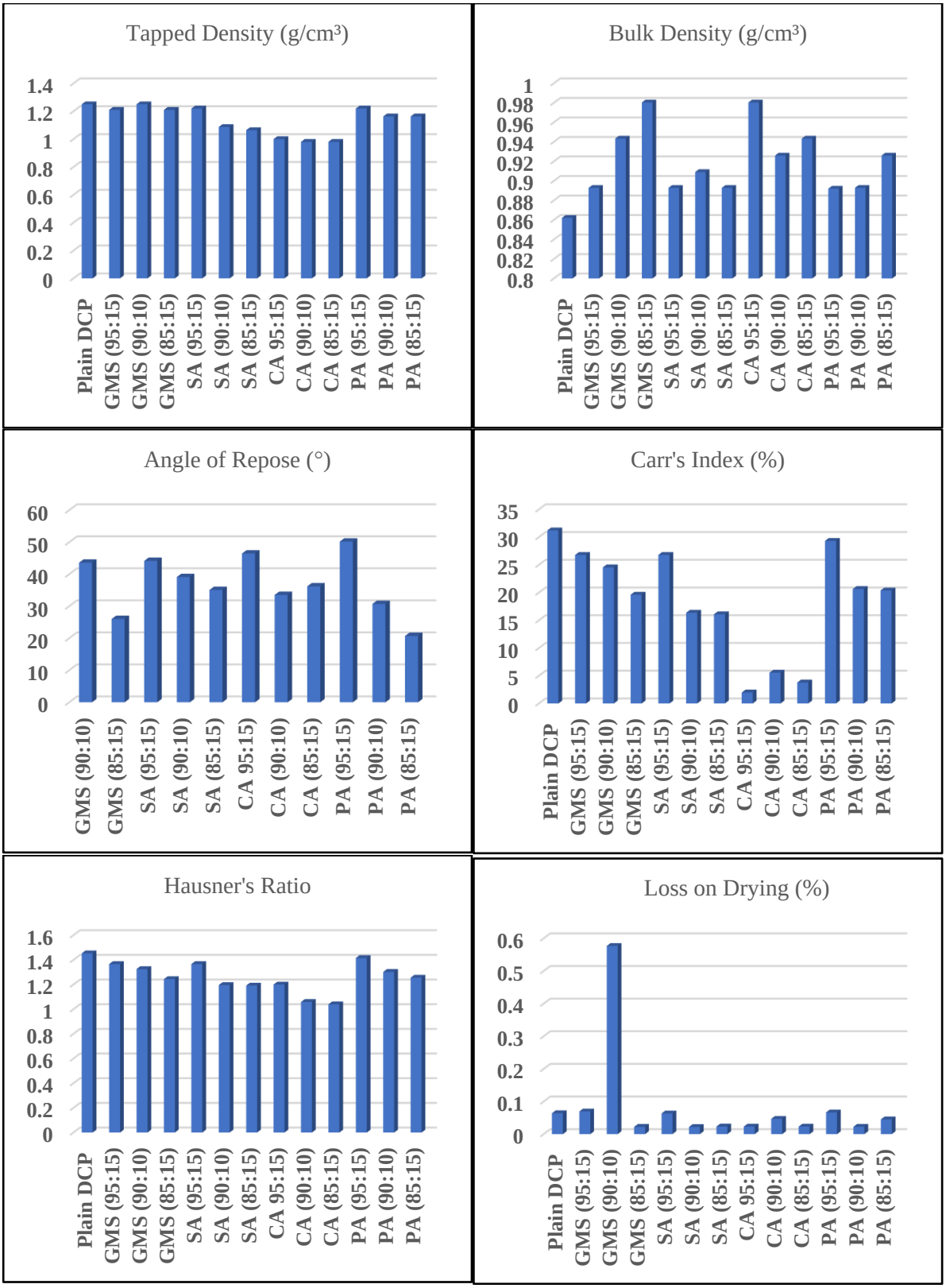

Figure 1: PCA Analysis of Flow Properties for Co-Processed Excipients

alcohol, and palmitic acid were used in subsequent preliminary trials (Table 1).

Developing final co-processed excipient involves two steps. In first phase, dicalcium phosphate and various quantities of lipid excipients were used in melt granulation, which was done in hot air oven at particular temperature. Granules were then dried at room temperature for an hour. In following phase, ratios of fatty excipients and dicalcium phosphate were calculated. The final co-processed excipients were determined to have intended co-processed excipient property—suitability for direct compression. Three sets of co-processed excipient were manufactured

Table 3: Evaluation parameters for Optimized Batch of co-processed excipients

Batch	C2
Ratio w/w(%)	90:10
Bulk density (g/ml)	0.9259
Tapped density (g/ml)	0.9803
Angle of Repose	33.52
Carr's index	5.5493
Hausner's ratio	1.0587
Loss on drying	0.04678

Table 4: Flow properties of blends of Caffeine tablets using CPE (CA 90:10)

Batch	Results
Bulk density (g/ml)	0.9820
Tapped density (g/ml)	1.1
Angle of Repose	32
Carr's index	10.72
Hausner's ratio	1.12
Loss on drying	0.0641

Table 5: Caffeine 200 mg tablet characterization of Formulation Batch C2

Parameters	Results
Physical Appearance	White coloured round tablets
Thickness (mm)	4.2
Hardness (kp)	5.4
Friability Test	0.92
Weight Variation (mg)	210
Disintegration time (mins.)	6mins. 20secs.

who's formula was referred in tablet no -1 each with varying proportions of Dicalcium Phosphate and lipid excipient as Glyceryl Monostearate, Stearic Acid, Cetyl Alcohol, Palmitic Acid for purpose of comparison.[5]

Application of Principle Component Analysis (PCA) for Selection of Optimum Lipid Based Co-Processed Excipient Product

Based on PCA studies the major parameters to consider for selecting most promising meltable lipid binder are improvement in densities, flow properties and minimum loss on drying values. In the development of co-processed excipients, four lipids—Glyceryl monostearate(GMS), stearic acid(SA), palmitic acid(PA), and cetyl alcohol(CA)—were evaluated, with cetyl alcohol showing the most promising results based on predetermined parameters like flow properties and compressibility. The concentration of the meltable lipid, cetyl alcohol, played a crucial role in formulation performance. It was observed that higher lipid content, when combined with dicalcium phosphate, led to increased sticking to both the upper and lower tablet punches during compression. To optimize density and flow parameters, three concentration ranges of cetyl alcohol—5%, 10%, and 15%—were selected for further development trials. These trials aimed to balance flowability, compressibility, and reduce sticking, improving the overall performance of the co-processed excipient[6].

Assessment of Lipid Based Co-processed excipient (CPE)

Analysis of Flow Properties of Lipid Based Co-Processed Excipient

Table 6: Evaluation parameters of formulation batches for Cetyl Alcohol

Formulation Batch Code		Batch C2
Evaluation Parameters	PhysicalAppearance	White to off white coloured round tablets
	Thickness of Tablet ± S.D. (mm)(n = 6)	2.1
	Hardness of Tablet ± S.D. (kp)(n = 6)	4.3
	Friability (%)	0.92
	Average Weight (n = 20)	208
	DT (mins.)	5mins. 47secs.

Table 7: % of drug release profile of tablet of Formulation Batch C2

Time Point (Mins.)	% DR of Batch C2
5	2.25
10	6.75
20	18
30	35.4375
45	47.25
60	56.25
90	74.25
120	96.75

The lipid-based Excipients that are co-processed were tested for their pre-compression properties, including bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose, loss on drying, and particle size analysis using a sieve shaker.

Fourier Transform-Infrared Spectroscopy (FT-IR)

The caffeine infrared spectrum was captured using a Fourier Transform Infrared spectrophotometer (Bruker), with % transmittance measured within the spectral range of 4000.00-200.00 cm-1, using a 4 cm-1 resolution and a scanning range of 40 cm-1.

X-Ray Diffraction Studies (pXRD)

Powder X-ray diffraction (pXRD) analysis was conducted using the Bruker Model D8 Advance. The sample was uniformly applied to an amorphous silica holder with a low-background design and positioned on the goniometer's sample stage. The instrument was operated in Bragg-Brentano (B-B) geometry, with data collected under a current of 40 mA and voltage of 40 kV.

Surface Morphology studies using SEM

Scanning electron microscopy (SEM) is an advanced technique used for detailed surface analysis in material characterization. In this study, the surface morphology of the extruded product was analyzed using a JEOL 390LV scanning electron microscope (Tokyo, Japan). A small extrudate, 10.00 mm in diameter, was affixed to specimen stubs with carbon tape, then coated with a thin layer of gold using the JFC 1600 ion sputter coater. The sputtering process enables quick and effective gold coating, improving the surface's visibility.

Melting Point Studies using DSC

Thermograms were obtained using a DSC analyzer (SDT Q600 V20.9 Build 20) in the temperature range of 30–

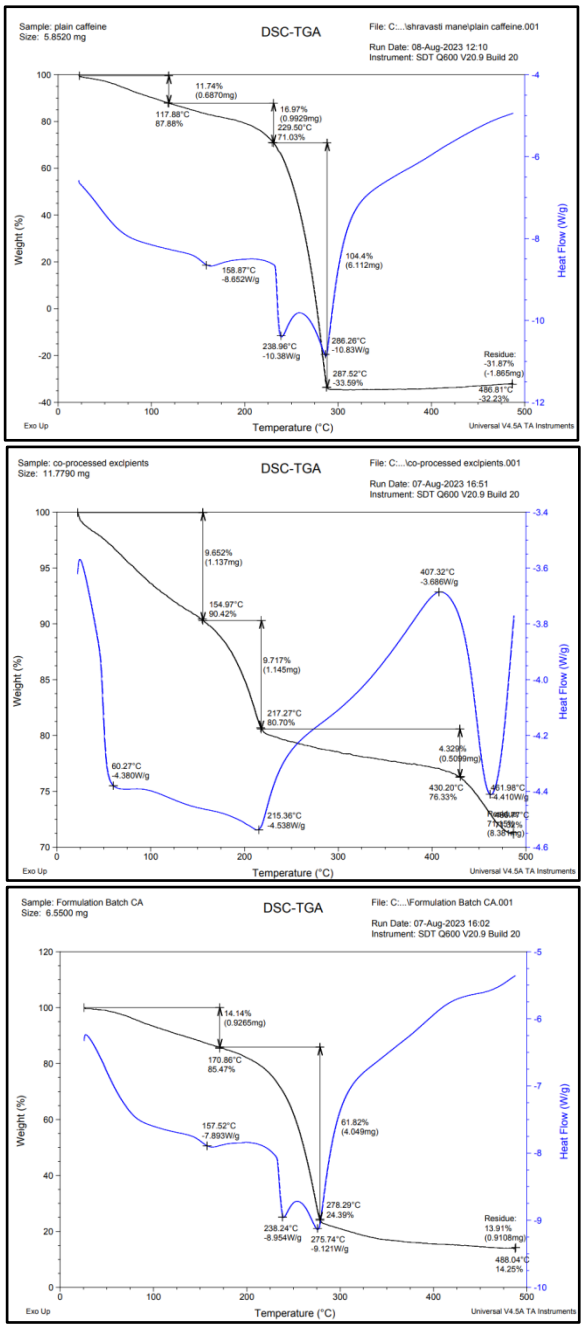

Figure 2: DSC thermogram of a. Caffeine, b. Co-processed excipients (CA 90:10), c. Caffeine Tablet Formulation (CA 90:10)

300°C. A 2–3 mg sample was heated at a rate of 10°C/min in sealed aluminum crucibles, with a nitrogen flow rate of 100 mL/min. Standards for zinc and indium were used to calibrate the DSC. For thermogravimetric analysis (TGA), a Shimadzu thermobalance (TGA-50) was utilized. Samples (3 mg) were heated at 10°C/min in open platinum crucibles under nitrogen flow (100 mL/min) from 30–600°C, calibrated with calcium oxalate. The thermal data was processed using TA60 software.

Development and Assessment of Immediate Release Caffeine Tablets by Prepared Co-processed excipients (CPE)

Table 8: Spectrum interpretation of Caffeine

Sr. No.	Functional groups	Observed wavelength (cm^{-1})	Reported wavelength (cm^{-1})
1.	-C=N ring stretching	1652.37	1661.29
2.	Aromatic C-H stretching	3094	3111.18 to 2953.02
3.	C=C stretching	1546	1548.84
4.	C-N stretching	1357.21	1350 to 1399

Table 9: Spectrum interpretation of Cetyl Alcohol

Sr. No.	Functional groups	Observed wavelength (cm^{-1})	Reported wavelength (cm^{-1})
1.	Intermolecular H bonds	3317.16	3324
2.	CH_2 Streching	1461.91	1468
3.	CH_2 Streching	1056.03	1060
4.	CH_2 Streching	721.54	724

Table 10: Spectrum interpretation of compatibility study of Co-processed excipients (CA 90:10)

Sr. No.	Functional groups	Observed wavelength (cm^{-1})	Reported wavelength (cm^{-1})
1.	CH_2 Streching	1061.54	1060
2.	C-N Streching	1346	1350 to 1399

To assess the efficacy of the co-processed excipient, tablet compression was carried out using caffeine as a model medication. Immediate release tablets were the product that was promoted for the drug substance. Micronized drug substances are employed because they have a limited solubility in water.

Formulation of Caffeine tablets by Direct Compression (DC)

The dispensing process involves accurately measuring and dispensing the active pharmaceutical ingredient (API) and excipients needed for the formulation. Once the ingredients are dispensed, the sifting stage begins, where caffeine, the model drug, is passed through a #40 sieve (Table 2). Similarly, excipients such as co-processed sodium starch glycolate, silicon dioxide, and starch are sifted individually through the same sieve size. Following sifting, the ingredients are mixed thoroughly for 5 minutes to ensure a uniform blend. For the lubrication stage, magnesium stearate and talc are weighed, filtered through a #80 sieve, and then added to the blend, which is further mixed for another 5 minutes. Finally, the lubricated blend is crushed into tablets using a tablet compression machine, finishing the procedure.[7]

Evaluation of Pre-Compressional Parameters

The blend used to develop immediate-release caffeine tablets was assessed for pre-compression characteristics such as bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose, and loss on drying., and particle size analysis using a sieve shaker. Tablet compression was carried out based on the powder's flow properties and compressibility index values.

Evaluation of Post-Compressional Parameters

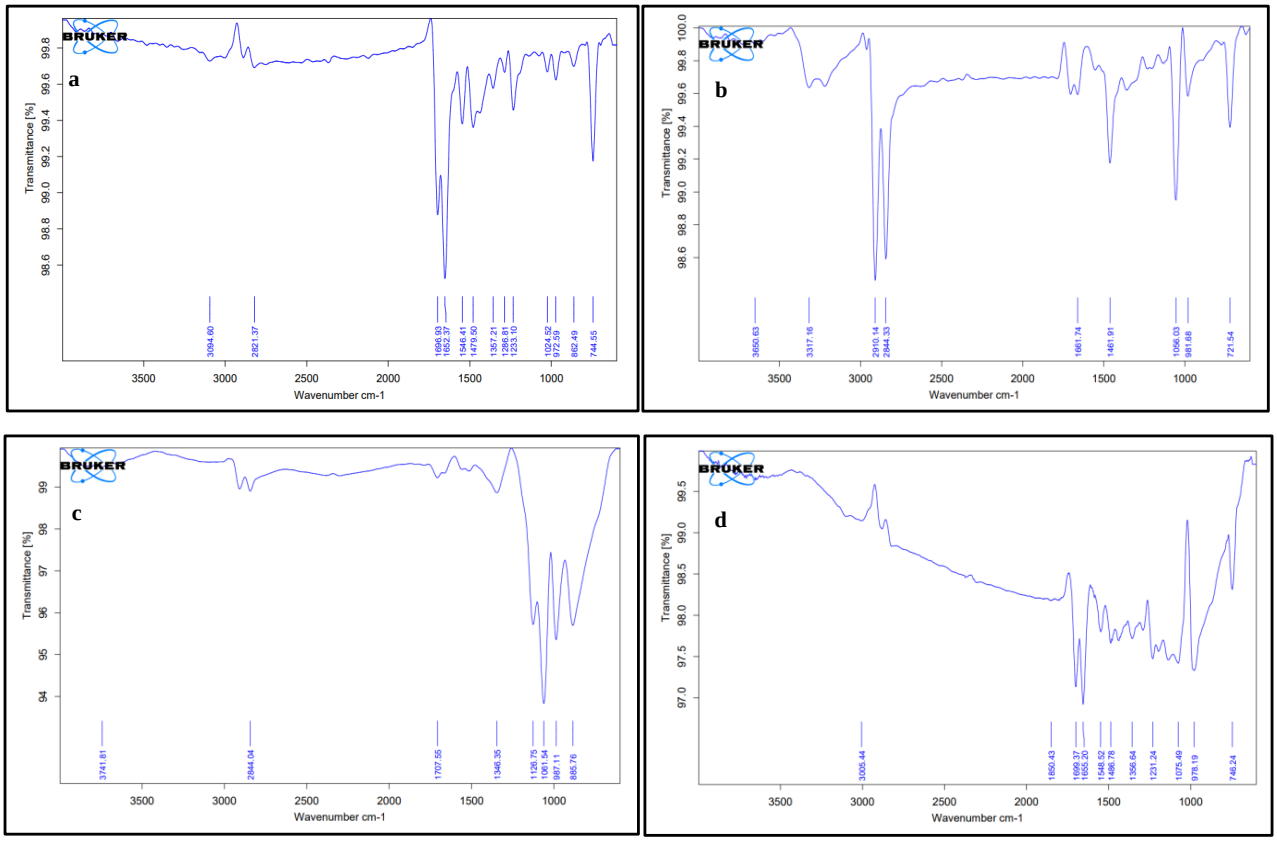

Figure 3: IR Spectrum of a. Caffeine, b. Cetyl Alcohol, c. Co-processed excipients (CA 90:10), d. Caffeine Tablet Formulation (CA 90:10)

Table 11: Spectrum interpretation of compatibility study of Caffeine Tablet Formulation (CA 90:10)

Sr. No.	Functional groups	Observed wavelength (cm^{-1})	Reported wavelength (cm^{-1})
1.	C-N Streching	1356.64	1350 to 1399
2.	CH_2 Streching	1489.78	1450 to 1500

The reference and compressed tablets were evaluated for appearance, weight, dimensions, hardness, thickness, and disintegration time. The tablets were stored in a dual-layer polybag, then sealed in a triple-layer Aluminum bag containing silica gel to protect them for subsequent testing.

Dissolution Studies

An in vitro dissolution study of pure caffeine and tablets containing physical mixtures (PM) was carried out using the USP Dissolution Apparatus II (Paddle) at 75 rpm in a phosphate buffer (pH 6.8). Three tablets were randomly selected and placed in 900 mL of dissolution medium. To maintain volume, samples were taken at 5-minute intervals and replenished with fresh phosphate buffer. After passing through 0.45 µm Whatman filter paper, the samples were examined. by UV-Visible spectrophotometry at 273 nm. The dissolution experiments were repeated three times[8].

Stability Studies

Studies on short-term stability were conducted on the formulated caffeine tablets. The tablets were stored at room temperature in a vacuum-sealed desiccator. After 30 days, their physicochemical stability was evaluated using pXRD, DSC, TGA, and FTIR techniques, focusing on drug content and solid-state characteristics.

RESULTS AND DISCUSSION

Many active pharmaceutical ingredients (APIs) used in formulations such as powders, granules, tablets, and capsules often exhibit poor flow properties, complicating both manufacturing and product consistency. To address this issue, there is a continuous pursuit of innovative excipients that are not only cost-effective but also designed to improve particle size control and distribution. Co-processing techniques optimize micromeritics and compressibility, enhancing the flowability of materials and making them easier to handle and process. This approach also increases the potential for dilution, enabling higher proportions of excipients to be used without compromising the tablet's integrity. Additionally, co-processed excipients minimize the formulation's sensitivity to lubricants, resulting in improved overall product performance. In the present study, Glyceryl Monostearate, Stearic Acid, Cetyl Alcohol, and Palmitic Acid were evaluated as meltable binders for developing a co-processed excipient specifically for dibasic calcium phosphate. The goal was to improve the physicochemical properties, including bulk density, tapped density, Carr's Index, and angle of repose. The optimized lipid-based co-processed excipient was then utilized to formulate and assess immediate-release caffeine anhydrous tablets. Caffeine anhydrous, a highly water-soluble drug, served as the model drug for this study.

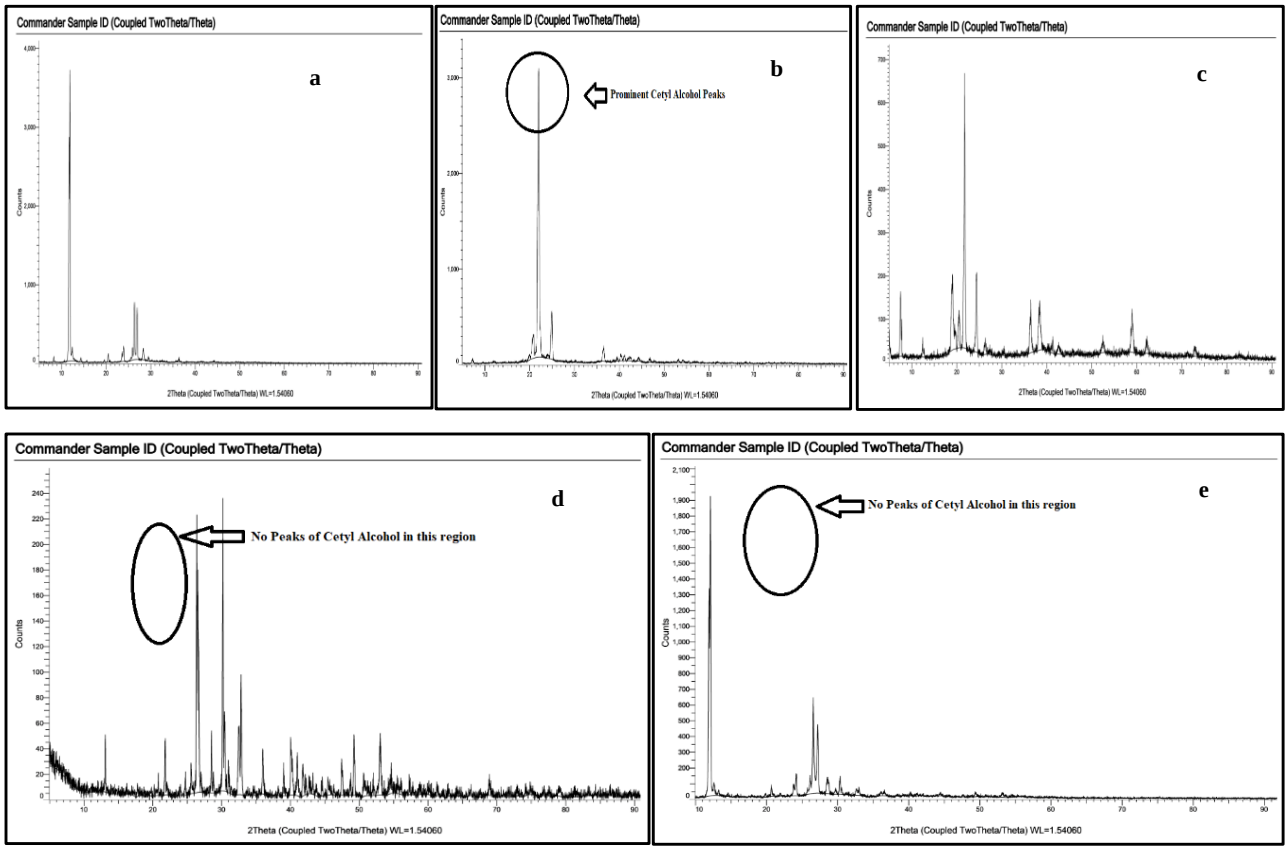

Figure 4: pXRD spectrum a. Caffeine, b. Cetyl Alcohol, c. Palmitic Acid, d. Co-processed excipients (CA 90:10), e. Caffeine Tablet Formulation (CA 90:10)

Table 12: Stability study of tablet of Formulation Batch C2

Test	First day	After 1 Month	After 3 Months
Description	White to off white coloured round tablets	White to off white coloured round tablets	White to off white coloured round tablets
Thickness	4.2	4.25	4.31
Hardness	5.4	5.42	5.50
Disintegration Time	6 Mins. 20secs.	5 Mins. 20secs.	5 Mins. 40secs.

Evaluation of Flow Properties of Lipid Based co-processed excipient

Based on PCA studies the major parameters to consider for selecting most promising meltable lipid binder are improvement in densities, flow properties and minimum loss on drying values. Out of the four lipids only cetyl alcohol (CA) shows promising results as per predetermined parameter values. The concentration of meltable lipid also plays very crucial role in the development of co-processed excipient. The higher the content of lipid with the dicalcium phosphate more sticking to upper as well lower tablet punches were reported. Based on improvement in density and flow parameters three concentration ranges *5%, 10% and 15%* were selected for further development trials (Figure 1, Table 3 to Table 7).[9]

Melting Behaviour Studies using DSC

The DSC endotherm of neat caffeine API shows a sharp endothermic peak at around 238.96 ºC due to melting. The sharpness and height of the peak can provide insights into purity and crystallinity of the sample. Data of analysis showed that co-processed granules at 215.36 ºC were in crystalline state, and crystalline peak of caffeine, was observed in Caffeine Tablet Formulation (CA 90:10) 275.74 ºC Peak (Figure 2).

FT-IR Fingerprint Studies

The IRspectra revealed consistent wavelengths between spectra derived from their compound formulation of Co-processed excipients and drug itself. These findings strongly suggest absence of any interaction among caffeine, cetyl alcohol, and accompanying excipients. Consequently, it can be inferred that these components are mutually compatible. This underscores viability of employing caffeine alongside lipid excipient, cetyl alcohol, in developing Co-processed excipients for pharmaceutical applications (Figure 3, Table 8 to 11).

Powder X-Ray Diffraction (pXRD)

The co-processed excipient only showed significant peaks of cetyl alcohol at 26.58°, 26.46°, 26.40° and 24.90°, 24.94° disappeared in Caffeine Tablet Formulation (CA 90:10). The pXRD analysis indicated that cetyl alcohol exists in an amorphous state, which facilitates rapid disintegration and smooth compression. Conversely, increased crystallinity of cetyl alcohol diminished the blend's compaction properties,

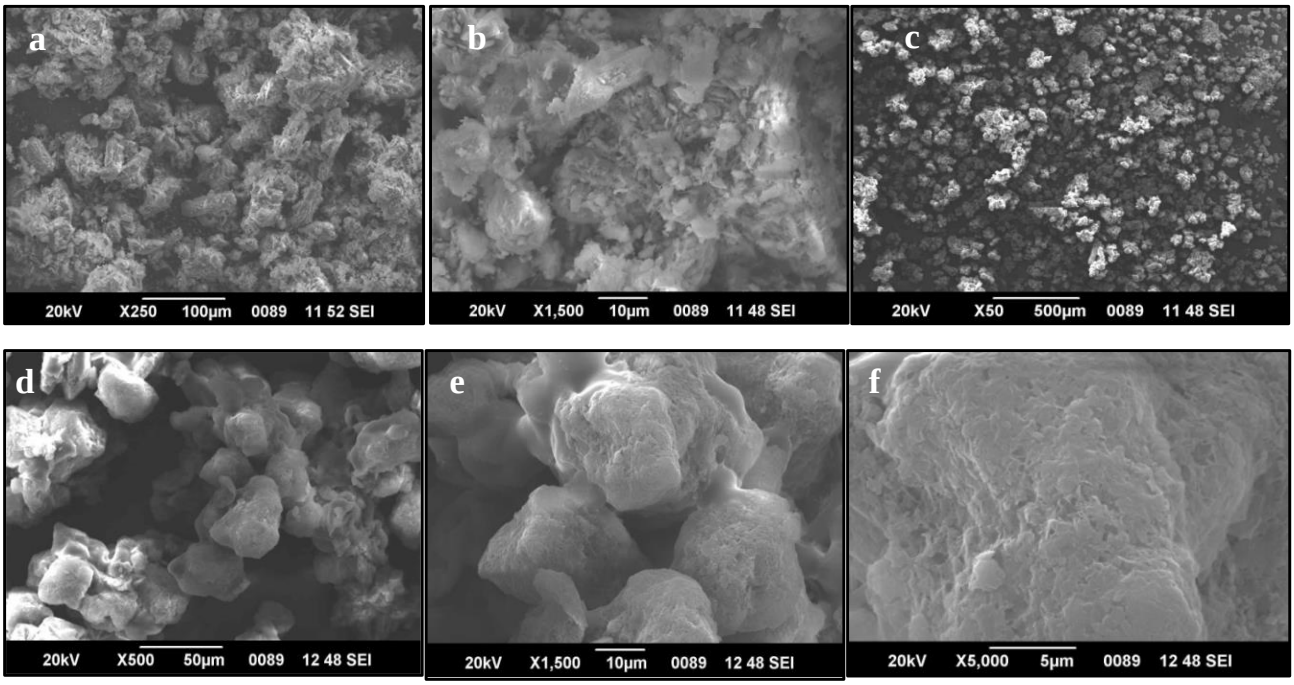

Figure 5: a. SEM of Dicalcium phosphate (X250), b. Dicalcium phosphate (X5000), c. co-processed granules (X50), d. co-processed granules (X500), e. co-processed granules (X1500), f. co-processed granules (X5000)

resulting in longer disintegration times and delayed dissolution (Figure 4).[10]

Surface Morphology Studies using SEM

The figure 5 display surface characteristics of both individual excipients and Co-processed excipients. Co-processed excipient exhibited surface characterized by porosity and rough texture. Upon zooming in at 5000X magnification, surface images of Co-processed excipients unveiled microcapillaries. These structures play significant role in facilitating rapid water absorption and capillary action. Notably, surface morphology of Co-processed excipients showed distinct alteration in characteristics of Dicalcium phosphate component. Notably absent were cubic crystal formations typically associated with Dicalcium phosphate[11,12].

Stability Studies

As per ICH guidelines, accelerated stability study was performed on prepared Optimized (co-processed excipients by using model drug caffeine) batch C2[13,14]. Optimized batch C2 has acceptable assay and cumulative drug release which can further progressed to be evaluated in *in vivo* study (Table 12)[15,16].

CONCLUSION

In summary, the development and assessment of co-processed excipients composed of lipids, incorporating ingredients like glyceryl monostearate, stearic acid, cetyl alcohol, and palmitic acid, have yielded promising outcomes in enhancing drug delivery. Particular attention was given to cetyl alcohol as a crucial element in the formulation. Utilizing caffeine as a model drug, this research highlighted the potential of these lipid-based excipients in enhancing drug solubility, dissolution, and overall bioavailability. The tablet for Formulation Batch C2 was manufactured using the dry granulation technique. Various evaluation parameters, including appearance, thickness, weight consistency, hardness, and friability, were employed to assess the compressional formulations. All the evaluation outcomes for the Formulation Batch C2 tablet fell within acceptable ranges. The pre-compression tests conducted on the tablet yielded satisfactory results. Specifically, the tablet's thickness, hardness, weight consistency, and friability all met the acceptable criteria. Notably, an enhanced formulation achieved an impressive 96.75% *in vitro* drug release within just 2 hours (120 minutes).

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