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RESEARCH ARTICLE

EXPLORATION OF NOVEL CO-PROCESSED MULTIFUNCTIONAL EXCIPIENT FOR TABLET DOSAGE FORM

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Abstract:
The aim of the present investigation is to formulate novel co-processed multifunctional excipient for tablet dosage form. Co- processed particles of chitosan, microcrystalline cellulose (MCC) and aerosil-200 were fabricated by wet granulation technique to be used as a directly compressible excipient in tablet formulation. The developed co-processed excipients (CPE) were evaluated for their excipient related and dosage form related parameters. As expected, all the prepared batches exhibited acceptable angle of repose (<35^0) and quick disintegration time (<1min). The "intimate" physical association between chitosan, MCC and aerosil-200 has created an insoluble, hydrophilic, highly absorbent material, resulting in superiority in water uptake, water saturation for gelling formation, and compactability among other superdisintegrants. The developed CPE could be act as a superdisintegrant and pharmaceutical filler at the same time.

Keywords: Co-processed excipients (CPE), direct compression, superdisintegrants

Introduction

Oral route of drug administration is perhaps the most appealing route for the delivery of drugs [1]. Among the various dosage forms administered orally, the tablet is a preferred dosage form by industrial pharmacists because of its known advantages and constant innovations both in the adjuvants and equipments. Direct compression technique has been one of the well-accepted methods of tablet manufacturing. A wide range of materials from various sources has been developed and marketed as directly compressible vehicles such as lactose, starch, cellulose derivatives, inorganic substance, polyalcohols, and sugar-based materials. In addition to the development of directly compressible excipients by the modification of a single substance, co-processing of 2 or more components can be utilize to produce composite particles or co-processed excipients (CPE).

The CPE are introduced to achieve better powder characteristics and tableting properties than a single excipient or the physical mixture of excipients [2].

Nearly all the co-processed excipients for direct compression are manufactured by granulation, agglomeration, co-crystallization, or spray-drying [3]. Chitosan, as an excipient has received considerable attention in tablet disintegration application [4, 5, 6]. Tablets containing chitosan show faster disintegration and greater dissolution than those containing sodium starch glycolate and croscarmellose sodium. However, chitosan powder shows poor bulk density and therefore poor flowability and compressibility, when large-scale handling of pharmaceutical blends is desired [7].

Among directly compressible fillers, microcrystalline cellulose (MCC) is to be considered as the most compressible and has the highest dilution potential. However, because of the high cost and poor fluidity when compared with that of most other direct compression vehicles, it is generally not used as the only diluent in tablet formulations but is usually combined with other direct compression vehicles to improve the flowability and reduce the cost of the product. Because of its high binding and good disintegrating properties, MCC is of interest to be combined with other less compressible excipients as an added component in CPE [8].

To overcome such weaknesses of both of them, their physical mixture has been modified by selective adsorption of aerosil-200 over them. The choice of aerosil-200 was based upon its unique high water absorption capacity and surface modification property when being co-processed with polymers. In practice, aerosil-200 (colloidal silicon dioxide) was proven to be an efficient additive for the processing of MCC and carboxymethyl cellulose [9, 10, 11]. Thus, aerosil-200 is an efficient candidate for the development and modification of highly compressible, highly compactable, and disintegrable excipients. A combination of chitosan, microcrystalline cellulose, and aerosil-200 has not been yet explored either by industry or by researchers.
The objective of the present investigation was to develop novel CPE of chitosan, MCC and aerosil-200 using wet granulation technique.

MATERIALS AND METHODS

Materials

Paracetamol was a gift from Relax Pharmaceuticals Ltd, Vadodara, India. MCC (Avicel PH-101), polyvinyl pyrolidone (PVP K-30), sodium starch glycolate (SSG), croscarmellose sodium (CCS), crospovidone (CP) and aerosil-200 (colloidal silicon dioxide) were received as a gift from Zydus Cadila Ltd., Ahmedabad, India. Chitosan was procured from Sigma- Aldrich Corporation, U.S.A. All the other ingredients and chemicals used were of analytical grade.

Experimental Design

A 3^2 full factorial design was employed to systematically study the joint influence of the effect of independent variables X_1 and X_2 on the dependent variable Y. Microcrystalline cellulose–chitosan mixture (X_1) and % of Aerosil-200 (X_2) were selected as independent variables [12].

Preparation and evaluation of CPE

A blend of chitosan, aerosil-200 and MCC were placed in mortar in geometric order. An alcoholic solution of PVP K-30 (3% w/v) was added just enough to bind the mass of excipients. The wet mass was allowed to pass through 10 mesh sieve and allowed to retain on 16 mesh sieve. The granules thus obtained were dried in hot air oven. The dried granules were further subjected to fine sieving and were kept in a tightly closed container till further use. The prepared CPE were evaluated for flow characteristics by measuring angle of repose, Carr's index and Hausner's ratio [13].

Preparation and evaluation of Tablets of CPE

The nine batches of tablets CPE-1 to CPE-9 were prepared by blending the prepared CPE (160 mg) with paracetamol (40 mg), 2% talc and 1% magnesium stearate for two minutes in polythene bag and directly compressed into tablets using a rotary punch (8 mm) tablet machine (Rimek tablet machine, RSB-4 Mini Press, India).

The prepared batches of tablets were evaluated for hardness, friability, disintegration time and in vitro drug release study. The disintegration time of tablet was determined in distilled water at 37°C ± 1°C using disintegration test apparatus (VTD-2W, Veego Ltd.) as per IP'96 [14]. The disintegration test was performed without disc. In vitro drug release study of Paracetamol tablets was perfomed at 37 ± 0.5 ˚C using USP type-II dissolution apparatus (Scientific USP standards DA-60) in 900 mL phosphate buffer pH-7.8 as dissolution medium and rotating paddle at 50 rpm for 30 min. The sample was withdrawn at suitable time intervals and analyzed using UV / VIS spectrophotometer (UV-1601, Shimadzu, Japan.) at 249 nm.

Check Point Batch

To confirm the validity of contour plot and equations generated by multiple regression analysis, two check point batches were prepared as shown in table 1.

Characterization of optimum batch

Batch CPE-1 was selected as optimum and further characterization carried out of this batch as mentioned below:

Scanning Electron Microscopy (SEM)

The morphological study of the particles of chitosan, aerosil-200, MCC PH-101 and CPE-1 was carried out by scanning electron microscopy. Double side carbon tape was affixed on aluminum stubs. Samples were sprinkled onto the tape. The aluminum stubs placed in the vacuum chamber of a scanning electron microscope (XL 30ESEM with EDAX, Philips, Eindhoven, Netherland). The samples were observed for morphological characterization using a gaseous secondary electron detector (working pressure: 0.8 torr, acceleration voltage: 30.00 kv).

Differential Scanning Calorimetry (DSC) studies
Paracetamol, physical mixture of Paracetamol with CPE-1 and CPE-1 itself were separately weighed and hermetically sealed in the aluminum pans. A thermal analysis system instrument DSC – pyris – 1 with intracooler, a refrigerated cooling system, as used. Indium standard was used to calibrate the DSC temperature and ml / min. Initially sample were held at 50ºC for 1 minute and after that heating was performed from 50ºC to 320ºC at a rate of 10ºC / min.

Fourier Transform Infrared spectroscopy (FTIR)
Fourier transform infrared spectroscopy (FTIR) was used to determine the molecular interaction between Chitosan, aerosil-200, MCC PH-101, and CPE-1 with Paracetamol. Samples were prepared using KBr (Spectroscopic grade) disks by means of hydraulic pellet press at a pressure of 7 to 10 tons. The samples were scanned from 4000 to 400 cm^{-1}.

Particle Size Distribution
Particle size analysis of CPE-1 was recorded using Laser Diffraction Particle Size Analyzer, Sympatec, Germany, X50, X90 and volume mean diameter were recorded.

Hygroscopicity
Different samples of CPE-1 (initial weight 2 gm.) were subjected to different humidity conditions of saturated salt solutions. The samples were placed in desiccators at ambient temperature (25ºC). The samples were stored in desiccators for 1 week until equilibrium was reached. The percentage gain in weight from the original weight was measured for each humidity reading.

Maximum Water Saturation
To 25 ml of water, under stirring using magnetic stirrer, prepared CPE-1 powder was added stepwise, at room temperature, until the saturation end point was reached, indicated by the formation of solid mass of the powder and no further stirring required. The maximum saturation power of CPE-1 was calculated by dividing the mass of the added powder by the fixed volume of water. This test was further performed on sodium starch glycolate (SSG), croscarmellose sodium (CCS), crospovidone (CP) superdisintegrants. Each set of experiments was repeated three times, and the average was calculated.

Water Penetration/Uptake Rate (Wetting time)
Samples (1, 5, 25, and 50% w/w) were prepared by physically mixing prepared CPE-1 with MCC (Avicel® 200). Samples with different percentage of CPE-1-MCC mixture were compressed in to tablets with average weight of 200 mg. The method described by Gohel et al was used for measurement of liquid uptake [15]. Briefly, a glass petridish was partially filled with dye solution (0.5%w/v methylene blue), and a tablet was placed on the surface of a band of filter paper supported on a glass slide. The uptake of dye solution occurred from the lower surface of the tablet. The time required for dye solution to reach the center of the upper surface of the tablet was noted as wetting time. This test was further performed on superdisintegrants SSG, CCS and CP.

Testing the Superdisintegration Power with other Commercial Superdisintegrants
About 100 g of a standard placebo mixture was prepared by mixing MCC and lactose at a mass ratio of 70 and 30%, respectively. Then 20 gm of mixture made from the standard placebo and a tested superdisintegrant was prepared before compaction using the rotary punch tablet machine (Rimek tablet machine, Ahmedabad, India). The superdisintegrants tested were CPE-1, CCS, SSG, and CP, all of which were added separately at different percentages (1, 5, 10, 25 and 50%) to the standard placebo mixture. Tablet disintegration was performed for each mixture and for the placebo powder itself (compacted under the same conditions as the tested mixtures). Disintegration time was measured using a disintegration tester (VTD-2W, Veego Ltd.).

Testing the Superdisintegration Power of CPE-1 over Conventional Method
The product's integrity was tested over wet granulation formulations. Tablets incorporating CPE-1 as disintegrant with conventional wet granulation method were prepared and evaluated.

Packability of Batch CPE-1

The Packability was evaluated by tapping the agglomerates in a measuring cylinder. The data were analyzed using Kawakita equation. 10g of sample was poured slowly and gently into a 25 ml measuring cylinder and tapped for 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100 and 1200 times. The packability was evaluated by the tapped density according to the Kawakita and Ludde equation as follows [16],

$$\frac{n}{C}=\left(\frac{1}{ab}\right)+\left(\frac{n}{a}\right) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where n is the tap number, C denotes the volume reduction which can be calculated according to following equation, $\frac{1}{a}$ defines the degree of volume reduction at the limit of tapping, termed compactibility and $\frac{1}{b}$ is a constant related to cohesion, termed cohesiveness.

$$C = \frac{(V_0 - V_n)}{V_0} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Where V_0 and V_n are the powder bed volume at initial and n^{th} tapped state respectively.

The plot of $\frac{n}{C}$ versus n is linear and the compactibility $\frac{1}{a}$ and cohesivity $\frac{1}{b}$ are obtained from the slope $\frac{1}{a}$ and the intercept ($\frac{1}{ab}$) of the plot.

Dilution potential

Dilution potential is the amount of poorly compressible drug that can be satisfactorily compressed in to a tablet with prepared CPE. Dilution potential of batch CPE-1 was calculated by using Paracetamol as a model poorly compressible drug. Two different ratios of CPE to drug (60:40, 50:50) were mixed and the mixture was compressed in to tablets. The tablets were evaluated for crushing strength, friability and disintegration time as per the procedure described earlier.

Effect of lubricant

In the present study different fraction of lubricant (Magnesium stearate) viz-1%, 2%, 3% were mixed with blend of drug, CPE-1 and talc and tablets were obtained. Parameters such as hardness, disintegration time and %drug dissolved are measured.

Effect of compression force

Tablets from the mixture of CPE-1 and Paracetamol were obtained, having different hardness values. The disintegration time was measured for each of them as per the procedure described earlier.

RESULTS AND DISCUSSION

The use of a one-body adjuvant is justified if it results in potentiation of the functionalities of the components compared with a physical blend of individual components. The synergistic effect may improve flow, compressibility, and tablet quality.

The samples of MCC, chitosan, aerosil-200, and a physical blend consisting of equal parts of the three adjuvants exhibited poor flow (angle of repose >37º and Carr's index >17). These poorly flowing materials are expected to give tablets of varying weight. Wet granulation was adopted for the size enlargement and subsequent flow improvement. Co-processing is generally conducted with one excipient that is plastic and another that is brittle. This particular combination prevents the storage of too much elastic energy during compression, which results in a small amount of stress relaxation and a reduced tendency of capping and lamination. Nine batches of CPE were prepared according 3^2 full factorial design to optimize proportion of all three excipients viz. MCC, chitosan, and aerosil-200.

Evaluation of CPE

Angle of repose measured by fixed funnel method, was found to be in the range of 24.92 to 30.12 (Table 2) reflecting free flowing properties of CPE and can be used for direct compression. The simplest method of measurement of free flow of powder was compressibility, an indication of the ease with which material can be induced to flow was given by Carr's index (CI). The value below 15% indicates a powder which usually gives rise to excellent flow characteristics, whereas above 25% indicate poor flowability. The CI was found in the range of 14.46 to 22.41**.** Hausner's ratio is also an indirect index of ease of powder flow. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25). Hausner's ratio was found to be in the range of 1.16 to 1.28.

Evaluation of Prepared Tablets

The hardness of tablet was determined using Monsanto hardness tester (Dolphin, Mumbai, India) and were found in the range of 3.4 to 5.8 kg / cm^2 (Table 2). Friability was found in the range of 0.30 to 1.02, indicating sufficient mechanical integrity and strength of prepared tablets. Disintegration time was found in the range of 7.9 to 14.26 sec for all nine batches.

From this results, it can be concluded that both the proportion of MCC: Chitosan and % of aerosil-200 are important variables for the preparation of directly compressible adjuvant with good flowability (low CI), and satisfactory tablet characteristics. As the amount of aerosil-200 in the blend increases, Angle of repose, Carr's index, Hausner's ratio and hardness increased, but the % friability and disintegration time was decreased.

The joint effect of important variables was further studied in the form of in vitro drug release study (Table 3). Dissolution is critical step to be measured because amount of drug dissolved in a given media is of paramount importance for both drug as well as dosage forms as it is a prerequisite for drug absorption.

Dissolution test is also utilized as a quality control tool to monitor the uniformity and reproducibility of production batches. Also dissolution test is utilized as research tool for optimizing the parameters and ingredients in any formulation as the amount of drug dissolved is associated with drug absorption and bioavailability. Considering in vitro drug released as more quantitative measure, amount of drug released over the period of 5 minute was taken as dependent variable (Table 4).

The results of multiple linear regression analysis show that the proportion of MCC : Chitosan (X_1) had less significant effect on % drug released in 5 minutes than the % of aerosil-200 (X_2).A quadratic equation of full model obtained as-

$$Y = 74.59 - 1.63X_1 - 6.826X_2 + 3.08 X_1^2 + 1.08 X_2^2 - 1.33 X_1X_2 \quad \ldots\ldots\ldots\ldots (3)$$

The contour plot of all the independent variables were generated (Fig.-1) to locate the area of common interest by statistical software in which the dependent variable Y was represented by a curvature as a function of Xi. The plots were found to be non linear in relationship between X_1 and X_2. This signifies no direct linear relationship among the selected independent variables. It was determined from the contour plot that a higher value of dissolution (≥ 80%) could be obtained at all the three levels of X_1 and with lower level of X_2.

To confirm the validity of contour plot and equations generated by multiple regression analysis, two check point batches were prepared. Good agreement was observed between observed and predicted values (Table 4).

Batch CPE-1 and CPE-7 still gave nearby result but considering the derived polynomial equation and contour plot as well as the values for auxiliary parameters such as angle of repose <25, Carr's Index <20, hardness >5kg/ cm^2 and friability <1%, CPE-1 was found to be most promising batch. Also the results for cumulative %drug released in 30 min and other formulation constraint such as the amount of binder needed to make the CPE (an increase in proportion of chitosan was associated with an increase in the requirement of granulating agent) indicates batch CPE-1 as best batch.

Characterization of Optimum batch CPE-1

The agglomerates of CPE-1 were screened by scanning electron microscopy (SEM) and the difference in their appearances was clear, as shown in fig. 2. Chitosan as well as MCC had no porous structure, whereas chitosan–MCC-aerosil-200 blend had more porous structure.

Thermal analysis is useful in the investigation of solid-state interactions. In the absence of any interaction, the thermograms of mixtures show patterns corresponding to those of the individual components. In the event that interaction occurs, this is indicated in the thermogram of a mixture by the appearance of one or more new peaks or the disappearance of one or more peaks corresponding to those of the components. Since the melting point peak of individual excipient in the prepared Co-processed excipient CPE-1 was not found to alter then their original peak position, it can be concluded that co-processing does not bring any chemical change in the excipient structure (Fig. 3A). And since the peak position of pure Paracetamol was also not found to alter in the physical mixture of Paracetamol with CPE-1, it can be concluded that the prepared CPE and Paracetamol are compatible with each other (Fig. 3B).The infrared spectra of chitosan, aerosil-200, MCC PH-101, and their intimate mixture in co-processed excipient CPE-1 are shown in fig. 4.

Chitosan showed split absorption bands at 1660 and 1620 cm^{-1} corresponding to the amide I region and an absorption band at 1560 cm^{-1} corresponding to the amide II region. Silica showed an absorption band at 800 cm^{-1} and 810 cm^{-1} which is due to Si-O-Si symmetrical stretching vibration. All these bands were identical in both the CPE-1 and individual excipient. This suggests no chemical reactivity present between chitosan and aerosil-200 when they undergo co-processing. A similar behavior was observed for the intimate association between MCC and aerosil-200 when they are co-processed. Apart from the band mentioned above characteristic stretching vibration for C=O 1750 -1735 cm^{-1}, for O-H stretching 3570 – 3450cm^{-1}, for N-H stretching 3500-3400cm^{-1}, N-H bending 1650-1500cm^{-1} etc are present in their native form indicating compatibility of prepared CPE (co-processed excipient) with drug, Paracetamol and compatibility of individual adjuvant in the prepared CPE indicating no chemical change has been taken place during co-processing (Fig. 4 (A) and 4 (B)).

Particle size and particle size distribution of the samples have considerable impact on the flow properties of powder. Fig. 5 shows the particle size distribution of batch CPE-1. Mean particle size of batch CPE-1 was 95.2 µm. About 98% particles are 387.26 µm, which may be the reason for the better flowability of granules of batch CPE-1 than that of the shelf powder or their physical blend. Because the mean particle size of individual adjuvant are available in the range of 30 µm, 7-16 µm and <200 µm for Chitosan, Aerosil-200 and MCC respectively [17]. This size enlargement aids in flowability and subsequently improves compressibility.

One of the important characteristics investigated for prepared CPE as a superdisintegrant was hygroscopicity. Disintegration power is dependent on water uptake, and alternatively, on powder hygroscopicity. Polymers with a higher moisture uptake capacity will be expected to be more prone to impairment of tablet disintegration time.

Fig. 6 clearly indicates that CPE-1 was capable of gaining moisture up to 30% of its initial weight. However, hygroscopicity was not highly significant when prepared CPE-1 was subjected to humidity below 70%. Such property may be taken as an advantage, where environmental conditions as anticipated are not a

real threat to integrity of such product. The moisture adsorptivity would be mainly attributed to aerosol-200 particles associated with chitosan and MCC or to the presence of the large number of hydroxyl sites on the surface.

As the concentration of all commercial superdisintegrants increases within the tablets, the swelling rate becomes so high that they form a gel-like layer that blocks the passage of water inside deeper layers.

The formation of the gel layer is a result of an increase in the viscosity of the medium surrounding the particles due to hydration of the particles. This makes common superdisintegrant play their role on the interface [18]. Therefore, it was essential to examine the maximum amount of the superdisintegrants added to a fixed volume of water needed to form the gel layer. Fig. 7 indicates that water can accommodate larger masses of prepared CPE before gelling occurs than is the case for the other commercial superdisintegrants like sodium starch glycolate (SSG), croscarmellose sodium (CCS), and crospovidone (CP).

Water penetration rate or wetting time of prepared CPE-1 and other superdisintegrants was determined to further highlight the mechanistic action of superdisintegrants; this is shown in Fig. 8. The choice of using Avicel® mixed with tested superdisintegrants was based on its free allowance to water passage without any hindrance due to gelling. It was clear that water could penetrate SSG and CCS only when their percentages were within their limits of use. This means that their presence within the limits cannot hinder the passage of water. It is only when their concentrations are increased above their limits (i.e., > 10%), water can no longer pass through due to the swelling action of SSG and CCS. CP showed good water penetration rate, nearly up to double the rate shown by MCC alone. However, this was only encountered when the CP concentration was 5–10%; at higher concentrations, there would be a decrease in the rate due to obstruction by the CP. CPE showed the highest water uptake rate without limits to its content within the MCC superdisintegrant mixture. Therefore, the action of CPE would be independent of its concentration within solid dosage forms.

Finally, the superdisintegration competence of the CPE-1 was set in parallel with selected commercial ones. The low concentration of CPE-1 in tablets was as efficient as, SSG, CCS and better as CP. The most interesting feature could be seen when disintegration time became elevated when the concentrations of the commercial superdisintegrants were increased above their limits. This result could be explained from the data obtained previously from the maximum water saturation and water capillary penetration, as shown in Fig. 7 and 8.

One important limitation to the use of swellable polymers in disintegration is in wet granulation formulation [19]. SSG and CP exhibit a significant decrease in the rate of water being absorbed into the tablet matrix following wet granulation. It was found that wet granulation did not alter the functionality of CPE-1 as a superdisintegrant, when added as both intrangranularly and extrangranularly. A release of more than 80% of the drug was obtained within 5 min of dissolution time at total concentration of 5% of CPE-1 when added both as intragranularly and extragranularly (Table 5).

The Packability was ascertained by comparing constant *a* and *b* in Kawakita's equation (fig.9) [20]. The constant *a* represents the proportion of the consolidation as closet packing is attained. The reciprocal of *b* represents the packing velocity. The constant *a* for agglomerates of selected batch of CPE (0.2225) was smaller than that of physical mixture of Chitosan Aerosil-200 and MCC PH-101 (0.399). This result indicates that the agglomerates of CPE-1 showed good packability even without tapping. The larger value of *b* for CPE-1 (0.0057) as compared to that of physical mixture (0.0027) proved that the packing velocity of the agglomerates by tapping was slower than that of powder blend. The slow packing velocity corresponds with a proportion of the consolidation of the powder bed per tap. As result of improved packability, agglomerates of batch CPE-1 showed improved property than that of physical mixture. Table 6 depicts the results of dilution potential study for the three different ratios tried in the present study. The minimum acceptable limits for hardness (>4 kg/cm^2), friability (<0.8%), disintegration time (<1 min) and %drug dissolved in 5min (>80%) were selected as criteria for selection of batches. The batch CPE-1A, CPE-1B, and CPE-1C met the selection criteria. It can be concluded that up to 50% of Paracetamol can be accommodated in the co-processed diluent.

The physicomechanical properties of excipients that ensure a robust and successful process are good flowability, good compressibility, low or no moisture sensitivity, low lubricant sensitivity, and good machineability even in high-speed tableting machinery with reduced dwell times. The material, CPE-1 was compressed into tablets at different compression forces, and the superdisintegration power was noticed to be independent of tablet' s hardness, as shown in Table 7.

FIGURES

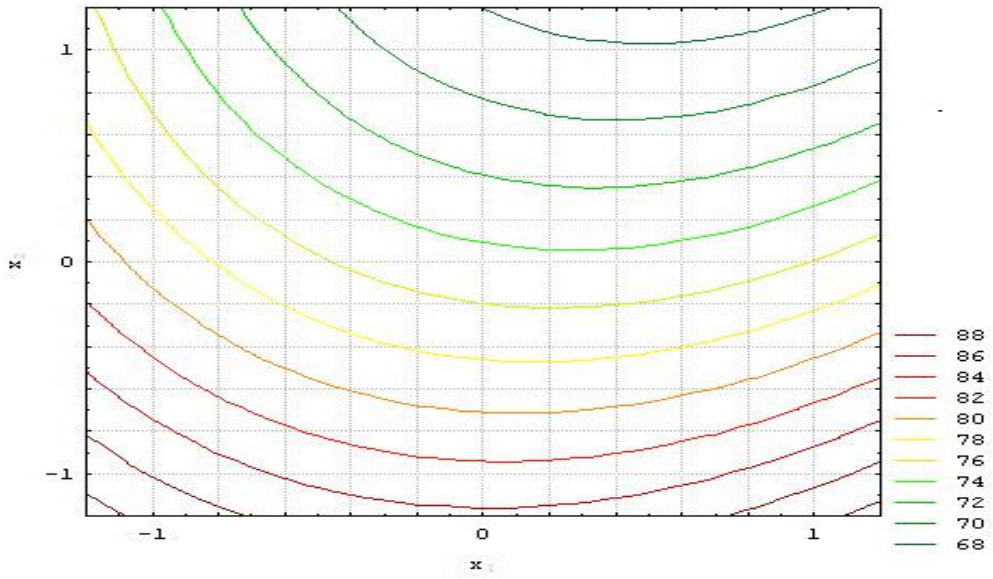


Figure 1 Contour plot of % drug dissolved in 5 minutes at different level of X_1 and X_2.

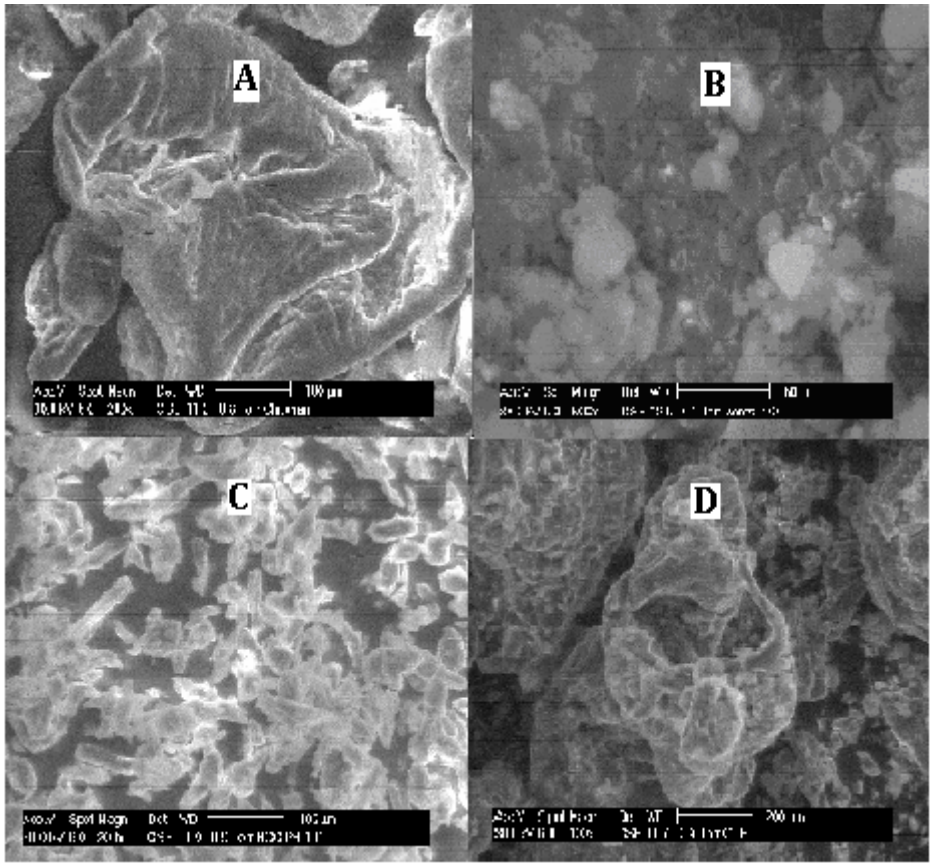


Figure 2. SEM of chitosan **(A)**, aerosil-200 **(B)**, MCC PH-101 **(C)** and CPE-1 **(D)**.

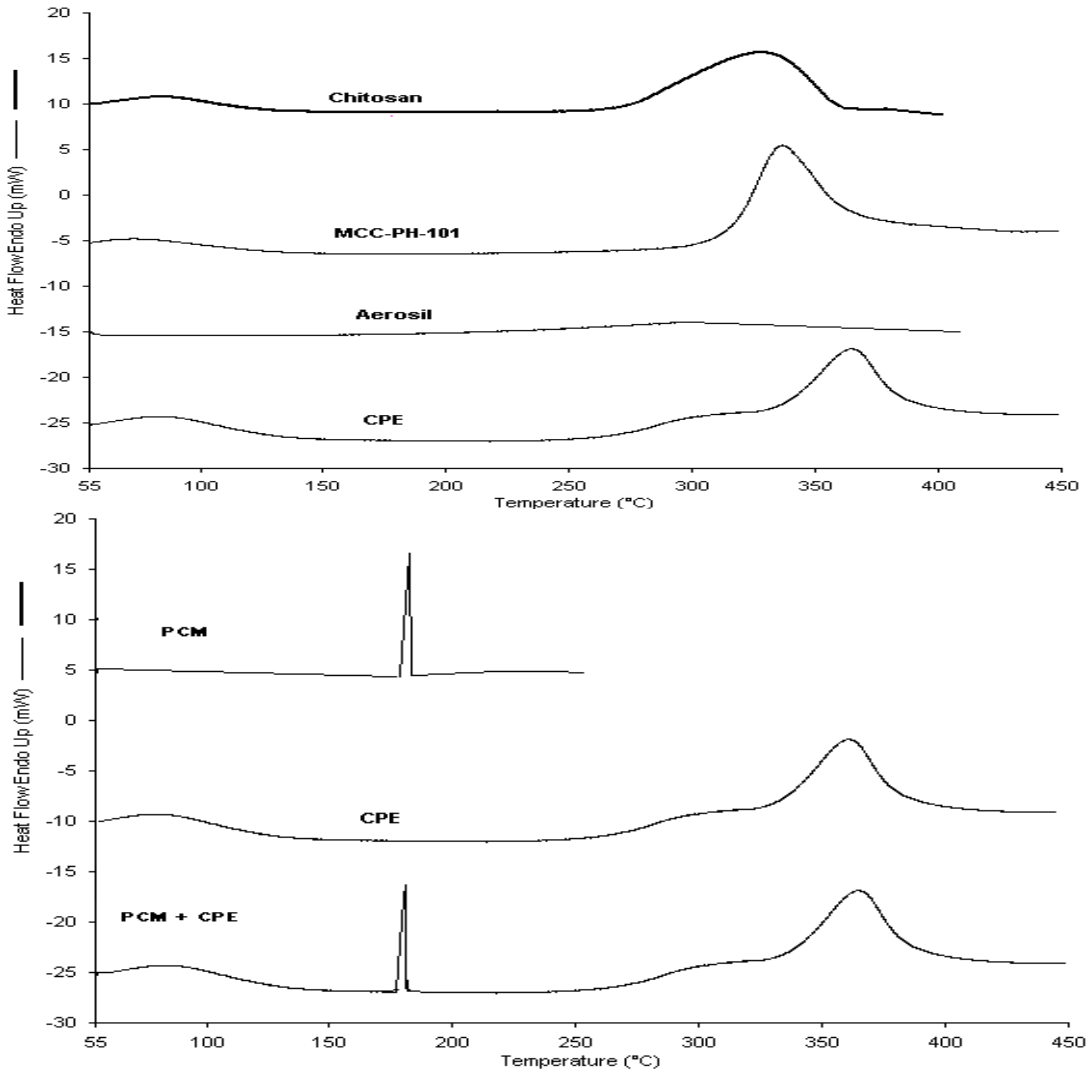
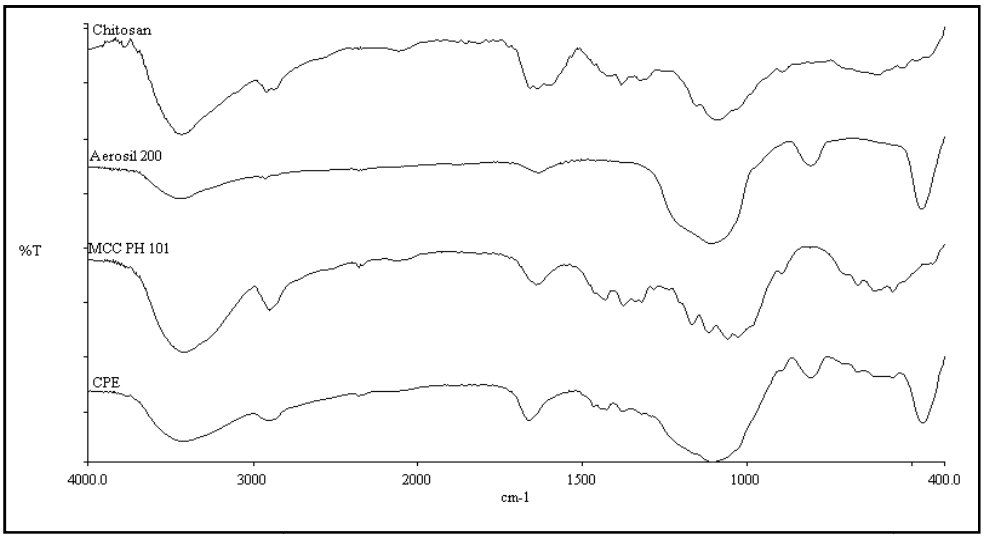
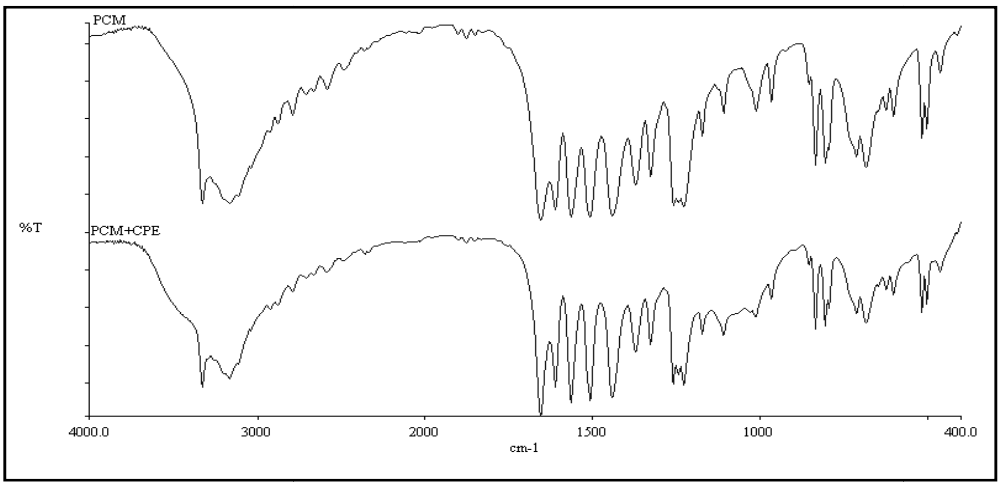


Figure 3. DSC studies overlay plot of chitosan, aerosil-200, MCC PH-101, CPE-1 **(A)**, and PCM, CPE-1, PCM + CPE-1 **(B)**.



(A)



(B)

Figure 4. Overlay spectra of FTIR studies for chitosan, aerosil-200, MCC PH-101, and CPE-1 **(A)** and PCM+CPE-1 with PCM **(B)**

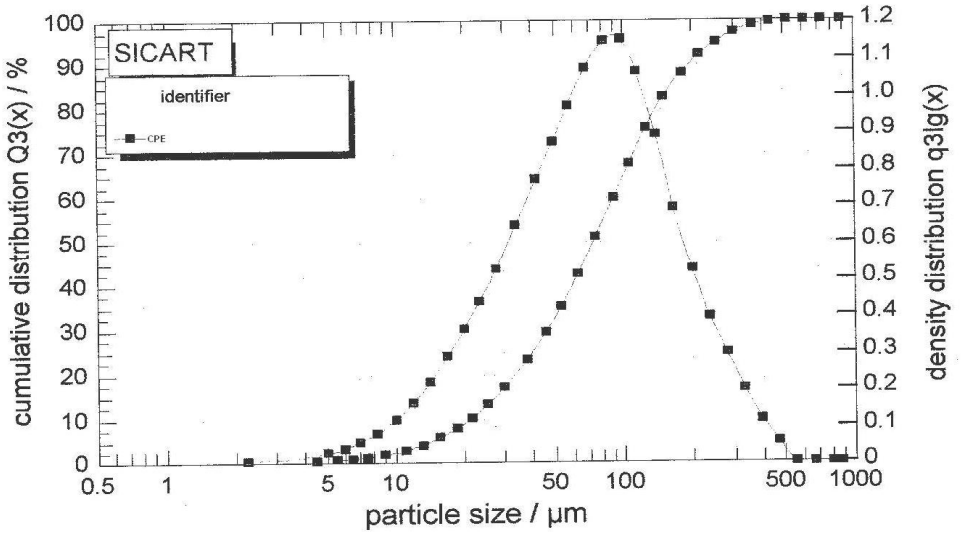


Figure 5. Particle size distribution of batch CPE-1

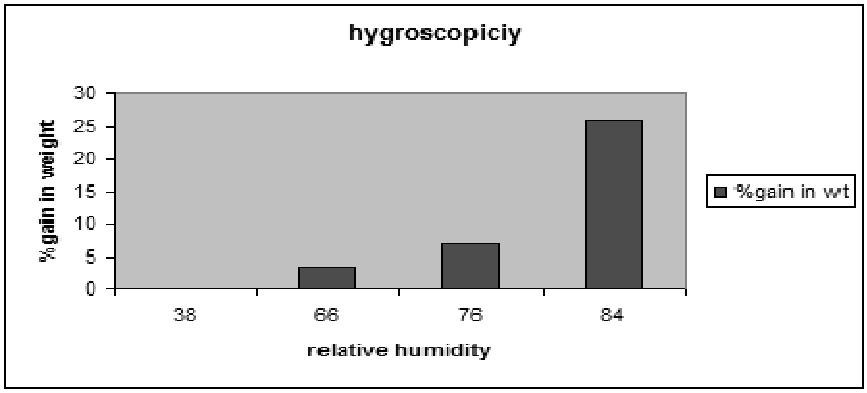


Figure 6. Hygroscopicity test for batch of CPE-1.

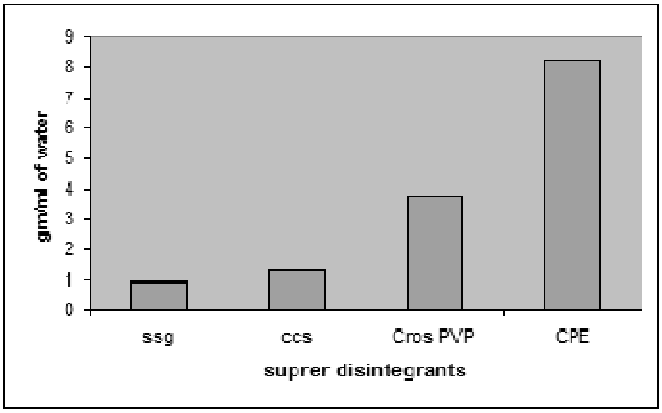


Figure 7. Maximum water of saturation test for various superdisintegrants

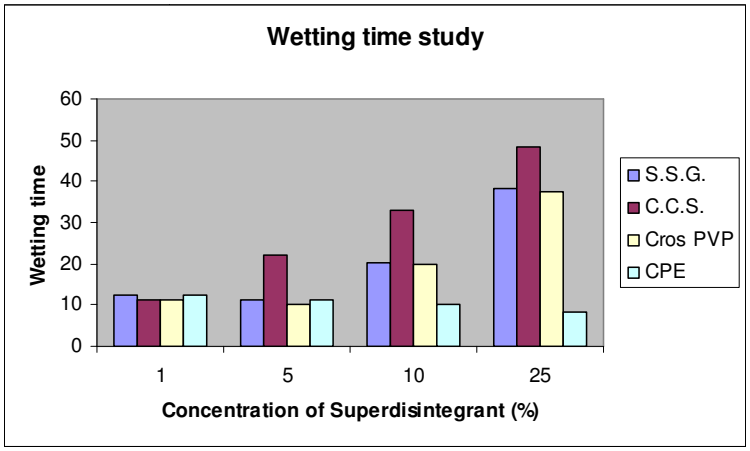


Figure 8. Water penetration rates of CPE-1 and other commercial superdisintegrants.

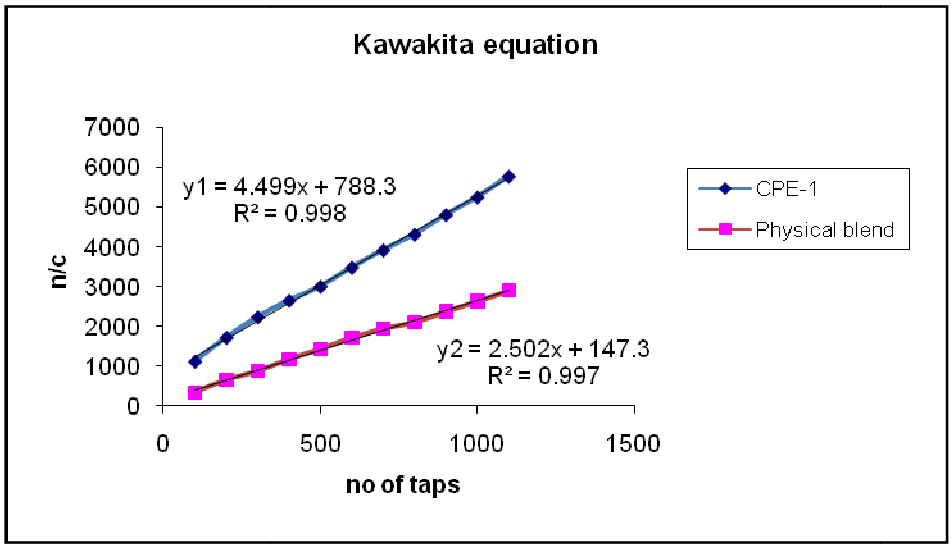


Figure 9. Packability of CPE-1 with respect to its physical mixture

TABLES

Table 1. Actual and Transformed Values of Nine Different Formulations as per 3^2 Full Factorial Design.

Batch code	Actual level		Coded level	
	X_1	X_2	X_1	X_2
	Ratio of MCC : Chitosan	% Aerosil-200	Ratio of MCC : Chitosan	% of Aerosil-200
CPE-1	2:1	10	-1	-1
CPE-2	2:1	20	-1	0
CPE-3	2:1	30	-1	1
CPE-4	1:1	10	0	-1
CPE-5	1:1	20	0	0
CPE-6	1:1	30	0	1
CPE-7	1:2	10	1	-1
CPE-8	1:2	20	1	0
CPE-9	1:2	30	1	1
CP-1	1.5:1	15	-0.5	-0.5
CP-2	1:1.5	25	0.5	0.5

CP-1 and CP-2 are checkpoint batch

Table 2. Evaluation of Nine Different Batches of 3^2 Full Factorial Design.

Batch code	Angle of repose (º)	Carr's index (%)	Hausner's ratio	Hardness (kg/cm^2)	Friability (%)	Disintegration time ' (sec)
CPE-1	24.92˚	14.46029	1.169048	5.80 (0.109)	0.309	12.01 (0.201)
CPE-2	26.89˚	17.46641	1.211628	4.28 (0.178)	0.354	10.39 (0.124)
CPE-3	27.18˚	18.14947	1.221739	3.8 (0.244)	0.421	8.59 (0.134)
CPE-4	25.43˚	15.44554	1.18267	4.6 (0.141)	0.319	11.29 (0.066)
CPE-5	25.18˚	17.28625	1.208989	4.16 (0.089)	0.485	10.33 (0.112)
CPE-6	28.18˚	18.96552	1.234043	3.28 (0.228)	0.39	8.68 (0.206)
CPE-7	28.82˚	16.95568	1.204176	5.66 (0.194)	0.507	12.08 (0.189)
CPE-8	26.25˚	16.69866	1.200461	5.12 (0.109)	0.574	9.40 (0.159)
CPE-9	30.12˚	22.41379	1.288889	4.64 (0.167)	0.993	8.55 (0.158)

Values in parenthesis indicate standard deviation '(n=6).

Table 3. Dissolution Study of Prepared Batches.

Batch code	Time in min*			
	5	10	15	30
CPE-1	85.57 (0.041)	88.82 (0.196)	92.12 (0.147)	97.62 (0.138)
CPE-2	78.46 (0.030)	81.69 (0.350)	85.68 (0.470)	91.50 (0.235)
CPE-3	76.08 (0.035)	79.02 (0.384)	82.91 (0.075)	88.58 (0.361)
CPE-4	82.76 (0.344)	85.79 (0.318)	89.73 (0.210)	91.62 (0.482)
CPE-5	77.07 (0.020)	79.60 (0.080)	80.97 (0.173)	86.47 (0.165)
CPE-6	66.13 (0.025)	67.57 (0.365)	70.08 (0.279)	82.27 (0.152)
CPE-7	85.36 (0.125)	87.04 (0.399)	88.14 (0.210)	92.94 (0.650)
CPE-8	74.43 (0.075)	83.29 (0.334)	85.35 (0.465)	89.97 (0.385)
CPE-9	70.52 (0.061)	78.75 (0.399)	83.18 (0.340)	86.65 (0.19)

Values in parenthesis indicate standard deviation* (n=3).

Table 4. Regression Input for 3^2 Full Factorial Design

Batch code	Actual level		Coded level		Y
	X_1	X_2	X_1	X_2	
	Ratio of MCC : Chitosan	% Aerosil-200	Ratio of MCC : Chitosan	% of Aerosil-200	
CPE-1	2:1	10	-1	-1	85.57 (0.041)
CPE-2	2:1	20	-1	0	78.46 (0.030)
CPE-3	2:1	30	-1	1	76.08 (0.035)
CPE-4	1:1	10	0	-1	82.76 (0.34)
CPE-5	1:1	20	0	0	77.07 (0.020)
CPE-6	1:1	30	0	1	66.13 (0.025)
CPE-7	1:2	10	1	-1	85.36 (0.125)
CPE-8	1:2	20	1	0	74.43 (0.075)
CPE-9	1:2	30	1	1	70.52 (0.061)
	Check point batches				
CP-1	1.5:1	15	-0.5	-0.5	78.85 (0.372)
CP-2	1:1.5	25	0.5	0.5	72.45 (0.369)

Values in parenthesis indicate Standard Deviations (n=3).

Table 5. Evaluation with Wet Granulation Technique of Batch CPE -1

Batch code	ˀHardness (Kg/cm^2)	ˀDisintegration time (sec)	%drug dissolved in 5 min*
CPE-1	5.8 (0.109)	12.01 (0.201)	85.57 (0.041)
WG-1	6.20 (0.37)	18.90 (0.23)	81.27 (0.21)

Values in parenthesis indicate Standard Deviation ˀ(n=6),* (n=3).

Table 6. Dilution Potential Study

Batch code	Drug:CPE-1	ˀHardness (Kg/cm^2)	Friability (%)	ˀDisintegration tome (sec)	*% drug dissolved in 5 min
CPE-1A	30:70	5.8 (0.109)	0.309	12.01 (0.201)	85.57 (0.041)
CPE-1B	40:60	5.12 (0.109)	0.485	11.29 (0.066)	84.76 (0.029)
CPE-1C	50:50	4.2 (0.244)	0.507	9.40 (0.159)	84.54 (0.28)

Values in parenthesis indicate standard deviation ˀ(n=6),* (n=3)

Table 7. Study of Effect of Compression Force.

Batch code	Hardness (Kg/cm^2)	Disintegration time (sec)
CF-1	3	<5
CF-2	4	<10
CF-3	5	<10
CF-4	6	<10

CONCLUSION

In summary, CPE-1 has demonstrated improved disintegration and dissolution functionality over conventional superdisintegrants. SEM revealed that silicon dioxide, in some manner, has been integrated with chitosan and MCC particles via a partial coating of the particles, without any chemical interaction of the two ingredients as evidenced by IR analysis. This association has been confirmed by X-ray diffraction. The result of Kawakita equation proves better packability of CPE-1 over the physical mixture of same individual adjuvants and hence proves the efficacy of co-processing. Dilution potential study indicated that the material could dilute up to 50% of Paracetamol, a poorly compressible drug. Moreover, the high hygroscopicity and high water capillary penetration turn to be the driving engine for such superdisintegration. Finally, the improved flow and the ability to be implemented in wet and dry granulation with no concentration limits of the superdisintegrant can impart further benefit in pharmaceutical applications. Thus, the new excipient could act as a superdisintegrant and pharmaceutical filler at the same time.

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