Research Article

Process and Development of Co-Processed Excipient Silicified Microcrystalline Cellulose and Manufacture Paracetamol Tablet by Direct Compression

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ABSTRACT

Co-processing is one of the ways to develop new excipients for the pharmaceutical industry. Co-processed excipients are a combination of established two or more excipients through physical mixing or co-process technology. Co-processed excipients has no change in chemical structure, it only changes physical properties of the final product. Co-processing technology could lead to formation of co-processed excipient with superior physical properties compared to simple physical mixtures of their components. In this study we will be manufacturing (HiCel™ SMCC) Silicified microcrystalline cellulose, which is a combination of two pharmaceutical excipients, one is colloidal silicon dioxide and second is (HiCel™) Microcrystalline cellulose. (HiCel™SMCC) Silicified Microcrystalline Cellulose is made by co-processed technology.HiCel™SMCC90M grade of Silicified microcrystalline cellulose is used to manufacture the Paracetamol (PCM) tablet using direct compression technology. It is a good choice of excipients for direct compression formulation. The main aim of co-processing is to obtain product with a benefit related to the ratio of it functionality or costing.

Keywords: Co-processed Excipients, Scanning electron microscopy of HiCel™ SMCC, Direct Compression of Paracetamol (PCM) tablet, *In Vitro* Evaluation of PCM tablet.

INTRODUCTION

Co-process technology is another way to introduce new excipients in pharmaceutical market without undergoing the rigorous safety testing of new product. In co-processing, modification of only physical properties of product is done, without altering the chemical structure of product. Co-processed excipient is a combination of two or more than two established excipients by an appropriate process[1]. It could lead to the formation of excipients with superior properties compared to the simple physical mixtures of their components. Development of co-processed directly compressible adjuvant starts with selection of excipients to be combined, their targeted proportion, selection of preparation method to get optimized product with desired physicochemical parameters and it ends with minimal batch-to-batch variations[2].A fixed and homogenous distribution for the component is achieved by embedding them within mini granules. Segregation is diminished by adhesion of the actives on the porous particles making process validation and in process control easy and consistent[3].

Many co-processed excipients have been launch in the pharmaceutical market in the past few years and a few formulations are commercially available. Many co-processed exicipents having trade mark HiCel™ available in market i.e. HiCel™SMCC, HiCel™MCG, and HiCel™HFE etc. Co- processed excipients are helpful for wet granulation and direct compression formulation[4], because co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, which is to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients. Thus, the use of the co-processed excipient combines the advantages of wet granulation with direct compression[5, 6]. The use of one-body components is justified if it results in increase of functionality over that of dry blend of the components prepared by gravity mixture. This synergistic effect should improve the quality of the tablet equally in all aspects ranging from hardness to dissolution[7,8]. In co-processed excipient have a limitations, the ratio of mixing excipients in the mixture is fixed. Co-processed adjuvant lacks the official acceptance in pharmacopoeia but is acceptable in pharmaceutical industries[9, 10].

In this study, the development of a co-processed excipient using co-processed technology is used. Colloidal silicon dioxide and HiCel™ Microcrystalline cellulose are used in a suitable proportion. This combination would be providing enhanced support to direct compressible formulation in respect of flow ability, compaction, and hardness and dissolution time. Using HiCel™SMCC as an excipient make PCM direct compressible tablets and thereafter evaluate quality parameter.

MATERIAL AND METHODS

MATERIAL

Colloidal silicon dioxides, HiCel™ Microcrystalline Cellulose are used to makes the (HiCel™ SMCC) Silicified microcrystalline cellulose. Paracetamol (PCM) was gifted by Meghmani LLP Dahej. All the chemical and reagent were the analytical grade.

METHOD

Preparation of Co-Processed Excipient HiCel™ SMCC [3, 11]

Take required quantity of Colloidal silicon dioxide (2%) and HiCel™ microcrystalline cellulose (98%) and the same are processed by using co-processed technology. Drying of the combination is done with the help of spray dryer. (Manufacturing process shown in the fig.1.

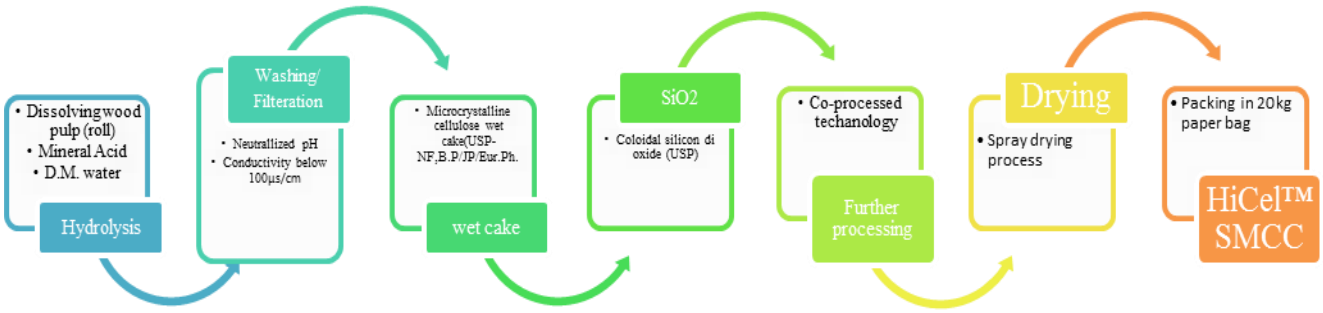

Figure 1: Manufacturing Process of HiCel™ Silicified microcrystalline cellulose

PHYSICAL PROPERTIES OF HICEL™ SMCC

Particle size distribution (PSD) [12]

Average particle size was analyzed by Sieve shaker, PSD software (Retsch-German instrument). PSD software operates through computer. Take cleaned mesh sieve with bottom pan and top cover. Check sieve shaker and set mesh sieve with sample being analyzed on sieve jet. Take weight of all required mesh sieve with bottom. Arrange the sieve mesh sequence from top mesh 60, mesh 200 and bottom. Weight accurately 10 gm of MCC powder with the help of weight balance (Mettler Toledo, Model no. ML802/A01) and put into top of sieve. Fill the initial weight of mesh sieve and bottom into PSD software table and start. After 5 minutes take out the sieves and again take weight of all sieve mesh with retain sample. Fill into the PSD software table.

Untapped Bulk Density [13]

Weight accurately 20g sample by using (Mettler Toledo, model no-ML802/A01) and poured slowly from side wall into 100 ml capacity Class A graduated measuring cylinder. Level the surface of sample in cylinder by slow movement and observed the occupied volume and calculate the untapped density by using equation1.

$$\text{Density} = \frac{\text{Weight of powder in gram}}{\text{Occupied volume in mL}} \quad (1)$$

Moisture content [13]

Heat the shallow bottle in a hot air oven (Model no. PNX-14) at 105°C for 30 minutes after that cool it in desiccator at room temperature. Tare weight the Shallow bottle and take about 1 gm of HiCel™MCC in shallow bottle, set oven at 105°C and keep for 3 hours. After 3 hours take out the shallow bottle allow to cool in desiccator at room temperature. When the shallow bottle is cool take weight again, calculate moisture content by using the following formula equation 2.

$$\text{Moisture content} = \frac{\textit{After drying weight of shallow bottle} - \textit{empty weight of shallow bottle}}{\textit{Sample weight in gram}} \times 100 \quad (2)$$

Angle of Repose [13]

Pour 30gm of dry MCC through pour on powder flow tester (#10 mesh size), powder comes on the S.S cylinder surface until a pile build on the top of S.S cylinder. Measure the total height (S.S cylinder & pile) by scales.

$$\text{Angle of Repose} = \frac{2h}{d} \quad (3)$$

Where
h = height of S.S cylinder
d = diameter of S.S cylinder

Scanning electron microscopy of HiCel™ SMCC 90M [14, 15]

Scanning electrode microscopy (gold coating Edwards sputter Coater) was carried out at Bombay IIT lab in Mumbai (India).

Compaction of Tablets [12]

Compacts of ~500 mg tablet of Paracetamol were made on 10 station proton mini press (Model no. MINI PRESS 10 "D") using D tooling dies and flat punches. Machine operating pressure ranges 10 to 60 KN. Formula of paracetamol tablet mention in the table no-1.

In Vitro Study of PCM Tablet

Weight variation of Tablets [16]

Random 10 tablets were taken from batch and each tablet was weighted individually using electronic digital balance (Mettler Toledo, Model No.-MS204S /A01).

Table 1: Paracetamol tablet manufacture formula

Name of material	Quantity in %
Paracetamol (PCM)	71.23
HiCel™SMCC (Silicified microcrystalline cellulose)	21.37
Sodium starch glycolate(SSG)	4.63
Magnesium streate	1.85
Purified talc	0.93

The average weights of all tablets were calculated following formula (equation 13). (Pharmacopoeia limit ±5 % for 500 mg tablet)

$$Averageweightoftablet = \frac{Totalweightoftablets}{Totalno.oftablets} (4)$$

***Hardness of Tablet*[12]**

Random 10 tablets were taken from batch. Electronic digital hardness test machine (Labindia tablet hardness tester, Model No.-TH1050 M) was used for hardness test. Individually, a tablet was placed between two anvils, force was applied to the anvils, and the crushing strength that just caused the tablet to break was recorded. Finally the reading was taken in kp[kgf] on display of hardness machine.

***Thickness of Tablet*[12]**

Random 10 tablets were taken from batch. Vernier caliper (M&W Precision tools serial no-11071909) was used for thickness test. Individually, a tablet was placed between two external jaws and take reading in millimeter (mm).

***Friability of Tablet*[12]**

At first 10 tablets were taken. The tablets were carefully dusted prior to testing, then the 10 tablets were weighted electronic digital balance (Mettler Toledo, Model no. ML802/A01).Which was considered as the initial reading. After weighing the tablets, all the tablets were placed in the drum of friability tester (Electrolab, model no-EF-Z) and rotated 100 times at 25 rpm. After 100 revolutions the 10 tablets were removed and re-weighted. This was the final reading. The percentage was calculated by following formula (equation 5). According to USP the tablets should not loose more than 1% of their total weight.

$$PercentageFriability = \frac{Tabletweightbeforefriability - TabletweightAfterfriability}{Tabletweightbeforefriability} \times 100 \quad (5)$$

***Disintegration of Tablet*[16]**

Disintegration is evaluated to ensure that the substance is fully available for dissolution and absorption from gastrointestinal tract. Disintegration was measured for six tablets by inserting disks using 900 ml of dematerialized water at 37±2 °C in disintegration apparatus (electrolab, model no-ED-ZL).

***Dissolution of Tablet*[17, 18]**

Dissolution of Paracetamol tablet was measured as per USP method, apparatus type 2 (paddle) used, paddle speed 50rpm per minute in 900 ml of pH 5.8 phosphate buffer(Potassium di-hydrogen ortho phosphate) solution at 37±2 °C. Check absorbance of paracetamol tablets by using UV VIS-Spectrophotometer (Shimadzu model no-1800). Each sample (n=6) was spectrophotometerically determined at 257 nm wavelength. Calculate percentage of dissolution using following formula.

10 ml Sample are taken at different time intervals 5, 10, 15, 20, 25, 30, 35, 40 minutes. Samples filter with whatman filter paper (42), after filtration the sample volume is 1.4 ml. The determination of the active ingredient is done by an UV Spectrophotometer at λ=257nm.

$$\%\ of dissolution = \frac{Sampleabsorbance}{Standardabsorbance} \times \frac{Standardconc}{Sampleconc} \times Purityofdrug \quad (6)$$

Where
Standard absorbance = 0.715
Sample concentration = 10 ppm
Drug purity (on dry basis) = 97.26 %

RESULTS AND DISCUSSION

Manufacturing process of HiCel™SMCC

The material is white color, crystalline and free flowing powder. After some technical changes in the spray dryer can makes different grade of SMCC. There are many grades of HiCel™ SMCC available in the market as HiCel™ SMCC 50M, HiCel™ SMCC LM50M, HiCel™ SMCC LM 90M, HiCel™ SMCC HD 90M and HiCel™ SMCC 90M. In this study only HiCel™SMCC 90Mpowder was used for manufacture of paracetamol tablets.

Physical properties of HiCel™SMCC

Particle size distribution (PSD)

Particle size of HiCel™ SMCC 90 M is 125µm.

Untapped bulk density

Untapped bulk density of HiCel™ SMCC 90 M is 0.28 g/CC.

Moisture content

After 3 hrs the moisture content of HiCel™SMCC 90M is 4.80 %.

Angle of Repose

Flow of HiCel™ SMCC 90M is excellent due to its co-processed technology. The Angle of repose of HiCel™ SMCC 90 M grade is 37°.

Scanning electron microscopy

Scanning electron microscopy of HiCel™ SMCC grade 90M shown in fig2.

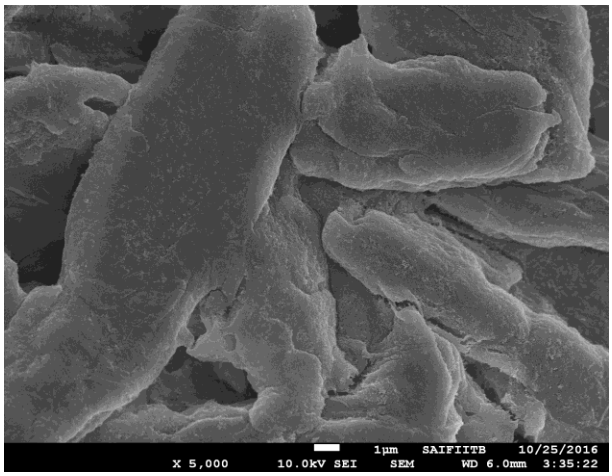

Figure 2: Scanning electron microscopy images of HiCel™ SMCC 90M

Compaction of tablet

Paracetamol tablets were manufactured by direct compression method at 35KN compaction force. All tablets were white colored and in round shape. Tablets are shown in the fig.3(e). General appearance of the tablets is free from defects (Capping, lamination, sticking and picking, mottling and weight variation). Weight variation of individual tablets has been brought out in the fig.4.

Figure 3: Paracetamol (PCM) Direct Compressible tablets

***In*-vitro Study of Paracetamol Tablet**

Weight Variation

Weight variation of Paracetamol(PCM) tablets were under pharmacopoeia limits ±5% of 702 mg. Individual weight of PCM tablets shown in the table no- 2 and fig.4. Average PCM tablet weight is 697.8 mg.

Hardness

Hardness of PCM tablets obtain under 5kp(kgf). Individual tablet hardness shown in the tablet no-2. Average hardness of tablet is 5.2kp (kgf).

Thickness

Thickness of the entire 10 tablets shown the table.2 and average thickness of PCM tablets are 4.46 mm.

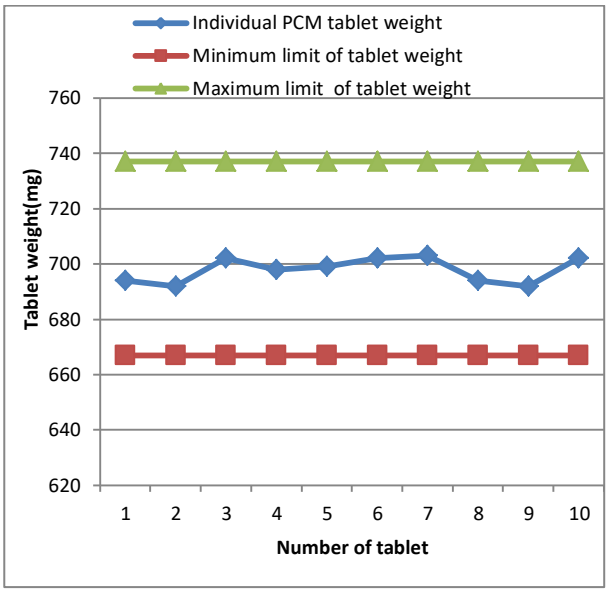

Figure 4: Weight Variation of tablets

Friability

Individual PCM tablet percentage of Friability shown in the table.2 and average percentage of friability is 0.093%.

Table 2: Weight, Hardness, Thickness and friability evaluation of PCM tablet

Number of tablets	Weight of tablet (mg)	Hardness [kp(kgf)]	Thickness (mm)	Percentage Friability (%)
1	694	5.0	4.5	0.1
2	692	5.0	4.4	0.08
3	702	5.1	4.5	0.07
4	698	5.0	4.5	0.1
5	699	5.0	4.5	0.09
6	702	5.1	4.4	0.1
7	703	5.0	4.4	0.1
8	694	5.0	4.5	0.09
9	692	5.0	4.5	0.1
10	702	5.1	4.4	0.1
Average	697.8	5.0	4.46	0.093

Disintegration

Disintegration time of Paracetamol tablet is mentioned in tablet no- 3. Average D.T is 122.67 Seconds.

Dissolution

Sample absorbance and percentage of dissolution shown in table no.3 and graph is mention fig.5.

Table 3: Disintegration Time and Dissolution profile of PCM DC tablet

Number of tablet	Disintegration Time(Seconds)	Dissolution profile	
		Absorbance λ(nm)	Percentage of dissolution (%)
1	123	0.583	97.10
2	122	0.584	97.26
3	123	0.584	97.26
4	123	0.585	97.43
5	123	0.585	97.43
6	122	0.585	97.43
Average	**122.67**	**0.5843**	**97.32**

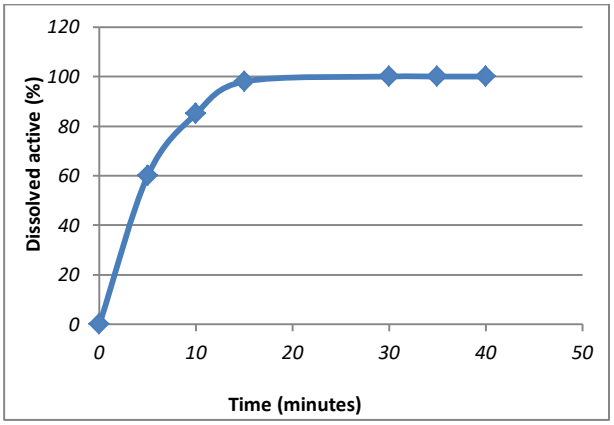

Figure 5: Dissolved active percentage at different time interval

CONCLUSION

Co-processed HiCel™SMCC has outstanding flow property. When it is used in formulations, it gives good compressibility at low compaction force. In this study, we manufactured PCM direct compressible tablet at 35KN compaction force. Tablets obtained were of satisfactory hardness with less weight variation and percentage friability. Content uniformity obtained by dissolution profile, all tablet carry same percentage of active. Dissolution and disintegration time is under pharmacopoeia limits. When HiCel™SMCC 90M used in formulation production, the cost would be reduced with the tableting process involving reduced steps. Additionally, the number of other excipients in the formulations would also come down, giving further savings.

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