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SILICIFIED MICROCRYSTALLINE CELLULOSE, MODERN CO-PROCESSED EXCIPIENT FOR LOW DOSE SOLID DOSAGE FORMS

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ABSTRACT
Low dose 75 mg aspirin tablets are widely used for adults in arthritis, rheumatic fever, pain and to reduce uric acid excretion. Low dose formulation are manufactured by wet granulation method, which is time consuming and laborious. However these days direct compression method is in trend. Direct compression method is cost effective and gives better productivity than wet granulation method. Micro-crystalline cellulose and silicified micro-crystalline cellulose are suitable excipients for direct compression method. Silicified microcrystalline cellulose is favorable for low dosage forms. It controls drug content uniformity in the tablets. Silicified microcrystalline cellulose has outstanding flow-ability, when it is mixed with API, material fills into die equally during tableting. In this study, we compared SEM analysis, flow-ability and tablet profile of Silicified microcrystalline cellulose with microcrystalline cellulose. We used HiCel™MCC and HiCel™SMCC to evaluate this study. Physical properties of HiCel™SMCC are novel for low dose tablet.

KEYWORDS: SEM analysis, Flow fraction, Mohr's stress circle, weight variation, content uniformity of drug,

INTRODUCTION
Aspirin comes under NSAIDs (Nonsteroidal anti-inflammatory drugs and antipyretic analgesics) drugs, it is acetyl derivative and chemical name is Acetylsalicylic acid.[1] It is used as analgesic, as anti-inflammatory, antipyretic and in acute rheumatic fever, rheumatoid arthritis and osteoarthritis. Aspirin is used as OTC (over the counter) drugs.[2] Two different low dosage aspirin tablets 75 mg and 81 mg are available in the market.[3] Low dosage Aspirin tablets can be manufactured by either wet granulation or roller compaction or direct compression (DC). Wet granulation method is very popular and old method for low dosages form. Direct compression method is used in pharmaceutical industries for making low dose, medium dose and high dose because direct compression is convenient and fast.[4] Without best quality excipients support, DC could be a difficult method for manufacturing tablets. It may deviate tablet profile parameters viz. Hardness, Friability and Disintegration time.[4] However, many pharmaceuticals excipients i.e. microcrystalline cellulose, silicified microcrystalline cellulose and lactose directly support direct compression method. These excipients improve the tablet profile such as weight uniformity, hardness, friability, disintegration time and dissolution profile.[5]

Microcrystalline cellulose belongs to cellulose group. It is a high degree polymer and through controlled hydrolysis, it converts to low degree polymer. Hydrolysis reaction is done in presence of mineral acid and neutralized with ammonia solution. Spray dried material in white color, granular, free flowing powder.[6] Different grades of MCC are available in market, which are used to manufacturing both DC and wet granulation formulation.[7] However, with some API's, there are functional problems like poor flow, reduced surface area for bonding etc, which could result in poor quality of tablets. To eliminate the functional problems outlined, it is suggested to use co-processing of MCC with other established excipients.[5] Co-processing MCC may improve the preference of materials which is used in direct compression. There are many co-processing exipients used to manufacture the direct compression formulation. This process produces a material with beneficial characteristics with respect to flowability, mechanical strength and disintegration.[8]

Silicified microcrystalline cellulose excipient is co-processed MCC. It is a combination of 98 % microcrystalline cellulose and 2% colloidal silicon dioxide, through wet mixing and dried by spray dryer.[9] Silicified microcrystalline cellulose has excellent flow properties and gives satisfactory tensile strength on less compaction force. In low dosages solid formulation it gives excellent weight uniformity. It absorbs very less moisture from environment.[10]

The main aim of study is find to direct compressible excipient for low dosages formulations. In this study comparative analysis of SEM, physical profile and tableting profile are done. Flow ability of both excipients HiCel^{TM}SMCC and HiCel^{TM}MCC are tested by FT4 powder rheometer. Flowability is represented by flow fraction (ff_c), shear stress, Mohr's stress circle and angle of repose. Select. Low dose Aspirin tablets are manufactured using two different excipients i.e. HiCel^{TM}MCC and HiCel^{TM}SMCC by direct compression.

EXPERIMENTAL SECTION

HiCel^{TM}MCC90M and HiCel^{TM}SMCC90M manufactured at "Sigachi Industries Pvt. Ltd" were used to investigate this study**.** Acetyl Salicylic acid was purchased from "The Andhra Sugars Limited". Povidone K-30 procured form "Anshul Life science" and Purified Talc were used for manufacturing dispersible Acetyl salicylic acid tablet.

SCANNING ELECTRON MICROSCOPE ANALYSIS[11]

HiCel^{TM}Silicified microcrystalline cellulose 90M SEM analysis was done at IIT Mumbai and HiCel^{TM}90M microcrystalline Cellulose analysis done at IIT Gandhinagar (Gujarat). 1 to 2 milligram sample was used for analysis. SEM images micrograph was taken at X 5000 magnification and particles surface visualized at 1µm. Same sample quantity of HiCel^{TM}Microcrystalline cellulose was mounted on double sided tape on aluminum stabs and sputter coated with platinum with the help of auto fine coater JEOL (JFC.1600). Micrographs were taken at appropriate magnification and particles surface visualization detailed analyzed by scanning electron microscope JEOL (JSM.76000 F).

FLOWABILITY ANALYSIS

Cohesion and Flow fraction analysis[12,13]

Particle size, Shape, Surface characteristic will greatly influence the flow of powder. Stress shear and flow fraction of microcrystalline cellulose samples were analyzed using FT4 Powder rheometer (Freeman technology). All samples were tested at 6 kpa shear and preshear, 23.5 mm blade and 25 mm×10 ml split vessel were used. Sample vessel made by Kulfimix Carragenan material.

The rotational Shear Cell module consists of a vessel containing sample (powder) and Shear head to induce both vertical and rotational stresses. The Shear head moves downward inserting the blades into the powder and induces a normal stress as the shear head face contacts the top of the powder. The Shear head continues to move downward until the required normal stress (σ)is stable. Slow rotation of the shear head then begins, inducing a Shear stress(τ). A Shear plane is established below the ends of blades.

When the powder bed resists the rotation of the Shear head, the Shear stress increases until the bed fails of Shears, at this time maximum Shear stress is observed and the normal Stress is maintained constant throughout the Shear step.

Flowability of bulk material is characterized mainly by its unconfined yield strength (σc), as a function of the consolidation stress($\sigma 1$) and the storage period (t). Cohesive powder will have higher Cohesion values and unconfined yield strength (σc) consequently a low flow fraction (ff_c), a high value of ffc indicates that the powder flow is free flowing[12]. ffc calculated by below equation-

$$ff_c = \frac{\sigma 1}{\sigma c} \quad (1)$$

$\sigma 1 =$ consolidation stress (CS)

$\sigma c =$ Unconfined yield strength (UYS)

Mohr Stress circles[14]

After performing a stress analysis on a material body assumed as a continuum, the components of the Cauchy stress sensor at a particular material point are known with respect to coordinate system. The Mohr circle is then used to determine graphically the stress components acting on a rotated coordinate system i.e., a differently oriented plane passing through that point.

The normal stress (σ) σ and Shear stress (τ) of each point on the circle, are the magnitudes of the normal stress and shear stress components, respectively, acting on the rotated coordinate system. In other words, the circle is the locus of points that represent the state of stress on individual plants at all their orientations, where the axis represent the principal axis of the stress element.

ANGLE OF REPOSE[15]

Pour 30g 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. Using following formula find the calculated value this value check natural tangents chart for angle of repose and reported. The angle of repose (θ) for samples was calculated using the below formula.

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

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

Preparation of dispersible Aspirin tablets[16]

Dispersible Aspirin tablet containing 75 mg Acetyl salicylic acid (Aspirin) was prepared by direct compression method. Each formulation, we have used different excipients in same quantity and manufacturing formula shown in table no.2. Required material was measured accurately and mixed uniformly. 150 mg Aspirin tablets were compressed with 10-station proton mini press tableting machine (Model no. MINI PRESS

10 "D") using D tooling dies and concave punches. Sigachi logo is on upper punch and "Sigachi" word embossing is on lower punch.

Table No-1: Dispersible Aspirin tablet manufacturing formula.

Ingredients	W/W (%)	Mass per tablet(mg)	
		F_1	F_2
Aspirin	50.00	75.00	75.00
Povidone K-30	9.67	14.50	14.50
Talc	0.33	0.50	0.50
HiCel™MCC 90M	40.00	-	60.00
HiCel™SMCC 90M	40.00	60.00	-
Total tablet mass	100%	150mg	150mg

MCC- Microcrystalline cellulose, SMCC- Silicified microcrystalline cellulose, F_1 – Silicified Microcrystalline cellulose containing formula, F_2 –Microcrystalline cellulose containing formula.

EVALUATION OF DISPERSIBLE LOW DOSE ASPIRIN TABLET

Physical appearance[17]

The general appearance of tablet is essential for consumer acceptance. The manufactured aspirin tablets were evaluated for size, shape and organoleptic properties like color and defects i.e. sticking, capping, lamination and picking.

Weight Variation Test[18]

10 tablets were taken from each batch and each tablet was weighted individually using the electronic digital balance (Mettler Toledo, Model No. ML802/A01). The average weight of all tablets was calculated and considered as the standard weight of the individual tablet. Than all the tablets were individually weighted and the percentage weight variation was calculated to determine whether the individual weight is within the range or not. As per USP limits ±7.5 % variation is allowed for 150 mg tablets. The tablets meet the USP test if not more than two tablets are outside the percentage limit and if no tablet differ by more than two times of the percentage limit.

Hardness Test[19]

Hardness is a force required to break a tablet, it is also known as crushing strength. It is an indication of its strength. Randomly 10 tablets were taken from each formula batch. Electronic digital hardness test machine (Labindia tablet hardness tester, Model No.-TH1050 M) was used to analyze hardness of tablets. Single tablet was placed between two anvils, force applied to the anvils, and the tensile strength that just required breaking the tablet is recorded. The values of hardness were expressed in kp[kgf] unit.

Friability Test[20]

Percentage friability was determined by using friability tester (LABINDIA, Model No. FT1020). 10 tablets were taken and weighed by using electronic digital balance which was considered as the initial weight. All the tablets were placed in the drum of friability tester and allowed to rotate 100 times at 25 rpm. After 100 revolutions, 10 tablets were removed and re-weighed which was considered as the final weight. As per USP, the tablets should not lose more than 1% of their total weight.

Disintegration Test of Tablet[21]

The tablet breaks down into smaller particles is called disintegration. This test was carried out at 37±2°C in 600 ml Demineralized water. A set of six tablets has taken and one-one tablet was introduced in each tubes, disk is placed and basket get positioned in one liter beaker containing 37±2°C temperature of water. Time noted when tablet was disintegrated into smaller particles.

Dissolution Test of tablet[22]

Dissolution test of aspirin tablet was performed as per USP method, apparatus type 1 (Basket type) used. Basket speed was fixed at 50rpm per minute in 500ml of 4.50±0.05 pH 0.05 M acetate buffer solution at 37±2°C. Checked the absorbance of aspirin tablets by using UV VIS-Spectrophotometer (Shimadzu model no-1800). Each sample (n=6) was determined at 265 nm wavelength. Calculated the percentage of dissolution using below given Eq.

10ml sample from each vessel was taken after 30 mins. All samples were filtered with whatman filter paper (No.42). 1ml sample from each was taken and determined the active ingredient concentration by UV VIS-Spectrophotometer at λ=265nm.

$$\text{Percentage of dissolution} = \frac{Sampleabsorbance}{standardabsorbance} \times \frac{standardconc}{sampleconc} \times Purityofdrug \quad (3)$$

STATIATICAL ANALYSIS[23]

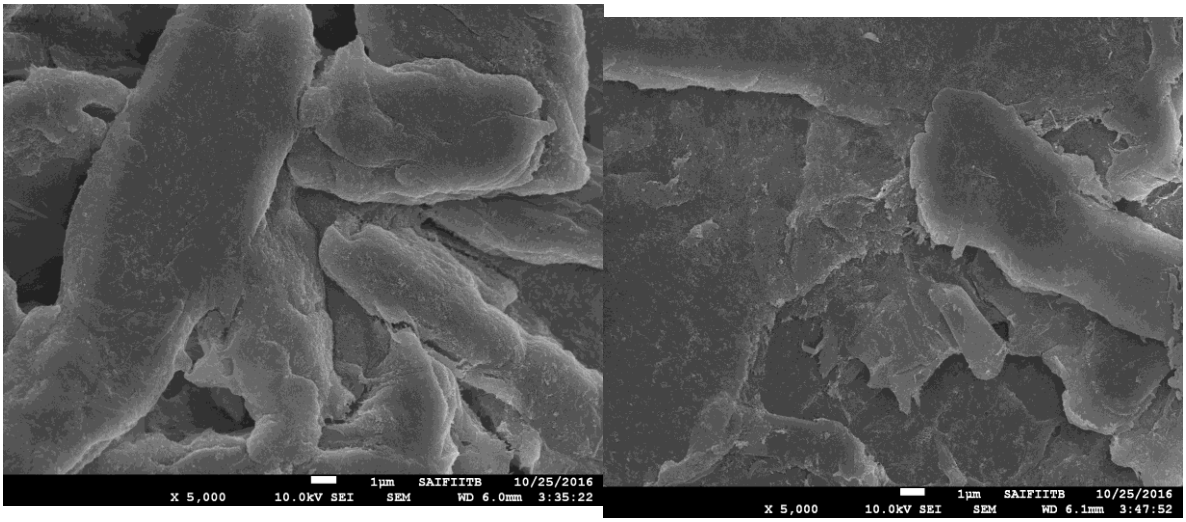
Low dose Aspirin tablet parameters (Weight variation, Hardness variation, disintegration time variation and drug content variation) were calculated using with the statistical techniques i.e. mean, standard deviation and relative standard deviation.

RESULT AND DISCUSSION

EVALUATION OF HICEL™SMCC AND HICEL™MCC

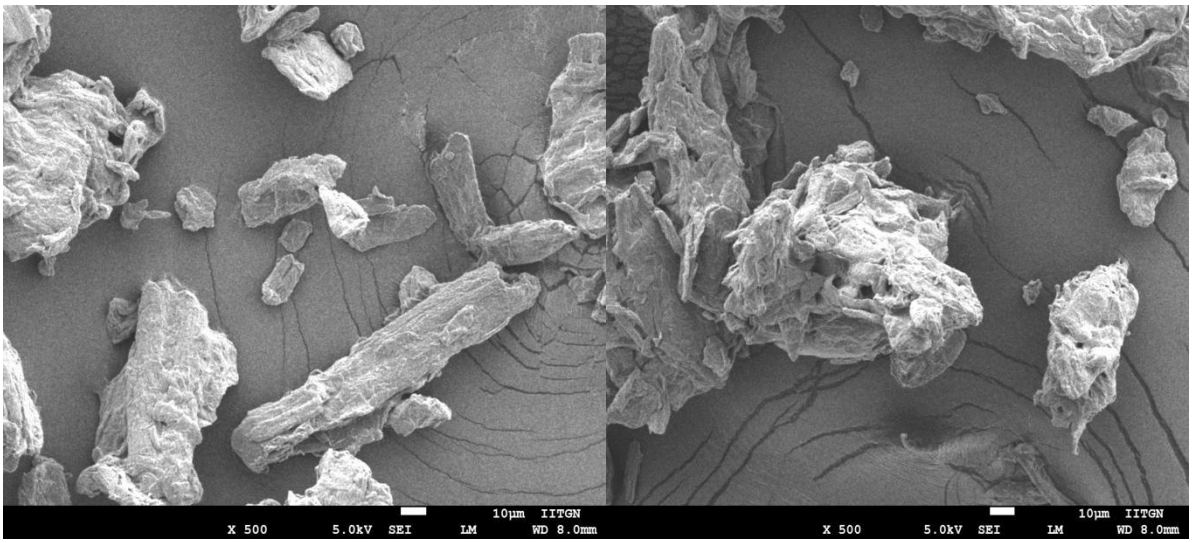
SEM ANALYSIS

In SEM images shows silicified microcrystalline cellulose and microcrystalline cellulose particles are rod shaped. SMCC particles surface smoother than microcrystalline cellulose particles images of both samples are shown in fig.1. and fig.2 respectively.



(a) **(b)**

Fig.1: a) and (b) SEM images of HiCel^{TM}Silicified microcrystalline cellulose at X 5,000 magnification.



(c) **(d)**

Fig. 2: (c) and d) SEM images of HiCel^{TM} Microcrystalline cellulose at X 500 magnification.

FLOW ANALYSIS

HiCel^{TM} SMCC has less cohesion, unconfined yield strength and high ff_C value shown in fig.3. Fig.4 (e and f) indicate the low shear stress (shifted and un-shifted) of HiCel^{TM} SMCC. Fig. 5 (g) Moher's stress circle of HiCel^{TM} SMCC also indicated that it has low shear stress than HiCel^{TM} MCC.

Table 2: Summary of result obtained by Shear and wall fraction test at 6kPa, using FT4 powder rheometer and their parameter measured during the shear test.

Name of Sample	Cohesion(kPa)	σc (kPa)	$\sigma 1$(kPa)	ffc ($\sigma 1/\sigma c$)	$\varphi e(°)$	$\varphi s(°)$	$\varphi(°)$
HiCel^{TM} Microcrystalline cellulose	0.37	1.47	12.09	8.22	49.02	36.96	40.11
HiCel^{TM} Silicified microcrystalline cellulose	0.10	0.35	9.86	28.40	32.03	29.44	31.16

σc: unconfined yield strength, $\sigma 1$:major principle stress, ffc: flow fraction, φe: effective angle of internal fraction, φs: Angle of internal fraction steady state,φ: angle of internal fraction.

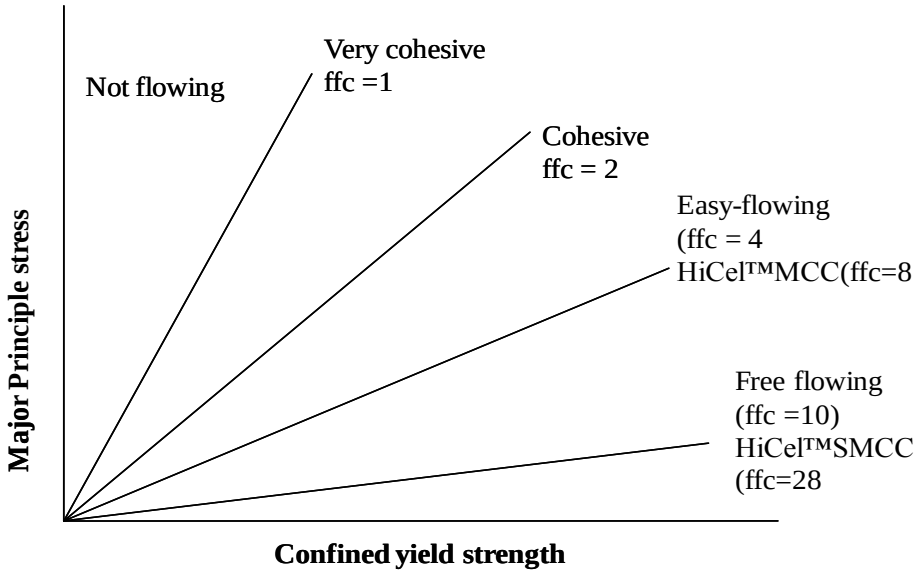
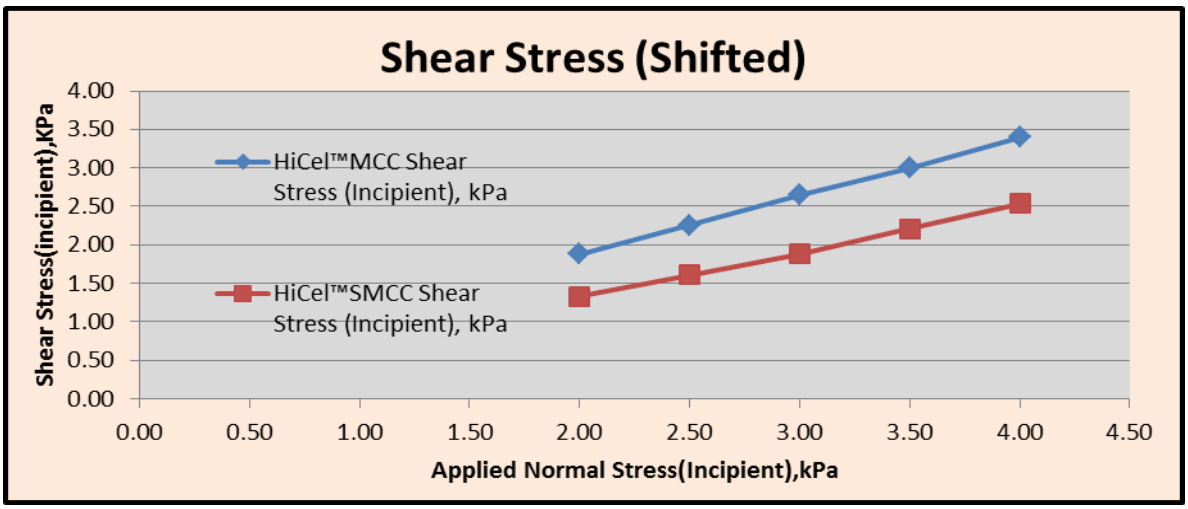
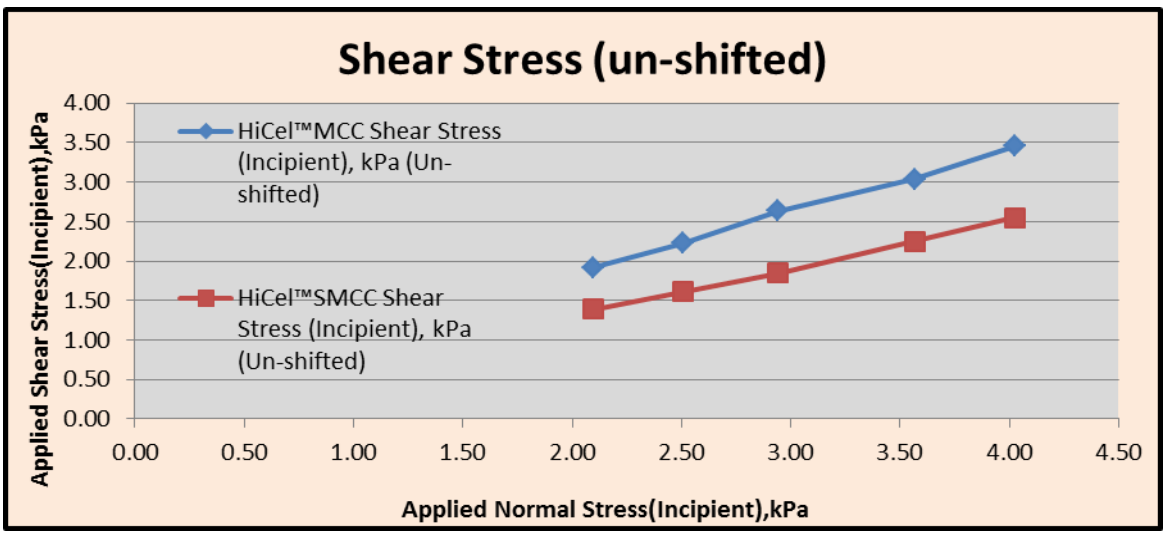


Fig.3: Instaneous flow function

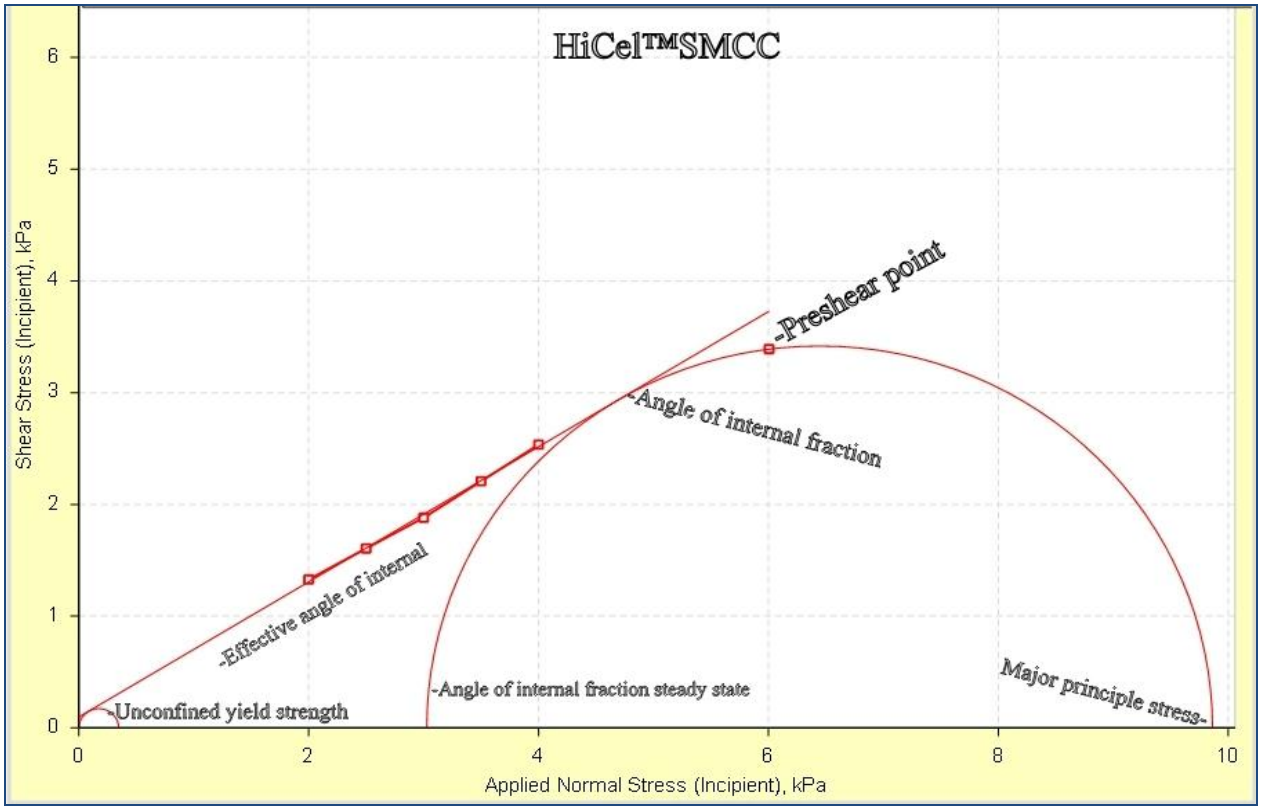


(e)

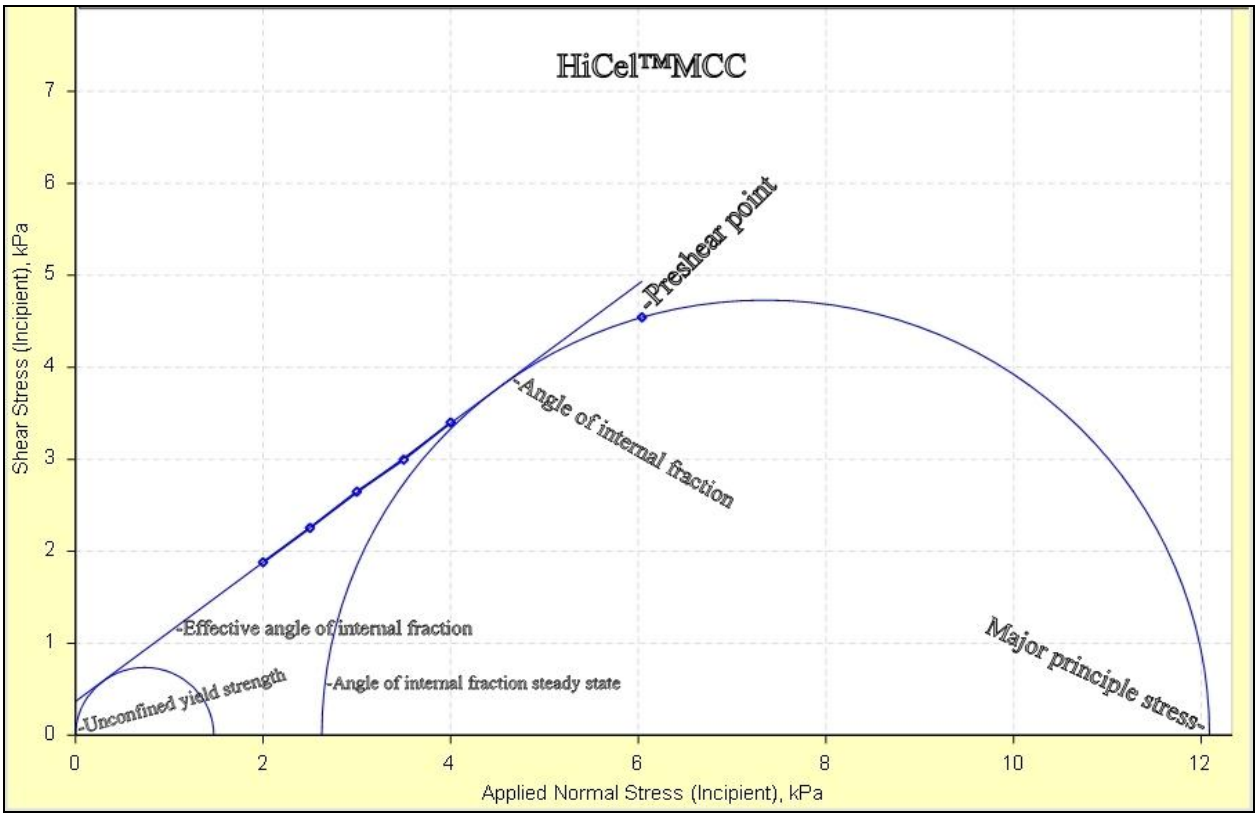


(f)

Fig. 4: (e) and (f) represent the Yield Loci of both samples HiCel™Silicified microcrystalline cellulose and HiCel™Microcrystalline cellulose.



(g) HiCel™SMCC: fig. shows unconfined yield strength circle (σc) length is 0 to 0.35kPa and major principle stress circle length is 3.0 to 9.86 kPa.



(h) HiCel™MCC: fig. shows unconfined yield strength circle (σc) length is 0 to 1.47kPa and major principle stress circle length is 2.8 to 12.09 kPa.

Fig.5: (g) and (h) represent the Mohr Stress circle of HiCel™Silicified microcrystalline cellulose and HiCel™Microcrystalline cellulose respectively.

ANGLE OF REPOSE

Silicified microcrystalline cellulose and Microcrystalline cellulose angle of repose results are mentioned in table no.4.

Table 4: Angle of repose details of both samples HiCel™SMCC and HiCel™MCC.

Name of sample	Peak height	Chart value (USP)	Angle of repose
HiCel™Silicified Microcrystalline Cellulose	10.75	0.6875	$34^0 40'$
HiCel™Microcrystalline Cellulose	10.90	0.750	37

EVALUATION RESULT OF DISPERSIBLE ASPIRIN TABLET

Weight Variation

SMCC containing Aspirin tablets (batch number F1) have weight uniformity. In F2 batch number weight variations have been found.

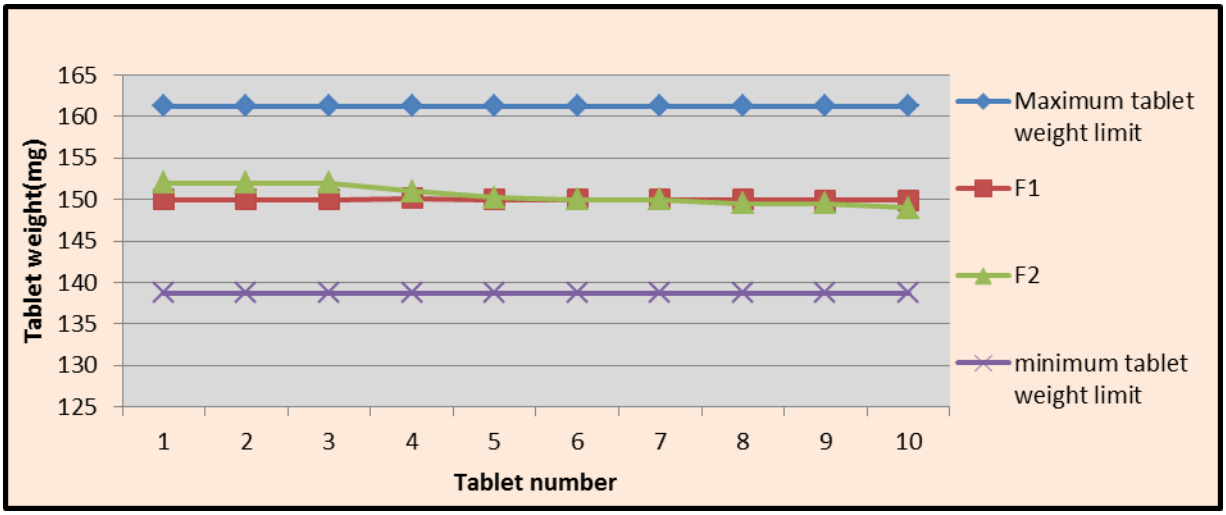


Fig.6: weight variation low dose of Aspirin tablet, F_1 _ Silicified Microcrystalline cellulose containing formula, F_2 Microcrystalline cellulose containing formula.

Hardness Test

HiCel™ SMCC containing tablets are found excellent hardness. Both batches hardness result shown in fig.7.

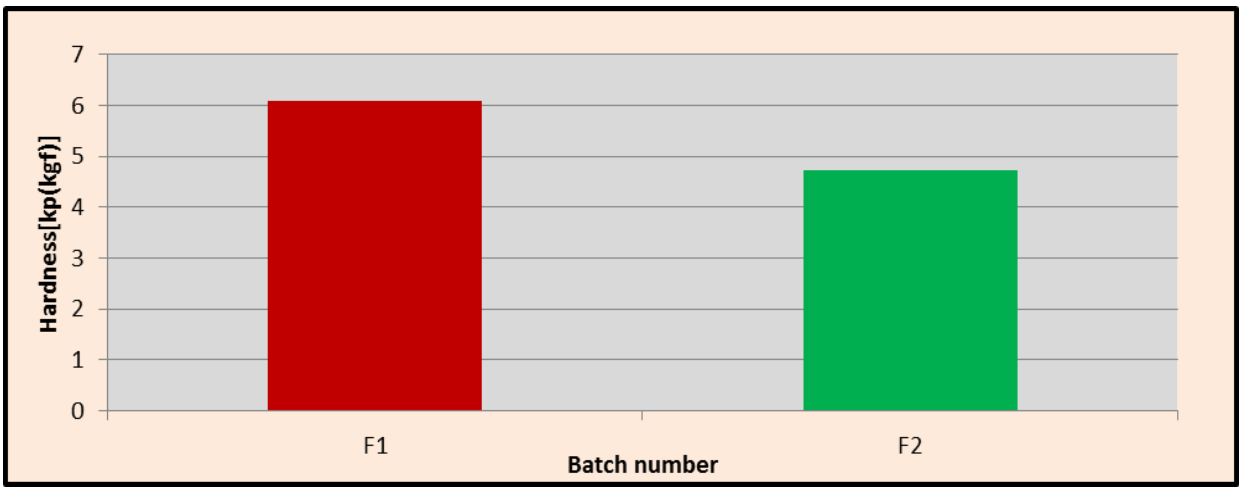


Fig.7: hardness variation of low dose Aspirin table, F_1 _ Silicified Microcrystalline cellulose containing formula, F_2 Microcrystalline cellulose containing formula.

Friability Test

Friability of test of both batches is under USP limit, and friability shown in fig.8.

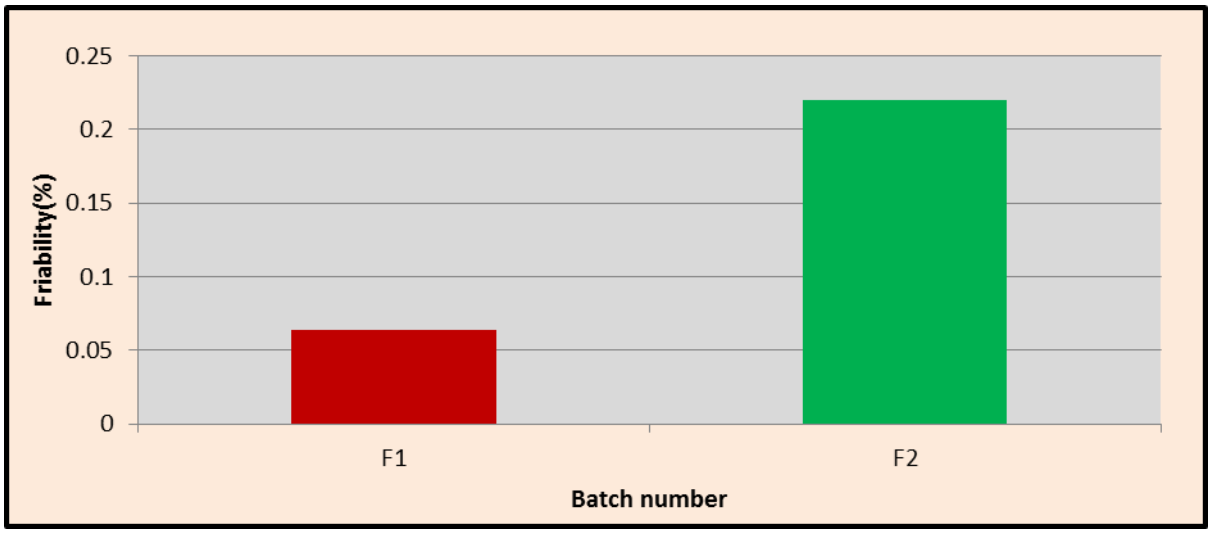


Fig. 8: Percentage friability of low dose Aspirin tablet, F_1 _ Silicified Microcrystalline cellulose containing formula, F_2 Microcrystalline cellulose containing formula.

Disintegration test

Disintegration test of both batches tablets have less than one minutes. Average D.T of tablets is mentioned in fig.9.

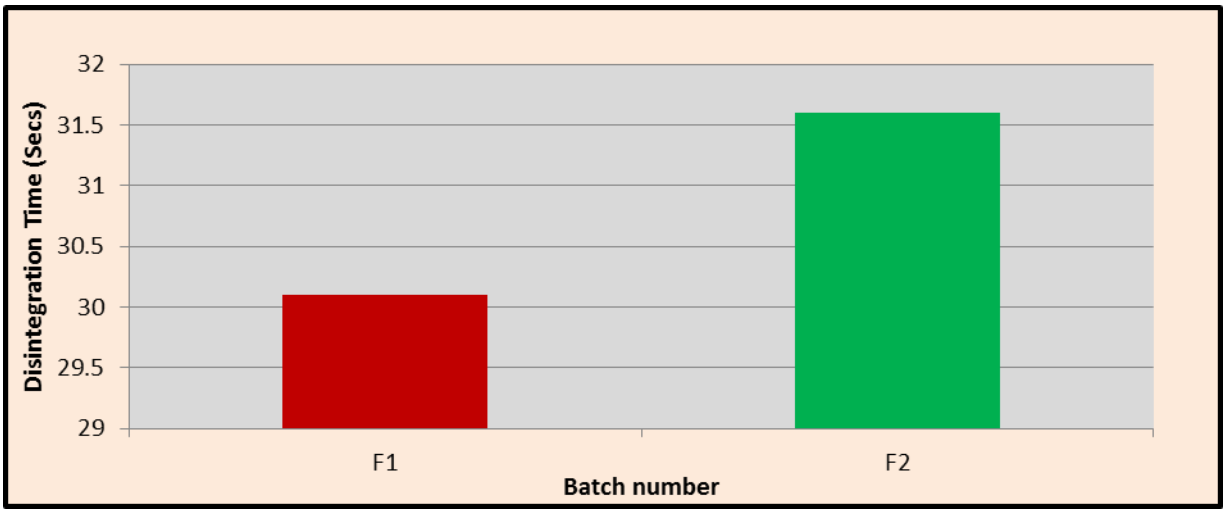


Fig.9: Disintegration time of low dose Aspirin tablet, F_1 _ Silicified Microcrystalline cellulose containing formula, F_2 Microcrystalline cellulose containing formula.

Percentage of drug present in tablet

This test carried out with dissolution test apparatus. All tablets dissolution time is 30 mints after 30 mints sample withdrawal from each beaker and dilute with same concentration of dilution take reading with UV Spectrophotometer. Calculate percentage of drug present into tablet.

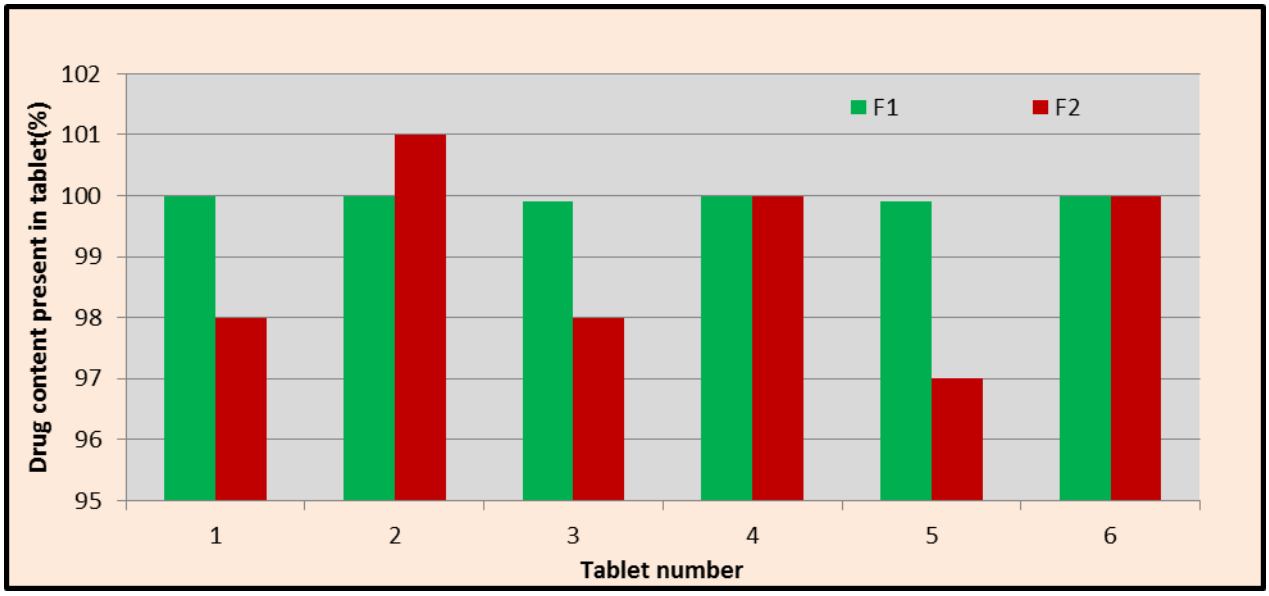


Fig. 10: Drug content uniformity of low dose aspirin tablet, F_1 _ Silicified Microcrystalline cellulose containing formula, F_2 Microcrystalline cellulose containing formula.

Table 5: Low dose Aspirin tablets weight variation, hardness variation, disintegration time variation and Aspirin content present in tablet variation calculated by standard deviation, relative standard deviation.

Name of test	F1 (HiCel™SMCC)			F2 (HiCel™MCC)		
	Mean	SD (σ)	R SD(%)	Mean	SD (σ)	RSD(%)
Tablet Weight (mg)	150.0	0.0568	0.0378	150.5	1.1468	0.7619
Hardness [kp(kgf)]	6.10	0.0422	0.6935	4.7	0.1033	2.1881
Disintegration Time (Sec)	30.2	0.4082	1.3533	31.7	1.2111	3.8244
Drug content present in tablet (%)	100	0.05164	0.0166	99	1.54919	1.5648

SD= standard deviation, RSD= relative standard deviation, SMCC= Silicified Microcrystalline cellulose, MCC= Microcrystalline cellulose

ABBREVIATIONS

API: Active pharmaceutical ingredient, B.D: Bulk density, ff_c: flow fraction, g: gram, LBD: loose bulk density, %: percentage, MCC: Microcrystalline cellulose, MC: moisture content, mg: milligram, PSD: Particle size distribution, TBD: tapped bulk density, SEM: scanning electron microscope, SV: sample volume, WS: sample weight, σ: sigma, USP: united states pharmacopoeia.

CONCLUSION

Presented study has proven that HiCel™SMCC is very good excipient for low dose direct compressible solid formulation in comparison to microcrystalline cellulose. It has excellent flow property which controls tablet weight variation and carries equal drug content. In SEM analysis, HiCel™SMCC particles surface are smooth whereas MCC surface is slightly rough. Low angle of repose and high flow fraction (ff_c value) both indicate that SMCC has excellent flowability. Silicified microcrystalline cellulose has high ff_c value, less cohesion and low shear stress compared to microcrystalline cellulose. HiCel™SMCC (Formula F1) has very good tablet profile, it has no weight variation, less friability, disintegration time, good tablet hardness and aspirin content uniformity in the all tablets.

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CONFLICTS OF INTERESTS

The authors state and confirm no conflict of interests. No direct funding was received for this study.

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