Evaluation of calcium magnesium silicate-date palm cellulose as a potential tablet excipient.

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ABSTRACT

A new excipient was prepared using natural resources and bio-wastes such as sodium silicate, brine and date palm cellulose. The prepared excipient is water-insoluble silicate salt precipitated in date palm cellulose (WISS-DPC). The aim of this study was to evaluate the potential use of this new material as an excipient for formulating oral solid dosage forms. Diclofenac sodium and paracetamol tablets were manufactured using direct compression and wet granulation methods, respectively. The surface of the tablets was studied using AFM and SEM. FTIR and DSC provided a guarantee of compatibility of the excipient with the model drugs. The prepared tablets passed Pharmacopeial and Non-Pharmacopeial tests. Tablets prepared using WISS-DPC were harder, had rapid disintegration and rapidly dissolved compared to those produced with microcrystalline cellulose. The compactibility of the WISS-DPC was not affected by dilution with drugs or wet granulation. This new excipient could be used in pharmaceutical industry.

KEY WORDS: Water-insoluble silicate salt, date palm cellulose, co-precipitate, excipients, tablets, oral solid dosage forms

INTRODUCTION

A new excipient was prepared using natural resources and bio-wastes available in Saudi Arabia. It was manufactured using brine obtained from a desalination plant, silica from desert sand and cellulose extracted from the date palm tree. In a previous study, the brine and sodium silicate were reacted together to produce water-insoluble calcium magnesium silicate salt (WISS) (1). This insoluble silicate salt was used for the production of a new pharmaceutical excipient after co-precipitation with cellulose from the date palm tree (DPC). The new product showed unique characteristics such as better flowability and compactibility. The objective of the study here was to evaluate the performance of the co-processed excipient for use in the formulation of oral solid dosage forms. Tablets are popular dosage forms as they have several advantages over other dosage forms (2). Powders are transformed, when compressed on a tablet machine, into tablets which increases the intermolecular forces between the particles. Fragmentation and plastic and elastic deformation are the main processes that increase particle bonding during compression (3). Ideal tablet diluents have balanced elastic and plastic

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properties (4). The compression process of WISS-DPC was studied further and it showed that WISS-DPC exhibit increased plastic flow and lower elastic recovery compared to DPC (1). Tablets prepared from WISS-DPC appear to have better compressibility and disintegration properties than DPC (1).

In this work, a new excipient was developed using Saudi Arabia biowastes to pepare diclofenac sodium (Diclo) and paracetamol (PAR) tablets. The tablets were evaluated and compared with tablets manufactured using an existing, well known, direct compression excipient i.e., microcrystalline cellulose (MCC).

Materials and methods

Materials

The date palm tree trunk, *Phoenix dactylifera*, family (Arecaceae, or Palmae), was obtained from an old tree in the city of Taif, KSA. Brine sea water (BSW) was obtained from Red Seawater after desalination from Shuaibah Desalination Plant, Jeddah, KSA. Diclofenac sodium, paracetamol, colloidal silica and microcrystalline cellulose (Avicel® PH 101) were obtained from Al Rai Company, a local Pharmaceutical Manufacturer in Jeddah, KSA. All chemicals and reagents used were of analytical grade and used as received.

Methods

Preparation of the WISS-DPC coprecipitate excipient using natural resources

A detailed description on the preparation of the new excipient has been previously published (1).

Drug/excipient compatibility

FTIR

The compatibility of drugs with the excipient was investigated using Fourier Transform Infra-Red Spectrometer (FTIR). Separately 5 mg of the pure drug or a physical mixture of 1:1 weight ratio of drug/excipient was mixed with 300 mg of KBr. Small portions of each mixture were compressed to form a disc and scanned from 400-4000 cm^{-1}.

Differential Scanning Calorimetry (DSC)

The thermal behavior was studied using DSC (STA 449 F1 Jupiter®NETZSCH, Germany). 5 mg of the samples (pure drug or the physical mixture of 1:1 weight ratio of drug/excipient) were heated from 25 to 300°C at a heating rate of 10°C min^{-1} in an open aluminum pan using an empty pan as a reference.

Preparation of Diclo tablets using direct compression method

The co-precipitated WISS-DPC powder was passed over a mesh of 300 μm**.** 25 mg of Diclo and 275 mg of WISS-DPC powders were mixed together for 5 minutes using a mortar and pestle. The mixture was compressed into a flat tablet using an Instron press (Model 3367, Instron Ltd, USA) with a compression load of 15 kgf. Tablets were prepared with MCC using the same method for comparison.

Preparation of PAR tablets by wet granulation

The co-precipitated WISS-DPC powder was passed over a mesh of 300μm. The drug and WISS-DPC (5:3 w/w) were mixed in a cube mixer for 15 minutes. The powder was transferred to a planetary mixer and sufficient water was added to form wet mass. During the addition of water, the mixture was continuously stirred which was continued for 10 minutes after all the water had been added. The wet mass was passed through a 2.5 mm sieve and dried in an oven at 50°C until the moisture content was less than 2% w/w. The dried granules were passed through a 0.8 mm sieve. An amount of granules equivalent to 500 mg PAR was weighed and compressed into tablets using an Instron press (Model 3367, Instron Ltd, USA) with a compression load of 15 kgf. PAR tablets were prepared from MCC using the same procedure for comparison.

Quality control tests

Weight variation

20 tablets were weighed individually using an analytical

balance (ALC 210.4 sartorius, Germany). The average weight and standard deviation were calculated. The individual tablet weight was compared with the average weight.

Diameter and thickness

The diameter and thickness of 10 tablets were determined using a Digital caliper apparatus (KINEX, China). Averages and standard deviations of their diameter and thickness were calculated.

Friability testing

According to USP 41-NF 36, for tablets with a unit mass of less than 650 mg, a sample of whole tablets corresponding to 6.5 g should be weighed. For tablets with a unit mass of more than 650 mg, a sample of 10 whole tablets should be weighed. 10 tablets of PAR (average weight > 650 mg) or 20 tablets of Diclo (average weight < 650 mg) were weighed using an analytical balance and then placed in the friability tester (FAB-25 Logan, USA) which rotated at 25 RPM. The tablets were re-dusted and weighed again. The difference in weight and % loss was calculated using Equation 1:

$$\%F = \left\{\frac{(W - W_0)}{W_0}\right\} x\,100 \qquad \text{Eq. 1}$$

where, %F = Friability in percent, W = Initial weight of tablet and W_0 = Weight of tablet after the test.

Determination of drug content

Assay of Diclo tablets

USP 41-NF 36 analytical method was used for the determination of drug content using high performance liquid chromatography HPLC (Shimadzu, Japan) apparatus. The conditions employed were: C18 column (Thermo); detection at 276 nm; eluent, methanol-phosphate buffer pH 2.5 (volume ratio 7:3). The flow rate was 1 ml/min and the sample size 100 µl. A calibration curve was constructed using pure Diclo and linearity was demonstrated by correlation coefficient. The sample was prepared as follows: 10 tablets were dissolved in 800 ml methanol (50%) shaken for 30 minutes, and sufficient amount of the mobile phase to produce 1000 ml, filtered through a 0.45 µm filter, diluted and assayed.

Assay of PAR tablets

Drug content was determined according to BP 2018 using UV spectrophotometer (P3000Optima, Japan) at 257 nm. The sample was prepared as follows: 20 tablets were weighed and crushed into powder. A quantity of the powder containing 0.15g of PAR was added to 50 ml of 0.1 M sodium hydroxide then diluted with 100 ml water, shaken for 15 minutes and sufficient water was added to produce 200 ml of the mixture. The mixture was filtered and 10 ml of the filtrate was diluted with 100 ml of water and assayed.

Dissolution testing

The dissolution of Diclo and PAR tablets was examined according to USP XXII paddle method at 37±1°C and 50 RPM using dissolution apparatus (DT 620 Erweka, Germany). The dissolution medium for Diclo was 900 ml phosphate buffer at pH 6.8 (prepared according USP 41-NF 36). For PAR, 900 ml of phosphate buffer at pH 5.8 was prepared according to BP 2012. At predetermined time intervals, 3 ml aliquots were withdrawn and immediately filtered through 0.45 µM Millipore filter. The same volume of fresh medium was added to the test medium. The concentration of Diclo in the filtrate was determined by HPLC method (USP 34) as mentioned in drug content section, while the concentration of PAR was determined spectrophotometrically at 257 nm.

Disintegration testing

One tablet was placed in each of the six tubes of the disintegration apparatus (Qc-21 Hanson, Japan). The disintegration medium was 900 ml of water at 37 ± 1°C (USP 41 - NF 36). The time required for tablet fragments to pass through 10 mesh screen was recorded. The average time of the six tablets and standard deviation were calculated.

Breaking force testing

10 tablets were tested using a hardness tester (TBH 225 Erweka, Germany). The force equired to fracture each tablet a long its diameter was recorded and the average and standard deviations were calculated. The literature refers this test as crushing strength or hardness test which is incorrect (5).

Atomic Force Microscopy (AFM)

The surface of the tablets (20x20 μm) from the center of the tablets were scanned using an AFM (Dimension® Edge TM Atomic Force Microscope, Bruker) under tapping mode operation.

Scanning Electron Microscope (SEM)

Tablet surfaces were scanned from the center of the tablets using a SEM (Model 6390 LA-Jeol, Japan).

Statistical analysis

A one-way ANOVA test was used for comparison. The difference was considered statistically significant when the probability value (P) was less than 0.05.

RESULTS AND DISCUSSION

Preparation of Diclo and PAR Tablets

In a previous study tablets were prepared using only the WISS-DPC aand their physico-chemical properties were characterized (1). In this study, the novel excipient (WISS-DPC) was added to the formulation with the drugs to investigate its performance with an active pharmaceutical ingredient (API). Two methods of tablets manufacturing were explored, direct compression to show that the compressibility of the WISS-DPC is not affected by adding the API and wet compression to confirm that the compressibility is retained after wet granulation. The Diclo tablets were manufactured using direct compression and the PAR tablets were prepared using wet granulation.

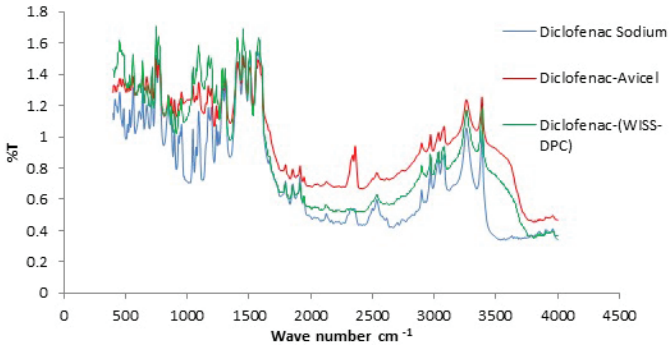

Figure 1 FTIR Spectra of pure diclofenac sodium and physical mixtures of diclofenac with excipients.

WISS-DPC drug compatibility

FTIR

To evaluate drug-excipient compatibility, FTIR scans were examined for the presence of major peaks of drugs, the presence of new peaks or the disappearance and shifting of peaks due to an interaction with the WISS-DPC. Figure 1 shows that the characteristics peaks in the FTIR spectrum for the Diclo were N-H stretching at 3200 cm^{-1}, Dichlorophenyl ring stretching at 1556 cm^{-1} and the carbonyl group at 1650 cm^{-1} (6). The FTIR of the physical mixture of the excipient component was run to illustrate the dilution effect. Both the Diclo-physical mixture and Diclo-co-precipitate exhibited the distinctive peaks of the pure drug (Figure 1), which confirmed the absence of interaction between the drug and the component of the WISS-DPC.

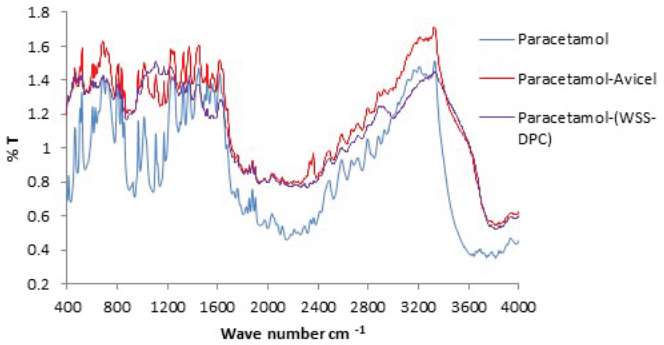

Figure 2 FTIR of pure paracetamol and physical mixtures of paracetamol with excipients.

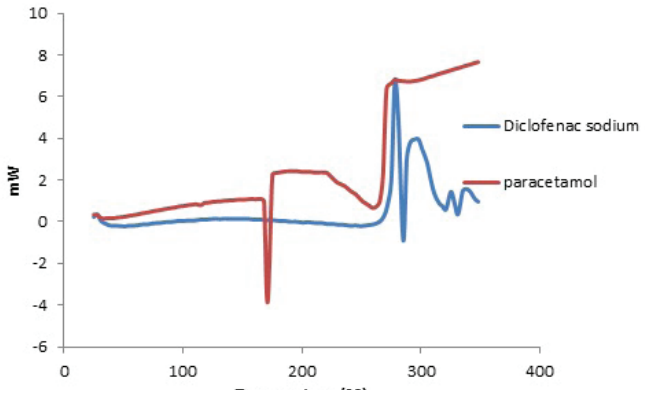

Figure 3 DSC thermograms of paracetamol and diclofenac sodium.

Figure 2 showed PAR peaks at 3360 cm^{-1} which was assigned to N-H amide stretch, 3000-3500 cm^{-1} due to phenolic OH stretch and the aromatic overtone region observed at 1840-1940 cm^{-1} (7). The nature of the peaks for the PAR-copreciptate were almost the same as the pure drug indicating the absence of any chemical interaction between PAR and WISS-DPC (Figure 2).

DSC

DSC was also used to investigate drug-excipient compatibility. Pure PAR melted at 170°C as shown in Figure 3. This result agrees well with previous studies (8, 9). PAR was mixed with MCC or WISS-DPC at a ratio of 1:1. The thermograms of the physical mixtures are shown in Figure 4. These were compared with theoretical thermograms calculated by taking the summation of the average of heat flow of both components. There was a high degree of similarity between the theoretical and practical thermograms. This suggests an absence of interaction between the two physical mixtures studied i.e., PAR and WISS-DPC or PAR and MCC. Other studies have shown compatibility between PAR and MCC (8, 10).

DSC thermogram of Diclo is shown in Figure 3. An exothermic peak appeared at about 300°C suggesting decomposition of Diclo before reaching its melting point. The same trend has been reported previously (11). Figure 4 indicates that Diclo was compatible with MCC and WISS-DPC.

The two methods, FTIR and DSC, show the compatibility of the two model drugs, Diclo as

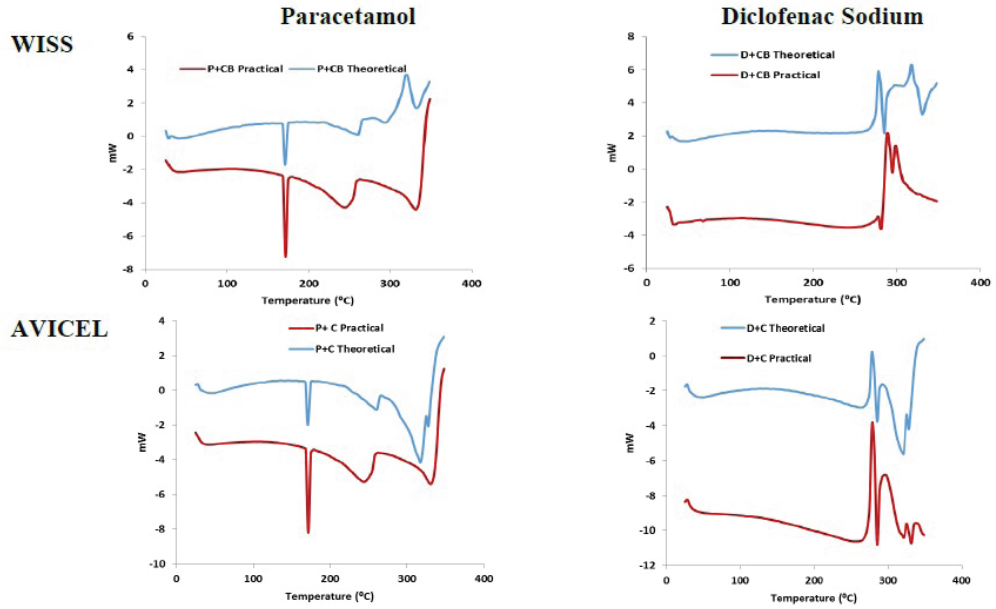

Figure 4 DSC thermograms of diclofenac sodium (D) and paracetamol (P) mixed with Avicel® (cellulose-C) and WISS (cellulose brine-CB) at a 1:1 w/w ratio carried out at a rate of 10°C/min. Theoretical calculations were carried out by taking the summation of the average of heat flow of both components.

an example of a salt form of drugs and PAR as an example of a parent drug with WISS-DPC and MCC.

Physical quality evaluation of Diclo and PAR Tablets

Weight uniformity test and content uniformity

The differences in tablet weights reflect the different weights of drug content, i.e., whether the tablets contained 25 mg or more of the drug. The total weight of a tablet is determined by the depth of the die cavity, bulk density of the granules or powder, and the uniformity of particulate flow (12). According to BP 2018 the acceptable deviation should be no more than 10% for the Diclo tablets (weight less than 80 mg) or 5% for the PAR tablets (weight more than 250 mg). Diclo and PAR tablets prepared with WISS-DPC or MCC complying with the BP Pharmacopeia requirements (shown in Table 1). Diclo and PAR were assayed using HPLC and UV-Spectrophotometer, respectively. The concentration of the API in the tablets was calculated from their respective calibration curves. The results showed that all studied tablets have an acceptable content uniformity ranging from 98-102% ± 2%.

Uniformity of diameter and thickness

A tablet's diameter depends on the integrity of the punches and dies of the tablet machine. The tablet's thickness should be controlled to smooth the process of packing. A tablet's thickness should be within a 5% variation of a standard value. The diameter and thickness of all tablets showed no significant deviation and the tablets pass the two tests as shown in Table 1.

Table 1 Physical Quality Evaluation of Diclo and PAR tablets

FORMULATION	WEIGHT (mg)	% FRIABILITY	THICKNESS (mm)	DIAMETER (mm)
Diclo-Coprecipitate	312.13 ± 2.43	0.56%	2.16±0.02	13.22 ±0.01
Diclo-MCC	315.34± 2.34	0.87%	1.82±0.01	13.17±0.02
PAR-Coprecipitate	792.29 ± 2.42	0.62%	5.1± 0.03	13.18±0.01
PAR-MCC	808.01± 2.65	0.567%	5.1± 0.05	13.2±0.01

Breaking force testing

Breaking force is the force required to break a tablet along its diameter by applying compression loading. Breaking force of the tablet is controlled by the degree of the pressure applied during the compression stage and concentration and type of binding agent (13). Breaking force is an important non-compendial test. If the tablet requires a high force to break, it may not disintegrate in the required period of time to meet the dissolution specifications. Conversely, if it is too soft, it may not be able to withstand the handling during subsequent processing such as during coating, packaging or shipping operations. Tablet breaking force should be between 6 – 10 kg. The breaking force values for the Diclo and PAR tablets are shown in Table 2. All tablets passed the test, however, tablets prepared with WISS-DPC needed a significantly higher force to break compared to those prepared using microcrystalline cellulose ($P<0.05$). This indicates that WISS-DPC compactibility was not affected by the dilution with Diclo. Another interesting result is that the breaking force of the tablets was unaffected by the production method. Some excipients produce weaker tablets with wet granulation method as has been stated previously (14).

Table 2 Breaking force of Diclo and PAR tablets

SAMPLE	HARDNESS (N)	P-VALUE
Diclofenac-coprecipitate	60.4 ± 2.83	0.00000137
Diclofenac-MCC	49.7 ± 2.90	
PAR-Coprecipitate	57.7 ± 3.13	0.00025459
PAR-MCC	51.9 ± 2.56	

Friability testing

Friability is the tendency of tablets to powder, chip or fragment due to external pressure during manufacturing, packaging or shipping. It is related to the breaking force of the tablet. The results of friability here are acceptable since the percentage friability ranges from 0.37-0.94% which is less than the compendial limit (below 1% as shown in Table 1).

Disintegration

Disintegration is the first step in dissolving the tablet to release the API. The time required for the tablets to break into particles are shown in Table 3. When WISS-DPC was added as an excipient, disintegration times were significantly shorter ($P<0.05$) compared to tablets made with MCC (shown in Table 3). These results agree with the results published previously, where the WISS-DPC was compressed alone without a drug and compared with MCC. In both experiments WISS-DPC was superior compared with MCC (1). This indicates that the properties of this novel excipient were unaffected by adding an API or the manufacturing technique applied. Tablets that have a higher breaking force are expected to take longer to disintegrate compared to tablets with a lower breaking force. The direct relationship between a tablet's breaking force and disintegration time has been confirmed by many previous studies (15, 16). However, this study showed an atypical scenario where the tablets with higher breaking force, the WISS-DPC containing tablets, disintegrated faster than tablets with lower breaking force, i.e., the MCC-containing tablets.

Table 3 Disintegration time of Diclo and PAR tablets

SAMPLE	DISINTEGRATION TIME (MIN)	P VALUE
Diclo-Coprecipitate	0.8 ± 0.55	0.000138
Diclo-MCC	4.10 ± 0.54	
PAR-Coprecipitate	1.13 ± 0.49	0.000109
PAR- MCC	7.77 ± 1.36	

The first step in disintegration is the liquid penetration into the tablet (17). The inclusion of porous silica appears to facilitate faster liquid penetration and hence improved disintegration. The results obtained in this study show that the excipient examined here produces tablets with high breaking force and rapid disintegration.

Dissolution

Dissolution testing provides the amount of drug in solution that is available for absorption. The percentage release of the APIs after 30 minutes and 45 minutes are shown in Table 4. The results for all tablets were in accordance with the USP 41-NF 36. However, after 30 minutes for the Diclo tablets and 15 minutes for the PAR tablets, those containing the WISS-DPC showed faster release compared to those containing MCC. This is to be expected since WISS-DPC disintegrated at a faster rate as discussed previously. Faster dissolution provides a rapid effect which is particularly important when a rapid onset of action is required. Both PAR and Diclo are pain killers so a rapid effect is a soughtafter property.

Table 4 Drug release from Diclo and PAR tablets

SAMPLE	% RELEASE AT 30 MINUTES FOR DICLO TABLETS AND AT 15 MINUTES FOR PAR TABLETS	% RELEASE AT 45 MINUTES FOR DICLO TABLETS AND AT 30 MINUTES FOR PAR TABLETS
Diclo-coprecipitate	67 ± 4.5	104 ± 1.6
Diclo-MCC	45 ± 5.1	98 ± 3.4
PAR-Coprecipitate	73 ± 1.9	101 ± 2.5
PAR- MCC	65 ± 2.8	99 ± 5.6

Tablet surface roughness

Al-khattawi *et al.* investigated powder interaction at the inter-particulate and intermolecular levels using Atomic Force Microscope (AFM) and Scanning Electron Microscope (SEM) in conjunction with the Heckel profile analysis to elucidate the underlying physico-chemical and mechanical mechanisms responsible for powder densification and product functionality (18). Heckel profiles were constructed in a previous study (1) and in this study AFM and SEM scans were carried out to understand the behavior of the new excipient. A tablet's surface roughness is affected by the powder properties and compression pressure. Higher compression pressure produces smooth tablets. The type and amounts of excipients also affect a tablet's roughness. Brittle excipients tend to produce smoother tablets than plastic excipients (19). Surface roughness may affect the final quality of tablets. It has been found that the surface roughness of uncoated tablets affects the dissolution rate of the tablets (20). Surfaces

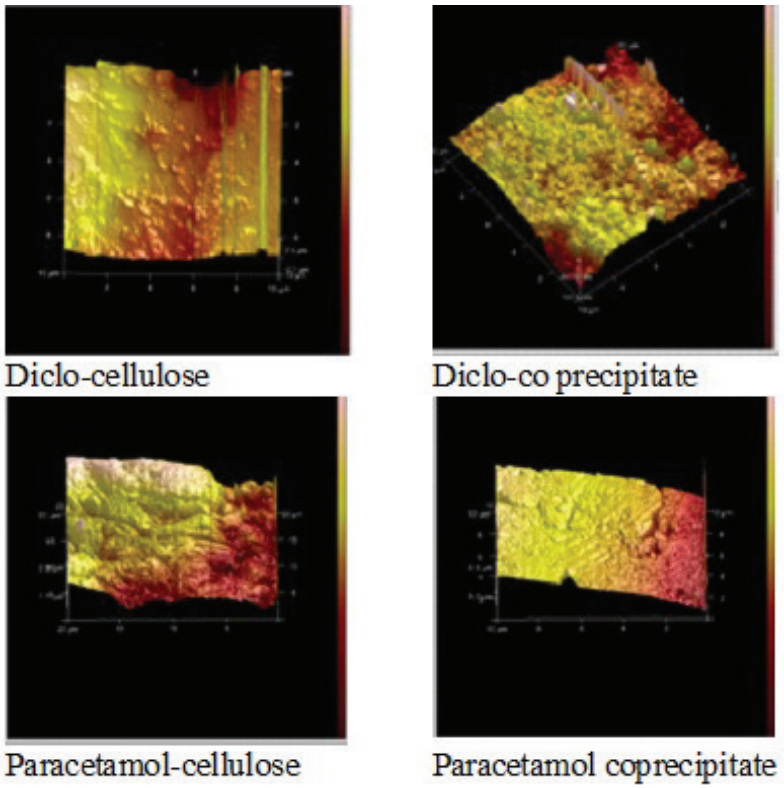

Figure 5 AFM 3D photos of dilcofenac-cellulose (Avicel®) compared to diclofena-coprecipitate (WISS-DPC). Similarly, AFM photos of paracetamol cellulose (Avicel®) compared to paracetamol-coprecipitate (WISS-DPC).

that have different roughness may have different dissolution rates due to differences in surface area (21). The surface of the tablets was investigated using AFM. Three dimensional images are shown in Figure 5 and roughness parameters are shown in Table 5. The average roughness (Ra) of the Diclo tablets prepared with MCC was higher than tablets formulated with WISS-DPC. However, the values of Rms and Rz were greater for WISS-DPC tablets compared with MCC tablets. Ra is the arithmetic mean of the absolute values of the height of the surface profile, while Rms is the root mean squared absolute values of surface roughness profile. Hence, it is more sensitive to peaks and valleys than the average roughness due to the squaring of the amplitude in its calculation (22). The Rz (ISO) is the arithmetic mean of the five highest peaks added to the five deepest valleys over the evaluation length measured which renders it more accurate than Ra. From the preceding discussion, Diclo-WISS-DPC tablets had a rougher surface compared with the Diclo-MCC tablets. This was confirmed by 3D pictures (Figure 5), where the surface of tablets made from MCC appeared smooth whereas tablets made from the coprecipitate showed different structures. In a previous study the authors attributed the higher breaking force of MCC compared to D-mannitol to its roughness which was 3 times that of D-mannitol (18). In contrast, the surface of WISS-DPC was rougher than the surface of MCC. This may explain the higher breaking force of WISS-DPC compared to MCC as discussed previously. Interlocking of different shaped structures of WISS-DPC may contribute to its high mechanical strength as has been explained previously (18). For the PAR tablets, the three parameters (Ra, Rms, Rz) values were greater than for the MCC tablets (Table 5). This may indicate that the granules of WISS-DPC were smoother than the MCC granules. Comparing direct compression and wet granulation tablets which contain WISS-DPC, wet granulation produced smoother surface than direct compression. This may be due to

the more uniform nature of the granules compared to the powder mix used for the direct compression batch as stated elsewhere (23). Since, AFM can scan only a limited area of a tablet (20x20 μm), SEM scans were performed to have provide an indication about larger surfaces of the tablets.

Table 5 AFM roughness parameters of tablets

TABLETS	ROUGHNESS PARAMETER		
	RA (NM)	RMS (NM)	RZ (NM)
Diclo-Cellulose	457	315.04	766.13
Diclo-Coprecipitate	267.92	706.87	883.91
PAR-cellulose	437.7	419.68	1738.6
PAR-Coprecipitate	292.66	224.74	785.91

SEM

SEM pictures of the tablets are shown in Figure 6. Circular particles appeared on the surface of the Diclo-WISS-DPC tablet. The high values of the AFM parameters (Rms, Rz) for these tablets may be due to the landing of the AFM probe on these circular structures. On the SEM pictures of the PAR tablets, a lot of irregular particles are shown. These structures were distributed evenly for the PAR-MCC tablets, whilst on the surface of the PAR-WISS-DPC some areas are smooth and others are rough. Therefore, the low values of AFM in these tablets may be due to just a chance of landing of probe on the smooth areas. The interlocking of different shaped structures of WISS-DPC ay result in better sticking of the surfaces which may contribute to lower surface roughness compared to that for cellulose.

CONCLUSIONS

Diclo sodium and PAR tablets were manufactured using WISS-DPC as an excipient. This new excipient improves the breaking force, disintegration and dissolution time of tablets and thus could be used in pharmaceutical industry.

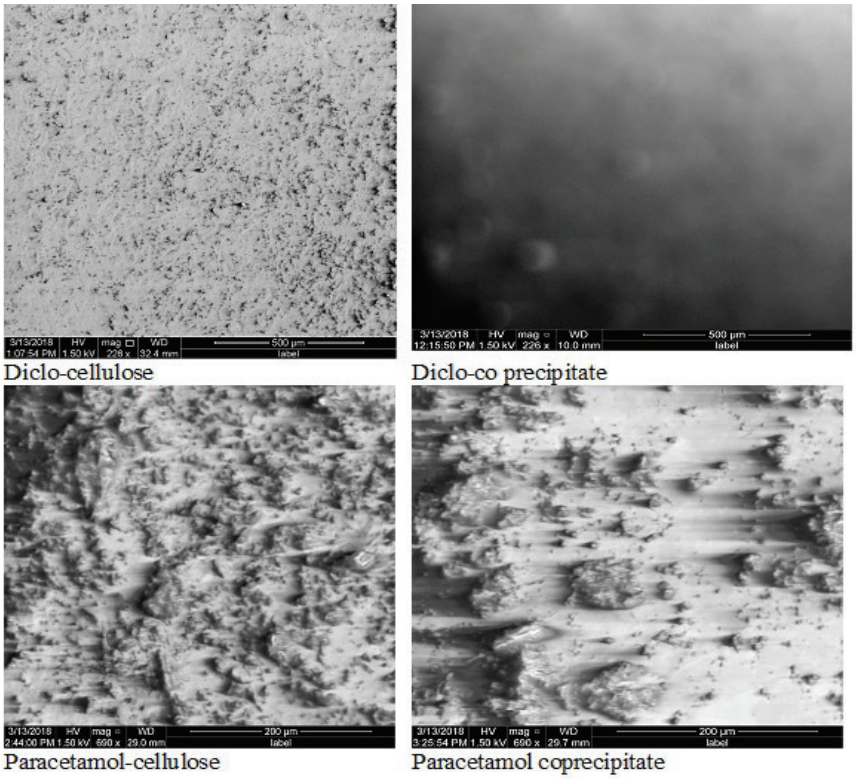

Figure 6 SEM photos of dilcofenac-cellulose (Avicel®) compared with diclofenac-coprecipitate (WISS-DPC). Similarly, SEM photos of paracetamol cellulose (Avicel®) compared to paracetamol-coprecipitate (WISS-DPC).

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