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Drug-Excipient Compatibility: Preformulation Study with New Grades of Microcrystalline Cellulose from Potential Non-Woody Sources, Sorghum and Andropogon

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ABSTRACT

Compatibility of Sorghum and Andropogon Microcrystalline Cellulose (MCC) with acetaminophen, ascorbic acid and metronidazole was examined using FTIR. Tablet characteristics of the binary blends were studied. Drug-excipient ratio was 70:30% w/w for acetaminophen and ascorbic acid while metronidazole was 67:33% w/w. Spectra of the polymer, drug and polymer-drug blends were studied within 400-4000 cm-1 wave number. Characteristic peaks were observed for functional group traits. Tablet batches were obtained for each drug using the derived MCC grades as dry binders, at three different pressure units. Tablets made at fixed pressure units were compared with those of Avicel PH 101. Disintegration, friability, crushing strength and dissolution profiles served as bases for assessment. Peaks of functional groups remained within reference range for the drugs in the drugpolymer blends; 1660-1590 (C=C), 1660-1590 (C=O) and 3650-3200 (OH) for acetaminophen; 1700-1630 (C=C), 3650-3250 (OH) for ascorbic acid and 1660-1590 (C=N), 1560-1500 (NO2) for metronidazole. Tablets formulated with the excipients exhibited acceptable hardness, crushing strength, friability and dissolution profiles. The t_{50} and t80 evaluation returned times of 4-11 and 11-29 min after 24 hrs and 6 months of storage respectively. The results are within acceptable range for non-coated tablets. The new MCC grades compared well with Avicel PH 101 as the mean standard variation for the evaluated tablet properties was less than 5%. Sorghum and Andropogon plants are potential none-woody sources of MCC.

Keywords: Drug-excipient compatibility; Preformulation study; FTIR; MCC; Sorghum; Andropogon

INTRODUCTION

Formulation of tablets usually involves a series of compromises in order to produce the desired properties. Correct selection and balance of excipient materials for each active or a combination of active ingredients is central to the formulator so as to achieve the desired objective (safe, effective, and highly reliable product). Increasing competition among manufacturers demands that products and processes are cost effective. Therefore, cost of a new material or a particular processing step must be considered before a final tablet formulation is selected. Tablet product design thus requires two major considerations; identification of excipient(s) most suitable for a prototype formulation and secondly, the level of such excipient (s) must be optimally selected to satisfy all process and product quality constraints. Pharmaceutical aid development must therefore aim at producing effective material that is cost effective and capable of competing favorably with available commercial equivalent. Drug excipient compatibility is of primary consideration in the selection of formulation aids [1-5]. Simon reported a accelerated approach, utilizing thermal analysis to identify incompatibility or otherwise of drug-excipient combinations. Differential Scanning Calorimetric (DSC), Fourier Transform Infra Red spectroscopy (FTIR), High Performance Liquid Chromatog-

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raphy (HPLC) and Thin Layer Chromatography (TLC) have been used to investigate the interactions between drugs and some commonly used tablet and capsule excipients [6]. In addition to compatibility with active ingredients, excipients that tend to improve flow (gallivants) and bond (binders) should be evaluated for use with poor flowing and poor bonding compounds respectively with careful selection of appropriate technique. Most powders cannot be compressed directly into tablets because they lack inherent bonding characteristics and often times exhibit poor flow ability. Wet granulation is the traditional means, which attempts to gather small particles into large, permanent aggregates resulting in improved flow and bonding potentials. Other methods include dry granulation and direct compression of which the later involves the least number of steps; blending and tableting. In previous studies, the compaction behavior of Sorghum MCC (SMCC) and Andropogon MCC (AMCC) has been established to be by plastic deformation similar to Avicel brand of MCC [7,8] the dilution capacity of these new filler binders has also been determined, in the range of 30-50 % w/w. In this investigation, the compatibility of these polymeric materials with some Active Pharmaceutical Ingredients (APIs) was determined using FTIR spectrophotometry [6]. Thereafter, binary blend formulations of ascorbic acid, acetaminophen and metronidazole were made using SMCC and AMCC as DC filler- binders. Tablet qualities of these formulations were determined while Avicel PH 101 served as comparator Direct Compression (DC) excipient.

MATERIALS AND METHODS

Drug Excipient Compatibility Test

The new SMCC and AMCC were obtained as previously described. Ascorbic acid, metronidazole and acetaminophen (Vision pharmaceutical company, China), Avicel PH 101 (FMC corporation, USA) were used as obtained from the manufacturers/suppliers. ATI Mattson Genesis (ATI instruments USA) Fourier Transform Infrared Spectrophotometer (FTIR) was used for the compatibility study. The spectra of SMCC, AMCC and Avicel PH 101 acetaminophen, ascorbic acid and metronidazole were produced over the range 400-4000 cm-1. Characteristic peaks were used as basis for comparison. Acetaminophen was mixed with SMCC, AMCC or Avicel PH 101 in a ratio of 70 to 30% while that of Ascorbic acid or Metronidazole was similarly done with each diluent binder. Spectra of the mixtures were recorded over the range 400-4000 cm-1. The wave numbers (cm) of characteristic peaks were determined and compared with those of the pure drug samples.

Formulations and Tableting

A single station tablet machine model THP ('basket' type) made by Shanghai Tianxina and Chentai (STC) pharma machinery company Ltd China was used. The carver hydraulic hand press model C (Carver Inc. USA). Erweka hardness tester model MT (Erweka GmBH. Germany) was used to determine diametric crushing strength for tablets made with the carver tablet machine. Tensile strength was calculated using the dimensions of the compacts or tablets and applying the equation $Ts=2P/\pi Dt$ where Ts is tensile strength, P is diametric crushing strength; D is diameter and t, thickness of tablet. The Eureka dual drum friabilator was used to determine tablet friability. The Eureka disintegration tester model EP 4-4 was used to determine Disintegration Time (DT). The eureka single station tablet dissolution tester model DT (paddle apparatus) was used. Dissolution test was performed on the tablets, analyzed spectrophotometric ally with the Shimadzu spectrophotometer UV-160A, Japan. All dissolution experiments were performed in triplicate and average values calculated. Drug content was determined for each batch of formulations 24 hrs and 6 months of storage as described in the official monograph. Assay was done using Beckman HPLC equipment consisting of programmable solvent module 126 and detector module 166. Formulations of acetaminophen, ascorbic acid and metronidazole were made using AMCC, SMCC or Avicel PH 101 as direct compression excipient. Acetaminophen tablets 250 mg were made with AMCC or SMCC or Avicel PH 101 in ratio of 70:30%. The drug filler-binder blends were compressed at pressure units of 11,12,13. The performance of tablets prepared at compression pressure level of 12.0 units using either of the new MCC grades was compared with the batch containing Avicel PH 101. Ascorbic or metronidazole 250 mg drug content was similarly formulated at ratio of 66.67:33.33 % drug-excipient with SMCC, AMCC and Avicel PH 101. Tablets were made using the basket type tablet press at different compression pressure levels of 8.0, 8.5, and 9.0 units for different batches containing the various grades of MCC. The performance of tablets prepared at 8.5 pressure units was compared with that containing Avicel PH 101.

RESULTS AND DISCUSSION

The FTIR spectra of SMCC, AMCC, Avicel PH 101 as well as acetaminophen, ascorbic acid and metronidazole, were examined. The characteristic peaks of the functional groups were noted for comparison with spectra of drug-excipient blends. The spectra for acetaminophen blends with the polysaccharides, ascorbic acid plus the filler-binders and that for metronidazole blends were similarly studied. (**Tables 1-3**) shows the peaks of characteristic bonds or group in acetaminophen, ascorbic acid, metronidazole, as well as their mixtures with SMCC, AMCC, or Avicel PH 101. The approximate range of occurrence is indicated similar to what has earlier been reported. There is no observable disappearance, reduction or appearance of new absorption bands in all the spectra. The table values indicate there's no major shift in the peaks of characteristic functional groups or bonds of these drugs. These indicate lack of untoward reaction between the APIs and the new filler-binders. The shift noticed in ascorbic acid binary blends with the new polymers and the comparator microcrystalline cellulose MCC, Avicel PH 101 at ethereal functional group (C-O-O-) in (**Table 1**) may be due to experimental error as this corresponds to vibration of aliphatic phosphates, P-O-C stretch in the range 1050-990 cm-2

Table 1: Effect of MCC grade on characteristic JR peaks (cm) for acetaminophen.

Sample	Aromatic gp C=C	C=O	OH
Acetaminophen, p	1608.10	1653.58	3332.22
P (70%)+SMCC (30%)	1605.26	1544.74	3333.33

P (70)+AMCC (30%)	1618.42	1657.89	3323.51
P (70)+Avicel PH 101 (30%)	1611	1658.44	3250.64
Wave number (cm-1) range	1660-1590	1700-1630	3650-3200

Table 2: Effect of SMCC and AMCC on characteristic IR peaks (cm-1) for ascorbic acid.

	C=C	-O-O-	OH
Ascorbic acid C (100%)	1644.74	907.89	3263.16
C (66.7%)+SMCC (33.3%)	1671.05	1024.74	3572.04
C (66.7%)+AMCC (33.3%)	1657.89	1010.78	3572.88
C (66.7%)+Avicel H 101 (33.3 %)	1697.37	1024.92	3405.96
Wave number (cm-1) range	1700-1630	890-820	3650-3250

Table 3: Effect of SMCC and AMCC on characteristic IR peaks (cm-1) for Metronidazole.

Sample	C=N	NO2
Metronidazole, M (100%)	1644.74	1506.54
M (66.7%)+SMCC (33.3%)	1657.89	1539.89
M (66.7%)+AMCC (33.3%)	1658.50	1538.47
M (66.7%)+Avicel PH 101 (33.3%)	1618.42	1535.53
Wave number (cm-1) range	1660-1590	1560-1500

Characteristic peaks for acetaminophen and metronidazole occur over the range 1600-1028. (**Tables 1-3**) shows that the blends of these polymers with any of the drugs do not cause any major shift in the peaks of the functional groups. Similar trends are noticeable in ascorbic acid and metronidazole blends. The blends of the new grades of MCC may be said to be interaction free with the examined drugs. Acetaminophen, ascorbic acid and metronidazole could therefore be deemed compatible with SMCC or AMCC. Pediatric acetaminophen tablets were produced using the new direct compression grades of MCC, while Avicel PH 101 served as reference diluent-binder, all at 30% w/w concentrations. The crushing strength profile of acetaminophen, ascorbic acid and metronidazole tablets made with different grades of MCC is presented in (**Figure 1**). It increased with compression pressure in all the batches. Tablets of paracetamol containing either SMCC or AMCC made at compression pressure unit of 12 with the basket type tableting press were compared with those containing Avicel PH 101. Other tablet properties evaluated include hardness, disintegration time, friability, dissolution rate and the results are presented in (**Tables 4 and 5**). Hardness of the acetaminophen compacts determined 24 hrs after production shows that those made with SMCC were off slightly higher strength values than those containing AMCC or Avicel PH 101. The variation in resulting data was not significant as the mean standard variation (SDVA) was in the range of 0.2-1.7 % the disintegration time and friability values are all within acceptable limits for directly compressed tablets. The in vitro dissolution profile of the tablets after 24 hrs of storage is shown in (**Figure 2**). The release characteristics of those made with SMCC or AMCC are similar to that containing Avicel PHI01. The t_{50} of the formulations 24 hrs of storage was in the order AMCC<SMCC=Avicel PH 101. After storage for 6 months, the same set of parameters were monitored and are found to be quite similar as in (**Tables 4 and 5**) as in (**Figure 1**). The error bars indicate the similarity in the crushing strength and dissolution profile of tablets made with the new grades of MCC SMCC, AMCC and the comparator Aviel PH 101.

Table 4: Tablet properties of acetaminophen formulations.

Cellulose grade	Crushing strength (KG)		Disintegration time (min)		Friability (F) % loss	
	24 h	6 m	24 h	6 m	24 h	6 m
SMCC	6.5	7	1.08	1	0.56	0.52
AMMC	6.1	7	2.5	1.5	0.42	0.84
Avicel PH 101	5.9	6.5	1.5	1.2	0.96	1.2
SDVA	0.3055	O.2887	0.7295	1.2	0.2802	0.3402

Table 5: *In vitro* dissolution characteristic of acetaminophen formulations.

Grade of cellulose	T50% (min)		T80% (min)	
	24 hrs	6 m	24 hrs	6 m
SMCC	7.7	7.7	16.3	15.9
AMCC	5.0	8.2	13.8	15.9
Avicel PH 101	7.7	8.4	16.8	16.8
SDVA	1.5588	0.3601	1.6076	0.5196

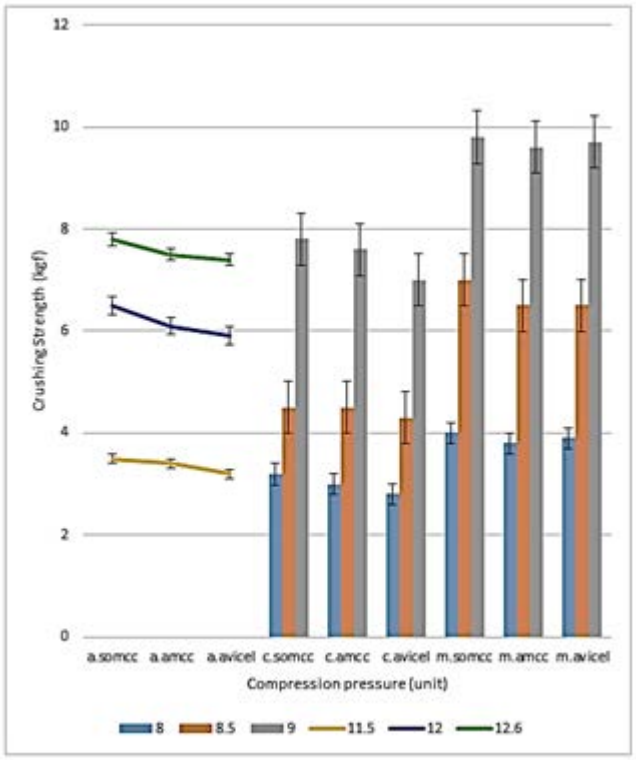

Figure 1: Crushing strenth profile of acetaminophen, ascorbic and metronidazole tablets with different grades of MCC.

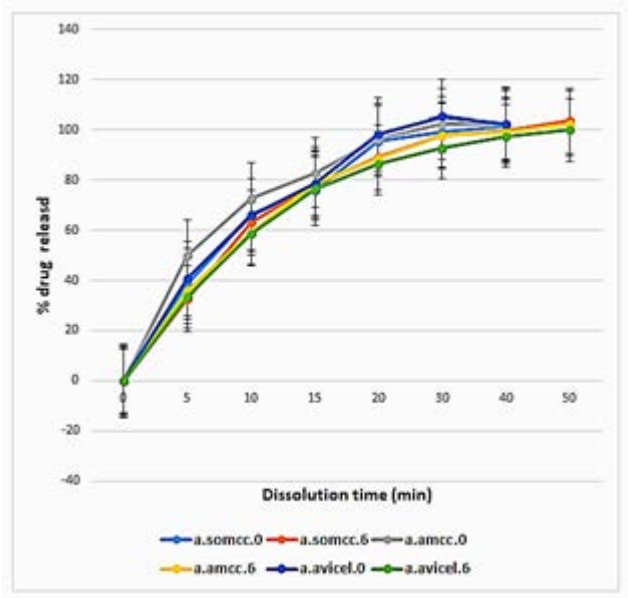

Figure 2: Dissolution profiles of acetaminophen (a): Polymer tablets 24 hrs (0) and 6 months of storage.

Hardness was seen to increase slightly on storage in all the samples which is consistent with behavior of compacts on aging. The release profiles of the formulations containing either grade of the new polymers was similar to that of Avicel PH 101 and they all showed no significant changes after storage for 6 months. Acetaminophen formulations containing SMCC or AMCC are therefore considered stable within the experimental conditions. Ascorbic acid tablets, USP (250 mg) have been formulated using Avicel PH 101 at 20% w/w concentration in addition to 17.5 % of starch 1500. The investigators also remarked that higher level of vitamin C could be tableted directly using more Avicel and less of the starch 1500. In this investigation, a modified formula was used. A 33.3% w/w concentration of either grade of cellulose was used to incorporate 66.67 w/w of ascorbic acid. This level of usage is deemed suitable as a minimum excipient concentration of 30 % was earlier determined for the new grades of MCC. The crushing strength profile of ascorbic acid tablets containing SMCC, AMCC, or Avicel PH 101 is presented in (Figure 1) with observable similar profiles. Tablets compressed at 8.5 compression pressure unit were compared. Disintegration was fast and friability was below 1% in all cases. Crushing strength of ascorbic acid tablets containing SMCC and AMCC compared favorably with that of tablets containing Avicel PH101. In vitro dissolution profile of ascorbic acid containing the new polymers is shown in (Figure 2). The release characteristic of AMCC was found to be similar to that of Avicel PH 101 and slightly better than those of tablets containing SMCC as seen in Tables. The $t_{80\%}$ for both AMCC and Avicel PH 101 formulated tablets is 10.9 minutes while that of SMCC is 15.2 minutes. The release pattern after 6 months of storage at room temperature shows no significant difference from that at 24 hrs post production storage as seen in Figure 3 and the corresponding disintegration times in (**Tables 6 and 7**).

Metronidazole powder has poor compressibility profile and different binders have been used to alter the tensile strength, disintegration and dissolution properties of tablets of this amoebicidal drug. An attempt to classify this powder using Heckle analysis failed as no compact was formed when the drug (alone) was compressed at pressure levels of 31.2 to 185.2 MNm2 with a hydraulic tablet press. However, incorporation of various levels of the new grades of MCC modified the compressibility greatly such that a minimum use level of 25.0% w/w of either of the new polymers was found adequate in obtaining tablets with no capping tendency.

A 33.3% concentration was thereafter selected for formulating metronidazole tablet containing SMCC, AMCC or Avicel PH 101. The crushing strength profile presented in (**Figure 1**) shows similarity in the compact strength of tablets made with different grades of the dry filler-binders. Other properties of tablets prepared at 8.5 compression pressure unit are compared as presented in (Table 8). Hardness was good enough for handling and disintegration in all cases was below 5 minutes, tablets containing SMCC and Avicel PH 101 were slightly faster in disintegrating than those of AMCC.

The friability was below 1% in all the formulations. The dissolution profiles of the tablets 24 hrs of storage are shown in **Figure 4**. As the dissolution progresses, $t_{50\%}$ and $t_{80\%}$ shown in Table 9 indicate that the batch containing Avicel PH 101 performed slightly better than tablets of SMCC or AMCC. The evaluated tablet properties did not show significant change after 6 months of storage. As indicated in (**Table 8**) and (**Figure 4**).

Table 6: Tablet properties of ascorbic acid containing different filler-binder.

Cellulose	Crushing Strength (kgf)		Disintegration time (min)		Friability (F) % loss	
	24 h	6 m	24 h	6 m	24 h	6 m
SMCC	4.5	5.5	1.1	1	0.67	0.43

AMCC	4.5	5.5	1.8	1.2	0.27	0.18
Avicel PH 101	4.3	5.2	0.93	1.03	0.27	0.6
SDVA	0.11547	0.173205	0.461122	0.107858	0.23094	0.211266

Table 7: *In vitro* dissolution characteristic of ascorbic acid tablets.

Cellulose	T_{50}		T_{80}	
	24 hrs	6 m	24 hrs	dissolution
SMCC	7.8	8	15.2	15.5
AMCC	5.9	5.75	10.9	11.5
Avicel PH 101	4.7	4.5	10.9	10
SDVA	1.563117	1.77365	2.482606	2.84312

Table 8: Tablet properties of metronidazole formulations.

MCC Grade	Crushing strength		Disintegration time (min)		Friability (F) % loss	
	24 h	6 m	24 h	6 m	24 h	6 m
SMCC	7	8.2	2.3	2.5	0.34	0.3
SMCC	6.5	7	4.7	3.9	0.23	0.35
Avicel PH 101	6.5	7.3	2.7	2.9	0.23	0.34
SDVA	0.288675	0.6245	1.28582	0.72111	0.063509	0.026458

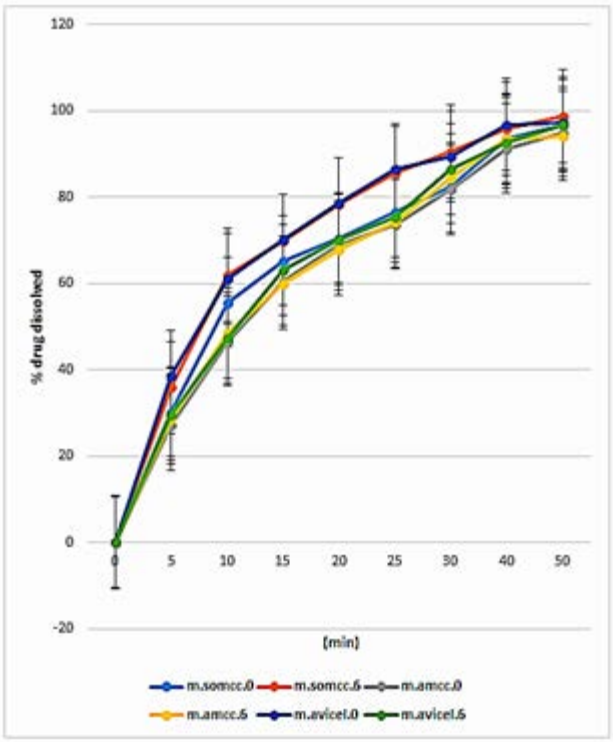

Figure 4: Dissolution profile of metronidazole-polymer tablet 24 hrs and 6 months of storage.

CONCLUSION

The results are within acceptable range for non-coated tablets. The new MCC grades compared well with Avicel PH 101 as the mean standard variation for the evaluated tablet properties was less than 5%. Sorghum and Andropogon plants are potential none-woody sources of MCC.

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