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Formulation and Evaluation of Ascorbic acid Tablets by Direct Compression using Microcrystalline Starch as a Direct Compression Excipient

Abstract

PURPOSE: To evaluate the tableting properties of microcrystalline starch (MCS) used as a direct compression excipient in the formulation of ascorbic acid tablets and to compare with the properties of tablets produced using microcrystalline cellulose (MCC).
METHODS: MCS was obtained by partial hydrolysis of cassava (*Manihot esculenta* Crantz) starch using the enzyme, α-amylase. The hydrolysis was allowed to proceed for 5 hr under controlled temperature and pH (56 °C, 6). The derived MCS was recovered by filtration after precipitation with ethanol (95%$^{v}/_{v}$). Powder properties were investigated and tablets of ascorbic acid were formulated using MCS and MCC as direct compression excipients.
RESULTS: Mechanical properties of tablets formulated with MCS were comparable to those of MCC. Tablets formulated with MCS disintegrated within 15 min and gave a 100% release of ascorbic acid within 30 min compared to MCC which disintegrated after 60 min.
CONCLUSION: MCS can be incorporated as a direct compression excipient in the formulation of heat and/or moisture sensitive drugs by direct compression.

Keywords: Microcrystalline cellulose, Powder properties, Mechanical properties, Partial hydrolysis, α-amylase.

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Introduction

Tablets at present, remains the most preferred oral dosage form because of the many advantages it offers to formulators as well as physicians and patients [1]. They offer a safe and convenient way of administering active pharmaceutical ingredients (API) with excellent physicochemical stability in comparison to some other dosage forms, and also provide means of accurate dosing. They are amenable to mass production with robust quality controls. The process of manufacturing a robust tablet dosage form and consistently maintain its quality is a major challenge to all formulators [1]. Hence, a careful design or selection of the manufacturing process

and formulation components take pivotal importance.

Direct compression has taken the centre stage in tablet manufacturing because the process avoids many of the problems associated with granulation methods. It is a simple, economical process and because heat or moisture is not required, it is suitable for unstable compounds. However, the success of the direct compression process is determined to a greater degree by the excipients chosen because they impart flow and compression characteristics to the powder blend for direct compression.

Microcrystalline cellulose (MCC) is a well known excipient for direct compression with excellent compaction properties [2]. It possesses good disintegrant properties but tends to lose this action when high compression load is applied. Due to this limitation as well as the increasing popularity of the direct compression process, there is a need to increase the range of excipients available for direct compression.

Starch is a versatile, cheap and readily available material obtained from renewable sources that has found wide application in tableting as a binder, disintegrant, diluent, lubricant and glidant. The native form of starch possesses poor flow and compression properties making it unsuitable for direct compression. Several researchers have made attempts to improve on the flowability and compressibility of starch by modification in order to make it adaptable for direct compression. The objective of this study is to modify starch by partial enzymatic hydrolysis and evaluate its tableting properties in the formulation of ascorbic acid tablets. Ascorbic acid is a poorly compressible water-soluble drug that is sensitive to moisture. This informed its choice as the model drug for this study.

EXPERIMENTAL

Materials

The materials used were stearic acid, talc, ethanol, ascorbic acid, xylene (BDH Chemicals Ltd Poole, England), sodium hydroxide (Avondale Laboratories Ltd Banbury, England), hydrochloric acid, α-amylase (Sigma-Aldrich laborchemikalien GmbH Germany), microcrystalline cellulose ph 101 (ATOZ Pharmaceuticals Ltd, Ambaltur, India). Cassava starch was extracted in the Process laboratory of the Department of Pharmaceutics and Pharmaceutical Microbiology, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria.

Methods

Extraction and modification of starch

Starch was extracted from freshly harvested tubers of cassava (*Manihot esculenta* Crantz) using a standard procedure described in literature. The method of Buwalda and Arends-Scholte [3] was adopted to prepare microcrystalline starch. Slurry containing 40% $^{w}/_{w}$ of starch was prepared in a beaker. The beaker was placed in a water bath (Digital thermostatic water bath Mcdonald Scientific International, Lagos, Nigeria) and the temperature brought to 56 ºC. The pH of the reaction mixture was adjusted to 6 using 0.1N HCl and 0.2%$^{v}/_{g}$ of α-amylase (BAN 240L) was introduced into the reaction mixture. The reaction was allowed to proceed for five (5) hours with constant stirring. The reaction was then terminated after 5 hr by lowering the pH to 2.5 with 0.1N HCl and subsequently neutralized by raising the pH to 7 with 0.1N NaOH. The reaction mixture was allowed to settle and the supernatant decanted. It was then washed several times with distilled water before adding 100 ml of Ethanol (95% $^{v}/_{v}$) to dehydrate the microcrystalline starch (MCS) formed. The MCS was recovered by decanting the supernatant and air-dried.

Determination of powder properties

Moisture content was determined by weighing five (5) grams of each powder sample and dried at 105ºC in the oven (Gallenkamp Oven BS Size 3, England) to constant weight. The % loss in weight was calculated as the moisture content. The angle of repose was determined using a method described by Alebiowu [4]. Twenty (20) grams of each powder sample was placed in a standing cylindrical tube. The cylinder was gently

raised to leave a free heap of the powder. The circumference of the base of the heap was outlined and its radius, r, measured. The height, h, of the heap was also measured. The angle of repose was calculated from the equation given below:

$$\theta = Tan^{-1}\frac{h}{r} \quad \text{……,,,,,,} \quad 1$$

The average of three determinations was recorded. The particle density was determined using a liquid displacement pycnometric method with xylene as the displacement fluid [5]. The bulk and tapped densities were determined in a glass measuring cylinder as a measure of packability [6]. Hausner's ratio was determined from the quotient of tapped density to bulk density. Carr's index was calculated from the equation:

$$Cl = \frac{Tapped \cdot density - Bulkdensity}{Tapped \cdot density} \times 100\% \cdot \text{.....} 2$$

The hydration capacity, swelling index and moisture sorption capacity were determined using established procedures [7-9].

Dilution Capacity

A binary mix of the drug and filler-binder was prepared in the following ratios: 10:90, 20:80, 30:70, 40:60, 50:50, 60:40, 70:30, 80:20, and 90:10. It was then compressed at varying compression loads on the Single Punch Tableting Machine (Type EKO, Erweka Apparatebau - G.m.b.H Heusenstamm, West Germany). The crushing strength of each binary mix was determined and recorded.

Tablet Formulation

The formula for ascorbic acid tablets is given below on Table 1. Tablets were prepared by the process of direct compression. A powder blend of the drug and direct compression excipient without the lubricant (Stearic acid) and glidant (Talc) was uniformly mixed for 5mins using a mortar and pestle. The predetermined quantities of the lubricant and glidant were then added and mixing continued for another 5mins. A single punch tableting machine (Type EKO, Erweka – Apparatebau - G.m.b.H Heusenstamm, West Germany) fitted with 12mm normal concave-faced punches was used for the tableting at varying compression loads. The tablets were stored over silica gel for 24 hr to allow for elastic recovery and hardening, and prevent false low yield values. The target tablet weight was 500mg.

Table 1: Tablet formula for ascorbic acid tablets

Batch	1	2
Ascorbic acid (40%$^{w}/_{w}$)	200	200
MCS/MCC (59%$^{w}/_{w}$)	295	295
Stearic acid (0.5%$^{w}/_{w}$)	2.5	2.5
Talc (0.5%$^{w}/_{w}$)	2.5	2.5
Total (mg)	500	500

MCS, microcrystalline starch; MCC, microcrystalline cellulose

Evaluation of tablet properties

The weights of 20 tablets for each batch were individually determined using an electronic balance (Mettler Analytical Balance, Philip Harris Ltd., England) and the mean was calculated. The crushing strength of 10 tablets for each batch was determined using a Mosanto hardness tester. Mean crushing strength was calculated and the tensile strength values were determined using the equation below:

$$Ts = 2Cs/3.14dt \text{ …….. } 3$$

where Ts is the tensile strength, Cs is the crushing strength, d and t is the diameter and thickness of the tablet respectively. Friability was determined using an Erweka friabilator. Ten tablets per batch were weighed and allowed to tumble in the drum of the friabilator which rotated at 25rpm for 4 minutes. The tablets were dusted and reweighed. The loss in weight expressed in percentage of the original weight of the ten tablets was calculated as the friability of the tablets.

Disintegration times of six tablets per batch were individually determined in distilled water at 37±0.5ºC using the Erweka disintegration test apparatus (Type ZT3, Erweka – Apparatebau - G.m.b.H Heusenstamm, West Germany). The mean disintegration times were calculated and the dissolution rate of the tablets from each batch was determined using Erweka dissolution apparatus.

(dissolution medium was 1000 ml of 0.01N HCl, maintained at 37±0.5 °C). The revolution of the basket containing the test tablet was 100 rpm. 10 ml of the sample was withdrawn at 5 min intervals for a period of 30 min. Each sample withdrawn was replaced with an equivalent volume of dissolution medium maintained at the same temperature. A ten fold (1:9) dilution with the dissolution medium was done for each sample withdrawn before absorbance values of the samples were read at 244 nm [14] using a UV/VIS Spectrophotometer (Helios Zeta UV – VIS Spectrophotometer, Thermo Fischer Scientific Inc., Cambridge, UK). The percentage drug released was plotted against time to generate a dissolution curve.

Results and Discussion

The powder properties of MCS and MCC were determined and the results obtained are presented on Table 2. The angle of repose of a powder provides an insight into the magnitude of the cohesiveness of the powder, and hence its flowability [10]. Mildly cohesive powders have angles of repose between 40 and 60° when measured by any of the standard methods [11]. The values obtained for angle of repose for both materials are greater than 40º. This implies that both materials possess poor flow property and therefore requires the inclusion of talc as a glidant to improve the flow of the formulation during tableting.

There is a significant difference in values obtained for bulk and tapped densities of both materials. The values recorded for MCS are higher than those of MCC indicating that MCS has a better packing behaviour compared to MCC. This is likely to affect the degree of consolidation of the formulation containing these materials as filler-binder during compression, with MCS ensuring a greater degree of consolidation compared to MCC. Particle densities for both materials were comparable though MCC is slightly heavier. Powder porosity gives an indication on the ease at which a powder consolidates and it is considerably lower for MCS (56%) compared to MCC (74%). Carr's index and Hausner's ratio as well as angle of repose are indices for predicting the flow property of powders [12]. High values indicate poor flow of the materials. These results support the poor flowability of both materials.

The value recorded for the moisture sorption capacity of MCS is a confirmation of its hygroscopic tendency and is likely to affect the stability of tablets formulated during storage compared to MCC with a lesser degree of moisture sorption (10%). There seems to be slight differences in the swelling power of MCS and MCC while the hydration capacity values for both materials are comparable. This variation in swelling and hydration capacities of these filler-binders will invariably affect the rate of disintegration of tablets formulated with these materials.

Table 2: Powder properties of MCS and MCC

Property	MCS	MCC
Angle of repose (º)	45.4±1.03	41.5±1.77
Bulk density (g/cm^3)	0.61±0.02	0.39±0.02
Tapped density (g/cm^3)	0.79±0.02	0.55±0.01
Particle density (g/cm^3)	1.38	1.48
Hausner's ratio	1.30	1.41
Carr's index (%)	23	29
Powder porosity (%)	56	74
Swelling power	1.50	1.31
Hydration capacity	0.82	0.84
Moisture sorption capacity (%)	19	10

MCS, microcrystalline starch; MCC, microcrystalline cellulose

The results for dilution capacity are given on Table 3. Dilution capacity of a DC excipient is the proportion of another ingredient that can be mixed with it while still obtaining tablets of acceptable quality [2]. Generally, there was a decline in the tensile strength values of the compacts as the proportion of the drug increased in the binary mix. Higher tensile strength values were observed with MCC compared to MCS for the same proportion of binary mix. This is an indication that MCC has a superior dilution capacity which can be attributed to its ability to deform plastically at low pressures and its porous surface structure allowing it to incorporate high proportions of a poorly compressible drug and still retain its compressibility [13].

Table 3: Dilution capacity of MCS and MCC

	MCS		MCC	
Binary mix ratio	CS (N)	TS (MN/m^2)	CS (N)	TS (MN/m^2)
10:90	87.5	2.10	130	4.75
20:80	87.5	2.01	130	4.50
30:70	87.5	1.95	120	4.50
40:60	80.8	1.93	120	4.30
50:50	77.5	1.82	120	4.10
60:40	75.0	1.78	96.7	3.80
70:30	-	-	80	3.00
80:20	-	-	26.7	1.00
90:10	-	-	18.3	0.70

MCS, microcrystalline starch; MCC, microcrystalline cellulose
10:90 *10% drug + 90% Filler-binder*
CS *Crushing strength*
TS *Tensile strength*
MCS *Microcrystalline starch*
MCC *Microcrystalline cellulose*
- *Poorly compressible*

The outcomes of tablet properties evaluated are given on Table 4. Both batches passed the weight variation test, not exceeding the limit of ±5% (475-525mg) [14]. The crushing strength values for batch 2 containing MCC as filler-binder was significantly higher than that of batch 1 containing MCS. This was also reflected in the tensile strength values determined using crushing strength data. This high value is related to the high bonding index of MCC.

MCC, a cellulose derivative is a straight chain polymer. Unlike starch, no coiling occurs in its structure and the molecules adopts an extended rod-like conformation and because of the microfibrillar structure of MCC, the multiple hydroxyl groups on the glucose residues hydrogen bond each other, holding the chains firmly together contributing to their high tensile strength [2]. Also, friability values were relatively lower for batch 2 tablets compared to batch 1. This can also be explained by the hardness of batch 2 tablets compared to batch 1.

Tablets in batch 1 disintegrated within 15minutes and much faster than tablets in batch 2 which took over 1hour to disintegrate. The dissolution studies confirmed the observations seen with disintegration time. Drug release was much faster for tablets containing MCS than for tablets containing MCC. A 100% drug release was achieved after 30minutes for tablets containing MCS compared to 27% recorded with MCC tablets. A graphical representation of the drug release is given as Figure 1. Other dissolution parameters extrapolated from the curve are displayed on Table 4.

Table 4: Tablet properties of MCS and MCC

Parameter	Batch 1	Batch 2
Uniformity of weight (mg)	495±14	506±13
Tablet thickness (mm)	3.78±0.09	3.64±0.06
Tablet diameter (mm)	12.04±0.08	12.07±0.01
Crushing strength (N)	82±0.4	100±0.00
Tensile strength (MN/m^2)	1.15±0.4	1.45±0.00
Friability (%w/w)	0.76	0.39
Disintegration time (min)	10.33±0.59	>60
D.E (30mins) (%)	100	27.15
$T_{50\%}$ (min)	16	40
$T_{90\%}$ (min)	25	-

MCS, microcrystalline starch; MCC, microcrystalline cellulose

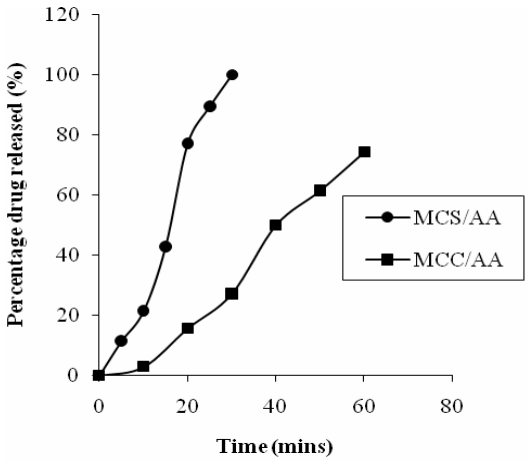

Figure 1: Drug release from microcrystalline starch (MCS) and microcrystalline cellulose (MCC) tablets

Conclusion

The study has shown that modification of native starch by enzymatic hydrolysis has been able to impart some desirable features required for direct compression. It therefore can be readily employed as a directly compressible excipient in the formulation of tablets containing heat or moisture sensitive drugs by direct compression.

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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