PERFORMANCE EQUIVALENCE STUDY OF SODIUM STARCH GLYCOLATE, MODIFIED MAIZE STARCH AND MAIZE STARCH AS DISINTEGRANTS IN PARACETAMOL TABLET FORMULATION

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SUMMARY: Fierce price competition informed the reappraisal and reformulation of paracetamol tablet. Sodium starch glycolate (SSG) was implicated in the high cost and needed to be replaced. The use of modified maize starch (MMS) produced by cold, dilute acid hydrolysis of maize starch (MS) offered good and cheaper alternative.

Evaluation of different disintegrants using 5 batch formulations coded SSG-3, MS-3, MMS-3, MMS-6 and MMS-9 and characterization of resultant tablets showed that interchanging SSG with MMS resulted in no deleterious therapeutic consequences. Inclusion of 6% MMS in the paracetamol formulation gave tablets that exhibited good mechanical and dissolution properties comparable to the tablets produced with 3% sodium starch glycolate.

Indeed, at 95% confidence level, t-test which compares the p-value (?0.05) of dissolution of the batch formulations returned values of 0.000056 for MS-3, 0.0182 for MMS-3, 0.0965 for MMS-6 and 0.1433 for MMS-9. The values confirmed the significant differences between batch SSG-3 and batches MS-3 and MMS-3 and no difference of any significance in batches MMS-6 and MMS-9. Hence MS and MMS at 3% level can not effectively replace SSG at 3% level. The poor friability (1.12%) as well as higher disintegration time (16 minutes, 54 seconds), both higher than official limits of <1% and ?15 minutes respectively, would not also allow the use of MMS at 3 and 9% level as substitutes for 3% SSG. Thus, only MMS at 6% inclusion level can interchange with SSG 3%.

Cost - benefit analysis showed that over 9% cost reduction is achieved by the replacement without compromising both physical and chemical qualities of the resultant tablets which include mean dissolution time (MDT) 50% of 4.5 minutes and dissolution of 103.87% in 30 minutes.

Key words: Formulation variables, Acid hydrolysis, Therapeutic consequences, Cost reduction, mean dissolution time.

INTRODUCTION

The use of starch as disintegrant in tablet formulation is as old as the history of tablet manufacture. The description of starch by formulation scientists and researchers is experience based. According to Mustapha (1), such descriptions include its being most widely used disintegrant and that most other disinte-

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grants owe their heritage to starch hence it is hard to beat. Omission of maize starch from consideration as a disintegrant would only show lack of prudence (1, 2).

Due to its physicochemical nature, relative inertness, abundance and economy of price, starch is described as an excipient of choice (including its use as intra-and extragranular disintegrant) and listed as one of the most popular eight tablet disintegrants that produce better disintegration (1,3).

Although the comparison of distribution of starch as internal or external disintegrant in formulation is debatable, the accruable merits from its use in both instances are widely reported in literature. Externally distributed starch is known to promote better aqueous absorption, penetration and wettability leading to quicker tablet disruption and faster disintegration and dissolution (1-3).

Irrespective of modification process, modified starch has been reported to perform better during processing than normal starch. The inference of Okor and Nelson (4) and other researchers (5) is not any different. By simple, cold, dilute acid hydrolysis of maize starch, a reduction effect on elastic and therefore gelling tendencies of maize starch is attained. This improves its use as disintegrant. Accordingly, defatting of starch was reported to lead to better granular properties which resulted in good flowability, better disintegrant property and lower friability (5).

When modified maize starch was incorporated intragranularly, improved processing and tablet characteristics better than starch USP were reported. Wet granulation process did not affect the quality of modified maize starch while granule flowability and tablet weight uniformity were better and exhibited slightly faster release rate. Granules and tablets with MMS were observed to be insensitive to processing changes. These and other reports confirm suitability of modified maize starch as good disintegrant and direct compressible excipient due to its free flowing characteristics (1).

Sodium starch glycolate according to manufacturers and drug formulation scientists is a high-tech disintegrant with remarkable rapid water penetration and extensive swelling capability due to increase in its granule size. Its inherent compressibility characteristics are in no doubt. SSG was reported to possess capability to absorb water and swell about 300 times its volume and not affected by increase in compression pressure. A super disintegrant, SSG maintains its disintegrant efficiency and improved dissolution even after the tablet has been reworked. All these attributes led to rapid disintegration and enhanced dissolution of tablet (1, 6, 7).

Replacement of SSG with modified maize starch without compromising the quality attributes of the product is considered enormous economical benefit bearing in mind the high unit price of SSG of =N=1500.0 per kg in comparison with MS (=N=150.0 per kg) and MMS (=N=185.0 per kg).

Paracetamol tablet, being a "me-too" product manufactured by over 80% of local pharmaceutical manufacturers in Nigeria is cheap and therefore could not adequately absorb the cost of an expensive, high-tech disintegrant such as SSG without increasing the unit cost of the product.

In this research work therefore, performance equivalence evaluation of effects of replacing SSG with MMS as disintegrant in paracetamol tablet formulation was done using maize starch USP as baseline. Five batch formulations with similar composition except for the disintegrants which were varied to reflect the effect of parameter being studied in the formulation. Characterization indices such as tablet weight uniformity and hardness (crushing strength), disintegration time and dissolution rate as well as friability were utilized to elucidate the consequence of the replacement and the attendant economic gain (8, 9). Cost- benefit analyses as well as statistical metric were engaged to confirm the significance of the differences. t-Test value of less than 0.05 is an indication of significant difference.

MATERIALS AND METHODS

Materials

Raw Materials and reagents used in this investigation include paracetamol powder (Wenzhou Pharma, China), microcrystalline cellulose (J. Rotten Maier and Sohnne, Germany), sodium starch glycolate (Explotab - Edward Mendell Co. Inc. NY), Polyvinyl pyrrolidone (BASF, Germany), Maize Starch (GATCO, Germany), Magnesium stearate (Vigenesh, India),

0.1N Hydrochloric acid (BDH, England), phosphate buffer pH 5.8 and methanol (Sigma-Aldrich, Germany). All these items were sourced through Roche (Nig.) Ltd., Lagos, Nigeria.

Methods

Preparation of Modified Maize Starch

250g of maize starch weighed and suspended in 500ml of 0.1N hydrochloric acid in a litre glass beaker. It was stirred until slurry is formed and left to stand at room temperature for 72 hours with occasional stirring at least two times in 24 hours. The slurry was decanted, washed several times with distil water until the last washing had a pH of around 6.5 determined with pH meter (Metrohm-632).

Filtered with sintered glass (type AG 17 x 2) that is attached to Waters Vacuum pump (type DOA), the wet mass was manually pressed through sieve of 1.4mm size, dried at 60°C using Ehret dryer (type TK/L10) for 2 hours. Dried granules passed manually through sieve of size 0.425mm and properly stored for further evaluation.

Evaluation of prepared Modified Maize Starch Powder

Moisture content was determined using Salvis oven. 20g of the powder was dried to constant weight at temperature of 105°C. Percentage loss was thus calculated. This was repeated for both maize starch and sodium starch glycolate. Using 2% mucilage of modified maize starch and maize starch respectively, viscosity was measured with Contrives Rheomat viscometer (type 108R) at shear rate of 1291 rpm for both materials. Average of three readings was computed.

The pH of modified maize starch was measured with Metrohm - 632 pH meter from 20% slurry of the material. Readings taken in triplicate and average found. The same was done for both maize starch and sodium starch glycolate.

Bulk density using 12g of modified maize starch and 20g of maize starch, accurately weighed with Mettler PM - 140 weighing balance was evaluated. Each was carefully transferred to graduated measuring cylinder and volume recorded. Three readings taken and average calculated in each case. The density is extrapolated from the ratio of weight and volume.

Preparation of Tablet

Five formulation batches were prepared. They differ only in the type and quantity of disintegrant used. The batches were coded SSG-3 with 3% SSG, MS-3 with 3% MS, MMS-3, MMS-6 and MMS-9 with 3%, 6% and 9% respectively of MMS. The weighing was carefully carried out using Mettler PM - 140 weighing balance (Mettler, Switzerland). Paracetamol powder and micro crystalline cellulose were dry-mixed for 3 minutes at 200rpm using Erweka AR 400 mixer (Erweka, Germany). Polyvinyl pyrrolidone was dissolved in 160 ml hot water to form binder solution which was allowed to cool to 40°C and then added to the powder mixture and kneaded for 2 minutes at 200rpm. The mixer is opened, scraped, closed and mixed for another one minute. The wet mass was carefully removed from the mixer, manually pressed through sieve number 10 (2.0mm size), dried at 60°C in Ehret dryer until the moisture content is around 1.2% determined with Ohaus moisture balance. The dried granule was manually pressed through sieve number 20 (1.4mm size). Each of sodium starch glycolate, modified maize starch, and maize starch was separately mixed with magnesium stearate in a nylon bag. The mixture was added to the granule in a litre plastic container which was manually rotated for 5 minutes to achieve blending.

Using single stroke tablet press (Korsh, Germany) fitted with 12.5mm flat punches and dies, granules were compressed into tablets having adjusted weight, thickness and compression force.

Determination of Tablet Parameters

Weight Variation: Individual weight of 20 tablets from each batch is checked using Mettler PM-40 analytical balance. Minimum, maximum, mean together with standard deviation were determined and recorded.

Friability Test

The test was done with Copley friabilator (Erweka - Germany). Average weight of 10 tablets was taken before the test. The tablets were fed into friabilator and allowed to rotate for 100 revolutions (i.e 4 mins at 25 rpm), the tablets carefully removed, dusted and re-weighed. Percentage friability calculated by comparing weight before and after test.

Hardness Test

The crushing strength of 10 tablets was determined individually using Schleuniger 2E hardness tester. Minimum, maximum, mean, standard deviation were extrapolated.

Disintegration Time

Copley distingration tester was used with water as medium at temperature of 37 ± 2°C maintained by thermostatically controlled water bath. A tablet was put in each tube, and the time it took to crumble into smaller particles that could pass through sieve no. 10 was determined. The mean and standard deviation of the six values were computed.

Dissolution Rate:

This was evaluated using Sotax AT-7 dissolution apparatus with six vessels and rotating paddle at speed of 75 rpm. Dissolution medium is phosphate buffer of pH 5.8 and temperature kept at 37 ± 1°C.

Table 1: Quality attributes of tablets of different batch formulations.

Attributes	SSG-3	MS-3	MMS-3	MMS-6	MMS-9
Weight Variation (mg) (n=20)	661.25 ± 7.73	640.15 ± 9.68	642.65 ± 9.04	668.55 ± 6.10	675.05 ± 7.92
Friability -%	0.76	0.68	0.51	0.62	1.12
Hardness - KP (n=10)	7.66 ± 1.18	11.42 ± 3.01	11.62 ± 1.61	9.86 ± 1.22	7.16 ± 0.81
Hardness/Friability Ratio	10.08	16.79	22.78	15.90	6.39
Disintegration time (Min: Sec), (n=6)	0:21 ± 0:1.1	3:07 ± 0:48	16:54 ± 0:21	4:32 ± 1:07	4:49 ± 0:32
MDT 50% (min)	0.5	33.8	6.4	4.5	3.20
Dissolution @ 30 min - % (n=6)	109.97 ± 1.98	44.64 ± 1.9	85.88 ± 2.17	103.87 ± 2.24	100.89 ± 2.1

Standard solution was prepared by dissolving 55.5mg of paracetamol in 100ml buffer. One ml of the solution was further diluted to 100ml with phosphate buffer.

Sample solution was prepared by putting a tablet in each of the six vessels containing 900ml of phosphate buffer. Paddle was put on at speed of 75 rpm. At stipulated time interval of 1, 5, 10, 20, 30, 40 minutes, 5ml sample was withdrawn from each vessel and replaced with dissolution medium. The sample was filtered and one ml of filtrate diluted to 100ml with phosphate buffer.

By means of Spectrophotometer (Spectronic 21, Milton Roy Coy), the absorbance of both standard and sample solutions was determined at wavelength of 249nm. The process was repeated for all the batches.

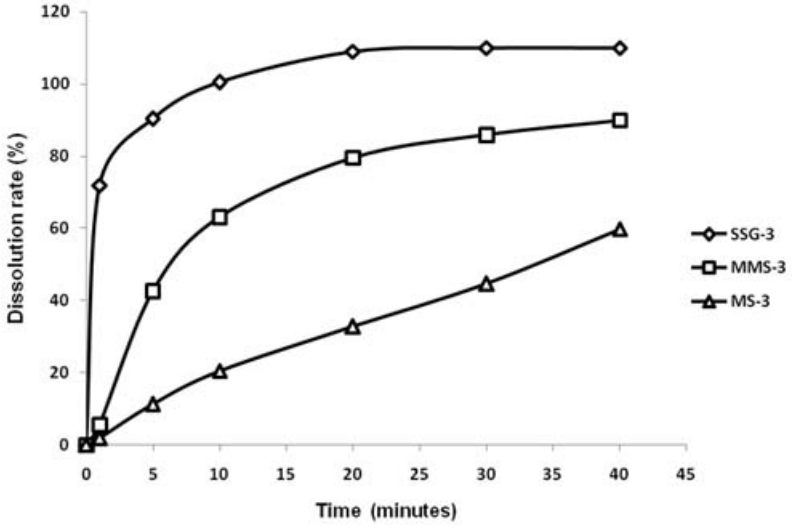
RESULTS

The results revealed that cold, dilute acid hydrolytic modification of maize starch produced better material in MMS with its viscosity reduced from 12 ± 0.46 to 11 ± 0.45 mPas and bulk density from 0.833 ± 0.018 to 0.600±0.015 g/ml. The results also showed that process performance efficiency of modified maize starch is better than maize starch. This is evident in the quality attributes of the final tablets shown in Table 1. Form weight variation to tablet friability, hardness to disintegration time, the parameters have comparable results. The dissolution rate as in Table 2 showed the superiority of MMS to MS and its inferiority

Table 2: Dissolution rate data of different batch formulations (%).

Time (Min)	SSG-3	MS-3	MMS-3	MMS-6	MMS-9
1	71.91	1.8	5.5	7.8	15.9
5	90.29	11.3	42.65	55.25	71.81
10	100.48	20.54	63.11	77.38	94.96
20	109	32.68	79.54	94.75	101.19
30	109.97	44.64	85.88	103.87	100.89
40	109.97	59.82	89.91	107.46	101.78
t- Test ($p \geq 0.05$)		0.000056	0.0182	0.0965	0.1433

Figure 1: Dissolution profiles of batches with 3% of different disintegrants.



to SSG in terms of drug release characteristics. The dissolution profile comparing the release rate of the batches with different types and different quantities of disintegrants were shown in Figures 1 and 2.

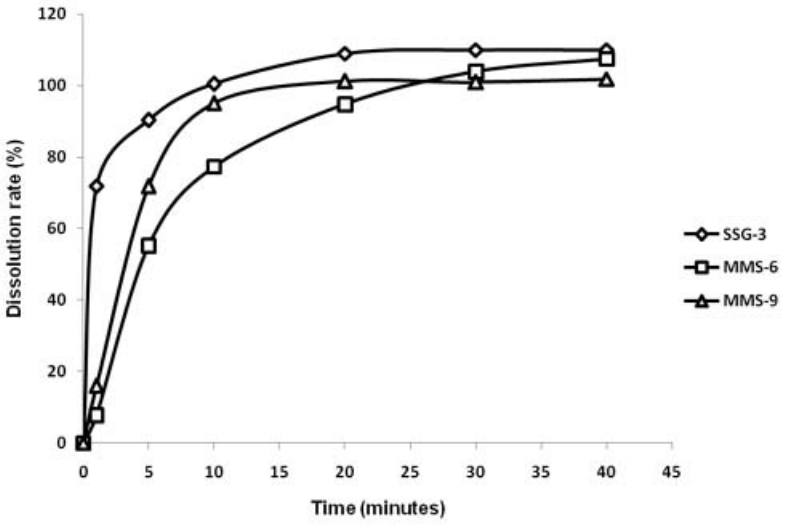
DISCUSSION

The use of starch in solid dosage form manufacture especially tablet, is not new (1-3). Its hydrolytic modification which reduced amylopectin and increased amylose content has shown that modified maize starch is a better disintegrant material than maize starch in terms of performance during processing and handling. This was in line with other previous research works done (4, 5). The modification has no detrimental effects on the overall quality of the tablet. The inclusion of MMS in the formulation has increased the plasticity of tableting materials thus making the granules to compress into tablets without any tendency of capping, chipping or lamination. The modification has indeed given the MMS additional property of a direct compressible material because of its crystalline nature. All these attributes make MMS to be superior to maize starch as indicated in Tables 1 and 2 and Figure 1. The dissolution at 30 minutes of batch with MS 3% is 44.64% as against 103.87% of batch with MMS 6%. The official specification is ≥ 80%.

Despite all these attributes however, results have shown that the qualities of MMS are inferior to sodium starch glycolate, a new generation, super disintegrant, so much so that its inclusion level has to be increased from 3 to 6% in order to provide drug release characteristics that will be comparable to SSG (6, 7). Incidentally, increase of MMS to 9% resulted in tablets that showed poor friability as depicted in table 1. This observation was however, in line with some earlier research investigations. It is concluded from the research work that increase in concentration of starch leads to decrease in crushing strength, increase in tablet porosity and friability and a decrease in disintegration time (11). The increase in starch concentration makes the tablet to be softer, porous and weak.

Table 1 showed that the physical parameters of tablets from all the batches were in conformity with standards. Variation in weight is less than 6% relative standard deviation limit in official books, given formulation weight of 650mg. It actually ranges from 1.2% in SSG-3, 1.5% in MS-3, 1.4% in MMS-3, 0.9% in MMS-6 and 1.17% in MMS-9. This assured content uniformity. Friability (except batch MMS-9 which has higher quantity of modified maize starch) and hardness were within their various limits. Tablets especially from batches SSG-3 and MMS - 6 are comparable at all levels while all the batches had tablets that are strong enough to withstand

Figure 2: Dissolution profiles of batches with different levels of disintegrant.



normal and abnormal stresses. The crushing strength and friability ratio also confirmed this assertion (12). Disintegration time except for batch MMS-3 is within the limit of official books (13).

The physico-chemical evaluation using dissolution which has been known to be a good predictor of bioavailability (10), was quiet revealing. The dissolution data and profiles shown in Table 2, Figures 1 and 2 revealed the superiority of modified maize starch over maize starch and it's potential to replace sodium starch glycolate as disintegrant in this paracetamol tablet formulation. At 95% confidence level, t- test which compares the p-value (0.05) of different batches at dissolution level returned values of 0.000056 for MS-3, 0.0182 for MMS-3, 0.0965 for MMS-6 and 0.1433 for MMS-9 respectively. The results showed that there were no significant differences among SSG-3, MMS-6 and MMS-9 hence were all the same. However, significant difference did exist among SSG-3, MS-3 and MMS-3 to the extent that both MS and MMS at 3% level can not replace SSG 3%. In the same vein, high friability of 1.12% as against official limit of less than 1% would not allow the use of MMS at 9% level as substitute for SSG 3% as it may not be able to withstand both normal and abnormal stresses during manufacturing and transportation. Thus, only MMS at 6% is a potential substitute for SSG 3%.

From cost - benefit analysis of the formulations, it makes economic sense to replace 3% sodium starch glycolate with 6% modified maize starch as the unit cost of the product is reduced by more than 9%, yet its dissolution profile at 95% confidence level (P = 0.0965) is comparable to that of 3% sodium starch glycolate. Both physical and chemical qualities of the resultant tablets are not in anyway compromised as mean dissolution time- MDT 50% for MMS-6 is 4.5 minutes with dissolution of 103.87% at 30 minutes. All these will engender therapeutic effects comparable to that of SSG-3.

CONCLUSION

Guided by the outcome of the evaluation of processes and data generated in the course of this research work and the limits of experimental conditions, it is evidence- based, data- supported and economically justified to replace 3% sodium starch glycolate with 6% modified maize starch as disintegrant in this formulation. The quality attributes of the resultant products such as hardness and friability, disintegration and dissolution were not in any way compromised.

However, care should be exercised during scale-up processes. Particular attention should be paid to com-

pression force, friability and disintegration time. Other studies have shown that improper storage of tablet with higher percentage of starch may lead to slight colour change and increase in hardness over time. This may lead to increase in disintegration time, decrease in dissolution rate and poor availability of paracetamol in the tablet.

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