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Research Article

Application of Acetylated Corn Starch as a Sustained Release Formulation in Metronidazole Tablets

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Abstract

Objective(s): This study aimed to assess the impact of acetylation on the disintegrant properties of corn starch and evaluate its effectiveness as a sustained release formulation in metronidazole tablets.

Design: Experimental study involving acetylation of corn starch using acetic anhydride.

Intervention(s): Formulation of granules with varying concentrations of acetylated corn starch as disintegrant, followed by tablet production.

Main Outcome Measure(s): Disintegration time, sustained release of metronidazole, tablet properties (friability, hardness, content uniformity), and release kinetics.

Results: Acetylated corn starch increased disintegration time, resulting in sustained release of metronidazole over several hours. Tablets met standard requirements for friability (<1% weight loss), hardness (>5 kg/cm^2), and content uniformity (>90% active ingredient). The release profile showed a controlled release pattern, indicating the potential of acetylated corn starch as a sustained release polymer.

Conclusion:

Acetylation successfully modified corn starch, making it an effective polymer for sustained release metronidazole tablets. This study demonstrates the potential of acetylated corn starch in formulation development for sustained release applications.

Keywords: Disintegration, Acetylation, Sustained Release.

INTRODUCTION

Sustained-release drug delivery systems are systems that prolong the duration of action of a drug by slowing its release [1]. They offer numerous advantages over conventional dosage forms which include reduction in the fluctuation of drug level that diminishes untoward side effects of the drug while improving therapeutic outcome as the reduction in dosing frequency enhances patient compliance. To be successfully used in sustained drug delivery formulations, a polymer material must be chemically inert, should not invoke an inflammatory or toxic response, should be readily processable and must have acceptable shelf life. In addition, the material should be capable of being metabolized in the body after fulfilling its purpose, leaving no trace.

A majority of investigations of natural polymers as matrices in drug delivery systems have focused on proteins and polysaccharides such as starch. In recent years, starches have been considered as new potential biomaterials for pharmaceutical applications because of their unique physicochemical and functional characteristics [2]. Improvement on the functional properties and applicability of starches has been achieved with various modifications. The process of starch modification involves the de-structurization of the semi-crystalline starch granules and the effective dispersion of the component polymer. In this way, the reactive site (hydroxyl groups) of the amylopectin polymer becomes accessible to reactants [3]. There are a number of chemical modifications made to starch to produce many different functional characteristics and these include acetylation, acidification, etherification, oxidation, cationization, cross- linking and grafting of starches. Acetylated starches are distinguishable through their high levels of shear strength; they are particularly stable to heat, acid and form flexible, water insoluble films [4]. As the degree of substitution increases, the nature of the starch acetate changes from hydrophilic to hydrophobic and simultaneously the inter-particulate bonding capacity increases greatly [5]. Official starches such as potato starch have been modified by acetylation and were reported to substantially retard the release of drug, thus allowing sustained drug release [6].

The objective of this project is to investigate and understand how the chemical modification process of acetylation affects the disintegrant properties of corn starch. It is also to evaluate the effectiveness of acetylated corn starch as a sustained release agent in metronidazole tablets, assessing its impact on drug release kinetics and overall formulation stability

The significance of this study is multifaceted. Firstly, by exploring the therapeutic advancement offered by a novel drug delivery approach, the research aims to enhance therapeutic outcomes for patients taking metronidazole. The potential for a sustained release formulation could improve patient adherence, thereby increasing the overall efficacy of the treatment [7].

Secondly, the study seeks to contribute to the optimization of pharmaceutical formulations. Identifying the optimal conditions for acetylated corn starch as a sustained release agent may lead to the development of more efficient and stable pharmaceutical products, advancing the field of pharmaceutical sciences [8].

Thirdly, the focus on patient compliance is pivotal. Successful implementation of sustained release tablets may reduce the frequency of drug administration, addressing a common challenge in healthcare. This could have a positive impact on patient adherence and consequently on treatment outcomes [9].

Despite the progress in pharmaceutical formulations, challenges persist in achieving optimal sustained release of metronidazole due to solubility and stability issues. The selection of an appropriate sustained release polymer is crucial to address these challenges and enhance therapeutic outcomes. While various polymers have been investigated for sustained release formulations, there is a research gap in exploring the potential of acetylated corn starch as a sustained release polymer for metronidazole tablets [10]. This study aims to fill this void by examining how acetylated corn starch influences drug release kinetics and the overall performance of sustained release formulations of metronidazole, contributing essential insights to the field of pharmaceutical formulation.

MATERIALS AND METHOD

Reagents Used

The materials used were Maize (procured from Igwuruta market, Rivers state, Nigeria), Acetic anhydride, Sodium hydroxide, 0.5M HCL, 75% Ethanol, 95% Ethanol, Distilled water, 0.5N Potassium hydroxide, Magnesium stearate, Talc, 0.1N HCL. This experiment was carried out in September 2023, at the University of Port-Harcourt, Rivers state.

Starch Extraction

Starch was extracted from local maize grains by soaking in distilled water after thorough washing. The mixture was milled to obtain a slurry that was strained through a muslin cloth followed by settling of the filtrate. The supernatant was decanted at 12 hours intervals and the starch slurry was re-suspended in distilled water. The starch cake was collected after 72 hours and dried in a hot air oven at 40°C for 48 hours. The dried mass was pulverized and then screened through a sieve of size 125µm [11].

Phytochemical Examination

Phytochemical screenings were carried out on the extracted corn starch to determine their compositions. The tests include confirmation test for starch and Molisch's test for carbohydrate.

Confirmation Test for Starch (Iodine Test)

A 0.1g of the dried isolated corn starch was placed on a clean crucible and a few drops of Lugol's solution was added. The color change was observed.

Molisch Test

A 2% dispersion of the isolated corn starch was prepared with distilled water. A 2ml of this dispersion was transferred into a test tube and a few drops of 10% alcoholic solution of Alpha Naphthol (Molisch reagent) was added. The test tube was inclined at an angle of 45° and 2ml of concentrated sulphuric acid was added cautiously, to form a layer beneath the starch dispersion. Observations were made and recorded.

Acetylation of Starch

A suspension of 50 g of starch in 112 mL of distilled water was subjected to shaking at 1500 rpm in a magnetic stirrer for 60 min at 25 °C. The pH of the suspension was adjusted to 8.0 with an aqueous 3.0 g/100g NaOH solution, and a slow addition of 5.5ml of acetic anhydride maintaining the pH between 8.0 and 8.4 with a 3.0 g/100g NaOH solution. After the complete addition of acetic anhydride, the reaction was continued for 15 min. The reaction was stopped by adjusting the pH to 4.5 with a 0.5 mol equi/L HCl solution. The final suspension was centrifuged for 3 min at 1000rpm and subjected to successive washings with 95 mL/L ethanol. The starch was dried in an oven with air circulation at 40 °C for 24 hours.

Determination of degree of substitution

One gram of starch acetate and 50 mL of 75 % ethanol were mixed in a flask with a loose stopper. The mixture was stirred in a water bath at 50°C for 30 min. After cooling to room temp, 40 mL of 0.5 N potassium hydroxide (KOH) solution was added to the mixture. The flask was fitted with a tight stopper and kept at room temperature with occasional shaking for 72 hours for complete saponification. An excess of alkali in solution was titrated with 0.5 N HCl solution using phenolphthalein as the indicator. A blank test was performed following the same procedure [12]. The percent of acetyl group and degree of substitution (DS) were calculated as shown:

$$\text{Acetyl group (\%)} = \frac{\text{(value of blank–value of sample) (ml) X Molarity of HCL X 0.043X100}}{Sample\ weight\ (g)}$$

$$\text{Degree of Substitution} = \frac{162 \text{ X Acetyl group}}{4300-(42\ X\ \%\ acetyl\ group)}$$

Where 162 is the molecular weight of the anhydro glucose unit, 42 is the molecular weight of replaceable acetyl group and 4300 is the molecular weight of the acetyl group attached with 100 anhydro glucose unit.

Preparation of granules

Granules were prepared by wet granulation method using acacia gum as the binder and acetylated corn starch as disintegrant at concentrations of 5, 7.5, 10, 15, 20 and 25% (w/w). Also, granules were prepared using 5% conventional corn starch as a disintegrant. Details of granulation are given in Table 1. Lactose was used as the diluent. The powder samples were dried and mixed in a ceramic mortar. The mixtures were moistened with the appropriate amount of binder solution that has been melted in warm water. The homogeneous wet mass was then screened through a 2.0mm sieve and the wet granules dried in a hot air oven at 40°c for 10 minutes. Thereafter, the granules were screened through a 1.0mm sieve and dried at 40°c for 10 minutes. Each batch of granules were transferred to already labelled dispensing jars and sealed properly.

Table 1: Composition of metronidazole tablet.

Ingredients	Batch A (5%)	Batch B (7.5%)	Batch C (10%)	Batch D (15%)	Batch E (20%)	Batch F (25%)	Batch G unacetylated corn starch (5%)
Metronidazole (mg)	200	200	200	200	200	200	200
Acacia gum(mg)	5	5	5	5	5	5	5
Acetylated corn starch(mg)	15	22.5	30	45	60	75	15
Magnesium stearate (mg)	3	3	3	3	3	3	3
Talc (mg)	3	3	3	3	3	3	3
Lactose(mg) to	300	300	300	300	300	300	300

Bulk density

A 10g weight of metronidazole granules A was weighed and transferred into a clean, dry 50ml measuring cylinder and the volume occupied was recorded. The bulk density was calculated using the formula below.

Bulk density= mass / volume

The procedure was repeated for batches B, C, D, E, F and G.

Tapped density

A 10g weight of granules batch A was weighed and transferred into a clean, dry 50ml measuring cylinder. The measuring cylinder was tapped for 5minutes on a padded tabletop to a fixed height and the tapped volume was recorded. The tapped density was calculated using the equation below.

Tapped density = mass / tapped volume

The procedure was repeated for batches B, C, D, E, F and G.

Flow rate

A 10g of granules batch A was poured into a blocked plastic funnel clamped on a retort stand. The blocked orifice was opened and the granules were allowed to flow out unaided. The time taken for the granule to exit the funnel was recorded.

The procedure was repeated for batches B, C, D, E, F and G.

Angle of repose

A plastic funnel was clamped on a retort stand at a fixed distance of 3cm from a flat surface. Sufficient granules of batch A was poured through the funnel until the tip of the heap touched the orifice of the funnel. The diameter of the heap was marked and measured. The angle of repose was calculated using the formula below.

Angle of repose, $(\theta) = \tan^{-1}(2h/d)$

Where; h= height of heap

d= diameter of the base of the heap

The procedure was repeated for batches B, C, D, E, F and G.

Hausner's ratio

This was calculated for all the batches using the formula below;

Hausner's ratio = tapped density / bulk density

Carr's index

This was calculated for all the batches using the formula below;

Carr's index = Tapped density - Bulk density /Tapped density X 100

Addition of exo-excipients

The exo-excipients (lubricant and glidant) were added to the granule based on the calculation in table 1. The

granules were mixed properly.

Compression of granules

After the addition of the exo-excipients, the mixed granules were compressed into tablets using a single punch tableting machine at a pressure of 4kg.F. The formed tablets were allowed to stay for 48hours before evaluation to allow for elastic recovery.

Quality control of tablets

Uniformity of Weight/ Weight Variation Test

Twenty tablets were randomly selected and weighed individually using an electronic balance. The weights were recorded and the mean as well as the variation in weight were determined.

Friability test

Ten tablets were randomly selected from each batch and dusted gently with a soft brush. The tablets were weighed together and placed in a friabilator set to rotate at 25rpm for 4minutes. The tablets were obtained, dusted again and reweighed together. The percentage friablility was calculated with the equation below;

$$\%\text{Friability} = \frac{(\text{initial weight of tablets} - \text{final weight of tablets})}{\text{initial weight of tablets}} \times 100\%$$

Hardness/ crushing strength test

The hardness of ten tablets from each of the 7 batches was determined using Erweka hardness tester. The mean crushing strength was determined.

Tablet thickness

Ten tablets were picked at random from each batch of the Metronidazole tablets. The thickness of the tablets was individually determined using a micrometer screw gauge. The mean and standard deviation for each determination was recorded [13]

Tablet diameter

Ten tablets were picked at random from each batch of the Metronidazole tablets. The diameter of the tablets was individually determined using a micrometer screw gauge. The mean and standard deviation for each determination was recorded [13]

Disintegration Test

The disintegration rate of six tablet selected at random from each of the batches was determined using a BP specified apparatus containing 0.1N HCL at 37 ± 0.5°C. The mean disintegration rate was calculated.

Dissolution test

The dissolution rates of the active drug from the tablet were determined using USP apparatus. A 900ml of freshly prepared medium (0.1N HCL) was transferred into the dissolution jars and maintained at a temperature of 37±0.5°C. The paddles were set to rotate at 100rpm. 10ml samples were withdrawn at 5, 10, 15, 20, 30, 40, 50, 60, 80, 100 and 120 minutes respectively and analysed spectrophotometrically for metronidazole at 277nm wavelength. The samples removed for analysis were replaced with fresh aliquots of the dissolution medium and the percentage drug dissolved was calculated as follows.

Preparation of standard calibration

A 0.05g weight of pure metronidazole powder was placed in a 50ml volumetric flask, dissolved with 0.1N HCL, and made up to the mark with the same solvent. Various dilutions of the stock solution were made to get 0.05, 0.10, 0.15, 0.20, 0.25 and 0.30mg/ml with 0.1N HCL and the absorbance determined by UV spectrophotometer at 240nm wavelength. A standard calibration curve was plotted (by plotting absorbance against concentration).

Content of active ingredient

Ten tablets were selected at random from each of the six batches, weighed and crushed to fine powder. The average of the powdered drug was calculated and transferred into a 50ml volumetric flask and dissolved with 0.1N HCL and made up to the 50ml mark with the same solvent. The solution was filtered and 1ml of the filtrate was transferred into a 10ml volumetric flask and made up to the mark with the 0.1N HCL. The drug content was determined by measuring the absorbance of the filtrate at 277nm wavelength, using the UV spectrophotometer.

RESULTS

Acetyl Content and degree of substitution

The acetyl content of the modified starch was approximately 43.30%, with a degree of substitution of 2.76.

Table 2: Preliminary Confirmation Test (Iodine Test)

Test	Observation	Inference
0.1g of starch in crucible + few drops of Lugol's solution	blue-black coloration	starch present

Table 3: Preliminary Confirmation Test (Molisch Test)

Test	Observation	Inference
2ml of 2% dispersion of corn starch in water + 2drops of alpha naphthol + 2 drops of conc H2SO4	Deep purple rung observed at the junction of two layers	Carbohydrate present

Table 4: Physical Characteristics of Metronidazole Granules

Batches	Average Bulk Density ± SD (g/cm^3)	Average Tapped density ± SD (g/cm^3)	Average Hausner's ratio ± SD	Average Carr's index ± SD (%)	Average Flow rate ± SD (g/s)	Average angle of repose ± SD (°)
A	0.51±0.00	0.66±0.03	1.30±0.06	23.00±0.82	10.84±1.21	49.41±0.43
B	0.54±0.00	0.60±0.01	1.11±0.02	10.00±0.77	26.11±1.20	36.00±0.42
C	0.51±0.02	0.68±0.01	1.34±0.06	25.37±0.79	14.91±0.93	48.37±0.34
D	0.53±0.00	0.71±0.00	1.36±0.00	26.33±1.02	14.08±2.41	51.05±0.00
E	0.48±0.01	0.62±0.03	1.29±0.03	22.58±0.67	21.01±1.92	49.09±0.45
F	0.46±0.00	0.59±0.00	1.29±0.00	22.90±0.39	23.81±0.00	48.49±0.01
G	0.43±0.05	0.55±0.10	1.30±0.01	25.20±0.00	20.56±0.10	43.89±0.09

Table 5: Physical Characteristics of Metronidazole Tablets

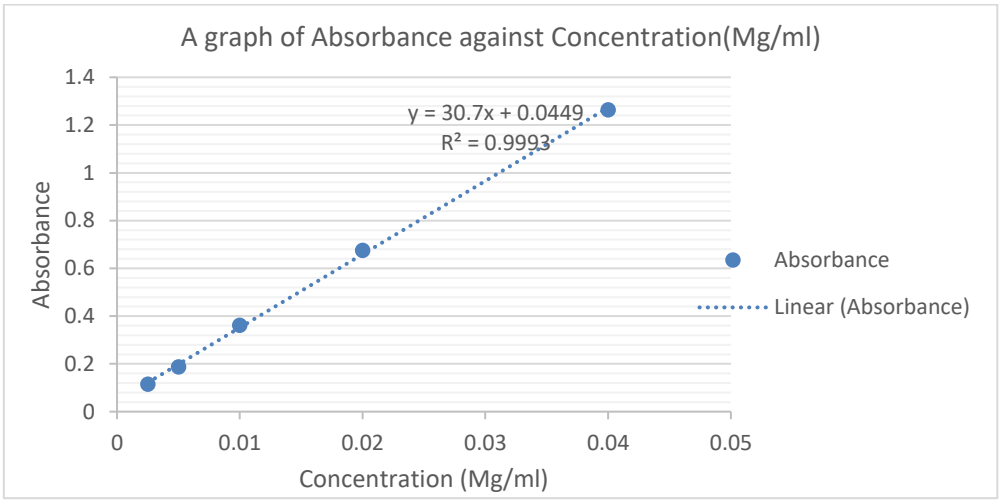
Batches	Tablet weight ± CV (mg)	Friablility (%)	Tablet Hardness (kg/F)	Tablet thickness (mm)	Tablet diameter (mm)	Disintegration time test (minutes)	Drug Content (%) assay
A	304.10±5.67	0.43±0.01	7.00±0.98	0.40±0.00	0.81±0.01	47.00±3.56	97.00
B	306.35±4.40	0.20±0.00	4.00±1.20	0.38±0.50	0.79±0.02	52.00±2.81	99.00
C	308.00±3.90	0.57±0.00	6.50±0.69	0.40±0.20	0.80±0.00	59.00±1.19	99.00
D	307.00±6.25	0.52±0.01	6.50±0.00	0.35±0.01	0.81±0.20	84.00±3.32	98.00
E	300.30±1.98	0.51±0.00	5.50±0.96	0.40±0.00	0.80±0.02	62.00±0.97	97.50
F	300.20±0.89	0.70±0.02	4.50±0.54	0.38±0.01	0.79±0.01	51.00±0.72	97.00
G	302.00±1.37	0.50±0.08	4.5±0.01	0.40±0.01	0.80±0.00	3.75±0.90	99.00

Table 6: Organoleptic properties of Metronidazole tablets

Batch	Color	Shape	Defect	Taste
A	White	Round	None	Bitter
B	White	Round	None	Bitter
C	White	Round	None	Bitter
D	White	Round	None	Bitter
E	White	Round	None	Bitter
F	White	Round	None	Bitter
G	white	Round	None	Bitter

Table 7: Absorbance value and Concentration for Beer's plot

Absorbance	Concentration (mg/ml)
1.264	0.04
0.675	0.02
0.362	0.01
0.1875	0.005
0.115	0.0025



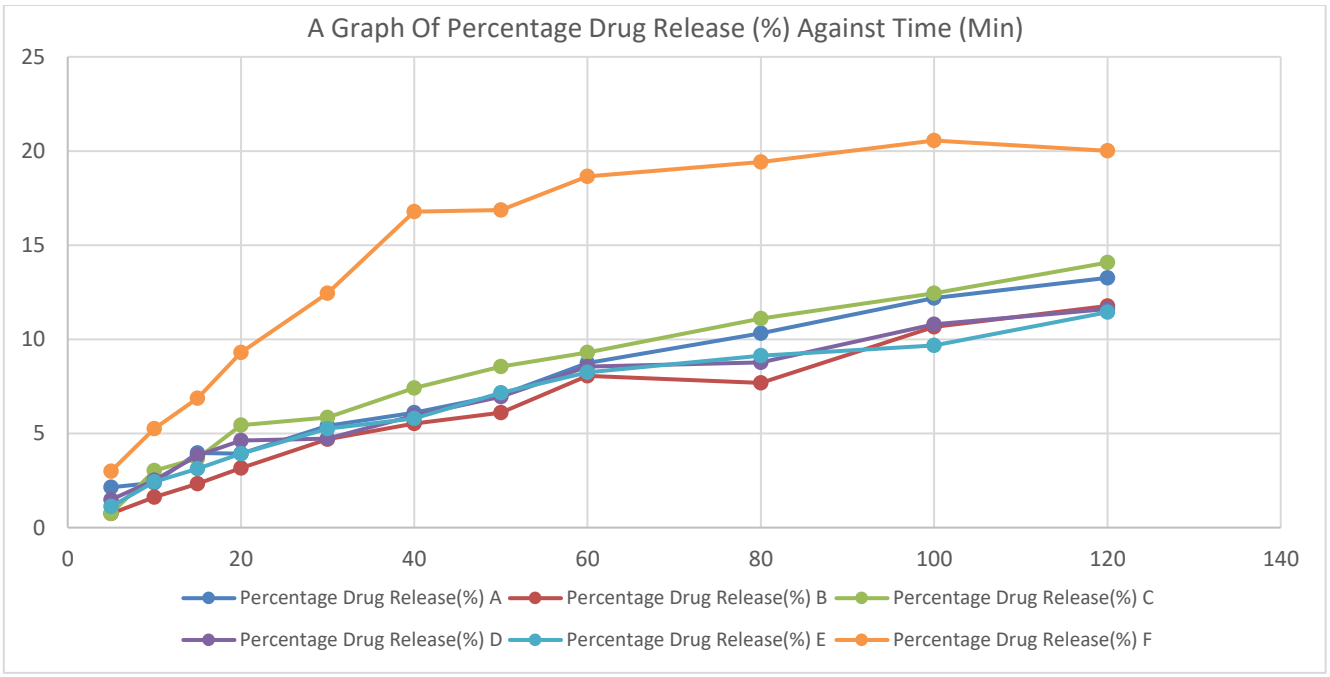


Figure 1: A Graph Showing the Percentage Drug Release Against Time

DISCUSSION

The isolated starch when subjected to preliminary confirmatory tests which include Molisch test and Iodine test produced an intense blue-black colouration when treated with Lugol's solution confirming the presence of starch. On treatment with Molisch's reagent, the appearance of a violet ring when treated with alpha naphthol confirmed the presence of a carbohydrate. The acetyl content of the modified starch was approximately 43.30%, with a degree of substitution of around 2.76. Starches with a higher degree of substitution (DS) exceeding 2 attract research attention due to their thermoplasticity and reduced swelling. [14], [15]. With increasing DS, the starch acetate transitions from hydrophilic to hydrophobic, enhancing inter-particle bonding and making them suitable as polymers for sustained release [5].

Metronidazole granules were formulated in 7 batches; batch A-F had acetylated corn starch as the disintegrant in 5%, 7.5%, 10%, 15%, 20% and 25% respectively whereas batch G contained 5% native corn starch as the disintegrant.

From the evaluation of granules, batch B had the highest bulk density, 0.54 g/cm^3 and batch G had the least bulk density 0.43g/cm^3 while batch D had the highest tapped density, 0.71g/cm^3 and batch G had the least 0.55g/cm^3.

The best flow property was seen in batch B which had a Hausner's ratio of 1.11, Carr's index of 10%, an angle of repose of 36° and a flow rate of 26.11g/s. The other batches had a passable flow property.

Table 8: Showing the scale of flowability

Carr's index	Flow property	Hausner's ratio	Angle of repose (°)
≤10	Excellent	1.00-1.11	25-30
11-15	Good	1.12-1.18	31-35
16-20	Fair	1.19-1.25	36-40
21-25	Passable	1.26-1.34	41-45
26-31	Poor	1.35-1.45	46-55
32-37	Very poor	1.46-1.59	56-65
>38	Very very poor	>1.60	>66

Source [16]

Some organoleptic tests were carried out on the tablets and they were found to be round in shape, white and had a bitter taste and they all lacked defects.

The weight variation test was carried out on twenty (20) randomly selected tablets from each batch. The average tablet weight across the 7 batches ranged from 300.20mg - 327.00mg. The percentage deviation ranged from 0.89-6.25. According to the USP, tablets from 130mg to 324mg should fall within a percentage deviation of ±7.5%. From the result obtained, the tablets of all batches were within this limit, hence they all passed the test.

Table 9: Limits of coefficient of variance

S.N.	Average weight	Coefficient of Variance
1	< 130mg	±10%
2	130mg - 324mg	±7.5%
3	> 324mg	±5.0%

Source [17].

The hardness of the tablets across all batches ranged from 4.5kgF-7.0kgF which according to the USP is within the standard range (4.0-10kgF).

The percentage friability for all batches were below 1%, hence all tablets passed the test and as such, tablets would be able to withstand transportation and handling.

The diameter of tablets across all batches ranged from 7.90mm - 8.10mm while the tablet thickness ranged from 3.50mm to 4.00mm.

The disintegration time of the tablets was found to increase as the concentration of the acetylated corn starch increased (47, 52, 59 minutes) and the peak disintegration time was observed in batch D (84minutes) having 15% acetylated corn starch. After this concentration, the disintegration time was found to reduce in batches E and F (62 and 51 minutes respectively).

This prolonged disintegration is attributed to the acetylation of the starch. Thus, tending to the formulation of a sustained release metronidazole tablet. The batch produced using the unacetylated starch disintegrated at 3.75 minutes which is in line with the USP standard.

The dissolution profile of the tablets showed that batch F had the highest percentage drug release, this is because it had the shortest disintegration time when compared to the other batches. The drug release from the tablets was sustained over a period of time as a result of the hydrophobic polymer network of the acetylated starch. The dissolution time was observed to increase with increase in amount of polymer. The percentage of active drug content across batches ranged from 97-99% which is within the standard.

CONCLUSION

From this experiment, all batches produced passed the evaluation test and thus are suitable for oral administration. Due to the acetylation process, the disintegration time of the tablets was greatly increased thus leading to a reduced release rate of the active ingredient. This implies that acetylation is an effective starch modification process that would produce stable sustained release metronidazole tablets. Acetylated corn starch is more effective as a disintegrant for sustained release tablets at concentrations not exceeding 20%w/w.

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