INTRODUCTION

Pharmaceutical products usually undergo series of changes in the course of storage and this is highly influenced by the nature of the material and the conditions under which they are stored (1). The physical, chemical and biological properties may be altered during storage leading to deterioration, and decrease in their therapeutic usefulness. In certain cases, such deterioration may result to toxicity of the drug substance (2, 3).

The knowledge of the various storage conditions for individual drug products and the need to provide such optimal storage conditions cannot therefore be over-stressed. Apart from the danger posed by such deteriorated drug substances, there is the problem of economic loss to the manufacturing firms who may need to recall such products.

Generally, pharmaceutical products undergo three types of deteriorations namely: physical, chemical and microbial (4, 5). Physical deterioration includes discolouration leading to inelegant products, change in flavour, viscosity and consistency of the formulation. Chemical deterioration is usually caused by series of chemical reactions involving the active ingredient and other adjuvants. Exposure to environmental conditions such as temperature, humidity, sunlight, pH, moisture and oxygen affect the rate and extent of drug chemical degradation. Microbial deterioration occurs when the product’s activity or appearance is altered due to an invasion or contamination by microbial agent.

Pharmaceutical products containing steroidal drugs are highly sensitive and need special storage conditions (6). In fact, the BPC recommends that pharmaceutical products containing steroids like

ABSTRACT

In this study, the effects of some environmental storage conditions – light, temperature and humidity on the stability of the steroidal drug, hydrocortisone sodium succinate injection were investigated. The drug samples were stored at varying conditions of light, temperature (0°C, 28°C and 60°C) and humidity, after which each sample was assayed at weekly intervals for their content of the drug using a UV –Vis spectrophotometer. From the results obtained, storage under light, at enhanced temperature and in the presence of moisture had pronounced degradative effects on the stability of hydrocortisone sodium succinate injection, calling for caution in the storage of this widely used anti-allergic and anti-inflammatory drug.

Key words: Hydrocortisone, storage conditions, stability, environmental conditions
prednisolone, cortisone acetate, dexamethasone, triamcinolone and hydrocortisone should be properly stored.

In this present study, the influence of various storage conditions of a typical widely used steroidal injection, hydrocortisone sodium succinate (11-β-17, 21 Trihydroxy-4-ene-3-20 dione-21) is studied. Hydrocortisone sodium succinate is an odourless, white, hygroscopic crystalline powder soluble at 20°C in 3 parts of water, in 34 parts of alcohol and 200 parts of dehydrated alcohol. It has a protein binding of 90%, melts at 17°C and should be stored in airtight containers. It is well absorbed after oral administration and has a plasma half-life of 80 – 120 min, which may be increased in patients with liver disease, hypothyroidism or in patients undergoing estrogen therapy. The drug is used as a replacement therapy in adrenal gland disease and as supplementary therapy for those with low endogenous production of hydrocortisone. It is also used in rheumatoid arthritis, polyarthritis nodosa, dermatomyositis, alphaltous ulcer, skin rashes, collagen disease and in rheumatoid fever.

**MATERIALS AND METHODS**

**Materials**

The following materials were used as procured from their respective manufacturers: hydrocortisone sodium succinate injection (RFI, Milan) and ethanol (M & B, England). Equipment used included electronic balance (Mettler, AE 240, England), spectrophotometer (Ref. Spec. 6000 Series, England), pH meter (Becmans, England), oven (Memmet, Karl Kolb, Germany) and viscometer (Becmans, England).

**Methods**

**Beer’s plot**

From a sample of the hydrocortisone injection powder, 10 mg was dissolved in 50 ml of 95% ethanol and 2 ml of this was made up to 50 ml with the ethanol to give a stock solution of 8 µg/ml. The following concentrations were subsequently prepared from the stock solution: 0.6, 3.2, 4.8, 6.4, 8.0 and 9.6 µg/ml. The absorbances of these prepared solutions were determined with the spectrophotometer at 246.2 nm, after appropriately diluting with 95% ethanol and employed to obtain the Beer’s plot.

**Effect of storage temperature on stability**

A 100 mg quantity of the hydrocortisone powder was stored at an elevated temperature of 60°C for six weeks, during which time, the drug content was analysed at weekly interval using the spectrophotometer. This procedure was also repeated for samples stored at 28°C and 0°C respectively.

**Effect of light on stability**

This was determined by exposing 100 mg of sample B to direct sunlight and another 100 mg to darkness in a dark cupboard. Their contents were analysed spectrophotometrically at weekly intervals for six weeks.

**Effect of humidity on stability**

A 100 mg quantity of hydrocortisone sample C was exposed to atmospheric humidity for six weeks while another 100 mg quantity was stored in a desiccator, inside the room at room temperature.
RESULTS AND DISCUSSION

Figure 1 shows the variations in the content of active ingredient upon storage at exposed light and in the dark. There was a very slight decrease in the concentration of hydrocortisone remaining upon storage for six weeks in the dark. The same was however not the case with the injections exposed to light. The decrease in concentration of active ingredient was more pronounced in the injection exposed to light. Light has been known as one of the causative factors that catalyse hydrolytic reactions that lead to instability in pharmaceutical formulations in a process termed photolysis (7). The energy of light is known to be capable of initiating oxidative or hydrolytic decomposition in drugs. The degradative power of light increases with decrease in the wavelengths essentially because the energy of light increases with decreasing wavelength such that the UV light with a lower wavelength (50 – 400 nm), has more energy (72 – 286 kcalmol⁻¹) than the visible light (400 – 750 nm) which in turn has more energy (36 – 72 kcalmol⁻¹) than the infra-red (1 – 36 kcalmol⁻¹) with a wavelength range of 750 – 10,000 nm. The natural light from the sun possesses the wavelength range of 290 780 nm and only the UV range of this can lead to photodegradation of drugs (8). Generally, when electromagnetic radiations are incident on molecules of solute, the later absorbs photons of light at typical wavelengths resulting to an increase in the energy state of the substance. The absorbed light energy will either lead to the degradation of the substance, or can be converted to heat, be retained or transferred, or can lead to the emission of light of a different wavelength such as fluorescence or phosphorescence. Hydrocortisone is one of the drugs subject to photodegradation, as well as prednisolone, ascorbic acid, riboflavin and folic acid (9).

Figure 2 shows the effect of storage temperature on the stability of the hydrocortisone injections. Increase in temperature led to increase in the amount of degradation of the active ingredient. Among the factors that affect drug stability is temperature. It has been shown that a 10°C rise in temperature leads to a two to five times increment in the amount of decay experienced by a drug (9). The presence of free energy typically increases the rate of chemical reaction. This increase follows an Arrhenius equation relationship (Equation 1) in which a plot of log rate of chemical reaction verses reciprocal of absolute temperature yields a straight-line curve.

\[ k = A e^{-E_a R T} \quad \text{... Eqn 1} \]

Or

\[ \log k = \log A - \frac{E_a}{2.303RT} \quad \text{...Eqn 2} \]

Where A is a constant called frequency factor; k is the rate constant; E_a is the activation is the activation energy; R is the gas constant and T is the thermodynamic temperature.

Thus the rate of chemical reaction at any given temperature can be deduced making it possible for the shelf life to be extrapolated. This forms the basis for the accelerated stability tests.
Figure 3 shows the effect of humidity on the stability of hydrocortisone sodium succinate. It is seen that the presence of humidity increased the rate of degradation of the drug. Humidity, like light and temperature is one of the factors responsible for drug instability. Moisture generally leads to hydrolysis in drug products. Such hydrolysis often occurs when water offers a nucleophilic attack on susceptible bonds in drugs like esters, amides and lactams when these drugs are in solutions (10 – 12'). Such nucleophilic attacks on drugs can equally be exhibited by solvents other than water in a process referred to as solvolysis.

CONCLUSION

It has been shown from this study that light, increased temperature and humidity decreased the stability of hydrocortisone sodium succinate. Care should therefore be taken in the storage of this drug and any drug formulation containing it, to preclude the presence of these degradative factors.

REFERENCES

INTRODUCTION

Starch is an important ingredient in the formulation and production of tablets where they act as binders, disintegrants and diluents. For instance, starches from banana spps and sago have been investigated for their disintegrant property by Patel and Chikkha (1). Underwood and Cadwallader (2) studied the influence of various starches namely, corn, rice, potato and arrow root, on the dissolution rate of salicylic acid from tablets. Effects of various starches as binders on the physical properties of sulfanilamide tablet formulation have been studied by Keshin et al (3). In 1967, Mital and Ocran (4) studied the use of cassava and yam starches as tablet disintegrants, using only lactose as the organic substance for the preparation of such tablets. Nasipuri (5) also studied the use of cassava starch as a binder and disintegrant in the formulation of tablets. Esezobo and Ambulam (6) evaluated the starch obtained form plantain as a binder and disintegrant for compressed tablets.
Due to their effect as powerful disintegrant, starches have been found useful in preparation of insoluble drug substances. Sakr et al (6) studied the effect of various starches on the physical standards of sulfaguanidine. They showed that all the starches caused a decrease in the disintegration time with increase in concentration. Osisiogu and Uzo (8) examined the industrial potentials of starch extracted for Dioscorea rotundata. They stated that the granule size and some rheological properties of this starch disposes it as a potential substitute starch.

Starches have also been used as suspending and emulsifying agents due mainly to the high viscosity of their mucilage (9). They have also occasionally been used for preparing enemas containing oils. Wheat starch is particularly good for this because of its demulcent, neutral and viscosity inducing properties (10).

Starches have also been applied in the production of pills as coating/dusting agent. It is equally used as a base for jellies and when added to gelatin and heated, produces starch glycerin used for the preparation of jelly with a gelatinised starch base (11). Sterilised starch BP is used as a lubricant for surgeon’s gloves. Sterilised starch is maize starch subjected to physical and chemical treatment so that it does not gelatinise on exposure to moisture. Potato starch is used as a raw material for nitro-starch manufacture, and as an attractant in insecticide mixtures, as well as a boiler feed treating agent.

Tablet binders are agents used to impart cohesive qualities to the powdered materials to ensure that the tablets remain intact after compression. They are substances that glue powders together and cause them to form granules (12).

In this present study, the starch obtained from a tropical plant tuber, Dioscorea dumetorum is evaluated as a binder in chloroquine phosphate formulations.

**MATERIALS AND METHODS**

**Materials**

The following materials used were of analytical grades chloroquine phosphate, maize starch, hydrochloric acid and lactose all from May and Baker, England, and magnesium stearate (Hopkins and Williams, UK). Dioscorea dumetorum was procured locally from Nsukka Central market.

**Methods**

The starch was extracted by light modifications of the methods of Shipman (13), Ocran (4) and Rasper et al (14). The tuber was washed free of soil with clean tap water and dried. This was peeled to remove the outer covers and cut into small pieces, washed with water and grated mechanically with an aluminium grater. The fine pulp obtained was macerated in clean distilled water for 6 h and later strained through a 100-mesh sieve and washed several times with clean water. The resulting starch slurry was collected, allowed to settle for 6 h after which the supernatant was discarded. The slurry was purified further by continuous washings with distilled water to remove soluble impurities while passing through a 100-mesh sieve. The larger impurities like fibres and hairs were removed by passing through a 200-mesh sieve. The resultant slurry was then spread in thin layers on flat trays and sun-dried. This was pulverized with an end runner mill (Paschall Engin., USA) and...
dried in hot air oven (Gallenkamp, England) at 50°C for 2 h.

**Defatting of starch**

A 500 g quantity of *D. dumetorium* starch was extracted for 24 h in a soxhlet extraction using 85 % v/v aqueous methanol as solvent. The defatted starch was oven-dried and the dried starch pulverized with pestle and mortar.

**Identification tests on the extracted starch**

A 1 mg quantity of the starch was boiled with 50 ml of distilled water and 1 ml of iodine solution added. A blue-black colouration confirms the presence of starch.

**Preparation of granules**

Chloroquine phosphate granules were prepared according to the following formula:

- Chloroquine phosphate: 250 mg
- Maize starch (disintegrant): 50 mg
- Lactose (diluent): 20 mg
- Maize/*D. dumetorium* starch (binder): 15, 20, 25%

The binder pastes were prepared by adding the respective starch to the required quantity of cold water and heating in a water bath with constant stirring for 5 min. The pastes were then used to form chloroquine granules. The granules were sieved, dried and re-sieved.

**Preparation of chloroquine tablets**

The wet granulation method was used to formulate chloroquine phosphate tablet according to the earlier given granule formula. The appropriate weights of active ingredient, disintegrant and diluent were added and mixed in a mortar using a pestle. The mixture was moistened gradually by adding drops of the solution of binder prepared to render it coherent but by no means wet. The damp mass so obtained was then granulated by passing through a No. 10 mesh sieve, dried at 60°C for 12 h and then re-sieved through a No. 16 mesh-sieve. The lubricant, magnesium stearate was then added by tumbling action. The lubricated granules were then compressed into tablets using a Korsh Single-punch tableting machine (Germany).

**Evaluation of granules**

**Angle of repose**

A measuring cylinder opened at both ends was placed on a smooth surface in a vertical position. A 10 g quantity of the granules was poured into it with the aid of a funnel. The cylinder was slowly and carefully withdrawn by raising it up to form a core of the granules. The height of the granules was measured with a cathetometer (Eberbach, Michigan). The angle of repose was determined from the angle formed by the sides of the heaps with the horizontal. A total of four determinations were made.

**Bulk and tapped densities**

The bulk densities of all the granules were measured by gently pouring through a short stemmed glass funnel into a 100 ml graduated cylinder, 20 g of each granule. The orifice of the funnel was aligned with the 100 ml mark. The volume occupied to the nearest 0.5 ml was noted and the bulk density deduced in g/cm³. The tapped density of the granules was measured by dropping the graduated cylinder containing 20g of granules, 20 times from a height of 2.5
cm onto a wooden bench and recording the volume. The tapped density was calculated in g/cm$^3$.

% fines

Using sieve No. 60, the dry granules were sieved and the fines produced for each batch weighed. The percentage on the basis of the total granules was calculated.

Flow rate

The flow rate of 40 g of each granule batch was determined four times using the flow rate apparatus and the mean taken.

Evaluation of chloroquine tablets

Hardness

The tablet to be tested was placed between the spindle and anvil of the Monsanto tester. Pressure was then applied by turning the knob gradually and gently until the tablet was just held in position. The pointer reading on the scale was then adjusted to zero. Pressure was further applied as uniformly as possible until the tablet was broken and the particular pressure noted. The average of ten determinations was taken.

Friability

The Erweka friabilator was set at 25 rpm. Ten randomly selected tablets from any batch were dusted free of any adhering particles and weighed. These were then introduced into sample bottles and placed in the chamber of the friabilator. The machine was then allowed to rotate for 4 min and the tablets de-dusted and re-weighed. The % loss in weight was calculated as the friability.

Disintegration

Five tablets were placed in the basket of an Erweka disintegration apparatus and lowered in such a way that the complete up and down movement is repeated thirty times a minute. The tablets were regarded as disintegrated when no particle remained above the gauze, which would not pass readily through it. The time taken for the tablets to disintegrate was noted. This was repeated five times.

Uniformity of weight

The BP specification for uniformity of weight was applied. The weights of twenty tablets were determined singly and collectively and the mean weight noted. The percentage deviation allowed by the BP for tablets containing 0.3 g and above was used to calculate the adherence or otherwise of the tablets to the limits for uniformity of weight.

Dissolution profile

The USP dissolution test apparatus was used for the test. A 500 ml quantity of 0.1 N HCl was placed in a 600 ml glass jar and placed on a hot plate with a magnetic stirrer. The system was allowed to attain a temperature of 37°C and then stirred with the magnetic stirrer at a speed of 100 rpm. One tablet from each batch was placed in the basket and 5 ml of the dissolution medium withdrawn at pre-determined time intervals. The volume withdrawn was replaced by pipetting 5 ml of 0.1 N HCl into the medium. The withdrawn volumes were
diluted serially with 0.1 N HCl and their chloroquine contents determined by measuring in a Pye Unicam UV-Vis spectrophotometer at a wavelength of 257 nm reference to a standard Beer’s plot.

RESULTS AND DISCUSSION

The extraction process yielded 12.5 % w/w of a light yellowish starch the colour of which was further lightened by defatting. The identification test confirmed the identity of the starch.

Table 1 shows the granule properties of the different granule batches produced by the different binder concentrations. Increase in binder concentration generally yielded increases in angles of repose. Angle of is an index of flow behaviours of granules and powders. The more cohesive granules are, the greater the angle of repose. Granules that do not flow present difficulty in the manufacture of compressed tablets. Generally, granules will not flow if the angle of repose exceeds 50° while materials having angle of repose near minimum circa 25°, flow easily (15). All the batches had generally good angles of repose.

The bulk and tapped densities however decreased with increasing concentration of binder. This is as a result of increase in granular size. Simultaneously, the voidage of the granules bed increases, accounting for the decrease in bulk density. The two types of starches showed similarities in both bulked and tapped densities. The table also shows that low binder concentrations of both starches produced more fines than the higher concentrations. Low percentages of fines indicate effectiveness of binder (16). The percentages of fines were also relatively similar for both starches though slightly lower in the granules produced from maize starch. Increase in binder concentration also yielded increases in flow rate of granules. Granulation is a way of improving the flow of powders.

Table 2 shows some of the characteristics of the formulated chloroquine phosphate tablets. Increasing the binder concentration increased the hardness of the tablets, generally. This is consistent with

<table>
<thead>
<tr>
<th>Granule properties</th>
<th>Binder concentration (D. dumetorium)</th>
<th>Binder concentration (Maize starch)</th>
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<tbody>
<tr>
<td></td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>Angle of repose (°)</td>
<td>20.5</td>
<td>21.8</td>
</tr>
<tr>
<td>Bulk density (g/cm³)</td>
<td>0.606</td>
<td>0.588</td>
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<tr>
<td>Tapped density (g/cm³)</td>
<td>0.699</td>
<td>0.657</td>
</tr>
<tr>
<td>% fine</td>
<td>12.2</td>
<td>11.7</td>
</tr>
<tr>
<td>Flow rate (g/sec)</td>
<td>9.1</td>
<td>12.5</td>
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previous works (17). The tablets generally had good hardness values of between 4 and 6 kgf. There was a decrease in friability as the binder concentration increased. This result is consistent with an earlier result (18). This is expected since friability is a measure of interparticulate cohesiveness in tablets and could be a function of tablet hardness. Again, the two batches of tablets produced by the two starches showed similar friability patterns. The tablets all disintegrated within the acceptable limit of 15 min. Increase in the concentration of binder however led to decrease in disintegration times.

Figure 1 shows the dissolution profiles of the tablets formulated with the different starches. All the tablets showed similar dissolution profiles with the tablets formulated with Dioscorea dumetorium showing higher initial dissolution rates. The dissolution times generally increased with increasing binder concentrations in all the batches.

REFERENCES
2. Underwood, T. W. and Cadwallader, D. E.

<table>
<thead>
<tr>
<th>Table 2: Tablet characteristics of the different tablets produced by the different binder concentrations</th>
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<tr>
<td>Tablet properties</td>
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<tr>
<td></td>
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<tr>
<td>Hardness (kgf)</td>
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<tr>
<td>% friability</td>
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<tr>
<td>Disintegration time (min)</td>
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<td>Mean weight (g)</td>
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