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Original Article

STABILITY STUDIES ON FLUCLOXACILLIN SODIUM IN CAPSULE DOSAGE FORMS

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ABSTRACT

Objective: Flucloxacillin is easily broken down by moisture and this raises stability concerns of the drug in a country where humidity is very high.

Stability studies on flucloxacillin sodium in capsule formulations were done with three pharmaceutical excipients. The studies sought to determine the best of three excipients for the formulation of flucloxacillin that gives the best stability in an environment of high humidity. The study also sought to establish if the amount of excipient influences the stability of flucloxacillin in the formulation.

Methods: Fixed amounts of flucloxacillin sodium were mixed with varying amounts of dried starch, undried starch and sodium carboxymethylcellulose (sodium cmc) in Petri dishes. The mixtures were exposed to humidity in a room for 12 w and iodimetry was used to monitor the amounts of flucloxacillin sodium in the mixtures for 12 w.

Results: It was noticed after 12 w that, the mixtures with the dried starch experienced the least breakdown or gave the most stable products, followed by those with the undried starch while those with sodium cmc experienced the most breakdown. Also, the higher the amounts of excipients used, the more stable the drug.

Conclusion: Dried starch should be preferred and in higher amounts in formulating capsule dosage forms of flucloxacillin sodium.

Keywords: Stability studies, Flucloxacillin sodium, Sodium carboxymethylcellulose, Dried starch, Undried starch, Iodimetry

INTRODUCTION

Antibiotics are naturally occurring substances that are produced by bacteria and fungi and are able to inhibit the growth of other bacteria and fungi [1].

Penicillin is one of the first antibiotics to be discovered by man. Its discovery was made by chance by Sir Alexander Fleming in 1928 when he noticed zones of inhibition around the blue-green moulds that were found in a medium he had inoculated with *Staphylococcus aureus* [2].

Penicillin acts on the bacteria to kill them by inhibiting their cell wall synthesis [3].

Flucloxacillin is isoxazolyl penicillin whose bulky side chain makes it resistant to beta-lactamases produced by susceptible bacteria [4]. It can be used in the treatment of boils, meningitis caused by methicillin-sensitive *Staphylococcus aureus* among other infections and can cause muscle pains as one of its side effects. Its use is contraindicated in persons who react to penicillins [5, 6].

Flucloxacillin as a drug comes in various forms; capsules, suspensions and injections usually as the sodium salt [7]. Flucloxacillin is an unstable drug which can be broken down by moisture, acids and bases. This implies that, formulations of the drug ought to be kept away from these factors that make them unstable [8]. It is however, difficult to keep totally formulations away from moisture because of the high humidity that persists in our environment. This therefore, means that there has to be a way of stabilizing the product in the presence of moisture.

The experiment was therefore aimed at investigating some excipients which when formulated with flucloxacillin sodium will slow down its breakdown by moisture by possibly sequestering the moisture in the formulation or product. The excipients considered were starch (dried and undried) and sodium cmc.

Starch when exposed is able to absorb moisture from the atmosphere. This moisture renders the starch polar and as a result, is able to absorb more moisture through hydrogen bonding from the air making it more hygroscopic than the dry form which has not been exposed or has the water molecules removed by heating. The study therefore, sought to find out the impacts of these two forms of starch on the stability of flucloxacillin sodium [9].

The effects of the different excipients on the stability or rate of breakdown of flucloxacillin sodium were assessed using the reaction rate constants. The reaction rate constant, k, is a very useful measure and an indicator of how rapidly a reaction occurs with time. A high value for k denotes a fast reaction rate which translates into a very rapid breakdown and an unstable product. A small value for k implies a slow reaction rate, a slow rate of breakdown and a very stable product [10].

MATERIALS AND METHODS

Materials

The following drugs, substances and chemicals of analytical grade were used: Sulphuric acid (98 %w/w), sodium thiosulphate, sodium hydroxide (99 %), formaldehyde and sodium acetate (all from BDH, Poole, England). Potassium iodide and starch mucilage powder (both from Finkem Laboratory Reagents), potassium iodate and copper sulphate pentahydrate (both from Fissons Scientific Equipment), iodine (Breckland Scientific Supplies, UK), hydrochloric acid (36% w/w) and glacial acetic acid (both from Philip Harris plc, Shaneson, England).

Pure flucloxacillin sodium powder, pure starch powder and the sodium cmc powder were obtained from Letap Pharmaceutical Company, Accra, Ghana.

Instruments

Adam–analytical weighing balance WA 210; 210/0.0001 g previously calibrated was used in all the weighings carried out. Sanyo drying oven MOV-112 was used in drying the starch.

Collection of capsule brands

The five different capsule brands used in the experiment were sampled from pharmacies in the Kumasi metropolis of Ghana and were labelled A, B, C, D and E.

All the capsules of the various brands employed in the experiment were all well sealed in their blisters, were clean and intact and had no physical defects upon a thorough visual examination. White and powdery capsule content and sometimes a yellowish tinge indicated that there were no physical and chemical signs of instability or breakdown in the products [11].

The average content of each of the capsule brand was found to help in determining the varying amounts of excipients that could be mixed with flucloxacillin sodium powder.

Identification tests

Pure flucloxacillin sodium powder and flucloxacillin sodium in the sampled capsule brands were chemically identified using sulphuric acid–formaldehyde solution and observed for the development of a yellowish green colour [11].

The starch powder and the presence of starch in the capsules were tested using iodine solution and observed for the development of blue-black colour [11].

The sodium cmc powder and the presence of it in the capsule brands were tested with a 5 % solution of copper sulphate pentahydrate and observed for the formation of a precipitate [12].

Preparation of dried starch

Dried starch was obtained by heating the starch sample at 130 °C for 90 min in a temperature regulated oven until a constant weight was obtained indicating the removal of all the water molecules that may be in it. The unheated starch sample was termed undried starch [7].

Preparation of 250 mg flucloxacillin sodium/excipient mixtures

Flucloxacillin sodium/excipient combinations of ratios of 250 mg flucloxacillin sodium/200 mg excipient, 250 mg flucloxacillin sodium/100 mg excipient and 250 mg flucloxacillin sodium/50 mg excipient were prepared using dried starch, undried starch and sodium cmc as excipients. Sufficient amounts of each excipient and pure flucloxacillin sodium powder in the above ratios of the combination were weighed, mixed and triturated with a porcelain mortar and pestle to obtain homogenous mixtures.

Each mixing ratio of each excipient and flucloxacillin sodium powder was exposed in a Petri dish in a room for 12 w. Controls of only each excipient of known weights were also exposed in Petri dishes also for 12 w. The experiment was carried out at room temperature and at a fairly constant humidity since the room in which the samples were exposed was airtight.

The combination ratios of 200 mg, 100 mg and 50 mg of excipient and 250 mg flucloxacillin sodium mixture were chosen using the average contents of the various brands of flucloxacillin sodium capsules as guides.

Assay of samples of 250 mg flucloxacillin sodium/excipient mixtures

Each sample of 250 mg flucloxacillin sodium/excipient combination was periodically assayed for the content of flucloxacillin sodium at predetermined time intervals for 12 w using iodimetry as the method of the assay [13]. A triplicate assay was done in each case, and the mean percentage content (% w/w) and the standard deviations (SD) were found.

Assay of capsule brands and pure flucloxacillin sodium powder

Sufficient amounts of contents of the various capsule brands and pure flucloxacillin sodium powder were also exposed in Petri dishes in a room for 12 w. They were also assayed periodically at predetermined time intervals for 12 w.

Some amounts of the contents of the capsule brands were not exposed but kept airtight and assayed after 12 w. The method of the assay was also by iodimetry [13].

A triplicate assay was done in each case and the mean percentage content (% w/w), and the standard deviations were found.

Statistical analysis

The percentage contents obtained for all the samples analyzed were expressed as mean±SD (n=3).

Conversion of concentration terms

Zero order rate of breakdown

The zero order rate of reaction equation is given as: $c= c_0 - kt$ and comparing with y= mx+c, y= c, x=t, m=-k and $c= c_0$

c= concentration after a certain period of time, t, c_0 = initial concentration and k = rate constant

Thus, a plot of c against time, t, is a straight line with intercept, c_0 and gradient,-k [14].

First order rate of breakdown

The first order rate of reaction is given as: $\ln c = \ln c_0 - kt$ and comparing with y= mx+c;

y= ln c, x=t, m=-k and $c= \ln c_0$ (ln means natural logarithm).

c= concentration after a certain period of time, t, c_0 = initial concentration and k = rate constant

Hence, a plot of ln c against time is a straight line with intercept, $\ln c_0$, and gradient,-k [14].

The mean contents (%w/w) of flucloxacillin sodium obtained for all the samples analyzed for 12 w were converted to concentration terms suitable for a zero order rate of breakdown and a first order rate of breakdown.

Graphs of concentration terms against time for both rates of breakdown were plotted using Microsoft Excel 2010 and the rate constants (gradient) and correlation coefficients were obtained from the graphs for all the samples analyzed.

Determination of the total moisture uptake by the excipients

This was determined for each of the excipients after 12 w. It was done for each excipient in the control Petri dishes by finding the difference in the weights of only the excipient at the start (i. e 0 w) and at the end (i.e. 12 w) of the study and expressing each as a percentage. A bar chart was used to represent this for each excipient using Microsoft Excel 2010.

RESULTS AND DISCUSSION

Determination of the order of breakdown

Zero and first order graphs were drawn for the samples investigated. It was observed that all the samples followed zero order kinetics except capsule brands B and E that followed first order kinetics. The full data used in plotting zero order and first order graphs for all the samples investigated are provided in Tables 1,2,3 and 4. The graphs were obtained by plotting the concentration terms against their corresponding times of assay [14].

The coefficients of correlation (R^2) obtained for the zero order graphs for these samples were higher than the R^2 for the first order graphs (Tables 5, 6 and 7).

R^2 shows the strength of correlation between y (concentration terms) and x (time) values. The higher the R^2, the stronger the correlation between the concentration terms and times of assay and vice versa. These showed there were stronger degrees of correlation between the concentration terms and times of assay for zero order than for first order for the samples [15]. The line graphs for zero order for these samples also looked better than those for their first order graphs (fig. 1 and fig. 2).

Capsule brands B and E however, followed first order kinetics with their coefficients of correlation higher than those for their zero order graphs (table 8). This implies that their concentration terms for first order showed a stronger and better correlation with time than those for zero order and also their first order graphs looked better than their zero order graphs.

Table 1: Values plotted for graphs for zero and first orders of reaction rates for flucloxacillin sodium breakdown in the various 250 mg flucloxacillin sodium/undried starch combinations

	200 mg undried starch mixture		100 mg undried starch mixture		50 mg undried starch Mixture	
Time of assay (w)	**Conc (% w/w)**	**In conc (% w/w)**	**Conc (% w/w)**	**In conc. (%w/w)**	**conc. (% w/w)**	**In conc (% w/w)**
0	97.20	4.577	99.44	4.600	100.29	4.608
1	89.22	4.491	90.05	4.500	89.22	4.491
2	84.75	4.440	86.01	4.454	87.82	4.575
4	73.80	4.301	75.40	4.323	72.20	4.279
8	55.60	4.018	50.68	3.926	44.03	3.785
12	36.78	3.605	26.57	3.280	18.45	2.915

Conc. is the concentration term for zero order rate of breakdown and In conc. is the concentration term for first order rate of breakdown. The mean % contents were converted to the desired concentration terms.

Table 2: Values plotted for graphs for zero and first orders of reaction rates for flucloxacillin sodium breakdown in the various 250 mg flucloxacillin sodium/sodium cmc combinations

	200 mg sodium CMC mixture		100 mg sodium CMC mixture		50 mg sodium CMC Mixture	
Time of assay (w)	**Conc (% w/w)**	**In conc (% w/w)**	**Conc (% w/w)**	**In conc (% w/w)**	**Conc (% w/w)**	**In conc (% w/w)**
0	95.97	4.564	98.34	4.588	97.51	4.580
1	87.34	4.470	88.41	4.482	87.22	4.468
2	83.27	4.422	76.17	4.333	82.16	4. 409
4	68.27	4.223	64.82	4.172	62.73	4.139
8	41.63	3.729	30.00	3.401	21.12	3.050
12	2.83	1.040	6.64	1.893	3.69	1.306

The mean % contents were converted to the desired concentration terms.

Table 3: Values plotted for graphs for zero and first orders of reaction rates for flucloxacillin sodium breakdown in the various capsule brands and pure flucloxacillin sodium powder

	Capsule brand A		Capsule brand B		Capsule brand C	
Time of assay (w)	**Conc (% w/w)**	**In conc (% w/w)**	**Conc (% w/w)**	**In conc (% w/w)**	**Conc (% w/w)**	**In conc (% w/w)**
0	115.0	4.745	87.15	4.468	92.25	4.525
1	105.66	4.660	77.86	4.355	88.31	4.481
3	99.63	4.601	64.58	4.168	73.19	4.293
4	95.24	4.556	60.76	4.107	61.25	4.115
8	84.75	4.440	15.71	2.754	7.73	2.045
12	47.68	3.865	6.48	1.869	0.00	

	Capsule brand D		Capsule brand E		Pure flucloxacillin sodium powder	
Time of assay (w)	**Conc (% w/w)**	**In conc (% w/w)**	**Conc (% w/w)**	**In conc (% w/w)**	**Conc (% w/w)**	**In conc (% w/w)**
0	86.59	4.461	55.23	4.012	91.14	4.512
1	78.97	4.369	44.53	3.796	82.04	4.407
3	78.60	4.364	37.64	3.628	76.88	4.342
4	71.46	4.269	31.73	3.457	74.17	4.306
8	19.64	2.978	9.82	2.284	20.87	3.038
12	0.73	-0.315	3.30	1.194	5.13	1.635

The mean % contents were converted to the desired concentration terms.

Table 4: Values plotted for graphs for zero and first orders of reaction rates for flucloxacillin sodium breakdown in the various 250 mg flucloxacillin sodium/dried starch combinations

	200 mg dried starch mixture		100 mg dried starch mixture		50 mg dried starch Mixture	
Time of assay (w)	**Conc. (% w/w)**	**In conc. (% w/w)**	**conc. (% w/w)**	**In conc (% w/w)**	**Conc. (% w/w)**	**In conc (% w/w)**
0	91.64	4.518	91.51	4.516	91.81	4.520
1	80.44	4.388	84.99	4.443	85.36	4.447
2	80.41	4.387	79.58	4.377	79.81	4.380
4	73.19	4.293	72.32	4.281	70.73	4.259
8	51.05	3.933	42.44	3.748	38.25	3.644
12	32.35	3.477	22.63	3.119	16.48	2.802

The mean % contents were converted to the desired concentration terms.

Table 5: Comparison of rate constants for zero and first orders of reaction and their correlation coefficients (R^2) for the various combinations of dried starch with 250 mg flucloxacillin sodium

Amount of dried starch (mg)	1ST order rate constant (%w/w/w)	Zero order rate constant (% w/w/w)	R^2 values for zero order	R^2 values for 1ST order
200	0.0833	4.7464	0.9875	0.9735
100	0.1158	5.8242	0.9934	0.9707
50	0.1415	6.4123	0.9942	0.9600

Table 6: Comparison of rate constants for zero and first orders of reaction and their correlation coefficients (R^2) for the various combinations of undried starch with 250 mg flucloxacillin sodium

Amount of undried starch (mg)	1ST order rate constant (% w/w/w)	Zero order rate constant (% w/w/w)	R^2 values for zero order	R^2values for 1ST order
200	0.0787	4.9116	0.9966	0.9908
100	0.1061	5.9416	0.998	0.969
50	0.1388	6.7604	0.9965	0.9538

Table 7: Comparison of rate constants for zero and first orders of reaction and their correlation coefficients (R^2) for the various combinations of sodium cmc with 250 mg flucloxacillin sodium

Amount of sodium CMC (mg)	1ST order rate constant (%w/w/w)	Zero order rate constant (%w/w/w)	R^2 values for zero order	R^2 values for 1ST order
200	0.2651	7.5622	0.9924	0.8211
100	0.2154	7.6279	0.9919	0.9400
50	0.2686	8.1789	0.9819	0.9452

Table 8: Comparison of rate constants for zero and first orders of reaction and their correlation coefficients (R^2) for the various capsule brands and pure flucloxacillin sodium powder

Capsule brands	1ST order rate constant (%w/w/w)	Zero order rate constant (%w/w/w)	R^2 values for zero order	R^2 values for 1ST order
A	0.0657	5.0465	0.9404	0.8879
B	0.2286	7.1655	0.9597	0.9617
C	0.3116	8.6260	0.9472	0.8620
D	0.3807	7.7561	0.9433	0.8454
E	0.2383	4.3352	0.9575	0.9759
Pure powder	0.2439	7.7083	0.9494	0.9258

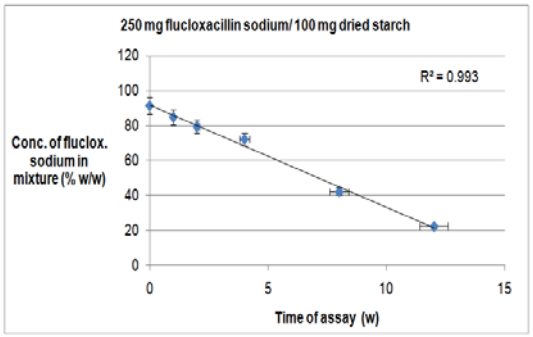

Fig. 1: Graph for a zero order rate of breakdown of flucloxacillin sodium in 250 mg flucloxacillin sodium/100 mg dried starch mixture

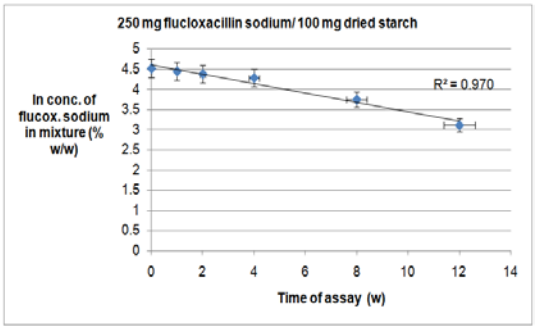

Fig. 2: Graph for a first order rate of breakdown of flucloxacillin sodium in 250 mg flucloxacillin sodium/100 mg dried starch mixture

Comparison of reaction rate constants (k) for the various flucloxacillin sodium/excipient mixtures

The concentration of flucloxacillin sodium in all the capsule brands and in the various excipient mixtures reduced with time upon exposure to moisture in air in a room (tables 9, 10, 11 and 12). This shows that flucloxacillin is susceptible to moisture-induced breakdown [8].

The rate constant is a measure of the degree of breakdown or degradation of a drug. The higher the value of the rate constant, the greater the degree of breakdown of the drug. The smaller the value of the rate constant, the smaller the degree of breakdown of the drug [14].

The zero order rate constant values were used since all the flucloxacillin sodium/excipient mixtures followed zero order kinetics.

The k (rate constant) values show that, the rate constants for the various amounts of dried starch were smallest followed by undried starch and then sodium cmc for the same amounts of each excipient (Tables 5, 6 and 7). Also, the zero order rate constant for pure flucloxacillin (7.7083 %w/w/w) provided in table 8 was higher than the zero order rate constants obtained for all the flucloxacillin sodium/excipient mixtures except that for 50 mg sodium cmc which gave a rate constant of 8.1789 %w/w/w (table 7). The zero order rate constant for any amount of dried starch or undried starch was smaller than all the zero order rate constants obtained for any proportion of sodium cmc with flucloxacillin sodium. All the zero

order rate constants obtained for all the proportions of dried and undried starch were lower than the zero order rate constant for only pure flucloxacillin sodium (table 8). The rate constants for all the excipient mixtures with 250 mg flucloxacillin sodium have been provided in Tables 5, 6 and 7.

It was observed that dried starch formed the most stable product with flucloxacillin sodium and sodium cmc gave the least stable product. The excipients therefore, gave some protection to the drug as its breakdown was slowed down when compared to the breakdown rate of only pure flucloxacillin sodium powder with time.

Table 9: % (w/w) contents of flucloxacillin sodium in the pure form and in the capsule brands determined for 12 w

Time of assay (w)	Capsule brand A	Capsule brand B	Capsule brand C	Capsule brand D	Capsule brand E	Pure powder
0	115.0±0.07 %	87.15±0.11 %	92.25±0.07 %	86.59±0.02 %	55.23±0.04 %	91.14±0.01%
1	105.66±0.04 %	77.86±0.03 %	88.31±0.05 %	78.97±0.02 %	44.53±0.02 %	82.04±0.04 %
2	99.63±0.16 %	64.58±0.03 %	73.19±0.02 %	78.60±0.02 %	37.64±0.071 %	76.88±0.02 %
4	95.24±0.04 %	60.76±0.04 %	61.25±0.12 %	71.46±0.02 %	31.73±0.02 %	74.17±0.02 %
8	84.75±0.05 %	15.71±0.01 %	7.73±0.02 %	19.64±0.02 %	9.82±0.05 %	20.87±0.02 %
12	47.68±0.02 %	6.48±0.02 %	0.00%	0.73±0.03 %	3.30±0.03 %	5.13±0.04 %

Data given in mean±SD (n= 3)

Table 10: % (w/w) contents of flucloxacillin sodium in the various 250 mg flucloxacillin sodium/dried starch mixtures determined for 12 w

Time of assay (w)	200 mg starch mixture	100 mg starch mixture	50 mg starch mixture
0	91.64±0.02 %	91.51±0.02 %	91.81±0.02 %
1	80.44±0.01 %	84.99±0.01 %	85.36±0.04 %
2	80.41±0.02 %	79.58±0.02 %	79.81±0.08 %
4	73.19±0.03 %	72.32±0.06 %	70.73±0.06 %
8	51.05±0.11 %	42.44±0.04 %	38.25±0.04 %
12	32.35±0.04 %	22.63±0.07 %	16.48±0.03%

Data given in mean±SD (n= 3)

Table 11: % (w/w) contents of flucloxacillin sodium in the various 250 mg flucloxacillin sodium/undried starch mixtures determined for 12 w

Time of assay (w)	200 mg starch mixture	100 mg starch mixture	50 mg starch mixture
0	97.20±0.22 %	99.44±0.01 %	100.29±0.01 %
1	89.22±0.04 %	90.05±0.11 %	89.22±0.07 %
2	84.75±0.05 %	86.01±0.02 %	87.82±0.02 %
4	73.80±0.01 %	75.40±0.08 %	72.20±0.11 %
8	55.60±0.03 %	50.68±0.03 %	44.03±0.09 %
12	36.78±0.03 %	26.57±0.04 %	18.45±0.07 %

Data given in mean±SD (n= 3)

Table 12: % (w/w) contents of flucloxacillin sodium in the various 250 mg flucloxacillin sodium/sodium cmc mixtures determined for 12 w

Time of assay (w)	200 mg CMC mixture	100 mg CMC mixture	50 mg CMC mixture
0	95.97±0.04 %	98.34±0.04 %	97.51±0.02 %
1	87.34±0.06 %	88.41±0.08 %	87.22±0.13 %
2	83.27±0.04 %	76.17±0.03 %	82.16±0.04 %
4	68.27±0.03 %	64.82±0.01 %	62.73±0.04 %
8	41.63±0.02 %	30.00±0.17 %	21.12±0.02 %
12	2.83±0.02 %	6.64±0.03 %	3.69±0.02 %

Data given in mean±SD (n= 3)

Hygroscopic nature of the excipients used

Starch and sodium cmc are hygroscopic substances and it was thought that their use would make flucloxacillin sodium more stable as they will take up any moisture present in the formulation thereby reducing moisture-induced hydrolysis of the drug.

A direct relation between water absorption and the rate of the breakdown was thus established. Over the period of study, the exposed dried starch, undried starch and sodium cmc respectively absorbed 0.84 % w/w, 2.82 % w/w and 12.50 % w/w of moisture (fig. 3).

Dried starch formed the most stable product because it absorbed the least amount of moisture making it the least hygroscopic. Sodium cmc formed the least stable product because it took up the most amount of moisture and proved to be the most hygroscopic. Undried starch formed a product less stable than that of dried starch but more stable than that of sodium cmc. Since undried starch was not heated to remove water molecules, the adhering water molecules readily associated with incoming ones to cause higher moisture absorption than dried starch [9].

Effect of excipient amount on the stability of flucloxacillin sodium

All the rate constants reduced for the various flucloxacillin sodium/excipient combinations with increase in the amounts of the excipients used (tables 5, 6 and 7).

Thus, the more the excipient used, the higher the protection offered to flucloxacillin sodium and the more stable the product.

The rate constant obtained for 250 mg flucloxacillin/50 mg sodium cmc combination was seen to be lower than that of pure flucloxacillin sodium (table 8). Thus, pure flucloxacillin sodium powder was more stable than the 250 mg flucloxacillin/50 mg sodium cmc mixture. Towards the end of the study, the 250 mg flucloxacillin/50 mg sodium cmc mixture formed a hardened substance whereas those for the 200 mg and 100 mg sodium cmc were quite powdery. This meant that the 50 mg proportion of sodium cmc was inadequate. At the end of the experiment (i.e.12 w), the 50 mg sodium cmc product yielded a 'caked' substance that retained a lot of moisture in its core and caused the fastest breakdown, even faster than pure flucloxacillin sodium powder [16]. This observation was not made for mixtures made with 200 mg and 100 mg sodium cmc which gave more stable products than pure flucloxacillin sodium powder.

Hence the higher the excipient/flucloxacillin sodium ratio, the more stable the product.

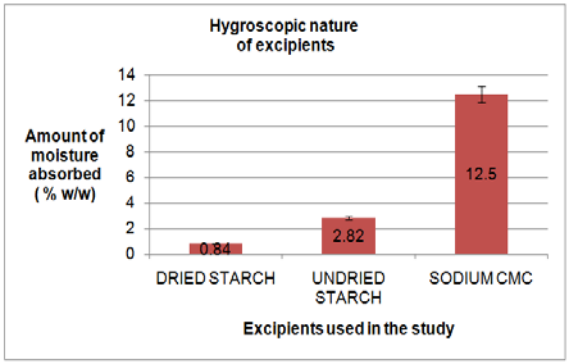

Fig. 3: The amount of moisture absorbed by each of the excipients used when exposed alone in a Petri dish for 12 w

Effect of excipients on the stability of flucloxacillin sodium in capsule brands

The capsule brands used contained flucloxacillin sodium (table 13). None of the capsule brands contained sodium cmc. Capsule brands C and D contained no starch (table 15). Capsule brands B and E followed a first order reaction while capsule brands A, C and D followed a zero-order reaction. For effective comparison and for feasibility, the zero order rate constants were used.

Capsule brand E was the most stable capsule brand with a rate constant of 4.3352 % w/w/w and capsule brand C was the least stable with a rate constant of 8.6260 % w/w/w (table 8).

Capsule brand E contained only a small amount of starch which was seen as blue-black specks with iodine (table 15). Capsule brand E also gave the lowest percentage content of 55.23±0.04 % w/w when first assayed at 0 w (table 9). The content of flucloxacillin sodium in a formulation should be between 95-105 % w/w [12]. This low amount of starch and low flucloxacillin sodium content implies a high starch/flucloxacillin sodium ratio. The stability of capsule brand E is therefore due to the starch present.

Capsule brand A was the second most stable with a rate constant of 5.0465 % w/w/w (table 8). It tested positive to the presence of starch which showed as intense blue-black coloration (table 15). It also had a high percentage content of 115±0.07 % w/w when first assayed at 0 w (table 9). This means that the ratio of starch to flucloxacillin sodium may be lower than that for E, hence the higher stability of flucloxacillin sodium in capsule brand E than in capsule brand A.

Capsule brands E and B actually followed first order kinetics and capsule brand E may have contained other chemical substances that increased its stability.

Capsule brand B was less stable than capsule brand A, but more stable than D which also showed a higher stability than capsule brand C. Both capsule brands B and D had similar active contents which were fairly high (i.e. brand B-87.15±0.11 % w/w and brand D-86.59±0.02 % w/w) but the small amount of starch present in capsule brand B may have made it more stable than capsule brand D which contained no starch (table 15).

Capsule brand B was less stable than capsule brand A because of a possible lower starch/flucloxacillin sodium ratio in capsule brand B than brand A.

Capsule brand C is the least stable among the capsule brands because of the following reasons: the absence of starch, formulation with moist or hydrated excipients and the presence of chemical substances that promoted breakdown. Capsule brands C and D with respective rate constants of 8.6260 % w/w/w and 7.7561 % w/w/w were less stable than pure flucloxacillin with a rate constant of 7.7083 % w/w/w (table 8).

Capsule brands A, E and B were more stable than the pure flucloxacillin sodium because they tested positive for the presence of starch which stabilized the flucloxacillin sodium present in them.

Capsule contents appearing white or white with a yellowish tinge was an indication that there were no signs of chemical or physical breakdown. Specks of blue-black coloration were an indication of the little amount of starch present while an intense coloration indicated the presence of a large amount of starch in the sample [12].

Stability of the airtight samples

The various capsule brands and pure flucloxacillin sodium powder that were not exposed to moisture in the air did not undergo any significant breakdown after 12 w (table 16). This further shows that flucloxacillin sodium is not stable to moisture.

Table 13: Results of flucloxacillin sodium identification in the various capsule brands and in the pure flucloxacillin sodium powder

Sample tested	Observation	Inference
Flucloxacillin powder (pure)	An intense yellow coloration was formed	Sample passed
Capsule brand A	An intense yellow coloration was formed	Sample passed
Capsule brand B	An intense yellow coloration was formed	Sample passed
Capsule brand C	An intense yellow coloration was formed	Sample passed
Capsule brand D	An intense yellow coloration was formed	Sample passed
Capsule brand E	An intense yellow coloration was formed	Sample passed

Sample passed implies it contained flucloxacillin sodium.

Table 14: Results of identification tests for the excipients used

Excipient tested	Observation	Inference
Starch powder	Blue–black color was seen	Sample passed
Sodium CMC powder	A precipitate was formed	Sample passed

The sample passed means it had the identity of the sample tested for.

Table 15: Results for the test of the excipients used in the investigation in the capsule brands

Capsule brand	Appearance of content	Test for starch	Test for sodium CMC
A	Content appeared white and powdery	Intense blue-black coloration	No precipitate was formed
B	Powdery white content with a very faint yellowish tinge	Specks of blue-black particles were seen	No precipitate was formed
C	Powdery white content	No blue-black coloration	No precipitate was formed
D	Powdery white content	No blue-black coloration	No precipitate was formed
E	Powdery white content but had a slight yellowish tinge and had some granules	Specks of blue, black particles were seen	No precipitate was formed

Table 16: % (w/w) contents of flucloxacillin sodium in the pure form and in the capsule brands determined for airtight samples after 12 w

Capsule brand	% Content (w/w)
A	114.52±0.02
B	86.87±0.01
C	91.74±0.02
D	86.50±0.02
E	54.82±0.01

Data given in mean±SD (n= 3)

CONCLUSION

Dried starch formed the most stable product, followed by undried starch and sodium cmc gave the least stable product. The higher the amount of excipient used the more stable the product. To obtain very stable products, high amounts of dried starch should be used in formulating capsule dosage forms of flucloxacillin sodium. The starch used in formulating moisture sensitive drugs should be heated in an oven to constant weight to drive off moisture before use.

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CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

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