Omdurman Journal of Pharmaceutical Sciences

https://journal.oiu.edu.sd/index.php/ojps

Formulation and Optimization of Stable Aspirin 100mg Tablets

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DOI: 10.52981/ojps.v2i3.2871 ISSN: 1858-506X

Abstract

Several moisture and temperature-sensitive medicines cannot be manufactured in Sudan due to extreme climatic conditions**.** Keeping these factors under control during production is difficult task. It is possible to overcome these difficulties by using excipients and utilizing technology in the production of the drug. This study aimed to adjust and improve the formulation of aspirin using different excipients and different technological approaches to produce stable aspirin tablets. Microcrystalline cellulose and lactose were used as fillers and stearic acid as a lubricant, four aspirin formulations, two formulations containing lactose and two formulations containing microcrystalline cellulose were prepared for aspirin 100 mg. For each formulation, wet granulation and direct compression techniques were applied separately, to study the effect of manufacturing technology and the role of excipients on the stability of the product. Prepared tablets were subjected to various quality control tests. Lactose had lower moisture content than MCC. But MCC has moisture scavenger characteristic. Direct-compression CDs with MCC shows less degradation than other tablet formulations. Addition of stearic acid as a substitute for magnesium stearate (a lubricant) changes the overall pH to more acidic which reduces hydrolysis.

Keywords: Direct compression, Lactose, Micro-crystalline cellulose (MCC), Stearic acid, Wet granulation.

Introduction:

According to USP, Tablet is defined as a compressed solid dosage form containing medicament with or without Excipients [1].

Tablet Ingredients and Excipients in addition to active ingredients, tablet contains a number of inert materials known as additives or excipients. Different excipients are: Diluents / Fillers, Binders and adhesives, Disintegrants, Lubricants and glidants, Coloring agents, Flavoring agents, sweetening agents [2].

Acetylsalicylic acid (Aspirin): first appeared as an analgesic in form of willow bark, and its antipyretic and analgesic effects have been recognized for more than 200 years [3]. It is an anti-inflammatory drug; it also reduces platelet aggregation. It is also commonly used anti platelet drug that can reduce the risk of recurrence of cancer-specific mortality. Long-term prophylactic use of low-dose of this drug reduced the incidence of heart attacks and strokes in cancer [4, 5].

Stability of aspirin: The drug which is salicylic acid ester becomes therapeutically active upon hydrolysis to form free salicylic acid (FSA). FSA is very irritating to gastric mucosa and is associated with dyspepsia and gastric bleeding [5]. Factors affecting stability of aspirin, including pH (Aspirin → Salicylic Acid + Acetic Acid). The rate of this reaction is said to be second order, as it is dependent not only upon the aspirin concentration, but also, upon solution pH. At pH = 7.5, but some authors have suggested that hydrolysis of aspirin is first order reaction and independent of pH, some of them suggested a range (4--8) within which, the hydrolysis is first order out this range will turn into pseudo first order reaction , which mean very alkaline and very acidic excipients will promote the hydrolysis [6]. Second factor are excipients: In a formulation, drugs have intimate contact with one or more excipients, which can affect drug stability. Moisture often plays a key role in the physical and chemical stability of a solid dosage form. The selection of excipients that minimize the moisture sensitivity of the product is important. The most common effect of moisture on chemical stability is hydrolysis [6]. Lactose is widely used excipients in solid dosage forms. Presently, there are several different grades of lactose are commercially available; these include anhydrous α-lactose, α-lactose monohydrate, and anhydrous β-lactose [7]. Micro-crystalline cellulose (MCC) is one of the most commonly used tableting excipients and many of its properties depend on its moisture content. However, moisture sorption by MCC has also been reported to cause stability problems for moisture sensitive drugs. Ordinary MCC is manufactured with 4–5% (w/w) moisture content. For moisture sensitive drugs, low moisture grades of MCC are available (1.5%, w/w, moisture in Avicel PH 112 and 3%, w/w, moisture in Avicel

PH 103, FMC Corp.), however, these appear to be hygroscopic [7, 8]. Third factor are environmental conditions**:** The process of preparation of the present invention helps improve the stability of aspirin tablets. Tablets prepared under controlled humidity condition, have significantly improved stability of the final formulation when tested under stability conditions. Thus, stable aspirin tablets of the present invention are prepared under controlled process parameters (temperature and pressure) without the need to use any additive to control the hydrolytic degradation of aspirin. This technique for improvingstability is simpler and less tedious as compared to those used in theart, and is more effective in controlling hydrolysis of aspirin [8].

Materials: Aspirin was kindly provided by Salah Medicinal Preparation Factory , Micro-crystalline cellulose, Stearic acid, Primojel, Pvp Polyvinyl pyrrolidone, Lactose, Ethanol, Ferric chloride (FeCl3), Ferric ammonium sulfate, Sodium hydroxide and Hydrochloric acid are originated in china and kindly provided by Wafra pharm , Origin china, Salicylic acid: kindly provided from Nados medical supplier.

Methodology:

Tablet manufacturing by direct compression: Two formulations were prepared. Aspirin was added to lactose (F1) and to microcrystalline cellulose (F2) during tumbling mixing. A total of 8 grams of stearic acid were sifted and sieved. 4 grams were incorporated into each powder bed. 2 grams of primo gel were included in each powder bed. Prior to formulation, angles of repose, Hausner ratios, and Carr's indices were calculated for both formulations (F1) and formulations (F2). A fixed funnel method was used to measure the angle of repose. When the powder pile reached 4 cm height, the angle of the resulting cone was measured. To calculate the Hausner ratio, powder tapped density (W/V) was divided by powder fluffy density (W/V). Carr's index was calculated by the equation (CI =100[ρT-ρB] ρB). Using an automatic single-punch machine, both formulations were directly compressed to produce tablets.

Tablet manufacturing by wet granulation method: Formulation (F3) and Formulation (F4) were prepared by mixing 40 grams of aspirin, 20 grams of microcrystalline cellulose (F3), and 40 grams of aspirin and 20 grams of lactose (F4), followed by the addition of polyvinyl pyrrolidone solution (2g/5 ml, using ethanol solvent 90%). The slugs were transformed into granules by sieving, and the granules were dried in an oven at 60°C for two hours. The flow ability and compressibility of the two powder beds were evaluated by calculating the angle of repose, the Hausner ratio, and Carr's index. 4 g of stearic acid powder and 2 g of Primo gel were added to each formulation

separately and mixed for ten minutes. Finally, the two formulas were compressed using an automatic single-bunch machine to produce tablets.

Quality Control tests:

Weight variation test: 20 tablets were weighed individually. The average weight was calculated, the standard deviation (SD) and (RSD) were calculated, RSD= (SD/ average weight) %, where RSD is relative standard deviation.

Hardness test: 10 tablets of each batch were tested individually by using hardness tester and the force required to crush the tablet were measured.

Friability test: 10 tablets of each batch were weighed together after removing loose dust with aid of air, tablets were placed in the friability tester drum, and the drum was adjusted at 25 RPM for 4 min. then removed and cleaned from the loose dust by the same methods. The tablets were weighed again and the percentage loss was calculated as flow, Friability (%) = W1- W2/ W1 x100, Where, w1= weight of tablets initial before tumbling& w2= weight of tablets after tumbling

Method of assay: Approximately 0.10 g of Acetylsalicylic acid was weighed. 5 ml of 1 M sodium hydroxide was added, which was gently heated until all solids were dissolved. The solution was diluted with deionized water to the 100.0 ml mark on the flask (stock solution). An aliquot of 0.5 ml of sodium salicylate stock solution was diluted to 10 ml with 0.02 M iron (III) chloride solution that is buffered to pH 1.6 (solution A). Similarly, solutions labeled B, C, D, and E were prepared with aliquots of 0.40, 0.30, 0.20, and 0.10 ml sodium salicylate solution. The amount equivalent to one tablet of each formulation F1, F2, F3, and F4 was weighed separately after crushing twenty tablets of each formulation. The powder portions were transferred to 125 ml. 5 ml of 1 M sodium hydroxide was added to each flask. These solutions were diluted to the 100.0 ml mark on the flask and labeled these flasks Sample 1 and Sample 2, 3, 4. Similarly, 0.3 ml of each solution was diluted to 10.0 ml with 0.02 M iron (III) chloride.

Measure Absorbance of Standards and Aspirin Samples1: The instrument was set to zero with an iron (III) chloride solution. The absorbance of standard solutions A, B, C, D, and E were measured and the absorbance of samples 1, 2, 3, and 4 were measured.

Tablets dissolution method: Each pecker was filled with 900 ml of deionized water. The stirrer was switched on. A spot about 4 cm below the surface of the water and 2 cm from the side of the beaker from which to collect samples were chosen. Aspirin tablets were dropped into the water. As soon as the stopwatch started, 1 ml of the sample was removed from each chamber and placed in a boiling tube labeled "zero time."

Another 1 ml of each sample was withdrawn and transferred to boiling tubes labeled (5 minutes), (10 minutes), (20 minutes), and (30 minutes) for each sample, and two drops of 0.1 M NaOH solution were added to each sample; these samples were diluted with 10 ml of 0.02 MOL/L iron(III) chloride solution. The absorbance of the solutions were measured and used to calculate the concentration of aspirin. Finally, the concentrations of aspirin in the solution were calculated.

Stability Testing: The tablets were prepared as per the method above then packed in plastic containers and kept for stability testing under the conditions given below. The temperature is 40°C, the relative humidity is 75%, and the duration is 3 months. Products will be tested for the **amount** of free salicylic acid generated in products at the initial stage, at the completion of 1 month, at the completion of 2 months, and at the completion of 3 months. Limit Test for free salicylic acid: 0.1g powdered Aspirin (i.e., active + excipients) was extracted with 2 ml of 95% ethanol. Water was added to give a final volume of 100.0 ml and mixed. 50.0 ml of the filtrate was transferred to a measuring cylinder and 1.0 ml of acidified ferric ammonium sulfate solution was poured in, mixed, and allowed to stand. The standard solution used was prepared for comparison as follows: To another measuring cylinder, 3.0 ml of freshly prepared 0.01% (w/v) salicylic acid was added, and then 2.0 ml of ethanol, 1.0 ml of acidified ferric ammonium sulfate solution and sufficient water to give a total volume of 51.0 ml. A violet color produced by the samples should not be more intense than that of the standard

Results

Table (1) powder characterization results for aspirin tablets 100 mg. It appears that the Granulation process with the MCC-containing formulation (F2, granulated F3) did not significantly change the flow ability and compressibility results, while significant change was observed with the lactose-containing formulationFf1, granulated F4).

Formulation No	Angle of repose	Carr's index	Hausner ratio	Expected flow
F1	32 °	11.1	1.1	Good
F2	26 °	12	1.2	good
F3	22 °	12	1.1	Good

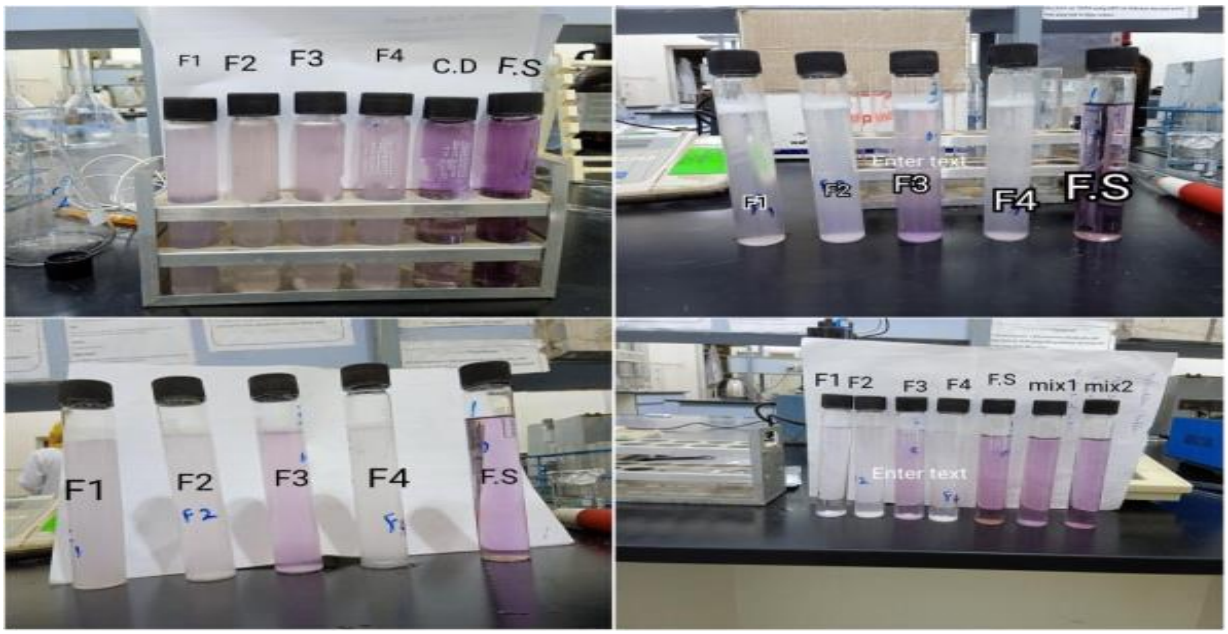
F4	18 °	8	1.07	Excellent

Figure (1) Cumulative release percent for formulation F1, F2, F3, F4 of aspirin tablets 100 mg.

Blue line refers to F1, Orange line refers to F2, Gray line refers to F3, and yellow line refers to F4. MCC containing formulation (F2, F3) showed lower cumulative release percent compared to lactose containing formulation (F1, F4)

Stability results for aspirin tablets 100 mg:

A **B**



C **D**

Figure (2). Limit test of aspirin

Figure (2). Picture (A) demonstrates the limit test result of aspirin tablets 100 mg at zero time, where F1, F2, F3, F4, Formulation number, F.S refer to free salicylic acid and. The color intensity of formulations F1, F2, F3, and F4 was less than the limit F.S. Picture (B) shows the limit test results one month after preparation. Formulations F1, F2, and F4 were less intense than the limit F.S. but F3 had a slight increase in its intensity. Picture (C) shows the limit test results two months after formulation. The formulation number refers to free salicylic acid. F1, F2, and F4 were less intense than the limit test, but formulation number F3 showed an intense color. Picture (D) in addition of the four formulations test tubes and free salicylic acid. This picture contains two additional tubes containing a mixture of F.S. with lactose and F.S. with MCC, to avoid turbidity effects. After three months, formulation F3 still had more color intensity, but the other formulation showed less color intensity compared with the limit F.S.

Table (2) Comparison of quality control results for aspirin tablets 100 mg at zero time:

Formulation No	Appearance	RSD	Friability	Hardness (N)	Limit test F.S.
Formulation 1	No change	3.04%	0.6 %	57.5 N	No color
Formulation 2	No change	4%	0.18 %	62.2 N	No color
Formulation 3	No change	3.2%	0.2 %	47 N	Slight color
Formulation 4	No change	2.44%	0.5 %	62 N	No color

Table (3) Comparison of quality control results for aspirin tablets 100 mg after completion of one month:

Formulation No	Appearance	RSD	Friability %	Hardness(N)	Limit test F.S.
Formulation 1	No change	3.3 %	0.57 %	50 N	No color
Formulation 2	No change	3.9 %	0.23 %	58 N	No color
Formulation 3	No change	3.7 %	0.3 %	41 N	Slightly increase in color
Formulation 4	No change	2.3 %	0.53 %	61 N	No color

Table (4) Comparison of results of quality control for aspirin tablets 100 mg. after completion of two months:

Formulation No	Appearance	RSD	Friability %	Hardness (N)	Limit test F.S.
Formulation 1	No change	3.9 %	0.6 %	52 N	No color
Formulation 2	No change	4 3 %	0.61 %	58 N	No color
Formulation 3	No change	4.2 %	0.67 %	37 N	Intense color
Formulation 4	No change	2.7 %	0.52 %	65 N	No color

Table (5) Comparison of quality control results for aspirin tablets 100 mg after completion of three months:

Formulation No	Appearance	RSD	Friability %	Hardness(N)	Limit test F.S.
Formulation 1	No change	4,1 %	0.67 %	47 N	No color
Formulation 2	No change	4.3 %	0.84 %	57 N	No color
Formulation 3	No change	4,4 %	0,91%	33 N	Intense color
Formulation 4	No change	2.7 %	0.51 %	63 N	No color

Discussion:

Physical properties of powder blends and granules: parameters studied were the angle of repose, Carr's index, Hausner's ratio, bulk density, and tapped density. The results showed the ease of compaction into a tablet dosage form for powder containing MCC over that comprising lactose. Across all formulations, weight variations, as well as Friability, appearance, and Hardness were acceptable. Friability was low in formulations f2, and f3 containing MCC compounds. This was shown to be due to the high binding index of MCC, which is considered a dry binder in direct compression as it improves compatibility and tablet ability [9]. The result of the disintegration time revealed an increase in the disintegration time of the batches prepared by wet granulation for both lactose and MCC compared to the batches prepared by direct compression for the same diluent, indicating that the granulation process may increase the hardness of the tablets in a way that can overcome the role of some material such as MCC which in fact is commonly used as Disintegrants [10]. Limit test showed a slight purple color. This indicates an increase in free salicylic acid. The appearance of a slight purple color in formulation F3 indicates an increase in free salicylic acid. This means the hydrolysis of some amount of aspirin. Since MCC absorbs water (hygroscopic material) while lactose does not [11]. The wet granulation method may work with lactose as a diluent but does not give acceptable

results with MCC, based on the moisture content of 0.0% lactose and 2.8% MCC, both materials were dried in an oven to remove moisture and then used in the preparation. The results from the dissolution test concluded that cumulative release percent for formulations made with lactose gave better results than those formulated with MCC. This was accompanied by the fact that the average weight of the tablets prepared using lactose was higher than the average weight of the tablets prepared with MCC. The latter has a low bulk density while lactose has a higher bulk density [12]. Using MCC alone might cause inconsistent die filling at higher press speeds due to low bulk density. According to the above results, we suggest that Formulation F3 is the least stable when subjected to an accelerated condition and the first candidate to be rejected. In the first month, there was no significant change in the results of all formulations. There was a slight increase in friability for all formulations, and a decrease in hardness not worth mentioning. Formulations F1, F2, and F4 still do not give color with the limit test, but formula F3 gives a light purple color that exceeds the F.S. limit. The results for the weight variation are still within the percentage difference range.

In the second month : It was found that formulas F1, F2, and F4 continue to give no color with ferric ammonium sulfate, while formula F3 intensified the violet color, which means that aspirin decomposition has progressed; formula F3 reduced hardness and disintegrated, which ensures its exclusion; other tests also indicated some changes. Friability % increased for formula F1 and hardness decreased. Formulation F2 increased friability while decreasing hardness. However, they are still within an acceptable range. Formulation F4 still has reasonable results, with a slight increase in friability, and a small decrease in hardness.

The third and final month: Formulation F1 was prepared by direct compression using lactose. The overall appearance was acceptable, friability increased, and hardness decreased, but still does not produce the violet color with ferric ammonium sulfate. Formulation F2 contains MCC and was prepared by direct compression. The overall appearance was acceptable, the weight variation was fair, and the friability and hardness were increased, but they were still within acceptable limits. No color was obtained with ferric ammonium sulfate. It appears that MCC acts as a moisture scavenger. Direct compression outperforms wet granulation for aspirin. Formulation F4 contained lactose and was prepared by wet granulation. There was no color produced with ferric ammonium sulfate, and the appearance of the product was satisfactory. The hardness was reduced and the friability increased.

MCC plays an active role in direct compression as a disintegrant and lubricant, especially since it has a low density. During compression, MCC does a better job than lactose at preventing capping [13].

Conclusion:

Aspirin preparation with lactose anhydrous is an acceptable and stable choice as in formulation F1. It is also stable when prepared by wet granulation since lactose does not absorb moisture. It was prepared with 90% ethanol. As in formulation F4, however wet granulation is not the most suitable method to produce aspirin. This is because ethanol is used instead of water in wet granulation which increases the cost, especially with mass production. The results of preparing aspirin with MCC (water scavengers) are different from those of direct compression and wet granulation. The wet granulation formulation F3 clearly deteriorated, possibly due to MCC absorbing moisture during granulation, while formulation F2 prepared by direct compression showed excellent stability. It could be due to MCC being still dry preserving its ability to act as a moisture scavenger. I would recommend formulation F2 as the first candidate. Also adding both MCC and lactose in various ratios may improve results.

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