Formula Optimization of 100 mg Chewable Ascorbic Acid Tablets

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ABSTRACT

Background: Ascorbic acid is a water soluble nigh dose drug that usually degrades in the presence of moisture with the formation of not so biologically active substances.. Pharmaceutical excipients have long been used to impart functionalities that improve stability and enhance patient compliance while increasing cost. Optimization therefore aims at achieving a compromise between a given set of constraints that yields the best formulation.

Objectives: The aim of this work is to produce optimised formulation of 100 mg chewable ascorbic acid tablet.

Methods: The lubricant was stearic acid at 0.25 %, 0.5% or 0.75 %. The direct compression excipient (DCE) used was Avicel® PH 102 with sorbitol as sweetener in the ratios of sorbitol to Avicel of 1:0, 0:1, 1:1 1:2, 1:3, 1: 4 respectively. The tablet weight was calculated such that the concentration of drug is 30-50% of the direct compression excipient (DCE). A step-wise optimization approach was employed. The best batch was selected as having the highest DCE dilution, hardness ≥4 kgf, minimal tablet defects, and acceptable weight variation, content and content variation.

Results: The optimal formula was obtained with the batch that has the following formula, 0.75 % stearic acid at a maximum DCE ratio of avicel: sorbitol of 4 :1 at dilution of 40 % w/w. The flow rate of the powder mix for this batch was 29.70 g/s, with Carr's compressibility index of 22%, and Hausner ratio of 1.28. The angle of repose determined by free flow from a height of 4 cm was 23°. Drug-excipient compatibility studies using DSC revealed no significant interaction between the tablet components except possible change in crystal structure.

Conclusion: The optimal formulation had the following formula: 0.75 % stearic acid, 4 Avicel: 1 sorbitol, and at a maximum DCE dilution of 40% w/w.

Keywords: Ascorbic acid; tablet; direct compression; sequential; optimal formula

Optimisation de la formule de 100 mg des comprimés d'acide ascorbique à croquer

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RESUME

Contexte: L'acide ascorbique est un médicament de dose hydrosoluble qui se dégrade habituellement en présence d'humidité avec la formation de substances qui ne sont pas si biologiquement actives. Les excipients pharmaceutiques ont longtemps été utilisés pour conférer des fonctionnalités qui améliorent la stabilité et augmentent la conformité du patient tout en augmentant les coûts. L'optimisation vise donc à réaliser un compromis entre un ensemble donné de contraintes qui donne la meilleure formulation.

Objectifs: Le but de ce travail est de produire une formulation optimisée de comprimé à 100 mg d'acide ascorbique à croquer.

Méthodes: Le lubrifiant était de l'acide stéarique à 0,25%, 0,5% ou 0,75%. L'excipient à compression directe (DCE) utilisé était Avicel® PH 102 avec sorbitol comme édulcorant dans les rapports de sorbitol à Avicel de 1:0, 0:1, 1:1 1:2, 1:3, 1:4 respectivement. Le poids du comprimé a été calculé de telle sorte que la concentration du médicament soit de 30 à 50% de l'excipient de compression directe (DCE). Une approche d'optimisation par étapes a été utilisée. Le meilleur lot a été choisi pour avoir la dilution DCE la plus élevée, la dureté ≥ 4 kgf, les défauts minimaux du comprimé et la variation acceptable du poids, de la teneur et de la variation du contenu.

Résultats: La formule optimale a été obtenue avec le lot qui a la formule suivante, 0,75% d'acide stéarique à un rapport DCE maximum d'avicel:sorbitol de 4:1 à la dilution de 40% p/p. Le débit du mélange en poudre pour ce lot était de 29,70 g/s, avec un indice de compressibilité de Carr de 22% et un rapport de Hausner de 1,28. L'angle de repos déterminé par l'écoulement libre à partir d'une hauteur de 4 cm était de 23 °. Des études de compatibilité de médicament excipient utilisant la DSC n'ont révélé aucune interaction significative entre les composants du comprimé à l'exception d'un changement possible dans la structure cristalline.

Conclusion: La formulation optimale a la formule suivante: 0,75% d'acide stéarique, 4 Avicel: 1 sorbitol, et à une dilution maximale de 40% en poids/poids dans l'ETCD.

Mots-clés: Acide ascorbique; comprimé; compression directe; séquentiel; formule optimale

INTRODUCTION

Ascorbic acid has received much attention from researchers, mainly because of its antioxidant properties. It has been reported to be essential in the biosynthesis of collagen, and also important in phenylalanine and tyrosine oxidation. It is also important in the conversion of pholacine to tetra-hydrophilic acid. It is also involved in the inflammatory reaction process. Furthermore, ascorbic acid is important for bioavailability of dietetic non-heminic iron.[1] The major active form is ascorbic acid (AA) but dehydroascorbic acid (DHA), which is its oxidized form, also shows biological function.[2] However, human beings cannot synthesize AA, and thus the major supply is through food. Vegetables and fruits are known to be the best sources of ascorbic acid and it is important to determine their AA and DHA contents. Obtaining reliable data regarding the vitamin C contents in vegetables has become very necessary since studies have shown that there is a positive correlation between intake and disease prevention. A diet deficient in ascorbic acid can lead to scurvy, which causes loosening of the teeth, an inability to heal wounds, haemorrhage, and eventually death. Ascorbic acid has several distinct physical properties.[2]

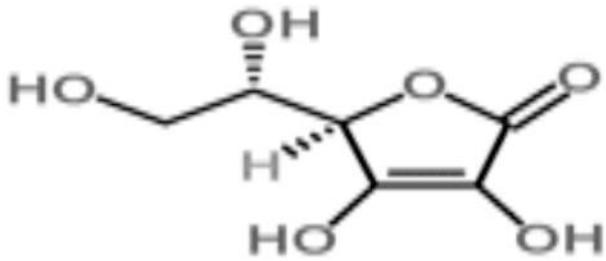

Fig 1: Structure of ascorbic acid [3]

Ascorbic acid has a chemical formula of $C_6H_8O_6$. The molecular weight of ascorbic acid is 176.1g/ mole.[3]

Direct compression method is better suited for production of ascorbic acid tablets because of stability issues. [4,5] It is also known that AA due to its poor flowability and lubricant properties does not lend itself well to direct compression at concentrations above 60%. [6] Sorbitol is a non-cariogenic and low caloric sugar that is highly compressible. These properties make it an attractive choice in the manufacture of chewable tablets made by direct compression. Avicel® has also been widely used as a good, though expensive directly compressible diluent. From the foregoing, it is apparent that AA requires low amount of diluent because it's a high dose drug and high amount of diluent because its poor flow properties. Optimization therefore becomes imperative Optimization has been defined as the implementation of systematic approaches to arrive at the best combination of product (or process variables) under a given set of conditions.[7] With respect to the drug formulations or pharmaceutical process, optimization is a process of finding the best possible composition or operating conditions respectively. Although several optimization procedures are available to the pharmaceutical scientist, not all is suited to pharmaceutical formulation and processing due to the absence of a clear relationship between formulation characteristics (output variable) and material and process variables (input variables).[8] In general the procedure consists of preparing, according to statistical model, a range of formulations, varying the concentrations of formulation ingredients in some systemic manner. These formulations are evaluated according to specified qualities, such as hardness, dissolution, appearance, stability, and taste. Based on the outcome of these evaluations, a particular formulation (or group of formulations) may be predicted to be optimal.[9,10,] Different methods are employed e.g. genetic algorithms (GA) and simulated annealing (SA).[11,12] Monte Carlo simulated annealing (MCSA), also known as the Metropolis algorithm ,[13] Random search [14], and optimization by factorial design.[15] A modification of factorial design and sequential search were employed in this work because of their simplicity to formulate 100 mg chewable ascorbic acid tablets with optimal parameters of minimal tablet defects and least variation in tablet weight. Another major reason for optimization in this work is to achieve maximal dilution of direct compression excipient without compromising quality. This helps to ensure only the minimal necessary quantities of excipients are used, and thus helps to reduce production costs.

MATERIALS AND METHODS

Reagents

The following reagent were used for the work: ascorbic acid (Shanufang Industries, China), micro crystalline cellulose (Avicel Chemical Industry, India), sorbitol (B.D.H England), stearic acid (Shanphai chemicals co. Ltd), iodine crystals, potassium iodide, soluble starch were gifts from Juhel (Pharma) Nigeria Ltd, Enugu, Nigeria. Distilled water was prepared in the Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka, Nigeria.

Drug-Excipient Compatibility Studies

Compatibility studies of ascorbic acid with the excipients was done by mixing ascorbic acid with sorbitol, Avicel or stearic acid and scanning using a differential scanning calorimeter (NETZSCH DSC 204 F1, Phoenix). A 1g quantity of ascorbic acid was mixed with 1g each of the excipients in a transparent glass sample bottle. Then, 1 mg mixture was carefully packed in a small aluminium pan, sealed and scanned with blank pan as reference. The procedure was repeated for each component alone, and their thermograms were each compared with that obtained from ascorbic acid. The scanning conditions are as stated below: Non isothermal measurements were taken at temperatures ranging from 25°C to 400°C with heating rate of 10K/min under a nitrogen purge flow of 2.2 to 2.7ml/min.

Preparation of powder mix

Granule batches were prepared to correspond to the tablet formulas developed. The drug in each tablet was calculated for 100 mg; lubricant was stearic acid at concentrations of 0.25 %, 0.5% or 0.75 %. The direct compression excipients (DCE) used were Sorbitol and Avicel PH 102 in the ratios of Sorbitol to Avicel of 1:0, 0:1, 1:1, 1:2, 1:3, 1: 4, respectively. The tablet weight was calculated such that the drug is 30, 40 or 50 % of the DCE. The corresponding weights of the microcrystalline cellulose (Avicel 102), ascorbic acid, sorbitol and stearic acid were weighed out for each of the batches as shown in Table 1. Then the stearic acid was added to the mixture and mixed in a low shear process for 2 minutes. The same procedure was followed for the batches containing sorbitol alone as the direct compression excipient. For the batches containing a mixture of sorbitol and microcrystalline cellulose in different ratios, the appropriate weights of the sorbitol crystal, microcrystalline cellulose and ascorbic acid were mixed in a specimen bottle in a high shear process for about 2 minutes and then the stearic acid was added to the mixture and mixed in a low shear process for another 2 minutes.

Powder flow rate and angle of repose

Free flow of 30g of each powder mix under gravity was used with a dry glass funnel supported by a retort stand at 4 cm and 10 cm distance from the tip of the funnel to the table. The time of flow was recorded in triplicates and used to calculate flow rate as 30g/time of flow (s). The angle of repose of the conical heap formed, Θ, was determined from equation 1

$$Tan\ 0 = \frac{Height\ of\ powderheap}{Raidius\ of\ powderheap} \quad (1)$$

Determination of bulk density, tapped density, compressibility index and Hausner ratio for the batches of granules

A 30g sample of each powder mix was weighed out and gently introduced into a 100 mL measuring cylinder. The cylinder was gently dropped on a wooden platform three times for 2 seconds. The volume occupied by the powder was noted as the bulk volume (V_B). The cylinder was tapped 200 times on the wooden platform to a constant volume of the powder. The volume occupied by the powder was noted as the tapped volume (V_T). The procedure was done three times. The Hausner ratio was calculated as V_B / V_T, while Carr's Index was calculated as $100(V_B - V_T) / V_B$.

Table 1: Composition of the tablet formulation batches

Batch code	AA (mg)	Dilution (%)	Avicel:Sorbitol ratio	Avicel (mg)	Sorbitol (mg)	Stearic acid	
						mg	%
A1	100	40	1:0	245.7	0.0	0.8	0.25
A2	100	40	1:0	253.2	0.0	1.3	0.50
A3	100	40	1.0	247.8	0.0	1.9	0.75
A4	100	30	1:0	336.1	0.0	0.8	0,25
A5	100	30	1:0	338.0	0.0	1.7	0.50
A6	100	30	1:0	341.8	0.0	2.6	0.75
A7	100	40	4:1	201.2	50.3	0.6	0.25
A8	100	40	4:1	202.6	50.6	1.3	0.50
A9	100	40	4:1	203.8	51.0	1.9	0.75
A10	100	30	4:1	268.9	67.2	0.8	0,25
A11	100	30	4:1	271.2	67.7	1.7	0.50
A12	100	30	4:1	273.5	68.4	2.6	0.75
A13	100	30	3:1	252.1	84.0	0.8	0.25
A14	100	30	3:1	254.3	84.8	1.7	0.50
A15	100	30	3:1	256.4	85.5	2.56	0.75
A16	100	40	0:1	0.0	251.5	0.6	0.25
A17	100	40	0:1	0.0	251.2	1.3	0.50
A18	100	40	0:1	0.0	254.8	1.9	0.75
A19	100	30	0:1	0.0	336.2	0.8	0,25
A20	100	30	0:1	0.0	339.0	1.7	0.50
A21	100	30	0:1	0.0	341.9	2.6	0.75

Dilution = dilution of direct compression excipient; quantities for Sorbitol to Avicel of 1:0, 1:1, 1:2, not shown because preliminary runs showed good compression at Avicel: sorbitol of 3:1 at maximal pressures conducive for the machine. Also, values for 50 % DCE dilution were not shown because preliminary runs showed excessive capping and lamination and overall failed tablets for all DCE mixes at this dilution. Values for Sorbitol retained for comparison and emphasis. Below 30% DCE not used because of jamming of the tableting machine during trial runs.

Compression of the powder mixes

The corresponding calculated weight for each tablet in the batches was used to set the die volume. The blend for each batch was compressed using Proton Minipress (Proton Engineering Rotary Tableting Machine, India). The compression was done separately for all the batches. The pressure was adjusted 49 kgf, which did not cause jamming of the machine. The setting was used for all batches.

Tablet weight uniformity test

The average tablet weight was determined by weighing 20 tablets individually using an electronic weighing balance (Ohaus, England). The mean, standard deviation and the coefficient of variation for each batch were calculated

Hardness determination or crushing strength

Ten (10) tablets were selected randomly from each batch and hardness was determined using Monsanto hardness tester. The mean and standard deviation for each batch was calculated.

Uniformity of weight test

Ten (10) tablets were individually weighed using an electronic balance (Ohaus, England). The mean, standard deviation and the coefficient of variation for each batch were calculated. According to the USP, as seen from table 2, not more than two tablets should deviate from the mean by more than the 5%, and no tablet should deviate by more than 10%[16]

Table 2: USP weight variation limits for tablets [16]

Tablet Weight	Limit
130 mg or less	10%
130 mg to 324 mg	7.5%
More than 324 mg	5%

Tablet friability test

Ten (10) tablets were selected at random from each batch and dedusted. The tablets were weighed together on an electronic balance. The dedusted tablets were placed in a friabilator (DBK friability test apparatus DBK 5020/7 India) and set to rotate at 25 rpm for 4 minutes. The tablets were thereafter removed from the friabilator, dedusted and weighed again. The loss in weight indicates the ability of the tablets to withstand this type of wear. The mean loss in weight was calculated for each batch and percent friability was calculated using equation 2

$$\text{Friability loss (\%)} = \frac{\text{Initialweight} - \text{Finalweight}}{\text{Initial weight}} \times 100 \qquad (2)$$

Assay of active ingredient

Redox titration method using iodine solution was used for the assay. [17]

Preparation of Standard Iodine Solution (0.005 mol/L): 2 g of potassium iodide and 1.3 g of iodine crystals were weighed into a 100 ml beaker. A 20 mL volume of distilled water was added and mixed for 5 minutes until iodine was dissolved. The iodine solution was transferred to a 1L volumetric flask and the solution was made up to the 1 L mark with distilled water.

Preparation of starch indicator solution. [17].

A 0.25 g quantity of soluble starch was weighed and dispersed in 20 mL hot water in a 50 mL conical flask and the volume made up to 50 mL and boiled to gelatinize. The gelled starch was stirred continuously and allowed to cool before use.

Titration of 100 mg of pure ascorbic acid

Twenty (20) tablets were selected at random from each batch, crushed together and a quantity corresponding to a single tablet weight was dissolved in 200 mL of distilled water in a volumetric flask. A 20 mL aliquot of the sample solution was pipetted into a 250 mL conical flask. A volume of 150 mL of distilled water and 1mL of the starch indicator solution were added to the flask. The sample was titrated with 0.005 mol/L iodine solution. The endpoint of the titration was identified as the first permanent trace of a dark blue-black colour due to the formation of starch-iodine complex. The procedure was repeated with 100 mg of the ascorbic acid powder whose endpoint was 15 mL of the standard iodine solution. The content of ascorbic acid in each tablet was calculated from equation 3

$$\text{Weight (mg) of ascorbic acid} = \frac{\text{Titrant volume for sample (ml)}}{\text{Titrant volume for 100mg ascorbic acid (ml)}} \text{ X } 100 \quad (3)$$

Determination of content uniformity of tablets

Ten (10) tablets were randomly selected from each of the batches. Each tablet was crushed and the titration procedure repeated as in the method for content of active ingredient. The mean drug content was calculated and the coefficient of variation, as well as the percentage deviation of each tablet.

Selection criteria

A step-wise optimization approach was employed. Highest DCE dilution, minimal tablet defects (capping and lamination, chipping, picking, sticking to die cavity or breaking), minimal tablet weight variation, minimal tablet hardness (not less than 4 KgF) and minimal DCE in the powder mix were used as selection criteria for the tablet batches.

RESULTS

Compatibility studies

The thermogram of ascorbic acid as recorded using the DSC is shown in Figure 2. There was a sharp endothermic peak at 198.2

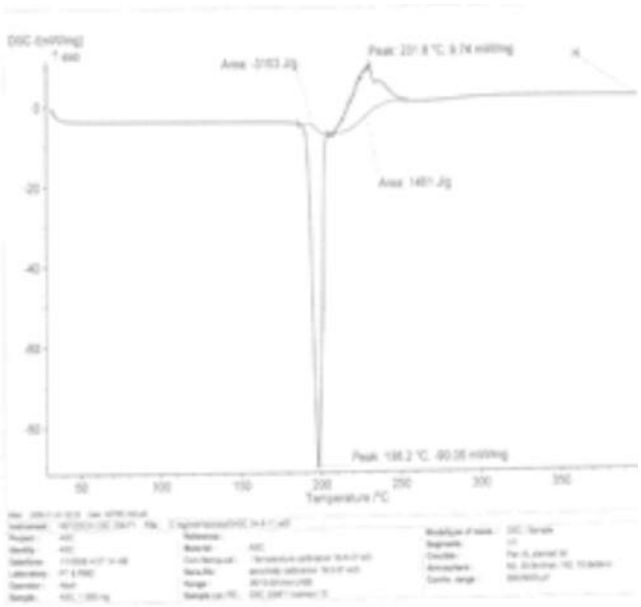

Figure 2: Thermogram of ascorbic acid

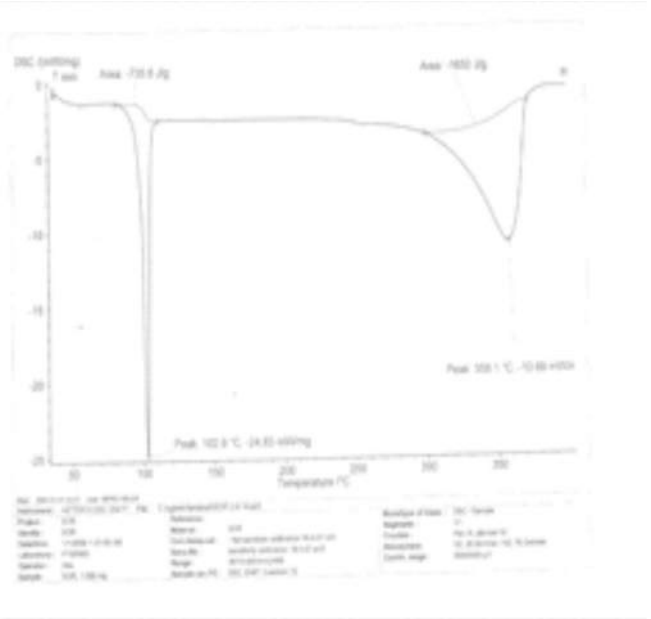

Figure 3: Thermogram of sorbitol

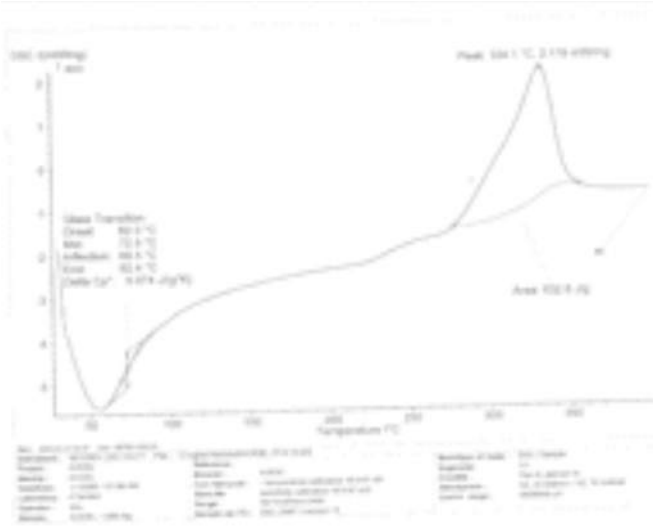

Figure 4: Thermogram of avicel

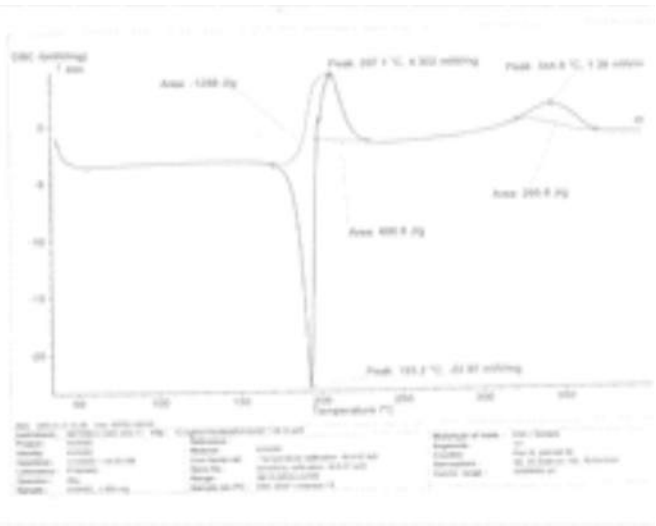

Figure 5: Thermogram of Ascorbic acid/Avicel Figure

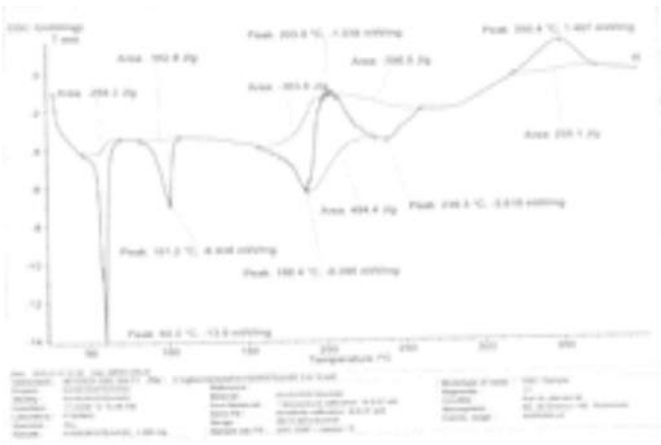

Figure 6: Thermogram of Stearic acid

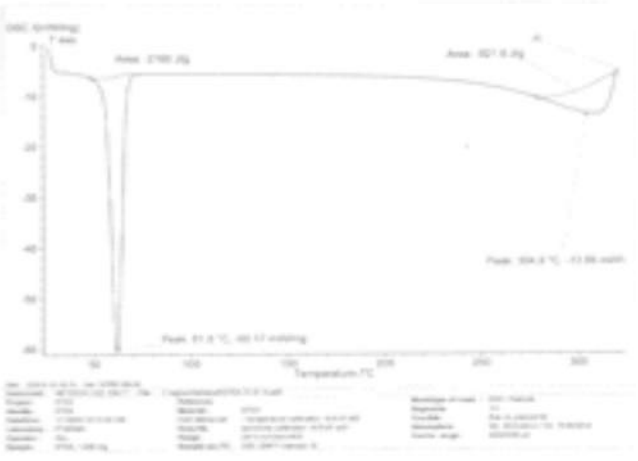

Fig.7: Thermogram of Avicel plus stearic acid

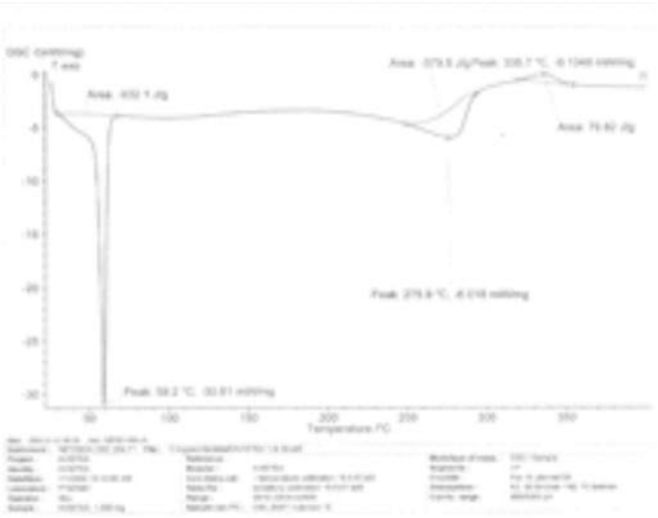

Fig. 8:Thermogram of Ascorbic acid/Avicel/Sorbitol/Stearic acid

Flow and compressibility properties of powder mixtures

The results of the evaluation of the flow properties of the powder mix from different batches is recorded in Tables 3, 4, and 5.

Table 3: Compressibility indices

Batch code	Hausner's ratio± SD	Carr's Index (%)± SD
A1	1.43± 0.01	30.00± 0.53
A2	1.33± 0.02	25.00± 0.95
A3	1.36± 0.02	26.53± 0.94
A4	1.39± 0.03	28.00± 1.31
A5	1.35± 0.01	26.00± 0.61
A6	1.34± 0.02	25.00± 0.88
A7	1.35± 0.01	26.00± 0.81
A8	1.19± 0.03	20.00± 2.10
A9	1.28± 0.01	22.00± 0.90
A10	1.24± 0.01	19.15± 0.86
A11	1.23± 0.01	18.75± 0.95
A12	1.24± 0.01	19.15± 0.75
A13	1.32± 0.01	24.90± 0.51
A14	1.32±0.00	24.00± 0.23
A15	1.35± 0.00	26.00± 0.23
A16	1.10± 0.01	19.76± 0.61
A17	1.08± 0.00	7.32±0.14
A18	0.87± 0.01	4.63± 0.98
A19	1.14± 0.01	11.90± 0.41
A20	1.14± 0.00	12.50± 0.29
A21	1.14± 0.00	11.90± 0.00

Table 4: Powder mix flow rate

Batches	**Flow rate (g/s) ± SD**	
	4 cm height	**10 cm height**
A1	26.09 ± 0.61	18.52 ± 0.99
A2	24.39 ± 0.42	22.39 ± 1.31
A3	27.78 ± 1.08	18.29 ± 2.10
A4	19.61 ± 0.13	18.63 ± 0.89
A5	18.75 ± 0.92	16.30 ± 1.14
A6	16.67 ± 0.99	16.68 ± 1.39
A7	27.20 ± 1.22	24.39 ± 2.07
A8	27.00 ± 0.89	27.03 ± 1.15
A9	29.70± 1.33	22.56 ± 0.00
A10	26.09 ± 0.99	24.39 ± 2.12
A11	27.27 ± 1.38	26.09 ± 1.28
A12	27.78 ±2.00	27.27 ± 2.01
A13	17.54 ± 0.83	15.54 ±0.13
A14	16.39 ± 1.31	15.71 ± 1.26
A15	26.79 ± 1.11	22.90 ± 1.27
A16	35.71 ± 1.76	29.13 ± 2.09
A17	40.00 ± 3.21	32.36 ± 2.15
A18	34.88 ± 3.00	25.00 ± 2.01
A19	41.10 ± 3.21	31.58 ±1.66
A20	27.27 ±0.98	24.79 ± 2.01
A21	19.61 ± 1.10	17.14 ± 0.09

Table 5: Angle of repose

Batch codes	Angle of Repose (degrees) ± SD	
	4 cm	10cm
A1	18.9 ± 2.13	14.3 ± 3.12
A2	22.0 ± 1.22	16.3 ± 3.44
A3	24.9 ± 2.40	7.8 ± 1.17
A4	27.1 ± 3.21	17.4 ± 2.46
A5	25.7 ± 1.78	19.7 ± 3.11
A6	25.4 ± 2.91	19.9 ± 3.08
A7	23.0 ± 1.25	14.5 ± 2.89
A8	20.6 ± 2.40	23.0 ± 3.06
A9	20.4 ± 2.31	17.8 ±1.35
A10	24.2 ± 1.91	16.8 ± 1.44
A11	26.6 ± 2.33	19.0 ± 2.90
A12	27.1 ± 2.61	17.7 ± 2.01
A13	25.5 ± 3.02	19.8 ± 3.00
A14	27.9 ± 3.10	16.1 ± 2.76
A15	26.0 ± 0.92	18.5 ± 2.99
A16	23.0 ± 1.91	14.0 ± 1.73
A17	23.0 ± 3.11	18.2 ± 2.88
A18	24.5 ± 1.29	20.4 ± 3.26
A19	21.3 ± 1.48	14.2 ± 1.44
A20	24.0 ± 2.19	19.3 ± 3.00
A21	22.8 ± 2.05	24.2 ± 3.21

Hardness of the compressed tablets

The hardness values of the tablets are shown in Table 6.

Table 6: Hardness test results

Batch code	Mean Hardness ± SD
A1	7.8 ± 0.9
A2	5.7 ± 0.9
A3	4.8 ± 0.9
A4	10.0 ± 1.2
A5	7.9 ± 0.7
A6	7.5 ± 1.0
A7	4.2 ± 0.8
A8	3.9 ± 1.0
A9	4.0 ± 0.9
A10	3.6 ± 0.7
A11	4.3 ± 1.1
A12	4.0 ± 1.1
A13	4.0 ± 1.1
A14	3.8 ± 1.2
A15	3.7 ± 0.8
Marketed brand	3.5 ± 0.1

Bold font shows tentatively selected batches based on taste and maximal DCE dilution with appreciable hardness. All batches made with only sorbitol eliminated at this stage because of poor compression and hygroscopicity. Friability of compressed tablets The results of the friability tests carried out on the selected batches are shown in Table 7.

TABLE 7: Friability test

Batches	% Friability
A1	0.91
A2	0.93
A3	1.39
A4	0.44
A5	0.33
A6	0.11
A7	3.71
A8	5.59
A9	0.00
A10	0.52
A11	0.41
A12	1.05
A13	0.45
A14	0.29
A15	0.43
Marketed AA tablets	0.47

TABLE 7: Friability test

Bold font shows tentatively selected batch based on low friability. This falls within batches already selected using hardness criterion in table 6. Other batches were retained for comparison.

Weight uniformity test

The result of weight uniformity tests carried out on selected batches is shown in Table 8.

Table 8: Tablet weights (D= dilution of direct compression excipient)

Batch codes	Mean weight ± SD (mg)	Coefficient of variation
A1	355.0 ± 8.5	2.4
A2	359.0 ± 8.8	2.4
A3	361.0 ±9.9	2.8
A4	418 ± 15.5	3.7
A5	418 ± 18.1	4.3
A6	456.0 ± 12.6	2.8
A7	353.0 ± 11.6	3.3
A8	357.0 ± 8.2	2.3
A9	354.0 ± 9.7	2.7
A10	432.0 ± 6.3	1.5
A11	436.0 ±8.4	1.9
A12	448.0 ± 15.5	3.5
A13	435.0 ± 8.5	2.0
A14	401.4 ± 6.2	1.4
A15	442.0 ± 11.4	2.6
Marketed AA tablets	290.0 ± 7.8	2.7

Bold fonts shows already tentatively selected batch based on hardness and low friability criteria in tables 6 and 7. This still conforms to D acceptable weight variation. Other batches retained for comparison.

Table 9: Uniformity of content test results

Batch	Mean ± SD	Deviation from 100mg stated dose (%)									
		1	2	3	4	5	6	7	8	9	10
A1	96.31 ± 3.1	2.13	3.07	3.73	0.73	11.93	3.87	3.67	3.73	2.00	2.00
A2	93.93 ± 1.45	7.60	8.13	6.20	7.27	4.53	4.53	6.00	7.33	4.60	4.53
A3	95.86 ± 1.92	3.07	4.53	7.53	7.20	4.40	3.07	2.60	2.00	2.47	4.53
A7	95.27 ± 3.42	11.3	8.00	4.67	0.67	2.67	3.33	7.33	5.33	2.67	2.67
A8	96.60 ± 2.97	2.67	1.33	5.33	8.67	4.00	3.33	0.00	2.00	6.67	2.67
A9	96.40 ± 1.84	5.33	3.33	2.67	1.33	2.67	1.33	8.00	3.33	2.67	2.67
A13	93.25 ± 1.88	7.40	6.60	4.80	10.33	9.33	6.67	6.67	6.00	4.87	4.80
A14	96.87 ± 3.68	13.3	0.93	1.67	2.33	0.60	1.93	2.53	2.00	4.00	2.00
A15	95.20 ± 2.61	4.53	1.27	2.60	7.00	10. 5	5.27	5.13	2.93	3.40	5.33
Marketed brand	98.00 ± 0.55	1.33	2.00	2.00	3.33	1.33	2.00	2.13	2.00	1.87	2.00

Bold fonts show final optimized batch based on hardness, low friability, weight variation and drug content criteria in tables 6, 7, 8 and 9. This still conforms to acceptable uniformity of content.

Table 10: Absolute drug content test results

Batch code	Drug content ± SD (mg)
A1	95.57 ± 4.33
A2	91.67 ±8.33
A3	97.00 ± 3.00
A7	94.53 ± 5.47
Ā8	94 80 ± 5.20
A9	97.67 ± 2 33
A13	95.20 ± 4.80
A14	98.27 ± 1.73
A15	95.47 ± 4.53
Marketed brand	98,73 ± 1.27

Bold font shows already tentatively selected batch based on hardness, low friability and weight variation criteria in tables 6, 7 and 8. This still conforms to acceptable drug content. Tablets with DCE dilution of 30 % eliminated because they had higher bulk that those of 40%. Other batches retained for comparison.

DISCUSSION

Trial compression runs involving either sorbitol alone or in mixtures with avicel in which it constituted higher than 35% of the mix showed less than optimal compression characteristics and hence were eliminated. This could be attributed to the physicochemical characteristics of the direct compression excipient particularly sorbitol's hygroscopicity.[20] Likewise, formulations that had 50% dilution of the direct compression excipient showed excessive capping and lamination of the tablets and were therefore eliminated early in the process.

Sorbitol is non-cariogenic sugar used as a sweetener but also doubled as a direct compressional excipient to aid the microcrystalline cellulose. In spite of the fact that avicel has high dilution potential in addition to excellent compressibility, and self lubricating, its flowability is still less than optimal.[21].

Excipients are always used in combination with other

materials or the API hence determining their compatibility is important.[22] Differential scanning calorimetry is one of the several methods used to determine the existence of active ingredient excipient interaction and excipient excipient interaction. The usual melting point of ascorbic acid is 190-192.[23] The shift in melting point from 192 to 198 is likely as a result of slight impurities.

The thermogram of binary mixture of Avicel and ascorbic acid gave two sharp endothermic peaks, one corresponding to that of ascorbic acid (though with a slight shift), and the other to that of the Avicel. This shift in the melting peak of ascorbic acid in the binary mixture is expected since the melting point of pure samples as determined in DSC is usually higher than that of the samples in binary mixtures. The nature of the shift indicates molecular rearrangement and change in crystal structure

The DSC shows no incompatibility between the excipients and the ascorbic acid. This is not surprising since avicel exhibits inherent compatibility due to its plastic deformation and elastic recovery.[24]

The compressibility indices (Carr's index and Hausner's ratio) and angle of repose reveal particle-particle interaction and powder bed consolidation. The more the ability to consolidate, the greater the likelihood of poor flow. [19] From Table 3, it was observed that all the batches of granules containing sorbitol alone at each dilution of the direct compression excipient have a Hauser's quotient less than 1.18 and a Carr's index less than 20%. This is indicative of excellent flow.[19] Generally, the compressibility indices values increased with increase in Avicel content of a batch. This may be attributed to the fact that Avicel has excellent compressibility and is one of the reasons it is one of the most widely used direct compression diluent. [20] In addition, the flow rate values (Table 4) shows that the more the Avicel, the poorer the flow indices. The batches that contain only Avicel at the different dilutions showed poorer flow. This also may be as a result of the poor flowability of Avicel. From Table 4 it is also observed that batches of powder mix containing sorbitol at the different concentration of stearic acid had excellent flow at both heights of 4cm and 10 cm respectively. The batch containing 0.75% stearic acid at 40% dilution showed the best flow. Generally, angle of repose of less than 30° indicates free flowing powders, though many factors affect the value and the use of angle of repose for flow indication is somewhat subjective.[19] All the batches had values less than 30° (Table 5).

All the tablet batches containing sorbitol had lower hardness than the batches formulated with Avicel. Batch A13 containing 0.25% of stearic acid at 30% DCE dilution at 3: 1 of Avicel: sorbitol produced the least hardness, while batch A4 containing 0.25% of stearic acid at 30% Avicel had the highest hardness. The batches with 4 Avicel: 1 sorbitol at 40 % dilution had good hardness profile. All the batches with only sorbitol as DCE had poor compression and were hygroscopic. Hence, they were eliminated. Lubricant presence and concentration has been shown to affect the tensile strength of compacts made with avicel negatively- a phenomenon known as lubricant sensitivity[25]. This refers to reduction in bonding between the plastically deforming particles of the powder due to the presence of the lubricant particles. The effect of the lubricant on the hardness of Avicel tablet batches is obvious from table 6. As the concentration of steric acid increased and that of Avicel decreased, the hard ness of the tablets also decreased. The hardness for the batch from the commercial product was below 4 kgf.

Friability of not more than 1% is generally accepted for a good tablet. [23] From Table 7 it was observed that most of the tablet batches passed the friability test, except for batches A3, A7 and A8 It is observed that the batch A9 containing 0.75% stearic acid at 40% dilution of Avicel to sorbitol at a ratio of 4:1 had the least friability result. The batch from the commercial preparation equally passed the test but has a friability that is higher than that of batch A9

The United States Pharmacopoeia states that for tablets of more than 324 mg weight, no two tablets should vary from the mean by more than 5 %. [23] Table 8 showed that the entire tablet batch passed the test for uniformity of weight. The tablet batch containing 0.25% stearic acid at 30% dilution of Avicel: sorbitol ratio of 4: 1 has the least mean deviation. The batch from the commercial preparation also met the specification.

For the assay of uniformity of content, the United States Pharmacopoeia states that when 10 tablets are assayed, not more than 1 dosage unit should fall outside the range of 85% to 115% of the label claim or the relative standard deviation of 10 dosage units is less than or equal to 6.0 %. If 2 or 3 dosage unit fall outside the range of 85% to 115% of the label claim but not outside the range of 75% to 125% or if the relative standard deviation is greater than 6% or both conditions prevails, 20 additional units should be tested. The requirement is met if not more than 3 units of the 30 fall outside the range of 85.0% to 125.0% of the label claim and the relative standard deviation of the dosage units does not exceed 7.8 % [16]. From Table 9, all the batches

met the requirement.

The United States Pharmacopoeia states, under the monograph for ascorbic acid, that the ascorbic acid content should not be less than 90% of the tablet claim and should not be more than 110% [16]. From Table 10, it can be seen that all the tablet batches met the official requirement. The deviation is highest with the tablet batch containing 0.5% stearic acid at 30% drug concentration of Avicel and least with the tablet batch containing 0.5% stearic acid at 40% drug concentration of Avicel.

CONCLUSION

In conclusion, therefore, the formula for ascorbic acid tablets was optimised using a combination of Avicel and sorbitol. The optimal formulation was the batch that has the following formula: 0.75 % stearic acid, 4 Avicel: 1 sorbitol, and at a maximum DCE dilution of 40% w/w. The optimized formulation had a good taste and a minimal content of direct compression excipients which is expected to lead to a corresponding minimal cost of production.

ACKNOWLEDGEMENT

We wish to appreciate Mr Nwobu Boniface of the Department of Pharmaceutics and Pharmaceutical Technology of Nnamdi Azikiwe University, Awka, Nigeria for his technical assistance in handling the tableting machine throughout the work. This work was privately funded and there are no competing interests.

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