Journal of Science and Practice of Pharmacy
December 2014; 1 (1): 25-30 Available at http://www.jsppharm.org

Original Research Article

Development and Evaluation of Novel, Multifunctional Co-Processed Excipients for Direct Compression of Paracetamol Tablets

Sylvester O Eraga*, Cynthia O Damisah, Michael U Uhumwangho and Magnus A Iwuagwu
Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, Benin City, 300001, Nigeria.

*For correspondence: *Email:* eragaso@uniben.edu Tel: +2348030884928

Abstract

Purpose: To develop a novel multifunctional pharmaceutical excipient for direct compression (DC) of paracetamol.
Methods: The novel excipient was prepared by co-processing gelatinized maize starch with sodium carboxyl methyl cellulose and microcrystalline cellulose in a ratio of 2:1:1, dried and pulverized into powder. DC was applied in preparing different batches of paracetamol tables with drug-excipient ratios of 1:1, 1:2, 1:3, and 1:4. Both the excipient powder, the blended mixture of paracetamol and the excipient powder and the tablets formulated were evaluated for their physicochemical properties including bulk, tapped and particle densities, Hausner's ratio, Carr's index, angle of repose, flow rate, moisture content, swelling index and hydration capacity while the tablets formulated were evaluated for uniformity of weight, dimensions, hardness, friability, disintegration time, moisture sorption and dissolution rate.
Results: The co-processed novel excipient exhibited excellent flow properties (angle of repose; 25º) with a high moisture content (9 %), good swelling index (15.10) and hydration capacity (5.26). The powder mix also showed good flow properties that were proportional to the concentration of the excipient. Formulated tablets were of good quality with regard to weight, hardness, drug content and disintegration time except friability where two batches failed the official specification.
Conclusion: The co-processed excipient developed in this study was found to be a promising directly compressible vehicle for the preparation of compressed tablets for poorly compressible drugs.
Keywords: flow properties, maize starch, sodium carboxyl methyl cellulose, microcrystalline cellulose, post-compression parameters

Indexing: Index Copernicus, African Index Medicus

Introduction

The compressed tablet is the most popular dosage form in use today. In the tablet compressing process, it is important that all ingredients be fairly dry, powdered or granular, somewhat uniform in particle size and freely flowing. In order to achieve this, the ingredients will need to undergo a granulation process. Both wet and dry granulation methods of tablet manufacture are complex multistage processes, but are necessary to convert the components of the formulation into a state that can be readily compressed into acceptable tablets. If however, the necessary degree of fluidity and compressibility is possessed by a major component of the formulation, granulation would not be necessary. This is the basis for the direct compression (DC) method of tablet manufacture [1].

Key components in the DC process are the excipients. They must not only possess those properties which are necessary for satisfactory tablet formulation but retain them when mixed together especially the active ingredients [2]. Excipients provide a wide variety of functionalities such as better processibility of different API into dosage forms; better tablet binding; better tablet disintegration; better API bioavailability [3]. They may also provide other functionalities, such as good flowability, compressibility, particle size distribution, hardness and taste masking that improve the manufacture and performance of tablets and capsules.

However, most of the excipients that are natural or synthetic products do not possess the functionalities that will impact on the API desired delivery system upon formulation. No single excipient possesses all the desired physico-mechanical properties for the

development of a robust drug delivery system (DDS) which can be scaled up easily. Hence, there is a need to have excipients with multiple characteristics built into them such as better flow, low/no moisture sensitivity, superior compressibility, and rapid disintegration ability [4].

The engineering of pharmaceutical excipients to give high functional ones (contribute at least two functions to the formulation through a single ingredient) can be achieved by developing new chemical excipients, new grades of existing materials, or by new combinations of existing materials. The latter two types are products of what is now called particle engineering [5].

Co-processing, a method of particle engineering, could lead to the formation of excipients with superior properties compared to the simple physical mixture of their components. The main aim of co-processing is to obtain a product with added value related to the ratio of its functionality/price [6]. Co-processed products have been developed primarily to address the issues of flowability, compressibility and disintegration potentials with filler-binder combination being the most commonly evaluated [7].

Particle engineering methods are encumbered with many disadvantages which include need for state-of-the-art facilities, use of expensive and/or environmentally unfriendly chemicals, need for high skilled technicians, additive high cost of production, etc. All these demerits have triggered the search for a simple and cheap particle engineering method that may be used in regions where hi-tech facilities are lacking. The aim of this research work was to formulate and characterize a novel pharmaceutical excipient using the simple method of co-processing and to determine the effect of the novel excipient on some physicochemical properties of paracetamol tablets.

Methods

Materials

These include maize starch BP, micro crystalline cellulose and sodium carboxymethyl cellulose, (Edo Pharmaceuticals, Benin City, Nigeria), α-lactose monohydrate (Fluka, Netherlands), concentrated HCl 37 % (BDH, UK), and paracetamol powder (Nomagbon Pharmaceuticals, Benin City, Nigeria). All other reagents used were of analytical grade and water was double distilled.

Preparation of the co-processed novel excipient (NE)

Maize starch BP (6 g) was dispersed in distilled water at 32 °C to make a 10 ml slurry in a 500 ml beaker. The slurry was well stirred to ensure that all the powder was properly wetted. Freshly boiled water (100 °C) was then added to the slurry to reach the 200 ml mark and stirred properly till a paste of uniform consistency was formed. Sodium carboxyl methylcellulose (2 g) powder was then dispersed in the paste, in little quantities at a time (to prevent lump formation), and stirred continuously until an even mixture was produced. Then, a solution containing 2 g of microcrystalline cellulose in 5 ml of distilled water was added to the mixture and stirred until a smooth paste of all three substances was obtained. The paste was then transferred into a transparent heat resistant plastic container, spread thinly and dried in the hot air oven at 60 °C for 48 h. The resulting flakes were pulverized using a dry kitchen blender (Phillips Switzerland) and stored in an air tight container over silica gel until use.

Characterization of the co-processed novel excipient

The co-processed novel excipient prepared was characterized by determining the bulk and tapped densities, compressibility index, Hausner's ratio, angle of repose, flow rate, moisture content, particle density, swelling index and hydration capacity.

Bulk and tapped densities: A 20 g quantity of the novel excipient powder was poured gently into a 100 ml graduated measure. The volume of the powder was read and the bulk density calculated. The measure containing the 20 g of the novel excipient powder was tapped 100 times on a wooden platform. The volume was noted and used in calculating the tapped density.

Carr's index and Hausner's ratio: The difference between the tapped and bulk density of the novel excipient powder divided by the tapped density was calculated and the ratio expressed as percentage to give the Carr's index. The ratio of the tapped density to the bulk density of the novel excipient powder was calculated as the Hausner's quotient.

Angle of repose: The hollow tube method was used. A short hollow tube of 3 cm in internal diameter sitting on a circular horizontal surface of same diameter was filled with the powders of the novel excipient. The tube was withdrawn vertically and excess powders allowed to fall off the edge of the circular horizontal surface. The height of the heap was measured. The angle of repose, θ, was calculated using Equation 1.

$$\theta = \tan^{-1} (h/r) \text{ - - - - - - - - - - - - - - - - } (1)$$

where h is the height of the heap of granules and r is the radius of the circular base.

Flow rate: An Erweka flow tester was used. The time taken for 50 g of the novel excipient powder to pass through its orifice was recorded. This was carried out in triplicates and the mean values recorded.

Particle density: A 25 ml specific gravity bottle (glass pycnometer) was filled with liquid paraffin, cleaned of any residual liquid paraffin and weighed (a). The bottle was emptied, rinsed with acetone and dried. About 1 g (b) of the novel excipient powder was poured into the bottle and then filled with liquid paraffin. It was weighed (c) after cleaning off the residual paraffin from the bottle. The various weights recorded were used to calculate the particle density of the novel excipient using Equation 2.

$$\rho = b/[(a+b)-c]S \quad \text{- - - - - - - - - - - - -} \quad (2)$$

where ρ is the particle density of the novel excipient and S is the specific gravity of liquid paraffin.

Moisture content: A 1 g quantity of the novel excipient was dried in a hot air oven for 4 h at 105 ºC. The initial weight of the granules and the weight after drying were recorded and used to calculate the moisture content.

Swelling index: One gram weight of the novel excipient powder with a tapped volume (Vi) in a 50 ml measuring cylinder was dispersed with 1 ml of ethanol 96 % and 25 ml of distilled water and thereafter made up to volume with more water. The cylinder was firmly closed and shaken vigorously every 10 mins for 1 h. The dispersion was allowed to stand for 3 h and the volume of the sediment (Vf) noted. The swelling capacity was computed with Equation 3.

$$\text{Swelling capacity} = Vf - Vi \quad \text{- - - - - - - - - - - - - - -} \quad (3)$$

Hydration capacity: A 1 g weight of the novel excipient was introduced into four 15 ml centrifuge tubes. The tubes were corked after 10 ml of water was added. The tube contents were shaken for about 2 min, allowed to settle for 10 min and centrifuged at 1000 rpm for 10 min using a bench centrifuge. The resulting supernatant was decanted and the sediment weighed. The hydration capacity was determined with Equation 4.

$$\text{Hydration capacity} = W_f / W_i \quad \text{- - - - - - - - - - - - - - -} \quad (4)$$

where W_f and W_i are the weights of the sediment and the dry starch sample, respectively.

Characterization of the powder blends

The powder blends excipient prepared were characterized by determining the bulk and tapped densities, compressibility index, Hausner's ratio, angle of repose, flow rate and moisture content. The method use under the novel excipients were repeated here.

Tablet formulation by direct compression

The paracetamol tablets were prepared by direct compression (DC) using the formulae in Table 1. The different batches of the tablets containing drug-novel excipient ratios of 1:1, 1:2, 1:3 and 1:4 were prepared by weighing the paracetamol powder, novel excipient, maize starch and lactose into a mixer and dry mixed for 5 mins. The powder mix was compressed into tablets using a single punch tableting machine (F-3 Manesty Machines, UK) at compression pressure of 32 kilonewton (KN). The die volume was adjusted to compress tablets of uniform weight by using powders weighing 650 mg. The tablets made were then kept in air tight containers and stored in a desiccator until evaluation

Table 1: Formula of prepared paracetamol tablets

Ingredients	Quantity (mg/tablet)			
	1:1	1:2	1:3	1:4
Paracetamol	100	100	100	100
Lactose	350	250	150	50
Maize starch	100	100	100	100
Novel Excipient	100	200	300	400
Total	650	650	650	650

Evaluation of tablets: The following tests were carried out on the compressed tablets using standard procedures: tablet weight uniformity, hardness, friability, disintegration time, moisture soption, content of active drug and dissolution studies.

Tablet weight uniformity: The weight of each of 20 tablets was determined from each batch using an electronic balance (College B154, Mettler Toledo, Switzerland) and the mean weight and standard error were computed.

Tablets hardness: The hardness of each of ten tablets per batch was determined (Campbell Electronics, Model HT-30/50, India). The mean hardness and ± standard deviation was calculated.

Friability test: The weight of ten tablets was determined on the electronic balance. The tablets were then placed in the drum of a friabilator (Erweka GmbH, Germany) revolving at 25 rpm which exposed the tablets to rolling and repeated shock resulting from free fall within the apparatus. After four minutes, the tablets were brought out, dedusted and reweighed. The weight was then recorded and friability calculated as percentage loss in weight.

Disintegration time: The disintegration times of six tablets per batch of the tablets were determined in distilled water at 37 ± 0.5 °C using the British Pharmacopoeia (BP) disintegration tester (MK IV, Manesty Machines, UK).

Moisture sorption: The moisture sorption properties of the tablets were determined using static gravimetric method. A tablet from each batch was dried at 80 °C for 4 h. The tablet was weighed, placed in a petri dish and exposed to a 100 % relative humidity condition for 48 h in a desiccator containing distilled water at 32 °C. The weight of the tablet at

the end of 48 h was recorded and moisture sorption calculated as percentage gain in weight.

Content of active drug: Some tablets (20) were randomly selected from each batch and crushed to fine powder. A quantity of the powdered tablets equivalent to 100 mg paracetamol was weighed and dissolved in 50 ml of 0.1N HCl in a 100 ml volumetric flask and made up to volume. Necessary dilutions were carried out to obtain a final concentration of 100 µg/ml, the solution was thereafter filtered through a Whatman No 1 filter paper and the absorbance of the filtrate determined at 245 nm using 0.1N HCl as blank.

Statistical analysis

Descriptive statistics was done for all data using Microsoft Excel (2007). Mean and standard deviations of triplicate determinations was computed and reported. Differences between mean was determined using ANOVA while $p < 0.05$ was considered significant.

Results and Discussion

Properties of the novel excipients

The physical properties of the co-processed novel excipient are shown in Table 2. Carr's index of 18.33 indicates good flow ability. The values of the Hausner's ratio, angle of repose and the flow rate also indicated that the excipient prepared has excellent flow properties. The particle density of 1.11 could be as a result of wide size range of its particles with the smaller particles filling the void spaces created by larger ones. This is in line with Newman [8] who showed that low densities result when void spaces created by powder particles are not filled by smaller particles, leading to consolidation of the powder particle. High moisture content of 9 % of the novel excipient is indicative of large particle sizes which may trap water and result in high moisture content [9] because moisture contents as high as 3 – 4 %w/w are appropriate to produce maximum disintegration and dissolution of tablets [10]. Swelling and hydration values of the excipient indicates a good candidate as a disintegrant. As the co-processed novel excipient possesses excellent flow properties and swelling character, it promises to be a good candidate as a directly compressible vehicle for DC of tablets.

Table 2: Physical properties of the co-processed novel excipient

Properties	Result
Bulk Density (g/ml)	0.49
Tapped Density (g/ml)	0.60
Carr's Index (%)	18.33
Hausner's Ratio	1.22
Angle of Repose (°)	25
Flow Rate (g/sec)	5.5
Particle Density (g/ml)	1.11
Moisture Content (%)	9.0
Swelling Index	15.10
Hydration Capacity	5.26

Properties of the powder blend

The physico-chemical properties of the powder blends (Table 3) show a direct proportionality between powder flow and excipient concentration. There was a general improvement in the flow properties of the blends with increasing excipient concentration. There is increase in As the flow rate and bulk densities increased the angle of repose, tapped densities, Carr's index and the Hausner's ratio decreased with increase in the concentrations of the novel excipients. This is consistent with the formation of larger granules as the concentration of excipient increased leading to larger voids in between the larger granules. This increase in particle sizes would also lead to decrease in surface free energy of the powder particles and decrease in frictional forces between the particles leading to faster flow [11]. The moisture loss of all the powder blends was between 3 – 4 %, which met the BP [12] specification that not more than 15 % of the granule weight should be lost on drying.

Tablet properties

Table 4 shows some physicochemical parameters of the paracetamol tablets formulated. The weight uniformity test on the tablets indicated no significant differences ($p>0.05$) in the weights of tablets from the various batches and hence conformed to the British Pharmacopoeia [13] specification, i.e., that not more than two of the individual weights should deviate from the average weight by more than ±5 %

Table 3: Some physicochemical properties of the powder mix

Batch	Bulk Density (g/L)	Tapped Density (g/L)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (°)	Flow Rate (g/sec)	Moisture Content (%)
1:1	0.42	0.51	17.64	1.21	36	3.68	4
1:2	0.44	0.50	12.00	1.14	33	3.85	4
1:3	0.45	0.49	8.16	1.09	30	4.33	3
1:4	0.45	0.48	6.25	1.07	28	4.52	3

Table 4: Some physicochemical characteristics of the paracetamol tablet

Batch	Tablet Weight* (g)	Tablet Dimensions (mm)		Tablet Hardness* (KgF)	Friability (%)	Disintegration Time* (min)	Moisture Sorption (%)	Content of Active (%)
		Diameter*	Thickness*					
1:1	0.65 (0.02)	12.34 (0.03)	4.14 (0.09)	4.88 (0.57)	1.7	4.30 (1.26)	11.05	99
1:2	0.64 (0.01)	12.28 (0.01)	4.32 (0.14)	4.16 (0.32)	1.3	5.29 (1.32)	16.42	98
1:3	0.64 (0.01)	12.31 (0.03)	4.41 (0.09)	4.12 (1.40)	0.9	6.10 (0.83)	18.33	99
1:4	0.65 (0.01)	12.30 (0.02)	4.42 (0.03)	3.47 (1.43)	0.6	7.55 (1.31)	21.40	101

**Standard deviation in parenthesis*

and none should deviate by more than ±10 %. Also, there were no significant differences amongst the tablet dimensions but there were amongst the tablet hardness friability. These differences could be attributed to the different amounts of the novel excipients used since no binder was used in the formulation. All the tablets from all the batches gave average hardness values between 3.47 – 4.88 KgF since hardness values greater than or equal to 4 KgF are is considered to be the minimum for a satisfactory tablet. [14]

The friability values of the tablets increased with decreasing concentrations of the disintegrant (Table 4). However, only tablets of two batches (1:3 and 1:4) met the BP specification of a maximum loss of 1 % of the mass of the tablets tested (BP, 1980) or a 0.8 – 1.0 % loss in weight of the tested tablets without capping, lamination or breaking up in the course of the test [15].

All the formulated tablets disintegrated within 15 minutes (Table 4) as specified by BP [16] for uncoated tablets, but the results showed an increase in the disintegration time with increase in the novel excipient concentration. Moisture sorption, one of the indices for understanding the capacity of a tablet to swell and disintegrate in the presence of water were found to increase with increasing concentration of the novel excipients.

The content of active drug in all the tablets were within the range prescribed by the pharmacopeia [16], that is, not less than 90.0 % and not more than 110.0 % of the labelled content.

The co-processed novel excipient exhibited excellent flow properties with a high moisture content and good swelling index. The powder mix also showed good flow properties that were proportional to the concentration of the excipient. Tablets were of good quality with regard to weight, hardness, drug content and disintegration time except friability where two batches failed the official specification.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authorship

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. MAI conceived and designed the study, SOE supervised the laboratory works, collection and analysis of data and write the manuscript, COD carried out the laboratory work, MUU co-supervised the laboratory works and analysis of data and participated in the manuscript writing. All authors read and approved the manuscript for publication.

References

1. Bolhuis, G.K., Chowhan, B.G. Materials for direct compression, In: Alderborn, G. and Nystrom, C. (eds), Pharmaceutical powder compaction technology. Marcel Dekker Inc. New York; 1996. pp. 419-500.
2. Armstrong, N.A. Tablet manufacture, In: James, Swarbrick and James, C. Boylan (eds), Encyclopedia of pharmaceutical technology, 2nd ed., Vol.3; Marcel Dekker Inc., New York; 2002. pp. 2713-2732.
3. Robertson, M.I. Regulatory issues with excipients. Int J Pharm 1999;187:273-276.
4. Avachat, A., Ahire, V.J. Characterization and evaluation of spray dried co-processed excipient and their application in solid dosage formulations. Ind J Pharm Sci 2007;69(1):647-668.
5. Moreton, R.C. Tablet excipients to year 2001: A look into the crystal ball. Drug Dev Ind Pharm 1996;22(1):11-23.
6. Gohel, M.C., Jogani, P.D. Functionality testing of a multifunctional directly compressible adjuvant containing lactose, polyvinylpyrrolidone, and cross carmellose sodium. Pharm Technol 2002;25:64-82.
7. Bansal, A.K., Nachaegari, S.K. Co-processed excipients for solid dosage forms. Pharm Technol 2004;28:52-64.
8. Newmann, B.S. The flow properties of powder. In: Bean, H.S., Beckett, A.H., Carless, J.E. (eds.), Advances in pharmaceutical sciences. Academic press, London; 1967. pp. 181-221.
9. Olayemi, O.J., Oyi, A.R., Allagh, T.S. Comparative evaluation of maize, rice and wheat starch powders as pharmaceutical excipients. Nig J Pharm Sci 2008;7:154-161.
10. Pilpel, N., Otuyemi, S.O., Kurup, T.R. Factors affecting the disintegration and dissolution of chloroquine phosphate starch tablets. J Pharm Pharmacol 1978;30:214-219.
11. Iwuagwu, M.A., Nwaoshai, C.A., Iseghohi, F.E. Investigations into the binding and disintegrants properties of starches from selected dioscoreaceae plants. Nig J Pharm Sci 1986;2:10-22.
12. British Pharmacopoeia Vol. I and II, Her Majesty's Stationery Office, London; 1980. p. A273.
13. British Pharmacopoeia Vol. I and 11. The Pharmaceutical Press, Her Majesty's Stationer Office, London; 2003. pp. 249-252.

14. Rudnic, E.D., Schwartz, J.D. Oral solid dosage forms. In: Alfonso, R. Gennaro (ed.), Remington: The science and practice of pharmacy, 20th ed., Lippincot Williams and Wilkins Inc., Philadelphia; 2000. pp. 858-893.
15. Ofoefule, S.I., Orisakwe, O.E., Ibezim, E.C., Esimone, C.O. Mechanism of nifedipine release from sustained release tablets with some polymeric materials. Boll Chim Farmae 1998;37:223-227.
16. British Pharmacopoeia Volume I & II. British Pharmacopoeia Commission. The Stationery Office Limited, London; 2007: 249-267.