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The Use of Nata de Coco Derived Bacterial Cellulose as a Potential Excipient for Directly Compressed Tablets

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ABSTRACT:

Introduction: Nata de coco is produced through the fermentation of coconut water using Acetobacter xylinum bacteria. Nata de coco is chemically high in fiber, consisting of bacteria-derived cellulose. Bacterial celluloses present a number of unique physical properties compared to plant celluloses including a relatively high purity and crystallinity, with mechanical strength. These properties lend Nata de coco to be extremely amenable to research.

Methods and Results: The current study attempts to assess the suitability of Nata de Coco derived bacterial cellulose in direct compression tablet formulation. Nata de coco, at various states of hydration, defined here as 0%, 'low' and 'high', achieved by both oven-drying and freeze-drying is incorporated into a low-dose loratadine powder blend for direct compression into tablets. The dissolution profile of these novel tablets was evaluated for release properties. The resulting tablets reveal freeze-drying, compared with oven-drying, markedly improve the properties of Nata de Coco for inclusion in a tablet formulation, producing tablets with improved disintegration times and dissolution profiles and retaining physical stability. Ovendried Nata de Coco, resulting in physically weaker tablets, with poor friability and hardness. The upper limit for water-content in both cases, similar to HPMC, appears to be 11%.

Conclusions: Freeze-dried Nata de Coco, therefore presents considerable promise for use as a tablet excipient to produce a rapid-release formulation.

Keywords: Nata de Coco; Acetobacter xylinum; Direct compression; Disintegration; Dissolution

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1. Introduction

Nata is white gelatinous bacterial cellulose produced by *Acetobacter aceti* ssp. *xylinum* through the fermentation of fruit juices or plant extracts [1]. Nata de coco is produced from the fermentation of coconut water [2] and has become popular in Southeast Asian countries because of its distinct textural properties and high fiber content [3]. From its initial industrial production in 1996, Nata de coco has been used as a food ingredient in China. For instance, diced Nata is added into milk products to enhance taste and texture. It has also been used in puddings, drinks, and meat products. Bacterial celluloses present a number of unique physical properties compared with plant celluloses including a relatively high purity and crystallinity, mechanical strength, a considerable capacity to absorb water as well as being non-toxic and biodegradable [3-6]. These properties lend Nata de coco to be extremely amenable to research [7] and have resulted in its evaluation for potential development and use as an ingredient not only within the food industry, but also in audio technology [8], as an artificial skin [9], for membrane separation [10], the paper industry [11], and materials for biomedical purposes [12]. The processing properties and the functional characteristics of Nata de coco have been firmly characterized [13], however little is known of its processing properties in a dehydrated state. The moisture in Nata de coco is reported to be more than 99.1% [14]. 0.3% of which is bound water and 98.8% free water. As a consequence of this large free water content, dehydrated Nata de coco can be easily rehydrated almost back to its original state. However, experiments have shown that completely dehydrated Nata de coco (0% moisture), cannot be reconstituted. It can also be

rehydrated to its initial state when the moisture content within the dehydrated samples remains above 8% [15]. Data for dehydration levels above 0.3% and below 8% are not available. The use of HPMC for example within tablet formulation has indicated that variation in HPMC moisture content over the range 2.25–10.85% has no significant effects on drug release profiles [16]. The current study considers the potential of Nata de Coco derived bacterial cellulose as a potential tablet excipient, the effects of drying method and moisture content on the processability of Nata de coco, together with dissolution profiles, disintegration and physical strength of the resulting tablets.

2. Materials *&* Methods

Nata de Coco derived bacterial cellulose was produced by drying (oven-drying and freeze-drying) Nata de Coco, to produce fibers with 0%, 'low' and 'high' water-content. 5kg of Commercially available Nata de Coco, in the form of gelatinous cubes, was washed and soaked multiple times in distilled water for a period of 2-weeks until a stable, near-neutral pH was achieved (pH 5-7). This was then blended to form a uniform, clear white gelatinous mass which was then spread evenly in a drying tray in preparation for oven or freeze-drying. Oven drying was achieved in a commercial oven, with the temperature set to a relatively low 55C. Although this considerably slowed down the drying process, it ensured no burning of the resulting bacterial cellulose. Three batches of 5kg Nata de Coco were prepared, and dehydrated down to 0%, 'low' and 'high' water-content. In a similar fashion, three batches of 5kg Nata de Coco were prepared by freeze-drying. Loratadine was chosen as a drug model since it is a low dose drug, only 10 mg per tablet, as the focus of the formulation was less on the drugs direct compression properties and more on the effects of using Nata de Coco derived bacterial cellulose on overall tablet physical stability and efficacy. An outline of the formulation for directly compressed tablets using both oven-dried and freeze-dried Nata de Coco, at each of the three levels of dehydration are indicated in Table 1.

Table 1. Summary of tablet formulation using dehydrated Nata de Coco derived bacterial cellulose.

	F1	F2	F3	F4
Loratadine 2%	10mg	10mg	10mg	10mg
Microcrystalline cellulose	Fixed percentage			
Magnesium Stearate	Fixed percentage			
Nata de Coco %	0	Increasing levels of Nata de Coco		
Lactose				
Tablet weight	500mg	500mg	500mg	500mg

A total of 22 different batches were produced, with batch F1, containing no Nata de Coco, sharing a common formulation at each water-content level since this was used as a control. Each tablet batched was mixed and subjected to direct compression, and if appropriate tablets' properties were evaluated for friability and hardness, uniformity of dose, disintegration time, and dissolution.

3. Results

The use of 0% and low water-content level Nata de Coco, oven-dried and freeze-dried resulted in the formation of tablets, albeit at a different levels of physical stability. In general, using freeze-dried Nata de Coco produced better, more physically stable tablets. The use of high water-content dehydrated Nata de Coco however either freeze-dried or oven-dried, we were unable to produce viable tablets. The higher water-content levels produced a mixture difficult to mix and compress. At the 0% water-content level, oven-dried Nata de Coco produced particles with relatively large particle size. Comminution proved successful to a point, however particles were generally larger compared to those obtained by freeze-drying, which was flat and oval in shape, with better flowability. Looking closely at 0% oven-dried Nata de Coco, direct compression tableting proved successful at all three levels of Nata de Coco content, going from F2 to F4 (Table 1). However, the resulting tablet quality dropped significantly in terms of both hardness and friability. Friability went from 1.31% loss in mass after tumbling in the F1 formulation without Nata de Coco, to 24.46% to 27.66% loss, going from F2 to F4, with increasing Nata de Coco content (Table 2). This trend was also revealed in tablet hardness, which almost halved going from F1 to F2, with a continued reduction in tablet strength with increasing Nata de Coco. This clearly indicates a disruption in the ability of particles within the formulation mixtures to adhere and cohere. This reduction in tablet strength is also reflected in the disintegration times, which go from 339s for formulation F1 to 58s for formulation F4 (Table 3). Though a reduction in disintegration time is looked upon favorably in tablet formulation, the current trend also points towards a decline in the tablet integrity and physical stability. The presence of Nata de Coco also appears to exert a positive effect on the dissolution profile of the tablets, with an increasing rate of dissolution, culminating in formulation F4 exhibiting a markedly increased dissolution time (Fig. 1). However, similarly to disintegration, this positive improvement in dissolution is marred by the significant reduction in the physical stability of the resulting tablets.

Table 2. Summary physical tests carried out on tablets produced using oven-dried Nata de Coco derived bacterial cellulose with 0% water-content.

Sample	Initial Weight 10 tablets / g	Final Weight 10 tablets / g	Friability %	Average Hardness / N
F1	10.62	10.48	1.03	59.61
F2	10.19	7.75	24.46	27.92
F3	9.94	7.68	22.73	25.13
F4	9.87	7.14	27.66	18.29

Table 3. Disintegration (BP) times for tablets produced using oven-dried and freeze-dried Nata de Coco derived bacterial cellulose at 0% and low water-content. Together with Loratadine tablets BP.

Sample/Disintegration Time / minutes	Oven dried 0% humidity	Oven dried 5% humidity	Freeze dried 0% humidity	Freeze dried 5% humidity
F1	5 minutes 39 s	6 minutes 42 s	5 minutes 10 s	6 minutes 16 s
F2	2 minutes 21 s	3 minutes 21 s	1 minutes 55 s	2 minutes 55 s
F3	1 minutes 45 s	2 minutes 45 s	1 minutes 28 s	2 minutes 28 s
F4	58 s	N/A	1 minutes 2 s	3 minutes 2 s
Loratadine Tablets BP	4 minutes 23 s			

Table 4. Summary physical tests carried out on tablets produced using oven-dried Nata de Coco derived bacterial cellulose with low water-content.

Sample	Initial Weight 10 tablets / g	Final Weight 10 tablets / g	Friability %	Average Hardness / N
F1	10.55	10.42	1.02	60.33
F2	10.26	10.08	1.75	47.93
F3	9.84	9.58	2.64	38.73
F4	N/A	N/A	N/A	N/A

Formulation F4, produced using low water-content level oven-dried Nata de Coco, proved unviable. The higher concentration of Nata de Coco within this system produced a sticky formulation that was difficult to process, had poor flow properties and was almost impossible to compress due to blockages within the tableting machine resulting from the adherence of the tableting mixture. Formulation F2 and F3 at this water-content level however, produced tablets with an improved dissolution profile and disintegration time relative to formulation F1 (Fig. 2). Crucially, the tablets demonstrated considerably better physical stability compared with the 0% oven-dried batch (Table 4). A complete lack of moisture possibly serves to retard the attractive forces between particles within the powder mixture, producing weaker tablets. Although hardness and friability did show a slight decline compared with formulation F1, the decline was far less than that exhibited with the 0% oven-dried batch.

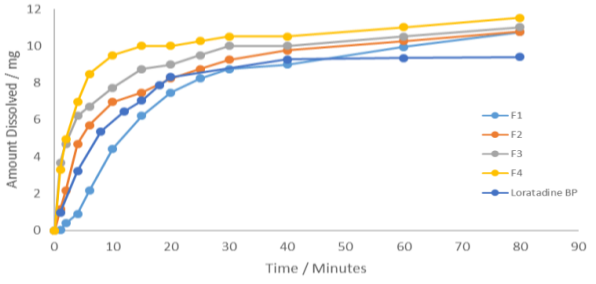

Figure 1. Dissolution testing of oven-dried Nata de Coco derived bacterial cellulose with 0% water-content, together with Loratadine tablets BP.

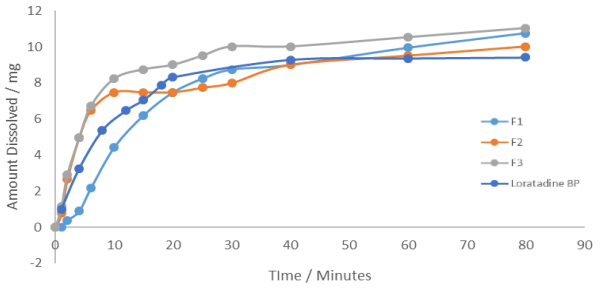

Figure 2. Dissolution testing of oven-dried Nata de Coco derived bacterial cellulose with low water-content together with Loratadine tablets BP.

The use of high water-content oven-dried Nata de Coco produced a batch that was difficult to mix, and ultimately proved unable to directly compress into tablets. The moisture content of the bacterial cellulose resulted in mixtures (F2, F3 and F4) that were sticky, with poor flowability that adhered to the tableting machine's die walls. Interestingly, the use of 0% water-content level freeze-dried Nata de Coco resulted in better tablet properties compared with the oven-dried cellulose at the same water-content level (Table 3), resulting in successful incorporation into the tablet formulation. Even at the highest concentration of Nata de Coco the freeze-dried mixture (F4) was relatively easier to process and had good flow properties and was also easier to compress. The resulting bacterial cellulose fibers from freeze-drying appeared to be less dense, almost sponge-like in appearance, which underwent comminution with ease, resulting in smaller, spherical fiber particles compared to the larger, flat, oval-shaped particles produced after oven-drying.

Table 5. Summary of physical tests carried out on tablets produced using freeze-dried Nata de Coco derived bacterial cellulose with 0% water-content.

Sample	Initial Weight 10 tablets / g	Final Weight 10 tablets / g	Friability %	Average Hardness / N
F1	9.5103	9.3993	1.07	59.34
F2	9.8283	9.1874	6.52	31.32
F3	9.7592	8.8978	8.83	29.19
F4	9.6993	8.9462	7.75	21.42

Directly comparing the 0% oven-dried and 0% freeze-dried batches (Table 3), the latter exhibited much better physical stability at all formulation water-content levels, F2, F3 and F4, with less significant changes in friability and hardness.

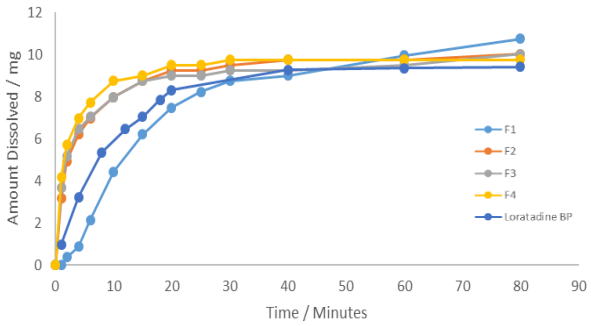

Figure 3. Dissolution testing of freeze-dried Nata de Coco derived bacterial cellulose with low water-content, together with Loratadine tablets BP.

Interestingly, the dissolution profiles and disintegration times for this freeze-dried batch (Fig 3) showed marked improvement compared with the standard formulation F1, and the oven-dried formulations (Fig. 1). This is a critical difference between the oven-dried and freeze-dried systems, where an improvement in dissolution and disintegration is not marred by significantly lower tablet physical stability. On a separate note, formulation F1, without Nata de Coco exhibited similar disintegration (table 3) and dissolution (figures 1-4) profiles to store-bought Loratadine BP tablets. In general, the use of freeze-dried Nata de Coco with low water-content produced a mixture with very good processing properties, resulting in successful incorporation into all three tablet formulations, including formulation F4, with 10% Nata de Coco content, unlike its oven-dried counterpart. Even at this higher proportion of Nata de Coco, the mixture was relatively easier to process, compared with the low water-content level oven-dried Nata de Coco, with better flow properties and was easier to compress. However, in a similar fashion to high water-content oven-dried Nata de Coco, the high water-content freeze-dried bacterial cellulose mixtures (F2, F3 and F4) proved to be very difficult to formulate, and we were unable to produce viable tablets at this level of dehydration due to poor processing ability of the mixtures. It does appear therefore; the presence of Nata de Coco derived bacterial cellulose plays a role in modifying the nature of particulate interactions within a powder mixture. The nature of this modification, either a simple disruption of cohesive forces or a complicated interplay between Nata de Coco, other tablet excipients and API, will need further investigation. The presence or absence of water-content is complicated by the use of oven or freeze-drying, as 0% freeze-dried Nata de coco produced tables with different properties to those produced to that which is 0% oven-dried. Within the current study however, the use of a low dose API served to minimize the effect of the drug on the mixture's flowability and compressibility. It is clear that oven-drying and freeze-drying both exert important and unique effects on Nata de Coco derived bacterial cellulose. Oven-dried Nata de Coco consistently produced softer tablets, which did not withstand the rigors of testing and handling. Freeze-dried Nata de Coco appears to have a much less disruptive effect on tablet hardness and friability, yet still has positive effects on disintegration and dissolution times. This paves the way for an easy to formulate, fast-acting, tablet formulation produced by using cheap, natural and readily available excipients.

Table 6. Summary of physical tests carried out on tablets produced using freeze-dried Nata de Coco derived bacterial cellulose with low water-content.

Sample	Initial Weight 10 tablets / g	Final Weight 10 tablets / g	Friability %	Average Hardness / N
F1	9.3003	9.1927	1.05	59.43
F2	9.7981	9.6847	1.16	41.66
F3	9.3951	9.2988	1.03	39.49
F4	9.4880	9.3560	1.40	31.11

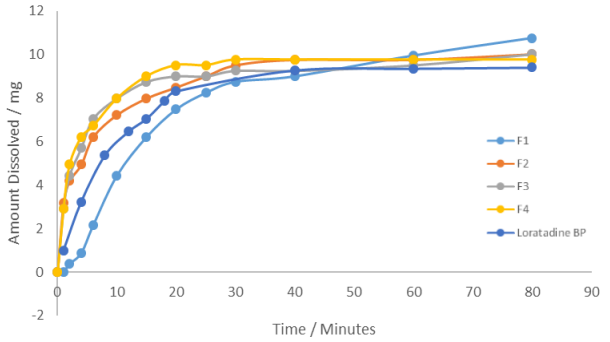

Figure 4. Dissolution testing of freeze-dried Nata de Coco derived bacterial cellulose with low water-content, together with Loratadine tablets BP.

4. Discussion and Conclusion

The presence of Nata de Coco derived cellulose within a tablet formulation appears to improve the dissolution profile and disintegration time. For Nata de Coco that has been dehydrated in an oven, this improvement is unfortunately accompanied by a significant loss in physical stability, possibly attributed to a weaker tablet compared with the Nata de Coco free formulation (F1), due to changes in the compatibility of the mixture. However, tablet formulations containing freeze-dried Nata de Coco with 'low' water-content levels, appear to possess improved dissolution and disintegration times,

with acceptable levels of tablet physical stability. Further testing is required to evaluate and optimize this apparent improvement in disintegration time and dissolution profile, and to find the optimum amount of freeze-dried Nata de Coco that can be incorporated into each tablet before tablet integrity is compromised. In general, the use of Nata de Coco appears to hold considerable promise as a tablet excipient to produce a rapid-release formulation.

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Conflict of interest

There is no conflict of interest.

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