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Formulation and Evaluation of Fast-Disintegrating Paracetamol (500 mg) Tablets Using Maize Starch and Croscarmellose Sodium as Disintegrants

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Abstract: Background: The physicochemical properties of granules and the performance of compressed tablets are influenced by the type and proportion of excipients used in their formulation. This study evaluated the effects of varying proportions of maize starch and croscarmellose sodium on the flow properties of granules and the physicochemical characteristics of fast-disintegrating paracetamol (500 mg) tablets prepared by wet granulation. Methods: Five batches of paracetamol granules and tablets were prepared using wet granulation, with 10% w/v hydroxypropyl methylcellulose (HPMC) mucilage as the binder. Batch A contained maize starch alone, while Batch B contained croscarmellose sodium alone. Batches C, D, and E contained maize starch and croscarmellose sodium at ratios of 75:25, 50:50, and 25:75, respectively. Pre-compression parameters assessed included bulk density, tapped density, Carr's compressibility index, Hausner's ratio, angle of repose, and flow rate. Post-compression evaluation comprised weight uniformity, tablet hardness, friability, and disintegration time. Data were analysed using one-way analysis of variance (ANOVA), with statistical significance set at $P < 0.05$. Results: Batch E exhibited the highest bulk and tapped densities (0.51 and 0.58 g/mL, respectively). Batch A demonstrated the most favourable Hausner's ratio (1.07) and Carr's compressibility index (6.5%), whereas Batch C exhibited the least favourable values (1.26 and 20.69%, respectively). Batch B recorded the lowest angle of repose (30.02°) and the highest flow rate (22 g/s). Tablet hardness ranged from 5.2 kgf in Batch A to 6.6 kgf in Batches B and C. All batches exhibited friability below 1%, with Batch D recording the lowest value (0.458%). Weight uniformity was acceptable across all batches, and Batch D had the lowest relative standard deviation (0.222%). Disintegration time differed significantly among the batches ($P < 0.001$), ranging from 102.67 ± 9.60 s in Batch A to 1,558.67 ± 356.47 s in Batch C. Batches D and E recorded disintegration times of 1,220 ± 0 s and 997.33 ± 57.15 s, respectively. Conclusion: Maize starch alone produced the most favourable granule flow characteristics and the shortest tablet disintegration time, whereas croscarmellose sodium alone was associated with greater tablet hardness and improved flow rate. Although the 50:50 blend (Batch D) demonstrated the lowest friability and the most consistent tablet weights, its prolonged disintegration time limits its suitability as an optimised fast-disintegrating formulation. Further optimisation of the disintegrant proportions and formulation parameters is therefore necessary to achieve a balance between mechanical strength, flow properties, and rapid **disintegration.**
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1. Introduction

The formulation of fast-disintegrating tablets (FDTs) using the wet granulation method has attracted increasing research interest because of the growing demand for immediate-release dosage forms, particularly for pain and fever management (Sharma et al., 2020). FDTs disintegrate rapidly in the oral cavity without the need for water, offering a convenient route of administration for patients with dysphagia, including paediatric and geriatric populations who often struggle to swallow conventional tablets (Sharma et al., 2020). Paracetamol (acetaminophen), one of the most widely used over-the-counter analgesics and antipyretics, is

well suited to this dosage form because rapid disintegration translates into a faster onset of therapeutic action (Jóźwiak-Bebenista & Nowak, 2020).

Globally, chronic and acute pain conditions affect approximately 1.5 billion people and contribute substantially to disability (International Association for the Study of Pain, 2021). In Sub-Saharan Africa, this burden is compounded by the high prevalence of febrile and infectious illnesses such as malaria, alongside limited access to healthcare professionals in rural settings (WHO, 2022; Bigna et al., 2020). Over-the-counter analgesics such as paracetamol remain the mainstay of pain management in these settings, yet difficulties with swallowing conventional tablets continue to limit patient compliance, particularly among children, the elderly and bedridden patients (Angibaud et al., 2024). Fast-disintegrating formulations of paracetamol therefore represent a practical strategy for improving access to rapid symptomatic relief.

Wet granulation remains one of the most widely used methods of tablet formulation because it improves the flow, compressibility and uniformity of powder blends prior to compression (Chen et al., 2022). During wet granulation, a liquid binder is used to agglomerate powder particles into granules, which are subsequently dried, sized and compressed. The choice and concentration of disintegrant used in this process critically determines the balance between the mechanical strength of the resulting tablet and its disintegration time (Sharma et al., 2020). Maize starch is a traditional disintegrant that swells on contact with water and promotes rapid tablet breakup, whereas croscarmellose sodium is a cross-linked cellulose-derived superdisintegrant known for its strong swelling and wicking action and its contribution to tablet cohesiveness (Goel et al., 2021).

Despite extensive literature on individual disintegrants, relatively few studies have systematically compared blends of a conventional disintegrant (maize starch) with a superdisintegrant (croscarmellose sodium) across a full range of mixing ratios within a single formulation matrix. Understanding how these two materials interact when combined in varying proportions is important for guiding rational formulation design, particularly because higher binder or disintegrant loads that improve mechanical strength may simultaneously delay disintegration (Sharma et al., 2020).

This study therefore aimed to formulate fast-disintegrating paracetamol (500 mg) tablets by wet granulation and to evaluate the effect of varying maize starch-to-croscarmellose sodium ratios on the pre-compression properties of the granules (bulk and tapped density, Carr's compressibility index, Hausner's ratio, flow rate and angle of repose) and on the post-compression properties of the resulting tablets (uniformity of weight, hardness, friability and disintegration time). The specific objectives were: (i) to compare the flowability and compressibility of granules prepared with maize starch alone, croscarmellose sodium alone, and combinations of the two at ratios of 75:25, 50:50 and 25:75; and (ii) to assess the post-compression quality attributes of the resulting tablets in order to identify a formulation that balances rapid disintegration with adequate mechanical strength.

2. Materials and Methods

2.1 Materials

Paracetamol powder, croscarmellose sodium, maize starch BP, talc, lactose and magnesium stearate were obtained from Edo Pharmaceuticals (Benin City, Nigeria) and used as supplied without further purification. Hydroxypropyl methylcellulose (HPMC) was used as a 10% w/v binder mucilage. British Standard sieves (Gallenkamp, UK) of aperture 1.00 mm and 1.25 mm were used for granulation. Equipment used included a hot air oven (Gallenkamp, UK), a 12-punch tableting machine (F-3 Manesty Machines, UK), a Monsanto hardness tester (Monsanto, UK), a Roche-type friabilator (Roche B&T, Germany), a disintegration tester (B&T DC-01, UK), and an analytical weighing balance (Electric Balance TIANFU-DT-1000, China).

2.2 Preparation of Paracetamol Granules

Five batches (A–E) of paracetamol granules were prepared by wet granulation, varying the ratio of maize starch to croscarmellose sodium as shown in Table 1. Batch A contained maize starch alone (100%, control), Batch B contained croscarmellose sodium alone (100%, control), and Batches C, D and E contained maize starch and croscarmellose sodium in ratios of 75:25, 50:50 and 25:75, respectively. For each batch, the required quantities of paracetamol powder and lactose, sufficient to produce 200 tablets, were dry-mixed in a mortar and pestle for 5 minutes. Half of the required quantity of disintegrant (10% w/w maize starch BP or croscarmellose sodium, as applicable) was incorporated intragranularly in geometric proportions during trituration. A sufficient quantity of 10% w/v HPMC binder mucilage was then added gradually to form a coherent wet mass, which was passed through a 1.25 mm sieve. The resulting granules were dried at 60 °C for 1 hour in a hot air oven, re-screened through a 1.00 mm sieve, and dried again at 60 °C for 30 minutes. The previously weighed glidant (talc) and lubricant (magnesium stearate) were

then blended with the dry granules in geometric proportions, and the finished granules were stored in airtight containers prior to analysis and compression.

Table 1: Formula for the preparation of paracetamol granules (mg per tablet)

Batch (Maize Starch : Croscarmellose Sodium)	Paracetamol	Croscarmellose Sodium	Lactose	Talc & Mg Stearate (10% w/w)	Maize Starch BP (10% w/w)	HPMC (10% w/v)	Total
A (100:0)	500	–	40	10	50	q.s.	610
B (0:100)	500	20	70	10	–	q.s.	610
C (75:25)	500	5	47.6	10	37.5	q.s.	610
D (50:50)	500	10	55	10	25	q.s.	610
E (25:75)	500	15	62.5	10	12.5	q.s.	610

2.3 Evaluation of Granule Flow Properties

Pre-compression properties of the granules were determined in triplicate using standard procedures, as described. Bulk and tapped density: Approximately 30 g of granules was gently poured into a 100 mL graduated cylinder, and the occupied volume was recorded as the bulk volume. The cylinder was then tapped 100 times on a flat surface until no further volume reduction occurred, and the resulting volume was recorded as the tapped volume. Bulk density and tapped density were calculated as the ratio of granule weight to bulk volume and tapped volume, respectively.

Carr's compressibility index (CCI) was calculated as: CCI (%) = [(Tapped density − Bulk density) / Tapped density] × 100. Hausner's ratio (HR) was calculated as the ratio of tapped density to bulk density (HR = Tapped density / Bulk density). Flow rate was determined using an Erweka flow tester (Model GT, GmbH, Germany). Fifty grams of granules were allowed to flow through the orifice of the apparatus, and the time taken was recorded in triplicate. Angle of repose was determined by the fixed-funnel (hollow tube) method. Granules were allowed to flow freely from a tube onto a flat circular surface, and the angle of repose (θ) was calculated from the height (h) and radius (r) of the resulting powder cone as $\theta = \tan^{-1}(h/r)$.

2.4 Compression of Granules into Tablets

Following granule evaluation, each batch was compressed into tablets using a 12-punch tableting machine (F-3 Manesty Machines, UK) at a compression pressure of 25.5 N, with the die volume adjusted to give a target tablet weight of approximately 660 mg. Each batch yielded approximately 100 tablets, which were stored in airtight containers in a desiccator pending further evaluation.

2.5 Evaluation of Tablet Properties

Uniformity of weight: Twenty tablets from each batch were selected at random and weighed individually using an analytical balance. The mean weight and standard deviation were determined and compared with British Pharmacopoeia limits for tablets weighing 250 mg or more, which permit not more than two tablets to deviate from the mean by more than ±5%, and none by more than twice that value (British Pharmacopoeia, 2012).

2.5.1 Hardness: The crushing strength of ten tablets from each batch was determined using a Monsanto hardness tester. A mean crushing strength of 4–8 kg/F is considered acceptable for uncoated tablets (British Pharmacopoeia, 2012).

2.5.2 Friability: Ten pre-weighed tablets from each batch were placed in the drum of a friability tester and rotated at 25 rpm for 4 minutes. The tablets were then de-dusted and reweighed, and percentage weight loss was calculated as [(Initial weight − Final weight) / Initial weight] × 100. Determinations were performed in triplicate.

2.5.3 Disintegration time: The disintegration test was carried out in accordance with the British Pharmacopoeia (2003) method using a B & T DC-01 disintegration apparatus. Six tablets from each batch were placed in the Perspex tubes of the apparatus basket, which was immersed in 800 mL of distilled water maintained at 37 ± 0.5 °C. The time taken for each tablet to disintegrate sufficiently to pass through the apparatus screen was recorded, and the mean

disintegration time for each batch was calculated. According to the European Pharmacopoeia, an orodispersible tablet is one that disintegrates within 3 minutes in the mouth prior to swallowing.

2.6 Statistical Analysis

Results were expressed as mean ± standard deviation (SD), with relative standard deviation (RSD) calculated as (SD/Mean) × 100. Comparisons among the five batches for weight uniformity and disintegration time were performed using one-way analysis of variance (ANOVA), with statistical significance set at $P < 0.05$. Statistical analyses were performed using GraphPad InStat version 3.10.

3. Results

3.1 Pre-Compression Properties of Granules

The bulk and tapped densities, Hausner's ratio, angle of repose and flow rate of granules from the five batches are presented in Table 2. Bulk density ranged from 0.43 g/mL (Batch A) to 0.51 g/mL (Batch E), while tapped density ranged from 0.46 g/mL (Batch A) to 0.58 g/mL (Batches C and E). Batch A, formulated with maize starch alone, displayed the most favourable Hausner's ratio (1.07), consistent with good flow, whereas Batch C (maize starch:croscarmellose sodium, 75:25) displayed the highest Hausner's ratio (1.26), indicating the poorest flow among the batches. The angle of repose was lowest, and therefore most favourable, for Batch B (30.02°), while Batch A recorded the highest angle of repose (34.64°). Flow rate measurements showed that Batch B granules flowed fastest (22 s for 50 g), while Batch D granules required the longest time to flow (63 s).

Table 2: Pre-compression granule analysis

Parameter	Batch A	Batch B	Batch C	Batch D	Batch E
Bulk volume (mL)	70	53	50	53	45
Tapped volume (mL)	65	45	40	47	40
Weight (g)	30	24	23	27	23
Tapped density (g/mL)	0.46	0.53	0.58	0.57	0.58
Bulk density (g/mL)	0.43	0.45	0.46	0.50	0.51
Angle of repose (°)	34.64	30.02	30.47	33.69	30.47
Hausner's ratio	1.07	1.17	1.26	1.14	1.14
Flow rate (s/50 g)	43	22	34	63	34

Carr's compressibility index, calculated from the bulk and tapped density data, is presented in Table 3. Batch A exhibited the lowest (most favourable) Carr's index (6.5%), indicative of excellent compressibility, while Batch C showed the highest value (20.69%), indicative of poor compressibility. Batches D and E showed intermediate, broadly similar values (12.28% and 12.07%, respectively), corresponding to fair-to-good compressibility according to standard flowability classifications.

Table 3: Carr's compressibility index of granules

Batch	Carr's Compressibility Index (%)
A	6.5
B	15.09
C	20.69
D	12.28
E	12.07

3.2 Post-Compression Properties of Tablets

Tablet hardness values for ten tablets per batch are shown in Table 4. Mean hardness ranged from 5.2 kg/F (Batch A) to 6.6 kg/F (Batches B and C), with Batches D and E recording mean values of 6.55 kg/F and 6.3 kg/F, respectively. All batches fell within the British Pharmacopoeia-acceptable range of 4–8 kg/F for uncoated tablets.

Table 4: Tablet hardness (kg/F)

Tablet No.	Batch A	Batch B	Batch C	Batch D	Batch E
1	6.5	8.0	5.0	7.0	5.5
2	6.0	6.0	7.0	8.0	6.0
3	4.5	7.0	6.5	8.0	7.5
4	6.0	7.0	9.5	5.0	6.5
5	4.0	5.0	5.0	5.5	6.0
6	5.0	5.5	6.5	5.5	7.0
7	4.0	8.0	7.0	6.0	6.0
8	4.0	7.0	6.0	7.0	5.5
9	6.5	7.0	7.5	5.5	6.5
10	5.5	5.5	6.0	8.0	6.5
Mean	5.2	6.6	6.6	6.55	6.3

Friability results (Table 5) showed that all batches lost less than 1% of their weight after 4 minutes of rotation, satisfying the standard pharmacopoeial requirement. Batch D recorded the lowest friability (0.458%), while Batch C recorded the highest (0.8%).

Table 5: Friability test results

Batch	Initial Weight, V (g)	Final Weight, Y (g)	Friability (%)
A	6.001	5.965	0.6
B	6.114	6.081	0.5
C	6.106	6.059	0.8
D	6.118	6.090	0.458
E	6.129	6.093	0.590

Weight uniformity testing of twenty tablets per batch yielded the mean weights, standard deviations and relative standard deviations summarised in Table 6. All batches met British Pharmacopoeia weight-variation criteria for tablets weighing 250 mg or more. Batch D showed the lowest RSD (0.222%), indicating the most uniform tablet weight, while Batch A showed the highest RSD (0.881%). One-way ANOVA indicated a statistically significant difference among the batch means ($P = 0.014$).

Table 6: Weight uniformity: mean tablet weight, standard deviation and relative standard deviation

Batch	Mean Weight (g) ± SD	RSD (%)
A	0.6092 ± 0.005367	0.881
B	0.6070 ± 0.003403	0.561
C	0.6035 ± 0.002947	0.488
D	0.6100 ± 0.001356	0.222
E	0.6081 ± 0.002929	0.482

One-way ANOVA: $P = 0.014$ (significant at the 5% level).

Disintegration time results (Table 7) showed marked differences among batches ($P < 0.001$). Batch A (maize starch alone) disintegrated fastest, with a mean time of 102.67 ± 9.60 seconds, well within the 3-minute orodispersible benchmark. Batch C (75:25 maize starch:croscarmellose sodium) disintegrated most slowly, with a mean time of 1558.67 ± 356.47 seconds. Batch B disintegrated in 873 ± 0 seconds, Batch D in 1220 ± 0 seconds, and Batch E in 997.33 ± 57.15 seconds.

Table 7: Disintegration time (seconds)

Tablet No.	Batch A	Batch B	Batch C	Batch D	Batch E
1	122	873	1054	1220	934
2	102	873	1146	1220	914
3	98	873	1788	1220	1034
4	98	873	1788	1220	1034
5	98	873	1788	1220	1034
6	98	873	1788	1220	1034

Table 8: Mean disintegration time and ANOVA

Batch	Mean (s) ± SD	RSD (%)
A	102.67 ± 9.60	9.36
B	873 ± 0	0.00
C	1558.67 ± 356.47	22.87
D	1220 ± 0	0.00
E	997.33 ± 57.15	5.73

One-way ANOVA: $P < 0.001$ (significant at the 5% level).

4. Discussion

This study evaluated the influence of varying ratios of maize starch and croscarmellose sodium on the pre- and post-compression properties of fast-disintegrating paracetamol tablets prepared by wet granulation. The bulk and tapped density data indicated that Batch E, formulated with the highest proportion of croscarmellose sodium (25:75 maize starch:croscarmellose sodium), achieved the highest packing densities (0.51 and 0.58 g/mL, respectively), consistent with the known swelling and cohesive character of croscarmellose sodium, which promotes closer particle packing during tapping. By contrast, Batch A, formulated exclusively with maize starch, exhibited comparatively looser packing, while Batch C, containing an intermediate ratio, displayed intermediate density values, illustrating the gradual influence of croscarmellose sodium content on granule packing behaviour.

Hausner's ratio and Carr's compressibility index provided complementary insights into granule flow and compressibility. Batch A displayed the most favourable Hausner's ratio (1.07) and the lowest Carr's index (6.5%), both indicative of excellent flow and compressibility, attributable to the inherent glidant-like properties of maize starch. Batch C, however, displayed the poorest flow (Hausner's ratio 1.26; Carr's index 20.69%), suggesting that the 75:25 maize starch:croscarmellose sodium combination may have produced irregular granule morphology that impeded flow. Batches D and E, containing balanced or croscarmellose sodium-predominant blends, showed intermediate and broadly similar Hausner's ratios (1.14), reflecting moderate flow performance. The angle of repose results was broadly consistent with these findings, with Batch B (croscarmellose sodium alone) recording the lowest angle (30.02°) and therefore the best flow by this measure, while Batch A and Batch D displayed comparatively higher angles. The relatively slow flow rate recorded for Batch D (63 s) further illustrates that granule composition and disintegrant interactions, rather than density alone, govern flow behaviour, and that different flow indices may not always rank batches identically.

With respect to post-compression properties, all batches achieved tablet hardness values within the pharmacopoeial range of 4–8 kg/F. Batches B and C achieved the highest hardness (6.6 kg/F), consistent with the binding contribution of croscarmellose sodium, while Batch A, containing maize starch alone, recorded the lowest hardness (5.2 kg/F), suggesting that maize starch alone provides comparatively weaker interparticulate bonding. Friability results mirrored this pattern only partially: although all batches met the friability criterion of less than 1%, Batch D (50:50 ratio) achieved the lowest friability (0.458%), suggesting that a balanced disintegrant blend may optimise binder-disintegrant interactions

for mechanical robustness, whereas Batch C's relatively higher friability (0.8%) points to a less favourable interaction at the 75:25 ratio despite its high hardness value.

Weight uniformity was acceptable across all batches, with RSD values below 1%, indicating generally consistent granule flow during die filling. Batch D again performed best on this measure (RSD 0.222%), and the ANOVA result ($P = 0.014$) indicated that the observed differences among batch means were statistically significant, likely reflecting subtle differences in granule flow and compression behaviour linked to disintegrant composition.

The disintegration time results were the most pharmaceutically consequential findings of this study. Batch A, containing maize starch alone, disintegrated fastest (102.67 ± 9.60 s), consistent with maize starch's well-documented rapid-swelling disintegrant action and confirming its suitability for immediate-release, fast-disintegrating formulations. Batch C, containing 75% maize starch and only 25% croscarmellose sodium, disintegrated most slowly (1558.67 ± 356.47 s), suggesting that this particular combination may produce a more cohesive granule matrix that resists water penetration despite the presence of maize starch. Batch D (50:50) disintegrated in 1220 ± 0 seconds, intermediate between the extremes, while Batch E (25:75) disintegrated somewhat faster, at 997.33 ± 57.15 seconds, than both Batch C and Batch D, indicating that a higher proportion of croscarmellose sodium relative to maize starch improved disintegration relative to the 75:25 blend, though it remained considerably slower than maize starch alone. Batch B, containing croscarmellose sodium alone at a lower total disintegrant concentration (4% w/w, as opposed to the 10% w/w used for maize starch in Batch A), disintegrated in 873 ± 0 seconds, suggesting that the lower concentration of croscarmellose sodium used in this control may have limited its disintegrant efficacy relative to its performance at higher inclusion levels. The ANOVA result ($P < 0.001$) confirmed that disintegrant type and ratio had a highly significant effect on disintegration time.

Taken together, these findings indicate that maize starch and croscarmellose sodium act through complementary but partially opposing mechanisms: maize starch promotes rapid disintegration but contributes comparatively less to tablet hardness, while croscarmellose sodium enhances hardness and granule packing but, particularly in combination with high proportions of maize starch, can delay disintegration. None of the five batches simultaneously achieved both the fastest disintegration of Batch A and the mechanical robustness of Batches B/C/D, underscoring the trade-off that formulators must navigate when selecting disintegrant systems for fast-disintegrating tablets. Among the blended formulations, Batch D (50:50) offered the most balanced overall profile, combining acceptable hardness (6.55 kg/F), the lowest friability (0.458%) and the best weight uniformity (RSD 0.222%), albeit with a disintegration time (1220 s) considerably longer than the European Pharmacopoeia's 3-minute orodispersible benchmark and longer than that of Batch A.

These results are broadly consistent with prior reports on superdisintegrant performance in fast-disintegrating formulations. For example, optimised formulations incorporating sodium starch glycolate have been shown to achieve rapid and near-complete drug release within 15–20 minutes (Mushtaq et al., 2021), while cetirizine fast-disintegrating tablets formulated with appropriate superdisintegrant concentrations achieved disintegration times of less than 50 seconds (Mhaske et al., 2023). The considerably longer disintegration times observed for several batches in the present study, particularly Batches B–E, suggest that the concentrations and/or combinations of croscarmellose sodium used here may not have been fully optimised for rapid orodispersible performance, and that further work on disintegrant concentration, granule size distribution and compression force is warranted.

This study has some limitations. Dissolution testing, which would provide direct evidence of in vitro drug release and bioavailability implications, was not performed. In addition, the relatively small sample sizes used for hardness, friability and disintegration testing, together with the zero-variance observed for Batches B and D in the disintegration test, suggest that some measurements may benefit from a larger number of replicates in future work. Granule morphology was also not directly characterised, despite its likely contribution to the flow and compressibility differences observed among batches.

5. Conclusion

This study demonstrated that the ratio of maize starch to croscarmellose sodium significantly influences the pre-compression flow properties of granules and the post-compression performance of fast-disintegrating paracetamol tablets prepared by wet granulation. Maize starch alone (Batch A) conferred the best granule flow and compressibility and produced the fastest-disintegrating tablets, while croscarmellose

sodium contributed to improved tablet hardness and granule packing but slowed disintegration, particularly when combined with a high proportion of maize starch (Batch C). A balanced 50:50 ratio of maize starch to croscarmellose sodium (Batch D) provided the most favourable combination of hardness, friability and weight uniformity among the blended formulations, while Batch A remained the only formulation to meet the orodispersible disintegration benchmark of under 3 minutes. These findings provide a basis for the rational selection and combination of disintegrants in the design of fast-disintegrating paracetamol tablets, and highlight the need to balance mechanical strength against disintegration performance according to the intended clinical application.

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