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## Effect of a co-processed excipient on the disintegration and drug release profile of ibuprofen tablets

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### Abstract

Tablets at present, remain the most preferred oral dosage form because of many advantages they offer to formulators as well as physicians and patients. The objective of this work was to determine the effect of co-processing on the disintegration and drug-release profile of ibuprofen tablets prepared from a co-processed excipient. The co-processed excipient (CE) containing lactose, gelatin and mucin in the ratio 90:9:1 was prepared using co-fusion. The excipient was evaluated for its physicochemical properties and then used to formulate tablets with the addition of a disintegrant by direct compression. The tablets were evaluated for their tablet properties and compared with tablets prepared with cellactose- 80<sup>®</sup> (CEL) and spray dried lactose<sup>®</sup> (SDL) and a physical mix (PM) of the co-processed ingredient. Results from evaluation of CE showed that flow rate, angle of repose, Carr's index and Hausner's ratio were 5.28 g/sec, 20.30°, 23.75 % and 1.31, respectively. Tablets prepared with CE had friability (0%), crushing strength (5.25) KgF, disintegration time (3 mins) and T<sub>50%</sub> (2 mins). For CEL, friability (0.4 %), crushing strength (7.25) KgF, disintegration time (1 min) and T<sub>50%</sub> (2 mins); SDL, friability (1.57 %), crushing strength (7.50) KgF, disintegration time (4 mins) and T<sub>50%</sub> (2 mins) and PM, friability (2.38 %), crushing strength (5.00) KgF, disintegration time (1 min) and T<sub>50%</sub> (2 mins). In conclusion, the disintegration time and drug release profile for CE was not superior but compared favorably with CEL, SDL and PM.

**Keywords: co-processing, disintegration, excipients, tablets, release profile.**

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### INTRODUCTION

Drug administration, through the oral route has been very popular for the usage of medicinal agents in managing diseases since it gives room for safety, permits self-medication, ease

of ingestion of drug product, etc. and these enhance patient compliance (Quodbach and Kleinebudde, 2016).The large surface area of the gastrointestinal tract which favors drug

absorption, provides sufficient fluid to facilitate disintegration of the dosage form and dissolution of the drug thereby making the oral route the most appealing route for drug delivery despite the advancements made in the new drug delivery systems (Desai *et al.*, 2016). According to Banker and Anderson, at least 90% of all drugs used to produce systemic effect are administered orally. Currently, controlled release and targeted drug delivery systems seem to be getting much attention within the solid dosage forms, although, solid dosage forms which when ingested, disintegrate to discharge their active pharmaceutical ingredients (API) instantly in the gastrointestinal tract have continued to enjoy much patronage. The tablet disintegration process is very critical for the immediate release dosage forms and consequent upon that, disintegrants are added to tablets to induce break-up when it comes in contact with the fluid (Sastry *et al.*, 2000). A disintegrant is described as an inert substance that is added to a solid dosage formulation such as a tablet or capsule to cause their breakup that will lead to the release and dissolution of the API. They act by increasing the surface area of the tablet and softening the binding agent through swelling which is often accepted as the key mechanism of tablet disintegration. This on its own, enhances the rate of dissolution in the media (Sharma *et al.*, 2019). Currently, starch and cellulose-based materials among others are utilized as disintegrants and could be incorporated intragranularly, extragranularly or by both procedures especially in a wet granulation method of producing tablets (Dave, 2008). Methods of producing uncoated tablets intended for rapid disintegration and release of the API could be wet granulation (WG), dry granulation (DG) or direct compression (DC) methods. The use of the DC method is currently widespread because its mode of application is simple and achievable in the shortest possible time frame. Its utilization enhances a cautious choice of an excipient which should demonstrate impressive flowability and compressibility (Gandhi and Akhtar, 2019). New combinations of existing excipients are interesting option for improving excipient functionality because all formulations contain multiple excipients. A much broader platform for the manipulation of excipient functionality is provided by co-processing or particle engineering of two or more excipients.

Co-processing, which is based on the novel concept of two or more excipients interacting at sub particle level, with an objective of providing a synergy of functionality improvement as well

as masking the undesirable properties of the individual excipients has become a method of interest because the products are in a special way physically modified without losing their chemical structure and stability (Nachaevari and Bansal, 2004). This concept of co-processing of excipients was introduced in late 1980s when microcrystalline cellulose and calcium carbonate were co-processed (Mehra *et al.*, 1988).

Previous studies on co-processing lactose, gelatin and mucin in the formulation of ibuprofen tablets exhibited superior characteristics required for tableting when compared to its parent excipient (lactose monohydrate) and the physical mix but however, failed disintegration as well as dissolution tests due to poor release, therefore, the aim of this research is to prepare a novel pharmaceutical excipient using the simple method of co-processing with the incorporation of a disintegrant (corn starch) and to determine its effect on the release profile of ibuprofen from tablets (Mohammed, 2017).

## **MATERIALS AND METHODS**

### **Materials**

Lactose, Maize starch (BDH Pharmaceuticals, Mumbai, India) Cellactose-80, Spray dried lactose (Ausmasco Chemicals Ltd, Xiamen-Fujia, China) Gelatin (May and Baker Ltd, Dagenham, England) Ibuprofen (Himedia laboratories Ltd, Mumbai, India). All other reagents used were of analytical grade and water was double distilled.

### **Extraction of mucin**

The extraction of mucin has been previously reported by Mohammed and Apeji., (2018) using fresh small intestines of cow obtained from the abattoir (Zango, Kaduna) and dissected starting from the beginning of the jejunum to the ileocaecal sphincter. The intestines sectioned into short lengths was flushed through with chilled saline and the mucosal surface was exposed by longitudinal dissection. Using a microscope slide, the mucus layer was gently scrapped off into the chilled saline. The mucus was precipitated using chilled acetone and dried (lyophilized). The resultant flakes were pulverized using a milling machine and stored in an air-tight container until used.

### **Excipient preparation**

The preparation of excipient has been previously reported in Mohammed and Apeji., (2018). Using the co-fusion method as

described by Adeoye and Alebiowu, 2014, a mix of lactose, gelatin and mucin was carried out in the ratio 90:9:1 by dispersing them in distilled water and heated on a water bath at 40°C for 15 mins following an outcome of a pre-formulation study using the design of experiment (DOE).

### Powder characterization

#### Angle of repose

The static angle of repose  $\theta$  was measured according to the fixed funnel and free-standing cone method (Ohwoavworhwa and Adelokun, 2005). A funnel was clamped with its tip 2cm above a graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the cone thus formed just reached the tip of the funnel. The heights (h) of the powder cones and the mean diameters (D) of the base of powder cones were determined and the tangent of the angle of repose calculated using the equation:

$$\tan \theta = \frac{2h}{D} \dots \dots \dots (i)$$

#### Bulk and tapped densities

A 2.0g quantity each of the powder sample was placed in a 10ml measuring cylinder and the volume, V<sub>0</sub> occupied by each of the samples

without tapping was noted. After 100 taps on the table, the occupied volume V<sub>100</sub> was read. The bulk and tapped densities were calculated as the ratio of the weight to volume (V<sub>0</sub> and V<sub>100</sub> respectively).

### Compressibility Index

$$\text{Compressibility index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100 \dots \dots \dots (ii)$$

### Hausner's ratio

This was calculated as the ratio of tapped density to bulk density of the samples. The same powder parameters evaluated for CE was repeated for the other powder blends and are referred to as formulations I, II, III and IV.

### Tablet formulation

The powders were compressed into tablets using a single punch tableting machine (Erweka GmbH, Langen, Germany) at different compression pressures ranging from 5-7 MT to produce 500 mg tablets. Four different formulations were prepared by direct compression method having a batch size of 60 tablets.

**Table 1: Tablet formula**

Ingredients (mg)	I	II	III	IV
Ibuprofen	200	200	200	200
Excipient	282	282	282	282
Maize starch	15	15	15	15
Magnesium stearate	3	3	3	3
Total	500	500	500	500

Key: I= Co-processed excipient (CE), II = Cellactose-80 (CEL), III = Spray dried lactose (SDL), IV = Physical mix (PM)

### Tablet evaluation

#### Friability

This was determined using a Roche friabilator as described in the USP 32/NF 27 (2009). Ten tablets were weighed (X) and transferred to the friability test apparatus at 25 rpm for 4 min. The tablets were removed, de-dusted and re-weighed (Y).

#### Disintegration test

The assembly (Erweka, Langen, Germany) was suspended in a 1000 mL beaker containing

distilled water. The volume of liquid was taken such that when the assembly was in highest position the wire mesh was at least 25 mm below the surface of the liquid and when the Assembly was in lowest position the wire mesh was at least 25 mm above the bottom of the beaker. One tablet was placed into each of the six tubes. The apparatus was operated with the BP method having the minimum expected time for disintegration as 15 mins, 900 mL of distilled

water and temperature at 37±2 °C. Time for complete disintegration of tablet was noted.

### **In-vitro drug release studies**

The dissolution profiles of Ibuprofen tablets were determined using the USP XXVIII basket method for the various batches of the tablets. A dissolution medium of 900 mL of phosphate buffer pH 7.2 solution for Ibuprofen maintained at (37±0.5) °C with a basket revolution of 50 r/min was used (USP/NF, 2009). A 5 mL volume of leaching fluid was withdrawn at predetermined time intervals (5, 10, 15, 20, 25 min) and replaced with an equivalent volume of the dissolution medium after each withdrawal. The withdrawn samples were filtered and diluted with an equal volume of phosphate buffer pH 7.2 solution. This was continued for 60 min.

The absorbance of the resulting solutions was measured spectrophotometrically at λ max 221 nm for ibuprofen. The percentage drug released at each interval was determined using the equation from the standard calibration plot obtained for the pure drug.

### **Statistical analysis**

All data obtained were expressed as mean ± SD. Statistical analysis was performed with one-way analysis of variance (ANOVA) comparison test of Graph pad prism 6. A confidence level of 95 % (p < 0.05) was

considered satisfactory for determining significant differences.

## **RESULTS AND DISCUSSION**

The powders so formed in the tablet formulation were observed to have excellent flow properties as presented on Table 2 with angles of repose of < 30°, except that of formulation IV that has value of 54.66°.

For good flow of granules, the British Pharmacopoeia (2010) specifies Hausner's ratio value of <1.25, Carr's index of > 5 ≤ 16. The Hausner's ratio for formulations I, II and III were within the standard specification. Carr's index for the granules for formulation III revealed good flow character, formulations I and II revealed passable flow character while formulation IV has very poor flow character.

For poorer flowing materials, there are frequently greater interparticle interactions and a greater difference between the bulk and tapped densities will be observed (Ajay *et al.*, 2012). Formulation IV had the highest difference (0.29 g/cm<sup>3</sup>) between bulk and tapped densities as seen on Table 2 compared to I (0.19 g/cm<sup>3</sup>), II (0.12 g/cm<sup>3</sup>) and III (0.13g/cm<sup>3</sup>). Therefore, formulation IV exhibited poor flow compared to formulations I, II and III with good flow. This goes a long way to show that co-processing or particle manipulation did not in any way result in the formation of a new compound and this is comparable to the work of Gramaglia *et al* (2005).

**Table 2: Micromeritic and flow properties of ibuprofen and excipients' mix**

<b>Properties</b>	<b>CE</b>	<b>CEL</b>	<b>SDL</b>	<b>PM</b>
Flow rate (g/sec.)	5.28 (0.01)	4.62(0.1)	6.25(0.03)	1.46 (0.2)
Angle of repose (°)	20.30 (0.55)	14.57(0.57)	17.22(0.1)	54.66 (3.18)
Bulk density (g/ml)	0.61 (0.43)	0.44(0.0)	0.74(0.0)	0.51 (0.03)
Tapped density (g/ml)	0.80 (0.01)	0.56(0.0)	0.87(0.03)	0.80 (0.03)
Carr's index (%)	23.75 (0.6)	21.43(0.01)	14.92(0.0)	36.25 (0.5)
Hausner's ratio	1.31 (0.27)	1.27(0.1)	1.18(0.11)	1.57 (0.57)

**Key:** I= Co-processed excipient (CE), II = Cellactose-80 (CEL), III = Spray dried lactose (SDL), IV = Physical mix (PM)

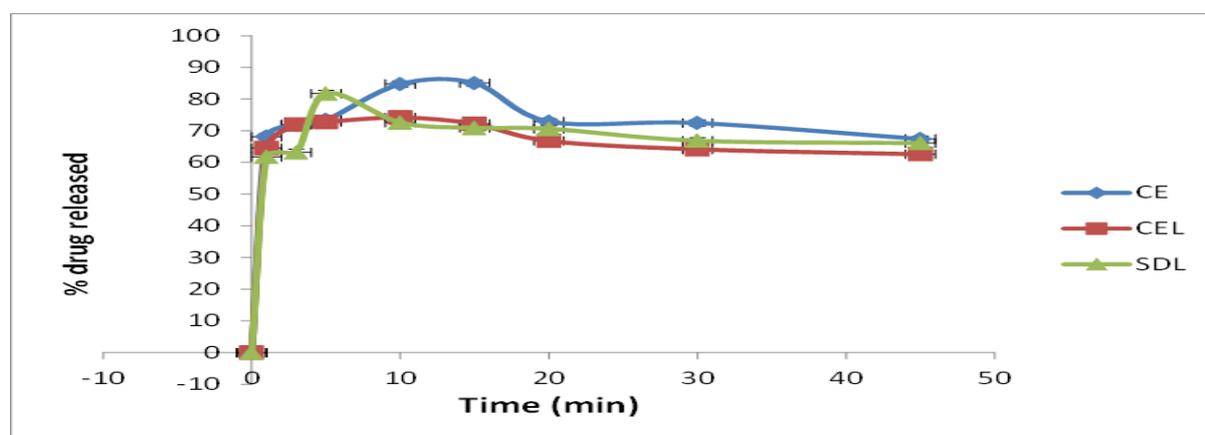
**Table 3: Physical properties of the formulated ibuprofen tablets**

Formulation	Ibuprofen Parameters								
	Weight (mg)	Thickness (mm)	CS (kgF)	TS (MN/m <sup>2</sup> )	BI	FR (%)	DT (min)	T <sub>50%</sub> (min)	T <sub>90%</sub> (min)
I	0.50 (0.01)	4.36 (0.04)	5.25 (0.50)	0.64	0.01	0.00	3	2	ND
II	0.50 (0.01)	4.50 (0.03)	7.25 (0.96)	0.85	0.01	0.40	1	2	ND
III	0.50 (0.01)	4.17 (0.03)	7.50 (1.29)	0.95	0.01	1.57	4	2	ND
IV	0.50 (0.01)	4.23 (0.05)	5.00 (0.96)	0.63	0.01	2.38	1	2	ND

**Key:** -I-Co-processed excipient; T<sub>50%</sub>-Time taken to release 50 % of the drug; II-Cellactose – 80; T<sub>90%</sub>-Time taken to release 90 % of the drug; III- Spray dried lactose; ND-Not determined; IV- Physical mix; CS- Crushing Strength; TS-Tensile Strength; BI-Bonding Index; FR-Friability; DT-Disintegration Time

The values for the average weight of tablets with reference to Table 3 for all formulations compressed were within B.P (2010) specification of  $\pm 5\%$ . A 12 mm punch was used, and the diameter of the tablets corresponded with this size. Thickness which is dependent on the volume of the die cavity, showed that the tablets had a thickness of approximately 4.17 mm – 4.50 mm. The crushing strength values ranged between 5 to 7.5 KgF which was within the accepted limit of 4 – 8 KgF, to enable the tablets disintegrate at a definite rate and withstand handling during packaging. The result of tablets friability test showed that formulations I and II had a friability value of  $< 1.0\%$ , while formulations III and IV had a friability of  $> 1.0\%$  (1.57% and 2.38% respectively).

This is explained by the fact that formulations III and IV as seen on table 3 did not go through co-processing, therefore, implying that co-processing enhances bonding and decreases the formation of friable tablets. The tablets disintegration time complied with B.P (2012) that uncoated tablets are expected to disintegrate within 15 min. The same amount of disintegrant (5% maize starch) was used for all formulations. All the tablets of the four formulations disintegrated in less than 5 mins which is a plus for conventional tablets. The disintegration test result is an improvement on the work done by Mohammed, (2017) in which the novel co-processed excipient (CE) failed the disintegration test having a disintegration time longer than 30 mins.



**Figure 1: In-vitro drug release profile for ibuprofen**

The drug release profile for CE, CEL and SDL as seen in figure 1 revealed that more than 70 % of the drug was released after a time period of 45 min. In SDL and CE however, more than 80 % of the drug was released, this agrees with the specification for drug release as indicated in the monograph for ibuprofen (USP/NF, 2009). The time taken to achieve 50 % drug release was same for all (CE, CEL and SDL) due probably to the rapid disintegration time observed. The extent of drug release by CE was higher than those of CEL and SDL, with CE exhibiting superior tensile strength. However, figure 1 result depicted that there was no complete release for any of the formulations due to known poor solubility of ibuprofen in water. This incomplete dissolution of the particles may have been affected by the intrinsic properties of the drug, its size and components of its formulation (Azam and Haider, 2008).

## CONCLUSION

The disintegration time and drug release profile for formulation I (CE) was not superior to but compared favorably with formulations II (CEL), III (SDL) and IV (PM). However, due to the known poor solubility of ibuprofen in water, there was no complete release for any of the formulations. In conclusion, co-processing impacted greatly by improving the release profile of ibuprofen.

## Conflict of interest

The authors have no conflict of interest to declare.

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