Diluent performance of a three component co-processed excipient for formulating ibuprofen tablets by wet granulation

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Abstract

Pharmaceutical tablets ingested orally remain the most popular dosage form in drug delivery, while the most frequently used route for administration of therapeutic agents remains the oral route. Recently, excipient development comprising a mixture of two or more materials assembled in a single frame by means of particle engineering, known as co-processed excipients, has gained enormous popularity.

To prepare ibuprofen tablets by co-processing and wet granulation method and evaluate its diluent property.

From the design of experiment (DOE), the optimized composition was obtained and ibuprofen granules were prepared for the newly developed co-processed excipient (lactose, mucin and corn starch BP) and starlac®, cellactose® and lactose as standards. The granules were evaluated for their micromeritic properties and compressed into tablets. Evaluation of the ibuprofen tablets for their physical properties and dissolution studies were done using British Pharmacopoeia methods.

The results obtained showed that ibuprofen granules were flowable and compressible. The compressed ibuprofen tablets had good physical properties: minimal weight variation (495±9.46 – 501mg ±23.15), hardness (5.50 ±0.55 – 6.50±1.05 KgF), disintegration "time" < 15 min±0.37 and "friability" < 1.0 % ±0.00 - >1.0±0.07. The dissolution of ibuprofen tablets complied with British Pharmacopoeia criteria.

The data obtained from the different evaluation parameters containing the co-processed excipient compared well with starlac, cellactose and lactose used as comparing standard. The co-processed excipient which performed better than starlac in terms of friability and lactose in terms of disintegration can serve as a good diluent in ibuprofen tablets.

Keywords: Diluent, co-processed excipient, wet granulation, ibuprofen tablets.

Introduction

Pharmaceutical tablets ingested orally remain the most popular dosage form in drug delivery, while the most frequently used route for administration of therapeutic agents remains the oral route (Desai et al., 2012). This popularity of tablets is connected to the many advantages of tablet dosage form which include accurate dosage administration of the drug, ease of self-medication which promotes a high degree of patient compliance, high level of therapeutic response and good shelf life of the product. Formulation of the pharmaceutical tablet is often done with the active pharmaceutical ingredient (API) in

combination with excipients that can enhance the functionality of the dosage form.

Ibuprofen belonging to the class of non-steroidal anti- inflammatory drugs (NSAIDs) is a chiral propionic acid derivative. It is used in the treatment of inflammatory conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, mild and moderate pain, dysmenorrhoea, vascular heads and fever as a result of its analgesic, antipyretic and anti- inflammatory actions. The dose as an anti-rheumatic for adults is about 1.2 to 3.2 g orally taken daily in 3 or 4 divided doses. Ibuprofen is readily absorbed by the gastrointestinal tract and its peak plasma levels are reached within 1 – 2 h (Halford *et al*., 2012).

Recently, excipient development comprising a mixture of two or more materials assembled in a single frame by means of particle engineering, known as co-processed excipients, has gained enormous popularity. These excipients are a combination of existing excipients, designed to physically modify their properties in a manner not possible by simple physical mixing. Therefore, a co-processed excipient that is ideal and intended for better tableting performance should be customized. Techniques such as spheronization, dry and wet granulation, co-crystallization, co-milling, melt extrusion, and spray drying are practiced for co-processing (Badwan *et al*., 2015). Wet granulation provides the adhesion needed to fuse the powders together in the form of granules, and improves compressibility when liquid binders are employed. The problem with binders is their ability to retard disintegration, and their use should be limited (Thoorens et al., 2014). The granule properties and tablet performance should be investigated to ensure a suitable manufacturing process, as well as acceptable drug delivery.

Improvement in specific attributes of a single excipient without compromising its other functionalities is difficult as they might contradict each other. For instance, enhancement in compactibility might affect the disintegration ability of the system. Co-processed excipients help to mitigate these difficulties and aid in gaining superior multifunctional properties than the individual ones (Galdon *et al*., 2016). To overcome the relatively poor compactibility of lactose, a co-processed excipient using a combination of lactose, mucin and corn starch BP was developed.

Diluents are commonly added to formulations to increase the bulk volume of the active ingredient and hence the size of the tablet suitable for handling. The selection of the diluent will depend on the type of plasticity and processing of materials to be used (Desai *et al*., 2016).

Lactose is widely used as a filler or filler-binder in the formulation of pharmaceutical tablets and capsules. The general properties of lactose that contribute to its popularity as an excipient include cost effectiveness; bland taste, low hygroscopicity, availability, compatibility with active ingredients and other excipients, excellent physical and chemical stability and water solubility (Emeje and Rodriguez, 2012). Lactose was chosen as one of the ingredients of the tri-component excipient system. Another component of the system was corn starch BP, which is an established disintegrant that works by a combination of wicking and swelling as well as a binder and bulking agent (Khainar *et al*., 2014).

Mucins, which is the third component, play a fundamental role in the gastrointestinal tract defense mechanism, the distribution of the different mucins throughout the gastro-intestinal tract has been widely studied for monogastric mammalians. However, in polygastric species, mucin distribution is still largely unclear coupled with the high cost involved in new excipient discovery and development. These are a few of the problems that need to be solved through

particle engineering (Momoh *et al.,* 2012). This work is targeted at formulating a three-component co-processed excipient and evaluating its diluent performance in ibuprofen tablets by comparing with cellactose, starlac and anhydrous lactose as standard diluents.

Materials and Methods

Ibuprofen was obtained from Shasun Chemicals and Drugs Ltd. Lactose anhydrous, Maize starch BP, Magnesium stearate was obtained from Signet Chemicals Ltd. Talc was obtained from Luzenac Pharma Ltd, Crosspovidone, Cellactose®, StarLac® were obtained from Ausmasco chemical Ltd, China.

Extraction of bovine mucin

The extraction of bovine mucin was carried out as described by Momoh *et al.,* (2012) with some slight modifications. The small intestines of freshly slaughtered cow were dissected into short lengths, 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 air-dried. The resultant flakes were pulverized using a milling machine and stored in air-tight container until used.

Design of experiments (DOE)

Determination of the precise amount of mucin and corn starch BP that would impart maximum hardness with minimum disintegration time was the key objective behind the implementation of DOE leading to the selection of the optimal ratio composition.

Table 1: Experimental design for ratio optimization

Run order	Lactose (%)	Corn starch BP (%)	Mucin (%)	Disintegration time (min)	Hardness (KgF)
B1	90	1	9	17.49	12.0
B2	90	2	8	14.21	7.7
B3	90	3	7	6.23	4.0
B4	90	4	6	11.42	8.3
B5	90	5	5	7.09	10.3
B6	90	6	4	6.46	9.0
B7	90	7	3	5.23	5.7
B8	90	8	2	6.38	7.0
B9	90	9	1	3.3	8.0

Preparation of co-processed excipient

The primary excipients (lactose, mucin and corn starch BP) were co-processed in the ratio 90: 5:5, by dispersing them in distilled water and heated in a water bath (Julabo – GmbH, Germany) to 40 ^{o} C. The dispersion was stirred for 15 min at the same temperature to form a paste. The resulting paste was then dried at 40 ^{o} C in a hot air oven (Gallenkamp B.S 3, England) for 2 h before screening and stored in a screw-capped bottle.

Tablet Preparation

Formulation of ibuprofen granules

Ibuprofen granules were prepared using the ingredients shown in Table 2. An amount of

each of the ingredients that were required to produce 200 tablets from the granules was calculated and weighed out (except crosspovidone, talc and magnesium stearate), added using the doubling up technique, blended to homogeneity and wet granulated. The granules were formed by wet screening the damp mass of ibuprofen and the co-processed excipient through a 2 mm sieve, dried in the oven [Gallenkamp, England] at 60 ˚C for 1 h, rescreened through a 1 mm sieve, further dried at 60˚C in the oven until a constant weight was attained.

Table 2: Formula for ibuprofen tablets

Ingredient	Batch 1	Batch 2	Batch 3	Batch 4
Ibuprofen (mg)	200	200	200	200
Co-processed excipient (mg)	270	-	-	-
Cellactose (mg)	-	-	270	-
Starlac (mg)	-	270	-	-
Lactose (mg)	-	-	-	270
Crosspovidone (mg)	21	21	21	21
Magnesium stearate (mg)	4.5	4.5	4.5	4.5
Talc (mg)	4.5	4.5	4.5	4.5
Total (mg)	**500**	**500**	**500**	**500**

Bulk density

Bulk density was determined by gently pouring 25 gm of granules into 100 ml graduated cylinder. The volume occupied by the sample was recorded. Bulk density was calculated as:

$$BD = \frac{weight\ of\ sample\ in\ gram}{volume\ occupied\ by\ the\ sample}$$ ----------eqn 1

Tapped density

An accurately weighed sample of powder was carefully added to the cylinder. Typically, the initial volume was noted, and the sample is then tapped (500, 750 or 1250 tapping) until no further reduction in volume is noted. Volume was noted and tapped density was calculated using the following formula.

$$TD = \frac{weight\ of\ sample\ in\ gram}{tapped\ volume}$$ ----------eqn 2

Carr's Compressibility Indexand Hausner's Ratio
The Carr's index (CI) and Hausner's ratio (HR) were computed from the bulk and tapped densities as:

$$\mathrm{HR} = \frac{TD}{BD} \quad \text{----------eqn 3}$$

$$CL = \frac{TD-BD}{TD} \times 100 \quad \text{----------eqn 4}$$

Angle of Repose
This is the maximum possible angle between surface of pile of powder or granules and the horizontal plane

$$\mathrm{Tan}\,\theta = \frac{h}{r} \quad \text{……..eqn 5}$$

where, θ = angle of repose, h = height, r = radius.
A funnel was fixed at a height approximately of 2-4 cm over the platform. The granules were passed slowly through the wall of funnel, till the cone of the powder formed. The angle of repose was determined by measuring the height of the cone of granules and radius of the heap of granules.

True density
The True density of each of the respective ibuprofen granules was determined by the solvent displacement method using xylene (Staniforth, 1988). A tarred 50 ml pycnometer (W) was filled with xylene and the weight was noted as (W1). The weight of the xylene was obtained by subtracting W from W_1. A quantity of 1 g of ibuprofen granule (W_3) and was transferred into the pycnometer bottle, the excess xylene displaced from the pycnometer was wiped off the body of the pycnometer and its content was weighed again (W4). Replicate determinations were done for each batch of ibuprofen granules. The True density, Pt was calculated using equation (6). Where *V* is the volume of the pycnometer.

$$\mathrm{Pt} = \left[\frac{w_3}{w_1+w_3} - w_4\right] \times S.G \quad \text{……..eqn 6}$$

Flow rate
The flow rate of the ibuprofen granules was determined by using a modification of the Ansel method (Ansel *et al.*, 2005). A quantity of 20 g of the ibuprofen granules was poured into a funnel that was clamped with the orifice of the efflux tube at a height of 3 cm above a flat surfaced platform. The orifice was closed with a cotton wool to prevent premature discharge of the granules. On removal of the cotton wool, the time it took for the granules to be completely discharged from the funnel was noted. Replicate determinations were done for each of the granules. The flow rate was determined using equation 7.

$$\mathrm{Fr} = \frac{weight\ of\ granules}{time} \quad \text{……..eqn 7}$$

Porosity

Porosity depicts the volume/pores present relative to the tapped volume that was used to calculate the tapped density. The porosity of ibuprofen granules depicts the number of inter and intra-particulate void spaces that exists within the granules and is determined using equation (8).

$$P = 1 - \left[\frac{BD}{TD}\right] \times 100 \quad \text{.....eqn 8}$$

Particle size

A series of standard sieves were stacked one above the other so that sieves with a larger pore size (less sieve number) occupy the top position followed by sieves of decreasing pore size (larger sieve number) towards the bottom. These sieves were arranged in ascending order. Weighed quantity of (30 g) was placed in the mesh. Sieve shaker was set for 15 min. The sieves are removed from the sieve shaker and weighed individually to note the quantity retained in each size of mesh.

Fourier transform – infrared spectroscopy

The Fourier Transform – infrared (FT – IR) spectrum of the sample, was recorded from 4000 to 650 cm^{-1} on an IR spectrometer (Shimadzu FTIR 8400s, USA). This was done by using potassium bromide (KBr) discs prepared from the mixture of the sample and dried KBr in the ratio of 1:200. The spectrum with the clearest identifiable peaks was chosen.

Compression of ibuprofen granules

The ibuprofen granules obtained from the four batches (Table 2) were compressed into ibuprofen tablets. The talc and magnesium stearate were added immediately prior to compression. A single station Manesty tablet press, Model F-3 (Manesty, England) fitted with a set of flat faced punches (12.5 mm diameter) and dies at a compression pressure of 7 Metric tonnes was used to compress 200 tablets per batch at a target tablet weight of 500 mg per tablet

Characterization of Ibuprofen Tablets

The ibuprofen tablets were characterized 24 h after they were tableted for their physical properties and drug release from the tablets using pharmacopoeia methods.

Uniformity of weight

The ibuprofen tablets were examined for variation in tablet weight by randomly selecting and individually weighing 20 tablets from each batch of the formulation.

Hardness

Through a process of random selection, 10 tablets from each batch of the ibuprofen formulation were collected and a Monsanto hardness tester was used to determine the pressure at which each tablet diametrically broke.

Disintegration time

The disintegration time of the ibuprofen tablets was determined by randomly selecting six tablets from each batch of the formulation and putting each tablet from any given batch into each of the six cylindrical holes of a model ZT-122 disintegration machine (Erweka, Germany). The disintegration medium was 500 ml of 0.1 N HCl held in a 1 L beaker that was immersed in a water bath. The temperature of both the medium and bath was maintained at 37 ± 0.5 ˚C.

Friability

Ten tablets were randomly selected from each batch of the ibuprofen tablet formulations were free of dust, collectively weighed (Wi) and put into one of the drums of the friability tester, model TAR 200

(Erweka, Germany). The machine was operated in a way that the drum rotated at 25 rotations per minute (rpm) for 4 min. The tablets were collected, de-dusted and reweighed (Wf) and the percentage friability (F) was calculated using equation 9:

$$F = \frac{w_i - w_f}{w_i} \times 100 \quad \text{.....eqn 9}$$

Thickness/Diameter

Ten tablets were also selected at random from each brand of ibuprofen tablets. The thickness and diameter of the tablets were individually determined using a micrometer screw gauge. The mean and standard deviation for each determination was recorded.

Dissolution of ibuprofen

The dissolution of ibuprofen tablets or its release profile from the tablets was carried out using a dissolution apparatus (Erweka®, Germany). A tablet from each batch was individually put in 900 ml of phosphate buffer (pH 7.2) solution contained in a 1 L flask kept in a water bath whose temperature was maintained at 37 ± 0.5 ˚C with a paddle speed set at 50 rpm. Five ml samples were withdrawn from the test media every 5 min, filtered through a filter paper and replaced after each sampling time. The filtrates were scanned at wavelength of 221 nm in the spectrophotometer and the absorbance readings obtained were converted to concentrations using the standard calibration equation earlier established (Gavura, 2019).

Statistical analysis

Statistical analysis was carried out with the IBM SPSS version 21 (SPSS Inc., Chicago, Illinois, USA) software using one-way analysis of variance (ANOVA). Results were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

Design of experiment

Trial compositions of the three excipients namely lactose, mucin and corn starch BP were prepared to optimize the co-processed excipient as shown in Table 1. From the outcome of the performance of the various combinations, batch B5 was selected as the optimized composition (Mohammed et al., 2019).

Some Micromeritic Properties of Ibuprofen Granules

Bulk and Tapped densities

The results of the bulk and tapped densities of the ibuprofen granule evaluations are shown in Table 3. The bulk densities were consistently lower than the tapped densities (Daraghmeh *et al.*, 2010) for all the ibuprofen granules containing co-processed excipient, starlac, cellactose and lactose which are indicative of volume reduction of the powder bed on agitation. Thus, they can be categorized as compressible granules. There was no significant difference ($p > 0.05$) in the bulk densities. A similar trend was observed in the tapped densities.

Flow rate

The results of the flow rates of the ibuprofen granules are reflected in Table 3. Batch 1 (co-processed excipient) had the highest flow compared to other batches. Generally, the granules had good flow attributes and would be good for the preparation of ibuprofen tablets with good physical properties such as uniform weight, content and hardness (Katdase and Chaubal., 2006).

Angle of repose

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is characteristically related to inter particulate friction or resistance to movement between particles. The angle of repose of the ibuprofen granules is shown in Table 3 and ranged from 30.00 ± 1.00 - 36.00 ± 1.00˚. There was a significant difference ($p < 0.05$) in the angle of repose of ibuprofen granules containing cellactose and lactose. However, there was no significant difference ($p > 0.05$) between the ibuprofen granules containing co-processed excipient and starlac. The granules generally can be classified as having an excellent flow (Kumar and Koh, 2012, Gohel et al., 2007). Based on their flowability, they would fill the dies properly during tableting, resulting in tablets with minimal variation in weight.

Table 3: Micromeritic properties of ibuprofen granules

Parameter	Batch 1	Batch 2	Batch 3	Batch 4
Angle of repose (^{O})	30.67 ± 1.53	30.00 ± 1.00	36.00 ± 1.00	31.33 ± 1.16
Bulk density (g/ml)	0.40 ± 0.01	0.40 ± 0.01	0.40 ± 0.01	0.39 ± 0.01
Tapped density (g/ml)	0.50 ± 0.01	0.50 ± 0.01	0.50 ± 0.01	0.48 ± 0.01
Carr's index (%)	20.00 ± 0.01	20.00 ± 0.01	20.00 ± 0.01	19.00 ± 0.10
Hausner's ratio	1.25 ± 0.60	1.25 ± 0.40	1.25 ± 0.10	1.23 ± 0.30
Porosity (%)	73.00 ± 0.60	73.00 ± 0.56	73.00 ± 0.54	74.00 ± 0.40
Flow rate (g/sec)	4.77 ± 0.21	3.93 ± 0.06	3.50 ± 0.06	3.63 ± 0.06
Particle size (µm)	297	220	173	296
True density (g/ml)	1.48 ± 0.20	1.50 ± 0.01	1.49 ± 0.10	1.51 ± 0.02

Hausner's quotient and Carr's compressibility Index

The Hausner's quotient of the ibuprofen granules was in the range of 1.23 ± 0.30 - 1.25 ± 0.10 and Carr's compressibility in the range of 19.00 ± 0.10 - 20.00 ± 0.01 % (Table 3). Generally, the granules can be classified as having good flow properties (Ansel et al., 2005; Kunle, 2016). These flow indices suggest that the ibuprofen granules would be reasonably discharged from the hopper to the die to aid the formation of well-filled and compressed tablets.

Porosity

The porosity evaluation results of the ibuprofen tablets are shown in Table 3. The porosity values support non-cohesiveness which indicated the good flow that was observed. A good flowability is desirable in powders/granules to enable proper die filling and production of tablets with minimal variation in weight. There was no significant change seen in their porosities. This is in consonance with the work of Ilic et al., 2009.

FTIR

Figure 1 shows the FTIR overlay spectra. Most of the peaks appearing in the final spectra (Co-processed excipient) are consistent with lactose which was the dominant excipient. The OH stretch bond, aliphatic C-H stretch and C-O stretch were all reflected in both the physical mix and co-processed excipient at the same wavenumber indicating that little heating of the co-processed excipients was not enough

to cause a significant chemical interaction or chemical change (Daraghmeh *et al.*, 2010).

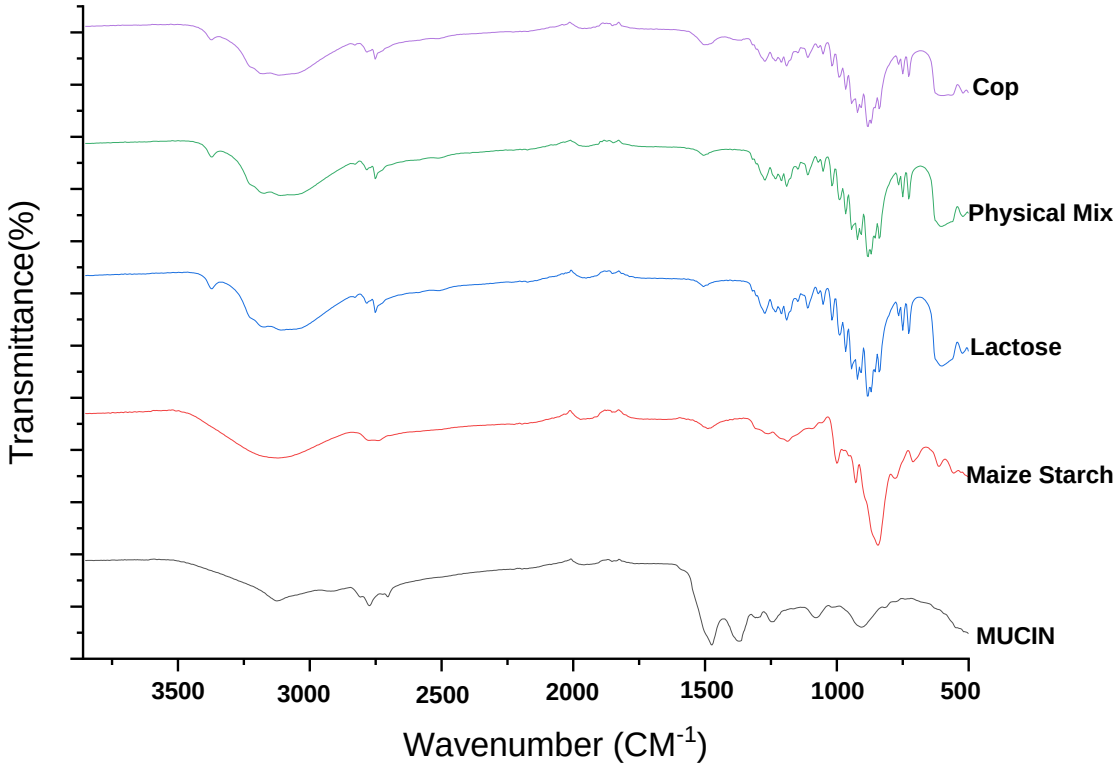

Fig 1: FTIR overlay spectra

Ibuprofen Tablet Parameters

Uniformity of weight

The result of the assessment of the tablets for uniformity of weight is shown in Table 4. The tablets showed minimal variation in weight and were found to comply with British

Pharmacopoeia specifications for uncoated tablets that weigh more than 250 mg. The permissible percentage variation for such tablets is stipulated to be within ± 5 % of the given tablet weight (BP, 2012).

Hardness

The hardness of the ibuprofen tablets was in the range of 5.50 ± 0.55 - 6.50 ± 1.05 kgF (Table 4). All the tablets met with the British Pharmacopoeia recommendation for uncoated tablets which is given as ≥ 4.00 kgF. Such hardness values imply good mechanical strength and physical integrity of the tablets as was reflected in the tensile strength (USP, 2009).

Disintegration time

The disintegration time result revealed that all the ibuprofen tablets disintegrated within 8 min except for batch 4 (Table 4) which is quite good for the different batches of tablets. The upper permissible limit by the British Pharmacopoeia is 15 min therefore, the tablets passed the test (BP, 2012). Uncoated tablets are expected to disintegrate within 15 min after oral ingestion to enable release of the active pharmaceutical ingredient for dissolution and possible absorption in the gastrointestinal tract.

Table 4: Physical parameters of ibuprofen tablets

Batch/Parameter	Batch 1	Batch 2	Batch 3	Batch 4
Uniformity of weight (mg)	495 ± 10.99	495 ±9.46	501 ± 23.14	496.5 ± 8.75
Hardness (KgF)	5.67 ± 0.82	5.50 ± 0.55	5.83 ± 0.75	6.50 ± 1.05
Tensile strength (Nm^{-2})	0.79 ± 0.71	0.77 ± 0.56	0.80 ± 0.27	0.82 ± 0.65
Disintegration time (min)	1.47 ± 0.37	8.70 ± 3.16	7.99 ± 1.72	15.00 ± 1.90
Friability (%)	0.20 ± 0.00	2.60 ± 0.07	0.02 ± 0.00	0.11 ± 0.00
Diameter (mm)	12.09 ± 0.04	12.04 ± 0.06	12.08 ± 0.04	12.05 ± 0.04
Thickness (mm)	3.76 ± 0.05	3.78 ± 0.06	3.82 ± 0.04	4.19 ± 0.09

Friability

The ibuprofen tablets were not friable except for batch 2 containing starlac as all the batches had friability in the range of batch 4< batch 1 and 3 < batch 2. This is a good attribute as it is an indication of the ability of the tablets to withstand the abrasive stresses that would be encountered during packaging, transportation and handling during use. Uncoated tablets are expected to have friability of ≤ 1.00 % (Nachegari and Bansal, 2004; Ohrem *et al*., 2014). The ibuprofen tablets passed the friability test except for batch 2.

Thickness/Diameter

The thickness/diameter of the ibuprofen tablets are shown in Table 4. There is no significant difference ($p > 0.05$) in the thickness and diameter of the different tablets. This suggests that there was fair uniform filling of the granules into the dies as well as uniform compression pressure during the tableting of the granules.

Dissolution of ibuprofen

The drug release profile of the ibuprofen tablets containing the co-processed excipient, cellactose, starlac and lactose as diluents is shown in Figure 2. There was a fast release of ibuprofen from the tablets ($T_{50\%}$) within 2 min for all batches except lactose which was at 4 min, thereafter the release increased gradually until 30 min. Most of the tablets released more than 70 % of their ibuprofen content within 30 min. At 30 min, there was no significant difference ($p < 0.05$) amongst all the batches except for Batch 1. Comparatively, Batch 1 of the ibuprofen tablets which contained co-processed excipient was the most released within 30 min lending credence to the advantage of co-processing. It was closely followed by the tablets containing starlac (Batch 2) while the tablets containing cellactose and lactose were the least released. All the batches met with BP requirements which stipulates that up to 50 % of ibuprofen must be released from the tablets within 30 min (BP, 2012).

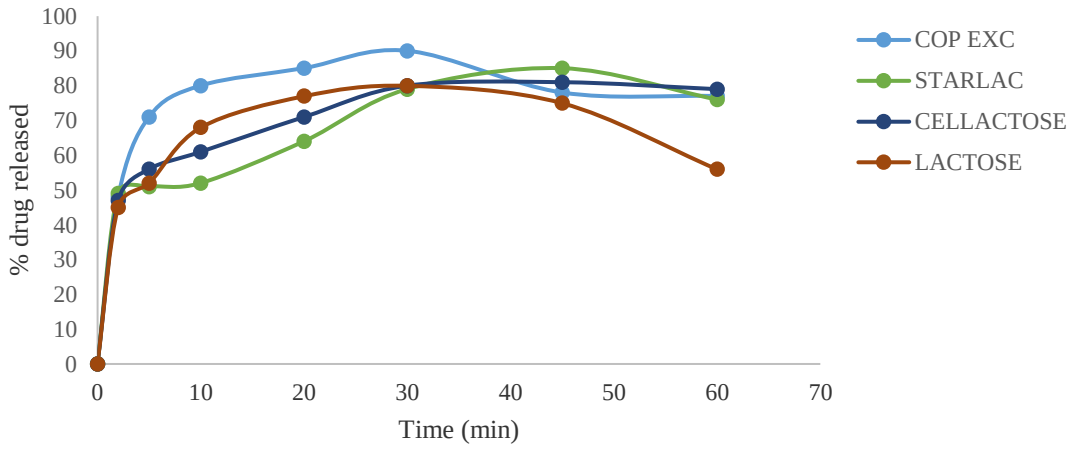

Figure 2: Dissolution profile of ibuprofen tablets.

Conclusion

Ibuprofen granules formulated with the different diluents had good flow and compressibility.

The tablets had minimal weight variation, good mechanical strength, friability and disintegration times. The content of ibuprofen in the tablets, and its release therefrom met with acceptable British Pharmacopoeia set limits. The data obtained from the different evaluation parameters containing the co-processed excipient compared well with starlac, cellactose and lactose which were used as comparing standards. The co-processed excipient performed better than starlac in terms of friability and lactose in terms of disintegration. The co-processed excipient served as a good diluent in ibuprofen tablets.

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Conflict of interest

The authors declare that there is no conflict of interest.

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