IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
December 2020 Vol.:20, Issue:1

Formulation and Evaluation of Fast Disintegrating Tablets of Diclofenac Potassium Using *Pleurotus tuber-regium* Powder

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Submitted: 01 November 2020
Revised: 20 November 2020
Accepted: 10 December 2020

Keywords: *Pleurotus, tuber-regium,* super-disintegrant, diclofenac release

ABSTRACT

Fast disintegrating tablets (FDTs) are tablets that dissolve rapidly when placed on the tongue. They are new trends in oral drug delivery systems resulting in quick disintegration of the administered medicine into solution or suspension when in contact with the saliva. This study aimed to formulate fast disintegrating tablets of diclofenac potassium using a combination of *Pleurotus tuber-regium* powder and a super disintegrant (croscarmellose sodium). Eleven (11) batches of diclofenac powder blends and tablets were prepared using *Pleurotus tuber-regium* powder, a super-disintegrant (croscarmellose sodium) and combinations of *Pleurotus tuber-regium* powder and croscarmellose sodium using the direct compression method. Granules from the powder blends and tablets formulated were characterized for their flow and tablet properties respectively. The diclofenac granules had passable flowability (angles of repose ≤ 37.56°, Hausner's ratios ≥ 1.29 and Carr's indices ≥ 22.00%). Disintegration times of the tablets decreased with increase in concentrations of *Pleurotus tuber-regium* powder and croscarmellose sodium with the highest disintegration time of 3.20 min from tablets prepared with the lowest concentration of *Pleurotus tuber-regium* powder. Tablets prepared with combinations of *Pleurotus tuber-regium* powder and croscarmellose sodium had the lowest disintegration times and the highest percentages of drug release with batch K having the least disintegration time of 10 sec and 100% drug release within 20 min. The formulated diclofenac tablets were fast disintegrating and had good dissolution profiles. *Pleurotus tuber-regium* powder acts as a super disintegrant at higher concentrations, whereas at a lower concentrations, it behaved like a conventional disintegrant.

INTRODUCTION:

Fast disintegrating tablets (FDTs) are oral drug delivery systems resulting in quick disintegration of the administered medicine into solution or suspension when in contact with the saliva. FDTs are commonly known as fast melt, orally disintegrating tablets, orodispersible system, fast/rapid dissolving tablets, mouth dissolving tablets (Kaur *et al.*, 2011), quick disintegrating tablet, rapid melt, melt in mouth, quick-dissolving and porous tablet.

These formulations have advantages of both solid and liquid dosage systems i.e., they are convenient as solid dosage and easy to swallow as a liquid formulation (Hartsell *et al.*, 2005). The fast-dissolving drug delivery system provides convenient means of administering tablets especially to pediatrics, geriatrics and patients having difficulty in swallowing conventional dosage form, thus improving compliance to dosage regime. FDTs are also useful when rapid disintegration and absorption of drug is needed thereby producing rapid onset of action (Reddy *et al.*, 2002). Diclofenac potassium is a commonly prescribed non-steroidal anti-inflammatory drug (NSAID) that is used as an analgesic, antipyretic and anti-inflammatory drug, and in treating various acute, chronic pain and inflammatory conditions. It is known to dissolve and absorbed faster than the sodium salt and is thus, recommended in treatment that needs quick onset of action mainly for its analgesic properties. While a quick action is required in immediate pain relief treatments, a prolonged action is useful in reducing inflammation. To achieve a fast onset of action, fast disintegrating tablets of diclofenac can be designed and formulated for quick absorption in the gastrointestinal tract.

Fast disintegration is usually achieved using super disintegrants. They have greater disintegrating efficiency than conventional disintegrants and are effective at low concentrations. Examples of super disintegrants include croscarmellose sodium, sodium starch glycolate, and crospovidone.

Pleurotus tuber-regium, known as the king tuber mushroom, is an edible fungus native to the tropics, including Africa, Asia, and Australia. This fungus has a history of economic importance in Africa as food and as a medicinal mushroom (Isikhuemhen and LeBauer, 2004). Some researchers have investigated the disintegrating activity of *Pleurotus tuber-regium*; (Iwuagwu and Onyekweli 2002, Ogor *et al.*, 2020). Since fast disintegrating tablets require very fast disintegration, a combination of super disintegrants may enhance fast

disintegration by synergistic effect. Therefore, this study aimed to formulate fast disintegrating tablets of diclofenac potassium using a combination of *Pleurotus tuber-regium* powder and super disintegrant (croscarmellose sodium).

MATERIALS AND METHODS:

MATERIALS:

Diclofenac potassium, mannitol, ascorbic acid, magnesium and talc (Edo Pharmaceuticals, Benin City, Nigeria), croscarmellose sodium (BDH Chemical Poole, UK), microcrystalline cellulose (Avicel-PH 101) (FMC Biopolymer, Philadelphia, USA), *Pleurotus tuber-regium* was purchased at a local market in Nigeria and processed into powder in the laboratory.

METHODS:

Preparation of *Pleurotus tuber-regium* powder

The fresh tubers of *Pleurotus tuber-regium* were collected and the brown outer layer of the tuber was peeled to expose the whitish inner sclerotia, which was diced and blended into powder using a blending machine (Kenwood Ltd, UK). The powder was dried at 60 °C for 30 min in a hot air oven (Kottermanns, Germany). The dried powder was then sieved through a 212 µm mesh screen.

Preparation of diclofenac potassium powder blends

The formula used in the preparation of the different batches of diclofenac powder blends and tablets is shown in Table 1.

Table No. 1: Formula for the prepared diclofenac powder blends and tablets

Ingredients (mg)	Batches										
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**
Diclofenac	50	50	50	50	50	50	50	50	50	50	50
Croscarmellose sodium	-	-	-	-	-	15	20	30	15	10	15
Pleurotus tuber-regium	10	15	20	30	35	-	-	-	15	25	20
Microcrystalline cellulose	5	5	5	5	5	5	5	5	5	5	5
Mannitol	30	25	20	10	5	25	20	10	10	5	5
Ascorbic acid	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Powder blends sufficient to produce one hundred tablets per batch of eleven (11) batches (A - K) were prepared by weighing the required amount of diclofenac potassium powder, microcrystalline cellulose, *Pleurotus tuber-regium* powder, and croscarmellose sodium into a mixer and mixed for 5 min. The amounts of mannitol and ascorbic acid were added and mixing continued for another 5 min and the resulting powder passed through a 212 µm sieve. Slugs were compressed from the powder blend (Koln Niehi, Germany) and then broken down into granules with a mortar and pestle before screening through a 710 µm sieve. The amounts of talc and magnesium stearate were added to the granules in geometric proportion and mixed intimately. The granules were analyzed for their flow properties and drug-excipients compatibility and kept in an airtight container until compression.

Granules analysis

Bulk and tapped densities

A 1.5 g of the granulation was poured gently into a 10ml graduated measuring cylinder. The volume of the granules was noted and the bulk density was calculated as the ratio of the weight of granules to the volume of granules. The measuring cylinder was then tapped 100 times on a wooden platform, and the final volume was recorded and used to calculate the tapped density of the diclofenac granules.

Carr's index (% Compressibility)

The difference between tapped and bulk density of the granules divided by the tapped density was calculated and the ratio (Carr's index) expressed as a percentage.

Hausner's ratio

The ratio of the tapped density to the bulk density of the granules was calculated as Hausner's ratio.

Angle of repose

The funnel method was used to determine the flow rate and angle of repose (flowability) of the granules. A funnel with an orifice diameter of approximately 0.8 cm was clamped to a retort stand with its tip, 5.0 cm above a flat surface. A 5.0 g granules were gently poured through the funnel forming a cone-like heap. The angle of repose (θ) was calculated using the mean diameter of the base of the cone and the height of the cone in equation 1.

$$\theta = \tan^{-1}(h/r) \quad \ldots. (1)$$

Compression of granules

The diclofenac granules were compressed into tablets at a compression of 30 arbitrary units, using a single punch tableting machine (F-3 Manesty Machines, UK). Tablets of uniform weight were compressed using granules weighing 100 mg. The tablets made were then kept in airtight containers and stored in a desiccator until evaluation.

Evaluation of the formulated tablets

The formulated diclofenac tablets were evaluated for the following parameters using standard procedures: weight uniformity, friability, hardness, disintegration time, and dissolution studies.

Weight variation

Ten (10) tablets were selected from each batch at random and weighed individually using an electronic weighing balance (College B154, Mettler Toledo, Switzerland). The mean weight and standard deviation were computed.

Friability

Ten (10) pre-weighed tablets were placed in a friabilator (Erweka GmbH, Germany) and rotated at a speed of 25 rpm for 4 min. The tablets were brought out, dusted, reweighed, and their percentage loss in weight was calculated. This was done in triplicate and the mean and standard deviation were reported.

Hardness

Five (5) tablets were selected at random from each batch and the compression force required to crack the tablets was determined using a motorized tablet hardness tester (Campbell Electronics, Model HT- 30/50, India) and the mean hardness and standard deviation were calculated.

Disintegration time

The disintegration time for the various batches of tablets was determined using the BP disintegration apparatus (MK IV, Manesty Machines, UK) containing distilled water and thermostated at 37 ± 0.5 °C. The time taken for six tablets per batch to disintegrate completely was noted. The mean or average time and standard deviation were calculated.

Dissolution studies

In vitro dissolution profiles of various batches of the diclofenac potassium tablets were determined using the USP dissolution test apparatus (USP- NF, 2011) containing 900 ml of 0.1 N HCl as the dissolution medium. For each batch, the tablets (100 mg) were placed in the dissolution medium rotated at a paddle speed of 100 rpm and maintained at a temperature of 37 ± 0.5 °C. A 5 ml volume solution was withdrawn at intervals up to 30 min and replaced with a fresh 5 ml dissolution medium maintained at the same temperature. The samples withdrawn were filtered using a Whatman No. 1 filter paper and suitably diluted with 0.1 N HCl solution. The absorbances of the sample solution were measured at λmax of 276 nm (T70, PG Instruments Ltd, USA). The concentration and the percentage of drug released at each time interval was determined using the equation from the standard calibration plot obtained from the pure diclofenac potassium.

Statistical analysis

The mean and standard deviations of replicate determinations were computed and reported. Using GraphPad InStat 3.10, the statistical differences in the granules and tablet parameters of the different batches were subjected to student's t-test at a 5 % level of significance.

RESULTS AND DISCUSSION:

RESULTS:

Diclofenac granules flow properties

The result from the granules analysis is shown in Table 2. Their bulk and tapped densities values were between 0.36 - 0.63 g/ml and 0.43 - 0.69 mg/ml, respectively. The angle of repose was between 28.50- 37.56°. Hausner's ratio was between 1.29-1.60. Carr's index of the granules was between 22.00 - 38.00%.

Table No. 2: Flow properties of granules

Batch	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (º)	Hausner's ratio	Carr's index (%)
A	0.39 ± 0.05	0.61 ± 0.04	33.24 ± 0.02	1.54 ± 0.02	35.47 ± 0.03
B	0.39 ± 0.05	0.58 ± 0.03	31.20 ± 0.02	1.47 ± 0.02	32.00 ± 0.03
C	0.42 ± 0.04	0.62 ± 0.03	30.01 ± 0.02	1.45 ± 0.02	31.40 ± 0.02
D	0.51 ± 0.05	0.68 ± 0.03	29.20 ± 0.03	1.33 ± 0.01	25.00 ± 0.03
E	0.53 ± 0.05	0.69 ± 0.05	28.50 ± 0.03	1.29 ± 0.01	22.00 ± 0.01
F	0.37 ± 0.04	0.59 ± 0.04	33.10 ± 0.05	1.57 ± 0.02	36.60 ± 0.02
G	0.36 ± 0.05	0.60 ± 0.04	34.35 ± 0.03	1.60 ± 0.02	38.00 ± 0.01
H	0.44 ± 0.05	0.64 ± 0.03	33.80 ± 0.03	1.45 ± 0.02	31.20 ± 0.01
I	0.38 ± 0.05	0.58 ± 0.05	31.40 ± 0.02	1.52 ± 0.01	34.00 ± 0.00
J	0.56 ± 0.04	0.69 ± 0.05	37.56 ± 0.02	1.32 ± 0.01	24.50 ± 0.01
K	0.63 ± 0.05	0.43 ± 0.05	32.50 ± 0.02	1.44 ± 0.01	30.61 ± 0.01

Tablet properties

The average weights of the prepared tablets were between 97.0 mg to 106.0 mg. The tablet friability ranges from 0.04 - 0.80% while the hardness of the tablets in batches A-K was between 1.04 - 2.00 kp. There was significant variation in the disintegration time of the diclofenac tablets which ranges from 0.10 - 3.05 min. Tablets in batches A, B, C, D, and E containing *Pleurotus tuber-regium* in increasing concentrations had an average disintegration time of 3.20, 3.05, 2.30, 1.30, and 1.15 min respectively. Tablets in batches F, G, and H containing croscarmellose sodium in increasing concentrations had an average disintegration time of 1.40, 1.20 and 0.8 min respectively. While, tablets in batches I, J and K containing combinations of croscarmellose and *Pleurotus tuber-regium* in varying concentrations had an average disintegration time of 70 sec, 30 sec and 10 sec respectively.

The dissolution profiles of the diclofenac tablets containing only *Pleurotus tuber-regium* and croscarmellose sodium and a combinations of *Pleurotus tuber-regium* and croscarmellose sodium is shown in Figure 1 (a and b) respectively. There was variable drug release across all batches with batches of tablets containing *Pleurotus tuber-regium* powder alone exhibiting the lowest percentage drug release except batch E tablets with the highest concentration having a drug release of 92.14% in 20 min. While, in Figure 1b containing varying concentrations of both *Pleurotus tuber regium* and croscarmellose sodium, it was observed that more than 60% of its drug contents was released in 5.0 min and a 100% release in 20 min.

Table No. 3: Post compression properties of the formulated tablets

Batch	Weight (mg)	Hardness (kp)	Friability (%)	Disintegration time (min)
A	103 ± 0.83	1.04 ± 0.61	0.66 ± 0.00	3.20 ± 0.45
B	97 ± 1.24	1.5 ± 0.33	0.5 ± 0.13	3.05 ± 0.12
C	104 ± 2.41	1.7 ± 0.26	0.67 ± 0.00	2.30 ± 0.31
D	105 ± 1.26	2.0 ± 0.44	0.42 ± 0.20	1.30 ± 0.60
E	105 ± 0.85	1.8 ± 0.25	0.8 ± 0.34	1.15 ± 0.27
F	100 ± 1.39	1.4 ± 0.46	0.04 ± 0.12	1.40 ± 0.11
G	102 ± 1.55	1.4 ± 0.10	0.36 ± 0.48	1.30 ± 0.23
H	99 ± 1.27	1.4 ± 0.35	0.06 ± 0.23	0.80 ± 0.08
I	106 ± 1.19	1.7 ± 1.20	0.7 ± 0.10	1.10 ± 0.09
J	100 ± 1.20	2.0 ± 1.10	0.22 ± 0.15	0.30 ± 0.03
K	106 ± 1.10	1.8 ± 0.37	0.5 ± 0.33	0.10 ± 0.07

DISCUSSION:

The bulk and tapped densities of the granules depends largely on the particle shape and particle size distribution and reflect the inter-particulate interaction between the granules. The angle of repose, Hausner's ratio, and Carr's compressibility index indirectly measure granules flowability. The established relationship between the angle of repose and flow properties of powders and granules indicates that an angle of repose < 20 shows an excellent flow, between 20-30° and 30-34° indicates good and passable flow and values > 34° shows a very poor flow (Carr, 1965). Batches C, D, and E have a good flow. Batch J has a poor flow while the others have a passable type of flow. The lower Hausner's ratio (< 1.25) indicates better flow properties of the granules than the higher ones (> 1.25) while Carr's index below 16% indicates good compressibility and flowability, values above 35% indicate cohesiveness and poor flow. Hence, the scale of flowability showed that Batch D, E, and J have a passable flowability while the others have poor flowability and the granules showed a passable to poor compressibility.

The tablets were found to be within the acceptable weight variation according to British Pharmacopeia specification states that the variation in the individual weight of the tablets

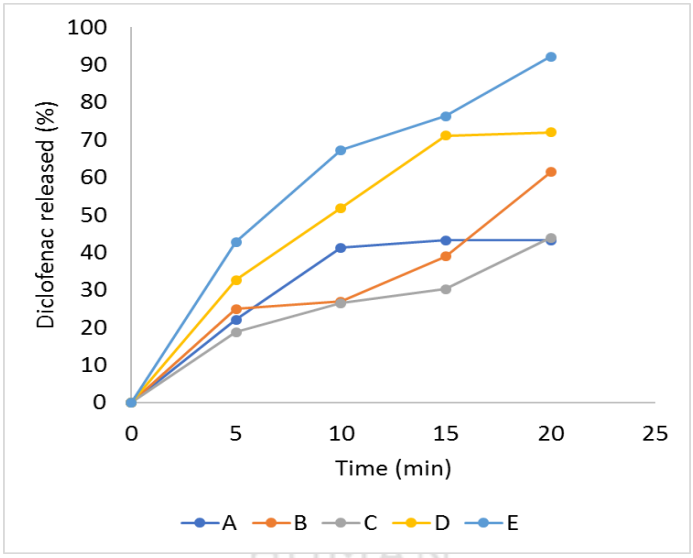
should not be more than ± 10% and not more than two of the 20 tablets should deviate from the average weight by more than ± 5% (BP, 2009). The variations in the tablet weights were not more than ± 10% of the individual weight with only two of the tablets weights deviating with more than 5% of the calculated mean weight. The friability results of the tablets showed that all the tablets were within the acceptable range of 0.8 - 1.0% loss in weight without the tablet capping or breaking up in the course of the test (BP, 2009). This indicates that the tablets are likely to stand abrasion during packaging, shipping/transport, storage, and handling. The BP specification for a satisfactory tablet hardness or crushing strength ranged between 5 - 8 kp. The hardness of the tablets were not satisfactory and this could be due to the relatively small tablet weights. It could also be due to the low compression pressure used in the tablet compression (Symecko and Rhodes, 1997).

The disintegration time of a tablet is a very essential parameter of FDTs. According to the European Pharmacopeia, a disintegration time of 3.0 min is expected for FDTs (EP, 2008). Except for batches A and B tablets which showed a slightly high disintegration time, all other formulated tablets passed the disintegration test for FDTs. Generally, the disintegration time results showed that the disintegration time decreased progressively as the concentration of the disintegrants (*Pleurotus tuber-regium*, croscarmellose sodium and *Pleurotus tuber-regium* + croscarmellose sodium) was increased. Across all the batches, the batch K tablets containing 15.0 mg of croscarmellose sodium and 20.0 mg of *Pleurotus tuber-regium* had the lowest disintegration time of 10 sec suggesting an optimum combination concentrations of the disintegrants for optimal disintegration time. Also, the low disintegration time will facilitate fast break up of tablet and consequent fast release and dissolution of tablet drug content for faster onset of drug action (Markl and Zeitler, 2017).

The variable drug release observed across the batches showed that the tablets (batch K) containing the optimal concentrations of both *Pleurotus tuber-regium* and croscarmellose sodium had more than 60% of their drug contents released within 5 min while 100% was released in 20 min. Thus, this high percentage of drug release may facilitate an enhanced absorption of the drug in the gastrointestinal tract, leading to higher drug bioavailability (Eraga *et al*., 2018).

In summary, a comparison of the disintegration and dissolution activity of the various batches of formulated diclofenac tablets with either *Pleurotus tuber-regium* powder or croscarmellose sodium or both combination showed that as the concentration of the disintegrants increases,

the disintegration time decreases and the dissolution rate increases whereas, as the disintegrants concentration decreases, the disintegration time increases and dissolution rate decreases. Batches of diclofenac tablets prepared with combinations of *Pleurotus tuber-regium* powder and croscarmellose sodium had the lowest disintegration times and the highest percentage of drug release across the batches. Hence incorporating optimal concentrations of both *Pleurotus tuber-regium* powder and croscarmellose sodium in the formulation of fast disintegrating tablets of diclofenac will cause a significant reduction in the disintegration time and an increase in the dissolution rate of diclofenac tablets.



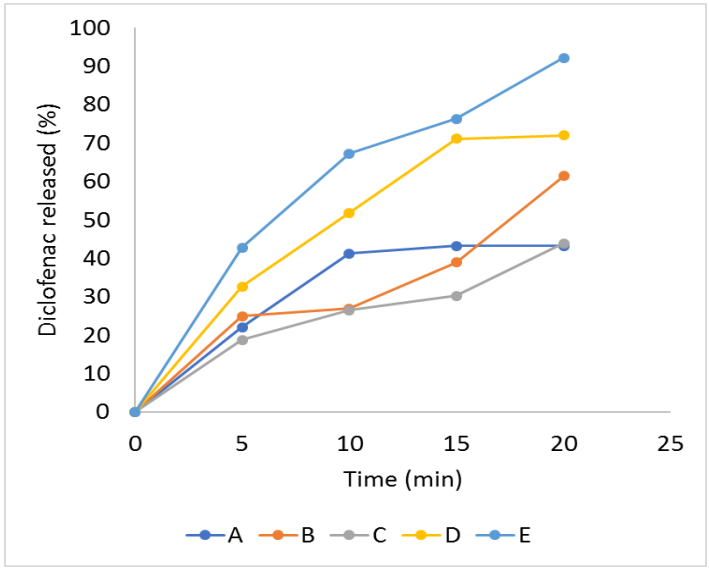


Figure No. 1a: Dissolution profile of batch A – E tablet containing varying concentrations of *Pleurotus tuber-regium*

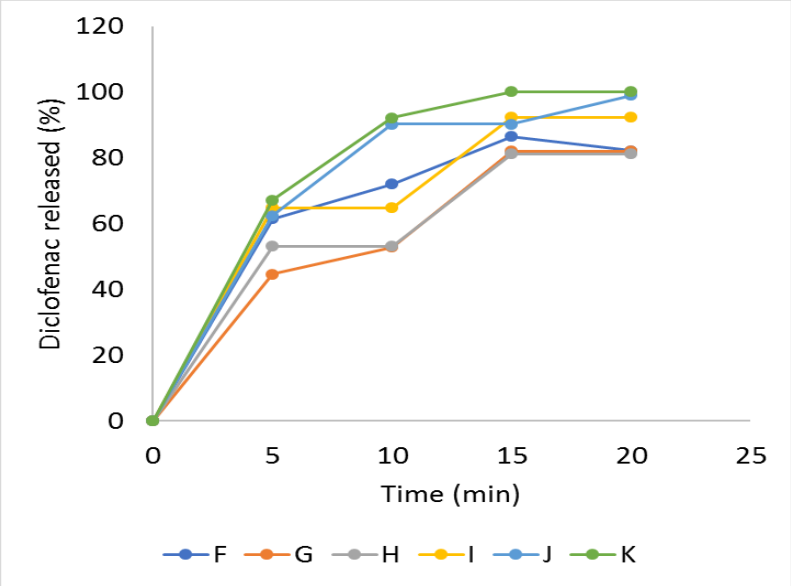


Figure No. 1b: Dissolution profile of batch F – K tablet containing varying concentrations of croscarmellose sodium and both *Pleurotus tuber-regium* and *croscarmellose sodium*

CONCLUSION:

The study has shown that it is feasible to formulate diclofenac into fast disintegrating tablets with the aim of rapid disintegration, dissolution, and absorption of the drug. *Pleurotus tuber-regium* powder acts as a super-disintegrant only at a much higher concentration, whereas at a lower concentration, it behaved like a conventional disintegrant. An optimal concentration of a combination of *Pleurotus tuber-regium* powder and croscarmellose sodium as disintegrants will produce fast disintegrating tablets and in turn, increase the dissolution rate of diclofenac tablets.

ACKNOWLEDGEMENT:

The authors acknowledge the technical support received from the laboratory staff of the Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, Benin City.

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