Nigerian Journal of Pharmaceutical and Applied Science Research, 6(2):1-7, September 2017

Optimization of disintegrant blends using Box Behnken design in the formulation of fast disintegrating tablets of diclofenac sodium

*Eraga Sylvester Okhuelegbe, Egharevba Precious Osayande and Iwuagwu Magnus Amara
Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, PMB 1154, Benin City, 300001, Nigeria.

ABSTRACT

The study aimed at formulating fast disintegrating tablets of diclofenac using a blend of disintegrants and to optimize the concentrations of the disintegrants for optimal tablet properties. Seventeen batches of diclofenac sodium tablets were prepared by direct compression using 17 combinations of three disintegrants (crospovidone, croscarmellose sodium and maize starch BP) generated by an experimental Box Behnken design model and subjected to disintegration and crushing strength tests to select four optimal batches. Granules and tablets of the optimal batches were bulk-prepared and subjected to flow properties and tablet evaluations. Drug-excipient compatibility studies were also carried out using DSC and FTIR. Granules of the optimal batches were free flowing. Disintegration times of the tablets were within 60 sec and were comparable with the disintegration times of the experimental study. The tablets were of crushing strength values > 4 kp and all the batches released 100 % drug content within 30 min. Compatibility studies revealed no interaction between diclofenac sodium and the excipients used. The Box Behnken optimization of three disintegrant concentrations to produce fast disintegrating tablets of diclofenac sodium with acceptable tablet properties was successful. The different combinations of the disintegrants affected the disintegration times and crushing strengths of the tablets.

Keywords: Box-Behnken, diclofenac, disintegrants, optimization, FDT

INTRODUCTION

Some patients experience difficulty in swallowing tablets and hard gelatin capsules and this usually leads to non-compliance to prescription resulting in incidence of ineffective therapy and treatment failure. Advances in drug delivery systems have also been directed at formulating convenient dosage forms for easy administration and to achieve better patient compliance (Shirsand *et al*., 2010). In line with recent efforts in developing drug dosage forms that are more convenient to use, pharmaceutical manufacturers have developed tablet formulations that can be ingested simply by placing them on the tongue (Reddy, 2002). These tablets known as fast disintegrating or fast dissolving tablets (FDT) are designed to disintegrate or dissolve rapidly on contact with saliva, thus eliminating the need to chew the tablet, swallow an intact tablet, or take the tablet with liquids (Indurwade *et al*., 2002, Iyad *et al*., 2008). This mode of administration was initially expected to be beneficial to paediatric, geriatric, bedridden or mentally challenged patients, but it has benefited patients with diarrhoea, persistent nausea or vomiting, travellers with little or no access to water and patients with condition of impaired swallowing. (Nachaegari and Bansal, 2004, Abdelbary *et al*., 2005).

Formulating a drug as FDT has the added advantage of increased bioavailability due to pre-gastric absorption of the drug in the oral cavity and oesophagus leading to faster onset of action. Also the amount of drug subjected to first-pass metabolism is reduced as compared to standard tablet (Kuchekar *et al*., 2003). Emergency drugs that are absorbed sublingually are the best candidates for FDTs but other drugs with short biologic half-life and undergo heavy first-pass metabolism have been formulated and studied (Narmada *et al*., 2009, Shirsand *et al*., 2009, Biswajit *et al*., 2011, Eraga *et al*., 2014). Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) used to treat pain or inflammation caused by arthritis or ankylosing spondylitis, muscle aches, backaches, dental pain, menstrual cramps and sports injuries. It also reduces pain, swelling and joint stiffness caused by arthritis. Diclofenac works by blocking the effect of cyclooxygenase (COX) enzymes, thereby inhibiting the production of prostaglandins which are produced at site of injury or damage and cause pain and inflammation. A fast disintegrating diclofenac tablet will ensure a quick onset of drug action and pain relief especially in an emergency situation.

*Correspondence author: E-mail: eragaso@uniben.edu Tel: +2348030884928

Superdisintegrants addition, one of the methods used in the formulation of FDTs involves choosing from a range of available (super) disintegrants. Given that the selected disintegrants will affect the cost of the final tablet products, efforts are made in getting the optimal amounts or concentrations of the disintegrants needed to achieve the desired tablet disintegration time. These optimal amounts or concentrations are usually arrived at by repetitive and random combinations of different amounts of the disintegrants, a process that can be wasteful and time consuming. The objectives of the study were to formulate fast disintegrating tablets of diclofenac using a combination of disintegrants and to optimize the concentrations of the disintegrants (crospovidone, croscarmellose sodium and maize starch powder) using the Box Behnken design for optimal tablet parameters.

MATERIALS AND METHODS

Materials

All materials were used as received from their suppliers. Diclofenac sodium powder (Sure Chem Ltd, England), crospovidone (ISP Technology, USA), croscarmellose sodium (FMC Bipolymer, USA), di-calcium phosphate anhydrous, (Innophos, Inc., NJ, USA), maize starch BP, magnesium stearate and talc (Edo Pharmaceuticals, Benin City). All other chemicals were of analytical reagent grade.

Methods

Preparation of granules and tablets

Experimental design

A preliminary Box Behnken Design (BBD) was developed using Design Expert® 10.0 (Statease, Inc. Minneapolis, USA) to determine the possible combinations of crospovidone, croscarmellose sodium and maize starch BP powders for maximizing the disintegration time and crushing strength of formulated tablets. The range and levels of variables (disintegrants) used are shown in Table 1.

The BBD combines the vertices of a hypercube whose coordinates are given by a 2^n factorial design to give 17 possible runs or combinations (Table 2). Each combination was treated as a batch and tablets for the 17 batches were prepared by direct compression and their disintegration times and crushing strengths determined in triplicate. The composition of the 17 experimental batches of tablets with their disintegration times and crushing strengths stated as mean ± SD are shown in Table 2. Batches B2, B10, B12 and B13 tablets were selected from Table 2 as optimum batches on the basis of their tablets having the lowest disintegration times and subjected to bulk production. A 100 tablets per batch were prepared by dry-mixing the calculated amounts of the ingredients in a mixer (Moulinex, France). The powder blend was passed through a 710 µm mesh screen (BSS Endecotts, England) and compressed into slugs using a heavy duty single punch tableting machine (Koln Niehi, Germany). The slugs were broken down into granules using a mortar and pestle. The granules were evaluated for pre-compression parameters and drug-excipients compatibility, before being directly compressed into tablets using a single punch tableting machine (Manesty Machines, UK) at a pressure of 35 arbitrary units (AU). The compressed tablets were kept in an air tight container until evaluation.

Evaluation of granules

The granules were evaluated for their bulk and tapped densities, angles of repose and flow rates following standard procedures. Carr's compressibility indices and Hausner's ratios of the batches of granules were thereafter calculated.

Compatibility studies

Drug-excipients compatibility studies were carried out on the granules and pure diclofenac sodium powder using DSC and FTIR analyses. The DSC analysis was carried out using the DSC822e Differential Scanning Calorimeter (Mettler Toledo, Switzerland). Four milligrams of the sample was weighed into the sample holding aluminium pan of the calorimeter and sealed. The seal of the pan was pierced and the pan placed in the calorimeter previously calibrated with indium and nitrogen as the purge gas. Heating of the sample was carried out at the rate of 10 °C per min from 30 to 350 °C under nitrogen at a flow rate of 70 ml/min. The FTIR analysis was done using FTIR-4100 Spectrophotometer (Shimadzu Co. Japan). Five milligrams of the granules was dry-mixed with potassium bromide to give a 200 mg weight powder. The mixed powder blend was compressed using a Sigma Press into a tablet. The tablet was placed in the sample compartment of the spectrophotometer and scanned over a range of 4000 - 1000 cm^{-1}.

Evaluation of tablets

Using standard procedures, the following tests were carried out on the compressed tablets: tablet weight uniformity, dimensions, crushing strengths, friability, disintegration time and dissolution studies (BP, 2003).

Weight uniformity

The weight of each of twenty randomly selected tablets of each batch was determined (Mettler Toledo, Switzerland) and the mean weight and standard deviations were computed.

Tablet dimensions

A micrometre screw gauge (Gallenkamp) was used to measure the thickness and diameter of each of ten tablets per batch and the mean values and standard deviations were recorded.

Friability

Ten pre-weighed tablets were placed in the drum of a friabilator (Erweka GmbH, Germany) revolving at 25 rpm. After 4 min, the tablets were brought out, de-dusted and reweighed. Friability was calculated as the percentage loss in weight.

Crushing strength

Using a motorized tablet hardness tester (Campbell Electronics, Model HT-30/50, India), the crushing strengths of ten tablets per batch were individually determined by diametrial compression of the tablet. Their mean values and standard deviations were recorded.

Disintegration time

The disintegration time for the batches of tablets was determined using the BP tablet disintegration test apparatus (Manesty Machines Ltd, UK). A tablet was placed in each of the six tubes of the apparatus. Distilled water, used as the disintegration medium was maintained at 37 ± 0.5 ºC and the time taken for the entire tablet to disintegrate completely was measured in seconds.

Dissolution studies

The dissolution tests were carried out using the BP paddle method. A dissolution test apparatus (Caleva ST7, UK) containing 900 ml of 0.1 M HCl solution maintained at 37 ± 0.5 °C with a revolution speed of 50 rpm was used. Six (6) tablets selected at random from each batch were used simultaneously for the study. A 5 ml aliquot was withdrawn from the dissolution medium at 5 min intervals for 30 min. The withdrawn fluid was replaced with an equivalent volume maintained at same temperature (37 ± 0.5 ºC). The aliquot was filtered and diluted with an equal volume of 0.1 M HCl solution. The absorbance of the resulting solution was measured at λmax 276 nm, using the UV/Visible spectrophotometer (T70, PG Instruments Ltd). The percentage of drug released was then calculated using the equation from the standard calibration plot obtained from the pure drug.

Statistical analysis

Descriptive statistics was done for all data using GraphPad InStat 3.10. Mean and standard deviations of replicate determinations was computed and reported. Differences between mean were subjected to Student's t-test at 5 % level of significance.

RESULTS

Granule properties

Results from the pre-compression analysis of the formulated granules of the four optimum batches are shown in Table 3. The bulk and tapped densities ranged from 0.610 to 0.688 g/cm^3 and 0.82 to 0.85 g/cm^3 respectively with angles of repose between 18.26 and 21.80°. The calculated compressibility indices and Hausner's ratios of the granules ranged from 21.53 to 25.61 % and 1.221 to 1.344, respectively. The granules also exhibited comparable flow rates with values ranging from 0.82 to 0.87 g/s. These flow parameter values would indicate good flowability of the granules (Carr, 1965, Mehta and Barker, 1994).

Table 1: Experimental range and level of the disintegrants

Independent variables (Disintegrants)	Symbol	Coded levels		
		-1	0	+1
		Actual levels (mg)		
Crospovidone	X_1	3.8	5	6.8
Croscarmellose sodium	X_2	7.2	9	10.8
Maize starch BP	X_3	3.2	4.2	5.3

Drug-excipients compatibility studies

Thermal analysis: Figure 1 (a) and (b) show the DSC thermograms of pure diclofenac sodium powder and its tablet granules respectively. The pure diclofenac sodium thermogram shows two endothermic troughs, a sharper one at 82 °C and a semi-broad one at 122 °C. The sharp trough may be attributed to the loss of water by the powder while the broader trough corresponds to the melting point of the amorphous diclofenac sodium powder. The thermogram of the granules showed the characteristic troughs seen in the pure diclofenac sodium thermogram, though not clearly well-defined, which may be due to the low content of diclofenac sodium in the tablet granules. But the absence of new troughs or shifts in the patterns indicates the absence of chemical interaction in the powder mixing and slugging processes.

FTIR: The FTIR spectrum of pure diclofenac sodium powder showed characteristic absorption bands at 758.38, 1502.55, 1568.13 and 3394.72 cm^{-1} (Figure 2 (a)). These bands observed for diclofenac remained unchanged when compared with the spectral data of the granules (Figure 2 (b)). The absence of any shift in the FT-IR bands suggests the absence of chemical interaction and complex formation between diclofenac sodium and excipients during the mixing and slugging processes.

Table **2:** Composition of experimental batches of tablets with their disintegration times and crushing strengths

Runs/ Batches	Factors						Responses	
	Coded values			Actual values			Disintegration time (sec)	Crushing strength (kp)
	X_1	X_2	X_3	X_1	X_2	X_3		
B1	0	-1	-1	5.0	7.2	3.2	120 ± 0.25	4.6 ± 0.55
B2	0	0	0	5.0	9.0	4.2	30 ± 1.10	4.3 ± 0.50
B3	+1	0	-1	6.8	9.0	3.2	90 ± 1.20	4.4 ± 0.55
B4	-1	+1	0	3.8	10.8	4.2	79 ± 0.40	4.2 ± 0.40
B5	0	-1	+1	5.0	7.2	5.3	140 ± 0.55	4.9 ± 0.90
B6	0	0	0	5.0	9.0	4.2	95 ± 0.65	4.2 ± 0.30
B7	+1	+1	0	6.8	10.8	4.2	80 ± 0.80	4.4 ± 0.60
B8	+1	0	+1	6.8	9.0	5.3	180 ± 0.50	3.2 ± 0.25
B9	0	0	0	5.0	9.0	4.2	85 ± 1.50	4.2 ± 0.15
B10	-1	-1	0	3.8	7.2	4.2	12 ± 2.20	5.6 ± 0.40
B11	0	0	0	5.0	9.0	4.2	160 ± 1.35	5.2 ± 0.20
B12	0	+1	-1	5.0	10.8	3.2	28 ± 1.20	4.9 ± 0.70
B13	-1	0	+1	3.8	9.0	5.3	41 ± 0.85	4.6 ± 0.25
B14	-1	0	-1	3.8	9.0	3.2	50 ± 1.65	4.6 ± 0.10
B15	0	0	0	5.0	9.0	4.2	110 ± 0.85	4.0 ± 0.45
B16	+1	-1	0	6.8	7.2	4.2	80 ± 1.10	4.2 ± 0.25
B17	0	+1	+1	5.0	10.8	5.3	90 ± 1.25	4.6 ± 0.70

X_1: amount of crospovidone (mg), X_2: amount of croscarmellose sodium (mg), X_3: amount of maize starch BP (mg). All batches contained 50 mg of diclofenac, 40-50 mg of di-calcium phosphate and 1.2 mg each of magnesium stearate and talc. Average weight of each tablet was 120 mg.

Table 3: Pre-compression parameters of formulated batches of granules

Parameters	Batches			
	B2	B10	B12	B13
Bulk density (g/cm^3)	0.63 ± 0.03	0.69 ± 0.01	0.67 ± 0.02	0.61 ± 0.04
Tapped density (g/cm^3)	0.83 ± 0.04	0.84 ± 0.03	0.85 ± 0.05	0.82 ± 0.03
Angle of repose (^{o})	18.26 ± 0.15	20.30 ± 0.10	20.56 ± 0.14	21.80 ± 0.09
Carr's index (%)	24.70 ± 0.02	18.10 ± 0.04	21.53 ± 0.02	25.61 ± 0.02
Hausner's ratio	1.33 ± 0.06	1.22 ± 0.02	1.27 ± 0.04	1.34 ± 0.03
Flow rate (g/s)	0.83 ± 0.07	0.87 ± 0.03	0.86 ± 0.04	0.82 ± 0.06

± Standard deviation

Table 4: Post compression parameters of the formulated batches of tablets

Parameters	Batches			
	B2	B10	B12	B13
Weight (mg)	118 ± 1.10	119 ± 0.74	120 ± 0.01	121 ± 0.71
Thickness (mm)	3.43 ± 0.01	3.41 ± 0.02	3.42 ± 0.01	3.42 ± 0.02
Diameter (mm)	6.32 ± 0.03	6.31 ± 0.02	6.30 ± 0.01	6.30 ± 0.03
Crushing strength (kp)	4.33 ± 0.33	5.25 ± 0.29	4.40 ± 0.25	4.25 ± 0.42
Friability (%)	2.48 ± 0.03	1.67 ± 0.02	1.75 ± 0.04	1.25 ± 0.01
Disintegration time (sec)	30.50 ± 1.25	50.00 ± 1.50	41.40 ± 0.25	12.50 ± 1.15

± Standard deviation

Tablet properties

Results from the post compression evaluations of the formulated four optimum batches of tablets are presented in Table 4. The average weight of the tablets ranged from 118 - 121 mg, while the thickness and diameter fell between 3.41 - 3.43 mm and 6.30 - 6.32 mm, respectively. The tablets exhibited crushing strength values between 4.25 - 5.25 kp and they were comparable to those obtained from the preliminary study while their friability values ranged from 1.25 - 2.48 % for the different batches.

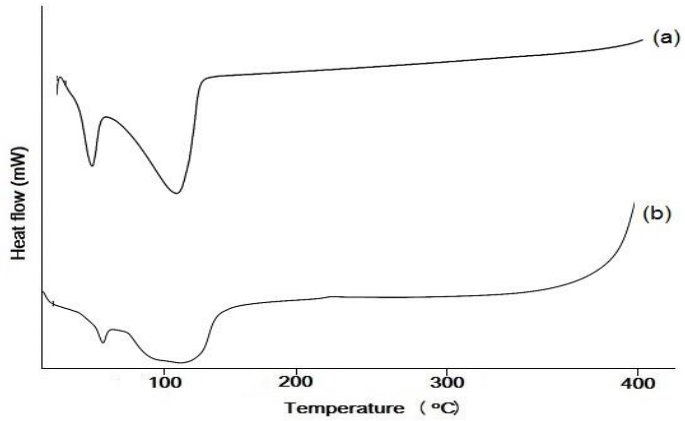

Figure 1**:** DSC thermograms of pure diclofenac sodium powder (a) and the tablet granules prepared by slugging (b).

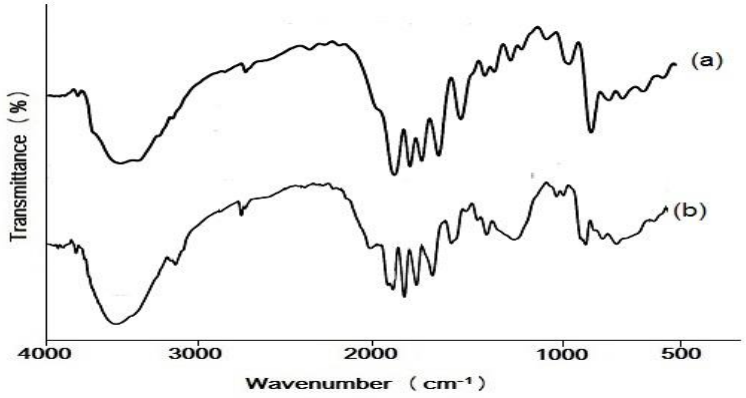

Figure 2: FTIR spectra of pure diclofenac sodium powder (a) and the tablet granules prepared by slugging (b).

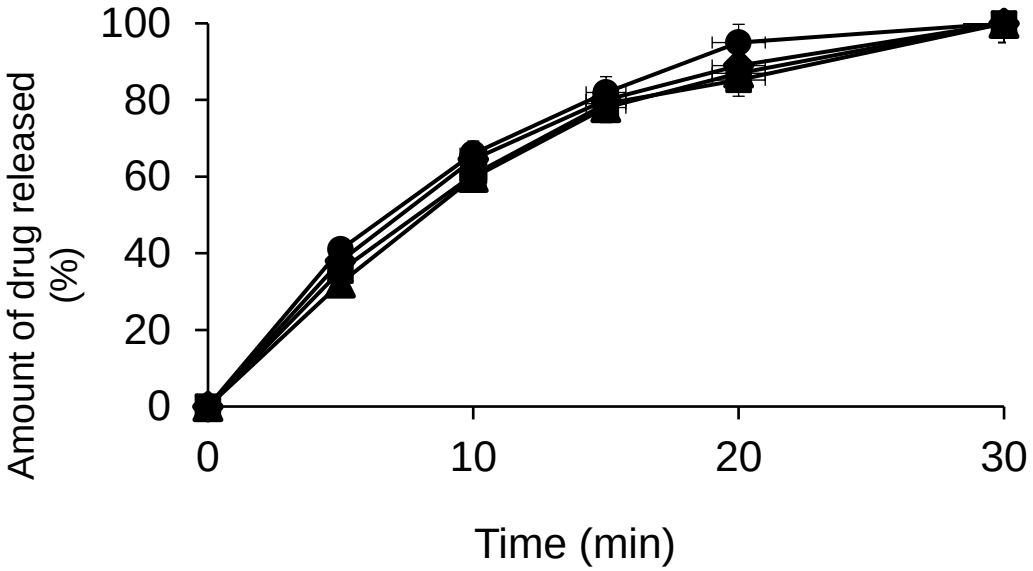

Figure 3**:** Dissolution profiles of the four batches of formulations.
(B2 (◆), B10 (■), B12 (▲), B13 (●))

All the tablets disintegrated within 60 sec with the B13 batch of tablets showing the lowest time of 13 sec and the B10 tablets with the highest time of 50 sec. The disintegration times of the bulk formulated tablets were not significantly different from the times obtained in the experimental preliminary study.

The *in vitro* dissolution profiles of the four optimal batches are presented in Figure 3. The tablets showed comparable release profiles with the cumulative percentage of drug release after 30 min of profiling at 100 % for all the batches of tablets. All the tablets achieved 70 % drug release within 10 min while the batch B13 tablets reached a 100 % drug release ahead of the other batches within 20 min.

DISCUSSION

The formulation of fast disintegrating tablets using disintegrant addition method requires that the amounts of the different disintegrants combined as a blend be properly chosen or optimized to effect optimal disintegration property when used in tablet formulation. In this study, the combination of three disintegrants at different concentrations ranges was carried out using a Box Behnken Design (BBD) model. Preliminary evaluations of tablets prepared from the combinational outcomes of the model revealed four disintegrant blends with optimal tablet disintegration times and crushing strengths.

The bulk produced tablets of these four optimal batches whose tablet parameters were further evaluated showed in their results, a non significant ($p > 0.05$) variations in tablet weights, thicknesses and diameters. The tablets weight variation being the most important of these parameters, fell within the BP specification of a maximum deviation of ±7.5 % from the average tablet weight (BP, 2009). The non-significant deviation in these tablet parameters could be attributed to the good flow of the granules resulting in uniform die filling and tablets of equal weights. Since tablet weight could be correlated with drug content, the uniformity in weight could also imply drug content uniformity in the batches of tablets. Also, their crushing strength values would suggest tablets of average hardness as values ranging from 5.0 - 8.0 kp have been recommended by the BP as optimum hardness values (BP, 2009), although a lower limit of 4.0 kp has been suggested by some researchers (Rudnic and Schwartz, 2006).

Furthermore, the average hardness of the tablets is reflected on the high friability values of the tablets. Since the BP recommends a 0.8 - 1.0 % friability for uncoated tablets (BP, 2009), these higher values would indicate tablets with poor friability. However, the European Pharmacopeia makes some allowance up to 2.0 % for tablets prepared by direct compression (EP, 2005). A tablet is expected to possess sufficient mechanical strength to withstand fracture and friabilation during handling and transportation (Carlin, 2008), while maintaining good disintegration and dissolution properties. The mechanical strength of FDTs is very important in its formulation as a balance between the tablet hardness and friability must be reached to prevent formulating a hard tablet that is difficult to break up in the mouth or a soft tablet that cannot withstand handling and transportation.

The disintegration time test, being the most important test in the evaluation of FDTs revealed that the disintegration times of all the batches of tablets did not only comply with the BP disintegration time specification of less than 15 min (BP, 2009) but also the European Pharmacopeia specification for FDTs of less than 3 min (EP, 2008). These short disintegration times of the tablets would ensure a rapid break down of the tablets into their primary particles, releasing their active pharmaceutical ingredient (API) and a quicker onset of action (Alebiowu and Adeagbo, 2009). As fast disintegrated tablets would necessarily lead to a fast drug dissolution, the dissolution profiles of the tablets can be said to follow the disintegration-dissolution theory that states that, the faster the disintegration of the tablet, the earlier the onset of drug dissolution. This postulation indicates that the disintegration time and the disintegration process are the limiting steps in the dissolution process since they determine when and how the tablet breaks up bringing the tablet particles in contact with liquid (Odeku and Itiola, 2003).

CONCLUSION

The study showed that the Box Behnken optimization of the different disintegrant concentrations to produce fast disintegrating tablets of diclofenac sodium with acceptable tablet properties was successful. It can therefore be stated that the combinations involving different concentrations of the disintegrants affected the disintegration times and crushing strengths of the tablets, and the right combination of the disintegrants can produce the intended result of disintegration time. Batch B14 tablets with average disintegration times of 12 sec and crushing strengths of 4.25 kp was superior to the other optimal batches.

REFERENCES

Abdelbary G, Eouani C, Prinderre P, Joachim J, Reynier J, Piccerelle P (2005). Determination of the *in vitro* disintegration profile of rapidly

disintegrating tablets and correlation with oral disintegration. *Int J Pharm* 292(1-2): 29-41.

Alebiowu G, Adeagbo AA (2009). Disintegrant properties of a paracetamol tablet formulation lubricated with co-processed lubricants. *Farmacia* 57(4): 500-510.

Biswajit B, Abhishek B, Sagar M, Vora V, Devraj B, Abhay D (2011). Formulation and evaluation of fast dissolving tablets of cinnarizine using superdisintegrant blends and subliming material. *J Adv Pharm Technol Res* 2: 266-273.

British Pharmacopoeia (2003). Vol. I and II. The Pharmaceutical Press, Her Majesty's Stationery Office, London, pp 249-252.

British Pharmacopoeia (2009). Vol III. The Pharmaceutical Press, Her Majesty's Stationery Office, London, pp 6578-6585.

Carlin BAC (2008). Direct compression and the role of filler-binders. Augsburger LL, Hoag SW (eds). Pharmaceutical Dosage Forms: Tablets, Informa Healthcare Inc., New York, pp 173-216.

Carr RL (1965). Evaluating flow properties of solids. *Chem Eng* 72: 163-168.

Eraga SO, Arhewoh MI, Ajah AI (2014). Evaluation of fast disintegrating tablets of nifedipine prepared by superdisintegrants addition and sublimation methods. *Dhaka Univ J Pharm Sci* 13(2): 199-205.

European Pharmacopoeia (2005). Supplement 5.0. European Pharmacopoeia Commission, Council of Europe, Strasbourg, p. 234.

European Pharmacopoeia (2008). Supplement 1.1. European Pharmacopoeia Commission, Council of Europe, Strasbourg, pp. 748-750.

Indurwade NH, Rajyaguru TH, Nakhat PD (2002). Novel approach-fast dissolving tablets. *Indian Drugs* 39(8): 405-409.

Iyad R, Mayyas A, Ala'a E, Adnan B (2008). Chitin silicon dioxide co-precipitate as a novel superdisintegrants. *J Pharm Sci* 97(11): 4955-4969.

Kuchekar B, Atul S, Badhan C, Mahajan HS (2003). Mouth dissolving tablets: A novel drug delivery system. *Int J App Bio Pharma Tech* 35: 7-9.

Mehta A, Barker CG (1994). Disorder, memory and avalanches in sand piles. *Europhys Lett* 27(7): 501-506.

Nachaegari SK, Bansal AK (2004). Co-processed excipients for solid dosage forms. *Pharm Technol* 28(1): 52-64.

Narmada GY, Mohini K, Prakash Rao B, Gowrinath DXP, Kumar KS (2009). Formulation, evaluation and optimization of fast dissolving tablets containing amlodipine besylate by sublimation method. *Ars Pharm* 50: 129-144.

Odeku OA, Itiola OA (2003). Effects of interacting variables on the tensile strength and the release properties of paracetamol tablet. *Trop J Pharm Res* 2: 147-153.

Reddy LH (2002). Fast dissolving drug delivery system: A review of the literature. *Indian J Pharm Sci* 64: 331-336.

Rudnic EM, Schwartz JB (2006). Oral solid dosage forms. In: Troy DB, Beringer P (eds). Remington - The Science and Practice of Pharmacy, Lippincott Williams and Wilkins, Baltimore, pp 889-928.

Shirsand SB, Sarasija S, Swamy PV (2009). Formulation design and optimization of fast dissolving clonazepam tablets. *Indian J Pharm Sci* 71: 567-572.

Shirsand SB, Sarasija S, Swamy PV, Para MS, Kumar DN (2010). Fast disintegrating tablets using disintegrant blends. *Indian J Pharm Sci* 72(1): 130-133.