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Simplex Lattice Optimization of Superdisintegrants in the Formulation of Fast Oral Dissolving Tablets of Ibuprofen

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Optimization of different superdisintegrants using the simplex lattice design in the formulation of fast disintegrating tablets of ibuprofen was studied. Seven formulations (F1 to F7) were prepared by direct compression of ibuprofen as the model drug and a combination of superdisintegrants–pre-gelatinized starch, croscarmellose sodium and crospovidone–utilizing the simplex lattice design. FTIR analysis of drug and excipients was carried out. Granules and tablets formulated were evaluated for pre- and post-compression parameters. The granules were fairly free flowing with angles of repose ranging from 42 - 49°, Carr's index < 24 %, and a Hausner's quotient < 1.3. The tablet hardness and friability were 4.00 - 5.99 kgF and < 1 %, respectively, while wetting and disintegration times were < 160 and < 76 s, respectively. Dissolution profiles showed all the tablets released over 60 % of drug within 5 min. FTIR analysis showed no interactions between ibuprofen and excipients. The simplex lattice design revealed that combination of superdisintegrants significantly affects the wetting and disintegration times as well as drug release.

Key words: Simplex lattice, fast disintegrating tablets, superdisintegrants.

INTRODUCTION

Fast disintegrating tablets (FDTs) or oral dissolving tablets are advantageous particularly for pediatric, geriatric and mentally ill patients as well as for persons experiencing difficulty in swallowing conventional tablets and capsules [1]. These dosage forms are placed in the mouth and allowed to disperse or dissolve in the saliva. They release the drug as soon as they come in contact with the saliva, thus obviating the need for water during administration. Water plays an important lubricating role when swallowing oral dosage forms and people usually experience discomfort when swallowing conventional solid dosage forms without water [2].

The United States Food and Drug Administration (FDA) has defined an FDT as "A solid dosage form containing medicinal substances or active ingredients which disintegrates rapidly within a few seconds when placed on the tongue". FDTs release medicament in the mouth allowing for absorption throughout the gastro-intestinal tract [3]. Among the various dosage forms developed to improve the ease of administration, the FDTs are the most widely preferred commercial products [4].

FDTs are a new generation of formulations which combine the advantages of both liquid and conventional tablet formulations and, at the same time, offer added advantages over both the traditional dosage forms. They provide the handling convenience of a tablet formulation and also afford the ease of swallowing provided by a liquid formulation [5]. Currently, FDTs are available in the market for the treatment of many disease conditions including hypertension, migraine, dysphagia, nausea, vomiting, Parkinson's disease, schizophrenia and pediatric emergencies [6-9].

Ibuprofen, a propionic acid derivative, is one of the most commonly used non-steroidal anti-inflammatory drug (NSAID) for its analgesic, anti-inflammatory and anti-pyretic properties [10,11]. It is used in the management of mild to moderate pain [12] and in acute or chronic pain [13] especially in dental practice. Ibuprofen is absorbed throughout the gastrointestinal tract [14]. Hence an FDT

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formulation of the drug will enhance absorption right from the mouth, especially when fast onset of action is needed.

The objective of the present investigation was to explore the feasibility of preparing a fast dissolving tablet brand of ibuprofen using different superdisintegrants and optimizing their concentrations when used together as a blend.

EXPERIMENTAL

Materials

Ibuprofen powder and magnesium stearate were gift samples from Edo Pharmaceuticals Ltd, Benin City, Edo State, Nigeria. Excipients employed in the formulation included croscarmellose sodium (BDH Chemicals, Poole, UK), crospovidone (ISP Technologies Inc., Wayne, NJ, USA), pre-gelatinised starch and dicalcium phosphate anhydrous (Innophos Inc., Cranbury, NJ, USA).

Preparation of tablets

Simplex lattice design

The simplex lattice design was developed by Scheffe [15] using the theory of statistics and experiments to obtain models that can be used to determine mix proportions for a specified criterion. In our design experiment, one criterion (disintegration) was evaluated by changing the concentrations of three superdisintegrants simultaneously while keeping their total concentration constant. A three-superdisintegrant system design will be represented by a two dimensional equilateral triangle with its three vertices representing a formulation containing the maximum amount of one superdisintegrant, with the other two superdisintegrants at a minimum level. The three midpoints between vertices represent a formulation containing the average of the minimum and maximum amounts of the other two superdisintegrants and a center point representing a formulation containing one third of each superdisintegrant.

Using this design, with our independent variables being the concentrations of each superdisintegrant, the various batches of tablets were prepared using the formula in Table 1. Seven formulations (batches) of ibuprofen containing the three superdisintegrants croscarmellose sodium, crospovidone and pre-gelatinized starch in different proportions were prepared using anhydrous dicalcium phosphate as diluent. Amounts of the ingredients calculated to produce 100 tablets per batch were mixed together. The powder blend was passed through a 710 μm mesh screen (Endecotts, London, UK) and the resulting blend evaluated for pre-compression parameters prior to compression into tablets using a single punch tableting machine (Manesty Machines, Liverpool, UK) at a pressure of 35 arbitrary units (AU).

Table 1: Composition of Superdisintegrants in Formulation

Batch Code	Transformed Fraction of Independent Variables		
	X_1	X_2	X_3
F1	1*	0	0
F2	0.5	0.5	0
F3	0	1	0
F4	0	0.5	0.5
F5	0	0	1
F6	0.5	0	0.5
F7	0.33	0.33	0.33

X_1: amount of croscarmellose sodium (mg), X_2: amount of crospovidone (mg), X_3: amount of pre-gelatinized starch (mg). *A value of 1, 0.5 and 0.33 represents 20, 10 and 6.67 mg respectively of the superdisintegrant. All batches contained 200 mg of ibuprofen, 176 mg of anhydrous dicalcium phosphate and 1% w/w of magnesium stearate. Average tablet weight = 400 mg.

Evaluation of powder blend

The granule bulk and tapped densities as well as the angle of repose were evaluated according to compendial specifications. Compressibility (Carr's) index and Hausner factor were thereafter calculated.

Compatibility studies

Drug-excipient interactions were studied using a Spectrum BX Fourier Transform Infrared Spectrophotometer (Perkin-Elmer, Beaconsfield, England). The drug, excipients and powdered tablet formulations were

separately pressed into KBr pellets and scanned at a range of 4000 - 350 cm^{-1}.

Evaluation of tablets

The tablet dimensions, weight uniformity, hardness and friability of the compressed tablets were evaluated as per standard procedures [16].

Wetting time: A piece of double-folded tissue paper was placed in a Petri dish containing 6 ml of water. The tablet was placed on the wet tissue paper and the time in seconds for complete wetting of the tablet surface was measured and recorded [17].

Disintegration test: The disintegration time for all formulations was measured using a tablet disintegration test apparatus (Manesty Machines Ltd, Liverpool, UK). A tablet was placed in each of the six tubes of the apparatus. Distilled water at 37 ± 0.5 ºC was used as the disintegration medium. The time in seconds taken for the tablet to disintegrate completely was measured and recorded.

Dissolution studies: The dissolution tests were carried out using a BP dissolution test apparatus (GB Caleva Ltd, Sturminster Newton, UK) fitted with a basket rotated at 100 rpm. The dissolution medium was 900 ml of phosphate buffer pH 6.8 maintained at 37 ± 0.5 ºC. Six (6) tablets selected at random from each batch were used simultaneously for the study. A 5 ml aliquot of leaching fluid was withdrawn at 5 min intervals for 30 min. The withdrawn fluid was replaced with an equivalent volume of phosphate buffer maintained at 37 ± 0.5 ºC. The aliquot was filtered and diluted with an equal volume of phosphate buffer. The absorbances of the resulting solutions were measured at λ_{max} 266 nm, using a UV/Visible spectrophotometer. The percentage of drug released was calculated from the absorbance. The dissolution profiles of two commercially available ibuprofen tablets were evaluated for comparison.

Statistical analysis

Descriptive statistics was performed for all data using Microsoft Excel (2007). Means and standard deviations of triplicate determinations were computed and reported. Differences between mean were determined using ANOVA and $p < 0.05$ was considered significant.

RESULTS AND DISCUSSION

The FTIR spectra of drug, excipients and formulated tablets are shown in Figure 1. The IR absorption spectra of the individual excipients and pure ibuprofen were found to be similar with that of the formulated tablet granules containing ibuprofen and the excipients, with no extra bands observed in the spectra. This finding confirmed that ibuprofen did not interact with any of the excipients used in this study, an indication that the drug and excipients were compatible with each other.

Pre-compression parameters

The flow properties of powder mixtures are important for the uniformity of the mass of the tablet. The angle of repose was between 42.93°-49.09º, indicating poor powder flow. However, other parameters put together gave a Hausner's ratio ranging from 1.170 to 1.319 as seen in Table 2, which is within the acceptable range. Consequently, flow still occurred despite the high angle of repose.

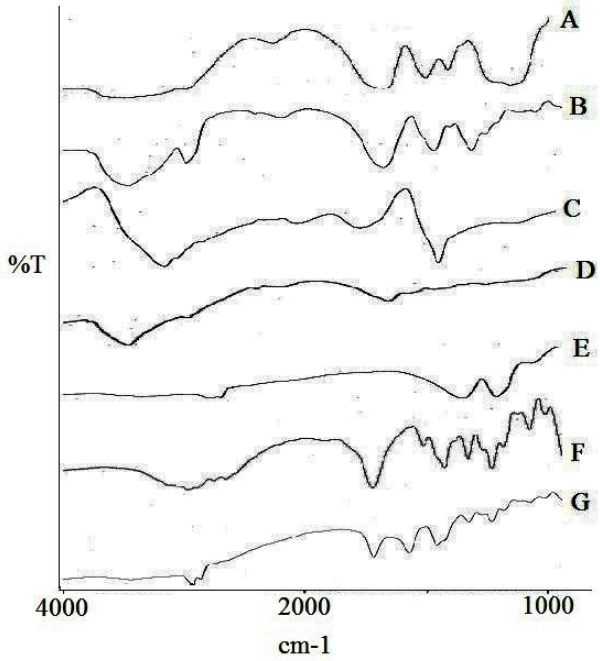

Figure 1: FTIR Spectra of ibuprofen, excipients and formulations

Key: A = croscarmellose sodium, B = crospovidone, C = anhydrous dicalcium phosphate, D = pre-gelatinized starch, E = magnesium stearate, F = ibuprofen, G = ibuprofen + excipients

Table 2: Pre-compression parameters of the powder blends of the various batches

Batch	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Angle of Repose (º)	Carr's Index (%)	Hausner Ratio
F1	0.500 ± 0.29	0.588 ± 0.18	43.95 ± 0.03	14.97 ± 0.56	1.176 ± 0.13
F2	0.435 ± 0.25	0.526 ± 0.27	45.64 ± 0.65	17.30 ± 0.67	1.209 ± 0.25
F3	0.488 ± 0.17	0.571 ± 0.13	49.09 ± 0.21	14.54 ± 0.45	1.170 ± 0.10
F4	0.490 ± 0.32	0.625 ± 0.22	45.00 ± 0.32	21.60 ± 0.33	1.275 ± 0.18
F5	0.481 ± 0.14	0.600 ± 0.10	43.60 ± 0.67	19.83 ± 0.56	1.247 ± 0.65
F6	0.496 ± 0.23	0.615 ± 0.23	47.94 ± 0.33	20.64 ± 0.54	1.240 ± 0.18
F7	0.444 ± 0.19	0.586 ± 0.42	42.93 ± 0.65	24.23 ± 0.43	1.319 ± 0.56

Post-compression parameters

The weight of the prepared tablets ranged between 390.22 and 409.34 mg. The weights did not vary significantly ($p > 0.05$) among themselves. The percentage friability of all the tablets was less than 1.0 % (Table 3) indicating the ability of the tablets to withstand abrasion in handling, packaging and shipment. The hardness of prepared tablets was between 4.0 to 5.0 kgF (Table 3). Tablet hardness of 4.0 kgF is considered to be the minimum for a satisfactory tablet [18]. These values were observed to be highest in F3 (5.0) and lowest in F5 (4.0). This finding is in agreement with Lachman *et al.* [19] who, in a similar study, observed a relative drop in the tensile strength of FDTs formulated with pre-gelatinized starch compared to those formulated with crospovidone and croscarmellose sodium as superdisintegrants.

Table 3: Post-compression parameters of the tablets formulated (Mean ± SD)

Batch	Weight Variation (mg)	Hardness (kgF)	Friability (%w/w)	Wetting Time (sec)	Disintegration Time (sec)
F1	1.520 ± 0.01	4.25 ± 0.14	0.70 ± 0.22	78 ± 0.34	20.34 ± 0.04
F2	0.756 ± 0.02	4.75 ± 0.09	0.80 ± 0.16	50 ± 0.14	12.05 ± 0.34
F3	2.439 ± 0.16	5.00 ± 0.33	0.90 ± 0.06	145 ± 0.25	60.05 ± 0.05
F4	1.234 ± 0.02	4.50 ± 0.45	0.80 ± 0.02	102 ± 0.45	32.25 ± 0.65
F5	0.982 ± 0.17	4.00 ± 0.66	0.96 ± 0.42	160 ± 0.82	75.45 ± 0.78
F6	1.112 ± 0.02	4.50 ± 0.12	0.88 ± 0.56	130 ± 0.90	39.45 ± 0.09
F7	0.789 ± 0.23	4.75 ± 0.33	0.62 ± 0.09	93 ± 0.56	26.18 ± 0.67

The wetting time of formulation F2 containing crospovidone and croscarmellose sodium in equal proportions was 50 sec (Table 3) and was lower than that of the other formulations. Deepali [20] achieved a similar result in his study on naproxen tablet formulations. Zhao and Augsburger [21] in their study showed that wetting time in addition to disintegration time affects dissolution time of drugs. The authors reported that increasing concentrations of crospovidone will decrease the wetting time of tablets (via its wicking action) while pre-gelatinized starch on the other hand will increase the wetting time but croscarmellose will have no observable effect on wetting time.

The most important parameter that needs to be optimized in the development of FDTs is the disintegrating time of the tablet (FDA approved value ≤ 3 min) [22]. In our study, it was observed that with increased concentration of pre-gelatinized starch, there was a relative increase in the disintegrating time of the formulated tablets: F5 (75.45 sec) compared to F6 (39.45 sec) and F4 (32.25 sec). This may have been due to the formation of a viscous gel layer by the swelling of pre-gelatinized starch at higher concentrations. The gel layer can be a barrier to the penetration of the disintegrating medium and possibly hinder disintegration or leakage of the tablet content.

In a similar work, Bolhuis *et al.* [23] concluded that disintegration time can be effectively reduced by using a combination of wick-type and swelling-dependent superdisintegrants with an even blend of croscarmellose and crospovidone (wick and swell type) giving the least disintegration time.

The optimum formulation which showed rapid disintegration was formulation F2 containing equal proportions of crospovidone and croscarmellose sodium. This rapid disintegration was due to the penetration of liquid into the pores of the tablets, leading to the swelling and wicking of superdisintegrants to create enough hydrodynamic pressure for quick and complete tablet disintegration. Both superdisintegrants exhibit good water uptake with high capillary action and rapid swelling. This combination of properties leads to fast tablet disintegration as was also observed in a similar work carried out by Seong *et al.* [24].

Wetting and disintegration times are critical to the dissolution profiles of FDTs. There is a correlation between wetting time, disintegration time and the drug release profiles of the formulated tablets (Figure 2).

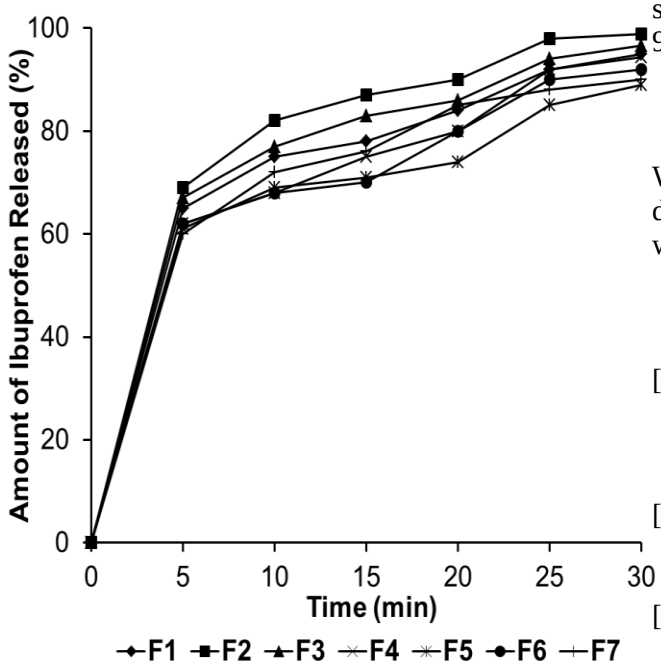

Figure 2: Ibuprofen Release Profile of Batch F1 – F7.

The F2 batch of tablets with shorter wetting and disintegration times exhibited the highest per cent drug release. The lowest per cent drug release occurred from the F5 batch with longer wetting and disintegration times. This slow release of the batch F5 tablets may be due to rapid swelling into primary particles of the pre-gelatinized starch forming a viscous gel layer that slowly releases the drug. Thus the differences in drug release profiles may be attributed to the difference in surface area exposed to the dissolving medium rather than the speed of tablet disintegration. Furthermore, the dissolution profile of batch F3 tablets containing crospovidone alone is dependent on the volume of the dissolution medium and surface area of the granules exposed to the medium.

CONCLUSION

The formulation containing crospovidone and croscarmellose sodium in equal proportions showed the fastest disintegration time when compared to the other formulations. Tablets with fast disintegration can be produced by selecting the proper amounts and combinations of disintegrants in tablet formulation. Although differences existed between superdisintegrants, FDTs of ibuprofen could be prepared using any of the superdisintegrants used here to achieve over 90 % drug release within 30 min.

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