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Original Investigation

Formulation Optimization and in-vitro Evaluation of Diclofenac Fast Disintegrating Tablets

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ABSTRACT

INTRODUCTION: Fast disintegrating tablets (FDTs) are solid dosage forms that disintegrate and dissolve in the mouth without the need for water within a matter of seconds. In the present study, a fast-disintegrating tablet of diclofenac sodium was prepared using WOWTAB (without water) technology, and its in-vitro characters were analyzed to prepare an optimum formulation. **MATERIALS AND METHODS:** Diclofenac sodium and its reference standard along with other excipients were collected. Softer tablets with hardness ranging from 1.493 to 1.522 kg/cm2 were prepared using Plackett-Burman (PB) design and central composite design (CCD). Various physicochemical parameters and in-vitro quality parameters of formulations were evaluated using standard methods. **RESULTS:** The disintegration time of the formulations ranged from 76 to 126 seconds. The in-vitro drug release was found to be from 96.31 to 99.94%. The study of contour plot and surface plot indicated that formulation with maltose concentration of 5 mg and mannitol concentration of 90 mg would produce an optimized formulation of diclofenac fast disintegration tablet with a rapid disintegration time of 1.2 to 1.4 minutes and dissolution percent at 30 minutes of 99.5 to 100%. **CONCLUSIONS:** Diclofenac FDT was prepared based on WOWTAB technology. Formulation containing maltose 5 mg and mannitol 90 mg would be an optimized formulation of diclofenac FDT, with a rapid disintegration time of 1.2 to 1.4 minutes and dissolution percent at 30 minutes of 99.5 to 100 %.

Keywords: Diclofenac sodium, fast disintegrating tablet, WOWTAB, optimized formulation

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INTRODUCTION

Fast disintegrating tablets (FDTs), also called mouth dissolving tablets (MDTs) are defined as solid dosage forms designed to dissolve in the mouth without water within seconds [1]. These dosage forms disintegrate instantly in the mouth and thus results in quick absorption and fast onset of clinical effect [2]. They are ideal for pediatric, geriatric, bedridden, and developmentally disabled patients and patients with persistent nausea, traveling, or little or no water access [3]. Various manufacturing techniques used for preparing MDTs are lyophilization, moulding, direct compression, spray drying, sublimation, and mass extrusion [4]. The direct compression method is the simplest and most cost-effective technique. The disintegration and dissolution of directly compressed tablets depend on the disintegrants used or any water-soluble excipients [5,6]. In the current study, WOWTAB technology was used for preparing diclofenac FDTs using mannitol as a low mouldability saccharide and maltose as a high mouldability saccharide. WOWTAB technology involves coating low mouldability saccharides with high mouldability saccharides to give tablets adequate hardness and quick disintegration in the mouth [3,7]. Diclofenac sodium is a traditional non-steroidal anti-inflammatory (NSAID), most extensively employed in rheumatoid arthritis and osteoarthritis, bursitis, ankylosing spondylitis, toothache, dysmenorrhoea, post-traumatic and post-operative inflammatory conditions [8]. It belongs to the BCS class II category and is an ideal candidate for FDTs [9]. Diclofenac is only 50% absorbed systemically and its peak plasma concentration is achieved approximately 1 hour after oral administration, which suggests the need for fast disintegrating tablet dosage form of diclofenac [3,10,11]. So, the present study is undertaken to prepare a fast-disintegrating formulation that will give rapid and more effective pain-relieving action.

MATERIALS AND METHODS

Active ingredient and excipients::

Diclofenac sodium and its reference standard (Potency: 99.45% and loss on drying: 0.22%), mannitol, maltose, lactose, saccharin, menthol flavor, and magnesium stearate were obtained from Chemidrug Industries Pvt. Ltd., Thankot, Kathmandu.

Chemical and reagents:

Phosphate Buffer pH 6.8

250 ml 0.20 M potassium dihydrogen phosphate was taken in a 1000 ml volumetric flask and added 100 ml 0.20 M sodium hydroxide. Volume was made up to 1000 ml with distilled water to prepare phosphate buffer pH 6.8 [12].

Simulated Salivary Fluid

2.38 g Disodium hydrogen phosphate (Na_2HPo_4), 0.19 g Potassium dihydrogen phosphate (KH_2PO_4), and 8.00 g Sodium chloride (NaCl) were dissolved in 1 liter of distilled water to prepare simulated salivary fluid, pH adjusted to 6.76 with phosphoric acid [13].

Standard Calibration Curve

A 100 mg reference standard of diclofenac sodium was taken and dissolved in 100 ml of pH 6.8 phosphate buffer to prepare a stock solution. 10 ml was pipetted out and diluted up to 100 ml. Again, 1.0, 2.0, 3.0, 4.0, and 5.0 ml were pipetted out and diluted up to 10 ml. The absorbance was measured using an ultraviolet (UV) spectrophotometer at 283 nm [8].

Formulation of diclofenac FDT

Diclofenac fast disintegration tablets were prepared by the wet granulation method. Twelve formulations based on the Plackett-Burman (PB) design and thirteen formulations based on the central composite design (CCD) were prepared using Minitab version 16 software. All the ingredients were weighed accurately, sieved through sieve number 40, and mixed together geometrically. The granules formed were dried at 500^{0}C for 20 minutes and then compressed using a Labpress 10-station tablet compression machine to prepare a fast disintegrating diclofenac tablet. The preparation and in-vitro evaluation of diclofenac FDTs were carried out at Chemidrug Industries Pvt. Ltd., Thankot and Lomus Pharmaceuticals Pvt. Ltd., Kathmandu.

Pre-compressional analysis of powder mixture:

Carr's Index: An amount of powder equivalent to 5.0 ml was weighed, taken in a glass tube, and bulk volume determined. After tapping the tube 100 times, the tapped volume was measured, and Carr's index (I) was determined. Values of "I" below 15 % usually give rise to good flow characteristics and above 25 % indicates poor flowability [14].

Hausner's Ratio: The Hausner's ratio is an indirect index of ease of powder flow. A lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25) [15,16].

Wetting Time: A piece of tissue paper was folded double and was placed in a Petri plate containing 6 ml of simulated salivary fluid. The tablet was placed on the paper and the time for complete wetting was measured [17].

In-vitro Analysis

Weight Variation: Twenty tablets were selected at random and the average weight was determined. Then, individual tablets were weighed and compared with average weight [18].

Friability: Pre-weighed samples of twenty tablets were placed in the Roche friabilator and were subjected to 100 revolutions, the final weight was measured, and friability was determined [18].

Hardness: Hardness was measured using a Monsanto tablet hardness tester (Electrolab). Six tablets were selected randomly from each batch and the hardness of each was measured [16].

In-vitro Disintegration test: Electrolab disintegration tester was used to determine the disintegration time of the formulations. Six randomly selected tablets were selected at random and disintegration time was determined using phosphate buffer pH 6.8 as the medium [19]. Minitab software was used to determine the effect of excipients on the disintegration time.

Drug Assay: Assay was carried out to determine the actual drug content in the tablet. A 20 µg solution of standard and test sample of diclofenac were prepared and the absorbance of both solutions was measured at 283 nm [19].

In-vitro Drug Release: In-vitro drug release studies were carried out for all the formulations using a tablet dissolution test apparatus (USP XXII paddle type) at 50 rpm and phosphate buffer pH 6.8 was used as the dissolution medium. 1 ml sample was withdrawn at 5, 10, 15, 20, 25, and 30 minutes and diluted to prepare a 20 µg solution. The final solution was filtered and analyzed for drug release using a UV spectrophotometer (Shimadzu) at 283 nm [19].

Statistical analysis:

The data was analyzed using SPSS software, and descriptive statistics (mean, SD, frequency and percentage) were applied.

RESULTS

Standard Calibration Curve

The absorbance measured for the serial strength of diclofenac sodium reference standard by UV/Visible spectrophotometer at 283 nm is shown in figure 1.

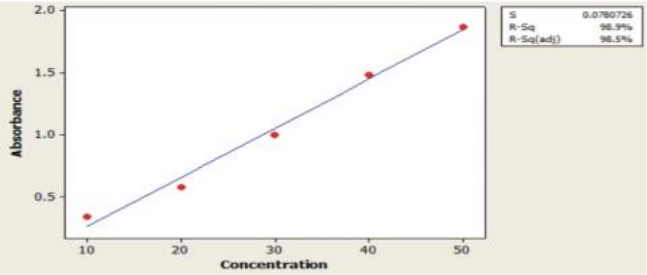

Figure 1: Standard calibration curve of diclofenac sodium (y = -0.1370 + 0.03970x)

Figure 1 shows a fairly linear relationship between the concentration (µg/ml) and absorbance with the R^2 value of 98.90%. This indicates that the absorbance increases linearly with the increase in concentration. This validates the assay procedure used to determine the drug content of each formulation.

In–vitro disintegration test

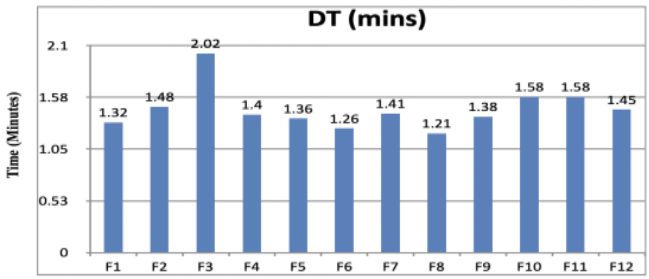

Figure 2: Disintegration time of different formulations based on PB design

All formulations except F3 disintegrated within the limit of two minutes. The disintegration time for F3 was 2.02 minutes, which may be due to the low amount of low mouldability saccharide, mannitol (40 mg), and high amount of high mouldability saccharide, maltose (16 mg).

Determination of factors influencing disintegration time

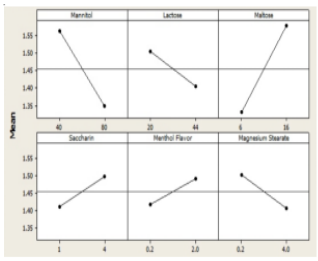

Figure 3: Main effect plot

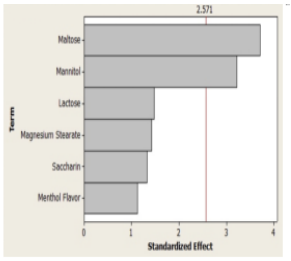

Figure 4: Pareto chart of the standardized effects(Alpha=0.05)

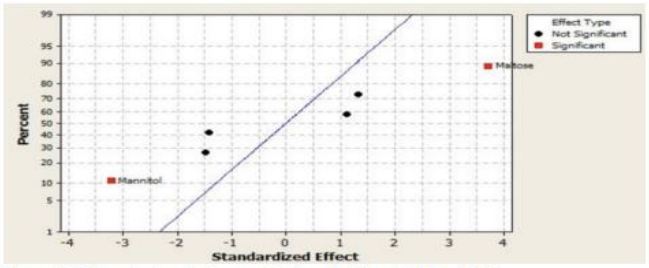

Figure 5: Normal plot of the standardized effects (Alpha=0.05)

The main effect plot, Pareto chart, and normal chart show that mannitol and maltose influence the disintegration time significantly while the other ingredients have an insignificant role in the disintegration time of the formulation at a 95% confidence interval. The disintegration time of tablet increases with an increase in maltose concentration and a decrease in mannitol concentration.

In-vitro Analysis

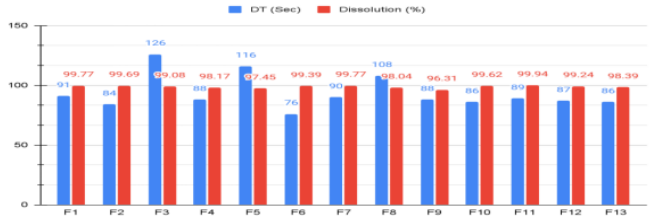

Figure 6: Disintegration time and dissolution of formulations based on CCD design

Table 1| Physico-chemical properties of CCD formulations

Formulation Code	Average Weight (mg) n = 20	±SD	Average Thickness (mm) n = 6	±SD	Average Diameter (mm) n = 6	±SD	Average Hardness (Kg/cm²) n = 6	±SD	Friability (%)	Assay n = 2	±SD	DT (Sec)	Dissolution (%)
F1	198.9	5.820	1.904	0.021	6.39	0.022	1.495	0.080	0.85	99.55	0.375	91	99.77
F2	199.8	3.795	1.909	0.02	6.4	0.014	1.498	0.048	0.92	99.41	0.700	84	99.69
F3	199	2.749	1.907	0.018	6.4	0.014	1.498	0.047	0.7	100.77	0.269	126	99.08
F4	199	1.826	1.913	0.022	6.4	0.014	1.522	0.037	0.4	98.64	0.396	88	98.17
F5	200	4.595	1.902	0.021	6.4	0.025	1.505	0.034	0.55	96.31	1.379	116	97.45
F6	198.3	4.448	1.914	0.023	6.4	0.008	1.478	0.038	1.1	100.8	2.588	76	99.39
F7	200	2.211	1.900	0.030	6.4	0.014	1.507	0.037	0.65	97.92	1.739	90	99.77
F8	200.4	2.503	1.898	0.040	6.4	0.014	1.498	0.021	0.25	101.86	1.994	108	98.04
F9	200.1	1.197	1.916	0.017	6.4	0.021	1.493	0.027	0.19	102.59	2.008	88	96.31
F10	199.2	1.874	1.903	0.015	6.4	0.008	1.503	0.033	0.1	101.47	1.676	86	99.62
F11	199.2	2.781	1.904	0.010	6.4	0.014	1.507	0.033	0.1	99.81	0.792	89	99.94
F12	199.9	1.912	1.885	0.054	6.4	0.028	1.500	0.046	0.35	99.49	0.629	87	99.24
F13	199.7	1.703	1.906	0.032	6.4	0.025	1.498	0.021	0.25	98.00	1.400	86	98.39

Table 1 shows various physicochemical properties of the CCD formulations such as weight variation, thickness, diameter, hardness, friability, assay, disintegration time, and dissolution. Softer tablets with hardness ranging from 1.493 to 1.522 kg/cm2 were prepared. The result is similar to the one obtained by Dor JN et al [7]. The study found that low mouldable sugar-coated with high mouldable sugar gave rise to tablets with a hardness of 1.0 – 2.0 kg/cm2.

All the formulations disintegrated within the specified limit of two minutes except for formulation (F3) whose disintegration time was found to be 2.06 minutes, which may be due to the lower amount of low mouldability saccharide, mannitol (50 mg), and a higher amount of high mouldability saccharide, maltose (19 mg). The in-vitro drug release after 30 minutes was found to range from 96.31 % to 99.94%. Dissolution was within the pharmacopoeial limit. The disintegration time was slightly higher than the one found by Dor JM et al [7].

Optimization of formulations

Contour and surface plot for disintegration time

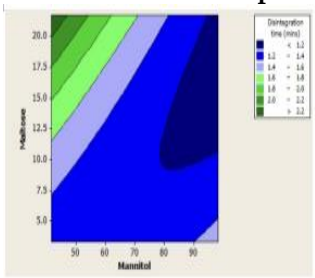

Figure 7: Contour plot for disintegration time of CCD formulations

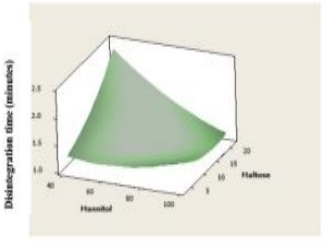

Figure 8: Surface plot for disintegration time of CCD formulations

The contour and surface plot of disintegration shows that as the concentration of maltose increases, disintegration time increases rapidly with an increase in maltose concentration and a decrease in mannitol concentration. Analysing the plots suggests that a formulation containing a mannitol concentration of 80 mg or more and a maltose concentration of 5.0 mg or less has an optimum disintegration of 1.5 or fewer minutes.

Contour and surface plot for dissolution

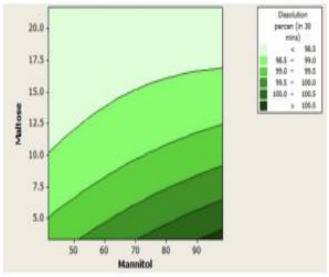

Figure 9: Contour plot for dissolution of CCD formulations

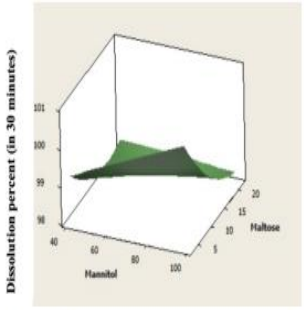

Figure 10: Surface plot of dissolution of CCD formulations

The contour and surface plot for dissolution show that the drug release from the tablet increases with the increase in the concentration of mannitol and the decrease in the concentration of maltose. The best drug release of 99.5% to 100% is shown by the dark green area in the plot that is obtained when the concentration of maltose is 5 mg or below and that of mannitol is 60% to 90%.

Thus, from the surface plot and contour plot of disintegration and dissolution, a formulation with a maltose concentration of 5 mg and mannitol concentration of 90 mg would produce an optimized formulation of diclofenac fast disintegration tablet with a rapid disintegration time of 1.2 to 1.4 minutes and dissolution percent at 30 minutes of 99.5 to 100%.

DISCUSSION

The study was carried out to prepare an optimized formulation of diclofenac FDT. The disintegration time obtained from the twelve PB formulations was found slightly higher than that obtained in the study by Dor JM et al. The study showed that low mouldable sugar-coated with high mouldable sugar gave a fast disintegration time of 1-40 seconds [7]. The disintegration time obtained in the present study was in the range of 1.21 to 2.02 minutes. The effect of formulation excipients on disintegration time was determined using the main effect plot, Pareto plot, and normal plot. All the plots indicate that disintegration time decreases with an increase in mannitol concentration and a decrease in maltose concentration, which is similar to the study carried out by Mizumoto et al. [20]. Similarly, with the use of mannitol and maltose, softer tablets with hardness ranging from 1.493 to 1.522 kg/cm2 were prepared, which is similar to the results obtained by Dor JN et al. The study found that low mouldable sugar-coated with high mouldable sugar gave rise to tablets with a hardness of 1.0 – 2.0 kg/cm2 [7].

CONCLUSIONS

Diclofenac fast disintegrating tablets were prepared based on WOWTAB technology, using mannitol as a low-mouldability saccharide and maltose as a high-mouldability saccharide. The evaluation of the effect of formulation excipients on disintegration time shows that the main factors influencing the disintegration time at a 95% confidence interval was mannitol and maltose. Evaluation of CCD formulation indicated that the disintegration time of the formulations ranged from 76 to 126 seconds and in-vitro drug release was found to be from 96.31 to 99.94%. From the contour plot and surface plot, formulation with maltose concentration of 5 mg and mannitol concentration of 90 mg was found to produce an optimized formulation of diclofenac fast disintegration tablet with a rapid disintegration time of 1.2 to 1.4 minutes and dissolution percent at 30 minutes of 99.5 to 100 %.

ADDITIONAL INFORMATION AND DECLARATIONS

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Data Availability: Data will be available upon request to corresponding authors after valid reason.

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