FORMULATION AND EVALUATION CELECOXIB TABLETS THROUGH HIGH SHEAR WET GRANULATION TECHNOLOGY

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ABSTRACT:

Celecoxib is BCS class II drug with low solubility and high permeability used in the treatment of pain and inflammation. In the current research Celecoxib was subjected for wet granulation process through High shear granulation process using various excipients. The angle of repose of the CEB blend was good. The loose bulk density, tapped density, Hausner's ratio, Carr's compressibility index had good flow properties. During post compression thickness, weight variation, hardness, disintegration time and the friability were satisfactory and within limits. The drug content uniformity by HPLC using UV detector at 254 nm was 99.65± 0.48. The finalized F4 formulation shows drug release up to 12th hr 99.3% and the marketed products release hours up to 9th hours 99.6%.

INTRODUCTION

A Novel Drug Delivery System (NDDS) can be defined as a new approach that combines innovative development, formulations, new technologies, novel methodologies for delivering pharmaceutical compounds in the body as needed to safely achieve its desired pharmacological effects. (1) Various novel drug delivery system technology includes Colloidal drug carrier systems such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles of 10–400 nm diameter show great promise as drug

delivery systems. High Shear Granulation Technology is a shaping process for granulation that has been enhanced for application in the pharmaceutical industry. A binder liquid is fed to the powder particles in a closed container with blending tools and a chopper. Dense granules are formed through the liquid and solid bridges that result. Advantages of High Shear Granulation Technology need a small quantity of the binder solution for the granulation process and granulation can be achieved within a shorter period. (2) The granulation endpoint can be predicted while using a high shear granulator leading to consistency along with short drying times. Celecoxib is 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide indicated for the treatment of osteoarthritis, rheumatoid arthritis, acute pain, musculoskeletal pain, painful menstruation, ankylosing spondylitis, juvenile rheumatoid arthritis, and to reduce the number of colon and rectal polyps in people with familial adenomatous polyposis. Celecoxib is BCS class II drug with low solubility and high permeability. Its effective half-life is approximately 11 hours when a single 200 mg dose is given to healthy subjects. The terminal half-life of Celecoxib varies because of its low solubility, which prolongs absorption. Apparent clearance (CL/F), single oral 200 mg dose, healthy subjects = 27.7 L/hr.(3)

MATERIALS AND METHODS

Celecoxib (Niksan Pharmaceutical), Lactose Monohydrate (Pharmatose 200M) (Rewine Pharmaceutical) , Crospovidone (Polyplasdone XL) (Rising Brothers, Sodium lauryl sulphate (Stepanol) (Matangi Industries), (Polyvinyl pyrrolidone K30(Kollidon 30)V and Purified water.

INSTRUMENTS AND METHODS

Electronic balance (Sartorius), Disintegration test (Electro lab), Hardness test (Electro lab), Moisture Analyser (Sartorius), Electromagnetic sieve shaker (Electro lab), Automated tab density shaker (Electro lab),Compression machine (Karnavati), Tablet Friabilator (Electro lab) , Rapid mixer Granulator (Anchor mark), Rapid dryer (Retsh), Vibratory shifter (Anchor mark), Automated tab density tester (Anchor mark), Dissolution apparatus (Electro lab), High performance liquid chromatography (Agilent) High shear mixer/granulator (Ss Laboratory High Shear Mixer Granulator, 415 Volts, Model Name/Number: Lirmg).

FORMULATION OF GRANULES

Granulation experiments were done in a small scale, bottom driven high shear mixer/granulator (Ss Laboratory High Shear Mixer Granulator, 415 Volts, Model Name/Number: Li-rmg) with a 2L stainless steel vessel equipped with base mounted two blade impeller and

vertically mounted a Christmas tree chopper design for de-aggregation of larger agglomerates. The batch size was 250 g in all runs resulting in approximately 50% fill volume. Lactose Monohydrate was layered on the top of Celecoxib and pre-mixed for 2 min. To this Sodium lauryl sulphate mixed for 2 min. The speed of impeller was retained constant (300 rpm) over pre-blending and process of granulation. Crospovidone was dissolved in the granulating liquid (Polyvinyl pyrrolidone K30 in water) and sprayed unto the powder blend using a binary spray nozzle and atomizing air pressure *via* a tube connected to a pre-calibrated pump. The speeds of chopper were kept on high (3000 rpm) at pre-blending and wet massing, while for the phase of wetting, the speed of chopper was fixed to low (1500 rpm).The nozzle putted 10 cm above the moving dry powder. After addition of binder solution, the material was wet massed for constant massing time of 10 min. (4,5)

***In Vitro* evaluation of CEB blend**

The flow properties of CEB blend were characterized by measuring angle of repose, bulk density and tapped density, Carr's compressibility index and Hausner's ratio and the results are tabulated in Table 1.

Angle of repose (6)

Angle of repose in the surface of a pile of blend and the horizontal plane were used to measure the frictional forces of the CEB blend. The funnel method was used to determine the angle of repose. In a funnel, 20 gm of the CEB blend was placed, the height of the funnel was adjusted, and the tip of the funnel just touched the apex of the granules blend heap (a distance of 10 cm from the flat surface). By removing the cotton plug from the 8 mm funnel orifice, the CEB blend was allowed to flow through, and the height of the heap (h) and radius of the heap (r) were measured. The CEB blend heap's diameter was measured, and the angle of repose was calculated using the following equation:

$$\theta = \tan (h/r)$$

Where, θ = Angle of repose, h = height of CEB blend and r = radius of CEB blend heap.

Bulk density and Tapped bulk density(7)

The following approach was used to determine the loose bulk density (LBD) and tapped bulk density (TBD) of the liquid solid mix of CEB blend. On a chemical balance, 20 gram of CEB blend was weighed and placed into a 100 ml measuring cylinder. The cylinder was dropped

three times at two-second intervals from a height of 2.5 cm onto a wooden platform. The bulk volume was defined as the volume occupied by the blend. After that, the cylinder was tapped on the wooden platform until the CEB blend's volume stayed steady. The tapping was then continued until there was no further change in volume. The following formulae were used to calculate LBD and TBD:

$$LBD = \frac{\text{Weight of the blend}}{\text{volume of the packing}}$$

$$TBD = \frac{\text{Weight of the blend}}{\text{tapped volume of the packing}}$$

The data generated were used in calculating the Carr's compressibility index and Hausner's ratio.

Carr's Compressibility Index (8)

Carr's compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of CEB blend because all of these factors can influence the observed compressibility index. The optimized CEB blend was evaluated for this study which influences the flow properties of the CEB blend. Compressibility Index (Carr's Index) was determined by using the following equation:

$$\text{Carr's compressibility Index (\%)} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio (9)

Hausner's ratio is a measure of the ease with which powder flows. The following formula is used to calculate it.

$$\text{Hausner's Ratio} = TD / BD$$

Where, TD=Tapped Density, BD = Tapped density.

Table: 1 Results of Flow properties of CEB blend

Sl.no	Ingredients	B1	B2	B3	B4	B5	B6
1	Celecoxib	100	100	100	100	100	100
2	Lactose Monohydrate (Pharmatose 200M	23	21	21.5	21.0	22.5	24
3	Crospovidone (Polyplasdone XL)	5.0	4.0	3.5	2.5	2.0	1.5
4	Sodium lauryl sulphate (Stepanol)	2.5	4.0	5.0	4.5	3.0	3.5
5	Polyvinyl pyrrolidone K30 (Kollidon 30)	2.0	3.5	2.5	4.5	5.0	3.5
6	Purified water	7.5	7.5	7.5	7.5	7.5	7.5
Pre lubrication part							
7	Crosspovidone	2	2	2	2	2	2
Lubrication part							
8	Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5
		143.5	143.5	143.5	143.5	143.5	143.5

Table: 2 Formulation of CEB granules

FORMULATION	F1	F2	F3	F4
Angle of repose (θ)	38.6±0.14	37.5±0.16	36.4±0.12	34.5 ±0.12
Bulk Density (g/ml)	0.48	0.42	0.61	0.62
Tapped Density (g/ml)	0.90	0.82	0.75	0.73
Compressibility Index (%)	47.20	49.39	18.92	15.29
Hausner Ratio (HR)	1.90	1.99	1.24	1.19

Evaluation of tablets (10-12)

Quality control tests of tablets is a systematic determination of physical, chemical and mechanical properties as per Pharmacopoeial standards, to design the perfect tablets and later monitor tablet production quality, quality control tests of tablets or evaluation of tablets' physical, chemical and invitro dissolution properties are essential.

Thickness of tablets

The thickness of the tablet is the only dimensional variable related to the tablet compression process. Generally, it is measured with a micrometer. 10 tablets are selected and then, the tests for diameter uniformity. The thickness should control within ±5% variation of a standard value and must control for patient acceptance and make the tablet packaging easier.

Weight variation test

A weight variation test is performed to determine the consistency of formulated preparations. It is a pharmacopoeial test for the evaluation of tablets. Weigh 20 tablet selected at random, each one individually.T1, T2, T3….Tz., determine the average weight T = (T1+T2+T3+…. + T z) / 20 using electronic weighing machine.

Hardness test

The breaking force of tablets is commonly called "hardness" in the pharmaceutical literature. Certainly, tablets require a definite amount of hardness to withstand mechanical shocks of handling in manufacture, packaging, and transportation without affecting the disintegration limit. Generally, oral tablets have a hardness of 4 to 10 kg. Hardness of tablets is measured by Monsanto tester.

Disintegration time

Disintegration is the process by which a solid oral dosage form such as a tablet breaks down into smaller particles or granules. The tablets must disintegrate and all particles must pass through the 10-mesh screen in the time specified. Tablet disintegration apparatus was used. Six tablets were taken and placed individually in tubes and properly covered. The temperature of medium was maintained at 37±2° and timely noted by thermometer. The time taken by the tablet to disintegrate completely was noted. It is a pharmacopoeial test for the evaluation of tablets or quality control tests of tablets.

Friability test

Friability of a tablet can determined by friability test apparatus at 25 rpm, for 4 min, dropping the tablets through a distance of six inches in the Friabilator, which is then operate for 100 rpm. Friability testing is used to test the durability of tablets during transit (packing, transportation). Friability of tablets was determined by using Roche Friabilator. Twenty tablets were weighed and placed in the drum of the friabilator and speed was adjusted at 25 rpm. The

tablets were allowed to revolve, fall from height of six inches for 4 min. Then tablets were de-dusted using muslin cloth and re-weighed.

The following formula was used to calculate percent friability (percent F):

$$\% F = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

Content uniformity test

The term "uniformity of dosage unit" is defined as the degree of uniformity in the amount of the drug substance among dosage units. To ensure the consistency of dosage units, each unit in a batch should have drug content within a narrow range around the label claim. It is a Pharmacopoeial test for the evaluation of tablets or quality control tests of tablets. CEB quantification was carried out using HPLC instrument (Agilent, 1200 series LC, Santa Clara, CA, USA) system with a C_{18} column (250 mm × 4.6 mm, 5 μm particle size). Methanol and water (75:25 v/v) mixture was used as the mobile phase at a flow rate of 1 mL/min at 30 ± 0.5 °C. The UV detector was set at 254 nm and the injection volume was set as 20 μL. The chromatograms were evaluated with Chem Station Software. CEB concentration was calculated using calibration curve consisted with seven different standards of CEB (R^2 = 0.999). All samples were measured in triplicate. (13)

Dissolution test

Dissolution studies of tablets were performed on USP type-II apparatus. The speed of apparatus was set at 50 rpm. Nine hundred milliliters of phosphate buffer solution of pH 7.4 was taken as dissolution medium in each vessel of the apparatus. A single tablet was dipped in each of the dissolution vessels and temperature of medium was kept at 37±0.5°. The dissolution sample was taken from each vessel at regular intervals and was replaced by equal quantity of freshly prepared media. Absorbance was measured by using UV/Vis spectrophotometer (UV 1700, Shimadzu, Japan).

Stability studies:

The stability studies of tablets were performed for a period of six months according to ICH (international conference on harmonization) guidelines. All the physical and *in vitro* tests were performed and any significant changes were observed. Studies were performed under following temperature and humidity conditions 37±1°, 40±1°, 50±1° and RH 75±5%. (14)

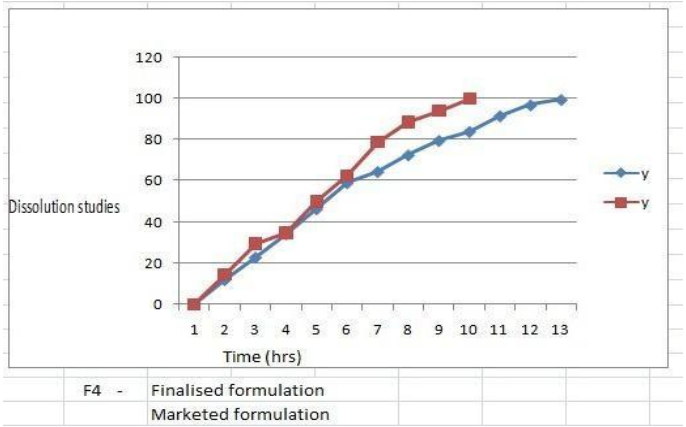
Table: 3 Post-Compression Parameters of tablet Formulation (F4)

Formulation (F4)	Average (N=6)
Thickness of tablets	4.01 ± 0.081
Weight Variation (mg)	143.92 ± 0.12
Hardness (kg/ cm 2)	6.4±0.12
Disintegrating Time (min)	4:37 ± 0.32
Friability (%)	0.24±0.15
Content uniformity test	99.65± 0.48

Table: 4 Comparative dissolution tests for finalized F4 and the marketed products

Time (hrs)	Finalized Formulation dissolution studies data % of drug release	Marketed Product dissolution studies data % of drug release
0	0	0
1	11.8	14.3
2	22.7	29.3
3	34.1	34.6
4	46.2	49.8
5	58.9	62.4
6	64.3	78.6
7	72.4	88.4
8	79.4	93.9
9	83.8	99.6
10	91.4	
11	96.7	
12	99.3	

Table: 4 Comparative graph for the dissolution tests finalized F4 and marketed products



Discussion:

In the current research Celecoxib was selected and subjected for High shear granulation process using lactose mono hydrate as a diluent in the formulation in order to maintain excellent flow property and compressibility as well as due its rheological properties. Cross povidone was selected as cross linking agent also a water insoluble super disintegrable agent it is always selected during granulation process. Sodium lauryl sulfate was used as a surfactant which is anionic nature. PVP is versatile excipients was used in the tablet binder process, having water soluble and maintains optimal viscosity. Cross povidone was selected as pre lubricant and magnesium stearate was uses as a lubricant.

The angle of repose of the CEB blend was observed to be 34.5 ±0.12, and the CEB blend prepared by adsorption proved to be good. The loose bulk density and tapped density of the prepared CEB blend are 0.62 (g/ml) and (g/ml), respectively. The CEB blend Hausner's ratio was 1.19, and the CEB blend Carr's compressibility index was 15.29 (%). The prepared blend had good flow properties based on these results. During post compression thickness of tablets of the tablets was found to be 4.01 ± 0.081 cm; and the weight variation is of 143.92 ± 0.12mg; the hardness of Celecoxib tablet was 6.4±0.12 kg/ cm 2; the disintegration time was 4:37 ± 0.32 min; and the friability was 0.24±0.15%, the drug content uniformity by HPLC using UV detector at 254 nm was 99.65± 0.48. The finalized F4 formulation shows drug release up to 12^{th} hr 99.3% and the marketed products release hours up to 9^{th} hours 99.6%. The stability studies of tablets resulted in no significant changes.

Conclusion:

Using high shear granulation technology a small quantity of the binder solution was used in the granulation process and granulation was achieved within a shorter period. The finalized F4 formulation shows drug release up to 12^{th} hr 99.3% and the marketed products release hours up to 9^{th} hours 99.6%. Thus we have achieved the formulation Celecoxib tablets through high shear wet granulation technology.

Conflicts of interest: None declared.

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