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Original Article

Preformulation Studies for development of a generic capsule formulation of Celecoxib comparable to the branded (Reference) Product

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Abstract

This study aims to provide preformulation information, which is an essential part in the development of a robust formulation for generic celecoxib capsules. Various preformulation studies were carried out including drug characterization, Reference product characterization, Drug-Excipients compatibility studies. The physical properties of the drug like Solubility profile, Bulk / tapped densities, flow properties and particle size were also studied. The Celecoxib drug was found to be having good compatibility with majority of excipients studied. The drug is found to be of fluffy nature due to low density and the drug was also observed to be having very poor flow characteristic, hence it was concluded that direct filling of powder mixture into capsules was not possible. Therefore, wet granulation method was considered for granulation in-order to improve bulk density and flow-ability of blend.

Keywords: Preformulation, Generic formulation, Drug characterization, compatibility, bulk/tapped density, flow properties, wet granulation.

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1. Introduction

Over the past decades, pharmaceuticals have made a major contribution in improving the health status of patients. At the same time, its expenditure has increased rapidly, with spending on medicines outpacing economic growth in many countries [1]. Since generic drug products are usually marketed at substantially lower prices than the original brand-name products and with the rising cost of healthcare; development of generics is an attractive option to healthcare providers and governments [2]. However since the regulatory expectations for approval of a generic drug product have become increasingly challenging and also to avoid setbacks at a later stages during the

development , it is very important that sufficient efforts are made on generating the preformulation data at the initial stages during the development work for a generic formulation.

A Generic drug product [3,4,5], is considered to be "essentially similar" or bioequivalent to an innovator (brand name) drug product. Bioequivalence implies that a generic drug product is essentially identical to the brand name drug (reference) drug product in term of active ingredient, strength, dosage form, route of administration, quality, safety, efficacy, performance characteristics and therapeutic effects.

Generic drug product development may or may not use a different approach and strategy compared to that used to develop branded drug product containing a new chemical entity.

This article summarizes some of the preformulation studies which have been carried out during the initial development work for a robust generic capsule formulation of Celecoxib. These preformulation studies provided a scientific understanding and a platform to develop a suitable strategy for subsequent stages of development for a generic Celecoxib Capsules which shall be stable ,comparable and bioequivalent to the US reference listed product i.e CELEBREX® Capsules (of GD Searle LLC a division of Pfizer).

2. Materials and Methods:

The Active ingredient was procured from Aarti Drugs India. Lactose monohydrate (Diluent) from DMV Pharm; Croscamellose Sodium (Disintegrant) from Dow Chemicals; Povidone K-30 (Binder) from ISP; Sodium Lauryl Sulphate (Wetting agent) from Stepan; Magnesium Sterate (Lubricant) from Mallincrodt.

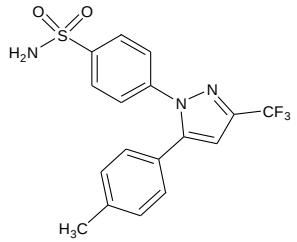
Preformulation Studies and Results:

Pre-formulation testing is designed to identify those physicochemical properties of drug substances and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product. A thorough understanding of physicochemical properties may ultimately confirm that no significant barriers are present for the formulation development. The preformulation studies included characterization of the active drug substance, evaluation of the reference listed product, and compatibiliy evaluation of the active drug with various excipients [9].

Drug Characterization: Celecoxib is chemically designated as 4-[5-(4-methylphenyl) -3-(trifluoromethyl)- 1H-pyrazol-1-yl] benzene sulfonamide and is a diaryl-substituted pyrazole. It is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic effects.

X- Ray *Diffraction pattern of Celecoxib*: X-ray crystallography is a method of determining the arrangement of atoms within a crystal, in which a beam of X-rays strikes a crystal and diffracts into many specific directions. From the angles and intensities of these diffracted beams, a crystallographer can produce a three-dimensional picture of the density of electrons within the crystal. From this electron density, the mean positions of the atoms in the crystal can be determined, as well as their chemical bonds, their disorder and various other information.

Physico-chemical characteristics of celecoxib active ingredient [06]

International Non Proprietary name (INN) of drug substance:	**:**	**Celecoxib**
Pharmacotherapeutic Group	**:**	Anti-inflammatory, Analgesic
Mol. Wt.	**:**	381.38
CAS Registry Number	**:**	169590-42-5
Empirical Formula	**:**	$C_{17}H_{14}F_3N_3O_2S$
Chemical Name	**:**	4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide
Chemical Structure	**:**	
Physical Description	**:**	White to off white crystalline powder
Solubility in water	**:**	Very low water solubility (3.3 mg/L)
Solubility in other solvents such as ether, mthanol, acetone etc.	**:**	Soluble in methanol
Melting Point	**:**	159 - 161 ^{o}C
pH of solution	**:**	5.2 - 6.5
Log P (Octanol/Water)	**:**	3.9
Polymorphism	**:**	Form II
PKa	**:**	11.1
Assay (By HPLC)	**:**	98.0 – 102.0 %
Heavy Metals	**:**	20 ppm
Sulphated Ash	**:**	0.1%

Impurity Profile limits. Impurity 0.1% Impurity B: 0.1% Isomer Impurity : 0.15% Single unknown Impurity : 0.1 % Total Impurities 1.0 %		
Hygroscopicity	**:**	No
UV Max	**:**	250 nm

Sr no	Bulk density (g/cc)	0.260 (fluffy nature)
1	Tapped density (g/cc)	0.431
2	Carr's index	39.68
3	Hausner ratio	1.66 (poor flow properties)
4	Particle Size (by Malvern)	D90 = 10.18 µm

Physical properties of Celecoxib

Sr. No.	Media	Solubility in mg/ml	Solubility in mg/250ml
1.	0.1 N Hydrochloric acid	0.028	7.0
2.	pH 4.5 Acetate Buffer	0.024	6.0
3.	pH 6.8 Phosphate Buffer	0.015	3.8
4.	pH 7.4 Phosphate Buffer	0.014	3.5
5.	pH 12 Tribasic sodium phosphate buffer	0.567	141.8

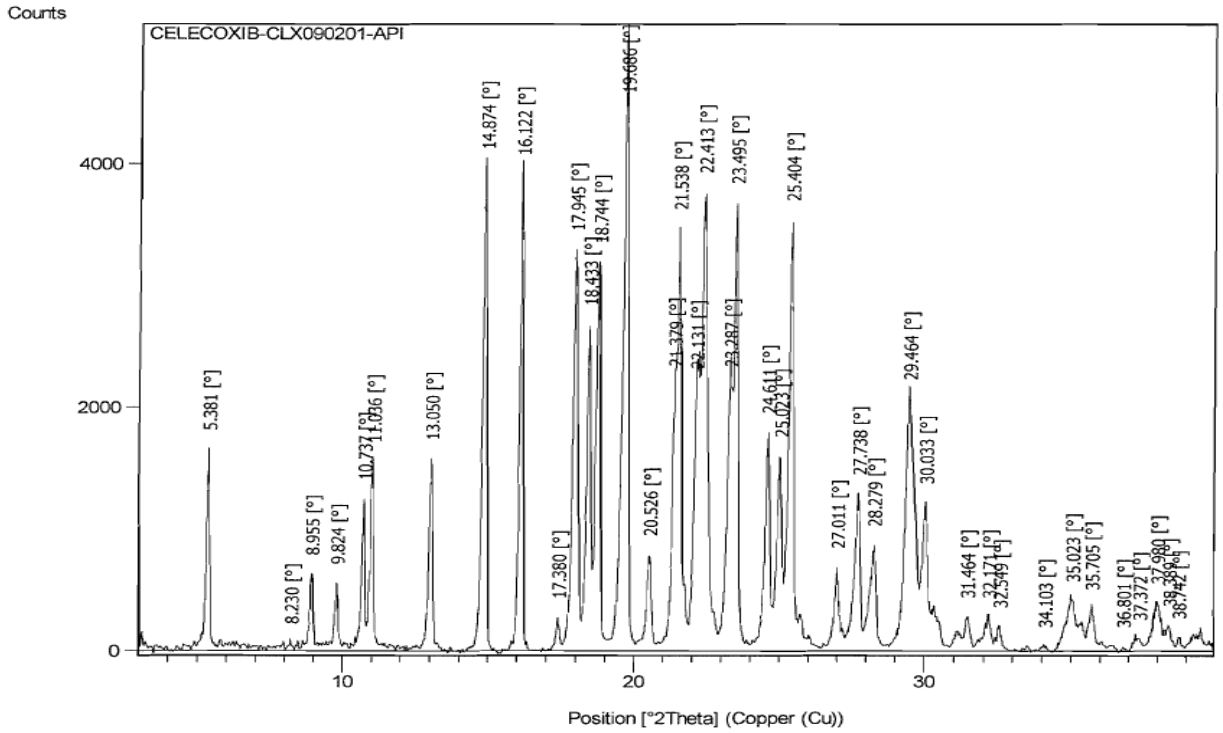
6.	Purified Water	0.018	4.5

Solubility profile of Celecoxib

Measurement Conditions:

Dataset Name	CELECOXIB-CLX090201-API
File name	C:\XRD Data\CELECOXIB\CELECOXIB-CLX090201-API.xrdml
Measurement Date / Time	11/26/2010 12:16:26 PM

Main Graphics, Analyze View:



X- Ray Diffraction pattern of Celecoxib

Peak List:

Pos. [°2Th.]	Height [cts]	d-spacing [Å]	FWHM Left [°2Th.]	Area [cts*°2Th.]	Rel. Int. [%]
5.381433	1658.011000	16.42227	0.117096	191.52	32.57
8.230382	64.131100	10.74299	0.133824	8.47	1.26
8.955333	628.748700	9.87488	0.100368	62.25	12.35
9.823696	555.006500	9.00386	0.100368	54.95	10.90
10.737010	1237.147000	8.23994	0.100368	122.49	24.31
11.036500	1546.204000	8.01700	0.117096	178.60	30.38
13.049800	1567.247000	6.78433	0.117096	181.03	30.79
14.874030	3953.990000	5.95612	0.133824	521.97	77.68
16.121650	3906.198000	5.49788	0.117096	451.20	76.74
17.379810	267.585400	5.10261	0.117096	30.91	5.26
17.945380	3284.231000	4.94306	0.150552	487.75	64.52
18.433400	2675.215000	4.81327	0.100368	264.87	52.56
18.744090	3186.970000	4.73419	0.150552	473.30	62.61
19.686360	5089.948000	4.50967	0.133824	671.93	100.00
20.525940	784.388700	4.32706	0.117096	90.60	15.41
21.378740	2181.608000	4.15635	0.083640	180.00	42.86
21.537540	3462.623000	4.12606	0.083640	285.69	68.03
22.130620	2161.317000	4.01681	0.100368	213.99	42.46
22.413190	3761.711000	3.96680	0.100368	372.44	73.90
23.287140	2174.583000	3.81987	0.100368	215.30	42.72
23.495450	3673.305000	3.78647	0.117096	424.30	72.17
24.611070	1788.676000	3.61730	0.167280	295.16	35.14
25.023490	1591.701000	3.55861	0.133824	210.12	31.27
25.403880	3535.155000	3.50618	0.133824	466.68	69.45
27.010960	682.383000	3.30112	0.133824	90.08	13.41
27.737920	1287.691000	3.21623	0.167280	212.49	25.30
28.278800	862.625400	3.15593	0.083640	71.17	16.95
29.463710	2063.042000	3.03166	0.234192	476.60	40.53
30.032760	1215.777000	2.97550	0.117096	140.43	23.89
31.463890	274.443000	2.84335	0.167280	45.29	5.39
32.170920	273.239500	2.78245	0.167280	45.09	5.37
32.549060	192.721800	2.75099	0.133824	25.44	3.79
34.102600	31.071270	2.62914	0.267648	8.20	0.61
35.022700	409.080200	2.56215	0.167280	67.50	8.04
35.704670	342.706700	2.51476	0.167280	56.55	6.73
36.800630	28.660870	2.44235	0.133824	3.78	0.56
37.372240	95.312450	2.40629	0.334560	31.46	1.87
37.980470	391.807400	2.36915	0.234192	90.51	7.70
38.388860	204.142100	2.34488	0.133824	26.95	4.01
38.742120	108.297200	2.32431	0.100368	10.72	2.13

3.2 Evaluation of the reference product in USA:

Celecoxib (a non-steroidal anti-inflammatory agent) marketed in USA under the brand name CELEBREX® by G.D. Searle LLC (Division of Pfizer Inc. NY). Celebrex (Celecoxib) capsules are available in four strengths (50, 100, 200 and 400 mg) in different packs. The brief evaluation of Celebrex® capsule 400mg (Reference Listed Product in USA) is given in the table below:

Active ingredient	Celecoxib
Dosage form	Capsule , oral
Strength	50, 100, 200 and 400 mg (RLD strength - 400mg)
Brand Name	CELEBREX®
Average weight (mg) (RLD)	631.6, 629.6, 625.5, 624.3 and 623.2 mg = 626.84 mg
Product	Celebrex Capsules
Size of capsule	Size of 50, 100 & 200 mg capsule = 2 Size of 400 mg capsule = 0
Lock length (mm) (RLD)	21.61, 21.66, 21.64, 21.72 and 21.57 mm = 21.64 mm
Disintegration Time (min)	Contents: 1.15 – 1.5 min / Capsule Shell: 12-15 min
Inactive ingredients	Croscarmellose sodium, lactose monohydrate, magnesium stearate, povidone and sodium lauryl sulfate, edible inks and gelatin.
Pack	Bottles of 60's and 100's . Unit dose blister pack

Celebrex Capsules				
App: USP Type II (Paddle), 50 rpm and 75 rpm for 400 mg				
Medium: 0.04 M Tribasic Sodium Phosphate Buffer, pH = 12 with 1% SLS; Volume: 1000 mL				
Time (min)	**Celebrex 400 mg**	**Celebrex 200 mg**	**Celebrex 100 mg**	**Celebrex 50 mg**

B. No.	C090960	C091104	C090841	C090160
10	54	42	73	89
15	67	64	85	92
30	81	90	87	97
45	95	91	90	96
60	101	96	91	99
Similarity factor	**F2**	**56.30**	**38.50**	**34.34**
Assay (% Label Claim)	98.2	98.4	97.8	97.1

Drug Release profile of reference product

Celebrex Capsules 400 mg (B. No. C090960)				
App: USP Type II (Paddle), 75 rpm				
Volume: 1000 mL				
Time points (hrs)	**Official media* pH 12**	**0.1 N HCl with 1 % SLS**	**4.5 pH Acetate Buffer with 1 % SLS**	**pH 6.8 Phosphate buffer with 1 % SLS**
10	54	60	53	54
15	67	69	67	69
30	81	80	79	85
45	95	88	86	88
60	101	90	90	92
Similarity factor	***F2***	**59.11**	**59.32**	**62.72**

Drug release profile of reference product in different medias.

* 0.04 M Tribasic Sodium Phosphate Buffer, pH = 12 with 1% SLS

3.3. Sources and selection of excipients

Some of the commonly used excipients which have been evaluated are tabulated below. These excipients have been chosen for the study based on the available information of reference product composition in package insert and the information available in patents.

Sr. No.	Ingredient	Maximum Limit as per IIG (mg)
1	Lactose monohydrate	586.00
2	Croscarmellose sodium	180.00
3	Povidone K30	80.00
4	Sodium lauryl sulfate	51.69
5	Magnesium Stearate	256.4

Maximum limit recommended as per USFDA inactive ingredient guidance (IIG) [8]

3.4. Drug-excipient compatibility studies

Compatibility Studies of celecoxib with various excipients: In early drug development phase, excipient compatibility studies are very important as it provides a rational basis for identification of low-risk excipients with physical and chemical compatibility to the drug substance. Drug excipient compatibility studies are critical for well-formulated final dosage forms where the drug reside in contact with one or more excipients during process scale-up from clinical trials through commercial to consumer. Performing these studies at the early development stage has the potential to both accelerate drug development and minimize the risk of drug product stability failure. The study designed as follows with different ratio for drug and excipients as per their functionality. The weighed amount of API mixed well with a proposed proportion of individual excipients. Blend was filled and sealed in 5 ml glass vials. Vials were subjected to 40°C ± 2°C/75% ± 5% RH for 4 weeks. The control samples were stored at 2-8^{o}C. The samples were observed for physical changes like discoloration, liquefaction and analysed for related substance by HPLC [7].

Conditions	Time Zero	1 week	2 weeks	4 weeks
40°C 75%RH	X Y	X	X	XY

Drug-Excipient time-point testing schedule.
X= Visual Observation; Y= RS by HPLC

Drug : Excipients	**RATIO**	**Initial**	**Observations**		
			40 °C/75 %RH		
			1W	**2W**	**4W**
Celecoxib (CLX)	1:0	White to off white powder	√	√	√
CLX : Lactose monohydrate (Pharmatose 200M)	1:1	White to off white powder	√	√	√
CLX : Microcrystalline cellulose PH 101	1:1	White to off white powder	√	√	√
CLX : Corn Starch	1:1	White to off white powder	√	√	√
CLX : HPC (Klucel LF)	1:0.5	White to off white powder	√	√	√
CLX : Povidone (PVP K-30)	1:0.5	White to off white powder	√	√	√
CLX : Crosspovidone	1:0.5	White to off white powder	√	√	√
CLX : Sodium starch glycolate	1:0.5	White to off white powder	√	√	√
CLX : Croscarmellose sodium (Ac Di Sol)	1:0.5	White to off white powder	√	√	√
CLX : Sodium stearylfumerate	1:0.2	White to off white powder	√	√	√

CLX : Magnesium Stearate	1:0.2	White to off white powder	√	√	√
CLX : Colloidal silicon dioxide (Aerosil 200)	1:0.2	White to off white powder	√	√	√
CLX : Sodium lauryl sulfate	1:0.05	White to off white powder	√	√	√

Drug- excipients compatibility study for celecoxib (physical observation). √= No physical change

Related Substances generated during compatibility studies:

Initial and1M (4 Week) 40°C/75 % RH samples were tested for change in related substances by HPLC method. The results are tabulated below:

Drug: Excipients	Diketone Impurity	Isomer Impurity	Total unknown impurities	Total Related Substance
Celecoxib (CLX)	0.000	0.081	0.000	0.081
CLX : Lactose monohydrate (Pharmatose 200M)	0.000	0.039	0.000	0.039
CLX : Microcrystalline cellulose PH 101	0.000	0.041	0.000	0.041
CLX : Corn Starch	0.000	0.040	0.000	0.040
CLX : HPC (Klucel LF)	0.000	0.051	0.000	0.051
CLX : Povidone (PVP K-30)	0.000	0.056	0.000	0.056
CLX : Crosspovidone	0.000	0.052	0.000	0.052
CLX : Sodium starch glycolate	0.000	0.048	0.000	0.048
CLX : Croscarmellose sodium (Ac Di Sol)	0.000	0.056	0.000	0.056
CLX : Sodium stearylfumerate	0.000	0.070	0.000	0.070
CLX : Magnesium Stearate	0.000	0.074	0.000	0.074

CLX : Colloidal silicon dioxide (Aerosil 200)	0.000	0.061	0.000	0.061
CLX : Sodium lauryl sulfate	0.000	0.076	0.000	0.076

Drug - excipient interaction (Chemical Compatibility) for Celecoxib– Initial

Drug : Excipients	Diketone Impurity	Isomer Impurity	Total unknown impurities	Total Related Substance
Celecoxib (CLX)	0.000	0.077	0.000	0.077
CLX : Lactose monohydrate (Pharmatose 200M)	0.000	0.041	0.000	0.041
CLX : Microcrystalline cellulose PH 101	0.000	0.044	0.000	0.044
CLX : Corn Starch	0.000	0.042	0.000	0.042
CLX : HPC (Klucel LF)	0.000	0.053	0.000	0.053
CLX : Povidone (PVP K-30)	0.000	0.054	0.000	0.054
CLX : Crosspovidone	0.000	0.054	0.000	0.054
CLX : Sodium starch glycolate	0.000	0.055	0.000	0.055
CLX : Croscarmellose sodium (Ac Di Sol)	0.000	0.054	0.000	0.054
CLX : Sodium stearylfumerate	0.000	0.068	0.000	0.068
CLX : Magnesium Stearate	0.000	0.067	0.000	0.067
CLX : Colloidal silicon dioxide (Aerosil 200)	0.000	0.078	0.000	0.078
CLX : Sodium lauryl sulfate	0.000	0.077	0.000	0.077

Drug- excipient interaction (Chemical Compatibility) for Celecoxib– after 4 Weeks (1M) 40°C/75%RH

Based on the observation of the data on compatibility studies it is observed that that celecoxib is compatible and stable with majority of excipients used.

Sr. No.	Excipients	Manufacturer	Specification	Function
1.	Lactose monohydrate	DMV Pharm	NF	Diluent
2.	Croscarmellose sodium	Dow	NF	Disintegrant

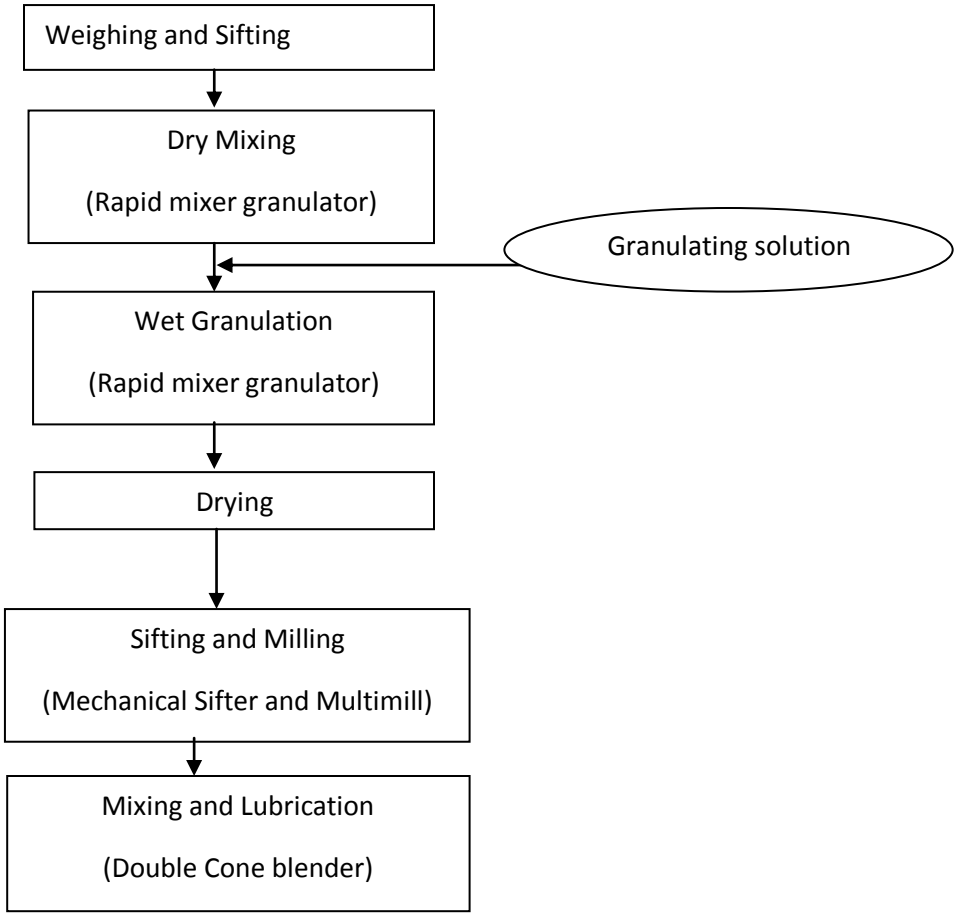
3.	Povidone K30	ISP	NF	Binder
4.	Sodium lauryl sulfate	Stepan	NF	Wetting agent
5.	Magnesium Stearate	Mallincrodt	NF	Lubricant
6.	Purified Water	In house	USP	Granulating agent

Selected raw materials for generic capsule formulation development.

Conclusion:

Developing a formulation strategy based on preformulation studies:

Objective of the project was to develop a stable generic product, which should be bio-equivalent to the reference drug product. The drug is found to be compatible with majority of excipients .The selected candidate Celecoxib is BCS class II drug and the dose required for therapeutic action is high. Hence, it was challenging to formulate a capsule dosage form to produce a bioequivalent product. Additionally, due to fluffy nature of API because of low bulk density, it was tough to select a proper method to formulate a capsule dosage form.



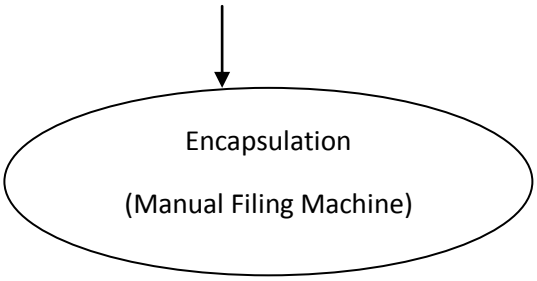


Fig: Flow diagram of manufacturing process adopted for Celecoxib capsules

Development of a generic product starts with the characterization of the API, evaluation of refernce product followed by compatibility studies, selection of process and equipment, formulation development experiments, optimization trials and bio-equivalent studies. In order to develop bio-equivalent generic formulation of selected drug candidate, initial requirement was to choose a suitable manufacturing process. As the preformulation studies indicated the fluffy nature of Celecoxib drug due to low density and also since it was observed to be having very poor flow characteristic, hence it was concluded that direct filling of powder mixture into capsules was not possible. Therefore, wet granulation method was considered for granulation in-order to improve bulk density and flow-ability of blend.

References

01 Simoens, S., Coster, S.D., 2006. Sustaining Generic Medicines Markets in Europe. Research Centre for pharmaceutical care and pharmaco - economics.1-106. Available at: at:http://www.assogenerici.org/articolihome/simoens-report_2006-04.pdf.

02 Retrieved from www.egagenerics.com/doc/ega_increase-patient-access_final.pdf.

03 Abbreviated New Drug Application updated on 20/08/2010, cited on 9/10/2010. Available from: http://www.fda.gov.

04 Retrieved from www.fda.gov/developmentApprovalprocess/.

05 Singh, D.P., 2010. Generic drug access in global scenario. J. Pharm. Sci. and Res.2, 90-98.

06. Retrieved from www.drugbank.ca/drugs/DB00482.

07. Kadri B.V., 2009, Drug- Excipients compatibility study will find the perfect partner to your API. Available at www.pharmaquality.com /MEZ/Audience/dirmod.asp.sid).

08. www.fda.gov/drugs/ information drugs/ucm113978.htm

09. Essentials of pharmaceutical preformulation by Mark Gibson.

10. Pharmaceutical Dosage Forms (Vol-3), Herbert A Lieberman and Leon Lachman.