"FORMULATION AND EVALUATION OF THE IMMEDIATE RELEASE DOSAGE FORM OF COX-2 INHIBITOR"

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BIOPHARMACEUTICS

BY

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UNDER THE GUIDANCE OF

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CERTIFICATE

This is to certify that ***Mr. RAVI C. PATEL*** *has prepared his thesis entitled "Formulation and Evaluation Of The Immediate Release Dosage Form Of COX-2 inhibitor", in partial fulfillment for the award of M. Pharm. degree of the Nirma University, under our guidance. He has carried out the work at the Formulation & development, Alembic Ltd. Pharma., Vadodara and at Institute of Pharmacy, Nirma University., Ahmedabad.*

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DECLARATION

I declare that the thesis "Formulation And Evaluation Of The Immediate Release Dosage Form Of COX-2 inhibitor", has been prepared by me under the guidance of Industrial guide Mr. CHIRAG SHAH, Group leader, Alembic research center, Vadodara & Academic guide Dr. TEJAL MEHTA, Professor, Department of Pharmaceutics & pharmaceutical technology, Institute of Pharmacy, Nirma University. No part of this thesis has formed the basis for the award of any degree or fellowship previously.

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Last, but not the least, I express my gratitude and apologize to anybody whose contributions, I could not mention in this page.

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Index

1. AIM OF PRESENT WORK

Aim:

The aim of present study is to formulate an immediate release dosage form of COX-II inhibitor as an active pharmaceutical ingredient with the aid of suitable excipients and evaluating its characteristics.

Strength of selected drug is 400 mg/capsule.

The formulation of API for effective oral administration to a subject has hitherto been complicated by the unique physical and chemical properties of the compound, particularly its low solubility and factors associated with its ***crystal structure, including cohesiveness, low bulk density and low compressibility***.

API is insoluble in aqueous media. Unformulated API is not readily dissolved and dispersed for rapid absorption in the gastrointestinal tract when administered orally, for example in capsule form.

In addition, unformulated API, which has a crystal morphology that tends to form long cohesive needles, typically fuses into a monolithic mass upon compressing in a tableting die. Even when blended with other substances, the API crystals tend to separate from the other substances and agglomerate together during mixing of the composition resulting in a non-uniformly blended composition containing undesirably large aggregates of API. Therefore, it is difficult to prepare a pharmaceutical composition containing API that has the desired blend uniformity.

Further, handling problems are encountered during the preparation of pharmaceutical compositions comprising API. For example, the low bulk density of API makes it difficult to process the small quantities required during formulation of the pharmaceutical compositions. Accordingly, a need exists for solutions to numerous problems associated with preparation of suitable pharmaceutical compositions and dosage forms comprising API, particularly orally deliverable dose units.

In particular, a need exists for orally deliverable API formulations possessing one or more of the following characteristics relative to unformulated API or other API compositions:

(1) improved solubility;
(2) shorter dissolution time;
(3) improved wettability;
(4) improved compressibility;
(5) improved flow properties of liquid and particulate solid compositions;
(6) improved physical stability of the finished composition;
(7) reduced capsule size;
(8) improved blend uniformity;
(9) improved dose uniformity;
(10) improved control of weight variation during encapsulation
(11) increased granule density for wet granulated compositions;
(12) reduced water requirement for wet granulation;

As is indicated herein below, API treatment is potentially indicated in a very wide array of cyclooxygenase-2 mediated conditions and disorders. It would therefore be of great benefit to provide a range of formulations having bioavailability characteristics tailored to different indications.

It would be of especial benefit to provide formulations exhibiting pharmacokinetics consistent with a more rapid onset effect than is possible with unformulated API.

Such formulations would represent a significant advance in the treatment of cyclooxygenase-2 mediated conditions and disorders.

Thus, the present study was aimed to formulate the immediate release capsule dosage form of selective COX II inhibitor (BCS class II drug) using various excipients which improve solubility and thereby bioavailability.

2 INTRODUCTION

2.1 INTRODUCTION TO IMMEDIATE RELEASE DOSAGE FORM:

It is defined as a dosage form for the immediate release of the drug. The drug should be released 75% in 30 min. [29]

Oral route of drug administration is perhaps the most appealing route for the delivery of drugs. Of the various dosage forms administered orally, the tablet is one of the most preferred dosage forms because of its ease of manufacturing, convenience in administration, accurate dosing, stability compared with oral liquids, and because it is more tamperproof than capsules.

The gastrointestinal tract provides sufficient fluid to facilitate disintegration of the dosage form and dissolution of the drug. The large surface area of gastric mucosa favors the drug absorption. Therefore, the oral route has continued to be the most appealing route for drug delivery despite the advancements made in the new drug delivery systems. Banker and Anderson stated that at least 90% of all drugs used to produce systemic effect are administered orally.

Bioavailability of a drug depends on absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluid and permeability of the drug across gastrointestinal membrane. The drugs solubility mainly depends on physical – chemical characteristics of the drug. However, the rate of drug dissolution is greatly influenced by disintegration of the tablet.

The drug will dissolve at a slower rate from a non disintegrating tablet due to exposure of limited surface area to the fluid. The disintegration test is an official test and hence a batch of tablet must meet the stated requirements of disintegration.

Disintegrants, an important excipient of the tablet formulation, are always added to a tablet to induce breakup of tablet when it comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrants.

The objectives behind addition of disintegrants is to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together in a tablet. **[4]**

Selection criteria for the drug to be developed as immediate release dosage form:

1) Longer half life.

2) Poor solubility.

3) To need the immediate action of the drug.

4) Absorption from mainly stomach.

5) Long elimination half life.

2.2 INTRODUCTION TO GRANULATION TECHNIQUES [4]

Introduction

Orally administered drug delivery platforms, such as tablets and capsules, are considered the preferred and most patient-convenient dosage forms available today. This is primarily because of the ease of administration, convenience of handling and increased stability compared with their liquid counterparts. Typically, solid dosage forms administered orally are an intricate blend of excipients (diluents, binders, disintegrants, glidants, lubricants and flavours) and APIs. To successfully manufacture acceptable pharmaceutical products, these materials must be adequately mixed and/or granulated to ensure that the resultant agglomerates possess the required flow and compressibility, and avoid de-mixing during post granulation processes.

Currently, the techniques in existence for the agglomeration and mixing of pharmaceutical powders involve either wet or dry methods. Although dry techniques lead to associated decreases in process time and the avoidance of wetting and drying processes, the inherent difficulties in compressing crystalline solids, the uneven and erratic flow properties of APIs, and the development costs associated with dry methods, culminates in wet granulation remaining the preferred and most widely accepted method for powder agglomeration. However, it is well accepted that there is an increasing need for alternative processes to dramatically improve particle processing to ensure acceptable and reproducible solid dosage forms.

Granulation may be defined as a size enlargement process which converts small particles into physically stronger & larger agglomerates.

Ideal characteristics of granules

The ideal characteristics of granules include uniformity, good flow, and compactibility. These are usually accomplished through creation of increased density, spherical shape, narrow particle size distribution with sufficient fines to fill void spaces between granules, adequate moisture (between 1-2%), and incorporation of binder, if necessary.

The effectiveness of granulation depends on the following properties

1. Particle size of the drug and excipients

2. Type of binder (strong or weak)
3. Volume of binder (less or more)
4. Wet massing time (less or more)
5. Amount of shear applied to distribute drug, binder and moisture.
6. Drying rate (Hydrate formation and polymorphism)

The most widely used process of agglomeration in pharmaceutical industry is wet granulation. Wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing and drying.

Important steps involved in the wet granulation

1. Mixing of the drug(s) and excipients
2. Preparation of binder solution
3. Mixing of binder solution with powder mixture to form wet mass.
4. Coarse screening of wet mass using a suitable sieve (6-12)
5. Drying of moist granules.
6. Screening of dry granules through a suitable sieve (14-20)
7. Mixing of screened granules with disintegrant, glidant, and lubricant.

Drugs are introduced into the body by several routes. They may be taken by mouth (orally); placed under the tongue (sublingually); sprayed into the nose and absorbed through the nasal membranes (nasally); breathed into the lungs, usually through the mouth (by inhalation); given by injection into a vein (intravenously), into a muscle (intramuscularly), into the space around the spinal cord (intrathecally), or beneath the skin (subcutaneously); inserted in the rectum (rectally) or vagina (vaginally); installed in the eye (by the ocular route); applied to the skin (cutaneously) for a local (topical) or body wide (systemic) effect; or delivered

through the skin by a patch (transdermally) for a systemic effect. Each route has specific purposes, advantages, and disadvantages.

Solid dosage forms are the least expensive, most popular and convenient methods for drug delivery. They can be produced in a non-sterile environment and the technology is well-known after more than 100 years of development. Most pharmaceuticals are produced in solid dosage forms.

2.3 INTRODUCTION TO COX-II INHIBITOR [21,22,25,30,31]

COX-2 inhibitors are a subclass of non steroidal anti inflammatory drugs (NSAIDs). NSAIDs work by reducing the production of prostaglandins, chemicals that promote inflammation, pain, and fever. Prostaglandins also protect the lining of the stomach and intestines from the damaging effects of acid, promote blood clotting by activating platelets, and also affect kidney function.

The enzymes that produce prostaglandins are called cyclooxygenase (COX). There are two types of COX enzymes, COX-1 and COX-2. Both enzymes produce prostaglandins that promote inflammation, pain, and fever; however, only COX-1 produces prostaglandins that activate platelets and protect the stomach and intestinal lining.

NSAIDs block the COX enzymes and reduce production of prostaglandins. Therefore, inflammation, pain, and fever are reduced by all COX inhibitors. Since the prostaglandins that protect the stomach and promote blood clotting also are reduced, NSAIDs can cause ulcers in the stomach and intestines, and increase the risk of bleeding. Unlike older NSAIDs that block both COX-1 and COX-2, the newer COX-2 inhibitors only block the COX-2 enzyme. Since COX-2 inhibitors do not block COX-1 (which primarily produces prostaglandins that protect the stomach and promote blood clotting) they do not cause ulcers or increase the risk of bleeding as much as the older NSAIDs. Nevertheless, COX-2 inhibitors are as effective as the older NSAIDs for treating inflammation, pain and fever.

COX-2 inhibitors are used for treating conditions that cause inflammation, mild to moderate pain, and fever. Examples include:

- sports injuries,
- osteoarthritis,
- rheumatoid arthritis,
- colorectal polyps, and
- menstrual cramps.

Unlike aspirin, also an NSAID, they are not effective for preventing strokes and heart attacks in individuals at high risk for such events.

API is the only COX-2 inhibitor currently available in the United States. Rofecoxib (Vioxx) and valdecoxib (Bextra) are no longer available because they increased the risk of heart

attacks and strokes with long term use. Rofecoxib was discontinued in 2004 and valdecoxib was discontinued in 2005.

Table 2.1: Side effects of API

Common side effects include	Other side effects include	
Abdominal pain,	Fainting,	Anxiety,
Headache,	Kidney failure,	Light sensitivity,
Nausea,	Aggravation of hypertension,	Weight gain,
Diarrhea,	Ringing in the ears,	Water retention,
Flatulence,	Bleeding,	Drowsiness,
Insomnia.	Blurred vision,	Weakness.

Allergic reactions also can occur. Individuals who have developed allergic reactions (rash, itching, difficulty breathing) from sulfonamides [for example, trimethoprim and sulfamethoxazole Bactrim)], aspirin or other NSAIDs may experience an allergic reaction to API and should not take API.

COX-2 inhibitors and other NSAIDs may increase the risk of heart attacks, stroke, and related conditions, which can be fatal. This risk may increase with duration of use and in patients who have underlying risk factors for disease of the heart and blood vessels. NSAIDs should not be used for the treatment of pain resulting from coronary artery bypass graft (CABG) surgery.

Other NSAIDs and, to a lesser extent, COX-2 inhibitors may increase the risk of serious, even fatal, stomach and intestinal adverse reactions such as bleeding, ulcers, and perforation of the stomach or intestines. These events can occur at any time during treatment and without warning symptoms. Elderly patients are at greater risk for these types of reactions.

- Concomitant use of API with aspirin or other NSAIDs [for example, Ibuprofen, Naproxen (Naprosyn, Naprelan), etc.) may increase the occurrence of stomach and intestinal ulcers. It may be used with low dose aspirin.
- Alcohol consumption increases the risk of developing stomach ulcers when taking NSAIDs; this may also apply to API.
- Fluconazole (Diflucan) increases the concentration of API (Innovator) in the body by inhibiting the elimination of API in the liver.

- API (Innovator) increases the concentration of Lithium (Eskalith) in the blood by 17% and may increase the blood thinning effect of Warfarin (Coumadin).

API (Innovator product) is the only COX-2 inhibitor available in the United States.

2.4 INTRODUCTION TO API [21,22,25,30,31]

Molecular formula : $C_{17}H_{14}F_3N_3O_2S$

Molecular weight : 323.412g/mol

Pka : 5.98

Category : Selective COX-II inhibitor.

Melting point : 159-160^{0}C

Log P/hydrophobicity : 3.9

Dose : 50mg, 100mg, 200mg, 400mg,

Description : White crystalline powder having no odor. practically insoluble in water

λmax: 254 nm in 0.1 N HCl (pH 1.2) with 1% SLS.

Loss on drying: Not more than 1%w/w.

Storage: Store at room temperature at 77 degrees F (25 degrees C) away from light and moisture.

PHARMACOLOGY

Mode of Action :

API is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of API is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2), and at therapeutic concentrations in humans, it does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme. In animal colon tumor models, API reduced the incidence and multiplicity of tumors.

Absorption:

Peak plasma levels of API occur approximately 3 hrs after an oral dose. Under fasting conditions, both peak plasma levels (Cmax) and area under the curve (AUC) are roughly dose proportional up to 200 mg BID; at higher doses there are less than proportional increases in

Cmax and AUC (see Food Effects). Absolute bioavailability studies have not been conducted. With multiple dosing, steady state conditions are reached on or before Day5.

The pharmacokinetic parameters of API in a group of healthy subjects are 81 shown in Table1.

Mean (%CV) PK Parameter Values				
C_{max}, ng/mL	**T_{max}, hr**	**Effective $t_{1/2}$, hr**	**V_{ss}/F, L**	**CL/F, L/hr**
705 (38)	2.8 (37)	11.2 (31)	429 (34)	27.7 (28)

Food Effects

When Innovator capsules were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%.Under fasting conditions, at doses above 200mg, there is less than a proportional increase in Cmax and AUC, which is thought to be due to the low solubility of the drug in aqueous media.Co-administration of Innovator with an aluminum and magnesium containing antacid resulted in a reduction in plasma API concentrations with a decrease of 37% in Cmax and 10% in AUC. Innovator, at doses up to 200 mg BID can be administered without regard to timing of meals. Higher doses (400 mg BID) should beadministered with food to improve absorption.

Distribution :

In healthy subjects, API is highly protein bound (~97%) within the clinical dose range. *In vitro* studies indicate that API binds primarily to albumin and, to a lesser extent, α1-acid glycoprotein. The apparent volume of distribution at steady state (Vss/F) is approximately 400 L, suggesting extensive distribution into the tissues. API is not preferentially bound to red blood cells.

Metabolism :

API metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors.Patients who are known or suspected to be P450 2C9 poor metabolizers based on a

previous history should be administered API with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Excretion :

API is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% was excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process making terminal half-life (t1/2) determinations more variable. The effective half-life is approximately 11 hours under fasted conditions. The apparent plasma clearance (CL/F) is about 500 mL/min.

Table 2: Pharmacokinetic parameters of API

Pharmacokinetic parameters	**Value from literature**
Absolute Bioavailability	22-40%
C_{max}	906.07 ng/ml
T_{max}	3 Hrs
$T_{½}$	11
V_d	400
Protein binding	97%

Indications :

Innovator is indicated:

1) For relief of the signs and symptoms of osteoarthritis.
2) For relief of the signs and symptoms of rheumatoid arthritis in adults.
3) For relief of the signs and symptoms of juvenile rheumatoid arthritis in patients 2 years and older.
4) For the relief of signs and symptoms of ankylosing spondylitis.
5) For the management of acute pain in adults.
6) For the treatment of primary dysmenorrhea.

7) To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance, surgery). It is not known whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients. It is also not known whether the effects of Innovator treatment will persist after Innovator is discontinued. The efficacy and safety of Innovator treatment in patients with FAP beyond six months have not been studied.

Relief of the signs and symptoms of osteoarthritis, ankylosing spondylitis, juvenile rheumatoid arthritis (JRA), and rheumatoid arthritis; management of acute pain; treatment of primary dysmenorrhea; to reduce the number of intestinal polyps in familial adenomatous polyposis (FAP).

Contraindications

Innovator should not be given to patients who have demonstrated allergic-type reactions to sulfonamides. Innovator should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarelyfatal, anaphylactic-like reactions to NSAIDs have been reported in such patients. Innovator is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

Use in pregnancy

Pregnancy Risk Factor C (prior to 30 weeks gestation)

Teratogenic effects have been observed in some animal studies; therefore, API is classified as pregnancy category C. The effects of this selective inhibition to the fetus have not been well studied and limited information is available specific to API. NSAID exposure during the first trimester is not strongly associated with congenital malformations; however, cardiovascular anomalies and cleft palate have been observed following NSAID exposure in some studies. The use of a NSAID close to conception may be associated with an increased risk of miscarriage. Nonteratogenic effects have been observed following NSAID administration during the third trimester including: Myocardial degenerative changes, prenatal constriction of the ductus arteriosus, fetal tricuspid regurgitation, failure of the ductus arteriosus to close postnatally; renal dysfunction or failure, oligohydramnios; gastrointestinal bleeding or perforation, increased risk of necrotizing enterocolitis; intracranial bleeding (including intraventricular hemorrhage), platelet dysfunction with

resultant bleeding; pulmonary hypertension. Because it may cause premature closure of the ductus arteriosus, the use of API is not recommended 30 weeks gestation. The chronic use of NSAIDs in women of reproductive age may be associated with infertility that is reversible upon discontinuation of the medication.

Use in lactation :

Small amounts of API are found in breast milk.The manufacturer recommends that caution be exercised when administering API to nursing women and hence it should not be used during lactation.

Warnings and Precautions

Cardiovascular events: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI and stroke. Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. May cause sodium and fluid retention, use with caution in patients with edema. Avoid use in heart failure. Long-term cardiovascular risk in children has not been evaluated. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular; alternate therapies should be considered for patients at high risk.

Coronary artery bypass graft surgery: API is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft surgery. Risk of MI and stroke may be increased with use following CABG surgery.

Adverse Reaction

Symptoms of overdose include breathing difficulties, coma, drowsiness, gastrointestinal bleeding, high blood pressure, kidney failure, nausea, sluggishness, stomach pain, and vomiting.

Overdosage:

Symptoms of overdose include breathing difficulties, coma, drowsiness, gastrointestinal bleeding, high blood pressure, kidney failure, nausea, sluggishness, stomach pain, and vomiting.

2.5.INTRODUCTION TO EXCIPIENTS [5]

1. Lactose monohydrate

Nonproprietary Names

BP: Lactose monohydrate

PhEur: Lactosum monohydricum

JP: Lactose

USPNF: Lactose monohydrate

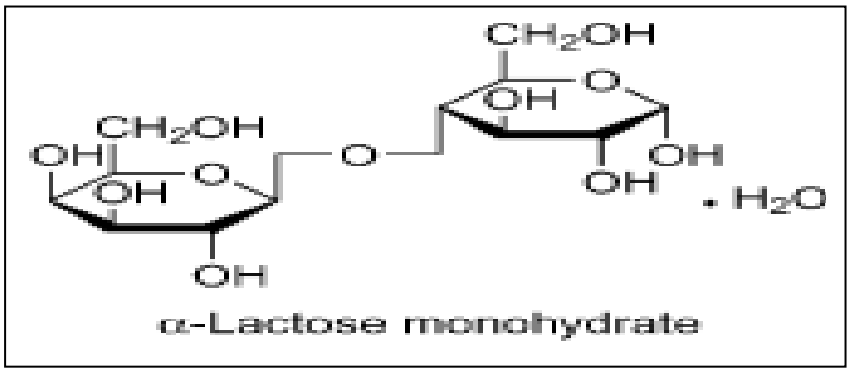
Chemical Name

O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate

Empirical Formula and Molecular Weight

$C_{12}H_{22}O_{11}\cdot H_2O$ and 360.31

Structural Formula



Functional Category

Binding agent; diluent for dry-powder inhalers; tablet binder; tablet and capsule diluent.

Description

In the solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e. α-lactose monohydrate, β-lactose anhydrous, and α-lactose-anhydrous. The stable crystalline forms of lactose are α-lactose monohydrate, β-lactose-anhydrous, and stable α-lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; α-lactose is approximately 20% as sweet as sucrose, while β-lactose is 40% as sweet.

Typical Properties

Density (true)

1.545 g/cc (a-lactose monohydrate)

Density (bulk)

0.540 g/cc (Granulac 200)

Density (tapped)

0.800 g/cc (Granulac 200)

Loss on drying Typically

0.2% for Monohydrate 80M, Monohydrate Impalpable; and 0.1–0.2% for Meggle products.

Melting point

201–202^{0}C

Moisture content

Lactose monohydrate contains approximately 5% w/w water of crystallization and normally has a range of 4.5–5.5% w/w water content.

Applications in Pharmaceutical Formulation or Technology

Lactose is widely used as a filler or diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas. Lactose is also used as a diluent in dry-powder inhalation. Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application; for example, the particle size range selected for capsules is often dependent on the type of encapsulating machine used. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size permits better mixing with other formulation ingredients and utilizes the binder more efficiently.

Other applications of lactose include use in lyophilized products, where lactose is added to freeze-dried solutions to increase plug size and aid cohesion. Lactose is also used in combination with sucrose (approximately 1 : 3) to prepare sugar-coating solutions. Direct compression grades of lactose monohydrate are available as granulated/agglomerated α lactose monohydrate, containing small amounts of anhydrous lactose. Direct-compression grades are often used to carry lower quantities of drug and this permits tablets to be made without granulation Other directly compressible lactoses are spray-dried lactose and anhydrous lactose.

Stability and Storage Conditions

Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions; The purities of different lactoses can vary and color evaluation may be important, particularly if white tablets are being formulated. The color stabilities of various lactoses also differ. Solutions show mutorotation; Lactose should be stored in a well-closed container in a cool, dry place

2. Microcrystaline cellulose:

Nonproprietary Names

BP: Microcrystalline cellulose

JP: Microcrystalline cellulose

PhEur: Cellulosum microcristallinum

USPNF: Microcrystalline cellulose

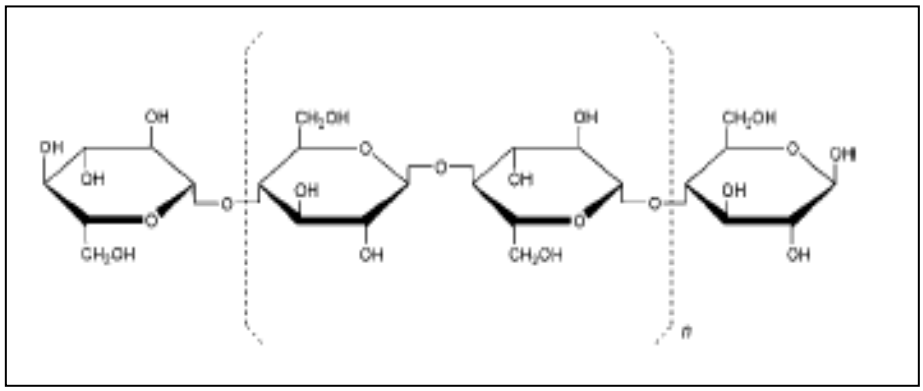
Synonyms

Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.

Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)n$ _36 000 where n _ 220.

Structural Formula



Functional Category

- Adsorbent
- suspending agent
- tablet and capsule diluent
- tablet disintegrant.

Description

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products.

Typical Properties

Angle of repose:

498 for Ceolus KG;

34.48 for Emcocel 90M.(9)

Density (bulk):

0.337 g/cm^3;

0.32 g/cm^3 for Avicel PH-101;

0.29 g/cm^3 for Emcocel 90M;

0.29 g/cm^3 for VivaPur 101.

Density (tapped):

0.478 g/cm^3;

0.45 g/cm^3 for Avicel PH-101;

Density (true):

1.512–1.668 g/cm^3

Melting point:

chars at 260–270°C

Moisture content:

Typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.

Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agents.

3. Polyvinyl Pyrrolidone:

Nonproprietary Names

BP: Povidone

JP: Povidone

PhEur: Povidonum

USP: Povidone

Synonyms

E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

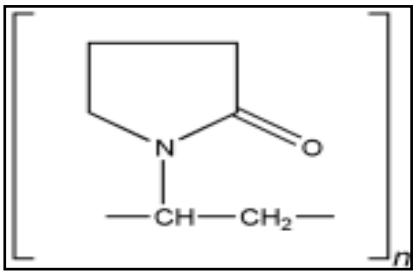
Empirical Formula and Molecular Weight

$(C_6H_9NO)n$ 2500–3 000 000

Table 3: Approximate molecular weights for different grades of povidone.

K- value	Approxi,mate Weight
12	2500
15	8000
17	10000
25	30000
30	50000
60	400000
90	1000000
120	3000000

Structural Formula



Functional Category

- Disintegrant
- Dissolution aid
- Suspending agent
- Tablet binder.

Applications in Pharmaceutical Formulation or Technology

In tableting, povidone solutions are used as binders in wet-granulation processes. Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. Povidone solutions may also be used as coating agents. Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

Table 2.4: Uses of Povidone

Use	**Concentration (%)**
Carrier for Drugs	10-25
Dispersing agent	Up to 5
Eye drops	2-10

Suspending agent	Up to 5
Tablet binder, tablet diluents, or coating agent	0.5-5

Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with *K*-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher *K*-value povidones are manufactured by drum drying and occur as plates.

Typical Properties

Acidity/alkalinity:

pH = 3.0–7.0 (5% w/v aqueous solution).

Density (bulk):

0.29–0.39 g/cm^3 for Plasdone.

Density (tapped):

0.39–0.54 g/cm^3 for Plasdone.

Density (true):

1.180 g/cm^3

Flowability:

• 20 g/s for povidone K-15;

• 16 g/s for povidone K-29/32.

Melting point:

softens at 150°C.

Moisture content:

povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative

humidities.

Particle size distribution:

• Kollidon 25/30: 90% >50 μm, 50% >100 μm, 5% >200 μm;

• Kollidon 90: 90% >200 μm, 95% >250 μm.7

Solubility:

freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

Viscosity (dynamic):

the viscosity of aqueous povidone solutions depends on both the concentration and the molecular weight of the polymer employed.

Stability and Storage Conditions

Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130°C; steam sterilization of an aqueous solution does not alter its properties. Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives. Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds;. Thevefficacy of some preservatives, e.g. thimerosal, may be adversely affected by the formation of complexes with povidone.

4. Hypermellose:

Nonproprietary Names

BP: Hypromellose

JP: Hydroxypropylmethylcellulose

PhEur: Hypromellosum

USP: Hypromellose

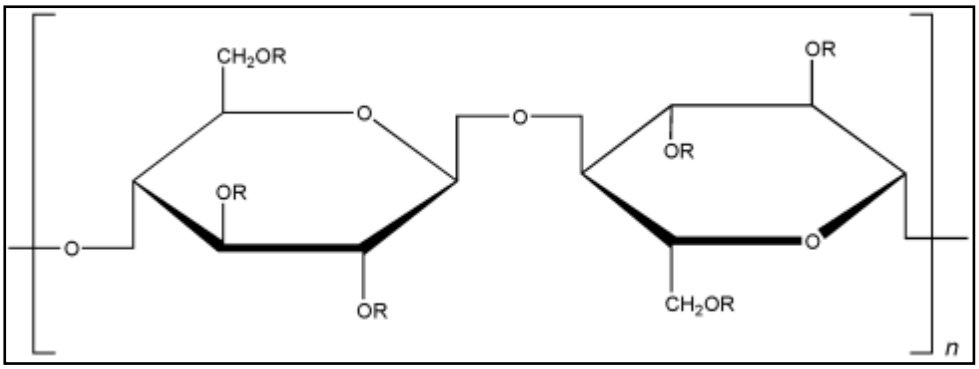
Synonyms

Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.

Empirical Formula and Molecular Weight

The PhEur 2005 describes hypromellose as a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20°C. Hypromellose defined in the USP 28 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH2CH(OH)CH3), calculated on a dried basis. It contains methoxy and hydroxypropoxy groups conforming to the limits for the types of hypromellose stated in Table I. Molecular weight is approximately 10 000–1 500 000. The JP 2001 includes three separate monographs for hypromellose: hydroxypropylmethylcellulose 2208, 2906, and 2910, respectively.

Structural Formula



where R is H, CH_3, or $CH_3CH(OH)CH_2$

Functional Category

- Coating agent
- Film-former
- Rate-controlling polymer for sustained release
- Stabilizing agent
- Suspending agent
- Tablet binder
- Viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulations.8–12 Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Examples of filmcoating materials that are commercially available include AnyCoat C, Spectracel, and Pharmacoat. Hypromellose is also used as a suspending and thickening agent

in topical formulations. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments. In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Description

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

Typical Properties

Acidity/alkalinity:

pH = 5.5–8.0 for a 1% w/w aqueous solution.

Density (bulk):

0.341 g/cm^3

Density (tapped):

0.557 g/cm^3

Density (true):

1.326 g/cm^3

Melting point:

Browns at 190–200°C; chars at 225–230°C. Glass transition temperature is 170–180°C.

Moisture content:

Hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.

Solubility:

Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water andalcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

Specific gravity: 1.26

Viscosity (dynamic):

A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous hypromellose solutions. Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions;

Teble 2.5 HPMC grades and viscosity

Methocel product	**USP designation**	**Nominal viscosity (mPa s)**
Methocel K3 Premium LV	2208	3
Methocel K100 Premium LVEP	2208	100
Methocel K4M Premium	2208	4000
Methocel K15M Premium	2208	15 000
Methocel K100M Premium	2208	100 000
Methocel E3 Premium LV	2910	3
Methocel E5 Premium LV	2910	5

Methocel E6 Premium LV	2910	6
Methocel E15 Premium LV	2910	15
Methocel E50 Premium LV	2910	50
Methocel E4M Premium	2910	4000
Methocel E10M Premium CR	2910	10000
Methocel F50 Premium	2906	50
Methocel F4M Premium	2906	4000
Metolose 60SH	2910	50, 4000, 10 000
Metolose 65SH	2906	50, 400, 1500, 4000
Metolose 90SH	2208	100, 400, 4000, 15 000

To prepare an aqueous solution, it is recommended that hypromellose is dispersed and thoroughly hydrated in about 20–30% of the required amount of water. The water should be vigorously stirred and heated to 80–90°C, then the remaining hypromellose should be added. Sufficient cold water should then be added to produce the required volume. When a water-miscible organic solvent such as ethanol (95%), glycol, or mixtures of ethanol and dichloromethane are used, the hypromellose should first be dispersed into the organic solvent,

at a ratio of 5–8 parts of solvent to 1 part of hypromellose. Cold water is then added to produce the required volume.

Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gel point is 50–90°C, depending upon the grade and concentration of material. Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage.13 However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative: when hypromellose is used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

5. <u>Croscarmellose sodium</u>

1. Nonproprietary Names

BP: Croscarmellose sodium

PhEur: Carmellosum natricum conexum

USPNF: Croscarmellose sodium

2. Synonyms

Ac-Di-Sol; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum;

Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

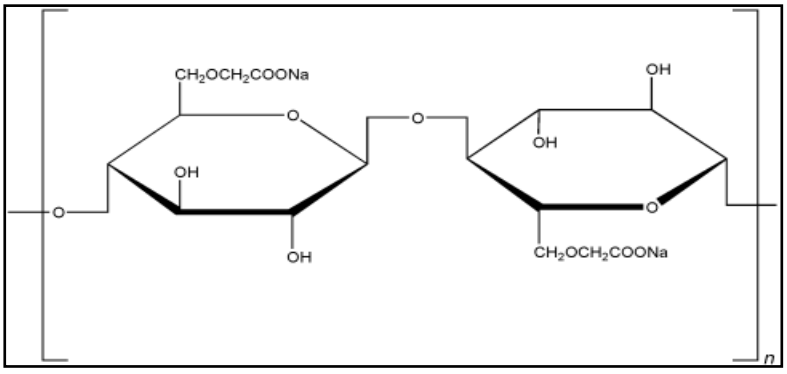
3. Chemical Name and CAS Registry Number

Cellulose, carboxymethyl ether, sodium salt, crosslinked

4. Empirical Formula and Molecular Weight

Croscarmellose sodium is a crosslinked polymer of carboxymethylcellulose sodium. The USP 28 describes carboxymethylcellulose sodium as the sodium salt of a polycarboxymethyl ether of cellulose. Typical molecular weight is 90 000–700 000.

5. Structural Formula



6. Functional Category

Tablet and capsule disintegrant.

7. Applications in Pharmaceutical Formulation or Technology

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules,1,2 tablets,3–13 and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized.11,12 Croscarmellose sodium atconcentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process. **Table I**

Table 2.6: Uses of croscarmellose sodium.

Use	Concentration (%)
Disintegrant in capsules	10-25
Disintegrant in tablets	0.5-5.0

8. Description

Croscarmellose sodium occurs as an odorless, white or grayish-white powder.

9. Typical Properties

Acidity/alkalinity:

pH = 5.0–7.0 in aqueous dispersions.

Density (bulk):

0.529 g/cm^3 for Ac-Di-Sol7

Density (tapped):

0.819 g/cm^3 for Ac-Di-Sol7

Density (true):

1.543 g/cm^3 for Ac-Di-Sol7

Particle size distribution:

• Ac-Di-Sol: not more than 2% retained on a #200 (73.7 μm) mesh and not more than 10% retained on a #325 (44.5 μm) mesh.

• Pharmacel XL: more than 90% less than 45 μm, and more than 98% less than 100 μm in size.

Solubility:

Insoluble in water, although croscarmellose sodium rapidly swells to 4–8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.

Specific surface area:

0.81–0.83 m^2/g

11. Stability and Storage Conditions

Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 30°C for 14 months.9 Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

12. Incompatibilities

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that hygroscopic excipients such as sorbitol.10 Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

6. Crospovidone:

1. Nonproprietary Names

BP: Crospovidone

PhEur: Crospovidonum

USPNF: Crospovidone

2. Synonyms

Crosslinked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL; Polyplasdone XL-10; polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer**.**

3. Chemical Name and CAS Registry Number

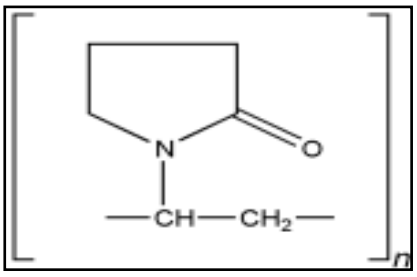
1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4. Empirical Formula and Molecular Weight

$(C_6H_9NO)n$ >1 000 000

The USPNF 23 describes crospovidone as a water-insoluble synthetic crosslinked homopolymer of N-vinyl-2-pyrrolidinone. An exact determination of the molecular weight has not been established because of the insolubility of the material.

5. Structural Formula



6. Functional Category

- Tablet disintegrant.

7. Applications in Pharmaceutical Formulation or Technology

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

8. Description

Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

9. Typical Properties

Acidity/alkalinity:

pH = 5.0–8.0 (1% w/v aqueous slurry)

Density:

1.22 g/cm^3

Density (bulk):

Table 2.7: Density values of commercial grades of crospovidone.

Commercial Grade	**Density (bulk) g/cm^3**	**Density (tapped) g/cm^3**
Kollidon CL	0.3-0.4	0.4-0.5
Kollidon CL-M	0.15-0.25	0.3-0.5
Polyplasdone XL	0.213	0.273
Polyplasdone XL-10	0.323	0.461

Moisture content:

Maximum moisture sorption is approximately 60%.

Particle size distribution:

Less than 400 μm for *Polyplasdone XL*; less than 74 μm for *Polyplasdone XL-10*. Approximately 50% greater than 50 μm and maximum of 3% greater than 250 μm in size for *Kollidon CL*. Minimum of 90% of particles are below 15 μm for *Kollidon CL-M.*

Solubility:

Practically insoluble in water and most common organic solvents.

Specific surface area:

Table 2.8: Specific surface areas for commercial grades of crospovidone.

Commercial grade	**Surface area (m^2/g)**
Kollidon CL	1.0
Kollidon CL-M	3.0–6.0
Polyplasdone XL	0.6–0.8
Polyplasdone XL-10	1.2–1.4

10. Stability and Storage Conditions

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

7. Sodium Starch Glycolate

Nonproprietary Names

BP : Sodium Starch Glycolate

PhEur: Carboxymethylamylum natricum

USPNF: Sodium Starch Glycolate

Synonyms

Carboxymethyl starch, sodium salt; Explotab; Primojel; Vivastar P

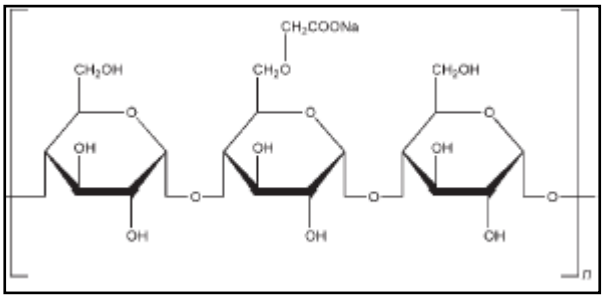
Chemical Name

Sodium carboxymethyl starch.

Empirical Formula

The USPNF 20 states that sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch. The PhEur 22 describes three types of material; Type A: equivalent to the USPNF 20 material, containing 2.8- 4.2 % of sodium.Type B: containing 2.0 -3.4 % of sodium.Type C: containing 2.8- 5.0 % of sodium.

Structural Formula



Molecular weight

5× 105_ × 1 × 106

Functional category

Tablet and capsule disintegrant.

Description

It is a white to off – white, odorless, tasteless, free- flowing powder. It consists of oval or spherical granules, 30- 100 µm in diameter, with some less spherical granules ranging from 10- 35 µm in diameter.

Typical properties

Acidity/ alkalinity

pH = 3.0- 5.0 or Ph = 5.5- 7.5 for a 3.3 % w/v aqueous dispersions.

True density

1.443 g/cm3

Bulk density

0.756 g/cm3

Tapped density

0.945 g/cm3

Melting point

Does not melt , but chars approximately 200˚ c

Particle size distribution

100% of particles less than 104 µm in size .Average particle size is 42 µm for Explotab

Specific surface Area

0.24m2/g

Solubility

sparingly soluble in ethanol (95%); practically insoluble in water. At a concentrations of 2 % w/v it disperses in cold Water and settles in the form of a highly hydrated water.

Swelling capacity

In water, it swells to up to 300 times its volume.

Application in pharmaceutical formulation or technology

It is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct- compression or wet- granulation processes. The usual concentrations employed in a formulations is between 2% and 8%, with the optimum concentrations about 4%, although in many cases 2% is sufficient.

Incompatibilities

It is incompatible with ascorbic acid.

Stability and storage conditions

Sodium Starch Glycolate is stable and should be stored in a well- closed container .

8. Sodium lauryl Sulfate:

Nonproprietary Names

BP: Sodium lauryl sulfate

JP: Sodium lauryl sulfate

PhEur: Natrii laurilsulfas

USPNF: Sodium lauryl sulfate

Synonyms

Dodecyl sodium sulfate; Elfan 240; sodium dodecyl sulfate; sodium laurylsulfate; sodium monododecyl sulfate; sodium monolauryl sulfate; Texapon K12P.

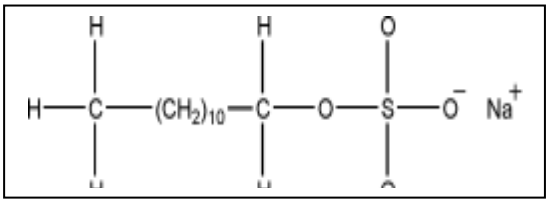
Chemical Name and CAS Registry Number

Sulfuric acid monododecyl ester sodium salt [151-21-3]

Empirical Formula and Molecular Weight $C_{12}H_{25}NaO_4S$ and 288.38

The USPNF 23 describes sodium lauryl sulfate as a mixture of sodium alkyl sulfates consisting chiefly of sodium lauryl sulfate $C_{12}H_{25}NaO_4S$.

Structural Formula



Functional Category

Anionic surfactant; detergent; emulsifying agent; skin penetrant; tablet and capsule lubricant; wetting agent.

Applications in Pharmaceutical Formulation or Technology:

Sodium lauryl sulfate is an anionic surfactant employed in a wide range of nonparenteral pharmaceutical formulations and cosmetics

Table 2.9: Uses of sodium lauryl sulfate

Use	**Concentration (%)**
Anionic Emulsifier, forms self emulsifying bases with fatty alcohols	0.5-2.5
Detergent in medicated shampoos	10
Skin cleanser in topical application	1
Solubilizer in concentration greater than critical micelle concentration	>0.0025
Tablet lubricant	1.0-2.0
Wetting agent in dentrifices	1.0-2.0

It is a detergent and wetting agent effective in both alkaline and acidic conditions. In recent years it has found application in analytical electrophoretic techniques: SDS (sodium dodecyl sulfate) polyacrylamide gel electrophoresis is one of the more widely used techniques for the analysis of proteins;1 and sodium lauryl sulfate has been used to enhance the selectivity of micellar electrokinetic chromatography (MEKC).2

Description

Sodium lauryl sulfate consists of white or cream to pale yellow-colored crystals, flakes, or powder having a smooth feel, a soapy, bitter taste, and a faint odor of fatty substances.

Typical Properties

Acidity/alkalinity:

pH = 7.0–9.5 (1% w/v aqueous solution)

Antimicrobial activity:

Sodiumlauryl sulfate has some bacteriostatic action against Gram-positive bacteria but is ineffective against many Gram-negative microorganisms. It potentiates the fungicidal activity of certain substances such as sulfanilamide and sulfathiazole.

Critical micelle concentration:

8.2 mmol/L (0.23 g/L) at 20°C

Density:

1.07g/cm^3 at 20°C

HLB value: ≈40

Interfacial tension:

11.8 mN/m (11.8 dynes/cm) for a 0.05% w/v solution (unspecified nonaqueous liquid) at 30°C.

Melting point:

204–207°C (for pure substance)

Moisture content:

≤5%; sodium lauryl sulfate is not hygroscopic.

Solubility:

Freely soluble in water, giving an opalescent solution; practically insoluble in chloroform and ether.

Wetting time (Draize test):

118 seconds (0.05% w/v aqueous solution) at 30°C

Stability and Storage Conditions

Sodium lauryl sulfate is stable under normal storage conditions. However, in solution, under extreme conditions, i.e., pH 2.5 or below, it undergoes hydrolysis to lauryl alcohol and sodium bisulfate. The bulk material should be stored in a well-closed container away from strong oxidizing agents in a cool, dry place.

Incompatibilities

Sodium lauryl sulfate reacts with cationic surfactants, causing loss of activity even in concentrations too low to cause precipitation. Unlike soaps, it is compatible with dilute acids and calcium and magnesium ions. Solutions of sodium lauryl sulfate (pH 9.5–10.0) are mildly corrosive to mild steel, copper, brass, bronze, and aluminum. Sodium lauryl sulfate is also incompatible with some alkaloidal salts and precipitates with lead and potassium salts.

9. Magnesium stearate:

Nonproprietary Names

BP: Magnesium stearate

JP: Magnesium stearate

PhEur: Magnesii stearas

USPNF: Magnesium stearate

Synonyms

Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

Empirical Formula and Molecular Weight

$C_{36}H_{70}MgO_4$ and 591.34

Structural Formula

$[CH_3(CH_2)_{16}COO]_2Mg$

Functional Category

Tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w.

Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin

Typical Properties

Crystalline forms:

High-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.

Density (bulk):

0.159 g/cm^3

Density (tapped):

0.286 g/cm^3

Density (true):

1.092 g/cm^3

Flash point:

250°C

Flowability:

poorly flowing, cohesive powder.

Melting range:

117–150°C (commercial samples);126–130°C (high purity magnesium stearate).

Solubility:

Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Specific surface area:

1.6–14.8m2/g

Incompatibilities

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation. No toxicity information is available relating to normal routes of occupational exposure. Limits for heavy metals in magnesium stearate have been evaluated in terms of magnesium stearate worst-case daily intake and heavy metal composition.(1) Toxicity assessments of magnesium stearate in rats have indicated that it is not irritating to the skin, and is nontoxic when administered orally or inhaled.(2,3) Magnesium stearate has not been shown to be carcinogenic when implanted into the bladder of mice.(4) LD50 (rat, inhalation): >2 mg/L(2) LD50 (rat, oral): >10 g/kg.

3. LITERATURE REVIEW

Newton JM, et al has done the prediction of the bulk densities of powder mixtures, and its relationship to the filling of hard gelatin capsules. From measurements of the properties of individual components, it has been found possible to predict the maximum tapped bulk density of two component mixtures of a range of particle size fractions of acetylsalicylic acid and lactose in varying proportions. This has been extended to the prediction of bulk density of such mixtures when filled into hard gelatin capsules by a system which results in the powders existing at the maximum tapped bulk density. Consequently the capsule fill weight can also be predicted for such systems. The method is less satisfactory for the prediction of the bulk density and capsule fill weight, when the capsules are filled by a process involving compression of the powder within the capsule shell.

Podczeck, F et al, They performed the experiments to study the possibility of predicting the bulk volume changes of a powder bed due to granulation and/or low compression, to aid the development of powder filled hard gelatin capsules. Granulation techniques used were a high speed mixer/granulator and an oscillating granulator. For each of a series of typical filler powders and the granules produced from them, the tapped volume and the Kawakita constant a were determined on the basis of tap density volumetry. Only the granules produced in the high speed mixer/granulator partly provided a reduced tap volume, whereas the processing by an oscillating granulator resulted generally in an increased tap volume. For the decrease in volume, a limiting value of the tap volume of the original powders of 1.4 cm(3)/g appears to exist. Powders with a tap volume below this threshold cannot be densified by granulation, whereas the degree of possible volume reduction increases with an increase in tap volume above the limiting value. A combination of granulation and compression to further densify a powder failed in providing smaller plug volumes. Hence, if a reduction in capsule size is the only reason to use a densification method, low compression is preferable to granulation.

S.B. Tan et al,. The flowability of size fractions of 5 pharmaceutical excipients has been related to their capsule filling performance. Using angular, packing and shear tests, the samples were ranked in different relative orders of flowability. The powders were filled in capsule. Capsule fill weight and weight uniformity were monitored and the coefficient of variation (Xcv) of the fill weight of 20 capsules was used as an indicator of capsule filling performance. Flowability was dependent on the particle size, morphology and bulk density of the powder. There was a significant correlation between the values of Xcv and the flow

parameters of Carr's compressibility, Hausner's ratio, angle of repose, Kawakita's equation constant (a) and Jenike's flow factor. Xcv was also related to the coefficient of variation of the powder bed bulk density and the variation in the compression stress. There was, however, no correlation between the values of Xcv and the angle of internal flow and the angle of effective friction.

Rajesh Patel et al The influence of the type and source of 8 microcrystalline cellulose samples on the capsule filling performance has been investigated. Different sources of fine, medium and coarse grade microcrystalline cellulose have been used. Several properties of the powders such as particle size, packing and flow were determined and related to the capsule filling behaviour and the capsule disintegration time. A fine grade microcrystalline cellulose such as Avicel® PH105 cannot be used in capsule filling because of unsatisfactory flow properties. Medium and coarse grade microcrystalline cellulose can be classified as a good capsule filling excipient, but not all sources are suitable. The Lüdde-Kawakita constant a and Hausner's ratio are good indicators of the capsule filling performance, especially in terms of interchangeability of different sources, possibility of filling above maximum bulk density and flow problems producing large coefficients of fill weight variation

R. N. Saha. et al A new UV spectrophotometric method (UV method) and a reversed phase liquid chromatographic method (LC method) for the quantitative estimation of API, a selective COX-2 inhibitor, in pure form and in solid dosage form were developed in the present study. The detection limit, as per the error propagation theory, was found to be 0.26 μg/ml and 25 ng/ml, respectively, for the UV and LC methods. The developed methods were employed with a high degree of precision and accuracy for the estimation of total drug content in three commercial capsule formulations of API. The results of analysis were treated statistically, as per International Conference on Harmonisation (ICH) guidelines for validation of analytical procedures, and by recovery studies. The results were found to be accurate, reproducible and free from interference and better than the earlier reported methods.

Block L.C. et al Metformin hydrochloride (MH) is an oral hypoglycaemic agent and a high-dose drug that has poor flow and compression properties. In this study, the feasibility of developing adequate, low cost 500mg tablets of metformin hydrochloride by wet granulation was tested with several binders (Starch / PVP K30; Starch 1500/PVP K30, PVP K30 and PVP K90). The drug powder was tested for ability to flow, by determining Carr’s Index (CI) and the Hausner ratio (HR). The size distribution, friability, flow properties and drug content of the granules were analyzed, as were the hardness, friability, disintegration, dissolution and

uniformity of the dosage form. The drug powder showed CI > 22% and HR > 1.25, characteristic of a poor flow powder, and no significant incompatibilities with the excipients. All the granules showed adequate flow properties and were suitable for pressing into tablets, all of which complied with pharmacopeial specifications. The starch /PVP K30 and starch 1500 /PVP K30 mixtures were best for producing 500 mg MH tablets.

M.A. Odeniyi et al. A research study was made on the compressibility and flow characteristics of Metronidazole in binary mixtures with Lactose and Microcrystalline cellulose powders as diluents. Binary mixtures of various proportions of Metronidazole with Lactose powder and Microcrystalline cellulose were prepared. The bulk and tapped densities, angle of repose, angle of internal flow, and compressibility index of the individual and powder mixtures were determined using appropriate parameters. The results obtained showed that the packing and cohesive properties of the binary mixtures depended on the nature of the diluent, particle shape and size, particle size distribution, and the concentration of the diluent. The results from the factorial experimental design showed that changing the diluent from low to high concentration in both mixtures served to increase the maximum volume reduction parameter, while no significant ($p > 0.05$) effect was observed when the diluent was changed from Lactose to Microcrystalline cellulose. However, changes in the nature and concentration of diluents caused an increase in the angle of internal flow. The results obtained would be useful in the handling and industrial processing of these powders and in the production of powders, tablets, capsules and other drug delivery systems with desirable and predictable flow properties.

4. EXPERIMENTAL WORK

4.1 PREFORMULATION STUDIES

4.1 Characterization of Active Pharmaceutical Ingredient

4.1.1 Description

API is a white to off white crystalline, odourless powder.

4.1.2 Solubility

Solubility study was performed at different pH and temp. 37˚C.

Table 4.1: Solubility study of API

Medium	Solubility of API without SLS (mg/ml)	Solubility of API with 1% SLS (mg/ml)
Water	0	0.3786
0.1 N HCl	0.0003	0.5839
pH 4.5 Acetate Buffer	0.0007	0.6698
pH 6.8 Phosphate Buffer	0.0006	0.6087

Result of solubility study shows that API is almost practically insoluble at all the pH i.e. it has pH independent solubility. It get solubilize in different media with 1% SLS.

4.1.3 Differential Scanning Calorimetry

The DSC thermograms of the API showed peaks at about 202° C.

4.1.4 Bulk Density

Bulk Density is the ratio of the weight of powder to the volume it occupies. It is expressed in g/cc. Volume occupied by the powder includes, volume of the solid portion of the particles and voids between the particles. Bulk density is important in determining the size of the

equipment needed for handling and processing. The bulk density of API is presented in the following table.

Table 4.2: Bulk density of API

Parameters	**Unit g/cm^3**
Bulk Density (Apparent (ρ1))	**0.22**
Tapped Density (ρ2)	**0.452**

Result of BD and TD shows that API is fluffy in nature.

4.1.5 Compressibility

Compressibility is indirectly related to the relative flow rate, cohesiveness and particle size distribution of the powder. Powders with compressibility values lesser than about 20% has been found to exhibit good flow properties.Tapped (ρ2) and Apparent (ρ1) bulk density measurements can be used to estimate the compressibility of a material.

$$\text{Carr's Compressibility index (\%)} = \frac{(\rho 2) - (\rho 1)}{(\rho 2)} \text{ X } 100.$$

Table 4.3: Flow properties

Compressibility Index (%)	**Flow Character**	**Hausner Ratio**
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, Very poor	>1.60

For the above lots, the mean Compressibility Index was found to be **51.32%.** Thus it is evident that API exhibits poor flow properties and thus it is necessary to improve the flow property.

4.1.6 Particle Size Analysis

Various physical and chemical properties of drug substance are affected by their particle size distribution and shape. In case of insoluble drugs, the particle size can affect the dissolution, which in turn can affect plasma concentration profile in Bio-equivalence studies. In solid dosage forms, particle size can affect the content uniformity and tablet characteristics like porosity and flow ability.

The particle size distribution of API is determined by Malvern Particle Size Analyser using dry method. The observation is tabulated in the following table.

Table 4.4: Particle Size Distribution of API

API	**Particle Size in µm (% of particles under size)**		
Lot No.	**90 %**	**50 %**	**10 %**
	50µm	30µm	20µm

4.1.7 Compatibility of drug and Excipient

Drug:Excipients were kept in different conditions (40°C /75%RH) and checked for compatibility

Table: 4.5 Compatibility of drug and Excipient

Sr. No.	Drug + Excipient	Ratio	Related Substances					
			INITIAL			4th WEEK (40˚C±2˚C, 75±5% RH)		
			Impurity%					
			Max known	Max unknown	Total	Max known	Max unknown	Total
1	API		0.084	0.034	0.118	0.083	0.034	0.117
2	API:Microcrystalline cellulose (Avicel PH 101)	1 : 1	0.081	0.034	0.118	0.080	0.034	0.114
3	API:Lactose monohydrate (granulac 200)	1 : 1	0.080	0.032	0.112	0.079	0.031	0.110
4	API:Crosscarmellose sodium	1: 0.5	0.085	0.034	0.119	0.085	0.034	0.119
5	API:Crospovidone XL	1: 0.5	0.081	0.033	0.114	0.081	0.033	0.114
6.	API:HPMC 6 cps	1 0.5	0.084	0.034	0.118	0.082	0.033	0.115
7.	API:PVP K-30	1 0.5	0.082	0.033	0.115	0.082	0.033	0.115
8.	API:Sodium lauryl sulphate	1:0.25	0.084	0.034	0.118	0.082	0.033	0.115
9.	API:Tween 80	1: 0.25	0.084	0.034	0.118	0.084	0.034	0.118
10.	API:Magnesium stearate	1 : 0.1	0.085	0.034	0.119	0.082	0.034	0.116
11.	API:Talc	1 : 0.1	0.083	0.033	0.116	0.081	0.033	0.114
12.	API:Aerosil 200	1 : 0.1	0.084	0.034	0.118	0.083	0.034	0.117

limit :- Known impurity- NMT 0.15 and Unknown impurity-NMT 0.10

Total impurity – NMT 0.50 %

Table 4.6 Compatibility of drug and Excipient

Sr. No.	Drug-excipient mixture	Result	
		Initial	After 4 week
1	API	White to off white crystalline powder	White to off white crystalline powder
2	API:Microcrystalline cellulose (Avicel PH 101)	Off white powder	Off white powder
3	API:Lactose monohydrate (granulac 200)	White to off white powder	White to off white powder
4	API:Crosscarmellose sodium	White to off white powder	White to off white powder
5	API:Crospovidone XL	White to off white powder	White to off white powder
6	API:HPMC 6cps	Off white powder	Off white powder
7	API:PVP K-30	Off white powder	Off white powder
8	API:Sodium lauryl sulphate	White to off white powder	White to off white powder
9	API:Tween 80	Pale yellow colour	Pale yellow colour
10	API:Magnesium stearate	White to off white powder	White to off white powder
11	API:Talc	White to off white powder	White to off white powder
12	API:Aerosil 200	White to off white powder	White to off white powder

Observation: No significant change was observed in impurity profile of API with all excipients in Drug-compatability study.

Results:

Based on the data, it was concluded that API is compatible with all the excipients studied.

4.2. MATERIAL AND METHODS

Table 4.7 List of ingredient used in process

Sr.No	Excipients	Function
1	API	COX II inhibitor
2	Lactose monohydrate (Granulac 200)	Diluent
3	Microcrystalline cellulose (Avicel PH101)	Diluent
4	HPMC 6cps	Binder
5	PVP K-30	Binder
6	Croscarmellose sodium	Disintegrant
7	Sodimu stach glycolate	Disintegrant
8	Crospovidone XL	Disintegrant
9	Sodium lauryl sulfate	Wetting agent
10	Magnesium stearate	Lubricant

Table 4.8 List of instruments/equipments used in the process with its manufacturer

Sr. No.	Instruments/Equipments	Manufacturer
1.	Electronic Weighing Balance	Mettler Toledo
2.	Rapid Mixer Granulator	Saral
3.	Fluidized Bed Drier	Reva pharma
4.	Tray Drier	Saral
5.	Multi Mill	Shakti
6.	Conta Blender	Saral Engineering
7.	Halogen Moisture Analyzer	Mettler Toledo
8.	Capsule Hand Filling Machine	Pam India
9.	Tap Density Tester	Electrolab Tap Density Tester USP
10.	Powder characterization system	Sartorius
11.	Sieve Analyser	Cisa®
12.	Disintegration tester	Electrolab Disintegration Tester USP
13.	Dissolution Tester	Electrolab Dissolution Tester USP
14.	Stainless steel Sinkers	8mm X 23mm

15.	UV Visible Spectrophotometry	Shimadzu 1800
16.	Differential Scanning Calorimetry	DSC60 Shimadzu, Japan

4.3 IDENTIFICATION OF API

4.3.1 Determination by melting point:

The thiel's tube method of melting point determination in liquid paraffin was used in present investigation.

No of trials	Melting point (˚C)	Average
1	160	160˚C
2	159	
3	160	

Result: The observed value was found nearly similar to that of reported value. This indicates the identity and purity of API.

4.3.2. Determination by UV Spectroscopy:

10µg/ml drug solution was prepared in 0.1 N HCl with 1% SLS and Absorbance was measured in UV. The wavelength maxima was found to be 254 nm.

Result: Thus, the absorption maxima of sample drug exactly matched to the reported value. This further confirmed the identity of API.

4.4 STANDARD CURVE

Standard Curve in 0.1 N HCl with 1% SLS

Preparation of Stock Solution:

25 mg of API was accurately weighed and transferred into 50 ml volumetric flask. 0.1 N HCl with 1% SLS was added to dissolve the drug and finally the volume were make up to the mark with the same. From this, 2 ml of solution was transferred into 10 ml volumetric flask and diluted by buffer upto the mark. The concentration of this solution was 100 µg/ml.

Preparation of Standard Curve:

From stock solution 1,3,5,7,9,11,13and15 ml was pipetted out and transferred to 100 ml volumetric flask followed by suitable dilution with 0.1 N HCl with 1% SLS so the final concentration is 1,3,5,7,9,11,13and15 µg/ml respectively.

Table 4.9 Standard curve.

Concentration µg/ml	Absorbance				
	Trial 1	Trial 2	Trial 3	Average	% RSD
0	0	0	0	0	0
1	0.051	0.05	0.052	0.051	1.961
3	0.101	0.100	0.101	0.101	0.572
5	0.149	0.148	0.149	0.149	0.387
7	0.249	0.248	0.249	0.249	0.232
9	0.370	0.369	0.371	0.370	0.27
11	0.498	0.497	0.497	0.497	0.116
13	0.613	0.612	0.612	0.612	0.094
15	0.73	0.73	0.72	0.73	0.791

Figure 4.1 Standard curve in 0.1 N HCl with 1 % SLS

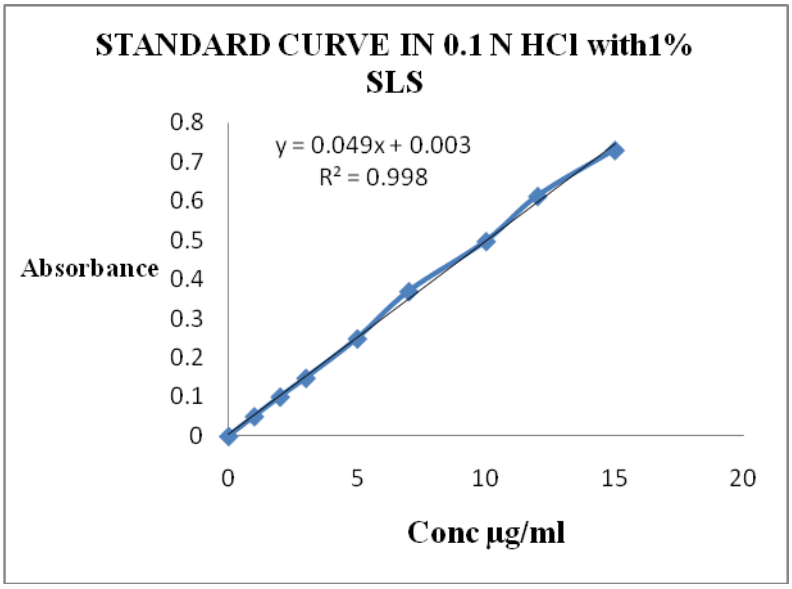


Table 4.10 Regression Analysis

OBSERVATION	
R^2	0.998
SLOPE	0.049
INTERCEPT	0.003

Standard Curve in (Water : Acetonitrile) (50 : 50)% v/v mixture

Table 4.11 Standard curve.

Concentration µg/ml	Absorbance				
	Trial 1	Trial 2	Trial 3	Average	% RSD
0	0	0	0	0	0
40	0.081	0.083	0.084	0.0827	1.847
120	0.182	0.181	0.181	0.1813	0.318
200	0.259	0.256	0.258	0.2577	0.593
280	0.322	0.32	0.321	0.321	0.312
360	0.426	0.425	0.425	0.4253	0.136
440	0.516	0.516	0.517	0.5163	0.112
520	0.619	0.615	0.618	0.6173	0.337
600	0.706	0.706	0.708	0.7067	0.163

Figure 4.2 Standard curve in Water : Acetonitrile (50 : 50) Mixture.

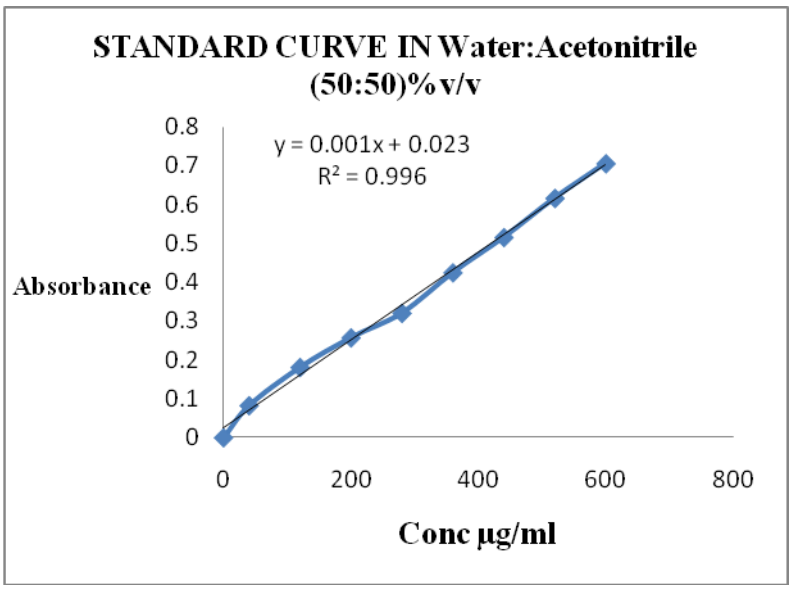


Table 4.12 Regression Analysis

OBSERVATION	
R^2	0.996
SLOPE	0.001
INTERCEPT	0.023

4.5 ESTIMATION OF API

Instrument : UV spectrophotometer

Wavelength : 254 nm

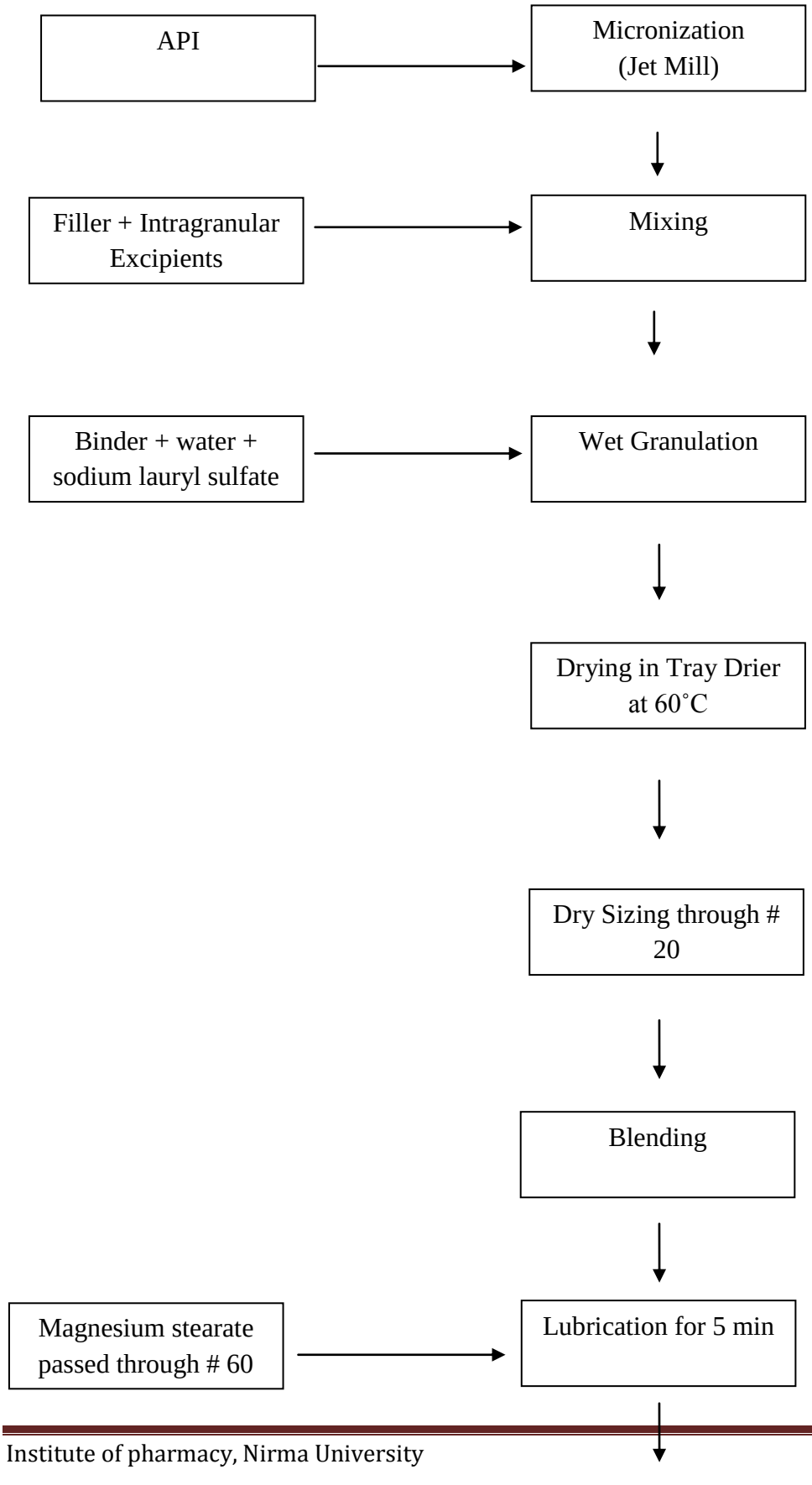
Medium : Water : Acetonitrile (50: 50)

Assay procedure for API

The amount of API present is determined by employing UV absorption at the wavelength of maximum absorbance at about 254 nm on portion of the test solution in comparison with the standard solution, using a 1- cm path length cell and Medium as the blank.

Assay = 99.9%

Process Flow Diagram:



Evaluation parameters of Capsule

Bulk Density

The bulk density of a solid is often very difficult to measure since the slightest disturbance of the bed may result in a diffferent bulk density. Bulk density is determined by measuring the volume of a known mass of powder sample, M that has been passed through a screen into a graduated cylinder. Carefully, level the powder without compacting, if necessary, and read the unsettled apparent volume, V_i to the nearest graduated unit. Calculate the bulk density in gm/ml by the formula :

$$\text{Bulk Density} = \frac{M}{Vi}$$

Tapped density

Tapped density is obtained by mechanically tapping a measuring cylinder containing a powder sample. Introduce a weighed quantity of powder sample in the glass graduated cylinder. Carefully, level the powder without compacting, if necessary, and read the unsettled apparent volume V_i to the nearest graduated unit. Mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using a suitable mechanical tapped density tester that provides a fixed drop of 14 ± 2 mm at nominal rate of 300 drops per minute. Tap the cylinder 250 times initially and measure the tapped volume, Va, Repeat the tapping for an additional 750 times and measure the tapped volume, Vb. If the difference between the two volumes is more than 2%, Vb is the final tapped volume Vf. Repeat in increments of 1250 taps, as needed, untill the difference between succeeding measurements is less than 2%.

Calculate the tapped density, in gm/ml by the formula:

$$\text{Tapped Density} = \frac{M}{Vf}$$

Angle Of Repose

The angle of internal friction is a measure of internal stress distribution and is the angle at which an applied stress diverges as it passes through the bed. It is the least slope at which a powder will slide down an inclined plane surface. The typical method is to pour the powder

in a conical heap on a level, flat surface and measure the included angle with the horizontal. It is denoted by θ.

$$\tan \theta = \frac{h}{r}$$

Where, θ = angle of repose, h = height of a pile, r = radius of pile.

Table 4.13 Flow Property

Flow Property	Angle Of Repose (θ)
Excellent	25-30
Good	31-35
Fair –aid not needed	36-40
Passable-may hang up	41-45
Poor –must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	>65

The powder mixture was allowed to pass through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

Loss On Drying

Mix and accurately weigh the substance to be tested, and conduct the determination on 1 to 2 gm. If the test specimen is in the form of large crystals, reduce the particle size to about 2 mm by quickly crushing. Dry the test specimen at the temperature 105˚C for 3min. This procedure determines the amount of volatile matter of any kind that is driven off under the conditions specified.

Particle Size Distribution

Sieving is one of the oldest methods of classifying powders and granules by particle size distribution. Mechanical sieving is most suitable where the majority of the particles are larger than about 75 µm. Tare each test sieve and place an accurately weighed quantity of test specimen on the top sieve and replace the lid. Agitate the nest of sieves for 5 minutes. Then

carefully remove each from the nest without loss of material. Reweigh each sieve, and determine the weight of material on each sieve. Total losses must not exceed 5% of the weight of the original test sample.

FINISHED PRODUCT PARAMETERS

Average weight

The weight variation of the capsule was carried out by taking the Average weight of 10 capsule. Theoretical Fill weight was 540 mg. The acceptable weight variation range is between 499.5 mg to 580.5 mg (±7.5%).

Disintegration

Complete disintegration is defined as the state in which any residue of the unit, except fragments of insoluble coating of capsule shell, remaining on the screen of the test apparatus or adhering to the lower surface of the disk, if used, is a soft mass having no palpably firm core. Place 1 dosage unit in each of the six tubes of the basket and operate the apparatus using water or the specified medium as the immersion fluid, maintained at 37 ± 2°C. Note the time required to disintegrate the dosage units.

Assay

Instrument : UV spectrophotometer

Wavelength : 254 nm

Medium : Water : Acetonitrile (50:50)v/v Mixture

Assay procedure

10 Capsules were taken and content were removed out, dissolved specified quantity of the material in 500 ml of medium from the stock solution above 5 ml was taken and diluted to 50 ml giving 20 µg/ml.

Determine the amount of API present is determined by employing UV absorption at the wavelength of maximum absorbance at about 254 nm

Content Uniformity

Instrument : UV spectrophotometer

Wavelength : 254 nm

Medium : Water : Acetonitrile (50:50)v/v

Capsule was taken and its content was extracted with 100 ml of the above medium. From this stock solution, 5 ml was taken and diluted to 25 ml giving 20 µg/ml.

Determine the amount of API present in individual capsule by employing UV absorption at the wavelength of maximum absorbance at about 254 nm and repeat the procedure for other 9 capsules.

InVitro Dissolution Profile

Dissolution parameter of API

Media : 0.1 N hydrochloric acid with 1% SLS

Apparatus : USP Type- II, Paddle with S.S sinker

rpm : 75 RPM

Volume : 1000 ml

Temperature : 37.0 °C ± 0.5 °C

Time Points : 5, 10, 15, 30, 45 and 60 min.

4.6. PRODUCT DEVELOPMENT OF IMMEDIATE RELEASE CAPSULE DOSAGE FORM.

Product development was initiated by taking preliminary trials with Lactose monohydrate (Granulac 200) as a Diluent, HPMC 6cps (Pharmacoat 606) as a binder, Croscarmellose sodium as a disintegrant, Sodium lauryl sulphate as a wetting agent and magnesium Stearate as a lubricant.

Micronized form of the API were used in order to improve the solubility.

Table 4.14 List of Trials

Sr no.	List of Trials
1	Physical Mixture
2	Wet Granulation
3	Selection of Diluent and Binder
4	Optimization of the concentration of surfactant
5	Selection of Disintegarnt
6	Optimization of the concentration of Disintegarnt
7	Optimization of the concentration of Lubricant
8	Scale up of optimized batch

TRIAL 1 :- PHYSICAL MIXTURE

Table 4.15 Composition of Trial 1

Sr. No.	Ingredients	mg/capsule	% weight w/w
1.	API	400	74.07
2.	Lactose monohydrate (Granulac 200)	80.6	14.93
3.	HPMC 6 cps (Pharmacoat 606)	27	5
4.	Croscarmellose sodium(AC-DI-SOL)	16.2	3
5.	Sodium lauryl sulphate	10.8	2
6.	Magnesium Stearate	5.4	1
	Total Weight	**540**	**100**

Procedure:

1. Drug, Lactose monohydrate (Granulac 200), HPMC 6 cps (Pharmacoat 606), Croscarmellose sodium (AC-DI-SOL), Sodium lauryl sulphate was weigh and sifted the through # 30. Above material was mixed for 15 min in polybag.
2. Magnesium Stearate was sifted through the # 60 and then lubricated with the above blend for 5 min in the polybag.
3. Blend was characterized for the physical parameters.

Table 4.16 Blend Characterization of Trial 1

Sr. No.	**Parameter**	**Results**
1	Bulk Density	0.233g/ml
2	Tapped Density	0.500g/ml
3	Carr's Index	55.35
4	Hausner Ratio	2.24
5	Angle of repose (θ)	58 (very poor)

Problems observed during the initial trials

Low Bulk Density – Fluffy in nature so finding difficulty to fill the filled weight.

Sticking as well as Poor flow property were observed

Result and discussion:

The blend of Physical mixture has poor flow property observed from the physical parameters As the drug is highly fluffy in nature it was difficult to filled it in the capsule so trials were done to prepare the granules.

So these problems were required to be solved to get the effective & robust formula. Wet granulation were proposed to improve the flow property and wetting property.

Trial 2:- WET GRANULATION

FORMULA OPTIMIZATION

SELECTION OF THE DILUENT AND BINDER

Table 4.17 Selection of the Diluent and Binder

Sr. No.	Ingredients	mg/capsule				% Weight w/w
		Batch A	Batch B	Batch C	Batch D	
1.	API	400	400	400	400	74.07
2.	Lactose monohydrate (Granulac 200)	80.6	80.6	-	-	14.93
3.	Microcrystalline cellulose (Avicel PH 101)	-	-	80.6	80.6	
4.	PVP K-30	27	-	27	-	5
5.	HPMC 6 cps	-	27	-	27	
6.	Croscarmellose sodium	16.2	16.2	16.2	16.2	3
7.	Sodium lauryl sulphate	10.8	10.8	10.8	10.8	2
8.	Purified Water	q.s	q.s	q.s	q.s	q.s
	Extragranular material					
9.	Magnesium Stearate	5.4	5.4	5.4	5.4	1
	Total Weight	**540**	**540**	**540**	**540**	**100**

Procedure:

1. Drug, Lactose monohydrate (Granulac 200), Croscarmellose sodium (AC-DI-SOL), were weighed and sifted through # 30. Above material was mixed for 15 min in polybag.
2. Binder solution was prepared by dissolving HPMC 6 cps (Pharmacoat 606), Sodium lauryl sulphate in purified water to get a clear solution.

3. Granulation of the mixture of step 1 was done using step 2 solution. Additional volume of the purified water were also used during granulation.

4. The above granules was dried in the tray drier at the temperature of 60°C until LOD achieve less than 2%.

5. The granules was passed through the sieve # 30 and magnesium stearate was passed through the # 60.

6. Finally the granules were lubricated with the magnesium stearate for 5 min in polybag.

7. Blend was characterized for the physical parameters and then filled in the capsule Size "0el". Fill weight of capsule is 540 mg.

Table 4.18 Blend Characterization of Trial 2

Sr. No.	Parameter	Results			
		Batch A	**Batch B**	**Batch C**	**Batch D**
1	% LOD	0.65	0.58	0.78	0.93
2	% Yield	91.83	84.25	92.01	94.25
3	Bulk Density	0.556	0.521	0.500	0.495
4	Tapped Density	0.652	0.666	0.636	0.656
5	Carr's Index	14.72	21.73	21.42	24.54
6	Hausner Ratio	1.17	1.28	1.27	1.33
7	Angle of repose	24.1	25.2	24.5	26

Table 4.19 Particle size distribution of lubricated granules of batch A, B, C, D.

Sieve no.	Size µm	% Retained			
		Batch A	**Batch B**	**Batch C**	**Batch D**
#40	450	51.25	39.10	52.76	46.92

#60	250	17.58	12.29	14.57	18.43
#80	180	9.54	9.49	13.56	16.75
#100	150	5.02	8.37	5.52	5.58
Base	-	16.58	30.72	13.56	12.29
Total		100	100	100	100

Table 4.20 Evaluation parameters of the Capsule

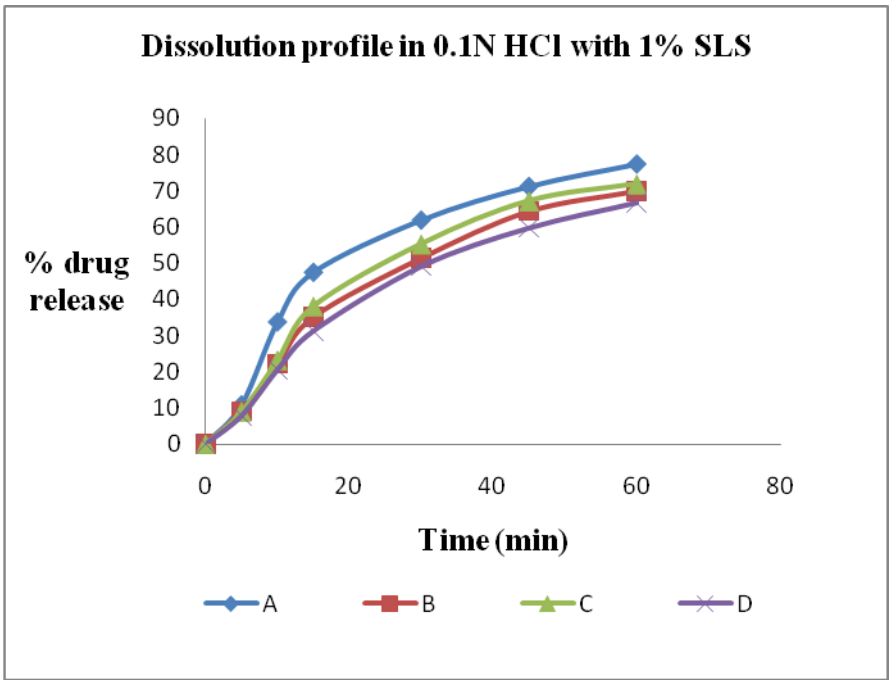
Parameters	**Batch A**	**Batch B**	**Batch C**	**Batch D**
Average weight (mg)	540.5	539.8	540.1	539.4
Assay %	98.9	97	97.9	98.1

InVitro Dissolution Profile

Table 4.21 Comparative dissolution profile in 0.1N HCl with 1% SLS of Trial 2

Dissolution Profile of the Test Product								
USP II (Paddle), 0.1 N HCl with 1% SLS								
Time(min)	**Batch A**		**Batch B**		**Batch C**		**Batch D**	
	CPR	**%RSD**	**CPR**	**%RSD**	**CPR**	**%RSD**	**CPR**	**%RSD**
0	0	0	**0**	0	**0**	0	**0**	0
5	10.9	20.3	9.1	23.1	9	23.3	7.9	21.3
10	33.8	19.7	22.2	20.8	23.2	18.9	20.6	17.9
15	47.5	9,6	35.1	10.1	38.1	9.9	31.3	10.0
30	61.9	7.9	51.3	7.6	55.3	7.3	49.1	9.3
45	71.2	4.6	64.2	4.8	67.2	3.9	59.7	3.9
60	77.4	3.6	69.8	2.2	71.9	3.2	66.7	3.2

Figure 4.3 Comparative dissolution profile in 0.1N HCl with 1% SLS of Trial 2



Result and discussion:

The blend of all **Batches** showed satisfactory flow property. All the batches passes disintegration test as per the standard. The Capsule of Batch A and B showed better dissolution compared to Batch C and D, but still it is not comparable to that of Innovator product. In Batch C and D more pressure was required to got the fill weight, it may be due to the less denser nature of MCC, and the granules were light and bulky in nature so it was difficult to get the filled weight.

From the above result, Lactose monohydrate and PVPK-30 **(Batch A)** were selected as diluents and binder respectively as it shows good flow property and dissolution profile compared to other batches.

Trial 3: OPTIMIZATION OF THE CONCENTRATION OF SURFACTANT

Batches were carried out with different concentration of surfactant.

Table 4.22 Optimization of the concentration of surfactant.

Sr. No.	Ingredients	mg/capsule			% Weight w/w
		Batch A	Batch A1	Batch A2	
1	API	400	400	400	74.07
2	Lactose monohydrate (Granulac 200)	80.6	75.2	69.8	-
3	PVPK-30	27	27	27	5
4	Croscarmellose sodium	16.2	16.2	16.2	3
5	**Sodium lauryl sulphate**	**10.8**	**16.2**	**21.6**	-
6	Purified Water	q.s	q.s	q.s	q.s
	Extragranular material				
7	Magnesium Stearate	5.4	5.4	5.4	1
	Total Weight	540	540	540	100

Table 4.23 Blend Characterization of Trial 3

Sr. No.	Parameter	Results		
		Batch A	Batch A1	Batch A2
1	% LOD	0.65	0.85	0.71
2	% Yield	91.83	94.75	92.60
3	Bulk Density	0.556	0.549	0.545
4	Tapped Density	0.652	0.668	0.690
5	Carr's Index	14.72	17.81	21.01
6	Hausner Ratio	1.17	1.21	1.26
7	Angle of repose (θ)	24.1	26.2	25.0

Table 4.24 Particle size distribution of lubricated granules of Trial 3

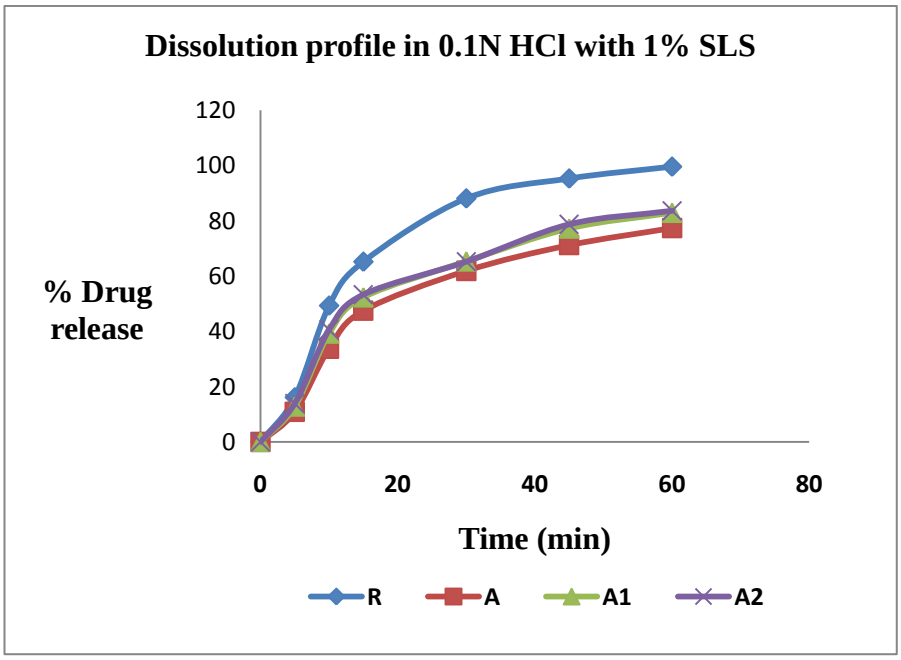
Sieve no.	Size µm	% Retained		
		Batch A	Batch A1	Batch A2
#40	450	51.25	49.50	38.50
#60	250	17.58	21.24	10.20
#80	180	9.54	10.01	32.70
#100	150	5.02	4.08	3.40
Base	-	16.61	15.17	15.20
Total		100	100	100

Table 4.25 Evaluation parameters of the Capsule

Parameters	Batch A	Batch A1	Batch A2
Average weight(mg)	540.5	540.1	539.4
Assay %	98.9	99.9	98.1

IN VITRO DISSOLUTION PROFILE

Figure 4.4 Comparative dissolution profile in 0.1N HCl with 1% SLS of Trial 3



Result and discussion:

The blend of all the batches showed satisfactory flow property with uniform particle size distribution. All the batches passes disintegration test as per the standard. **Batch A1** shows better dissolution profile compared to other batches. But the dissolution of this batch was not found satisfactory in comparison of the Innovator product.

From the above result, 3% Sodium lauryl sulfate was selected as an optimum concentration of surfactant as a wetting agent.

Trial 4: SELECTION OF THE DISINTEGRANT

Batches were carried out with two different disintegrants a) **Croscarmellose sodium** and b) **Crospovidone XL**.

Table 4.27 Selection of the disintegrant.

Sr. No.	Ingredients	mg/capsule			% Weight w/w
		Batch A1	Batch G	Batch H	
1	API	400	400	400	74.07
2	Lactose monohydrate (Granulac 200)	75.2	75.2	75.2	13.93
3	PVPK-30	27	27	27	5
4	**Croscarmellose sodium**	**16.2**			**3**
5	**Crospovidone XL**		**16.2**		
6	**Sodium Starch Glycolate**			**16.2**	
7	Sodium lauryl sulphate	16.2	16.2	16.2	3
8	Purified Water	q.s	q.s	q.s	q.s
	Extragranular material				
9	Magnesium Stearate	5.4	5.4	5.4	1
	Total Weight	**540**	**540**	**540**	**100**

Table 4.28 Blend Characterization of Trial 4

Sr. No.	Parameter	Results		
		Batch A1	Batch G	Batch H
1	% LOD	0.85	0.78	0.71
2	% Yield	94.75	92.01	91.0
3	Bulk Density	0.549	0.530	0.555
4	Tapped Density	0.668	0.636	0.660
5	Carr's Index	17.81	16.66	15.90

6	Hausner Ratio	1.21	1.20	1.19
7	Angle of repose (θ)	26.2	25.6	26.7

Table 4.29 Particle size distribution of lubricated granules of Trial 4

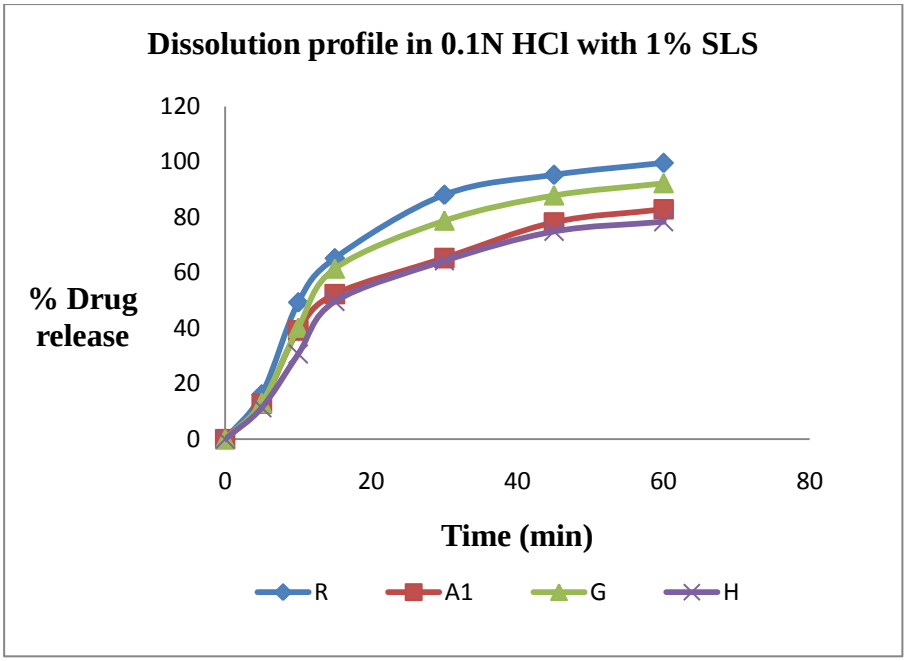
Sieve no.	**Size µm**	**% Retained**		
		Batch A1	**Batch G**	**Batch H**
#40	450	49.50	52.76	51.7
#60	250	21.24	14.57	11.87
#80	180	10.01	13.56	12.44
#100	150	4.08	5.52	8.88
Base	-	15.17	13.59	15.11
Total		100	100	100

Table 4.30 Evaluation parameters of the Capsule

Parameters	**Batch A1**	**Batch G**	**Batch H**
Average weight(mg)	540.1	539.8	540.2
Assay %	99.9	98.0	99.2

IN VITRO DISSOLUTION PROFILE

Figure 4.5 Comparative dissolution profile in 0.1N HCl with 1% SLS of Trial 4



Result and discussion:

The blend of both the **batches** showed satisfactory flow property and uniform particle size distribution. The dissolution of **Batch G** was found to be satisfactory in comparison to the **Batch A** and **H**, but not found satisfactory as compared to the Innovator product. All the batches passes disintegration test as per the standard.

From the above result, **Crospovidone XL** were selected as a disintegrant and dissolution improver, and further optimization of the disintegrant concentration was required to achieve comparative dissolution profile to that of the Innovator product.

Trial 5: DISINTEGRANT OPTIMIZATION

Batches were carried out with four different concentration of disintegrant- Crospovidone XL.

Table 4.32 Optimization of concentration of disintegrant

Sr. No.	Ingredients	mg/capsule				% Weight w/w
		Batch G	Batch I	Batch J	Batch K	
1.	API	400	400	400	400	74.07
2.	Lactose monohydrate	75.2	69.8	64.4	59.0	-

	(Granulac 200)					
3.	PVP K-30	27	27	27	27	5
4.	**Crospovidone XL**	**16.2**	**21.6**	**27**	**32.4**	
5.	Sodium lauryl Sulfate	16.2	16.2	16.2	16.2	3
6.	Purified Water	q.s	q.s	q.s	q.s	q.s
	Extragranular material					
7.	Magnesium Stearate	5.4	5.4	5.4	5.4	1
	Total Weight	**540**	**540**	**540**	**540**	**100**

Table 4.33 Blend Characterization of Trial 5

Sr. No.	**Parameter**	**Results**			
		Batch G	**Batch I**	**Batch J**	**Batch K**
1	% LOD	0.78	0.61	0.98	0.73
2	% Yield	92.01	91.83	90.01	90.25
3	Bulk Density	0.530	0.526	0.540	0.544
4	Tapped Density	0.636	0.642	0.676	0.685
5	Carr's Index	16.66	18.06	20.11	20.58
6	Hausner Ratio	1.20	1.22	1.25	1.26
7	Angle of repose (θ)	25.6	25.8	26	27

Table 4.34 Particle size distribution of lubricated granules of Trial 5

Sieve no.	**Size µm**	**% Retained**			
		Batch G	**Batch I**	**Batch J**	**Batch K**
#40	450	52.76	48.25	49.10	46.92
#60	250	14.57	10.58	12.29	15.43
#80	180	13.56	15.54	10.49	16.75
#100	150	5.52	9.02	8.37	5.58

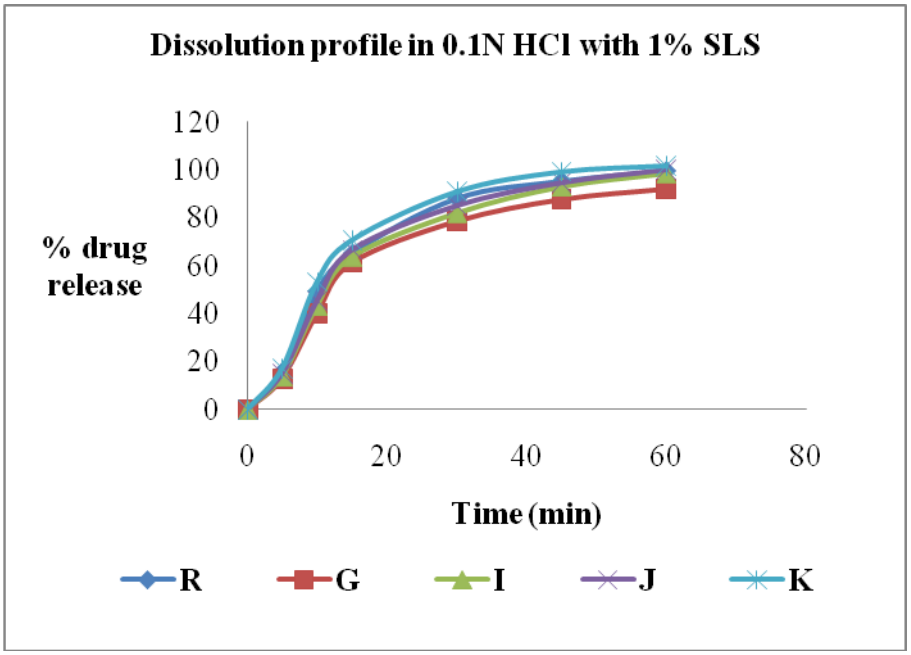
Base	-	13.56	16.61	19.75	15.29
Total		100	100	100	100

Table 4.35 Evaluation parameters of the Capsule

Parameters	**Batch G**	**Batch I**	**Batch J**	**Batch K**
Average weight(mg)	539.8	540	539.9	539.6
Assay %	98.0	98.7	98.19	98.41

IN VITRO DISSOLUTION PROFILE

Figure 4.6 Comparative dissolution profile in 0.1N HCl with 1% SLS of Trial 5



Result and discussion:

The blend of all the **Batches** showed satisfactory flow property but it was observed that as the concentration of disintegrant increases the flow properties were affected. The dissolution of the **Batch J** was found to be satisfactory in comparison to the Innovator product. All the batches passes disintegration test as per the standard.

Trial 6: LUBRICANT OPTIMIZATION

Batches were carried out with three different concentration of lubricant- magnesium stearate.

Table 4.37 Optimization of concentration of lubricant.

Sr.No.	Ingredients	mg/capsule			% Weight
		Batch J	Batch K	Batch L	
1.	API	400	400	400	74.07
2.	Lactose monohydrate (Granulac 200)	75.2	77.9	72.5	
3.	PVP K-30	27	27	27	5
4.	Crospovidone XL	27	27	27	5
5.	Sodium Lauryl Sulfate	16.2	16.2	16.2	3
6.	Purified Water	q.s	q.s	q.s	q.s
	Extragranular material				
7.	**Magnesium Stearate**	**5.4**	**2.7**	**8.1**	
	Total Weight	**540**	**540**	**540**	**100**

Table 4.38 Blend Characterization of Trial 6

No.	Parameter	Results		
		Batch J	Batch K	Batch L
1	% LOD	0.61	0.65	0.78
2	% Yield	91.83	90.10	91.01
3	Bulk Density	0.526	0.520	0.523
4	Tapped Density	0.642	0.644	0.639
5	Carr's Index	18.06	19.25	18.15
6	Hausner Ratio	1.22	1.23	1.22
7	Angle of repose (θ)	26.0	26.2	26.3

Table 4.39 Particle size distribution of lubricated granules of Trial 6.

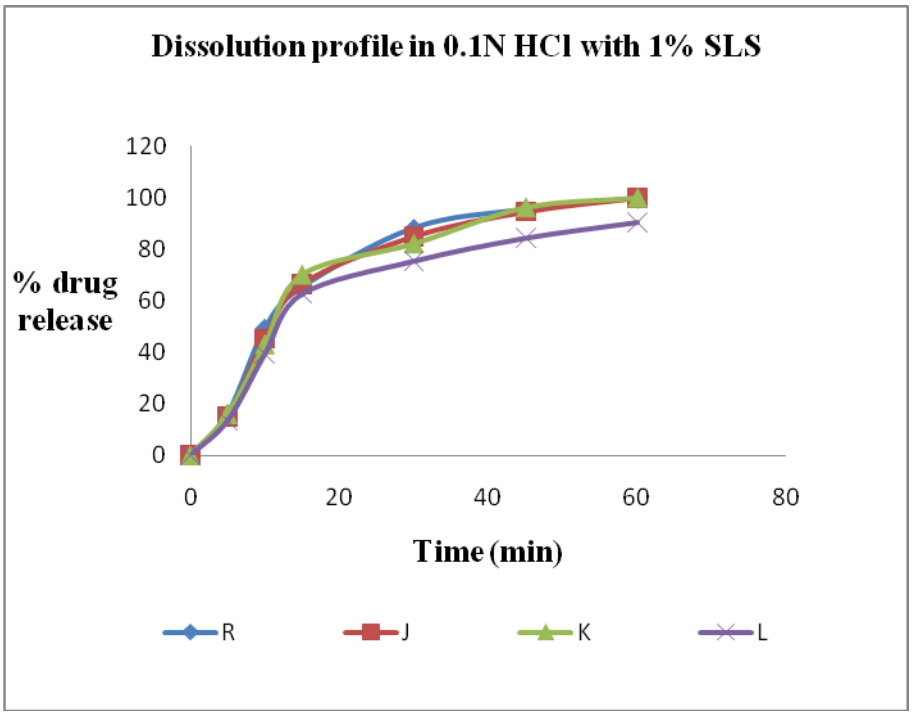
Sieve no.	Size µm	% Retained		
		Batch J	Batch K	Batch L
#40	450	39.10	39.10	39.10
#60	250	12.29	12.29	12.29
#80	180	9.49	9.49	9.49
#100	150	8.37	8.37	8.37
Base	-	30.72	30.72	30.72
Total		100	100	100

Table 4.40 Evaluation parameters of the Capsule

Parameters	Batch J	Batch K	Batch L
Average weight (mg)	539.8	540	538.8
Assay %	98.0	97.0	97.90

IN VITRO DISSOLUTION PROFILE

Figure 4.7 Comparative dissolution profile in 0.1N HCl with 1% SLS of Trial 6



Result and discussion:

The blend of all the **Batches** showed satisfactory flow property but it was observed that as the concentration of lubricant decreases from 1 to 0.5 sticking problem arises where as in **Batch J** and **K** there were no sticking issue so finally 1% lubricant was selected. The dissolution of the **Batch J** was found to be satisfactory in comparison to the Innovator product. All the batches passes disintegration test as per the standard.

Trial 7: SCALE UP OF THE OPTIMIZED BATCH

Scale up of the optimized batch i.e. Batch J was done with large Batch size (1000 capsule). Granulation was done in the RMG, drying was done in the fluidized drier, dry sizing was done using multi mill and blending was done in the conta blender.

Table 4.42 Composition of Scale up Batch.

Sr. No.	Ingredients	mg/capsule	% Weight w/w
1.	API	400	74.07
2.	Lactose monohydrate (Granulac 200)	75.2	13.93
3.	PVP K-30	27	5
4.	Crospovidone XL	27	5
5.	Sodium lauryl sulphate	16.2	3
6.	Purified water	q.s	q.s
	Extragranular material		
7.	Magnesium Stearate	5.4	1
	Total Weight	**540**	**100**

Table 4.43 Blend Characterization of Trial 7

Sr. No.	Parameter	Results	
		Batch J	Scale up Batch
1	% LOD	0.98	0.91
2	% Yield	90.01	93.45
3	Bulk Density	0.540	0.596
4	Tapped Density	0.676	0.713
5	Carr's Index	20.11	16.40
	Hausner Ratio	1.25	1.19
	Angle of repose (θ)	26.0	25.1

Table 4.44 Particle size distribution of lubricated granules of Trial 7.

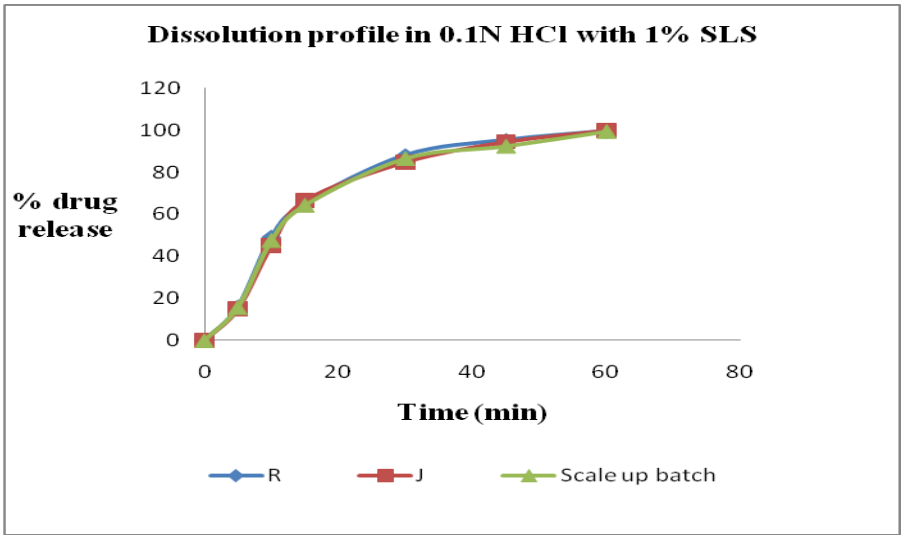
Sieve no.	Size µm	% Retained	
		Batch J	Scale up Batch
#40	450	39.10	45.19
#60	250	12.29	10.12
#80	180	9.49	11.39
#100	150	8.37	6.50
Base	-	30.72	26.8
Total		100	100

Table 4.45 Evaluation parameters of the Capsule

Parameters	Batch J	Scale up Batch
Average weight (mg)	539.8	540
Assay %	98.0	99.2

IN VITRO DISSOLUTION PROFILE

Figure 4.8 Comparative dissolution profile in 0.1N HCl with 1% SLS of Trial 7



Result and discussion:

The blend of all the **Batches** showed satisfactory flow property and particle size distribution. The dissolution profile of the **Batch J** and **scale up batch** was found to be satisfactory in comparison to the Innovator product. All the batches passes disintegration test as per the standards.

COMPARISON OF DISSOLUTION PROFILE BY MODEL INDEPENDENT METHOD (SIMILARITY AND DISSIMILARITY FACTOR)

DISSOLUTION PROFILE:

Definition :-

It is graphical representation [in terms of concentration vs time] of complete release of A.P.I. from a dosage form in an appropriate selected dissolution medium.i.e. in short it is the measure of the release of A.P.I from a dosage form with respect to time.

IMPORTANCE OF DISSOLUTION PROFILE :-

Dissolution profile of an A.P.I. reflects its release pattern under the selected condition sets. i.e, either sustained release or immediate release of the formulated formulas.

For optimizing the dosage formula by comparing the dissolution profiles of various formulas of the same API.

Dissolution profile comparison between pre change and post change products for SUPAC (scale up post approval change) related changes or with different strengths, helps to assure the similarity in the product performance and green signals to bioequivalence.

In continuation to above point. FDA has placed more emphasis on dissolution profile comparison in the field of post approval changes and biowaivers (e.g. Class I drugs of BCS classification are skipped off these testing for quicker approval by FDA).

The most important application of the dissolution profile is that by knowing the dissolution profile of particular product of the BRAND LEADER , we can make appropriate necessary change in our formulation to achieve the same profile of the BRAND LEADER.,

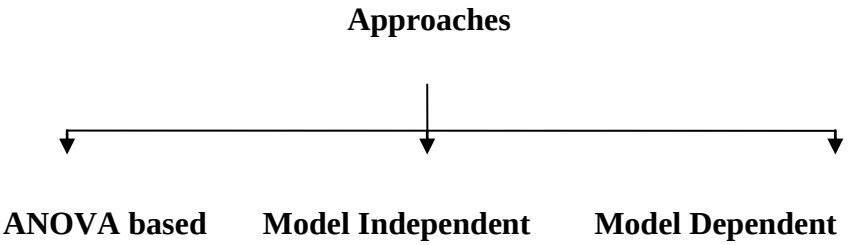
This is required as FDA or equivalent authorities' worldwide demands the drug release data of our product which is compared with the initiative one of that particular product under the same conditions for the approval of our product in that respective part of the world.

As there are 'n' number of different dosage forms of same A.P.I. the dissolution pattern of the A.P.I. will be different and so the dissolution profile will differs.

However the dissolution profile is governed by various physical characteristics of the dosage forms and hence it is difficult to propose a single model which would consider all these physical parameters.

Therefore, great variety of mechanistic and empirical mathematical models has been used to describe the in vitro dissolution profiles and different criteria have been proposed for the assessment of similarity between two dissolution profiles

Basically 3 main approaches are there for the comparison



Approaches	Methods	Parameters/equations
ANOVA-based	➢ Multivariate ANOVA	Statistical method (Uses formulation and time as class variable)
	➢ Multiple unvariate ANOVA	”
	➢ Level & Shape approach	-
MODEL INDEPENDENT	➢ Ratio test procedure	○ ratio of % dissolved ○ ratio of area under the dissolution curves ○ ratio of mean dissolution time
	➢ Pair wise procedures	○ difference factor (f_1) ○ similarity factor (f_2) ○ index of Rescigno (ξ_1 ξ_2)
MODEL DEPENDENT	➢ Zero order	% dissolved = k * t
	➢ First order	% dissolved = 100(1- e^{-kt})

	➢ Hixson – Crowell[a,b] a : from $M_o^{-1/3} - M^{-1/3} = K \times t$ where M_o = 100 mg. b : from physical pharmacy MARTIN	% dissolved = 100 [1 – (1 – $\frac{k \times t}{4.616 mg^{1/3}}$)^3]
	➢ Higuchi model	% dissolved = $k \times t^{0.5}$
	➢ Quadratic model	% dissolved= $100 \times (k_1 t^2 + k_2 t)$
	➢ Gompertz model	% dissolved=$A \times e^{-k-k(t-\gamma)}$
	➢ Logistic model	%dissolved = $A/[1+e^{-k(t-\gamma)}]$
	➢ Weibull model	%dissolved = $100[1-e^{-(t/\tau)\beta}]$
	➢ Korsemeyar and peppas model	$Mt/Ma = Kt^n$

PAIR WISE PROCEDURE

DIFFERENCE FACTOR (f_1) & SIMILARITY FACTOR (f_2)

These factors are introduce by **MOORE AND FLANNER** in 1996. This approach is adopted by Center for Drug Evaluation and Research (CDER) of US-FDA and also by Human Medicine Evaluation Unit of European Agency for Evaluation of Medicinal Products (EMEA) as criteria for assessment of similarity between 2 dissolution profiles.

The **difference factor (f_1)** as defined by FDA calculates the % difference between 2 curves at each time point and is a measurement of the relative error between 2 curves.

where, n = number of time points

R_t = % dissolved at time t of reference product (prechange)

$$f_1 = \left\{ \frac{\left\{ \sum_{t=1}^{n} |Rt - Tt| \right\}}{\sum_{t=1}^{n} Rt} \right\} \times 100$$

T_t = % dissolved at time t of test product (postchange)

The f1 equation is the sum of the absolute value of the vertical distance between the test and reference mean values, i.e. lRt-Ttl at each dissolution time point , expressed as percentage of sum of mean fraction released from reference formulation at each time point.

The f1 equation is zero(0) when the mean profile are identical and increases proportionally as the difference between the mean profile increase.

The **similarity factor (f_2)** as defined by FDA is logarithmic reciprocal square root transformation of sum of squared error and is a measurement of the similarity in the percentage (%) dissolution between the two curves.

$$f2 = 50 \times \log\left[\left\{ 1 + \frac{1}{n} \sum_{r=1}^{n} wt(Rt - Tt) \right\}^{-0.5} \times 100 \right]$$

Here idea of weight (Wt) is to provide more weighting to some dissolution time point than others. If it is not appropriate to weight time profile Wt may be set to one at each time point.

1. Determine dissolution profile of 12 units of each of the test and reference product.
2. Using Mean dissolution values for both curves at each time intervals and calculate f_1 and f_2.
3. f_1 close to zero and f_2 close to 100 are considered as similar profiles. Generally **f_1 between 0 - 15 and f_2 between 50 - 100** ensures equivalence.

Why f_2 limit is 50 – 100 ?

When both the profiles are identical (Rt – Tt) = 0

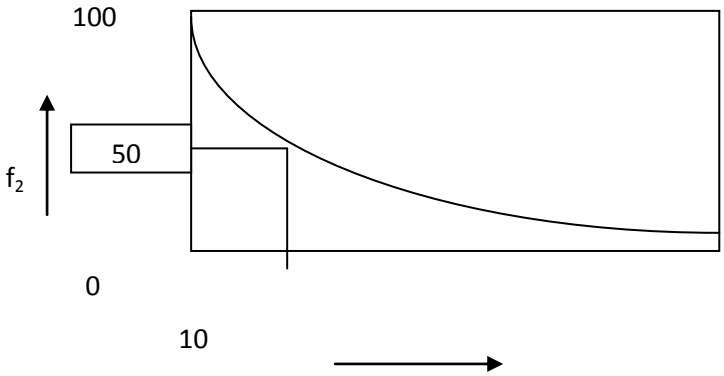
So, f_2 = 50 X log 100 = 50 x 2 = 100

When both the profile are unidentical to the extent that dissolution of any of one product completes before other begins, (Rt – Tt) = 100

So, f_2 = 50 X log { [1+1/n$(100)^2$]$^{-0.5}$ x 100 } = -0.001 ~ 0

So, range of f_2 is 0 – 100

Average difference of not more than 10 % at any sampling time point between reference and test may be acceptable. And when 10 % average absolute difference is substituted in equation of f_2, value of f_2 comes to 50.



So, finally acceptable limit defined as 50 – 100.

Recommendations to be taken in consideration

1. Dissolution measurement of both products made under exactly same conditions and sample withdrawal timing should be also same.
2. Dissolution time points recommended for immediate release products are 15, 30, 45 and 60 minutes and for extended release products are 1, 2, 3, 5 and 8 hours.
3. f_2 value is sensitive to the number of dissolution time points, so only one measurement should be considered after 85 % dissolution of product.
4. For products which are rapidly dissolves, i.e. more than 85 % release in 15 minutes or less, profile comparison is not necessary.
5. The mean dissolution value for Rf should be derived preferably from the last prechanged (Reference) batch.
6. To allow the use of mean data, % coefficient of variation (% CV) at earlier time points (e.g. 15 minutes) should be not more than **20 %** and at other time points should not more than **10 %.**

Advantages

(1) They are easy to compute

(2) They provide a single number to describe the comparison of dissolution profile data.

Disadvantages

(1) The f1 and f2 equations do not take into account the variability or correlation structure in the data .

(2) The values of f1 and f2 are sensitive to the number of dissolution time point used.

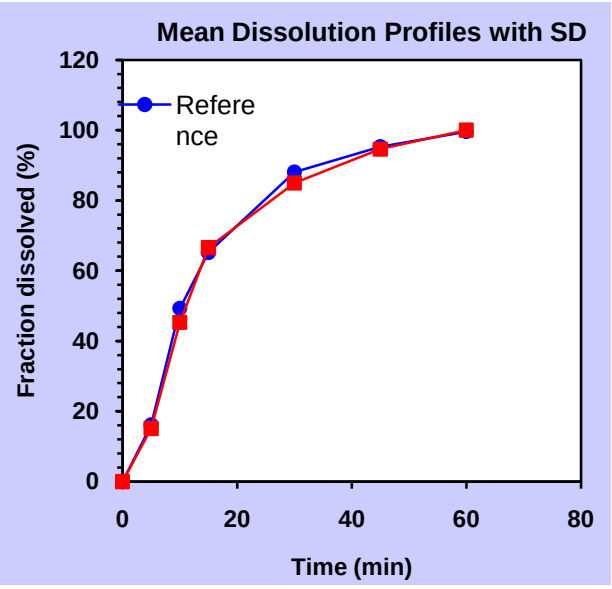
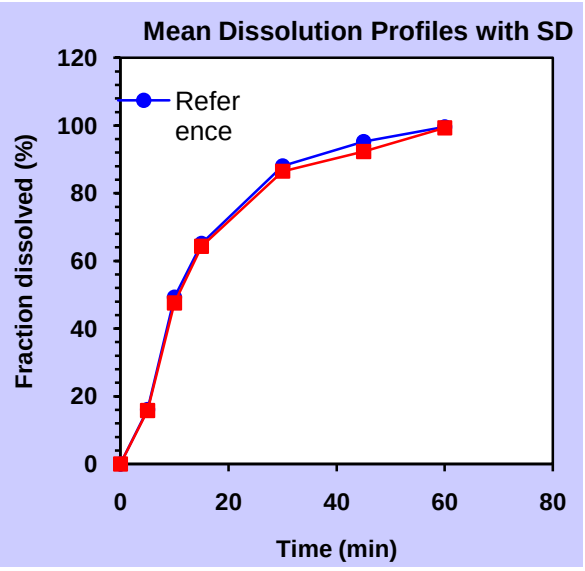
(3) If the test and reference formulation are inter changed , f2 is unchanged but f1 Is not yet differences between the two mean profile remain the same.

The basis of the criteria for deciding the difference or similarity between dissolution profile is unclear.

Similarity factor (f_2) is dependent on sampling scheme from apparatus means selection and determination of number of dissolution time points.

So that when we have same reference and test product, but if number and time of dissolution time points are different, they shows different results.

Comparison of the dissolution profile of the Innovator product and the optimized batch (Batch J)

Figure 4.9 comparison of dissolution profile (Reference vs Batch J)	Figure 4.10 comparison of dissolution profile (Reference vs Scale up batch)
	

Result and Discussion

Similarity factor (f2) value of the Innovator product and Optimized batch was found to be 82.15 and with Scale up batch was found to be 87.35. According to the reference standard for the similarity in the dissolution profile F2 Value should be greater than 50. The results indicates that both the batches were found to similar to that of Innovator product.

5. STABILITY STUDIES

Stability testing study design:-

The Stability study program provides evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light.

Stability

The ability of a pharmaceutical product to retain its chemical, physical, microbiological and biopharmaceutical properties within specified limits throughout its shelf-life .

Shelf-Life

The period of time during which a drug product, if stored correctly, is expected to comply with the specification as determined by stability studies on a number of batches of the product. The shelf-life is used to establish the expiry date of each batch.

Accelerated Stability Testing

Studies designed to increase the rate of chemical degradation and physical change of a drug or drug product by using exaggerated storage conditions as part of the formal stability-testing programmed. The results of accelerated testing studies are not always predictive of physical changes.

Real-Time (Long-Term) Stability Studies

Experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of a drug, during and beyond the expected shelf-life and storage periods of samples under the storage conditions expected in the intended market. The results are used to establish the shelf-life, to confirm the projected shelf-life, and to recommend storage conditions.

Main Climatic Zones:

"Stability Testing of New Drug Substances and Products."

The Guideline "Evaluation of Stability Data" describes when and how an extrapolation of the data can be undertaken in order to establish the re-test period for a drug substance or the shelf

life for a drug product beyond the observed range itself, based on the data resulting from the long-term stability testing.

The Guideline on stability testing for Climatic Zone III and IV takes up a proposal made by WHO and now defines not only storage conditions for stability testing relevant for the ICH tripartite regions (Europe, USA, Japan), but also completes the recommendations for the standardization of the storage conditions for the Climatic Zones III (dry-hot) and IV (very hot/humid). For these Climatic Zones, the following standard conditions are recommended:

- Long-term testing: 30°C / 65% RH
- Accelerated conditions: 40°C / 75% RH

This means that the "accelerated conditions" remain the same as in the Guideline and only the "long-term storage conditions" have to be modified

General case:

Table 5.1 Stability study conditions

Study	**Storage condition**	**Minimum time period covered by data at submission**
Long term*	25˚C ± 2˚C / 60% ± 5%RH or 30˚C ± 2˚C / 65% ± 5%RH	12 months
Intermediate**	30˚C ± 2˚C / 65% ± 5%RH	6 months
Accelerated	40˚C ± 2˚C / 75% ± 5%RH	6 months

*** it is up to the applicant to decide whether long term stability studies are performed at 25˚C ± 2˚C / 60% ± 5%RH or 30˚C ± 2˚C / 65% ± 5%RH.**

**** if 30˚C ± 2˚C / 65% ± 5%RH is the long term condition then there is no intermediate condition.**

Four climatic zones can be distinguished for the purpose of worldwide stability testing, as follows:

Table 5.2 Four Climatic Zones

Climatic zone	**Description**	**Derived Storage Conditions (For real time studies)**
zone I	Temperate	21ºc 45%RH
zone II	Subtropical	25ºc 60%RH
zone III	Hot and dry	30ºc 65%RH
zone IV	Hot and humid	30ºc 65%RH

Conditions for real time stability testing of relatively stable drug substance and its drug product for

Table 5.3 Stability Testing For Zone I, II And III

Storage Temperature (°C)	Relative humidity (%)	Duration of studies (months)
25 ± 2	60 ± 5	3,6,9,12,18,24,36,48 & 60

Table 5.4 Stability Testing For Zone IV

Storage temperature(°C)	Relative humidity (%)	Duration of studies(months)
30 ± 2	65 ± 5	3,6,9,12,18,24,36,48 & 60

Purpose of Stability Programme

1. Helps predict and extend shelf life,
2. Provides information on extent and degree of the stability of products and degradability,
3. Helps determine the impurity profile on storage,
4. Helps confirm the suitability and integrity of packing / container-closure system,

5. Helps confirm the storage conditions, *and*
6. Useful in regulatory submissions.

Stability Testing

Stability studies are essential to every phase of drug life cycle. They not only documented that a product will maintain its stated shelf life, but that it will do so under variety of storage condition. The protocol for stability testing was developed Approved Stability Protocol is a detailed study plan which describes evaluation of physical, chemical, biological, and microbiological characteristics of a drug substance and a drug product as a function of time.

The objective of this stability study is to assess the shelf life of the product at different temperature / humidity conditions and to establish a recommended storage condition. The scope of this stability protocol is applicable for following packs of the-

Accelerated stability study of optimized dosage form.

According to the ICH guidelines Accelerated stability study were carried out for 6 months. 1 month stability data were showed below.

Capsules were packed in HDPE Containers accelerated stability study at 40°C±2°C/75%RH±5%RH. The physical and chemical parameters were studied at different time intervals are found to be satisfactory.

Trial Batches with final formulation and process were evaluated for the accelerated stability study at 40˚C / 75% RH

Table 5.5 Stability Data of the Optimized Batch

Stability Data of the Optimized Batch			
Batch no.	**Scale up Batch**		
Stability condition	**Accelerated Stability 40˚C ± 2˚C / 75% ± 5%RH**		
Pack	**HDPE Bottle**		
		With 2 gm silica gel pillow pack	**Without 2 gm silica gel pillow pack**
Test	**Initial**	**1 Month**	**1 Month**
Description : Opaque white hard gelatine capsule size '0el' filled with white to off white granular powder.			
Description	As above	Complies	Complies
% water by KF	1.592 %	1.608 %	1. 810 %
Average fill weight (mg)	540	540	540
Assay	100.2	99.8	98.8
Disintegration time (min)	6 min 40 sec	6 min 50 sec	6 min 40 sec
Related substances			
Impurity I	0.019 %	0.018 %	0.017 %
Impurity II	0.039 %	0.031 %	0.031 %
Impurity III	ND	ND	ND
Highest unknown	0.007 %	0.010 %	0.011 %
Total impurities	0.065	0.059	0.059

Total impurities = NMT 0.50 % **ND = Not Detected**

RESULTS:

There were not any significant changes found in assay, in-vitro dissolution studies, disintegration time, appearance, when kept for stability studies till 1 months in the HDPE container with 2 gm silica gel pillow pack.

But the capsule kept in the HDPE container without silica gel pillow pack showed increase % water by KF, decrease the dissolution and the outer shell become soft, and hence it was decided to store the capsule in the container with silica gel pillow pack. The product showed the stability as per the ICH guidelines.

6. SUMMARY

The aim of present study was to formulate an immediate release dosage form of COX-II inhibitor as an active pharmaceutical ingredient with the aid of suitable excipients and evaluating its characteristics.

Further, handling problems are encountered during the preparation of pharmaceutical compositions comprising API. For example, the low bulk density of API makes it difficult to process the small quantities required during formulation of the pharmaceutical compositions. Accordingly, a need exists for solutions to numerous problems associated with preparation of suitable pharmaceutical compositions and dosage forms comprising API, particularly orally deliverable dose units.

In particular, a need exists for orally deliverable API formulations possessing one or more of the following characteristics relative to unformulated API or other API compositions: improved solubility; shorter dissolution time; improved wettability; improved compressibility; improved flow properties improved; physical stability of the finished composition; reduced capsule size; improved blend uniformity; improved dose uniformity; improved control of weight variation during encapsulation increased granule density for wet granulated compositions; reduced water requirement for wet granulation;

It would be of especial benefit to provide formulations exhibiting pharmacokinetics consistent with a more rapid onset effect than is possible with unformulated API. Such formulations would represent a significant advance in the treatment of cyclooxygenase-2 mediated conditions and disorders.

Thus, the present study was aimed to formulate the immediate release capsule dosage form of selective COX II inhibitor (BCS class II drug) using various excipients which improve solubility and thereby bioavailability.

Immediate release dosage form is defined as a dosage form for the immediate release of the drug. The drug should be released 75% in 30 min.

Selection criteria for the drug to be developed as immediate release dosage form: longer half life, poor solubility, to need the immediate action of the drug, absorption from mainly stomach, long elimination half life.

COX-2 inhibitors are a subclass of non steroidal anti inflammatory drugs (NSAIDs). NSAIDs work by reducing the production of prostaglandins, chemicals that promote inflammation, pain, and fever. Prostaglandins also protect the lining of the stomach and intestines from the damaging effects of acid, promote blood clotting by activating platelets, and also affect kidney function.

Preliminary trials were initiated with the physical mixture but due to low bulk density and fluffy nature of the formulation, fill weight was not achieved so trials were carried out with wet granulation as it improved the flow property and wetting property.

From the initial trial lactose monohydrate and PVPK-30 were selected as a diluent and binder respectively because the granules obtained showed satisfactory flow property with optimum fill weight were as in case of MCC extra pressure were required to fill the granules in the capsule as the granules are light in weight.

Surfactant concentration were optimized and finally 3% were selected as a optimized concentration as further increase in the concentration had no major difference in the dissolution profile.

Crospovidone XL were selected as a disintegrant as Crospovidone XL has Porous morphology, small particle Size with large surface area and thereby increases interfacial activity and increases dissolution. Hypothetically it has solvent like chemistry.

Disintegarnts	**Surface area m2/g**	**Average particle size (µ)**
Crospovidone XL	1.4	30-50
Croscarmellose sodium	0.7	50
Sodium starch glycolate	0.2	50

Disintegrant concentration were optimized and finally 5% were selected as a optimized concentration as dissolution profile was matched with that of Innovator product.

Lubricant concentration were optimized and finally 1% were selected as a optimized concentration as further increase in the concentration leads to decrease in the dissolution profile and on the lower side sticking problem arises.

Dissolution profile of the optimized batch as well as scale up batch and Innovator product were compared, f2 value were found to be 82.15 and 87.35 and f1 value were found to be 2.56 and 1.89 respectively, so it indicated that the dissolution profile of optimized batch matched well with the dissolution profile of the Innovator product.

FUTURE PROSPECTIVE

- To perform full stability study in different packs.
- Plan for the bio study of the scale up batch.
- Development of same dosage form for there other strength-50, 100, 200 mg/capsule.
- Plan for Exhibit batch and generate full stability data and bioequivalence data.
- Filling

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