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IBUPROFEN: A PHARMACEUTICAL STUDY

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ABSTRACT

Analgesic drugs are widely used for the management of pain, inflammation, and fever. Among them, ibuprofen is a commonly used non-steroidal anti-inflammatory drug (NSAID) that exhibits analgesic, antipyretic, and anti-inflammatory properties by inhibiting cyclooxygenase (COX-1 and COX-2) enzymes and reducing prostaglandin synthesis. The present study focuses on the formulation and evaluation of ibuprofen hard gelatin capsules along with the preformulation studies required for successful dosage form development. Preformulation studies were carried out to evaluate the physicochemical properties of ibuprofen such as solubility, melting point, pKa, partition coefficient, polymorphism, hygroscopicity, and flow properties including angle of repose, bulk density, tapped density, Hausner's ratio, and Carr's index. Compatibility and stability studies were also performed to ensure the suitability of the drug for capsule formulation. The formulation process involved the selection of suitable excipients including diluents, binders, lubricants, glidants, and disintegrants for efficient capsule filling and drug release. Different capsule filling methods such as manual, semi-automatic, and fully automatic techniques were studied. Evaluation tests including weight variation, content uniformity, dissolution test, disintegration test, moisture content, microbial testing, and stability studies were carried out to assess the quality, safety, and efficacy of the formulated capsules. The study concludes that proper preformulation, formulation, manufacturing, and evaluation processes are essential for developing stable and effective ibuprofen capsules with good therapeutic performance and patient compliance.

KEYWORDS: Analgesic, ibuprofen capsule.

PAINANDANALGESIA

Pain isaprotectivephysiologicalresponsethatsignalsactualorpotentialtissueinjuryand prompts the body to avoid further harm. It acts as a protective warning signal and may be classified as acute or chronic, and as nociceptive or neuropathic based on its origin.

Analgesiais the relief of pain without loss of consciousness. It is achieved by analgesic drugs thatacteitherperipherallybyinhibitinginflammatorymediators orcentrally bymodifyingpainperceptionin the central nervous system. Effective analgesia is essential for patient comfort and improved therapeutic outcomes.

Analgesic drugsare agents used to relieve pain without causing loss of consciousness. They act by reducing painperceptionat peripheral sites, the central nervous system, or both. Analgesics are widely used in conditions associated with inflammation, injury, and disease.

CLASSIFICATION

1. Non-OpioidAnalgesics

Non-opioid analgesics are commonly used for mild to moderate pain and are effective in inflammatory conditions.

Examples:Paracetamol,Aspirin,Ibuprofen,Diclofenac,Celecoxib. Mechanism of Action:

Acetaminophenmainlyactson thecentralnervous system to reducepainand feverbut has minimal anti-inflammatory effects.

NSAIDs reduce the production of prostaglandins, which are chemicals involved in pain, inflammation,andfever,byinhibitingcyclooxygenase(COX)enzymes. Uses:

Usedformildto moderatepain suchas headachesand muscleaches.

2. Opioid Analgesics

Opioidanalgesics arepotentpainrelievers used formoderatetoseverepain,especiallyin postoperative care, trauma, and cancer-related pain.

Examples:Morphine,Codeine,Tramadol,Fentanyl,Buprenorphine. Mechanism of Action:

It binds with the opioid receptors in the brain and spinal cord and reduces the perception of pain.

Uses:

Used formoderate to severepainsuch aspost-surgicalor cancer-related pain.

3. AdjuvantAnalgesics

Adjuvantanalgesicsaredrugsthatenhancepainrelieforareusefulinspecificpain conditions like

neuropathic pain.

Examples: Amitriptyline (Antidepressants), Gabapentin & Pregabalin (Anticonvulsants), Dexamethasone (Steroids).

MechanismofAction:

Workthroughmechanismsthattargetnervepainorchronicconditions. Uses:

Commonlyusedfornerve-relatedpain(e.g.,diabeticneuropathyorfibromyalgia).

4. LocalAnalgesics

Localanalgesicsaredrugsthatrelievepainataspecificsiteofapplicationwithoutcausing loss of consciousness or affecting sensation in other parts of the body.

Examples:Lidocaine,Bupivacaine. Mechanism of Action:

Theyblockvoltage-gatedsodium(Na^+)channels innervemembranes,preventing initiation and conduction of nerve impulses.

Uses:

Oftenemployedaslocal anestheticinsurgeriesor tomanage chronicpainthroughtopical application

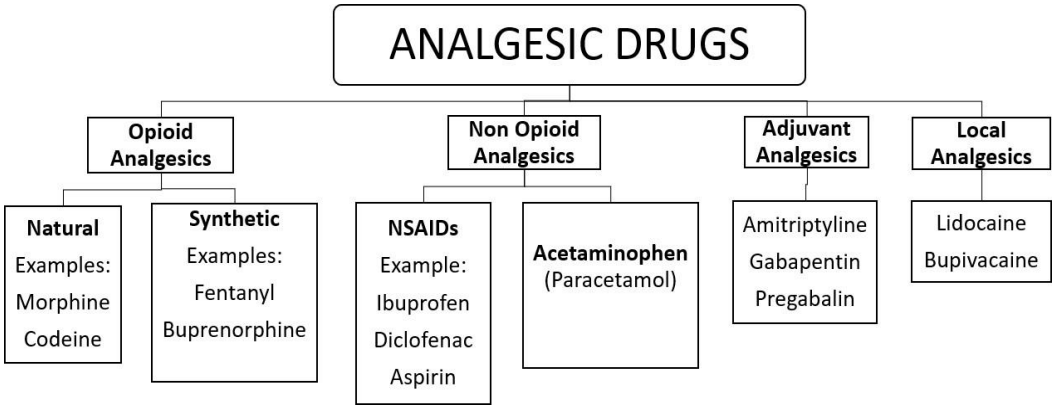

Fig1.1ClassificationofAnalgesics.

IBUPROFEN

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that produces analgesic, antipyretic, and anti-inflammatory effects by inhibiting cyclooxygenase (COX-1 and COX-2) enzymes, thereby reducing the synthesis of prostaglandins involved in pain, inflammation, and fever.

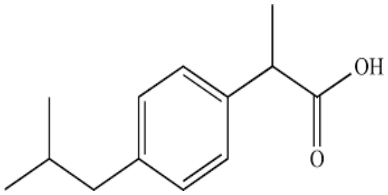

Figure1.2Structureof ibuprofen.

Molecular Formula: $C_{13}H_{18}O_2$ **Molecularweight:**206.28g/mol **BCS Classification:** Class II

MECHANISMOFACTION

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) that produces analgesic (pain-relieving), anti-inflammatory, and antipyretic (fever-reducing) effects primarily by interfering with the synthesis of prostaglandins, which are key mediators of inflammation and pain.

1. **Inhibitionofcyclooxygenaseenzyme(COX-1andCOX-2)**

Ibuprofen reversibly inhibits both **COX-1** and **COX-2** enzymes**,** which are responsible fortheconversionofarachidonicacidintoprostaglandinH_2(PGH_2)—theprecursorfor various prostaglandins and thromboxanes involved in inflammation, pain, fever, and platelet function.

2. **ReducedProstaglandinProduction:**

By blocking COX activity, ibuprofen reduces the synthesis of pro-inflammatory prostaglandinssuchas**PGE_2**,whichnormallysensitizepainreceptorsandamplify inflammatory responses.

3. **Analgesic,Anti-Inflammatory,andAntipyreticEffects:**

- **Analgesia:**Lowerprostaglandinlevelsdecreasesensitivityofpain-sensing neurons.
- **Anti-inflammation:**Reducedprostaglandinproductionlowersvasodilationand vascular permeability at sites of injury.
- **Antipyresis:**Prostaglandinsinthehypothalamusraisethebody'stemperature set-point; their reduction helps normalize fever.

4. **Reversibleandnon-selective:**

UnlikesomeNSAIDs(e.g.,aspirinwhichirreversiblyinhibitsCOX),ibuprofen's inhibition is reversible and affects both COX-1 and COX-2.

PHARMACOKINETICS

Table1:PharmacokineticsofIbuprofen.

Parameter	**Description**
Absorption	Rapid
Bioavailability	80-100%
Tmax	1-2hours

Effectsof Food	Delaysabsorption
Distribution	Widelydistributed
Protein Binding	99%(albumin)
Metabolism	Extensivehepaticmetabolism
Excretion	Mainlyrenal
Halflife	2 hours

DOSAGEFORMS

Table2:Dosage Formof Ibuprofen.

Dosage	Strength	Uses
Tablet	200 mg	Pain,headache,fever,toothache, menstrual pain
Capsule	200 mg	Painrelief,fever reduction
Chewabletablet	100 mg	Feverandmildpainin children
Oralsuspension	100 mg/5mL	Feverandpainininfantsandchildren
Topical gel/cream	5%w/w	Localizedmusclepainandjoint pain
IVInjection	100 mg/mL	Shorttermmanagementofpainand fever

ADVERSEDRUGREACTIONS

Table3:AdverseDrugReactionsof Ibuprofen.

SystemAffected	CommonADRs	Serious/RareADRs
Gastrointestinal	Nausea,vomiting, heartburn, abdominalpain,indigestion	Gastriculcer,GIbleeding, perforation
Cardiovascular	Fluidretention,mildincrease in blood pressure	Increasedriskofheart attack (MI),stroke,heart failure
Renal	Mildincreaseincreatinine	Acutekidneyinjury,renal failure
Hypersensitivity	Rash,itching,mildallergic reaction	Anaphylaxis, angioedema, bronchospasm(especiallyin asthmatics
Liver	Mildelevationofliver	Hepatitis
	enzymes	
CentralNervousSystem (CNS)	Headache,dizziness	Asepticmeningitis(rare,more common in autoimmune disorders
Skin	Mildrash	Stevens–Johnsonsyndrome, toxicepidermalnecrolysis(very rare)

THERAPEUTICUSES

- **Rheumatoidarthritis**
  - To reducejoint pain, swelling, and stiffness.
- **Osteoarthritis**
  - Forreliefofpainand inflammationindegenerativejoint disease.
- **Ankylosingspondylitis**
  - Torelieveinflammationandimprovemobility.
- **Acutegouty arthritis**

- Forreductionofpainand inflammationduringacuteattacks.

- **Primary dysmenorrhea**
- Torelievemenstrual painby inhibiting prostaglandin synthesis.

- **Fever (Pyrexia)**
- Forloweringelevatedbodytemperatureinadultsandchildren.

- **Mildtomoderatepain conditions**
- Suchasheadache,dentalpain,musculoskeletal pain,backpain,andpost-operativepain.

- **Upperrespiratorytractinfectionsymptoms**
- Reliefoffever,sorethroat,and body aches.

CONTRAINDICATIONS

- Heartfailure
- Renal impairment
- Hepaticimpairment
- Thirdtrimesterof pregnancy
- Activepepticulcerdisease

DRUGINTERACTION

- **Anticoagulants(warfarin)**–IncreasesBleedingrisk
- **Aspirin/otherNSAIDs**–IncreasesGIulcer&bleeding
- **Corticosteroids**–IncreasesGI bleeding
- **ACEinhibitors/ARBs/Diuretics** –Reduces Antihypertensiveeffectandincreasesrenalrisk
- **Lithium**–IncreasesLithium toxicity
- **Methotrexate**–IncreasesMethotrexate toxicity

PREFORMULATIONSTUDIES

Preformulation studiesare carried outto evaluate the physicochemical properties of ibuprofenbeforeformulationintosuitabledosageformstoensurestability,efficacy,andmanufacturability.

OBJECTIVES

- Todeterminephysicochemicalproperties (solubility,pka,meltingpoint).
- Toevaluatestabilityunderdifferentconditions.
- Tocheckdrug–excipientcompatibility.

- Toassessflowandparticlepropertiesforcapsule filling.
- Topredictdissolutionandbioavailability.

PARAMETERSEVALUATED

1. **OrganolepticProperties**

- Whiteoralmostwhite crystallinepowder
- Characteristic odor
- Practicallyinsolubleinwater;solubleinorganicsolvents

2. **PhysicalProperties**

a. Solubility

- Practicallyinsolubleinwater
- Freelysolubleinethanol,methanol,acetone, chloroform
- Slightlysolubleinalkalinesolutions(duetoacidicnature) Poor solubility of ibuprofen can be improved by:
- Reducingparticlesize
- Forming salts
- Using surfactants
- Makingsolid dispersions
- Usinglipid-basedformulations

b. MeltingPoint

- Around75°C–78°C
- Sharpmeltingpointsuggest a**purecrystalline**substance

Procedure

- **PowdertheSample:**Finelygrindibuprofen.
- **FillCapillaryTube:**Insert2-3mmofpowdereddrugintoasealed capillarytube.
- **Placein Apparatus:**Insertthetubeintoameltingpoint apparatus.
- **HeatGradually:**Increasethetemperatureslowly.
- **Observe:**Notethetemperaturerangefromthefirstsignofmeltingtocomplete liquefaction.
- **Record:**Reportthemeltingpoint asarange.

c. Hygroscopicity

- Ibuprofenis**non-hygroscopic**
- Doesn’treadily absorbmoisturefromtheenvironment

Idealforlongterm storage,but protectfrom humidityto avoid degradation

3. Chemical Properties

a. pKaValue

- Approx.**4.4**
- Weaklyacidicdrug; mostlyunionizedintheacidicenvironmentofthestomach.

Procedure

The pKa of Ibuprofen can be determined by the potentiometric titration method during preformulation studies. In this method, an accurately weighed quantity of ibuprofen (about 0.2–0.5 g) is dissolved in a small volume of ethanol to enhance solubility and then diluted with distilledwater.Thesolutionisstirred continuously,andthepHmeteriscalibratedusing standard buffer solutions before use. The drug solution is titrated with standardized 0.1 N sodium hydroxide (NaOH), added gradually from a burette while continuously recording the pH after each addition. A titration curve is plotted between pH and volume of NaOH added. The equivalence point is identified from the sharp rise in pH, and the half-equivalence point is determined from the graph. According to the Henderson–Hasselbalch principle, at the half-neutralizationpointthepHofthesolutionequalsthepKaofthedrug.ThepHvalueatthispoint isthereforetakenasthepKa,whichforibuprofenistypicallyfoundtobearound4.4–4.9, confirming its weak acidic nature.

b. PartitionCoefficient(logP)

- LogP ≈ 3.3 -3.9
- Highlylipophilicand goodmembranepermeability

Procedure

The partition coefficient of ibuprofen is determined using the shake-flask method. Equalvolumes of n-octanol and water (or buffer) are taken in a separating funnel and pre-saturatedwith each other to ensure equilibrium conditions. A known amount of ibuprofen is added to the mixture, and the system is shaken vigorously for a fixed period to allow the drug to distribute between the two phases. The mixture is then allowed to stand until complete phase separation occurs. The aqueous layer is carefully separated and analyzed spectrophotometrically to determine the drug concentration. The concentration in the octanol phase is calculated by subtractingtheaqueousconcentrationfromtheinitialamountadded.Thepartitioncoefficient(P) is

calculated as the ratio of drug concentration in the octanol phase to that in the aqueous phase, and the logarithm of this value gives the log P.

c. StabilityStudies

Stabilitystudiesareconducted todeterminehowthequality,safety,and efficacyofibuprofen.

Objective

- Todetermineshelflife
- Toestablishstorageconditions
- Toevaluatedegradationpattern
- Toensureproductsafety and potency

Procedure

A known amount of ibuprofen is dissolved separately in acidic solution (e.g., 0.1 N HCl) and alkaline solution (e.g., 0.1 N NaOH). The solutions are kept at room temperature or elevated temperature for a specific time, and samples are withdrawn at intervals and analyzed using UV spectrophotometry to measure drug content. The remaining drug concentration is compared with the initial concentration to determine stability in each medium.

4. Polymorphism

- Ibuprofenexistindifferentcrystalline forms.
- Polymorphsdifferinsolubility, stability,andmeltingpoint.

5. Table4:Polymorphism

Polymorph	Key Characteristics
FormI	More stable
FormII	Lessstable;mayconverttoFormIover time
Amorphous	Non-crystalline;highersolubilitybutless stable.

6. FlowProperties

a. ParticleSizeand Shape

- Ibuprofenisapoorly flowing,hydrophobiccrystallinepowder.
- Ittypicallyhas:
- Irregularcrystal shape
- Broadparticlesizedistribution

b. Angleof Repose

Table5: Angle of Repose.

Angleof Repose	Flowcharacter
<30	Excellent
30-35	Good
35-40	Fair
>40	Poor

Procedure

- Afunnelisfixedata certainheight (h)
- Ibuprofenpowderisallowedtoflowthroughthefunnelontoaflatsurface.
- Aconicalheapforms.
- Measure:
  - Heightofpile (h)
  - Radiusofbase(r)

Formula:

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

$$\theta = \tan^{-1}(h/r)$$

c. Bulk Density

The bulk density of ibuprofen is determined by taking a clean, dry graduated cylinder (typically 100 mL or 250 mL) is weighed, and a known mass of ibuprofen powder is carefully introduced without compacting, using a funnel if necessary to avoid loss. The powder is allowed to settle naturally under gravity, and the unsettled volume (V_0) is recorded. The bulk density is then calculated by dividing the mass of the powder by this initial volume.

BulkDensity=Massofpowder/Initialvolume

d. Tapped Density

The tapped density of ibuprofen is determined by tapping a powder containing measuring cylinder mechanically until the volume becomes constant.

TappedDensity=Massofpowder/Tappedvolume

e. Hausner'sRatio

Hausner'sratioofibuprofenpowderwascalculatedbyusingtheequationbelow.Hausner'sratio which is less than 1.25 shows good flowing properties more than higher ones. Hausner's

ratios whicharefrom1.25 to1.6showmoderateflowingproperties.Hausner'sratio whichismore than 1.6willshowmorecohesive powders.

Hausner'sratio=Tappeddensity/Bulk density

Table 6: Hausner'sratio.

Hausner'sRatio	Flow
1.2-1.3	Excellent
1.3-1.4	Good
1.4-1.5	Fair
1.5-1.6	Poor

f. Carr'sIndex

Tapped andbulk density measurements can be used to estimate thecarr's index ofa material.Carr's index was determined by,

Carr'sIndex=[(TappedDensity-Bulkdensity)/Tappeddensity] *100

Table7: Carr'sIndex.

Carr'sIndex	Flow
5-15	Excellent
12-16	Good
18-21	Fair
23-35	Poor
35-38	Verypoor
Morethan 40	Extremelypoor

7. FTIR(FourierTransformInfrared Spectroscopy)

FTIR(FourierTransformInfraredSpectroscopy)identifiesfunctionalgroupsbasedonhow molecular bonds absorb infrared radiation at specific wavenumbers (cm^{-1}). Eachfunctionalgroupinibuprofenabsorbsatcharacteristicregions→givinga"fingerprint spectrum."

Ibuprofencontains:

- Carboxylicacid(–COOH)
- Aromaticring (benzene)
- Alkylgroups(–CH_3,–CH_2)

ThesegroupsproducethekeyFTIR peaks.

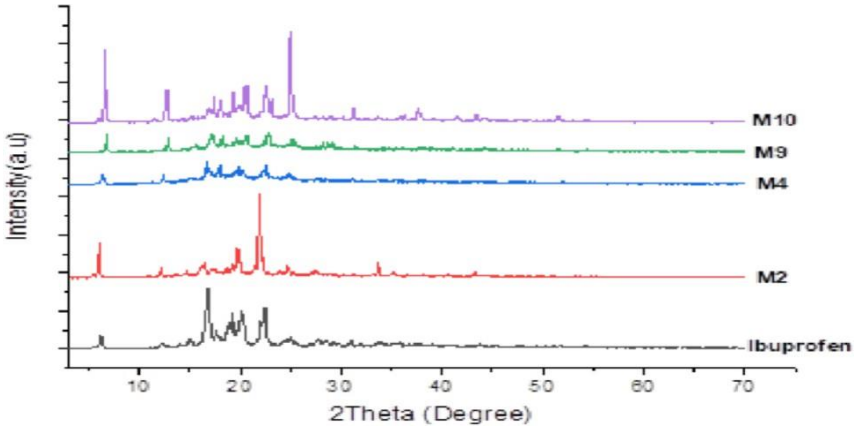

Fig2.1:FTIRSpectraof Ibuprofen.

FORMULATIONOFIBUPROFENCAPSULE

FormulationofHardGelatinCapsules

Table8:Formulationof HardGelatinCapsules.

1.ACTIVEPHARMACEUTICALINGREDIENT			
2.CAPSULESHELLMATERIALS			
	INGREDIENTS	**EXAMPLES**	**PURPOSE**
1.	Gelatin	Collagenobtaiedfrom skin	Primarycomponent,protect the contents from light, atmospheric oxygen, contaminationetc
2.	Plasticizer	Glycerin, Sorbitol	Improve flexibility and softnessofcapsuleshell; prevent brittleness
3.	Coloring agent	Titaniumdioxide,Iron oxides, FD&C dyes	Provide color for identification,branding,and patient appeal
4.	Opacifyingagent	Titanium dioxide	Make the capsule/tablet opaque;protectdrugfromlight
5.	Preservatives	Methylparaben, Propylparaben,Sodium benzoate	Preventmicrobialgrowth, especially in liquid formulations
3.MATERIALSFORFILL			
	EXCIPIENT	**EXAMPLES**	**PURPOSE**
1.	Diluents(Fillers)	Lactose, Microcrystalline cellulose,Dicalcium phosphate	Increasebulktomakedosage form manageable and ensure uniform dose
2.	Binders	Starch,PVP,HPMC	Holdpowderparticlestogether and ensure consistency
3.	Lubricants	Magnesiumstearate, Stearic acid	Preventstickingtomachinery during compression
4.	Glidants	Colloidalsilicon dioxide	Improvepowderflowduring manufacturing
5.	Disintegrants	Croscarmellosesodium, Sodiumstarchglycolate	Help the capsule break apart and release the active ingredientonceitreachesthe digestive tract

MANUFACTUREOFCAPSULE

1. MANUFACTUREOFHARDGELATINCAPSULESHELL:

Hard gelatin capsules are manufactured using a dip-coating method and the various stages involved are as follows:

Step1:Preparationofthegelatinsolution(dipping solution)

A concentrated solution of gelatin is prepared by dissolving the gelatin in demineralized water which has been heated to 60-70°C in jacketed pressure vessels. This solution contains 30-40% w/w of gelatin and is highly viscous, which causes bubbles as a result of air entrapment. To remove the air bubbles, a vaccum is applied to the solution. Following the above steps, colorants and pigments are added to attain the desired final capsule appearance. At this stage, added sodium lauryl sulphate to reduce tension. The solution viscosity is measured and adjusted as needed with hot demineralized water to achieve the target specification.

Step2:Dip-coatingthegelatinsolutionontometalpins(moulds)

Capsule shells are manufactured under strict climatic conditions by dipping pairs (body and cap) of standardized steel pins arranged in rows on metal bars into an aqueous gelatin solution (25-30%w/w)maintainedat about50°Cinajacketed heatingpan.Becausethemouldsarebelowthe gelling temperature, the gelatin begins to form a thin gelatin layer or film on the moulds. The rows of pins are arranged so that caps are formed on one side of the machine while bodies are simultaneously formed on the opposite side of the machine.

Step3:Rotationofthedip-coatedpins

Followingadsorptionofthegelatinsolutionontothesurfaceofthepins,thebarcontaining the pins are removed and rotated several times to evenly distribute the solution around the pins.

Step4:Dryingofthegelatin-coatedpin

Oncethegelatinisevenlydistributedonthemoulds,ablastofcoolairisusedtosetthegelatin on the mould. At this point, the gelatin is dried, and the pins are then passed through several drying stages to achieve the target moisture content.

Step5:Strippingandtrimming

Afterthegelatin isdried,the capsuleisstripped offthemould andtrimmedto theproperlength.

Step6:Joiningofthetrimmedcapsuleshell

Oncetrimmed,thetwohalves(thecapandbody)arejoinedtothepre-closedpositionusingapre lock mechanism. At this point, printing is done if needed before packing in cartons for shipping.

Step7:Printing

After formation, the capsule shells can be printed to improve identification. Printing can be achieved using one or two colors, containing information such as product name or code number, manufacturers name or logo and dosage details.

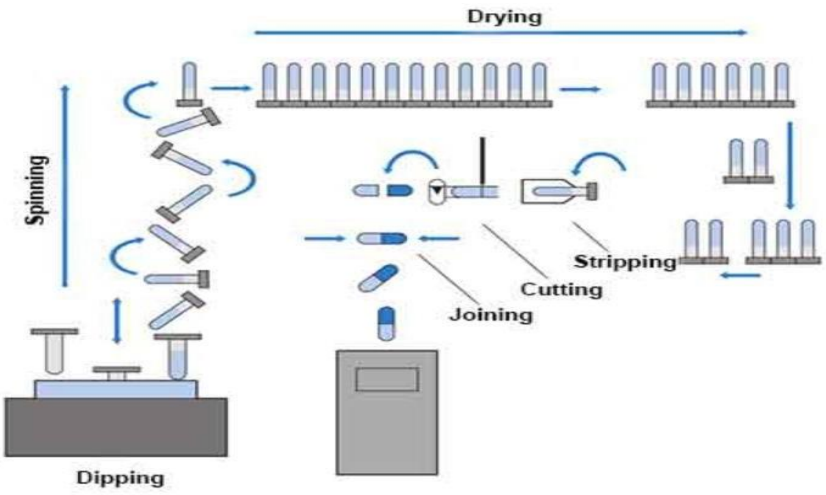

Fig3.1ManufacturingprocessofHardGelatinCapsule Shell.

2. CAPSULEFILLINGMETHODS:

a. Manualcapsulefilling method

b. Semi-automaticcapsulefillingmethod

c. Fully-automaticcapsulefilling method

a. MANUALCAPSULEFILLING METHOD

Weigh therequired quantity of APIand excipients using an analytical balance. Mix the powders uniformlyusingmortarandpestleorapowderblender.Selecttheappropriatecapsulesizebased on the bulk density of the formulation. Separate the capsule cap and capsule body manually.

Place the capsule bodies into the holes of a manual capsule tray (if available) for ease and consistency. Use a spatula or funnel to fill the powder into the body of each capsule. Gently tap or settle the tray to allow powder to settle in the capsules. Use a tamper to compressthe powder if needed, then top off with more powder. After filling, replace the cap of each capsule by hand. Press gently to lock the capsules securely. Clean the filled capsules using a soft cloth or a piece clean tissue to remove excess powder. Store capsules in a moisture-proof container.

Fig3.2:ManualCapsule FillingMachine.

Advantages

- Lowcost,Simpletooperate,FlexibleandisPortable Disadvantages
- SlowProduction
- InconsistentFilling-canleadtounevenamountsofpowderineachcapsule
- Labor-Intensive-requiremoremanuallabor

b. SEMIAUTOMATICMACHINEFILLING

In a semi-automatic capsule filling machine, the process is a mix of manual work and machineassistance.

Preparation:First,thepowdereddrug(API)andotheringredients(excipients)arecarefully mixed together. This blend is then loaded into the machine.

LoadingCapsules:Emptycapsules(thebodiesandcaps)areplacedintothemachine.The machine automatically separates the caps from the bodies, so they are ready for filling.

Filling:Thepowderisthenautomaticallyfilledintothecapsulebodies bythemachine.Asystem inside the machine compresses the powder to make sure each capsule gets the correct amount.

Closing the Capsules: Once the capsules are filled, the machine automatically puts the caps back on the bodies. The operator presses a button to lock them together.

Finishing:Finally,thefilledcapsulesareejectedfromthemachine,cleanedofanyexcess powder, and checked for quality.

Fig3.3:Semi-AutomaticCapsuleFillingMachine.

Advantages

- Faster,moreaccurate,Goodformedium-sizedproduction,lessmanualwork Disadvantages:
- Needssomeskill,require regularmaintenance,notveryflexible

C.FULLYAUTOMATICFILLING METHOD

In a fully automatic capsule filling machine, the entire process is handled by the machine, requiring little to no manual intervention.

Loading the Capsules: Empty hard gelatin capsules are placed into the machine's hopper which automatically orients them so they are all in the same direction. The machine then separates the capsules bodies from the capsule caps.

Filling the Capsules: The powder blend (medicine + excipients) is loaded into the machine's filling system. There are two main filling methods:

a. Tamping Pin Method: The powder is compressed into a small slug by tamping pins and then inserted into the capsule body.
b. Dosator Method: The powder is drawn into a tube (dosator), and the exact amount is pushed into the capsule body.

Locking the Capsules: After the bodies are filled, the machine automatically aligns the caps and bodies, and they are securely locked together.

Ejecting and Cleaning: The filled and locked capsules are ejected from the machine and move to a cleaning system where excess powder is removed. They may also undergo a polishing step to improve their appearance.

Final Inspection: The capsules are inspected automatically for defects like cracks, weight

inconsistency, or incomplete filling. Some systems also check the dissolution rate.

Fig3.4:Fully AutomaticCapsuleFillingMachine.

Advantages

- Veryfast,highlyaccurate,Lowhumaneffort,Greatforlargeproductionmanufacturing

Disadvantages:

- Expensive,needstrainedoperators,notflexibleforsmallbatches,Hardtoadjust

FACILITIESREQUIREDFORTHEMANUFACTURINGPROCESS

1. Cleanroom Facility
2. RawMaterialStorage Area
3. WeighingandDispensingAre
4. GranulationorBlendingRoom(forpowder fill)
5. CapsuleFillingArea
6. CapsulePolishingandInspectionArea
7. Drying area
8. In-ProcessandQualityControlLabs
9. Finishedproductstoragearea
10. PackagingArea
11. HVAC System
12. Utilities
13. PersonnelFacilities

EVALUATIONOFIBUPROFENCAPSULE

1. PHYSICALEVALUATION

Thisinvolvescheckingtheappearanceandsizeofthecapsulestoensureuniformity.

ColourandAppearance:Thecapsulesshouldbeconsistentincolourandappearance.Any deviation might indicate contamination or issues during manufacturing.

ShapeandSize:Capsulesshouldhaveaconsistentshapeand sizetoensureaccurate dosing.

2. WEIGHTVARIATIONTEST

Thistestchecksthe uniformityofthecapsule's content.

Ten hard gelatin capsules are usually weighed individually and the contents are removed. The emptied shells are individually weighed and the net weight of the contents is calculated by subtracting the weight of the shell from the respective gross weight. The content of active ingredient in each capsule may be determined by calculation based on the per cent drug content in the formulation.

3. CONTENT UNIFORMITY

This test is performed only when the content is specified in the individualmonographs and when capsules fail weight variation test. If the weight of capsules is completely filled no need of this test. The amount of active ingredient should be within in the range of 85% to 115% of the label amount for 9 of 10 capsules, with no unit outside the range of 70% to 125% of label amount.

4. DISSOLUTIONTEST

Drug absorption and physiological availability depend on the drug substance being in the dissolved state at the site of drug absorption. The rate and extent of dissolution of the drug from the capsule dosage form is tested by a dissolution test. This test provides means of qualitycontrol in ensuring that, different batches of the drug product have similar drug release characteristics and also, a given batch has similar dissolution as the batch of capsules that was shown initially to be clinically effective.

5. DISINTEGRATIONTEST

Disintegration of hard gelatin capsules is evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. 6 capsules are placed in thebasket-rackassembly,whichisrepeatedlylowered30timesperminuteintoa thermostatically controlled bath of fluid at 37 ± 2 ˚C and observed over the time described in the individual monograph. If 1 or2 capsules fail to disintegratecompletely, thetest is repeatedon an additional 12 capsules, and the requirements is met if not fewer than 16 of the total 18 capsules disintegrate completely.

6. MOISTURECONTENTTEST

Moisture content is the amount of water present in an ibuprofen capsule, which can affect its stability and shelf life. It is determined by weighing the sample, drying it in an oven at about 105°Cforafewhours,coolingitinadesiccator,reweighingit,andcalculatingthelossinweight as the percentage of moisture.

7. MICROBIALCONTENT

The capsules are tested to ensure lack of growth of bacteria and mould by microbiological tests. These tests are usually carried out by incubation of the capsule contents in a growth medium and counting the colonies formed after a predefined period of time. Selection of the growth medium and duration of the test, as well as maintenance of aseptic conditions during the testing, are critical to successful assessment of microbial contamination by this method.

8. STABILITYTESTING

It is performed to determine the physicochemical stability of the drug substance in the finished drug product under specified package and recommended storage conditions intrinsic stability of the active drug molecule and the influence of environmental factors (e.g., temperature, humidity, light), on formulation components, and the container and closure system.

PACKAGINGOFIBUPROFENCAPSULE

Capsule packaging refers to how pharmaceutical capsule are enclosed for distribution and use. It includesprimary packaging(e.g. blister cavities or bottles) and secondary packaging(outer cartons, boxes, and labels that further protect and identify the product). Good capsule packaging must protect the drug from moisture, light, and contamination, ensure stability through shelf-life, and meet regulatory requirements. The primary packaging of pharmaceutical capsules – iscritical forproduct protection, compliance, and patient safety: It keeps capsules dry, uncontaminated, and clearly labeled. For instance, blister packs and amber bottles are known to be ideal for moisture-sensitive medicines. The right packaging also supports patient compliance (unit-doseblisterdosing,child-resistantbottles,clearlabeling).Afterchoosingaprimarypack, capsules are usually placed intosecondary packaginglike carton boxes orshrink-wrappedcases. Cartons provide extra protection during shipping, allow additional labeling (drug info, branding, tamper-evident seals), and help organize multi-pack products

Fig4.1:HDPEBottlePackaging

Fig4.2: BlisterPackaging

LABELLINGOFIBUPROFENCAPSULE

Table9:LabellingInformationofIbuprofenCapsule.

LabelComponent	Description
ProductName	IbuprofenCapsules(e.g.,Ibuprofen200mg)
ActiveIngredient	SolubilisedIbuprofen
DosageStrength	Clearindicationofthstrengthpercapsule (e.g.,200 mg)
BatchNumber	Uniquebatchidentification code
Expiry Date	ExpirydateinMM/YYYYformat
Manufacturerdetails	Name,address,and contactinformationofthemanyfacturer
StorageInstructions	Directionforproperstorage(storeat20°to 25°C)
DirectionforUse	BasicusingInstructions(e.g.,donot takemorethan directed)
Warnings	Safetywarnings(e.g.,Keepoutofreachof children)

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