FORMULATION DEVELOPMENT AND IN VITRO CHARACTERIZATION OF FLURBIPROFEN SUSTAINED RELEASE MATRIX TABLETS

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Abstract- **In the present work, an attempt has been made to develop Sustained release matrix tablets of Flurbiprofen by selecting natural polymers Tragacanth, Acacia gum, and Xanthan gum as release rate retarding polymers. All the formulations were prepared by direct compression method. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density, etc. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits**

Index Terms- **Flurbiprofen, Tragacanth, Acacia gum, Xanthan gum and sustained release tablets**

I. INTRODUCTION

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamics and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form. Sustained-release medications are usually labeled with "SR" at the end of their name. These medications prolong the medication's release from a tablet or capsule so that you'll get the medication's benefits over a longer period of time. Sustained-release medications should not be used alone to adjust or titrate a patient's uncontrolled pain. Using them for titration unduly prolongs the process to bring the pain under control. However, once the pain is controlled, changing to a sustained-release product may enhance the patient's quality of life and improve compliance and adherence due to the decreased frequency of dosing. Probably the earliest work in the area of sustained drug delivery dosage forms can be traced to the 1938 patent of Israel Lipowski. This work involved coated pallets for prolonged release of drug and was presumably forerunner to the development of the coated particle approach to sustained drug delivery that introduced in the early 1950s.

II. DRUG SELECTION FOR ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEMS

The biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery system requires knowledge on the absorption mechanism of the drug form the G. I. tract, the general absorbability, the drug's molecular weight, pKa, solubility at different pH and apparent partition coefficient.

Table1.1. Parameter for drug selection:

Parameter	Preferred value
Molecular weight/ size	< 1000
Solubility	> 0.1 µg/ml for pH 1 to pH 7.8
Pka	Non ionized moiety > 0.1% at pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability	From all GI segments
Release	Should not be influenced by pH and enzymeS

The pharmacokinetic evaluation requires knowledge on a drug's elimination half- life, total clearance, absolute bioavailability, possible first- pass effect, and the desired steady concentrations for peak and trough.

Table1.2. Pharmacokinetic parameter for drug selection

Parameter	Comment
Elimination half life	Preferably between 0.5 and 8 h
Total clearance	Should not be dose dependent
Elimination rate constant	Required for design
Apparent volume of distribution Vd	The larger Vd and MEC, the larger will be the required dose size.
Absolute bioavailability	Should be 75% or more
Intrinsic absorption rate	Must be greater than release rate
Therapeutic concentration Css av	The lower Css av and smaller Vd, the loss among of drug required
Toxic concentration	Apart from the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.

Advantages of Sustained release drug delivery system over the conventional dosage form

- Reduced dosing frequency
- Dose reduction.
- Improved patient compliance.
- Constant level of drug concentration in blood plasma.
- Reduced toxicity due to overdose.
- Reduces the fluctuation of peak valley concentration.
- Night time dosing can be avoided.

The IR drug delivery system lacks some features like dose maintenance, sustained release rate & site targeting. The oral Sustained drug delivery has some potential advantage like Sustained release rate & dose maintenance in plasma. The SR formulations have some swelling polymer or waxes or both which controls the release rate. The use of reservoir system is also well known for controlling release rate. (Figure1) shows the relation between plasma concentration verses time

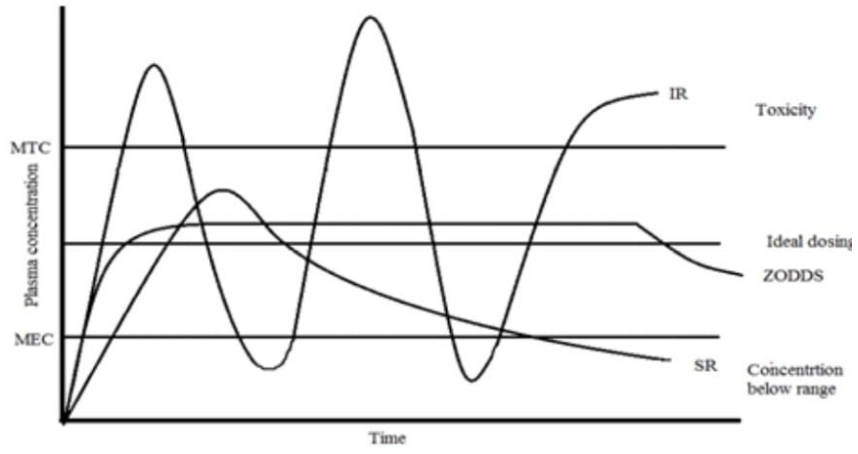


Figure 1: Ideal Plasma Concentration Curves For Immediate Release, Zero Order Release, Sustained Release Drug Delivery System

FACTORS AFFECTING THE FORMULATION OF ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEM

Physicochemical factors

- **Aqueous Solubility**

the drugs are weak acids or weak bases Drugs with low water solubility will be difficult to incorporate into sustained release mechanism. For a drug with high solubility and rapid dissolution rate, it is often quite difficult to retard its dissolution rate. A drug of high water solubility can dissolve in water or gastrointestinal fluid readily and tends to release its dosage form in a burst and thus is absorbed quickly leading to a sharp increase in the blood drug concentration compared to less soluble drug. It is often difficult to incorporate a highly water soluble drug in the dosage form and retard the drug release especially when the dose is high. The pH dependent solubility particularly in the physiological pH range would be another problem for Sustained release formulation because of the variation in the pH throughout the gastrointestinal tract and variation in the dissolution rate. The biopharmaceutical classification system (BCS) allows estimation of likely contribution of three major factors solubility, dissolution and intestinal permeability which affect the oral absorption.

- **Partition coefficient (P (o/w)**

Partition coefficient is defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Drugs that passes though biological membrane, if partition coefficient of drug influences shows very much bioavailability because lipophilic nature of biological membrane. Drugs that have lower partition coefficient are not suitable for oral CR drug delivery system and drugs that have higher partition coefficient are also not suitable for oral SR drug delivery system because they will not partition out of the lipid membrane once it gets in the membrane

- **Drug pKa and ionization at physiological pH**

Drugs existing largely in ionized form are poor candidates for oral Sustained release drug delivery system. Absorption of the unionized drugs are well whereas permeation of ionized drug is negligible because the absorption rate of ionized drug is 3-4 times less than that of the unionized drug is pH sensitive is around 3.0-7.5 and pKa range for basic drug whose ionization is pH sensitive is around 7.0-11.0 are ideal for optimum positive absorption. Drug shall be unionized at the site to an extent 0.1-5.0% .

- **Drug stability**

Drugs undergo both acid/base hydrolysis and enzymatic degradation when administered oral route. If the drug in the solid state the degradation will occur in reduced rate, for the drugs that are unstable in stomach that prolong delivery to the entire GI tract are beneficial. If drug is administered in extended release dosage form that are unstable in small intestine may demonstrate decreased bioavailability

- **Molecular size and diffusivity**

Diffusivity depends on size & shape of the cavities of the membrane. The diffusion coefficient of intermediate molecular weight drug is 100-400 Daltons; through flexible polymer range is 10-6- 10-9 cm2/sec. For drugs having molecular weight > 500 Daltons, the diffusion coefficient in many polymers are very less i.e. less than 10-12 cm2/sec.

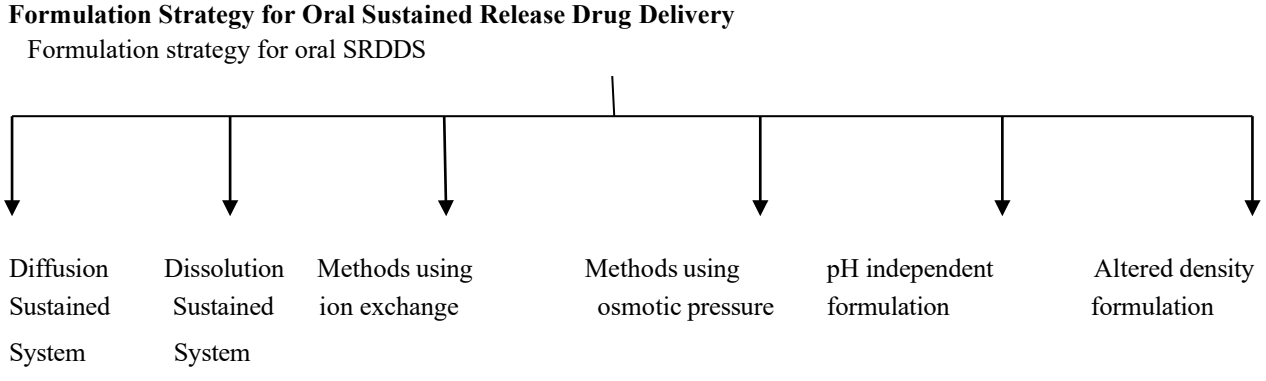


Figure 2: Formulation Strategy for Oral Sustained Release Drug Delivery System

) Diffusion sustained system

Diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration

Diffusion reservoir system

In this system, a water insoluble polymeric material covers a core of drug. Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media.

- **Diffusion matrix system**

The matrix system is defined as a well mixed composite of one or more drugs with gelling agent. hydrophilic polymers. Matrix systems are widely used for sustaining the release rate. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed

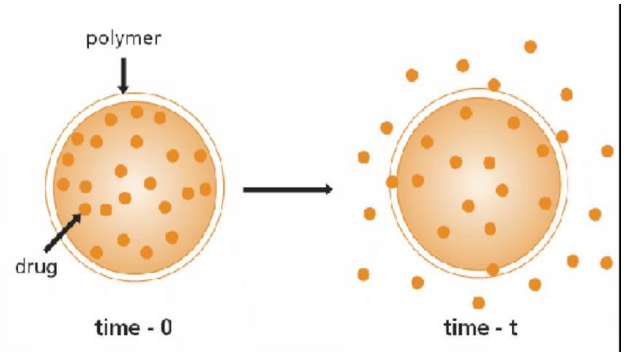


Figure 3: Schematic Representation of Diffusion Type Reservoir System

2) Dissolution sustained systems

A drug with a slow dissolution rate is inherently sustained and for those drugs with high water solubility, one can decrease dissolution through appropriate salt or derivative formation. These systems are most commonly employed in the production of enteric coated dosage forms. To protect the stomach from the effects of drugs such as Aspirin, a coating that dissolves in natural or alkaline media is used

- Soluble reservoir system
- Soluble matrix system
- Dissolution- sustained pulsed delivery system

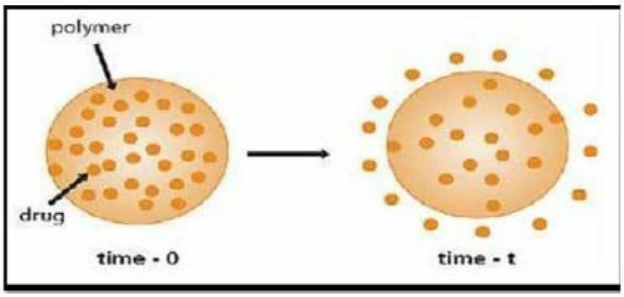


Figure 4: Schematic Representation of Diffusion Type Matrix System

3) Ion exchange resins sustained release

Ion exchange resins are cross-linked water insoluble polymers carrying ionisable functional groups. The resins have been used in various pharmaceutical applications, primarily for taste masking and controlled release systems. In tablet formulations, ion exchange resins have been used as disintegrant, because of their swelling ability. It forms irreversible complex with ionisable drugs upon prolonged exposure of the drug to the resin. A resin bound drug is removed when appropriate ions are in contact with ion exchanged groups. the addition of ion exchange resin to HPMC matrices due to formation of complex between drug and resin.

4) Methods using osmotic pressure

In this method, the release controlling factor that must be optimized is the osmotic pressure gradient between inside the compartment and the external environment. The simplest and most predictable way to achieve a constant osmotic pressure is to maintain a saturated solution of osmotic agent in the compartment. This technology provides zero order release used for hydrophilic drugs. Drug may be osmotically active or combine with osmotically active salt eg

NaCl. Osmotic pressure is the hydrostatic pressure produced by a solution in a space divided by a semi permeable membrane due to difference in concentration of solutes. A semi permeable membrane is placed around a tablet, particle or drug solution that allows transport of water into the tablet with eventual pumping of drug solution out of the tablet through a small delivery aperture in tablet coating.

5) pH Independent formulations

Most drugs are either weak acids or weak bases. The release from Sustained release formulations is pH dependent. However; buffers such as salts of amino

acids, citric acid, phthalic acid phosphoric acid or tartaric acid can be added to the formulation to help to maintain a constant pH thereby rendering pH independent drug release.

6) Altered density formulation

Several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract. The delivery system remains in the vicinity of the absorption site until most, if not all of its drug contents is released. In high density approach, the density of the pellets must exceed that of normal stomach content and should therefore be at least 1 - 4g/cm3. In low density approach, the globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of drug for sustained release purpose.

III. MATRIX TABLETS

A matrix tablet is formed when an active drug is homogeneously dispersed (embedded) in an inert material. Matrix materials are often swellable hydrophilic or non-swellable hydrophobic polymers.

Classification of Matrix Tablets

1. Based on Polymer Used:

A) Hydrophilic Matrix Tablets:

1. Utilize hydrophilic carriers to control drug release rate.
2. Prepared by direct compression or wet granulation.
3. Examples of polymers:

Cellulose derivatives (e.g., HPMC, sodium carboxymethyl cellulose, methyl cellulose).

Non-cellulose polymers (e.g., agar-agar, alginates, chitosan, modified starches).

Acrylic acid polymers (e.g., Carbopol 934).

Other hydrophilic materials (e.g., alginic acid, gelatin, natural gums).

B) Fat-Wax Matrix Tablets:

1. Incorporate drugs into fat-wax granulations.
2. Prepared by:

Spray congealing in air.

Blend congealing in aqueous media (with or without surfactants).

Classification of Matrix Systems by Porosity Types:

A) Macro Porous Systems:

- Pore size: 0.1 to 1 μm.
- Drug diffusion: Occurs through large pores, larger than the diffusing molecule size.

B) Micro Porous Systems:

- Pore size: 50-200 Å (angstroms).
- Drug diffusion: Occurs through small pores, slightly larger than the diffusing molecule size.

C) Non-Porous Systems:

- No pores: Molecules diffuse through the polymer network meshes.
- Only polymer phase: No pore phase exists, drug release occurs through the polymer matrix.

Drug Release Kinetics from Matrix Systems

A. Zero-Order Kinetics:

1. Equation: Qt - Q0 = K0t
2. Characteristics: Constant rate of drug release, independent of initial drug concentration.
3. Plot: Cumulative percent drug release vs. time (linear plot indicates zero-order kinetics).

B. First-Order Kinetics:

1. Equation: Log Qt = Log Q0 - K1t/2.303
2. Characteristics: Rate of drug release is proportional to the amount of drug remaining.
3. Plot: Log cumulative percent drug remaining vs. time (straight line indicates first-order kinetics).

C. Higuchi's Model:

1. Equation: $Q = \sqrt{(D\delta/\tau)(2C - \delta Cs)Cst}$
2. Characteristics: Describes drug release from matrix devices by diffusion.
3. Factors influencing release: Diffusion coefficient, porosity, tortuosity, solubility, and time.

Factors Influencing Drug Release from Polymeric Matrices

Swelling Property of Polymer:

1 . Polymer dissolution involves water absorption, polymer-polymer linking rupture, and swelling.

2. Study of polymer hydration/swelling is crucial for understanding drug release.

Drug Solubility:

1. Molecular size and water solubility determine drug release.
2. Drugs with:
   a) Reasonable solubility: Release occurs by dissolution in infiltration medium.
   b) Poor solubility: Release occurs by both dissolution and erosion of the matrix.

Solubility and Sink Conditions:

1. In vitro studies should mimic in vivo sink conditions (e.g., hemoperfusion).
2. Perfect sink conditions ensure accurate drug release profiles.

Polymer Diffusivity:

a) . Energy-activated process dependent on:
   - Polymer chain segment length.
   - Cross-linking.
   - Crystalline nature of polymers.

b) Influenced by:
   - Polymer particle size.
   - Polymer viscosity.

c) Polymer concentration.

d) Thickness of Polymer Diffusional Path:
   - Controlled release governed by Fick's law of diffusion.
   - Thickness of the diffusional path affects drug release rates.

Biological Factors Influencing Sustained Release Formulations

Biological Half-Life:

1. Determines suitability for sustained release formulations.
2. Short half-life drugs (e.g., < 2 hours): Excellent candidates for sustained release (e.g., reduce dosing frequency).
3. Drugs with very short half-life (e.g., furosemide, levodopa): May not be suitable due to challenges in maintaining therapeutic levels.

Absorption:

1. Transit time in GI tract: 8-12 hours; maximum half-life for absorption should be 3-4 hours.
2. Strategies to enhance absorption:

1. Gastroretentive systems (e.g., slow release in stomach).
2. Low-density pellets or capsules (e.g., floating in stomach).
3. Bioadhesive materials (e.g., sticking to GI tract mucosa).

Metabolism:

1. Pre-systemic metabolism: Drugs significantly metabolized before absorption may show decreased bioavailability in sustained release formulations.
2. Impact on formulation design: Consideration of metabolic pathways is crucial for successful sustained release formulations.

Factors Influencing Drug Release from Matrix Systems

A) Polymer Hydration:
- Important to study polymer hydration/swelling process.
- Involves water absorption, polymer-polymer linking rupture, and swelling.

B) Drug Solubility:
- Molecular size and water solubility determine drug release.
- Drugs with:

Reasonable solubility: Release occurs by dissolution.

Poor solubility: Release occurs by both dissolution and erosion.

C) Solution Solubility:
- In vitro studies should mimic in vivo sink conditions.
- Maintaining sink conditions ensures accurate drug release profiles.

D) Polymer Diffusivity:
- Influenced by polymer chain segment length, cross-linking, and crystallinity.
- Affected by: Polymer particle size. , Polymer viscosity.

E) Thickness of Polymer Diffusional Path:
- Controlled release governed by Fick's law of diffusion.
- Thickness affects drug release rates.

F) Thickness of Hydrodynamic Diffusion Layer:
- Drug release profile affected by variation in layer thickness.
- Increasing thickness decreases drug release rate.

G) Drug Loading Dose:
- Affects release kinetics, especially for poorly soluble drugs.
- Increasing initial drug loading: Decreases relative release rate (poorly soluble drugs) ,
  Increases absolute release rate.

H) Surface Area and Volume:
- Rate of drug release dependent on surface area.
- Smaller tablets release faster than larger ones.

I) Diluent's Effect:
- Water-soluble diluents (e.g., lactose) increase drug release rate.
- Insoluble diluents (e.g., dicalcium phosphate) decrease Fickian diffusion.

J) Additives:
- Non-polymeric excipients can increase release rate.
- Soluble excipients (e.g., lactose) have a greater effect.

Rationale for Sustained Release Matrix Devices:

1. Extend duration of action.
2. Reduce dosing frequency.
3. Minimize plasma level fluctuations.
4. Improve drug utilization.
5. Reduce adverse effects.

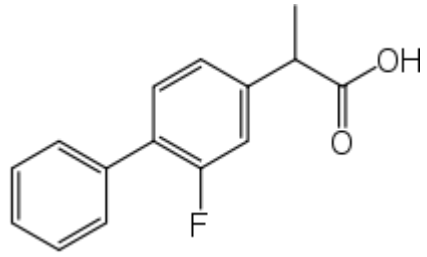
Polymers Used in Matrix Tablets:

1. Hydrogels: PHEMA, PVA, PVP, PEO, PA.
2. Soluble polymers: PEG, PVA, PVP, HPMC.
3. Biodegradable polymers: PLA, PGA, PCL, polyanhydrides.
4. Non-biodegradable polymers: PVA, PDS, PEU, PVC, CA, EC.

5. Mucoadhesive polymers: Polycarbophil, sodium CMC, polyacrylic acid.
6. Natural gums: Xanthan gum, guar gum, karaya gum.

IV. DRUG PROFILE

Drug: Flurbiprofen
Synonym : (+-)-2-Fluoro-alpha-methyl-4-biphenylacetic acid
Drug category: Nonsteroidal Anti-inflammatory Compounds



Structure

Chemical name/ Nomenclature / IUPAC Name:
2-(3-fluoro-4-phenylphenyl)propanoic acid
Molecular Weight: 244.2609 gm/mole. **Official Pharmacopoeia :** USP
Molecular Formula $C_{15}H_{13}FO_2$
PHYSICOCHEMICAL PROPERTIES:
Description(Physical State): Solid
Solubility: Water Solubility 0.0249mg/mL
Dosage: Tablet
Melting point: 110-111 **Log P:** 3.57

PHARMACOKINETIC PROPERTIES:
Half-life : 4.7-5.7 hrs
Absorption : Fluribiprofen is rapidly and almost completely absorbed following oral administration. Peak plasma concentrations are reached 0.5 - 4 hours after oral administration.
Volume of Distribution : 14 L Protein binding : > 99 % Metabolism : Hepatic
Excretion : Renal

Mechanism of Action:
1. Reversible inhibition of cyclooxygenase (COX): Decreases prostaglandin synthesis, leading to anti-inflammatory, analgesic, and antipyretic effects.
2. Non-selective COX inhibitor: Inhibits both COX-1 and COX-2.

Therapeutic Efficacy/Indications:
1. Rheumatoid arthritis: Acute and long-term treatment.
2. Osteoarthritis: Symptomatic treatment.
3. Ankylosing spondylitis: Symptomatic treatment.
4. Pain management: Dysmenorrhea, mild to moderate pain with inflammation.
5. Ophthalmic use: Prevents intraoperative miosis.

Contraindications:
1. Systemic mastocytosis: Increased risk of adverse reactions.
2. Bleeding disorders: Increased risk of bleeding.
3. Cardiovascular conditions: High blood pressure, heart attack, stroke, blood clot.

Interactions:
Drug Interactions:
1. Acetazolamide: May decrease flurbiprofen serum levels.
2. Allopurinol: May increase allopurinol serum levels.
3. Benazepril: Increased risk of renal failure, hyperkalemia, and hypertension.
4. Betamethasone: Increased risk of gastrointestinal irritation.

Food Interactions:
1. Alcohol: Avoid consumption.
2. Food: Take with food to reduce gastric irritation.

SR . .No	Drug name	Label Claim	Brand name	Company
1	Flurbiprofen	100 mg	Ansaid	Pharmacia & Upjohn Inc.

V. DRUG FORMULATION

Table 7.3: Ingredients and Uses

Ingredients	Uses
Flurbiprofen	API
Tragacanth	Binding & release controlling Agent
Acacia gum	Binding & release controlling Agent
Xanthan gum	Binding & release controlling Agent
PVP-K 30	Binding Agent
Aerosil	Anti tacking agent
Magnesium Stearate	Lubricant
Lactose	Diluent

INGREDIENTS (MG)	FORMULATION								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Flurbiprofen	100	100	100	100	100	100	100	100	100
Tragacanth	50	100	150	-	-	-	-	-	-
Acacia gum	-	-	-	50	100	150	-	-	-
Xanthan gum	-	-	-	-	-	-	50	100	150
PVP-K 30	10	10	10	10	10	10	10	10	10
Aerosil	5	5	5	5	5	5	5	5	5
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Lactose	131	81	31	131	81	31	131	81	31
Total Weight	300	300	300	300	300	300	300	300	300

Table 7.4: Formulation composition for tablets

Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

1. Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Table 7.5: Pharmacopoeial specifications for tablet weight variation

Average weight of tablet (mg) (I.P)	Average weight of tablet (mg) (U.S.P)	Maximum percentage difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than 250 or More	More than 324	5

2. **Hardness:** Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.
3. **Thickness:**
   Important for reproducing appearance and ensuring uniformity.
   Calculated as average thickness with deviation for core and coated tablets.
   Friability:
   Measures mechanical strength of tablets.
   Conducted using a Roche friabilator at 25 rpm for 4 minutes (100 rotations).
   Calculated as percentage weight loss: % Friability = [(W1 - W2) / W1] × 100.
4. **Drug Content:**
   Tablets tested for drug content uniformity.
   Powdered tablet sample analyzed using UV-Vis spectrophotometry.
   Drug concentration calculated from calibration curve.
5. In Vitro Drug Release Studies:
   Apparatus: USP-II (Paddle Method).
   Dissolution Medium: 0.1 N HCl (pH 1.2) for 2 hours, followed by pH 6.8 phosphate buffer for 10 hours.
   Sampling Intervals: 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 hours.
   Analysis: Samples analyzed using UV-Vis spectrophotometry at 246 nm.
6. **Release Rate Kinetics:**
   Models Tested:
   - Zero-order kinetics: F = Ko t.
   - First-order kinetics: Log (100 - F) = kt.
   - Higuchi model: F = k t^1/2.
   - Korsmeyer-Peppas model: Mt / M∞ = K t^n.
   - Hixson-Crowell model: (100 - Qt)^1/3 = 100^1/3 - KHC t.
7. **Drug-Excipient Compatibility Studies:**
   FTIR Spectroscopy: Detects compatibility between drug and excipients.
   Spectra Range: 4000 cm^-1 to 400 c

VI. RESULTS & DISCUSSION

The present study was aimed to developing sustained release tablets of Flurbiprofen using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release study.Analytical method
Graphs of Flurbiprofen were taken in 0.1N HCL and in pH 6.8 phosphate buffer at 246nm and 268nm respectively.

Table 8.1: Observations for graph of Flurbiprofen in 0.1N HCL

Concentration (µg/ml)	Absorbance
0	0
5	0.165
10	0.312
15	0.449
20	0.586
25	0.69

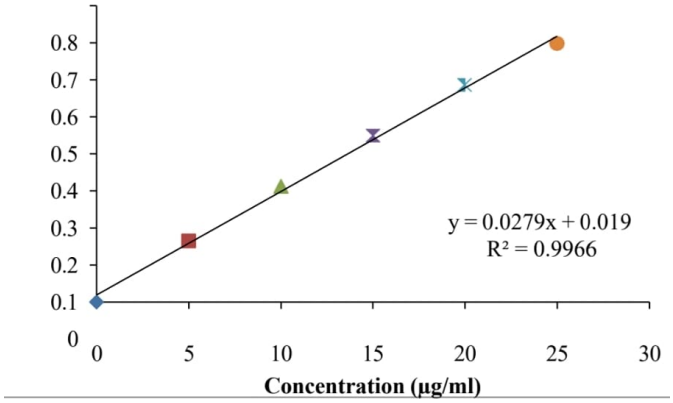


Fig 8.1: Standard curve of Flurbiprofen

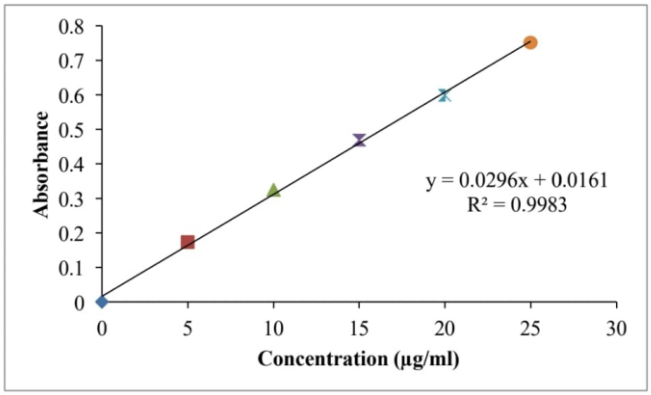


Fig 8.2: Standard curve of Flurbiprofen

Table 8.2: Standard graph values of Flurbiprofen at 268 nm in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
5	0.173
10	0.324
15	0.468
20	0.598
25	0.751

Preformulation parameters of powder blend

Table 8.3: Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.76±0.3	0.53±0.01	0.61±0.01	10.91±0.8	1.17±0.02
F2	24.87±0.3	0.55±0.01	0.65±0.03	10.63±0.5	1.15±0.03
F3	25.56±0.2	0.57±0.06	0.69±0.03	10.34±1.0	1.13±0.06
F4	23.20±0.1	0.54±0.21	0.67±0.12	10.83±0.5	1.11±0.06
F5	22.46±0.1	0.61±0.02	0.55±0.02	11.53±0.8	1.15±0.05
F6	23.19±0.2	0.58±0.04	0.63±0.04	11.24±0.6	1.19±0.03
F7	26.94±0.1	0.59±0.04	0.64±0.05	10.72±0.7	1.14±0.09
F8	23.67±0.3	0.56±0.12	0.58±0.04	10.43±1.0	1.18±0.07
F9	24.34±0.4	0.52±0.02	0.56±0.01	10.13±0.8	1.16±0.02

All the values represent n=3

Tablet powder blend was subjected to various preformulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range showing that the powder has good flow properties. The compressibility index of all the formulations was found to be 10.13 to 11.53 which show that the powder has good flow properties. All the formulations have shown the hausner's ratio

1.11 to 1.19 indicating the powder has good flow properties.

Tablet quality control tests such as weight variation, hardness, friability, thickness, and drug release studies in different media were performed on the compression tablet.

Table 8.4: Quality control parameters for tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (% loss)	Thickness (mm)	Drug content (%)
F1	300.02	5.3	0.51	3.11	98.32
F2	299.87	5.5	0.45	3.49	99.57
F3	296.50	5.7	0.39	3.77	100.00
F4	299.75	6.8	0.38	3.82	95.94
F5	299.85	5.9	0.26	3.58	96.57

F6	300.05	6.4	0.22	3.25	99.61
F7	297.61	5.6	0.44	3.28	97.44
F8	298.47	5.1	0.57	3.91	98.12
F9	299.83	5.8	0.43	3.32	95.80

❖ **Weight variation test:**

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet. The average weight of the tablet is approximately in range of 296.50 to 300.05 mg, so the permissible limit is ±7.5% (>300 mg). The results of the test showed that, the tablet weights were within the limit.

❖ **Hardness test:**

Hardness of the five tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 8.4. The results showed that the hardness of the tablets is in range of 5.1 to 6.8 kg/cm2, which was within IP limits.

- **Thickness:**

Thickness of five tablets of each batch was checked by using Micrometer and data shown in Table-8.4. The result showed that thickness of the tablet is raging from 3.11 to 3.91 mm.

- **Friability:**

Tablets of each batch were evaluated for percentage friability and the data were shown in the Table-8.4. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

- **Drug content:**

Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within

95.80 – 100.00 %

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

IN VITRO DRUG RELEASE STUDIES

Table 8.5: Dissolution data of Flurbiprofen tablets F1-F9

Time (H)	% OF DRUG RELEASE								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
0.5	17.41	18.07	12.72	10.35	8.72	8.79	7.82	10.17	7.68
1	28.38	36.14	25.38	20.65	17.31	17.38	15.38	20.21	15.31
2	34.22	39.63	32.79	22.16	20.23	25.43	24.45	21.07	23.03
3	39.39	41.82	46.88	33.98	25.96	36.86	28.59	24.17	25.12
4	47.85	54.40	49.54	46.29	38.35	37.75	36.83	33.56	30.13
5	52.34	57.09	53.17	59.73	43.02	44.46	49.26	46.58	37.09
6	62.13	68.46	66.62	68.22	56.75	55.13	53.15	54.27	45.17
7	70.91	75.02	75.93	71.73	59.13	68.16	66.29	59.68	59.24
8	76.28	79.59	78.87	75.40	64.84	69.77	67.76	66.37	63.36

9	80.96	82.36	81.26	87.01	72.22	72.85	70.27	72.77	64.81
10	85.21	85.11	84.15	89.58	80.09	84.49	74.19	75.42	73.63
11	88.56	93.78	89.02	91.96	83.56	88.88	80.64	84.12	79.43
12	92.13	95.19	90.14	92.63	94.75	93.16	90.49	89.28	85.19

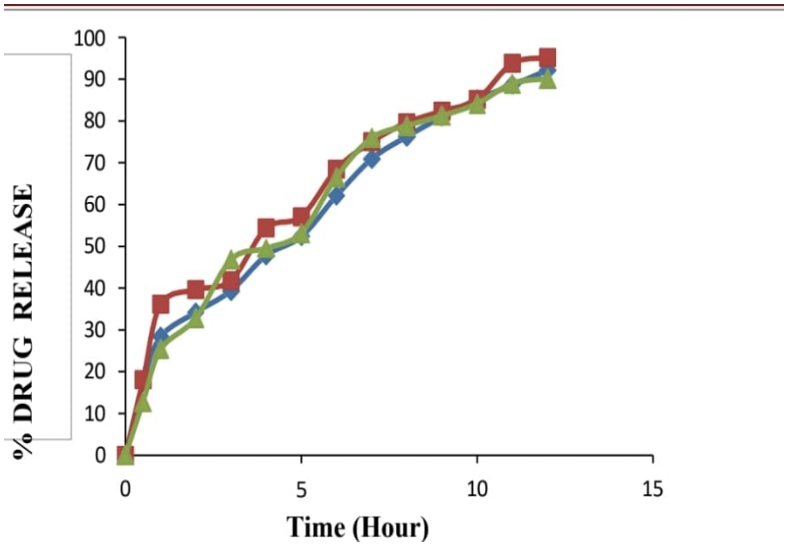


Fig 8.3: Dissolution profile of Flurbiprofen (F1, F2 and F3 formulations).

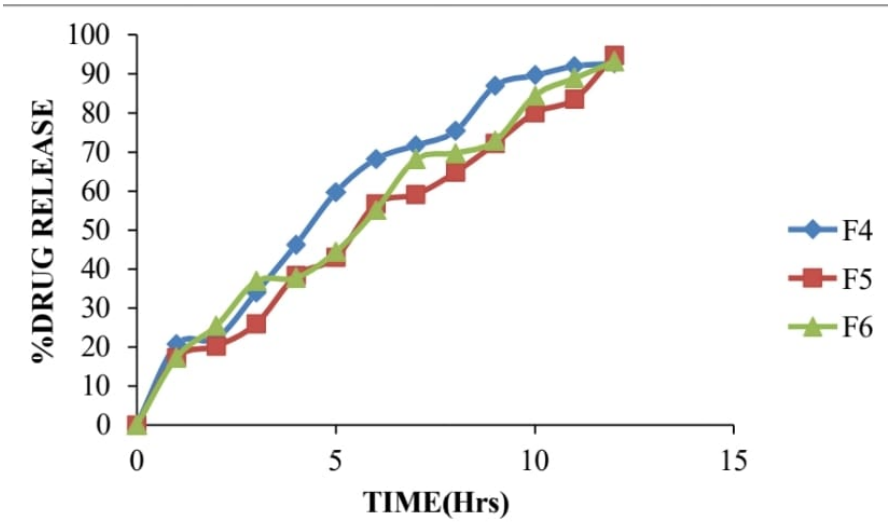


Fig 8.4: Dissolution profile of Flurbiprofen (F4, F5 and F6 formulations).

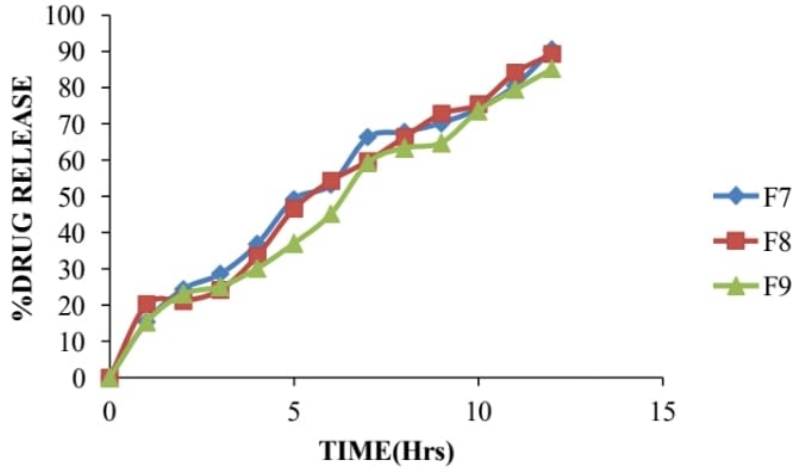


Fig 8.5: Dissolution profile of Flurbiprofen (F7, F8 and F9 formulations

Formulation Development and Optimization

Formulations Prepared:

- F1-F3: Tragacanth polymer at ratios 1:1, 1:2, and 1:3.
- F4-F6: Acacia gum polymer at ratios 1:1, 1:2, and 1:3.
- . F7-F9: Xanthan gum polymer at ratios 1:1, 1:2, and 1:3.

Drug Release Results:

❖ Tragacanth (F1-F3):

1. F1 (1:1): 92.13% drug release at 12 hours.
2. F2 (1:2): 95.19% drug release at 12 hours.
3. F3 (1:3): 90.14% drug release at 12 hours.

❖ Acacia Gum (F4-F6):

1. F4 (1:1): 92.63% drug release.
2. F5 (1:2): 94.75% drug release.
3. F6 (1:3): 93.16% drug release.

❖ Xanthan Gum (F7-F9):

1. F7 (1:1): 90.49% drug release at 12 hours.
2. F8 (1:2): 89.28% drug release at 12 hours.
3. F9 (1:3): 85.19% drug release at 12 hours.

Optimized Formulation:

1. F2: Selected as the best formulation with 95.19% drug release in 12 hours.
2. Conclusion: F2 formulation with Tragacanth polymer at a 1:2 ratio was considered the optimized formulation.

Table 8.6: Release kinetics:

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM % RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3 - Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
36.14	1	1.000	1.558	0.000	1.805	36.140	0.0277	-0.442	63.86	4.642	3.997	0.645
39.63	2	1.414	1.598	0.301	1.781	19.815	0.0252	-0.402	60.37	4.642	3.923	0.719
41.82	3	1.732	1.621	0.477	1.765	13.940	0.0239	-0.379	58.18	4.642	3.875	0.767

54.4	4	2.000	1.736	0.602	1.659	13.600	0.0184	-0.264	45.6	4.642	3.573	1.069
57.09	5	2.236	1.757	0.699	1.633	11.418	0.0175	-0.243	42.91	4.642	3.501	1.141
68.46	6	2.449	1.835	0.778	1.499	11.410	0.0146	-0.165	31.54	4.642	3.160	1.482
75.02	7	2.646	1.875	0.845	1.398	10.717	0.0133	-0.125	24.98	4.642	2.923	1.718
79.59	8	2.828	1.901	0.903	1.310	9.949	0.0126	-0.099	20.41	4.642	2.733	1.909
82.36	9	3.000	1.916	0.954	1.246	9.151	0.0121	-0.084	17.64	4.642	2.603	2.038
85.11	10	3.162	1.930	1.000	1.173	8.511	0.0117	-0.070	14.89	4.642	2.460	2.181
96.78	11	3.317	1.986	1.041	0.508	8.798	0.0103	-0.014	3.22	4.642	1.477	3.165
95.19	12	3.464	1.979	1.079	0.682	7.933	0.0105	-0.021	4.81	4.642	1.688	2.954

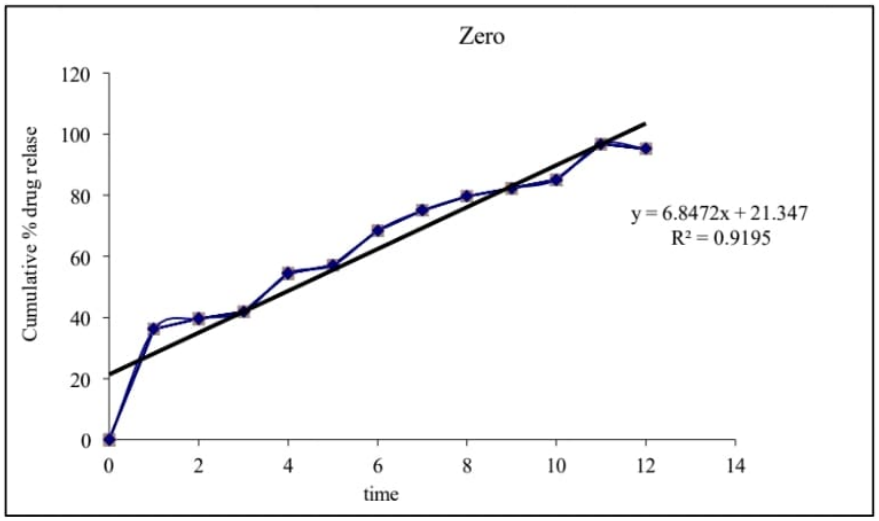


Figure 10.6: Zero order release kinetics graph

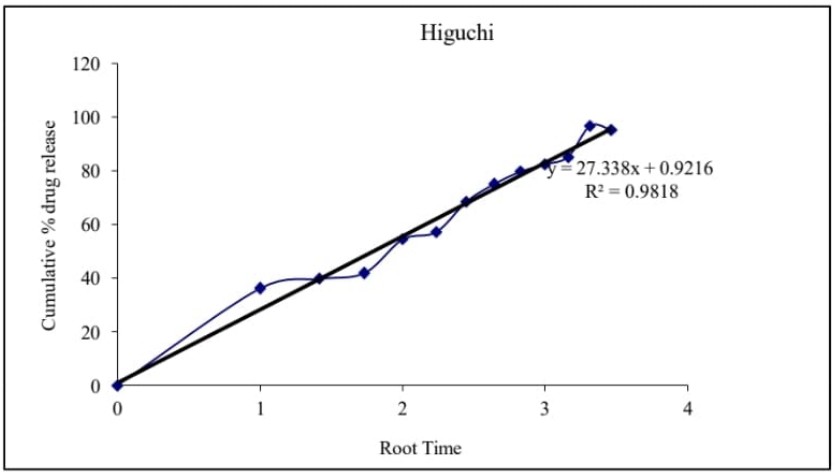


Figure 8.7: Higuchi release kinetics graph

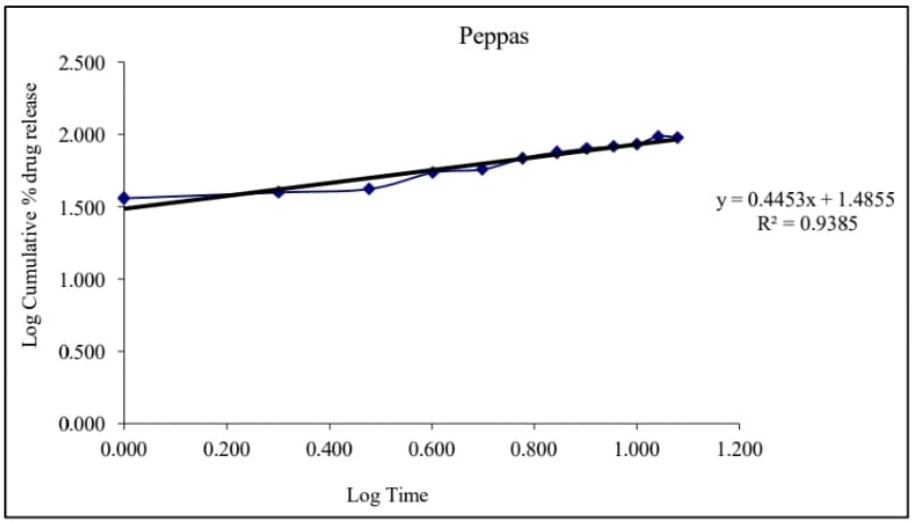


Figure 8.8: Peppas release kinetics graph

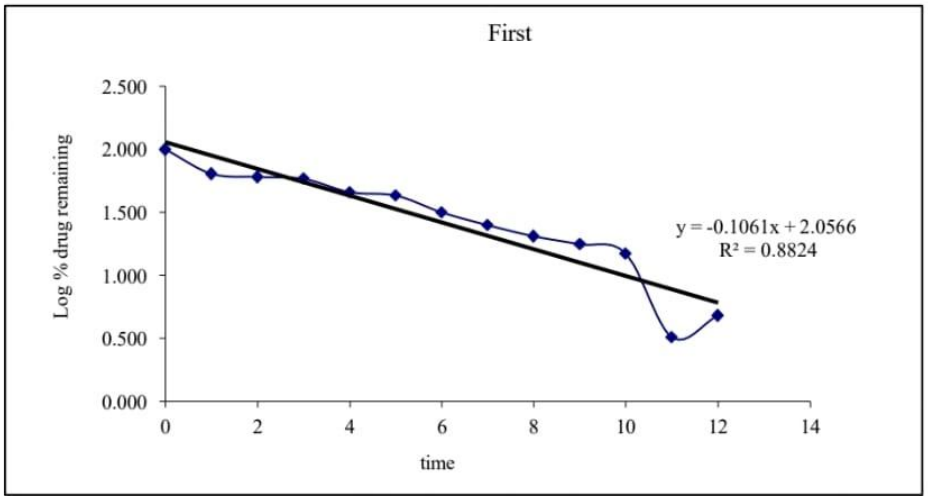


Figure 8.9: First order release kinetics graph

The above graphs it was evident that the formulation F2 was followed Higuchi release kinetics mechanism.

Table 8.7: kinetics Correlation coefficient values

Release kinetics	Correlation coefficient values
Zero order release kinetics	$R^2 = 0.919$
Higuchi release kinetics	$R^2 = 0.981$
Peppas release kinetics	$R^2 = 0.938$
First order release kinetics	$R^2 = 0.882$

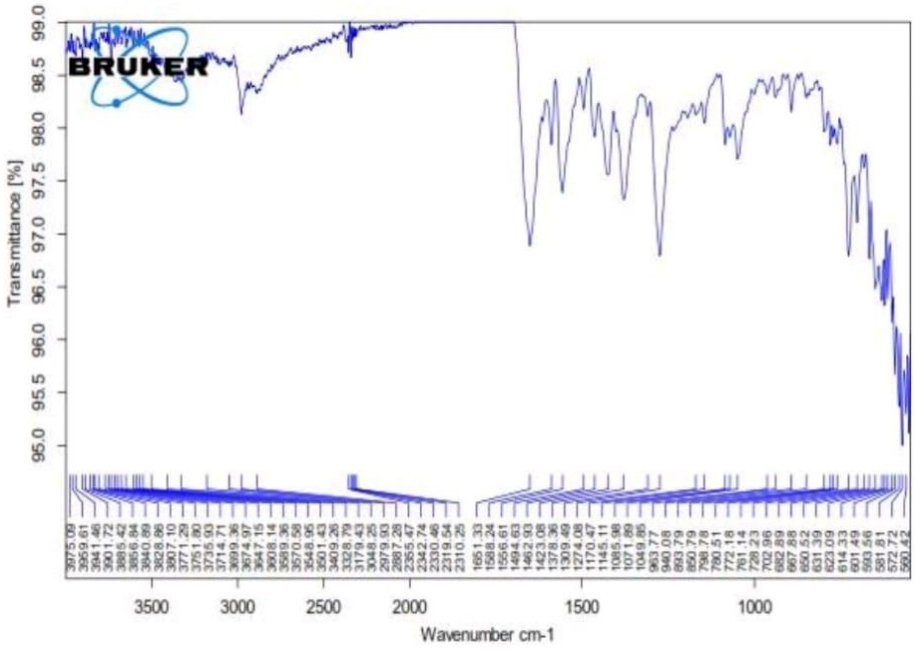


Figure 8.10: FT-TR Spectrum of Flurbiprofen pure drug

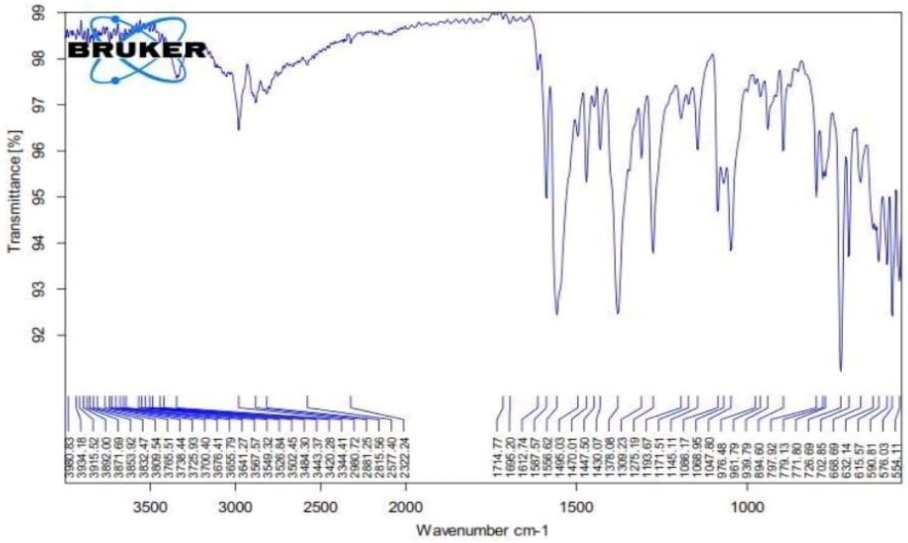


Figure 8.11: FT-IR Spectrum of Optimized Formulation

From the above studies it was found that there was no shifting in the major peaks which indicated that there were no significant interactions occurred between the Flurbiprofen and excipients used in the preparation of different Flurbiprofen Sustained release formulations. Therefore the drug and excipients are compatible to form stable formulations under study. The FTIR spectra of Flurbiprofen and physical mixture used for optimized formulation were obtained and these are depicted in above figures. From the FTIR data it was evident that the drug and excipients does not have any interactions. Hence they were compatible

VII. CONCLUSION

The present study was carried out to evaluate the natural polymers for its matrix forming ability due to formation of thick gel structure when comes into contact with the aqueous media. The present study was also carried out to evaluate the usage of direct compression technique for the formation of sustained release matrix tablets using natural gums. Blends of all the formulations shown good flow properties. All the post compression parameters of the formulations were found to be within the Pharmacopoeial limits. We conclude that Tragacanth, Acacia gum and Xanthan gum formulated tablets made by direct compression technique were found to be effective in sustaining the drug release up to 12 hrs more economically with less labor. During this study, it was also found that polymer concentration influencing the drug release behaviour. Drug Excipient Compatibility studies revealed that there was no considerable change in the drug and formulation. FT-IR studies resulted that all peaks corresponding to different functional groups of pure drug were present in the drug-excipient mixture and no interaction taken place between the drug and excipients. It can be concluded that stable formulation could be developed by incorporating Tragacanth polymer in a definite proportion, so that the desired sustained released profile can be obtained. Release model of optimized formulation was found to follow Higuchi release kinetics mechanism with high linearity.

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