### 3. MATERIALS & METHOD

Table No.: 9. List of Materials used

<table>
<thead>
<tr>
<th>SLNo.</th>
<th>Material</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Carbamazepine USP</td>
<td>Gujarat Mitul Petro- Pharma(Pvt.) Ltd, Gujarat.</td>
</tr>
<tr>
<td>2</td>
<td>HPMC K 4 M</td>
<td>Rubicon Research Pvt.Ltd., Mumbai</td>
</tr>
<tr>
<td>3</td>
<td>HPMC K100 M</td>
<td>Dr.Reddy Lab, Hyderabad</td>
</tr>
<tr>
<td>4</td>
<td>Ethyl cellulose</td>
<td>Sd fine Chem.,Ltd ,Mumbai</td>
</tr>
<tr>
<td>5</td>
<td>Povidone K-30</td>
<td>Rubicon Research Pvt.Ltd., Mumbai</td>
</tr>
<tr>
<td>6</td>
<td>Avicei-101</td>
<td>Ozone International ,Mumbai</td>
</tr>
<tr>
<td>7</td>
<td>Di-Calcium phosphate</td>
<td>Rubicon Research Pvt.Ltd., Mumbai</td>
</tr>
<tr>
<td>8</td>
<td>Sodium starch glycolate</td>
<td>Sd fine Chem.,Ltd ,Mumbai</td>
</tr>
<tr>
<td>9</td>
<td>Ferric oxide</td>
<td>Sd fine Chem.,Ltd ,Mumbai</td>
</tr>
<tr>
<td>10</td>
<td>Aersil</td>
<td>Qualigen Chemicals ,Mumbai</td>
</tr>
<tr>
<td>11</td>
<td>Magnesium Sterate</td>
<td>NR Chem ,Mumbai.</td>
</tr>
<tr>
<td>12</td>
<td>Talc</td>
<td>Qualikem fine Chem. Pvt.Ltd ,Mumbai</td>
</tr>
<tr>
<td>13</td>
<td>Hydrochloric acid (HCL)</td>
<td>Merck specialties Pvt.Ltd ,Mumbai</td>
</tr>
<tr>
<td>14</td>
<td>Sodium hydroxide (NaoH)</td>
<td>Sd fine Chem.,Ltd ,Mumbai</td>
</tr>
<tr>
<td>15</td>
<td>Methanol</td>
<td>Qualikem fine Chem. Pvt.Ltd ,Mumbai</td>
</tr>
<tr>
<td>16</td>
<td>Potassium dihydrogen ortho phosphate</td>
<td>Merck specialties Pvt.Ltd ,Mumbai</td>
</tr>
<tr>
<td>17</td>
<td>Acetone</td>
<td>Sd fine Chem.,Ltd ,Mumbai</td>
</tr>
</tbody>
</table>
**EQUIPMENT OR INSTRUMENTS USED:**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>List of Instrument</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>12 Station multi-tooling Compression machine</td>
<td>Cadmach Machinery Co Ltd., Ahmedabad</td>
</tr>
<tr>
<td>3.</td>
<td>Mechanical Sifter with Sieve 22, 24, 40, 60, 80 and 100,</td>
<td>Bhushan Engineering &amp; Scientific traders</td>
</tr>
<tr>
<td>4.</td>
<td>Hardness Tester</td>
<td>SQC &amp; Insp. instruments, Mumbai</td>
</tr>
<tr>
<td>5.</td>
<td>Double drum friability test apparatus</td>
<td>Electrolab, Mumbai</td>
</tr>
<tr>
<td>6.</td>
<td>Disintegration tester</td>
<td>Dolphin Instruments, Hyderabad</td>
</tr>
<tr>
<td>7.</td>
<td>Digital Dissolution test apparatus</td>
<td>Labindia Instruments Pvt. Ltd., Thane</td>
</tr>
<tr>
<td>8.</td>
<td>Digital weighing balance (BT 124S)</td>
<td>Sartorius Biotech (India) Pvt. Ltd., Bangalore</td>
</tr>
<tr>
<td>9.</td>
<td>Hot air oven</td>
<td>Thermolab</td>
</tr>
<tr>
<td>10.</td>
<td>Stability chambers M-722</td>
<td>Thermolab</td>
</tr>
<tr>
<td>11.</td>
<td>Electronic Single Pan Balance</td>
<td>Mettler Toledo, Mumbai</td>
</tr>
<tr>
<td>12.</td>
<td>Vernier Calipers</td>
<td>Mitutoyo, China made</td>
</tr>
<tr>
<td>13.</td>
<td>Tapped density USP, ETD-1020</td>
<td>Electrolab, Mumbai</td>
</tr>
<tr>
<td>14.</td>
<td>Analytical Sieve Shaker, EMS-8</td>
<td>Electrolab, Mumbai</td>
</tr>
<tr>
<td>15.</td>
<td>Mechanical stirrer</td>
<td>Remi motors, Mumbai</td>
</tr>
</tbody>
</table>
Table No.: 10. List of Analytical Instruments used

<table>
<thead>
<tr>
<th>SL.No</th>
<th>EQUIPMENT</th>
<th>MANUFACTURER</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pH meter</td>
<td>Datla Instruments, Hyderabad</td>
</tr>
<tr>
<td>2</td>
<td>Moisture analyzer</td>
<td>Advance Research Instruments</td>
</tr>
<tr>
<td>3</td>
<td>UV Visible Spectrophotometer</td>
<td>Elico</td>
</tr>
<tr>
<td>4</td>
<td>DSC</td>
<td>Perkin-Elmer instruments</td>
</tr>
<tr>
<td>5</td>
<td>FTIR</td>
<td>Shimadzu</td>
</tr>
</tbody>
</table>
Drug profile

CARBAMAZEPINE

IUPAC Name: 5-Carbamoyl-5H-dibenz [b,f] azepine

CAS Registry number: 298-46-4.

Molecular weight: 236.27

Molecular formula: C\textsubscript{15}H\textsubscript{12}N\textsubscript{2}O

Melting Point: 189 to 193°C

Structure:

![Structure of Carbamazepine](image)

**Appearance:** White and hygroscopic powder.

**Solubility:** Freely soluble in alcohol and acetone and insoluble in water.

**Half Life:** 25-65 hours.

**Functional category:** Anticonvulsant.

**Storage:** Preserved as in tight closed containers.

**Pharmacokinetic**

**Absorption**

Carbamazepine has a slow rate of dissolution, which is believed to result in slow, erratic, and unpredictable absorption in humans. Peak levels are usually seen between 3 and 8 hours after ingestion. However, there is considerable intra- and inter-subject variability, and peak levels have been reported to occur much later after dosing. The absorption of...
Carbamazepine does not follow a simple first order process. Absorption may be prolonged in the upper and lower part of the intestine, resulting in several secondary and tertiary peaks of absorption. Absorption of carbamazepine may be slower following evening dose. The absorption from oral tablets estimated to be about 85 to 90%. The chewable tablets and immediate release tablets are equivalent to bioavailability and may be interchanged without a change in dose or dose interval. The bioavailability of the suspension is equal to bioavailability immediate release tablets. However, the suspension is absorbed at a faster rate. Therefore, the total dose of carbamazepine is the same using either immediate release or suspension formulation. However, to avoid wide floculation in peak to trough concentrations with possible side effects or breakthrough seizures, the formulation of sustained release has bioequivalent to the immediate release formulation but provided a more even serum concentration curve.

**Distribution**

Carbamazepine binds to albumin and $\alpha_1$-acid glycoprotein (AAG). AAG very with the presence of inflammation, concurrent antiepileptic drug therapy, and age. The amount of free or unbound drug available in the plasma and the need of drug monitoring. The free fraction of carbamazepine estimated as 25% but reports in epileptic patients have ranged from 10 to 50%. There is a small decrease in protein binding of carbamazepine in neonates, but binding rates in all other age groups are compatible. Unbound drug decreases with increasing total concentrations. Monitoring of the free fraction may be indicated when clinical presentation of patients. For example, the presence of side effects, the lack of response or does not concide with plasma concentration.

Carbamazepine cross the placenta, achieving a concentration in the fetus equal to the concentration in plasma of the mother. The concentration of carbamazepine in the saliva and tears approximates the unbound concentration.

- **Protein Binding** 76%.
- **Cerebrospinal fluid (CSF)**, the CSF/serum ratio 0.22
- **Volume of Distribution** is 0.8 to 2 L/kg

**Metabolism**

The metabolism of carbamazepine follows four pathways: oxidation, hydroxylation, direct conjugation with glucuronic acid, and sulfur conjugation. The oxidation and hydroxylation
pathways account for 65 % of metabolism of carbamazepine. The most important of carbamazepine metabolites is the 10,11-epoxide because it is felt to be active and may contribute to the efficacy and toxicity of carbamazepine. In the recent study carbamazepine was reported by 10,11-epoxide metabolites without a loss of efficacy. The metabolism of carbamazepine may be altered by other drugs and by itself. Carbamazepine is unique in that it can induce its own metabolism. The epoxide metabolite is partly responsible for carbamazepine intoxication.\textsuperscript{196}

**Metabolism Sites and Kinetics**

- It is metabolized by Liver, 98%
- Carbamazepine induced its individual metabolism during treatment and also completed in three to five weeks with a fixed dosing regimen.
- With increasing carbamazepine doses, a dosedependent autoinduction process was needed.
- Carbamazepine metabolism occurs via cytochrome P450 3A4

**Excretion**

- Mainly excreted by kidney. Renal Excretion 72%
- Total Body Clearance 3.85 L/hr
- Clearance in children was reported to be 2.37 liters/hour. Clearance increases with increasing doses. Clearance decreases with increasing age
- Patients older age having a decreased clearance by approximately 70%.

**Pharmacodynamics**

Carbamazepine acts by prevent repetitively firing of action potentials in depolarised neuron via use of voltage dependent sodium channel.

**Mechanism of action of Carbamazepine**\textsuperscript{197}

- Carbamazepine increases latency, decreases responsivity and suppress the polysynaptic pathway associated with cortical and limbic function.
- It also reduces post–tetanic potentiation
MATERIALS & METHODS

✓ It is a Na$^+$ channel blockers that slows the rate of recovery of Na$^+$ channel from the inactivated state to closed state. This has the effect of suppressing a seizure focus as well as preventing rapid spread of activity from the seizure.

**Therapeutic Endpoints.**$^{198}$

The desired therapeutic endpoint for carbamazepine is abolition of seizures. As carbamazepine is the model drug for suitable for partial seizures and also used in generalized seizures, assessments of therapeutic outcomes may require both careful patient history and EEG. Carbamazepine may control seizures as monotherapy in about 75% of patients.

**Adverse Reactions.**$^{199}$

Neurologic side effects are associated with carbamazepine. The first week of treatment such as nausea, vomiting, and anorexia, ataxia, giddiness, and serious adverse effects are jaundice, peripheral neuritis, agranulocytosis, thrombocytopenia. During long-time-taking drug may cause fluid retention and insidious development sluggishness and both mental and physical stress. Severe exfoliative forms and Steven-Johann syndrome, blood dyscrasias including bone marrow suppression and aplastic anemia.

**Drug-Drug Interaction**$^{200}$

Carbamazepine an enzyme inducer and may enhance the metabolism of many drugs under going Phase –I metabolism. Because carbamazepine is generally metabolized by the liver and metabolism may be affected by other drugs that induce or inhibit liver microsomal enzymes. A potential synergistic effect is seen with lithium when carbamazepine is used in patients with bipolar depression.

**Disease - Drug Interaction**$^{201}$

Congestive heart failure that causes gut edema may contribute to variable absorption of carbamazepine. Carbamazepine may cause sodium and water, aggravating congestive heart failure. Fever (increased metabolism) and pulmonary disease (decreased metabolism) have been associated with alterations of antiepileptic drug clearance. Protein binding may be altered postoperatively. The change in protein binding and altered metabolism were felt to be responsible for carbamazepine toxicity that followed cardiothoracic surgery and myocardial infarction. Clearance of antiepileptic drugs...
increases during the third trimester of pregnancy and the concentration of carbamazepine
should be closely monitored during this period.

**Therapeutic Regimen**

**Initial Dose**

It is preferable to begin therapy with one fourth to one third of anticipated maintenance
dose and to titrate the dose to individual patients’s response. Doses may be increased by
one fourth to one third at weekly intervals until the patient becomes seizure free or side
effects are intolerable. This allows tolerance to the central nervous system side effects to
develop and allows for anticipation of autoinduction.

**Maintenance Dose**

Because of autoinduction the serum concentration of CBZ and patient’s seizure
frequency should be monitored for at least 1 to 2 months after the achievement of a
therapeutic dose and adequate serum concentration. The usual maintenance doses are 7 to
15 mg/Kg/d for patients older than 15 years and 11 to 40 mg/Kg/d for patients less than
15 years.

**Dose Interval**

Based on the half life of carbamazepine may be dosed twice a day and many patients will
tolerate this dosing frequency. This gives higher peaks, however and in some patients this
peak may exceed the threshold for side effect. Therefore, some patients may need a three-
or four times a day dosing schedule with conventional immediate release tablets. The
suspension, which is absorbed more quickly, should be given at least three or four times a
day. The sustained release formulation of carbamazepine may be given twice a day.

**Therapeutic Range**

Carbamazepine monotherapy is mostly suitable for optimum seizure control in
patients, to occur concentration of drug levels at plasma is 4–12 mg/L. The conversion
factor from mg/L to m mol/L for carbamazepine is 4.23 while that of carbamazepine
10,11-epoxide, it is 3.96. The exact concentration that will be therapeutic for a given
patient must be individually determined. The final target concentration is a balance
between seizure control and tolerable side effect. There is poor *in vitro* correlation
between doses of drug and serum concentration.
Therapeutic Drug Monitoring

Optimum seizure control of carbamazepine monotherapy for patent is most possible to occur at plasma carbamazepine levels of 4 to 12 mg/L. The upper boundary of the reference range for carbamazepine-10,11-epoxide is 9 m mol/L. The conversion factor for carbamazepine is from mg/L to m mol/L is 4.23, while that of carbamazepine 10, 11-epoxide, it is 3.96.

Excipients profile

MICROCRYSTALLINE CELLULOSE

Nonproprietary Name:
BP: Microcrystalline cellulose
IP: Microcrystalline cellulose
PhEur: Cellulose microcristalline
USPNF: Microcrystalline cellulose

Synonyms: Avicel PH, Celex, Ethispheres, Emcocel, Pharmacel, Tabulose

Chemical Name: Cellulose

Empirical Formula: \((\text{C}_6\text{H}_{10}\text{O}_5)^n\) where \(n \approx 220\)

Structure:

![Cellulose Structure](image)

Molecular Weight: \(~36\,000\)

**MATERIALS & METHODS**

**Description:** MCC is purified and partly depolymerized cellulose that occurs as a white amorphous, odorless, tasteless powder composed of porous particles. Their different particle sizes and moisture grades are applicable to different dosage form.

**Solubility:** Somewhat soluble in 5% w/v sodium hydroxide solution & insoluble in water as well organic solvents.

**Stability and Storage Conditions:** It is a stable and hygroscopic material. The bulk material stored in a well closed container, cool and dry place.

**Incompatibilities:** It is incompatible with strong oxidizing agents.

**Applications:** It is widely used in diluent/filler in oral dosage form formulations. It is popularly used for wet and dry granulation techniques. The direct compression characteristics are excellent. It rarely used as lubricant and disintegrant properties that make for tableting. It is normally used as cosmetics as well as food industry. Mainly it varies according to the concentration as following table

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adsorbent</td>
<td>20-90</td>
</tr>
<tr>
<td>Antiadherent</td>
<td>5-20</td>
</tr>
<tr>
<td>Tablet disintegrant</td>
<td>5-15</td>
</tr>
<tr>
<td>Tablet and capsule</td>
<td>5-15</td>
</tr>
<tr>
<td>binder/diluent</td>
<td>20-90</td>
</tr>
</tbody>
</table>

**Related Substances:** Microcrystalline cellulose, carboxy methyl cellulose sodium, microcrystalline cellulose, guar gum, and powdered cellulose.

**DI CALCIUM PHOSPHATE 204**

1. **Nonproprietary Names:**
   - BP: Anhydrous Calcium hydrogen phosphate
   - JP: Dibasic Calcium phosphate Anhydrous
   - PhEur: Calcium hydrogen phosphate
   - USP: Dibasic calcium phosphate Anhydrous

2. **Synonyms**
   - A-TAB, Calcii hydrogenophosphas anhydricus, Calcium monohydrogen phosphate, Calcium orthophosphate, Dical-cium orthophosphate, Fujicalin, Phosphoric acid calcium salt.

3. **Chemical Name:** Dibasic calcium phosphate
4. **CAS Registry Number**: 7757-93-9

5. **Empirical Formula**: CaHPO₄

6. **Molecular Weight**: 136.06

7. **Functional Category**: Tablet and capsule diluent.

8. **Description**

   It is mainly a white, odorless, tasteless and crystalline solid. It occurs as triclinic crystals.

9. **Applications in Dibasic calcium phosphate**

   DCP is used as an excipient as well as source of nutritional supplements. It is excellent for water sensitive drugs, provided that the bound water is not released under any elevated storage conditions to which the product might be exposed. It is used mainly because of its the good flow properties of the coarse grade materials and compaction properties for solid dosage formulation. The major deformation mechanism of coarse grade of dibasic calcium phosphate is brittle fracture and reduces the rate of strain that helps compassion of the materials. It is an abrasive and a lubricant is necessary for tableting. It is stable and nonhygroscopic at room temperature. It doesn’t form hydrate to dihydrate. It is also used for abrasive properties toothpaste and dentifrice.

10. **Stability and Storage Conditions**

    It doesn’t form hydrate to the dehydrate due to stable and non hygroscopic material as well as high humidity. It should be stored in a dryplace as well closed container place.

11. **Incompatibilities**

    It shouldn’t be used in the formulation tetracycline. The surface of milled anhydrous dibasic calcium phosphate is alkaline & it should n’t have used with active drugs that are susceptible to alkaline pH. For the surface alkalinity or acidity between the milled and un milled grades are differentiated. When the particle size of this excipients might be expected to change. There is a difference has been important indication for drug stability, mainly when reformulating from, e.g. roller compaction to direct compression.

12. **Related Substances**:

    Calcium phosphate, Di-basic dehydrate, Calcium phosphate and Tribasic calcium sulfate.
POVIDONE

Nonproprietary Name:
  BP: Povidone
  JP: Povidone
  PhEur: Povidone
  USP: Povidone

Synonyms: Kollidon, Plasdone, Polyvinylpyrrolidone (PVP)

Chemical Name: 1-Vinyl-2-pyrrolidinone homopolymer

Empirical Formula: \((C_6H_9NO)_n\)

Chemical Structure:

![Chemical Structure](image)

Molecular Weight: 2500–3,000,000

Functional Category: Disintegranting agent, Dissolution enhancer, Suspending agent, Binder in wet granulation process.

Description: It mainly as a fine, white to creamy white, odorless powder and hygroscopic pH 3 to 7. Povidone K30 are manufactured by spray drying techniques as well as K90 are manufactured by drum drying techniques.

Solubility: Povidone is soluble in waters, acids, chloroform, ethanol (95%), methanol, ketones and insoluble in ethers, hydrocarbons, and mineral oils.

Stability and Storage Conditions: On heating at 150°C, with a reduces in aqueous solubility. The stability of povidone is nearly at 110–130°C. It may be stored without undergo either decomposition or degradation under normal conditions. The physical
characteristics of excipient is hygroscopic, so it should be stored in an airtight container in a cool & dry place.

**Incompatibilities:** It is compatible broad range of inorganic salts, natural & synthetic resins. The molecular adducts were formed in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital and tannin.

**Applications:** Povidone is mainly used in a tablet filler or diluent and coating agent in the concentration of 0.5 to 5%. It is used as a suspending and dispersing agent in the concentration of 5% in suspension.

**Related Substances:** Crospovidone.

**SODIUM STARCH GLYCOLATE**

1. **Nonproprietary Names**
   - BP: Sodium Starch Glycolate
   - PhEur: Sodium Starch Glycolate
   - USP-NF: Sodium Starch Glycolate

2. **Synonyms**
   - Carboxymethyl starch, Carboxymethyl amylopectin, Explosol, Explotab, Glycolys, Primojel, Starch carboxymethyl ether.

3. **Chemical Name:** Sodium carboxymethyl starch

4. **CAS Registry Number:** 9063-38-1

5. **Empirical Formula and Molecular Weight depends upon the Type**
   The USP32-NF27 described two types of sodium starch glycolate: Type A and Type B and a carboxymethyl ether of starch of sodium salt or a crosslinked carboxymethyl ether of starch. The PhEur described three category of material: Type A, B & C. Among these two Type A and Type B are sodium salt of a crosslinked & partly O-carboxymethylated potato starch and Type C is sodium salt of a partly O-carboxymethylated starch & crosslinked by physical dehydration. Types A, B, and C are differentiate by either their pH, sodium, sodium chloride content. It may be characterized by the degree of substitution and crosslinking.
5. Structural Formula

![Structural Formula Diagram]

**Description**

It is a white hygroscopic and free flowing powder. According to PhEur, when granules are examined under a microscope showing irregular shaped, pear-shaped / ovoid particle size having 30-100 mm, if rounded 10-35 mm in particle size and compound granules consisting of 2 to 4 components occur rarely. The granules have an eccentric hilum and concentric striations. Between crossed nicol prisms & a dissimilar black cross striations intersecting at the hilum. The granules having significant swelling in contact with water.

**8. Applications in Sodium starch glycolate**

It is widely used in oral solid dosage form as a disintegrating agent in manufacturing of tablets and capsules. Generally it is used for tablets formulations either by direct compression or wet granulation processes. The concentration range in between 2% and 8%

The principle of disintegration acts via swelling mechanism, which can swell dramatically during water uptake and thus quickly and effectively break the tablet. It may also be incorporated as both intra granular and extra granular portion. It is also applicable for suspending vehicle.

**9. Solubility:** It is insoluble in methylene chloride & gives a transparent suspension in water.

**10. Stability and Storage Conditions**

Sodium starch glycolate has good storage properties due to hygroscopic nature powder and to protected from different stability conditions like temperature and humidity, which
causes caking. The physical properties of these excipient remain unchanged for up to 3 years. If it is stored moderate at temperatures and humidity it should be stored in a well closed container.

11. Incompatibilities

It is incompatible with ascorbic acid and interact with glycopeptide antibiotic, basic drugs and to increase the photostability of norfloxacin.


HYPROMELLOSE

a) Nonproprietary Names

BP: Hypromellose
JP: Hypromellose
PhEur: Hypromellose
USP: Hypromellose

b) Synonyms

Methocel, Benecel MHPC, Hydroxy propyl methylcellulose, Hypromellosum, Pharmacoat, Methyl cellulose propylene glycol ether, Methyl hydroxypropylcellulose, Metolose, Tylopur, Tylose MO

c) Chemical Name

Cellulose hydroxypropyl methyl ether

CAS Registry Number: 9004-65-3

d) Empirical formula & Molecular weight

The PhEur describes hypromellose as a partly O-methylated and O-(2-hydroxypropylated) cellulose. The first two digits refers to methoxy group (OCH$_3$) the estimated and the second two digits referes to of the hydroxypropoxy group (OCH$_2$CH(OH)CH$_3$) calculated on a dried basis. It contains methoxy and hydroxypropoxy groups that indicates the different types of hypromellose.

Molecular weight: It is approximately 10 000–1 500 00
e) Structural Formula:

![Chemical Structure of Hypromellose](image)

Where R is H, CH₃, or CH₃CH(OH)CH₂

f) Functional Category:

Bioadhesive material, coating agent, controlled, sustained, extended and modified release agent, Dispersing agent, Dissolution modifier, Emulsifying agent, agent, Film former agent, mucoadhesive agent, Solubilizer, suspending agent for suspension, Tablet binding agent, Thickening and Viscosity modifyier agent.

g) Applications of Hypromellose

Hypromellose is widely used as formulations of oral, ophthalmic, nasal, and topical. In HPMC is rarely used as a tablet binding agent but mostly in film coating agent and as a matrix tablet for used in extended-release formulations. The concentrations of binding agent having the up to 2% to 5% w/w either wet & dry granulation processes. High-viscosity grades of HPMC of concentration 10–80% w/w used for retard the drug release from a matrix tablets and capsules.

It is also used as liquid oral dosage forms as a suspending and thickening agent at concentrations ranging from 0.25–5.0% as well as concentrations of 2 to 20% w/w are used as film-forming solutions for film-coating tablets. Higher-viscosity grades like HPMC K4 M, HPMC K100 M used as rate controlling polymer. The concentrations in between 0.45–1.0% w/w used as a thickening agent to vehicles. For the eye drops and pharmaceutical tear solutions 0.1%. is necessary liquid nasal formulations. It is used as an emulsifying, suspending and stabilizer for topical gels and ointments. It is prevented...
droplets and particles from coalescing or agglomerating. So it inhibit the formation of sedimentation. It is also formulate time release capsules and as a wetting agent for hard contact lenses. HPMC is sustainable polymer for bilayer, inlay and compressed coated tablets.

**h) Description**

It is white to creamy white, odorless, tasteless and fibrous or granular powder.

**i) Stability and Storage Conditions**

Although it is hygroscopic after drying, hence it is a highly stable material. The solutions are stable at pH 3 to 11. It undergoes a reversible sol–gel transformation upon heating and cooling. Depending upon the grade and molecular weight of material it will differ. The gelation temperature is 50–90°C. Below the gelation temperature, decreases the viscosity of the solution with increase in temperature. So gelation temperature inversely proportional to viscosity. Aqueous solutions are enzyme-resistant during long term storage condition, so these solutions are responsible for microbial spoilage and the antimicrobial preservative is necessary. When HPMC is used as a viscosity enhancer in ophthalmic solutions, benzalkonium chloride is used as the preservative. It should be stored in a well closed container, in a cool and dry place.

**J) Incompatibilities**

It is nonionic so it is incompatible with oxidizing agents and should n’t complex with metallic salts or ionic organics to form insoluble precipitates.

**l) Safety**

It is generally used as an excipient in oral, ophthalmic, nasal, and topical formulations. Even though it is a nontoxic and nonirritating material, so the excessive oral utilization having the more laxative effect. For the increase the strength of hypromellose are for treated for different of metabolic syndromes.

Hypromellose dust may be irritating to the eyes and production of excessive dust should be avoided to reduce the risks of explosion.

**m) Related Substances**

Ethylcellulose, Hydroxyethyl cellulose, Hydroxyethylmethyl cellulose, Hydroxypropy cellulose, Hypromellose acetate succinate, Hypromellose phthalate, Methylcellulose
ETHYL CELLULOSE

1. Nonproprietary Name

BP: Ethyl cellulose
PhEur: Ethylcellulose
USP-NF: Ethylcellulose

2. Synonyms
Aquacoat ECD, Aqualon, Ashacel, Ethocel, Ethyl cellulosum, Surelease.

3. Chemical Name: Cellulose ethyl ether

CAS Registry Number: 9004-57-3

4. Empirical Formula and Molecular Weight

Ethylcellulose is ethoxyl substitution (DS=3) is \( C_{12}H_{23}O_6 \) \( (C_{12}H_{22}O_5)\_n \) \( C_{12}H_{23}O_5 \) where \( n \) can vary to provide different of molecular weights. It is an ethyl ether of cellulose is a long-chain polymer of anhydrous glucose units joined together by acetal linkages.

5. Structural Formula

![Structural Formula of Ethyl Cellulose]

Functional Category
Coating agent, flavoring agent, diluents & binding agent tablets and viscosity enhancer.

Applications of Ethyl cellulose
Ethylcellulose coatings are used to modify the releasing rate of a drug and masking the unpleasant taste. It improve the stability of formulations of dosage form. Modified release matrix tablet formulated by using ethylcellulose as a polymer.

Ethylcellulose coating modified to change their solubility by the adding of hypromellose or a plasticizer. Polymer dispersion / latex with aqueous solution ethylcellulose such as aquacoat or Surelease be used to prepare ethylcellulose films, without the need for organics solvents. The ethylcellulose coated dosage forms can be controlled by diffusion mechanism. It protects the coating from fracture during compression. High viscosity grades of ethylcellulose are applicable for drug micro encapsulation and drug release from an ethylcellulose microcapsule is a utility of the microcapsule wall thickness and surface area. Ethylcellulose also suitable for as a binding agent for tablet formulation. It is also having the characteristics of tablets with low friability and poor dissolution rate. In topical formulations like in creams, lotions or gels used as a thickening agent. It used as a stabilizer for o/w or w/o type of emulsions.

**Table 2: Uses of ethylcellulose.**

<table>
<thead>
<tr>
<th>SL.No</th>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Microencapsulation</td>
<td>10.0-20.0</td>
</tr>
<tr>
<td>02</td>
<td>Sustained-release tablet coating</td>
<td>3.0-20.0</td>
</tr>
<tr>
<td>03</td>
<td>Tablet coating</td>
<td>1.0-3.0</td>
</tr>
<tr>
<td>04</td>
<td>Tablet granulation</td>
<td>1.0-3.0</td>
</tr>
</tbody>
</table>

**Stability and Storage Conditions**

Ethylcellulose is a stable and quite hygroscopic material. It is resistant chemically to acidic materials as well as alkalis like dilute, concentrated & salt solutions. Ethylcellulose is to be oxidative degradation in the presence of sunlight / UV light at elevated temperatures. Ethylcellulose prevented by antioxidant and chemical additives that absorb light 230 to 340 nm in the range. It should be stored at a temperature not exceeding 32°C, away from all heat sources. It should not be stored subsequently to peroxides or oxidizing agents.

**Incompatibilities**

Incompatible with waxes of paraffin & microcrystalline.

**COLLOIDAL SILICON DIOXIDE**

93
Nonproprietary Name:
- BP: Colloidal Anhydrous Silica
- JP: Light Anhydrous Silicic Acid
- PhEur: Silica, Colloidal Anhydrous
- USP-NF: Colloidal Silicon Dioxide

Synonyms: Aerosil, Cab-O-Sil, Colloidal silica

Chemical Name: silica

Empirical Formula: SiO₂

Molecular Weight: 60.08


Description: Colloidal silicon dioxide having amorphous powder, with silica having particle size of about 15 nm. It is a weight less, light bluish white colored, odorless and tasteless.

Solubility: It is soluble in hot solutions of alkali hydroxide and insoluble in water and organic solvents except hydrofluoric acid. The solubility of aerosil in water is 150 mg/L at 25°C at pH 7.

Stability and Storage Conditions:
It is quite hygroscopic, so adsorbs large quantities of water without liquefying. It should be stored in a tight fitting and well closed container.

Incompatibilities: Aerosil incompatible with diethylstilbestrol formulation.

Applications: Aerosil having the thixotropically control viscosity and thicken and stabilize emulsions as well as suspending agent for semisolid preparations. Due to its small particle size and large specific surface area, give it excellent flow properties the The flow properties necessary as tableting and capsule filling. It acts as both glidant & adherent depends upon the concentration as subsequently 0.1-1% and 1-2%. It is used a thickening agent for topical preparations. Recently it is used nanocapsules and nanosphere suspension to the freeze-drying. It is an adsorbent during the preparation of wax microspheres.
MAGNESIUM STEARATE

1. Nonproprietary Name:
- BP: Magnesium stearate
- IP: Magnesium stearate
- PhEur: Magnesii stearas
- USPNF: Magnesium stearate

Synonyms: Dibasic magnesium stearate, Magnesium distearate, Magnesia stearas, Magnesium octadecanoate, Octadecanoic acid,

Chemical Name: Octadecanoic acid magnesium salt

CAS Registry Number: [557-04-0]

Empirical Formula: C\textsubscript{36}H\textsubscript{70}MgO\textsubscript{4}

Structure:

\[
\begin{array}{c}
\text{C}_{36}\text{H}_{70}\text{MgO}_{4}
\end{array}
\]

Molecular Weight: 591.24

Functional Category: Solid dosage form lubricating agent

Description: It is a very light white fine powder having low bulk density as well as odour of stearic acid and. The powder is slippery to the touch and easily adheres to the skin.

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerosols</td>
<td>0.5-2.0</td>
</tr>
<tr>
<td>Emulsion stabilizer</td>
<td>1.0-5.0</td>
</tr>
<tr>
<td>Glidant</td>
<td>0.1-1.0</td>
</tr>
<tr>
<td>Suspending and thickening agent</td>
<td>2.0-10.0</td>
</tr>
</tbody>
</table>
Solubility: It is almost insoluble in ethanol, ether and water as well as slightly soluble in hot benzene and ethanol (95%).

Stability and Storage Conditions: It is stable and should be stored in a cool and dry place as well as closed container.

Incompatibilities: Incompatible with strong acids, alkalis and iron salts and to avoid mixing with strong oxidizing materials. It can’t be used in dosage form containing vitamins & alkaloidal salts.

Applications: It is generally effective of a lubricant manufacturing of in tablet and capsule having the concentration in between 0.25 % to 5.0 % w/w. It is also used as barrier creams in cosmetic.

Related Substances: Calcium stearate, Magnesium aluminum silicate, Stearic acid & Zinc Stearate.

TALC

1. Nonproprietary Names
   BP: Purified Talc
   JP: Talc
   PhEur: Talc

2. Synonyms
   Altalc, Hydrousmagnesiumcalciumsilicate, Hydrous magnesium silicate, Imperial, Luzenac Pharma, Magnesium hydrogen metasilicate, Magsil Osmanthus, Magsil Star, powdered talc, Purified french chalk, Purtalc, Soapstone, Steatite, Superiore, Talcum.

3. Chemical Name: Talc

CAS Registry Number: 14807-96-6

4. Empirical Formula and Molecular Weight
   Talc is a purified, hydrated magnesium silicate, approximating to the formula Mg₆(Si₂O₅)₄(OH)₄. It may contain small, variable amounts of aluminum silicate and Iron.

5. Functional Category:
   Anticaking agent, Glidant, Tablet and capsule diluents and lubricant
MATERIALS & METHODS

6. Description

Talc is a very fine amorphous powder. Odorless and white to grayishwhite. It adheres readily to the skin and is soft to the touch and free from grittiness.

7. Applications of Talc in Pharmaceutical Formulations:

Talc is used in oral solid dosage formulations i.e. tablets & capsules as a lubricant. More ever it is used as a retard the dissolution products. Powder coating is used for modified release pellets and an adsorbant. It is used as a dusting powder, for topical preparations and more ever it should not be used to dust surgical gloves. It is a natural material and should be sterilized when used as a dusting powder in cosmetic industry for example manufacture of body powder, compact powder and cleansing lotion.

Uses of Talc:

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dusting powder</td>
<td>90.0-99.0</td>
</tr>
<tr>
<td>Glidant and tablet lubricant</td>
<td>1.0-10.0</td>
</tr>
<tr>
<td>Tablet and capsule diluent</td>
<td>5.0-30.0</td>
</tr>
</tbody>
</table>

8. Stability and Storage Conditions

Talc is a stable product & sterilized by heating at 160°C for NLT 1hour. It sterilized by exposure to ethylene oxide or Y- irradiation. It is stored in closed container in a cool & dry place.

9. Incompatibilities

Incompatible with quaternary ammonium compounds.

10. Safety

Talc is n't absorbed systemically oral ingestion, therefore it is fundamentally nontoxic material. However, intranasal or intravenous abuse of products containing talc can cause granulomas in body tissues, particularly the lungs. Contamination of wounds or body cavities with talc may also cause granulo mass. It may causes irritation and respiratory distress in infants on inhalation of talc. However, talc contaminated with asbestos proved to
be carcinogenic in humans, and asbestos free grades should therefore be used in pharmaceutical products. Also, long-term toxic effects of talc contaminated with large quantities of hexachlorophene caused serious irreversible neurotoxicity in infants accidentally exposed to the substance.

**Related Substances**

Bentonite, Magnesium aluminum silicate, Magnesium silicate, Magnesium trisilicate.

**PREFORMULATION STUDIES**

The initial step of preformulation for the development of oral dosage for a drug substance. The goal of preformulation study is to create significant information for developing stable & bioavailable dosage forms. Preformulation studies can be broadly classified into two classes, the first one is fundamental properties & second one is derived properties. Fundamental preformulation properties are dependent on physical characteristics and the chemical structure of the drug molecule. Fundamental preformulation properties include (i) Solubility studies performed during solubility assessment include solubility in different solvents, dissociation constant (pKa), salt formation, partition or distribution coefficient (log P or log D), pH solubility profile and dissolution and rate of kinetics release (ii) permeability (iii) Solid state properties like solid structure, polymorphism, solvated forms & amorphous form and (iv) Solid state and solution state stability, pH stability data and photo stability are examined.

Derived preformulation properties for solid oral dosage form like tablet include (i) categorization of particle properties like morphology and particle size, (ii) bulk density, (iii) flow properties and (iv) compaction behavior. The derived preformulation properties are specific to the intended dosage form to be developed. Compatibility studies are performed in wherein the physical and chemical stability of the drug molecule and excipients like polymer interaction were analysed. The suitable of excipients is indicated by the type of dosage form to be developed.

Preformulation study are considered to identify those physio-chemical properties and excipients that may influence the design and suitable of techniques for formulation and resulting the pharmacokinetic, biopharmaceutical characteristics of the dosage form. Following studies
performed for in the preformulation study.

**Description** : White or almost white crystalline powder.

**Solubility**

Drug & their product of solubility of was examined by different solvents such as water, 0.1 N HCl, and different buffers such as acetate buffer, phosphate buffer 6.8, 7.2, & 7.4 and different concentration of SLS.

**a) Bulk density**

Weighed accurately 5 gm of carbamazepine drug, which were passed through 22# sieve no. and was transferred to 50 ml graduated glass cylinder. The Drug powder was carefully leveled without compaction and estimate the unsettled apparent volume (V₀). The apparent bulk density was calculated by the following formula:

\[
\text{Bulk density} = \frac{\text{Weight of the powder}}{\text{Bulk Volume}}
\]

**b) Tapped density**

Exactly weighed 5 gm of carbamazepine were passed through 22# sieve was transferred in 50 ml graduated cylinder. Then the glass cylinder containing the sample were tapped by raising the cylinder and allowed it to drop under its own weight using tapped density tester that provides a fixed drop of 14 ±2 mm at a normal rate of 300 drops per minute. The graduated cylinder was tapped for initially for 500 times and the volume was denoted as (V₁) and the frequency of tapping was repeated for 750 times, then the volume was measured as (V₂). The variation between the two tapped volumes is less than 2% then final volume (V₂) should be taken as consideration. The tapped density in gm/ml by the following formula:

\[
\text{Tapped density} = \frac{\text{Weight of the powder}}{\text{Tapped Volume}}
\]

**Angle of repose**

\[\text{Angle of repose} = \theta\]
**MATERIALS & METHODS**

It is the angle between the horizontal base of the surface and the edge of pile of powder or granules. The angle of repose was determined by glass funnel having the diameter of the orifice was 10 mm and the height funnel was 111 mm to end of orifice. The glass funnel was fixed at 4 cm above from the working surface. After the cone from which 5 g of samples were builted. The height of the sample forming the height of the cone (h) and the radius (r) of the base were measured. The angle of repose (θ) was calculated as follows:

\[ \theta = \tan^{-1} \left( \frac{h}{r} \right) \]

**Compressibility Index and Hausner Ratio**

The compressibility index influenced to bulk density, tapped density, size and shape of sample, particle size, particle surface area, moisture content, and cohesiveness of materials. The compressibility index was determined by measuring both the bulk volume and the tapped volume of a powder. The Compressibility index and Hausner ratio may be calculated using measured values for bulk density (\( \rho_{\text{bulk}} \)) and tapped density (\( \rho_{\text{tapped}} \)) as follows:

\[
\text{Compressibility Index} = \frac{\rho_{\text{tapped}} - \rho_{\text{bulk}}}{\rho_{\text{tapped}}}
\]

**Hausner Ratio** = It is ratio between tapped density to bulk density

The **Carr index** is related to the Hausner ratio, another indication of flowability, by the formula.

\[
\text{CI} = (1 - 1/H) \times 100
\]

Where CI= Carr’s Index

H= Hausner ratio
MATERIALS & METHODS

Dispersibility 117

It is the ability to flow or pour easily over a plane of any material. Dispersibility, dustiness and flood ability are interrelated terms. Weight approximately 10 g of the carbamazepine, the material is dropped en mass from a total height (610 mm) on to a tarred watch glass (diameter 102 mm) through a hollow cylinder (330 × 102 mm) placed vertically 102 mm above the watch glass. The cylinder is secured to a supported stand by 102 mm diameter support rings placed above and below the cylinder. The drop point is approximately 178 mm vertically above the cylinder. The material landing within the watch glass is weighed. Any loss of powder during the fall is the result of dispersion. The % of dispersibility is calculated using the relationship.

\[
\text{Dispersibility (\%)} = \frac{\text{Weight of powder in watch glass}}{\text{initial weight of sample}} \times 100
\]

cale of Flowability

<table>
<thead>
<tr>
<th>Flow Characteristics</th>
<th>Angle of repose ((\theta))</th>
<th>Consolidation Index (%)</th>
<th>Hausner’s Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>25-30</td>
<td>&lt;10</td>
<td>1.00-1.11</td>
</tr>
<tr>
<td>Good</td>
<td>31-35</td>
<td>11-15</td>
<td>1.12-1.18</td>
</tr>
<tr>
<td>Fair</td>
<td>36-40</td>
<td>16-20</td>
<td>1.19-1.25</td>
</tr>
<tr>
<td>Passable</td>
<td>40-45</td>
<td>21-25</td>
<td>1.26-1.34</td>
</tr>
<tr>
<td>Poor</td>
<td>46-55</td>
<td>26-31</td>
<td>1.35-1.45</td>
</tr>
<tr>
<td>Very Poor</td>
<td>55-65</td>
<td>32-37</td>
<td>1.46 -1.59</td>
</tr>
<tr>
<td>Very Very Poor</td>
<td>&gt;66</td>
<td>&gt;40</td>
<td>&gt;1.6</td>
</tr>
</tbody>
</table>

Loss on drying

Determine the amount of water and volatile matters present in a sample, when dried under specified conditions. The loss on drying of was determined (2g) of blend by using electronic moisture apparatus at 105°C. The limit of LOD is not more than 2 %.

Compatibility studies
The objective of study were to select appropriate excipients for the formulation. The interaction between drug-excipient compatibility is an significant method for optimize stable dosage form and incompatibility between drug and excipients can alter the stability and bioavailability. It is affecting its safety and efficacy of dosage form.

The screening was done by only 1mg of drug in a 50% physical mixture with the excipients to know about interaction between drug excipients. These interaction can be identify by these following DSC, XRD, FTIR.

**Formulation of Inlay Tablet:**

Both a sustained release portion and immediate release granules were prepared by different proportions of polymers by wet granulation technique.

**A. Formulation of Immediate Release granules**

Carbamazepine drugs were shifted through 60 #mesh and all excipients were by 40 # mesh. The model formulations were consist of Carbamazepine, Avicel-101, Sodium starch glycolate. Loaded the materials of into V cone blender and mix for 20 mins. The binding solutions were prepared by dissolving povidone K30 in boiled water. After addition of binder solution with drug and excipients mixed until to got granules. Then the wet granules passed 20# sieve and loaded the wet granules of into hot air oven, dry until the moisture content of granules is NMT 1.0%. The dried granules again passed through 1.5 mm screen and sifted through # 20mesh sieve. Sifted Talc, magnesium stearate by # 40 mesh, into V-blender and mixed for 3 minutes at slow speed. Immediate release granules were prepared by wet granulation technique using different concentration of disintegration agent. The **(Table 3)** showing formulation of immediate release granules.
**B. Formulation of Sustained release Core Tablets:** All ingredients except magnesium stearate and aerosil were weighed properly and mixed separately in mortar in geometric order. The carbamazepine was sifted through #60 mesh, rest of all material by 40 # mesh. The model formulations consisted of drug like carbamazepine and polymers like ethyl cellulose, HPMC K 4 M, HPMC K 100 M, DCP. Loaded the materials into V cone blender in and mix for 20 mins. The binding agents were prepared by dissolving povidone K30 in boiled water and mix with ferric oxide. After addition of binder solution with drug and excipients were mixed until to got granules. Then the wet granules passed through 20# sieve, loaded the wet granules of into hot air oven, dry until the moisture content of granules is NMT 1.0%. The dry granules are screened 1.5 mm and sifted through 20 # sieve. Lastly colloidal silicon dioxide, magnesium stearate passed through 40 # mesh and lubricants into V blender. Mixed for 3 minutes at slow speed. After SR granules prepared followed by compressed through Cadmec presscoatoa machine.（Table-4）

<table>
<thead>
<tr>
<th>SL. No</th>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>*F10</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Carbamazepine</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>200</td>
</tr>
<tr>
<td>2.</td>
<td>Di Calcium phosphate</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>3.</td>
<td>HPMC K4M</td>
<td>70</td>
<td>80</td>
<td>90</td>
<td>10</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>4.</td>
<td>HPM C100M</td>
<td>65</td>
<td>55</td>
<td>45</td>
<td>35</td>
<td>60</td>
<td>70</td>
<td>80</td>
<td>**</td>
<td>**</td>
<td>***</td>
</tr>
<tr>
<td>5.</td>
<td>Ethyl Cellulose</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>55</td>
<td>45</td>
<td>35</td>
<td>55</td>
<td>45</td>
<td>35</td>
</tr>
<tr>
<td>6.</td>
<td>Povidone K-30</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>7.</td>
<td>Aerosil</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>8.</td>
<td>Magnesium Stearate</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>375</td>
</tr>
</tbody>
</table>

**Carbamazepine Immediate Release Granules**
C. Formulation of Inlay Tablet:
The final formulation of Inlay tablet includes both SR core tablet and IR granules. Half of immediate release granules of carbamazepine is placed on lower of the die cavity and then sustained release core were putting being placed centrally over the Immediate release granules and it was compressed by using 16×32’’ round flat plain upper and lower punches. Feed frame was adjusted until optimized weight and hardness of the tablet results and Inlay tablets were formulated.

PHYSICAL EVALUATION OF TABLETS

1. Determination of Thickness
Tablet thicknesses of were measured by a vernier caliper. Randomly selected five tablets from each batch taken as consideration. The average thickness and standard deviation of tablets were calculated. Tablet thickness should be controlled within ±5% variation of a standard value.

2. Weight variation
To ensure the tablet contains the proper amount of drug by these evaluation test. Any variation in weight of tablets leads to either under or overdose of medicament. This is most important, when the drugs are potent or low dose. Twenty tablets were selected randomly from the batch and average weight was calculated. Then the percent deviation were calculated of individual weights from the average weight and then standard deviation was calculated. The weight variation for uncoated tablets as per USP are as shown in the table.

<table>
<thead>
<tr>
<th>Average weight (mg)</th>
<th>% deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>130 mg or less</td>
<td>± 10</td>
</tr>
<tr>
<td>More than 130 mg and less than 324mg</td>
<td>± 7.5</td>
</tr>
<tr>
<td>More than 324 mg</td>
<td>± 5.0</td>
</tr>
</tbody>
</table>
Improper flow of granules from hopper into the die is responsible for weight variation. The optimised amount of fines also improves the flow and maintained uniform weight of tablets. Uniformity of weight is also important in achieving consistency of tablet strength, as there is a relationship between the quantity of powder in the die and the compaction pressure required to compress it to a given thickness, which is what the tablet machine is effectively doing. If the quantity of powder in the die is reduced to a lower compaction, pressure will be applied, producing a weaker tablet. Variation in strength of tablet may in turn lead to variability in the disintegration and dissolution properties of the dosage form.

**Hardness:**

It is the force required to fracture a tablet across the diameter. This is significant test, which might influence disintegration and dissolution of tablets. It differs depending on the type & concentration of the binding agents. Monsanto hardness tester consists of a barrel containing a compressible spring held between two plungers. Then lower plunger is placed in contact with the tablet and a zero reading is taken. The upper plunger is then forced against or spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer. The limits of hardness is ± 5 kg/cm²
Friability:
Roche friabilator is used to measure the friability of tablets. The tablets are dedusted previously to testing. Ten tablets are weighed initially $W_1$ gm and placed in the plastic chamber which revolves at 25 rpm dropping the tablets a distance of six-inches having 4 minutes. The tablets are agin dusted and reweighed i.e $W_2$ gm to find out the % of loss in weight. Tablets with a unit weight equal to or less than 650 mg, take a sample of whole tablets corresponding as near as possible to 6.5 g. For tablets with a unit weight of more than 650 mg, take a sample of 10 whole tablets. If tablets cracked, cleaved, or broken after tumbling, the sample fails the test. If the results are difficult to interpret or if the weight loss is greater than the targeted value, the test should be repeated twice and the mean of the three tests determined. The standard deviation, weight loss from the three samples of not more than 1.0% is considered as acceptable. The friability of the tablet is determined by the formula given below.

\[
\text{Friability} = \frac{\text{Initial weight - Final Weight}}{\text{Initial weight}} \times 100
\]

Assay of the tablets:
These assay test are carried out initially twenty tablets were powdered and weighed. The amount of 60 mg of carbamazepine powdered drug was boiled with 25 ml of 96% ethanol for a 5 minutes. The boiling mixture was stirred in a flask with for 10 minutes and filtered through sintered glass. The flask and the filter were washed with 96% ethanol and with excess amount of 96% ethanol was added and cooled filtrate to produce 100 ml. From this 5 ml of aliquot solution was diluted to 250 ml with 96% ethanol and the the drug content of carbamazepine was calculated taking the value of A (1%, 1cm) at the $\lambda_{\text{max}}$ of
285 nm. of absorbance of the carbamazepine solution was measured using an UV spectrophotometer.

**Release Kinetic**

*In-vitro* kinetic release was evaluated to check the goodness of fit to different kinetic equations for the release tablets. Mainly the kinetic models used were zero order, first order, Higuchi and Korsmeyer-Peppas model. The goodness of fit was evaluated by coefficient of correlation values ($R^2$).

**a) Zero order of Kinetics**

It follows the system in which the drug releasing rate is independent of its concentration.

$$Q_t = Q_0 + K_0 t$$

Where $Q_t$ = Amount of drug dissolved in time ‘t’

$Q_0$ = Initial amount of drug in solution in time zero

$K_0$ = Zero order rate constant

If Zero order of drugs release kinetics is obeyed, then a plot of $Q_t$ vs time will be a straight line with a slope of $K_0$ and intercept at zero.

**b) First order Kinetics**

It describes the drug release rate is dependent on concentration.

$$\log Q_t = \log Q_0 + Kt / 2.303$$

Where $Q_t$ = Amount of drug released in time ‘t’

$Q_0$ = Initial amount of drug in solution in time zero

$K$ = First order rate constant

If the first order kinetics is satisfied, then a plot of $\log Q_0$, $Q_t$ versus time will be linear, with a slope of $Kt / 2.303$ and having intercept at $t=0$ of $\log Q_0$.

**c) Higuchi Model**

This model is used to identify the release of water and poorly soluble drugs incorporated in solid matrices. The drug particles dispersed in a uniform matrix behaving as the
diffusion media, hence the mathematical expression was obtained. To examine the dissolution from a homogeneous matrix, the relation obtained is as following

\[ f(t) = Q = K_H \times t^{1/2} \]

Where, \( K_H \) is the Higuchi model dissolution constant.

d) Korsmeyer-Peppas model.

The data obtained is to be plotted as cumulative percentage drug release versus square root of time. The drug release mechanism was observed that first 60% drug release data is to be fitted in Korsmeyer-Peppas model.

\[ \frac{M_t}{M_\infty} = k t^n \]

Where \( \frac{M_t}{M_\infty} \) is a fraction of drug released at time t, K is the release rate constant and n is release exponent. In this model, the value of n characterizes the release mechanism of drug. For the case of cylindrical tablets, \( 0.45 \leq n \) corresponds to a Fickian diffusion mechanism. Special cases identify the transport mechanism

I. \( n < 0.89 \) to non-Fickian transport,
II. \( n = 0.89 \) to Case II (relaxational) transport,
III. \( n > 0.89 \) to super case II transport.
IV. \( \frac{M_t}{M_\infty} < 0.6 \) should only be used
In-vivo study

In-vivo study was performed by different gender of rats of weighing between 18-22gms. The Institutional Animal Ethical Committee approved the experimental of protocol clearance /resolution number: VIP/IAEC/2011-12/116. of Veerayatan Institute of Pharmacy. The animals were maintained under standard conditions of temperature and relative humidity are respectively 24°C & 45-50%. The animals have been free to access the standard diet, water and housed in the polypropylene cages. All animals were kept fasting 12 hrs previous to the experiment but allowed to free access to water. Invivo test was performed by two models to evaluate the anti convulsant activity

A.Maximal Electric Shock induced Convulsion (MES)
B.Chemical Method: Pentylenetetrazole induced Convulsion (PTZ)
Maximal Electroshock Seizure (MES) Test

This model is functional for screening of drugs effective against primary and secondary generalized tonic clonic seizures.

**Procedure:** Groups of eight rats are used per dose of a drug. Electrical stimulation to corneal or ear electrodes with a stimulator that delivers constant voltage at a frequency of 50-60/sec. The electrodes are moistened with saline solution before application. The rats are stimulated with supra maximal current strength that is 2 to 5 times the threshold current strength. With uniform current stimulators, typical stimulation parameters include 150 mA in rats, 50 to 60/sec current delivered via corneal electrodes uniform voltage stimulators 750 V for 0.2 sec to the rat. The resultant seizure passes through various phases; phases of tonic limb flexion about 1.5 sec duration followed by phase of tonic limb extension lasting about 10 sec and finally followed by a variable short clonic interval which may lead to physical death in some animals.

Chemconvolants inducing generalized seizures after systematic administration, eg. pentylenetetrazol, bicuculline, picrotoxin, isoniazid, pilocarpine etc.

**Pentylenetetrazol (PTZ)**

Pentylenetetrazol is a tetrazol derivative with consistent convulsive effect in rat. It is believed to act by antagonizing the inhibitory GABAergic neuro transmission.

**Procedure**

Groups of eight rats are used per dose of a drug. 1% of solution of PTZ is administered by continuous iv. infusion at the rate of 0.3 ml/min. The rat developed the seizures in the one or more isolated jerks followed immediately by generalized clonic seizures with loss of righting reflexes, followed by maximum tonic clonic seizure after long a certain time lag. The end point of generalized clonic seizures with loss of righting reflex. Threshold is calculated as the mean dose of PTZ that induces seizures and 50 mg/kg for clonic and 90 mg/kg for maximal tonic clonic seizures.

**There are different stages of convulsion.**

1. **Flexion:** The bending movement of a joint in a limb that decreases the angle between the bones of the limb at the joint.

2. **Extensor:** A muscle that serves to extend or straighten a part of the body.
3. **Clonus**: Alternating of a series of contractions and partial relaxations of a muscle that in a few nervous diseases occurs in the form of convulsive spas involving complex groups of muscles and is believed to result from change of the normal pattern of motor neuron discharge.

4. **Stupor**: Lack of critical cognitive function and level of consciousness wherein a suffer is entirely unresponsive and only responds to base stimuli, such as pain.

(Flexion Stage of convulsion)

(Extensor)
MATERIALS & METHODS

(Clonus)

(Stupor)

(PTZ-induced convulsion)
The duration of flexion, extensor, clonus, and stupor phases were noted.

**STABILITY TESTING**

Stability is defined as the lapse of time during which the finished product retains the physical and chemical properties and it possessed at the time of manufacture. The stability of a product is expressed as the as the expiry period or shelf life.

WHO Guidelines recognized finished products for stability testing of as drug. The stability studies carried out during storage and to influence quality, safety and efficacy. For instance, in case of tablets: appearance, hardness, friability, content uniformity as well as *in vitro* drug release.

Storage condition are acceptable variations in temperature and relative humidity of storage facilities for stability studies.

Recommended storage condition:

- Shelf life for the drug product
- Quality of a drug substance or drug product

The extent to which a product retains, within specified limits and throughout its shelf-life, the same properties and characteristics that it overcome at the time of its manufacture. In general five types of stability recognized are shown in the following table.

<table>
<thead>
<tr>
<th>Type of Stability</th>
<th>Conditions for maintained throughout the shelf life of drug product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Chemical</td>
<td>Each active ingredient retains its chemical integrity and labeled potency, within the specified limits.</td>
</tr>
<tr>
<td>2. Physical</td>
<td>The original physical properties, including appearance, palatability, uniformity, dissolution, and suspend ability, are retained.</td>
</tr>
<tr>
<td>3. Microbiological</td>
<td>Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents that are present retain effectiveness within the specified limits.</td>
</tr>
<tr>
<td>4. Therapeutic</td>
<td>The therapeutic effect remains unchanged.</td>
</tr>
<tr>
<td>5. Toxicological</td>
<td>No significant increase in toxicity occurs.</td>
</tr>
</tbody>
</table>
MATERIALS & METHODS

(Drug product general Case)

<table>
<thead>
<tr>
<th>Storage temperature (0°C)</th>
<th>Relative humidity (%)</th>
<th>Minimum time period covered data at submission (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accelerated: 40±2</td>
<td>75±5 RH</td>
<td>6</td>
</tr>
<tr>
<td>Intermediate: 30±2</td>
<td>65±5 RH</td>
<td>12</td>
</tr>
<tr>
<td>Long term: 25±2</td>
<td>60±5 RH</td>
<td>12</td>
</tr>
</tbody>
</table>

(Storage in Refrigerator)

<table>
<thead>
<tr>
<th>Storage temperature (0°C)</th>
<th>Relative humidity (%)</th>
<th>Minimum time period covered data at submission (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long term: 5±3</td>
<td>40±5 RH</td>
<td>12</td>
</tr>
<tr>
<td>Accelerated: 25±2</td>
<td>60±5 RH</td>
<td>6</td>
</tr>
</tbody>
</table>