5.1. DRUG PROFILE: (55-77)

**Name:** Zolpidem tartarate

**Chemical name:** [N, N, 6 – trimethyl – 2 – (4 – methyl phenyl) imidazo [1, 2 – a] pyridine – 3 – acetamide], tartarate salt

**Chemical structure:**

![Chemical Structure](image)

**Molecular weight:** 764.9

**Category:** Sedative, Hypnotic

**Melting point:** 193-198°C

**Log P:** 3.316

**pKa:** 6.2

**Solubility:** Soluble in 0.1N HCl. Sparingly soluble in alcohol, propylene glycol and water.
Description:
The drug substance, zolpidem tartrate is a white to off-white crystalline powder. It is a non-benzodiazepine, utilized as a sedative-hypnotic in shorter-term treatment of insomnia. At higher doses than the hypnotic dose, zolpidem tartrate produces muscle relaxation and anticonvulsant effects and hence it is utilized in treatment of antipsychotics inducing parkinsonism.

Though, zolpidem tartrate has a different structure than other non-benzodiazepines it is useful for selective action. The drug has rapid absorption and peak plasma levels are achieved within three hours. Bioavailability decreases to 70% due to first pass metabolism. The most of the drug eliminated from liver and only 1% appears non-changed in urine. A minimum dose is suggested for elderly patients and those with hepatic impairment. Zolpidem tartrate has a 2 h half life, but its hypnotic impact can remains upto 6 h. Drug substance had a rapid onset of action. The possibilities of residual coming day impacts from extended or more sedation reduces due to short half life. CNS depression is not observed after administration of zolpidem tartrate. Zolpidem tartrate has received FDA approval in 1993. A supplemental NDA was filed in January 2002 by Biovail Pharmaceuticals for approval. Sustain release drug (Ambien CR™) was approved by FDA on September 2, 2005.

Pharmacokinetics:

Absorption:
It is administer orally and is immediately absorb from GIT. Peak medication impacts occur in 90 min of a single units. In single unit study, in subjects administering with 5 mg and 10 mg drug, the mean peak concentrations ($C_{\text{max}}$) were 59 (range: 29-112) and 121 (range: 58-271) ng/mL, respectively, occurs at a mean time ($T_{\text{max}}$) of 1.6h for both strengths.

Distribution:
It is about 92% bound to plasma proteins. Absorption decreases in presence of food which extends the time to reach maximum concentration, delays onset of sleep. Hence, zolpidem tartrate must be taken on empty stomach versus after meal. The apparent volume of distribution of zolpidem tartrate was 0.54L/Kg after administration of 10mg oral dose. A single dose of zolpidem tartrate is eliminated from plasma within hour. The mean elimination half-life of zolpidem tartrate for 5 mg strength and 10 mg strength was 2.6
(range: 1.4-4.4) and 2.5 (range: 1.4-3.7) hours respectively, in volunteers or patients with normal hepatic and renal function.

**Metabolism:**
Zolpidem tartarate undergoes first-pass metabolism. It produces inactive metabolites which get excreted through urine.

**Excretion:**
The elimination rate constant of 10 mg dose was 0.277 per hour. It is converted to inactive metabolites and eliminated by renal excretion i.e. in urine and faeces.

**Mechanism of action:**
The important site of action is situated within GABA-A receptor complex on alpha-subunit, which is called as benzodiazepine (BZ) or the omega receptor. At least 3 subtypes of omega receptor have been find out within CNS. Sleep studies is carried out in humans and animals which shows that drug normally maintains deep sleep (stage 3 and 4) in relation to placebo and any small changes in REM sleep which occur non-consistently. After drug dosages of >= 10mg, a decrease in the new morning recall may observe, as per the news obtained during the times of peak medication impact (i.e. 90min post-dose). As with the benzodiazepines, flumazenil, a benzodiazepine antagonist, may antagonize sedative effect of drug.

**Special precautions:**
The pharmacokinetic parameters of zolpidem tartarate by rapid release and modified release are changed with advance age and due to variation in hepatic function, but were not significantly changed in individuals with renal impairment. The mean half-life of both products increased to roughly 3h in elderly patients. The doses of zolpidem tartarate should be minimized in elderly patients who receives immediate release or extended release product. Although extended release zolpidem tartarate has not formally evaluated in individuals with hepatic impairment, dosage adjustments are also recommended for this dosage form.
**Dosage:**

It is administered in the doses of 5-6.5 mg twice a day or 10 mg once daily. It has fast onset of action after administration.

The immediate-release forms of zolpidem are Ambien, Intermezzo, Edluar, and Zolpimist, which are used to help you fall asleep.
EXCIPIENTS PROFILE

1.2. Povidone⁷⁸,⁷⁹:

Nonproprietary Names:  BP: Povidone, USP: Povidone

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

Chemical Name and CAS Registry Number:

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

Empirical Formula and Molecular Weight:  \((\text{C}_6\text{H}_9\text{NO})_n\) 2500–3 000 000

The USP mentioned povidone as a synthetic polymer consist of linear 1- vinyl-2-pyrrolidinone groups, polymers of various molecular weights data due to differing degree of polymerization.

Functional Category:

Disintegrant; suspending agent; dissolution improver; tablet binding agent.

Uses:

Povidone is widely used in pharmaceutical formulations, usually in solid forms. In tablets, povidone dispersions are utilized as binders for wet- granulating processes. Povidone is also utilized as a solubilizing agent in oral and parenteral compositions to improve dissolution of poorly soluble active substance from solid-dosage units. Povidone solutions may be utilized as coating.
Description:

Povidone occurs as a fine, white to creamy-white powder, odorless, moisture sensitive. Povidone with $K$-values equal or less than 30 are prepared by spray-warming technique and with higher $K$-value or equal to 90 are prepared by drum drying technique.

Typical Properties:

Acidity/alkalinity: $\text{pH} = 3.1 – 6.9$ (5% w/v aqueous solution).

Density (bulk): 0.29–0.38 g/cm$^3$ for Plasdone.

Density (tapped): 0.39–0.53 g/cm$^3$ for Plasdone.

Density (true): 1.179 g/cm$^3$

Flowability: 20 g/s for povidone K15; 16 g/s for povidone K29/K32.

Melting point: softs at 150°C.

Moisture content: Povidone is moisture sensitive.

Particle size distribution:

Kollidon 25/30: 90% >50 μm, 50% >100 μm, 5% >200 μm; Kollidon 90: 90% >200 μm, 95% >250 μm

Viscosity (dynamic):

Viscosity of water loving solvents based on concentration and molecular weight of substance.

Solubility:

Freely soluble in chloroform, acids, methanol, ethanol (94.9%), ketones and water; practically non-soluble in hydrocarbons, ether and mineral oil. In water, solution concentration is restricted by viscosity of resulted material.
**Stability and Storage Conditions:**

On heating at 150°C, povidone slightly get darken and reduces aqueous solubility. Aqueous solvents are prone to mold growing and adding of useful preservatives is recommended. Povidone can stored at normal situations without any degradation or decomposition. However, due to its hygroscopic nature, it may be store in air-tight container in dry or cool location.
5.3 HYPEROMELLOSE:

**Nonproprietary Names:** BP: Hypromellose, USP: Hypromellose

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

**Chemical Name and CAS Registry Number:** Cellulose hydroxy propyl methyl ether [9004-65-3]

**Empirical Formula and Molecular Weight:** Hypromellose defined in USP specifies the substitution type by using 4-digit number to non-proprietary name: e.g., hypromellose 1828. In which initial 2 digits refer to methoxy group (OCH₃). % content and second two digits refer to hydroxy propoxy group (OCH₂CH(OH)CH₃) percentage content measured on dried basis. Molecular weight is approximately 10 000–1500 000.

**Functional Category:**
Film-former; Coat forming agent; rate-maintaining material for extended release; stabilizer; suspending material; binder; viscosity-enhancing material.

**Applications:**
Hypromellose is generally utilized in oral, topical and ophthalmic dosage form. In oral dosage forms it is utilized as a tablet binding agent, and as a matrix for in modified-release dosage forms. It is recommended to use in 2% & 5% w/w as a binding solution in wet granule forming processes. To retard the drug release a high viscosity grades have been used while in aqueous coating of film lower-viscosity range excipients are used.

**Description:**
It is an odorless and tasteless, white or creamy-white granular or fibrous powder.

**Typical Properties:**
**Acidity/alkalinity:** pH = 5.6 – 7.9 for 1% w/w aqueous solution.

**Ash:** 1.6–2.9%, based on grade and viscosity.

**Auto ignition temperature:** 360°C

**Density (bulk):** 0.340 g/cm$^3$

**Density (tapped):** 0.556 g/cm$^3$

**Density (true):** 1.325 g/cm$^3$

**Specific gravity:** 1.25

**Melting point:** It become brownish at 190–199°C; chars at 224–229°C. Glass transition temperature is 169–179°C.

**Moisture content:**
It is hygroscopic in nature.

**Viscosity (dynamic):**
Aqueous solutions are less viscous than solutions prepared by using organic solvents.

**Solubility:**
Soluble in cold water, forms a viscous colloidal solution; practically non-soluble in ethanol (94.9%), chloroform and ether but soluble in mixtures of organic solvents like ethanol and DCM etc.

**Stability and Storage Conditions:**
Stable powder, hygroscopic over drying. Solutions are well stable at pH 3–11. However, aqueous solvents are susceptible to microbiological spoilage and hence preservatives are used during storage.
5.4. EUDRAGIT NE 40 D³¹-³²:

Nonproprietary Names: Polyacrylate Dispersion 40 Per Cent Ph. Eur.

Description:
Milky-white liquid of lower viscosity with faint characteristic odor. It is highly permeable polymer and is very flexible polymer. It is available in the 40% dispersion form and it already contains plasticizer, so there is no need to add plasticizer in the formulation containing Eudragit NE 40 D.

Solubility:
The aqueous dispersions are miscible with water in any ratio, the milky-white appearance being retained. When 1 part Eudragit NE 40 D is mix with five portions of organic solvent like acetone, a clear to slight cloudy, viscous solution is observed. When mix with 1 N NaOH in ratio of 1: 2, dispersion did not get dissolve and milky-white appearance is remained.

Viscosity: Max. 150 mPa. s.

pH: 5.5 - 8.6.

Uses:
The eudragit NE 40 D is mainly use in modified release formulation. It can be used in layering technique in which the active material and polymer will coat parallaly on sugar spheres at optimize speed to avoid extrusion spheronization process and to avoid drug loading process by wurster technique.
It can also be use in granulation before extrusion and spheronization process as release retarding polymer.
It is generally use for pH independent release pattern as it is neutral polymer and does not show pH dependent dissolution profile.
In is widely use in modified release formulation and eudragit recommend N series grades for modified release formulations.
Storage and handling: Protect from high temperatures (USP, General Notices). Protect from freezing. Freezing needs to be avoided because it is 40% dispersion and it will get settled during freezing leads to uneven distribution.
5.5. POLETHYLENE GLYCOL\textsuperscript{83}:

**Nonproprietary Names:** BP: Macrogols, USPNF: Polyethylene glycol

**Synonyms:**
Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; PEG; Pluriol E; polyoxyethylene glycol.

**Chemical Name and CAS Registry Number:**
\(\alpha\)-Hydro-\(\omega\)-hydroxypoly (oxy-1,2 ethanediyl) [25322-68-3]

**Empirical Formula and Molecular Weight:**
\[\text{HOCH}_2(\text{CH}_2\text{OCH}_2)_n\text{CH}_2\text{OH}\] where \(m\) shows the number of oxyethylene groups.

**Functional Category:**
Plasticizer; base of ointment; solvent; base of suppository; capsule and tablet lubricant.

**Uses:**
Polyethylene glycols (PEGs) are generally utilized in a different medicinal dosage form involving parenteral, topical, rectal, oral, and ophthalmic formulations. It is used in controlled drug delivery system as biodegradable polymeric matrices and also used in film coating. Solid grades of PEGs are used as plasticizers coating solution. Liquid grades of PEGs are useful to increase water permeability of coating solution. It is also used to avoid rupture of the coating film in microencapsulated products.

Polyethylene glycols (PEGs) are useful in controlled release drug delivery it helps to form uniform film over pellets during curing which affect the drug release pattern of active substance. Many coating material manufacturers used it as a key agent in the coating material.

**Description:**
The USP shows polyethylene glycol as additional polymer of water and ethylene oxide. PEG have different grades of from 200 to 600 are liquids; grades from 1000 and more are solids at ambient temp. Liquid grades (PEG 200–600) are colorless, clear or slight yellowish colored, viscous liquids. Having less properties odor and bitter taste. Grades of PEG six thousand have free-flowing mill materials.
Typical Properties:

**Density:**
- \(1.10–1.13 \text{ g/cm}^3\) at 25°C for liquid PEG
- \(1.14–1.20 \text{ g/cm}^3\) at 25°C for solid PEG

**Melting point:**
- 51–58°C for PEG 4000;
- 55–63°C for PEG 6000;

**Moisture content:**
They are hygroscopic in nature and hygroscopic property reduces with increase in MW. Solid grades e.g. PEG four thousand and above, are non-hygroscopic.

**Solubility:**
They are soluble in aqueous material and miscible with other PEG grades. Liquid PEG are soluble in organic solvents like alcohols, acetone, glycerin, benzenes, and glycols, while solid PEGs are soluble in acetone, DCM, ethanol (94%), and methanol.

**Stability and Storage Conditions:**
They do not support microbial growth. Ideally PEG should be store in proper-closed containers in a cool or dried place.
5.6. ISOPROPYL ALCOHOL


Synonyms: IPA; Di-methyl carbinol; 2-propanol; iso-propanol; petrohol; sec-propyl alcohol.

Chemical Name and CAS Registry Number: Propan-2-ol [67-63-0]

Empirical Formula and Molecular Weight: C\textsubscript{3}H\textsubscript{8}O

Functional Category: Disinfectant; solvent.

Uses:
IPA (propan-2-ol) is utilized in cosmetics and pharmaceuticals. It is utilized as solvent in topical compositions, tablet granulation and film coating.

Description:
It is a clear, volatile, colorless, flammable solvent with a specific odor having slightly bitter taste.

Typical Properties:

Boiling point: 82.4°C
Melting point: −88.5°C

Moisture content: 0.1–12.9% w/w for commercial grades (13% w/w relates to water azeotrope).

Solubility:
It is miscible with chloroform, benzene, ethanol (94.99%), glycerin and water. Soluble in acetone and not soluble in salty solutions. Forms an azeotrope with water, having 87.3% w/w IPA (boiling point 79.99°C).
Specific gravity: 0.787

Vapor pressure: 133.3 Pa (1 mmHg) at −26.1°C; 4.32 kPa (32.4 mmHg) at 20°C; 5.33 kPa (40 mmHg) at 23.8°C; 13.33 kPa (100 mmHg) at 39.5°C.

Viscosity (dynamic): 2.43 mPa s (2.43 cP) at 20°C

Stability and Storage Conditions:
IPA may be kept in an airtight container in a dried or cool place.
5.7. SODIUM LAURYL SULPHATE 86.87:

Nonproprietary Names : BP: Sodium lauryl sulfate
USPNF: Sodium lauryl sulfate

Synonyms : Dodecyl sodium sulfate; Elfan 240; sodium dodecyl sulfate; sodium lauryl sulfate; sodium monododecyl sulfate; sodium monolauryl sulfate; Texapon K12P.

Chemical Name and CAS Registry Number: Sulfuric acid monododecyl ester sodium salt [151-21-3]

Empirical Formula and Molecular Weight: \( C_{12}H_{25}NaO_4S \) 288.38
The USPNF 23 describes sodium lauryl sulfate as a mixing of sodium alkyl sulfates having chiefly of SLS (\( C_{12}H_{25}NaO_4S \)).

Table 3: Uses of sodium lauryl sulfate.

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anionic emulsifying agent, forms self-emulsifying bases with fatty alcohols</td>
<td>0.5–2.5</td>
</tr>
<tr>
<td>Detergent in medicated shampoos</td>
<td>≈10</td>
</tr>
<tr>
<td>Skin cleanser in topical uses</td>
<td>1</td>
</tr>
<tr>
<td>Solubilizer in concentrations more than critical micelle concentration</td>
<td>&gt;0.0025</td>
</tr>
<tr>
<td>Tablet lubricating agent</td>
<td>1.0–2.0</td>
</tr>
<tr>
<td>Wetting agent in dentrifices</td>
<td>1.0–2.0</td>
</tr>
</tbody>
</table>

It is a detergent and wetting agent efficient in both alkaline and acidic stages.

Functional Category:

Anionic surface active agent; emulsifier; detergent; skin penetrant; capsule and tablet lubricating agent; wetting material.
Applications:
It is an anionic surface active agent employed in wide range of non-parenteral pharmaceutical compositions and cosmetics.

Description:
It has white or cream colored crystal forms or powder having a smooth feel, faint odor and bitter taste.

Typical Properties:

- **Acidity / alkalinity**: pH = 7.0–9.5 (1% w/v aqueous solution)
- **Acid value**: 0
- **Antimicrobial activity**: Sodium lauryl sulfate having bacteriostatic effect against gram-positive bacteria’s but it is not effective in many gram-negative microbes.
- **Critical micelle concentration**: 8.2 mmol/L (0.23 g/L) at 20°C
- **Density**: 1.07 g/cm³ at 20°C
- **HLB value**: ≈ 40
- **Interfacial tension**: 11.8 mN/m (11.8 dynes/cm) for 0.05% w/v solution (non-specified non-aqueous solvent) at 30°C.
- **Melting point**: 203–207°C (for pure material)
- **Moisture content**: ≤5%; sodium lauryl sulfate is non-hygroscopic.
- **Solubility**: Easily soluble in water, practically insoluble in chloroform and ether.
- **Spreading coefficient**: −7.0 (0.05% w/v aqueous solution) at 30°C
- **Surface tension**: 25.2 mN/m (25.2 dynes/cm) for 0.05% w/v aqueous solution at 30°C
- **Wetting time (Draize test)**: 119 seconds (0.05% w/v aqueous solution) at 30°C
Stability and Storage Conditions:

It is stable at room storage stage. However, it undergoes hydrolysis to lauryl alcohol and sodium bisulfate under extreme conditions.

The bulky unit may be store in a well-closed container far from strong oxidizer in a cool, dried place.
5.8. SODIUM BICARBONATE:


Synonyms: Baking soda, monosodium carbonate, natrii hydrogenocarbonas, Sal de Vichy.

Chemical Name and CAS Registry Number: Carbonic acid monosodium salt [144-55-8]

Empirical Formula and Molecular Weight: NaHCO₃, 84.01.

Functional Category: Source of CO₂ in effervescent granules and tablets.

Applications: In effervescent granules or tablets, sodium bicarbonate is generally designed with tartaric and/or citric acid. Individual citric acid creates a sticky mix which is tough to granulate, while granules with tartaric acid alone looses the firmness, hence combining of citric and tartaric acid are often referred in compositions. A chemical reaction occurs, when the granules or tablets come in contact with water and carbon dioxide is evolved, and product get disintegrate. Melt granule formation in a fluidizing bed dryer has been given as single-step method for effervescent granules manufacturing which consist of citric acid (anhydrous) and sodium bi-carbonate, for subsequent compression into units. Solid units might be manufactured with sodium bicarbonate alone as acid of gastric fluid is much more to cause disintegration and effervescence. Sodium bicarbonate also utilized in tablet compositions for buffering drug materials which are weak acids, thereby improving dissolution of solid dosage form and by minimizing gastric irritation.

Description: Sodium bicarbonate observes as an odorless, white, crystalline powder with slight basic taste. The crystal structure is mono-clinic prisms.

Typical Properties:

Acidity/alkalinity:

pH = 8.3 for a newly manufactured 0.1 M aqueous solution at 25°C; basic improves on heating or agitation.
**Density (bulk):** 0.869 g/cm³  
**Density (tapped):** 1.369 g/cm³  
**Density (true):** 2.173 g/cm³  
**Freezing point depression:** 0.381°C (1% w/v solution)  
**Melting point:** 270°C (with degradation)  
**Moisture content:**
Below 80% RH, the moisture content is below 1% w/w. Above 85% RH, sodium bicarbonate instantly absorbs more quantity of water and may initiate to degrade with loss of carbon dioxide.  
**Osmolarity:** A 1.39% w/v aqueous solution is isosmotic with serum.  
**Refractive index:** $n_{D}^{20} = 1.3344$ (1% w/v aqueous solution)  

**Stability and Storage Conditions:**
When heated at 50°C, sodium bicarbonate starts to dis-associate into CO₂, sodium carbonate, and water; on heating to 250–300°C for a less time, sodium bicarbonate is totally switch into anhydrous sodium carbonate. However, procedure is both temperature and time dependent, with conversion 90% total within 75 min at 93°C. The reaction goes via surface-controlled kinetics; when sodium bicarbonate crystals are warmed for short time, very small needle-shape crystals of anhydrous sodium carbonate are prepared on sodium bicarbonate surface. Sodium bicarbonate is shows stability in dried air but get degrades smoothly in moist air and should hence be kept in a well-close container in a dried or cool place.
5.9. TALC:


Synonyms:  Altalc, hydrous magnesium silicate, hydrous magnesium calcium silicate, magnesium hydrogen metasilicate, steatite, talcum.

Chemical Name and CAS Registry Number:  Talc [14807-96-6]

Empirical Formula:  \( \text{Mg}_6(\text{Si}_2\text{O}_5)\text{OH}_4 \).

Functional Category:
Glidant; tablet and capsule lubricant; anticaking agent; capsule and tablet diluent.

Application:
Talc is popularly utilized in solid compositions as a lubricant, glidant, and diluents, though today it is less commonly utilized. However, it is widely utilized as a drug release retardant in developing of modified-release materials. It is also utilized as lubricant in a new powder coat forming for modified-release spheres and adsorbent.

In topical compositions, talc is utilized as a dusting powder, although it may not be utilized to dust surgical gloves. Talc continues to be widely used in coatings, and the ratio of talc to polymer is important in the releasing rate of a active substance from coated beads. Talc has also shown to be useful in oral disintegrating tablets as it is insensitive to tablet hardness unlike other lubricants.

Description:  Talc occurs as a very small, white to grayish-white, odorless powder. It adhering easily to the skin and is free from gritty appearance.

Typical Properties:
Acidity/alkalinity:  \( \text{pH} = 7 - 9.9 \) for a 20% w/v aqueous dispersion.
Solubility:  Practically non-soluble in dilute alkalis and acids, organic solutions and water.
Moisture content:  It absorbs water at 25°C and RH up to about 90%.
Refractive index:  \( n^{D}_{20} = 1.54-1.59 \)
Stability and Storage Conditions:
It is a stable in nature, sterilize by heating at 160°C for NLT 1 hour. It can sterilize by gamma irradiation or by exposure to ethylene oxide. It may be kept in well-closed container in a dried or cool place.
DESIGN OF MULTIPLE UNIT DRUG DELIVERY SYSTEMS

The goal of constructing multiple unit dosage system is to design a suitable composition which is having advantages over single unit formulations and avoid chances of change in active substance release pattern and approach of composition due to less units to units type variation, differ in pH of gastro – luminal membrane and population of enzyme. A commonly accepted approach is that multiple unit systems give good performance in vivo as compare to single unit delivery system, due to less irritation through the length of the intestine, have a lower transit time through the organ called colon and provide a highly reproducible release of drug to develop multiparticulates colon targeted drug release pattern in presence of selected populations of bacteria within colon and enhancing pH has been widely explored as triggering type system in order to start colon targeted release of active substance.

Multiple unit crystalline type active substance composition

A multiple unit for specific modified release pattern of a active substance consist of a drug with crystalline nature, a glyceride which have minimum one alkylate type substituent of maximum than 16 components of carbon and poloxamer, wherein minimum 69% of the active moiety is in crystalline form. The multiple units consisting drug particles which are in crystalline form mixed in the poloxamer. The poloxamer type is very uniformly reached over the glycerides and is available as a individual type phase from the glycerides.
Multiparticulates as NDDS

Incorporating available drug product into a novel type delivery of drug (NDD) can marginally enhance its output in terms of safety, effectiveness and to improve expectations of patient. In NDDS, an existing active moiety may get new source of delivery which increases its market value over extended period of life.

Intestinal Protective Drug Absorption System

Intestinal protective type absorption of drug system (IPDAS) is a multiple unit type tablet technique which has designed to improve gastric toleration ability of highly irritant or ulcer producing type drugs like the NSAIDs. It involves beads of higher density modified release which compacted in the form of tablet. The beads can be prepared by process like extrusion-spheronization technique and modified release of drug can be reach by using various polymer processes to coat the targeted pellets.

On other hand, active moiety may also coat into carrier material like sugar seeds to reflect immediate release multiple units. Modified release behavior can be achieved by the formation of modified release membrane of polymers over the immediate release multiple units. Once the IPDAS tablet is administered, it easily distributed and dispersion of sugar beads consisting the active moiety in the stomach that easily passes in the duodenum through the GI tract in a gradual or modified fashion, irrespective of the feeding stage. Release of drug substance through the multiple units results through a diffusion technique either by membrane of polymers and /or the macro-environment of the material or active moiety prepared in the extruding/Spheronizer type multiple units.

There is proper prevention of IPDAS by ways of the multiple unit potential of composition which confirms highly large distribution of irritant type active substance throughout the GI system. Naprelan®, marketed US, used IPDAS techniques.

This invention type composition of drug is a very selective modified release type composition recommended for actual and chronical pain.
Spheroidal Oral Active Substance Absorption Process

Spheroidal Oral Drug Absorption System (SODAS) is a multiple units techniques which enables the manufacturing of selective dosage forms which gives response to individual active substance. It may also show multiple tailored drug release patterns which includes rapid release of active substance follows by controlled/modified release to show rapid onset of action to be maintained for one day. Parallaly, the opposite scene may be obtained by delaying release of drug for long time.

Programmable Oral Active Substance Absorption System

Programmable oral drug absorption System (PRODAS) consist of multiple mini type tablets kept in hard or soft gelatin capsule and combines the advantages of technology of tableting within capsule. It is comfortable to include multiple number of different mini tablets, each mini tablet designed singly and positioned to release of active substance at various locations in the GI tract. Combinations may includes delayed release, immediate release pattern, and/or extended or modified release mini tablets. For high drug loading it is convenient to add mini tablets of various size ranging from 1.50 to 4.0 mm in diameter.

Diffucaps

In such multiple unit system, drug patterns are subjected to layering by active moiety over neutral beads like sugar beads, granules or crystals which are then followed by applying rate-monitoring type useful membrane. Based on individual needs, the coating components may be soluble in water, depend on pH or not dependent on pH or not water soluble based on the single requirement of compound. The targeted pellets are smaller in size approx. 1.0 mm or less than 1.0 mm in diameter. Combination release pattern can be targeted by incorporating varying active substance release pattern beads into hard or soft gelatin capsule shell. It is necessary to sort out any mixture of controlled release, immediate release and pulsatile release patterns depend on product requirement.

Process of layering of drug can be initiated from aqueous or non aqueous based solvents of drug. Eurand which has designed a composition technique which provides the active
substance release offering by diffucaps techniques which improve the soluble ability of drug which are insoluble in water in the GI tract. Scientist is using this type of process to achieve a controlled delivery which goes beyond one technique. Diffucap beads are minimum size, approx. 1.0 mm in diameter; they are encapsulated in a capsule to provide the optimum dose. Seeds of different release pattern of drug can be smoothly encapsulated in a one capsule and shows more levels of control to release parameters. Different drugs diffucaps type beads easily combined with each other to prepare very optimum unique dosage forms for different treatments.

Minitabs

The Eurand MINITABS type technique is also selective in which it provides benefits of a combination of tablet with a multiple unit drug form. Eurand MINITABS are small (2.0 mm x 2.0 mm) tablets consist of excipients which forms gel that control rate of active substance release. To control release rate more membranes to be applied. The tiny size of minitabs of Eurand explains that it may be incorporated into particular capsules as a optimum dosage units. Which result, the materials may be designed to permit multiple release patterns within only single capsule.

Minitabs of Eurand offer more active substance loading, the potential to optimize rate of release for targeted delivery system and uniformity of dosage units for highly optimize dosing. Minitab of scientist Eurand offer more active substance loading, a highest scale of release rates and optimization of such range of release. The capsule may be easily open and the material utilized as a "sprinkle" type formulating aid.

Stabilized Pellet Delivery Process

Stabilized pellet delivery system (SPDS) technique utilizes useful polymers or a various combines of selective additives and functional type polymer, like composite polymeric components for drug delivery to a optimum absorption site with the intestinal tract. The drug is added in multiple units like Eurand MINITABS or DIFFUCAPS, which get coated with pH not dependancet/ dependent polymeric type membranes to release the active substance at specific site of action. These are after encapsulated into hard or soft gelatin capsules.
SPDS technique is developed mainly for highly not stable drugs which entered a core of spheres consisting of active moiety and highly preventive outer layer(s) of polymer.

**Pelletized Delivery Process**

Pelletized type Delivery System (PDS) is a delayed or modified delivery system by utilizing spheres or beads made by spheronization/pelletization/marumerization technique or powder-layering or solution layering on placebo spheres. Release retarding ingredients are spraying over spheres by various coating system. Spheres which are coated are encapsulated into soft or hard gelatin caps. Release of active pharmaceutical excipients was done by diffusive system and connecting with bio-erodable or by osmotic procedure via the surface over layering. The system of active pharmaceutical excipients release might be pH-dependant or not depend on pH. The beads can be formulated to give first or zero order release kinetics.

**Pelletised tablet**

Pelletised tablet (Peltab®) type of system applied active substance coated with polymer or pellets of drug. They are successfully compacted into tablets. In respect to provide sustained or modified pattern of release, a polymer which is not soluble in water is used for coating discrete active substance crystals or pellets, to resist fluids action in the GI tract. This technique provides a high coating of polymer which enables compressing of the coated pellets into tablet dosage form without breakage significantly.

**Multiparticle Drug Dispersing type Shuttle**

Multiparticle active substance dispensing (Multipart®) type includes a carrying part of tablet for controlled release of pellets or spheres via the GI tract; it confirms the inte-grity and drug releasing characteristics of seeds. A proper distributing of seeds is reflected by test like disintegration of tablets carrying part within stomach. Release of active substance from the seeds is reflected by disintegrating of solid dosage form. It may be pH-dependant or not
depend on pH and may shown with osmosis or disintegration. The seeds may be designed to create zero order or first order model.

**Macrocap®**

Macrocap® type includes rapid release seeds prepared by pelletization/ extruding or spheronizing process or by powder or solution layering over placebo seeds. Polymers which controlled the release are sprayed over seeds by utilizing different coating process. The pellets which are coated are encapsulated in hard or soft gelatin capsules. Release of drug achieved by diffusion connected with bio-erosion or by process called osmosis through surface membrane. The mechanism of release pattern could be pH-dependant or not depend on pH. The seeds could be composited to prepare zero or first order model.

**Orbexa®**

Orbexa® type process is multiple unit process which provides more drug loading and is useful for materials requiring process called granulation. This type of process manufacture controlled size seeds and bulk density parameter by using process like granulation, extrusion type and spheronization technology. Orbexa process is very selective which allows for more loading of active substance than other type of mechanism, It is user friendly and flexible with sensitive type materials like enzymes.

**KV/24**

KV/24 type is a patent selective, multiple unit delivery system which en-capsulate number of drug components to reach targeted release in a pre-calculated pattern for a time period of 24-hour after administered orally. KV/24 technique is basically depend on neutral seeds coating (placebo type bead) with a active substance, then in row a spaying with single or multiple polymers to reach a desired OD pattern of release. Active substance may either be incorporated into the process of coating or combined with basic neutral core.

**Flashtab**
Flashtab type technique is a rapidly dissolve or disintegrate type of solid oral composition. It is a mixture of specific excipients with masking of taste of multiple unit active drug which get compacted in tablet dosage form. A agent which get disintegrate and swell are utilized in combining with active substances which get coated in this composition to prepared tablet which disintegrates in the oral cavity within minute. These oral dispersible tablets get dispersed before swallowing by the individual.

**InnoHerb**

This type of technology is utilized for pellet coating inside the capsule, called InnoHerb Phytogranules. The multiple unit consisting of small beads or micropellets containing which contains active substance which is herbal in nature. The particular spaying for each of the extract of plant maintain high standardised quality type extracts who confirms safety and effectiveness of semipermeable membranes, enhances the stability, nullify smell or taste and provide gastro protection and deliver modified or sustained release of active substance, availability optimum and good site specific absorption.

**Layering stages for multiparticulates dosage units**

Layering type stages include solid internal materials loading with excipients and/or drugs. Core material, situated in a suitable type vessel like a fluid bed or coating pan, can be layered based on different methods. Some methods involve solution/suspension layering over the cores containing both binding agent and drug. While some are depend on drug layering to powdered form in which loading of drug is occur by adhesion and gravity which confirmed by binder solution coated over core particles.

The layering stage is mainly flexible for manufacturing of very tiny size active substance coated beads, such multiple units are inserted into capsule shell for transport to patient. During case of round internal cores like placebo seeds, the technique of coating from suspensions/solution manufacture very uniform active substance coated beads, it maintain nearly round shape. Hence which are useful for uniform coating to achieve target weight with the objective of achieving a targeted pattern of release of drug.
Delayed release oral polypeptides

In this type, the formulation consists of an internal core. The internal core may be, for example, a pellets, granules or beads consist of starch, sugar, MCC or any other medicinally useful type of inert ingredient. A recommended internal core is a typical carbohydrate, like monosaccharide, disaccharide, or poly-saccharide, i.e., an excipient consisting of 3 or more than two sugar components. Sucrose is an example of a useful carbohydrates. In some conditions, sucrose is available in composition with concentration of 60.0-75.0%. The biologically active polypeptide like IL-11, the IL-11 layering is usually served with the stabilizing agent like phosphate buffer and tween 80, and the medicinally acceptable type binder, like povidone, HPMC or HPC. The composition may externally include single or multiple medicinal type ingredients. Such pharmaceutical ingredients involve, e.g., disintegrants, binders, plasticizers, diluents, glidant, anti-adherents, spraying and dispersing/suspending agents.

In few cases, the formula is provided as a number of sub-units which includes enteric type coating plurality, IL-11 spraying type seeds in oral solid dosage units. An enteric coating IL-11 seeds have internal core, like a seeds of carbohydrates, IL—11 layering and enteric type spraying layer. The enteric type spraying may involve, e.g., polymers which depend on pH, a plasticizer and glidant/ anti adhering material. Useful excipients like, HPMC phthalate, cellulose acetate phthalate, methacrylic acid type copolymer, poly-vinyl acetate phthalate, carboxymethyl cellulose. Ideally, an internal seal coating is available in formulation as carrier in enteric coat and IL-11 layers. The inert seal coats can be e.g. HPMC, povidone, HPC or other medicinally acceptable type solution as binder. Useful controlled release type polymers involve, e.g., methacrylate - ethacrylate amino copolymers (Eudragit RS and RL), HPMC or EC.

In few cases, the copolymer of methacrylic acid is depend on pH type anionic polymer solubilized greater than the pH 5.50. A copolymer of acid of methacrylic may be available in disperse state and composition at a 10-20% w/w concentration. A preferred methacrylic acid-copolymer to maintain pH 5.5 is Eudragit® L30D-55.
**Multiparticulate mucoadhesive formulations**

In such type of formulation, the flow of ingredients which develops gas and a multiple film-type, stacked type single moiety that having oral adhesive, drug having layer and back type membrane which controls drug movement, these individuals being situated within the polymer closure this is very resistant to juice having gastric pH but highly permeable to juice having intestinal pH. Drug substances are coated in the film-type ingredients. The technique for manufacturing of a juice having gastric pH resistant formulation, it consist of minimum one drug component in multiple unit preparation with oral adhesive characteristics, and of a blowing type individuals this in contact with solution manufactures individual gas components which closed by a juice that is pH of gastric resistant and liquid having intestinal pH -soluble type ingredients.

(a) movement of a polymeric substance in unique form to the twining board consisting bores, application of vacuum for developing polymer compacting closure;

(b) filling in the drug component and the blowing type component having formulation;

(c) super imposing a next number excipients, and by closing with application of pressure and heat closing the compartments;

(d) by punching or cutting, separating the individual devices.

**Advantages** of multiparticulates are as follows

1. Rejection of the dose dumping.
2. Faster Gastric type emptying.
3. Highlights enhanced transit time reproducibility and highest rate of dispersion in digestive system.
4. Well dispersed and very few likely to cause irritation locally.
5. Enhance comfortness of patient
7. Shows better stability.

Recently, concentration is on the designing of multiple units delivery in single unit pattern due to its useful benefits like

1. Improved Bioavailability,
2. Decrease risk of irritation locally and systemic toxicity
3. Targeted emptying of gastric portion.

This system has some limitations like,

1. Less drug loading capacity,
2. Higher requirement of ingredients,
3. Lack of processing variables,
4. More stages of technical variables,
5. Number of manufacturing stages,
6. Production cost is more,
7. Advanced technology is required,
8. Properly rain, experienced person need for development.
9. Liquid multiparticulate system suffers from chemical and physical stability issues like caking and sedimentation of multiple units or drug degradation.
10. The release pattern may very due to the coating material leaching out into the carrier vehicle and to overcome this problem reconstitutable multiparticulate system was developed.

A broad range of drug delivery opportunities are available using oral multiparticulate technology like pellets, granules, beads, spheroids and microspheres. Drug delivery by pelletization technique is most widely used technique during formulating the dosage form because we can control the release pattern by using various grades of release controlling polymer.

The drug is mostly released from multiparticulates by following mechanism.

1. Erosion –
Coating with the erodible polymers to erode smoothly with time hence releasing the active component in particle. Drug release mostly depends on the characteristics of polymer which shows the erosion and responsible for drug release. It shows zero or first order kinetics.

2. Osmosis –

Pressure of osmosis can construct within the particle to allow solution to enter. The active substance is pressure out of particle into external surface through coating. Osmotic pressure is responsible for drug release in which drug passes via more to minimum concentration via semi permeable layer.

3. Diffusion-

In contact with soluble components in Gastro intestinal tract, solution diffuses the particle internal surface. The release of active substance occurs and active solution diffuses through the external release surface. A diffusion principal shows release which depends on concentration and drug. It shows the zero order kinetics.

Modified release drug delivery\(^6,7,8\):

The design of useful delivery systems of active substance has currently become new approach for the designing of new formulations. The aim is to supply a therapeutic quantity of medicines to the targeted site of action to reach the predetermined effect and keep such effect for the overall period of treatment.

Multiple efforts have made currently in the designing of unique processes for delivery of active substance. Such processes have ability to monitor the scale of delivery of active substance, controlling the time of therapeutical process, and/or specific drug delivery to a particular site. Such type of system could provide number of below advantages:

1. Administering of a therapeutical dose at a controlled rate.
2. To maintain concentration of active substance for treatment of specific duration.
3. To maximize effectiveness to dose relationship.
4. To reduce toxic effects and dose frequency.
5. Improvement of patient compliance.

**Nomenclature to describe modified release dosage forms**:  
A multiple terms were utilized to mention the oral dose system consisting extended release characteristics; which having sustained or extended or delayed and controlled release.

A summary of main terminology which shows various controlled release dose units are described below.

1. **Modified release dosage forms (MRDF):**

   Those units which active substance release properties of timing course or/and site is selected to achieve therapeutic effectiveness which was not achieved by traditional dose system.

2. **Controlled release (CR):**

   The active substance is pass at a same interval and quantity of active substance obtained after administering is maintained with time.

3. **Delayed release:**

   The active substance is pass through body at interval different than immediate release after the administering.

4. **Extended release (ER):**

   Slowly drug release to keep plasma concentrations at therapeutic level for a longer time.

5. **Prolonged release:**
Absorption of drug for longer time period.

6. **Repeat action:**

   Shows that immediate administration of first dose followed by subsequent administration of second and third dose.

7. **Sustained release (SR):**

   Slow release of drug at a rate designed by the delivery pattern.

   Controlled release (CR) technology is continuously improving from last three decades, it provides innovative approaches to transfer drug in systemic circulation at a precalculated rate. The selection of active substance to be deliver and pharmacokinetic parameters of drug are main factors in designing of sustained release compositions. Even though a various dosage units have designed for manufacturing of orally modified release compositions, they mainly divided into 2 parts: one is single unit system and second is multiple unit system \(^{10,11}\).

**Single unit dosage forms:**

Single unit dosage units contains single units with single dose of the active substance and designed to be take at a single interval. Advantages of single unit dosage form includes easy and low cost processing, the stock of a number of ingredients and excipients for maintaining release of active substance.\(^{12}\)

**Multiple unit dosage forms:**

Such forms known as oral solid dosage forms have multiple small particles, each having particular properties. Such characteristic units show the modified release pattern of drug. Pelletization is agglomeration technique which converts fine granules or powders of active substance and ingredients into easy-flowing, small, round shape units. Pellets or round shape units are developed by agglomerating finer powders of active substance and ingredients with a solution consist of binder.
Regardless of which preparation system is utilized, spheres needs to fulfill the below needs.

1. Pellets to be close to spherical with smoother surface.
2. The size of particles of pellets or spherical units to be uniform.
3. Size of pellets should be optimum for pharmaceutical use.
4. The pellets must contain maximum possible drug substance to kept final dosage form size within selective limits.

Spheres provide a highest flexibility in developing oral dosage units. Spheres composing of number of drugs which are chemically compatible and goes to the site of action. The spheres can easily disperse in GIT and gives maximum absorption of active substance and avoid peak plasma fluctuation. 

Oral solid dosage forms releases in controlled manner are developed to deliver active substance at a targeted organ within the GI tract or to control action of drug for prolonged time period. Along pellets, the modified release of active substance can be reach by different coating materials to provide desired release and effect.

Sphericity of sphere should be uniform to coat the pellets uniformly which will impact on dissolution pattern.

**Rationale for Pelletization**:

Technique of pelletization is likely utilized technique in pharmaceutical organization. Pelletizing units offer flexible dosage units and enhance effectiveness and safety of active substances.

Such technique makes possible the formulation of round beads or round pellets having mean size diameter in scale from 0.51 to 1.80 mm. Spheres might be coated with typical functional
coat and utilized in controlled or modified drug delivery pattern which involves extended release type dosage units, controlled release type dosage units, fast release type dosage units, floating drug delivery, colon targeted drug delivery units etc.

Process of pelletization generally enhances mixing characteristics, appearance and flow characteristics by improving physical or chemical characteristics of fine powders.

Making of pellets may be explained as procedure of segregation (size-enlargement) which converts finer powder units or fine components of a bulk active substances and ingredients into very smaller, easy flowing, and minimum or maximum sphere shape units, known as pellets.

Process of granule formation is also well known as pelletization technique agglomeration process or typical spheronizing process, and the units collected are known to be granules, pellets, agglomerates or spheroids.

The general terminology like “pelletizing procedure” and like “granule forming process” are commonly used parallel and no any clear change looked among them.

Usually, if a process of size-enlarging gives segregates of a size distributes in range of 0.12 to 1.78 mm and a very high porosity (about 19.0-49.0%), the procedure may be called as “granule formation”, and the resulted agglomerates are called as “granulates”.

“Pelletizing process” can reference to as a process of size-enlarging which involves the production of agglomerates with a comparatively narrow range of size, generally with average size from 0.52 to 1.79 mm, called “spheres”. Spheres also have free flowing properties with a minimum porosity (about 10.0 %).

The term “spheronization” is very typical, generally connected with round shaped particles which prepared by a procedure called enlarging of size which involves a stage of spheronizing in which extrudes or agglomerates are rounded which tumbles on a rotating type frictional type of spheronizing plate, called as “spheres”.

Spheronization of wet mass needs to be optimize to prepare uniform spheres and to avoid pore formation on spheres. It is well known that use of lactose monohydrate in dry mix along with active material will avoid formation of pores during spheronization. Use of
microcrystalline cellulose in dry mix helps to form uniform spheres but along with microcrystalline cellulose, lactose monohydrate also used to avoid formation of pores.

A SHORT HISTORY OF PELLETS

Although various organizations have commonly utilized processes of pelletization since 20th century in order to prepare particles with defined shapes and sizes, it was in the 1950’s, to sustain release of drug for an extended time interval, that the pharmaceutical organizations created a keen interest in pelletization technology.

In 1949, pharmaceutical scientists named Smith Kline & French (SF) understood the ability of candy like beads in preparation of controlled-release dosage forms and started the designing of very small size active substance spheres or granules which may be encapsulated into capsules.

Meanwhile, lot of research was carried out to develop pelletization process and major resources were allocated towards enhancing methods that were faster, cheaper and more useful, both in respect to formulation and processing equipment. The trend is nearly to continue in the new innovation.

Also, role of spheres or pellets, especially of spheroids, in oral solid dosage form design and development has improved in recent decades.

Currently, spheres having the drug substance are taken in different form like solutions, tablets or capsule, a various number of such pharmaceutical products being available in the market. Also, pelletization technique is utilized in different industries, like agriculture (herbicides and fertilizers), mineral type processing (iron ore pelletization process), detergent and food industry.
REASONS FOR PELLETIZATION

The pharmaceutical organization has developed lot of changes in pelletizing process due to multiple units:
– improving content uniformity by preventing segregation of co-agglomerated components,
– Avoidance of dust formation, which leads to improving safety of process, as small powders may create explosions of dust and the respiring these fines may cause health issues;
– improving density of bulk and lowering volume of bulk;
– the selective weight and shape enhances appearance of product;
– due to the free-flowing properties it improves handling characteristics,
– improving tensile strength and spheres friability;
– modified release pattern of spheres due to minor area of surface to area of volumes ratio which gives an unique type shape for film coatings uses.
All these reasons can be considered as technological advantages for pelletization.

Additionally, the preparation of modified-release multiparticulates oral dosage units using granules or spheroids, designed to deliver drugs at a targeted part in the GI tract or over long time interval, which provides series of therapeutic advantages over conventional type oral dosage forms (tablets or capsules), like:
– pellets can be disperse freely throughout GI tract after administering and subsequently the absorption of drug is increased as a high portion of GI surface is included in this technique;
– drug plasma level may be minimized by using round shape particles with various release ratio; without affecting bioavailability of drug; major adverse effects are decreased
– the large distribution of round shape units in the GI tract controls localized build-up of drug, preventing the irritant effect of drugs in the gastric mucosa;
modified release multiple unit dosage units are short susceptible to dumping of dose compare to single unit dosage forms.

But pellets also present some limitations:
– often pellets or spheres can not be pressed into the tablets as they are too rigid. In such case, pellets needs to be filled into the capsules.
– the manufacturing of spheres is often an costly technique and / or requires highly specialized robust equipment.
– the manufacturing process control is tough (example. water amount to be included is very critical for the spheres quality or pellets and over wet process can observe rapidly).

Pelletization shows significant benefits over single unit system.

**Advantages of pelletization:**

1. Free dispersion of pellets in the GIT and improve absorption of drug, minimize peak plasma fluctuation and reduce major side effects.
2. Variations in rates of gastric emptying can be reduce by pellets and minimize inter and intra subject variability of plasma patterns.
3. When designed as controlled-release dosage units, spheres are minor prone to dumping of dose than a single unit, reservoir-type compositions.
4. Significant properties of flow, narrow distribution of particle size, minimum friability of dosage form and optimum packing.
5. Pellets can be compressed to form tablets and tablets will be coated to achieve the desired drug release.

**PROPERTIES OF PELLET**

1) Particle size distribution

Distribution of size of particle needs to be as minimum as possible, to confirm less change in thickness of coating; enhance blending type system if different types of blending of spheres are needed. Evaluation of sieve study using shaker is generally accepted method for calculating distribution of size of particle.
Microscopy is commonly used technique for calculating distribution of size of particle. Scanning and optical electron microscopy was utilized to identify the diameter of pellets. Patappe. W. in 2004 recommended the utilization of vernier calliper to measure pellet size.

Particle size of pellets should match with reference standard to avoid its impact on physical properties like bulk density as well as chemical properties like dissolution profile.

2) Surface area

The properties of spheres, which restricting area of surface, are importantly porosity, shapes, size and roughness of surface. There are 3 different processes of calculating the area of surface of the pellets. This will be measured from distribution of particles sizes by calculating mean diameter, as area of surface is equal or near to $\pi d^2$. However, such type of measurement did not consider for inclusions of surface part develops from different type of properties, like surface roughness, porous nature and shape, size of spheres. Hence, two techniques, i.e. adsorption of gas and permeability of air, indicate surface area calculation.

Methods of air permeability are mostly utilized for measurement of surface area, mainly to avoid batch to batch type changes. The process of resistance to the fluid flow - like air – via a plug of the compressed substance is nothing but surface area of that substance. The gas adsorption process (generally known as BET process) were prepared by Emmett, Teller and Brunauer (1937). In such process nitrogen volume which is absorbed through substance having an evacuated glassy bulb is calculated at varying pressures, it’s outcome were plotted like $P/ V (p_0 - p)$ versus $p/ p_0$ to create the parallel plot in which $V$ was gas vol. in cm$^3$ absorbed each gm of substance at a pres. $p$ and $p_0$ is the saturating type vapours pres. of liquefy NO$_2$ at the temp. of practical. A slope with intercept of plots shows figures $V_m$ and b. A specific surface (sw) of spheres is after produced by utilizing the equation: $SW = 4.35 * V_m$

3) Porosity

Porosity of pellets enhances releasing rate of active substances from spheres through impacting capillary type process of the dissolved active substance. Pellets porosity could be
calculated qualitative using electron (scan) type microscopy (SEM) and quantitative using the mercury porosity-metry. The pellets porosity may be measured quantitatively and by utilizing scanning electron and optical microscopy in combination along image.

4) Density

Pellets density may be influenced by changing in the composition and/or process, it may impact another factors, like coating, filling of capsule and blending. Bulk density of spheres may be calculated utilizing automating tapper. Density (true) shows compactness and/or extent of densification of particles. Pellets true density can be calculated using a helium pycnometer, air-comparison type pycnometer solvent dis-placement process.

5) Hardness and Friability

These parameters measurement of spheres is required due to the spheres needs to stand while shipping, handling, storing and different processes like spraying. A machine like Kaul pellet hardness checker gives comparative tensile strength values and pellets friability are measured by utilizing turbula mixer or erkewa type friabilator of tablets for a limited time period in combination with beads (glass) of specific dia. in response to create abrasiveness. Calculation of friability could be performed utilizing air stream during wurster process in fluidized bed coater.

6) Tensile strength

Pellets hardness is calculated by utilizing hardness instrument with 5000 g loading cell, the spheres are strained till failing observes. The loading is calculated and the tensile power is measured by utilizing specific figure for a failing load and radia of pellets.
Now pelletizing technique shows a constructive way for production of delivery of drug. The literature enforce on rarely utilized pelletizing process to preparing spheres for novel delivery via administration through oral route. Every technology has its own benefits and limitations. Process of layering has widely utilized over number of days for pellets preparation. Many such individuals have emphasizes there work on optimizing or refining current pelletizing process and viewed on designing of new type techniques along with processes of preparing spheres using new composition and role of instrument. This type pelletizing process may have large effect on designing different types of new type active substance transfer systems. If the tensile strength of pellets is low then it will distract during coating at high atomization air or at high fluidization blower speed.

A multiple spheres substances were developed to improve in vivo role of medications available easily and to comply regulatory needs.
ROLE OF EUDRAGIT IN MULTIPARTICULATE DRUG DELIVERY SYSTEM:

Eudragit is famous trade-mark of a Rohms GmbH & Co. KG. Darmstadt placed in Germany, initially distributed in early 1949s. It is manufactured by polymerizing process of methacrylic and acrylic acid or its ester, e.g., dimethyl amino-ethyl or butyl ester. Eudragit polymers are type of co-polymers which originated from esters of methacrylic and acrylic acid, which physico-chemical characteristics are found by functionally active parameters (R). Type of eudragit grades are present in large limits of various physical units (organic solution granules, water prone dispersion and powder mixtures).

CLASSES OF EUDRAGIT POLYMERS

1. Soluble Poly(meth)acrylates

They are highly soluble in gastric fluids by formation of salt. Examples are- Eudragit S, L, E and FS polymers. These polymers with alkaline or acidic groups allows release which depend on pH of the active pharmaceutical material.

Uses: from easy masking the taste via gastric resistance to extended or modified distribution of active substance in all parts of intestine.

2. Insoluble Poly(meth)acrylates

These are not soluble but easily permeating in digestive solution. Some of the standards are- Eudragit RS and RL grades with basic and Eudragit NE grade with more neutralize groups
permits limited interval distributing of the extended release material by pH- nondependent swelling characteristics.

**Uses:** sustained & delayed distribution of active substance.

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**EUDRAGIT POLYMERS – PHARMACEUTICAL CHARACTERISTICS**

Poly-(meth)-acrylates are well understood worldwide in the pharmaceutical organization under the trade mark called as Eudragit. Such polymers permit the active in solid type dosage form to act at the passage of a human body. The flexible ability of combination a different excipients allows to achieve an expected distribution of active substance pattern by loosing the active substance at the right location and at the targeted time and, if required, over a targeted interval of time. Other needful uses are prevention from moistures (outer influences) or odor/ masking of taste to improve compliance of patient. The range of substance portfolio gives total flexibility for site specific active substance release patterns by offering very good performance for enteric release, protective or extended-release characteristics.

**Enteric formulations**

**Gastro resistance and GI Targeting**

For protection of active substance from gastric type fluid and to improve effectiveness of drug– Eudragit L and S polymers are chosen grades of coating units. It makes possible of targeting typical sites of the intestine. Excipients of coating grade offers a wide portfolio of product of anionic types of Eudragit which get disperse at improving values of pH. More preferably, the different types may be combine to each other, which makes it easy to maintain the pH of dissolution medium, and hence to get the needed GI targeting for an active pharmaceutical materials. Site targeted drug distribution pattern in colon is necessary for local action of disorders of intestine such as ulcerative colitis, intestinal cancer or crohn’s disease. It is also needed for drug substance which are low soluble in the upside of GI tract.
More likely, the gastric-resistance of coat forming confirms an oral doses is very compliance to patient. The referred coating material is EUDRAGIT FS 30 D, which shows release in the colonic system with the below technical benefits:

Process using aqueous solution
More flexible coatings
Useful for multiple unit formation of tablet

**Protective formulations**

**Protection from moisture and Odor/Taste Masking**

The active pharmaceutical material require to protect from light or moisture to improve compliance of patient. Eudragit E grades help to coat sensitive active material and raises compliance of patient by masking odors and tastes. Even thinly type layers of eudragit can also give the targeted effect, makes it an extremely eco-friendly use.

**Sustained-release formulations**

**Time-limited drug release**

When release of active substance is required for a limited period or one would like to utilize from the advantage of multiple unit or matrixing formulations – eudragit grades may cooperate to achieve targeted release pattern. Delivery of active substance can be modified or extended through the overall GI tract to improve its impact and complies with patient. Eudragit NE and NM classes are neutrally esters dispersions which may not need adding of new plasticizer.

**Formulation process for time controlled drug release**

1. **Matrix formulation**
Eudragit keeps as a type of matrix in which the pharmaceutical ingredient is added. The structure of matrix is obtain using granulation, compression by DC process, or by melty extrude formation. Eudragit NM 30 D grade is specifically useful for typical granule formation processes in the preparation of matrixing tablet.

2. Multiparticulate formulations

Eudragit is behave as a coating unit, typically for spheres coating or particles which gets compact in tablet or filling in capsules. Such units or spheres behave as diffusional cell in the digestive tract and moves an active pharmaceutical ingredient with consistent amount per unit time (multiple dosage forms).

ADVANTAGES OF EUDRAGIT POLYMERS

**Eudragit provides remarkable advantages for enteric type coatings**

Release of active substance depend on pH
Protection of active substance which are favorable to gastric fluids
Protecting from gastric type mucosa’s from relevant substances
Improve efficiency of active substance
Better stability during storage
Colon and GI targeting

**Benefits of protective eudragit coatings**

Release of active substance depend on pH
Protection of sensible active substance
Odor and Taste masking
Avoid from moisture
Eco-friendly application
Improved dosage form passage
Very smooth and shiny surface, better color type coating
Advantages from Eudragit coat forming with sustained release

Time-bound release of drug substance.
Theoretically very customized profile of release
More compliance of patient due to less dosing number to be taken
Less cost for processing

ROLE OF EUDRAGIT IN TARGET SPECIFIC DRUG DELIVERY

Targeting the proximal colon

Eudragit and other enteric type coatings are mainly utilized to prepare formulations which is resistant to acid, and with proper release control time of drug which might be especially efficient in achieving drug release pattern in the non-descending colon. For colonic type delivery, Eudragit S and L, which are not non-ionic type co-polymers of methyl methacrylate & methacrylic acid, has used widely. These polymers are highly insoluble at minimum pH but forms salt form and disperse above pH 5.9 and 6.9, respectively. Eudragit L 100–55, a co process polymer of ethyl acrylates and acid of methacrylate, is not water insoluble it restricts the need for organic type solutions in the coating procedure.

The initial study which employes Eudragit S type coating for targeting colon utilized sulphapyridine as a marking for release of drug. Hard gelatin caps having the active substance, and barium sulphate to aid radiological type visualize formation, which were coated with the typical material and administered to six volunteers who swallows six caps. 12 hrs after administering, 4 capsules were crack in the distal illeum, 23 in the colonic site and 9 remains as such.

The similar approach were utilized with 5-amino-salicylic acid (5-ASA) but the thickness of coating of polymer was lower from 119 to 81 micron. This forms the base of the traditional type composition of 5- ASA tablet. There is at least one type report of volunteer who takes 5-
ASA and showing the transfer of overall tablets in its stools. It is due to a result of the more pH at which the Eudragit S-type coatings get dissolved.

The study of Eudragit S type coating tablets (10 mm in dia.) in 7 different volunteers utilizing gamma scintigraphy which yields some useful updates. In some cases, stasis’s at the illeocaecal port was observed. Another subjects had fast transfer over the colon, leads the typical editors to speculates whether the variation in transition meant which a pH-depend coating was not suitable meaning of drug delivery to the colonic system.

**Intestinal Drug Delivery**

Sustained release intestinal drug delivery was designed which may bypass the stomach portion and release the drug loading material for sustained time into the intestine by using eudragit polymer as a coating material.

Eudragit S & L are 2 different forms of traditionally available enteric type acrylic resin. Both of it prepare films which restricted to gastric fluid. Eudragit S & L is very soluble in intestinal fluid at pH six & seven concurrently.

Eudragit L type polymer is present as organic type solution (Isopropanol), aqueous or solid dispersions.

Eudragit S type is present only as organic type solution (Isopropanol) and material of solids. Rahman et. al. manufactured sodium para amino-salicylate type pellets which are coat with Eudragit L30 D55 by utilizing fluidizing bed processor and checked for a *in vitro* drug release pattern in pH 1.2 for first 2 hrs and after that medium is replaced towards pH of 6.8phosphate buffers. 59% w/w percent of spraying built up of the eudragit grade like L 30 D55 was manufactured highly expected outputs as compare to acidic type coating.

**Ophthalmic Drug Delivery**
A main issue being challenged in ocular type therapies is achievement of optimum quantity at main acting location. Very less bio-availability of drug substance in ocular type dose units is especially due to non-productive absorbing process, tears productivity, transit time of residence, and corneal epithelium im-permeability. Eudragit also having very proper behavior, like absence of toxicity, positive type charge and extended or modified release patterns which keep them useful for ophthalmic type use.

**Vaginal Drug Delivery**

Eudragit RS100 type vaginal suppository which contains sildenafil, and another ingredients which give useful release. Intravaginal type tablets were produced with 1:1 ratio of Eudragit E100 to lactic acid, tablets gets disintegrate in a gelly form at physico-logical pH range of 3.80-4.40. Such gels which possesses an acid keeps that may be get ableto which get diluted the more of basic available in major vaginary type infections.

**Transdermal Drug Delivery**

The mechanical characteristics of Eudragit E100 films are checked for combination effect of 2 cohesion promoters (citric or succinic acid) and a triacetin as a type of plasticizing agent. The manufactured films were individual-adhesive, elastic, transparent type and a slight yellow in color. Eudragit E100 type material were observed to shown in wrinkles-zero transparent type films with better adhesive nature to skin. Kinetics of release from transdermal type theoretical system were shown due to rapid eroding nature of hydrophilic Eudragit E100 type polymer, and 100% rapid releasing rate was found in 20 min.

Preparation of transdermal film is major challenge in pharma industry because the excipients used in preparation are very costly and it is very tough to reproduce the batch due to various external parameters. The commonly use polymer are from eudragit grades, it is also recommended to use only one grade of eudragit in formulation instead of multiple grades in single formulation because multiple grades will behave drastically different in vivo as compare to in vitro and based on in vivo results it will become difficult to understand impact of individual grade among multiple grades.

**Gene Delivery**
The series of multiple hereditary disorders may be revised by genes type delivery. To addition, much acquiring disorders like multi-genetic type diseases and those disorders which affected by viral type genes may be treating with genetic type process. Nano size particles which manufactured by mixing PLGA with a methacrylic acid copolymer (Eudragit (R) E100) may safely and efficiently pass encoding of plasmid DNA a mouse inter-leukin-10 leads to preventing of the auto-immune type diabetes’s.

Nanoparticles of anionic type are produced by Eudragit L100-55 supply a unique type area for adsorption on protein surface and a very efficient system of delivery especially at a time of high maintenance of biological proactive type confirmation is needed for efficient vaccination. Antisense oligo-deoxynucleotides are effectively passed by nano size particles produced by Eudragit RS100, L100.

**Vaccine Delivery**

Anionic type surface active agents-free polymorphic core-shell microspheres and nanospheres are produced by Eudragit L30-D55 grade. Vaccines are easily provided by various routes, like subcutaneous, intranasal or intramuscular and results are checked to immunizing with Tat type single or with Tat type passed with the adjuvant alum. The follow up shows that micro and nano spheres/Tat type compositions are very sensitive and provide very tough and deep-lasting humoral and cellular characters in mice after mucosal and/or systemic type immunization. Weighing ratio of Eudragit S-100 and Noveon had a very efficient effect on adhesive time of typical double layer films. Post-loaded plastid DNA and bata-gal type kept very stable after passed from bilayer type films (releases 61 - 79% in initial two hours each).

Buccal type immunization utilizing novel type bi-layer films (108 +/- 7-μm thickness) having plastid DNA get to very comparative antigen-targeted IgG titter to that of subcutaneous type injection of protein. All rabbits get immunizing with plastid DNA via buccal type route but no one by other like subcutaneous route with protein type antigen demonstrating splenocyte proliferation type immunization responses.