2. INTRODUCTION

2.1 INTRODUCTION TO HOT MELT GRANULATION
Melt granulation is one of the most widely applied processing techniques in the array of pharmaceutical manufacturing operations. Melt granulation process is currently applied in the pharmaceutical for the manufacture of variety of dosage forms and formulation such as immediate release and sustained release pellets, granules and tablets. Industrial application of the extrusion process dates back to 1930’s. Hot-melt extrusion is one of the most widely applied processing technologies in the plastic, rubber and food industry. Currently, more than half of all plastic products, including plastic bags, sheets and pipes are manufactured by this process. Recently melt extrusion has found its place in the array of the pharmaceutical manufacturing operations. Several research groups have evaluated this technology to achieve enhancement in dissolution rates for poorly water soluble drugs, to modify drug release and transdermal passage of the drug. Extrusion is the process of converting a raw material into a product of uniform shape and density by forcing it through a die under pressure\(^1\,^2\).

Advantages:
- Neither solvent nor water used in this process.
- Fewer processing steps needed thus time consuming drying steps eliminated.
- There are no requirements on the compressibility of active ingredients and the entire procedure simple, continuous and efficient.
- Uniform dispersion of fine particle occurs.
- Good stability at varying pH and moisture levels.
- Safe application in humans due to their non-swellable and water insoluble nature.

Disadvantages:
- Requires high energy input.
- The melt technique is that the process cannot be applied to heat-sensitive materials owing to the elevated temperatures involved.
- lower-melting-point binder risks situations where melting or softening of the binder occurs during handling and storage of the agglomerates.
• Higher-melting-point binders require high melting temperatures and can contribute to instability problems especially for heat-labile materials.

**Applications in the pharmaceutical industry:**

• In pharmaceutical industry the melt extrusion has been used for various purposes, such as
  Improving the dissolution rate and bioavailability of the drug by forming a solid dispersion or solid solution.
• Controlling or modifying the release of the drug.
• Masking the bitter taste of an active drug.

**2.1.1 Materials Used In Lipid Matrix Systems:**

Lipids are considered as an alternative to polymer in the design of sustained drug delivery systems due to their advantages such as the low melt viscosity (thus avoiding the need of organic solvents for solubilization) absence of toxic impurities such as residual monomer catalysis and initiators, potential biocompatibility and biodegradability. The various meltable binders used for the sustained drug delivery systems\(^3,4\) are mentioned in the table no. 2.1.1 and 2.1.2.

<table>
<thead>
<tr>
<th>Hydrophilic Meltable Binder</th>
<th>Typical Melting Range (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelucire 50/13</td>
<td>44 - 50</td>
</tr>
<tr>
<td>Poloxamer 188</td>
<td>50.9</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>42–53</td>
</tr>
<tr>
<td>3000</td>
<td>48–63</td>
</tr>
<tr>
<td>6000</td>
<td>49–63</td>
</tr>
<tr>
<td>8000</td>
<td>54–63</td>
</tr>
<tr>
<td>10000</td>
<td>57–64</td>
</tr>
<tr>
<td>20000</td>
<td>53–66</td>
</tr>
<tr>
<td>Stearate 6000 WL1644</td>
<td>46–58</td>
</tr>
</tbody>
</table>
Table 2.1.2: Hydrophobic Meltable Binders in the Melt Granulation Technique\(^5\).

<table>
<thead>
<tr>
<th>Hydrophobic Meltable Binder</th>
<th>Typical Melting Range (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beeswax</td>
<td>56–60</td>
</tr>
<tr>
<td>Carnauba wax</td>
<td>75–83</td>
</tr>
<tr>
<td>Cetyl palmitate</td>
<td>47–50</td>
</tr>
<tr>
<td>Glyceryl behenate</td>
<td>67–75</td>
</tr>
<tr>
<td>Glyceryl monostearate</td>
<td>47–63</td>
</tr>
<tr>
<td>Glyceryl palmitostearate</td>
<td>48–57</td>
</tr>
<tr>
<td>Glyceryl stearate</td>
<td>54–63</td>
</tr>
<tr>
<td>Hydrogenated castor oil</td>
<td>62–86</td>
</tr>
<tr>
<td>Microcrystalline wax</td>
<td>58–72</td>
</tr>
<tr>
<td>Paraffin wax</td>
<td>47–65</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>46–69</td>
</tr>
<tr>
<td>Stearicalcohol</td>
<td>56–60</td>
</tr>
</tbody>
</table>

**Melt Extrusion Technology:**

Melt extrusion technology has proven to be a suitable method for the production of controlled release reservoir systems consisting of polyethylene vinyl acetate (EVA) co-polymers. Based on this technology, two controlled release systems Implanon\(^\text{®}\) and Nuvaring\(^\text{®}\) have been developed. Manketal., reported in 1989\(^10\) and 1990\(^11\), the extrusion of a number of thermoplastic polymers to produce sustain-release pellets. A melt extrusion process for manufacturing matrix drug delivery system was reported by Sprockel and co-workers. In 1994\(^13\) Follonier and co-workers investigated hot-melt extrusion technology to produce sustained-release pellets. Diltiazem hydrochloride, a relatively stable, freely soluble drug was incorporated into polymer-based pellets for sustained-release capsules. Four polymers were considered for extrusion trials, namely ethylcellulose, cellulose acetate butyrate (CAB), polyethylene-co-vinyl acetate and polymethacrylate derivative. The plasticizers included triacetin and diethyl phthalate.
The porosity of the formulations was assessed using mercury porosimetry. The pellets produced, exhibited a smooth surface and low porosity. The in-vitro release of the drug was biphasic, with the CAB and EVAC pellets giving the lowest release rate.

In a later study, Follonier et al. examined different parameters influencing the release of diltiazem hydrochloride from hot melt extruded pellets. These parameters included polymer type, drug/polymer ratio, and pellet size. The authors incorporated various polymer excipients such as croscarmellose sodium (Ac-Di-Sol) and sodium starch glycolate (Explotab) into the formulations to vary the drug-release rate\(^1\). These pellets could be applicable for incorporation into hard gelatin capsules. With optimization techniques and formulation, it is apparent that hot-melt extrusion of these and other sustained-release pellets is a viable drug delivery technology\(^6\).

Another application of hot-melt extrusion was described by Miyagawa, Sato, and coworkers in 1996 and 1997\(^7,8\). They studied the controlled release and mechanism of release of diclofenac. These researchers utilized a twin-screw compounding extruder to prepare wax matrix granules composed of carnauba wax, the model drug, and other rate controlling agents. Their first investigation showed that a wax matrix with high mechanical strength could be obtained even at temperatures below the melting point of the wax. Dissolution release profiles of diclofenac from wax matrix granules were strongly influenced by the formulation of the granules. The rate controlling additives that were varied in the formulations included hydroxypropyl cellulose, methacrylic acid copolymer (Eudragit L-100), and sodium chloride. The authors emphasized the advantages of using twin-screw extruder for wax matrix tablets, such as low temperatures, high kneading and dispersing ability and low residence time of the material in extruder. The investigators concluded in a second study that selection of rate-controlling agents based on physicochemical properties (solubility and Swelling characteristics) had significant impact on the properties of wax matrix granules prepared by this extrusion process. Similar study was conducted by Zhang and McGinity in 2000. The objective of this study was to investigate the properties of poly vinyl acetate (PVA) as a retardant polymer and to study the drug release mechanism of theophylline from matrix tablets prepared by hot-melt extrusion. The release rate of the drug was shown to be dependent on the granule size, drug particle size, and drug loading in the tablets. As the size of hot-melt extruded theophylline/PVAc granules was increased, there was a significant decrease in the release rate of the drug. Higher drug loading in the hot-melt granules also showed higher release rates of drug\(^9\).
**Melt Agglomeration:**

Melt agglomeration is a process by which the solid fine particles are bound together into agglomerates, by agitation, kneading, and layering, in the presence of a molten binding liquid. Dry agglomerates are obtained as the molten binding liquid solidifies by cooling. Typical examples of melt agglomeration processes are melt pelletization and melt granulation. During the agglomeration process, a gradual change in the size and shape of the agglomerates would take place. It is usually not possible to clearly distinguish between granulation and pelletization. Thus granulation is considered a pelletization process when highly spherical agglomerates of narrow size distribution are produced. Conversely, an unsuccessful pelletization process may be classified as granulation.

The equipment for melt agglomeration include rotating drums or pans, fluid-bed granulators, low-shear mixers such as Z-blade and planetary mixers, and high-shear mixers. Presently, the more popular agglomeration equipment for industrial-scale production are high-shear mixers and fluid-bed granulators. In both methods, a gradual buildup of agglomerates occurs during the process. The marked difference between the methods is the absence of shearing forces in the fluid-bed process, whereas very high shearing forces are generated in high-shear mixing.

During a melt agglomeration process, the meltable binder may be added as molten liquid, or as dry powder or flakes. In the latter, the binder may be heated by hot air or by a heating jacket to above the melting point of the binder. Alternatively, the melt agglomeration process exploits an extremely high shear input, of a high-shear mixer, where the heat of friction alone raises the temperature of the binder and effects melting. Typically, the melting points of meltable binders range from 50°C to 80°C. A lower-melting-point binder risks situations where melting or softening of the binder occurs during handling and storage of the agglomerates.

In assessing the influence of meltable materials on the formative and growth processes of melt agglomerates, it is imperative to have a thorough understanding of the melt agglomeration process. The mechanism of melt agglomeration is similar to that of wet agglomeration.
Modes of melt agglomeration:

[Fig 2.1.1: Modes of melt agglomeration: (a) Distribution and (b) Immersion]

These are based on the elementary mechanisms have been proposed—distribution and immersion. In agglomeration by the distribution mode, a distribution of molten binding liquid on the surfaces of primary particles will occur, and agglomerates are formed via coalescence between the wetted nuclei (Fig. 2.1.1). In agglomeration by the immersion mode, nuclei are formed by immersion of the primary particles onto the surface of a droplet of molten binding liquid (Fig. 2.1.1). The distribution of molten binding liquid to surfaces of nuclei has to be effected by densification prior to coalescence between the nuclei. Depending on the relative size between the solid particles and the molten binding liquid droplets, the distribution will be a dominant mode when the molten binding liquid droplets are smaller than the solid particles or of a similar size. On the other hand, the immersion mode will dominate when the molten binding liquid droplets are larger than the solid particles. The distribution mode is promoted by a low molten binding liquid viscosity. In the case of immersion, it is more favorable for molten binding liquid of high viscosity, which could resist breakup by dispersive forces.
2.1.2 Techniques for Melt Granulation:

Spray Congealing:

Spray congealing is a melt technique of high versatility. In addition to manufacture multiparticulate delivery system, it can be applied to process the raw meltable materials into particles of defined size and viscosity values for the melt agglomeration process. Processing of meltable materials by spray congealing involves spraying a hot melt of wax, fatty acid, or glyceride into an air chamber below the melting point of the meltable materials or at cryogenic temperature. Spray-congealed particles (10–3000 µm in diameter) are obtained upon cooling. The congealed particles are strong and nonporous as there is an absence of solvent evaporation. Ideally, the meltable materials should have defined melting points or narrow melting ranges. Viscosity modifier, either meltable or non-meltable at the processing temperature, may be incorporated into the meltable matrix to change the consistency of the molten droplets\textsuperscript{11,12}.

Tumbling Melt Granulation:

A newer melt agglomeration technique, i.e., tumbling melt granulation, for preparing spherical beads has been reported. A powdered mixture of meltable and non-meltable materials is fed onto the seeds in a fluid-bed granulator. The mixture adheres onto the seeds with the binding forces of a melting solid to form the spherical beads. In preparing the spherical beads, both viscosity and particle size of the meltable materials should be kept at an optimum value. The particle size of a meltable material should be 1/6 or lower than the diameter of the seeds. High-viscosity meltable materials should not be employed to avoid agglomeration of seeds and producing beads of low sphericity.

Both particle size and viscosity of the meltable materials play a significant role in the melt agglomeration process. The control of the melt agglomeration process is best initiated by using meltable materials of controlled properties. For the melt pelletization and melt granulation processes, it is desirable that meltable materials have a high viscosity to improve the mechanical strength of the agglomerates, but a reduced particle size to prevent uncontrollable agglomerate growth. In tumbling melt granulation, small meltable particles with sufficient viscous binding forces are obligatory for the production of spherical beads\textsuperscript{13-19}.
[Fig 2.1.2: Process of Tumbling Melt Granulation]

**Conclusions:**

Today melt extrusion technology represents an efficient pathway for manufacture of drug delivery systems. Resulting products are mainly found among semi-solid and solid preparations. The potential of the technology is reflected in the wide scope of different dosage forms including oral dosage forms, implants, bioadhesive ophthalmic inserts, topical films, and effervescent tablets. In addition, the physical state of the drug in an extrudate can be modified with help of process engineering and the use of various polymers. The drug can be present in crystalline form for sustain release applications or dissolved in a polymer to improve dissolution of poorly water-soluble drugs. The possible use of a broad selection of polymers starting from high molecular weight polymers to low molecular weight polymers and various plasticizers has opened a wide field of numerous combinations for formulation research.

Drawbacks of the technology are often related to high energy input mainly related to shear forces and temperature. This is where process engineering becomes significant. The design of screw assemblies and extruder dies are two major areas, which have significant impact on product quality and degradation of drug and polymers. Drugs which are sensitive to elevated temperatures can be processed successfully when the residence time is short compared to conventional processes like sterilization. Work in this field is increasing and the literature published reveals many novel and interesting aspects of this technology such as in-situ salt formation, fast dispersing systems with foam like structures, complex formation in the melt, and nanoparticles released from molecular dispersions manufactured by melt extrusion.

Extrusion process has gained world wide attention because it is a simple and fast processing technology for mixing and designing moldable materials. This process is
well known in the polymer and food industry and is now being used for pharmaceutical manufacture due to its financially viable and environmental advantages and the prospect to create novel new formulations. The most relevant technologies for the manufacture of solid dispersions are melting of excipients or fusion method, embedding of drug by means of spray drying, co-evaporation, coprecipitation, freeze-drying, and roll-mixing or co-milling. In 1974, Sekiguchi and Obi were first to report the melting or fusion method as a new field of pharmaceutical technique and its principles role in increasing dissolution, absorption and therapeutic efficacy of the drug. The bioavailability of an orally administered drug mainly depends on its solubility and permeability. Due to introduction of high throughput screening in the drug discovery process the resultant compounds are often high molecular weight and highly lipophilic hence exhibits poor solubility. Also the controlled and sustained release of drug application within the pharmaceutical industry require consistent smooth surface with a narrow size distribution, to ensure uniform coating and accurate free flow of granules for filling operations like capsule filling, and all this can be achieved by melt extrusion technique. The main objective of the extrusion is to produce pellets of uniform size with high drug loading capacity. Extrusion is a multiple process of wet mass extrusion to produce uniform size spherical particles, called as spheroids, pellets, beads or matrix pellets depending upon the material as well as processed for extrusion. Extrusion has been used in various industries like agrochemicals, detergent additives, sweeteners, food and more recently in pharmaceuticals. The process is useful when uniform spherical shape, uniform size, good flow properties, reproducibility in packing, high strength, low friability and smooth surface of granules is desired. The pellets or beads produced by the extrusion offer several advantages over conventional drug delivery system. Like; it produces spheroids with high loading capacity of active ingredient without producing extensively large particles. In pharmaceutical industry the melt extrusion has been used for various applications like,

- Improving the dissolution rate and bioavailability of the drug by forming a solid dispersion or solid solution.
- Controlling or modifying the release of the drug.
- Masking the bitter taste of an active drug.

It produces particles of uniform size with narrow size distribution and good flow properties. Successful coating is applied to spheroid because of its spherical shape and
low surface area to volume ratio. Pellets composed of different drugs can be blended and formulated in single unit dosage form that facilitates delivery of two or more chemically compatible or incompatible drug at the same or different site in GI tract. Pellets are frequently used in controlled release delivery system as it facilitates free dispersion of spheroids in the GI tract and offer flexibility for further modification. It improves the safety and efficiency of active ingredient. It helps to increase bioavailability of drugs by controlling or modifying the release rate of drugs. HME offers several benefits over the traditional formulation which makes it more attractive with respect to commercialization and ease of operations.\(^{39-42}\)

**Advantages**

- Small equipment
- Economic continuous process and scale up flexibility
- Solvent-free manufacture
- High mixing efficiency
- Closed process unit to prevent cross contamination
- Short processing time
- Easily controlled process parameters
- Possibility of online analytics for process control

**Disadvantages**

- Thermal process (drug/polymer stability)
- Flow properties of the polymer are essential to processing
- Limited number of available polymers
- Requires high energy input\(^{43-47}\)
- The melt technique is that the process cannot be applied to heatsensitive materials owing to the elevated temperatures involved This process is anhydrous thus avoids any potential drug degradation from hydrolysis following the addition of aq. or alcoholic granulating media. During hot-melt extrusion, a matrix is formed due to the polymer melt acting as a thermal binder. In addition, poorly compactible materials can be incorporated into tablets produced by cutting an extruded rod thus eliminating any potential tableting problems seen in traditional compressed dosage forms.
2.1.3 The HME process (HME)

HME has been widely used technique in plastic processing industries and now it is used in pharmaceutical industries for developing formulation of sustained release 48-50 controlled release and transdermal as well as transmucosal drug delivery system. Polymer, API, equipment selection, excipients and processing conditions all play important roles in the success of a HME formulation. Most of the compounds used in the production of hot-melt extruded pharmaceuticals have been used in the production of other solid dosage forms such as tablets, pellets, and transdermal film. FDA guidance also facilitates the introduction of new technologies like HME to the pharmaceutical industry for the enhancement and modernization of formulation process using HME to improve the efficiency and effectiveness of manufacturing process design, control and quality assurance 51. While doing HME for developing formulation ingredient like polymer, release modifying agents, bulking agents and processing agents are required with the help of which can be a the single- and twin-screw extruders.52,53 Simple single screw arrangements consist of only a single rotating screw inside a stationary extruder barrel, whereas more advanced machines involve twin-screw systems utilizing either a co-rotating or counter-rotating screw configuration. It is common for the extrusion screw to be characterized by the length/diameter (L/D) ratio, which typically ranges from 20 to 40:1. Typical pilot plant extruders have diameters ranging 18–30 mm, whereas production machines are much larger with diameters typically exceeding 50 mm. Irrespective of the complexity of the machine, the extruder must be capable of rotating the screw(s) at a selected speed while compensating for the torque generated from the material being extruded. Single-screw extrusion is the simplest form of polymer processing mainly used to increase pressure within a polymer melt, allowing extrusion through a die or injection into a mould. Although a relatively simple process, single screw extrusion does not possess the mixing capability of a twin-screw machine and is, therefore, not the preferred approach for the production of pharmaceutical formulations. While twin-screw extrusion offers a rapid, continuous process with much efficient mixing capability than single screw extrusion 54. Also, twin screw extrusion provides a more stable melting process, shorter residence times and significantly greater output. As an initial evaluation, the thermal, chemical, and physical properties of the drug and other ingredient must be characterized before and after processing. Depending on the
physical and chemical properties of the drug substance (API) and the other ingredient in the formulation, the drug may be present as undissolved particles, a solid solution, or a combination in the final dosage form. An extruder for HME process consists of a platform that supports a drive system, an extrusion barrel; a rotating screw arranged on a screw shaft and an extrusion die for defining product shape. Typically, process parameters are controlled via connection to a central electronic control unit. In hot melt extrusion process, extrusion channel is conventionally divided into three sections that are feed zone, transition zone, and metering zone. The monitor and controlling parameter in HME are barrel temperature, feed rate, screw speed, motor load and melt pressure. Extruder consist of two rotating screw inside a stationary cylindrical barrel. And an endplate die connected to the end of barrel determines the shape and size of extruded products. The function of the feeding section is to transfer the solid material forward into the melting section where it gradually melts as it enters the melting section. Initially, melting results from the heat transferred to the barrel from the heating devices. The geometric design of the metering section is an important factor in determining output rate of the extruder. The materials used in the production of hot-melt extruded dosage forms must meet the same levels of purity and safety as those used in traditional dosage forms and should maintain the same properties before and after the process. The state of the drug in the dosage form may have a severe impact on the heat hence cooling device is provided at the outer side of barrel. The molten mass is continuously pumped through the metering section with homogeneous mixing and passed through the die in a variety of shape and size. The thermal stability of each individual compound and the composite mixture should be sufficient to withstand the processing environments. The selection of an appropriate carrier compound is important in the formulation and design of a hot-melt extruded dosage form as the properties of the ingredient material often decide the processing conditions necessary for the production of the dosage unit, and the physical and chemical properties of the ingredient often modulate the release of the active compound from the final dosage form. To produce granules or tablets via hot-melt extrusion, a pharmaceutical grade polymer must be selected that can be processed at a relatively low temperature because of the thermal sensitivity of most drugs. HME is continuous process as it does not require a lengthy drying stage since it does not involve addition of water or other solvent. The absence of water may prevent drug
degradation as many drugs are unstable in presence of water. It produces a spherical shape pellets with narrow range particle size distribution. Reduce the loss of coating material during the coating process associated with wet mass extrusion process. It is a convenient technology for preparation of solid dispersion and solid solution for delivery of poorly soluble drug as it offers an advantage of solvent free formulation of solid dispersion. It helps to mask the bitter taste of the active ingredient. Poorly compatible materials can be incorporated into tablets produced by cutting an extruded rod.

**Formulation development by HME**

The selection of an appropriate carrier compound is important in the formulation and design of a hot-melt extruded dosage form. Depending on the physical and chemical properties of the drug substance and the other excipients in the formulation, the drug may be present as undissolved particles, a solid solution, or a combination in the final dosage form. The state of the drug in the dosage form may have a profound impact on the processability and stability of the product. The thermal stability of each individual compound and the composite mixture should be sufficient to withstand the production process. The properties of the carrier material often dictate the processing conditions necessary for the production of the dosage unit, and the physical and chemical properties of the carrier often modulate the release of the active compound from the final dosage form. To produce granules or tablets via hot-melt extrusion, a pharmaceutical grade polymer must be selected that can be processed at a relatively low temperature because of the thermal sensitivity of most drugs. The selection of polymer for hot-melt extrusion process mainly depends on drug–polymer miscibility, polymer stability and function of final dosage form. A variety of carrier systems have been studied or used in hot-melt extrusion dosage forms.

Many commercially available, pharmaceutical-grade polymers like synthetic cellulose derivatives (ethyl cellulose, hypromellose, hydroxypropylmethyl cellulose, cellulose acetate butyrate), methacrylates, polyethylene oxides, polyvinylacetate, poly(lactide–co-glycolide), starch, lipids and waxes (possibly in combination with a plasticizer to optimize the thermoplastic properties of the polymer) etc. are known for drug delivery and also used in HME formulations. Hot-melt extruded dosage forms are complex mixtures of active drug and functional excipients like matrix carriers, release modifying agents, bulking agents, and various additives. The excipients can impart
specific properties to melt extruded pharmaceuticals in manner similar to those in traditional dosage form. Initially projected as significant disadvantages of HME process like residence time within the extruder and high processing temperatures to melt the polymeric carrier were resolved by modification of screw configuration, coupled with the use of plasticizing agents and the introduction of twin screw extruders, removed such concerns. Typical plasticizing agents for HME include PEGs, triacetin, citrate esters and citric acid. Typically, conventional plasticizer such as triacetin or polyethylene glycol is used in concentration range of 5-30% weight of the extrudate that lowers the processing temperature. Carbon dioxide can act as temporary plasticizer. During extrusion carbon dioxide is transformed in gaseous phase. As a consequence carbon dioxide escapes from extrudate and does not appear in final product. In some of the cases API have been reported as effective plasticizers which occupy sites along the polymer chain, reduce polymer–polymer chain secondary bonding and provide more mobility for the macromolecules, resulting in a softer, more easily deformable mass thus improving process ability. Various studies have been conducted using this technique to produce sustained release pellets of Diltiazem hydrochloride using polymers such as ethyl cellulose, cellulose acetate butyrate, poly ethylene co vinyl acetate.

**Table 2.1.3: various drug and Excipients used in HME process**

<table>
<thead>
<tr>
<th>Excipients used</th>
<th>Drug used</th>
<th>Reference no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG 6000, PVP or vinylpyrrolidine-vinylacetate-copolymer</td>
<td>17β Estradiol hemihydrate (17β E2)</td>
<td>27</td>
</tr>
<tr>
<td>Hydroxypropylmethylcellulose</td>
<td>Itraconazole</td>
<td>28</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose and poly(ethylene oxide)</td>
<td>Clotrimazole</td>
<td>29</td>
</tr>
<tr>
<td>Polyethylene oxide</td>
<td>Chlorpheniramine maleate</td>
<td>30</td>
</tr>
<tr>
<td>Etilcellulose, Polyethylene glycol and polyethylene oxide</td>
<td>Metoprolol tartrate</td>
<td>31</td>
</tr>
<tr>
<td>Polysorbate 80, sodium lauryl sulfate, citric acid and malic acid</td>
<td>Itraconazole</td>
<td>32</td>
</tr>
<tr>
<td>Etil cellulose</td>
<td>Ibuprofen</td>
<td>33</td>
</tr>
<tr>
<td>Polyethylene oxide and hydroxy propyrcellulose</td>
<td>Tetrahydrocannabinol (THC)</td>
<td>34</td>
</tr>
</tbody>
</table>
Table 2.1.4: Properties of polymer used in HME process

<table>
<thead>
<tr>
<th>Polymers</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly(ethylene oxide)</td>
<td>Is a white hydrophilic powder with 100,000-7,000,000 Da M.W. used for controlled-release, solid-dose matrix systems, transdermal delivery systems, and mucosal bioadhesive. It has a broad processing window with melting point $\sim 70^\circ C$, and does not exhibit weight loss until $\sim 350^\circ C$, e.g. Polyoxs WSR.</td>
</tr>
<tr>
<td>Ethylcellulose</td>
<td>Is a hydrophobic ethyl ether of cellulose used for encapsulation of API, controlled-release systems, taste masking, solvent and extrusion granulation, tablet binding, and for coating for tablets and beads. EC is available in various molecular weights, and has a $T_g$ of 129-133 $^\circ C$ and a melting point $\sim 180^\circ C$, e.g. Ethocel®.</td>
</tr>
<tr>
<td>Hypermellose</td>
<td>It is hydrophilic cellulose ether that is available in a range of viscosities and substitutions and used for controlled-release matrices, tablet coatings, and granulation binders. HM exhibits a narrow processing window because of a high $T_g$ of 160-210 $^\circ C$.</td>
</tr>
<tr>
<td>poly (ethylene-co-vinyl acetate)</td>
<td>poly (ethylene-co-vinyl acetate) (EVA) is a polar copolymer with low processing temperature. Their properties depend mainly on ratio of ethylene to vinyl acetate. Thus, VA content is an important parameter of the copolymer, and needs to be known before the material is put into use. its $T_g$ is $\sim 36^\circ C$, Evisol®.</td>
</tr>
<tr>
<td>cellulose acetate butyrate (CAB)</td>
<td>The functional properties of CAB depend upon its degree of substitution as well as the distribution pattern of the two ester substituent groups on the (1→4)-d-glucopyranosyl residues of the polysaccharide. CAB is a water insoluble polymer, $T_g$ of 125-127 $^\circ C$.</td>
</tr>
</tbody>
</table>

The resulting pellets exhibited smooth surface, low porosity and showed slow drug release. Utilization of a ram extruder in the preparation of fast release dosage form with uniform shape and density, containing carbamazepine as poorly soluble model drug and PEG 4000 as a hydrophilic carrier and low melting binder, revealed that the extruded mixture of equal composition exhibited more rapid release than simple physical mixture. Controlled release theophylline pellets were prepared by hot melt extrusion method using eudragit, microcrystalline cellulose and polyethylene glycol 8000 powder. The evaluation studies showed that pellet follows diffusion controlled drug release which is influenced by polymer swelling and pH dependent dissolution. Sustained release matrix tablets of chlorpheniramine maleate were prepared by hot melt extrusion method using polyethylene oxide as drug carrier, the evaluation studies revealed that drug release was controlled by erosion of matrix and the diffusion of drug took place through swollen gel layer at surface of the tablet.

2.1.4 CONCLUSION

Today melt extrusion technology represents an efficient pathway for manufacture of drug delivery systems. Incorporation of a drug in a polymer matrix is often used to sustain drug release. To produce these sustained-release matrices, HME is becoming a widely-used technology in the pharmaceutical industry. Its major advantage over conventional techniques for manufacturing of sustained-release matrices is the continuity of the hot stage extrusion technique as the different process steps like...
mixing, melting, homogenizing and shaping can be carried out on a single machine. This offers many opportunities for automation of the production process, allows a high throughput, limits material loss and yields matrices with excellent homogeneity. In addition, the physical state of the drug in an extrudate can be modified with help of process engineering and the use of various polymers. The drug can be present in crystalline form for sustain release applications or dissolved in a polymer to improve dissolution of poorly water-soluble drugs. The possible use of a broad selection of polymers starting from high molecular weight polymers to low molecular weight polymers and various plasticizers has opened a wide field of numerous combinations for formulation research. The design of screw assemblies and extruder dies are two the major areas, which have significant impact on product quality and degradation of API due to mechanical, thermal and oxidativedergradation associated with the high energy input mainly required for the to shear forces and temperature. Work in this field is increasing and the literature published reveals many novel aspects to overcome issues related with HME technology.

REFERENCES:


20. Patel PS, Mundargi RC, Ramesh Babu V, Jain D, Rangaswamy V, Aminabhavi TM. Microencapsulation of doxycycline into


35. FDA Guidance for Industry — Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach, September 2004;.


38. NewYork: Marcel Dekker, Inc.; 2003;.


60. Follonier N, Doelker E, Cole ET. Evaluation of hot-melt extrusion as a new technique for the production of polymer-based pellets for sustained release.


2.2 INTRODUCTION OF DRUG DELIVERY

2.2.1 Concept of Sustained Release

Dr. Paul Ehrlich’s ‘magic bullet’ concept though realized late, offers a logical solution to the age-old problem of unrelated and unwanted effects of therapeutic agents and optimizing the drug therapy in its true sense. Although sustained/controlled drug delivery can be considered as the progenitor of magic bullet concept in practice, The term sustained/controlled has been used with the widest possible meaning. Probably the earliest work in the area of sustained drug delivery dosage forms can be traced to the 1938 patent of Israel Lipowski. This work involved coated pallets for prolonged release of drug and was presumably forerunner to the development of the coated particle approach to sustained drug delivery that introduced in the early 1950s.

Ideally, a drug should arrive rapidly at the site of action (receptor) in the optimum concentration, remain for the desired time, be excluded from other sites, and be rapidly removed from the site when indicated i.e. the basic goal of the therapy is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. Generally, the time course of a dosage form (pharmacokinetics) in man is considered to be controlled by the chemical structure of the drug. Decreasing the rate of absorption and/or changing the dosage form provide a useful adjunct. When it is feasible or desirable to modify the drug compound on a molecular level, often sought is a product that will require less frequent administration to obtain the required biologic activity time profile; for example, a tablet that has the same clinical effect when administered every twelve hours. In another instance, it may be desirable to decrease the absorption rate in order to obtain a more acceptable clinical response. Tablets are one of the most stable and commonly administered oral dosage forms. Since the later part of nineteen-century, tablets have been widespread and their popularity continues. Tablets remain popular as dosage form because of the advantages afforded both to the pharmaceutical manufacturers and patients. These includes: simplicity and economy of preparation, stable and convenient in packing, ease of transporting and dispensing, accuracy of single dosage regimen, compactness and portability, and blandness of taste and ease of administration. The goal in designing sustained or controlled delivery systems is to reduce frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required, providing uniform drug delivery. If one were to imagine the ideal
drug delivery system, two prerequisites would be required. First, it would be a single
dose for duration of treatment, whether it is for days of weeks, as with infection, or
for lifetime of the patient, as in hypertension or diabetes. Second, it should deliver the
drug directly to the site of action, thereby minimizing or eliminating side effects. This
may necessitate delivery to specific receptors or to localization to cells or to specific
areas of the body. Oral ingestion has long been the most convenient and commonly
employed route of drug delivery. Indeed, for sustained release systems, oral route of
administration has received most of the attention with respect to research on
physiological and drug constraints as well as design and testing of products. This is
because of the fact that there is more feasibility in dosage form design for oral route
than for parenteral or any other route. The design of oral sustained release delivery
systems is subject to several intercalated variables of considerable importance.
Among these are the types of delivery systems, the disease being treated, the patient
and the length of therapy and the properties of the drug. In conventional drug therapy,
it can be seen from the Figure 2.2.1 that the administration of drug by either
intravenous injection or an extra vascular route e.g. orally, intramuscularly, or rectally
does not maintain drug blood level within the therapeutic range for an extended
period of time. The short action is due to the inability of conventional dosage forms to
control temporal delivery.  

![Drug blood level vs. time profile for intravenous injections and extra vascular route of administration](image)

[Figure 2.2.1 Drug blood level vs. time profile for intravenous injections and extra vascular route of administration]
Conventional dosage forms are associated with many disadvantages such as -

- Poor patient compliance; increased changes of missing the dose a drug with short half life for which frequent administration is necessary.
- A typical peak-valley plasma concentration-time profile is obtained which makes Attainment of steady state condition difficult.
- The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the steady state concentration values fall or rise beyond the therapeutic range.
- The fluctuation in drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index whenever overmedication occurs.

2.2.2 Modified-release drug delivery systems

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of modified release drug delivery systems. The modified-release delivery systems may be divided conveniently into four categories.4, 5-9

1. Delayed release
2. Sustained release
3. Site-specific targeting
4. Receptor targeting

(1) Delayed release system

Delayed-release systems are those that use repetitive, intermittent dosing of a drug from one or more immediate-release units incorporated into a single dosage form.

Examples:

Delayed-release systems include repeat-action tablets and capsules, and enteric-coated tablets where timed release is achieved by a barrier coating.
[Figure 2.2.2 Typical drug blood level time profiles for delayed release drug delivery by repeat action dosage form\textsuperscript{10}]

(2) Sustained release system
Sustained-release systems include any drug-delivery system that achieves slow release of drug over an extended period of time. If the systems can provide some control, whether this is of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells, it is considered a controlled-release system.

(3) Controlled Release system
If the system is successful at maintaining constant drug level in the blood or target tissues, it is considered as a controlled release system. Drug delivery systems from which therapeutic agents may be automatically delivered at predefined rates over a long period of time are called as controlled drug delivery systems.

(4) Prolonged Release system
If without maintaining constant level, the duration of action is extended over that achieved by conventional delivery; it is considered as a prolonged release system. This is illustrated in Fig. 2.2.3.
Figure 2.2.3 Drug blood level time profile showing the relationship between controlled release-(a), prolonged release-(b), and conventional release-(c)  

(5) Site-specific targeting
Site-specific and receptor targeting refer to targeting of a drug directly to a certain biological location. In the case of site-specific release, the target is adjacent to or in the diseased organ or tissue.

(6) Receptor targeting
For receptor release, the target is the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug-delivery systems.

2.2.3 Sustained Release Drug Delivery Systems
During the past few years, conventional dosage forms of drugs are rapidly being replaced by the new and the novel drug delivery systems. Amongst, these the controlled release/sustained release dosage forms have become extremely popular in modern therapeutics. The basic rationale for sustained release drug delivery is to alter the pharmacokinetics and pharmacodynamics of drugs by using novel drug delivery systems or by modifying the molecular structure or physiological parameters inherent in a selected route of administration. It is desirable that the duration of drug action becomes more a design property of a rate controlled dosage form and less or not at all a property of the drug molecule’s inherent kinetic properties. Thus, optimal design of a sustained/ controlled release system necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drug. When the drug is administered
in a conventional dosage form, it results in a fluctuation of drug concentration at the site of action (peak and valley pattern) and therefore in systemic circulation and tissue compartment. Figure 2.2.4 shows the difference between the conventional and sustained release dosage forms.

Figure 2.2.4 Plasma drug concentration vs. time profile: (A) Conventional delivery with multiple dosing (B) Sustained delivery

Sustained release drug administration means not only prolongation of duration of drug Delivery, similarly to the action in the sustained and prolonged release, but the term also implies the predictability and reproducibility of drug release kinetics. The controlled release of drug substances and their effective transport to sites of action can be exploited to maximize the beneficial clinical response and to minimize the incidence of unbenevolent adverse reactions and side effects.
Advantages of sustained release drug delivery

Following are the potential advantages of sustained release products

- Decrease incidence and/or intensity of adverse effects and toxicity.
- Predictable and reproducible release rates for extended duration.
- Maintenance of optimum therapeutic drug concentration in the blood with minimum fluctuations.
- Delivery of drug in the vicinity of site of action.
- More efficient utilization of active agent.
- Improved patient compliance.
- Elimination of frequent dosing and wastage of drug, inconvenience of nighttime administration of drug.
- A greater selectivity of pharmacological activity.
- Reduction in GI irritation and other dose-related side effects.
- Enhanced bioavailability.
- Reduction of the incidences and degree of toxic and side effects and irritation of gastro intestinal tract caused by some orally administrated drugs.
- Greater effectiveness in treatment of chronic conditions.
- Enhanced duration of activity for short half-life drugs.

Disadvantages of sustained release drug delivery

The disadvantages of sustained release drug delivery system are

- Toxicity due to dose dumping.
- Increased cost.
- Unpredictable and often poor in vitro- in vivo correlation.
- Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).
- Local irritation or damage of epithelial lining (lodging of dosage forms).
- Need for additional patient education and counseling.
- Increased potential for first- pass clearance $^{10,11}$
2.2.4 Classification of oral sustained/controlled release systems

[1]. Diffusion controlled Systems

(a) Reservoir devices
A core of drug (reservoir) surrounded by a polymeric membrane characterizes them. The nature of the membrane determines the rate of drug release. The characteristics of reservoir diffusion systems are
1. Zero order drug release is possible.
2. The release rate is dependent on the type of polymer.
3. High molecular weight compounds are difficult to deliver through the device.

(b) Matrix devices
It consists of drug dispersed homogenously in a matrix. The characteristics of matrix diffusion systems are
1. Zero order release cannot be obtained.
2. Easy to produce than reservoir devices.
3. High molecular weight compounds are delivered through the device.

[2]. Dissolution controlled systems

(a) Matrix dissolution controlled systems
Aqueous dispersions, congealing, spherical agglomeration, etc. can be used.

(b) Encapsulation dissolution controlled systems
Particles, seeds, granules can be coated by techniques such as microencapsulation.

(c) Diffusion and dissolution controlled systems
In a bioerodible matrix, the drug is homogenously dispersed in a matrix and it is released either by swelling controlled mechanism or by hydrolysis or by enzymatic attack. 12-14

2.2.5 Sustained Release Matrix Tablets
One of the least complicated approaches to the manufacture of sustained release dosage forms is the direct compression of drug, release retardant, and additives to form a tablet in which drug is embedded in a matrix core of retardant. Alternatively drug retardant blend may be granulated prior to compression. Such tablets are called as matrix tablets. Three classes of release retarding materials are used for the formulation of matrix tablets. 15-23

Insoluble inert polymers have been used as basis for many marketed formulations. Tablets prepared from these materials are egested intact and not break apart in GI tract. The rate-limiting step in controlling the release of drug from these formulations is
liquid penetration into the matrix unless channeling agents are included in the formulation to promote permeation of water into the matrix. This allows drugs dissolution and diffusion from the channel created in the matrix. In these tablets, drug bioavailability is dependent on polymer-ratio. The bioavailability may be modified by addition of diluents such as lactose. These forms of matrix tablets are not useful if dose of drug is high or if the drug is insoluble in water. Waxes, lipids and related materials form matrices that control the release through both pore diffusion and erosion. Release characteristics are more sensitive to digestive fluid composition than the tablets preparation by insoluble material. Total release of drug from the wax-lipid matrices is not possible, since a certain fraction of the dose is coated with impermeable wax films. For dispersion of drug with the base, three methods are used, which include the fusion technique. In absence of additives, the drug release is non-linear from these systems. Additives like polyvinyl pyrrolidone or polyoxyethylene lauryl esters can lead to apparent zero-order release. The third group of matrix formers represents nondigestible materials, which form gels in situ. The release of drug from these systems is controlled by penetration of water through a gel layer produced by hydration of polymer and diffusion of drug through the swollen, hydrated matrix, in addition to the erosion of gelled layer. The extent to which the erosion or diffusion controls the release depends on polymer selected as well as on the drug-polymer ratio used in the formulation. High drug polymer ratios results in formulations from which drug release is controlled attrition.

Matrix Tablets release the drug in continuous manner. These release the drug by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non-swellable hydrophobic materials or plastic materials.

2.2.5 Classification of Matrix Tablets

A. On the Basis of Retardant Material Used: Matrix tablets can be divided in to five types.

1. **Hydrophobic Matrix (Plastic matrix):** The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Sustained release is
produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles.\(^{30-39}\)

Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

2. **Lipid Matrix:** These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

3. **Hydrophilic Matrix:** The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients, is of particular interest in the field of controlled release. Infect a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems.\(^{40-41}\)

The polymers used in the preparation of hydrophilic matrices are divided into three broad groups

1. Cellulose derivatives: methylcellulose 400 and 4000 cPs; hydroxyethylcellulose; hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000 cPs; and sodium carboxymethylcellulose.
2. Noncellulose natural or semisynthetic polymers: agar-agar; carob gum; alginates; molasses; polysaccharides of mannose and galactose; chitosan and modified starches.
3. Polymers of acrylic acid; corbopol 934, the most used variety.

In this type of controlled drug delivery system, the drug reservoir results from the homogeneous dispersion of the drug particles in either a lipophilic or a hydrophilic polymer matrix.
Zone 1: Undissolved drug, glassy polymer layer.
Zone 2: Undissolved drug, gel layer.
Gel layer thickness = Difference between erosion and swelling front position.
A hydrophilic matrix, controlled release system is a dynamic one involving polymer wetting, polymer hydration, gel formation, swelling, and polymer dissolution. At the same time, other soluble excipients or drugs will also wet, dissolve, and diffuse out of the matrix while insoluble materials will be held in place until the surrounding polymer/Excipients/drug complex erodes or dissolves away. The mechanisms by which drug release is controlled in matrix tablets are dependent on many variables. The main principle is that the water-soluble polymer, present throughout the tablet, hydrates on the outer tablet surface to form a gel layer.
4. Biodegradable Matrix: These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage
in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by nonenzymetic process in to olegomers and monomers that can be metabolised or excreted.

Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

5. Mineral Matrix: These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaeophyceae) by the use of dilute alkali.

B. On the Basis of Porosity of Matrix Matrix system can also be classified according to their porosity and consequently, macroporous; microporous and non-porous systems can be identified:

1. Macroporous Systems: In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusant molecule size.

2. Microporous System: Diffusion in this type of system occurs essentially through pores. For microporous systems, pore size ranges between 50 – 200 Å, which is slightly larger than diffusant molecules size.

3. Non-porous System: Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.\(^{40-45}\)

➢ Advantages of Matrix Tablets
  - Easy to manufacture
  - Versatile, effective and low cost
  - Can be made to release high molecular weight compounds

➢ Disadvantages of the matrix systems:
  - The remaining matrix must be removed after the drug has been released.
  - The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.
Polymers used in Matrix Tablets

- **Hydrogels**
  - Polyhydroxyethyl methacrylate (PHEMA)
  - Cross-linked polyvinyl alcohol (PVA)
  - Cross-linked polyvinyl pyrrolidone (PVP)
  - Polyethylene oxide (PEO)
  - Polyacrylamide (PA)

- **Soluble polymers**
  - Polyethylene glycol (PEG)
  - Polyvinyl alcohol (PVA)
  - Polyvinyl pyrrolidone (PVP)
  - Hydroxypropyl methyl cellulose (HPMC)

- **Biodegradable polymers**
  - Polylactic acid (PLA)
  - Polyglycolic acid (PGA)
  - Polycaprolactone (PCL)
  - Polyanhydrides Polyorthoesters

- **Nonbiodegradable polymers**
  - Polyethylene vinyl acetate (PVA)
  - Polydimethyl siloxane (PDS)
  - Polyether urethane (PEU)
  - Polyvinyl chloride (PVC)
  - Cellulose acetate (CA)
  - Ethyl cellulose (EC)

- **Mucoadhesive polymers**
  - Polycarbophil
  - Sodium carboxymethyl cellulose
  - Polyacrylic acid
  - Tragacanth
  - Methyl cellulose
  - Pectin
Natural gums
- Xanthan gum
- Guar gum
- Karaya gum

2.2.6 Drug Release from Matrix systems
Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.\textsuperscript{46}

Derivation of the mathematical model to describe this system involves the following assumptions:

a) A pseudo-steady state is maintained during drug release;

b) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix;

c) The bathing solution provides sink conditions at all times.

The release behaviour for the system can be mathematically described by the following equation:

\[
\frac{dM}{dh} = Co \cdot dh - \frac{Cs}{2} \quad \text{(1)}
\]

Where,

- \(dM\) = Change in the amount of drug released per unit area
- \(dh\) = Change in the thickness of the zone of matrix that has been depleted of drug
- \(Co\) = Total amount of drug in a unit volume of matrix
- \(Cs\) = Saturated concentration of the drug within the matrix.

Additionally, according to diffusion theory:

\[
\frac{dM}{dt} = \frac{(Dm \cdot Cs / h) \cdot dt}{1} \quad \text{(2)}
\]

Where,

- \(Dm\) = Diffusion coefficient in the matrix.
- \(h\) = Thickness of the drug-depleted matrix
- \(dt\) = Change in time

By combining equation 1 and equation 2 and integrating:

\[
M = [Cs \cdot Dm \cdot (2Co - Cs) \cdot t]^{1/2} \quad \text{(3)}
\]

When the amount of drug is in excess of the saturation concentration, then:
\[ M = [2Cs. Dm. Co. t^{1/2}] \] (4)

Equation 3 and equation 4 relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores. The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix:

\[ M = [Ds.Ca.p/T. (2Co – p.Ca) t^{1/2}] \] (5)

Where,
- \( p \) = Porosity of the matrix
- \( t \) = Tortuosity
- \( Ca \) = solubility of the drug in the release medium
- \( Ds \) = Diffusion coefficient in the release medium.
- \( T \) = Diffusional pathlength

For pseudo steady state, the equation can be written as:

\[ M = [2D.Ca .Co( p/T)t]^{1/2} \] (6)

The total porosity of the matrix can be calculated with the following equation:

\[ p = pa + Ca/ \rho + C ex/ \rho ex \] (7)

Where,
- \( p \) = Porosity
- \( \rho \) = Drug density
- \( Pa \) = Porosity due to air pockets in the matrix
- \( \rho ex \) = Density of the water soluble excipients
- \( Cex \) = Concentration of water soluble excipients

For the purpose of data treatment, equation 7 can be reduced to:

\[ M = k. t^{1/2} \] (8)

Where,
- \( k \) is a constant, so that the amount of drug released versus the square root of time will be linear, if the release of drug from matrix is diffusion-controlled. If this is the case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters:
  - Initial concentration of drug in the matrix
  - Porosity
• Tortuosity
• Polymer system forming the matrix
• Solubility of the drug.

**Bimodal Release**

In certain systems there is a bimodal or anomalous release of the active ingredient. In these systems there is diffusion; additionally, the extended release polymer may become hydrated and begin to dissolve leading to release upon erosion. These systems are complex and difficult to mathematically model since the diffusional path length undergoes change due to the polymer dissolution. A series of transport phenomena are involved in the release of a drug from a swellable, diffusion/erodable matrix:

a.) Initially, there are steep water concentration gradients at the polymer/water interface, resulting in absorption of water into the matrix.

b.) Due to the absorption of water, the polymer swells, resulting in dramatic changes of drug and polymer concentration, increasing the dimensions of the system and increasing macromolecular mobility.

c.) Upon contact with water the drug dissolves and diffuses out of the device.

d.) With increasing water content, the diffusion coefficient of the drug increase substantially.

e.) In the case of a poorly water-soluble drug, dissolved and undissolved drug coexist within the polymer-matrix

f.) Finally, the polymer itself dissolves. These systems are described in terms of fronts. The following fronts have been defined, with regard to anomalous release systems:

• The “swelling front”, the erosion front, and the diffusion front. The swelling front separates the rubbery region (swelling polymer area) which has enough water absorbed within the polymer to lower the $T_g$ of the polymer below the respective environmental temperature allowing for macromolecular mobility and swelling, from the non-swelling polymer region (where the polymer exhibits a $T_g$ that is above the respective environmental temperature).

• The “Erosion front” separates the matrix from the bulk solution and is the interface between the unstirred layer with polymer concentration gradient and the well stirred medium.

• The “Diffusion front” is between the swelling and erosion front and separated the areas of non- dissolved drug from the area of dissolved drug.
With regard to swelling matrix systems, alternate models have been proposed to describe the diffusion, swelling, and dissolution processes occurring with into the system and these phenomena lead to drug release. The gel strength is important in the matrix performance and is controlled by the concentration, viscosity and chemical structure of the rubbery polymer. This restricts the suitability of the hydrophilic polymers for preparation of swellable matrices. Polymers such as carboxymethylcellulose, hydroxypropylcellulose or tragacanth gums do not form the gel layer quickly. Consequently, they are not recommended as excipients to be used alone in swellable matrices.\(^{43-47}\)

In 1985 Peppas introduced a semi-empirical equation describing the drug release behaviour from anomalous-release, hydrophilic matrix systems:

\[
Q = k \cdot t^n \\
\text{Where,}
\]

\(Q\) = Fraction of drug release in time \((t)\)
\(k\) = Rate constant (incorporates characteristics of polymer system and drug)
\(n\) = Diffusional exponent the value of \(n\) is indicative of the drug release mechanism.

In order to describe relaxational transport, then modified equation 9 in order to account for relaxational transport:

\[
Q = k_1 \cdot t^n + k_2 \cdot t^{2n} \\
\text{Where,}
\]

\(k_1\) = Fickian diffusion constant
\(k_2\) = Relaxational mechanism constant If the surface area of the system is fixed, which is unlikely, the value of \(n\) should be 0.5 and equation 10 is transformed to:

\[
Q = k_1 \cdot t^{0.5} + k_2 \cdot t \\
\text{The first term of this equation accounts for diffusional phenomena, while the second term of this equation accounts for polymer erosion.}
\]

**Effect of Release Limiting Parameter on Drug Release**

The mechanistic analysis of controlled release of drug reveals that partition coefficient; diffusivity; diffusional path thickness and other system parameters play various rate determining roles in the controlled release of drugs from either capsules, matrix or sandwich type drug delivery systems.

**A. Polymer hydration:**

It is important to study polymer hydration/swelling process for the maximum number of polymers and polymeric combinations. The more important step in polymer
dissolution include absorption/adsorption of water in more accessible places, rupture of polymer-polymer linkings with the simultaneous forming of water-polymer linkings, separation of polymeric chains, swelling and finally dispersion of polymeric chain in dissolution medium.

B. Drug solubility:
Molecular size and water solubility of drug are important determinants in the release of drug from swelling and erosion controlled polymeric matrices. For drugs with reasonable aqueous solubility, release of drugs occurs by dissolution in infiltrating medium and for drugs with poor solubility release occurs by both dissolution of drug and dissolution of drug particles through erosion of the matrix tablet.

C. Solution solubility:
In view of in vivo (biological) sink condition maintained actively by hemoperfusion; it is logical that all the in vitro drug release studies should also be conducted under perfect sink condition. In this way a better simulation and correlation of in vitro drug release profile with in vivo drug administration can be achieved. It is necessary to maintain a sink condition so that the release of drug is controlled solely by the delivery system and is not affected or complicated by solubility factor.

D. Polymer diffusivity:
The diffusion of small molecules in polymer structure is energy activated process in which the diffusant molecules moves to a successive series of equilibrium position when a sufficient amount of energy of activation for diffusion Ed has been acquired by the diffusant is dependent on length of polymer chain segment, cross linking and crystallinity of polymer. The release of drug may be attributed to the three factors viz,

i. Polymer particle size
ii. Polymer viscosity
iii. Polymer concentration.

i. Polymer particle size: Malamataris stated that when the content of hydroxypropyl methylcellulose is higher, the effect of particle size is less important on the release rate of propranolol hydrochloride, the effect of this variable more important when the content of polymer is low. He also justified these results by considering that in certain areas of matrix containing low levels of hydroxypropyl methylcellulose led to the burst release.

ii. Polymer viscosity: With cellulose ether polymers, viscosity is used as an indication of matrix weight. Increasing the molecular weight or viscosity of the
polymer in the matrix formulation increases the gel layer viscosity and thus slows drug dissolution. Also, the greater viscosity of the gel, the more resistant the gel is to dilution and erosion, thus controlling the drug dissolution.

iii. Polymer concentration: An increase in polymer concentration causes an increase in the viscosity of gel as well as formulation of gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore reduction in drug release. The mechanism of drug release from matrix also changes from erosion to diffusion as the polymer concentration increases.\(^{49}\)

E. Thickness of polymer diffusional path: The controlled release of a drug from both capsule and matrix type polymeric drug delivery system is essentially governed by Fick’s law of diffusion:

\[
JD = D \frac{dc}{dx} \quad \text{(12)}
\]

JD is flux of diffusion across a plane surface of unit area where D is diffusibility of drug molecule, \(\frac{dc}{dx}\) is concentration gradient of drug molecule across a diffusion path with thickness dx.

F. Thickness of hydrodynamic diffusion layer: It was observed that the drug release profile is a function of the variation in thickness of hydrodynamic diffusion layer on the surface of matrix type delivery devices. The magnitude of drug release value decreases on increasing the thickness of hydrodynamic diffusion layer \(\delta_d\).

G. Drug loading dose: The loading dose of drug has a significant effect on resulting release kinetics along with drug solubility. The effect of initial drug loading of the tablets on the resulting release kinetics is more complex in case of poorly water soluble drugs, withincreasing initial drug loading the relative release rate first decreases and then increases, whereas, absolute release rate monotonically increases. In case of freely water soluble drugs, the porosity of matrix upon drug depletion increases with increasing initial drug loading. This effect leads to increased absolute drug transfer rate. But in case of poorly water soluble drugs another phenomenon also has to be taken into account. When the amount of drug present at certain position within the matrix, exceeds the amount of drug soluble under given conditions, the excess of drug has to be considered as non-dissolved and thus not available for diffusion. The solid drug remains with in tablet, on increasing the initial drug loading of poorly water soluble drugs, the excess of drug remaining with in matrix increases.

H. Surface area and volume: The dependence of the rate of drug release on the surface area of drug delivery device is well known theoretically and experimentally.
Both the in vitro and in vivo rate of the drug release, are observed to be dependent upon surface area of dosage form. Siepman et al. found that release from small tablet is faster than large cylindrical tablets.  

I. Diluent’s effect: The effect of diluent or filler depends upon the nature of diluent. Water soluble diluents like lactose cause marked increase in drug release rate and release mechanism is also shifted towards Fickian diffusion; while insoluble diluents like dicalcium phosphate reduce the Fickian diffusion and increase the relaxation (erosion) rate of matrix. The reason behind this is that water soluble filler in matrices stimulate the water penetration in to inner part of matrix, due to increase in hydrophilicity of the system, causing rapid diffusion of drug, leads to increased drug release rate.

J. Additives: The effect of adding non-polymeric excipients to a polymeric matrix has been claimed to produce increase in release rate of hydrosoluble active principles. These increases in release rate would be marked if the excipients are soluble like lactose and less important if the excipients are insoluble like tricalcium phosphate.

2.2.7 Factors influencing Oral Sustained-Release Dosage Form Design:

Biological factors influencing oral sustained-release dosage form design:

1) Biological half-life:
Therapeutic compounds with short half-lives are excellent candidates for sustained-release preparations, since this can reduce dosing frequency.

2) Absorption:
The absorption rate constant is an apparent rate constant, and should, in actuality, be the release rate constant of the drug from the dosage form. If a drug is absorbed by active transport, or transport is limited to a specific region of the intestine, sustained-release preparations may be disadvantageous to absorptions.

3) Distribution:
The distribution of drugs into tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending on time course of drug disposition. For design of sustained/ controlled release products, one must have information of disposition of drug.
4) **Metabolism:**
Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during a specific period, allowing more complete conversion of the drug to its metabolite.

- **Physicochemical factors influencing oral sustained-release dosage form design:**

1) **Dose Size:**
In general, single dose of 0.5 – 1.0 g is considered maximal for a conventional dosage form. This also holds true for sustained-release dosage forms. Another consideration is the margin of safety involved in administration of large amounts of drug with a narrow therapeutic range.

2) **Ionization, pKa, and aqueous solubility:**
Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pKa of the compound and the absorptive environment. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of drug in the aqueous media. For dissolution or diffusion sustaining forms, much of the drug will arrive in the small intestine in solid form, meaning that the solubility of the drug may change several orders of magnitude during its release. The lower limit for the solubility of a drug to be formulated in a sustained release system has been reported to be 0.1 mg/ml.

3) **Partition coefficient:**
Compounds with a relatively high partition coefficient are predominantly lipid-soluble and, consequently, have very low aqueous solubility. Furthermore these compounds can usually persist in the body for long periods, because they can localize in the lipid membranes of cells.

4) **Stability:**
Orally administered drugs can be subjected to both acid-base hydrolysis and enzymatic degradation. For drugs that are unstable in the stomach, systems that prolong delivery over the entire course of transit in the GI tract are beneficial.
Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form.

5) **Molecular size and diffusivity:**

The ability of drug to diffuse through membranes is called diffusivity & diffusion coefficient is function of molecular size (or molecular weight). Generally, values of diffusion coefficient for intermediate molecular weight drugs, through flexible polymer range from 10-8 to 10-9 cm²/sec with values on the order of 10-8 cm²/sec. being most common for drugs with molecular weight greater than 500, the diffusion coefficient in many polymers frequently are so small that they are difficult to quantify i.e. less than 10-12 cm²/sec. Thus high molecular weight drugs and / or polymeric drugs should be expected to display very slow release kinetics in sustained release device using diffusion through polymer membrane.

6) **Protein binding:**

It is well known that many drugs bind to plasma proteins with a concomitant influence on the duration of drug action. Since blood proteins are for the most part recirculated and not eliminated, drug Protein binding can serve as a depot for drug producing a prolonged release profile, especially if a high degree of drug binding occurs. Extensive binding to plasma proteins will be evidenced by a long half-life of elimination for drugs and such drugs generally most require a sustained release dosage form. However drugs that exhibit high degree of binding to plasma proteins also might bind to bio-polymers in GI tract which could have influence on sustained drug delivery. The presence of hydrophobic moiety on drug molecule also increases the binding potential.  

2.2.8 **Drug selection for oral sustained release drug delivery systems**

The biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery system requires knowledge on the absorption mechanism of the drug form the G.I. tract, the general absorbability, the drugs molecular weight, solubility at different pH and apparent partition coefficient.
### Table 2.2.1: Physicochemical Parameters for Drug Selection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preferred Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight/ size</td>
<td>&lt; 1000</td>
</tr>
<tr>
<td>Solubility</td>
<td>&gt; 0.1 mg/ml for pH 1 to pH 7.8</td>
</tr>
<tr>
<td>Apparent partition coefficient</td>
<td>High</td>
</tr>
<tr>
<td>Absorption mechanism</td>
<td>Diffusion</td>
</tr>
<tr>
<td>General absorbability</td>
<td>From all GI segments</td>
</tr>
<tr>
<td>Release</td>
<td>Should not be influenced by pH and enzymes</td>
</tr>
</tbody>
</table>

### Table 2.2.2: Pharmacokinetic Parameters for Drug Selection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination half life</td>
<td>Preferably between 0.5 and 8 h</td>
</tr>
<tr>
<td>Total clearance</td>
<td>Should not be dose dependent</td>
</tr>
<tr>
<td>Elimination rate constant</td>
<td>Required for design</td>
</tr>
<tr>
<td>Apparent volume of distribution $V_d$</td>
<td>The larger $V_d$ and MEC, the larger will be the required dose size.</td>
</tr>
<tr>
<td>Absolute bioavailability</td>
<td>Should be 75% or more</td>
</tr>
<tr>
<td>Intrinsic absorption rate</td>
<td>Must be greater than release rate</td>
</tr>
<tr>
<td>Therapeutic concentration $C_{ss av}$</td>
<td>The lower $C_{ss av}$ and smaller $V_d$, the less amount of drug required</td>
</tr>
<tr>
<td>Toxic concentration</td>
<td>Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.</td>
</tr>
</tbody>
</table>

### Table 2.2.2: Pharmacokinetic Parameter of Drug Selection

#### 2.2.9 Factors influencing the in vivo performance of sustained release dosage formulations:

There are various factors that can influence the performance of a sustained release product. The physiological, biochemical, and pharmacological factors listed below can complicate the evaluation of the suitability of a sustained release dosage formulation.\(^57, 58\)

- **Physiological:**
  - Prolonged drug absorption
  - Variability in GI emptying and motility
• Gastrointestinal blood flow
• Influence of feeding on drug absorption
• Pharmacokinetic/ biochemical
• Dose dumping
• First- pass metabolism
• Variability in urinary pH; effect on drug elimination
• Enzyme induction/ inhibition upon multiple dosing
• Pharmacological
• Changes in drug effect upon multiple dosing

➢ Pharmacokinetic/ biochemical
• Dose dumping
• First- pass metabolism
• Variability in urinary pH; effect on drug elimination
• Enzyme induction/ inhibition upon multiple dosing

➢ Pharmacological
• Changes in drug effect upon multiple dosing
• Sensitization/ tolerance.
REFERENCES:


44. Hogan, JE. Hydroxypropyl methylcellulose sustained release technology, Drug Dev Ind Pharm 1989; 15(6-7):975-999.
55. Yie W., Chien, Rate controlled drug delivery systems. 2nd Ed.; Marcel Dekker; New York, Revised and expanded, 2005;.

2.3 INTRODUCTION TO DISEASE

Hypertension (HTN) or high blood pressure, sometimes called arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is elevated.\(^1\) This requires the heart to work harder than normal to circulate blood through the blood vessels. Blood pressure is summarized by two measurements, systolic and diastolic, which depend on whether the heart muscle is contracting (systole) or relaxed between beats (diastole). Normal blood pressure at rest is within the range of 100-140mmHg systolic (top reading) and 60-90mmHg diastolic (bottom reading). High blood pressure is said to be present if it is persistently at or above 140/90 mmHg.

Blood pressure is the force of blood pushing up against the blood vessel walls. The higher the pressure the harder the heart has to pump. Hypertension can lead to damaged organs, as well as several illnesses, such as renal failure (kidney failure), aneurysm, heart failure, stroke, or heart attack. Researchers from UC Davis reported in the Journal of the American Academy of Neurology that high blood pressure during middle age may raise the risk of cognitive decline later in life. According to Medilexicon's medical dictionary, hypertension means "High blood pressure; transitory or sustained elevation of systemic arterial blood pressure to a level likely to induce cardiovascular damage or other adverse consequences."

The normal level for blood pressure is below 120/80, where 120 represent the systolic measurement (peak pressure in the arteries) and 80 represents the diastolic measurement (minimum pressure in the arteries). Blood pressure between 120/80 and 139/89 is called pre hypertension (to denote increased risk of hypertension), and a blood pressure of 140/90 or above is considered hypertension. Hypertension may be classified as essential or secondary. Essential hypertension is the term for high blood pressure with unknown cause. It accounts for about 95% of cases. Secondary hypertension is the term for high blood pressure with a known direct cause, such as kidney disease, tumors, or birth control pills.

Some 70 million adults the United States are affected by hypertension. The condition also affects about two million teens and children. According to a report issued by the Centers for Disease Control and Prevention (CDC) in September 2012, over half all Americans with hypertension do not have their high blood pressure under control.
Hypertension is classified as either primary (essential) hypertension or secondary hypertension; about 90–95% of cases are categorized as "primary hypertension" which means high blood pressure with no obvious underlying medical cause. The remaining 5–10% of cases (secondary hypertension) are caused by other conditions that affect the kidneys, arteries, heart or endocrine system.

Hypertension is a major risk factor for stroke, myocardial infarction (heart attacks), heart failure, aneurysms of the arteries (e.g. aortic aneurysm), peripheral arterial disease and is a cause of chronic kidney disease. Even moderate elevation of arterial blood pressure is associated with a shortened life expectancy. Dietary and lifestyle changes can improve blood pressure control and decrease the risk of associated health complications, although drug treatment is often necessary in people for whom lifestyle changes prove ineffective or insufficient.

**Signs and symptoms**

Hypertension is rarely accompanied by any symptoms, and its identification is usually through screening, or when seeking healthcare for an unrelated problem. A proportion of people with high blood pressure reports headaches (particularly at the back of the head and in the morning), as well as lightheadedness, vertigo, tinnitus (buzzing or hissing in the ears), altered vision or fainting episodes. These symptoms however are more likely to be related to associated anxiety than the high blood pressure itself.

On physical examination, hypertension may be suspected on the basis of the presence of hypertensive retinopathy detected by examination of the optic fundus found in the back of the eye using ophthalmoscopy. Classically, the severity of the hypertensive retinopathy changes is graded from grade I–IV, although the milder types may be difficult to distinguish from each other. Ophthalmoscopy findings may also give some indication as to how long a person has been hypertensive.

**Hypertensive crisis**

Severely elevated blood pressure (equal to or greater than a systolic 180 or diastolic of 110 sometime termed malignant or accelerated hypertension) is referred to as a
"Hypertensive crisis", as blood pressures above these levels are known to confer a high risk of complications. People with blood pressures in this range may have no symptoms, but are more likely to report headaches (22% of cases)\(^7\) and dizziness than the general population. Other symptoms accompanying a hypertensive crisis may include visual deterioration or breathlessness due to heart failure or a general feeling of malaise due to renal failure. Most people with a hypertensive crisis are known to have elevated blood pressure, but additional triggers may have led to a sudden rise.\(^8\)

A "hypertensive emergency", previously "malignant hypertension", is diagnosed when there is evidence of direct damage to one or more organs as a result of the severely elevated blood pressure. This may include hypertensive encephalopathy, caused by brain swelling and dysfunction, and characterized by headaches and an altered level of consciousness (confusion or drowsiness). Retinal papilloedema and/or fundal hemorrhages and exudates are another sign of target organ damage. Chest pain may indicate heart muscle damage (which may progress to myocardial infarction) or sometimes aortic dissection, the tearing of the inner wall of the aorta. Breathlessness, cough, and the expectoration of blood-stained sputum are characteristic signs of pulmonary edema, the swelling of lung tissue due to left ventricular failure an inability of the left ventricle of the heart to adequately pump blood from the lungs into the arterial system.\(^8\) Rapid deterioration of kidney function (acute kidney injury) and microangiopathic hemolytic anemia (destruction of blood cells) may also occur. In these situations, rapid reduction of the blood pressure is mandated to stop ongoing organ damage. In contrast there is no evidence that blood pressure needs to be lowered rapidly in hypertensive urgencies where there is no evidence of target organ damage and over aggressive reduction of blood pressure is not without risks. Use of oral medications to lower the BP gradually over 24 to 48 h is advocated in hypertensive urgencies.\(^8\)

**In pregnancy**

Hypertension occurs in approximately 8-10% of pregnancies.\(^6\) Most women with hypertension in pregnancy have pre-existing primary hypertension, but high blood pressure in pregnancy may be the first sign of pre-eclampsia, a serious condition of the second half of pregnancy and puerperium.\(^6\) Pre-eclampsia is characterised by increased blood pressure and the presence of protein in the urine.\(^6\) It occurs in about
5% of pregnancies and is responsible for approximately 16% of all maternal deaths globally. Pre-eclampsia also doubles the risk of perinatal mortality.[6] Usually there are no symptoms in pre-eclampsia and it is detected by routine screening. When symptoms of pre-eclampsia occur the most common are headache, visual disturbance (often "flashing lights"), vomiting, epigastric pain, and edema. Pre-eclampsia can occasionally progress to a life-threatening condition called eclampsia, which is a hypertensive emergency and has several serious complications including vision loss, cerebral edema, seizures or convulsions, renal failure, pulmonary edema, and disseminated intravascular coagulation (a blood clotting disorder).[9]

**In infants and children**

Failure to thrive, seizures, irritability, lack of energy, and difficulty breathing[10] can be associated with hypertension in neonates and young infants. In older infants and children, hypertension can cause headache, unexplained irritability, fatigue, failure to thrive, blurred vision, nosebleeds, and facial paralysis.[10,11]

**Cause**

Though the exact causes of hypertension are usually unknown, there are several factors that have been highly associated with the condition. These include:

- Smoking
- Obesity or being overweight
- Diabetes
- Sedentary lifestyle
- Lack of physical activity
- High levels of salt intake (sodium sensitivity).

According to the American Heart Association (AHA), sodium consumption should be limited to 1,500 milligrams per day, and that includes everybody, even healthy people without high blood pressure, diabetes or cardiovascular diseases. AHA's chief executive officer, Nancy Brown said "Our recommendation is simple in the sense that it applies to the entire U.S population, not just at-risk groups. Americans of all ages, regardless of individual risk factors, can improve the heart health and
reduce their risk of cardiovascular disease by restricting their daily consumption of sodium to less than 1,500 milligrams." The recommendation was published in the journal Circulation Insufficient calcium, potassium, and magnesium consumption

- Vitamin D deficiency
- High levels of alcohol consumption
- Stress
- Aging
- Medicines such as birth control pills
- Genetics and a family history of hypertension - In May 2011, scientists from the University of Leicester, England, reported in the journal Hypertension that some genes in the kidneys may contribute to hypertension.
- Chronic kidney disease
- Adrenal and thyroid problems or tumors

Statistics in the USA indicate that African Americans have a higher incidence of hypertension than other ethnicities.

### 2.3.1 Primary hypertension

Primary (essential) hypertension is the most common form of hypertension, accounting for 90–95% of all cases of hypertension. In almost all contemporary societies, blood pressure rises with aging and the risk of becoming hypertensive in later life is considerable. Hypertension results from a complex interaction of genes and environmental factors. Numerous common genetic variants with small effects on blood pressure have been identified as well as some rare genetic variants with large effects on blood pressure but the genetic basis of hypertension is still poorly understood. Several environmental factors influence blood pressure. Lifestyle factors that lower blood pressure include reduced dietary salt intake, increased consumption of fruits and low fat products (Dietary Approaches to Stop Hypertension (DASH diet)), exercise, weight loss and reduced alcohol intake. Stress appears to play a minor role with specific relaxation techniques not supported by the evidence. The possible role of other factors such as caffeine consumption and vitamin D deficiency are less clear cut. Insulin resistance, which is common in obesity and is a component of syndrome X (or the metabolic syndrome), is also
thought to contribute to hypertension.\textsuperscript{[22]} Recent studies have also implicated events in early life (for example low birth weight, maternal smoking and lack of breast feeding) as risk factors for adult essential hypertension, although the mechanisms linking these exposures to adult hypertension remain obscure.\textsuperscript{[23]}

**Secondary hypertension**

Secondary hypertension results from an identifiable cause. Renal disease is the most common secondary cause of hypertension. Hypertension can also be caused by endocrine conditions, such as Cushing's syndrome, hyperthyroidism, hypothyroidism, acromegaly, Conn's syndrome or hyperaldosteronism, hyperparathyroidism and pheochromocytoma.\textsuperscript{[6][24]} Other causes of secondary hypertension include obesity, sleep apnea, pregnancy, coarctation of the aorta, excessive liquorice consumption and certain prescription medicines, herbal remedies and illegal drugs.\textsuperscript{[25]}

### 2.3.2 Pathophysiology

Pathophysiology of hypertension

[Fig 2.3.1: A diagram explaining factors affecting Arterial pressure\textsuperscript{[27]}]

In most people with established essential (primary) hypertension, increased resistance to blood flow (total peripheral resistance) accounting for the high pressure while cardiac output remains normal.\textsuperscript{[26]} There is evidence that some younger people with prehypertension or 'borderline hypertension' have high cardiac output, an elevated heart rate and normal peripheral resistance, termed hyperkinetic borderline hypertension. These individuals develop the typical features of established essential hypertension in later life as their cardiac output falls and peripheral resistance rises with age.\textsuperscript{[27]} Whether this pattern is typical of all people who ultimately develop hypertension is disputed.\textsuperscript{[28]} The increased peripheral resistance in established hypertension is mainly attributable to structural narrowing of small arteries and
arterioles,\textsuperscript{[29]} although a reduction in the number or density of capillaries may also contribute.\textsuperscript{[30]} Hypertension is also associated with decreased peripheral venous compliance\textsuperscript{[31]} which may increase venous return, increase cardiac preload and, ultimately, cause diastolic dysfunction. Whether increased active vasoconstriction plays a role in established essential hypertension is unclear.\textsuperscript{[32]}

Pulse pressure (the difference between systolic and diastolic blood pressure) is frequently increased in older people with hypertension. This can mean that systolic pressure is abnormally high, but diastolic pressure may be normal or low — a condition termed isolated systolic hypertension.\textsuperscript{[33]} The high pulse pressure in elderly people with hypertension or isolated systolic hypertension is explained by increased arterial stiffness, which typically accompanies aging and may be exacerbated by high blood pressure.\textsuperscript{[34]}

Many mechanisms have been proposed to account for the rise in peripheral resistance in hypertension. Most evidence implicates either disturbances in renal salt and water handling (particularly abnormalities in the intrarenal renin-angiotensin system)\textsuperscript{[35]} and/or abnormalities of the sympathetic nervous system.\textsuperscript{[36]} These mechanisms are not mutually exclusive and it is likely that both contribute to some extent in most cases of essential hypertension. It has also been suggested that endothelial dysfunction and vascular inflammation may also contribute to increased peripheral resistance and vascular damage in hypertension.\textsuperscript{[37],[38]}

**Diagnosis**

Hypertension may be diagnosed by a health professional who measures blood pressure with a device called a sphygmomanometer - the device with the arm cuff, dial, pump, and valve. The systolic and diastolic numbers will be recorded and compared to a chart of values. If the pressure is greater than 140/90, you will be considered to have hypertension. A high blood pressure measurement, however, may be spurious or the result of stress at the time of the exam. In order to perform a more thorough diagnosis, physicians usually conduct a physical exam and ask for the medical history of you and your family. Doctors will need to know if you have any of the risk factors for hypertension, such as smoking, high cholesterol, or diabetes. If hypertension seems reasonable, tests such as electrocardiograms (EKG) and
echocardiograms will be used in order to measure electrical activity of the heart and to assess the physical structure of the heart. Additional blood tests will also be required to identify possible causes of secondary hypertension and to measure renal function, electrolyte levels, sugar levels, and cholesterol levels.

**How is hypertension treated?**

The main goal of treatment for hypertension is to lower blood pressure to less than 140/90 - or even lower in some groups such as people with diabetes, and people with chronic kidney diseases. Treating hypertension is important for reducing the risk of stroke, heart attack, and heart failure. High blood pressure may be treated medically, by changing lifestyle factors, or a combination of the two. Important lifestyle changes include losing weight, quitting smoking, eating a healthful diet, reducing sodium intake, exercising regularly and limiting alcohol consumption. Medical options to treat hypertension include several classes of drugs. ACE inhibitors, ARB drugs, beta-blockers, diuretics, calcium channel blockers, alpha-blockers, and peripheral vasodilators are the primary drugs used in treatment. These medications may be used alone or in combination, and some are only used in combination. In addition, some of these drugs are preferred to others depending on the characteristics of the patient (diabetic, pregnant, etc.). If blood pressure is successfully lowered, it is wise to have frequent checkups and to take preventive measures to avoid a relapse of hypertension.

Hypertension is diagnosed on the basis of a persistently high blood pressure. Traditionally, this requires three separate sphygmomanometer measurements at one monthly intervals. Initial assessment of the hypertensive people should include a complete history and physical examination. With the availability of 24-hour ambulatory blood pressure monitors and home blood pressure machines, the importance of not wrongly diagnosing those who have white coat hypertension has led to a change in protocols. In the United Kingdom, current best practice is to follow up a single raised clinic reading with ambulatory measurement, or less ideally with home blood pressure monitoring over the course of 7 days. Pseudohypertension in the elderly or noncompressibility artery syndrome may also require consideration. This condition is believed to be due to calcification of the arteries resulting abnormally high blood pressure readings with a blood pressure cuff while intra arterial measurements of blood pressure are normal.
Once the diagnosis of hypertension has been made, physicians will attempt to identify the underlying cause based on risk factors and other symptoms, if present. Secondary hypertension is more common in preadolescent children, with most cases caused by renal disease. Primary or essential hypertension is more common in adolescents and has multiple risk factors, including obesity and a family history of hypertension. Laboratory tests can also be performed to identify possible causes of secondary hypertension, and to determine whether hypertension has caused damage to the heart, eyes, and kidneys. Additional tests for diabetes and high cholesterol levels are usually performed because these conditions are additional risk factors for the development of heart disease and may require treatment.

Serum creatinine is measured to assess for the presence of kidney disease, which can be either the cause or the result of hypertension. Serum creatinine alone may overestimate glomerular filtration rate and recent guidelines advocate the use of predictive equations such as the Modification of Diet in Renal Disease (MDRD) formula to estimate glomerular filtration rate (eGFR). eGFR can also provide a baseline measurement of kidney function that can be used to monitor for side effects of certain antihypertensive drugs on kidney function. Additionally, testing of urine samples for protein is used as a secondary indicator of kidney disease. Electrocardiogram (EKG/ECG) testing is done to check for evidence that the heart is under strain from high blood pressure. It may also show whether there is thickening of the heart muscle (left ventricular hypertrophy) or whether the heart has experienced a prior minor disturbance such as a silent heart attack. A chest X-ray or an echocardiogram may also be performed to look for signs of heart enlargement or damage to the heart.
Adults

<table>
<thead>
<tr>
<th>Classification (JNC7)</th>
<th>Systolic pressure</th>
<th>Diastolic pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td>kPa</td>
</tr>
<tr>
<td>Normal</td>
<td>90–119</td>
<td>12–15.9</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120–139</td>
<td>16.0–18.5</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>140–159</td>
<td>18.7–21.2</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>≥160</td>
<td>≥21.3</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>≥140</td>
<td>≥18.7</td>
</tr>
</tbody>
</table>

In people aged 18 years or older hypertension is defined as a systolic and/or a diastolic blood pressure measurement consistently higher than an accepted normal value (currently 139 mmHg systolic, 89 mmHg diastolic). Lower thresholds are used (135 mmHg systolic or 85 mmHg diastolic) if measurements are derived from 24-hour ambulatory or home monitoring. Recent international hypertension guidelines have also created categories below the hypertensive range to indicate a continuum of risk with higher blood pressures in the normal range. uses the term prehypertension for blood pressure in the range 120-139 mmHg systolic and/or 80-89 mmHg diastolic, while ESH-ESC Guidelines (2007) and BHS IV (2004) use optimal, normal and high normal categories to subdivide pressures below 140 mmHg systolic and 90 mmHg diastolic. Hypertension is also sub-classified: JNC7 distinguishes hypertension stage I, hypertension stage II, and isolated systolic hypertension. Isolated systolic hypertension refers to elevated systolic pressure with normal diastolic pressure and is common in the elderly. The ESH-ESC Guidelines (2007) and BHS IV (2004), additionally define a third stage (stage III hypertension) for people with systolic blood pressure exceeding 179 mmHg or a diastolic pressure over 109 mmHg. Hypertension is classified as "resistant" if medications do not reduce blood pressure to normal levels.
Children

Hypertension in neonates is rare, occurring in around 0.2 to 3% of neonates, and blood pressure is not measured routinely in the healthy newborn. Hypertension is more common in high risk newborns. A variety of factors, such as gestational age, postconceptional age and birth weight need to be taken into account when deciding if a blood pressure is normal in a neonate.

Hypertension occurs quite commonly in children and adolescents (2-9% depending on age, sex and ethnicity)\(^5^1\) and is associated with long term risks of ill-health. It is now recommended that children over the age of 3 have their blood pressure checked whenever they attend for routine medical care or checks, but high blood pressure must be confirmed on repeated visits before characterizing a child as having hypertension. Blood pressure rises with age in childhood and, in children, hypertension is defined as an average systolic or diastolic blood pressure on three or more occasions equal or higher than the 95th percentile appropriate for the sex, age and height of the child. Prehypertension in children is defined as average systolic or diastolic blood pressure that is greater than or equal to the 90th percentile, but less than the 95th percentile. In adolescents, it has been proposed that hypertension and pre-hypertension are diagnosed and classified using the same criteria as in adults.\(^5^2\)

Prevention

Hypertension can best be prevented by adjusting your lifestyle so that proper diet and exercise are key components. It is important to maintain a healthy weight, reduce salt intake, reduce alcohol intake, and reduce stress. In order to prevent damage to critical organs and conditions such as stroke, heart attack, and kidney failure that may be caused by high blood pressure, it is important to screen, diagnose, treat, and control hypertension in its earliest stages. This can also be accomplished by increasing public awareness and increasing the frequency of screenings for the condition.
Hypertension speeds up brain aging

Young and middle aged people with high blood pressure have a higher risk of accelerated brain aging, scientists from the University of California Davis reported in The Lancet (November 2, 2012 issue). The risk appears to be there even for those whose elevated blood pressure is not considered enough for medical intervention. The authors say their findings should encourage doctors to control patients’ blood pressure early on event hypertensive ones. The team, led by Professor Charles DeCarli, said they found evidence of structural damage in white matter, and also volume of gray matter among people with high blood pressure, including prehypertensive patients in their 30s and 40s. They wrote that "(brain injury) develops insidiously over the lifetime with discernible effects".

Much of the disease burden of high blood pressure is experienced by people who are not labelled as hypertensive. Consequently, population strategies are required to reduce the consequences of high blood pressure and reduce the need for antihypertensive drug therapy. Lifestyle changes are recommended to lower blood pressure, before starting drug therapy. The 2004 British Hypertension Society guidelines\(^{[53]}\) proposed the following lifestyle changes consistent with those outlined by the US National High BP Education Program in 2002\(^{[54]}\) for the primary prevention of hypertension:

- maintain normal body weight for adults (e.g. body mass index 20–25 kg/m\(^2\))
- reduce dietary sodium intake to <100 mmol/day (<6 g of sodium chloride or <2.4 g of sodium per day)
- engage in regular aerobic physical activity such as brisk walking (≥30 min per day, most days of the week)
- limit alcohol consumption to no more than 3 units/day in men and no more than 2 units/day in women
- consume a diet rich in fruit and vegetables (e.g. at least five portions per day);

Effective lifestyle modification may lower blood pressure as much an individual antihypertensive drug. Combinations of two or more lifestyle modifications can achieve even better results.
Management

Lifestyle modifications

The first line of treatment for hypertension is identical to the recommended preventative lifestyle changes and includes: dietary changes, physical exercise, and weight loss. These have all been shown to significantly reduce blood pressure in people with hypertension. If hypertension is high enough to justify immediate use of medications, lifestyle changes are still recommended in conjunction with medication. Different programs aimed to reduce psychological stress such as biofeedback, relaxation or meditation is advertised to reduce hypertension. However, in general claims of efficacy are not supported by scientific studies, which have been in general of low quality.

Dietary change such as a low sodium diet is beneficial. A long term (more than 4 weeks) low sodium diet in Caucasians is effective in reducing blood pressure, both in people with hypertension and in people with normal blood pressure. Also, the DASH diet, a diet rich in nuts, whole grains, fish, poultry, fruits and vegetables promoted in the USA by the National Heart, Lung, and Blood Institute lowers blood pressure. A major feature of the plan is limiting intake of sodium, although the diet is also rich in potassium, magnesium, calcium, as well as protein.

Medications

Several classes of medications, collectively referred to as antihypertensive drugs, are currently available for treating hypertension. Prescription should take into account the person's cardiovascular risk (including risk of myocardial infarction and stroke) as well as blood pressure readings, in order to gain a more accurate picture of the person's cardiovascular profile. Evidence in those with mild hypertension (SBP less than 160 mmHg and /or DBP less than 100 mmHg) and no other health problems does not support a reduction in the risk of death or rate of health complications from medication treatment.

If drug treatment is initiated the Joint National Committee on High Blood Pressure recommends that the physician not only monitor for response to treatment but should
also assess for any adverse reactions resulting from the medication. Reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischaemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease.\textsuperscript{65} The aim of treatment should be to reduce blood pressure to $<140/90$ mmHg for most individuals, and lower for those with diabetes or kidney disease (some medical professionals recommend keeping levels below 120/80 mmHg).\textsuperscript{63,66} If the blood pressure goal is not met, a change in treatment should be made as therapeutic inertia is a clear impediment to blood pressure control.\textsuperscript{67}

Guidelines on the choice of agents and how best to step up treatment for various subgroups have changed over time and differ between countries. The best first line agent is disputed.\textsuperscript{68} The Cochrane collaboration, World Health Organization and the United States guidelines supports low dose thiazide-based diuretic as first line treatment.\textsuperscript{68,69} The UK guidelines emphasise calcium channel blockers (CCB) in preference for people over the age of 55 years or if of African or Caribbean family origin, with angiotensin converting enzyme inhibitors (ACE-I) used first line for younger people.\textsuperscript{70} In Japan starting with any one of six classes of medications including: CCB, ACEI/ARB, thiazide diuretics, beta-blockers, and alpha-blockers is deemed reasonable while in Canada all of these but alpha-blockers are recommended as options.\textsuperscript{68}

**Drug combinations**

The majority of people require more than one drug to control their hypertension. ESH-ESC guidelines \textsuperscript{49} advocate starting treatment with two drugs when blood pressure is $>20$ mmHg above systolic or $>10$ mmHg above diastolic targets. Preferred combinations are renin–angiotensin system inhibitors and calcium channel blockers, or renin–angiotensin system inhibitors and diuretics.\textsuperscript{71} Acceptable combinations include calcium channel blockers and diuretics, beta-blockers and diuretics, dihydropyridine calcium channel blockers and beta-blockers, or dihydropyridine calcium channel blockers with either verapamil or diltiazem. Unacceptable combinations are non-dihydropyridine calcium blockers (such as verapamil or diltiazem) and beta-blockers, dual renin–angiotensin system blockade (e.g.
angiotensin converting enzyme inhibitor + angiotensin receptor blocker), renin–angiotensin system blockers and beta-blockers, beta-blockers and centrally acting agents.\textsuperscript{[71]} Combinations of an ACE-inhibitor or angiotensin II–receptor antagonist, a diuretic and an NSAID (including selective COX-2 inhibitors and non-prescribed drugs such as ibuprofen) should be avoided whenever possible due to a high documented risk of acute renal failure. The combination is known colloquially as a "triple whammy" in the Australian health industry. Tablets containing fixed combinations of two classes of drugs are available and while convenient for the people, may be best reserved for those who have been established on the individual components.\textsuperscript{[72]}

**In the elderly**

Treating moderate to severe hypertension decreases death rates and cardiovascular morbidity and mortality in people aged 60 and older.\textsuperscript{[73]} There are limited studies of people over 80 years old but a recent review concluded that antihypertensive treatment reduced cardiovascular deaths and disease, but did not significantly reduce total death rates.\textsuperscript{[73]} The recommended BP goal is advised as \(<140/90\) mm Hg with thiazide diuretics being the first line medication in America,\textsuperscript{[74]} and in the revised UK guidelines calcium-channel blockers are advocated as first line with targets of clinic readings \(<150/90\), or \(<145/85\) on ambulatory or home blood pressure monitoring.\textsuperscript{[70]}

**Resistant hypertension**

Resistant hypertension is defined as hypertension that remains above goal blood pressure in spite of concurrent use of three antihypertensive agents belonging to different antihypertensive drug classes. Guidelines for treating resistant hypertension have been published in the UK\textsuperscript{[75]} and US.\textsuperscript{[76]}

**2.3.3 Epidemiology**

Disability adjusted life year for hypertensive heart disease per 100,000 inhabitants in 2004.\textsuperscript{[77]} As of 2000, nearly one billion people or \(~26\%\) of the adult population of the world had hypertension.\textsuperscript{[78]} It was common in both developed (333 million) and undeveloped (639 million) countries.\textsuperscript{[78]} However rates vary markedly in different
regions with rates as low as 3.4% (men) and 6.8% (women) in rural India and as high as 68.9% (men) and 72.5% (women) in Poland.\[^79\]

In 1995 it was estimated that 43 million people in the United States had hypertension or were taking antihypertensive medication, almost 24% of the adult United States population.\[^80\] The prevalence of hypertension in the United States is increasing and reached 29% in 2004.\[^81\],\[^82\] As of 2006 hypertension affects 76 million US adults (34% of the population) and African American adults have among the highest rates of hypertension in the world at 44%.\[^83\] It is more common in blacks and Native Americans and less in whites and Mexican Americans, rates increase with age, and is greater in the southeastern United States. Hypertension is more prevalent in men (though menopause tends to decrease this difference) and in those of low socioeconomic status.

In children

The prevalence of high blood pressure in the young is increasing.\[^84\] Most childhood hypertension, particularly in preadolescents, is secondary to an underlying disorder. Aside from obesity, kidney disease is the most common (60–70%) cause of hypertension in children. Adolescents usually have primary or essential hypertension, which accounts for 85–95% of cases.\[^85\]

Prognosis

![Diagram illustrating the main complications of persistent high blood pressure.](Fig 2.3.2)

[Fig 2.3.2: Diagram illustrating the main complications of persistent high blood pressure.]
Hypertension is the most important preventable risk factor for premature death worldwide.\textsuperscript{[86]} It increases the risk of ischemic heart disease\textsuperscript{[87]} strokes, peripheral vascular disease,\textsuperscript{[88]} and other cardiovascular diseases, including heart failure, aortic aneurysms, diffuse atherosclerosis, and pulmonary embolism. Hypertension is also a risk factor for cognitive impairment and dementia, and chronic kidney disease. Other complications include hypertensive retinopathy and hypertensive nephropathy.

2.3.4 History

Modern understanding of the cardiovascular system began with the work of physician William Harvey (1578–1657), who described the circulation of blood in his book "De motu cordis". The English clergyman Stephen Hales made the first published measurement of blood pressure in 1733.\textsuperscript{[89],[90]} Descriptions of hypertension as a disease came among others from Thomas Young in 1808 and especially Richard Bright in 1836.\textsuperscript{[89]} The first report of elevated blood pressure in a person without evidence of kidney disease was made by Frederick Akbar Mahomed (1849–1884).\textsuperscript{[91]} However hypertension as a clinical entity came into being in 1896 with the invention of the cuff-based sphygmomanometer by Scipione Riva-Rocci in 1896.\textsuperscript{[92]} This allowed the measurement of blood pressure in the clinic. In 1905, Nikolai Korotkoff improved the technique by describing the Korotkoff sounds that are heard when the artery is ausculated with a stethoscope while the sphygmomanometer cuff is deflated.\textsuperscript{[90]}

Historically the treatment for what was called the "hard pulse disease" consisted in reducing the quantity of blood by blood letting or the application of leeches.\textsuperscript{[91]} This was advocated by The Yellow Emperor of China, Cornelius Celsus, Galen, and...
In the 19th and 20th centuries, before effective pharmacological treatment for hypertension became possible, three treatment modalities were used, all with numerous side-effects: strict sodium restriction (for example the rice diet[89-92]), sympathectomy (surgical ablation of parts of the sympathetic nervous system), and pyrogen therapy (injection of substances that caused a fever, indirectly reducing blood pressure).[93] The first chemical for hypertension, sodium thiocyanate, was used in 1900 but had many side effects and was unpopular.[89] Several other agents were developed after the Second World War, the most popular and reasonably effective of which were tetramethylammonium chloride and its derivative hexamethonium, hydralazine and reserpine (derived from the medicinal plant Rauwolfia serpentina). A major breakthrough was achieved with the discovery of the first well-tolerated orally available agents. The first was chlorothiazide, the first thiazide diuretic and developed from the antibiotic sulfanilamide, which became available in 1958[94]

Society and culture

Awareness

[Fig 2.3.4: Graph showing, prevalence of awareness, treatment and control of hypertension compared between the four studies of NHANES]

The World Health Organization has identified hypertension, or high blood pressure, as the leading cause of cardiovascular mortality. The World Hypertension League (WHL), an umbrella organization of 85 national hypertension societies and leagues, recognized that more than 50% of the hypertensive population worldwide is unaware of their condition.[95] To address this problem, the WHL initiated a global awareness campaign on hypertension in 2005 and dedicated May 17 of each year as World Hypertension Day (WHD). Over the past three years, more national societies have been engaging in WHD and have been innovative in their activities to get the message to the public. In 2007, there was record participation from 47 member countries of the
WHL. During the week of WHD, all these countries – in partnership with their local governments, professional societies, nongovernmental organizations and private industries – promoted hypertension awareness among the public through several media and public rallies. Using mass media such as Internet and television, the message reached more than 250 million people. As the momentum picks up year after year, the WHL is confident that almost all the estimated 1.5 billion people affected by elevated blood pressure can be reached.\footnote{96}

### 2.3.5 Economics

High blood pressure is the most common chronic medical problem prompting visits to primary health care providers in USA. The American Heart Association estimated the direct and indirect costs of high blood pressure in 2010 as $76.6 billion.\footnote{83} In the US 80% of people with hypertension are aware of their condition, 71% take some antihypertensive medication, but only 48% of people aware that they have hypertension are adequately controlled.\footnote{83} Adequate management of hypertension can be hampered by inadequacies in the diagnosis, treatment, and/or control of high blood pressure.\footnote{97}Health care providers face many obstacles to achieving blood pressure control, including resistance to taking multiple medications to reach blood pressure goals. People also face the challenges of adhering to medicine schedules and making lifestyle changes. Nonetheless, the achievement of blood pressure goals is possible, and most importantly, lowering blood pressure significantly reduces the risk of death due to heart disease and stroke, the development of other debilitating conditions, and the cost associated with advanced medical care.\footnote{98}
REFERENCES


18. Dickinson, HO; Mason, JM; Nicolson, DJ; Campbell, F; Beyer, FR; Cook, JV; Williams, B; Ford, GA. "Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials.". Journal of hypertension24 , 2006 ;(2): 215-33.
22. Lawlor, DA; Smith, GD. "Early life determinants of adult blood pressure". Current opinion in nephrology and hypertension14, 2005; (3): 259–64.


47. Luma GB, Spiotta RT. "Hypertension in children and adolescents". Am Fam Physician 73, 2006; (9): 1558–68.


66. Eni C. Okonofua; Kit N. Simpson; Ammar Jesri; Shakaib U. Rehman; Valerie L. Durkalski; Brent M. Egan. "Therapeutic Inertia Is an Impediment to Achieving the Healthy People 2010 Blood Pressure Control Goals". Hypertension 47, 2006; 345–51.


84. Luma GB, Spiotta RT. "Hypertension in children and adolescents". Am Fam Physician 73 (9): 1558–68.


96. Alcocer L, Cueto L "Hypertension, a health economics perspective". Therapeutic Advances in Cardiovascular Disease 2 (3): 147–55.
2.4 INTRODUCTION OF DRUG
METOPROLOL SUCCINATE

2.4.1 Generic name: Metoprolol succinate

2.4.2 Chemical Name: \((\pm)-1-(Isopropyl amino)-3-[p-(2-methoxyethyl) phenoxy]-2-Propanolsuccinate\ (2:1)\ (salt)

2.4.3 Structure:

\[
\text{OCH}_2\text{CHCH}_2\text{NHCH(CH}_3)\text{CH}_2\text{OCH}_3
\]

\[
\text{COOH}
\]

\[
\text{CH}_2
\]

\[
\text{CH}_2
\]

\[
\text{COOH}
\]

2.4.4 Chemical Formula: \((C_{15}H_{25}NO_3)_2\cdot C_4H_6O_4\)

2.4.5 Molecular Weight: 652.8

2.4.6 Melting point: 136°C-137°C

2.4.7 Description: White crystalline powder

2.4.8 Solubility: freely soluble in water, soluble in methyl alcohol, slightly soluble in alcohol. Very soluble in ethyl acetate. \(^1\)\(^2\)

2.4.9 Mechanism of action:
Metoprolol is a beta1-selective (cardioselective) adrenergic receptor blocking agent also inhibits beta2-adrenoreceptors, chiefly located in the bronchial and Vascular musculature. Metoprolol has no sympathomimetic activity.

2.4.10 Clinical pharmacology:
Clinical pharmacology studies have confirmed the beta-blocking activity of Metoprolol in man as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

2.4.11 Dose: 25 to 100 mg

2.4.12 Dosage form: 25 to 100 mg Extended release Tablets and capsules
Table 2.4.1: Pharmacokinetic parameters of Metoprolol succinate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein binding</td>
<td>12%</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>50%</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>3-4 hours</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>4.2 L/Kg</td>
</tr>
<tr>
<td>Steady state concentration</td>
<td>25 ± 18 ng/ml</td>
</tr>
<tr>
<td>Biotransformation</td>
<td>Hepatic</td>
</tr>
</tbody>
</table>

2.4.13 Pharmacokinetics: [3-4]

Absorption:
Metoprolol Succinate is rapidly and almost completely absorbed from the GI tract; absorption of a single oral dose of 20–100 mg is complete in 2.5–3 hours. After an oral dose, about 50% of the drug administered as conventional tablets appears to undergo first-pass metabolism in the liver. Bioavailability of orally administered metoprolol succinate increases with increased doses, indicating a possible saturable disposition process of low capacity such as tissue binding in the liver. Steady-state oral bioavailability of extended-release tablets of metoprolol succinate given once daily at dosages equivalent to 50–400 mg of metoprolol succinate is about 77% of that of conventional tablets at corresponding dosages given once daily or in divided doses.

Distribution:
Metoprolol is widely distributed into body tissues. The concentration of the drug is greater in the heart, liver, lungs, and saliva than in the plasma. Metoprolol is 11–12% bound to serum proteins, apparently only to albumin. Following therapeutic doses, metoprolol concentrations in erythrocytes are about 20% greater than those in plasma, but the drug is available for elimination from these two sites at the same rate. Metoprolol crosses the placenta, and maternal and fetal blood concentrations are about equal. The drug crosses the blood-brain barrier; the concentration of metoprolol in CSF is about 78% of the simultaneous concentration in plasma.
Metabolism:
Metoprolol is metabolized by the cytochrome P-450 (CYP) microsomal enzyme system, predominantly by the 2D6 isoenzyme (CYP2D6). When administered orally, metoprolol exhibits stereo selective metabolism that is dependent on oxidation phenotype. Metoprolol does not inhibit or enhance its own metabolism. Three main metabolites of the drug are formed by oxidative deamination, O-dealkylation with subsequent oxidation, and aliphatic hydroxylation; these metabolites account for 85% of the total urinary excretion of metabolites.

Elimination:
Elimination of metoprolol appears to follow first-order kinetics and occurs mainly in the liver; the time required for the process apparently is independent of dose and duration of therapy. In healthy individuals and hypertensive patients, the elimination half-life of both unchanged drug and metabolites is about 3–4 hours.

Indications and usage:
Hypertension: metoprolol succinate extended release tablet is indicated for treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Angina pectoris: metoprolol succinate extended release tablet is indicated in the long term treatment of Angina pectoris.

Heart failure: metoprolol succinate extended release tablet is indicated for the treatment of stable, symptomatic heart failure of ischemic, hypertensive, or cardiomyopathic origin.

Contraindications:
Metoprolol succinate extended release tablets are contraindicated in severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome.

Side effects: dizziness, lightheadedness, drowsiness, tiredness, diarrhea, ataxia, trouble sleeping, nausea, headache etc.

REFERENCES
1) www.drugs.com
2) European Pharmacopoeia 5.0 :2032
4) http://www.medscape.com
2.5 INTRODUCTION TO POLYMER AND EXCIPIENTS

2.5.1 CARNAUBA WAX

1. Nonproprietary Names

- BP: Carnauba wax
- JP: Carnauba wax
- PhEur: Cera carnauba
- USPNF: Carnauba wax

2. Synonyms

Brazil wax; caranda wax; E903.

3. Chemical Name and CAS Registry Number

Carnauba wax [8015-86-9]

4. Empirical Formula and Molecular Weight

Carnauba wax consists primarily of a complex mixture of esters of acids and hydroxy acids, mainly aliphatic esters, \(\omega\)-hydroxy esters, \(p\)-methoxycinnamic aliphatic esters, and \(p\)hydroxycinnamic aliphatic diesters composed of several chain lengths, in which C26 and C32 alcohols are the most prevalent. Also present are acids, oxypolyhydric alcohols, hydrocarbons, resinous matter, and water.

5. Functional Category

Coating agent, for sustained action

6. Applications in Pharmaceutical Formulation or Technology

Carnauba wax is widely used in cosmetics, certain foods, and pharmaceutical formulations. Cosmetically, carnauba wax is commonly used in lip balms. Carnauba wax is the hardest and highest-melting of the waxes commonly used in pharmaceutical formulations and is used primarily as a 10% w/v aqueous emulsion to polish sugar-coated tablets. Aqueous emulsions may be prepared by mixing carnauba wax with an ethanolamine compound and oleic acid. The carnauba wax coating
produces tablets of good luster without rubbing. Carnauba wax may also be used in powder form to polish sugarcoated tablets. Carnauba wax (10–50% w/w) is also used alone or with other excipients such as hypromellose, hydroxypropyl cellulose, alginate/pectin-gelatin, Eudragit, and stearyl alcohol to produce sustained-release solid-dosage formulations.\textsuperscript{3–10} additionally, carnauba wax has been experimentally investigated for use in producing microparticles in a novel hot air coating (HAC) process developed as an alternative to conventional spray-congealing techniques.\textsuperscript{11}

7. Description

Carnauba wax occurs as a light brown- to pale yellow-colored powder, flakes, or irregular lumps of a hard, brittle wax. It has a characteristic bland odor and practically no taste. It is free from rancidity. Various types and grades are available commercially.

8. Pharmacopeial Specifications

<table>
<thead>
<tr>
<th>Test</th>
<th>JP 2001</th>
<th>PhEur 2005</th>
<th>USPNF 23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characters</td>
<td>+</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Identification</td>
<td>—</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Appearance of solution</td>
<td>—</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Melting range</td>
<td>80–86°C</td>
<td>80–88°C</td>
<td>80–86°C</td>
</tr>
<tr>
<td>Acid value</td>
<td>≤10.0</td>
<td>2–7</td>
<td>2–7</td>
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<tr>
<td>Saponification value</td>
<td>78–95</td>
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<td>78–95</td>
</tr>
<tr>
<td>Total ash</td>
<td>—</td>
<td>≤0.25%</td>
<td>≤0.25%</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>—</td>
<td>—</td>
<td>≤20 μg/g</td>
</tr>
<tr>
<td>Organic volatile impurities</td>
<td>—</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>Iodine value</td>
<td>5–14</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>0.990–1.002</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 2.5.1: Pharmacopieal Specifications of carnauba wax
9. Typical Properties

**Flash point:**

270–330°C

**Refractive index:**

\[ n_{90D} = 1.450 \]

**Solubility:**

Soluble in warm chloroform and in warm toluene; slightly soluble in boiling ethanol (95%); practically insoluble in water.

**Specific gravity:**

0.990–0.999 at 25°C

**Unsaponified matter:**

50–55%

10. Stability and Storage Conditions

Carnauba wax is stable and should be stored in a well-closed container, in a cool, dry place.

11. Incompatibilities

Not any incompatibility found with carnauba wax.

12. Method of Manufacture

Carnauba wax is obtained from the leaf buds and leaves of the Brazilian carnauba palm, Copernicia cerifera. The leaves are dried and shredded and the wax is then removed by the addition of hot water.

13. Safety

Carnauba wax is widely used in oral pharmaceutical formulations, cosmetics, and certain food products. It is generally regarded as an essentially nontoxic and nonirritant material.\textsuperscript{12–14} there have been reports of allergic contact dermatitis from
carnauba wax in mascara. The WHO has established an acceptable daily intake of up to 7 mg/kg body-weight for carnauba wax.\textsuperscript{15-16}

14. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

15. Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

16. Comments

In cosmetics, carnauba wax is mainly used to increase the stiffness of formulations, e.g. lipsticks and mascaras. The EINECS number for carnauba wax is 232-399-4.

17. Specific References


15. Chowdhury MM. Allergic contact dermatitis from prime yellow carnauba wax and coathylene in mascara. Contact Dermatitis 2002; 46(6): 244.

2.5.2 CETOSTEARYL ALCOHOL

1. Nonproprietary Names

- BP: Cetostearyl alcohol
- USPNF: Cetostearyl alcohol

2. Synonyms

Cetearyl alcohol; CrodaCol CS90; Lanette O; Tego Alkanol 1618; Tego Alkanol 6855.

3. Chemical Name and CAS Registry Number

Cetostearyl alcohol [67762-27-0] and [8005-44-5]

4. Empirical Formula and Molecular Weight

Cetostearyl alcohol is a mixture of solid aliphatic alcohols consisting mainly of stearyl (C18H38O) and cetyl (C16H34O) alcohols. The proportion of stearyl to cetyl alcohol varies considerably, but the material usually consists of about 50–70% stearyl alcohol and 20–35% cetyl alcohol, with limits specified in pharmacopeias. The combined stearyl alcohol and cetyl alcohol comprise at least 90% of the material. Small quantities of other alcohols, chiefly myristyl alcohol, make up the remainder of the material. Two emulsifying grades of cetostearyl alcohol are recognized by the PhEur 2005 and contain at least 7% surfactant, with Type A containing sodium cetostearyl sulfate and Type B containing sodium lauryl sulfate1-2.

5. Structural Formula

Stearyl (C18H38O) and Cetyl (C16H34O) alcohols.

6. Functional Category

Emollient; emulsifying agent; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Cetostearyl alcohol is used in cosmetics and topical pharmaceutical preparations. In topical pharmaceutical formulations, cetostearyl alcohol will increase the viscosity and impart body in both water-in-oil and oil-in-water emulsions. Cetostearyl alcohol
will stabilize an emulsion and also act as a co-emulsifier, thus decreasing the amount of surfactant required to form a stable emulsion. Cetostearyl alcohol is also used in the preparation of nonaqueous cream and sticks. Research articles have been published in which cetostearyl alcohol has been used to slow the dissolution of watersoluble drugs. In combination with surfactants, cetostearyl alcohol forms emulsions with very complex microstructures. These microstructures can include liquid crystals, lamellar structures, and gel phases.

8. Description

Cetostearyl alcohol occurs as white or cream-colored unctuous masses, or almost white flakes or granules. It has a faint, characteristic sweet odor. On heating, cetostearyl alcohol melts to a clear, colorless or pale yellow-colored liquid free of suspended matter.

9. Pharmacopeial Specifications for cetostearyl alcohol

<table>
<thead>
<tr>
<th>Test</th>
<th>PhEur 2005</th>
<th>USPNF 23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
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<td>+</td>
</tr>
<tr>
<td>Characters</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Appearance of solution</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Melting range</td>
<td>49–56°C</td>
<td>48–55°C</td>
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<tr>
<td>Acid value</td>
<td>≤1.0</td>
<td>≤2.0</td>
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<tr>
<td>Iodine value</td>
<td>≤2.0</td>
<td>≤4</td>
</tr>
<tr>
<td>Hydroxyl value</td>
<td>208–228</td>
<td>208–228</td>
</tr>
<tr>
<td>Saponification value</td>
<td>≤2.0</td>
<td>—</td>
</tr>
<tr>
<td>Assay of C₁₈H₃₈O</td>
<td>≥40.0%</td>
<td>≥40.0%</td>
</tr>
<tr>
<td>of C₁₆H₃₄O and C₁₈H₃₈O</td>
<td>≥90.0%</td>
<td>≥90.0%</td>
</tr>
</tbody>
</table>

Table 2.5.2: Pharmacopeial Specifications of cetosteary alcohol

10. Typical Properties

Solubility:

Soluble in ethanol (95%), ether, and oil; practically insoluble in water.
11. Stability and Storage Conditions

Cetostearyl alcohol is stable under normal storage conditions. Cetostearyl alcohol should be stored in a well-closed container in a cool, dry place\textsuperscript{10-13}.

12. Incompatibilities

Incompatible with strong oxidizing agents and metal salts.

13. Method of Manufacture

Cetostearyl alcohol is prepared by the reduction of the appropriate fatty acids from vegetable and animal sources. Cetostearyl alcohol can also be prepared directly from hydrocarbon Sources.

14. Safety

Cetostearyl alcohol is mainly used in topical pharmaceutical formulations and topical cosmetic formulations.

Cetostearyl alcohol is generally regarded as a nontoxic material, although it is essentially Nonirritating, sensitization reactions to cetostearyl, cetyl, and stearyl alcohols\textsuperscript{13–14} have been reported.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Cetostearyl alcohol is flammable and on combustion may produce fumes containing carbon monoxide.

16. Regulatory Status

Accepted as an indirect food additive and as an adhesive and a component of packaging coatings in the USA. Included in the FDA Inactive Ingredients Guide (oral tablets and topical emulsions, lotions, ointments, vaginal suppositories). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17. Related Substances

Anionic emulsifying wax; cetyl alcohol; sodium lauryl sulfate; stearyl alcohol\textsuperscript{14–15}. 
18. REFERENCES


2.5.3 WAX, WHITE

1. Nonproprietary Names

- BP: White beeswax
- JP: White beeswax
- USPNF: White wax

2. Synonyms

Bleached wax; E901.

3. Chemical Name and CAS Registry Number

White beeswax [8012-89-3]
4. Empirical Formula and Molecular Weight

White wax is the chemically bleached form of natural beeswax. Beeswax consists of 70–75% of a mixture of various esters of straight-chain monohydric alcohols with even-numbered carbon chains from C24 to C36 esterified with straight-chain acids\textsuperscript{16-18}. These straight-chain acids also have even numbers of carbon atoms up to C36 together with some C18 hydroxy acids. The chief ester is myricyl palmitate. Also present are free acids (about 14%) and carbohydrates (about 12%) as well as approximately 1% free wax alcohols and stearic esters of fatty acids\textsuperscript{1-2}.

5. Structural Formula

Beeswax consists of 70–75% of a mixture of various esters of straight-chain monohydric alcohols with even-numbered carbon chains from C24 to C36 esterified with straight-chain acids.

6. Functional Category

Controlled-release vehicle; stabilizing agent; stiffening agent\textsuperscript{3}.

7. Applications in Pharmaceutical Formulation or Technology

White wax is a chemically bleached form of yellow wax and is used in similar applications: for example, to increase the consistency of creams and ointments, and to stabilize water-in-oil emulsions. White wax is used to polish sugar-coated tablets and to adjust the melting point of suppositories. White wax is also used as a film coating in sustained-release tablets. White beeswax microspheres may be used in oral dosage forms to retard the absorption of an active ingredient from the stomach, allowing the majority of absorption to occur in the intestinal tract. Wax coatings can also be used to affect the release of drug from ion-exchange resin beads\textsuperscript{4,8}.

8. Description

White wax consists of tasteless, white or slightly yellow-colored sheets or fine granules with some translucence. Its odor is similar to that of yellow wax but is less intense.
9. Pharmacopeial Specifications

<table>
<thead>
<tr>
<th>Test</th>
<th>JP 2001</th>
<th>PhEur 2005</th>
<th>USP8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characters</td>
<td>+</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Drop point</td>
<td>60–67°C</td>
<td>61–66°C</td>
<td>62–6°C</td>
</tr>
<tr>
<td>Acid value</td>
<td>5–9 or 17–22</td>
<td>17–24</td>
<td>17–2°C</td>
</tr>
<tr>
<td>Ester value</td>
<td>—</td>
<td>70–80</td>
<td>72–75</td>
</tr>
<tr>
<td>Ester value : acid value ratio</td>
<td>—</td>
<td>3.3 : 4.3</td>
<td>—</td>
</tr>
<tr>
<td>Saponification value</td>
<td>80–100</td>
<td>87–104</td>
<td>+</td>
</tr>
<tr>
<td>Ceresin, paraffins, and certain other waxes</td>
<td>—</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Glycerols and other polyols</td>
<td>—</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Saponification cloud test</td>
<td>—</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>Purity</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Relative density</td>
<td>—</td>
<td>≈0.960</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 2.5.3: Pharmacopeial Specifications of beeswax\(^{11}\).

10. Typical Properties

Arsenic: ≤3 ppm

Density:

0.95–0.96 g/cm\(^3\)

Flash point:

245–258°C

Heavy metals:

≤0.004%

Iodine number:

8–11
Lead:

≤10 ppm

Melting point:

61–65°C

Peroxide value:

≤8

Solubility:

soluble in chloroform, ether, fixed oils, volatile oils, and warm carbon disulfide; sparingly soluble in ethanol (95%); practically insoluble in water.

Unsaponified matter:

52–55%

11. Stability and Storage Conditions

When the wax is heated above 150°C, esterification occurs with a consequent lowering of acid value and elevation of melting point. White wax is stable when stored in a well-closed container, protected from light.

12. Incompatibilities

Incompatible with oxidizing agents.

13. Method of Manufacture

Yellow wax (beeswax) is obtained from the honeycomb of the bee (Apis mellifera Linné (Fam. Apidae)); Subsequent treatment with oxidizing agents bleaches the wax to yield white wax.9

14. Safety

White wax is used in both topical and oral formulations, and is generally regarded as an essentially nontoxic and nonirritant material. However, although rare,
hypersensitivity reactions to beeswax (attributed to contaminants in the wax) have been reported.\textsuperscript{10-12}

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16. Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets, rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients\textsuperscript{13-14}.

17. Related Substances

Yellow wax

18. Reference


2.5.4 HYDROXY PROPYL METHYL CELLULOSE (HPMC)

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

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

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

4. **Typical properties**

   Melting point : 190-200°C

   Molecular weight : 10000-1,500,000

   pH : 5.5-8.0 for a 1% w/w aqueous solution.

   Density (bulk) : 0.341 g/cm³

   Density (true) : 1.326 g/cm³

   Viscosity : a wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared; increasing concentration also produces more viscous solutions. The Typical viscosity values for 2% (w/v) aqueous solutions of Methocel (Dow Chemical Co.) are shown in table.¹
<table>
<thead>
<tr>
<th>Methocel Product</th>
<th>Nominal viscosity mPa s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methocel K100 Premium LVEP</td>
<td>100</td>
</tr>
<tr>
<td>Methocel K4M Premium</td>
<td>4000</td>
</tr>
<tr>
<td>Methocel K15M Premium</td>
<td>15 000</td>
</tr>
<tr>
<td>Methocel K100M Premium</td>
<td>100 000</td>
</tr>
<tr>
<td>Methocel E4M Premium</td>
<td>4000</td>
</tr>
<tr>
<td>Methocel F50 Premium</td>
<td>50</td>
</tr>
<tr>
<td>Methocel E10M Premium CR</td>
<td>10 000</td>
</tr>
<tr>
<td>Methocel E3 Premium LV</td>
<td>3</td>
</tr>
<tr>
<td>Methocel E5 Premium LV</td>
<td>5</td>
</tr>
<tr>
<td>Methocel E6 Premium LV</td>
<td>6</td>
</tr>
<tr>
<td>Methocel E15 Premium LV</td>
<td>15</td>
</tr>
<tr>
<td>Methocel E50 Premium LV</td>
<td>50</td>
</tr>
<tr>
<td>Metolose 60SH</td>
<td>50, 4000, 10 000</td>
</tr>
<tr>
<td>Metolose 65SH</td>
<td>50, 400, 1500, 4000</td>
</tr>
<tr>
<td>Metolose 90SH</td>
<td>100, 400, 4000, 15 000</td>
</tr>
</tbody>
</table>

Table 2.5.4: Typical Viscosity Values for 2% (w/v) Aqueous Solutions of Methocel (Dow Chemical Co.). Viscosities Measured at 20°C².

5. **Incompatibilities:** Incompatible with oxidizing reagents.

6. **Health and safety:** Hydroxypropyl Methylcellulose is generally regarded as a nontoxic and nonirritant material.

7. **Storage and handling:** Hydroxypropyl Methylcellulose is a stable material although it is hygroscopic after drying. It is stored in a well closed container in cool and dry place.

8. **Applications in pharmaceutical formulation or technology:**

In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulations. Concentrations
between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes.²

Hypromellose is also used as a suspending and thickening agent in topical formulations. Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. It is also widely used in cosmetics and food products.

REFERENCES
