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REVIEW ARTICLE

Site Specific Oral Drug Delivery System

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ABSTRACT

The oral route remains the most considered one for administration of drugs. Several reasons can be pointed out to support this fact, namely ease of administration and full control of administration by the patient, together with a high degree of flexibility on dosing. In recent years a wide variety of newer oral drug delivery system like sustained/ controlled release dosage forms are designed and evaluated in order to overcome the limitation of conventional therapy. This review mainly focused on various site specific oral drug delivery systems and detailing about Buccal Patches, Medicated chewing gums, Colon targeted drug delivery system, Osmotic tablets, Pulsincap system, Egalet technology etc.

KEYWORDS

Oral route, Buccal mucosa, Oral drug delivery system, Medicated chewing gum, Colon targeted drug delivery system

INTRODUCTION

A drug can be administered via a many different routes to produce a systemic pharmacological effect. The most common method of drug administration is via per oral route in which the drug is swallowed and enters the systemic circulation primarily through the membrane of the small intestine. The oral route of drug administration is the most important method of administering drugs for systemic effect. The parenteral route is not routinely used for self–administration of medication. It is probable that at least 90 % of all drugs used to produce systemic effects are administered by the oral route. Absorption of drugs after oral administration may occur at the various body sites between the mouth and rectum.

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In general, the higher up a drug is absorbed along the alimentary tract, the more rapid will be its action, a desirable feature in most instances. A drug taken orally must withstand large fluctuation in pH as it travels along the gastrointestinal tract, as well as resist the onslaught of the enzymes that digest food and metabolism by micro flora that live there. It is estimated that 25% of the population finds it difficult to swallow tablets and capsules and therefore do not take their medication as prescribed by their doctor resulting in high incidence of non-compliance and ineffective therapy. Difficulty is experienced in particular by pediatrics and geriatric patients, but it also applies to people who are ill bedridden and to those active working patient who are busy or travelling, especially those who have no access to water. In these cases oral mucosal drug delivery is most preferred[1, 2].

Oral Mucosal Drug Delivery System

The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. As indicative by the wide range in this reported value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosa.[2] In general, the permeability's of the oral mucosa decrease in the order of sublingual greater than buccal and buccal greater than palatal.

This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and on-keratinized, the buccal thicker and nonkeratinized, and the palatal intermediate in thickness but keratinized. It is currently believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called 'membrane coating granules'. When cells go through differentiation, Membrane Coating Granule start forming and at the apical cell surfaces they fuse with the plasma membrane and their contents are discharged into the intercellular spaces at the upper one third of the epithelium.[2, 3]

Buccal Routes for Drug Absorption

There are two permeation pathways for passive drug transport across the oral mucosa: paracellular and transcellular routes. Permeants can use these two routes simultaneously, but one route is usually preferred over the other depending on the physicochemical properties of the diffusant. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubilities in this environment. The cell membrane, however, is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to a low partition coefficient. Therefore, the intercellular spaces pose as the major barrier to permeation of lipophilic compounds and the cell membrane acts as the major transport barrier for hydrophilic compounds.[3]

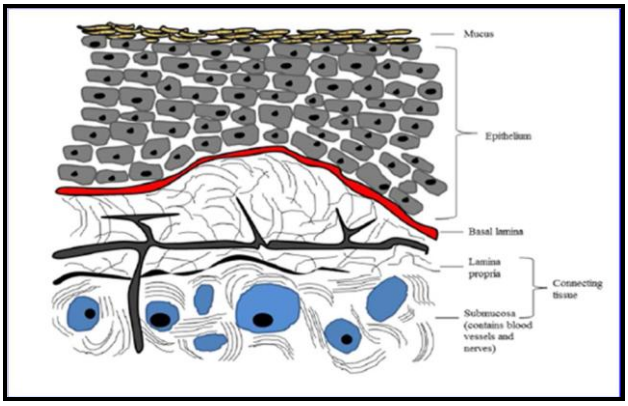

Figure 1: Structure of Buccal Mucosa[4]

There are three different categories of drug delivery within the oral cavity (i.e., sublingual, buccal, and local drug delivery). Selecting one over another is mainly based on anatomical and permeability differences that exist among the various oral mucosal sites. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailabilities of many drugs, and is convenient, accessible, and generally well accepted. The sublingual route is by far the most widely studied of these routes. Sublingual dosage forms are of two different designs, those composed of rapidly disintegrating tablets, and those consisting of soft gelatine capsules filled with liquid drug. Such systems create a very high drug concentration in the sublingual region before they are systemically absorbed across the mucosa. The buccal mucosa is considerably less permeable than the sublingual area, and is generally not able to provide the rapid absorption and good bioavailabilities seen with sublingual administration. Local delivery to tissues of the oral cavity has a number of applications, including the treatment of toothaches, periodontal disease, bacterial and fungal infections, aphthous and dental stomatitis, and in facilitating tooth movement with prostaglandins.

Advantages of Buccal Patches

1. The oral mucosa has a rich blood supply. Drugs are absorbed from the oral cavity through the oral mucosa, and transported

through the deep lingual or facial vein, internal jugular vein and braciocephalic vein into the systemic circulation.

2. The area of buccal membrane is sufficiently large to allow a delivery system to be placed at different occasions, additionally; there are two areas of buccal membranes per mouth, which would allow buccal drug delivery systems to be placed, alternatively on the left and right buccal membranes.
3. Buccal patch has been well known for its good accessibility to the membranes that line the oral cavity, which makes application painless and with comfort.
4. Patients can control the period of administration or terminate delivery in case of emergencies. The buccal drug delivery systems easily administered into the buccal cavity.[5]

Mechanism

Buccal drug absorption occurs by passive diffusion of the nonionized species, a process governed primarily by a concentration gradient, through the intercellular spaces of the epithelium. The passive transport of non-ionic species across the lipid membrane of the buccal cavity is the primary transport mechanism. The buccal mucosa has been said to be a lipoidal barrier to the passage of drugs, as is the case with many other mucosal membrane and the more lipophilic the drug molecule, the more readily it is absorbed[4]. The dynamics of buccal absorption of drugs could be adequately described by first order rate process. Several potential barriers to buccal drug absorption have been identified. Dearden and Tomlison (1971) pointed out that salivary secretion alters the buccal absorption kinetics from drug solution by changing the concentration of drug in the mouth.[6]

Composition of Buccal Patches

Active Ingredient Polymers (Adhesive Layer)

Hydroxy ethyl cellulose, hydroxyl propyl cellulose, polyvinyl alcohol, carbopol and other mucoadhesive polymers.

Diluents

Lactose DC is selected as diluent for its high aqueous solubility, its flavouring characteristics, and its physico-mechanical properties, which make it suitable for direct compression. Other example microcrystalline starch and starch.

Sweetening Agents

Sucralose, aspartame, mannitol, etc.

Flavouring Agents

Menthol, vanillin, clove oil, etc.

- Backing layer: Ethyl cellulose, etc.
- Penetration enhancer: Cyano acrylate, etc.
- Plasticizers: PEG-100, 400, propylene glycol, etc.

Medicated Chewing Gum

Medicated chewing gum has a history for about a century. Now-a-days it is considered to be a potential and convenient modified release drug delivery system which can be used in pain relief medication, smoking cessation, travel illness, freshening of breath, prevention of dental caries, alleviation of xerostomia, vitamin or mineral supplementation etc. Medicated chewing gums are prepared by using a water insoluble gum base with water soluble bulk portion.[7,8]

A medicated chewing gum is solid, single-dose preparation that is intended to be chewed for a certain period of time, deliver the drug and which may contain one or more than one active pharmaceutical ingredient. Chewing gums are not swallowed and the remaining mass after chewing is discarded. During chewing the drug contained in the gum is released into the saliva. The released drug has got two fates; either it could be absorbed through the oral mucosa or may reach the stomach for GI absorption. In fact both these two fates may occur simultaneously. So, medicated chewing gums offer both local and systemic effect. This drug delivery system offers two absorption pathways. Drug absorbed directly via the buccal membrane avoids metabolism in the gastrointestinal tract and thus the chance of first pass effect of the liver. As a result drug formulation as medicated chewing

gum may require reduced dose compared to other oral drug delivery systems.[9]

Benefits

Medicated chewing gums offer a range of advantages as identified by the classic review work of Imfeld in 1999. The advantages may be summarized as bellow:

- Chewing gum can be used without water, at any time, and everywhere.
- As the incorporated therapeutic agents are protected from oxygen, light, and water, product stability is good.
- Chewing gum can produce both local effects in the mouth (local delivery) and systemic effects after the active agents have been swallowed or (preferably) after they have been absorbed through the oral mucosa. The later is of special interest with respect to bio-availability, since it avoids metabolism of the drug in the gastrointestinal tract and the so called liver-first-pass effect, because oral veins drain into the vena cava.

Colon Targeted Drug Delivery System

The colon has gained attention on the delivery of drugs not only for the treatment of local diseases associated with the colon but also for its potential for the delivery of proteins and therapeutic peptides sensitive to the enzymes in both the stomach and small intestine. The proximal or ascendant colon is considered as the optimum site for colon-target delivery of drugs. The successful delivery to the colon requires the exploration of a unique feature of the colonic environment: consideration of transit times in the digestive tract (e.g. formulation of timed release systems, drug with a carrier, bioadhesive system and osmotic controlled drug delivery systems), pH (e.g. coating with pH sensitive polymers) and enzymes produced by colonic bacteria.[10]

Why Colon Targeted Drug Delivery System Needed?

To ensure direct treatment at the disease site, lower dosing and fewer systemic side effects. Colon-specific formulation could also be used to prolong the drug delivery. It should be considered as beneficial in the treatment of colon diseases. The colon is a site where both local or systemic drug delivery could be achieved. Topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's Disease. Such inflammatory conditions are usually treated with glucocorticoids and Sulphasalazine. A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon. Formulations for colonic delivery are also suitable for delivery of drugs which polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.[10]

Colon-Targeted Delivery Capsule Based on pH Sensitivity and Time-Release Principles

The system contains an organic acid that is filled in a hard gelatin capsule as a pH-adjusting agent together with the drug substance. This capsule is then coated with a three-layered film consisting of an acid-soluble layer, a hydrophilic layer, and an enteric layer (Figure 6). After ingestion of the capsule, these layers prevent drug release until the environmental pH inside the capsule decreases by dissolution of the organic acid, upon which the enclosed drug is quickly released. Therefore, the onset time of drug release is controlled by the thickness of the acid-soluble layer.

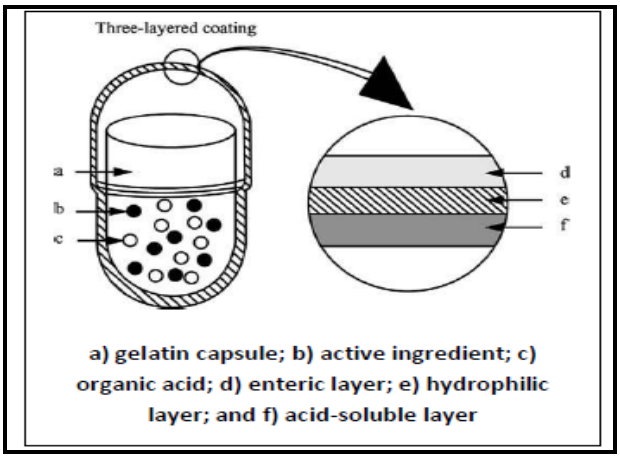

Figure 2: Design of the colon targeted delivery capsule[11]

Approaches for Colonic Drug Delivery

Prodrug Approaches

Prodrug is a pharmacologically inactive derivative of a parent molecule that requires enzymatic transformation in the biological environment to release the active drug at the target site. This approach involves covalent linkage between the drug and its carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine, and after reached in the colon, enzymatic cleavage regenerate the drug.

Azo Bond Conjugate

These azo compounds are extensively metabolized by the intestinal bacteria, both by intracellular enzymatic component and extracellular reduction. The use of these azo compounds for colon-targeting has been in the form of hydrogels as a coating material for coating the drug cores and as prodrug. In the latter approach the drug is attached via an azo bond to a carrier. This azo bond is stable in the upper GIT and is cleaved in the colon by the azo-reductases produced by the microflora.

Amino Acid Conjugation

Due to the hydrophilic nature of polar groups like -NH2 and -COOH, that is present in the proteins and their basic units (i.e. the amino acids), they reduce the membrane permeability of amino acids and proteins. Increase in hydrophilicity and chain length of carrier amino acid; decrease the permeability of amino acids and proteins. So the amino acid conjugate show more enzymatic specificity for hydrolysis by colonic enzyme.

Polymeric Prodrugs

Newer approaches are aimed at use of polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers are used for this purpose. Subsynthetic polymers have used to form polymeric prodrug with azo linkage between the polymer and drug moiety.[11]

Osmotic Tablets

Osmotic systems utilize the principle of osmotic pressure for the delivery of drugs. Drug release from these systems is independent of pH and other physiological parameter to a large extent and it is possible to modulate the release characteristic by optimizing the properties of drug and system.

The oral osmotic pumps have certainly came a long way and the available products on this technology and number of patent granted in the last few years makes it presence felt in the market. They are also known as gastro intestinal therapeutic system.[12]

Osmotic Drug Delivery Devices

They fall in two categories

1. Implantable

- ✓ The Rose and Nelson Pump
- ✓ Higuchi Leeper Pump
- ✓ Higuchi Theuwes pump
- ✓ Implantable Miniosmotic pump

2. Oral osmotic Pump

- ✓ Single chamber osmotic pump
- ✓ Elementary osmotic pump
- ✓ Multi chamber osmotic pump
- ✓ Push pull osmotic pump

Osmosis

Osmosis refers to the process of movement of solvent molecules from lower concentration to higher concentration across a semi permeable membrane. Osmosis is the phenomenon that makes controlled drug delivery a reality. Osmotic pressure created due to imbibitions of fluid from external environment into the dosage form regulates the delivery of drug from osmotic device. Rate of drug delivery from osmotic pump is directly proportional to the osmotic pressure developed due to imbibitions of fluids by osmogen.[12]

Basic Component of Osmotic Pumps[13]

1. Drug
2. Osmotic agent
3. Semi permeable membrane

Drugs

- ✓ Short biological half-life {2-6h}
- ✓ Highly potent drug
- ✓ Required for prolonged treatment. E.g. Nifedipine, Glipizide, Virapamil.

Osmotic Agents

Osmogents used for fabrication of osmotic dispensing device are inorganic or organic in nature a water soluble drug by itself can serve the purpose of an osmogent.

Inorganic Water-Soluble Osmogents

- ✓ Magnesium sulphate
- ✓ Sodium chloride
- ✓ Sodium sulphate
- ✓ Potassium chloride

Organic Polymer Osmogents

- ✓ Sodium carboxymethyl cellulose
- ✓ Hydroxypropylmethyl cellulose
- ✓ Hydroxyethylmethylcellulose
- ✓ Methylcellulose
- ✓ Polyethylene oxide
- ✓ Polyvinyl pyrollidine

Semi Permeable Membrane

The semi permeable membrane should be a stable both to the outer inner environment of the device. The membrane must be sufficiently rigid so as to retain its dimensional integrity during the operational lifetime of the device. The membrane should also be relatively impermeable to the contents of dispenser so that osmogent is not lost by diffusion across the membrane finally, the membrane must be biocompatible.

The elementary osmotic pump is a new delivery system for drugs. It delivers the agent by an osmotic process at a controlled rate. Control resides in the:

a) Water permeation characteristics of a semi permeable membrane surrounding the formulating agent

b) Osmotic properties of the formulation

Elementary Osmotic Pump

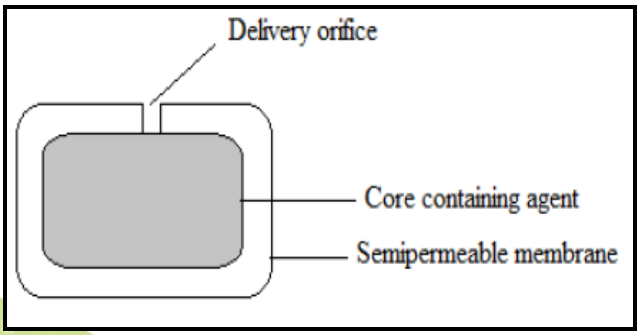

Figure 3: Elementary osmotic pump[13]

In its simplest embodiment the system is constructed by coating an osmotically active agent with the rate controlling semipermeable membrane. This membrane contains an orifice of critical size through which agent is delivered. The dosage form after coming into contact with aqueous fluids, imbibes water at a rate determined by the fluid permeability of the membrane and osmotic pressure of the core formulation. This osmotic imbibitions of water result in formation of a saturated solution of drug within the core, which is dispensed at controlled rate from the delivery orifice in the membrane.

Push Pull Osmotic Pump

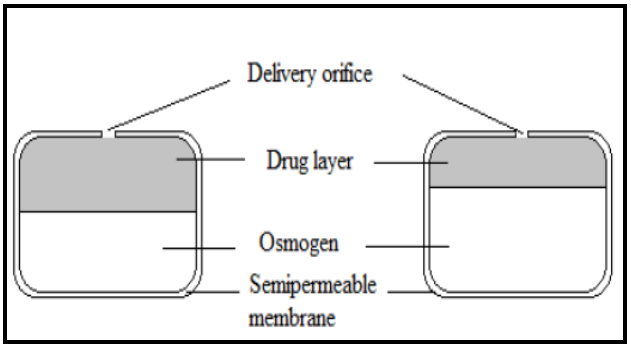

Figure 4: Pull push osmotic pump[13]

Push pull osmotic pump is a modified EOP. Through, which it is possible to deliver both poorly water-soluble and highly water soluble drugs at a constant rate. This system resembles a standard bilayer coated tablet. One layer (depict as the upper layer) contains drug in a formulation of polymeric, osmotic agent and other tablet excipients. This polymeric osmotic agent has the ability to form a suspension of drug in situ. When this tablet later imbibes water, the other layer contains osmotic and colouring agents, polymer and tablet excipients.

These layers are formed and bonded together by tablet compression to form a single bilayer core. The tablet core is then coated with semipermeable membrane. After the coating has been applied, a small hole is drilled through the membrane by a laser or mechanical drill on the drug layer side of the tablet. When the system is placed in aqueous environment water is attracted into the tablet by an osmotic agent in both the layers. The osmotic attraction in the drug layer pulls water into the compartment to form in situ a suspension of drug.

Liquid Oral Osmotic System

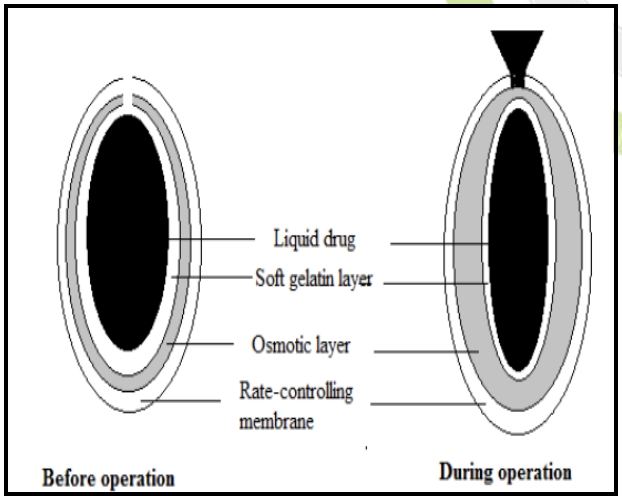

Figure 5: Liquid oral osmotic system[13]

Liquid OROS are designed to deliver drugs as liquid formulations and combine the benefits of extended release with high bioavailability. They are of three types: -

i. L OROS hard cap,

ii. L OROS soft cap

Delayed Liquid Bolus Delivery system

Each of these systems includes a liquid drug layer, an osmotic engine or push layer and a semipermeable membrane coating. When the system is in contact with the aqueous environment water permeates across the rate controlling membrane and activate the osmotic layer. The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system, thereby forcing the liquid formulation to be delivered from the delivery orifice. Whereas L OROS hardcap or softcap system is designed to provide continuous drug delivery, the L OROS delayed liquid bolus drug delivery system is designed to deliver a pulse of liquid drug.

The delayed liquid bolus delivery system comprises three layers: a placebo delay layer, a liquid drug layer and an osmotic engine, all surrounded by rate controlling semi permeable membrane. The delivery orifice is drilled on the placebo layer end of the capsule shaped device. When the osmotic engine is expands, the placebo is released first, delaying release of the drug layer. Drug release can be delayed from I to 10 hour, depending on the permeability of the rate controlling membrane and thickness of the placebo layer[12]

Delayed Delivery Osmotic Device

Because of their semi permeable walls, an osmotic device inherently show lag time before drug delivery begins. Although this characteristic is usually cited as a disadvantage, it can be used advantageously. The delayed release of certain drug (drugs for early morning asthma or arthritis) may be beneficial.

Pulsincap System

Pulsatile systems are achieving a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed based on the circadian rhythm of the body. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is

not desired. Products available as once-a-daily formulation based on Pulsatile release like Pulsincap®, Ritalin®, and Pulsys®.[14]

Components of Pulsincap System

R. R. Scherer (International Corporation, Michigan, US) developed Pulsincap. This system comprises of a water-insoluble capsule enclosing the drug reservoir. Seal the drug contents into the capsule body, a swell able hydrogel plug was used. It swelled, when this capsule came in contact with the dissolution fluid and after a lag time, the plug pushed itself outside the capsule and rapidly released the drug (Fig. 13). Various polymers used for designing of the hydrogel plug were various viscosity grades of hydroxyl propyl methyl cellulose, polymethyl methacrylates, polyvinyl acetate and poly ethylene oxide. The length of the plug and its point of insertion into the capsule controlled the lag time.

Pulsincap was studied in human volunteers and was reported to be well tolerated. As the swelling hydrogel polymer plug replaced the erodible tablet, the dependence of the dimensional accuracy between the plug and the capsule for the pulling mechanism of the plug from the capsule was also overcome. A release profile is characterized by a period during which no release followed by rapid and complete drug release. Release using this system was found to be reproducible in-vitro and in-vivo. When gastrointestinal transit of the formulations was carried out by gamma scintigraphy, it was found that in six of the eight subjects that the device reached the colon before drug was released.[15]

Enterion & Egalet Technology

The Enterion capsule has recently been developed by Phacton Research, Nottingham, UK, for targeted delivery of a wide range of different drug formulations into any region of the gut. It is a 32-mm long, round-ended capsule and contains a drug reservoir with a volume capacity of approximately 1 ml. The capsule can be loaded with either a liquid formulation (e.g. Solution, Suspension) or a particulate formulation (e.g., powder, pellets, in sit affects etc.) through an opening 9 mm in diameter, which is then sealed by inserting a push-on Cap fitted with a silicone O-ring.[16]

Figure 6: Design of enter-ion capsule[16]

A radioactive marker is placed inside a separate sealed tracer port to allow real time visualization of the capsule location using the imaging technique of gamma Scintigraphy. When the capsule reaches the target location in the gastrointestinal tract, the contents are actively ejected by the external application of an oscillating magnetic field. The frequency of the magnetic field is set in the low MHz region, low enough so that there is negligible absorption of the energy by the body tissues but sufficiently high enough to induce unable power in a tuned coil antenna embedded in the capsule wall. The power induced in the coil by the magnetic field is fed to a tiny heater resistor located within a separate sealed electronics compartment inside the capsule.

Although the power is only a few tenths of a wall, the small size of the heater (less than 1mm3) means that heat build up is extremely rapid. The heater resistor is in direct contact with the restraining filament, causing it to softer and breaks with the increase in temperature. This is turn, releases the spring and driver the piston. The resulting increase in pressure within the drug reservoir forces off the O-ring sealed cap and rapidly ejects the drug or drug formulation into the surrounding GI fluids. The piston motion is stopped near the end of the capsule, which maintains a seal and presents contact of the internal electronic compartments with the GI fluids. The movement of the piston also operates a switch, which directs some of the electrical energy away from the heater and

uses it to transmit a weak radio signal at a precise frequency. Detection of this signal externally confirms that the capsule has opened successfully.[16]

Components Involved in Egalet Technology

Egalet technology is used for a series of controlled release products developed by Egalet Ltd. Egalet technology works by incorporating the active ingredient into a polymeric matrix that is eroded by body fluids at a constant rate. The tablet is made by way of injection molding techniques involving only few steps. Egalet technique breaks new ground because it can be used for virtually any type of medicine and because it provides controlled release with unusual precision and reliability. Egalet additionally holds various proprietary drug delivery technologies that enable it to develop products for special populations and controlled release formulations with extreme precision for chronotherapy. Egalet has several opioid compounds in development, but currently the development focus is Egalet oxycodo.[17]

Mechanism of Action

Egalet Ltd. has developed one of the world's first erosion based pill that allows for the controlled release of drugs. The unconventionally shaped pill is made up of an inner matrix which contains the active ingredient and an outer coating shell made up of specific polymers.

The Matrix

The inner matrix has been designed for improved bioavailability, for specific situations where an insoluble active substance is needed, and to prevent abuse or misuse of the matrix. The matrix composition is made up of the following: 1. a mixture of a first (polyethylene glycols and/or polyethylene oxides) and second polymers (block co-polymer of ethylene oxide and/or propylene oxide) that have plasticizing characteristics. The melting points of the polymers are at the most 200 Celsius. The combination of the polyethylene oxides and the blocking co-polymer enable the control of the amorphous state. Some examples of the second block polymers used include poly(ethylene-glycol-b-(DL-lactic acid-co-glycolic acid)-b-ethylene glycol (PEG-PLGA PEG), poly((DL-lactic acid-co-glycolic acid)-g-ethylene glycol) (PLGA-g-PEG), poloxamers and polyethylene oxide-polypropylene oxide (PEO-PPO), a therapeutically, and/or diagnostically active substance.[17]

Polymer

The first polymer is a polyethylene glycol and/or a polyethylene oxide. Polyethylene glycols (which are denoted as polyethylene oxides when the molecular weight is above about 100,000) are mixtures of condensation polymers of ethylene glycol. In preferable conditions, the first polymer has a molecular weight of about 35,000 Daltons. Mixtures of PEG's may be used to get the ideal molecular weight for specific formulations.[17]

CONCLUSION

In recent years a wide variety of newer oral drug delivery system like sustained/ controlled release dosage forms are designed and evaluated in order to overcome the limitation of conventional therapy. These products are able to maintain steady drug plasma levels for extended periods of time as a result the variation of the drug levels in the blood are prevented and minimized drug related side effects. Buccal Mucosa Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods.

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