CHAPTER II

LITERATURE ON CONTROLLED RELEASE DRUG DELIVERY SYSTEMS
(MICROCAPSULES AND MATRIX TABLETS)

Controlled release drug delivery systems \(^1\) are those dosage formulations designed to release an active ingredient at rates, which differ significantly from their corresponding conventional dosage forms. The controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of the drug to a tissue. Drug release from these systems should be at a desired rate, predictable and reproducible.

Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or active agent in such a way that the active agent is released from the material in a predesigned manner. The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events. Controlled release drug delivery systems provided one or more of the following advantages.

1. Maintenance of optimum therapeutic drug concentration in the blood with minimum fluctuations.

2. Predictable and reproducible release rates for extended duration.
4. Elimination of side effects, frequent dosing and wastage of drugs.
5. Optimized therapy and better patient compliance.
6. To mask the unpleasant taste and odour of drugs.
8. Alteration of site of absorption.
9. Elimination of incompatibilities among the drugs.

The ideal drug delivery system should be inert, biocompatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from accidental release, simple to administer and remove, and easy to fabricate and sterilize.

In recent years, controlled drug delivery formulations and the polymers used in these systems have become much more sophisticated, with the ability to do more than simply extend the effective release period for a particular drug. For example, current controlled-release systems can respond to changes in the biological environment and deliver-or cease to deliver – drugs based on these changes. In addition, materials have been developed that should lead to targeted delivery systems, in which a particular formulation can be directed to the specific cell, tissue or site where the drug it contains is to be delivered. While much of this work is still in its early stages, emerging technologies offer possibilities that scientists have only begun to explore.
2.1 ORAL CONTROLLED RELEASE SYSTEMS

The oral route is the most convenient and common mode for administration of controlled release systems.

Oral route has been the most popular and successfully used for controlled delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design (possible because of versatility of g.i. anatomy and physiology) and ease of production and low cost of such a system. These systems have gained importance because of the technological advances made in fabrication, which help to achieve zero order release rates of therapeutic moiety. The majority of oral controlled release systems rely on dissolution, diffusion or a combination of both mechanisms to generate slow release of drug to the gastrointestinal milieu. Starting with limited data on a drug candidate for sustained release, such as dose, rate constants for absorption and elimination, some elements of metabolism and some physico-chemical properties of the drug, one can estimate a desired release rate for the dosage form, the quantity of the drug needed, and a preliminary strategy for the dosage form to be utilized. The advantages of oral drug delivery systems are i) Reduced dosing frequency, ii) Better patient convenience and compliance, iii) Reduced gastro-intestinal side effects and toxic effects, iv) Less fluctuating plasma drug level, v) Most uniform drug therapeutic effect, vi) Better stability of the drug.

The following are the major types of controlled release systems intended for oral use.
1. Matrix tablets

Matrix tablets are monolithic systems in which drug is homogeneously dispersed throughout a rate controlling medium. To control the release of the drugs, hydrophobic and hydrophilic matrices have been used. For water soluble drugs; the hydrophobic and hydrophilic matrices are mixed. For moderately or poorly soluble drugs hydrophilic matrices are used. The drug dissolution is controlled by controlling the rate of penetration of dissolution fluid in to the matrix by altering the porosity of tablet, decreasing its wettability or by itself getting dissolved at slower rate. The widely used hydrophobic and hydrophilic materials for the preparation of matrix tablets are bees wax, hydrogenated castor oil, hydroxy propyl methyl cellulose, xanthum gum and ethyl cellulose.

2. Mucoadhesive tablets

Mucoadhesive tablets are the controlled release drug delivery systems, bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the gastric retention time of drug delivery system in the stomach. These systems prolong the intimacy and duration of contact of drug with the biological membrane. Mucoadhesive polymers used in the preparation of tablets utilize the property of adhesive interaction with a biological or gastrointestinal mucosal surface. The characteristics of a mucoadhesive polymer are molecular flexibility, hydrophilic functional groups, specific molecular weight, chain length and conformation. These dosage forms are readily localized in the region applied to enhance the bioavailability of drugs. These dosage forms facilitate intimate contact of the formulation with the underlying absorption surface. This allows modification of tissue permeability for absorption of drugs. Mucoadhesive polymers are water insoluble and water soluble polymers, which form swellable
networks jointed by the cross linking agents. The commonly used polymers are sodium carboxy methyl cellulose, carbopol, polycarbophil, sodium alginate, hydroxy propyl methyl cellulose and gelatin.

The mucoadhesive drug delivery systems in the form of tablets, patches, films and solutions have been developed for oral, buccal, vaginal, rectal and ocular routes for enhancing bioavailability and for controlled release.

3. Microcapsules and microspheres

Microcapsules and microspheres are polymeric particles ranging in size from 1-1000 µm. Microencapsulation is the process used to encase liquids, solids and gases enclose within the polymeric embryonic membrane. The mechanism of release is either by dissolution or diffusion of drug and the formulations are either as encapsulated (microcapsules) or matrix (microspheres) form. Various methods such as interfacial polymerization, coacervation-phase separation are used to prepare microcapsules/microspheres. The thickness of the microcapsule coat can be adjusted from 1 µm to 200 µm by changing the amount of coating material applied from 3-30% of total weight. The coating material can be selected from a wide variety of natural and synthetic polymers depending on the material to be coated and the release characteristics desired. Microcapsules posses additional advantage that sustained release of drug can be achieved with taste masking and better g.i. tolerability.
4. **Ion-exchange resins**

The use of ion exchange resins is an attractive method for sustained drug delivery. These types of systems are developed by embedding the drug molecules in the ion-exchange resin matrix. In these systems drug release characteristics largely depend only on the ionic environment of the resins containing drug. Ion exchange based drug delivery systems are better suitable for drugs that are highly susceptible to degradation by enzymatic processes. Ion exchange resins can be divided into cation exchange resins and anion exchange resins. The most widely used and safe ion-exchange resin is divinyl benzene sulphonate.

5. **Film coated tablets**

Coating of the tablets by using film forming polymers can control the dissolution rate of drug from the tablets. Various polymers such as hydroxy propyl methyl cellulose (HPMC), ethyl cellulose and eudragit have been used for the polymeric film coating of the tablets. The polymer coatings act as diffusion controlling mechanisms. By using both hydrophilic and hydrophobic polymers one can accelerate the drug release. Thickness of the polymer coat is the important parameter for the desired dissolution rate.

6. **Floating tablets**

Increased gastro intestinal transit time is the consequent property of floating tablets. Floating tablets are used for local action in the proximal g.i. tract. These systems are designed to have lesser specific gravity than the gastric contents, thereby float on the gastro intestinal fluid for extended period. Poorly soluble and unstable as well as poorly absorbable (in intestine) drugs are suitable
for floating dosage units. Hydrodynamically balanced systems are the typical examples of floating tablets.

7. Swellable tablets

Swellable tablets are developed in a size, which can be swallowed and when they reach stomach fluid, swell quickly and attain considerably larger size. The dosage form is larger than the pylorus opening; it cannot pass through pylorus, thereby, the residence time in stomach increases. The gastric emptying of the swellable tablets is affected by their physical properties such as size, shape and flexibility. In addition to the swelling, the gel forming property of the polymer can retain the drug molecules within dosage form, there by sustaining the release of drug from the formulations. Swellable tablets are prepared in various shapes such as disk, string, pellet and tetrahedron. The tetrahedron shaped tablets showed an increased residence time in stomach than tablets of other shapes. The commonly used materials are gum karaya, guar gum, hydroxyl ethyl methacrylate and polyethylene glycol.

8. Osmotic tablets

The osmotic tablets are comprised of a drug contained in a rigid, semi permeable membrane in which an aperture (300 µm approx.) is created by a mechanical drill or a laser beam. These systems are suitable for the controlled release of water soluble drugs. The dispersion of drug molecules in the hydrogel with in the tablet leads to controlled release. When water penetrates through the semi-permeable membrane into the tablet mass by osmosis, osmotic pressure is developed with in the tablet and as a result saturated solution of drug is forced out of the tablet through the aperture. The two major factors, which control the
release, are the membrane permeability and the quality and quantity of hydrogel polymer. Semi-permeable polymers such as cellulose acetate, ethyl carbamate, polyamide and polyurethane are widely used.

9. **Micro and multiple emulsions**

Micro or sub-micron emulsions are having the dispersed phase diameter less than 0.1µm and appear translucent or transparent and they are thermodynamically stable compared to conventional emulsions. Multiple emulsions are containing three phases either o/w/o or w/o/w type. The selection of type of emulsion depends on the hydrophilic or lipophilic nature of the drugs. Lipid soluble drugs are more suitable to these systems for improved absorption.

10. **Electrically stimulated release devices**

These are monolithic devices prepared by using polyelectrolyte gels which swell when an external electrical stimulus is applied, causing a change in pH. The release could be modulated, by the current, giving a pulsatile release profile.

11. **Bioadhesive systems**

Bioadhesive can be defined as any substance that can adhere to a biological membrane and remain there for an extended period of time. If the membrane substrate is then the polymer is referred to as mucoadhesive. The bioadhesives increase the residence time and contact time at the area of absorption and provide a high concentration gradient across the membrane.
Among the various techniques, microencapsulation and matrix tablets have been widely accepted for controlled release. In the present work microencapsulation and matrix tablet by starch acetate and EVA was tried for obtaining controlled release of glipizide. An overview of literature on microencapsulation and matrix devices is given here.

2.2 MICROENCAPSULATION AND MICROCAPSULES

Microencapsulation may be defined as the process of surrounding or enveloping one substance within another substance on a very small scale, yielding capsules ranging from less than one micron to several hundred microns in size. Microcapsules may be spherically shaped, with a continuous wall surrounding the core, while others are asymmetrically and variably shaped, with a quantity of smaller droplets of core material embedded throughout the microcapsule. Types of microcapsules are shown in Fig. 2.1. All three states of matter (solids, liquids, and gases) may be microencapsulated. This allows liquid and gas phase materials to be handled more easily as solids, and can afford some measure of protection to those handling hazardous materials.

Microencapsulation may be achieved by a myriad of techniques, with several purposes in mind. Substances may be microencapsulated with the intention that the core material be confined within capsule walls for a specific period of time. Alternatively, core materials may be encapsulated so that the core material will be released either gradually through the capsule walls, known as controlled release or diffusion, or when external conditions trigger the capsule walls to rupture, melt, or dissolve. The substance that is encapsulated may be called the core material, the active ingredient or agent, fill, payload, nucleus, or
internal phase. The material encapsulating the core is referred to as the coating, membrane, shell, or wall material. Microcapsules may have one wall or multiple shells arranged in strata of varying thicknesses around the core.

Fig. 2.1: Various Types of Microcapsules
Applications:

There are almost limitless applications for microencapsulated material. Microencapsulated materials are utilized in agriculture, pharmaceuticals, foods, cosmetics and fragrances, textiles, paper, paints, coatings and adhesives, printing applications, and many other industries.

Historically, carbonless copy paper was the first marketable product to employ microcapsules. A coating of microencapsulated colorless ink is applied to the top sheet of paper, and a developer is applied to the subsequent sheet. When pressure is applied by writing, the capsules break and the ink reacts with the developer to produce the dark color of the copy.

Today’s textile industry makes use of microencapsulated materials to enhance the properties of finished goods. One application increasingly utilized is the incorporation of microencapsulated phase change materials (PCMs). Phase change materials absorb and release heat in response to changes in environmental temperatures. When temperatures rise, the phase change material melts, absorbing excess heat, and feels cool. Conversely, as temperatures fall, the PCM releases heat as it solidifies, and feels warm. This property of microencapsulated phase change materials can be harnessed to increase the comfort level for users of sports equipment, military gear, bedding, clothing, building materials, and many other consumer products. Microencapsulated PCMs have even been used in NASA-patented thermal protection systems for spacecraft.

Pesticides are encapsulated to be released over time, allowing farmers to apply the pesticides less often rather than requiring very highly concentrated and
perhaps toxic initial applications followed by repeated applications to combat the loss of efficacy due to leaching, evaporation and degradation. Protecting the pesticides from full exposure to the elements lessens the risk to the environment and those that might be exposed to the chemicals and provides a more efficient strategy to pest control.

Ingredients in foods are encapsulated for several reasons. Most flavorings are volatile; therefore encapsulation of these components extends the shelf-life of products by retaining within the food flavors that would otherwise evaporate out and be lost. Some ingredients are encapsulated to mask taste, such as nutrients added to fortify a product without compromising the product’s intended taste. Alternatively, flavors are sometimes encapsulated to last longer, as in chewing gum. The amount of encapsulated flavoring required is substantially less than liquid flavoring, as liquid flavoring is lost and not recovered during chewing. Flavorings that are comprised of two reactive components that, when encapsulated individually, may be added to the finished product separately so that they do not react and lose flavor potential prematurely. Some flavorings must also be protected from oxidation or other reactions caused by exposure to light. Many varieties of both oral and injected pharmaceutical formulations are microencapsulated to release over longer periods of time or at certain locations in the body. Aspirin, for example, can cause peptic ulcers and bleeding if doses are introduced all at once. Therefore aspirin tablets are often produced by compressing quantities of microcapsules that will gradually release the aspirin through their shells, decreasing risk of stomach damage.
**Microencapsulation Processes:**

Microencapsulation processes can be classified as follows:

I. Chemical processes
   i) Interfacial polymerization
   ii) *In situ* polymerization
   iii) Orifice method

II. Physico-chemical processes
   i) Coacervation - phase separation from aqueous solution
   ii) Coacervation - phase separation in organic solution
   iii) Complex coacervation
   iv) Complex emulsion
   v) Meltable dispersion
   vi) Powder bed

III. Mechanical processes
   i) Air suspension or fluidized bed coating
   ii) Pan coating
   iii) Spray - drying
   iv) Spray - congealing
   v) Electrostatic bonding

Microencapsulation processes are usually categorized into two groupings: chemical processes and mechanical or physical processes. These labels can, however, be somewhat misleading, as some processes classified as mechanical might involve or even rely upon a chemical reaction, and some chemical
techniques rely solely on physical events. A clearer indication as to which category an encapsulation method belongs is whether or not the capsules are produced in a tank or reactor containing liquid, as in chemical processes, as opposed to mechanical or physical processes, which employ a gas phase as part of the encapsulation and rely chiefly on commercially available devices and equipment to generate microcapsules.

**Chemical Methods:**

Capsules for carbonless paper and for many other applications are produced by a chemical technique called complex coacervation. This method of encapsulation takes advantages of the reaction of aqueous solutions of cationic and anionic polymers such as gelatin and gum arabic. The polymers form a concentrated phase called the complex coacervate. The coacervate exists in equilibrium with a dilute supernatant phase. As water-immiscible core material is introduced into the system, thin films of the polymer coacervate coat the dispersed droplets of core material. The thin films are then solidified to make the capsules harvestable.

Interfacial polymerization (IFP) is another chemical method of microencapsulation. This technique is characterized by wall formation via the rapid polymerization of monomers at the surface of the droplets or particles of dispersed core material. A multifunctional monomer is dissolved in the core material, and this solution is dispersed in an aqueous phase. A reactant to the monomer is added to the aqueous phase, and polymerization quickly occurs at the surfaces of the core droplets, forming the capsule walls. IFP can be used to prepare bigger microcapsules, but most commercial IFP processes produce
smaller capsules in the 20-30 micron diameter range for herbicides and pesticide uses, or even smaller 3-6 micron diameter range for carbonless paper ink.

Polymer-polymer incompatibility, also called phase separation, is generally grouped with other chemical encapsulation techniques, despite the fact that usually no actual chemical reaction is involved in the process. This method utilizes two polymers that are soluble in a common solvent; yet do not mix with one another in the solution. The polymers form two separate phases, one rich in the polymer intended to form the capsule walls, the other rich in the incompatible polymer meant to induce the separation of the two phases. The second polymer is not intended to be part of the finished microcapsule wall, although some may be caught inside the capsule shell and remain as an impurity.

*In situ* polymerization is a chemical encapsulation technique very similar to interfacial polymerization. The distinguishing characteristic of *in situ* polymerization is that no reactants are included in the core material. All polymerization occurs in the continuous phase, rather than on both sides of the interface between the continuous phase and the core material, as in IFP. Examples of this method include urea-formaldehyde (UF) and melamine formaldehyde (MF) encapsulation systems.

Centrifugal force processes were developed in the 1940s to encapsulate fish oils and vitamins, protecting them from oxidation. In this method an oil and water emulsion is extruded through small holes in a cup rotating within an oil bath. The aqueous portion of the emulsion is rich in a water-soluble polymer, such
as gelatin, that gels when cooled. The resulting droplets are cooled to form gelled polymer-matrix beads containing dispersed droplets of oil that are dried to isolate.

Similar in concept to centrifugal force processes, submerged nozzle processes produce microcapsules when the oil core material is extruded with gelatin through a two-fluid nozzle. The oil droplets are enveloped in gelatin as they are extruded through the nozzle. Then the capsules are cooled to gel the walls, before being collected and dried.

**Physical Methods:**

Spray drying is a mechanical microencapsulation method developed in the 1930’s. An emulsion is prepared by dispersing the core material, usually an oil or active ingredient immiscible with water; into a concentrated solution of wall material until the desired size of oil droplets are attained. The resultant emulsion is atomized into a spray of droplets by pumping the slurry through a rotating disc into the heated compartment of a spray drier. There the water portion of the emulsion is evaporated, yielding dried capsules of variable shape containing scattered drops of core material. The capsules are collected through continuous discharge from the spray drying chamber. This method can also be used to dry small microencapsulated materials from aqueous slurry that are produced by chemical methods.

Fluid bed coating, another mechanical encapsulation method, is restricted to encapsulation of solid core materials, including liquids absorbed into porous solids. This technique is used extensively to encapsulate pharmaceuticals. Solid particles to be encapsulated are suspended on a jet of air and then covered by a
spray of liquid coating material. The capsules are then moved to an area where
their shells are solidified by cooling or solvent vaporization. The process of
suspending, spraying, and cooling is repeated until the capsules’ walls are of the
desired thickness. This process is known as the Wurster process when the spray
nozzle is located at the bottom of the fluidized bed of particles. Both fluidized bed
coating and the Wurster process are variations of the pan coating method. In pan
coating, solid particles are mixed with a dry coating material and the temperature
is raised so that the coating material melts and encloses the core particles, and
then is solidified by cooling; or, the coating material can be gradually applied to
core particles tumbling in a vessel rather than being wholly mixed with the core
particles from the start of encapsulation.

Centrifugal extrusion processes generally produce capsules of a larger size,
from 250 microns up to a few millimeters in diameter. The core and the shell
materials, which should be immiscible with one another, are pushed through a
spinning two-fluid nozzle. This movement forms an unbroken rope which
naturally splits into round droplets directly after clearing the nozzle. The
continuous walls of these droplets are solidified either by cooling or by a gelling
bath, depending on the composition and properties of the coating material.

Another mechanical encapsulation process is rotational suspension
separation, or the spinning disk method. The internal phase is dispersed into the
liquid wall material and the mixture is advanced into a turning disk. Droplets of
pure shell material are thrown off the rim of the disk along with discrete particles
of core material enclosed in a skin of shell material. After having been solidified
by cooling, the microcapsules are collected separately from the particles of shell material.

2.3 CONTROLLED RELEASE THROUGH MICROENCAPSULATION

Microencapsulation has been widely employed in the design of controlled release dosage forms. The capsule shells can be designed to release their ingredients at specific rate and/or under specific set of conditions. Microencapsulation is perhaps the most widely accepted technique for oral and parenteral controlled release. The use of microencapsulation for the production of oral SR dosage forms has been widely employed in the last 50 years since the successful introduction by Smith, Kline and French (SKF) in the early 1950s of their ‘spansule’ products. These products usually consist of large number of microencapsules, having variable release rates because of the composition or amount of the coating applied, filled into hard gelatin capsule shells. Upon ingestion the outer shell quickly disintegrates in the stomach to liberate up to 1000-3000 microcapsules, which spread over the g.i. tract, thus ensuring more reproducible drug absorption with less local irritation that occurs with many non-disintegrating tablets designed for sustained release. Less frequently, microcapsules are tabletted because of the risk of capsule rupture during compression. Microcapsules have been formulated into suspensions having controlled drug release properties.

Microencapsulation is the most promising technique for the design of controlled release products for parenteral administration. The structure of the microcapsules varies according to the process of preparation, but generally, there
are two distinctive types. The reservoir type possesses a central core of drug coated with thin membrane of the polymer, whereas in the monolithic type (or microspheres) the drug is dispersed homogeneously through out a polymeric matrix. Polymers utilized for parenteral products must meet certain qualities regarding their tissue compatibility, mechanical characteristics, drug permeability and the specific property of being biodegradable (or bio-erodible).

The mechanism by which the active ingredient is released from the microcapsules includes diffusion of the drug through the polymeric matrix, its direct release through the pores of the polymer or as the polymeric material erodes. In the case of reservoir microcapsules, the release rate is constant (i.e. zero order rate), where as in monolithic microcapsules, the release rate generally decreases with time.

A wide variety of medicaments were investigated for microencapsulation majorly for obtaining sustained and controlled release. The medicaments studied in the recent past (1995-2011) for oral controlled release include anti-infective drugs (pyrimethamine, isoniazid, norfloxacin, cephalexine, tetracycline), analgesic and anti-inflammatory drugs (aspirin, indomethacin, ibuprofen, diclofenac, naproxen, pentazocin, ketoprofen, apomorphine, acetaminophen), anti-asthmatic and anti-allergic drugs (salbutamol, theophylline, aminophylline), cardio-vascular drugs (nifedipine, nicardipine, isosorbide dinitrate, captopril, diltiazem, propranolol) and miscellaneous drugs such as lactobacilli (anti-diarrhoeal), chlorpromazine (anti-emetic), and cimetidine (anti-ulcer), chloroquine phosphate (anti-malarial), isoxxuprene (uterine sedative), cephadrine (anti-microbial) and
sulphadiazine\textsuperscript{58} (anti-bacterial), doxifluridine\textsuperscript{59}, protein (bovine serum albumin\textsuperscript{60}),
gliclazide\textsuperscript{61}, tebuconazole\textsuperscript{62}, metronidazole\textsuperscript{63}, amifostine\textsuperscript{64}, vancomycin\textsuperscript{65,86},
nifedipine\textsuperscript{66}, doxorubicin\textsuperscript{67}, insulin\textsuperscript{68}, clozapid\textsuperscript{69}, vitamin D\textsubscript{2}\textsuperscript{70}, amoxicillin\textsuperscript{71,72},
feldipine\textsuperscript{73}, alkamin\textsuperscript{74}, bupivacaine\textsuperscript{75}, lycopene\textsuperscript{76}, dexamethasone\textsuperscript{77}, verapamil\textsuperscript{78},
atenolol\textsuperscript{79}, zidovudine\textsuperscript{80}, haloperidol\textsuperscript{81}, ethopropazine\textsuperscript{82}, thymopentin\textsuperscript{83}, isosorbide
dinitrate\textsuperscript{84}, tetracycline\textsuperscript{85}, zidovudine\textsuperscript{87}, celecoxib\textsuperscript{88}, melatonin\textsuperscript{89}, paclitaxel\textsuperscript{90},
metformin\textsuperscript{91}, capreomycin sulfate\textsuperscript{92}, salbutamol\textsuperscript{93}, diltiazem hydrochloride\textsuperscript{94},
lamivudine\textsuperscript{95}, clarithromycin\textsuperscript{96} and famotidine.\textsuperscript{97}

Among the drugs that have been incorporated in microcapsules for parenteral administration are steroids, especially contraceptives such as nor-ethisterone and high molecular weight compounds such as peptides and proteins. Water-soluble antibiotics with short half-lives such as ampicillin have also been microencapsulated to achieve long acting therapeutic effect in an effort to prevent infection and improve methods of treating wounds.

Research in microencapsulation has been receiving increasing attention for controlled release and drug targeting. Many studies with biodegradable polymers as coat materials were aimed at targeting. Polymers such as polylactide (PLA), polyglycolide (PGA) and polyglactin 370 (PLGA) have been extensively studied as microencapsulating materials.

Among the medicaments, biotechnology based protein drugs were extensively investigated for controlled release and targeting through microencapsulation. Biotechnology based drugs such as proteins as vaccine adjuvants\textsuperscript{98}, β-glucuronidase recombinant hepatitis B antigen\textsuperscript{99}, hepatocytes\textsuperscript{100},
recombinant human erythropoietin\textsuperscript{101}, nerve growth factor\textsuperscript{102} (NGF), soneatropin\textsuperscript{103}, recombinant human interferon-gamma\textsuperscript{104}, immunoglobulin Y\textsuperscript{105}, interleukin-2\textsuperscript{106}, transforming growth factor-beta (TGF-beta)\textsuperscript{107}, recombinant human growth hormone (rhGH)\textsuperscript{108} and hormones\textsuperscript{109} like α-ovine leutinizing hormone, β-human chorionic gonadotropin, recombinant aminopeptidase (PepN)\textsuperscript{110} interferon alpha-2B\textsuperscript{111}, DNA vaccine\textsuperscript{112}, ciliary Neurotrophic factor (CNTF)\textsuperscript{113} and tetanus toxoid\textsuperscript{114,115} were microencapsulated and were investigated.

Much research work on microencapsulation was carried out with known coat materials such as gelatin, gelatin-acacia, ethyl cellulose, cellulose acetate phthalate, shellac, eudragits (RS100, RL100), albumin, calcium alginate and poly (DL-lactide). In a few studies new substances such as propylene glycol rosin ester\textsuperscript{116}, abietic acid-sorbitol derivatives\textsuperscript{117}, cellulose acetate\textsuperscript{118-122}, poly(epsilon-caprolactone)\textsuperscript{123}, hGH dextran\textsuperscript{124}, Alginate-cellulose sulphate-oligocation\textsuperscript{125}, ethyl cellulose\textsuperscript{126}, poly (lactide-co-glycolide) (PLG)\textsuperscript{127}, poly(D,L-lactide-co-glycolide)\textsuperscript{128}, gellan gum\textsuperscript{129}, olibanum resin\textsuperscript{130}, colophony\textsuperscript{131}, chitosan\textsuperscript{132}, bharagum\textsuperscript{97} and polystyrene\textsuperscript{133} were evaluated as microencapsulating materials.

In the present study starch acetate, a new modified starch and EVA have been evaluated as microencapsulating agents and to prepare starch acetate and EVA coated microcapsules of glipizide for controlled release.
2.4 CONTROLLED RELEASE THROUGH MATRIX (MONOLITHIC) DEVICES

Matrix (monolithic) devices are possibly the most common of the devices for controlling the release of drugs. This is possibly because they are relatively easy to fabricate, compared to reservoir devices, and there is not the danger of an accidental high dosage that could result from the rupture of the membrane of a reservoir device. In such a device the active agent is present as a dispersion within the polymer matrix, and they are typically formed by the compression of a polymer/drug mixture or by dissolution or melting. The dosage release properties of monolithic devices may be dependent upon the solubility of the drug in the polymer matrix or, in the case of porous matrices, the solubility in the sink solution within the particle's pore network, and also the tortuosity of the network\(^{134}\) (to a greater extent than the permeability of the film), dependent on whether the drug is dispersed in the polymer or dissolved in the polymer. For low loadings of drug, (0 to 5% w/v) the drug will be released by a solution-diffusion mechanism (in the absence of pores). At higher loadings (5 to 10% w/v), the release mechanism will be complicated by the presence of cavities formed near the surface of the device as the drug is lost; such cavities fill with fluid from the environment increasing the rate of release of the drug.

It is common to add a plasticizer (e.g. a poly ethylene glycol), or surfactant, or adjuvant (i.e., an ingredient which increases effectiveness), to matrix devices (and reservoir devices) as a means to enhance the permeability (although, in contrast, plasticizer may be fugitive, and simply serve to aid film formation\(^ {135}\) and, hence, decrease permeability - a property normally more desirable in polymer
paint coatings). It was noted that the leaching of PEG acted to increase the permeability of (ethyl cellulose) films linearly as a function of PEG loading by increasing the porosity, however, the films retained their barrier properties, not permitting the transport of electrolyte\textsuperscript{136}. It was deduced that the enhancement of their permeability was as a result of the effective decrease in thickness caused by the PEG leaching. This was evidenced from plots of the cumulative permeant flux per unit area as a function of time and film reciprocal thickness at a PEG loading of 50\% w/w plots showing a linear relationship between the rate of permeation and reciprocal film thickness, as expected for a (Fickian) solution-diffusion type transport mechanism in a homogeneous membrane. Extrapolation of the linear regions of the graphs to the time axis gave positive intercepts on the time axis; the magnitude of which decreased towards zero with decreasing film thickness. These changing lag times were attributed to the occurrence of two diffusional flows during the early stages of the experiment (the flow of the 'drug' and also the flow of the PEG), and also to the more usual lag time during which the concentration of permeant in the film is building-up.

Efentakis \textit{et al}\textsuperscript{137} investigated the effects of added surfactants on (hydrophobic) matrix devices. It was thought that surfactant may increase the drug release rate by three possible mechanisms namely (i) Increased solubilization, (ii) Improved ‘wettability’ to the dissolution media and (iii) Pore formation as a result of surfactant leaching.

For the system studied (Eudragit\textsuperscript{®} RL 100 and RS 100 plasticized by sorbitol, flurbiprofen as the drug, and a range of surfactants) it was concluded that improved wetting of the tablet led to only a partial improvement in drug release
(implying that the release was diffusion, rather than dissolution, controlled), although the effect was greater for Eudragit® RS than Eudragit® RL, whilst the greatest influence on release was by those surfactants that were more soluble due to the formation of ‘disruptions’ in the matrix allowing the dissolution medium access to within the matrix. This is of obvious relevance to a study of latex films which might be suitable for pharmaceutical coatings, due to the ease with which a polymer latex may be prepared with surfactant as opposed to surfactant-free. Differences were found between the two polymers - with only the Eudragit® RS showing interactions between the anionic/cationic surfactant and drug. This was ascribed to the differing levels of quaternary ammonium ions on the polymer.

Matrix properties of a new plant gum in controlled drug delivery were investigated by V. D. Kalu et al. A new plant gum, Okra (extracted from the pods of Hibiscus esculentus), has been evaluated as a controlled-release agent in modified release matrices, in comparison with sodium carboxy methyl cellulose (NaCMC) and hydroxy propyl methyl cellulose (HPMC), using paracetamol as a model drug. Okra gum matrices provided a controlled-release of paracetamol for more than 6h and the release rates followed time-independent kinetics. The release rates were dependent on the concentration of the drug present in the matrix. The addition of tablet excipients, lactose and Avicel, altered the dissolution profile and the release kinetics. Okra gum compared favourably with Na CMC, and a combination of Okra gum and Na CMC or on further addition of HPMC resulted in near zero-order release of paracetamol from the matrix tablet.

Formulation of sustain release matrix systems of highly water soluble drugs was investigated by S. Siddique et al. Matrix systems are of favour
because of their simplicity, patient compliance etc., than traditional drug delivery which have many drawbacks like repeated administration, fluctuation in blood concentration level etc. Developing oral sustained release matrix tablets for highly water soluble drugs, if not formulated properly, may readily release the drug at a faster rate, and are likely to produce toxic concentration of the drug on oral administration. Hydrophilic polymer has become material of choice as an important ingredient for formulating sustained release formulations of highly water soluble drugs. Drug release to matrix system is determined by water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion. Highly water soluble drugs like metoprolol tartrate, diltiazem, primodol, ranitidine has been formulated as sustained release matrix tablets.

**Drug release from matrix device:**

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 solid drug moving toward the interior. Obviously, 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.

![Fig. 2.2: Drug Delivery from a Typical Matrix Drug Delivery System](image-url)
The equations, which describe the rate of release of drugs dispersed in an inert matrix system have been derived by Higuchi. The following equation can be written

\[
\frac{dm}{dh} = dC_0 dh - Cs/2 \quad (1)
\]

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 the matrix.

\( Cs \) = saturated concentration of the drug within the matrix.

From the diffusion theory:

\[
\frac{dm}{h} = Dm Cs/h dt \quad (2)
\]

where: \( Dm \) is the diffusion coefficient in the matrix.

Equating equations (1) and (2), integrating and solving for \( h \) gives

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

when the amount of drug is in excess of the saturation concentration, that is \( Co >> Cs \)

\[
M = (2CsDmCo)^{1/2} \quad (4)
\]

which indicates that the amount of drug released is a function of the square root of time. In a similar manner, the drug release from a porous or granular matrix can be described by

\[
M = [DsC2 p/t (2c^0 - pc^2)]^{1/2} \quad (5)
\]

where

\( p \) = porosity of the matrix

\( t \) = tortuosity
C2 = solubility of the drug in the release medium

Cs = diffusion coefficient in the release medium

This system is slightly different from the previous matrix system. In that the drug is able to pass out of the matrix through fluid-filled channels and does not pass through the polymer directly.

For purposes of data treatment, equation (4) or (5) can be reduced to

\[ M = Kt^{1/2} \]

where K is a constant.

So that a plot of amount of drug release versus the square root of time will be linear, if the release of drug from the matrix is diffusion controlled. If this is the case, then, by the Higuchi model, one may control the release of drug from a homogeneous matrix system by varying initial concentration of drug in the matrix, porosity, tortuosity, polymer system forming the matrix and solubility of the drug.

In the present study starch acetate and EVA have been evaluated as release retarding and rate – controlling polymer in matrix tablets for controlled release of glipizide.
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