Formulation Development and Evaluation of Chloramphenicol Microencapsule by Ionotropic Gelation Method

A dissertation submitted to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University in the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (B. Pharm.)

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APPROVAL

This Project **"Formulation Development and Evaluation of Chloramphenicol Microencapsule by Ionotropic Gelation Method"** submitted to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, has been accepted as satisfactory for the partial fulfilment of the requirements for the degree of Bachelor of Pharmacy and approved as to its style and contents.

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Declaration

I hereby declare that, this project report is done by me under the supervision of **Dr. Sharifa Sultana, Associate Professor,** Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy. I am declaring that this Project is my original work. I also declare that neither this project nor any part thereof has been submitted elsewhere for the award of Bachelor or any degree.

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Author

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Dedication

I dedicate this work at first to my God then to my parents and to my teachers and my friends.

ABSTRACT

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The advantages of microencapsule is to prevent the sensitive drug from contamination and to ensure the controlled or sustained release of drug. It has a purpose to ensure the targeted drug delivery to avoid the gastrointestinal fluid and enhance flow, compaction and core compression characteristics. Chloramphenicol is an effective antibiotic for certain bacterial infections which includes the usage of conjunctivitis as an eye treatment and meningitis, plague, cholera and typhoid fever are treated by oral or injections into the vein. The aim of the study as Chloramphenicol is X category drug for pregnant women then we can prevent the teratogenic properties of this drug by micro encapsulant formulation. Ionotropic gelation method is one of the safest and cost effective technique for microencapsulation. It is the easiest and effective method for the Chloramphenicol micro encapsulant. Sustained release oral product namely microbeads for Chloramphenicol prepared by ionotropic gelation technique using Sodium alginate alone and combination with Hydroxypropyl methyl cellulose as release rate modifiers, and investigated for in vitro drug release potential. While increase in the concentration of sodium alginate and other polymer dispersions increased, the amount release of drug is controlled due to time interval . In vitro drug release was dependent on the pH of the medium and concentration of polymer dispersions. Among the six formulation batches F4, F5 and F6 were found to show optimum sustained effect 99.984%, 99.598% and 99.1972% respectively. The mechanism of drug release from the microbeads was found to be followed super case-II transport. Finally it has been determined that when the concentration of the polymers increase it can ensure more controlled release of drug.

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Chapter – 1

Introduction

1.1 Microencapsulation Definition

- Micro-encapsulation means the technique of producing the continuous coating around an interior matrix which is entirely embedded in the wall of the capsule and is a core of embedded material. [1]
- Micro-encapsulation is a process wherein solids, liquids or even gasses build thin layers around the components in tiny particle creation. [2]
- Micro capsulation is a technique in which a very tiny droplet may be trapped, covered or encircled by a polymeric particle, such as solids, liquids or even gas. [3]
- Microencapsulating may also be used to lower the dose frequency and avoid degradation of medicines to solid and liquid or gas within a micrometric wall composed of hard or soft soluble film. [4]
- Enveloping tiny solid particles, liquid goutlets or gasses into a coat called microencapsulation. Small (1-1000 μm) microcapsules may have several shapes. [5]
- Including micron-sized parts in a polymeric shell is a process called microencapsulation. [6]
- Microencapsulation is a tiny 1 to 5000 μm of diameter, covering of liquid goplets or small solid particles. Special procedures have been created to consider the material to be encapsulated and the planned use of the capsules for the manufacture of those capsules. The covers, constructed of natural or synthetic polymers, are permeable, semi-permeable or impenetrable. There are therefore several ways in which an encapsulated reactive material may be regulated by, for example, enveloping destruction or permeation: alternatively, reactions inside the microcapsules could take place. [7]
- Micro capsulation includes the laying or entanglement, in the size range of 1–1000 μm, of a core material with polymer material. The semi-permeable polymeric matrix containments of microbial cells permits the physical separation of cells from outside while retaining a friendly interior micro environment.[8]
- Microencapsulation is a process of establishing a functional barrier for the provenance of chemical and physical interactions between the core and wall material and

maintaining biological, functional and physicochemical characteristics of key components. [9]

- Microencapsulation is a technique used to protect, stabilize and delay core material release.[10]
- Microencapsulation's may be characterized as package technology with thin polymer coverings of solids, liquids or gasses creating miniature microcapsules.[11]
- The micro-encapsulation provides a simple and cost-effective technique to enclose in the semi-permeable polymer membrane bioactive materials such as medicines and cells for the protection of bioactive substances, and the regulated release of the adjoined chemicals and their products. [12]
- Micro capsulation is a technique by which very tiny particles or droplets of solid or liquid substance are covered in a continuous polymer material film or are surrounded by them. These microcapsules offer a variety of advantages, including the conversion of liquids to solids, environmental protection, reactive chemicals being separated and the improvement of material handling. [13]
- Microencapsulation is a method aimed at protecting chemicals likely to decay or decrease owing to differing degradation responses (i.e., oxidation, hydrolysis, etc.). Various wall materials, including certain carbohydrates, prevent items from reacting with the protected material from the unfavorable heat, pH, humidity, oxygen and other components. [14]
- Micro capsulation is a method using microcapsules as small containers of liquid or solid substances which are released for a specified purpose. A coating works in a microcapsule as the wall, shell or membrane to encapsulate the substance that may be released in many ways according to the capsule wall's properties including physical pressure, friction, diffusion, wall disintegration and biodegradation. [15]

1.2 History

The development of a live cell started microencapsulation. The miracles of microencapsulation live in most single plants or animals. These natural capsular membranes serve certain roles with remarkable success. Protection of the inside material (core) and regulation of the material

flow through the cell membrane are among the most essential tasks. Plant seeds and bacterial spores have stayed alive for more than 100 years because of their exterior protection [16].

In unfavorable settings, black pigmentation inside the walls protects fungal spores by sunlight. Charged fluids frequently function as valves for permeability. Cytoplasmic membrane water permeability can be 1010 times greater than ion [17]. Even a chicken egg was made of a protective wall, thick as possible to shield it from incubation, and still thin enough to allow a rupture during the hatching process. An attempt by a man to mimic nature started at the laboratory in Dayton, Ohio. In the late 30s, the paucity of knowledge on solid-spread liquid in the colloid area was interested by Barrett Green, a young chemist fresh out of school. He had already identified the utility in photography applications of such scattered systems. Barrett Green went to his new ideas on dispersions when his business needed a product that would offer numerous paper copies without carbon paper. By 1940, no carbon paper was produced for the first time, but that was only the start. In 1942 Bungenberg de Jong's coercion experiments were investigated. His breakthrough was made. [18, 19]

In one article, solid gelatin spheres were made, whereas in another paper, oil phases were included in the gelatin conceive. Both principles were applied by Mr. Green and the first gelatin microcapsules were developed. The creation of a viable product from this primitive beginning took 9 hard years. A colorless teal base in the oil droplets and a second sheet of paper covered with acidic clay activated this novel printing technique. [20] One of the earliest proofs of transplanted cells in the immuno-protective membrane to replace organs was in 1933 when Bisceglie contained and transplanted the tumor cells into the abdominal cavity of a pig. [21]

The results revealed that the cells had lived enough long to infer that the immune system was not destroyed. Thirty years later, the phrase 'artificial cells' was used by Chang to describe it as an encapsulation for the immuno-protection of transplanted cells. [22] In the 1970s and 1980s, this technique was effectively implemented in order to immobilize xenograft islet cells in small animal models to help manage diabetic glucose. [23, 24]

Since then, huge efforts have taken place throughout the world to promote biological, genetic, plasma and pharmacological technological knowledge. The aim was to produce new

microencapsulates and to replace a restricted supply of source tissue with more appropriate cell lines, thereby enhancing local or systemic long-term therapeutic peptides. As a consequence, a broad variety of therapeutic therapies including renal failure, [25] diabetes, and hemophilia's have been treated using cell embellishment [27]. The results of small and large animal models have been the basis of a number of clinical studies, including an encapsulation of allogeneic islets for the treatment of diabetes [28] or the most recent studies involving the immobilization of P450 cytochrome expressing cells for pancreatic cancer elimination [29].

1.3 Future perspectives

In medicine and biotechnology, microencapsulation, including agricultural and environmental applications, has a potentially important future. However, cell micro-encapsulation technology still faces numerous major obstacles. Dosage, for instance, should be carefully regulated by the use of only limitedly growing and proliferating cells, therefore limiting uncontrolled cell development and cell overpopulation in the immune system. In order to meet biosafety and effectiveness criteria consistently, component Polymers should be standardized for physicochemical properties/composition, degree of purity, reaction conditions and source repeatability.[30] In fact, in the same way as in the case of enzymes employed, for example, in tissue digestion, transplant-level biomaterials that are identified by their batch numbers are necessary. The scaling up of the process while maintaining a regulated environment, operational discipline and stringent quality standards is another difficulty. This phase will be crucial for the introduction of human clinical trials and therefore a true clinical treatment approach in cell micro capsulation technology. The irretrievability of the microcapsules and the banking and culture of the appropriate cell are another significant field of investigation. For the development of this technique, it is crucial to develop protocols for the production of donor cells with appropriate number and quality. The next stage will entail the production of super specialized Microcapsules, each containing cells or pharmaceutical substances that interfere positively with the "main" cell product, that represent numerous micro-compartments, dynamically interacting with one another. Such capsules are not more complicated, chemical or biological but are based on simple components that have been manufactured and constructed correctly. Finally, cell life expectancy and functionality should be continually improved and

ultimately cell recovery patterns should be developed, in order to deal with socially significant illnesses, such as diabetes, Parkinson's disease or Alzheimer's [31].

1.4 Reasons for Microencapsulation

1) As in isolating vitamins from degrading effects,
    - Retraining evaporation of a volatile core, in certain situations the core should not be separated from its environment.
    - Enhance the manageability of a sticky substance.
    - Isolation of a chemical assault reactive core.
2) The purpose in other situations is not to fully isolate the core but to regulate, as in the controlled release of medicines or pesticides, the speed at which it escapes the micro-capsule.
3) The taste or smell of the core concealing,
4) As difficult as improving adsorption or extraction selectivity.

1.5 Benefit of Microencapsulation

1) Immobilization of the microorganism and enzymes –
    - Enzymes were embodied in cheeses to speed up maturity and taste.
    - The enzymes are shielded against low pH and strong cheese ion strength.
    - Microorganism encapsulation was utilized to enhance the stability of the starting crops.
2) UV protection, heat, oxidation, acid, bases UV protection (e.g. colorant sand vitamins). E.g. vitamin A/glutamate monosodium.
3) Improved shelf life because degrading processes are avoided (dehydration, oxidation).
4) Taste or smell masking.
5) Improved ingredient manufacturing, texture and waste.
    - Hygroscopy monitoring
    - Improve flow and dispensability
    - Powder free dust
    - Solubility improved

6) Management of liquids like solids.
7) Nutritious meals are increasingly required for youngsters, providing them with vitamins and minerals that are very essential in the age of growth. The highly required components in youngsters can be provided using microencapsulation in the friendly and appetizing manner.
8) Improve aesthetic element and philosophy of marketing.
9) The textile industry uses microencapsulated materials today in order to improve the characteristics of completed products. The addition of microencapsulated phase change materials is an increasingly used application (PCMs). Materials of phase transition absorb and release heat in response to ambient temperature variations. The phase changes material, which absorbs excess heat and feels cold when the temperatures increase. On the other hand, the PCM emits heat when it solidifies and feels warm when temperatures drop.
10) Farmers can use these pesticides less than the requirements of extremely highly concentrated and toxic first treatments followed by repeated applications to counteract efficiency loss caused by liquid leaching, evaporation and degradation in an overtime manner.
11) For a number of reasons, food ingredients are encapsulated.
    - Most aromatic substances are volatile and consequently these components encapsulated enhance their shelf-life.
    - Certain components, such as nutrients used to strengthen the products, have been encapsulated to conceal taste without compromise the desired taste of the product.
    - Because otherwise, occasionally the tastes can be contained for longer than.
12) Controlled and targeted release of active components
    - Many types, both oral and injectable, are micro-encapsulated to release over a lengthy period or at particular areas in the body.
13) Microencapsulation enables incompatible chemicals to be mixed. The mechanisms of micro encounter are typically divided into two groups: mechanical and physical processes, and chemical processes [33-38]. But these designations can be somewhat

deceptive because many processes labeled as mechanical could entail or even depend on a chemical reaction. One clearer indicator as to the type of the encapsulation technique is whether or not the capsules, as in chemical processes with a gas phase used as the encapsulation portion, are generated in a tank or reactor containing liquids as opposed to mechanical or physical procedures [39,40,41].

1.6 Advantages and Disadvantages of Microencapsulation

Advantages –

1) Conversion of liquid to a solid free flowing and pseudo-solid improving handling and storage such as eprazinone, clofibrate, chest oil, cod-liver oil, and more.
2) Reduces volatility of methyl salicylate, peppermint oils, tastes, fragrances and other compounds.
3) Avoid inconsistencies in combinations of medicines such as maleate aspirin and chlorpheniramine, eutectics, etc.
4) Unpleasant taste masks of drugs such as penicillins such as ampicillin, aminophylline, cod liver oil, etc.
5) Mask the smell of core such as beaver oil, cod liver, methionine, cysteine etc. Unpleasant or inacceptable.
6) Reduces gastritis caused by irritants such as ferrous Sulphate, potassium chloride, paracetamol, phenylbutazone, indomethacin, nitrofurantoin, and other medications.
7) Reduce core hygroscopicity, such as chloride sodium, etc.
8) Provides continuous/extended/delayed/control medicine release.
9) Reduces the risk to operators for hazardous substances such as insecticides, pesticides, sensitizers such as penicillins and other products.
10) Enhance flow, compaction and core compression characteristics such as vitamins, etc.
11) For the stabilization and retention of activities of enzymes.
12) Incompatible chemicals such as Aspirin can manufacture citric acid in a single form.

Disadvantages –

1) Quite costly

2) Not all the core materials can be adapted to the process
3) Sometimes coating is uncompleted
4) All core materials cannot use a single technique
5) Unable to utilize Sensitive Pharmaceuticals due to insufficient stability and shelf life
6) Individual design strategy is necessary for various cores and applications
7) Coated items might have unstable and unstable releasing characteristics, can be excessively voluminous
8) Limited range of materials that are safe, authorized, biocompatible and biodegradable
9) May, through mechanical stress such as the compression, harm the coat or product, Compacted, packaged, transported, handled etc.
10) Parenteral use micro particles may not be acceptable owing to size limitations
11) Need to be sterilized, need not be an allergic carrier, biocompatible and biodegradable, etc.
12) Most knowledge on microencapsulation remains copyrighted and so the choice of appropriate techniques and methodologies for each application may be challenging
13) Scale up and large-scale production of processes may provide problems.

1.7 Application of Microencapsulation

In such industrial applications it is not a matter of fully isolating the core, but of checking the pace of leaving the microcapsule, such as the checked release in food and chemical pharmaceutical and agro-industrial citric acid. Actually about every area in the industry might beneficiate from microencapsulation technology. In many domains, microencapsulation can be discovered (Figure 1).

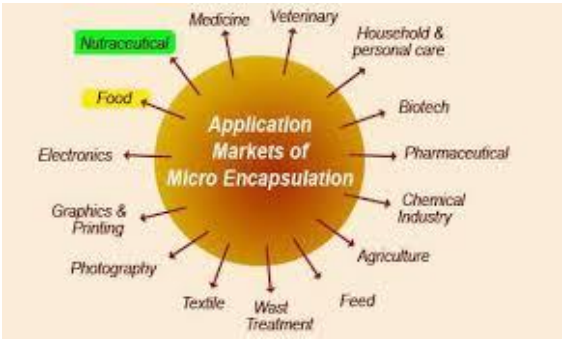


Figure-1: Application of Microencapsulation [3]

A. Microencapsulation of Vitamins, Minerals, and Nutraceuticals for Food Applications

- **Importance of Microencapsulation in Fortified and Functional Food Development:**

Action is required –

(1) To ensure stability of compounds during processing, handling and storage as well as in the gastrointestinal tract, and

(2) To facilitate controlled release at the GI tract site for proper absorption [45] to benefit from the advantages of consuming critical micronutrients and nutraceuticals.

Most of these chemicals, however, are limitedly soluble and stable [46] or are highly reactive and can interact with many other foods [47]. Furthermore, many have a disagreeable taste and color, which undermines food appeal [48]. These characteristics put various constraints on the direct addition of micronutrients and nutraceuticals to food, which has led to an increasing urgency in the food industry to create effective delivery systems. An efficient delivery method should be developed such that the physical chemicals and organoleptic characteristics of final food products contained are not negatively affected, while the active components are desired to be absorbed and bioavailable [49]. This has resulted in several efforts to build food supply systems for encapsulating, protecting and supplying nutraceuticals and micronutrients by using new food items. A proper selection of encapsulation methods alleviates many of the issues associated with adding bioactive chemicals to food directly. Microcapsules are able to protect, remove or minimize sensitive compounds, incorporate time relief mechanisms into final formulations, preserve desired aromas or masks that have an unsatisfactorily flavor and appearance, and convert powerful plant or grass extracts into liquid or solid microcapsules, making them easy to handle [50]. All of this has been utilized in the pharmaceutical sector in medication and vaccine delivery and is used more and more to add value to new food items of the food business. Micro capsulation is not a new notion; it is a technology used for more than 50 years in the domains of pharmaceuticals, biology. It is a technique, in short, by enshrining the functional components in a protective layer material and producing particles of just few nanometers to several millimeters in diameter from their surroundings. The encapsulated

component might be called the active ingredient or core ingredient, whilst the protective compounds are known as coatings or shells. The material used in food items should be food grade encapsulates that are capable of creating a barrier that protects the active agent from harmful effects of moisture, heat, lighting, oxygen and other reactive compounds contained in the food matrix [51,52]. The latest developments in medication supply are rooted in fundamental micro capsulation, while technology has opened up a wide variety of applications in other sectors. Unlike medicines the added criteria of food items should not negatively influence the sensorial qualities of the food vehicle or modify them by adding encapsulated bioactive components [45]. Micro capsulation was long considered to be far too costly for the food industry to use, until recent advances presented ever increasingly cost-effective preparation methods and scalable mass production lines that contribute to an affordable supply of different bioactive ingredients to the use of new value-added foodstuffs by micro capsulation technologies [53]. As various reviews have highlighted, micronutrients, enzymes and micro microorganisms, antioxidants, sprinklers and nutrients, as well as antioxidant agents and nutrients, have been utilized for protective and modifiable supplies of many dietary components.

- **Microencapsulation Technologies for Developing Fortified and Functional Foods:**

A variety of microencapsulation techniques for use in the food sector have been developed which are promising to provide fortified and functional products. Micro particular formation techniques may consist of the development of a single or double emulsion by a spray dry process (including the process of spray drying, spray cooling, extrusion, rotating pan and fluidized bed coating) and the development of chemical processes (including co-care, gelatination, co-crystallization, molecular inclusion and interfacial/in situ polymerization) [54].

Every approach of micro capsulation has benefits and downsides, as predicted. Physical methods are often less costly and easier to magnify but have relatively limited payload and poor particle characteristics. They are not very efficient. Conversely, chemical procedures entail complex ideas and expensive, but can usually produce well-defined particle shapes and desirable release characteristics. In developing medication delivery systems or producing value

added goods, chemical processes are frequently described. In particular, physical encapsulation methods are widely employed in the field of food applications for the protection and/or efficient provision of different ingredients [55].

The development of the microencapsulated system involves an effective combination of suitable coating materials and encapsulation techniques, because it plays a vital role in the physically and chemical properties of the resulting micro particles such as particle size, porosity, density, flow ability, integrity, reactance and release properties [56].

B. Microencapsulation in food industry

Bioactive components are micro-encapsulated by using various materials, such as water and oil. A normal water-oil-water emulsion consists of tiny water droplets, which are distributed in big oil droplets in the outer aqueous phase. The functional component may be enclosed in the interior, oil or external water stages after drying and numerous functional components may be included in a single delivery system. Micro emulsions are generated by micro-fluidization and micelle generation processes with droplets of a diameter of less than 500 nm. ME can effectively be utilized for the entanglement of natural substances such as essential oils (EO's) or plant extracts containing well-known antibacterial polyphenols. This aspect provides a key starting point for industries that are able to test new natural and safe materials or packaging systems that are capable of extending food shelf life, such as high-perishable foodstuffs (fruits, vegetables, meat, etc.) without reducing their quality and hygienic characteristics. ME may also be viewed as a real resource for food packaging to conceal undesirable tastes and smells or to provide obstacles to the environment between sensitive bioactive components (represented by food or oxygen). Many EOs have antibacterial effects against various foodborne pathogens and may perhaps be employed in various food diets, including meat products. [57, 58] Encapsulation enables the efficiency of EOs to be increased and its sensory influence on meals to be decreased. EOs are usually produced in two phases through micro capsulation. In a watery dispersion of a wall material, the volatile compound emulsion also serves as the emulator. In order to reduce the loss of the encapsulated substance via volatilization, the microencapsulated emulsion must next be dried under controlled conditions [59]. Rosemary EO encapsulation proved a more efficient antibacterial action in pig liver sausage compared to rosemary EO alone

[60]. The L. monocytogenes and O157: H7 are very effective with eugenols and caracole encapsulated in the micelles of non-ionic surfactant, due to a larger amount of antibiotic substances exposed to the bacterial surface in such a form [61, 62]. E. coli O157:H7 was effectively implanted in cooled, diced beef packed under nitrogen [63] and microencapsulated EOs were also evaluated satisfactorily. In food quality, safety and human health, polyphenols play a well-known fundamental role. Food science might increase their stability by encapsulating and drying by spraying, which might prevent them from oxygen, water or any conditions affecting their stability [64]. For the drying of pulp sprays several encapsulating agents (starch, maltodextrain, maize syrup and gum Arabic), lipids (stearic acid, mono and diglycerides) and proteins (gelatin, casein, milk serum, soybeans and weed) [65] are employed. Inulin is an intriguing potential encapsulant that would also make ME beneficial in the creation of functional meals thanks to its nutritional and prebiotic characteristics [66, 67].

C. Microencapsulation of Electronics

Micro capsulated electrical displays (MEPD) in electronic displays are a relatively recent technology. Microencapsulation innovation enables the particles in the screen to be permanently dispersed over the viewing area, which solves a major difficulty with earlier particle-based displays. Additional reliability problems have previously been troublesome with electrophoretic displays, such as particle adherence to electrodes and dispersion stability [69].

D. Microencapsulation in graphics, printing and photography

The main production parameters of microencapsulation technology in the printer industry are investigated in this study as well as possible printing methods for the transfer of microcapsules, the basic characteristics of the microcapsules, their applications in the printing and paper sector as well as the properties of printed materials with the help of MICs. The study also examines microcapsule fundamental properties (their size, morphology, mechanical characteristics, and basic material release properties), methods for characterizing microcapsules, techniques for determining spatial distribution in the coating layer of microcapsules, and durability of the microcapsules applied. Most researchers have previously worked towards developing new methods for the production of microcapsules to achieve improved (especially mechanical)

properties, improvements in methods of characterization of the microcapsule, and examine the dynamics of core material releases (for microcapsules with permeable or semi-permeable shells).

Very few scientists report on the qualities of the microcapsule transfer printer processes and their impacts on the properties and functions of printed microcapsules and the effects of printed microcapsules on the material's own imprint properties. A large number of transferred microcapsules affect the surface of the substratum as well as the uniformity of the microcapsules and their condition in the ink/varnish printing layer, thus affecting the level of microcapsules function. The method of the microcapsule transfer, i.e. the applied printing technologies. The main aim of this study paper is therefore to provide an in-depth understanding of the mechanisms of printing microcapsules, the behavior of microcapsules during printing processes and their conditions in foal products and thus reveal the most appropriate printing technique for the particular type and substrate materials of the microcapsules [70].

E. Microencapsulation in textile

In the early 1980s, micro-encapsulation was applied in order to enhance the thermal barrier characteristics of clothing, in especially for use in space missions, by the National Aeronautics and Space Administration (NASA). They enclosed PCMs in order to reduce the impact of severe temperature fluctuations experienced by astronauts during their space flights The technology was ultimately not included in the space program. However, its potential was recognized and the inventor, the Triangle Research and Research Co., located in Boulder, Colorado, licensed the work after additional development. For all kinds of materials especially outdoor gear (sparks, chests, thermals, snow suits and pants) and household blankets, couches, mattresses and pillow cases, Outlast has exploited the technology in textile fibers and fabric coatings and PCM capsules. In addition to its cold control function, PCM-containing textiles also contribute to the fight against overheating, therefore the effect may be characterized in general as thermal regulation. Microcapsules are smaller than 1 m in wall thickness and generally have a diameter of 20–40 m with a PCM load of 80–85%. The tiny capsule has a comparatively big heat transmission surface. The pace at which the PCM reacts to changes in

external temperatures is therefore quite fast. The previously established fiber-integration technique of the Outlate microcapsules has been created by Courtaulds Fibres in Bradford, UK, which loaded the fiber with 5 to 10 percent of Cox microcapsules, 1998. Late injection technique utilized for the production of the antibacterial fibers Amicor is also used in the procedure. The PCM is permanently trapped within the fiber; the processing of fiber (spinning, knitting, dyeing, etc) does not require any modification and the fiber shows its typical drapes, softness and strength [71].

For many years, the addition of scents to textile has been made in form of fabric washing and tumble-drying conditioners, all of which have been designed to give the textile a fresh aroma. However, the impact is generally short-lived, regardless of the quality of the technology utilized to transmit the smell. Many try to add scents directly to fiber and fabrics, but everyone does not last one or two wash cycles. Perfumes can remain on a garment for an important portion of his life only through microencapsulation. Micro capsulation of essential oil tastes, notably for kid's clothing, has led to several new uses, but it has permitted exposure to the therapeutic benefits of Aromatherapy at home and at work. The scent of branded perfumes may be fashioned clothing in the future, particularly when numerous perfume houses are entering the field of high fashion.

RT Dodge from Dayton, Ohio has worked in the research and production of microcapsules for a wide array of sectors since 1979. Over the last few years, Microcapsules for textiles have gathered a wealth of experience. Most of the work was in "scratch and sniff' micro-encapsulated T-shirts and in feminine shirts. The composition of the microcapsules has not been disclosed however the shirts remain washable (usually 8-20 cycles) depending on the active substance contained. In typical tumble dryers the capsules also withstand drying. Well-established methods for the production of capsules are utilized for in-site and interfacial polymerization [71].

F. Microencapsulation in veterinary medicine

In the veterinary sector, the main fields of medication include illness prevention and control, growth stimulation, estrogen syncs and nutrients. There are a variety of commercial devices

that use controlled release technologies to manage medicines to animals. The bolus Paratect is intended for an anthelmintic oral administration. The medication is supplied for a long time (about 90 days) and is designed to stop gastrointestinal worms from developing in livestock over the whole growth season. Spanbolet II is an example of a range of products for controlled sulfa release. These items may or may not be loaded, but all of them will disintegrate slowly in the rumen over a period of around three days. Liquamycin LA is an example of a tetracycline product with an extended service life. At the injection site, it is insoluble and releases slowly from the muscle. Sendran, which is worn as a flea and tick necklace, is another example. For cats and dogs a series of such products are available [72].

In the veterinary sector, the other main field of drug use is growing. The meal usually provides antibiotics to prevent illness transmission. A side advantage of this therapy is the increase in control growth. For example, tetracycline's, penicillins and ionophors, such as monensin, are used for the treatment of antibiotics. Ionophores are very powerful medicines that have both coccidiostat and antibacterial action. One of the main advantages of the usage of ionophores is that they are not utilized in people, thus the issue of bacterial resistance is less important. Steroid hormones like testosterone and estradiol are another important class of chemicals used to promote growth. The promotion of growth has also been proven to be synthetic substances like zeranol [73-75].

Trace nutrients are provided as the final area of application of controlled release technology. As with people, animals need a balanced, nutrient-friendly diet. This may include adding supplements to the basic food that vary according to the species and type of the feeding program. Swine and poultry diets, for example, are complemented with vitamins and amino acids like lysine and methionine. Cattle are generally capable of synthesizing all the required amino acids and vitamins, although trace nutrient supplementation such as cobalt, zinc, copper and selenium may be needed in some regions. These items are frequently given as boluses that dissolve in the rumen slowly [76].

G. Microencapsulation of household and personal care

In various goods, fragrance compounds are utilized to improve the pleasure of consumers. Added to consumer items including wash detergents, soap fabrics, soaps, personal care products like shampoos, body washers, deodorants, etc. [77] The encapsulation is used to prevent heat, light, moisture and exposure to perfumes or other active agents from oxidizing them over their lives.

It has also been used to inhibit evaporation and regulate the release rate of volatile chemicals. [78] Different elements such as temperature can affect the capsule shell to provide the contents when the capsule begins to melt. Otherwise, physical pressures, such as crushing, or other methods that affect the integrity of the capsule may jeopardize the capsules. The contents of the capsule can also be provided over the required time interval by means of diffusion through the capsule wall [79].

H. Microencapsulation in Biotech

Animal cells were treated using encapsulation technique in the early 1980s. The monoclonal antibodies produced in perforated mammalian cells did not build up in perforations, but flowed into the growing media. Mammalian cells leaking from pearls and growing in the media above a specific cell density boundary. However, 60 000 sand cells and monoclonal antibodies were included into the capsule for the weight cuts of the capsule membrane generated using Lim's two-step technique. In the capsule, the monoclonal antibody concentration was up to 1250 g/mL with 2 3 107 cell/mL cell density. A big reactor of 5000 L needed conventional suspension culture in order to generate 20g of antibodies while just a tiny reactor of 40 L required a micro-encapsulation technique to produce the same number of antibodies within 2 or 3 weeks. Another advantage of the microencapsulation technique was the traditional suspension culture by facilitating the separation process and increasing the recovery yield by the enclosure of antimicrobial agents. The pure antibody was 98 percent and the output of the standard suspension culture was roughly 100 times higher. A genuine analog seed is artificial seed or synthetic, produced with a polymer matrix by covering a somatic embryo. The immobilized somatic embryo can germinate and produce a full plant given appropriate

development circumstances. Polymer covering should physically protect the somatic embryo during storage, transit, and planting, and contain the germination and conversion nutrients. The idea of artificial seed was developed in 1977[80], with data published since 1986 [81, 82, 83, 84, 85, 86, 87] for the conversion of artificial seed. Many issues have to be addressed, though. In the presence of air, the traditional Alginate bead is not mechanically robust and dries fast. It can also not contain a lengthy duration of nutritional media. The immobilized somatic embryo conversion ratio diminishes over the preservation period. Somatic carrot embryos in drug capsules enables the nutritional medium to be contained in the mechanically powerful membrane [88]. In a membrane consisting of polyvinyl chloride, polyvinyl acetate and bentone thickener, over 90% of somatic embryos are germinated and 65% were formed from the membrane of the capsule. The performance of pharmaceutical capsules as an artificial seed barrier has established a preeminence in the manufacturing of artificial seeds for encapsulation technologies.

I. Microencapsulation in Agriculture

The field of crop protection [89-95] is one of the most significant applications for microencapsulated goods. Insect pheromones are now a potential alternative to traditional harsh pesticides. as a bio-rational alternative. In particular, attractive pheromones of sex can lower the populations of insects by interrupting the process of combination. Small amounts of particular pheromones are distributed during the mating season, which increases the pheromone background level to the point that the plum pheromone generated by its female partner is hidden [93, 95]. Polymer microcapsules, polyurea, gelatin and gum arabic[95] provide an effective supply to provide the pheromone by dispersing the capsule. In addition, encapsulation protects the pheromone during storage and release against oxidation and lighting.

J. Microencapsulation in Pharmaceutical

Pharmaceutical/biomedical for controlled/sustained drug administration are one of the primary uses in encapsulating techniques [96-103]. A possible uses of this drug delivery scheme include the replacement and usage of AIDS[110-112], tumors[113,114], cancer[115] and diabetes[116-118] vaccinations (not taken orally today as an insulin),[104,105] gene therapy[106-109] and

the treatment vaccine. A number of examples of medications that might benefit from the novel type of oral supply are protein, such insulin, growth hormone [119,120] and erythropoietin [121,122] (used to treat anemia). The provision of plasmid DNA remedy gene sequences [123] might enable simple treatment for a number of hereditary disorders such as cystic fibrosis [124,125] and hemophilia [126]. The spheres are designed to adhere closely to the gastrointestinal tract and even enter the lines prior to transmitting their contents over time to circulatory systems [127].

K. Microencapsulation in cell technology

The method for cell encapsulation is based on cell immobilization in a semi-permeable membrane. The membrane shields the inner cells against both mechanical stress and immunological systems, while permitting nutrition, oxygen and waste bidirectional dissemination. The fact that it might lead to a reduction or even a failure to administer immunosuppressant's in chronic form could be seen as a significant advantage because of the substantial adverse effects in patients in organ transplantation. In general, entirely bioconsistent materials should be used which do not interfere with cell activity. The encapsulation of cells rather than medicinal materials permits a longer length of time for delivery of the substance since cells constantly release the products. In addition, cell encapsulation permits non-human cells to be transplanted and can be seen as an alternative to a limited supply of donor tissue. In order to express any desirable protein in vivo, genetically engineered cells can also be immobilized without modifying the host's DNA. Cell immobilisation is of major benefit in comparison with protein encapsulation, because it enables the sustainable and regulated administration of therapeutic products 'de novo' to a constant extent, leading to increased physiological concentrations. Furthermore, the toxicity induced by the rapid release of high levels of the medication might be prevented if the encapsulating device is broken. However, the host's immune system might assault them to compromise their existence by cells leaving the encapsulating apparatus. The tiny size of the capsules (from 100 m to 500 microns) allows for intimate interaction with the blood stream which might be helpful for the long-term operating characteristics of the contained cells in certain applications subsequently addressed owing to the increased transport of oxygen into the capsules. In the comparison of various

immobilizing scaffolds, microcapsules have a greater surface/volume ratio that increases oxygen and nutrient permeability [128].

L. Microencapsulation in cell immobilization [129]

Microencapsulation in plant cell cultures enhances efficiency in manufacturing the many metabolites utilized for medicinal, pharmaceutical and aesthetic reasons by replicating the natural cell environment. Human tissues are transformed by encapsulating in natural polymers into biological artificial organs and are transplantated to prevent hormone deficiency conditions such as diabetes and serious hepatic insufficiency instances. In continuous fermentation procedures, cell density, productivity and the washing of biological catalysts out of the reactor are increased by immobilization. This has been utilized in the manufacture of ethanol, solvent and sugar or wastewater.

M. Beverage Production [129]

Today, production of wine, beer, wine and other beverages uses real estate to enhance output, improve quality, modify flavor, and so on.

N. Protection of Molecules from Other Compounds [129]

Microencapsulation is frequently required to address basic problems such as chemical problems (detergents hazardous if exposed directly to human skin) and other inactive or incompatible molecules when combined in any formulation. Micro-encapsulation is sometimes necessary. In addition, micro capsulation also enables many formulations to be prepared with reduced chemical loading, therefore considerably lowering process costs.

O. Drug Delivery [129]

Microencapsulation has allowed controlled release systems after the creation of the proper biodegradable polymers. These innovative methods enable the pace, duration and distribution of the active medication to be controlled. These systems are used to provide an active medication in a specific method for micro particles sensitive to the biological environment (stomach, colon, specific organs). Protecting sensitive drugs from the drastics (pH) and

reducing the number of patient medication delivery are among the primary advantages of these systems.

P. Quality and safety in food, agricultural & environmental sectors

Encapsulating bio-systems for the management of pollutants, the food cold chain have improved the development of the "biosensors" (abnormal temperature change).

Q. Soil Inoculation

Rhizobium, for example, is a very fascinating bacteria which increases adsorption and conversion of nitrate. However, inoculation is typically ineffective, given that cells are washed away by rain. Continued inoculation and greater cell concentration can be maintained by cell encapsulation techniques. This list is not complete; the field of nutraceuticals may be the last listed because of the growing interest and demand in health benefit ingredients which frequently need their efficiency and stability (e.g. probes, vitamins, etc.) to be protected and to target the release of active substances.

R. Applications of microcapsules in building construction materials

An examination of science papers and patent materials reveals that various possibilities of the incorporation in building materials of micro-encapsulated active substances such as cement, lime, concrete, mortar, marble, sealants and paints, as well as of functional textiles are provided (Figure 2).

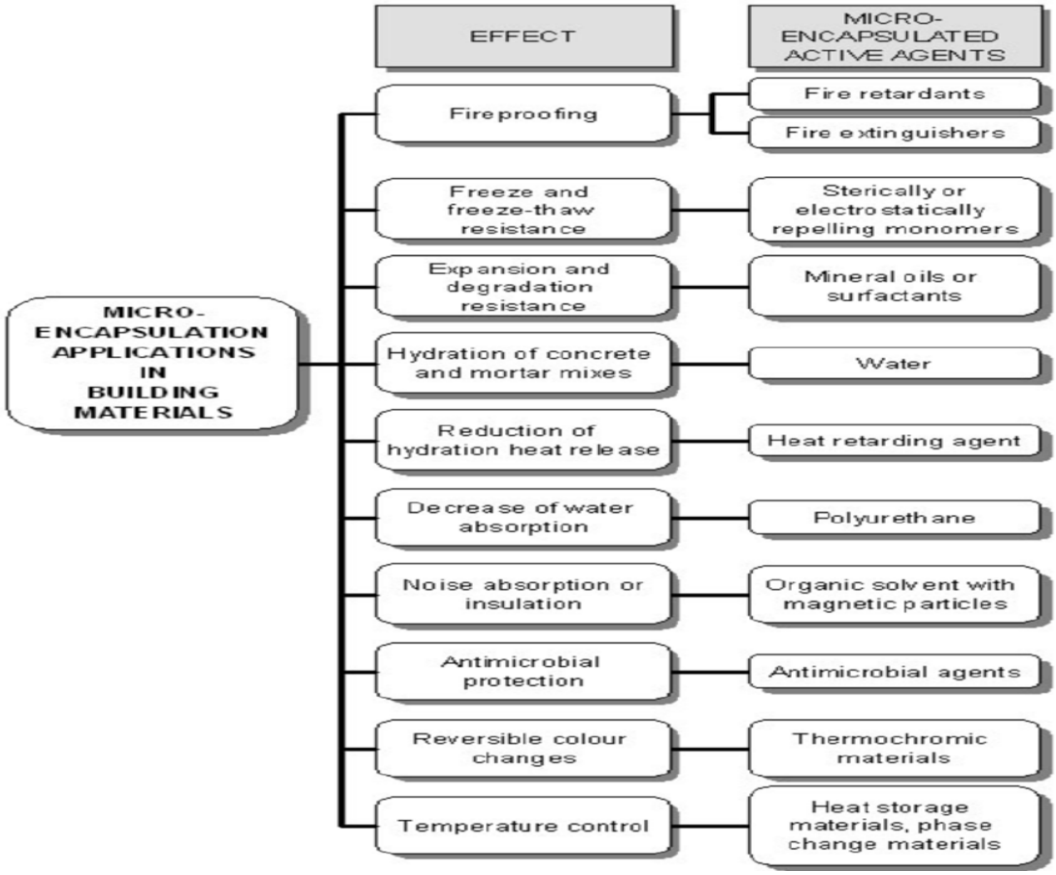


Figure 2: Applications of microcapsules in building construction materials [267]

1.8 Materials involved in microencapsulation

The technique of micro capsulation means the surrounding, or covered by a continuous layer of polymeric (the shell) particles or droplets of solid or liquid substance, which may be used for producing capsules within the micrometer-to-millimeter range known as microcapsules [129](Figure 3)

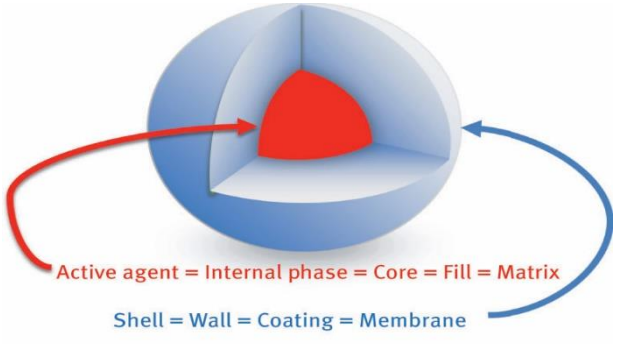


Figure 3: Microcapsule with core and coat [129]

1.8.1 Core materials in microencapsulation

The core material is the specific substance that might be liquid or solid in form to be coated. As the liquid core might comprise dispersed and/or dissolved components, the composition of the core material can change. The solid core is an active ingredient, a stabilizer, a dilatant, an excipient, and an accelerator. The ability to change the composition of the core materials gives a definite flexibility and use frequently allows the required microcapsule characteristics to be designed and developed [130].

1.8.2 Coating Materials for Microencapsulation

For the purpose of micro-encapsulation, core materials, such as lipophilic and hydrophilic nutraceuticals are utilized. Hydrophilic chemicals are water soluble, but in lipids and organic solvents insoluble, while in water lipophilic compounds are lipophilic, and lipid and organic solvent solutions are water soluble. Some hydrophilic microencapsulates are ascorbic acid, polyphenols, and so forth. [131,132,133,134].

The cover should be able to create a layer that is cohesive with the core material; chemically compatible and non-reactive, and offer the required couches such as strength, flexibility, impermeability, optical characteristics and stability. In certain respects, the coating materials employed in the process of microencapsulation can be modified in situ. The ideal properties of coating material include: core material stabilization, inert to the active components, regulated releases, film formation, malleable, tasteless, stable and non-hygroscopic, non-high viscosity, economically soluble in aqueous medium or solvent and it should be flexible, brittle, hard, thin etc. melting and coating [135].

1.8.3 Core Material Criteria [129]

- The material to be coated
- It may be liquid or solid
- Liquid core may be dissolved or dispersed material
- Composition of coating material:
- Drug or active constituent
- Additive like diluents

- Stabilizers
- Release rate enhancers

1.8.4 Coating Material Criteria [129]

1) Inert substance which coats on core with desired thickness
2) Compatible with the core material
3) Stabilization of core material.
4) Inert toward active ingredients.
5) Controlled release under specific conditions.
6) The coating can be flexible, brittle, hard, thin etc.
7) Abundantly and cheaply available
8) Composition of coating
    - Inert polymer
    - Plasticizer
    - Coloring agent

1.8.5 Examples of coating materials

Synthetic polymers –

- **Non-biodegradable polymers** e.g. Poly methyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate, Epoxy polymers [136,137]
- **Biodegradable polymers** e.g. Lactides, Glycosides & their co polymers [138], Poly alkyl cyanoacrylates, Polyanhydrides.

Natural polymers

- **Gums:** Gum Arabic, sodium alginate, carrageenan [129]
- **Celluloses:** Carboxy methyl cellulose, methylcellulose [129]
- **Lipids:** Bees wax, stearic acid, phospholipids [129]
- **Proteins:** Albumin, gelatin and collagen [139]
- **Carbohydrates:** Agarose, carrageenan, chitosan, starch [140] and
- **Chemically modified carbohydrates:** Poly dextran, poly starch [141]

Table 1: Core material and its characteristics [142]

Core material	Characteristic property	Purpose of encapsulation	Final product
Acetaminophen	Slightly water soluble solid	Taste-masking	Tablet
Activated charcoal	Adsorbent	Selective absorption	Dry powder
Aspirin	Slightly water soluble solid	Taste masking, sustained release; reduce gastric irritation; separation of incompatibles	Tablet or capsule
Islet of Langer Hans	Viable cells	Sustained normalization of diabetic condition	Injected
Isosorbide di nitrate	Water soluble solid	Sustained release	Capsule
Liquid crystals	Liquid	Conversion of liquid to solid; stabilization	Flexible film for thermal mapping of anatomy
Menthol/methyl salicylate camphor mixture	Volatile solution	Reduction of volatility; sustained release	Lotion
Progestin	Slightly water soluble solid	Sustained release	Varied
Potassium Chloride	Highly water soluble solid	Reduced gastric irritation	Capsule
Urease	Water soluble enzyme	Perm selectivity of enzyme, substrate and reaction products	Dispersion

Vitamin A palmitate	Non-volatile liquid	Stabilization to oxidation	Dry powder

1.9 Morphology of microcapsules [129]

Microcapsule shape largely depends on the core material and shell deposition technique.

1) Mononuclear- The shell around the core is contained in Mononuclear (core-shell) microcapsules.
2) Polynuclear- Includes multiple cores inside the shell of polynuclear capsules.
3) Matrix encapsulation- Encapsulation of the matrix in which the core material is uniformly distributed in the shell.

In addition to these three fundamental morphologies, microcapsules with multiple shells may also be mononuclear, or microcapsule clusters.

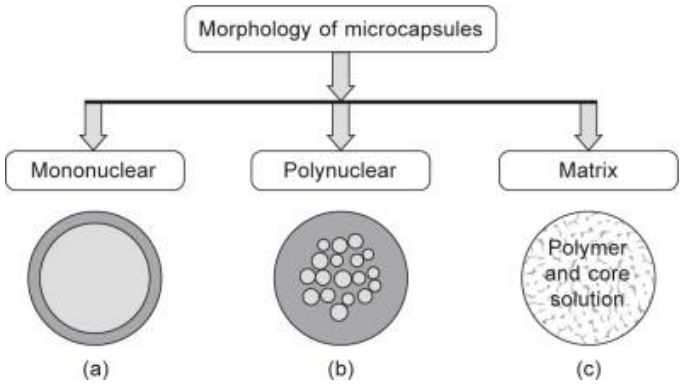


Figure 4: Morphology of microcapsules [131]

1.10 Reason for microencapsulation and release mechanism

There are innumerable reasons for microencapsulation. In some situations, as with the isolation of vitamins against the degrading effects of oxygen, the core has to be isolated from its surroundings, the evaporation of volatile core, improvements in handling of an adhesive substance, or the isolation of a reactive core from a chemical attack. In others, it is not the goal of totally isolating the core, but to regulate, like the controlled release of medicines or

pesticides, the rate at which it releases the microcapsule. It may be so simple as to conceal the taste, smell or complexity of the core or to increase adsorption or extract selectivity. John Franjione, Ph.D., and Niraj Vasishtha, Ph.D. outline the reasons for micro capsulation: "The work of a garment designer is like micro-encapsulation. He chooses the design, cuts the towel and sews the cloth according to his customers' desirability and age, plus the location and the environment where the cloth is used. By comparison, capsules are conceived and manufactured using microencapsulation to satisfy all needs with appropriate regard for the characteristics of the core material, the intended use of the product and the storage environment "There was a mistake. Various end products based on microcapsules require various microcapsule properties. In selecting raw materials and microencapsulation methods, the size and form of microcapsules, their chemical characteristics and their degradability, biocompatibility and permit ability need to be taken into account. Usually, permeability defines the goal of microencapsulation. In products where isolation of active ingredients is required and rapid release under specific conditions is employed microcapsules with impermeable walls. Impermeable micro capsulation effects include: separation of reactive components, environmental protection of sensitive chemicals, reduced volatility of extremely volatile materials, conversion of the liquid ingredient into a solid state, taste and odor masking, and toxicity reduction. On the other hand, permissible wall microcapsules permit the extended release into the environment of active components, e.g. in the case of prolonged release medicines, fragrances, deodorants, repellents etc. Examples include microencapsulated fertilizers and regionally restricted releases of pesticides to prevent leakage of chemical and biotechnological activities into grounds water, or microencapsulated catalysts and enzymes [143].

In advance are prepared the release methods for encapsulated materials and rely on the goal. The first developed and often used external pressure mechanism that breaks down the microcapsule wall and releases the liquid from the core was shown by an analyses of hundreds of patents. This approach is utilized in pressure-sensitive copying documents (pen ball or typography head pressure), multi-component stickers (pressure activation), deodorants and footwear fungicide (mechanical walking pressure), polished pasta (rubbing), chewing gum

scents and sweets (chewing). The wall of the microcapsule in various applications due to inner pressure, for example for light-plastic products and synthetic leather, the microcapsule wall breaks down. Microcapsules dissolve in water in immediate drinks. [144] For microencapsulated catalysts and medicines, dissolution of the specified pH value is beneficial. The enzyme breakdown of edible microcapsules can result in the release of drugs, vitamins, minerals, vital amino acids, fatty acids and even whole meals into the gastrointestinal system. The core material can be released for the grinding and cutting of additives by abrasion of the wall of a microcapsule, e.g. in antistatic fabrics and perfumes, (abrasion in washers and dryers). Kernwerkstoffe are emitted by heat in various applications. The effect of melting of the microcapsule wall is based on heat-sensitive recording papers (eg. telefax paper), temperature indicators of frozen foods, heat-sensitive adhesives, textile softeners and fragrances in dryers' formulas, body temperature cosmetic components and baking and tea-and-baking aromas. Fireproof materials contain micro-encapsulated fire retardants or extinguishers based on release of microcapsule walls. These sorts of microcapsules are utilized for wall paper, tapestry, ribbons, fire clothing and for electrical devices and wires in plastics and coatings. Microcapsules, light-sensitive documents and toners are disintegrated (or toughened) by light on specific photographic emulsions for photocopiers. When the wall is allowed, the content of the core is released slowly. This method can be used on medication release goods, aromas, perfumes, pesticides and fertilizers that are regulated. High molecular compounds of weight can be maintained in microcapsules for microencapsulated cells and enzymes in biotechnology, whereas low molecular by-products and substratum residues are removed by semipermeable microcap walls. The microencapsulated phase change materials for active heat collection and release from textiles, shoes are a specific example. They must remain within the impermeable and mechanically robust microcapsule wall for the entire lifetime of a product in order to be functioning during a number of phase transition cycles [129].

1.11 Technologies of microencapsulation

1) Physical Method
    - Pan coating
    - Centrifugal extrusion

- Vibrational nozzle
- Spray drying

2) Physicochemical method
    - Ionotropic gelation
    - Concertation-phase separation
3) Chemical methods
    - Interfacial poly condensation
    - Interfacial cross linking
    - In situ polymerization
    - Matrix polymerization

Physical Method

Pan Coating – In the pharmaceutical business, the pan-coating method is one of the oldest processes in the manufacture of tiny, coated parts or tablets. The particles are thrown into a pot or other equipment as the coating material is gently applied. In pot-clothing solid particles are mixed with dry-coated material and the temperature is increased to melt and enclose the core parts, and then reinforced with cooling, or to apply the coating material gradually on core particles that are dropped in a vessel rather than wholly mixed from the beginning of the encapsulation with core particles. (Figure 5) [129]

Advantages of Pan Coating –

- Suitable for larger particles
- Sustain release preparation.

Disadvantages of Pan Coating –

- Time consuming
- High material waste

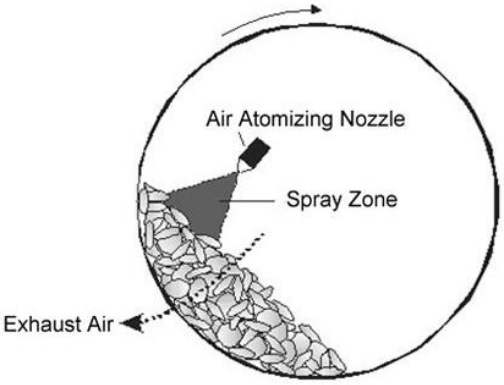


Figure 5: Pan Coating Techniques [133]

Centrifugal extrusion –

Centrifugal extrusion techniques usually create huge capsules of up to a diameter of 250 microns. A spinning, two-liquid pin is driven into the core and shell material, which should be unmissable with each other. This action creates an unbroken corpus that breaks into circular droplets immediately after the nozzle is clean. Depending on the composition and characteristics of the material, the continuous walls of these droplets are either reinforced by a cooling or by a cooling bath.

- A dual fluid flow of fluid core and core materials is pushed into concentrate pipes and into vibrational droplets.
- The shell is subsequently toughened by chemical cross-linking, cooling and/or solvent evaporation.
- To improve the process, different types of extrusion nozzles were designed.

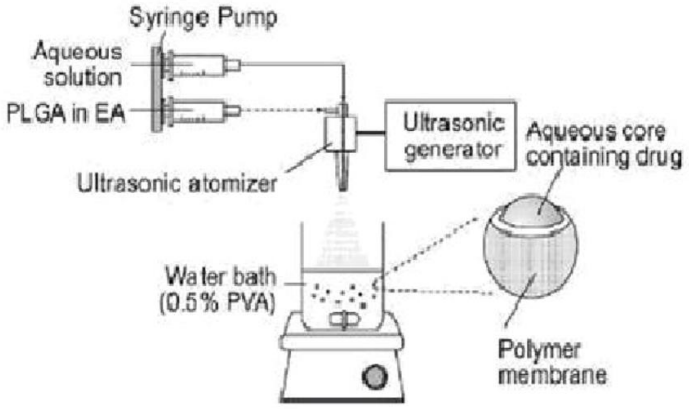


Figure 6: Centrifugal Extrusion Techniques [135]

Advantages of Centrifugal Extrusion Techniques – [135]

- The material is completely enclosed by the wall material
- Any leftover core is removed from the exterior
- The entanglement technique is relatively low temperature.

Disadvantages of Centrifugal Extrusion Techniques – [135]

- The capsule must be removed and dried from the liquid bath
- Capsules in very viscous melting's of carrier material are difficult to produce.

Vibrational Nozzle –

One of the most often used ways of manufacturing microspheres and microcapsules [149] is the vibrating jet technique, which is generally referred to as the vibrating nozzle technology or pilling [146-148] The process is based on the laminar jet disintegration concept, applying a vibrate frequency with a certain amplitude to the extruded jet. In a case with a flux extruded into a dump, a laminar jet is produced which can be divided freely by natural irregular disturbances into short lengths (provided these perturbations reach a threshold; otherwise, little or no break-up occurs). Those segments produce spherical droplets because of the tension of the surface. However, it can be irregular and not completely controllable to natural split by axial symmetric vibrations, leading to the production of droplets which are not of equal size and shape [150].

Lord Rayleigh has shown that the controlled breakup of laminar flow into uniform droplets of identical size may be done simply by using a specified frequency persistent sinusoidal force in the jet, thereby forming one droplet every hertz of applied frequency. This very frequent and reproductive disintegration only occurs with vibrational frequencies close to the naturally occurring frequency for the jet itself [150]. The properties of produced drops are dependent on the nozzle diameter, laminar jet flow rate, frequency size at specified amplitude and extrude liquid viscosity [151].

The sinusoidal force may either be used by vibrating the tube (vibrational nozzle), pulsing polymer in the chamber prior to passing through the nozzle (vibrational chamber method) or by changing the tube/orifice diameter periodically during extrusion [147,152,153]. The authors indicate that these many methods of applies the sinusoidal force collectively to the luminary jet are called "vibrating jet techniques." Although no consensus exists. Depending on the system it is applied to the choice of technique to deliver the vibratory force. For example, in fluid-liquid systems, pulsing of fluid has been proved to be the ideal approach, whereas the three strategies may be effectively used to create the microsphere in a gas phase [152] (Figure 7).

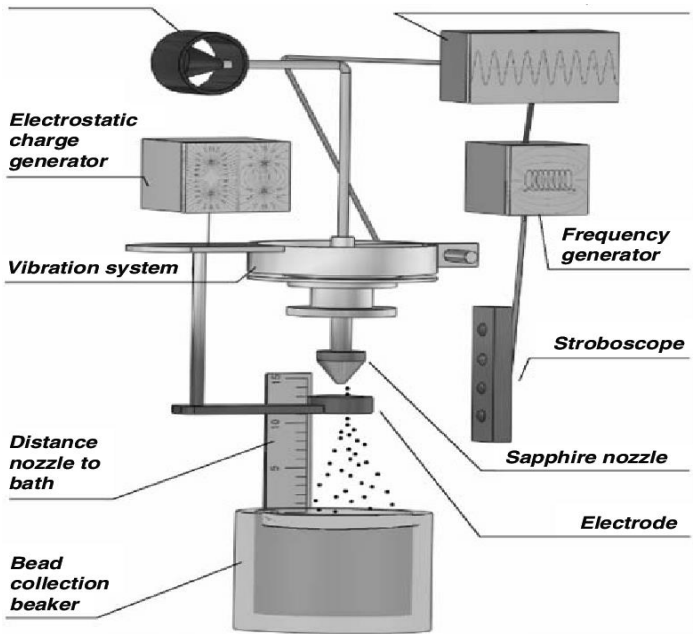


Figure 7: Vibrational nozzle [141]

Spray drying/ Fluid bed coating –

Another technique of mechanical encapsulation of fluid bed coating is confined to the encapsulation of solid core materials, including liquids absorbed in porous solids. This method is widely used for pharmaceutical encapsulation. Solid particles to be enclosed are suspended on an air jet and then sprayed with a liquid layer [154]. The capsules are then transferred to a location with a cooling or solvent vaporization solidifying their shell. This operation is continued until the walls of the capsule are of the appropriate thickness. The Wurster process is called when the pulverize is positioned at the bottom of the fluidized particle bed. Two variants in the pan coating methods, fluidized bed coating and Wurster process. The liquid coating is sprayed over the particles and quick evaporation helps to develop an external particle layer. The coating thickness and formulas can be provided on request. Top spray, bottom spray and tangential spray are different types of fluid bed coaters. The laminated material is sprayed down to the fluid bed in the top spray system, such that the solid or porous particles migrate into the labeling area. Enhanced enclosure effectiveness and cluster formation avoidance are achieved by opposing fluxes of materials and particles. Cluster formation the dripping of the coated particles relies on the coating substance composition. Top spray coaters generate better yields than both base and tangential sprays of encapsulated particles. In honor of its creation by Prof. D.E. Wurster [155] the lower spray is also known as the "Coater of Wurster." This method employs a cylindrical nozzle and a perforated floor plate in the covering chamber. For the spraying of the coating substance, the cylindrical dust is employed. The particles are enclosed by the coating material, as they travel upward through the perforated base plate and pass through the nozzle region. By evaporating the solvent, or chilling the embedded particle, the covering material adheres to the particle surface. This procedure remains so long as the necessary thickness and weight are achieved. The multi-layer coating technique helps to reduce particulate flaws, however it takes time. The spray is a revolving disk, which has the same diameter at the bottom of the covering chamber as the chamber. The disk is elevated to form a space between the chamber's edges and the disc during the operation. The tangential dust is put over the revolving disco, which releases the covering material. The particles travel into and are

encapsulated through the space within the spray zone. The amount of encapsulated particles increases as they traverse a minimal distance [129] (Figure 8).

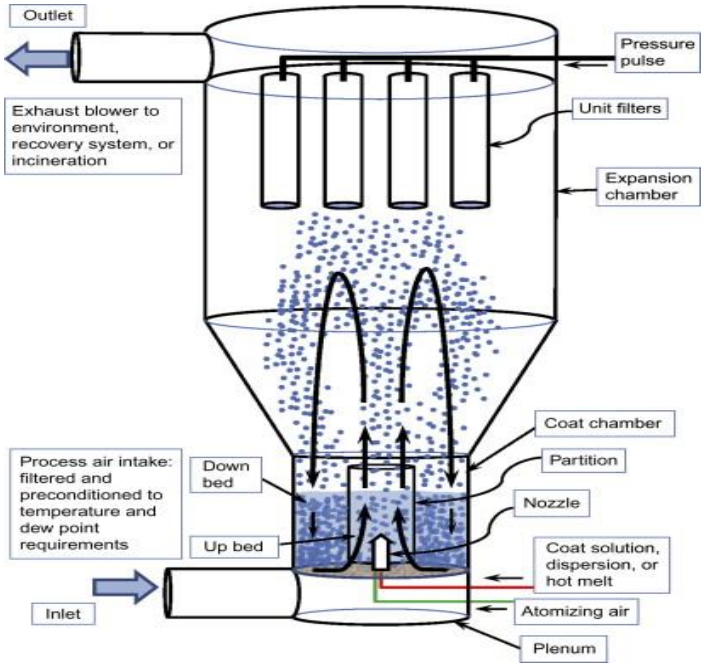


Figure 8: Fluid bed technology [145]

Physicochemical Method

Ionotropic gelation –

Ionotropic gelation is based on polyelectrolytes' capacity to cross links to create hydrogel beads in the presence of counter-ion ions, commonly known as gel spheres. Gelysophytes are hydrophilic, spherically interlaced polymers which have the ability to thoroughly gelato and expand in simulated biological fluids and release medication by means of polymer relaxation regulated. Hydrogel beads are generated by dropping an aqueous solution of versatile cations with a drug-powered polymer solution. The cations spread into the drug laden polymer droplets producing an ionic ally interlinked movement in a three-dimensional lattice.

In moderate circumstances, biomolecules can also be injected into these gel spheres to maintain their three-dimensional structure. [156,157] Due to their biological compatibility and biodegradability, natural polymers have become more important in the ionotropic gelation technology. This approach is frequently used for the encapsulation of natural or semisynthetic polymers such as alginates, galvanic gum, chitosan, and pectin and carboxymethyl cellulose

[158]. These natural polyelectrolytes are formed in their chemical structures with specific anions and cations, and in combination with counter ions, they form a mesh structure and create gelations by cross-connection.

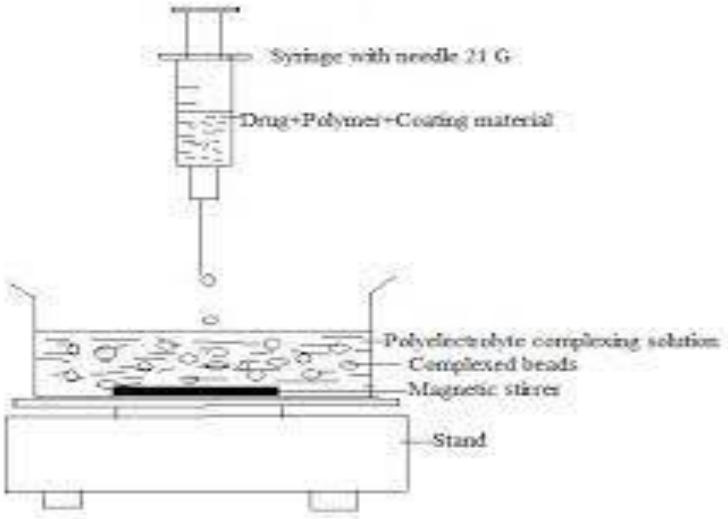


Figure 9: Ionotropic gelation method [151]

Natural polymers used in ionotropic gelation method

Alginates –

Alginate is a natural non-toxic polysaccharide produced by some species, which is biodegradable, derived from coastal brown algae. Sodium alginate is the natural polysaccharide and linear polymer of sodium salt of alginic acid, constituted of residual 1, 4-related β-Dmannuronic acid (M) and α-D-gluronic acid (G), in different quantities and configurations. Sodium alginate is water-soluble and forms a cross-linking structure that may be cross-linked to insoluble meshwork using divalent or versatile cations. For the cross-linking of acid groups of alginate, calcium and zinc cations have been observed. [159,160]

Gellan gum –

Gellan gum is a commercially manufactured bacterial exopolysaccharide produced by an aerobic sphinomone fermentation. In order to cause Gellan gelation, a concentrated water solution of Gellan gum has been warmed up. The chain changes from random spirals to double

helicopters as the temperature is lowered (coil-helix transition). The double helicopters are then rearranged and the hydrogel becomes organized joining zones (sole-gel transition).

Chitosan –

Chitosan, which has structural properties comparable to glycosaminoglycans, is a natural poly (amino saccharide), is not poisonous and is easy to bio absorb. [161,162] Chitosan avoids or weakens medication irritation in the stomach because of its anti-acid and antiulcer properties (163). Chitosane is a biopolymer that may be utilized in preparation with natural polyanes such as xanthan, algaenate and carrageenan for different polyelectrolyte complex products. Among them, the most significant drug supply hydrogel system may be the complex, chitosan-alginate complex.

Carboxymethyl cellulose –

Carboxymethyl cellulose can be changed as a plant product of a carboxymethylation procedure (CMC). The interactions between carboxylic groups of CMC and multivalent metal ions, which are mostly stabilized by electrostatic interactions, can be used to produce ionotropic ionic gels. Moreover, the interactions between the OH polymer groups and the ions help to stabilise these polymer aggregates and to ensure their insolubility in water. To obtain organic hydrogel beads the CMC can be combined with ferric/aluminum salt. By covering these hydrogels with chitosan/gelation and by cross-linking it may also be enhanced by controlling the release pattern.

Pectin – [164]

Pectin has been taken as a food additive, thickener and gallery, and is a cheap, nontoxic polysaccharide derived from citrus peels or pomaces. It is essentially a polymer having 1-4 links of aD-galacturonic acid.

Synthetic polymers –

- Hydroxyethylmethacryate (HEMA)
- N-(2-Hydroxy propyl) methacrylate (HPMA)
- N-Vinyl-2-pyrrolidone (NVP)

- N-Isopropylacrylamide (NIPAMM)
- Vinyl acetate (VAc)
- Acryolic acid (AA)
- Methacrylic acid (MAA)
- Polyethylene glycol acrylate/methacrylate
- (PEGA/PEGMA)
- Polyethylene glycol diacrylate/dimethacrylate

Multivalent cations –

Calcium (Ca+2 Potassium (K) + Ferric (Fe) +2), Barium (BA+2) Sodium (Na+) Magnesium (Mg+2) Aluminum (Al+3 Zinc (Zn) +2)

Factors affecting ionotropic gelation method – [165]

- **Polymer and crosslinking electrolyte concentration**

The concentration of polymer and electrolyte mostly affects ionotropic gelation technique in the bead formulations. In the ratio determined from the number of crosslinks the concentration of both should be. The efficacy of percent trapping depends on the electrolyte type, as well as the electrolyte concentration.

- **Temperature**

Temperature also influences the size of beads produced by ionotropic gelation and the duration of cure, i.e. time needed to be linked together.

- **pH of crosslinking solution**

The pH of the cross-connection solution also has a significant impact on reaction rate, shape and size of the beads during formulation.

- **Drug concentration**

Drug to be imprisoned into beads should be in the correct relation to polymer, because the medicinal concentration significantly affects the efficiency of the imprisonment, when

medicine exceeds the range, the rupture may then be observe, the gelispheric density improves, and so does the size and shape of the gel spheres.

- **Gas forming agent concentration**

In order to create pore-like gel sperms that have an enormous effect on gelispheric formation, gas producing agents such as calcium carbonate and sodium bicarybarbonate are used. As gas produces porous gel spheres, the lining of gel spheres cracks and leads to an uneven surface.

Advantages

- Organic solvents and severe temperature and pH conditions are prevented.

Disadvantages

- Utilized mostly on a lab scale
- In general, the capsules are very porous and encourage extensive bursting.

Concertation-phase separation –

A coacervate is a small spherical droplet of various organic molecules (particularly lipid molecules), which is kept together from the surrounding fluid by hydrophobic forces. The coacervate are between 1 and 100 micrometers in width and have osmotic characteristics and spontaneously produce organic solutions from specific dilutes. Their name comes from the Latin coacervate that is to be assembled or clustered together. They were proposed once that they played an important part in the development of cells and therefore of life itself. It spontaneously coaxes when a protein interacts with Arabic gum, for example gelatin. They are not only fascinating because they create a spatially separated environment, but because their borders allow simple organic molecules to be absorbed by themselves selectively from their surroundings. This is a basic kind of metabolism according to Oparin. Bernal said "the closest to our cells is to approach, without adding any biological – or biological – material, in any case living." However it does not exist as living systems because of a lack of any mechanisms by which Coacervate might replicate them [135].

Chemical Method

Interfacial poly condensation –

Three main interface types are typically employed: liquid-solid interfaces, fluid-liquid interfaces, and liquid-in-liquid emulsion interfaces; interfaces that are the most often utilized. [166] either one or both phases may include monomers inside the fluid-liquid and liquid-in-liquid emulsion interfaces. [166] [168] other interface types, including liquid gas, solid gas and solid solid-solid, are also seldom utilized. [166] Polymerization starts at the contact with a liquid-solid interface, resulting in a polymer bonded to the solid phase surfaces. Polymerization happens on just one side of the interface on the liquid-liquid interface with the monomer dissolved at the same stage, whereas polymerization occurs at the liquid-liquid interfaces with the monomer dissolved at both stage. [167] A stirred or non-rust polymerization interfacial reaction can occur. The two steps are coupled with intense agitation in an agitated reaction, which results in a greater interface area and a higher polymer output. [167] [168] the size of the capsule is controlled by the emulsion rhythm directly for capsule manufacturing. [167] while interfacial polymerization seems a very simple procedure, numerous experimental factors may be changed to develop particular polymers or vary polymer properties. [167] [168] The identity of the organic solvent, the concentration of a mono, reactivity, solubility, interface stability and the number of functional groups on the monomers are among of the most significant factors. [167] [168] It influences a number of parameters, such as monomer transport, reaction rate, polymer solubility and permeability, as well as the identity of the organic solvent. [168] It also has a major effect on the architecture of the polymer: a sub-substituted monomer produces linear chains, whereas a tri- or tetra substituted monomer creates branching polymers. [168]

In order to offer a further mechanical strength, the majority of interfacial polymerizations are done on porous substrate so as to make delicate Nano films suitable for industrial applications.[167] In this scenario, pores between 1 and 100 nm would be a good support. [167] By contrast, free films don't use support or manufacture distinctive topologies like micro- or Nano capsules. [167] Especially for polyurethanes and polyamides, the film can be continually

peeled from the interface to produce "rops" of polymeric film. [168] [169] The polymer can be continually removed as the polymer precipitates.

Interestingly, because of the large concentrations of monomers in the interfacial site, the molecular weight range of polymers produced via interfacial polymerization is wider than the Flory-Schulz distribution [170]. As the two solutions utilized for this reaction are unmistakable and the reaction rate is high, this reaction process generates a modest number of lengthy high molecular weight polymer chains. [171]

In situ polymerization –

Various techniques for encapsulating rely on the in situ polymerization process and numerous reviews have been briefly covered. The core stage, which is disseminated to appropriate size in such a process, is supplemented by a solution from the monomeric and oligomer materials. Controlled deposition and precipitation by precipitant or pH, temperature, or solvent quality changes at the interface. [174] In situ polymerization depending on the solubility of the monomer and the polymer, Arshady and George identified three situations. Suspension polymerization occurs if the monomer in the dispersion media is insoluble and produces suspended monomer droplets that polymerize to produce polymer micro particles. The polymerization reactor and stirring rate are therefore key criteria for a uniform distribution of size. In another example, a polycondensation of precipitation occurs when the monomer is soluble in the dispersion medium but not the polymer. As the reaction progresses, flocculation and add-on of a (low molar mass) polymer produce particles with an irregular form and a distinctive wide dispersion. Finally, when the dispersion medium is a good solvent to the monomer but a poor polymer solvent, the dispersion polycondensation occurs. The polymer is swollen instead and the microcapsule grows by adding the monomer and oligomer to the particle over time. Under these circumstances, micro particles with a small dispersion in size are produced [174].

Matrix polymerization –

During the creation of the particles, many processes involve a core material in a polymeric matrix. Spray drying in which the particle is produced by evaporation of the solvent from the

material of the matrix is a basic method of this type. Nevertheless, a chemical change might also induce the solidification of the matrix.

1.12 Coating effect enhancement

The flexibility of microencapsulation technologies enables limitless combinations of core and shell materials for their manufacture in a large variety of applications. To date, few studies were conducted on probable use of microcapsules in the creation of functional coatings. Microcapsules on surfaces are applied in several methods. For instance, they can be sprayed through an existing coating layer, possibly so that lubricants or fragrances are released immediately. Microcapsule application into coatings involves including them in a coating formulation or electrolytic co-deposition with metal ions, the two most frequent processes [129].

Compatibility of the shell material with the binder is necessary when combining microcapsules with coated binders. Microcapsules are generally employed in coatings for controlled release applications, however they can also be trapped inside a coating matrix comprising micro-capsules carrying active components such as biocides which sluggishly release material over time. The employment of micro-capsules in the creation of self-healing layers is another intriguing example. For this purpose, monomer, linker or catalyst microcapsules are included in a coating matrix such that the microcapsules open and release their contents when a coating breaks.

The monomer then polymerizes the links and plugs the damage, stopping future spread. The use of microencapsulated phase-change (PCM) particles in inside building coating is an innovative example. The core material melts and stores heat every day as the temperature increases. In the evening, when the temperature drops, heat is stored in the capsules and therefore reduces energy use [129].

1.13 Parameters should we check in microencapsulation

- Morphology
- Drug content
- Determination of % drug entrapment

- Bulk density
- Angle of repose
- Particle size determination
- In vitro dissolution test
- Diffusion study
- Floating capacity
- Bio adhesion
- In vitro study-PK and PD
- Stability study

1.14 Introduction Chloramphenicol

It reliably penetrates the central nervous system; it is usually bacteriostatic ally, but bactericidal for Haemophilus influenzae, Streptococcus pneumonia, or Neisseria meningitides; it is metabolized in the liver and serum levels of medicines should be monitored in liver disease patients and in neonates Chloramphenicol has certain notable characteristics. The use of this medication is restricted by potential toxicity. Death from aplastic anemia has been estimated in one of 24,500-40,800 therapy sessions. After parenteral treatment the incidence of aplastic anemia is unclear, however relatively few instances have been recorded. In preterm and newborn children with high or unaltered levels of chloramphenicol, the gray baby syndrome has occurred. The decrease of dose and the monitoring of drug levels in these children's serum can prevent this problem. Most frequently, the reversible dose-related suppression of the bone marrow identifies reticulocyte serial monitoring and the entire count of blood cells. Many indices of the usage of the medication remain contentious as studies that compare chloramphenicol with other antibiotics are not harmful and effective. [175]

The first broad-spectrum antibiotic, chloramphenicol, was introduced in 1949. It was easily produced and cost-effectively, and was considered to have no substantial toxicity, orally and parenterally available. In 1950, however, aplastic anemia was observed by Rich et al. [176], while volini et al.[177] showed bone marrow suppression related to dosage; chloramphenicol was connected with both disorders. The gray baby syndrome of preterm babies and new-borns receiving high-dose chloramphenicol's treatment first documented in 1959 by Sutherland

[178]. The usage of chloramphenicol was decreased and indications for use reduced as a result of the toxicity of this medicine and the introduction of safer alternative antibiotics. Recently, chloramphenicol has reemerged as an essential antibiotic with the advent of Haemophilus influenzae, an ampicillin-resistant disease, and improved understanding of Bactericides fragilis pathogeny in pelvic and in abdominal infections. Our objective is to evaluate this drug's pharmacology, activity range, toxicity and clinical uses.

1.15 Pharmacology of Chloramphenicol

Chloramphenicol as the parent ingredient is accessible as oral capsules. Unmodified chloramphenicol may not be administered readily as a sudden suspension, because it is highly bitter. The usage of the two esters of chloramphenicol helps overcome these difficulties. The palmitate of Chloramphenicol is tasteless and can be used by people with capsules that cannot swallow. Success chloramphenicol is a water-soluble ester for intravenous administration. These esters do not have anti-microbial activity [179-181] but are hydrolyzed at varying, but typically fast rates following oral or iv dosage [179-181]. The liver, lungs, and kidneys hydrate chloramphenicol succinate. In newborns 170/0 of the medication remains chloramphenicol sucinate 1 hour after iv injection, whereas 83% remain unesterified in the serum [182]. Palmitate chloramphenicol is degraded before gastrointestinal absorption by chloramphenicol. The average drug level of 25 mg/kg chloramphenicol is 1"\.119 lig/ml after 2 hours after delivery, compared to the average of 25 mg/kg dosage of iv chloramphenicol succinate at 28 ug/rnl at 30 min after administration [8]. There is, however, no significant difference between oral chloramphenicol palmitate and IV chloramphenicol succinate in the overall mean drug levels in blood (area below the curves) [183]. The serum's antibacterial activity [179-181] and dose-related toxicity [178, 184] are responsible for non-estherified chloramphenicols. The metabolization of chloramphenicol in chloramphenicol glucuronide happens mostly in the hepatic [185]. The antimicroscopic action of chloramphenicol glucuronide [10] is not known to induce toxicity [184]. Chloramphenicol is released from about 5070-10070 in urine, but not metabolized [185, 186]; 0.14070 in biles is released unchanged [184]. Chloramphenicol glucuronide is mostly eliminated by renal tubular secretion, whereas glomerular filtration is used for the excretion of active unesterified chloramphenicol [185]. Consequently, inactive

chloramphenicol glucuronide levels in blood are increasing whereas the treatment of probenecid does not alter active chloramphenicol levels. Chloramphenicol levels in serum can be determined by biological usage [187, 188], enzyme [189-191] and chromatographic testing [192]. These tests assess the active parent and not its precursors and inactive metabolites. Oral chloramphenicol formulations have been absorbed [178, 193] and are not reduced in diarrhoea patients [181]. Due to its consistent uptake, oral chloramphenicol was suggested to be taken whenever feasible in the package insert. Clinical failures [194] can occur in contrast to the reliables absorption of both oral formulations with poor and unsafe absorption of succinate chloramphenicol [194, 195]. Chloramphenicol has a half-life of 1.6-3.3 hr for adults [196] and a mean of 5.94 hr [197] for children and babies. Half-life rises very little in anuric adults between 3.2 and 4.2 hours (196) and chloramphenicol glucuronide accumulates as harmless metabolite. The rate of metabolism of chloramphenicol may be lowered [198, 199] in individuals suffering from liver illness or immature hepatic function (premature babies and neonates). Half-life of this medication can rise to 3-12 hours in patients with advanced circFeder, Osier, and Maderazo rhosis [196]. The prolonged half-life might be linked to the increased bilirubin level and reduced albumin level in blood (198-199). Chloramphenicol levels in the blood cannot be accurately anticipated for individuals with immature liver function or liver disease, and these levels should be monitored in order to minimize dose-related toxicity. Maintaining a serum dosage of 25 mg/kg a day may generally prevent toxicity, whereas the recommended dose is 50 mg/kg a day for children two to four weeks old. In babies below four weeks old, however, chloramphenicol concentrations in serum are unpredictable [201,202]; hence, serum concentrations must be monitored in order to prevent the hazardous build-up in this medicinal product (numbers > 25 ug/ml), [200] and to ensure therapeutic levels.

1.16 Toxicity of Chloramphenicol

Its toxicity limits the usage of chloramphenicol. This medication is potentially deadly for two forms of toxicity: aplastic anemia, which is idiosyncratic, and dose-related Gray baby syndrome. A dose-related suppression of the bone marrow is a third kind of toxicity. A first instance of aplastic anemia with chloramphenicol was notified in 1950 by Rich et al. [176] and this disease happened in the 63-year-old pyurian who had gotten the medicine for three months

at an intermittent time. There have been since this study "-'700 blood dyscrasies associated with chloramphenicol [203-208] in the US. Most were aplastic anemia patients. Unfortunately, the monitoring of blood cell counts cannot anticipate chloramphenicol-related aplastic anemia, and it often happens within weeks or months after the medication has been used. The death rate for patients with chloramphenicol-related aplastic anemia is "-'50 percent; however, the prognostics are poorest if, following the use of the medicine, there is aplastic anemia two months or longer[209].

The US Food & Drug Administration (FDA) carried out a national blood dyspraxia survey in 1952 on aplastic anemia linked with chloramphenicol [203]. Of 296 instances of aplastic anemia documented, 139 had had chloramphenicol before the disease was developed, and 68% had intermittent or extended chloramphenicol therapy for this reason Feder, Osier and Maderazo. Following this survey, labels were needed to warn of intermediate or extended usage of chloramphenicol related to blood dyscrasias and of the drugs not to be used for small or indiscriminate illnesses. Only 80 instances were related to chloramphenicol in a 1954 study of 349 cases of aplastic anemia and, in majority of them, the medicine had been obtained before the warning of 1952[204]. Therefore, the number of instances of chloramphenicol-related aplastic anemia declined between 1952 and 1954, possibly due to reduced medication use. In 1953, the U.S. Medical Association created the Blood Dyscrasies Registry, which gathered information on medicines related with aplastic anemia. Blood dyscrasy from chloramphenicol from 1953-1964 was best examined [206] for 408 instances. He observed that this medicine was administered for ineffective or trivial illnesses including cold, bronchitis, amber, acne. Chloramphenicol was administered intermittently in 39070 of the cases. Of these 6, 2070 instances examined with Best Affected Women, it is not unexpected, because this medicine was prescribed more commonly for women than males. Finally, Best [206] found "50070 mortality, and patients who were non-white were better than white ones. In 1970, the Blood Dyscrasies Registry was disbanded, although it was not discouraged without argument [210]. The majority of studies on chloramphenicol blood dyscrasies lacked information on the usage of chloramphenicol. However the link between the usage of chloramphenicol and aplastic fatal anemia in California between 1963 and 1964 was investigated by Wallerstein et al.[207] in

1969. They calculated that fatal aplastic anemia linked with this medicinal product happened in one of 24,500-40,800 treatment sessions, and discovered that fatal aplastic anemia was 13 times more prevalent in chloramphenicol-treated patients that year. They also observed an increase in the incident (unrelated to chloramphenicol) of idiopathic aplastic anemia with age. Unfortunately, no information was provided on the use of chloramphenicol by age groups and, thus, no age correction was done. Consequently, the apparent clustering of chloramphenicol-associated aplastic anemia in the elderly could not be concluded. Wallerstein et al. [207] have also identified all of their instances of chloramphenicol-related aplastic anemia in black individuals, in contrast to earlier observations of Best [206]. After oral dosing, most instances of aplastic anemia linked to chloramphenicol occurred [211,212].

Indeed, we understand that in literature only six instances have occurred following parenteral exposure to chloramphenicol-associated aplastic anemia [207, 208, 213-216].

41 instances of aplastic anemia have been reported to the FDA since 1971 (Personal communication; M. Dreis, U.S. Food and Drug Administration, Drug Experience Division, Rockville, Md.). In three such cases, only parenteral administration was involved. A comprehensive record has been provided to the FDA in one of these three situations. This was a 66-year-old guy, who received iv chloramphenicol succinate prophylactically for surgery on the coronary artery bypass. The patient developed aplastic anemia around 10 days after the medication was stopped. Two weeks later the patient died of sepsis and a diagnosis of aplastic anemia was confirmed by an autopsy. The definite association of aplastic aemia with parenteral administrative anemia in this patient, as in all previously isolated cases reported, has led some clinicians to administer this pharmaceuticals exclusively via iv route, now the preferred route for inpatients, as the association of aplastic anemia with oral chloramphenicol preparations [211, 212]. Thus, only four individuals got oral preparation in a university research with 100 patients who took chloramphenicol [217]. At a trial of 202, only four patients got oral chloramphenicol in a community hospital [218]. Aplastic anemia may be associated with oral medication partly because a greater percentage of patients took oral medicines. Unfortunately, statistics on the occurrence of aplastic anemia following oral vs. parenteral chloramphenicol are not available, and so definite determinations on their relative safety cannot be formed.

1.17 Clinical Indications of Chloramphenicol

For rare infections, chloramphenicol is the medicine of choice. Initial treatment of severe H. influenzae ampicillin-resistant infections is suggested [220]. Chloramphenicol is the medicine used for meningitis caused by H. influenzae, S. pneumoniae, or N. meningitidis in individuals allergic to penicillins [221]. As an initial treatment [222] for children suffering from meningitis, which may be caused to H. influenzae, a combination of chloramphenicol and ampicillin has been advised; chloramphenicol can also be stopped if the organism is proven to be ampicillin-sensitive. While chloramphenicol alone is a successful first meningitis therapy[116] for H. influenzae, S. pneumoniae, or N. meningitidis, ampicillin addition is advised for children as a result of uncommon H. influenzae resistance to chloramphenicol [224-226]. But in recent years, when meningitis was discovered to be chloramphenicol and ampicolin resistant to type b influenzae, the futility of such a method (which attempted to cover all possibilities of medication resistance) was clearer[227]. A recent [228] report on 1,885 cases of H. influenzae meningitis indicated that 180/0 are ampicillin-resistant and none chloramphenicol-resistant. As chloramphenicol's resistance to H. influenzae is relatively rare [224-226] and if it can be promptly determined [229], an alternative strategy is recommended for treating bacterial meningitis in children and babies. We would recommend a first therapy with chloramphenicol alone, and a continuation of or a shift to ampicillin, to prevent possible antagonisms between chloramphenicol and ampicillin (if the organism is sensitive). To determine the optimum therapy of meningitis related to H. influenzae, studies evaluating alternative therapeutic methods are required. Some physicians consider chloramphenicol to be the medication of choice for typhoid [230,231] and enteric fevers [212, 230] if these diseases are caused by chloramphenicol-prone bacterial strains [232]. Recent oral-therapy research has revealed that trimethoprim-sulfamethoxazole [233-235] or amoxicillin [236] are equally efficacious as typhoid fever with chloramphenicol. However, no major trials on iv chloramphenicol and other antibiotics have been completed using this method. Chloramphenicol is one of the medicines of choice for treating brain abscesses [231,237-240] before identification of the causative organisms due to its capacity to cross the blood brain barrier and its activities against organisms which generally lead to brain abscess (specially B. fragilis). It is shown to be resistant to either

ampicillin or other antibiotic antibiotics that enter the central nervous system by gram negative bacillins and other infections of the central nervous system. However, throughout therapy chloramphenicol resistance may develop [241, 242]. An alternative to chloramphenicol, amino glycosides are weakly penetrated by the brain [243] when parenterally administered. Unfortunately, aminoglycosides have not increased the survival rates of the newborns with meningitis owing to gram negative bacillis above the survival rate of those treated on the parenteral route only if given intrathecally [244] or intraventricular [245]. When other antibiotics can be provided, chloramphenicol is contentious. The choice of which antibiotic is less toxic and clinically more successful is often challenging. The chloramphenicol or clindamycin has demonstrated efficacy for anaerobic infection in both in vitro and clinical studies [244–249]. Due to the common causation of anaerobic pelvic and abdominal sepsis, including B. fragilis, chloramphenicol or clindamycin, in the first treatment. Anaerobes, including mostly B. fragilis, also work effectively with carbenicillin, cefoxitin and metronidazole. However, there are no major controlled clinical trials comparing these antibiotics with chloramphenicol. Chloramphenicol, clindamycin and ticarzilline were similarly beneficial for a newer controlled research [258] comprising 175 patients with severe abdominal or pelvic sepsis owing to combined aerobic and anaerobic pathogens. Even when B. Fragilis is present, anaerobic lung infections typically respond to penicillin alone,[239] therefore routine treatment of chloramphenicol for these infections is unnecessary. For rickettsia infections either chloramphenicol or tetracycline are effective [249-252]. Chloramphenicol should be used in small children or females whose tetracycline is contraindicated. Although a few effective treatment cases have been reported for chloramphenicol [253, 254], it is not advised for bacterial endocarditis treatment since it is typically bacteriostatic. There have been poor clinical outcomes for these infections [253-256]. For patients outside the hospital, chloramphenicol has limited indications. Unfortunately, it was administered in certain individuals to treat minor infections and aplastic anemia occurred in a few of these [207, 209]. In a 1973–1974 Tennessee ambulatory study [257], the overuse of chloramphenicol was underlined. Of the 1,061 chloramphenicol prescriptions, only one was considered to be appropriate.

Chapter – 2

Literature Review

Zien E, Ghorab M, Gad S, Yassin H. Design and characterization of diclofenac sodium microspheres prepared by ionotropic gelation technique for oral controlled drug delivery. Int. J. Adv. Pharm. Bio. Chem. 2015;4(2):321-9.

Micro beads for diclofenac sodium prepared using sodium alginate and combined with the use of Hydroxypropyl methyl cellulose, chitosan, Pectin as release rate modifications, for the sustained release oral product, i.e. for the use of ionotropic gelation technique, and investigating flow behavior, size of particles, swelling properties, SEM surface studies, and in vitro drug release potentials. While sodium alginate and other polymer dispersions rise in their concentration, sphericity, size and average particle size rise. The effectiveness of drug trapping is close to 95%. Increased concentration of calcium chloride lowers microbeads' median diameter, no noticeable morphological changes and drug release pattern. The pH of the medium and concentration of the polymer dispersions was dependent on in vitro medication releases. Of the 9 formulae F5 (sodium alginate 3%, calcium chloride 5%, HPMC 1%), F7 (sodium alginate 3%,calcium chloride 5%,chitosan 1%) and F9(sodium alginate 3%,calcium chloride 5% and pectin 2%) the optimal sustainability was identified. Super case-II transport was detected in the process of drug release from microbeads. [259]

Mandal S, Kumar SS, Krishnamoorthy B, Basu SK. Development and evaluation of calcium alginate beads prepared by sequential and simultaneous methods. Brazilian journal of pharmaceutical sciences. 2010 Dec;46(4):785-93.

The study was conducted with a natural polymer carrier to produce a sustain release dose pattern of trimetazidine (TMZ). The TMZ was trapped in the calcium alginate bead produced utilizing calcium chloride as a cross-linking agent with sodium alginates by the ionotropic gelation process. The beads were assessed using optical microscopy and SEM for particle size and surface morphology. Simultaneously, the concentration of drugs was greater when CaCl2 and polymers were raised but less when drug concentrations were raised. The crystalline drug was modified with crystalline in XRD investigations. After the formulation, the drug became amorphous. Calcium alginate beads manufactured using a sequence-based approach at varied CaCl2 (1-3% w/v) concentrations are approved for release. Drug release in SGF for 2 h was sustained, from 38% to 30%, and in SIF fluid from 89% to 82% up to 9 hours at increased

concentration of CaCl2.As the cross linker concentration grew, drug release reduced in the sequential process. Drug release. Beads produced with 3 percent w/v CaCl2 demonstrated the longest release impact because more cross-linkage led to a rigider gel network and hence better continuous release features.TMK releases were maintained from 30% to 37% in SGF at 2 hours and from 93% to 8 hours in the simultaneous process. During the in vitro drug release investigation, the effect of medication concentrations did not influence the release of calcium alginate bead medicinal products. The drug levels varied from 2% to 3% w/v for drug release studies. TMZ release in drug-prepared beads (batch C3), containing 2% w/v TMZ, has a sustained impact of around 62% with drug loading. However a more lasting impact with drug charges of roughly 58% was apparent in the case of the simultaneous technique, which comprises 3 percent w/v drugs. [260]

Bhadke SE. Formulation and Development of Repaglinide Microparticles by Ionotropic Gelation Technique (Doctoral dissertation).

Repaglinide is a meglitinide class medicine used to control type-II diabetes mellitus, an anti-diabetic, orally decreasing blood glucose medication. The present study comprises the creation and assessment of repaglinide micro particles as models for the extended drug release. In order to supply the medication sustained or regulated in the gastro-intestinal tract and subsequently in systemic circulation, the attempting was made to manufacture micro-particles of repaglinide using ion tropical gelation techniques. The calcium chloride cross-linking technique was used to create the micro particles utilizing different levels of Hydroxy Propyl Methyl cellulose and Chitosan by dropping the drug polymer solution with sodium alginate in calcium chloride solution. The micro particles generated were assessed for flow conduct, compatibility studies, and efficiency of drugs trappings, in vitro dissolution, electron microscopic scanning and screening process. Of the seven formulations F1 and F4 developed and assessed, good results were observed. Prepared micropartments demonstrate 78.62% to 91.25% trapping efficiency Infrared spectroscopy. The lack of any drug polymer interaction was verified infrared spectroscopy. In-vitro release experiments conducted at 1.2 pH and with 7.2 pH phosphate buffer solution reveal 93.78% and 91.78% respectively. The in-vitro release experiments demonstrate that F1, F2 and F3 are released at 91.99 percent after 12 hours, correspondingly

81.66 percent and 71.66 percent. The releases in formulations F4, F5 and F6 are 92.11%, 81.93% and 81.76%. The combination of Hydroxy propyl methyl cellulose and Chitosan, formula F7 exhibits 71.88% of drug releases. [261]

Prasad BS, Gupta VR, Devanna N. Formulation and Evaluation of Micro particulate system for controlled delivery of nateglinide by Ionotropic Gelation Method

Oral controlled release of nateglinide microspheres manufactured by Ionotropic Gelation Technique to avoid unwanted effects connected to drugs, such as gastrointestinal discomfort, enhance bioavailability under diverse pH values in gastrointestinal circumstances. A mix of sodium alginate and carbopol, HPMC and chitosan were used to manufacture a total of 24 packages for drug release, in different quantities, and to examine the features of physiochemical or pharmaceutical release. All properties researched have been successful. While sodium and other polymer concentrations increase, sphericity, size, flow and mid-diameter of microspheres rise. The effectiveness of drug entanglement of micro particles has been measured at 86%. The drug release is greatly increased by concentration in the alginate gel matrix in concentrative of other hydrophilic polymers such as Carbopol and HPMC (To 4.5 hours) as compared with alginate micro-particles (ALG). Study in Invitro shows a greater pH of medication release. The release of drugs was quicker than F4, F5 and F6 in batch F1, F2 and F3. But in the batch C1 – C8, H1 – H8 and E1 – E4 including Carbopol, HPMC and Chitosan-coated sodium alginate, optimal regulated release was observed. Case – II transport was observed to follow the drug release process from microspheres. The study found that controlled release by the use of an ionotropic gelation technique may be created successfully. [262]

Pillay V, Dangor CM, Govender T, Moopanar KR, Hurbans N. Ionotropic gelation: encapsulation of indomethacin in calcium alginate gel discs. Journal of microencapsulation. 1998 Jan 1;15(2):215-26.

The methodology used to construct a modified release multi-unit oral system of medicine distribution was ionotropic gelation via divalent metal contact. In order to stimulate the spontaneous synthesis new calcium alginate gel discs, a cross-linking of the indomethacin-sodium alginate sample with calcium ions was carried out. A preformulatory step for

optimizing the curing conditions and determining the potential of the gel disk played a major role in the certification of the integrity of the system. To identify key curing parameters, a three-phase methodology was designed. The appropriate concentration of calcium chloride (phase 1) and crosslinking reaction-time (phase two) had to be calculated, as the treatment entailed crosslinking of the sodium alginate with calcium ions. In addition, in the third phase, the air-drying time for the gel disks was optimized. The stability of the features of in vitro drug discharge was utilized as an indicator of optimal interconnection efficiency. Phase 3 was predicated on complete drying of the gel disks at 21^0 C under an extractor at a constant weight.

The investigation demonstrated that 1% w/v calcium chloride solution for 24 hour and air-dried for 21^0C under an extractor were optimally cross linked for 48 hours. Methanol, sodium citrate (1% w/v) and phosphate buffer pH 6.2 were the three solvent / solution systems examined for their capacity to release medication entirely from the matrix system. In addition to its capacity to expand calcium alginate gel disks, the phosphate buffer offered excellent drug removal. In addition, the use of greater levels of sodium alginate in formulations boosted drug loading. [263]

Linder C, Ziv G. Encapsulated forms of slow-release dry cow products of rapidly absorbed antibiotics. Journal of veterinary pharmacology and therapeutics. 1983 Mar;6(1):33-40.

After drying treatments with salts of these antibiotics suspended in common oil bases, the persistence of chloramphenicol, cephacetrile, and clindamycin in udders of dry cows was investigated the dry udder secretions collected 3 to 5 days following therapy did not detect any antibiotic action. Following the suspension of equivalent doses of encompassed chloramphenicol in the same oil base and the drying out, most medicines remained bound within the microcapsules; chloramphenicol levels above 10pg/ml of secretion were retained for 3-4 weeks, but the free medicine was very rapidly absorbed from the udder after the microcapsule had been released. A drying-off, suspended in the same sort of oil basis and with similar dosages to the no capsulated preparations, was inhaled into microcapsulating formulations of cephacetrile and clindamycin. The free medicine was maintained constantly for 2-3 weeks but the overall concentrations of the medication (bound and free) in the udder,

significantly greater than those of free drugs, were gradually and significantly lowered. It was apparent that the rates of drug release from the depot were equal to the absorption rate of the free drug from the udder when micro capsulated pre-parathions were infused with cephacetrile and clindamycin. Dry udder secretions as a time dependent extractable concentration chloramphenicol-col for formulations either infused with mineral oil or arachis oil. A simple or mono-exponential decreased medication concentration did not result. Together with 1,0 g chloramphenicol preparations were injected into mineral oil, total drug concentrations inside the udder were greater than 10 pg/ml for over 29 days. Suspended in arachis oil, infusions with that same encapsulated formulation led to lower overall concentrations of drugs. However, in both cases the in vitro release research showed a fair rank correction. In the first place chloramphenicol was emanated more rapidly in vitro and the overall drug concentrations in the udder were lower. This quick first in vitro release is linked in the first 7 days following infusion with a comparable in vivo release. The consequence for the rest of the test time is a reduced concentration of encapsulated medicine. Free concentrations in the filtrate drugs were low (below the MIC) and continued only 5 days after treatment following treatment with the encapsulated chloramphenicol formulations. No antibacterial activity occurred 5 days following the infusion of 1 °G non-encapsulated chloramphenicol in unfiltered or filtered secretion samples. [264]

Onur MA, Vurai I, Kaα HS, Hincal AA, Coskun T, Kanra G, Tümer A. Decrease in the placental transfer of chloramphenicol when administered in albumin microspheres into rats. Journal of microencapsulation. 1993 Jan 1;10(3):367-74.

Chloramphenicol is a humanly placental antibiotic that has a teratogenic impact on the fetus. When that antibiotic is caught in albumin microspheres and given intravenously to pregnant rats, placental transfer is considerably less than free drug transport. Alternative means for avoiding negative effects of medications in the event of intake during pregnancy include proposed drug amendments including imprisonment. The purpose of the study is to provide an alternate way of employing systems for medication delivery to prevent the transfer or at least to minimize of teratogenic medicines through the placenta. Chloramphenicol, an antibiotic, was captured and injected into preñed rats in albumin microphones. The medication was then

transferred to the side of the fetus and the free drug was compared. The placental passage of chloramphenicol is known to have adverse consequences on your fetus. Chloramphenicol is really an example of this study. This technology (albumin microphones) is not particular to this medicine and may be utilized for any medications known to be dangerous to the fetus that are trappable in this field. Used as a free form in microspheres. The cause for this might be due to the histological features of hemochorial placenta, in which fetal microvilli are in mother's blood pools. Microsphere may be washed away from the area easily and fast during free pharmaceutical periods. In conclusion, our results show that modifications to medicines such as the imposition of albumin microspheres could be beneficial and that the benefit is twofold: the medicine will be strongly reduced on the maternal side and will increase its therapeutic effect (by local accumulation); and the risk of teratogenicity will also be avoided due to low placental transfer. [265]

Manvi FV, Gadad AP, Mastiholimath VS, Patil MB, Balamuralidhara V. Microencapsulation of Verapamil Hydrochloride by Ionotropic gelation technique. Indian journal of pharmaceutical sciences. 2004;66(5):631.

A methodology of ionotropic freeze employing sodium alginate as well as hydroxypropylmethylcellulose and hydroxypropylcellulose was developed for verapamil hydrochloride micro pellets. For flow conduct, drug trapping efficiency, in-vitro dissolution and stability experiments, including electron microscope scanning and optical microscopy, prepared micro pellets were examined. Of the nine formulations F3, F6 and F9 created and assessed, good results were observed. Different mathematical models have also been used to evaluate the release of the medication from micro pellets following non Fickian diagnosis; the coefficient of diffusion and the correspondence were used. From the research, the use of ion-gelation technology might be used successfully for extended release of verapamil hydrochloride micro pellets. [266]

Chapter – 3
Purpose of study

3.1 The main objective of study:

- Microencapsulation has been done to protect the sensitive drug to prevent contamination. As Chloramphenicol is a sensitive drug so it has formulated in microencapsulation.
- Chloramphenicol is available in the market in tablet, capsule and eye drops but it is not available in microcapsule form so I want to formulate new dosage form. Moreover no formulation has been found of chloramphenicol in research papers so it makes more curiosity to work on it.
- Chloramphenicol 250 mg capsule is an effective drug used when other medicinal products are not successful or are incapable of delivering the required outcomes for severe illnesses caused by bacteria. Chloramphenicol is X category drug for pregnant women because it has teratogenic properties. One study shows if it is administered in microencapsule form then it can remove teratogenic property.
- Microencapsulation ensure extended release of the drug. When it is microencapsulated for chloramphenicol then it will change the release pattern of chloramphenicol.
- The ionic gelation or ionotropic gelation is a good approach using several encapsulation methods. The rationale is that this process is deemed cheap and does not require specialist materials, organic solvents, and high temperatures.

Chapter – 4

Materials and Methods

4.1 Reagents are required for palletization

- Sodium Alginate-polymer [SBH Foods Pvt. Ltd. (India)]
- HPMC (Hydroxypropyl methylcellulose)-polymer [Eminence Chemical (India)]
- Water
- Calcium Chloride (Cacl2) [SaiChem Industries (India)]
- Chloramphenicol (API)-250mg [Anuh Pharma Ltd. (India)]

4.2 Apparatus

- Weighing balance [Sartorius, Germany]
- Spatula
- Foil papers
- Volumetric flasks
- Water bottles
- Beakers
- Syringes-Size 22needles
- Filter papers
- Stands
- Funnels
- Glass rod
- Water Bath [Memmart, Germany]

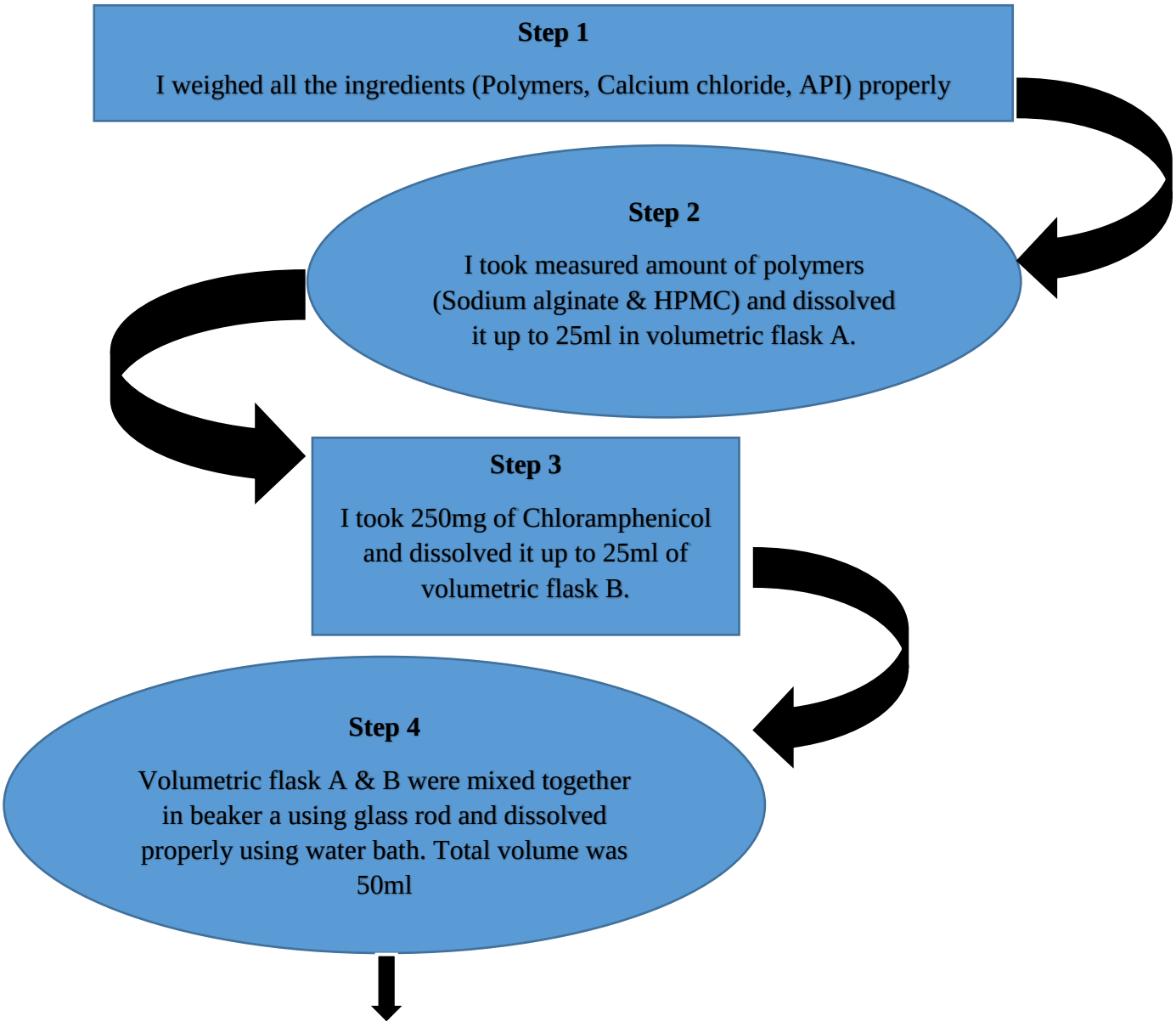
Table 2: Formulation for chloramphenicol pellets

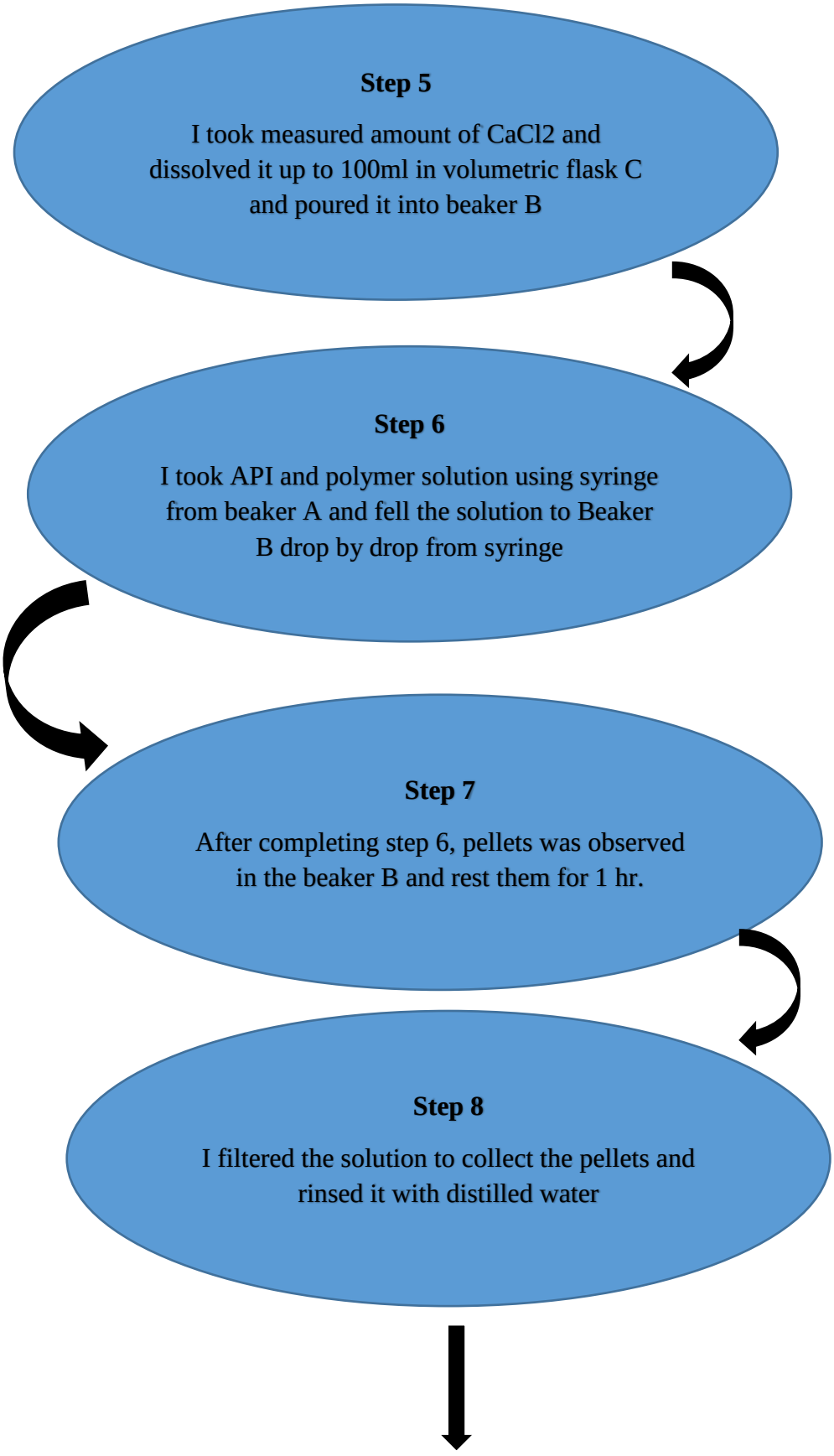
Serial No	Concentration of calcium chloride	Concentration of sodium alginate	Concentration of HPMC	Amount of drug
F1	1%	1.5%	1%	250mg
F2	1.5%	2%	1.5%	250mg

F3	2%	2.5%	2%	250mg
F4	2.5%	3%	2.5%	250mg
F5	3%	3.5%	3%	250mg
F6	3.5%	4%	3.5%	250mg

4.3 Methods of Palletization

I have used ionotropic gelation technique –





Step 9

I dried the pellets within 1/2 hrs.

Step 10

I collected the pellets and stored it into air tight containers

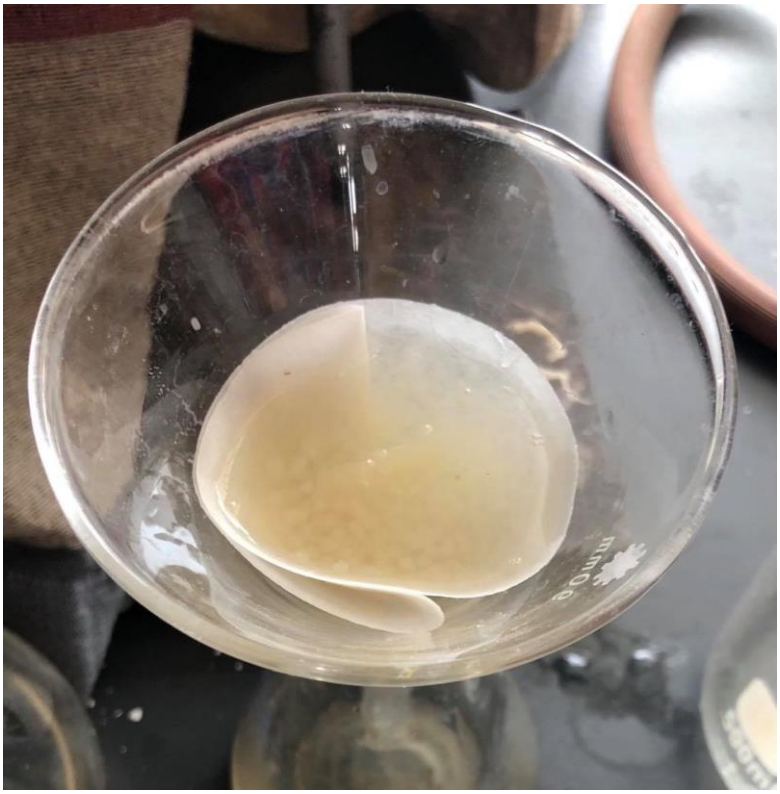


Figure 10: Filtration of pellets

Figure 11: After filtration of the pellets

Figure 12: After drying of 6 samples pellets

4.4 Evaluation test: Preparation of standard curve for chloramphenicol

Reagents

- Chloramphenicol API
- HCl (0.1 N)

Apparatus

- Beaker
- Test tubes
- Weighing Balance [Sartorius, Germany]
- Quarter cell
- Volumetric flask
- Dissolution tester [Pharmatest, Germany]
- Dropper
- Pipette
- UV spectrophotometer.

Procedure

- Step 1: Preparation of 0.1N HCl; 0.83ml HCl was dissolved up to 100ml volumetric flask.
- Step 2: 25mg of chloramphenicol was dissolve in 50ml volumetric flask.
- Step 3: Preparation of 16 microgram /ml concentrated 10 ml solution from step 2 solution. I took 0.32 ml from step 2 solution and added 0.1N HCl up to 10ml.
- Step 4: Preparation of 8 microgram /ml concentrated 10 ml solution from step 3 solution. I took 5 ml from step 3 solution and added 0.1N HCl up to 10ml.
- Step 5: Preparation of 4 microgram /ml concentrated 10 ml solution from step 4 solution. I took 5 ml from step 4 solution and added 0.1N HCl up to 10ml.
- Step 6: Preparation of 2 microgram /ml concentrated 10 ml solution from step 5 solution. I took 5 ml from step 5 solution and added 0.1N HCl up to 10ml.
- Step 7: I used UV-spectrophotometry to take absorbance at 278nm

- Step 8: I plotted a standard curve with the concentration and absorbance using MS Excel.

4.5 Dissolution test for solid dosage form of chloramphenicol 250mg

Apparatus

- Dissolution apparatus
- Test tubes
- Weighing Balance [Sartorius, Germany]
- Filter paper
- Pipette
- Volumetric flask
- UV-spectrophotometry

Reagents

- Pellets of chloramphenicol
- Distilled water
- 0.1N HCl

Procedure

8.33ml HCl dissolved in up to 1000ml

900ml of 0.1N HCl taken in the apparatus

Pellets were taken to the dissolution apparatus

It started to rotated at 75 RPM

It was noted the time when the paddle was started to move

After time interval 5ml of sample was collected and the apparatus was filled with another 5 ml 0.1N HCl

I filtered the solution

2ml of sample was collected after filtration and filled it up to 100ml

Then absorbance was take 278nm

I calculated the amount of drug release with intervals of time.

Figure 13: Dissolution tester

Figure 14: Dissolution Apparatus

Figure 15: Samples collection after dissolution

Chapter – 5

Result & Discussion

5.1 Result

Table 3: Weight of the sample

Samples	Weight
F1	1g
F2	0.96g
F3	0.99g
F4	1.02g
F5	1.18g
F6	1.24g

Standard curve for Chloramphenicol

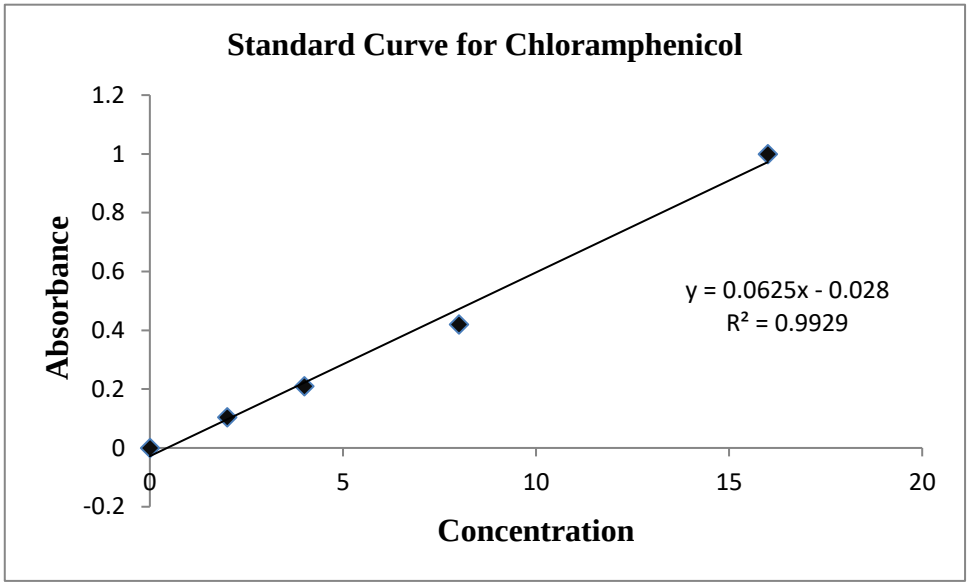


Figure 16: Standard curve for Chloramphenicol

Table 4: F1 formulation

Samples	Time interval (hrs)	Amount of drug release (mg)	Percentages (%)
F1	1	10.25	4.1
F1	2	25.45	10.18
F1	3	51.25	20.5
F1	4	100.05	40.02
F1	5	175.05	70.02
F1	6	240.24	96.096

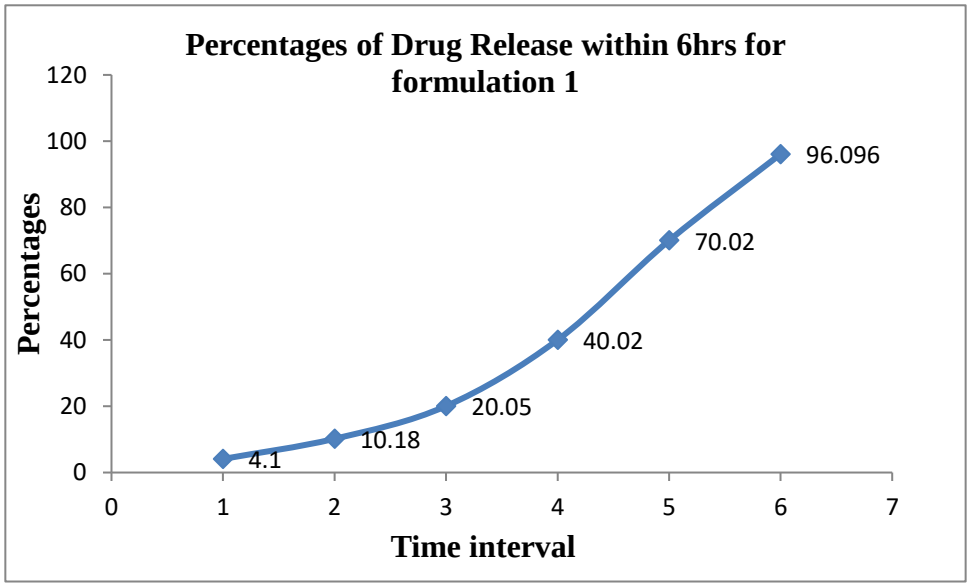


Figure 17: Percentages of drug release for formulation 1

Table 5: F2 formulation

Samples	Time interval (hrs)	Amount of drug release (mg)	Percentages (%)
F2	1	9	3.5
F2	2	23.20	9.28
F2	3	40	16
F2	4	75.5	30.2
F2	5	150.12	60.048
F2	6	237.80	95.12

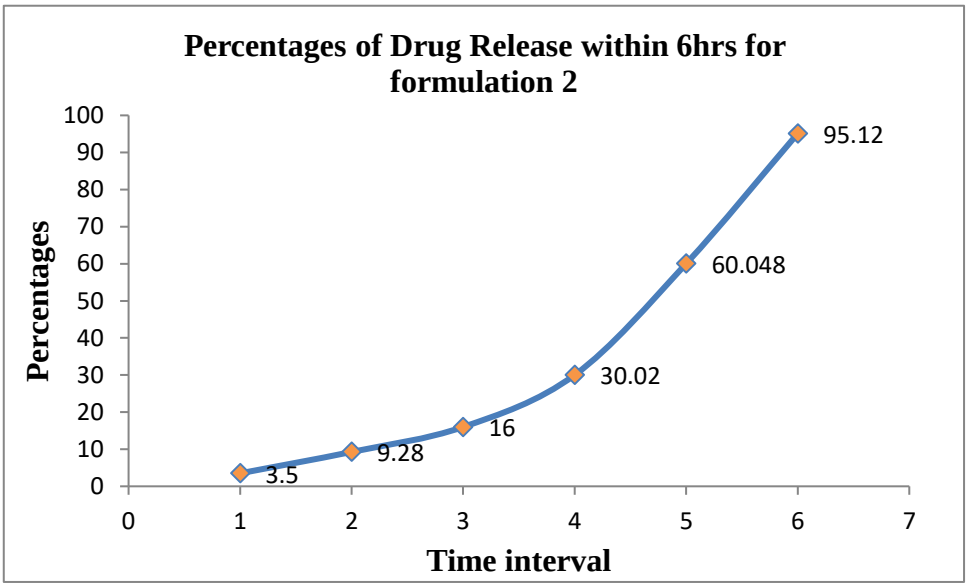


Figure 18: Percentages of drug release for formulation 2

Table 6: F3 Formulation

Samples	Time interval (hrs)	Amount of drug release (mg)	Percentages (%)
F3	1	7.075	2.83
F3	2	27.30	10.92
F3	3	43.39	17.356
F3	4	63	26
F3	5	190	76
F3	6	235.75	94.3

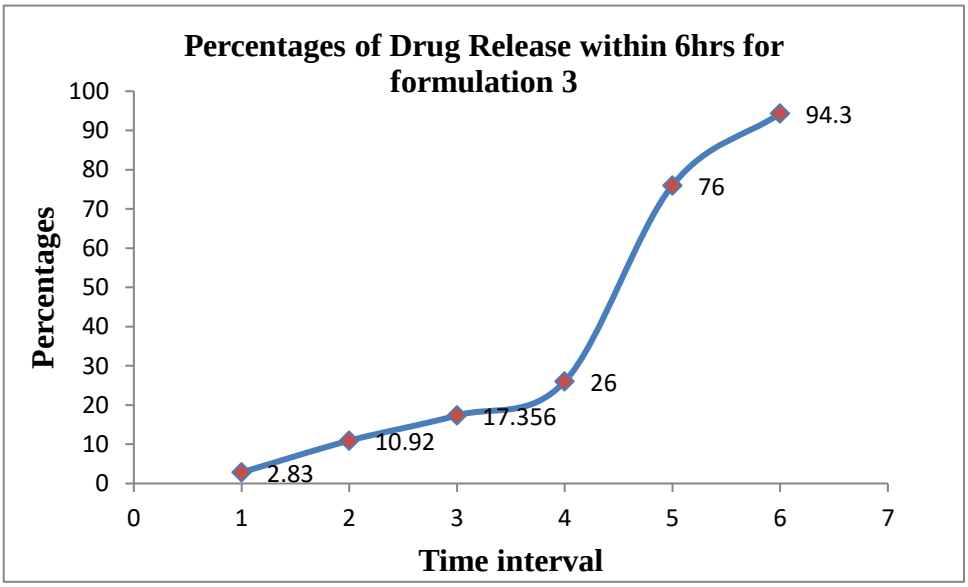


Figure 19: Percentages of drug release for formulation 3

Table 7: F4 Formulation

Samples	Time interval (hrs)	Amount of drug release (mg)	Percentages (%)
F4	1	7.043	2.8172
F4	2	23.12	9.248
F4	3	37.509	15.0036
F4	4	46.239	18.4956
F4	5	60.190	24.076
F4	6	75.925	30.37
F4	7	95.705	38.282
F4	8	120.139	48.0556
F4	9	150.930	60.372
F4	10	175.095	70.038
F4	11	200.395	80.158
F4	12	249.960	99.984

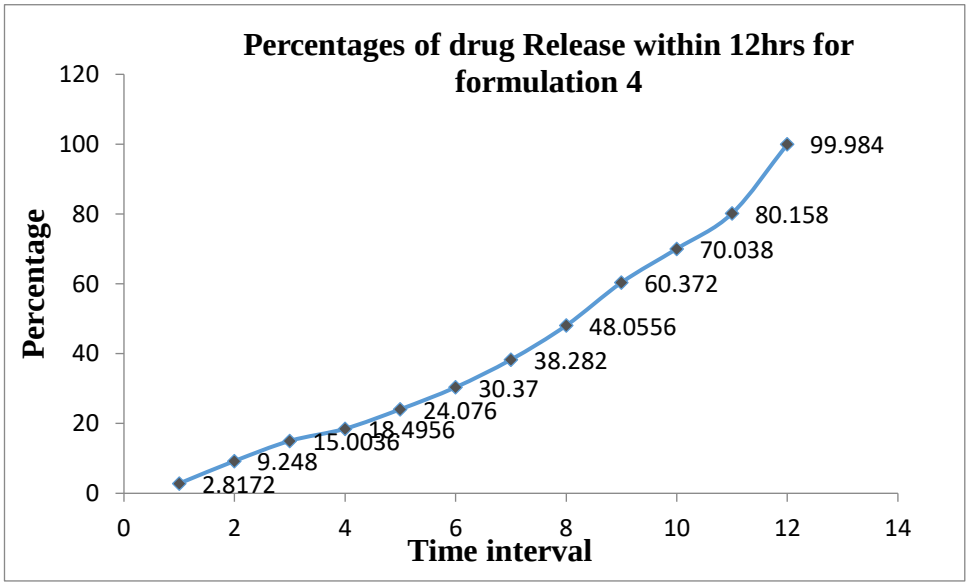


Figure 20: Percentages of drug release for formulation 4

Table 8: F5 Formulation

Samples	Time interval (hrs)	Amount of drug release (mg)	Percentages (%)
F5	1	6.96	2.784
F5	2	22.095	8.838
F5	3	31.0631	12.42524
F5	4	44.239	17.6956
F5	5	60.023	24.0092
F5	6	73.392	29.3568
F5	7	93.094	37.2376
F5	8	115.339	46.1356
F5	9	145.065	58.026
F5	10	172.367	68.9468
F5	11	199.950	79.98
F5	12	248.990	99.598

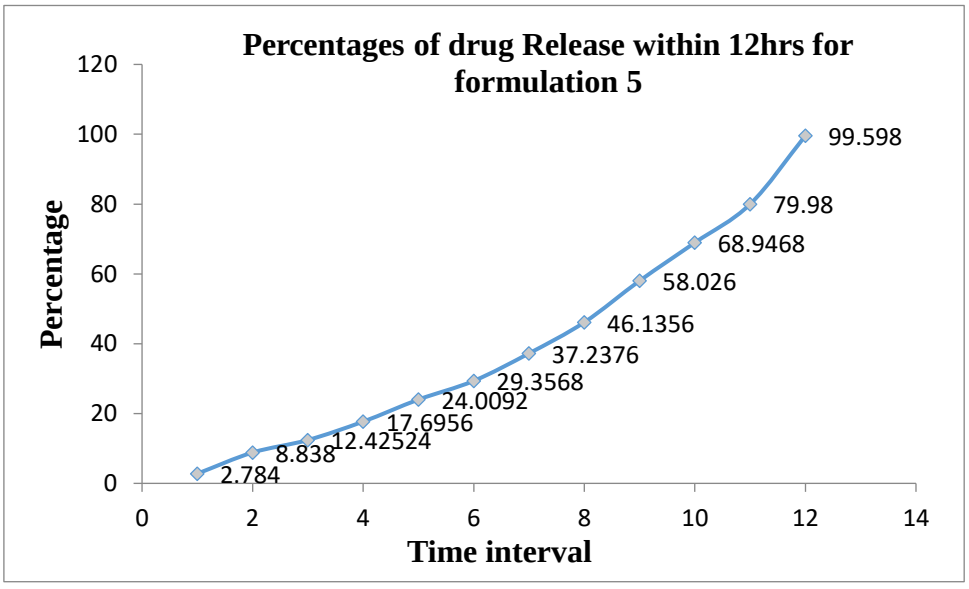


Figure 21: Percentages of drug release for formulation 5

Table 9: F6 Formulation

Samples	Time interval (hrs)	Amount of drug release (mg)	Percentages (%)
F6	1	6.780	2.712
F6	2	18.563	7.4252
F6	3	27.6432	11.05728
F6	4	43.950	17.58
F6	5	55.653	22.2612
F6	6	72.321	28.9284
F6	7	91.059	36.4236
F6	8	112.409	44.9636
F6	9	142.390	56.956
F6	10	170.679	68.2716
F6	11	180.021	72.0084
F6	12	247.993	99.1972

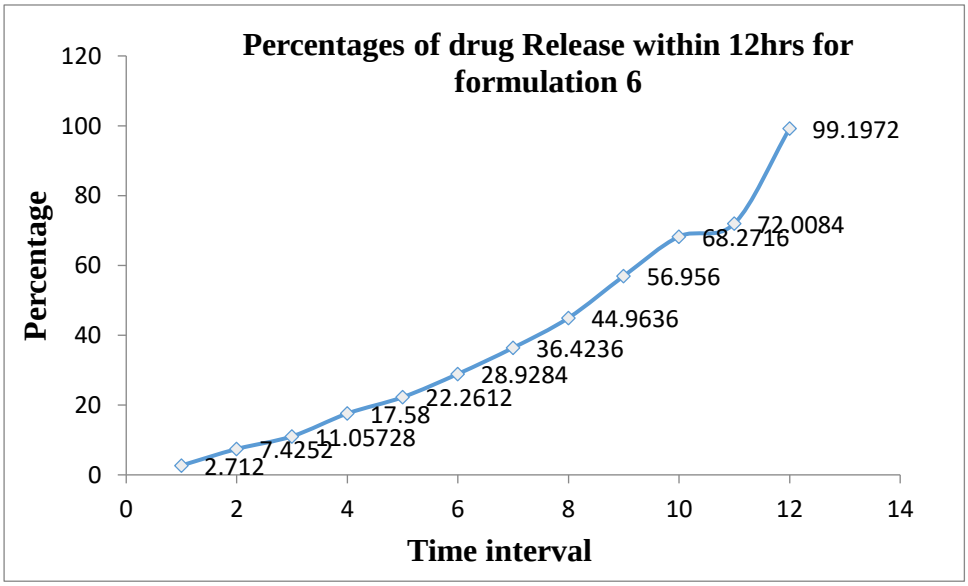


Figure 22: Percentages of drug release for formulation 6

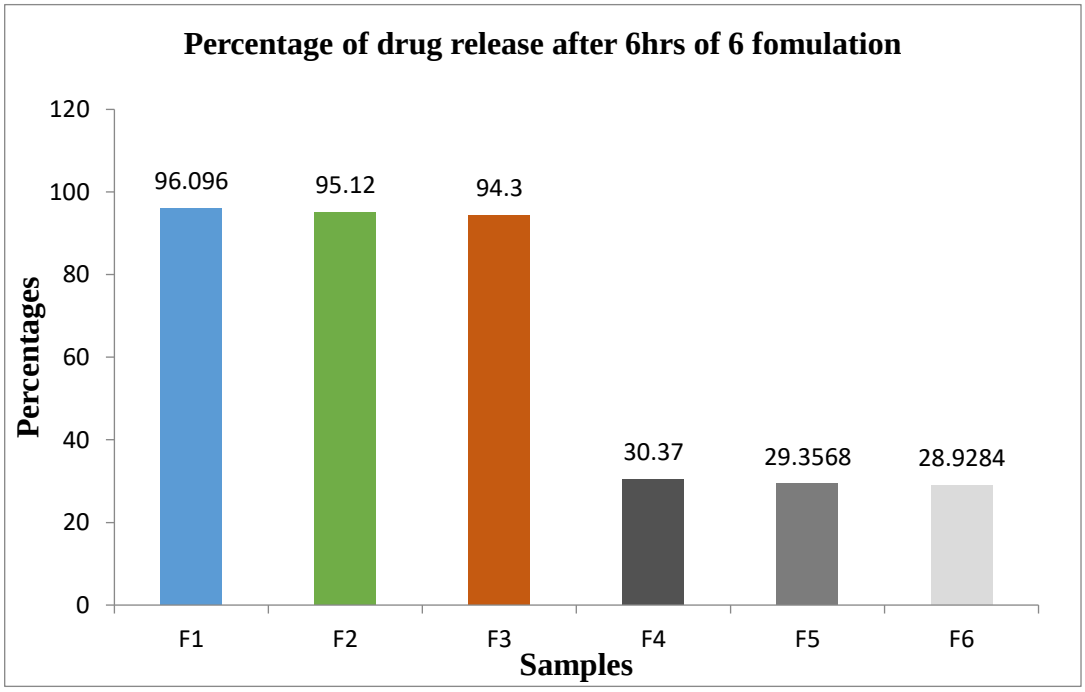


Figure 23: Percentages of drug release after 6hrs of formulation 6

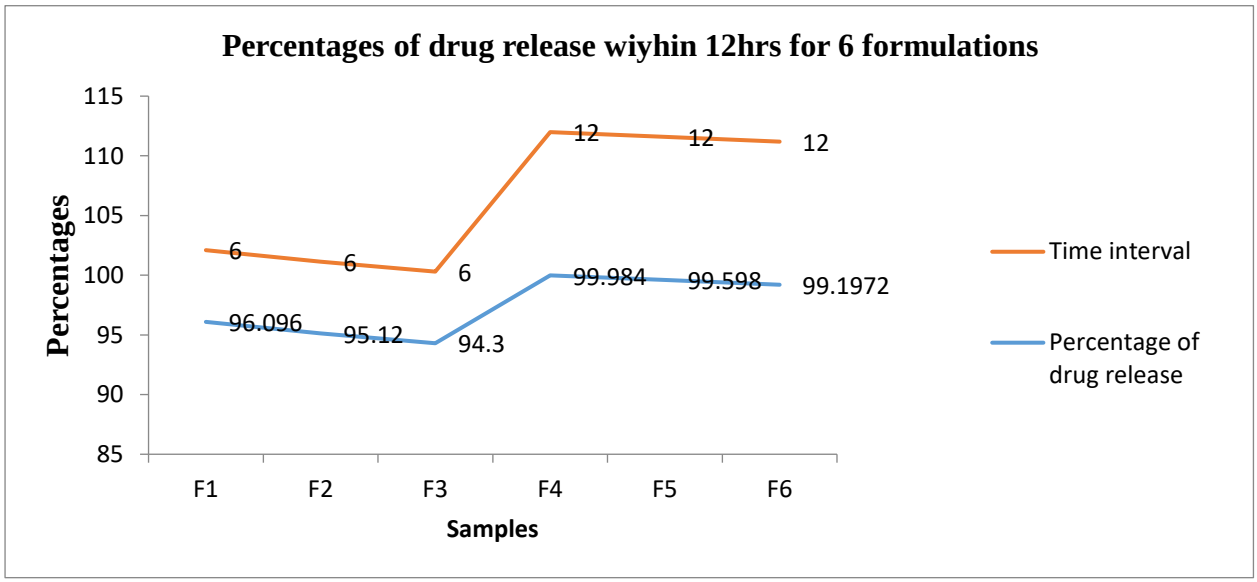


Figure 24: Percentages of drug release after 12hrs of formulation 6

5.2 Discussion

Dissolution studies of all the formulations were carried out using dissolution tester. The dissolution studies were conducted by using dissolution media with 0.1N HCl.

The data obtained in the in-vitro dissolution studies were grouped according to modes of data treatment as follows:-

Cumulative percent drug release V/s. Time (Zero-order).

The results of the in-vitro dissolution studies of formulations F1 to F6 are shown in Table 2. The plots of Cumulative percentage drug release V/s. Time, Time were drawn and represented

Graphically as shown in Figure No. 17 to 22, respectively. The amount of drug release in mg is shown in Table 4 to 9.The percentages of drug release over 12 hrs has shown in Figure 24.The weight of the pellets has shown in Table 3.

F1 formulation contains 1.5% Sodium alginate, 1% Hydroxy Propyl Methyl Cellulose along with 1% CaCl solution and its amount of drug release with repeatedly 1hr time interval almost 6hrs respectively 10.25mg, 25.45mg, 51.25mg, 100.05mg, 175.05mg and 240.24mg shown in tablet 4.

F2 formulation contains 2% Sodium alginate, 1.5% Hydroxy Propyl Methyl Cellulose along with 1.5% CaCl solution and its amount of drug release with repeatedly 1hr time interval almost 6hrs respectively 9mg, 23.20mg, 40mg, 75.5mg, 150.12mg, 237.80mg shown in tablet 5.

F3 formulation contains 2.5% Sodium alginate, 2% Hydroxy Propyl Methyl Cellulose along with 2% CaCl solution and its amount of drug release with repeatedly 1hr time interval almost 6hrs respectively 7.075mg, 27.30mg, 43.39mg, 63mg, 190mg and 235.75mg shown in tablet 6.

F4 formulation contains 3% Sodium alginate,2.5% Hydroxy Propyl Methyl Cellulose along with 2.5% CaCl solution and its amount of drug release with repeatedly 1hr time interval almost 12hrs respectively 7.043mg 23.12mg, 37.509mg, 46.239mg, 60.190mg, 75.925mg, 95.705mg, 120.139mg, 150.930mg, 175.095mg, 200.395mg and 249.960mg shown in tablet 7.

F5 formulation contains 3.5% Sodium alginate,3% Hydroxy Propyl Methyl Cellulose along with 3% CaCl solution and its amount of drug release with repeatedly 1hr time interval almost 12hrs respectively 6.96mg, 22.095mg, 31.0631mg, 44.239mg, 60.023mg, 73.392mg, 93.094mg, 115.339mg, 145.065mg, 172.367mg, 199.950mg, 248.990mg shown in tablet 8.

F6 formulation contains 4% Sodium alginate, 3.5% Hydroxy Propyl Methyl Cellulose along with 3.5% CaCl solution and its amount of drug release with repeatedly 1hr time interval almost 12hrs respectively 6.780mg, 18.563mg, 27.6432mg, 43.950mg, 55.653mg, 72.321mg, 91.059mg, 112.409mg, 142.390mg, 170.679mg, 180.021mg, 247.993mg shown in tablet 9.

The 6 formulation pellets weight respectively 1g, 0.96g, 0.99g, 1.02g, 1.18g and 1.24g shown in table 3.

The formulation F1, F2 and F3 Containing 1.5%, 2% and 2.5% Sodium alginate and 1%, 1.5% and 2% Hydroxy Propyl Methyl Cellulose respectively showed a release of 96.096%, 95.12% and 94.3% after 6 hours. This shows that more sustained release was observed with the increase in percentage of Hydroxy Propyl Methyl Cellulose and Sodium Alginate. In this way we can assume that within 7 hrs the drug will release totally. Our aim is to extended time release of the pellets but in the formulation F1, F2, F3, those cannot fulfill our requirements.

The formulation F4, F5 and F6 Containing 3%, 3.5%, and 4% Sodium Alginate and 2.5%, 3% and 3.5% respectively showed a release of 30.37%, 29.3568% and 28.9284% after 6 hours. Moreover the drug release are 99.984%, 99.598% and 99.1972% respectively after 12 hrs. As our intention is extended time drug release so F4, F5 and F6 can able to release nearly 100% after 12hrs.So, these formulations can fulfill our desire. This shows that more sustained release was observed with the increase in percentage of Sodium Alginate.

The formulations F4, F5 and F6 containing 3%, 3.5%, and 4% Sodium Alginate respectively showed a release that more sustained release was observed with the increase in percentage of Sodium alginate after 12 hours. This indicates that the release rate is further retarded due to addition and in percentage of Sodium Alginate because of the strong bonds between the HPMC and sodium alginate. As the percentage of HPMC increased the release was further sustained.

As our purpose of the study is to extend time release of Chloramphenicol to the pregnant women so formulation F4, F5 and F6 are more reliable. The release pattern has changed with the concentration increase of polymers.

Chapter – 6

Conclusion

6.1 Conclusion

In comparison with traditional medication delivery methods, micro encapsulant system has potential advancement. Micro- and microcapsules have been developed for various medicinal products as unique carrier systems that may be adapted to attach to specified systems. As well as for controlled release, micro-capsules and microspheres may thus also be employed to provide medicines to a certain location in the body. Despite important progress in the field of microencapsulation, numerous hurdles are yet ahead. The development of cheaper micro capsulation biopolymers, as well as the creation of generally recognized assessment techniques, are of particular relevance. Therefore, in future, a thorough study of the biological and technical elements of these systems is required for the creation of safe and efficient special systems. Chloramphenicol 250 mg pill is an efficient medicine used when other medicines fail to give the needed results for serious diseases caused by germs. For pregnant women, chloramphenicol is X because it has teratogenic effects. One study indicates if microencapsulated then teratogenic property can be removed. The micro encapsulation ionotropic gelation technique is inexpensive, prevented drug related adverse effects and used to formulate oral controlled release formulations for Chloramphenicol using HPMC and Sodium Alginate as controlled drug release modifiers. As the concentration of polymers increase then the controlled drug release will more effective. Among six formulations, three formulations F4, F5, and F6 are more effective than rest of the three formulations F1, F2 and F3.These formulations can effective in the large industrial scale. The recommendation of the study, if we follow the formulation F4, F5 and F6 then it should be an effective formulation.

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