NOVEL DRUG DELIVERY: FOCUS ON PREFORMULATION STUDIES

Shivshankar R[1], Tusara Kanta Behera[1], Ashi Varshney[1], Srijana Sharma[1], Vishal Singh[1], Shubham Bisht[1]

[1] School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India

Abstract

At various stages during development, it is essential to understand the physicochemical characteristics of compounds or biological entities that can affect their development into final products. Data acquired from such preformulation studies forms an important basis for understanding the potential pharmacokinetics of a drug in humans and animals and the opportunities and limitations for process change as the product is scaled up in manufacture. Preformulation studies are also performed to predict the stability of the formulation during manufacture, transport and storage and thus determine the shelf life of the marketed product. The chapter covers the measurement of solubility and dissolution rate, molecular dissociation, pK_a, diffusion, partition and permeability; and how these can be included in a biopharmaceutical classification system. Moisture uptake and sorption; the classification of hygroscopicity and evaluation of polymorphism and crystallinity is outlined together with methodology, such as differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and powder X-ray diffraction. Assessing the stability of active ingredients and excipients, both in isolation and in combination, is covered using stress testing, including the effect of pH, temperature, humidity, light and oxidizing agents.

Keywords: Novel drug delivery, Lipid based drug delivery, Preformulation, Formulation by design, Nanoparticles

1. INTRODUCTION

Drug delivery has become one of the greatest challenges in cancer therapy. By facilitating the selective accumulation of compounds in tumour tissue, nanocarriers reduce the toxicity of active pharmaceutical ingredients (API) while they maintain their therapeutic efficacy (1). In the past few decades, Lipid-based drug delivery systems gained increased attention due to their biodegradable and biocompatible property, nontoxicity, ability to improve safety, efficacy, and ability to penetrate through physiological barriers which can present challenges for drug delivery particularly blood-brain barrier (2). Nanoparticles are promising carriers for drugs due to their tuneable dimensions and shape. There are several factors that influence the particle size, particle distribution, surface charge, homogeneity and shape of nanometre-sized drug delivery systems (3). Currently, the field of nanotechnology is intensely exploited for drug delivery technology for passive and active targeting via various routes of administration. The application of nanotechnology in transdermal and topical drug delivery has proclaimed a new domain in the delivery of pharmaceuticals via the skin. Nanoparticles are defined as colloidal particulate systems having dimensions between 10-1000 nm (4). Recently, a new generation of small-molecule drugs has been developed for targeting the molecular pathways in cancer progression. In addition, some existing drugs originally indicated for noncancer diseases have been “repurposed” for cancer treatment. (5).In the latest century, Nanotechnology is one of the fastest increasing technological fields. Recent advances in the development of new materials with unique properties have provided exciting new opportunities in different areas, including environmental applications where nano adsorbents are gaining importance due to their remarkable capacities to uptake a wide variety of pollutants (6). Targeted drug delivery system

(T.D.D.S.) is the goal oriented drug delivery in which the delivery is designed in such a way that it only signifies targeted compartment, either with the help of carrier, ligand, polymer, proteins (components through which the drug can be targeted) or by altering the molecular weight, size or shape of formulation the science of targeted drug delivery is burgeoning with new information and explosive growth of technology and methodology in this area. The delivery of drug can be done with the help of molecule that bind either with receptor or antigens targeting (7). Lipid-based delivery systems have been in the forefront of the research towards conferring the desired attributes to a pharmaceutical drug candidate. Be it oral, dermal, parenteral, rectal, or nasal routes of drug delivery, nanostructured lipid carriers (NLCs) have established their mark as the most versatile system in the domain of pharmaceutical formulations (8). The oral route is still considered the most convenient and safest route of drug administration with higher patient compliance, lesser complications, and lower cost, in comparison with parenteral drug delivery (9). Drug-excipient compatibility studies showed that lopinavir was stable and compatible with most of the excipients proposed in the formulation of nanocarriers. First order degradation kinetics was observed for the drug in solution state across the pH conditions. Characterization using DSC and FTIR further supported the data obtained from these studies (10). Lipid-based delivery systems have several benefits over solid dispersions, complexation, and micronization especially for the delivery of highly lipophilic drugs because they are manufactured with biocompatible and GRAS excipients and their development are cost-effective, facile, and feasible for large scale-up production. The oral bioavailability of drugs including but not limited to fenofibrate, duloxetine, quercetin, lovastatin, and cyclosporine has been potentiated significantly using such approaches (11). Oral delivery of drugs exhibiting poor and inconsistent bioavailability gets thwarted owing to their poor aqueous solubility, low permeability, extensive hepatic first-passeffect, intestinal metabolism by cytochrome P450 and/or P-glycoprotein (P-gp) efflux. A number of conventional techniques available for manipulation of oral bioavailability like, micronization, solid dispersions, inclusion complexes, co-crystals, complexation with hydrophilic polymers and super saturable systems tend to address the issues of poor solubility only (12). Such Preformulationprofiling will not only dictate many of the subsequent events such as the selection of excipients, formulation strategy and processing development, but also provide a rationale for a robust dosage form that can sustain the rigors of processing and shelf life (13). However, the success of the treatment is dependent of the pharmaceutical dosage form used for its administration in the oral cavity, sincere it is important to maintain the drug concentration higher than the minimal inhibitory concentration in the salivary fluid, over an extended period of time. Among novel mucoadhesive drug delivery systems, tablets and films are the most prominent. In previous works, we designed mucoadhesive tablets containing nystatin, in which swellable polymers were responsible for bio adhesion and release modulation (14).The overall concept of preformulation is to create useful information which can be used by the innovator and/or industry to develop a stable formulation and marketable DDS. It is the primary process toward the final stage of formulation development, i.e., design of a DDS. Overall, it includes thorough understanding of the various physical and chemical properties of the drug right from development of an API, mixing with suitable excipients until the end design of a stable, safe, effective, and affordable DDS (15-17).

2. PREFORMULATION CONSIDERATION

Preformulation studies (physicochemical and biopharmaceutical properties) play a significant participate in drug discovery and development programs as they provide important information on drug use during the identification of lead and efficacy. The role of pre-preparation data means different things in different groups in the acquisition and development stages. In the chemical group, preformulation testing provides indicators of increased chemical composition in terms of solubility, availability and durability (18). Since the number of experiments increases considerably with a greater number of parameters that are included into the experimental design, preformulation studies were conducted and key parameters with a major impact on product characteristics were identified. First experiments included the evaluation of solvent-to-non-solvent (SNS) ratio, absolute flow rate, and the type of the stabilizing agent. The impact of SNS ratio

on precipitation efficiency was investigated by mixing solutions of PLGA–PEG in acetone (5%, w/v) and Pluronic1 F-68 (0.1%, w/v) at ratios of 1:1, 1:5, and 1:10. These compositions were incubated in a Thermomixer (Eppendorf, Hamburg, Germany) for 30 min, followed by centrifugation of the suspension for 10 min at 20,800 rcf and microgravimetric analysis of the supernatant. There were no significant differences in the amounts of non-precipitated polymer observed. Consequently, PLGA–PEG nanoparticles were prepared at a defined SNS ratio of 1:10 in the microreactor system (19). In this case, the formulation parameters play an important role on the mean diameter of the nanoparticles. Our primary concern was to obtain an optimal particle size distribution with a diameter less than 200 nm and a polydispersity index lower than 0.2; therefore, the corresponding parameters were thoroughly assessed. The effect of different organic solvents used in the organic phase on the mean particle size and polydispersity index (PDI) of blank amphiphilic CD nanoparticles. It is clearly seen that among the various water-miscible solvents (required for the nanoprecipitation technique), ethanol is the optimal solvent in this study in terms of mean diameter and PDI for all CD nanoparticle formulations. The nanoprecipitation method is mainly based on interfacial turbulence between a miscible organic phase and an aqueous phase (20). The preformulation studies were carried out by simultaneous estimation of both drugs by UV–Visible spectrophotometer and HPLC method. Further to ensure the compatibility of cisplatin and imiquimod for combination therapy, the various modern techniques have been applied at preformulation step (21). The overall concept of preformulation is to create useful information which can be used by the innovator and/or industry to develop a stable formulation and marketable DDS. It is the primary process toward the final stage of formulation development, i.e., design of a DDS. Overall, it includes thorough understanding of the various physical and chemical properties of the drug right from development of an API, mixing with suitable excipients until the end design of a stable, safe, effective, and affordable DDS (22). A preferred microbicide formulation should retain its aesthetic characteristics, performance and stability during various phases of production, distribution, storage, and use. Types of microbicide formulations to be pursued for an active compound are governed by several factors, including preferences and health care economics of the targeted population, the cultural environment, regional geographical and climatic conditions with reference to temperature and humidity, and functionality (with and without contraceptive activity) (23).

2.1 Properties

2.1.1. Solubility

Solubility of a drug substance is a fundamental property that should be evaluated early in the discovery phase. A direct relationship exists between solubility of a molecule and its dissolution rate. Drug penetration through lipid membranes depends on the lipophilicity of the molecule and, thus, may be correlated with the partition coefficient value. Absorption of a drug depends on the correct balance between these two opposite properties. A lack of solubility affects the ability of drug to achieve efficacious and toxicologically relevant exposures in animals. The solubility of compounds to be tested is critical for all high-throughput screening (HTS) test system (24). The extent to which a drug substances dissolves and exists nonionized in a particular solvent is referred to as its intrinsic solubility. Several parameters such as polarity of the solvent and drug, particle size of the drug, temperature and agitation of the solution process, etc., may affect the solubility of the drug to a significant extent. The intrinsic solubility of the drug substance can be determined by analysing the drug content in a saturated solution. An ideal microbicide compound should immediately disperse or dissolve in vaginal fluids and disperse throughout the cavity(25).The aqueous solubility of EDR based on pH was conducted between pH 2-10 by using universal buffer (pH 2-8) and alkaline borate buffer systems (pH 9-10) and compared with milli water(26). One of the principal objectives of preformulation is to keep the drug in solution form as this eventually leads to enhanced therapeutic efficacy. Besides, the solution form facilitates maximum amount of drug in the systemic circulation. Various solvents have been explored for analysing the solubility of

drug at room temperature, like distilled water, 0.9% sodium chloride, hydrochloride acid (0.01 and 0.1 M), 0.1 M sodium hydroxide, and buffers (pH 7.4) (27).

2.1.2. Solubility versus pH

The pH-dependent solubility of DIM-D was assessed using the shake-flask method by adding excess amount of the drug to phosphate buffer of pH values of 1.2, 4.5, 6.8, and 7.4. The mixtures were placed in centrifuge tubes and were shaken at room temperature for 24 h. The mixtures were then centrifuged and the supernatant was analysed by HPLC (28). Solubility measurements were carried out according to the CheqSol method20. JFD was titrated from pH 2.0, where it was fully dissolved at a concentration of 2.2mM under aqueous conditions towards its pKa to induce precipitation. When the precipitate started to appear (kinetic solubility), small aliquots of 0.5M HCl or KOH solution were added to induce and cycle between slight sub saturation and supersaturation, resulting in dissolution with a positive pH gradient (dpH/dt) or precipitation with a negative dpH/dt, respectively(29). In brief, the solubility of a drug in a solvent depends on pH of the solvent, temperature of the solution in which drug is dissolved, ionic strength of the drug in a particular solvent, and effect of buffer concentration(30).

2.1.3. Stability

Stability studies during preformulation are prerequisite for the quantitative determination of chemical stability of a new drug. This study is carried out during toxicological studies, formulation as solution state, DDS in solid state. As per the ICH guidelines Q1A(R2), the stability studies are conducted as either accelerated or long-term stability studies depending upon the climatic zones(31). A standard solution of clotrimazole, 1 mg/ml in acetonitrile was prepared. It was further diluted with USP buffers of pH 1.2, 4.5, 6.8 and 7.5, each to 10 ml. These solutions were incubated for 2, 4 and 24 h at 37 ◦C. In order to achieve adequate solubility levels; aqueous samples were prepared with acetonitrile as a cosolvent at an effective final concentration of 10% (v/v). The samples were assayed for drug content by validated HPLC method (32).One of the most important features of lipid nanoparticles is the ability to retard the chemical degradation of actives by photochemical, hydrolytic and oxidative pathways. It has been noted in research that actives that are incorporated in the imperfections at the less crystalline lipid matrix of NLC provide prolonged physical stability (33).

2.1.4. pH dependent stability

The determination of a stability profile could help to decide the suitable conditions for the pharmaceutical dosage form. Since we would like to develop an oral liquid formulation of EDR, we have used conditions like different pH, temperatures, presence of light and oxygen and effect of initial concentration. The process of the breakdown of a compound in presence of water is called Hydrolysis. It is considered as one of the most common reactions involved in the degradation process. The range of pH from acidic to basic using different buffer conditions could trigger the process of hydrolysis. We have used a universal buffer system (pH 2–8) containing citric acid, boric acid and phosphoric acid (Wang et al., 2015); and alkaline borate buffer system (pH 9-10) to cover the broad range of pH 2 – 10(34)There was negligible change in the measured drug amount remaining after 24 h incubation at both acidicand basic pH ranges (Fig. 1b). The overall calculated drug remaining after 24 h was >96 % of the starting amount. These projects the relative stability of DIM-D to possible pH-dependent degradation during transport in both the GI tract and blood circulation after oral administration (35).

2.1.5. Compatibilities with excipients

While developing a DDS, the basic information on drug-excipient interactions is highly critical for the selection of apt excipients. Although this information is available for the already existing marketed drugs, for the new molecules this is vital and it is usually generated during the preformulation. For example, formulation of tablet for a new molecule may consists of binders, disintegrants, lubricants, etc. Thus,

compatibility screening of two or more variants in the different excipients is important. The compatibility studies for the drug excipient are important in view of the following;

• Increasing the stability of a DDS as any physical or chemical interaction between drug and excipient can substantially modify the bioavailability of a drug.

• It facilitates in understanding the last-minute problems just before the final DDS.

• It correlates drug discovery (i.e., designing a new molecule) with the drug development.

(36-37).

2.1.6. Polymorphic behaviour

Polymorphs: The phenomenon of the existence of more than one crystalline form of a drug is termed as polymorphism and the forms are known as polymorphs. This atomic rearrangement causes the formation of different polymorphs with varying internal lattice and crystal forms. Owing to this rearrangement, the polymorphs differ in their physicochemical properties. For example, riboflavin has three different forms, i.e., I, II, and III forms of which form III has 20 times more aqueous solubility than form I. Polymorphismcan be differentiated into two types, i.e., monotropes and enantiotropes. This differentiation is based their stability on varying the temperature and pressure(38). The polymorphic form of a drug shows variation in solubility, melting point, density, hardness, crystal shape, optical and elemental properties (e.g., vapor pressure etc.). Moreover, relative bioavailability of solid compounds may vary markedly from one form to another. The crystal structure affects stability and developability of the crystallized product. The ritonavir story illustrates the importance of transitions among crystal forms (conformational polymorphism). Although polymorphic behaviour alters the solubility of drugs, it does not necessarily alter the bioavailability evidenced by phenylbutazone (39). Lipids has the ability to aggregate in a variety of ways giving rise to different polymorphic forms. This can be in form of micelles, lamellar phase, tubular arrangement or cubic phases. Wide angle and small angle X ray scattering techniques are utilized to explore the layer arrangements, crystal structure, phase & polymorphic behaviour of lipid and drug molecules. It also gives an idea regarding length of the short and long spacing of lipid lattice46 and localization of drug in it (40).

2.1.7. Crystallinity

Most of the drugs which are formulated are available as solids. Solid drug moleculesexist in two forms, namely amorphous and crystalline. The presence of either amorphousor crystalline form of the drug molecule in a formulation can influence the stability andbioavailability of the formulation. Generally, the amorphous forms are more soluble andless stable than the crystalline forms. Comparisons of physicochemicalproperties of amorphous or crystalline form are shown in Table (41).

Comparison of Physicochemical Properties of Different Crystalline Forms

Properties	Crystalline	Amorphous
Arrangements of atoms	Regular arrangements of atoms orgroupings of atoms in a lattice	Arrangement of atoms are irregular
Thermodynamic energy	Low thermodynamic energy	Thermodynamic energy is high compare to crystalline form
Solubility	Lesser solubility	Increased solubility as compared to crystalline forms
Melting point	Sharp melting point	Do not have sharp melting point
Cleavage pattern	Cleaved along definite planes	Undergo irregular and conchoidal Cleavage
Nature	Anisotropic in nature	Isotropic in nature

The nature of the crystalline form of a drug substance may affect its stability in the solid state, its solution properties and its absorption in vivo. Thus, sufficient care should be taken to determine polymorphic tendencies of a new drug substance during formulation development(42). Crystallization behaviour and lipid polymorphism are the two important parameters to be assessed in lipid-based nanoparticles to obtain stable NLC because crystallization behaviour and lipid modification influence the entrapment efficiency and release profiles of the drug (43).

2.1.8. Partition coefficient

It is defined as the ratio of concentration(s) of compound drugs distributed between organic and aquatic phases, during equilibrium. The drug concentration in the organic phase is generally determined by employing n-octanol and chloroform. Further, this parameter has a significant influence on drug properties as the drug molecules having higher KO/W are said to be highly lipophilic. It is a direct indicator of a drug's ability to traverse through the lipophilic cell membrane. Various methods of finding the partition coefficient include chromatographic method, shake-flask method, probe methods (counter current and Tomlinson's filter) and micro-electrometric titration method. The concept of partition coefficient is applied for the following:

1. Measurement of Lipophilicity.
2. Recovery of antibiotics following fermentation.
3. Drug sampling from biological fluid for therapeutic monitoring.
4. Drug absorption from different DDS, e.g., tablets, creams, suppositories, etc.
5. Distribution of essential and volatile oils while preparing emulsions (44). Although the drug substance dissolves easily in the body's pH's, its ability to transmit membranes may depend heavily on its ability to separate and cross lipophilic clusters, e.g. parts of cell walls. This lipophilicity can be calculated for comparative purposes by determining its PPo / w = (Coil) / (Cwater) equilibrium equilibrium which is a measure of drug distribution combined between the liquid phase and the equilibrium phase (45).

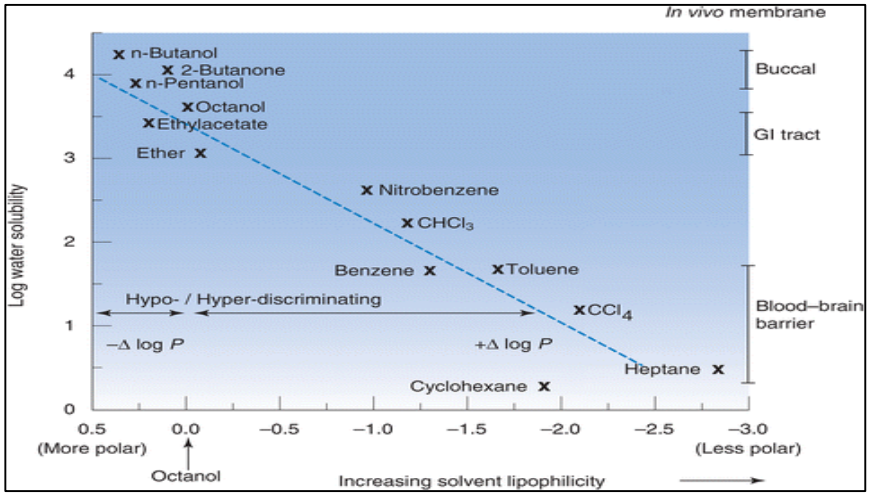

Figure- Distinguishing coefficients in solvents of increasing lipophilicity. Published with permission from Aulton's Pharmaceutics, Michale Aulton and Kevin Taylor, Chapter 23: Preformulation Pharmaceutical, 367-395, Copyright 2013, with permission from Elsevier (45).

2.1.9. Ionization constant

Although, a drug either weakly acidic or basic ionizes in the gastrointestinal tract (GIT) environment, it is only the unionized form that is rapidly absorbed. This correlation is given by the Henderson-Hasselbalch equation which provides an estimation of the ionize and unionized drug concentration at a particular pH. The pKa of a drug can be estimated by either detecting the spectral shifts by UV or visible spectroscopy at varying pH or by potentiometric titration (46). The liquid solubility of a compound depends, among other things, on its ionization state, including the ionized ratio and the union union. The ionization level can be measured using the Henderson - Hassel Bach equation which is a potent acidic compound (HA) of pKa = pH + log [HA] / [A−] or in its reconstituted form pH pKa + log [A -] / [HA] where Ka is the ionisation of constant separation. And with weak primary compounds (BH) pKa = pH + log [BH +] / [B] OrpH = pKa + log [B] / [BH +] pKa is obtained by measuring the pH change of the solution during potentiometric titration using either a weak foundation. or weak acid. When pH = pKa compound is 50% ionized. PKa can be calculated from internal melting data; re-measuring using a variety of strategies e.g. conduction, potentiometry and spectroscopy. The pKa value provides a useful indication of the region of the intestinal tract where the drug will be in ionized or unionized state and, therefore, there are indications of possible absorption characteristics (47-48).

2.1.10. Permeability

Most of the proteins and peptides carry positive charge on their surface which when it interacts with the negatively charged GIT membrane facilitates their permeability. In fact, distribution of charge is more significant as compared to partition coefficient while assessing the permeability of these large molecules across GIT mucosa. (49). Once you have a solution for body fluids e.g. gastric or plasma juices, the drug must replenish cells and tissues to reach the target. This will include passive and / or active routes. Overexpression of the drug will need to be separated from the lipid molecules of the cells and / or propagated through aqueous pores in the tissues. An indication of its availability can be obtained in vitro by measuring the availability of a model bullet at a constant temperature. The total amount of drug in this cell can be measured at different times. Different types of membranes can be selected for their lipid composition. The level of penetration will also depend on other physicochemical properties of the solutions (e.g. water temperature, viscosity, density) (50).

2.1.11. Diffusion

Once you have a solution in an organ or cell in organic fluid, e.g. synovial fluid, vitreous humour, mucous etc. The degree to which a drug can be dispersed depends on a variety of body types such as the viscosity of the liquid in which it is dispersed, the temperature of the liquid, the gradient concentration across the fluid — and hence the amount of the drug in solution and its contact area.. Pre-distribution studies can be performed using Franz's cell. In addition to determining the dose and quantity of a drug already ingested, the distribution coefficient provides an alternative to comparing the related chemicals with those known for in vivo symptoms (51). In this technique, solvent and water are mutually saturated to maintain initial thermodynamic equilibrium(52). In this method, the NLC's are prepared by incorporating the drug in organic solvents along with lipid mixture and lipophilic surfactant at elevated temperature, then the resulting organic solution containing drug is instantly dispersed with high mechanical agitation at 25 ◦C until the NLC's are obtained. The residual organic solvent from the prepared dispersion is evaporated by placing the dispersion in vacuum desiccators for 24 hours (53).

2.1.12. Particle size distribution

Particle shape and size affect both primary and bulk powder properties and play a decisive role in controlling dissolution. Knowledge of particle size and size distribution, flow properties and dissolution are key aspects that should be studied in the field of dissolution science and during the formulation development process (54). Particle size distribution of effervescent formulations was assessed in triplicate using an automatic sieve shaker (Bertel, Brazil) and different sieves of mesh size from 62 μm to 850 μm. The mean equivalent diameter and standard deviation were estimated by probit transformation (55). Particle size distribution, poly dispersity index (PDI) and zeta potential analysis of the protransfersome gel were performed by Malvern Zetasizer. The gel network was destroyed by appropriate hydration of formulation (100 mg) using phosphate buffer saline, pH 7.4 (10 ml) with manual shaking for 5 min at room temperature. Then, the size distribution profile of transfersomes was determined by employing the DTS0012-Disposable polystyrene cuvette (56). The particle size of drug molecule influences the dissolution rate of its dosages form. The dissolution rate, in turn, influences the absorption and bioavailability of drug. As the particle size decreases (by micronization), the effective surface area increases. Consequently, the higher the effective surface area, the greater will be the contact between the drug particle's surface and the aqueous solvent and hence, the quicker the dissolution(57). Particle charge determines the physical stability of the nano emulsion. Particle charge is quantified as zeta potential value which is measured via electrophoretic mobility of particles in an electrical field (58). Particle size of NLC is generally determined by photon correlation spectroscopy (PCS) using Zetasizer which works on Mie theory. Photon correlation spectroscopy (alias dynamic light scattering or quasi-elastic light scattering) is based on the measurement of the fluctuations in scattered light arising from Brownian motion.41 It provides the average particle size (z-average) and polydispersity of the system as a measure of the particle size distribution. It characterizes particles of few nanometres to about 3 microns. Laser diffractometer (LD) can characterize a wide range from the nanometre to the micrometre range particles. This evaluation is based on the diffraction pattern depicting particle shape and size (59). Particle size and the polydispersity index indicates the quality of nanoparticle with respect to size distribution. Rate of drug release, bio distribution profile, mucoadhesion, cellular uptake of water and buffer exchange to the interior of the nanoparticles, and protein diffusion affected by particle size(60).

2.1.13. Hygroscopicity

Moisture is considered to be the vital factor that drastically affects the stability of a drug and its DDS. This process depends on the relative humidity of the surroundings. The properties such as crystal structure, powder flow, compaction, lubrication, dissolution rate, and polymer film permeability are some of the instances which are affected by moisture adsorption. Hygroscopicity is characterized by Karl Fischer, gravimetric, TGA, or gas chromatography methods (61). Chemical and biological materials have different ability to advertise and extract desorb water (called "hygroscopicity") depending on the chemical and physical condition. Drugs and consumables will be stored in storage before being processed, and they will be stored in a variety of humid areas during processingHygroscopicity data can be used to select the inclusion of a final dosage form that can protect the product from exposing too many wet areas that may be exposed during transport and storage. The moisture content in the equilibrium at a certain space is called equilibrium humidity content (emc). The data can be presented as a moisture-absorbing graph

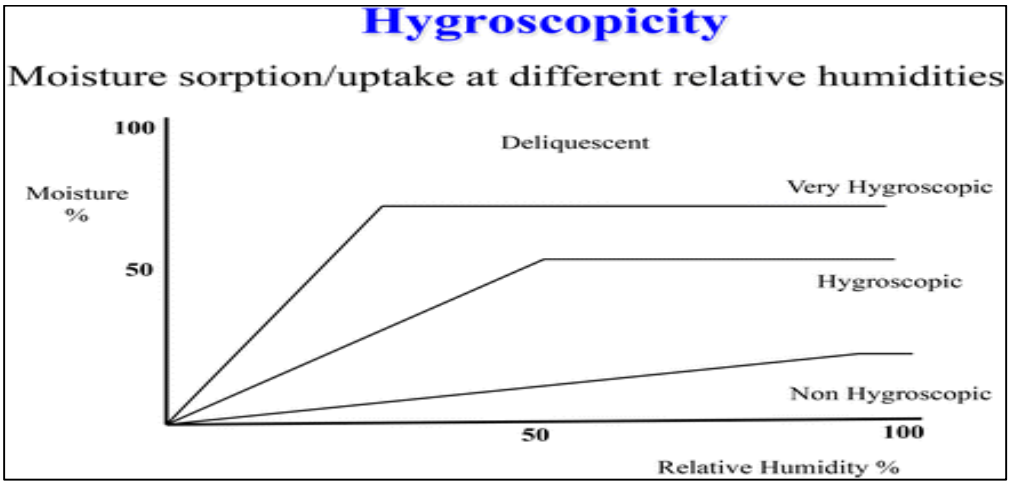

Fig. Hygroscopicity (62).

Hygroscopicity and classifications

Various attempts have been made to quantify the terminology used in classifying hygroscopicity. The most commonly used words are:

Deliquescent
Very hygroscopic
Hygroscopic
Non-hygroscopic

However, no isolation is commonly observed

Class I non-hygroscopic

In fact, no increase in humidity occurs in the relative humidity of less than 90%. In addition, the increase in moisture content after storage for one week above 90% relative humidity (RH) is less than 20%.

Class II is a little hygroscopic

In fact, no increase in humidity occurs in the relative humidity of less than 80%. Increased moisture content after one week of storage above 80% RH is less than 40%.

Class III moderately hygroscopic

The moisture content does not increase by more than 5% after being stored in a relative moisture content of less than 60%. Increased moisture content after one week of storage above 80% RH is less than 50% (62).

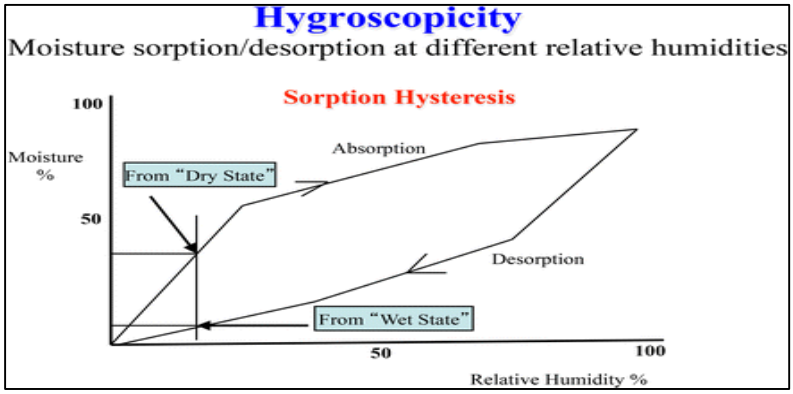

Fig. Sorption hysteresis (62).

2.1.14. Dissolution

Dissolution is an important step during preformulation studies because drug dissolution of a drug will exert a direct impact on bioavailability and drug delivery aspects The modified Noyes_Whitney equation describes the drug dissolution in which surface area is constant during disintegration.

Dc/dt=DA/hv (CS-c 2C)

Where,

D=diffusion coefficient of the drug in the dissolution medium.

h=5thickness of the diffusion layer at the solid/liquid interface.

A=surface area of drug exposed to dissolution medium.

V=volume of the medium.

CS=Concentration of saturated solution of the solute in the dissolution medium at the experimental temperature.

C=Concentration of drug in solution at time t.

When A=constant and CScC the equation can be rearranged to

dC/dt=DA/hv (CS

where,

k=D/h

W=weight (mg) of drug dissolved at time t.

K=intrinsic dissolution rate constant (mg/min cm2) (63).

3. NOVEL DRUG DELIVERY SYSTEM

3.1. Type of novel drug delivery

The way the drug is administered can have a profound effect on its effectiveness. Some drugs have a high concentration of high blood pressure, and focusing too much on or below the list may be harmful or counterproductive. On the other hand, slow progress in the effective treatment of complex diseases, has raised the growing need for multidisciplinary approaches to the delivery of targeted therapies. From this, new ideas were developed to regulate pharmacokinetics, pharmacodynamics, indirect toxicity, immunogenicity, biorecognition, and drug performance. These new methods, commonly referred to as drug delivery systems (DDS), are based on a variety of methods including polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology. To reduce the decline and loss of drugs, prevent harmful side effects and increase the availability of drugs and drug paraphernalia in the required area, various drug delivery systems and drug identification programs are still being developed. Controlled Drug Control and Novel that was a dream or even better is now a reality. For the past eleven and a half years, pharmacologists and other scientists have conducted extensive and in-depth research into the field of drug research Two major approaches can be differentiated into addressing the desired areas of drug withdrawal:

(i) Passing again;

(ii) Active identification

An example of a case study was the special collection of chemotherapeutic agents in strong tissues as a result of strong bone marrow tension compared to healthy tissues. A strategy that would allow for effective identification involves the internal functioning of drug carriers by ligands that are selectively detected by receptors on the surface of interest cells. Since ligand-receptor interactions are highly selective, this may allow for more direct orientation of the interest site (see values provided).

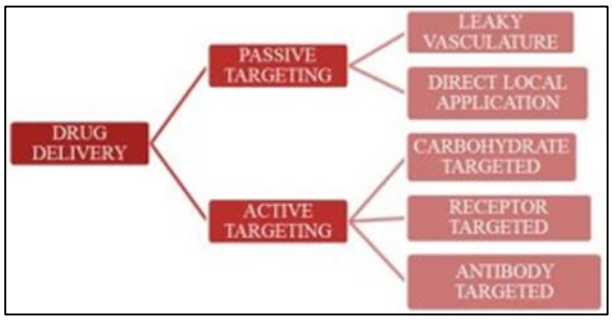

Fig.Drug delivery type (64).

Any drug delivery system can be defined as a system that contains:
a) Drug formation
b) A medical device or form of measurement / medicine to carry a medicine inside the body
• Increased drug effectiveness
• Direct site delivery
• Reduce toxins / side effects
• Easy increase
• Remedies for previously untreated diseases
• Potential printing systems
• Better patient compliance.
Therefore, the set of most appropriate drug delivery systems is reduced as follows:
Various Drug Delivery Programs:

Carrier Drug Delivery Program:
A) Liposomes
B) Nanoparticles
C) Microspheres
D) Monoclonal antibodies
E) Noisome
F) Erythrocytes have been studied as carriers of the drug
Transdermal Drug Delivery Programs:
A) Sonophoresis
• Mucoadhesive delivery systems
• Supramolecular delivery systems
• Flexible delivery systems
B) Osmotic Pump
C) Microencapsulation
Drug Delivery Carriers: Colloidal drug delivery systems such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions containing small particles of 10-400 nm diameter show great promise as drug delivery systems. The inserted drug plays a role in subcutaneous formation, and can affect it due to cell adhesion, especially if the drug has amphiphilic and / or optical properties (see diagram)

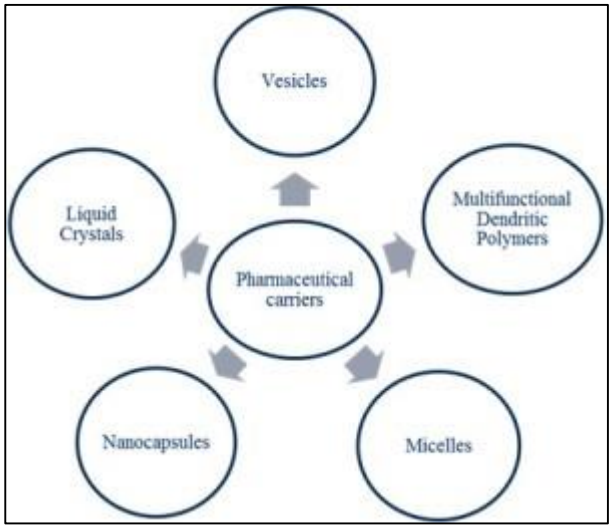

Figure: Different pharmaceutical carriers (64).

Pharmaceutical Carriers: Micelles are composed of a combination of amphiphilic block copolymers (5-50 nm) in aqueous solutions that are of great interest in drug delivery applications. Drugs can be physically absorbed into the block of copolymer micelles and transported to areas that can be subjected to internal water melting. As a result, the contents of the hydrophobic spine are effectively protected from hydrolysis and enzymatic degradation.

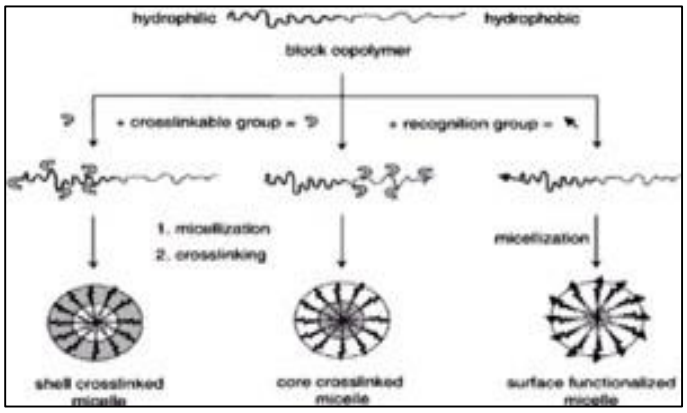

Figure: Mechanism of micelle formation (64)

Liposomes: Liposomes are a type of vesicles that contain many, few or one of the phospholipid bilayers. The polar letter of the liposomal spine causes cold drug molecules to be inserted internally. Amphiphilic and lipophilic molecules are soluble within the phospholipid bilayer according to their affinity with phospholipids. Therefore, nanocage-functionalized drugs and channel proteins are effectively protected against premature degradation by proteolytic enzymes. The drug molecule, however, is able to spread through the channel, driven by the concentration difference between the inside and outside of the nanocage (see fig.).

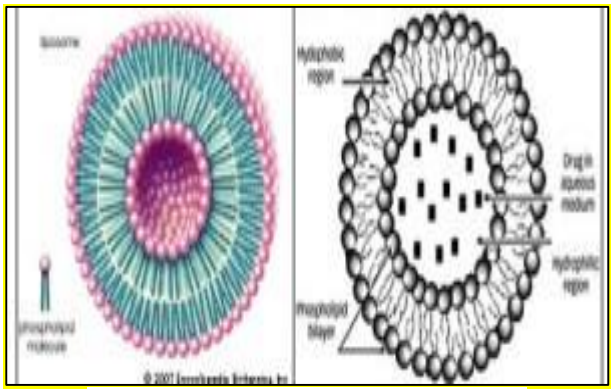

Figure: Structure of liposome (64)

Table 1: examples of patents for liposomes

Patent Number	Assignee/Inventors	Filed On	Title
US20100209492[5]	SDG, Inc, Cleveland, OH	January 14,2010	Targeted Liposomal Drug Delivery System
US20070286898[6]	Astellas Pharma Inc., Tokyo, JP	August 30,2005	Intracellular Drug Delivery Improving Liposome

Table 2: some commercially available marketed liposomal based products

Trade Name	Trade Name	Manufacturer	Indication
AmBisome	Amphotericin B	Nexstar Pharmaceuticals	Systemic fungal infections
Abelcet	Amphotericin B	The Liposome Company	Systemic fungal infections

Nanoparticles: Nanoparticles (including nanospheres and nano capsules size 10-200nm) are solid and amorphous or crystals. They are able to market and / or combine drugs, thus protecting us from chemical and enzymatic damage. In recent years, polymeric nanoparticles have attracted more attention as drug delivery devices due to their applications in controlled drug delivery, targeting specific organ / tissue, such as DNA carriers in gene therapy, and their ability to deliver protein peptides and genes genetically. of the road.

Nanomaterial Separation:

A) Nanotubes - Hallow cylinders made of carbon atoms. They can also be filled and sealed, forming test tubes or potential drug delivery devices.

B) Nanowires- The light silica nano wire is wrapped around a single tent of human hair. It looks weak. Nearly five times more than viral applications for nano wires including early detection of chest and ovary injuries.

C) Nanocantilever- The honey comb mesh behind this small carbon lamp is above the eye of a fly. Cantilevers are bars that are tied to the other side only. In the nano world they act as sensors ready to detect the presence of very small molecules in living organisms.

D) Nanoshells- Nanoshells are empty silica spaces covered with gold. Scientists can attach antibodies to their locations, enabling them to identify specific molecules as cancer cells. Nano shells will one day also be filled with drugs that contain polymers.

E) Quantum dots - Quantum dots are miniscule semiconductor particles that can act as signals for specific types of cells or molecules in the body. They can do this because they emit different wavelengths of radiation depending on the type of cadmium used in their cores. Cadmium sulphide ultraviolet to blue, cadmium selenide in bulk of the visible spectrum and cadmium telluride red infrared and near infra-red.

F) Nano pores- Nano pores contain cancer research and treatment applications. Formed into particles, they are so tiny that DNA molecules can pass through a single strand at a time allowing for more precise and efficient DNA sequence. With the engineering of nanopores on the surface of a drug capsule that is slightly larger than cell-based drugs, drug manufacturers can also use nanopores to control the rate of drug distribution in the body.

Applications- Bucky balls can see widespread use in products and future uses, from cancer drug delivery vehicles to ultra-strong wear and military damage. Bucky Ball- Antibody combination brings anti-inflammatory drugs.

• Bucky balls to fight allergies.
• Bucky balls as powerful antioxidants and are also HIV positive.

Requirements:

• Bucky balls damage cells.
• Bucky balls have a high concentration of live tissue accumulation.
• Difficulty in identifying the location of drug delivery.

Carbon nanotubes: Carbon nanotubes can be converted to circulate more efficiently in the body. Such modifications can be achieved by binding or non-covalent bonding. Modification can increase or decrease the cycle time in the body. Carbon nanotubes are less toxic when they are converted to dissolve in body fluids. They easily get into the cells. Cancer cells in tumours are larger than normal cells as they are well converted to dissolve in body fluids. They easily get into the cells. Prostate cancer cells are larger than normal cells and show leaks. Large molecules circulating slowly can enter and accumulate in the cancer cell. Carbon nanotubes containing active substances have been shown in animal studies to do this. Researchers have used carbon tubes to produce pre-existing active drugs called prodrug. e.g. Cisplatin.

Microspheres: Microspheres are flow-free powders that contain proteins or polymers that are easily degraded naturally and have particles of less than 200 μm. The materials used to prepare Microspheres are polymers. They are divided into two types:

1. Synthetic Polymers
2. Natural polymers

1. The composite polymers are divided into two types.

1. Non-perishable polymers

• Poly methyl methacrylate (PMMA)
• Glycidyl methacrylate
• Epoxy polymers

1. Decaying polymers

• Lactides, Glycosides and their polymers
• Poly alkyl cyano acrylates
• Too many anhydrides

Erythrocytes studied as drug carriers: Erythrocytes, the most abundant cells in the human body, have the ability to regulate drug delivery. Erythrocytes are biologically active, decaying organisms, have a very long half-life distribution of human life and can be loaded with various chemical and biological agents using a variety of chemical and physical mechanisms. erythro = red and cytes = cell Erythrocyte is a red cell. Erythrocyte is a biconcave disc, an antiviral Full of haemoglobin
(Hb), a protein used in gas transport. It contains plasma protein spectrin.

Healthy old man = 4.5millions / μml
Healthy adult woman = 4.8million / / ml the immature RBC is called reticulocytes.

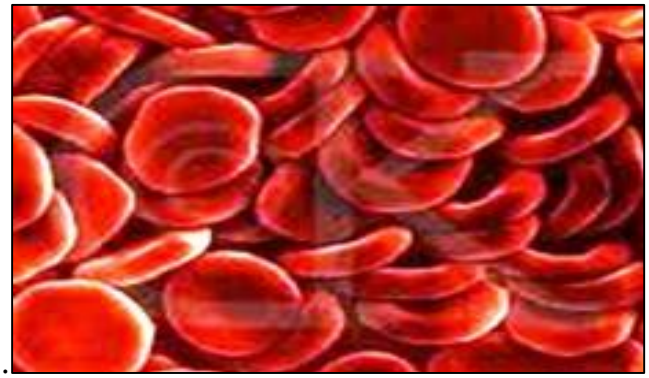

Figure: Erythrocytes (64)

Features of a closed erythrocyte of a drug carrier:

1) The drug must be removed from the target area in a controlled manner.

2) It should be the right size, shape and should allow for the passage of capillaries. And minor drug leaks should occur.

3) It should be biocompatible and should have minimal toxicity.

4) Must have the ability to manage a broad spectrum of drugs.

Profit:

1) They are a natural part of the body, so they decompose through decay.

2) Drug arrest does not require chemical modification of the drug

3) Drug seizures also do not require the chemical modification of the substance to be binding.

4) They are not active in the body and can be targeted to body tissues / organ.

Disadvantages: -

1) They have limited capacity as carriers of non-phagocyte target tissue.

2) There may be cell adhesion and dose disposal.

Drug-laden Erythrocytes: This is one of the growing and powerful systems for the delivery of drugs and enzymes. Erythrocytes are intermittent, degenerative, have a long half-life and can be loaded with a variety of biological agents. Carrier erythrocytes are designed to collect blood samples from the body of interest and to separate erythrocytes from plasma. By using various physiological and chemical mechanisms the cells are broken and the drug is trapped in the erythrocytes, eventually regenerated and subsequent carriers are termed "closed erythrocytes". When regenerated drug-laden erythrocytes act as a deplete depot depicting the drug in the reticulo-endothelial system. Niosomes: In Niosomes, ampicules that make up an amphibian are non-ionic like Span-60 which are usually stabilized by the incorporation of cholesterol and a small amount of anionic surfactant such as dicetyl phosphate. Niosomes and liposomes are equivalent in drug delivery and both increase drug performance compared to that of free drugs.

Transdermal Drug Delivery System: Transdermal Drug Delivery is defined as self-contained, different dosage forms, when applied to the appropriate skin, delivering the drug, through the skin at a controlled rate in the distribution system. The Transdermal Drug Delivery Program (TDDS) has established itself as an integral part of new drug delivery systems. Transdermal delivery is an exciting option because the transdermal route is convenient and safe.

The best features of the drug delivery to the skin to achieve systemic effects are:

• Avoiding the practice of first passing

• To prevent intestinal incompatibility

• Predictable and extended work time

Sonophoresis is a process that increasingly enhances the absorption of compounds (transdermal delivery) to the epidermis, dermis and skin rejuvenation by ultrasonic power. Ultrasound parameters such as duration of treatment, durability, and frequency are all known to affect automatic absorption, with the latter being the most important. Sonophoresis occurs because ultrasound waves trigger small vibrations within the epidermis of the skin and increase the kinetic energy of all molecules forming topical agents. Ultrasound probably enhances drug transport by cavitation, low radiation and heat.

Mucoadhesive Drug Delivery Programs: Bio adhesion can be defined as a state in which two substances, at least one of which is natural, are held together for a long time by the assembling forces. In medical science, where the adhesive paste can contract or mucous membranes, this practice is called mucoadhesion. The strength of mucoadhesive polymers has been demonstrated in ocular, nasal, vaginal and buccal drug delivery systems leading to a very long duration of continuous delivery systems in the mucosal membrane abdomen (GI) will offer a variety of benefits.

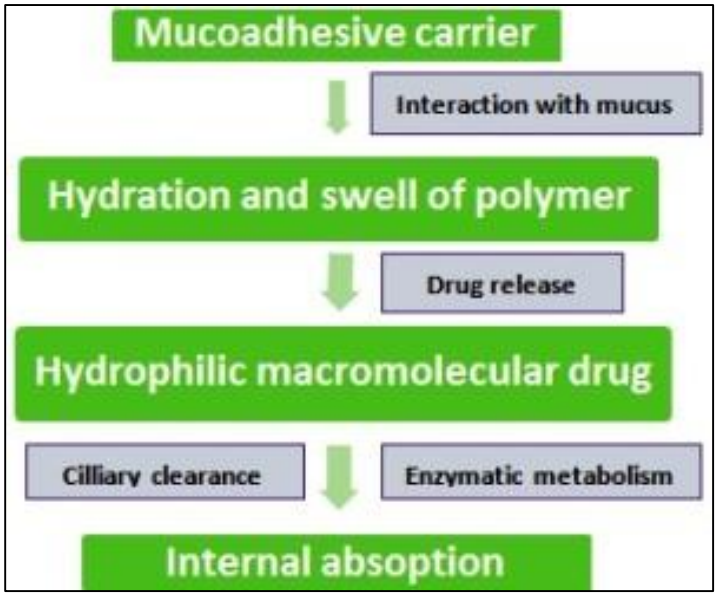

Figure: Mechanism of mucoadhesion (64)

- Supramolecular Drug Delivery Systems: The supramolecular system is made up of two or more bombs of cells held together and arranged using intermolecular non-covalent binding bonds. Supramolecular structures involving macrocyclic compounds have attracted great interest not only as models in understanding the natural supramolecular integration and molecular recognition, but also as precursors for the design of nanomaterials electronic novels, natural uses and pharmaceuticals.
- Osmotically Controlled Drug Delivery Programs: Osmotic Pressure is used as the driving force behind these programs to deliver a drug in a controlled manner. The Osmotic drug delivery process is the most interesting and widely accepted among all other technologies used for the same. Extensive research has been done on osmotic systems and many patents are also being published. The development of osmotic drug delivery systems was initiated by Alza and holds a large number of patented patents and also sells many products based on the osmotic principle. These systems can be used for both oral and parental management. Oral osmotic systems are known as gastrointestinal tract (GITS). Delivery of Parenteral osmotic drugs includes pumps that can be installed.

  Species: Controlled osmotic porosity pump, Osmotic bursting osmotic pump, Liquid OROS, Delayed Delivery Osmotic device, Telescopic capsule, Oros ct (colon targeting), Sandwiched oral Therapeutic system, Osmotic pump for insoluble, Monolithic osmotic system and OSMAT.

  Advantages

  The Osmotic drug delivery system for oral and parental use offers a different and more effective benefit than other delivery methods. The following benefits have contributed to the popularity of osmotic drug delivery systems.

  • They usually provide a release order profile after the initial withdrawal.
  • Delivery may be delayed or beaten if desired.
  • Drug release does not depend on abdominal pH and hydrodynamic status.
  • They look good and are understandable.
  • Removal methods do not depend on the drug.

Disadvantages:

• It is expensive

• If the coating process is not properly controlled there is a risk of film damage, which leads to dropping the the dose Size hole is important

• Loss of volume

Recovery treatment is not possible in the event of unexpected adverse events.

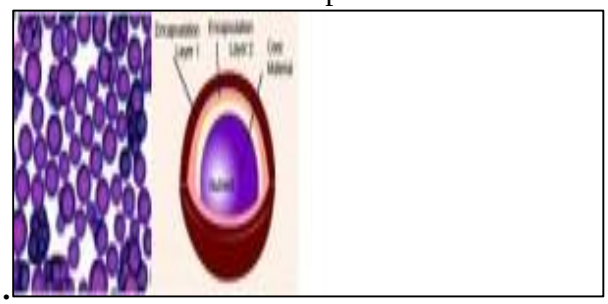

FIGURE: ENCAPSULATION (64).

4. NOVEL DRUG UNDER CLINICAL STUDIES

Designing a novel drug delivery system by incorporating an existing medicine into a new system can significantly improve its performance in terms of efficacy, safety, and improved patient compliance. The need for design of novel drug delivery devices with the aim to enhances their efficiency and minimize the side effects has encouraged pharmaceutical companies to engage in the development of new drug delivery systems.

4.1Present scenario

Through novel ways drugs can be delivered to a patient by different delivery systems. Most of the drugs are delivering through these delivery systems. The advances in the human genome and biotechnology enable most of the companies to develop a large number of macromolecules. Now, the protein- and peptide-based drugs constitute more than half of the new drugs available in the market, and more than 80% of these protein drugs are antibodies. Many biotech companies are involved in drug delivery task; hence, gene therapy is also likely to be one of the most exciting growth sectors. Currently, several genetically engineered cells are in Phase III clinical trials (65). Drug discovery is a continuous process due to the prevalence of many diseases. Research and development play a vital role in drug discovery as well as the drug development process. Once scientists confirm interaction with the drug target, they typically validate that target by checking for activity versus the disease condition for which the drug is being developed. After careful review, one or more lead compounds are chosen (66).

5. FUTURE REMARKS AND CONCLUSION

In the pharmaceutical product development lifecycle, the preformulation stage plays an integral part. It supports the fabrication/designing of the dosage form for any new drug and its quality control process results in an effective pharmaceutical(67). Recent advancements in the understanding of the structure and biochemistry of peptides and proteins has intensified the research in the field of recombinant technology in the pharmaceutical industry. Further advancements in the science and understanding of physicochemical properties of drugs and proteins as well as the biological system of the human body would facilitate the design and development of novel DDS or formulations circumventing the various limitations associated with the current drug or peptide therapies(68). There is a continuous growth in the market of drug delivery systems and will continue to grow at an impressive rate in future also. The advanced drug delivery technologies today enable us to formulate the novel drug delivery devices by incorporating the drug molecules into new delivery systems, thus providing numerous therapeutic and commercial advantages. It is evident from the increased number of novel products in the market and the number of patents granted in the recent past that a large number of companies are involved in the development of new drug delivery systems. The drugs which come into market in future will be more challenging and may present difficulties in the development of delivery systems, and pharmaceutical

scientists will have to be ready for a difficult task ahead(69). In summary, the article has provided critical account on the significance of preformulation studies in the drug development process. To facilitate clinical development and to reduce attrition rate, a thorough study of physicochemical properties of drug candidates is desired. This also serves as the foundation for developing robust formulations (70).

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