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Inclusion Complexes of Cyclodextrins with Anticancer Drugs: A Critical Review

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ABSTRACT:
One of the leading causes of death is cancer. Chemotherapy is a popular treatment method that uses a combination of drugs to either destroy or stop the growth of cancer cells. However, formulation is difficult because most cytotoxic chemotherapy drugs are insoluble in water. Among the cyclic oligosaccharides that have been studied the most are cyclodextrins (CDs) due to their unique inclusion capability, low toxicity, high biodegradability, and biocompatibility, as well as ease of chemical modification. In order to combine the benefits of both biomaterials for the better delivery of anticancer drugs in cancer treatment, polymers have recently been added to CDs. Together with the many, distinctive characteristics of cyclodextrins, the ability to build reversible inclusion complexes between them and other guest molecules offers a route to the development of incredibly complex nanostructures with substantial promise for the treatment of cancer. Stabilizing, encouraging controlled release, improving drug bioavailability, solubilizing, and successfully masking disagreeable tastes and smells are just a few of their many uses. The resultant nanomaterials take advantage of CDs' remarkable qualities, such as their capacity to stabilize labile drugs, increase bioavailability for better therapeutic efficacy.

Keywords: Drug delivery systems, Nanoparticles, Chemotherapy, Cytotoxic drug.

I. INTRODUCTION

1 1. Cyclodextrins [1]:

Cyclodextrins, also referred to as CDs, are cyclic oligosaccharides that form inclusion complexes with a variety of molecules. Their distinctive toroidal shape has a hydrophilic exterior and a hydrophobic interior. They can envelop guest molecules thanks to their structure, creating stable complexes. The three-dimensional form of cyclodextrins resembles a hollow torus, and their outer and interior surfaces have distinct polarity. The small rim has its primary hydroxyl group, whereas the wider rim has its secondary hydroxyl group. While secondary hydroxyls create robust hydrogen bonds and give cyclodextrin rigidity, primary hydroxyls can spin and decrease the diameter of cyclodextrin. Furthermore, the visitor may be subject to additional forces, including van der Waals and dipole-dipole interactions. By adding non-polar molecules with the right size to the cavity, CDs can increase the molecules' solubility in water. This encapsulating feature is highly beneficial for use in a variety of industries, including agrochemistry and medicine. The chemical structure of α, β, & γ cyclodextrin is present in Figures 1, 2 & 3, respectively.

The specific "R" group and the degree of substitution (the quantity of such groups added) can have a significant impact on the cyclodextrin's properties and ability to form inclusion complexes. The "R" group is typically connected to the hydroxyl (OH) groups on the cyclodextrin molecule, which can be primary (at the narrower end) or secondary (at the wider end).

The "R" group is just a hydrogen atom in natural cyclodextrins such as alpha-cyclodextrin (α-

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CD), beta-cyclodextrin (β-CD), and gamma-cyclodextrin (γ-CD). The "R" group in hydroxypropyl-β-cyclodextrin (HPβCD) is a hydroxypropyl group that is added when propylene oxide reacts with the cyclodextrin. Cyclodextrins' water solubility can be improved by adding substituents, which is crucial for pharmaceutical applications. The stability and selectivity of inclusion complexes produced with guest molecules can be influenced by the kind and extent of substitution.

1. 2. Cancer:

Cancer is a complex disease that is characterized by abnormal cell division. Common types include melanomas, lymphomas, leukemias, sarcomas, and cancers. Carcinomas, sarcomas, leukemias, lymphomas, and melanomas are common types. Anticancer medications, sometimes referred to as antineoplastic or chemotherapeutic treatments, are substances that stop cancer cells from growing. Anticancer medications can be categorized according to the kind of cancer they treat, as well as their chemical makeup, mode of action (e.g., microtubule inhibitors, DNA-damaging compounds), and cytotoxicity (direct toxicity to cells), or targeting (specificity to cancer cells). The normal cell development and abnormal cell growth are present in Figures 4 & 5, respectively.

1.3. Inclusion complex formation [2]

Cyclodextrins have a non-polar hole within and hydroxyl groups on the outside. Hydrophobic compounds are mostly included through hydrophobic interactions between the cyclodextrin cavity walls and guest molecules. Even though complexation with cyclodextrins involves a lot of pressure and variables, the process of creating complexes is fairly simple. The inclusion complex formation from cyclodextrin and an anticancer medication is present in fig 6.

II. INCLUSION COMPLEXES OF CYCLODEXTRINS WITH ANTICANCER DRUGS – MECHANISM

First, the interaction between cyclodextrin and the active ingredient is a key component in the mechanism of cyclodextrin complex formation. Through physical interactions like van der Waals forces, cyclodextrin molecules bind to a lipophilic molecule. When the guest molecule and host cavity have the same dimensions, a complex is formed. Absorption is restricted to hydrophobic elements whose normal sizes are less than the diameter of the inner cavity. The creation of inclusion complexes requires a dynamic association/dissociation equilibrium between the complex, free guest molecules, and uncomplexed CDs; the direction of this reversible process is determined by the Kf constant (formation/stability constant). In particular, a complex is more stable and less likely to dissociate if its Kf value is higher. The release of conformational strain and complementary contacts (such as van der Waals forces, hydrogen bonds, electrostatic interactions, and hydrophobic interactions) can have an impact on complex formation.

The hydrophobic molecule is contained in a basket-like structure that resembles a clathrate, with the H-bonds reoriented tangentially to the surface to minimize the number of broken physical bonds. Water molecules are ejected from the CD cavity to increase the system's entropy, while the hydrophobic molecule moves within the CD cavity to form the inclusion complex.

Another important feature of CDs is that they are non-toxic, which is why the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) allowed their use in pharmaceutical formulations. For that reason, they are safe to employ as excipients to increase the bioavailability and stability of medications that are not highly hydrophilic. Additional positive benefits on guest medications include extending the drugs' shelf life, minimizing (or getting rid of) bad taste and odor, and avoiding interactions between drugs or excipients.

The method of controlled disintegration of inclusion complexes is based on a pH change that causes hydrogen to be lost between the host and guest molecules. A different way to disassemble glucose units is by heating them or by cleaving the α-1,4 bonds between them with an enzyme. The guests are not always released in the same proportion as in the initial (pre-formation) guest mixture for inclusion complexes that contain several guest components or distinct cyclodextrin types.

To be more specific, CDs can be used as vehicles to deliver targeted ligands and receptors to the surface of tumor cells, where certain receptors (such as the folate, biotin, and glucose receptors) are over expressed.

Drug bioavailability, drug permeability through biological membranes, and the aqueous solubility of poorly soluble medications are all

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enhanced by the use of natural CDs and their derivatives as enabling pharmaceutical excipients. By creating inclusion complexes that increase drug solubility, stability, and bioavailability, cyclodextrins (CDs) increase the effectiveness of anticancer medications.

The percentage of the active ingredient that enters the bloodstream without transforming when given by a method other than intravenous delivery is known as bioavailability. Crossing cell and tissue membranes and structural changes brought on by the active ingredients' metabolism are physiological variables that impact bioavailability.

The Biopharmaceutical Classification System (BCS) classifies drugs into four groups called Class I, II, III, and IV according to how soluble and membrane-piercing they are. Class I drugs have high permeability and solubility. Class II drugs have both high permeability and low solubility, Class III drugs have both low permeability and high solubility, and Class IV drugs have both low permeability and low solubility. When medications and natural or modified cyclodextrins form inclusion complexes, the drugs' water solubility and bioavailability are enhanced.

III. INCLUSION COMPLEXES OF CYCLODEXTRINS WITH ANTICANCER DRUGS – SOLUBILITY

The topic of anti-cancer drugs is particularly relevant because most cytotoxic compounds are classified as BCS class IV and have very low solubility and penetrability in aqueous fluids. These substances are toxic even at low quantities. Thus, a great deal of research has been done on the function of cyclodextrins—both natural and modified—as well as cyclodextrin-based polymers in their delivery.

Furthermore, a lot of anti-tumor medications are very lipophilic, which makes it occasionally challenging to get the concentration needed to provide the intended effect, even when given intravenously. Because of its limited water solubility, phenoxodiol, an anti-tumor flavone derivative, has much less efficacy. Its cytotoxic activity against neuroblastoma and breast cancer cell lines is enhanced and its side effects are more than five times decreased by building inclusion complexes with β-CD. Improved solubility can be achieved in a variety of ways, including solid dispersion, size reduction, cosolvency, polymorphism, and the creation of complexes or prodrugs that dissolve in water.

Cyclodextrin (CD) complexation is one of the most researched methods to improve drug solubility and, thus, bioavailability. The native CDs are called α-, β-, and γ-CDs, respectively, and contain six, seven, or eight D-glucose units. The industry currently offers hundreds of semi-synthetic derivatives of native CDs, expanding the molecules' potential uses. CD complexation in a liquid state is frequently characterized using phase-solubility investigations. This approach offers helpful information regarding stoichiometry and complicated stability. The small rim of the CD molecule contains hydrophilic primary hydroxyl groups, whereas the wider rim contains secondary hydroxyl groups. The octanol/water partition coefficient, or LogPo/w, of CDs has a large negative logarithmic value due to their hydrophilic outer surface and abundance of hydrogen bond producers and acceptors. Despite being stable in alkaline environments, CDs are vulnerable to acid hydrolysis in low pH aqueous solutions, which causes ring opening and the formation of different linear oligosaccharides and glucose units. At pH 12, the hydroxyl groups on the rim begin to deprotonate. Based on the assessment method and the location of the hydroxyl groups, the pKa values of the natural CDs are reported to vary between 12.1 and 13.5.

Aside from the size of their core chamber, the three natural CDs differ mostly in how soluble they are in water. Despite being the least soluble, βCD has the best cavity size for complex formation with a wide range of medications. The CD molecule's molecular stiffness and the impact of intermolecular hydrogen bonding in the crystal state can be utilized to explain the poor solubility.

In particular, the creation of hydrogen bonds between nearby C2-OH and C3-OH in the βCD molecule results in the so-called complete secondary belt, which makes the βCD molecule less flexible and less able to create intermolecular hydrogen bonds with nearby water molecules. Molecular dynamics simulations show that the βCD molecule is surrounded by a high water density and a strong ordering of water molecules. In contrast, γCD has a non-coplanar structure while αCD has an incomplete hydrogen bond belt. Thus, both αCD and γCD have a higher solubility in water. To increase the native CDs' solubilizing potential, particularly their complexation capacity, CD derivatives have been developed by reacting the molecule's main and/or secondary OH groups with

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a variety of substituents. However, arbitrarily methylated and hydroxypropylated CDs, as well as sulfobutylether CDs, are manufactured on an industrial scale and are commonly present in medicinal goods. As a result, they may become more than 100 times more soluble in water.

Because of the electrostatic repulsion that these anionic chains produce, the hydrophobic core cavity is extended, increasing its solubilizing potential. The degrees of substitution DS has a major impact on the complex-forming ability and physicochemical properties of CDs. CD derivatives have cavity diameters that are comparable to those of their parent CDs. However, it has been observed that the substituent's location affects the cavity volume. It has been noted that replacing OH groups at the O-6 location lowers the water density inside the CD cavity, while hydroxypropylation of OH groups at the O-2 site produces a more dispersed form. Unlike original CDs, which have relatively little surface activity, some CD variants behave in this way. It has been demonstrated that methylated and hydroxyalkylated CD molecules reduce the surface tension of water. Surface activity is not significantly impacted by derivatives having polar ionic groups, such as carboxylate and sulfobutyl groups.

CDs have the ability to both help and hinder drugs from passing through biological membranes. The bulk of drug molecules are transported across biological membranes via passive diffusion, despite active drug transport. Generally, the gradient of chemical potential, a continuous function across interfaces, rather than the concentration gradient, drives passive diffusion across an aqueous environment (such as mucus) into and through membranes (such as mucosa). In a similar manner, the chemical potential controls how drug molecules enter the outermost membrane layer and dissociate from the membrane's outside. The greatest quantity of drug penetration occurs when the drug is saturated on the outside of the aqueous membrane. However, the concentration of dissolved medication at the membrane's exterior also affects how much drug flows through it[7].

IV. INCLUSION COMPLEXES OF CYCLODEXTRINS WITH ANTICANCER DRUGS – STABILITY

Camptothecin is an anticancer topoisomerase inhibitor that is both lipophilic and chemically unstable due to its lactone ring, which is readily hydrolyzed at physiological pH. This made it an especially difficult case. The stability of camptothecin within cyclodextrin cavities leads to a significant increase in anticancer activity in several tumor cell lines. An alternative is to formulate the active ingredient as nanocapsules with chemically modified cyclodextrins (heptakis(6-O-hexanoyl)cyclomaltoheptose) and coat them with a cationic polymer based on chitosan, which has been shown to improve camptothecin's stability and effectiveness in vitro. Inclusion complexes can be formed in aqueous solutions by the entry of small lipophilic molecules and the lipophilic moieties of larger ones into the lipophilic environment produced by the CD cavity. Complex formation is governed by relatively weak non-covalent interactions, such as hydrogen bonds, van der Waals forces, and hydrophobic contacts; no covalent bonds are formed or broken during the inclusion process. In diluted aqueous solutions, one drug (D) molecule most often forms a compound with one CD molecule. Next, we define the equilibrium constant (K1:1) as follows: It is stated that the stoichiometry is 1:1.

$$K1:1 = [D - CD] / [D \times CD]$$

where [D], [CD], and [D-CD] represent the concentrations of the free drug, free CD, and complex, respectively, in the solution. The physicochemical characteristics of pharmaceuticals, including their chemical stability, can be impacted by the formation of drug-CD complexes. When CDs are added to drug formulations, chemical stability is often increased, while stability may occasionally be lowered. In aqueous CD solutions, free drug molecules and drug molecules encased in CD complexes are in dynamic equilibrium. Drug-CD complexes are constantly forming and dissociating at rates that are quite near to the diffusion-controlled limits. If a 1:1 drug-CD complex forms and, by first-order kinetics, drug degradation takes place both in the complex and in the free form, the following kinetic paths exist:

$$kobs = (kf + kc \cdot K1:1 [CD] T) / (1 + K1:1 [CD] T)$$

Where K1:1 is the equilibrium constant for the complex formation (also called the stability constant), kf is the observed first-order rate constant for the degradation of the free drug (D), and kc is the recorded first-order rate constant for the drug degradation within the complex (D-CD). The weighted average of kf and kc is the observed first-order rate constant (kobs) for drug degradation in the aqueous complexation medium. Assuming

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that the total CD concentration is significantly higher than the total drug concentration (i.e., [CD]T > [D]T and [CD] [CD]T), [CD]T represents the total concentration of dissolved CD in the aqueous complexation medium. The value of kf is present in the complexation medium when CD is not present. In the absence of CD, the complexation medium contains the value of kf. K1:1 and kc are then obtained by non-linearly fitting the results of calculating kobs at fixed drug concentrations but variable CD concentrations. As an alternative, linear fitting techniques like the Lineweaver-Burk plot can be used to determine K1:1 and kc.

$$(1 / kf – kobs) = [1 / K1:1 (kf – kc)]. [1/ (CD)T] + [1 / (kf – kc)]$$

Plotting (kf-kobs) -1 versus ([CD])-1 yields a straight line, from which one can determine K1:1 from the slope and kc from the intercept. Numerous investigations have examined the effect of CDs on drug stability. In most situations, where kc is less than kf, CD complexation stabilizes the drug and prolongs the medicinal product's shelf life. However, in other cases, CD complexation accelerates drug degradation when kc is greater than kf. The intriguing natural macrocyclic oligosaccharides known as cyclodextrins (or CDs) have a characteristic basket form and are made up of 6–8 D-glucopyranose units that are intricately linked with α-1,4-glucosidic bonds. These amazing compounds have many fascinating properties and are biochemical wonders that result from enzymatic conversion during starch degradation. With a hydrophilic shell surrounding a hydrophobic core, CDs have a special set of characteristics that make them incredibly adaptable. They are the best option in a variety of chemical domains due to their solubility, capacity to form inclusion complexes (ICs), non-toxicity, affordability, renewable supply, and abundance of hydroxyl groups. Notably, complexation can occur without the use of covalent connections thanks to their remarkable ability to accommodate a variety of guest molecules inside their hydrophobic recesses. These cavities' varied sizes play a crucial part in controlling the growth and stability of ICs, highlighting the almost limitless potential of CDs in a variety of applications. After 30 days in the sun, the curcumin-β-cyclodextrin inclusion complex can withstand 2 hours of isothermal heating at 100–150°C and is 18% more stable than the pure active metabolite. Additionally, it demonstrated good chemical and physical stability at three distinct temperatures (−15°C, 4°C, and 25°C) of about 99%.

V. CONCLUSION

The toroidal structure, which is made up of glucose units connected by α-1,4-glycosidic linkages, is what distinguishes cyclodextrins. CDs are highly versatile in a variety of medical applications due to their distinct toroidal form and dual nature, which consists of a hydrophilic exterior and a hydrophobic inside. Stabilizing, encouraging controlled release, improving drug absorption, solubilizing, and successfully masking disagreeable tastes and smells are just a few of its many uses. To take advantage of these inherent benefits, CDs have been included in a number of nanoscale drug delivery devices. By utilizing the exceptional qualities of CDs, the resulting nanomaterials demonstrate biocompatibility and versatility, participate in supramolecular complexation for engineered nanomaterials, increase bioavailability for improved therapeutic efficacy, stabilize labile drugs, solubilize hydrophobic drugs for significant drug loading, and more.

Conflict of Interest:
We state that we have no conflicts of interest. We alone are responsible for the content and writing of this article.

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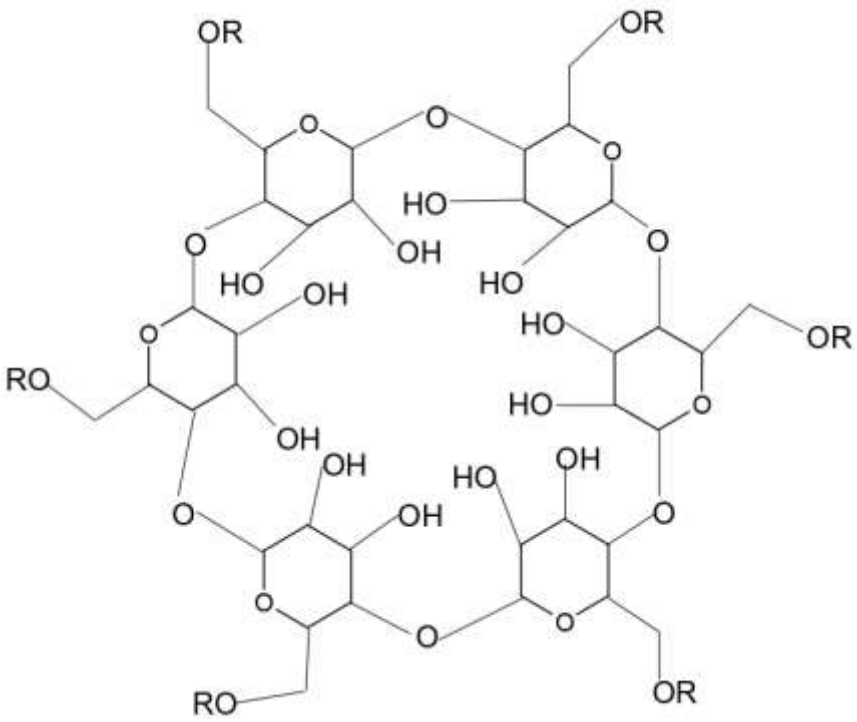

Fig 1: Alpa Cyclodextrin

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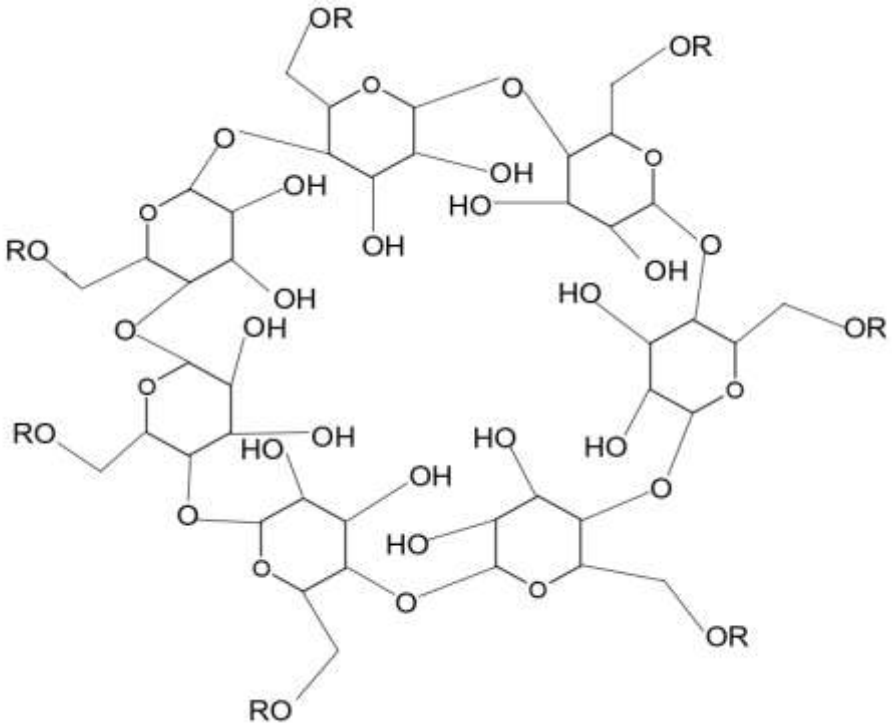

Fig 2: Beta Cyclodextrin

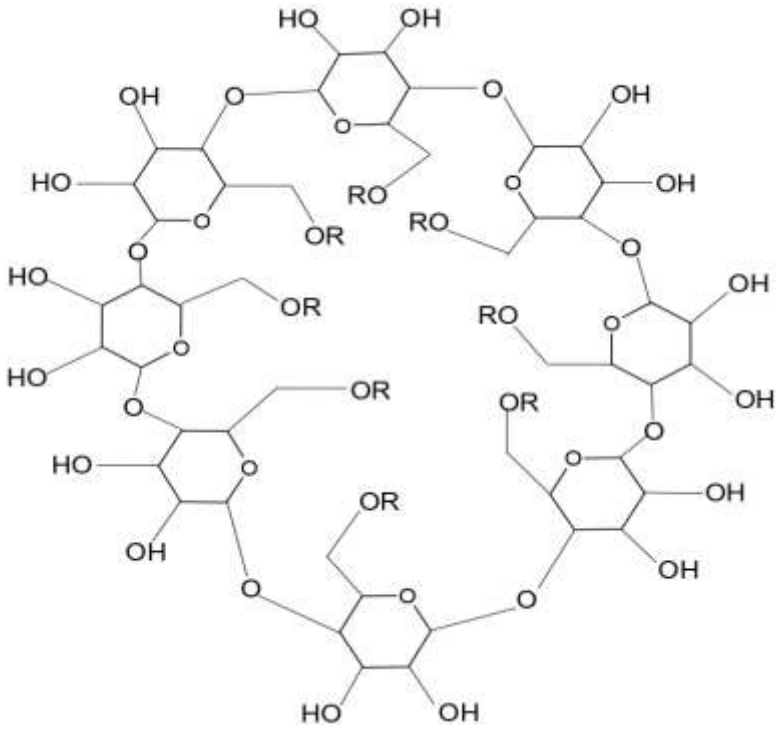

Fig 3: Gamma Cyclodextrin

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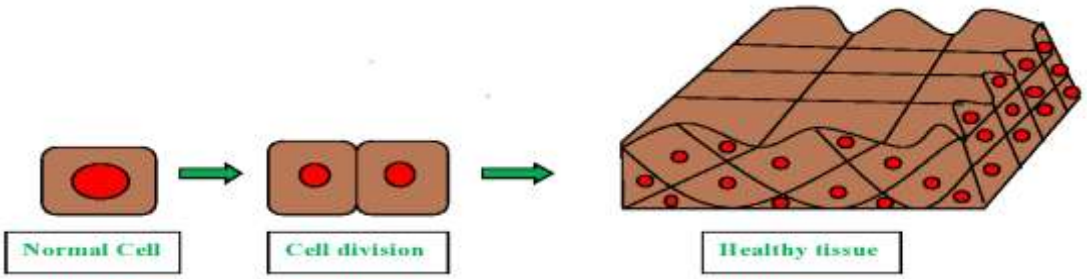

Fig 4: Normal Cell Development

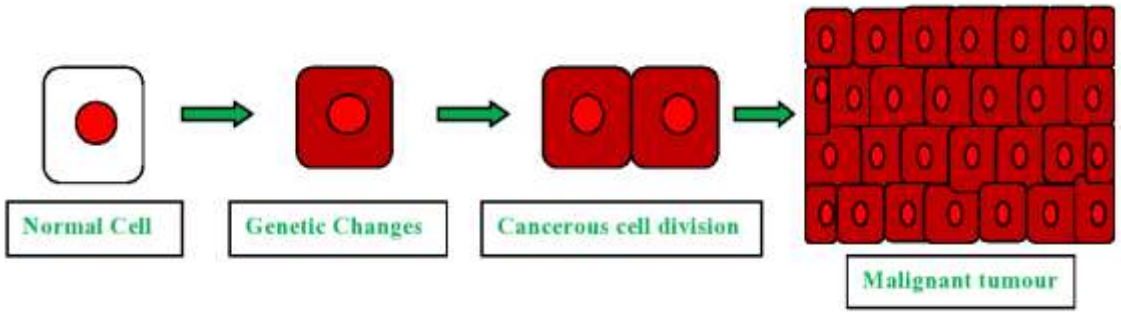

Fig 5: Abnormal Cell Growth

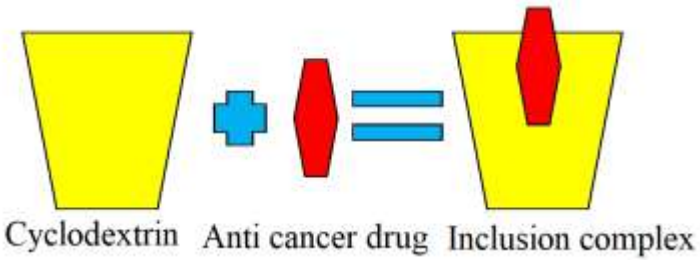

Fig. 6: Inclusion complex formation of Cyclodextrin and Anticancer drug