Lec 8 5th stage

Organic Pharmaceutical Chemistry IV

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Targeting of polymeric drugs

Drug targeting is the ability of the drug to accumulate in the target organ or tissue selectively and quantitatively, independent of the site and methods of its administration. Drug targeting is important to resolve the problem associated with systemic drug administration.

The main problems associated with systemic drug administration are:

1. Distribution of pharmaceuticals throughout the body.
2. The lack of drug specific affinity toward a pathological site.
3. The necessity of a large total dose of a drug.
4. Non-specific toxicity and other adverse side-effects.

Advantages of drug targeting are:-

1. Drug administration protocols may be simplified.
2. Drug quantity may be greatly reduced as well as the cost of therapy.
3. Drug concentration in the required sites can be sharply increased without negative effects on non-target compartments.

The targeted drug acts like a **'magic bullet'** selectively killing the villain and sparing the innocent. The targeting of a drug delivery system is especially important for cancer chemotherapy, mainly because of the high toxicity of anticancer drugs currently being used.

Two approaches are generally used to target polymeric anticancer drugs to the tumor or cancer cells:

1. Passive tumor targeting
2. Active tumor targeting

Passive tumor targeting

Passive targeting approaches include:

(a) The enhanced permeability and retention (EPR) effect

(b) The use of special conditions in tumor or tumor-bearing organ

(c) Topical delivery directly to the tumor.

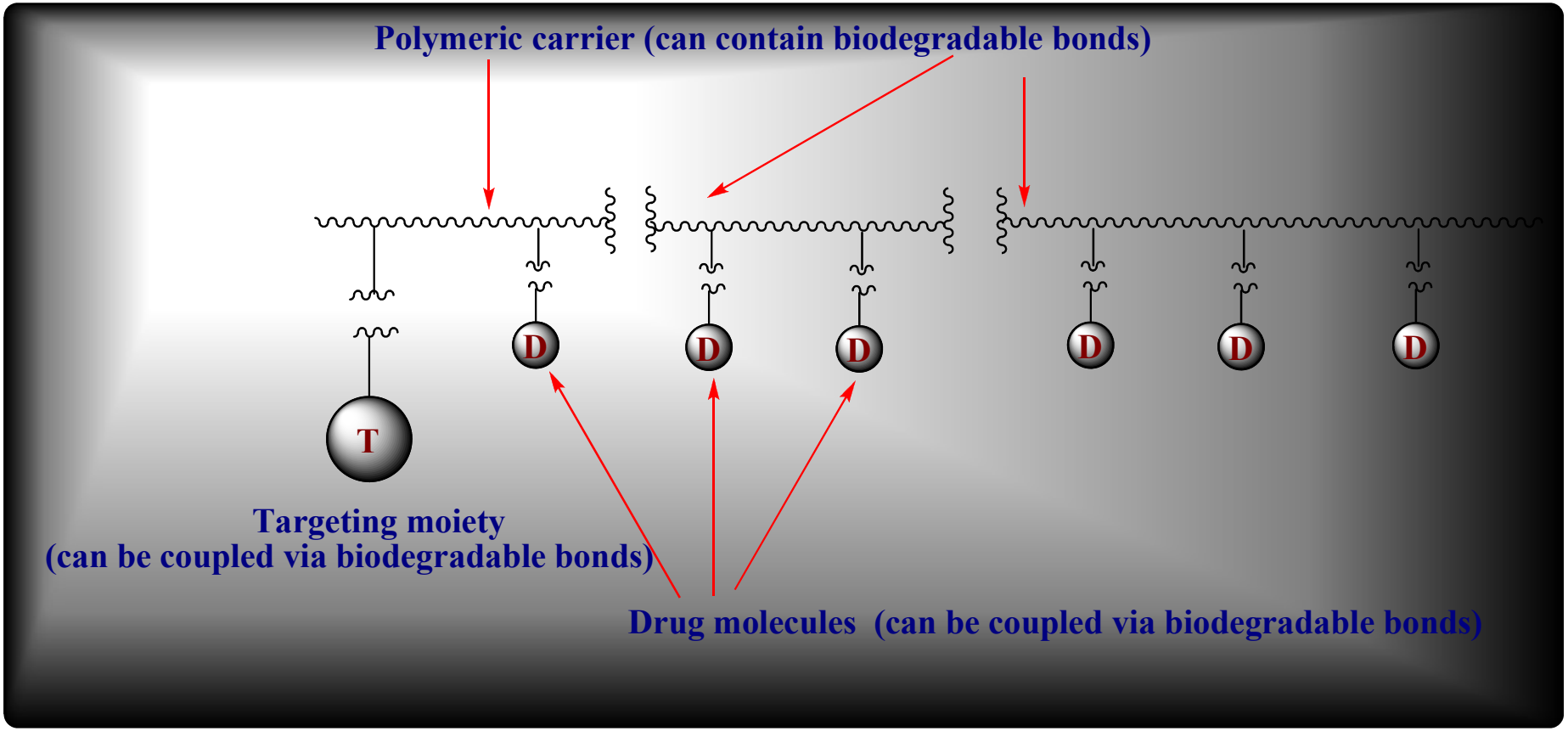
Many solid tumors display unique pathophysiology features including;-

1. High permeable vascular.

2- Impaired lymphatic drainage, that are absent in normal tissues. High molecular weight polymer–drug conjugates extravasate into the tumor tissues but not the normal tissues with less permeable vessels. Once inside the tumor tissues, the polymer–drug conjugates do not readily return to the general circulation because of the poor lymphatic's drainage.

Active targeting

Active targeting employs specific modification of a drug/drug-carrier nanosystems with “active” agents having selective affinity for recognizing and interacting with a specific cell, tissue or organ in the body.



The active targeting includes a coordinated behavior of three components:

1-Pharmaceutical carrier:-Carrier can be loaded with multiple active moieties and then conjugated additionally with the targeting unit.

a. Polymers
b. Microcapsules
c. microparticles
d. Cells
e. Lipoproteins
f. liposomes
g. micelles

2-Drug (which provide a therapeutic action in this target)

3-Targeting moiety (ligand): Which recognizes and binds the target.

The active targeting approach is based on the interactions between a ligand and target. In most cases, a targeting moiety in a polymeric drug delivery system is focused on the :-

1. specific receptor .
2. Antigen overexpressed in the plasma membrane.
3. Intracellular membrane of the targeted cells.

1. Targets

(a) Receptors: The presence of receptors on cell membranes potentiates active targeting by not only allowing specific interaction of drug carrier system with cells but also facilitating its uptake via receptor mediated endocytosis.

1. Folic Acid Receptor

Folic acid - a vitamin essential for de novo nucleotide synthesis is taken up by cells via cell membrane folate receptor. Folate receptor is a potential molecule target for tumor selective drug delivery .since the folate receptors is found in only a limited range of normal tissues but commonly over expressed by malignant cells.

1. LDL Receptors

Low density lipoprotein (LDL) receptors are a family of nine endocytic receptors that transport cholesterol rich lipoproteins (LDL) into cells via receptor mediated endocytosis. Many drugs and some lipid-based systems such as liposomes and cholesterol rich emulsions have been proposed to interact with these receptors.

3- Peptide Receptors

A large number of peptide receptors are expressed in large quantities in certain tumor cells. Peptides/peptide analogs can be conjugated to a drug carrier system to allow tumor specific targeting of cytotoxic agents, following interaction with peptide receptors.

Receptors for peptides such as:-

1. somatostatin analogs
2. vasoactive intestinal peptide
3. gastrin related peptides,
4. cholecystokinin,
5. leutanising hormone releasing hormone have been localized on tumor cells.

b. Lipid Components of Cell Membranes

Lipid components of cellular membranes are emerging as novel targets for antineoplastic drugs. Interaction of synthetic phospholipid analogs with cellular membranes changes the lipid composition, membrane permeability and fluidity, thereby influencing signal transduction mechanisms and inducing apoptotic cell death.

There is two such phospholipid analogs can selectively kill malignant cells and thus offer promising approaches in cancer chemotherapy.

- Edelfosine
-Miltefosine

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b. Surface Antigens/Proteins

Expression of different proteins on the surface of cells constitutes the biochemical writing on the cells, which can be deciphered using monoclonal antibodies against these proteins.

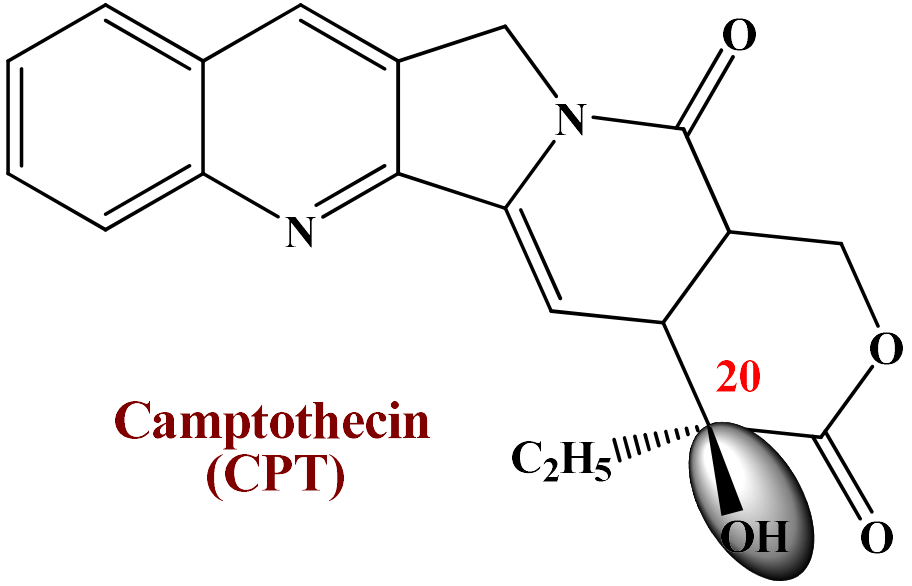
Targeting Ligands

Active targeting of drugs can be realized by the use of active agents or ligands which interact with the specific targets/receptors identified on particular cell types. Targeting ligands include:-

1. **folic acid**
2. **peptides**
3. **Antibodies:-** Antibodies are used as targeting moieties, against specific antigens/proteins expressed on the surface of cells.

Examples of targeting polymeric drugs

Two approach was demonstrated using the drug, **camptothecin (CPT)**, and two different targeting agents—**leutanising hormone-releasing hormone (LHRH) and BCL2 homology 3 (BH3) peptide.** **LHRH peptide** was targeted to extra-cellular LHRH receptors over expressed in several cancer cells in order to: increase the cancer specificity of the drug, reduce adverse drug side effects, and enhance drug uptake by cancer cells. **BH3 peptide** was targeted to intracellular controlling mechanisms of apoptosis used to suppress the cellular anti-apoptotic defense to enhance drug anticancer activity.



Camptothecin (CPT)

conjugate site in CPT- hydroxyl at C_{20}

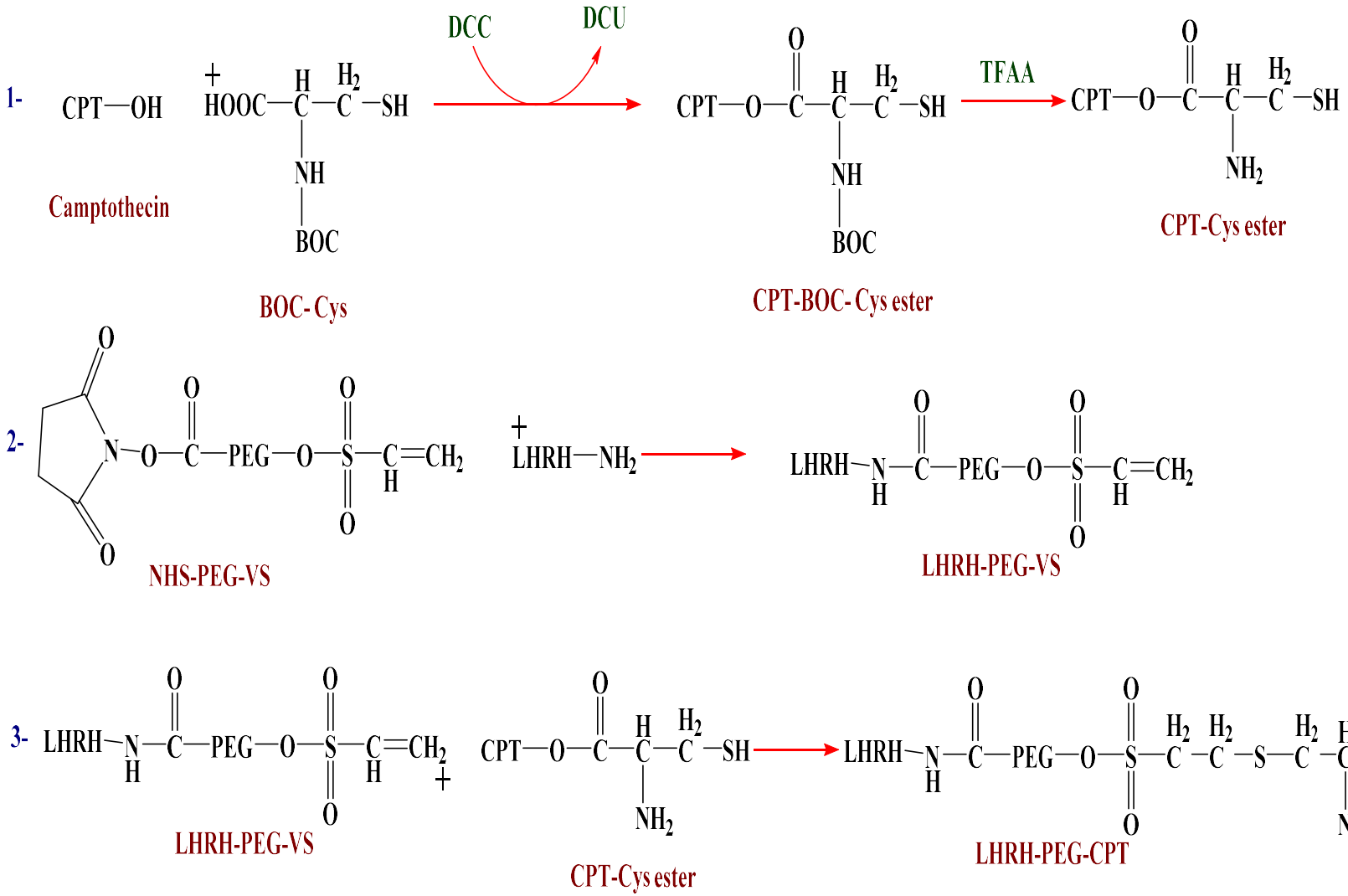
Preparation of LHRH-PEG-CPT

CPT was first coupled to an amino acid via a biodegradable ester bond • to the hydroxyl group at position 20, using Boc-Cys amino acid. Dicyclocarbodiimide, was used as a coupling agent and protecting groups were removed using trifluoroacetic acid.

In tumor tissue, spacers are necessary to be incorporated between the drug and its carrier in order to enable the release drug from that carrier either in slightly acidic extracellular fluids or, after endocytosis, in endosomes or lysosomes of cancer cells.

1-The LHRH analog- (Gln-His-Trp-Ser-Tyr-**DLys-**Leu-Arg-Pro-NH-Et), which had a reactive amino group only on the side chain of the lysine at position 6, was first reacted with one equivalent of NHS–PEG–VS in DMF.

2- CPT-Cys was then added to obtain the thioether bond formation between the VS group and the thiol group.


1-
CPT—OH
Camptothecin
HOOC—C(H)(NH—BOC)—C(H)(H)—SH
BOC- Cys
DCC
DCU
CPT—O—C(=O)—C(H)(NH—BOC)—C(H)(H)—SH
CPT-BOC- Cys ester
TFAA
CPT—O—C(=O)—C(H)(NH2)—C(H)(H)—SH
CPT-Cys ester
2-
NHS-PEG-VS
LHRH—NH2
LHRH—NH—C(=O)—PEG—O—S(=O)—C(H)=CH2
LHRH-PEG-VS
3-
LHRH-PEG-VS
CPT-Cys ester
LHRH—NH—C(=O)—PEG—O—S(=O)—C(H)(H)—C(H)(H)—S—C(H)(NH2)—C(=O)—O—CPT
LHRH-PEG-CPT

LHRH–PEG–CPT conjugate is an example of such targeted anticancer drug delivery system . In this system, LHRH peptide is used as a targeting moiety to the corresponding receptors overexpressed in several cancer cells, PEG polymer—as a carrier and CPT—as an anticancer drug. The use of a targeting moiety not only provides targeting of the whole system to the targeted cells limiting adverse side effects, but also facilitates cellular uptake of the whole conjugate by receptor-mediated endocytosis.

The interaction of such molecules with their receptor initiates receptor- mediated endocytosis; an active process that requires a significantly lower gradient of internalized substance across the plasma membrane when compared with simple endocytosis.

By conjugating the drug delivery system with molecules that are recognized by extracellular plasma membrane receptors, it is possible to enhance the influx of whole conjugate by receptor-mediated endocytosis.

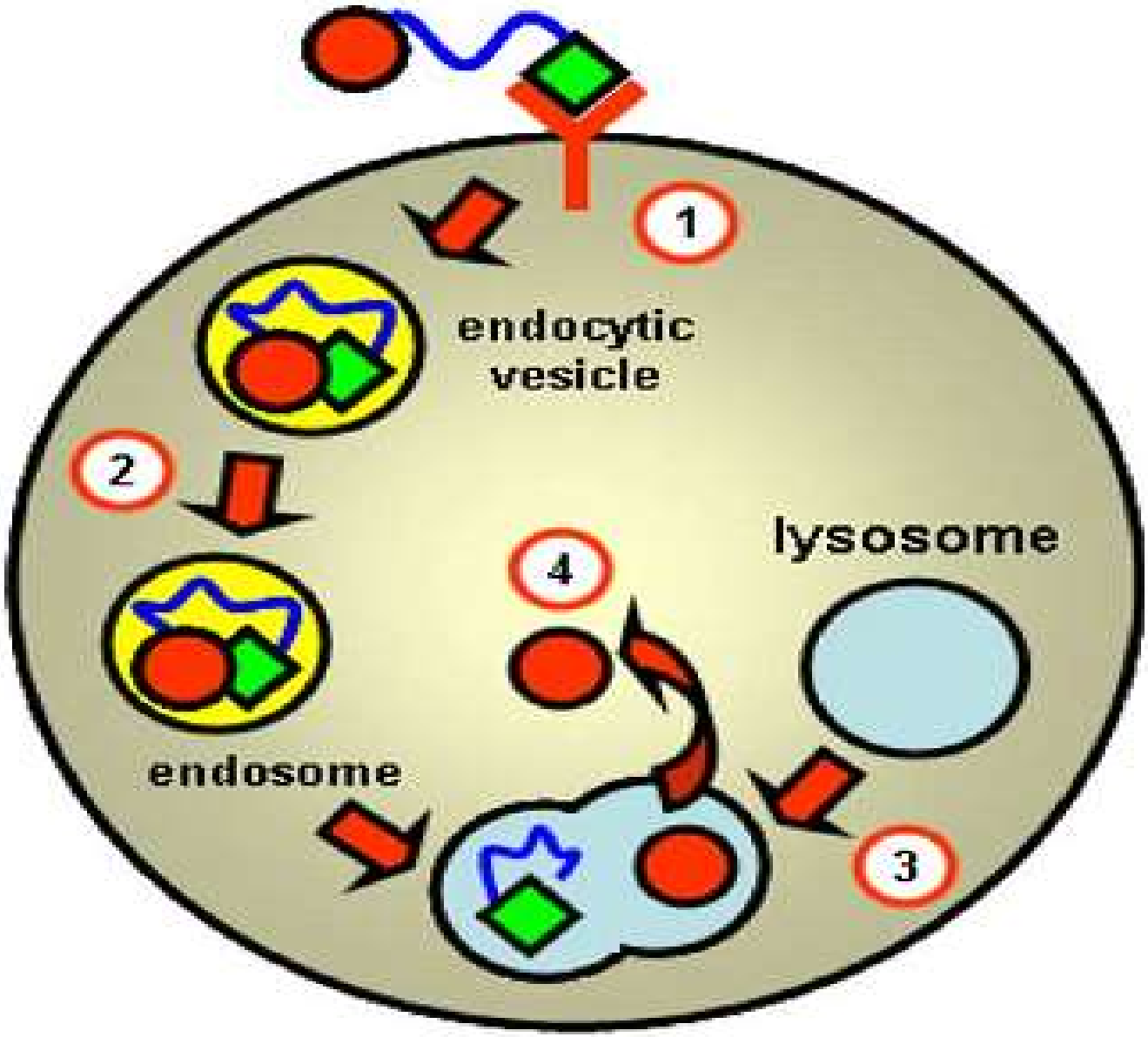
This process can be divided into several distinct steps as schematically presented in following fig.

1. **Interaction of a targeted carrier with a corresponding receptor leads to the engulfing of the plasma membrane inside the cells and the formation of a coated pit.**

1. **The pit then pinches of from the plasma membrane and forms an endocytic vesicle and endosomes-membrane-limited transport vesicles with a polymeric delivery system inside.**

1. **Transport inside the membrane-coated endosome prevents drugs from degradation by cellular detoxification enzymes and therefore preserves its activity.**

1. **Endosomes move deep inside the cell and fuse with lysosomes forming secondary lysosomes. If the bond between the targeting moiety (or targeted carrier) or spacer is designed in such a way that lysosomal enzymes are capable of breaking it, the drug is released from the drug delivery complex and might exit a lysosome by diffusion.**


1
endocytic
vesicle
2
endosome
4
lysosome
3