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RESEALED ERYTHROCYTES: A NOVEL AND PROMISING DRUG CARRIER

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ABSTRACT: Targeted drug delivery, known as smart drug delivery focuses on targeting the medicaments by increasing the residence time and the concentration of drug at the target site of the body (organs, cells, tissues) thus improving the efficacy of treatment and reducing the side effects. Various carriers that can be used in this type of delivery are liposomes, nanoshells, erythroosomes and resealed erythrocytes. In this Innovation era, resealed erythrocytes have become the choice of drug delivery system because of its excellent biocompatibility, biodegradability and ability to entrap several molecules. The promising aspect of resealed erythrocytes makes them useful as a drug carrier. They have reduced toxicity, improved pharmacokinetic properties that help in transport of active ingredient to the targeted site. This property makes them superior as compared to the conventional drug delivery system. The method of isolation involves collection of sample from the interest, then separating the plasma and finally resealing it. Erythrocytes are prepared by using methods like hypotonic dilution, hypotonic dialysis, pre-swelling, osmotic lysis, endocytosis and chemical penetration. The tremendous potential to achieve site specific drug delivery makes them as first choice of drugs in areas like enzyme therapy, cancer, hepatic tumours and antiviral. The present article includes methods, applications, evaluation, future aspects of resealed erythrocytes and highlights its applications with particular stress in areas of cancer, hepatic tumours and enzyme therapy.

INTRODUCTION: The drug delivery is a method in which the pharmaceutical ingredient is transported to the targeted site without loss of the chemical entity. Targeted drug delivery, sometimes called smart drug delivery, is a method of delivering drug to the patient in a manner that increases the concentration of drug in targeted parts of the body. Targeted drug delivery system is based on a method which delivers a certain amount of a therapeutic agent for a prolonged period of time to a targeted area within the body¹.

It helps in minimizing the side effects and results in improved efficacy and therapeutics thus eventually maintains a safe concentration of drug in the plasma. The very slow progress in the treatment of severe diseases has led to the alternate of a multidisciplinary approach to the targeted delivery and release of drugs, using nanotechnology, carriers, microspheres, liposomes, resealed erythrocytes etc. On the basis of types of targets they are classified as:

Active Targeting: Specific ligand receptor interaction occurs for intracellular localization after blood circulation. Example of active targeting is use of monoclonal antibody the treatment of cancer.

Passive Targeting: Accumulation of drug or drug carrier system in specific area of the body *e.g.*

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Include targeting of anti-malarial drugs for treatment of leishmaniasis, brucellosis and candidiasis.

Dual Targeting: Here the drug molecule has its own therapeutic efficacy thus leading to synergistic effects. *e.g.* antiviral drugs.

The Approaches in Active Targeting are: ^{1, 2}

First Order Targeting: refers to distribution of the drug carrier systems to the capillary bed at a predetermined target site, organ or tissue *e.g.* compartmental targeting in lymphatics, peritoneal cavity, plural cavity, cerebral ventricles and eyes, joints.

Second Order Targeting: refers delivery of drug to specific types of cells such as tumour cells and not to the normal cells *e.g.* selective drug delivery to kupffer cells in the liver.

Third Order Targeting: refers to drug delivery specifically to the intracellular site of targeted cells *e.g.* receptor based ligand mediated entry of a drug complex into a cell by endocytosis. Need of targeted drug delivery system is explained in **Fig. 1**.

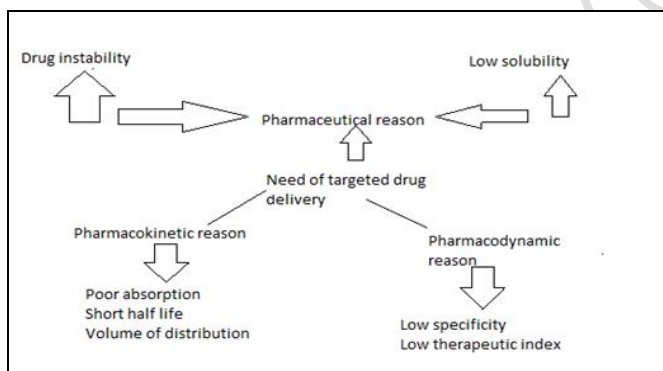


FIG. 1: REQUIREMENT FOR TARGETED DRUG DELIVERY SYSTEM

Ideal Characteristics of Targeted Drug Delivery System:

- Targeted drug delivery system should be biochemically inert (non-toxic), non-immunogenic.
- It must be physically and chemically stable *in vivo* and *in-vitro* conditions.
- It must restrict the drug distribution to the targeted site only without affecting normal cells.

- It must have a predictable and controlled drug release.
- There should be minimal drug leak from transit
- Carrier used should be biodegradable or readily eliminated from the body without any problem and no carrier should induce modulation of diseased state.

Components of Targeted Drug Delivery:

Target: It means specific organ or a cell or group of cells, which are treated in chronic or acute condition.

Carrier or Marker: Carriers are one of the special molecules essentially required for effective transportation of drug to the selected sites. They are engineered vectors, which retain drug inside or onto them *via* encapsulation or *via* spacer moiety.

Carriers of Targeted Drug Delivery System:

Liposomes: A liposome is spherical vesicle containing at least one lipid layer and composed of phospholipids in which the drug is entrapped. A liposome has an aqueous solution core surrounded by a hydrophobic membrane, in the form of a lipid bilayer and the hydrophilic solutes dissolve in the core cannot readily pass through the bilayer. The composition of liposomes consists of phosphatidylcholine, phosphatidyl-ethanolamine surrounded by a lipid layer. The mechanism by which liposome elicits its therapeutic action is by fusing the lipid bilayer with that of cell membrane thus leading to ejection of liposomes on to the targeted site. **Fig. 2** represents the structure and the composition of liposomes ².

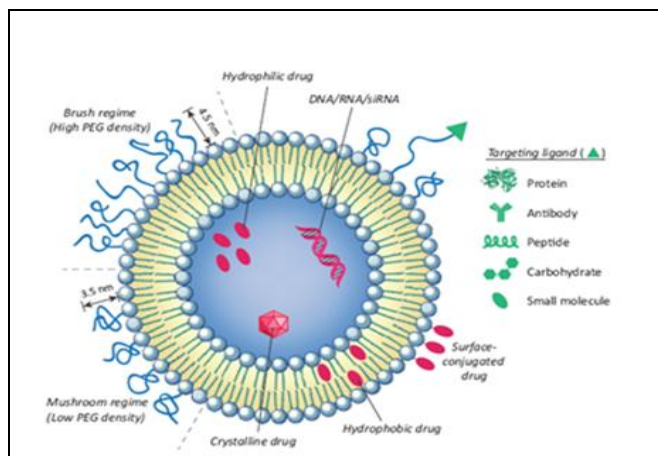


FIG. 2: SCHEMATIC REPRESENTATION OF LIPOSOMES

Some of the commercially available liposomes are enlisted in the table as follows

TABLE 1: COMMERCIALY AVAILABLE LIPOSOMES ²

Name	Trade Name	Company	Indications
Liposomal amphotericin B	Abelcet	Enzon	Fungal infection
Liposomal danorubicin	DaunoXome	Gilead sciences	HIV related Kaposi sarcoma
Liposomal morphine	DepoDur	Endo	Postsurgical analgesia
Liposomal doxorubicin	Myocet	Zeneus	Metastatic breast cancer

Microspheres: Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). They are also called as micro particles. Usually they are free flowing powders consisting of proteins and synthetic polymers. Mainly the composition of microspheres includes polystyrene or polyethylene and silica as a polymer. Polystyrene microspheres have their application in the field of biomedical as they are capable of immune precipitation and cell sorting. The mechanism by which they act is absorption of protein onto their surface. Polyethylene microspheres usually are used as temporary filler; due to their lower melting point they create porous structures in ceramics and other materials. The polyethylene microspheres find their application in electronic paper and digital display. The ceramic microspheres are also an emerging type which finds their application in grinding media. **Fig. 3** represents the structure of microspheres ³.

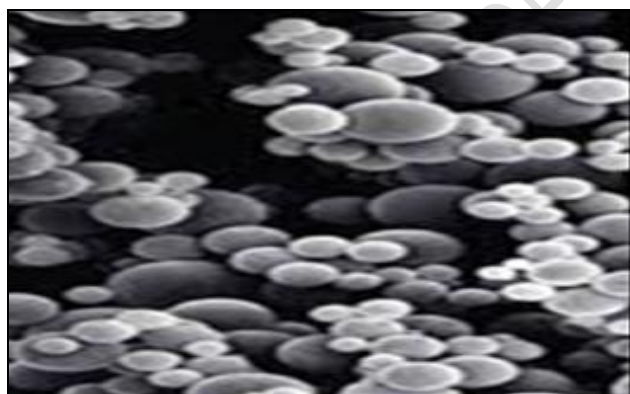
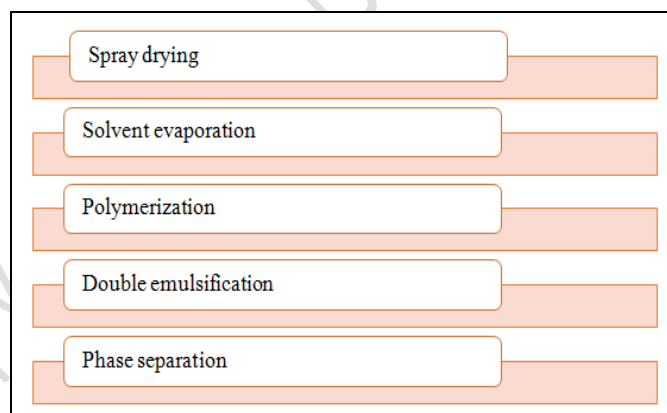


FIG. 3: SCHEMATIC REPRESENTATION OF MICROSPHERES

Nanotubes: Nanotubes are the one which have unique chemical, size, optical, electrical and structural properties which make them a choice and alternative for drug delivery systems. They also serve as an important platform for treatment of various diseases. Due to their nanoscale dimensions and electron transport in carbon, nanotubes will only propagate along the axis of the tube and elicit the quantum effect. Mostly carbon nano tubes are

used in treatment of cancer, ulcers, etc. Nano shells also have an application in field of targeted drug delivery which are composed of dielectric core usually silica and they have ability to absorb UV and infrared light ⁴.

The methods incorporated to prepare microspheres are as follows:



Resealed Erythrocytes: The substances that are used to transport a drug to the target site are called as drug carriers. Mainly they aim to decrease the toxicity and prolong *in vivo* action with improved pharmacokinetic properties. The cellular carriers are identified to have great potential and merits in various modules of drug delivery system. One of the most widely used carriers is erythrocytes which are non-immunogenic, non-pathogenic whose circulation can be controlled with time.

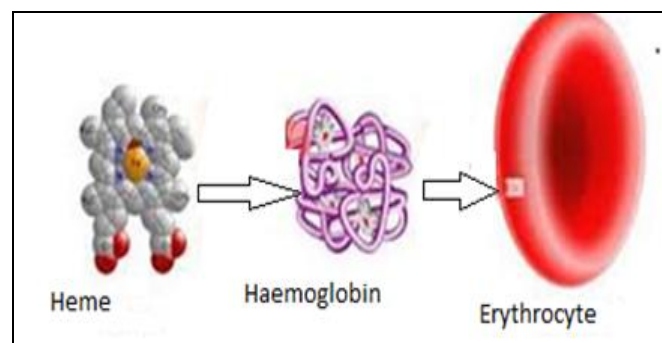


FIG. 4: SCHEMATIC REPRESENTATION OF RESEALED ERYTHROCYTES

Red blood cells also called as erythrocytes are responsible for delivering oxygen to the body *via* circulatory system to provide higher therapeutic benefits. Resealed erythrocytes are defined as entrapping the drug loaded carrier by simply collecting the blood from organism following separation of plasma and then eventually resealing the resultant cellular carrier^{1, 5, 6}.

Advantages:

- Biocompatible and no possibility of triggered immune response.
- Easily biodegradable with lowest toxicity.
- Drug loading is usually higher and is inert in nature.
- Entrapment of variety of chemicals is possible within the molecule which provides targeted drug delivery system.
- Relatively easy to maintain plasma concentration with decrease in fluctuation in concentration.
- Prolonged activity of drug with greater time of residence in body.
- Targeting to the organ of the RES.
- Entrapment of drug can be possible without chemical modification of the substance to be entrapped.
- Relatively inert intracellular environment can be encapsulated in a small volume of cells.
- They enable incorporation of protein and nucleic acid in eukaryotic cells by cell infusion with RBC.

Disadvantages:

- Limited potential as carrier to non-phagocyte target tissue.
- Possibility of clumping of cells and dose dumping problem may arise.
- Relatively costly.

Properties of Resealed Erythrocytes as Drug Carriers:⁷

- The drug should be released at targeted site in a controlled manner.
- It should have appropriate size and shape and should permit the passage of drug through capillaries.
- Minimum leakage of drug should take place.

- It should be biocompatible and should have minimum toxic effect.
- It should possess the ability to carry a broad spectrum of drug and must also possess specific physicochemical properties by which desired target size could be recognized.
- The degradation product of the carriers system, after release of the drug at the selected site should be biocompatible.
- It should be physico-chemically compatible with drug.
- The carrier system should have an appreciable stability during storage and treatment there on

Need of Resealed Erythrocytes: Erythrocytes offer a better drug delivery system which is non-toxic, biocompatible and safe to use.

Anatomy, Composition and Physiology of Resealed Erythrocytes: RBCs are biconcave disc with a diameter of 7.8 μm and thickness near 2.2 μm . Mature RBCs have a simple structure and are elastic in nature their plasma membrane is strong and flexible so that they can squeeze through narrow capillaries without deformation. RBCs lack nucleus and other organelles and can neither reproduce nor carry on extensive metabolic activities. **Fig. 5** illustrates the shape and dimensions of RBC's⁶.

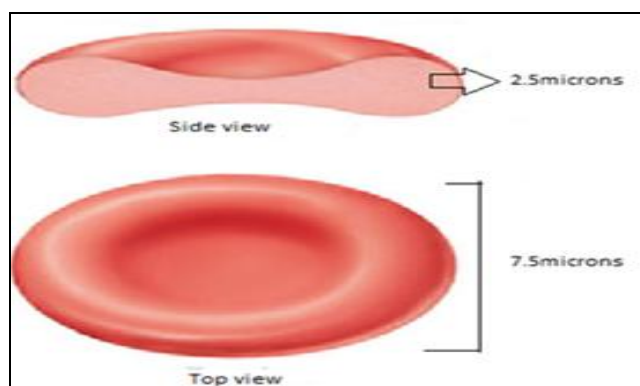


FIG. 5: SCHEMATIC REPRESENTATION OF RBC'S

RBCs are highly specialized for their oxygen transport function, because their mature RBCs have no nucleus, all their internal space is available for oxygen transport. The red blood cell membrane is associated with energy metabolism and maintains the permeability cell characteristics by various anions and cations. Each RBC contains about 280 million haemoglobin molecules which composed of protein called globin, containing four polypeptide

chains, a ring like non-protein pigment called a heme, bound to each of the four chains. The heme ring combines reversibly with oxygen molecule.

Composition of RBCs: RBCs include water (63%), lipids (0.5), glucose (0.8%), mineral (0.7%), non-haemoglobin protein (0.9%), meth haemoglobin (0.5%), and haemoglobin (33.67%)

Isolation of Erythrocytes:

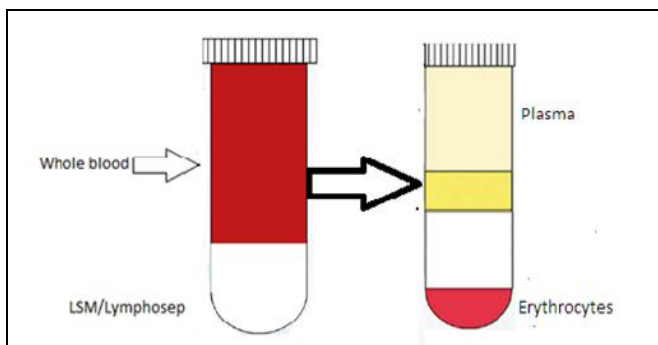
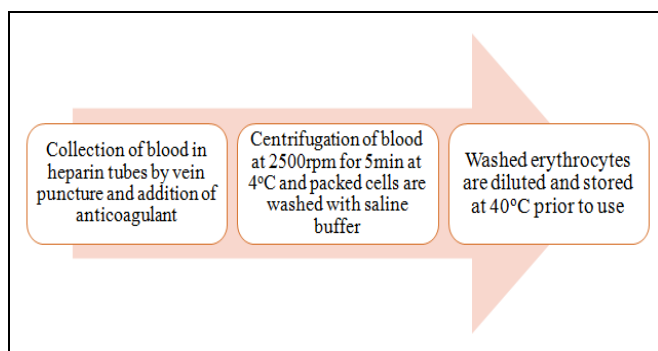


FIG. 6: SCHEMATIC REPRESENTATION OF ISOLATION OF ERYTHROCYTES

Methods of Drug Loading: ^{8,9}

Electroporation	Endocytosis
Methods of drug loading	
Osmotic based like hypotonic dilution, dialysis, osmotic lysis	Chemical perturbation

Hypo-osmosis Lysis Method: In this method the intracellular and extracellular solute of erythrocytes is exchanged by osmotic lysis and resealing takes place thus encapsulating the drug within the RBC's.

Hypotonic Dilution Method: 2-20 ml of aqueous solution of drug is diluted with a volume of packed erythrocytes and the tonicity is restored by adding

hypertonic buffer. The mixture is then centrifuged and supernatant is discarded, and the pellet is washed with isotonic solution. As shown in **Fig. 7**, the erythrocytes are first washed by saline solution and then combined with water to encapsulate the drug followed by centrifugation. A hypotonic solution is also added to restore the tonicity. This is one of the simplest and fastest method of drug encapsulation.

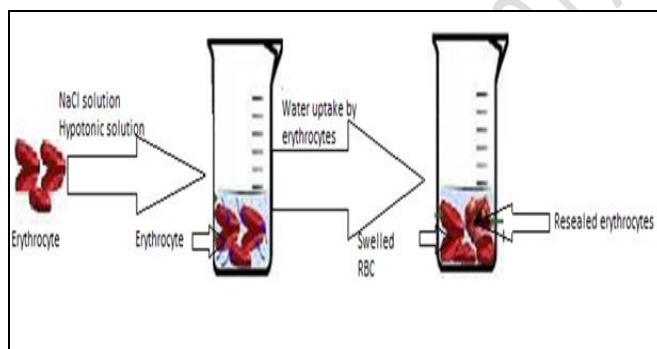


FIG. 7: SCHEMATIC REPRESENTATION OF HYPOTONIC DILUTION METHOD ⁸

Hypotonic Dialysis Method: In the process, an isotonic, buffered suspension of erythrocytes with haematocrit value of 70-80 is prepared and placed in a conventional dialysis tube. It is immersed in 10-20 volumes of a hypotonic buffer and the medium is agitated for 2 hours. The tonicity of the dialysis tube is restored by directly adding a certain amount of a hypertonic buffer to the surrounding medium. The drug to be loaded is added in the buffer and the process is continued until the drug dissolves. Drugs like gentamycin, furamycin, adiramycin, inositol enzymes have been incorporated by this method. **Fig. 8** represents the apparatus of the dialysis method.

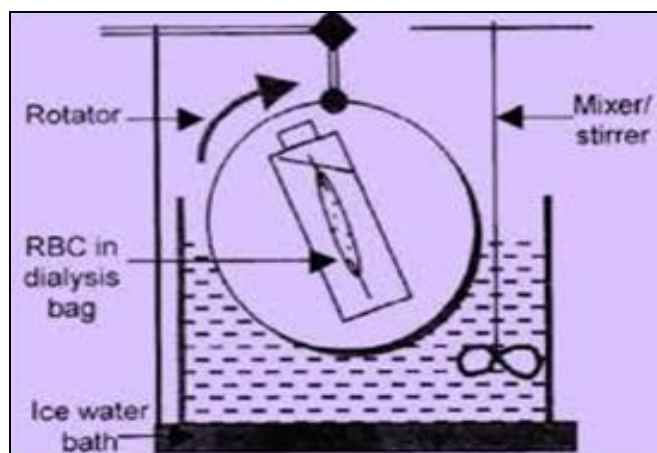


FIG. 8: SCHEMATIC REPRESENTATION OF HYPOTONIC DIALYSIS METHOD ⁸

Hypotonic Pre-swelling Method: This is method based on the principle of swelling the erythrocytes first without lysis by placing them in hypotonic solution. This method was developed by Rechsteiner in 1975. The swollen cells are allowed to recover by centrifugation at low speed. Relatively small volumes of aqueous drug solution are added at the point of lysis. This method is simpler and faster than other methods, causing minimum damage to cells. Due to gravitational force the supernatant layer is discarded and the detection point is considered when the boundary between the cell lines and supernatant disappears.

By adding a calculated amount of hypertonic buffer, the tonicity of a cell mixture is restored at the lyses point. To reseal the erythrocytes, the cell suspension is incubated at 37 °C. Such cells have a long circulation half-life comparable to that of normal cells. Drugs encapsulated in erythrocytes using this method include propranolol, levothyroxine, Metronidazole, Levothyroxine, Elaprnailat, and Isoniazid cortisol-21-phosphate, prednisolone-21-sodium, cyclophosphamide, α -1 antitrypsin, interferon alpha-2, insulin.

Isotonic Osmotic Lysis Method: This method, also known as the osmotic pulse method, involves isotonic hemolysis which is done by chemical or physical method. If erythrocytes are incubated in a solution with high membrane permeability, the solute will diffuse into the cells because of the concentration gradient. This process is followed by an influx of water to maintain osmotic equilibrium. Chemicals such as urea solution, polyethylene glycol, and ammonium chloride have been used for isotonic hemolysis. However, this method is not immune to changes in membrane structure composition. Hence a method was developed that involves suspending erythrocytes in an isotonic solution of dimethyl sulfoxide (DMSO). The suspension was diluted with an isotonic-buffered drug solution following separation of cells and resealing them at 37-42 °C.

Electro-Insertion or Electro Encapsulation Method: This method is also called as electroporation method is based that electrical shock brings about irreversible changes in an erythrocyte membrane. In this method erythrocyte membrane is open by a dielectric breakdown;

subsequently the pore of erythrocyte can be resealed by incubation at 37 °C in an isotonic medium. The various chemical encapsulated into the erythrocytes are primaquine, tetracaine and Vitamin A.

As shown in **Fig. 9**, the system consists of electrically charged chamber with two electrodes that one of which supplies isotonic solution to the jet capillary followed by resealing of erythrocytes. The RBC's are subjected to 2.2 KV current followed by addition of suspension. This loaded RBC's are then mixed with buffer and injected to the capillary. A capacitor is also attached externally to provide fixed voltage and control the rate of resealing and wave potential.

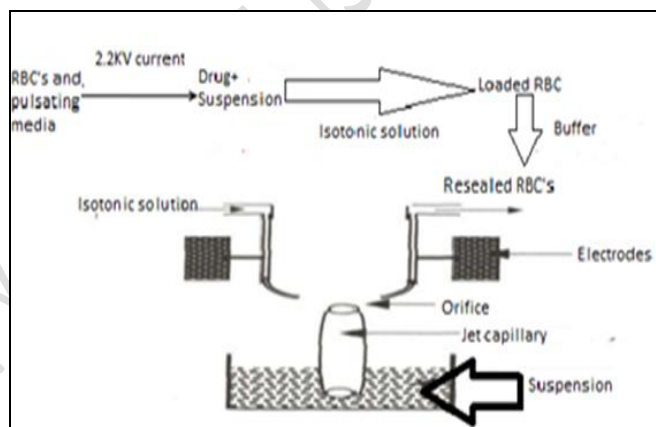


FIG. 9: SCHEMATIC REPRESENTATION OF ELECTRO INSERTION TECHNIQUE METHOD'

Use of Red Cell Loader: This method was developed to entrap non-diffusible drugs into the erythrocytes with the help of red cell loader. 50ml of blood sample containing active compounds is entrapped onto the erythrocytes within 2 hrs. The process is based on two sequential hypotonic dilutions of washed erythrocytes followed by concentration with a hem filter and an isotonic.

Lipid Fusion Method: The lipid vesicles containing a drug can be directly fused to human erythrocytes, which lead to an exchange with a lipid entrapped drug. This method is useful for entrapping inositol monophosphate to improve the oxygen carrying capacity of cells and entrapment efficiency of this method is very low (~1%). **Fig. 10** illustrates the process of lipid fusion where red blood cells are placed in hypotonic solution where in lysis takes place followed by drug entrapment followed by resealing.

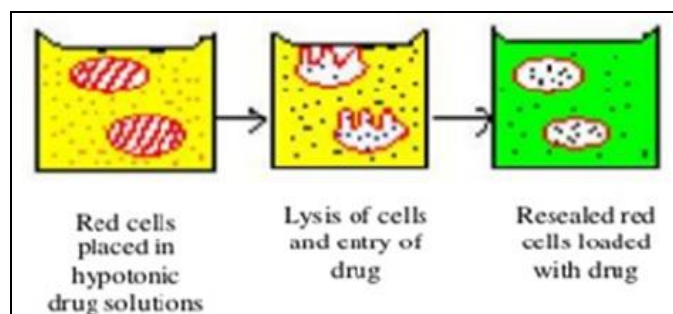


FIG. 10: SCHEMATIC REPRESENTATION OF LIPID FUSION TECHNIQUE METHOD¹⁰

Entrapment by Endocytosis: It involves the addition of one volume of washed packed erythrocytes to nine volume of buffer containing 2.5mM ATP, 2.5mM MgCl₂ and 1mM CaCl₂, followed by incubation for 2 minute at room temperature. The pores are resealed by using 154mM of NaCl and incubated at 3700 °C for 2 minutes. Several chemicals are entrapped in erythrocytes by this method are primaquine and related 8- aminoquinoline, vinblastin, chlorpromazine, and related phenothiazines, hydrocortisone, tetracaine and Vitamin A.

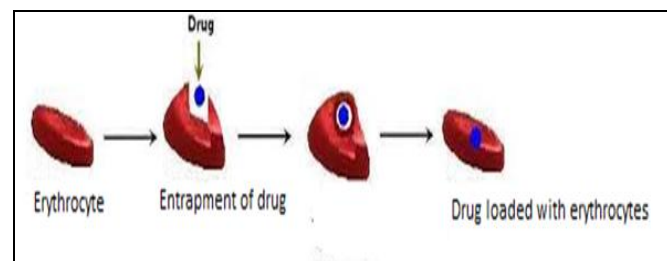


FIG. 11: SCHEMATIC REPRESENTATION OF ENDOCYTOSIS^[9]

Chemical Perturbation of the Membrane: This method is developed to enhance the permeability of cells on exposure to various chemicals. The permeability of erythrocyte membrane increases upon exposure to polyene antibiotic such as amphotericin B. Danorubicin an antineoplastic agent can be delivered by this method. However, these methods induce irreversible destructive changes in the cell membrane and hence not used widely⁹.

Evaluation of Resealed Erythrocytes:⁹⁻¹¹

Osmotic Fragility: This test detects the abnormal fragility of RBCs, by exposing the untreated and loaded erythrocytes to the hypotonic solutions and allowing them to swell. Rathod *et al.*, (2010) reported that normal erythrocytes released 50% to that of cellular haemoglobin at 0.33% concentration

of sodium chloride whereas drug loaded erythrocytes released the same amount but at 0.5% concentration of sodium chloride. As per the reports the solutions were diluted to different concentration and checked subsequently.

Shape and Surface Morphology: The morphology of erythrocytes is important as it decides their life after administration. The morphology of erythrocytes is studied using SEM, TEM and phase contrast microscopy. The vesicle size and distribution can be also found out by TEM

Drug Content: This method determines the entrapment efficiency, in which the deprotonization of packed cells is done with 2ml of acetonitrile and centrifugation takes place at 2500rpm for 10 min. The clear supernatant layer is taken for analysis by radio labelling or assay method.

Erythrocyte Sedimentation Rate (ESR): It is an estimate of suspension stability of RBC's in plasma that relates to the size and the concentration of fibrinogen, globulin that are set as standards.

Cell Counting and Cell Recovery: This involves counting the number of red blood cells per unit volume of whole blood, by using an automated machine. This determines the number of intact cells per cubic mm of packed erythrocytes before and after loading the drug.

Osmotic Shock: For osmotic shock study, erythrocytes suspension was diluted with distilled water (5ml) and centrifuged at 300 rpm for 15 minutes. The supernatant was estimated for percent haemoglobin release analytically

Determination of Magnetite Content: Atomic absorption spectroscopic method is used to determine the concentration of metal in a particular sample. HCl is added to a fixed amount of magnetite bearing erythrocytes and content is heated at 6000 °C for 2 hours, then 20 %w/v trichloro-acetic acid is added and supernatant obtained after centrifugation is used to determine magnetite concentration¹².

Shelf Life, Stability and Cross-Linking of Released Erythrocytes: The shelf life of the carrier erythrocytes is improved by storing the cells in powdered form and then they are filled in amber

glass vials. Lyophilizer is used to determine the cross linking efficiency by preparing the erythrocyte suspension. The temperature maintained must be -40°C with pressure 0.01 torr.

Haemoglobin Release: The content of haemoglobin can be estimated by altering the permeability of the erythrocytes. The red cell suspension the haemoglobin leakage can be tested.

Applications of Resealed Erythrocytes: ^{11, 12, 13}

Targeting the Bioactive Agents to RES:

Damaged erythrocytes are rapidly cleared off, from the circulation by the phagocytic cells in liver and spleen, the drug targeting minimizes this side effect and also the dose to be administered. Modification on the erythrocytic membrane using various proteins, antibody and chemical substances can enhance the therapeutic efficacy. Some of the examples are:

Glutaraldehyde: The treatment of drug loaded erythrocytes with glutaraldehyde increases the osmotic fragility, stability, sensitivity towards RES particularly suitable for organs like liver, spleen.

Biotin: Surface modification with N-hydroxy-succinamide and phenylhydrazine increases the macrophage uptake of loaded erythrocytes in both *in-vivo* and *in-vitro* conditions.

Erythrocytes as Circulating Bioreactors: This method enables the enzymes to be used as carriers to serve as circulating bioreactors. By decreasing the level of circulating metabolites the erythrocytes enter the site to elicit pharmacological action *e.g.* antiviral drugs

Erythrocytes in Controlled Release System: Controlled and sustained release dosage forms are designed to provide prolonged therapeutic action. As carrier erythrocytes have long span they can be used as circulating depots for antitumor, antibiotics and cardiovascular drugs. Various bioactive agents can be encapsulated to develop a sustained release formulation.

Resealed Erythrocytes in Cancer Therapy: Resealed erythrocyte act on acute lymphoblastic leukaemia, cancer of the white blood cells, the cells that normally fight infections. In patients of this condition, the bone marrow produces excess

immature white blood cells, called lymphoblasts, which are unable to help the body fight infections. L-asparaginase is used as a choice of drug. ASNase is an enzyme which hydrolyzes amino acid L-asparagine (ASN) to L-aspartic acid and ammonia. Most human tissues can self-synthesize ASN from L-glutamine by the action of asparagine synthetase (AS). Systemic depletion of ASN by ASNase would therefore impair protein biosynthesis in these cells, leading to their deaths through cellular dysfunction.

The L-asparaginase gets entrapped in *E. coli* to reduce immunological reactions and protect the proteins. Also preservative is added to give the final product. It is available under the trade name GRASPATM. It is reported by Jangde *et al.*, (2011) that the product minimizes the anaphylactic reaction, improves half-life of the drug and lengthens the plasma suppression. The steps by which drug gets entrapped are summarized as follows ¹⁴⁻¹⁶:

- RBCs are washed with a saline solution and L-asparaginase is added to the RBCs suspension following dialysis method.
- The RBCs swell and pores appear on their membrane allowing the L-asparaginase to enter erythrocytes.
- To restore isotonicity, a hypertonic solution is added online and the RBCs recover their initial shape and the membrane pores reseal.
- The RBCs loaded with L-asparaginase are washed to eliminate cell ghosts and extracellular elements.

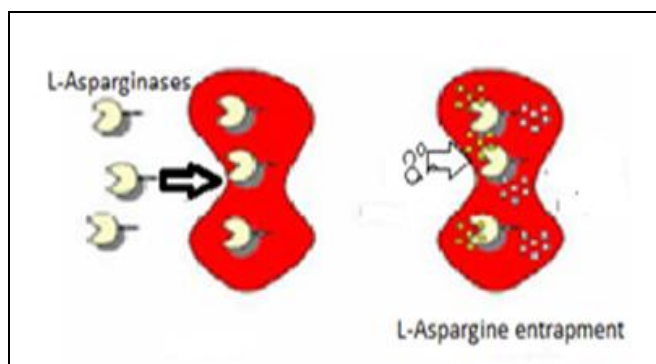


FIG. 12: SCHEMATIC REPRESENTATION OF ENTRAPMENT OF DRUG IN CANCER ¹⁶

In Multiple Myeloma: Also called as Kehler's disease is the cancer of plasma cells that lead to production of lesions due to inflammation.

Adiramycin is classic drug belonging to class of anthracycline is an antibiotic used in antineoplastic chemotherapy because of its remarkable cytotoxicity toward several solid tumors.

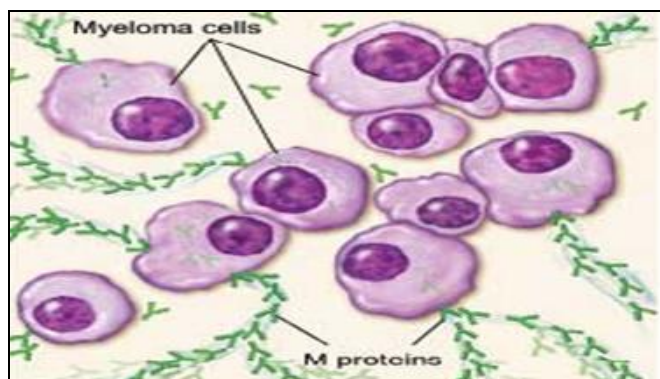


FIG. 13: SCHEMATIC REPRESENTATION OF MYELOMA CELLS¹²

It is closely related to intercalation of DNA. Due to its serious side-effect the drug is given by resealed erythrocytes technique. Mainly dialysis method is used to entrap the drug following its isotonic resealing. The dose that can be entrapped is 1.6 mg with 80% encapsulation with each ml pack of resealed erythrocytes. They are given parentally and act by activating Topoisomerase II thus also leading minimization of cardio-toxicity when given by oral route. The steps of entrapment are explained in the below Fig. 14.

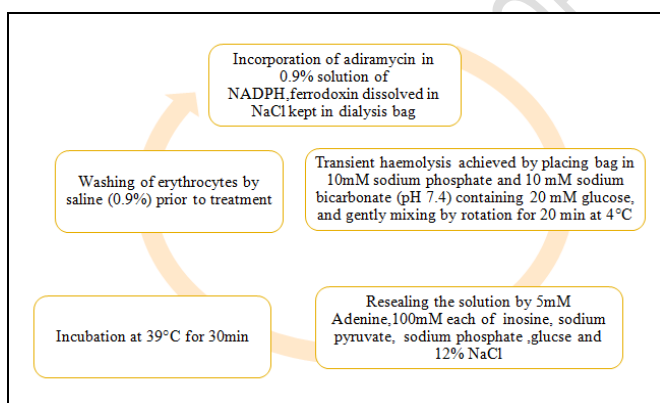


FIG. 14: SCHEMATIC REPRESENTATION OF DRUG ENTRAPMENT IN KEHLER'S DISEASE

Resealed Erythrocytes in Hepatic Tumours:

Hepatic tumors are one of the most prevalent types of cancer. Antineoplastic drugs such as methotrexate, bleomycin, asparaginase and Adriamycin have been successfully delivered by erythrocytes. By endocytosis method as shown in Fig. 15, the drug can be encapsulated that has improved therapeutics^{17, 18}.

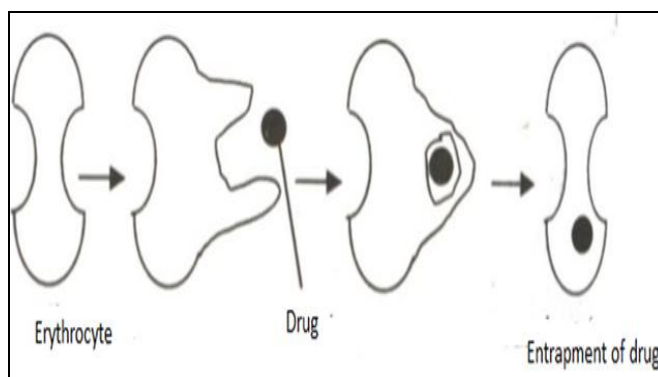


FIG. 15: SCHEMATIC REPRESENTATION OF DRUG ENTRAPMENT IN TREATING HEPATIC TUMOU¹⁷

Enzyme Therapy: Enzymes are widely used in clinical practice as replacement therapies to treat diseases associated with deficiencies like Gaucher's disease, galactosuria and degradation of toxic compound secondary to some kind of poisoning like cyanide, organophosphorus, Enzyme loaded resealed erythrocytes release enzymes into circulation upon haemolytic act as a "circulating bioreactors" in which substrates enter into the cell, interact with enzymes, and generate products or accumulate enzymes in RES upon haemolytic for future catalysis.

The first report of successful clinical trials of the resealed erythrocytes loaded with enzymes for replacement therapy is that of β -glucoserebrosidase for the treatment of Gaucher's disease. The disease is characterized by in born deficiency of lysosomal β -glucoserebrosidase in cells of RES thereby leading to accumulation of β -glucoserebrosides in macrophages of the RES¹⁹.

Iron Chelators: In thalasemic patients where regular blood transfusion is required the carrier erythrocytes can be incorporated in desferrioxamin which has shown improved therapeutics. RES is the main site of destruction of erythrocytes and iron in these patients.

Advances in Resealed Erythrocytes:^{20, 21}

Erythrosomes: These are specially engineered vesicular systems that are chemically cross-linked to human erythrocytes support upon which a lipid bilayer is coated. This process is achieved by modifying a reverse-phase evaporation technique. These vesicles have been proposed as useful encapsulation systems for macromolecular drugs.

Nanoerythroosomes: These cell based carrier systems were derived from erythrocytes after complete haemolysis and carefully engineered to produce nanoerythroosomes. Nanoerythroosomes are vesicles formed by the extrusion of red blood cell ghosts and the average diameter is $0.1\mu\text{m}$ ²².

CONCLUSION: The review focusses on the need, properties, isolation, preparation and applications of resealed erythrocytes. Resealed erythrocytes are the promising drug carriers that can be used for targeted drug delivery systems minimizing the side effects of the conventional dosage form. It can be prepared by different techniques and also characterized easily. Due to the several potential advantages over other drug delivery system with varied range of applications in areas of enzyme therapy, hepatic tumours, cancer, bacterial infections this drug loaded erythrocytes seems to be a promising delivery system. However more emphasis should be given on the novel approaches like nanoerythroosomes and erythroosomes so that it can be utilized in routine drug delivery system. Thus resealed erythrocyte is a promising approach for the delivery of drugs and biopharmaceuticals.

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CONFLICTS OF INTEREST: Nil

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