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Review Article

An Advanced Review on Resealed Erythrocytes

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ABSTRACT

Now a days there are numerous applications have been proposed for the use of resealed erythrocytes as carrier for drugs, enzyme replacement therapy etc. Until other carrier systems come of age, resealed erythrocytes technology will remain an active field for the further research. The use of resealed erythrocytes shows potential for a safe and effective delivery of various bioactive molecules for effective targeting. In coming future, erythrocyte based drug delivery system with their capability to afford controlled and site specific drug delivery have been developed for disease management. Erythrocyte carriers are **"Nano devices in the field of Nanotechnology**". A large amount of valuable work is needed so as to utilize the potentials of erythrocytes in passive as well as active targeting of drugs in diseases like cancer. At present erythrocytes are most effective carriers in novel drug delivery systems considering their tremendous potential. Hence the present article is reviewed about method of drug loading, evaluation and applications of RSE.

Keywords: resealed erythrocytes technology, Erythrocyte carriers, Nano devices, drug loading.

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INTRODUCTION:

Generally a drug is administered into the body with a motive to get the required actions of that drug on a specific target. But the fact is that apart from its actual target, the drug also acts on some non-target sites, resulting in adverse drug reactions-which are commonly called as side effects. Ideally a perfect drug should exert its pharmacological activity only at the target site, using the lowest concentration possible and without negative effects on non-target compartments. Target specificity would also reduce the dosage and frequency of administration. Present pharmaceutical scenario is aimed at developing drug delivery systems that maximize the drug targeting along with high therapeutic benefits for safe and effective management of diseases. The reasons for this increasing interest in drug delivery are due to the increasing need of safe drugs, capable of reaching the target and with minimal side effects. The various drug delivery systems available today aim at the target of making the drug exhibits its pharmacological action only on the specified target site. Drug targeting can be approaches by either chemical modification or by appropriate carriers. The delivery systems currently available enlist carriers that are either simple, soluble macromolecules (such as monoclonal antibodies, soluble synthetic polymers, polysaccharides, and biodegradable polymers) or more complex multicomponent structures (microcapsules, micro particles, cell ghosts, lipoproteins, liposomes, erythrocytes).[1]

Erythrocytes have been the most interesting carrier and have found to possess great potential in drug targeting. Resealed erythrocytes are gaining more popularity because of their ability to circulate throughout the body, biocompatibility, zero order release kinetics, reproducibility and ease of preparation.[2]

Most of the resealed erythrocytes used as drug carriers are rapidly taken up from blood by macrophages of reticuloendothelial system (RES), which is present in liver, lung and spleen of the body.

Erythrocytes are probably the most common cells found in the human body. After long research, we found their intense

application as a drug carrier in the drug delivery system. The resealed erythrocytes are biodegradable, biocompatible, non-immunogenic, non-pathogenic, self-degradable, reproducible, easy to prepare, possess prolonged circulation half-life and can be used to incorporate a wide variety of active drugs. All such properties make them a revolutionary drug carrier which can efficiently be used to increase the therapeutic effect of the drug as well as to prevent any possible toxic effects.[3]

ERYTHROCYTES:

Red blood cells (also referred to as erythrocytes) are the most common type of blood cells and the vertebrate organism's principal means of delivering oxygen (O2) to the body tissues via the blood flow through the circulatory system.

They take up oxygen through the lungs and release it while squeezing through the body's capillaries. These cells are rich in hemoglobin, an iron-containing biomolecule that can bind to oxygen and is responsible for the blood's red colour. Erythrocytes are natural products of body, biodegradable in nature, solation of erythrocytes is easy and large amount of drug can be loaded in small volume of cells, non-immunogenic in action and can be targeted to disease tissue or organ, prolong the systemic activity of drug while residing for a longer time in the body, protect premature degradation, inactivation and excretion of proteins and enzymes, act as a carrier for number of drugs, target the drugs within the reticulo-endothelial system (RES) as well as non RES organs/sites. They have capacity to carry large amounts of drug can behave as slow-release long acting systems.[4]

COMPOSITION OF ERYTHROCYTES:

- Blood contains about 55% of fluid portion (plasma) 45% of corpuscles or formed elements.
- Normal blood cells have extensile, elastic, biconcave and non-nucleated configuration with a diameter ranging from 6-9microns and the thickness is nearly 1-2microns.
- Erythrocytes have a solid content of about 35% most of which is Hb and rest 65%being water.

ELECTROLYTE COMPOSITION OF ERYTHROCYTES:

- The concentration of k+ is more in erythrocytes and Na+ in plasma.
- The osmotic pressure of interior of the erythrocytes is equal to that of the plasma and termed as isotonic (0.9% NaCl or normal physiological saline)
- The morphology of the cells change with the osmotic pressure of the medium surrounding the red blood cells.
- If the medium is Hypertonic (i.e. higher osmotic pressure than 0.9%Nacl) they will shrink and become irregular in shape.
- If the medium is Hypotonic water diffuses into the cells and they get swelled and eventually lose all their hemoglobin content and may burst.
- Balanced ion solutions like Ringer's and Tyrode solution which are isotonic to that of body fluids are used in erythrocyte related experiments.[6]

SOURCE OF ERYTHROCYTES:

Different mammalian erythrocytes have been used for drug delivery, including erythrocytes of mice, rats, rabbits, monkeys, chicken and sheep.

ISOLATION OF ERYTHROCYTES:

- Blood is collected into heparin-zed tubes by vein-puncture.
- Blood is withdrawn from cardiac/splenic puncture (in small animal) and through veins (in large animals) in a syringe containing a drop of anti-coagulant.
- The whole blood is centrifuged at 2500rpm for 5min at 4+/- 10 degrees in a refrigerated centrifuge.[7]
- The serum and buffy coats are carefully removed and packed cells are washed three times with phosphate buffer saline (pH=7.4).
- The washed erythrocytes are diluted with PBS and stored at 40 degrees centigrade for as long as 48hrs before use.

ERYTHROCYTES CAN BE USED AS CARRIERS IN TWO WAYS:

Targeting particular tissue/organ:

This method is used only if erythrocyte membrane is used. This is obtained by splitting the cells in hypotonic solution and after introducing the drug into cells, allowing them to reseal into spheres. Such erythrocytes are called as Red cell ghosts.[20]

For continuous or prolonged release of drugs:

They can also be used in continuous or prolonged release systems which provide prolonged drug action.Many methods are available for encapsulation of drugs within erythrocytes. They remain in the circulation for prolonged periods of time (till 120 days) and release the drug at a slow and steady rate.

RESEALED ERYTHROCYTES:

For drug loading carrier erythrocytes are prepared simply by collecting blood samples from the suitable organism, separating erythrocytes from plasma, entrapping drug in the erythrocytes and resealing the cellular carriers. Hence these carriers are called as resealed erythrocytes. The overall process is based on the response of these cells under osmotic conditions.

ADVANTAGES OF RESEALED ERYTHROCYTES:

- A remarkable degree of biocompatibility, particularly when the autologous cells are used for drug loading.
- Their complete biodegradability with no generation of toxic products from the carrier biodegradation.
- The considerable uniform size and shape of the carrier.
- Considerable protection of organism against toxic effects of the encapsulated drug,
- E.g. antineoplasts.
- A wide variety of chemicals can be entrapped.
- Prevention of degradation of the loaded drug from inactivation by endogenous chemicals.

- Remarkably longer life-span of the carrier erythrocytes in circulation in comparison to the synthetic carriers.
- Possibility of targeted drug delivery to the RES organs.
- Possibility of zero order kinetics of drug release.
- Relatively inert intracellular environment.
- Availability of knowledge, techniques and facilities for handling, transfusion and working with erythrocytes.
- The lack of occurrence of any undesired immune response against encapsulated drug.
- A considerable increase in drug dosing interval with drug residing in therapeutic window region for longer time.
- Modification of pharmacokinetic and pharmacodynamics parameters of the drug.
- Remarkable decrease in concentration fluctuations in steady state in comparison to the conventional methods of drug administration.
- A decrease in side effects of the drugs.
- Easy control during life span ranging from minutes to months.[10]

DISADVANTAGES OF RESEALED ERYTHROCYTES:

- The rapid leakage of certain encapsulated substances from the loaded erythrocytes.
- Given that they are carriers of biological origin, encapsulated erythrocytes may present some inherent variations in their loading and characteristics compared to other carrier systems.
- Possibility of clumping of cells and dose dumping may be there.
- They have limited potential as carrier to non-phagocyte target tissue.
- Possible contamination due to the origin from blood, the equipment used and the loading environment.
- Rigorous controls are required for the collection and handling of the erythrocytes.
- The major problem encountered in the use of biodegradable materials or natural cells as drug carriers is that they are removed in vivo by the RES. This in some cases may pose toxicological problems.
- The storage of the loaded erythrocytes is a further problem involving carrier erythrocytes for their possible use in therapeutics.[11]

METHODS OF DRUG LOADING IN ERYTHROCYTES:

1. **Hypo-osmotic lyses method**

a) Dilution method

b) Dialysis method

c) Pre-swell method

d) Isotonic osmotic lyses method

2**. Endocytosis method**

3. **Membrane perturbation method**

Hypo-osmotic lyses method

In this process, the intracellular and extracellular solutes are exchanged by osmotic lysis and resealing. The drug present will be encapsulated with in the erythrocytes membrane.

a) Dilution method

Hypotonic dilution was the first method investigated for encapsulation of chemicals into erythrocytes and is the simplest and fastest. In this method the volume of packed erythrocytes is diluted with 2-20 volumes of aqueous solution of a drug. The solution toxicity is then restored by adding a hypertonic buffer. The resultant mixture is then centrifuged, the supernatant is discarded and the pellet is washed with isotonic buffer solution. This reduces the circulation half-life of the loaded cells. These cells are readily phagocytosed by RES macrophages and hence can be used for targeting RES organs. Hypotonic dilution is used for loading enzymes such as galactosidase and glucosidase, asparginase. The major drawbacks of this method include low entrapment efficiency and a considerable loss of hemoglobin and other cell components.[14]

Examples of encapsulated agents: Beta-glucosidase, asparaginase arginase.

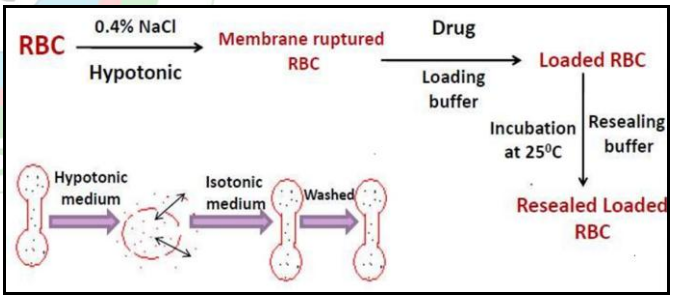


Figure 1: Method of drug loading in erythrocytes by hypotonic Dilution method

b) Dialysis method

In this method, erythrocyte suspension + Drug solution, loaded in dialysis tube with 25% air bubble and both ends are tied with thread. This tube is placed in bottle containing 100ml of swelling solution, stored at 4°C for lysis. After, the dialysis tube is transferred to 100ml resealing solution (isotonic PBS, pH 7.4) at room temp. (25-30°C) forresealing. These resealed cells are removed and washed with PBS at 4°C and finally suspended in PBS solution. High entrapment efficiency (30-40%) is attained by carrying out lysis and resealing in the same dialysis tube. Large molecular weight substances are entrapped by using low hematocrit erythrocyte suspension.

Eg: DMSO, monosaccharides, sucrose.

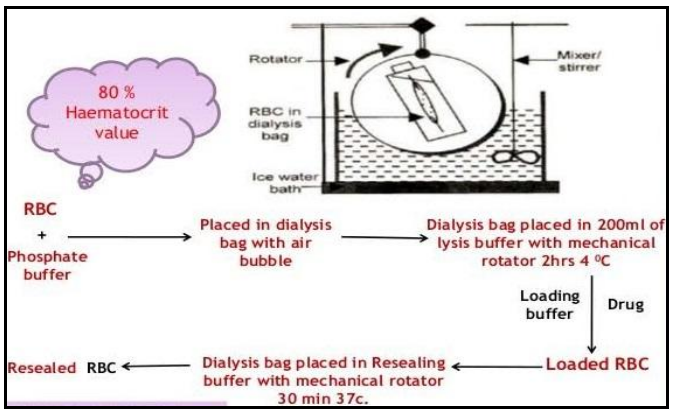


Figure 2: Method of drug loading in erythrocytes by hypotonic Dialysis method

c) Pre-swell method

This technique is based upon initial controlled swelling of RBC without lysis in hypotonic buffered solution. Erythrocyte suspension (2ml, 50% hematocrit), centrifuged at 1000 rpm for 10 min at 4°C to obtain packed RBC. Remove supernatant. Collect packed RBC + 4 ml of 0.65% NaCl (hypotonic pre-swelling solu.) and centrifuge 600 rpm for 5 min to collect swollen RBC cells. To swollen RBC, add small volumes of drug solution until they reach the point of lysis. Point of lysis is detected by appearance of thin layer of white ghosts on centrifugation. After 10 min hypertonic saline solu. Is added and suspension is incubated at 37°C for 10 min to restore isotonicity and resealing. Cells are washed thrice with washing buffer to remove hemoglobin and unentrapped drug. Cells are finally suspended in PBS buffer. This techniques results in good retention of cytoplasmic constituents, high drug entrapment (72%) and good in-vivo survival.

Eg: Thyroxin, Ibuprofen, etc.

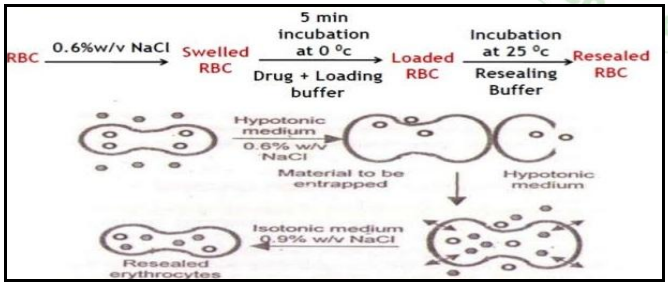
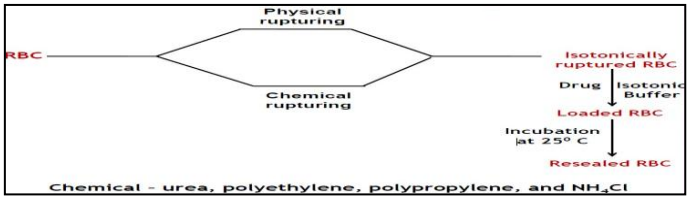


Figure 3: Method of drug loading in erythrocytes by hypotonic Pre-swell method

d) Isotonic osmotic lysis method

In this technique, hemolysis in isotonic solution can be achieved by either chemical or physical means or both. Propylene glycolincreases transient permeability and drug diffusion through erythrocyte wall without disturbing isotonicity. The lysed erythrocytes are resealed under isotonic condition by dilution with a glycol free medium.

Eg: DMSO, monosaccharides, sucrose.



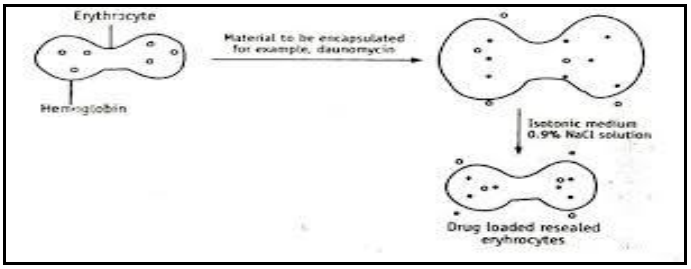


Figure 4: Method of drug loading in erythrocytes by hypotonic isotonic osmotic lysis method

2) Endocytosis method

Intra cellular vesicles with small molecules, drugs, enzymes, viruses (100 nm) can be induced in erythrocytes. The vesicle membrane separates the endocytosed substance from the cytoplasm, thus drug which are sensitive to inactivation of cytoplasmic enzyme are protected. In this method, 1vol. of packed erythrocytes + 9 vol. of buffer (containing 2.5mM ATP, 2.5mM $MgCl_2$ and 1mM $CaCl_2$) and incubated for 2min at room temperature. The pores created in this method are resealed by using 154mM of NaCl and incubate at 37°C for 2min.The entrapment of drug was obtained by endocytosis. Endocytosis can be induced by exposure to certain membrane activated drugs as given below.

Eg: 8-amino quinolones, Vinblastine, Chlorpromazine, Phenothiazine's, hydrocortisone, propranolol, tetracine, Vit-A, etc.,

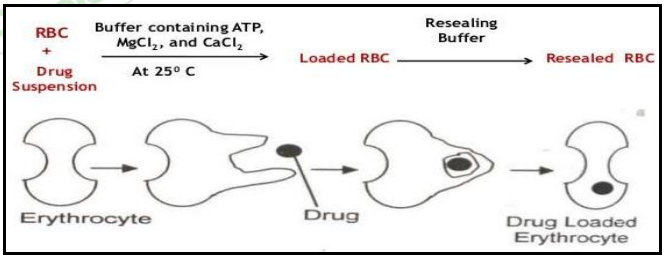


Figure 5: Method of drug loading in erythrocytes by Endocytosis method

3) Membrane Perturbation

Antibiotics such as **amphotericin-B** damage micro-organisms by increasing the permeability of their membrane to metabolites and ions. This property could be exploited for loading of drug intoerythrocytes. Amphotericin-B was used to load erythrocytes with anti-leukemic drug **daunomycin**. Amphotericin-B interacts with the cholesterol of the plasma membrane of eukaryotic cells causing change in permeability of the membrane.

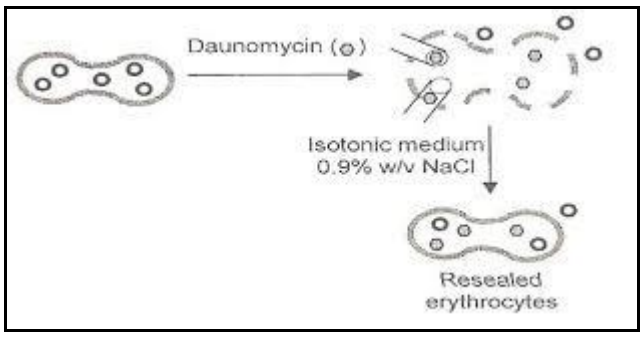


Figure 6: Method of drug loading in erythrocytes by Membrane Perturbation

CHARACTERIZATION OF RESEALED ERYTHROCYTES

In vitro Characterization of Resealed Erythrocytes:

Drug content quantification: To determine the drug content, packed loaded cells are deproteinized with acetonitrile after centrifugation at 3000rpm for a fixed time interval. The clear supernatant liquid is analyzed spectrophotometrically.[23]

In-vitro drug release and hemoglobin content study: In-vitro release of drugs and hemoglobin are monitored periodically from drug loaded cells. The cell suspension (5% hematocrit in PBS) is stored at 40 degrees C in amber coloured glass containers. Periodically the clear supernatant is withdrawn using a hypodermic syringes equipped with 0.45 m filter.[24]

%Hemoglobin release =As40 of sample-As40 of background/As40 of 100% hemoglobin

Percent cell recovery and Morphological study: Percent cell recovery may be determined by counting the no, of intact cells per cubic mm of packed erythrocytes before and after loading the drug. Phase contrast or electron microscope may be used for normal and drug loaded erythrocytes.

Osmotic fragility and Osmotic shock study; To study the effect of different tonicities, drug loaded erythrocytes are incubated separately in normal saline solution at 37+/- 2 degrees C for 10 minutes, followed by centrifugation at 2000rpm for 10 min. For osmotic shock study, dispersing the resealed erythrocyte suspension in distilled water and centrifuged at 300rpm for 15 min. The supernatant is estimated for percent hemoglobin release spectrophotometrically.[25]

Turbulence shock study: It is a measure of simulating destruction of loaded cells during injection. Normal and drug loaded cells are passed through a 23 gauge hypodermic needle at a flow rate of 10 ml/min which is comparable to the flow rate of blood. It is followed by collection of an aliquot and centrifugation at 2000rpm for 10 minutes. The hemoglobin in withdrawn sample is estimated. Drug loaded erythrocytes appear to be less resistant to turbulence, probably indicating destruction of cells upon shaking.[26]

Erythrocyte sedimentation rate (ESR): It is an estimate of suspension stability of RBC in plasma and is related to the number and size of red cells and to relative concentration of plasma protein, especially fibrinogen and alpha, betaglobulins. This test is performed by determining the rate of sedimentation of blood cells in a standard tube. Normal blood ESR is 0 to 15mm/hr. higher rate is indication of active but obscure disease processes.

Entrapped magnitude study: The hydrochloric acid is added to a fixed amount of magnetite bearing erythrocytes and contents are heated at 600 degrees C for 2hr.Then 20% w/v trichloro-acetic acid is added and supernatant obtained after centrifugation is used to determine magnetite concentration using atomic absorption spectroscopy.[27]

Shelf life, Stability and Cross linking of Released Erythrocytes: Glutaraldehyde (0.2%) treated erythrocytes in a sintered glass funnel (G-4) are collected by filtration and dried in vacuum (200mm Hg) for 10hr.Alternatively the erythrocyte suspension is filled into vials and lyophilized at -400 degree C to 0.01 torr using a laboratory lyophilizer. The dried powder is filled in amber colour glass vials and stored at 40 degree C for a month. Improvement in shelf life of carrier erythrocytes is achieved by storing the cells in powder form,ready for reconstitution at 40 degree C.

Particle size and zeta potential analysis: Using the particle size and zeta analyzer the size distribution of the sample was estimated. It was set with a dry accessory system in which a drop of sample is diluted with ten times of double distilled water and the sample is taken in cuvettes and was analyzed.[28]

In vivo Characterization of Resealed Erythrocytes:

Stability studies: Resealed erythrocytes were tested for stability. All the preparations were divided into three sets and were stored at 5+/-3 degrees C, 30+/-2 degrees C and 65%+5% RH and at room temperature, in thermostatic damp control over. After 2 weeks and 1 month, drug release of the optimized formulation and the percentage of drug content were determined for all the formulations.

APPLICATIONS OF RESEALED ERYTHROCYES:

In Vitro Applications:

- Carrier RBC'S have proved to be useful for a variety of in vitro tests.
- For in vitro phagocytosis cells have been used to facilitate the uptake of enzymes by phagolysosomes. An inside to this study shows that enzyme content within carrier RBC could be visualized with the help of cytochemical technique.
- When antibody molecules are introduced using erythrocytic carrier system, they immediately diffuse throughout the cytoplasm. Antibody RBC auto injected into living cells have been used to confirm the site of action of fragment of diphtheria toxin.

In Vivo Applications:

These include the following:

Slow drug release:

Erythrocytes have been used as circulating depot for the sustained delivery of anti-neoplastic, anti-parasitic,

veterinary, antiamoebics, vitamins, steroids, antibiotics and cardiovascular drugs.[11]

Drug targeting:

Ideally drug delivery should be site specific and target oriented to exhibit maximal therapeutic index with minimal side effects. Resealed erythrocytes can act as drug carriers and targeting tools as well. Surface modified erythrocytes are used to target organs of mononuclear phagocytic system/RES because the change in membrane is recognized by macrophages.

Targeting reticulo-endothelial system (RES) organs:

Surface modified erythrocytes are used to target organs of mononuclear phagocytic system/reticulo endothelial system because the changes in membrane are recognized by

Macrophages.

The various approaches used include:

i) Surface modification with antibodies

ii) Surface modification with glutaraldehyde

iii) Surface chemical cross-linking

Targeting the liver deficiency/therapy:

Many metabolic disorders related to deficient or missing enzymes can be treated by injecting these enzymes. However the problems of exogenous enzyme therapy include shorter circulation half-life of enzymes, allergic reactions and toxic manifestations. These problems can be successfully overcome by administering the enzymes as resealed erythrocytes. The enzymes used include P-glucosidase, P-glucuronidase and P-galactosidase.[9]

Treatment of parasitic disease:

The ability of resealed erythrocytes to selectively accumulate within RES organs make them useful tool during the delivery of anti-parasiticagents. Parasitic diseases that involve harboring parasites in the RES organs can be successfully controlled by this method.Results were favorable in studies involving animal models for erythrocytes loaded with antimalarial, anti-leishmanial and anti-amoebic drugs.

Removal of toxic agents:

Cannon et al. reported inhibition of cyanide intoxication with murine carrier erythrocyte containing bovine rhodanase and sodium thiosulphate. Anatomization of organophosphorus intoxication by released erythrocyte containing a recombinant phosphodiesterase also has been reported.[21]

Treatment of hepatic tumor's:

Antineoplastic drugs such as methotrexate (MTX),bleomycin, asparginase and adiramycin have been successfully delivered by erythrocytes.Eg.in a study, the MTX showed a preferential drug targeting to liver followed by lungs, kidney and spleen.

Delivery of antiviral agents:

Several antiviral drugs have been entrapped in resealed erythrocytes for effective delivery and targeting. Because most of the antiviral drugs are nucleotides their entrapment and exit through the membrane needs careful consideration.[22]

Targeting Non RES:

Erythrocytes loaded with drugs have also been used to target outside the RES.The various approaches for targeting non-RES organs include:

I. Entrapment of paramagnetic particles along with the drug
II. Entrapment of photosensitive material
III. Use of ultrasound waves
IV. Other approaches include fusion with liposome, lectin pre-treatment of resealed cells etc.

Enzyme Therapy: Enzymes can be injected into the blood stream to replace a missing or deficient enzyme in metabolic disorders or to degrade toxic compounds accumulated in the blood due to a disease likewise environmental, lysosomal storage disorders such as Gaucher's disease, hyperargininemia, hyperuricemia and kidney failure are only few examples of metabolic disorders that can be treated by administration of enzymes.[7]

Improvement in oxygen delivery to tissues:

Hemoglobin is the protein responsible for the oxygen-carrying capacity of erythrocytes. Under normal conditions,95% of hemoglobin is saturated with oxygen in the lungs whereas under physiologic conditions in peripheral blood stream only 25% of oxygenated hemoglobin becomes deoxygenated. Thus the major fraction of oxygen bound to hemoglobin is recirculated with venous blood to the lungs.

RECENT DEVELOPMENT:

Nanoerythrosomes: Nanoerythrosomes are vesicles prepared by the extrusion of RBC ghost, the average diameter of these vesicles being 100nm.The process gave small vesicles with the size of liposomes. These spheroid particles were named as 'Nanoerythrosomes' and appear to be stable and maintain both the cytotoxic and antineoplastic activity of daunorubicin (DNR) against mice leukemia P338-D-cell.Antiviral drugs can be pretreated to deliver drug directly to macrophages.

Erythrosomes : Erythrosomes are specially engineered vesicular systems in which chemically cross-linked human erythrocyte cytoskeletons are used as sport upon which a lipid bilayer is coated. This can be achieved by a modification procedure normally adopted for reverse phase evaporationErythrosomes are proposed as useful encapsulation system for drug delivery particularly for macromolecular drugs.[6]

CONCLUSION:

Now a days there are numerous applications have been proposed for the use of resealed erythrocytes as carrier for drugs, enzyme replacement therapy etc. Until other carrier systems come of age, resealed erythrocytes technology will remain an active field for the further research. The use of resealed erythrocytes shows potential for a safe and effective

delivery of various bioactive molecules for effective targeting.

In coming future, erythrocyte based drug delivery system with their capability to afford controlled and site specific drug delivery have been developed for disease management. Erythrocyte carriers are **"Nano devices in the field of Nanotechnology**".

A large amount of valuable work is needed so as to utilize the potentials of erythrocytes in passive as well as active targeting of drugs in diseases like cancer. At present erythrocytes are most effective carriers in novel drug delivery systems considering their tremendous potential. Genetic engineering aspects can be coupled to give a newer dimension to the existing cellular drug carrier concept. Using RBC'S we can transplant steroids and hormones to the targeting site by reducing their side effects. Erythrocytes are **"Golden eggs in novel drug delivery systems**".

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