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Artificial Intelligence: Microchip Based Drug Delivery Through Resealed Erythrocytes

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Abstract

In present scenario, the Artificial Intelligence in performing sophisticated tasks and computations has gradually led it to be introduced to solve many problems for betterment of a patients. Cellular carriers possess a great potential in various modules of drug delivery. Among such cellular carriers, erythrocytes have been found to possess huge merits for the targeted and controlled drug delivery system and could be manipulated with reference to time. Introduction of a wireless microchips in some of resealed erythrocytes can be thought to target the thrombus. In several cases, post-operative formation of a repeated thrombus is a common problem. If we target those thrombi by loading the antithrombotic drug with biosensor or by video monitoring, as like of an angioplasty, higher therapeutic success can be achieved. If same can be done by inserting wireless microchip with camera and biosensor so that when erythrocytes pass from the thrombus, it will give some indication to controlling device which will break or burst the erythrocytes over thrombus which contains the antithrombotic agents so that clot will dissolve and this can be monitored by wireless devices. This may helpful to prevent various blockages occurring due to clots, which otherwise lead to strokes or other life threatening complications.

It is hypothesis that we can use these devices and can prevent the stroke which may lead to further complications. This assumption if made possible, it will provide better compliance to the patients.

Keywords: Resealed erythrocyte; Thrombus; Microchips

Introduction

Cells are smallest functional units of the body, which form various tissues like blood, bones and muscles and perform specialized functions. When these different tissues are grouped, they form organs like heart, lungs, liver, stomach, and these together form systems like digestive, cardiovascular etc. According to this, blood is a connective tissue, which communicates between the cells of different parts of the body. Blood is about 7% of the body weight of an average individual, i.e. near about 5.6 litre blood in an average 70 kg man. This ratio or proportion does vary to a little extent according to age and gender. Blood, which is present in blood vessels is always in motion or in flow due to continuous pumping action of heart. Blood is composed of plasma (55%) and cells (45%) of total volume. Blood contains various blood cells namely, erythrocytes (RBC), Platelets (thrombocytes) and leucocytes (WBC) [1]. The process by which blood cells are formed is

called as haemopoiesis and occurs in bone marrow. Erythrocytes are one of the main components of blood with a life span in circulation near about 100-120 days. Development process of RBC's called as erythropoiesis. Transportation of oxygen from lungs to the tissues and carbon dioxide from the tissues to the lungs for process of excretion is the major function of blood and components of blood. It also carries various nutrients to the various living tissues and organs [1].

Resealed erythrocytes do have a great impact on the patient compliance. RBCs are extensively studied for their potential carrier ability of entrapped drug [2]. As they are biomolecules so that there will be no possibility of immunogenic reactions, which makes them most suitable carriers for targeting the drug. Resealed erythrocytes pose several advantages over other targeted drug delivery system, like nanosomes or liposomes. Resealed erythrocytes is one of the novel approaches towards the drug delivery. Even challenges come in the formulation and manufacturing or during loading of drug in erythrocytes, resealed erythrocytes are the most important carrier system for delivery of drugs may be of a chemical or a biological origin.

Drug carrying potential of erythrocytes

Erythrocytes were discovered in 1658. The RBCs which are under developing phase has a capacity to synthesize hemoglobin while adult RBCs don't have this capacity, they only serve as a carrier for a hemoglobin [2]. The use of cells as drug delivery systems was firstly realized in early 1970. The drugs which are used in cells are unable to permeate the membrane and made available to cross the membrane without causing any irreversible changes in the membrane, structure and permeability. Cells must be able to release drug when reached to target. Resealed erythrocytes are the carriers which are used for the targeting various disease. RBCs has a capacity of synthesized hemoglobin [3]. These are the one of the best carrier system that ever discovered.

Methods of drug loading in erythrocytes: FIG. 1 gives a schematic representation of different drug loading methods in erythrocytes.

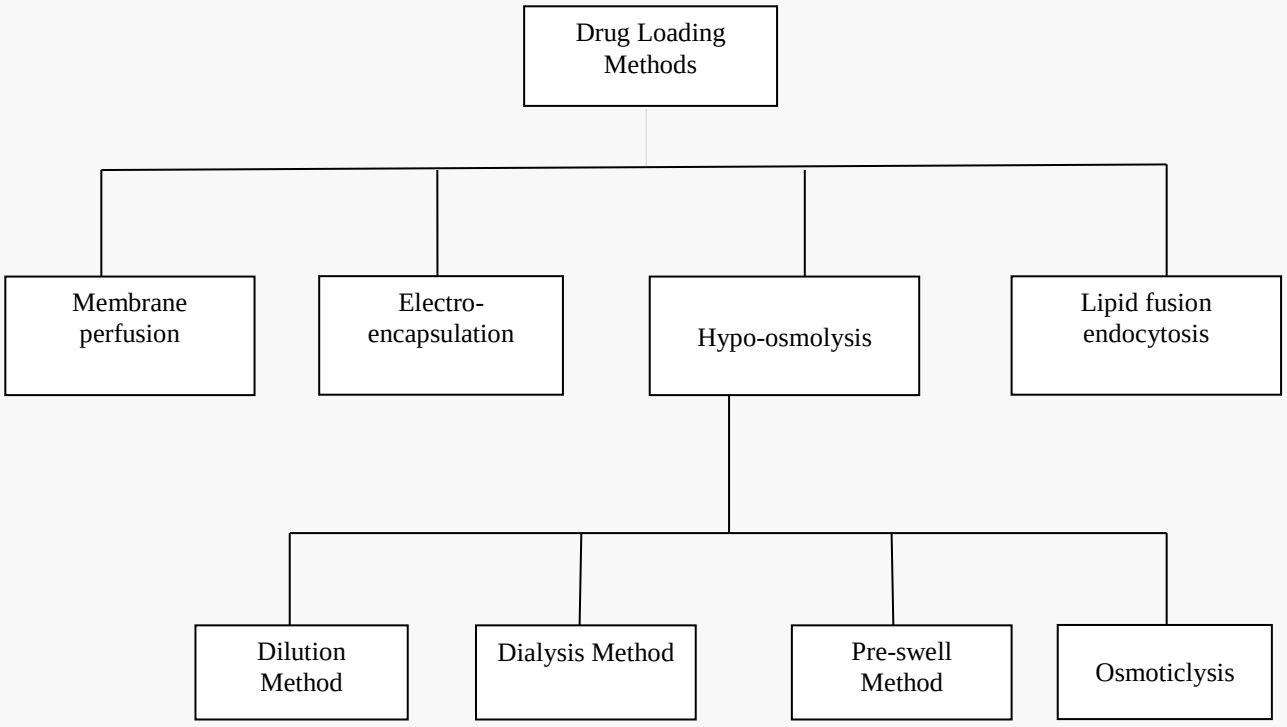

FIG. 1. **Methods of drug loading in erythrocytes.**

Hypo-osmolysis

In this process, intracellular and extracellular fluids are exchanged with the help of osmotic pressure so that pores of cells get opened and drug is loaded in erythrocytes [3,4]. These methods are further classified into following types: The diagrammatic flow charts of these methods are mentioned as FIG. 2-5 respectively.

a. Dilution Method
b. Dialysis Method
c. Pre-swell method
d. Osmotic lysis

a. Dilution Method

1. RBCs exposed to hypotonic Solution (0.4% NaCl)
↓
2. Swelling of cells up to its 1.6 times of original and appearance of pores 200 A° to 500A°
↓
3. Loading of drug in erythrocytes
↓
4. Increased strength to isotonicity and incubate cell at 37°C pores closed and osmotic pressure is restored in cell

FIG. 2. **Representation of dilution method of resealed erythrocytes.**

Advantages - Easy to load the drugs. Efficient for encapsulation of lower molecular weight drugs. Entrapment efficiency is quite good.

Disadvantages - Time consuming method. Sizes of loaded drugs are not found homogeneous.

b. Dialysis method

1. Hematocrit is washed with erythrocyte suspension and phosphate buffer of pH 7.4 containing drug [5]
↓
2. This mixture is placed in dialysis bag with proper tied with thread, placed in 200ml of dialysis buffer solution and placed on mechanical rotator at 4°C for 2 hrs
↓
3. Dialysis tube is then placed in solution isotonic to the erythrocytes for resealing at room temperature 25°C to 30°C
↓
4. Washed loaded RBCs with phosphate buffer solution at 4°C finally erythrocytes are re-suspended

FIG. 3. **Representation of dialysis method.**

Advantages - Entrapment of drug is more easy loading of drugs

Disadvantages - Time consuming process is complicated than dilution method.

c. Pre-swell Method

1. Erythrocytes are first swell by placing it in slightly hypotonic solution
↓
2. Centrifuged the swollen cells and recovered them at low speed
↓
3. When there will be minimum loss of constituents add a solution containing drug at a point of lyses

FIG. 4. **Representation of pre-swell method.**

Advantages - Simplest and quicker method than the dialysis. Resealed erythrocytes can be survive in optimum conditions for longer period

d. Isotonic osmotic lyses technique

1. Erythrocytes are placed in solution for incubation with high trans erythrocyte permeability
↓
2. Due to chemical potential, gradient solution diffuses the cells
↓
3. Transits permeability of erythrocytes can be produced using propylene glycol which helps drug to diffuse in cell
↓
4. Resealed the erythrocytes by using isotonic solution

FIG. 5**. Representation of Isotonic osmotic lyses techniques.**

2. Electro-encapsulation method: FIG. 6 gives a brief idea of steps involved in this method.

1. Suspend the erythrocytes in isotonic buffer solution in electrical discharge chamber
↓
2. The components are entrapped in the cells when electrical pulse of a greater threshold voltage 1 kV/cm to 10 kV/cm for 20 sec to 160 sec
↓
3. Resealed erythrocytes by using osmotic medium [5,6]

FIG. 6. **Representation of electro-encapsulation method.**

3. **Membrane perfusion method:** FIG. 7 gives a brief idea of steps involved in this method.

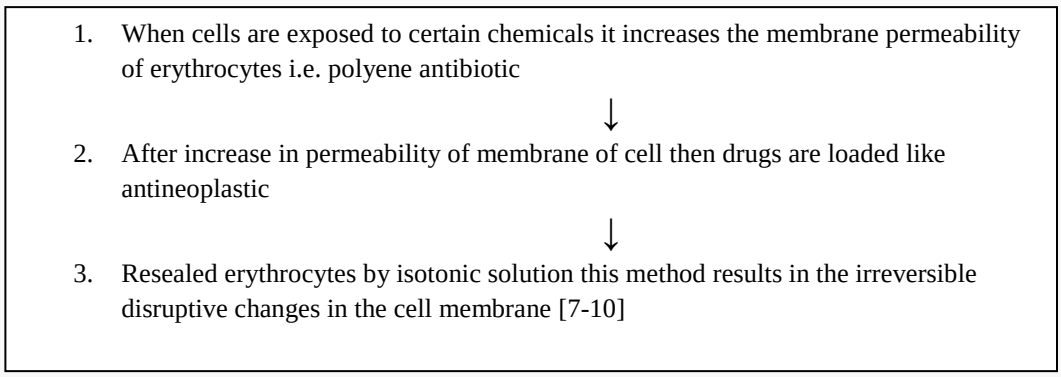

FIG. 7**. Representation of membrane perfusion method.**

4. **Lipid fusion endocytosis:** FIG. 8 gives a brief idea of steps involved in this method.

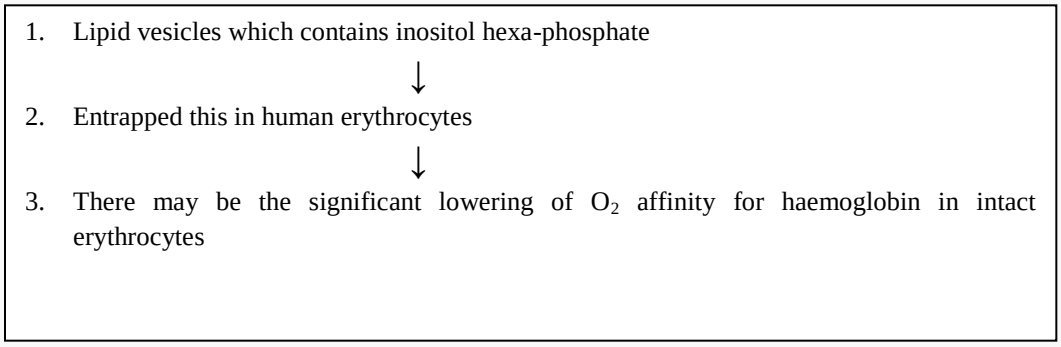

FIG. 8. **Representation of lipid fusion endocytosis.**

Efficiency of loading drug is very low in this method.

Advantages of resealed erythrocytes - These are biodegradable, biocompatible drug targeted carrier system. Having uniform size and shape of carrier. The wide variety of drugs or chemicals can be entrapped. There may be the modification of pharmacokinetic and pharmacodynamics parameter of drug. Having a longer life span in the blood circulation around 120 days. Decreased in side effect. Plasma concentration can be achieved [2-11].

Disadvantages of resealed erythrocytes - Complicated process of manufacturing of resealed erythrocytes. Entrapment of drug in erythrocytes difficult one rapid leakage of incorporated drug may take place. Contamination may be the problem due to biological origin. Some chemical molecules may alter the physiology of erythrocytes. As moreover they are targeted to RES system increased chances of toxicity if potent drugs are entrapped. May activate RES before maturity-Immunogenesis [12].

Thromboembolism

Blood clot that has formed inside a blood vessel subsequently breaks off, travels through the blood stream, and plugs another blood vessel, causing organ damage. Thrombus and embolus are a blood clot that forms inside the vascular system is called thrombus. When this thrombus breaks of leads to travelling all over the blood flow. This moving blood clot is referred to as an embolus. Thromboembolism is one of the major and common cause for the mortality [13]. Generally, it affects 0.1% to 0.2% of population every year. Men having a higher risk of thromboembolism than the women. FIG. 9 gives a diagrammatic presentation of thromboembolism.

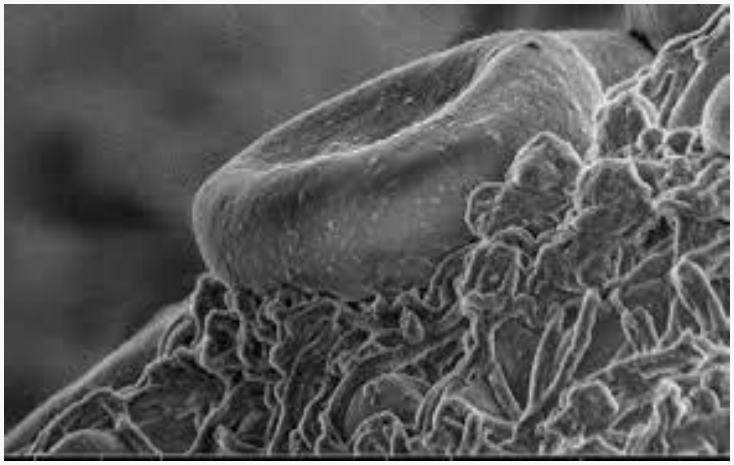

FIG. 9. **Thrombus showing RBC entrapped in surrounding platelets and fibrin meshwork.**

Causes of thromboembolism

Thromboembolism may be caused due to the various factors which can directly or indirectly affect the process [13]. These factors are as follows:

1. **Genetic factors**
    - Deficiency of antithrombin
    - Defects in fibrinolysis
    - Mutation in Factor V
2. **Acquired factors**
    - Use of oral contraceptives
    - Immobilization
    - Smoking
3. **Clinical condition**
    - Atherosclerosis
    - Heart diseases
    - Cancer
4. **Endothelial damage**
    - Surgery
    - Trauma

Embolism

It a process in which partial or complete obstruction or detached part of the cardiovascular system which carries mass in the circulation [14,15]. It is an intravascular part detaches from the site and moves in blood circulation is called as embolus [16]. There are various types of embolism depending upon the causes of thromboembolism [17].

Types of thromboembolism

1. **Depending on the matter in the emboli**
    - Solid e.g. tumour clump, athromatus
    - Liquid e.g. Fat globules, amniotic fluid
    - Gases e.g. air or other gases
2. **Depending upon whether infected or not**
    - Bland-When sterile
    - Septic-When Infected
3. **Depending upon source of emboli**
    - Cardiac emboli-Left side of arm emboli originating from atrium and atrial appendages
    - Atrial Emboli-In systemic arteries, in brain, spleen, kidney, intestine
    - Venous Emboli-Pulmonary arteries
    - Lymphatic Emboli
4. **Depending upon flow of blood**
    - Paradoxial-Embolus moves from venous site of circulation to the atrial side or it may be vice versa
    - Retrograde embolus-This type of embolus travels against the blood flow. e.g. metastatic deposition in the spine

Treatment for thromboembolism

Up till now there are various treatments used for the diagnosis and treatment of a thromboembolisms. This stage of disease are mainly occur in old age patients. For treatment, most commonly used therapy is anticoagulants. Anticoagulants may prevent the extension of clot. Duration of this therapy is up to 6 weeks [18,19]. There are various marketed preparations used for the treatment of thromboembolism are listed in TABLE 1.

TABLE 1. **Drugs used for treatment of thromboembolism.**

Sr. No.	Name of drugs	Dose	Site of action
1	Apixaban	5 mg or 2.5 mg	Venous thromboembolism
2	Dabigatrun	75 mg	Stroke
3	Edoxaban	15 mg, 30 mg, 60 mg	Stroke

4	Heparin	40 mg or 80 mg	Postoperative venous thromboembolism
5	Rivaroxaban	10 mg, 15 mg, 20 mg	Orthopaedic surgery
6	Warfarin	10 mg	Pulmonary embolism

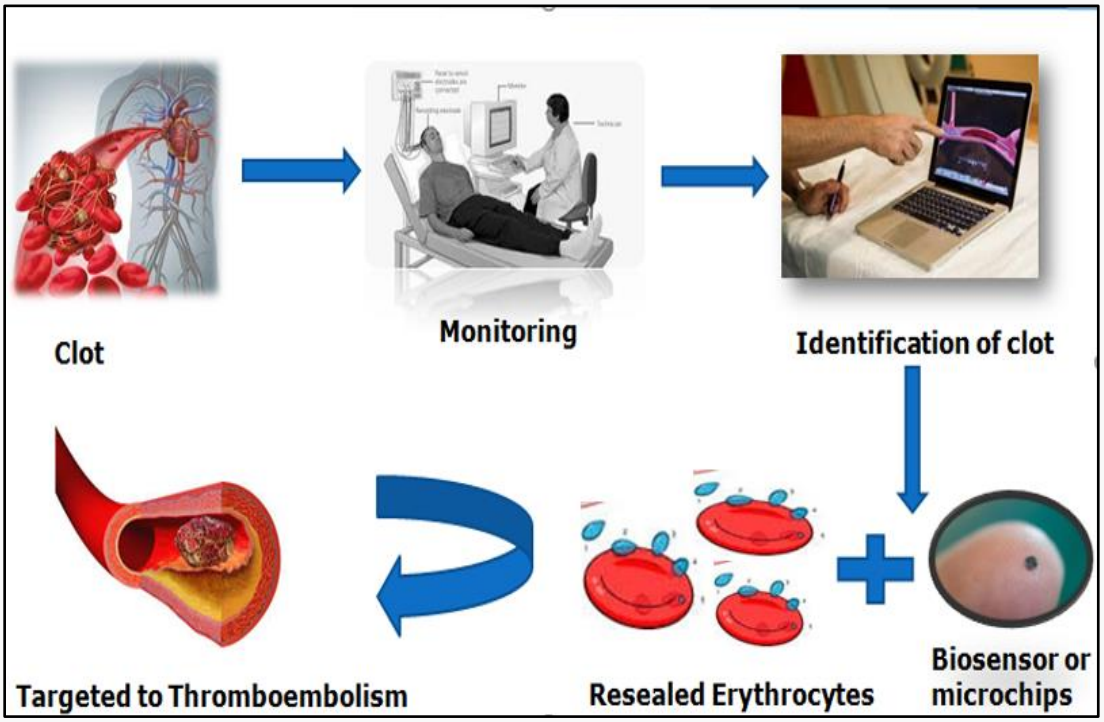

FIG. 10**. Hypothesis of resealed erythrocytes targeting using microsensors.**

Hypothesis

As shown in FIG. 10, collect the blood from either from the human origin or from the animal origin then go for the isolation of erythrocytes by the centrifugation method then collected erythrocytes are treated and removal of hemoglobin and now this erythrocytes are used for the loading of drugs as a carrier. Here various methods are used for loading of drug in erythrocytes here while loading the anticoagulant drug in erythrocytes there will be loading of biosensor or micro or nanochip which can be further use full for the detection of embolus in circulation and where it detects resealed erythrocytes should be able to burst and there itself released the drug and that embolus will dissolve from its original size or there may be completely dissolve embolus. These may be very much useful for prevention of a secondary complications and reduction in the mortality rate.

Conclusion

According to the hypothesis if this happens, it will provide more compliance for the patients and reduced in the secondary complications. It will be beneficial for treating various types of Thromboembolism and increase patient compliance.

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