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TARGETED DRUG DELIVERY SYSTEM OF NAPROXEN

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ABSTRACT

Naproxen and albumin microspheres were prepared by using water-in-oil emulsion technology. The in vitro release profile of targeted delivery system was studied by means of converting numerous processing and method parameters to offer a controlled launch of drug from the microspheres. Targeted drug delivery system was chosen to increase the concentration of delivered drug to the targeted body part of interest only (organs/tissues/ cells) which in turn improves efficacy of treatment by reducing side effects of drug administration. The inherent benefit of this method leads to administration of required drug with its reduced dose and decreased its side impact. The aim of targeted drug delivery is to prolong, localize, target and have a protected drug interaction with the diseased tissue. Quantum of drug at targeted drug delivery site was determined by taking samples at special site via UV spectrophotometer method.

KEYWORDS

Drug delivery, Drug carrier system and Therapeutics.

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INTRODUCTION

Targeted drug delivery is a form of miraculous drug delivery that brings medicine to a patient.

This drug delivery system undergoes the absorption of the drug throughout the biological membrane, whereas the intended release mechanism is that the drug is released in the form of doses[1,2].

Targeted drug delivery system is a method that brings a certain amount of long-term therapeutic agent to a specific disease within the body. This helps maintain the required level of plasma and tissue of the drug; therefore, to avoid any damage to healthy tissue with the drug. When using a targeted release program, the design process needs to be

considered: drug properties, adverse drug reactions, drug delivery route, target location, and disease[1,3,4].

The products found in such a delivery system are prepared by considering the specific characteristics of the target cells, the nature of the marker or carriers of vehicles or vehicles that transmit the drug to specific receptors and ligands and physically modified components. Targeted drug delivery systems must be biological (non-toxic), require antibodies, must be physically and chemically stable in vivo and in vitro conditions, and must have limited drug distribution to target cells or tissues or organs and demand. With the same distribution of capillary. It should have a manageable and predictable level of drug release and drug release should not affect drug movement. It should have a therapeutic value for drug release and should have minimal drug leakage during transport[5,4] .

Used carriers should not rot or have problems removed from the body. Delivery system maintenance should be simple or easy, duplicate and inexpensive. Targeted drug delivery system is preferred over standard drug delivery systems for three important reasons. The Ist is the reason for making medicines. Ordinary drugs have a lower rate of solubility and drug resistance compared to targeted drug delivery systems. 2nd Medications are usually poorly absorbed, have a short shelf life and require a large amount of circulation. These are its pharmacokinetic properties. Reason 3 includes the pharmacodynamic properties of the drug. Conventional drugs have a lower specificity and lower treatment dosage compared to the targeted drug delivery system. For these reasons the targeted drug delivery system is preferred over the standard drug delivery systems[1,3,4].

TYPES OF TARGETED DRUG DELIVERY

Targeting a drug in a particular area not only increases the therapeutic potential of the drug but also aims to reduce drug-related toxicity by allowing the dose of the drug to be used medically. To achieve such conditions, two widely used methods are also known as targeted drug categories[6,7,1] .

Passive Targeting

Refers to the accumulation of a drug or drug delivery system in a particular area such as antineoplastic drugs whose meaning may be attributed to the physicochemical or pharmacological properties of the disease. Therefore, in the event of arthritis treatment the size and surface areas of drug delivery of nanoparticles need to be controlled mainly to avoid detection using a reticuloendothelial system (RES) to increase circulation times and targeting ability. The key is called passive targeting. Drug withdrawal or drug actions are limited to selected sites within the body but not in the liver. Other examples include the administration of antimalarial drugs for the treatment of leishmaniasis, brucellosis, candidiasis.

Active targeting

Active targeting refers to the interaction of a specific type of ligand-receptor to locate intracellular intake that occurs only after blood circulation and additional release. This effective identification method can be further divided into 3 different targeting levels-

Refers to the limited distribution of drug administration systems in a capillary bed of a predetermined target area, organ or tissue e.g. partial orientation to lymphatics, peritoneal cavity, plural cavity, ventricles of the brain and eyes, joints.

Refers to the selective delivery of drugs to specific cell types such as tumour cells and not to normal cells e.g., Selected drug delivery to Chuffer cells in the liver.

Refers to direct delivery of the drug to the intracellular area of target cells e.g. receptor based ligand mediated entry of complex drug into cell by endocytosis[7].

COMPONENTS OF TARGETED DRUG DELIVERY

A drug delivery system primarily constitutes a target and drug carriers or markers. Target means specific organ or a cell or group of cells, which in

chronic or acute condition need treatment. Route of administration involves drug carrier as important targeting moiety and after its leakage from its carrier/markers to reach the drug to the specific or targeted site via biological metabolism with its clearance as well as not to reach at non targeted site to make this delivery system more site specific with reduced side effects of drugs and its quantity too. Carrier is one of the special molecule or system essentially required for effective transportation of loaded drug up to the preselected sites. These are engineered vectors which retain drug inside or onto them either via encapsulation and/ or via spacer moiety and transport or deliver it into vicinity of target cell[8,6,7].

Drug delivery vehicles

Drug delivery vehicles are also referred as drug vectors which are most important entity required for successful transportation of the loaded drug. Drug vectors transports and retains the drug to be delivered it within target. They are made capable of performing such specific functions which can be attributed by slight structural modification[9,7,4].

CHARACTERISTICS OF AN IDEAL DRUG VEHICLE

An ideal drug vehicle should be able to cross blood brain barriers and in case of tumour chemotherapy tumour vasculature. It must be recognized by the target cells specifically and selectively and must maintain the specificity of the surface ligands. The drug ligand complex should be stable in plasma, interstitial and other bio-fluids. The drug vehicle used should be non-toxic, non- immunogenic and biodegradable. After recognition, the carrier system should release the drug moiety inside the target organs, tissues or cells, selected and targeted chemotherapy[5].

Targeting Moieties includes antibodies, lectins and other proteins, Lipoproteins, Hormones, Charged molecules, Polysaccharides and Low molecular-weight ligands[9-11,4].

Liposomes

Liposomes are small artificially designed vesicles composed of phospholipid bilayers surrounding with the size ranging from 20 to 10,000nm. Many liposome formulations are rapidly taken up through macrophages and this could be exploited either for macrophage-specific transport of medicine or for passive drug focused on which allow sluggish release of the drug over time from those cells into the overall move. Cationic liposomes and lipoplexes have been considerably researched for non-viral vector mediated gene therapy[12].

Monoclonal antibodies and fragments

Most techniques based on antigen detection by antibodies are developed primarily to treat cancer. These strategies are usually aimed at the presence of tumour-related antigens on the body or in the specific term expressed by tumour cells. Antibody-drug conjugates (ADC) is a complex drug containing a monoclonal antibody that provides specialized identification of large numbers of cells or lymphomas. The drug is released by linker enzymatic cleavage under physiological conditions. Conjugates are currently being investigated in clinical trials[13].

Modified (plasma) proteins

Modified plasma proteins can be a smart drug transport vehicle due to its melting and small molecular weight. They can be easily altered by attaching different molecules such as peptides, sugars and other ligands to transport the desired drugs making them an ideal route for drug delivery.

Microspheres and nanoparticles

Microspheres and nanoparticles contain compatible polymers and are not soluble or soluble. microspheres and nanoparticles commonly used in selective drug delivery of cells, have found many of these days studied for their use in oral delivery of peptides and peptidomimetics[15-17,10].

Lipoproteins

Lipid particles such as LDL and HDL containing lipid and apoprotein moiety are called natural targeted liposomes and their core can be used to combine lipophilic or lipophilic pro-drugs and does not require a strong bond with the drug. Adjustments to the level of glycolipid insertion can be used to introduce new target components. Most studies on the use of LDL and HDL particles have

been performed and improved at the drug-targeting level[18].

Transdermal approach to drug transport

The Transdermal drug delivery system is systematically controlled by drugs in the form of leaflets delivering systemic drugs at a fixed and controlled rate. A transdermal drug delivery device or vehicle may be of functional or non-functional structure and is a device that provides an alternative to controlling an interested drug locally and delivering the drug to the entire skin barrier as well.

PREPARATION OF ALBUMIN MICROSPHERES

Several methods for the production of albumin microspheres have been reported. Many methods include emulsion technology and suspension.

The common formulation of these particles uses an aqueous solution of protein, a therapeutic agent in its solubility of fats and vegetable oils suitable to form a w/o emulsion. The emulsion solidified after transfer to an oil tank to solidify and subsequently separate the protein particles. Two methods of stabilizing albumin microspheres were used-

Temperature fluctuations at a temperature of between 100 and 180^{o}C for 2.5 minutes to 24 hours and chemical reactions using a suitable binding agent, such as formaldehyde.

Drug Entrapment

Inclusion of a healing agent 'Naproxen' within albumin microspheres was done using two techniques:

Drug addition inside the aqueous section before emulsification with the oil section and drug addition and equilibration with a suspension of preformed placebo albumin microspheres.

Preparation of Magnetic Microspheres

They are biodegradable microspheres ranging in size from 1-4um containing ultrafine magnetic particles "magnetite (Fe3O4}", the drug and the biodegradable coating materials e.g., albumin. The reaction takes place for Magnetite preparation is as following:

$FeSO_4 + 2NaOH \rightarrow Fe(OH_2) + Na_2SO_4$;$Fe(OH_2) + O \rightarrow Fe_3O_4 + 3H_2O$

Localization of the drug and magnetite bearing microspheres at the desired site, i.e. in-vitro; achieved by the application of an external magnetic field of appropriate strength. Magnetite can be easily introduced into microspheres physically without altering the chemical and physical properties of the polymer. Amount of magnetite which could be incorporated is 20-50% of the drug weight of drug carrier complex. The rationale for selecting magnetite size in albumin microspheres is that it should permit microspheres of size range 1-4um to render capillary level distribution and perfusion of the target. It should be biodegradable, non-toxic and non-immunogenic. It should have magnetic responsiveness to technically achievable external local fields and gradient flow rates found in physiologic system. The Estimation of drug from the targeted site was accomplished using UV spectrophotometer.

RESULTS AND DISCUSSION

Determination of drug content in microspheres

10 mg of the prepared microspheres digested with 1ml of 50%v/v trichloroacetic acid (TCA) and kept for 24 hours in order to precipitate the protein. The digested homogenate was centrifuged for 5 minutes and the naproxen content in the supernatant was determined by measuring the absorbance at 330nm, after suitable dilutions.

***In-vitro* Magnetic Responsiveness**

Magnetic responsiveness can be defined as the magnitude of response of microspheres when placed in a magnetic field.

An apparatus was fabricated to study the in-vitro magnetic responsiveness of the magnetite containing microspheres. The apparatus employed a syringe pump that deliver the solution through a polyethylene tube at a constant flow rate of 1-10cm/sec. The weighed quantity of microspheres (25mg) suspended in 0.15M NaCl were introduced and flow rate was adjusted with the help of a flow regulator. The retention of microspheres was evaluated by placing a bipolar magnet (8000 Oe strength). The fraction of microspheres retained and that passed with stream were collected, weighed,

and analysed for drug content, which gave the percent drug retained at the site where the magnetic field was applied.

The magnetic responsiveness of magnetite and drug bearing microspheres was studied by varying the magnetite content in the microspheres. The magnetite content was changed as 20%, 25% and 30% w/w based on BSA weight.

***In-vitro* release rate studies**

10ml suspension of accurately weighed quantity (25mg) of BSA microspheres was taken in a hollow tube which was tide at one and with treated cellophane membrane. This tube was clamped in a 100ml of beaker having 50ml of PBS (7.4) and maintained at 37+/- 2°C on a hot plate cum magnetic stirrer. 5ml of sample was withdrawn at hourly intervals for 6 hours. After each sampling the volume was replaced with an equal volume of fresh buffer. The drug content in the withdrawn samples was determined spectrophotometrically at 330nm, after suitable dilutions. Cumulative percent drug release was calculated at different time intervals.

It was observed that the temperature used for the stabilization of BSA microspheres exhibited an important effect on both the size and shape of the microspheres. At lower temperature 115+/-5°C microspheres of somewhat bigger size were obtained. The microspheres stabilized at 140+/-5^{o}C were regular in shape with narrow range of size distribution (Av. size 3.8µ).

On increasing the stirring rate relatively smaller microspheres were obtained due to subdivision of dispersed phase. The stirring speed of 1200rpm was found to be optimum stirring rate at which microspheres of smaller size (Av. size 4.07µ) were obtained.

At drug concentration 110mg/ml the average particle size of microspheres was found to be 4.05µ. However, on increasing the drug concentration upto 130mg/ml, microspheres of bigger size (Av. size 5.08µ) were obtained. 100-110mg/ml drug concentration was noted to be optimum.

***In-vitro* release profile study revealed that**

The release of drug was dependent on microsphere size. Microspheres prepared at higher stabilization temperature exhibited lesser release rate which may be attributed to the formation of more compact and rigid structure of microspheres.

The variation in stirring rate was noted to affect the size of microspheres and as a result the products prepared with variation in stirring rate showed significant difference in drug release.

It was found that at 25% magnetite concentration, the heat stabilized microspheres showed higher magnetic responsiveness (83%) on applying an external magnetic field of 8,000Oe. On increasing the concentration magnetite, magnetic responsiveness was increased accordingly.

Naproxen content of drug loaded BSA microspheres

S.No	Variables	% Drug Content
1	**At t Stirring Rates (rpm)**	
	(i) 400rpm	28.3
	(ii) 800rpm	21.7
	(iii) 1200rpm	24.2
2	**At t Stabilization Temperature**	
	(i) 115 +/- 5°C	17.1
	(ii) 130 +/- 5°C	19.4
	(iii) 140 +/- 5°C	22.3
3	**At Drug Concentration**	
	(i) 110mg	19.2
	(ii) 130mg	24.6
4	Magnetic microspheres	21.8

***In-vitro* Magnetic Responsiveness**

S.No	% Magnetite concentration	% Microspheres retained BSA heat stabilized
1	20	67
2	25	83
3	30	91

***In-vitro* release rate profile of heat stabilized BSA microsphereps prepared at different stabilizing temperatures**

Time (Hours)	% Drug Released		
	115 +/- 5°C	130 +/- 5°C	140 +/- 5°C
1	8.0	5.2	3.5
2	12.5	11.5	9.0
3	20.0	16.8	15.8
4	24.0	21.0	19.0
5	28.8	25.0	22.5
6	33.5	30.5	27.0

***In-vitro* release rate profile of heat stabilized BSA microsperes prepared at different stirring rates**

Time (Hours)	% Drug Released		
	400rpm	800rpm	1200rpm
1	3.0	4.8	6.0
2	5.0	7.8	13.9
3	10.2	13.5	17.0
4	18.0	19.7	22.5
5	20.8	24.8	27.4
6	24.5	26.0	34.0

***In-vitro* release rate profile of heat stabilized BSA microspheres prepared at different drug concentrations**

Time (Hours)	% Drug Released	
	110mg	130mg
1	3.2	4.0
2	7.5	9.5
3	14.8	17.0
4	20.0	22.4
5	23.7	29.2
6	28.0	36.4

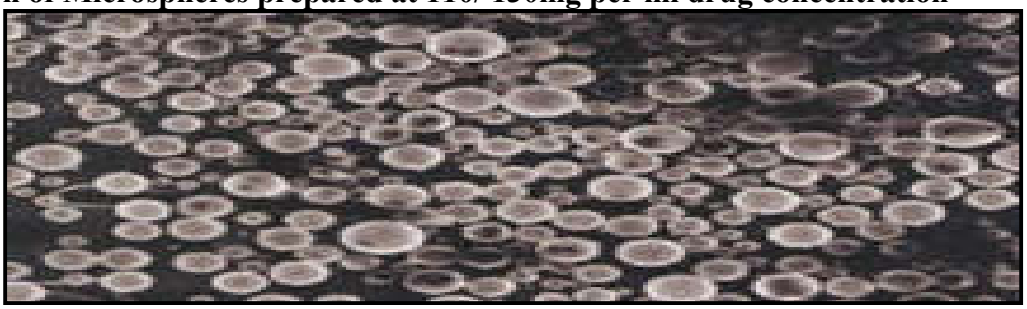
Size distribution of Microspheres stabilized at 115/130/140 (Temperature °C)

Photomicrograph of heat stabilized BSA microspheres prepared at 140°C

Size distribution of Microspheres prepared at 400/800/1200rpm stirring rates

Photomicrograph BSA microspheres prepared at stirring rate 1200 rpm

Size distribution of Microspheres prepared at 110/ 130mg per ml drug concentration



Photomicrograph of heat stabilized BSA microspheres prepared using Naproxen concentration 110mg/ml

CONCLUSION

It can be concluded from the present study, that naproxen bearing BSA microspheres can be used as a promising parenteral, targeted sustained release drug delivery carrier in diseased condition of rheumatoid arthritis. If the process variables are adjusted to their optimum values, microspheres of desired physico-chemical properties could be obtained. Furthermore, in the coming years, combining expertise in the drug targeting field with the technological developments in molecular biology and molecular medicine will facilitate the elucidation of the cellular and molecular processes underlying disease[1,9].

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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