International Journal of Engineering and Advanced Technology (IJEAT)
ISSN: 2249-8958 (Online), Volume-7 Issue-1, October 2017

Cell Encapsulation Technology-Applications in Therapy

Divya Sanganabhatla

Abstract: ***Entrapment of mammalian cells in physical membranes has been practiced since the early 1950s when it was originally introduced as a basic research tool. The method has since been developed based on the promise of its therapeutic usefulness in tissue transplantation. Encapsulation physically isolates a cell mass from an outside environment and aims to maintain normal cellular physiology within a desired permeability barrier. Numerous encapsulation techniques have been developed over the years. These techniques are generally classified as microencapsulation (involving small spherical vehicles and conformally coated tissues) and macroencapsulation (involving larger flat-sheet and hollow-fiber membranes). This review is intended to summarizes the state-of-the-art successes of microencapsulation, specifically with regard to the encapsulation of microorganisms, mammalian cells in treatment of various diseases.***

Index Terms: Microencapsulated cell, Probiotic Bacteria, Alginate Solution, Liver Cell.

I. INTRODUCTION

Microencapsulation has gained importance in the fields of cell and tissue engineering, as well as in the development of drug formulations and oral delivery systems. There are a number of already marketed microencapsulated products for the delivery of pharmaceutics [1]. The term microencapsulation, in this work, encompasses the terms microcapsules, microparticles, microspheres, and microemulsions. Generally, the term microsphere is employed for a homogeneous structure made of one continuous phase, and the term microcapsule is used for a reservoir-like structure with a well-defined core and envelope/coat. There exist a variety of microcapsules which can differ in size, composition, and function. The characteristics of the microcapsules ultimately depend on the final goal of the encapsulated product, as they can be used to entrap all sorts of substances: solids, liquids, drugs, proteins, bacterial cells, stem cells, and so forth. With such a range of substances that can be entrapped, one can conclude that microcapsules can have an assortment of objectives and applications, whether for drug delivery, enzyme retrieval, artificial cell and artificial tissue delivery, and delivery of microorganisms. This paper provides an up-to-date review of microencapsulation of cells and its latest developments in treatment of various diseases. Specifically, this paper comprehensively discusses the use of microencapsulated microorganisms in renal diseases, cardiovascular diseases, colorectal cancer, inflammatory bowel disease, and others.

Manuscript published on 30 October 2017.
***** Correspondence Author (s)
Divya Sanganabhatla*, Research Scholar, University College of Technology, Osmania University, Hyderabad (Telangana), India. E-mail: divya.dharba@gmail.com

Microencapsulation for mammalian cells is described for diabetes, hepatic diseases,
Parathyroid insufficiency, anemia, cancer, and neurodegenerative diseases.

II. MICROENCAPSULATED MICRO ORGANISM

Microencapsulation has been widely used for the encapsulation and immobilization of microorganisms [2]. Bacterial cell encapsulation is a process that can occur naturally as bacteria proliferate and produce exopolysaccharides, high-molecular-weight polymers composed of sugar residues. The exopolysaccharide structure can act as a protective capsule and reduce the permeability and bacterial exposure to potential adverse environmental factors. Early research used microencapsulation for the immobilization of bacterial cells in the food and dairy industry, as discussed in other reviews [3]. In recent years, the microencapsulation of probiotic cells, “live microorganisms, which, when administered in adequate amounts, confer a health benefit on the host,” has gained interest for the treatment of a number of gastrointestinal and other health disorders [4]. However, orally delivered probiotic cells must be delivered and remain viable through the harsh conditions of the upper GIT. Hence, microencapsulation can be used as a protection for the delivery of the cells. Research focused on microencapsulation of probiotics has proven successful in the contexts of renal failure, cardiovascular diseases, and in colon disorders, as described later.

A. Microencapsulated Microbes In Renal Failure

Early research in the field of microencapsulated microorganisms was undertaken, by Prakash and Chang, using a genetically modified Escherichia coli strain (DH5) containing a urease gene from Klebsiella aerogenes [5]. The encapsulation was performed by gelation of alginate in calcium chloride, followed by coating steps with polylysine and alginate, to give rise to alginate-polylysine-alginate (APA) microcapsules containing E. coli cells. When administered orally to uremic rats, the encapsulated E. coli successfully lowered the levels of plasma urea and ammonia back to normal levels, as well as modulating many markers of renal failure [6]. This was the first report that recorded the use of polymeric membrane artificial cells for the oral delivery of genetically engineered organisms. This research also highlighted microencapsulation as a method to isolate the delivered microorganisms through the GIT transit until excretion, eliminating safety issues associated with the delivery of microorganisms. Research was also undertaken, in vitro, with the same E.

Coli but using polyvinyl alcohol microcapsules which have a significantly higher mechanical strength than APA microcapsules [7]. Supplemental research was also performed with Lactobacillus delbrueckii capable of removing urea, to respond to concerns of toxicity associated with the use of the genetically engineered E. coli strain [8].

Research by Prakash et al. provided the first research investigating the use of microencapsulated yeast cells, Saccharomyces cerevisiae, in renal failure [9]. The research group investigated the oral administration of live yeast cells in APA microcapsules in a renal failure uremic rat model. The study demonstrated that the microencapsulated yeast cells were retained in the microcapsules through the GIT transit but allowed urea to diffuse through the semipermeable membrane of the microcapsule and were acted upon by yeast urease More importantly, a significant 18% decrease was noted for the urea levels during the 8-week treatment period, demonstrating the efficacy of the formulation as a therapeutic for eliminating the elevated levels of metabolites present in renal failure.

B. Microencapsulated Microbes In Hypercholesterolemia And Cardiovascular Diseases

Microencapsulation of bacterial cells has recently gained interest for the treatment and prevention of hypercholesterolemia. Early work by Garofalo et al. investigated the use of Pseudomonas pictorummicroencapsulated with alginate-polylysine and open pore agar [11]. Microencapsulated P. pictorum was shown to have significant cholesterol depletion activity, with the highest activity by the open pore agar microcapsule formulation. Continuing the same type of work, Jones et al. investigated APA microencapsulated genetically modified bile-salt-hydrolase (BSH-) active Lactobacillus plantarum 80 (pCBH1) for its capability to break down and remove bile acids [12]. This research established the use of BSH-active microencapsulated organisms for lowering blood serum cholesterol. Following this work, Martoni et al. demonstrated that APA microencapsulated naturally BSH-active Lactobacillus reuteri can be successfully delivered to the colon and remain enzymatically active, using a simulated human gastrointestinal model [13]. This probiotic formulation can contribute to a significant cholesterol-lowering effect in cardiovascular diseases, by contributing to the deconjugation of bile salts in the intestine. Further research by Jones et al. demonstrated the use of APA microencapsulated BSH-active L. reuteri in a human clinical study, administered as a yogurt formulation [14]. The formulation was shown to reduce low-density lipoprotein (LDL) cholesterol, total cholesterol, apolipoprotein B-100 (apoB-100), and non-high-density lipoprotein (HDL) cholesterol in hypercholesterolemic patients more efficiently than traditional probiotic therapy and other cholesterol-lowering ingredients.

Research by Bhathena et al. also investigated the use of APA microencapsulated bacteria, specifically feruloyl esterase (FAE) active L. fermentum, to lower triglyceride and cholesterol levels, major risk factors for coronary artery disease. Research was undertaken with regard to the viability and enzymatic activity of microencapsulated FAE-active L. fermentum under simulated gastrointestinal conditions [15].It was demonstrated that, following gastrointestinal exposure, there was a significant 2.5 log difference in viability between the free and microencapsulated L. fermentum cells [16]. The presence of a higher probiotic viability and FAE activity resulted in significant reductions in serum total cholesterol, LDL cholesterol and serum triglyceride levels in diet-induced hypercholesterolemic hamsters. Similar studies were also performed with microencapsulated L. fermentum for the treatment and prevention of metabolic syndrome [17].

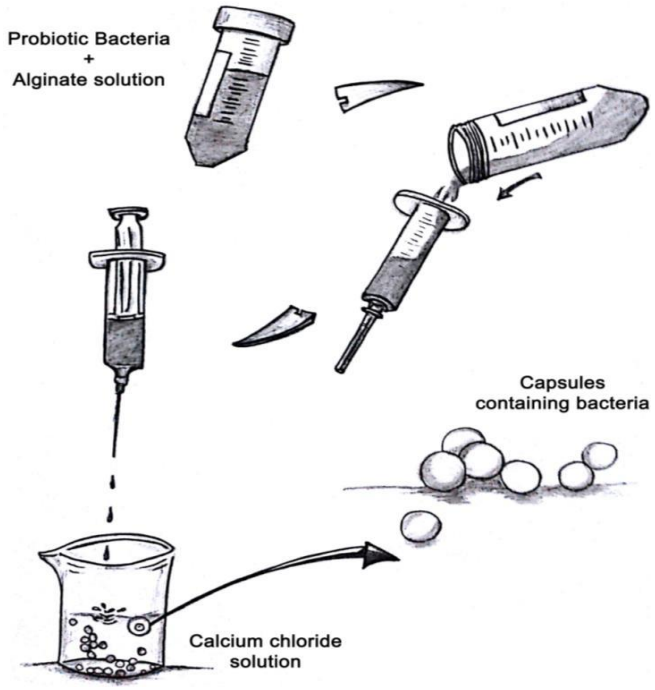

Fig 1: Microencapsulated Bacteria for Treatment of Various Diseases

C. Microencapsulated Lactobacilli In Colon Diseases

Microencapsulated microbes have also gained interest for the modulation of colonic inflammation, specifically with regard to colon cancer, but potentially for other colonic inflammatory disorders, such as inflammatory bowel syndrome (IBS) and inflammatory bowel disease (IBD). Urbanska et al. investigated the antitumorigenic properties of APA microencapsulated Lactobacillus acidophilus in Min (multiple intestinal neoplasia) mice that carry a germline Apc mutation which spontaneously develop numerous pretumoric intestinal neoplasms [18]. Administration of the probiotic led to a significant reduction in the number of adenomas and gastrointestinal neoplasias in the treated animals, suggesting that the microencapsulated bacteria could have a role in the development of a successful colon cancer therapeutic. Further research investigated the ability of APA microencapsulated L. acidophilus to suppress intestinal inflammation in mice, for potential applications in chronic inflammatory gut diseases such as IBS and IBD [19]. The administration of the microencapsulated formulation led to significant lowering of proinflammatory cytokine levels.

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Markers linked to colonic epithelial cell survival were also increased by the microencapsulated L. acidophilus formulation .Previously mentioned studies, with regard to FAE-active microencapsulated microbes, have shown significant antioxidant properties, which could also prove beneficial for colon inflammatory disorders [20,21]. Research into microencapsulated microorganisms is demonstrating great potential for the treatment and prevention of a number of health disorders, and they are summarized in Table 1.

Table 1: Microencapsulated Microorganism Formulations for Therapeutic Applications.

Disease condition	Microcapsule type	Encapsulated cells type	Delivery method and models
Renal diseases	Polyvinyl alcohol	E. coli DH5	In vitro
	APA	Saccharomyces cerevisiae	Rat intragastric gavage
	Alginate chitosan alginate	E. coli DH5	In vitro
	APA	Lactobacillus fermentum	Hamster intragastric gavage
Cardiovascular diseases	APA	Bifidobacterium longum	In vitro
	APA	Lactobacillus reuteri	In vitro
	APA	Lactobacillus reuteri	Human, incorporated in yogurt
Colorectal cancer	APA	Lactobacillus acidophilus	Mouse intragastric gavage
	Alginate-chitosan	Lactobacillus acidophilus	In vitro
Inflammatory bowel syndrome/ inflammatory bowel disease	APA	Lactobacillus acidophilus	Mouse intragastric gavage
Others	Gelatin	Bifidobacterium bifidum	Rat intragastric gavage
	Reconstituted skim milk with prebiotics	Bifidobacterium BB-12	In vitro

III. MICROENCAPSULATED MAMMALIAN CELL

Regenerative medicine is a field focused on the replacement of lost tissue and organs. The delivery of mammalian cells has been proposed to promote the regeneration of organs such as the liver, pancreas, heart, and kidney. Unfortunately, the in vivo delivery of mammalian cells raises a number of challenges. These include (1) immune rejection by the host, (2) a loss in cell survival due to aggregation and impaired nutrition, (3) impaired cellular function due to inadequate gene expression, (4) a requirement for a large amount of readily available cells, and (5) a shortage of human cell donors [22,23]. Due to a shortage of human donors, research has turned to nonhuman mammalian cells, but the aforementioned impediments of immune rejection, impaired cellular function, and readily available cells remain present.

Microencapsulated cells can provide an alternative approach to resolve the aforementioned obstacles. One of the earliest works in this field was by Bisceglie, in the 1930s, who demonstrated the use of a polymer membrane to encase mouse tumour cells [24].These were injected in a pig's abdominal cavity and were shown to successfully survive attacks by the host immune system [25]. Since then, a lot of research has been undertaken in this field. This section presents a synopsis of the most significant research with regard to microencapsulation in cell-based therapies, focusing on the applications of diabetes and hepatic disease.

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A. Microencapsulated Pancreatic Cells To Treat Diabetes

Type 1 diabetes is a growing concern, with an escalating rate of disease prevalence. With the present lack of a successful therapeutic the delivery of insulin secreting pancreatic islet cells (PICs) has proven promising for the treatment of type 1 diabetes [26]. Unfortunately, the routine use of immunosuppressive drugs to prevent the rejection of implanted PIC predisposes patients to infections and increases the risk of cancer development in the late posttransplant period [27,28]. Microencapsulation can act as a barrier, shielding the delivered pancreatic cells from the host's defences, eliminating the need for immunosuppressive drugs. The first study evaluating the morphology and function of encapsulated islet cells was performed by Lim and Sun in 1980 [29]. This research demonstrated that islet cells remained intact morphologically and functionally for 4 months, in vitro. The encapsulated cells were shown to secrete insulin when stimulated with glucose. Further investigations by Lim and Sun involved the intraperitoneal transplantation of encapsulated islet cells in streptozotocin-induced diabetic Wistar Lewis rats. The transplanted encapsulated islet cells maintained normoglycemia for 3 weeks .The rats transplanted with nonencapsulated cells had normoglycemia for only 6–8 days, demonstrating the potential of microencapsulation for the treatment of type 1 diabetes.

Studies have investigated the use of microencapsulated PICs to maintain normoglycemia in diabetic animal models. Kobayashi et al. investigated the therapeutic advantage of using encapsulated PIC versus free PIC in the diabetes animal model, nonobese diabetic mice [29]. PICs were encapsulated in 5% (w/w) agarose hydrogel and injected directly into the peritoneal cavity and the omental pouch, without any immunosuppressive drug administration The control group was injected with free PICs. Two weeks following transplantation, the control group was diabetic, as confirmed by intraperitoneal glucose tolerance tests and blood glucose levels It is to be noted that the free PICs were no longer viable at this time .On the other hand, encapsulated PICs were able to maintain normal blood glucose levels for over 100 days following transplantation Omer et al. demonstrated similar results with encapsulated porcine neonatal pancreatic cell clusters (NPCCs) capable of differentiating into insulin producing cells when transplanted into streptozotocin-induced diabetic B6AF1 male mice [30]. Microcapsules, containing 1-2 NPCCs, were manufactured using highly purified alginate cross-linked by barium chloride The diabetic mice were intraperitoneally transplanted with 10,000 islet equivalent (IE) encapsulated NPCCs in the test group and the equivalent number of nonencapsulated NPCCs in the control group, with no addition of immunosuppressive therapy. The NPCCs were removed 2, 6 and 20 weeks following transplantation .The control group (nonencapsulated NPCCs) remained hyperglycemic while the test group (encapsulated NPCCs) was normoglycemic until the completion of the trial .The function of the transplanted NPCCs was confirmed by the reoccurrence of hyperglycemia following their removal at weeks 2 and 6 .The functionality of the NPCCs was further demonstrated by an insulin upsurge and an improvement in the ratio of β cell area to total cellular area at week 20, confirming the differentiation of NPCCs into β cells .Like Kobayashi et al., Omer et al. confirmed that microencapsulation successfully provides the encapsulated islet cells with immune protection, without the need for immunosuppression. Moreover, Omer et al. showed the differentiation of NPCCs into insulin producing β cells, providing great therapeutic potential for the treatment of type 1 diabetes.

Clinical studies are few, but research by Tuch et al. investigated the transplantation of barium alginate microcapsules containing human islet cells in four type 1 diabetic patients [31]. This group successfully demonstrated the safety of this method, with little C-peptide detected, normal renal function, little cytokine release, and no major infection detected during the trial .Unfortunately, the research group makes the point that the efficacy of the method needs improvement for the therapy to be used clinically, although a decrease in glycemia was observed .Notably, the retrieval of the microcapsules following 16 weeks demonstrated that the encapsulated cells were no longer viable .

With respect to future human studies, there is a significant shortage of human insulin secreting cells and so the proposal for xenotransplantation. Xenotransplantation brings about concerns of host immune rejection, an obstacle that microencapsulation could potentially overcome. Abalovich et al. performed a preclinical study investigating the potential of encapsulated pig islet cells for xenotransplantation. Type 1 diabetic dogs were transplanted with encapsulated PICs and demonstrated a significant reduction (20%–80%) in insulin necessity after transplantation [32].Moreover, there was an upsurge of plasma insulin following 6–12 months of transplantation, along with a significant decrease in glycosylated hemoglobin. Thus, Abalovich et al. demonstrated that microencapsulation may be used for xenotransplantation of PICs in humans [32]. Elliott et al. evaluated the function of PIC APA microcapsules in a single type 1 diabetic patient [33]. Following the intraperitoneal implantation of 15,000 IE/kg bodyweight, at week 12, insulin requirement levels were decreased by 30%. The recovery of the microcapsules, following 9.5 years indicated that the PICs were still viable and secreting small levels of insulin The research by Elliott et al. demonstrates the potential long-term survival of microencapsulated xenogeneic PIC transplanted without the need for immunosuppression.

The presented research provides optimism for the future of microencapsulated PICs for the treatment of type 1 diabetes. However, there still is a need for continuing research to demonstrate the cell viability, functionality with respect to insulin secretion, and safety associated with the xenotransplantation and allotransplantations of microencapsulated PICs using long-term clinical studies.

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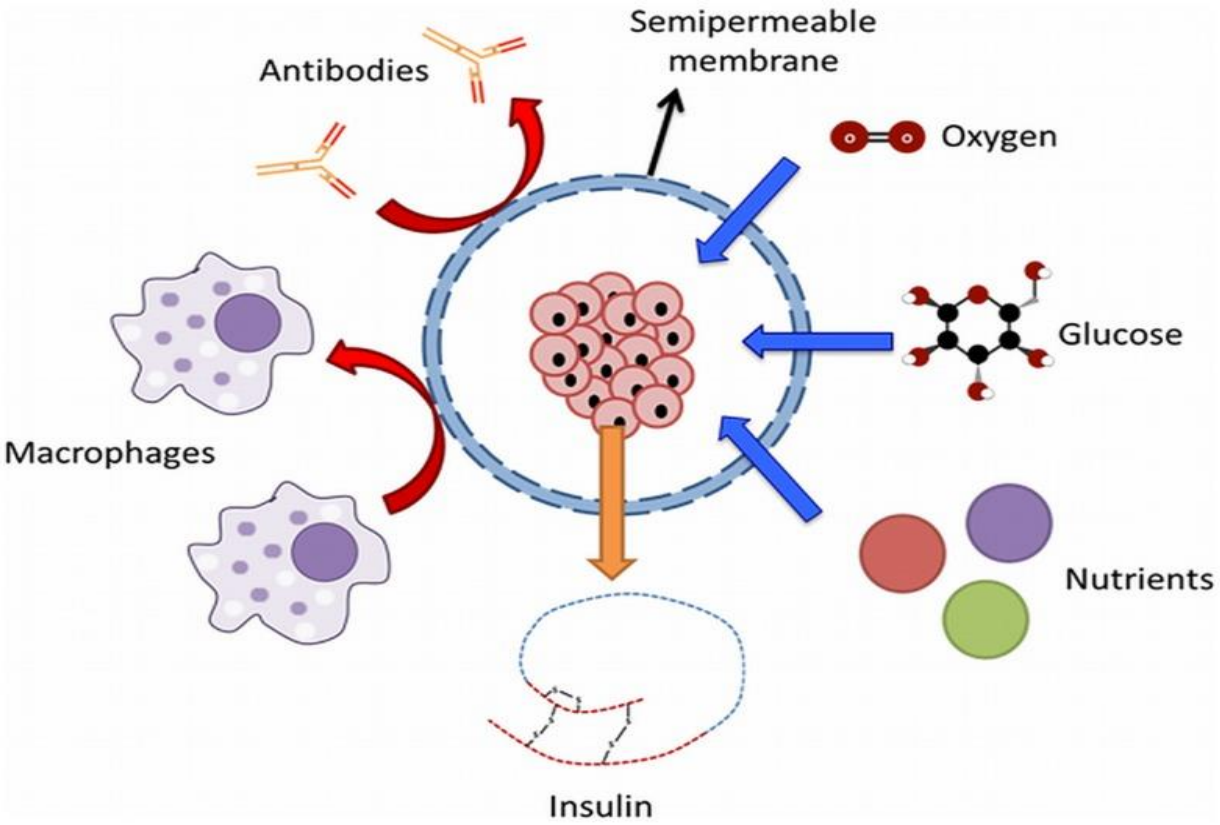

Fig 2: Microencapsulated Pancreatic Cell to Treat Diabetes

B. Microencapsulated Hepatic Cells to Treat Liver Disease

Hepatic diseases, including acute liver failure, chronic liver disease, and congenital metabolic liver disease, require the restoration of liver function [34]. Orthotropic liver transplantation is currently the only effective treatment for end-stage liver disease [35]. However, the shortage of organs, the requirement for immunosuppressive therapy, and the numerous complications associated with liver transplantation limit the overall effectiveness of transplantation [36]. Recent studies have investigated liver cell transplant (LCT) as a potential therapeutic but, for effective LCT transplantation, immunosuppression is still a requirement [37]. Microencapsulation has been proposed as a method to address these shortcomings, with some important research presented here. The first study evaluating the therapeutic potential of microencapsulated hepatocytes was performed by Sun et al. Rat hepatocytes, encased in APA microcapsules, were shown to secrete urea and albumin in vitro, two molecules secreted by the normal healthy liver. The encapsulated hepatocytes were transplanted into normal Wistar rats and rats with galactosamine-induced fulminant hepatic failure and still remained viable following 35 days.

A recent study performed by Teng et al. demonstrated the regeneration of liver cells in BALB/C mice with acute liver failure (ALF) by 70% hepatectomy, using a mixture of microencapsulated rat hepatocytes and human fetal liver stromal cells (FLSCs) supplemented with basal fibroblast growth factor (bFGF) bFGF was added to increase the metabolic activity of hepatocytes and to promote the self-renewal of human embryonic stem cells . The combined treatment of encapsulated rat hepatocytes, FLSCs, and bFGF enhanced the survival rate by over 86% when compared to the controls with a significant increase in liver mass following 72 hours Furthermore, immunohistochemical inspections showed decreased levels of necrotic liver cells with increased levels of proliferating liver cells in the periportal areas This study concluded that a mixture of encapsulated rat hepatocytes and FLSCs supplemented with bFGF improved the survival of mice with ALF, without the requirement for any immunosuppression The encapsulated cells were also protected from any host immunoreactions, demonstrating the potential for encapsulated hepatocyte xenotransplantation.

Table 2: Microencapsulated Mammalian Cell Formulations for Therapeutic Applications.

Disease condition	Microcapsule type	Encapsulated cells type	Delivery method and models
Type 1 diabetes mellitus	Alginate polylysine	Rat PICs	Rat intraperitoneal transplant

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Hepatic disease	APA	Rat hepatocytes	Rat intraperitoneal transplant
Cardiovascular disease	APA	CHO cells	Rat intramyocardial injection
Parathyroid insufficiency	Barium alginate	Human parathyroid tissue	Human forearm and leg transplant
Anemia	Polyether-sulfone	Mouse myoblast cells	Mouse dorsal flank transplant
Cancer	Alginate-polylysine	Human genetically engineered fetal kidney cells	Mouse subcutaneous flank injection
Neurodegenerative diseases	APA	Baby hamster kidney cells	Mouse cerebral cortex implantation
	Alginate	Neonatal porcine choroid plexus cells	Rat intracranial transplantation

IV. CONCLUSION

Microencapsulation has been applied in a wide variety of products from different areas, and studies have shown an enormous potential to provide the core with advantageous features,. In overall the live drug delivery system offers a safe and manufacturable method for systemic delivery of biologically active products from genetically engineered cells. As long as cells are viable and functional they are able to release desired product in more physiological manner. The technological approach associated woth emergence of reliable cell sources for delivery of protein offers new perspectives in cell therapy approaches of various diseases. Thus, immune isolated cell transplantation holds promise for controlled and sustained delivery of recombinant proteins. However, much effort through research and development is still needed to identify and develop new wall materials and to improve and optimize the existing methods of encapsulation for the better use of microencapsulation and its potential applications.

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