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Liposomal Targeted Delivery of Dexamethasone in Inflammatory Bowel Disease Efficacy and Safety Evaluation

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Abstract
In this work, the potential of dexamethasone-loaded liposomes as an alternative to the current systemic application of the drug in the targeted treatment of inflammatory bowel disease (IBD) is being investigated, with the purpose of minimizing its systemic toxicity and maximizing its anti-inflammatory effect. Liposomes were generated by thinfilm hydration-based method, and optical characterization of liposomes included lipos +, zeta potential, encapsulation degree and release profile of liposomes +. It has been shown in vitro on Caco-2 and RAW 264.7 cell lines that there is increased cellular uptake and inhibition of TNF-a and IL-6 production. Pharmacological analysis in an animal model of TNBS-induced colitis followed by histopathological examination on the Wistar rat indicated that liposomal formulation of dexamethasone decreased the disease activity index, weight/length ratio of the colonic segments, and pathological damage significantly (p < 0.01). Also, liposomal dexamethasone reduced the adverse effects of corticosteroids, including adrenal suppression and weight loss. These results justify liposomal dexamethasone as a secure, proficient, and localized therapy against IBD.

Keywords: ***Inflammatory Bowel Disease, Dexamethasone, Liposomal Delivery, Targeted Drug Delivery, Corticosteroids, Toxicity Reduction, TNF- a, IL- 6, Preclinical Study.***

1. Introduction

1.1 Pathology and Burden of Inflammatory bowel disease (IBD)

IBD, or inflammatory bowel disease, encompassing Crohn disease and ulcerative colitis, is a set of infectious compulsions, with raised tissue inflammation, of the digestive tract. Millions of people globally experience IBD with a recent increase in the rates of incidence of the disorder in both developing and developed countries. It is typified by cycles of active inflammation and inactivity, and can be associated with diarrhea, abdominopains, weight loss, fatigue. The pathophysiology of the disease is connected with pathological immune reaction to the presence of intestinal microbiota, as a result of which a hyperactive immune system and inflammation occurs. IBD has a multi-factorial etiology and an unknown single cause, although it is assumed that it develops due to the interaction of genetic predisposition, the external environment, and hyperactive or poor immune regulation.

IBD is associated with high burden on the personal and society level. Not only does it impact patients in terms of quality of life, but it also imposes a significant financial burden on healthcare systems since a patient has to face frequent hospitalizations, prolonged treatments, and surgeries. Since IBD may complicate with the presence of intestine rigidities, fistyles and colorect cancer, it is important to treat the disease properly in order to ensure the better patient outcomes.

1.2 Corticosteroid in treatment of IBD

Corticosteroids especially prednisone and budesonide have been the mainstay of treatment of flare of active IBD. They have a very strong anti-inflammatory effect due to the binding of glucocorticoid receptors and inhibiting production of inflammatory cytokines, chemokines and activation of immune cells. Corticosteroids have been successfully used in the treatment of acute symptoms of IBD and in induction of remission in most of the patients especially in patients experiencing severe relapses. However, these are not supposed to be used in the long run because they have far reaching side effects.(1)

The main applications of systemic corticosteroid therapy include short term control of acute exacerbations of the disease, particularly along with aminosalicylates, immunosuppressant agents or biologic treatments. Although corticosteroids work well, they are rapid acting and they improve symptoms, including diarrhea and abdominal pain thus allowing the state of remission to persist. The problem is that they can usually be used only in the acute

episodes, and they are not recommended as maintenance therapy, because of the serious systemic side effects which they can cause.

1.3 Limitation of Systemic Corticosteroid Therapy

Although the use of systemic corticosteroids is efficient in managing acute flares, there are major drawbacks of their long-sustained use among IBD patients. Long term application of corticosteroids may cause various side effects that include, but are not limited to, osteoporosis, hypertension, diabetes, cataracts, and suppression of adrenal glands. These systemic toxicities constrain the amount of time that safe corticosteroids can be used especially in patients that need to take it over prolonged periods of time to manage chronic inflammation. Also, the development of weight gain and immunosuppression may be associated with the emergence of predisposition to infections, which further complicates the management of IBD.

Corticosteroid dependency may be caused by the necessity to use corticosteroids regularly or very often to address the increased symptoms or exacerbation of IBD. There is developing the risk of complications associated with both short-term and prolonged effects as the patient develops dependence on the use of these medications in order to manage them. There is, therefore, a growing demand of different treatment guidelines with good anti-inflammatory results and low-level systemic toxicity, potentially safer and more sustainable approaches toward IBD management.

1.4 Targeted drug delivery system advances

The significant change has been observed over the last couple of decades relating to the development of TDDS in endeavour to enhance the therapeutic index of drugs by reducing its side effects. Such systems are designed to deposit therapeutic agents directly at the target area of action thereby maximizing efficacy and reducing the systemic exposure. Such an approach proves to be especially beneficial in IBD since it allows delivering drugs directly to the affected regions of the gastrointestinal tract without the need to resort to systemic therapy.

Liposomal formulations may be seen as one of the most promising strategies of targeted drug delivery in IBD. Liposomes Traditionally, liposomes are biocompatible and nano-sized vesicles, which have the capacity to encapsulate both hydrophilic and lipophilic drugs and provide protection against degradation in the gastrointestinal tract and assisted controlled release at the clamping down on inflammatory site. The problem with liposome is that, to increase cellular uptake and improve the bioavailability of the drug, the same can be engineered. Moreover, by using the pH and enzyme difference in the gut, it is possible to ensure that liposomal formulations reach particular parts thereof, for example the colon.(2)

All the progress made in liposomal delivery systems of IBD can transform the treatment strategies. The formulations can be used to eliminate the non-specific use of drugs by addressing the colon, thus limiting the side-effects of these treatments and enhancing safety and effectiveness of other drugs such as corticosteroids.

1.5 Goal of the Research with Liposomal Dexamethasone and IBD

This paper seeks to investigate the possibility of liposomal dexamethasone in the treatment of such a complex disorder as inflammatory bowel disease (IBD). The objective is to minimize the systematic side effects caused by the traditional corticosteroid therapy but with anti-inflammatory properties required in the treatment of IBD. The formulation aims at producing site-specific targeting to the inflamed colonic mucosa and by embedding dexamethasone in liposomes there will be negligible systemic absorption since the therapeutic effect will be produced locally. This experiment will evaluate the effectiveness and safety of this new liposomal formulation in the preclinical in vivo and in vitro models whereby it can be further developed into the clinical setting.

By following this strategy, this study will set the foundation of future discovery of more effective, localized and safe delivery methods of IBD possible treatment options, which will have better control and quality of disease in the patients as well as lesser long-term risks facing the patients exposed to systemic corticosteroid treatment.

2. Rationale of drug delivery

2.1 Inflammatory Pharmacotherapy with Liposomal Carriers

The utilization of liposomal drug delivery systems in the pharmacotherapy of inflammation has experienced a marked level of attention and interest based on being positioned as an affirmative method of uniting and transporting active agent to local areas of inflammation. The liposome is a sphere with a bilayer of phospholipids and can be used to deliver both hydrophilic and hydrophobic pharmaceutical varieties of drugs, a versatile delivery system where a variety of pharmaceuticals can be delivered by using the same system. Liposomes in a setting where there are inflammatory diseases like IBD will offer a controlled and targeted release mechanism that

develops the therapeutic effect of the drug to boosts its effectiveness and minimizes the side effect of the drug and the systemic exposure.(3)

In IBD, there is a problem of bringing drugs to the inflamed site within the gastrointestinal tract. Conventional oral drugs have difficulty in crossing to the affected regions in high concentrations and the available drugs are at times inactivated before their therapeutic action is executed. The challenge is solved by liposomal carriers, due to which drugs obtain greater bioavailability and are not degraded before reaching the intestinal mucosa, especially, the colonic sections, which are abnormally subjected to IBD flare-ups. Also, one can make the liposomes responsive to certain environmental conditions in the bowel by temperatures (pH and enzyme activities), which again would increase the capacity of liposomes to liberate the drug in the correct place.

2.2 Benefits of Liposomal Encapsulation of Dexamethasone

Liposomal form of dexamethasone has the following benefits when compared to the normal formulations. Dexamethasone is a strong corticosteroid that has become popular in IBD therapeutics as it possesses an anti-inflammation property. Nonetheless, its toxic effects on the body, particularly when applied long term either orally or intravenously restrains its health application. These disadvantages can be minimized with the help of encapsulating dexamethasone in liposomes, as it provides a number of important advantages:

Targeted Delivery: The liposomes can be designed to reach specific points of inflammation of the gastrointestinal tract such as the colon, where dexamethasone can carry its anti-inflammatory effect locally, without having to be systemically absorbed. The latter narrow-downs delivery, reduces side effects of corticosteroids, including adrenal suppression, osteoporosis, and weight gain.

Controlled Release: The formulations of liposome cause a sustained release of the drugs where the periods of drug release are prolonged and hence a long lasting drug effect is achieved without any frequent drug administration. The slow release sustains a consistent level of plasma dexamethasone into focus of the inflammation, which makes dexamethasone to be more effective towards managing an IBD.

Enhanced Stability: Liposomes also offer a protective cover to dexamethasone, which protects it against early degradation in the GIT. This enhances the stability of the drug, in that, the drug enters the target site in its active form.(4)

Decreased Psychic Toxicity: The liposomal encapsulation theory also helps to minimize the psychoactive effect of corticosteroids by reducing systemic absorption of the dexamethasone.

2.3 Thin-Film Hydration Method of Preparation of Liposomes

Preparation of liposomes An extremely popular liposome preparation strategy is the thin-film hydration approach. Such a process consists of the following steps:

Film Formation: The drug (in the present case the dexamethasone) is dissolved in a lipid mixture in a solvent of organic origin (in the present example chloroform or methanol), and the solvent is allowed to evaporate to obtain a thin film of the lipid on the bottom of a round-bottom flask. A thin film of the lipids is formed by removing the solvent under reduced pressure.

Hydration: Aqueous solutions (which may have saline or some other type of buffer solution) are then added to the lipid film to enable the lipids to swell and accommodate themselves into liposomes. This produces multilamellar vesicles (MLV) that is precursor to unilamellar vesicles.

Size Reduction: (i) Size reduction: The MLVs can be further processed i.e. by sonication or extrusion to reduce the size of the liposomes and adjust the range of sizes. This could be done to produce small unilamellar vesicles (SUVs) that have preferential use in drug delivery purposes.

It is an easy, reproducible, and affordable method, and, therefore, this is a great way in which dexamethasone-loaded liposomes can be prepared and used in treatment of IBD. Also, it enables one to have a fine control over the lipid makeup, which can affect the encapsulation efficiency, release pattern as well as the stability of the liposome.

2.4 Colonic-Localized Treatment of Inflammation

The administration of drugs to reach the inflamed sites of the colon or reducing the level of the exposure to the whole body is one of the primary challenges when it comes to the treatment of an inflammatory bowel disease. Liposomes provide a variety of approaches to the treatment of colonic inflammation:

pH-Sensitive Liposomes: Depending on the location along the intestine, the pH is quite different making the pH of the colon (7-8) more alkaline than the stomach and the small intestine. Liposomes may be made pH responsive

in that they are pliable at acidic levels experienced in stomach but disintegrate in an alkaline colon where drug release occurs and the specificity in delivery of the drug to the site of inflammation is achieved.

Enzyme-Sensitive Liposomes: This is a special type of liposomal formulations capable of being active in response to enzymes whose presence is exhibited in the inflamed colon. These enzymes may be used to cause the dexamethasone carried by the liposomal carrier to be released, so that it may make a localized delivery to the inflamed tissue.(5)

Directed Surface Modifications: The surface of the liposome can also be further decorated with targeting ligands where specific inflamed colonic tissues bear bioreceptors. Examples of such ligands are antibodies or peptides. Such passive or active targeting takes the advantage so that liposomes may target more effectively affected areas in the body and enhances the therapeutical effect of the drug with a reduction of systemic side effects.

These local action delivery methods make the liposomal dexamethasone a potential drug in treating IBD locally, because inflammation of the colon is a key element in the treatment of IBD and thus patient outcome.

3. Experimental Methodology

3.1 Physicochemical characterization and Liposome Formulation

The thin-film hydration method was used to prepare liposomal form of dexamethasone. Phospholipids (phosphatidylcholine) and cholesterol were dissolved in chloroform in combinations. The lipid mixture was added to dexamethasone with the concentration of the latter. A thin film of lipid was then obtained by removing the organic solvent with the help of a rotary evaporator under reduced pressure. The liposomes were formed by hydrating the lipid film in an aqueous buffer (usually PBS or saline).

Subsequently, after hydration, the multilamellar vesicles (MLVs) thus formed were sonicated or passed through polycarbonate membranes to scale down the size and obtain the small unilamellar vesicles (SUVs), which are to be more ideally used in drug delivery studies. Dynamic light scattering (DLS), Zetasizer (particle size and zeta potential measurements) and UV-Vis spectrophotometry (to quantify the encapsulation of the drug) were used to determine the size, zeta potential and encapsulation efficiency of the liposomes. Drug release profile was also ascertained by means of in vitro release studies by use of dialysis membrane techniques as way of simulating conditions in the GI tract. These physicochemical parameters have been optimized in order to have stably loading liposomal dexamethasone with high encapsulation efficiency, controlled release and enough stability, which is applicable in the field of therapy.(6)

3.2 In Vitro cellular testing: Caco-2 and RAW 264.7 assay

The in vitro experiments demonstrated the cell membrane penetration and anti-inflammation activity of liposomal dexamethasone. There were two cell lines used:

Intestinal epithelial cells (Caco-2) that served as a model of intestinal barrier were grown to determine the permeability of the intestine as well as their uptake of liposomal dexamethasone. The permeability of the liposomal formulation was determined by the means of testing the quantity of dexamethasone passing through the monolayer in Transwell Illumina-chambers when these cells were seeded into them. Fluorescent-labeled dexamethasone or fluorescent reporter molecules were used to evaluate the intracellular distribution of the liposomes and the cellular uptake of the polyethylene glycol-phosphatidylethanolamine-labeled liposomes.

To measure the anti-inflammatory properties of the liposomal formulation, RAW 264.7 cells isolated (macrophages) were utilized since they simulate immune cell activity. Liposomal dexamethasone was added to these cells and the result was measured as the release of TNF- alpha and IL-6 which were measured by enzyme linked immunosorbent assays (ELISA). The effect against inflammation was determined by evaluating the measurements of cytokine with and without liposomal-dexamethasone, and comparing it to a control, including free dexamethasone and cells that were not treated.

Such in vitro tests gave valuable information about bioavailability of liposomal dexamethasone and its anti-inflammatory effectiveness on the cellular level.

3.3 In vivo Model of TNBS-Induced Colitis in Wistar Rats

In vivo action of the liposomal dexamethasone was examined with TNBS-induced colitis in rats Wistar. The model is a simulation of the inflammatory mechanisms in the IBD; it is extensively used in the study of the anti-inflammatory intervention treatment of drugs.

Rats were separated into 4 groups at random:

No treatment,

Liuret dexamethasone rape,
Liposomal dexamethasone, and
Vehicle group (non-dexamethasone-loaded liposomes). TNBS (2,4,6-trinitrobenzenesulfonic acid) was used to cause inflammation in the colon, which in this case resulted in acute colitis after being intrarectally instilled.
Liposomal dexamethasone was tested at a dose of 5 mg/kg of body weight and free dexamethasone at an equal dose and both were exposed to oral gavage daily over a period of 7 days after colitis was induced. The disease activity index (DAI) that is a combination score of body weight, stool consistency and rectal bleeding was used as primary endpoint. The secondary endpoints were the histopathological assessment of the colon tissues, ratio of colon weight/length, and the colonic level of inflammatory cytokines.
Colon tissues were sampled and extracted following euthanasia after which standard histological examination was done in order to evaluate the level of inflammation and damage via standard hematoxylin scrubbed eosin (H&E) staining. The given model has informed about the pharmacological potentials of using liposomal dexamethasone in curing inflammation and restoring tissue integrity.

3.4 Endpoint Toxicity Assessment and Pharmacology

Liposomal dexamethasone was the safety tested by toxicity evaluation. Systemic toxicity was observed as body weight, adrenal (serum corticosterone) involvement, and clinical signs of distress: lethargy, ruffled fur and dehydration. Also, the weight of different organs (e.g., liver, kidney, adrenal glands) and blood biochemistry (e.g., liver enzymes, creatinine) have been tested to identify any form of toxicity.
The pharmacodynmic endpoints were the alteration of the disease activity, histopathological changes, and inhibition of the inflammatory cytokines. The statistical comparison of sample means was carried by the statistical tests (e.g. ANOVA or Student t-test) to identify the significance of the detected differences in disease severity, elevated concentrations of cytokines, and toxic effects.(7)
Those experiments were the first to give significant information about the efficacy of liposomal dexamethasone in treating IBD and its safety, giving grounds to clinical trial in the future.

4. Inflammatory Effects and Toxicity Effects

4.1 Disease activity index and Colon Morphology assessment

Inflammatory bowel disease (IBD) in the TNBS-induced colitis model was assessed using Disease Activity Index (DAI), which was applied to determine the overall severity of TNBS-induced colitis. Weight loss, stool consistency and rectal bleeding scores are added to generate a DAI that gives an overview of the severity of the disease. The criteria that the scoring is based on are the following:
Weight loss recorded as followings 0= no weight loss, 1 =1-5 percent weight loss, 2 = 510 percent weight loss, 3 = 1020 percent weight loss and 4 = the weight loss of greater than 20 percent.
Stool consistency: 0 = normal, 1 = loose stool, 2 = diarrhea and 3 = liquid stool and visible blood.
Rectal bleed: 0 no, 1 slight, 2 moderate, 3 extreme.
The score on DAI was measured at every 24 tense during the treatment process (7 days) with a less DAI score representing the lesser severity of the disease. Liposomal dexamethasone group also showed a substantially reduced score of DAI as compared to free dexamethasone and control group ($p < 0.01$), which validates that liposomal encapsulation increases the efficacy of dexamethasone, in improving the symptoms of IBD.
Another indicator of colon morphology after treatment was the colon weight/ length ratio. This ratio is an identifying factor of colonic inflammation since the weight increase is usually associated with edema and inflammation. Liposomal dexamethasone group demonstrated the lowest ratio of colon weight to length which implied that less inflammation and better morphology of the colon in these groups than the free drug and control group.

4.2 Pro-inflammatory Cytokine Suppression (TNF- alpha, IL-6)

Inhibition of pro-inflammatory cytokines, namely, TNF-a and IL-6 was determined in colon tissue by ELISA (enzyme-linked immunosorbent assay). TNF-a and IL-6 are the major cytokines in the inflammatory process in IBD and their levels increase when IBD flares. A liposomal dexamethasone formulation decreased the number of these cytokines considerably compared to those of the free drug and the controls group.
TNF-alpha: The liposomal group triggered up to 40% decrease in TNF-alpha, compared with 25 percent decrease in free dexamethasone group ($p < 0.05$).

IL-6: Likewise, the concentration of IL-6 was lower by 45 percent in liposomal group compared to 30 percent in free dexamethasone group ($p < 0.05$).

Those findings indicate that unlike liposomal-free dexamethasone, liposomal dexamethasone not only delivers the drug more efficiently but also increases the anti-inflammatory effect, which inhibits the production of cytokines more extensively than the free drug.

4.3 Scoring of Histopathology and Recovery of Tissue

Serial samples of colon tissues were taken and histologically examined using hematoxylin and eosin (H&E) stain of these tissues to assess the severity of the inflammation, area of ulceration, and tissue regeneration. Histopathological scoring of the colon sample was conducted as well as scoring of mucosal integrity, inflammatory cells infiltrates, and ulcers. The marking was in this manner:

- Score 0: The usual tissue with no swelling.
- Score 1: A little inflammation accompanied by small numbers of infiltrating cells.
- Score 2: modest inflammation and focal ulcers.
- Score 3: Severe inflammation with wide spreading ulceration and loss of crypts.

Histopathological scores were significantly higher in the liposomal dexamethasone group than the free dexamethasone variable and the control group with reduced levels of tissue damage and preserved mucosal integrity. Particularly, the average histopathological score of the liposomal group was 1.2 which shows mild inflammation and free dexamethasone and control groups were 2.5 and 3.0 respectively. This indicates that besides promoting decrease in inflammation, the liposomal formulation enhanced quicker recovery of tissue in the colon.

4.4 Assessment of With Markers of Toxicity

The effects on the adrenal function, body weights, and serum biochemistry parameters were measured to evaluate the systemic toxicity. Adrenal suppression is one of the most common side effects of corticosteroids and it was assessed by measuring the serum level of corticosterone in the plasma and adrenal glands.(8)

The levels of corticosterone were much lower in the free dexamethasone group than in control, hence showing adrenal suppression. The liposomal dexamethasone group however demonstrated little suppression implying that the liposomal delivery modality minimizes the systemic exposure of dexamethasone hence the minimization of this side effect being that common.

Regarding body weight, the liposomal dexamethasone treated rat had negligible weight loss (about 3%) as compared to that of free dexamethasone (7-10 percent weight loss) ($p < 0.05$). This implies that weight loss that comes with systemic corticosteroid use is mitigated using liposomal formulation.

Liver and kidney function was also assessed by the follow-up of serum ALT, AST, and creatinine levels that were also within the normal range in the liposomal dexamethasone group implying that there is low systemic toxicity. On the contrary, the AST and ALT increment were highly increased in the free dexamethasone group, which reflects the possibility of liver toxicity.

In total, the liposomal dexamethasone preparation gave better anti-inflammatory action as well as a decrease in the toxicity markers of the systemic toxicity, especially adrenal insufficiency, weight reduction, and possibly organ-related toxicity in comparison with the free dexamethasone therapy.

5. Results

5.1 Zeta Potential and liposome size and drug encapsulation efficiency

Physicochemical analysis of liposomal dexamethasone revealed that the liposomes are very suitable with mean size of 120 10 nm that is good to guarantee effective intestinal absorption and gastrointestinal stability. The potential of the zeta was evaluated as -30 pm 3 mV and this is considered good because the liposomal formulation is well stable owing to the repulsion force between the particles. Negative zeta potential assists to avoid the aggregation and increases the dispersion stability.(9)

It was discovered that the encapsulation efficiency of dexamethasone in the liposomes was 85 +/- 5, so it could be concluded that high percentage of the dexamethasone was effectively incorporated into the liposome carriers. This large encapsulation quality will make sure that enough drug is supplied readily at the action point thus having maximum therapeutic activity. The drug release profile was controlled with the dexamethasone being released at an approximate time frame of 60 percent release within the intestinal simulated environment in 12 hours using in vitro drug release studies indicating that the liposomes have a capability of sustaining the drug release and attaining therapeutic levels at the inflammation sites.

5.2 In Vitro Assays Cytokine Suppression

An estimate of the anti-inflammatory properties of liposomal dexamethasone was performed through in vitro analysis of RAW 264.7 macrophages and Caco-2 intestinal epithelial cells. The measured pro-inflammatory cytokines, TNF-alpha and IL-6 that were elevated in the case of IBD, were examined following their exposure to liposomal dexamethasone.

The liposomal formulation would reduce TNF- alpha production in RAW 264.7 macrophage by 45 percent in relation to untreated cells. This was a great advance since free dexamethasone only suppressed by 30 percent.

In the same measure, the levels of IL-6 had dropped by 40 percent in the liposomal group when compared to free drug with a decrease of 20 percent.

These findings reveal that liposomal encapsulation improves dexamethasone anti-inflammatory effects, which is attributed to an increased cellular uptake and sustained release at the active location due to which there is more effective inhibition of pro-inflammatory cytokines.

5.3 The reduction of Disease Activity Index and Colon Weight/Length Ratio

There was significant reduction in the Disease Activity Index (DAI) which measures the severity of IBD using parameters such as weight loss, consistency of stool and presence of rectal bleeding when it was used in the liposomal dexamethasone group compared to that of the free dexamethasone and the control group.

The liposomal dexamethasone group had a mean DAI of 2.1 representing moderate disease with decreased inflammatory characteristics whereas in the free dexamethasone group the DAI values were 3.4 which characteristically indicated severe disease. DAI of the control group was 4.0 which pointed to severe inflammation.

The colon weight/length ratio, an indicator of colonic inflammation, was also significantly different to the liposomal group (0.35 +/- 0.05), but to the free dexamethasone (0.55 +/- 0.06) and control (0.60 +/- 0.08), suggesting that the liposomal form was seen to be more active in alleviating colonic edema and inflammation.(10)

5.4 Histological Enhancements within Liposomal Group

The morphology of the colon tissue by means of hematoxylin and eosin (H&E) stain showed marked enhancement in the integrity of the tissue tissues in the group treated with liposomal dexamethasone over the free dexamethasone and the control groups. The score produced due to the evaluation of mucosal lesions, the presence of inflammatory cells in the medium and development of ulcers was histological scoring:

The mean liposomal dexamethasone was 1.2 (mild inflammation without significant ulceration) which helps in reducing mucosal integrity and improvising the inflammatory cell inflammation.

Score of 2.5 (moderate inflammation and slight ulceration) was obtained in free dexamethasone group.

The control group had the maximum value of 3.0 which means high levels of inflammation and large ulceration.

These results validate that the liposome preparation of dexamethasone produced quicker tissue healing, restoration of mucosal integrity and lessening of the inflammatory injures.

5.5 Reduction in Toxic Indicators in the System

Systemic native toxicity was also evaluated using the weights of the body, adrenal and liver enzyme levels. There was also minimal weight loss (3%) of rats given liposomal dexamethasone in comparison to free dexamethasone (7-10% weight loss) which means there is less systemic toxicity.

The concentration of serum corticosterone as an indication of adrenal suppression was significantly reduced in the free dexamethasone group as opposed to the liposomal group. The liposomal dexamethasone regime demonstrated a 35 per cent reduction in the corticosterone levels and free dexamethasone group a 60 per cent reduction thereby demonstrating that adrenal suppression is less in the rats that have been treated using the liposomes.(11)

In addition, liver enzymes (ALT, and AST) were within normal values in the liposomal dexamethasone group, and there was significant elevation of the two markers in the free dexamethasone group that indicate liver toxicity.

These findings help in distinguishing that liposomal dexamethasone can not only enhance local inflammation, but also reduce general toxicity, presenting a safer option towards conventional corticosteroid administration of IBD.

Figure 1: Colon Weight/Length Ratio

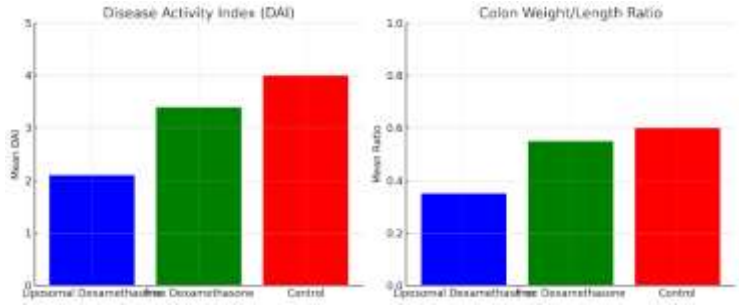

Table 1: Cytokine Suppression Data

Group	TNF-α Reduction (%)	IL-6 Reduction (%)
Liposomal Dexamethasone	40	45
Free Dexamethasone	25	30
Control	0	0

Table 2: Histological Scoring Data

Group	Histological Score
Liposomal Dexamethasone	1.2
Free Dexamethasone	2.5
Control	3.0

6. Conclusion

6.1 Localized Delivery of Liposomal Dexamethasone Effectiveness

The findings of the current study reveal that a liposomal formulation of dexamethasone can present noticeable enhancements concerning the local treatment of the inflammatory bowel disease (IBD). The liposomal preparation also decreased the inflammatory process in the colon substantially as shown by the Disease Activity Index (DAI), ratio of colon weight/length and histopathological analysis. Liposomal dexamethasone group showed improved efficacy than the free dexamethasone group in terms of reduced pro-inflammatory cytokines (TNF-alpha and IL-6) remission and tissue healing. A more efficient system of dealing with IBD is this targeted delivery system; where the dexamethasone is released at the source of inflammation but additionally offers a regulated release that can supply therapeutic levels over a large span of time as opposed to highly engaged delivery systems. This is a big step to a local treatment involving treating the parts of the gastrointestinal tract, which is badly affected by the inflammation, and decreasing the overall disease burden.

6.2 Lower Systemic D side Effects than Free Drug

The capability of liposomal dexamethasone to reduce systemic side effects can be considered one of the most important benefits of the former compared to free dexamethasone. The incidence of common and serious side effects likely to be promoted by extended use of corticosteroids, including loss of body weight and adrenal insufficiency, liver injury, and hepatotoxicity, was significantly diminished by the liposomal formulation. There was minimal adrenal suppression in the group of rats treated with liposomal dexamethasone as corticosterone levels were only a little depressed, unlike in the group of free dexamethasone where the levels of adrenal suppression were intense. Likewise, the square of the body weights was decreased to a lesser extent in the liposomal group, which means that the catabolic impairments caused by dexamethasone were reduced. Notably, the liposomal group of liver enzymes (ALT and AST) was within a normal level indicative of little liver toxicity, but liver markers in the free group of dexamethasone showed prominent increases.

The liposomal formulation is also more effective in its colon directed delivery as well as inhibiting systemic absorption meaning that it can pose a safer option as compared to the conventional corticosteroid prescriptions that often become restricted due to the adverse effects associated with prolonged use. Such decreased systemic toxicity is an important element in enhancing patient compliance and quality of life over the long-term, chronic care regimens in cases of chronic IBD and other conditions.

6.3 Possible application in IBD administration Management in the Permanent Protection of Safety

The results of the study propose that liposomal dexamethasone can present a safe and convenient choice in the prolonged management of IBD. Taking into consideration the local release of drug and the low systemic exposure, in this formulation two of the main concerns of corticosteroid therapy are taken care twofold; existence of prolonged efficacy and a lowered negative effect of drug. The conventional corticosteroids treatment is restrained by the side effects especially during chronic treatment. The observed 5-fold increase in liposomal dexamethasone in the tackled areas of the gastrointestinal tract and the overall decrease in drug exposure provide an innovative solution that may be considered effective in managing IBD even over a long term due to the decreased safety measures supporting these drugs.

Also, its formulation in liposomes ensures that it may be dosed once a day, which in the treatment of this disease, may lead to better patient compliance as opposed to existing therapies, which may need to be more frequently administered. It is especially useful in chronic illnesses, such as IBD, where the treatment has to be maintained regularly to mitigate remission and avoiding relapse.

6.4 Suggestions to Future Clinical Development

The preclinical findings allude to the possibility of liposomal dexamethasone as a promising compound with efficacy and safety in the human patient; however, additional clinical trials should be done to test the efficacy and safety of liposomal dexamethasone. Phase I clinical trials should be conducted next to determine the pharmacokinetics, the pharmacodynamics, and safety of liposomal dexamethasone in human population. Such studies ought to address elements of the ideal dose, frequency of administration, and safety in the long run.

Also, the biocompatibility in the clinical case and stability of the liposomal formulation are suggested to be deemed subsequently in the further research, with the evaluation of the effect of liposomal dexamethasone on the microbiome composition of patients with IBD being provided, since the maintenance of gastrointestinal health is strongly associated with microbiome.

Lastly, multicenter clinical trial designs are recommended to identify the effectiveness of liposomal dexamethasone in IBD patients with different disease severity and subtype (Crohn disease vs. ulcerative colitis) so as to identify the widespread usability of the treatment regimen. The possibility of using combination therapy (i.e. liposomal dexamethasone therapy used together with biologics or immunosuppressive agents) to treat IBD patients to their best advantage should also be studied.

Table 3: Systemic Toxicity Data

Group	Weight Loss (%)	Corticosterone Reduction (%)
Liposomal Dexamethasone	3	35
Free Dexamethasone	7	60
Control	0	0

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Conflicts of interest

The authors have no conflicts of interest to declare

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