

Novel Oral Drug Delivery Systems for Steroids: Overview and Recent Updates

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ABSTRACT

This review summarises the oral route of drug delivery of steroids. Oral drug delivery is widespread owing to its non-invasive nature which complements high patient compliance. This article summarises the problems associated with oral delivery of steroids including bioavailability. In this review, a brief description of the novel types of drug delivery systems of steroids such as microspheres, nanoparticles, solid lipid nanoparticles, multi-matrix tablets, pellet technology, liposomes are presented. The review also presents the latest innovations and advances that have been achieved in recent years.

Key words: Steroids, Oral delivery, Novel drug delivery, Drug carriers, Controlled release, Patient compliance.

INTRODUCTION

Oral delivery of the drugs is the most popular and preferred route of drug administration. Liquid and solid dosage forms are generally administered orally.¹ With respect to the physical as well as chemical stability of liquids and semi-solids, they can be converted into solid particles (powders or granules) which can be packed into capsules or compacted into tablets by selecting the appropriate particles. Steroids include the drugs used to relieve swelling and inflammation such as prednisolone and cortisone, sex hormones such as testosterone and estradiol, etc. Examples of oral steroids are glucocorticoids (prednisolone, beta-methasone, dexamethasone, hydrocortisone, methyl prednisolone, deflazacort) and mineralocorticoids (fludrocortisone). Steroids are used for the treatment of allergies, asthma, chronic obstructive pulmonary disease, autoimmune disease (systemic lupus erythematosus), inflammatory bowel disease (Crohn's disease, ulcerative colitis, etc.),

various types of cancers, Addison's disease and so on. The side effects associated with the prolonged use of steroids include: osteoporosis, hyperglycemia and hypertension. There is a high risk of developing cataracts and onset of duodenal ulcers. However, the oral type of drug delivery has certain disadvantages and the drug's bioavailability often varies due to the first-pass effect, gastrointestinal absorption and hostile intestinal environment. To avoid this problem, many novel methods are developed which help in increasing bioavailability and reducing the side effects of steroidal drugs. The development of new drug delivery systems has been an exponential interest in recent years. These new drug delivery systems can allow noteworthy advantages over conventional drug delivery in terms of high specificity, high stability, high drug loading capacity, controlled release behavior, possibility of use in various delivery routes and capacity.²

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Table 1: Oral delivery of various steroidal drugs by using novel drug delivery systems.

Steroidal Drug	Indication	Carrier	References
Prednisolone	Inflammatory bowel disease	Microparticles	33
Beclomethasone	Asthama	Coated microspheres	34
Betamethasone	Inflammatory bowel disease	Coated capsules	35
Dexamethasone	Inflammatory bowel disease	pH sensitive hydrogels	36
Hydrocortisone	Inflammatory bowel disease	Microparticles	37
Deflazacort	Ulcerative colitis	Microspheres	38
Fludrocortisone	Addison's disease	Microparticles	39

Various novel technologies for delivery of steroidal drugs

The different new drug delivery systems for steroidal drugs are shown in Table 1. Some of the novel technologies are discussed below.

Microspheres

Microspheres are significant vehicles for delivery of drugs in controlled manner due to their potential to load a variety of drugs, high bioavailability, biocompatibility and long-term drug release property. Microspheres have an advantage of the reduction of dosing frequency, solubility enhancement of poorly soluble drugs and provide a constant and prolonged therapeutic effect.³

Fabrication of polymeric microspheres involve three fundamental methods: (1) Interfacial polymerization methods like suspension polymerization, emulsion polymerization, dispersion polymerization and other methods like compressed anti-solvent precipitation and photo-polymerization; (2) emulsion-solvent extraction/evaporation and (3) extrusion.

Prajapati *et al.* (2015) developed highly spherical, smooth, crosslinked chitosan microspheres loaded with progesterone. Microspheres were produced by cross-linking with glutaraldehyde in aqueous acidic medium of chitosan containing progesterone in a non-aqueous medium containing liquid paraffin and 45–300 ml of sorbitan sesquioleate stabilized by petroleum ether. The extent of drug release depended on the cross-linking capacity of the microspheres. The highly cross-linked microspheres released around 35% of the loaded steroid in 40 days; whereas the lightly cross-linked spheres releasing around 70% of the incorporated steroids in 40 days.⁴

Liu Y and co-workers (2015) developed budesonide microspheres for colonic delivery by using guar gum. Guar gum is a natural polysaccharide that retards the release of the drug and also reduces its sensitivity to colonic region degradation. To minimize the side effects and provide efficacy, safety and targeted therapy, colonic

drug delivery has been developed. Budesonide loaded guar gum microspheres have been developed using the technique of emulsion cross-linking. The formulation's particle size and entrapment efficiency were determined using the particle size analyzer for laser diffraction and high-performance liquid chromatography respectively. The results showed that the microspheres were spherical in shape and $15.21 \pm 1.32 \mu\text{m}$ was found to be the mean particle size of the formulation. The formulation's drug loading and entrapment efficiency was found to be $17.78\% \pm 2.31\%$ and $81.6\% \pm 5.42\%$ respectively. The *in vitro* release studies were conducted using USP–II type apparatus. The drug release from microspheres was observed in a sustained manner, whereas the fast release was achieved in budesonide suspension form. The pharmacokinetics studies were conducted in the Sprague Dawley rats using two formulations, prepared budesonide microsphere formulation and budesonide suspension formulation for comparison. The extended half-life, increased residence time and thus reduced the total clearance of budesonide microspheres compared to the budesonide suspension indicated that budesonide microspheres could extend the time of *in vivo* budesonide compared to budesonide suspension. Microspheric budesonide AUC_{0-t} was 2.15 times higher compared to colon suspensions. Based on all the results the authors concluded that prepared formulation could be an effective and promising strategy for the treatment of colonic diseases.⁵

Guo *et al.* (2017) developed 2-methoxyestradiol (2-ME) loaded micelles and microspheres for oral delivery which serves as pH responsive delivery system. The 2-ME micelles showed particle size of 58 nm and high drug loading upto $7.94 \pm 0.23\%$. The developed formulation showed excellent drug release behavior and higher cytotoxicity than free drug on 4T1 cells. The prepared pH-sensitive microspheres prolonged the blood retention time compared to the 2-ME micelles and thus, increased the oral bioavailability upto 121.68 %.⁶

Multimatrix tablets (MMX®)

Multimatrix formulation (MMX®) was prepared for the long-term release of the drug. The MMX® matrix has a polymeric structure and was designed for slow and homogenous release of the active drug at a controlled rate throughout the target site (eg. Budenocide MMX® tablets). Budenocide belongs to steroid class with low bioavailability. It helps to bring cutback in patients with mild to modest ulcerative colitis. Budenocide MMX® tablets are preferred over the topical budenocide preparations for the treatment of inflammation and asthma as topical steroids are extensively eliminated by first-pass metabolism and result in low bioavailability. MMX® oral tablets have been developed for the homogenous drug release of budenocide along the entire length of the colon at a controlled rate for the treatment of inflammatory bowel disease (IBD).⁷ MMX® tablets consisted of two components, such as hydrophilic and lipophilic excipients, contained within a pH-dependent coating that is resistant to gastric disintegration and requires the release of drugs to be delayed until the terminal ileum where the pH is 7.0 or higher. When the coating collapses, intestinal fluids intermingle with the tablet, initiating it to swell, forming an external viscid gel mass. As the tablet goes through the colon, the external gel mass breaks from the tablet core of the drug.⁸ MMX® tablets can achieve targeted drug delivery and maintain long-term drug release. It can reduce the effects of systemic corticosteroids on hyperglycemia, mood changes, hypokalemia, moon face, sleep disorders etc.

Pellet technology

Pellet (or bead) technology offers various drug delivery profiles to be achieved by coating with various polymers a 'core' of drug and excipient. The drug cores are spherical in shape and range from 300 to 1,700 µm in diameter. Two types of processes are used for producing spheroidal particles: (1) extrusion granulation: This technique can keep up to 90% of the drug's potency. The drug is granulated with excipients in this process and extruded to form core spheroid granules then coated by polymer. (2) spheronization: using binder drug particles, the core coated with a polymer is attached to the outside layer. For example, drug powers of up to 60 percent may be possible (for example: budenocide pellets).

To avoid the premature drug release of budenocide in the stomach and gastrointestinal tract, pellet technology was established, which helps in releasing the drug at the target site. Using the extrusion spheronization method, the pellet cores were prepared and sequentially layered with xanthan gum (barrier layer), the combination

of Eudragit NE30D and L30D55 (inner layer) and Eudragit FS30 (as entry layer) to attain the essential release profile. With the help of cectose or pearlitol, the coated pellets are compressed into tablets. Different polymers used in the pelletization process for controlled delivery of the drug include: Gelucire, pectins, carbapol, alginates, resins, crosscarmellose sodium, sodium starch glycolate etc. The various advantages of pellets include: they are less prone to dose dumping and, drug safety and efficacy can be improved. The most important reason why multiple unit products are widely accepted is the rapid increase in the popularity of dosage forms for oral pellets. Oral solid dosage forms of pellets are usually intended either to deliver the drug at a specific location within the gastrointestinal tract or to maintain the action of drugs over a longer period of time.⁹

Liposomes

Liposomes are lipid based drug carriers and have been emerged as one of the novel drug delivery carriers. Liposomes are spherical bilayer vesicular structures containing phospholipids that are amphiphilic in nature. Amphiphilic phospholipids form spherical bilayer structures on contact with water, orienting their hydrophobic part facing each other (inward) and externally facing hydrophilic part. Hydrophilic substances can be incorporated in the aqueous inner spaces of globules; hydrophobic medicines can be incorporated into fatty acids inner layers.¹⁰ Liposomes are also used as a solubilizing or suspending medium for lipophilic drugs to be delivered as a micro-emulsion in soft gel capsules for oral dosage units. Liposome incorporated steroid ester (Budenocide-21-palmitate) helps in treating the inflammation and allergic reactions. Liposomes acts as carrier for sustained and controlled release drug delivery. It can increase the efficacy and therapeutic index of many drugs. It also provides selective passive targeting to tumour tissues.¹¹

Hiremath *et al.* (2009) developed a exemestane proliposomal formulation by solvent evaporation. This development was aimed at improving the oral absorption of the drug by enhancing intestinal permeability. The effect of phospholipid composition was studied on *in vitro* performance of proliposomes. Proliposomes were characterized by Differential Scanning Calorimetry (DSC) and dissolution behavior for their particle size distribution. For *in vitro* permeation studies of formulated proliposomes, various models such as rat intestine model, Parallel Artificial Membrane Permeability Assay (PAMPA) and Caco-2 cells were used. The results showed that the proliposomes increased exemestane dissolution by incorporating

phospholipid bilayers and changing from crystalline to amorphous physical condition. The *in vitro* studies in rat intestine, PAMPA and Caco-2 models showed that the proliposomes were useful in improving exemestane transport. The combined effect of enhanced solubility/dissolution and increased liposome absorption through intact cell membranes resulted in an improved *in vitro* permeation. Based on the results, the authors concluded that the developed formulation could improve oral bioavailability of the drug.¹²

In another study, Wang *et al.* (2017) formulated chitosan-modified cholesterol-free liposomes encapsulated with progesterone (CS-Lipo/Prog). This was developed to improve the drug's oral bioavailability. Progesterone is a poorly water-soluble drug and has a short half-life and high first-pass metabolism which result in variable bioavailability. Chitosan was coated onto the liposomes to protect them from gastric pH and enzymatic degradation. Chitosan is also helpful in transporting the cells across the epithelial tight junctions and improve the transport of hydrophobic drug. The particle size of the prepared formulation was studied and the results showed that these particles were beneficial to facilitate lymphatic drug transport and positive zeta charge suggested intestinal absorption of progesterone. The entrapment efficiency of the drug was found to be 80%. By using the dialysis method, the *in-vitro* cumulative release profiles of the drug from chitosan coated cholesterol-free liposomes containing progesterone were calculated. The results showed a sustained release profile without any burst release. The *in vitro* stability results showed that chitosan coated cholesterol-free liposomes could protect progesterone in harsh gastrointestinal environments. The pharmacokinetic and bioavailability studies of CS-Lipo/Prog (liposomes coated with chitosan) and Lipo/Prog (liposomes without chitosan coating) and progesterone were studied. The results revealed that the $AUC_{0-\infty}$ and Mean Residence Time of CS-Lipo/Prog were higher compared to other two and the relative bioavailability of CS-Lipo/Prog was found to be 6.03-fold higher than progesterone and 2.08-fold higher than Lipo/Prog. The authors concluded that cholesterol-free chitosan-modified liposomes could be a promising alternative to improve progesterone's oral bioavailability.¹³

Solid lipid nanoparticles (SLN)

SLN combines the benefits of polymeric nanoparticles such as controlled drug release and drug leakage avoidance with emulsion and liposome benefits such as low toxicity, good biocompatibility and increased bioavailability. Solid lipid nanoparticles (SLN) are used to overcome

the problems associated with poor water-soluble drugs like steroids (eg. progesterone). These are biocompatible and biodegradable carriers used for controlled drug delivery and specific targeting. They have the potential to carry water soluble and lipid soluble drugs. Controlled and targeted release of the incorporated drug can be achieved by using SLN. SLNs can enhance the bioavailability of entrapped bioactives. The usage of organic solvents can be minimized with SLN. SLNs of 120–200 nm size range are not detected by the reticuloendothelial cells (RES) and thus bypass the liver and can avoid first-pass metabolism. But, SLNs have poor drug loading capacity. There may be chances of drug expulsion during the period of the storage after the polymeric transition.¹⁴

Zur Mühlen *et al.* (1998) prepared prednisolone loaded SLNs in order to investigate the prolonged drug release potential. SLNs were prepared by cold and hot homogenisation techniques. The drug release potential was studied by using the USP XXII paddle method. Shape and surface texture of the solid lipid nanoparticles was studied by using atomic force microscopy. The solid SLNs prepared by cold homogenisation technique showed prolonged drug release along with minor burst release up to 5 weeks. On the other hand, drug release from SLNs prepared by hot homogenisation technique showed initial fast release followed by a prolonged drug release.¹⁵

Nanoparticles

Nanoparticles are solid colloidal particles of 1 to 100 nm in size, consisting of micro-molecular materials in which the active ingredient is dissolved or encapsulated or adsorbed.¹⁶ Nanoparticles are solid colloidal particles of 1 to 100 nm size, consisting of micro-molecular materials in which the active ingredient is dissolved or encapsulated or adsorbed. Nanoparticles are classified by size, morphology, physical and chemical properties into different types. Some of them are nanoparticles based on carbon nanoparticles, ceramic nanoparticles, metal nanoparticles, semiconductor nanoparticles, polymeric nanoparticles and lipidic nanoparticles. There are two main steps in many methods of preparing nanoparticles. The preparation of an emulsified system is the first step, while during the second step of the process, the nanoparticles are formed. This second step is achieved either by precipitation or gelation of a polymer, or by polymerization of a monomer. Various polymers used in the preparation of nanoparticles are: synthetic homopolymers like poly (lactide), poly (lactide-co-glycolide) etc., natural polymers like alginate, gelatine, albumin, chitosan and co-polymers like poly (lactide)-

poly (ethylene glycol), poly (epsilon-caprolactone)-poly (ethylene glycol) etc. nanoparticles are less toxic and inexpensive. They can be used for targeted drug delivery. They can easily cross the biological membranes such as blood brain barrier.¹⁷

Liu *et al.* (2016) formulated nanocrystals of diosgenin, which was isolated or extracted from *Dioscorea Nipponica Makino* and *Dioscorea Zingiberensis Wright*, by media milling method. They initiated the development of nanocrystals to bypass the problems of low oral bioavailability of diosgenin because of its high hydrophilicity. They used amalgam of Pluronic F 127 and sodium lauryl sulphate which is used as surface stabilizer in development of nanocrystals. The physicochemical parameters were studied and it was found that there was no change in the chemical structure and original crystalline state of diosgenin molecule. They conducted pharmacokinetic studies of diosgenin coarse suspension and formulated diosgenin nanocrystals in rats for comparative study. The AUC of prepared diosgenin nanocrystals was found 2.55 folds more than that of diosgenin coarse suspension. The C_{max} of the diosgenin nanocrystals was found to be 2.01 times more than that of diosgenin coarse suspension. Considering these parameters the authors concluded that the therapeutic action of formulated nanocrystals is a promising strategy for oral administration of diosgenin because of increased dissolution rate and bioavailability of diosgenin.¹⁸

Zhang *et al.* (2016) formulated ergosterol loaded poly (lactide-co-glycide) nanoparticles to improve its oral bioavailability and anti-tumor as well as the anti-angiogenic activities. They developed ergosterol-loaded PLGA nanoparticles because of the high lipophilicity of free ergosterol form. By using the method of emulsion/solvent evaporation, PLGA nanoparticles loaded with ergosterol were produced. The physicochemical properties of drug-charged nanoparticles were characterized and their anti-tumor activity against human cancer cell lines was evaluated using MTT assay. The pharmacokinetics studies of ergosterol-loaded PLGA nanoparticles were conducted in rats and tissue distribution studies were conducted in mice. Based on the results of MTT assay, they stated that drug-loaded nanoparticles exerted stronger anti-tumor activity against human cancer cells in comparison to free ergosterol. The prepared nanoparticles showed significantly reduced half maximal inhibitory concentration IC_{50} values in glioma U251 cells, in breast cancer MCF-7 cells; and in hepatoma HepG2 (immortalized cell line) cells. The pharmacokinetic results in rats on single dose showed that there was about 4.9- fold increase in the oral bioavailability

from formulated nanoparticles compared to free ergosterol. Studies of tissue distribution in mice showed that ergosterol was rapidly distributed in the form of nanoparticles in the stomach, renal, hepatic portion, brain, spleen and virtually non-existent in the heart and lungs. It was found that the existence of nanoparticles in the brain was particularly more in contrast with the free ergosterol. The authors concluded that formulated nanoparticles serve as an efficient carrier for low-soluble ergosterol and improve its bioavailability, bio-distribution and anti-tumor activity *in vitro*.¹⁹

Tween 80 coated PLGA nanoparticles that deliver estradiol to the brain through oral administration were formulated by Mittal and Carswell. Nanoparticles containing estradiol were produced using a single emulsion method. To these nanoparticles, Tween 80 coating was applied by incubating the re-constituted nanoparticles at different levels of Tween-80 concentrations. Tween 80 aids to cross the blood-brain barrier by the mechanism of endocytosis. The apolipoprotein E and/or B from the blood stream is adsorbed to the surface of the nanoparticles and acts as natural low-density lipoproteins (LDL) that interact with the LDL receptor in the capillary endothelial cells of the brain, followed by endocytotic absorption. In the ovariectomized rat of Alzheimer's disease, which mimics the postmenopausal conditions, the Tween 80 coated nanoparticles were examined. Compared to uncoated nanoparticles administered orally, Tween 80 coated nanoparticles administered through the same route showed significantly more estradiol levels in the brain after a day at a dose of 0.2 mg/ rat. This proved the importance of surface coating of nanoparticles with Tween 80. Moreover, these brain estradiol levels of the same dose of drug administered through both oral route (nanoparticles) and intramuscular route (drug suspension) were found to be identical, indicated an increased fraction of bioavailable medicine that reaches the brain when orally administered. With the administration of nanoparticles in the rat group, the expression of amyloid beta-42 (A β 42) immunoreactivity in the brain hippocampus region was successfully prevented. With the added benefits of patient compliance and reduced peripheral drug burden, the authors concluded that Tween 80 coated estradiol polylactide-co-glycide nanoparticles could be a prospective therapeutic approach in the treatment of post-menopausal Alzheimer's disease.²⁰

Jayapal *et al.* (2017) formulated and evaluated nanoparticles charged with exemestane for the treatment of cancer. Exemestane is an oral medicine used to treat cancer of the breast. Exemestane helps in preventing estrogen synthesis. By simple controlled gelation technique, the

exemestane was loaded into alginate nanoparticles. The exemestane encapsulation efficiency studies showed high encapsulation efficiency of the drug into the nanoparticles. The SEM results showed that the size was in nano-scale with rough surface morphology. *In vitro* drug release studies of exemestane loaded alginate nanoparticles were conducted and the results showed that there was a controlled manner of drug release from the nanoparticles. *In vitro* cytotoxicity studies of drug-loaded nanoparticles were conducted using Dalton's lymphoma ascites cells and the results confirmed that exemestane loaded alginate nanoparticles help in the treatment of breast cancer.²¹

Jang *et al.* (2014) developed a nanocrystal formulation of megestrol acetate to overcome the problems associated with the oral suspension of megestrol acetate formulation such as low bioavailability. Megestrol acetate is a synthetic form of progesterone, acts as an antineoplastic agent for the treatment of various types of cancers. Megestrol acetate helps for improving hunger and for increasing body weight in humans affected with cancer-associated anorexia. The studies were conducted in 93 healthy subjects and pharmacokinetics and tolerability of nanocrystal formulation and oral suspension were evaluated in fed and fasting states. After the dose, the blood samples from subjects were collected and pharmacokinetic parameters were studied up to 120 hr. The results showed that the megestrol acetate nanocrystal formulation was rapidly absorbed in both fed and fasting conditions. The systemic exposure was comparable between both nanocrystal formulation and oral suspension; while in fasting state the C_{max} of nanocrystal formulation was 6.7-fold higher than oral suspension and the AUC was 1.9-fold more than oral suspension. Based on the above results the authors stated that, with oral administration of nanocrystal formulation, systemic exposure to megestrol acetate is less affected by the lack of concomitant intake of food and the authors concluded that megestrol acetate's nanocrystal formulation could be more effective in treating patients with cachexia.²²

Use of orally administered steroids

Prednisone can cause partial remissions (PR) and complete remissions (CR) when given daily, in adults with primary focal segmental glomerulosclerosis (FSGS), but recurrences are common and adverse events occur. Cho *et al.* (2019) carried out the study to investigate the effectiveness and tolerability. In the first study, a combined CR-PR rate of 36% was found with the involvement of 13 number of subjects with FSGS and 1 subject with a minimally change disease. The 8

subjects were involved in the second study with 29% CR-PR combined rate. A combined CR-PR rate of 33% was found in the analysis when both studies combined. Almost 32% of the involved subjects showed adverse events. No adverse events which are serious were reported in the study. We can thus conclude that adults with idiopathic nephrotic syndrome with high dose oral dexamethasone are well tolerated and may be effective.²³

In another study, Ho *et al.* (2019) evaluated the medical treatment responses to frontal fibrosing alopecia (FFA) and proposed a clinical management approach. The therapy response was evaluated by the reported hair loss to stop or slow down. Oral prednisone was used rarely and rapid hair loss was only provisionally delayed. In conclusion, they found that the natural path of FFA varies and frontal hair recession can stabilize irrespective of treatment. But, early intervention in active disease is encouraged because hair loss is supposed to continue and treatment could alter the course of the disease.²⁴

Nishijima *et al.* (2019) examined the subacute sensory ataxic neuropathy, a known form of paraneoplastic syndrome. The patient participated in the study had left-dominant ataxia in four limbs because of decreased extremity sensations. After investigation, it was found that the patient had sensory ataxic neuropathy with invasive thymoma. First, i.v. immunoglobulin treatment, then thymectomy and again i.v. immunoglobulin treatment was failed in neurological symptoms treatment. Subsequently, prednisolone was started, which resolved neurological symptoms.²⁵

Campieri *et al.* (2003) investigated the effectiveness and safety in treating severe or left-sided ulcerative colitis by using beclomethasone dipropionate (BDP) in a controlled release oral formulation vs. 5-amino salicylic acid (5-ASA). A decrease in Disease Activity Index (DAI) (endoscopic mucosal appearance and clinical symptoms) was the main efficacy variable. In 63% of patients of BDP group, clinical remission was achieved compared to 62.5% patients of 5-ASA group. In patients suffering from severe disease, improvement in the disease activity index score was seen in favor of beclomethasone dipropionate. In conclusion, oral BDP provided treatment for patients suffering from ulcerative colitis. It did not show systemic side-effects.²⁶

Van Assche *et al.* (2015) conducted the double-blind trial in the fields of mild-to-moderate ulcerative colitis (UC) to compare the effectiveness and safety of beclomethasone dipropionate (BDP) to prednisone (PD). In total, 282 patients were randomized to administer beclomethasone dipropionate extended release 5 mg

tablets once a day for four weeks and then for further four weeks every other day or oral prednisone of 40 mg once a day for first two weeks with reduction of 10 mg every two weeks during the eight-week trial period. In conclusion, in the treatment of active UC, BDP was not below PD with both groups showing a good safety profile.²⁷

Dellon and co-workers (2019) conducted a study that involved, whether oral viscous budesonide (OVB) was effective than fluticasone multi-dose inhaler (MDI) for primary treatment in patients suffering from eosinophilic esophagitis (EoE). This study showed a decrease in counts of esophageal eosinophil and improved endoscopic features and dysphagia in the primary treatment of eosinophilic esophagitis with either oral viscous budesonide or fluticasone multi-dose inhaler. However, OVB was inferior to MDI, so either is an acceptable treatment for EoE.²⁸

Miller *et al.* (2008) conducted the study with the objective to review the role of oxandrolone in patients with serious thermal burn injury in pediatric patients. Oxandrolone increased the strength of the muscles during post-burn rehabilitation period, particularly when combined with exercise. To conclude, the benefits in long-term post-burn rehabilitation periods and acute post-burn injury have been shown by additional oxandrolone therapy in severely burned pediatric patients.²⁹

Gault *et al.* (2011) investigated the effects of oxandrolone and the time of pubertal induction on final height in girls diagnosed with Turner's syndrome receiving a growth hormone. Final height was the main measurement outcome. Oxandrolone also had a positive impact on girls final height suffering from Turner's syndrome which was treated with growth hormone, like late induction of puberty at age 14 years with ethinylestradiol. These effects, were not additive, so they had no benefit when both used. Therefore, oxandrolone may be offered to increase final height for girls suffering from Turner's syndrome in alternative to late pubertal induction.³⁰

Check and co-workers (2016 and 2019) investigated oral effects of mifepristone. In Case 1 of a research study with mifepristone given orally to stop non-small cell lung cancer of stage IV, the tumor which was lacking targeted markers was found to be ECOG zero and healthy for more than 3 years. Case 2 was a 68-year old female with non-small cell lung cancer of stage IV whose tumor was positive for the programmed death ligand-1 (PDL1) marker. In addition to three rounds of multi-agent chemotherapy the patient's cancer had advanced in spite of treatment with a check-point inhibitor. Patient's cancer remained stable (with tumor

regression) after treatment for 1½ years with mifepristone. Thus, treatment with mifepristone may be a method to stop metastatic lung cancer which was positive for the PD-L1.^{31,32}

CONCLUSION

As discussed, different types of formulations of steroids can be made to achieve targeted and controlled release of steroidal drugs and hormones. Results for disease treatments are on positive hand due to treatment with steroid as they act as a signalling molecule and can be found in human body rather than using chemical drugs. Therefore, recently, focus has been given on novel delivery technologies for steroid administration to treat various diseases.

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CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.

ABBREVIATIONS

2-ME: 2-methoxyestradiol; **5-ASA:** 5-Amino salicylic acid; **AUC:** Area under the curve; **Aβ42:** Amyloid beta-42; **BDP:** Beclomethasone dipropionate; **CR:** Complete remissions; **CS-Lipo/Prog:** Chitosan-modified cholesterol free liposomes encapsulated with progesterone; **DSC:** Differential Scanning Calorimetry; **EoE:** Eosinophilic esophagitis; **FFA:** Frontal fibrosing alopecia; **FSGS:** Focal segmental glomerulosclerosis; **IBD:** Inflammatory bowel disease; **LDL:** Low-density lipoproteins; **MMX:** Multimatrix formulation; **MTT:** 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; **OVB:** Oral viscous budesonide; **PAMPA:** Parallel Artificial Membrane Permeability Assay; **PD:** Prednisone; **PDL1:** Programmed death ligand-1; **PLGA:** Poly (lactide-co-glycolic acid); **PR:** Partial remissions; **RES:** Reticuloendothelial system; **SLC:** Solid lipid nanoparticles; **UC:** Ulcerative colitis; **USP:** United States Pharmacopoeia.

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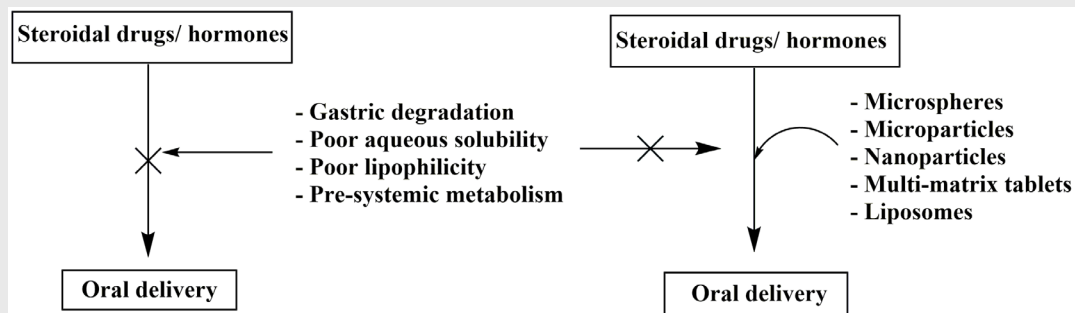
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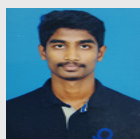
SUMMARY

- Variety of steroidal drugs and hormones are used to treat various inflammation related disorders.
- The oral delivery of steroidal drugs may undergo pre-systemic metabolism, degradation due to gastric acid, remained unabsorbed due to poor aqueous or lipid solubility.
- Use of various delivery platforms such as microspheres, nanoparticles, solid lipid nanoparticles, multi-matrix tablets, pellet technology, liposomes etc. can enhance the oral bioavailability of steroidal drugs.
- Novel delivery technologies can be used to achieve targeted and controlled delivery of steroidal drugs and hormones.

PICTORIAL ABSTRACT



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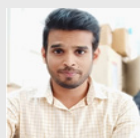
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