CHAPTER – IV

LITERATURE ON PREDNISOLONONE
PREDNISOLONE

Chemical name: (11, 17-dihydroxy-17- (2-hydroxyacetyl)-10, 13-dimethyl-6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17-dodecahydrocyclopenta [a]phenanthrene 3-one).

Structure:

Molecular formula: C_{21}H_{28}O_{5}.

Molecular weight: 360.444 g/mol.

Description:

It is a white or almost white, crystalline powder, hygroscopic, very slightly soluble in water, soluble in alcohol and in methanol, sparingly soluble in acetone, slightly soluble in methylene chloride. It has a molecular weight of 360.444 g/mol and melting point of 235°C. From the literature, aqueous solubility of prednisolone was found to be 0.215 – 0.753 mg/ml. Its hydrophobicity is given by experimental log P value of 1.705. It is readily absorbed by gastrointestinal tract, peak plasma concentration being reached 1-2 hours after administration. 


Pharmacokinetic and Pharmacodynamic profile of Prednisolone:

Glucocorticosteroids (GCCS) have been widely used in therapy of inflammatory diseases (both acute and chronic) for many years. Long-term therapy with these drugs is often necessary to control the symptoms of many rheumatic conditions. Long-lasting usage of GCCS in therapy causes many undesirable effects on cardiovascular system and bone metabolism. Bone loss is the most frequent side effect of a long-lasting application of GCCS. The mechanism underlying anti-inflammatory activity of GCCS are very complicated. They interfere with the function of several systems. In addition to the potential dangers associated with long-term use of GCCS at supraphysiological concentrations, there are problems associated with the withdrawal from steroid therapy. Because GCCS are the best anti-inflammatory agents available to date, therapeutic use would benefit greatly from a reduced undesirable side effects. The major limitation to the use of oral GCCS has always been about their safety.

Glucocorticosteroids are effective when given orally, and obviously this is the preferred mode of administration for prolonged therapy. However, parenteral administration is required in certain circumstances. For example, intramuscular injection of water-soluble ester produces peak plasma steroid levels within 1 hr. The Glucocorticosteroids are considered to be generally poorly water soluble and have demonstrated unpredictable dissolution rates.
Prednisolone is a corticosteroid anti-inflammatory, analgesic agent used in treatment of inflammatory diseases\textsuperscript{6}. It is indicated for treatment of primary or secondary adrenocortical insufficiency, such as congenital adrenal hyperplasia and thyroiditis. It is also used to treat psoriatic arthritis, rheumaoid arthritis, ankylosing spondylitis, bursitis, acute gouty arthritis and epicondylitis. Additionally it is indicated for treatment of systemic lupus erythematousus, pemphigus and acute rheumatic carditis. It can also be used to treat leukemias, lymphomas, thrombocytopenia purpura and autoimmune hemolytic anemia. Drug therapy of celiac diseases, insulin resistance, ulcerative colitis and liver disorders also includes prednisolone\textsuperscript{2}.

Prednisolone decreases inflammation by inhibition of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability. It suppresses the immune system by reducing the activity and volume of the lymphatic system.

The toxicity of prednisolone is given by the LD50 of 500 mg/kg (oral, rat). Its short-term side effects include high blood glucose levels and fluid retention and long term side effects include Cushing’s syndrome, weight gain, osteoporosis, glaucoma,Type II diabetes and adrenal suppression. It is highly protein bound (>90\%) and excreted in the urine as either free or glucoconjugate. It has half life of 2-4 hours. It is insoluble in aqueous solutions and causes gastric irritation upon oral administration\textsuperscript{2,7,8}. 
The adverse drug reactions of prednisolone include Cushing’s syndrome and growth retardation in child; osteoporosis, fractures. Peptic ulceration; glaucoma, cataracts; hyperglycaemia, pancreatitis; increased appetite, obesity. Topical: Thinning and atrophy, systemic absorption with prolonged use over large surface, broken skin or under occlusive dressing. Intradermal/intrlesional: Local hypopigmentation of hyperpigmented lesions. Ophthalmic: Raised intraocular pressure and reduced visual function.
PAST WORK ON SOLUBILITY ENHANCEMENT OF

PREDNISOLONE

Enhancement of prednisolone dissolution properties using liquisolid compacts was done by Spiro Spireas and Srinivas Sadu.

The in-vitro release characteristics of prednisolone, a very slightly water soluble glucocorticoid, formulated in directly compressed tablets and liquisolid compacts, were studied at different dissolution conditions. According to the new formulation method of liquisolid compacts, liquid medications such as solutions or suspensions of water insoluble drugs in suitable non-volatile liquid vehicles, can be converted into acceptably flowing and compressible powders by blending with selected powder excipients. It has been speculated that such systems exhibit enhanced release profiles due to the increased wetting properties and surface of drug available for dissolution. In the present study, the potential of liquisolid systems to improve the dissolution properties of water-insoluble agents was investigated using prednisolone as the model drug. Several liquisolid tablet formulations were prepared using a new mathematical model to calculate the appropriate quantities of powder and liquid ingredients required to produce acceptably flowing and compressible admixtures. Liquisolid compacts demonstrated significantly higher drug release rates, in different dissolution media and volumes, compared to tablets prepared by the direct compression method. It was also observed that the drug dissolution rate from liquisolid tablets was independent of the volume of dissolution medium,
in contrast to the plain tablets which exhibited declining drug release patterns with decreasing dissolution volumes.

Solubility and Stability Enhancement of Poorly-Soluble Drugs Clarithromycin and Prednisolone by Combination with Other Drugs was done by Neelam Seedher and Purshotam Sharma\textsuperscript{10}. An attempt has been made to enhance the solubility and stability of two poorly-soluble drugs, clarithromycin and prednisolone by forming their combinations with three widely consumed non-prescription drugs: paracetamol, caffeine and ibuprofen. For solubility enhancement, three methods; Solution phase studies, solid dispersions and physical mixtures were used. It is seen that paracetamol produced significant enhancement in solubility of both clarithromycin and prednisolone by all the three methods. A comparison of different methods showed that solid dispersion method produced maximum enhancement for both the drugs. However, as compared to clarithromycin, the magnitude of enhancement was smaller in the case of prednisolone. With increase in ionic strength of the medium, a small decrease in solubility was observed in each case. Paracetamol was also found to be most effective combination drug in enhancing the stability of clarithromycin as well as prednisolone.
PAST WORK ON CONTROLLED RELEASE OF 

PREDNISOLONE

Controlled release of prednisolone from suppository prepared using powder of pulverized tablet was done by Tatsumi A et al\textsuperscript{11}. Prednisolone suppositories have been used successfully for the treatment of ulcerative colitis in hospital settings. However, the raw material of prednisolone suppository, JP prednisolone powder (JP Powder), was recently removed from the market. Therefore we studied the effects of raw material and suppository base on the release of prednisolone suppository for the purpose of designing a new suppository with similar effects to those of suppository prepared using JP powder (old suppository). New suppositories consisting of the powder of pulverized tablet as raw material and Witepsol H-15 and Witepsol E-75 as suppository base were prepared according to the fusion method. Suppository release test was performed by reciprocating dialysis tube method with tapping (RDT method) and dialysis tubing method (DT method). Both RDT method and DT method were performed using a suppository dissolution apparatus (modified JP disintegration apparatus) and a JP15 paddle apparatus, respectively. The test fluid was 50 mM phosphate buffer solution (pH 7.4) maintained at 37+/-0.5 °C. The results of release test by RDT method were similar to those of DT method. Release rate of prednisolone from the new suppository was much faster than that of old suppository. The addition of Witepsol E-75 to new suppository base markedly delayed the release of prednisolone from the new suppository. Release rate of prednisolone from the
new suppository, consisting of pulverized tablet and Witepsol H-15 and Witepsol E-75 (76:24), corresponded well with that of the old suppository. It was suggested that this suppository could be used as incoming preparation of suppository prepared using JP powder.

K. Sharma et al\textsuperscript{12} had controlled the prednisolone release from copolyurethane monolithic devices. Monolithic controlled release devices have been designed to take advantage of the two-phase morphology of a block copolyurethane. The release of prednisolone from copolyurethane devices fabricated by two different methods (solution casting and swelling in saturated solute solutions) was characterized. Higher release rates were obtained when prednisolone was primarily loaded in the hydrophilic polyether matrix as compared to being loaded throughout the copolyurethane. The release mechanisms were different from the two devices. As a possible contributing variable to the release mechanisms, intermolecular interactions between the solute and copolymer were also investigated. Intermolecular interactions between prednisolone and the urethane segment of the copolyurethane contributed to the lower release rates from the solution-cast devices. These interactions were absent in the devices loaded by swelling, which exhibited higher release rates.

Design and In Vitro Evaluation of Prednisolone Tablets as a Potential Colon Delivery System was done by Mohanad Naji Sahib. Prednisolone is a corticosteroid drug that is used to treat many diseases. The present investigation was concerned with the formulation of prednisolone as an oral
modified release tablet for colonic targeting. Many trials were performed to prepare a satisfactory formula using the wet granulation method with various additives and coatings. We found that lactose as a diluent provided the most reasonable release for prednisolone among other diluents. In addition, the formula containing 1% Eudragit RS PM was the best with regard to 100% release of drug in comparison with other concentrations and other retardant types. Avicel was used as a canalizing agent, and the results showed that the formula containing 30% Avicel PH 302 demonstrated faster release. Eudragit S 100 provided the best release of drug in phosphate buffer, pH 7.4. The effect of the percent of binding agent polyvinylpyrrolidone (PVP) (5%, 10%, and 15%) was studied, and the best results were obtained with a concentration of 10%. The trials in this study successfully formulated prednisolone-modified release tablets (coated matrix) using a wet granulation method as a potential colon delivery system.
References


