2. Review of Literature

2.1 18 β-glycyrrhetinic acid

**Phytochemical and Pharmacological study**

*Obolentseva GV et al.* reported constituents of licorice, including 40-50% water soluble extractives containing triterpene saponin, flavonoid, polysaccharide, pectin, simple sugar, amino acid, mineral salt and various other substances. The sweet taste of licorice root is due to glycyrrhizin, a triterpenoid. This compound represents a mixture of potassium-calcium and magnesium salts of glycyrrhizic acid (2-25%). Glycyrrhizic acid is composed of a hydrophilic part (two molecules of glucuronic acid) and hydrophobic fragment (18 β-glycyrrhetinic acid)\(^1\).

*Rhosan Asha et al.* mentioned 18 β-glycyrrhetinic acid inhibits 11 β-hydroxy steroid, responsible for converting cortisol into its inactive metabolites. Also increase cortisol level and potentiate the glucocorticoid receptor. Hydrocortisone secreted from adrenal cortex is responsible for the anti-inflammatory action\(^2\).

*Li YJ et al.* studied pentacyclic triterpenoid, 18 β-glycyrrhetinic acid (0.5-20%) obtained from the hydrolysis of glycyrrhezic acid, obtained from liquorice\(^3\).

*Anonymous* mentioned each licophar logenze made up of glycyrrhiza extract 51.2mg shown stronger anti inflammatory action due to 18 β-glycyrrhetinic acid\(^4\).

*Chung-Yi W et al.* studied in vitro anti-inflammatory effects of 18 β-glycyrrhetinic acid from liquorice in a lipopolysaccharide stimulated macrophage model. The results showed that treatment with 20–75μM 18 β-glycyrrhetinic acid inhibited the production of nitric oxide and prostaglandin E\(_2\).The result suggested that 18 β-glycyrrhetinic acid, serves as potential agents for the treatment of inflammatory mediated diseases\(^5\).

*Peter JA et al.* studied 18 β-glycyrrhetinic acid in the range 0.1-10%, showed better anti-inflammatory actions by inhibiting prostaglandin E\(_2\) synthesis\(^6\).

*Li SA et al.* formulated the liposomal gel with 0.9% 18 β-glycyrrhetinic acid showed excellent anti-inflammatory activity against econazol cream\(^7\).

*Anonymous* reported the oral LD\(_{50}\) of 18 β-glycyrrhetinic acid in rats was 610mg/kg\(^8\).

*Trivedi A et al.* investigated HPTLC method for estimation of 18 β-glycyrrhetinic acid using toluene:ethyl acetate:glacial acetic acid 12.5:7.5:0.5 as mobile phase with \(R_f\) 0.51. It was quantified at the wavelength of maximum absorption of 260\(^9\).

**Pharmacokinetic study**

*Sun Hao-yang et al.* reported pharmacokinetic parameters of 18 β-glycyrrhetinic acid.
By administering oraly 15mg/kg (rat) showed AUC$_{0-t}$ 9.79μg·h/ml, AUC$_{0-\infty}$ 10.30μg·h/ml, C$_{max}$ 2.09μg/ml, t$_{max}$ 1.58h. t$_{1/2}$ was 2.95h showed poor bioavailability.$^{10}$

2.2 Boswellic acid

**Phytochemical and Pharmacological study**

Pardhy RS, Bhattacharya SC. identified the β -boswellic acid, acetyl- β -boswellic acid, 11-keto- β -boswellic acid, and acetyl-11-keto- β -boswellic acid from B. serrata Roxb.$^{11}$

Gupta VN. showed anti-inflammatory, anti-rheumatic activities, anti-pyretic effect and no ulcerogenic effect of boswellic acids when it administered in the dose dose 2g/kg (p.o) in mice. It improved blood supply to joints and restores integrity of vessels obliterated by spasm of internal damage. It is superior over conventional drugs because it is a natural constituents being used since ages and is absolutely free from side effects.$^{12}$

Sharma A et al. reported oral administration of B. serrata extract (200mg/kg) suppresses inflammation by inhibiting leukotrine synthesis.$^{13}$

HPT Ammon et al. reported anti inflammatory effect of alcohol extract of B. serrata$^{14}$. Francesco Di Pierro. studied topical formulations containing 0.001-5% boswellia extract with 60% boswellic acids used for symptomatic relief of musculoskeletal disorder$^{15}$. Goyal S et al. reported LD$_{50}$ for boswellic acid was > 2g/kg$^{16}$.

Rachh et al. reported non aqueous titration method for estimation of boswellic acid using 0.1N potassium methoxide and 0.3%w/v thymol blue as indicator$^{17}$. Ramakrishnan G et al. reported anti-inflammatory activity of different extracts of Boswellia serrata in Wistar albino rats$^{18}$.

2.3 Piperine

**Phytochemical and Pharmacological study**

Stohr J R et al. studied the pungency of black pepper and long pepper was due to piperine alkaloid, had also acquired anti-inflammatory activity.$^{19}$

Kaushal Neeraj et al. determined permeation of antidiabetic drug repaglinide through rat skin was enhanced by 8 fold in the presence of piperine (0.008%w/v)$^{20}$. Harle U N et al. determined piperine worked as a bioavailability enhancer in the range of 1-30mg and increased C$_{max}$ and AUC of phenytoin, theophylline and propranolol$^{21}$. Goswami DS, Singh V et al. reported piperine (0.5%) enhanced bioavailability of aceclofenac by inhibiting metabolizing enzymes as well as drug penetration via partial extraction of stratum corneum lipid and interaction with keratin. This shown piperine enhanced the therapeutic efficacy of the concurrently administered drugs$^{22,23}$. 
Trivedi A et al. studied HPTLC method for estimation of piperine using toluene:ethyl acetate:glacial acetic acid 12.5:7.5:0.5 as mobile phase with \( R_f \) 0.55 and wavelength of maximum absorption 331nm.

### 2.4 Excipients review

**Carbopol 934**

Zhen Yang et al. formulated reservoir type patch of bufalin. 10% limonene, 40% ethanol, 30% propylene glycol, 15% carbopol 934 gel base shown best release of bufalin.

Mutalik Shrinivas et al. developed reservoir type patch of glibenclamide using drug containing carbopol as reservoir and ethyl vinyl acetate (9%, 19%) as rate controlling membrane.

**Ethyl cellulose**

Patel RP et al. developed a matrix type transdermal patch using aceclofenac with different ratios of hydrophilic (hydroxyl propyl cellulose): hydrophobic (ethyl cellulose) polymers and 15%w/w of dibutyl phthalate as plasticizer by the solvent casting technique. Different amount of oleic acid and isopropyl myristate were used as penetrating enhancer to increase permeation of aceclofenac.

Bharkatiya M et al. developed matrix type transdermal patches containing Metoprolol tartrate were prepared by solvent casting method employing a mercury substrate by using the combinations of EC-PVP and Eudragit RL100-PVP in different proportions.

Jasuja Nakuleshwar Dut et al. developed matrix type transdermal patches of a potent anti-atherosclerotic botanical *Emblica officinalis*. Four formulations were prepared using different ratio of polymers, plasticizer and penetration enhancers. Formulations E-1, E-2, E-3 and E-4 were composed of EC and HPMC with the ratios of 6:4, 7:3, 8:2 and 9:1.

Lewis Shaila et al. prepared two types of patch (monolayer, bilayer) by using ethyl cellulose layer (200-300mg) regulates the release of nicotine to the skin. It showed a flux of 95μg/cm^2/h and delivers 27mg of nicotine for 24h from 12cm^2 patch.

**HPMC E50**

Vishwakarma AK et al. extracted turmeric oil and incorporated into transdermal formulation. Turmeric oil was obtained from the rhizomes of *Curcuma longa*. Extraction was carried out by hydro distillation using clevenger’s apparatus following the method of Guenther at room temperature. The \( R_f \) value for curcumin determined by TLC was 0.70 that assured the purity of turmeric oil. Transdermal patches containing turmeric oil was formulated and evaluated. The transdermal patches were prepared using HPMC E50 and
poly vinyl alcohol in different ratio using polyethylene glycol as plasticizer\textsuperscript{30}.

**Menthol**

Morimoto H, Jain AK et al. reported \textit{l}-menthol has been used to facilitate \textit{in vitro} permeation of morphine hydrochloride as well as diffusion of imipramine hydrochloride through hairless rat skin\textsuperscript{31,32}.

Kannikannan N et al. developed transdermal patch of melatonin with 5% of menthol and limonene as permeation enhancer\textsuperscript{33}.

**Glycerine (Glycerol)**

Sahoo B et al. formulated the diclofenac transdermal patch by the solvent evaporation technique using of hydrophilic (hydroxyl propyl methyl cellulose) : hydrophobic (ethyl cellulose) polymers in different ratios and glycerol as plasticizer. Different concentrations of oleic acid and isopropyl myristate were used to enhance the permeation of diclofenac\textsuperscript{34}.

2.5 Recent formulations of selected Phytopharmaceuticals

Lei Y et al. prepared nanocrystals(220nm) of glycyrrhetinic acid with anti-solvent precipitation-ultrasonication method followed by freeze-drying\textsuperscript{35}.

Jia HJ et al. developed 18 β-glycyrrhetinic acid liposome using PEG-7 glyceryl cocoate with encapsulation efficiency was 91.9 ± 2.43%. \textit{In-vitro} study showed lower release rate and higher deposition in epidermis\textsuperscript{36}.

Djekic L et al. formulated 1% 18 β-glycyrrhetinic acid phytosomes using 1% Carbopol\textsuperscript{®}980 and Carbopol\textsuperscript{®}Ultrez 10, 0.4% sodium hydroxide, 10% glycerol, 1% Sepicide\textsuperscript{®}HB (preservative). Carbopol\textsuperscript{®}980 hydrogel was more sensitive\textsuperscript{37}.

Bhardwal A et al. formulated self microemulsifying drug delivery system with 3.5% tween80, 12.5% PEG 400, 50% oil which increased dissolution of boswellic acid >90%\textsuperscript{38}.

Bairwa K e al. developed nanoparticle of 11-keto-β-boswellic acid (152.6nm) by emulsion diffusion evaporation method having 79.7% entrapment efficiency and 60.8% inhibition of rat paw edema\textsuperscript{39}.

Ahmad FJ et al. formulated nanogel of Boswellic acid (22.93nm) with tween 80 as surfactant, labrasol (cosurfactant), 1% carbopol 980 and isopropyl myristate as oil phase by water titration method\textsuperscript{40}.

Ganga Raju et al. formulated synergistic nutraceuticals, pharmaceuticals and diatery supplements anti-inflammatory compositions made up of 11-AKBA and Boswellia serrata non acidic resin extract\textsuperscript{41}. 
References


