Supplementary material

Table S1. Summary of study characteristics.

Active ingredient	Dosage form	In vitro / In vivo study	Carrier material	Other enhancers	Essential oil as Enhancer	Study characteristics	Ref.
Ondansetron HCl	Matrix type transderma l patch	In vitro	Tween20, glycerin, dibutyl phthalate		Menthol oil, Eucalyptus oil, Clove oil, Lemon grass oil	A matrix type transdermal patch of ondansetron was developed using the technique of solvent evaporation. The optimised formulation which contained menthol and Tween 20 demonstrated the maximum release of ondansetron and higher stability. The formulated type patch was shown higher efficacy and bioavailability.	[54]
Celecoxib	Solution	In vitro	Polyethylene glycol 400/ propylene glycol (PEG 400/PG)		Copaiba oil	Copaiba is an essential oil composed mainly of sesquiterpenes and diterpenes. The optimal release and the highest permeation of celecoxib was for a formulation composed of 25% of copaiba oil. The in vitro release and permeability of celecoxib was done using a maximum of Polyehylene glycol 400 / propylene glycol (PEG400/PG) across the membrane and pig ear skin.	[143]
Aceclofenac	Emulgel	In vitro / Ex vivo	Carbopol 940		Clove oil, Mentha oil	The formulation of aceclofenac emulgel was developed using Carbopol 940. The optimised formulation included clove oil and mentha oil as permeation enhancers. The formulation was characterised and the effects of different variables such as spreading coefficient, drug release and viscosity of preparation were assessed.	[70]
Diclofenac Potassium	Gel	In vitro / Ex vivo	CPM		Turpentine oil, Olive oil	A gel formulation of diclofenac potassium was developed using carboxypropyl methylene. The optimised formulation was composed of 1.5% w/v diclofenac, 10% turpentine or olive oil. The physical properties of gel were studied as well as in vitro and in vivo permeation study using Franz diffusion cell. The study found greater flux ability of diclofenac gel containing with turpentine as compared to olive oil.	[25]
Diclofenac sodium	Gel	In vitro / Ex vivo	Ethanol, Carbopol934P		Myristica fragrans	A transdermal gel of diclofenac sodium was developed using Carbopol 940. Methanol and chloroform extract of Myristica fragrans were incorporated into the formulation. The physicochemical properties of the formulation were evaluated as well as in vitro and ex vivo studies . Mystrica fragrans was shown to have a greater cumulative release and permeation enhancing effects as compared to the synthetic enhancers.	[144]
Curcumin	Hydrogel	In vitro	CPM	Tween80	Olive oil	A transdermal hydrogel formulation of curcumin was developed. The optimised formulation contained curcumin 2%, olive oil 2% and Tween 80. The in vitro permeation was evaluated using Franz diffusion cellsand showed good permeation across both artificial and rabbit skin.	[145]

Sumatriptan	Transdermal film	In vitro	Eudragit polymer, triacetin	Oleic acid	Eucalyptus oil	Transdermal film of sumatriptan was developed, characterised and assessed using HPLC method. Triacetin is an optimal plasticizer used in the formulation. The optimised formulation incorporated eucalyptus oil and oleic as permeation enhancers. The in vitro permeation study showed permeation enhancement of sumatriptan compared to formulation without enhancer. The study was found no significant difference in bioavailability while the extent of bioavailability was significantly increased	(2)
Ziprasidone hydrochloride monohydrate	Gel	In vivo / Ex vivo	Carbopol 940, water, ethanol, TEA		Tulsi oil	Ziprasidone hydrochloride monohydrate was formulated as a topical gel using Carbopol 940 with various concentration of tulsi oils. Sonophoresis was used to investigate the permeation of drug using abdominal rat skin. The ultrasonic waves result in disruption of lipid bilayer of the skin and enhancement of the delivery of various substances through the skin. The use of sonophoresis and tulsi oil produce a synergistic permeation enhancing effect.	[146]
Elemene	Matrix type transdermal patch	Ex vivo	Polyvinyl alcohol, sodium carboxymethyl cellulose	Azone, Azone:PG, oleinic acid, leurinol	Eucalyptus oil	A matrix type transdermal patch of elemene was formulated using polyvinyl alcohol and sodium carboxymethyl cellulose in concentration of 30% w/w. The optimisde formulation incorporated to the various penetration enhancers namely AzoneAzone, oleinic acid, eucalyptus and laurinol. The best permeation enhancement was established by using 2% AzoneAzone and 2% propylene glycol (in 1:1 ratio). Moreover, the permeation of elemene was greatly affected by the amount of polyvinyl alcohol and sodium carboxymethyl cellulose in matrices.	[147]
Ketorolac tromethamine	Reservoir type transdermal patch	In vitro	HPMC, PVA, glycerine, EC		Olive oil, d-limonene	A reservoir type transdermal patch of ketorolac tromethamine was developed using HPMC and PVA polymer. The optimised formulation consists of 1:1 ratio of drug to polymer and 10% d-limonene oil. The in vitro permeation and release study wfound better permeation and release of ketorolac incorporated to terpenes than vegetable oils.	[74]
Curcumin	Nanoemulsion	Ex vivo	Soybean lecithin lipoid75, sodium dodecyl sulfate (SDS)		Jojoba oil, Sunflower oil	A nanoemulsion of curcumin was formulated for transdermal delivery of drug using lecithin and sodium dodecyl sulfate (SDS) separately. The study reported lower in vitro toxicity with better permeation ability of curcumin from formulation-based lecithin as compared with SDS based formulation. Also, the type	[132]

						of oil used plays an important role in determination of the depth of penetration of curcumin across stratum corneum.	
Nemsulide	Gel	In vitro	Carbopol 940, TEA, water		Olive oil, Almond oil	A transdermal gel of nemsulide based on Carbopol 940 was developed. Two penetration enhancers, almond and olive oils were incorporated into the formulation at various concentrations. The formulation was characterised for its physicochemical characteristics and stability optimised formulation was composed of 1% nemsulide, 2% Carbopol, 2.5% olive oil and 2.5% almond oil. The in vitro permeation study was performed through a semipermeable membrane using Franz diffusion cells. The study reported a higher permeation from transdermal gel containing a penetration enhancer as compared to formulation without enhancers. It was also shown that the highest permeability of drug (up to 99.5%) was when olive oil and almond oil used together in the formulation.	[27]
Calcipotriol and methotrexate	SLN, NLC, Lipid emulsion	In vitro / In vivo	Myverol 18-04K, Pluronic F68	Precirol ATO 5	Squalene	Calcipotriol and methotrexate, antipsoriatic drus, were incorporated to precirol alone and precirol+squalene for the preparation of solid lipid nanoparticles (SLN), nanostructure lipid carrier (NLC) and lipid emulsion (LE). These formulations were used to study the effects of lipid colloid system on the permeation of the mentioned drugs through the skin. The formulation inner lipid phase carried calcipotriol while the aqueous phase entrapped methotrexate. The formulations were characterised, optimised and evaluated. The permeation study across the mouse skin found an increase in the permeation of calciporiol to a lesser extent than methotrexate. Both drugs permeated in the order NLC>LE>SLN. The study concluded that there are different factors playing a key role in enhancement of permeation such as rate of release of drug, drug partitioning to skin and the presence of the penetration enhancers.	[148]
Oryzanol	Penetration enhancer containing vesicles (PEVs)	In vivo / Ex vivo	Transcutol and Labrasol		Bisabolol	A nanovesicle (penetration enhancer containing vesicle, PEVs) of oryzanol was developed and optimised using penetration enhancers, labrasol and Transcutol with the aid of bisabolol. Labrasol containg formulation was more stable with a s particle size of 296 nm and zeta potential of about -31 mV. Also, it demonstrated superiority in the wound healing over other formulation and marketed product of	[149]

						oryzanol. This made the combination of oryzanol with bisabolol oil a promising strategy in healing of wounds.	
Febuxostat	Transdermal film	In vitro / In vivo / Ex vivo	Tween20 : PEG400, HPMC		Lemon oil	A transdermal film of febuxostat was formulated using the technique of self-nanoemulsifying drug delivery system (SNEDDS). A factorial design was used to optimise the formulation. The effects of ratios of lemon oil, Tween 20 and PEG-400 were evaluated. The optimised formulation was that with the smallest globule size, which contained 20% oil, 40% Tween 20 and 40% PEG 400. The study recommended this technique as a successful method for the improvement of the solubility and permeability of febuxostat through the skin.	[150]
Ketoprofen	Hydrogel	In vitro	Carbopol940, TEA, ethanol		Almond oil	A hydrogel formulation of ketoprofen was developed and characterised. The in vitro permeation was evaluated after incorporation of almond oil. The study showed a positive effect of increasing of almond oil concentration on the percentage of ketoprofen released and permeated.	[29]
Curcumin	Nanoemulsion	In vitro	MCT : terpene, Tween80, soybean lecithin		Eucalyptol, Pinene	A low-energy nanoemulsion of curcumin was developed using spontaneous emulsification. The optimised formulation contained 0.3% curcumin, 10% oil (eucalyptus, pinene, medium chain triglyceride), 10% (polysorbate 80:soybean lecithin, 9:1). The smallest droplet size was produced by the formulation with monoterpene oils. Both the in vitro release and in vivo permeation studies revealed an enhancing effect of eucalyptus oil on solubility and permeation of curcumin across the skin.	[75]
Flurbiprofen	Microemulgel	In vitro / In vivo	Tween80 : ethanol : water, Carbopol940		Galangal oil	A microemulgel of flurbiprofen was prepared using a galangal oil as the oil phase and penetration enhancer. The characterised formulation was showed a greater enhancement ratio (4.06) as compared to flurbiprofen solution with a higher AUC of flurbiprofen (>4 fold) with more than 96% relative bioavailability as compared to oral flurbiprofen.	[151]
Ketoconazole	Microemulsion loaded hydrogel	Ex vivo	HPMC K100M, Carbopol971, Carbopol974, Carbopol980, sodium alginate	Caproyol: nigella, Transcutol: PG	Nigella oil	A formulation of microemulsion-loaded hydrogel of ketoconazole was developed and incorporated nigella oil as a penetration enhancer. The optimised formulation was composed of 54.97% capryol:nigella, 36.07% Transcutol:propylene glycol and 7.13% water which were based on a polymeric gel. The formulation demonstrated thermodynamic stability, sustained release characteristic and enhanced permeability due to the presence of nigella oil. The formulation was considered a good carrier for treatment of fungal infection.	[152]

Timolol maleate	SLN incorporate-d transderma-l patch	–	SLN: Lutrol F68, Tween80, compritol 888ATO, HPMC, EC		Almond oil	A solid lipid nanopaticle of timolol maleate was formulated using a solvent evaporation method. The formulation was a transdermal patch optimised using a factorial design. The optimised patch formulation contained 200mg Hydroxypropyl methylcellulose (HPMC), 100mg ethylcellulose (EC) and 3ml of almond oil. The study found that the increase in HPMC concentration resulted in rapid dissolution of matrix. In addition, almond oil facilitate permeation of timolol transdermally.	[126]
5-Fluorouracil, osthole, paeonol	Solution	In vitro	PEG400/saline		White mustard seed (Sinapis alba L.) volatile oils	The mechanism of penetration enhancement of white mustard seed (Sinapis alba L.) volatile oils (SVO) was investigated using 3 model drugs, 5-fluorouracil, osthole and paeonol. ATR-FTIR spectroscopy and TEM were confirmed the ability of white mustard oil in inducing the disorder of the transdermal lipid structure and increasing the gap between the stratum corneum. The cellular studies found an inhibitory effect of SVO on Ca+2 ATPase. The study was found that SVO were a natural safe product used in transdermal penetration enhancement.	[142]
Metoprolol tartrate	Matrix type transderma l patch	In vitro	Chitosan, lactic acid, PEG400	Urea, SLS	Basil oil	A matrix type transdermal patch of metoprolol was developed using chitosan and PEG 400. Different types of penetration enhancers (synthetic and natural) were investigated through incorporation to the patch. The optimised formulation was composed of 360mg metoprolol, 630mg chitosan, 0.27ml lactic acid, 0.45ml PEG 400 and 1.5% basil oil. Basil oil enhanced the transdermal permeation effectively and improved the release profile of drug.	[153]
5-Fluorouracil, lidocaine, ibuprofen	Solution	Ex vivo	Crude Palm Oil (CPO)		Crude Palm Oil (CPO), Tocotrienol Rich Fraction (TRF) of Palm Oil	The investigation of the activity of transdermal permeation of Crude Palm Oil (CPO) and Tocotrienol Rich Fraction (TRF) of Palm Oil was carried out using 3 model drugs, 5-fluorouracil, ibuprofen and lidocaine. The in vitro permeation study was established using diffusion Franz cell across the full thickness of human skin. The study found a significant increase in permeation of ibuprofen combined with both oils.	[136]

Lopinavir	Liposome	In vitro / Ex vivo	Phospholipid, cholesterol		Olive oil, Peppermint oil	A liposomal cream of lopinavir loaded spray dried powder (L-SDP) was developed for increasing bioavailability and penetration enhancement across the skin. The optimal liposome consisted of liponavir, phospholipon 85G and cholesterol in a ratio of (3:2.5:0.3) respectively transformed into spray dried powder. The optimised L-SDP showed the best properties in term of size, shape, zeta potential and entrappment efficiency%. According to the ex vivo permeation study, liposomal cream resulted in a tenfold increase in the release s compared to traditional cream. In addition, peppermint oil aided the liposome permeation enhancement of lopinavir.	[85]
Aceclofenac	Microemulsion	In vitro	Tween80, ethanol, castor oil		Menthol oil	A microemulsion of aceclofenac 2% was formulated by a titration method. A range of concentrations of oil, surfactant, cosurfactant and water were combined with menthol as a penetration enhancer in order to optimise the formulation. The in vitro permeation studies showed about a 3-fold increase in the transdermal flux due to the effect of 8% menthol in the formulation.	[92]
Caffeine	Microemulsion	Ex vivo	Tween20 : ethanol, water		Grapefruit oil	A caffeine loaded grapefruit microemulsion was developed using a titration method. The formulation was characterised for its physical properties and characteristics such as pH, viscosity, particle size, polydispersity and ex vivo permeation. An optimised formulation was composed of 5% grapefruit oil, 50% (Tween 20:ethanol 9:1) and water. The study considered the formulation as an excellent vehicle for drug carrier and cosmetic preparation.	[154]
Felodipine	Niosome	In vitro	Span60 : cholesterol		Clove oil, Eucalyptus oil, Lemon oil	The effect of essential oils on the transdermal permeation of felodipine was investigated through integrating essential oils into the niosome formulation. The optimised formulation of niosome was composed of felodipine, a blend of Span 60 : cholesterol (2:1) and essential oil. with optimal particle size, shape and entrapment efficiency%. The membrane fluidizing effect of essential oils especially clove and eucalyptus were highlighted by thermal analysis. This effect plays a key role in enhancing the penetration of felodipine through the skin.	[61]
Propanol HCl	Matrix type transdermal patch	In vitro / Ex vivo	EC : PVPK30, DBP, PG		chamomile oil	A matrix type transdermal patch of propranolol was developed with different ratios of Eudragit grades using the technique of solvent evaporation. The formulation was characterised, optimised and evaluated. The in vitro permeation study showed an increase in the percentage of cumulative permeation, flux and ratio of enhancement when the formulation included with 6% chamomile oil.	[155]

Hippophae rhamnoides Linn oil	Nanoemulsion	In vitro	Cremophor EL: lTranscutol p		Hippophae rhamnoides Linn oil	An o/w type nanoemulsion of Hippophae rhamnoides Linn oil was developed, characterised and evaluated. The optimised formulation contained IPM : cremophor EL : Hippophae rhamnoides Linn oil in a ratio (5:16:20). The technique of CLSM found that that nanoemulsion of Hippophae rhamnoides Linn oilhas exhibited stronger fluorescence than tradition topical formulations such as ointment or cream. This indicated that Hippophae nanoemulsion increases the stability of drug and improve its skin permeation.	[156]
Tacrolimus	Microemulsion or Microemulgel	In vitro	Cremophor EL, Transcutol P, water, Carbopol940, oils		Menthol oil, Camphor	A microemulsion of tacrolimus was formulated by incorporating tacrolimus into a eutectic solution of menthol:camphor. The microemulsion formulation was optimised and characterised. The in vitro permeation study showed the superiority of this formulation over the marketed product of tacrolimus. The integration of eutectic menthol:camphor into the formulation of microemulsion provided a synergistic boost on the permeation effect through the skin.	[94]
Terbinafine	Emulgel	In vitro	Span20, liquid paraffin, Tween80, Carbopol 934, Carbopol 940, HPMC E5, HPMC E15, PG, ethanol, propyl paraben, trimethanolamine		Clove oil, Peppermint oil	A emulgel formulation of terbinafine was prepared and characterised for topical antifungal therapy. The emulgel which contained penetration enhancer, clove oil or peppermint oil, was based on 0.5% of Carbopol 934 and 3% of HPMC E5. The optimised formulation demonstrated the highest drug release with the acceptable physicochemical properties.	[66]
Aniba canelilla (H.B.K.) Mez essential oil	Solution	Ex vivo	_		1-nitro-2-phenylethane (Aniba canelilla(H.B.K.) Mez essential oil), methyleugenol (Aniba canelilla(H.B.K.) Mez essential oil)	A bioanalytical method was validated and optimised using microextraction of solid-phase in gas chromatography headspace mode with the aid of detector of flame ionization. This method was used for identification and quantification of 1-nitro-2-phenylethane and methyleugenol derived from the oil of different samples obtained from the skin permeation study such as the layers of porcine ear skin (stratum corneum, epidermis and dermis) and receptor fluid. The method showed gradual increase and dosage dependent penetration. 1-nitro-2-phenylethane and methyleugenol were retained in the skin in the following order: receptor fluid > dermis > epidermis > stratum corneum suggesting their role in deep penetration of skin.	[157]

Tacrolimus, cyclosporin	Nanoemul gel	In vitro / In vivo / Ex vivo	Cremophor RH40 : PEG400		Kalonji oil	Tacrolimus and kalonji oil were formulated as s nanoemulsion for quality characterisation. A nanoemulgel of tacrolimus and kalonji oil was prepared for physicochemical properties and in vitro study of cellular toxicity. A suitable particle size and polydispersity index was exhibited by nanoemulsion. The acceptable spreadability and sustained release with in vitro bioavailability improvement was found using the nanoemulgel.	[158]
Hesperetin, Rutin	Nanocrysta l	In vitro	Urea, PG, ethanol, DMSO		Olive oil	Hesperitin and rutin were formulated as a nanocrystal with different sizes and polydispersity index. The transdermal permeation of the drugs in nanocrystals was investigated using different types of excipients. The study showed a decreasing effect of penetration of drugs due to the hydrophilic excipient such as urea, glycerol and ethanol whereas, the oil vehicle, olive oil, played a positive role in transdermal permeation.	[112]
Ketorolac tromethamine	Solution	In vitro	Potassium phosphate monobasic		Eucalyptus oil, Olive oil, Menthol oil	The effect of different penetration enhancers (chemical and natural) on the transdermal permeation of ketorolac tromethamine was investigated using Franz diffusion cells. The in vitro permeation study was conducted using rat skin and the permeability parameters were evaluated. The study found a higher effectivity of urea, eucalyptus oil, olive oil and menthol in permeation of ketorolac through the skin.	[59]
Celecoxib	Solution	In vitro / In vivo	PEG400/PG		Copaiba oil	The effect of copaiba oil at different concentrations on the permeability of celecoxib was investigated. Porcine ear skin was used in in vitro permeation study. The study showed that the formulation containing 25% copaiba oil resulted in the highest permeation ability of celecoxib across the skin.	[159]
Minoxidil	Nanoemuls ion	In vitro	Volpo-N10 (Brij96v), ethanol, oleic acid, PBS		Eucalyptol	An o/w nanoemulsion of minoxidil 2% was prepared using penetration enhancers, eucalyptol or oleic acid. Franz diffusion cells were used in the in vitro permeation study which was conducted human skin. The optimised formulation of minoxidil nanoemulsion resulted in a significant enhancement in skin permeation as compared to aqueous solution. The study concluded that eucalyptol is more effective penetration enhancer than oleic acid.	[79]

Glimepiride	Matrix type transdermal patch	In vitro / Ex vivo	Eudragit RS100:RL100, PVA	IPM, span80, tween20	Eucalyptus oil, Limonene	A formulation of matrix type transdermal patch of gliumepride was based on Eudragit RL100 and Eudragit RS100. Different types of penetration enhancers, IPM, Span 80, Tween 20, eucalyptus oil and limonene, were incorporated into the formulation. The in vitro permeation study conducted using rabbit skin in Franz diffusion cells. The study found that release rate and transdermal permeation of glimepride were effectively increased by the penetration enhancer. IPM is the most effective penetration enhancer used followed by eucalyptus oil, Span 80, Tween 20 and limonene.	[50]
Meloxicam	Matrix type transdermal patch	In vitro	Chitosan and thiolated chitosan, EC, PVP, Eudragit		Flaxseed oil, Coriander Oil	A transdermal patch of meloxicam was prepared using different types of polymers and the penetration enhancers, coriander or flaxseed oil. The optimised formulation was composed of chitosan:thiolated chitosan (0.3:1.7), ethylycellulose:polyvinyl pyrrolidone (3:1) or Eudragit:polyvinyl pyrrolidone (5:1). The physicochemical properties of the patches were evaluated and the in vitro release and permeation study was conducted in rabbit skin. The maximum flux was shown with the formulation containing coriander and flaxseed at concentration of 5 and 10%, respectively.	[160]
Fluconazole	Hydrogel	In vitro / In vivo	Chitosan, HPMC		Clove oil, Cinnamon oil	A hydrogel formulation of fluconazole was developed and characterised for drug content, pH and rheological characteristics. The optimised formulation which contained 3 or 5% of cinnamon oil or 5% of clove oil, was based on a gelling agent of a combination of chitosan/HPMC. The in vitro release study showed sustained release of fluconazole with the highest flux through the synthetic membrane.	[69]
Indomethacin	Matrix type transdermal patch	In vitro	HPMC, PVP K30, PEG400		Patchouli oil	A matrix type transdermal patch of indomethacin was developed using patchouli oil as a penetration enhancer through the epidermis of rat. The optimised formulation which contained 1% of patchouli oil has satisfactory physicochemical properties and a potential enhancement activity of patchouli oil which was comparable to standard enhancer, DMSO.	[161]

Quercetin	Microemulsion	In vitro	Cremophor EL, 1,2-propanediol, oils		Peppermint oil, Clove oil, Rosemary oil	An essential oil-based nanoemulsion of quercetin was developed in order to improve the solubility of quercetin, protect from light and alkaline pH and enhance transdermal permeation. The optimised blank nanoemulsion was composed of cremophor EL, 1,2-propanediol and essential oil at ratios (47:23:30, w/w). Three essential oils, peppermint, clove and rosemary oil, were ncorporated into the formulation. The formulated quercetin nanoemulsion demonstrated better solubility, greater stability at alkaline pH and more photoprotective ability. Also, the in vitro permeation study found an increase in the transdermal permeation of quercetin, double or triple fold as compared to the aqueous solution.	[67]
Flurbiprofen	Gel	In vitro / In vivo	Hydroxypropyl-β-cyclodextrin (HPβCD) inclusion complex, CCarbopol940, glycerine / TEA		Turpentine oil	A CarbopolCarbopol 940 gel of flurbiprofen / Hydroxypropyl-β-cyclodextrin (HPβCD) inclusion complexes with or without turpentine oil as a penetration enhancer was formulated. The in vitro permeation study was conducted using abdominal skin of rats. It was found that there was a ignificant enhancement of permeability using the formulation with turpentine oil. The cumulative release of flurbiprofen / HPbCD inclusion complex was 103% which is 10-fold higher compared to flurbiprofen alone. The in vivo pharmacokinetic study found double Cmax, shorter Tmax with a relative bioavailability comparable to the marketed flurbiprofen	[106]
Paraffin, petrolatum, almond and jojoba oil	Solution	In vivo	Liquid paraffin, petrolatum, jojoba, almond oil		Almond oil, Jojoba oil	The impact of the oils derived from plants and minerals on the depth profile of the stratum corneum intercellular lipid was investigated. The mechanism of the interaction between the oils and intercellular structure of stratum corneum was assessed by confocal Raman spectroscopy. The study reported a different response of stratum corneum to oil. Both types of oil were deposited in the superficial stratum corneum, 0-20% of the depth. A significant increase in disturbance of the lateral and lamellar packing order of intercellular structure was shown as compared to intact skin. Plant oils disturbed intercellular structure in depth of 30% and 70-90% of the stratum corneum thickness.	[128]

Miconazole	Solution	In vitro	Acetylcysteine, alcohol, camphor, EDTA, HPC, starch phosphate, purified water, Magnesium aluminium silicate, menthol, propylene carbonate, PG, NaOH, Na thioglycolate, strontium chloride,	Tea tree oil, thymol, urea	Menthol oil, Thymol, Tea tree oil, Eucalyptus oil	Three in vitro model assays were used for the investigation of the penetration ability of a novel formulation of miconazole into the nail. Different penetration enhancers were tested in the formulation of miconazole solution such as eucalyptus oil, thymol, menthol and tea tree oil.	[162]
Chlorhexidine	Solution	Ex vivo	IPM		1,8-cineole	A solution of 2% chlorhexidine containing isopropyl alcohol was prepared with and without 1,8-cineole as a penetration enhancer. An ex vivo permeation study was conducted through human skin using Franz diffusion cells. The study found a significant increase (about 33%) in chlorhexidine permeation as compared to solution without enhancer.	[81]
5-Fluorouracil	Biodegradable polymeric nanogel	In vivo / Ex vivo	PLGA-chitosan		Eucalyptus oil	A double walled biodegradable polymer of PLGA-chitosan nanogel loaded with 5-fluorouracil was formulated and coated using 1% eucalyptus oil for topical application. The formulation was optimised and characterised for size, polydispersity index, shape and rheological properties. The ex vivo permeation study using porcine skin showed enhanced permeation potential of eucalyptus oil coated formulation. The in vivo and ex vivo results were suggested the biodegradable nanogel as a promising potential for skin cancer treatment.	[40]
Paeoniflorin	Glycerosome	In vitro / In vivo	Phospholipid, cholesterol, glycerol		Speranskia tuberculata essential oil	The formulation of glycerosome containing essential oil was developed and loaded with paeoniflorin in order to improve the transdermal administration of drug and enhance the absorption into synovium. The optimised formulation contained 5% w/w phospholipid, 10% w/v glycerol, 0.6% w/v cholesterol and a penetration enhancer, 2% v/v Speranskia tuberculata essential oil (STO). The in vitro permeation study reported a superiority of glycerosome containing STO over liposome, glycerosome and tinctures. This was confirmed by an imaging study with the greatest synovial accumulation of drug from STO-glycerosome.	[163]

Glabridin	Nanoemulsion	In vitro / In vivo	Tween80 : glycerol, IPM, water		Menthol oil, Camphor	A nanoemulsion of glabridin was developed using a eutectic mixture of menthol:camphor (1:1, w/w) in order to enhance the permeation of drug. The optimised formulation, which consisted of 0.25% glabridin, 5% oil, 5% glycerol, 10% Tween and 79.75% water, had satisfactory particle size with long-term stability. The in vitro permeation study results were supported by an in vivo permeation study and onfirmed the higher permeability of glabridin from nanoemulsion using eutectic mixture as compared to glabridin solution and nanoemulsion formulated with IPM.	[95]
Diclofenac diethanolamine	Matrix type transdermal patch	In vivo / Ex vivo	Sodium CMC, PVP-K30, Di-n-butylphthalate		Turpentine oil, Sesame oil	A matrix type transdermal patch of diclofenac was developed using sodium carboxymethyl cellulose and polyvinyl pyrrolidone K30 with penetration enhancers such as turpentine oil and sesame oil. The formulation was optimised and characterised for its physicochemical properties. The ex vivo permeation study was conducted across abdominal skin of rat using Franz diffusion cells. The study showed higher permeation enhancement effect of turpentine oil as compared to sesame oil. The study reported a preference of the diclofenac transdermal film for its therapeutic effect as compared to sustained release tablet.	[103]
Flurbiprofen	Matrix type Transdermal patch	In vitro / In vivo / Ex vivo	PVA, EC, PVP, ethanol, Di-n-butyl phthalate		Milk thistle oil	A flurbiprofen transdermal patch was developed using permeation enhancers, milk thistle oil and olive oil. The formulation was optimised and characterised for its physicochemical properties. The in vitro skin permeation study, which was conducted through synthetic membrane and rabbit skin, found enhanced release of drug from formulation with 5-10% milk thistle oil. The formulation with 10% milk thistle oil had higher permeation ability through the rabbit skin as compared to olive oil. The in vivo permeation study was conducted across rabbit skin for further evaluation of pharmacokinetic parameters.	[164]
Ibuprofen	Solution	In vitro	PG:IPA	Azone	Turpentine oil, Angelica, Chuanxiong, Cyperus, Cinnamon oil, Clove oil	The enhancement effect of various essential oils on the permeation of ibuprofen was investigated. Among these essential oils, turpentine, Angelica chuanxiong, Cyperus, cinnamon and olive oils were used at 3%concentration. The in vitro permeation study was conducted through the abdominal skin of rat using Franz diffusion cell. The study was shown a higher enhancing effect of these oils on the permeation of ibuprofen as compared to Azone through disturbing the lipid bilayer.	(12)

Indomethacin	Ointment	In vitro	White petrolatum	Tween80	Palm kernel oil	A hydrocarbon-based ointment of indomethacin was developed using Tween 80, kernel oil, hydrolysed or transesterified derivative of kernel oil. The in vitro skin permeation study was conducted in rabbit skin using Franz diffusion cells. The study wfound a higher permeation of indomethacin with Tween 80 at a concentration as low as 5%. However, kernel oil and its derivatives enhanced indomethacin permeation in a concentration-dependant manner	[165]
Lornoxicam	Microemulsion based gel	In vitro / In vivo	Cremophor EL : isopropanol, Carbopol940		Pine oil	A microemulsion of lornoxicam was developed using pine oil, cremophor RH40, isopropanol and water. The formulation was optimised and evaluated using Box-Behnken design. The optimised formulation was incorporated into carbomer 940 gel to form a microemulsion based gel in order to sustain the transdermal permeability. Upon comparison, the microemulsion based gel showedn significant anti-inflammatory difference from gel and in vivo bioavailability behaviour from oral tablet.	[166]
Imiquimod	Solid nanoemulsion	In vitro / In vivo	Squalene / tocopherol, medium chain triglyceride (MCT)	Squalene / tocopherol	Avocado oil, Jojoba wax, Squalene	A solid nanoemulsion loaded imiquimod was combined with a peptide antigen model, SIINFEKL. Different oils, medium chain triglyceride, jojoba wax, squalene and avocado oil were incorporated into the formulation. The in vitro permeation study using Franz diffusion cell found a reduction in the permeation of imiquimod through murine skin as compared to a cream formulation of imiquimod. However, the in vivo performance of the solid nanoemulsion containing squalene/tocopherol was better than imiquimod cream although it was comparable to medium chain triglyceride containing formulation of imiquimod.	[133]
Phycocyanin	Santosome	In vitro / In vivo	Hydrogenated phosphatidylcholine, Pg, cholesterol, PBS		Santolina insularis terpenes	Santosome, a biocarrier, was developedusing a combination of Santolina insularis and hydrogenated phosphatidylcholine. The formulation entrapped phycocyanin and was incorporated into propylene glycol as a penetration enhancer. The in vitro study reported no toxicities against cells, and the in vivo study revealed inhibition of oedema confirming the wound healing potential of phycocyanin.	[167]

Toluidine Blue O	Microemulsion	In vitro	Tween80: glycerol, EDTA, water		Eucalyptus oil	A microemulsion based essential oil was developed and entrapped a photosensitizer, Toluidine Blue O. The physicochemical features of the formulation were characterised and evaluated. CLSM was used to evaluate the permeation of toluidine blue O through the stratum corneum of porcine ear skin.The microemulsion was effective in enhancing the toluidine blue O permeability through the skin. This suggested toluidine blue O-microemulsion had potential in inactivation of topical pathogens.	[57]
Caffeine, Naproxen	Nanoemulsion	In vitro	Volpo-N10 (Brij96v), ethanol	Oleic acid	Eucalyptol	An o/w nanoemulsion of caffeine and naproxen was developed separately using oleic acid and eucalyptol as an oil phase and penetration enhancers. The optimised formulation was composed of 3% of caffeine or 2% naproxen, and a mixture of surfactant (Volpo-N10), co-surfactant (ethanol) and oil phase in a ratio of 1:1:0.6. The in vitro skin permeation study was carried out through epidermal membrane using Franz diffusion cells. The study found a significant increase in the transdermal permeation of caffeine and naproxen nanoemulsion as compared to aqueous solution.	[76]
Metoprolol tartrate	Matrix type transdermal patch	In vitro / In vivo	EC: ERL100, dibutyl phthalate	IPM, DMSO, span20, tween20	Eucalyptus oil	A matrix type transdermal patch of metoprolol was developed using various chemical enhancers, The matrix patch was composed of ethylene cellulose and Eudragit RL100 in a ratio of 8:2. The formulation ncorporated 10% of IPM, Span 20, Tween 20, DMSO or eucalyptus oil as well as 40% of plasticizer, dibutyl phthalate. The formulation was characterised for its physicochemical properties, evaluated and optimised. The diffusion study was carried out through rabbit skin using Franz diffusion cells. The study found the highest permeation enhancement using a formulation containing IPM followed by Tween 20, span 20, DMSO and eucalyptus oil. The in vivo study analysed pharmacokinetic parameters in comparison to the oral administration.	[51]
Diclofenac sodium	Emulsified microemulsion	In vitro	Monolinolein		R-(+)-limonene	An emulsified microemulsion of diclofenac sodium was developed using 60% R-(+)-limonene and 35% monolinolein. The formulation was characterised using small angle x-ray scattering (SAXS). Franz diffusion cell and in vitro tape stripping were used for assessment of permeation of drug across porcine skin. The studies found higher permeation of diclofenac loaded emulsified microemulsion as compared to cubic and hexagonal phases.	[99]

Santolina insularis	Penetration enhancer containing vesicles (PEVs)	In vitro	Phosphatidylcholine and ethylene or PG, water		Santolina insularis oil	A penetration enhancer containing vesicles (PEVs), a nanocarrier, was developed using phosphatidylcholine and propylene glycol or ethylene glycol with 10% water. Santolina insularis, an essential oil, was incorporated into the PEVs and the physicochemical characteristics and stability of formulations were evaluated. CLSM was used to show superiority of PEVs in enhancing Santolina insularis permeation into skin as compared to controla such as liposomea.	[168]
Ketorolac tromethamine	Matrix type transdermal patch	In vivo / Ex vivo	Carbopol934, EC, di-n-butyl phthalate, PVA, PVP		Turpentine Oil	A matrix type transdermal patch of ketorolac was prepared using Carbopol 934 and ethylcellulose with and without penetration enhancer, turpentine oil. The formulation was characterised and optimised. An ex vivo skin permeation study and in vivo inflammatory tests were performed. The studies found higher drug permeation as well as anti-inflammatory activity as compared to the formulation without penetration enhancer.	[105]
Flurbiprofen	Emulgel, hydrogel, foam	In vitro	span60, Tween80, methyl paraben, propyl parabens, PEG400, xanthan gum	Emu oil, crocodile, liquid paraffin	Olive oil, Coconut oil, Grape seed oil, Avocado oil	An emulgel of flurbiprofen was developed using 6 different natural oils and compared to liquid paraffin-containing emulgel and hydrogel. The effect of the various oil on transdermal permeation of drug were studied using Franz diffusion cells and a tape stripping method. Based on the transdermal flux of emulgel, the results reported effectiveness in the following order: hydrogel>>>olive oil>>liquid paraffin>>coconut oil>>grape seed oil>>avocado oil≥crocodile oil>>emu oil.	[23]
Indomethacin, benzocaine	Microemulsion	In vitro / In vivo	Tween80, ethanol, water		Eucalyptus oil	A microemulsion formulation was developed using eucalyptus oil, Tween 80, ethanol, and water in ratios 20:30:30:20. Indomethacin and benzocaine were selected as model drugs and incorporated separately or in combination into formulations. The in vitro and in vivo studies found enhanced transdermal flux of both drugs with shortened lag time as compared to an aqueous solution. The study reported a high potential of microemulsion in transdermal administration of both drugs.	[58]
Osthole, ferulic acid, puerarin, geniposide, tetramethylpyrazine	Solution	In vitro	PG : water		Zanthoxylum bungeanum	The transdermal permeation enhancement effect of Zanthoxylum bungeanum oil and its principal constituents were investigated and compared. Five model drugs (osthole, tetramethylpyrazine, ferulic acid, puerarin and geniposide) from traditional Chinese medicine were selected. These drugs were used inan in vitro skin permeation study across abdominal skin of rats using Franz diffusion cells. The study reported the highest permeation impact of drug by Z. bungeanum oil followed by limonene, 1,8-cineole and terpinen-4-ol.	[169]

Celecoxib	Gel	In vitro	Carbopol940	PG	Tulsi oil	The formulation of transdermal gel was developed using Carbopol 940 in propylene glycol. The gel was entrapped with celecoxib and combined with penetration enhancers such as turpentine oil and tulsi oil. The formulation was optimised, characterised and evaluated. The in vitro skin permeation study was conducted through the rat skin using Franz diffusion cells. The study found significant penetration enhancement of celecoxib from formulation containing tulsi oil compared to turpentine oil.	[170]
Hydrocortisone acetate	Microemulsion based gel	In vitro / In vivo / Ex vivo	Tween80 : ethanol, Carbopol940		Eucalyptus oil, Clove oil, Lemon grass oil	A microemulsion of hydrocortisone acetate was developed using Tween 80 and ethanol and containing natural penetration enhancer such as eucalyptus, clove and lemon grass oil. The optimised formulation was composed of natural enhancer (2.5%), Tween 80 (15%) and ethanol (45%). A microemulsion based gel was formulated by incorporating Carbopol 940 into the optimised microemulsion. The resultant microemulsion based gel showed better retention of drug in skin layers than the marketed product.	[56]
Phentolamine	Gel	In vitro / In vivo	HPMC	Azone	Peppermint oil	A transdermal gel of phentolamine was developed using different types of penetration enhancers, sodium dodecyl sulfate, Azone, pharmasolve, Transcutol P, propylene glycol, Labrasol, peppermint oil (hydrophilic and lipophilic) and oleic acid. The formulation was characterised for its physicochemical properties, stability and in vivo studies. Ane in vitro skin permeation study was carried out through rabbit skin. The study reported a significant enhancement of drug permeation through the skin from the formulation containing hydrophilic peppermint oil.	[17]
Tretenoin	Microemulsion	In vitro	Tween80 : PG : water		Olive oil	A microemulsion of tretinoin was developed using a phase diagram study. The optimised formulation was composed of 15% olive oil, 33% Tween 80, 12% propylene glycol and 40% water. The study investigated the effect of variables on the formulation characteristics. The in vitro release study was carried out using Franz diffusion cella across dialysis membrane. It reported an enhanced release of tretinoin as compared to marketed cream and gel.	[119]

Ascorbic acid	Ointment	In vitro	Glycerine, ethanol, sodium metabisulfite, vaseline album	Tween80	Palm kernel oil	The effect of Tween 80 and palm kernel oil on the skin permeation of ascorbic acid was investigated. Various formulations of ointment containing 10% ascorbic acid were prepared, characterised and optimised. The optimised formulation was composed of Tween 80 (2.5-5%) and palm kernel oil (35%). The in vitro skin permeation study using Franz diffusion cell through rabbit skin reported a penetration enhancement effect of Tween 80 and palm kernel oil on the permeability of ascorbic acid.	[171]
Olanzapine	Matrix type transdermal patch	In vitro / In vivo	ERL100:ERS100	Sodium lauryl sulphate, Benzalkonium chloride, span20	Olive oil	A matrix type transdermal patch was formulated using Eudragit RL100 and Eudragit RS100 in different ratios (3:2). The formulation entrapped olanzapine and contained a penetration enhancer. A number of penetration enhancers were selected and investigated in the formulation. The in vitro skin permeation study showed highest permeation of drug from formulation containing Span 20 as a penetration enhancer. The study considered this formulation as an optimised one and assessed it by further in vivo tests using rabbit as a model animal.	[120]
Clotrimazole	Gel	In vitro	Tween80, TEA, ethanol, carboxy polymethylene (CPM)	Tween80	Almond oil	A clotrimazole gel was prepared incorporating almond oil and Tween 80. The formulation was characterised, optimised and evaluated. The effect of almond oil and Tween 80 was assessed by the in vitro skin permeation study using Franz diffusion cells. The permeation of clotrimazole through the rabbit skin was increased with increasing Tween 80 concentration and decreasing almond oil concentration. The study reported a synergistic effect of the combination of almond oil and Tween 80.	[124]
Diclofenac diethanolamine	lotion	In vitro / In vivo	Carbomer980, ethanol, phosphate buffered saline	PG	Turpentine oil	A topical lotion formulation of diclofenac diethylamine was developed using different penetration enhancers, turpentine oil and propylene glycol. The formulation was subjected to characterisation of the physical properties and both in vitro and in vivo studies. The in vitro permeation study was carried out through synthetic membrane and rabbit skin using Franz diffusion cells. The study reported the maximum flux of diclofenac from the formulation containing 4% v/v propylene glycol and turpentine oil.	[172]

Calcium thioglycolates	Cream	In vitro	Liquid paraffin, span60, cetylalcohol, propyl paraben, lanolin, bees wax, PG, Tween80, DMSO, ethanol		Peppermint oil, Orange oil	The effect of different penetration enhancers on depilation time of calcium thioglycolate was investigated. The study showed a twofold reduction in tear resistance time by using ethanol, peppermint oil and DMSO. Also, an increase of temperature to 37°C and hydration reduced tear resistant time by 4 and 1.5 times, respectively. These results were claimed to decrease skin irritation and increase the user's compliance.	[86]
2,3,5,6-Tetramethylpyrazine	Reservoir type transdermal patch	In vitro / In vivo	Carbopol934p, ethanol		Eucalyptus oil	A reservoir type transdermal patch of tetramethylpyrazine was developed using eucalyptus oil as a penetration enhancer. The in vitro permeation study was performed through the dorsal skin of rats. It found the greatest extent of permeation using the formulation containing 5% eucalyptus oil as compared to control. An in vivo study demonstrated satidfactory pharmacokineticssiand it was considered that this formulation could be a better alternative for oral and intravenous administration.	[53]
Menthol and methyl salicylate	Ointment	In vivo	Castor oil, PEG4000, liquid paraffin, PEG400		Clove oil	Five different bases of ointment were used for the formulation of ointment. All the batches were composed of 5% menthol, 15% methyl salicylate and 1% clove oil as a penetration enhancer. The physical properties were determined and optimised. A water miscible-based ointment was considered the optimal formulation for its greatest anti-inflammatory activities as compared to a commercial formulation.	[173]
Risperidone	Matrix type transdermal patch	In vitro / In vivo	ERL100:ERS100		Olive oil, Groundnut oil, Jojoba oil	A matrix type transdermal patch of risperidone was developed containing different penetration enhancers. The formulation was characterised for physicochemical properties and an in vitro study of permeation was undertaken. The optimised formulation was composed of 20% of risperidone, film of Eudragit-based polymer (ERL100:ERS100, 3:2) and a mixture of jojoba oil and olive oil. The in vitro skin permeation study was conducted using Franz diffusion cells through rat skin. Risperidone had high permeation from the optimised formulation and the e formulation is further assessed for pharmacokinetic characteristics.	[30]

Benzoyl peroxide	Emulgel	In vitro	Tween20, Span60, Carbopol940, PG, Methylparaben, propyl paraben, disodium EDTA, butylated hydroxyl toluene		Almond oil, Jojoba oil, Sesame oil, Wheat germ oil	An emulgel of benzoyl peroxide was formulated using 4 different natural oils: jojoba, sesame, almond and wheat germ oil. The formulation was characterised for its physicochemical properties and an in vitro permeation study was done. The optimised formulation was composed of 5% of benzoyl peroxide, 1.5% Carbopol 940, 6% sesame oil, 2% Tween 20, 2.5% Span 60 and 5% propylene glycol. The optimised formulation hsd the greatest release of drug, antimicrobial activity and the least irritation of the skin.	[127]
Ondansetron HCl	Matrix type transderma l patch	In vitro / Ex vivo	ERS100, PVP, TEC (Triethylcitrate), DBS (dibutyl sebacate)	castor oil	Linseed oil, Eugenol	A matrix type transdermal patch of ondansetron was developed using a solvent casting method. The optimised formulation was composed of polymeric base of Eudragit RS100 and polyvinyl pyrrolidone in a ratio of 2:1, 20% dibutyl sebacate as a plasticizer and 3% linseed oil. The in vitro skin permeation and release studies were investigated using Franz diffusion cells. It was shownthat the release of drug was higher with increased concentration of polyvinyl pyrrolidone and dibutyl sebacate.	[174]
Lipid and water soluble vitamines (A, E, B6 and C)	Emulsion	In vitro	A and E: Prunus amygdalus dulcis oil, glycerol oleate, cera alba, tocopherol, retinyl acetate. B6 and C: Prunus amygdalus dulcis oil, glycerol oleate, cera alba,Polyacrylami de C13-14 , isoparaffin laureth-7 acsorbic acid, pyridoxine.		Lemon (Citrus limon, Burm.f.) essential oil	O/w and w/o emulsions of a number of lipophilic and hydrophilic vitamins were developed incorporaitng lemon essential oil. The permeation of vitamin A, E, B6 and C from the formulation were conducted through human skin using Franz diffusion cells. The study found an enhancement effect of lemon oil on the permeation of vitamin A, E, B6 and C by 4.1, 9, 3.4 and 5.8-fold, respectively. The study recommended lemon oil as a safe and effective penetration enhancer.	[175]

Curcumin	Solution	In vitro	Soybean oil, liquid paraffin, petrolatum, jojoba, avocado, almond oil	Soybean oil, liquid paraffin, petrolatum	Almond oil, Jojoba oil	The penetration behaviour of natural oils soybean oil, liquid paraffin, petrolatum, jojoba, avocado and almond oil) across the stratum corneum was investigated using confocal laser scanning microscopy. The transepidermal water loss measurement was also used for evaluation of the occlusion capability of oils. An in vivo study was conducted and reported the ability of the vegetable oils and paraffin oil in penetrating the first upper part of the stratum corneum. Also, the oils, except jojoba oil werefound to occlude the skin surface in a similar way. Petrolatum was shown to have the most effective occlusive ability.	[129]
Huperzine A, Ligustrazine phosphate	Microemulsion based transdermal patch	In vitro	Cremophor RH40, ethanol, oleic acid, PVA124, PVP K90, sorbitol		1,8-cineole	A microemulsion-based transdermal patch was developed for the delivery of huperzine A and ligustrazine phosphate simultaneously. The formulation was composed of oleic acid, Cremophor RH40 and ethanol with a penetration enhancer, 1,8-cineole. The in vitro skin permeation was conducted through abdominal rat skin using Franz diffusion celsl. The study reported the enhancing effect of microemulsion on the permeation rate of both drugs as compared to control.Release from the patch followed zero order kinetic behaviour and a pharmacodynamic study found a synergistic effect between the two drugs.	[77]
Ketoconazole	Transfersomal gel	In vitro / Ex vivo	Lecithin, Tween80, dichloromethane, Carbopol		Eucalyptus oil	A transfersome-based gel of ketoconazole was developed, evaluated and characterised for its physicochemical features and stability. Different essential oils were incorporated into the formulation as penetration enhancers. The in vitro permeation was studied through cellulose membrane using Franz diffusion cells. The drug release and permeation were improved significantly from the formulation containing eucalyptus oil.	[55]
Ketoprofen	Matrix type transdermal patch, gel	In vitro / Ex vivo	Gel: CPM, TEA, ethanol Patch: Eudragit, ethanol, PG		Almond oil	A transdermal gel and patch of ketoprofen were developed using a natural penetration enhancer, almond oil. The formulations were evaluated and characterised for their physicochemical characteristics and stability. The in vitro skin permeation study was conducted through synthetic membrane and rabbit skin using Franz diffusion cells. The study showed a significant enhancing effect of almond oil on the permeation of ketoprofen at a concentration of 3%.	[125]

Mefenamic acid	Emulgel	In vitro / In vivo / Ex vivo	Carbopol940, liquid paraffin, Tween20, Span20, PG, ethanol, Methylparaben, ethyl paraben		Mentha oil, Clove oil	An emulgel of mefenamic acid was prepared using Carbopol 940 as a gelling agent. The penetration enhancers, mantha oil and clove oil, were incorporated in the formulation. The formulation was evaluated and characterised for its physicochemical characteristics, in vitro and ex vivo release and biological activity. The study recommended the formulation containing 6% mentha oil or 10% clove oil as an optimised formulation and comparable with the commercial gel of diclofenac.	[68]
Zinc phthalocyanine tetrasulfonate (ZnPcSO4)	Microemulsion	In vitro / In vivo	Span80/Tween80, PG : water		Canola oil	A microemulsion of zinc phthalocyanine tetrasulfonate (ZnPcSO4) was developed using ternary phase diagrams. The optimised formulation was composed of canola oil, (Span 80/ Tween 80) and (propylene glycol / water) in a ratio of 47:38:15. The formulation was characterised for its rheological and physicochemical properties. An in vitro skin permeation study was carried out through porcine ear using Franz diffusion cells. The permeation of $ZnPcSO_4$ was increased significantly in the stratum corneum and epidermis+dermis, by a factor of 33 and 28, respectively as compared to drug in solution. This result was supported by in vivo studies which found a 1.6- and 5.6-fold increase in concentration of $ZnPcSO_4$ in stratum corneum and (epidermis + dermis).	[176]
Ibuprofen	Hydrogel	In vitro / Ex vivo	CPM, TEA, ethanol		Turpentine oil	A carboxypoly methylene hydrogel was developed and entrapped ibuprofen with and without turpentine oil, as a penetration enhancer. The formulation was evaluated and characterised for its physical properties. The in vitro and ex vivo skin permeation studies were carried out across cellulose membrane and abdominal skin of rats using Franz diffusion cells. The study found the highest flux of ibuprofen from the formulation with 3% turpentine oil.	[104]
Ketorolac tromethamine	Reservoir type transdermal patch	In vitro / In vivo	HPMC, PVP polymer		d-limonene, Cineole, Olive oil, Menthol oil, Linseed oil, Sunflower oil	A reservoir type transdermal patch of ketorolac tromethamine was developed. The patch film was formulated by a solvent casting technique using HPMC and polyvinyl alcohol and glycerin as plasticizer. A number of natural penetration enhancers were incorporated into the formulation such as cineole, d-limonene, olive oil, menthol, sunflower and linseed oil. The in vitro skin permeation study was performed through the abdominal skin of rats using Franz diffusion cells. The study found that the greatest permeation of ketorolac was from the formulation containing d-limonene. The skin permeation of ketorolac was enhanced by penetration enhancers as follows: cineole > olive oil > menthol > linseed>sunflower oil.	[177]

Cinnamaldehyde	Solution	In vitro	Ethanol, aqueous ethanol, PG, Acetone:olive	Acetone:olive	Olive oil	The penetration of trans-cinnamaldehyde and its vehicle was monitored inside skin using confocal Raman spectroscopy. Different vehicles, propylene glycol, aqueous ethanol, olive oil and acetone, were assessed and showed different rate of penetration of cinnamaldehyde. The study reported the superiority of acetone over other vehicles followed by aqueous ethanol, propylene glycol and olive oil. The study selected the combined solvent of acetone:olive oil for local lymph node assay.	[110]
Curcumin	Microemulsion	In vitro	Tween80 : ethanol : water		Eucalyptol	A microemulsion formulation of curcumin was developed containing 25% eucalyptol, 12.5% Tween 80, 37.5% ethanol and 25% water. An in vitro permeation study was conducted across porcine ear skin using Franz diffusion cells. The study found a 15.7-fold increase in the permeation of curcumin from the formulated microemulsion as compared to eucalyptol only (control).	(14)
Celecoxib	Matrix type transdermal patch	In vitro / In vivo	PVP : HPMC, glycerol	Isopropyl alcohol	Eucalyptus oil	A matrix type transdermal patch of celecoxib was developed using a film casting technique. The formulation was prepared, optimised and characterised for its physicochemical properties, in vitro release and permeation studies and in vivo studies. The optimised formulation was composed of 2% celecoxib, 3% polyvinyl pyrrolidone, 10% eucalyptus oil and glycerol with 20% of polymer. The in vitro release study, using paddle over disk method, found 99.68% of the drug was released. The in vitro permeation study using Keshary-Chien diffusion cells through artificial membranes and rat skin reported 96.01% drug permeated. The optimised formulation was used in in vivo studies for anti-inflammatory activities.	(13)
Collagen	Solution	Ex vivo	ZnO nanoparticle	Liquid paraffin, DMSO, THF	Sunflower oil, Olive oil, Coconut oil	The effect of a combination of zinc oxide nanoparticles and different penetration enhancer oils on the transdermal permeation of collagen was investigated. This was carried out using an ex vivo permeation study across animal skins using diffusion cells. The study showed n a synergistic effect of the combination of liquid paraffin with zinc oxide nanoparticles on improving the transdermal permeation of collagen.	[121]

Ketoprofen	Acrylic pressure-sensitive adhesive (PSA) transdermal patch	In vitro	Siliconized paper and polyolefin backing membrane. Acrylax ER-7306		α-pinene, Limonene, Menthone	A matrix type transdermal patch of ketoprofen was developed using a solvent casting method. The formulation was composed of acrylic pressure-sensitive adhesive and the ppenetration enhancers, terpenes. The formulation was evaluated and characterised for its physicochemical features and stability. The optimised formulation which was used in an in vitro permeation study was shown a significant increase in the flux of ketoprofen with an increase in the polymer content and the inclusion of terpenes.	[80]
Clotrimazole	Matrix type transdermal patch	In vitro	Eudragit, ethocel, PG, ethanol + acetone		Olive oil	A matrix type transdermal patch of clotrimazole was developed using a solvent evaporation method. The formulation, which was based on a matrix, composed of Eudragit and Ethocel (1:1) with propylene glycol as a plasticizer. The formulation incorporated with olive oil in a range of concentrations. The formulation was optimised and characterised for its physicochemical characteristics and in vitro permeation study. The in vitro skin permeation study was carried out through artificial membrane and rabbit skin using Franz diffusion cells. The study reported the highest permeation of clotrimazole from the formulation containing 3% olive oil.	[28]
Kaempferia parviflora	Microemulsion, Microemulgel, Pluronic lecithin organogel	In vitro	ME: oleic acid, Tween20, PG, water. MEG: ME, xanthan gum. Pluronic lecithin organogel: lecithin, oleic acid, IPM, poloxamer407, water.		Limonene	A extract of Kaempferia parviflora 10% was loaded in 3 different formulations, microemulsion, microemulgel and Pluronic lecithin organogel. Limonene, as a penetration enhancer, was incorporated into each formulation which were evaluated and characterised for stability and in vitro permeation study. The in vitro skin permeation was carried out through porcine skin using Franz diffusion cells. All of the formulations resulted in high skin permeability of extract and in the following order: microemulsion > microemulgel > pluronic lecithin organogel.	[100]
All trans retenoic acid	SLN, NLC, Nanoemulsion	In vitro	MCT, oleic acid, cetylpalmitate, Transcutol P, butylated hydroxytoluene, Tween20, Tween80		Limonene, 1,8-cineole	All-trans retinoic acid was formulated as a lipid nanoparticle, solid lipid nanoparticle (SLN), nanostructure lipid carrier (NLC) and nanoemulsion using terpenes, limonene and 1,8-cineole. Both SLN and NLC, which incorporated terpenes, exhibited satisfactory physicochemical characteristics, stability and toxicity. CLSM showed the highest skin permeation of all-trans retinoic acid from SLN containing 10% limonene. The study also reported the ability of SLN and NLCto enhance epidermal penetration of rhodamine B.	[98]

Pseudoephedrine HCl	Gel	In vitro	TEA, ethanol, Carbopol934p		Thyme oil	A gel formulation of pseudoephedrine was developed using thyme oil as a penetration enhancer. The formulation was characterised for its physicochemical properties, stability and in vitro skin permeation study. The in vitro release and permeation studies were performed through cellulose membrane and rabbit skin using Franz diffusion cells. The studies found an improvement in transdermal permeation of drug from the formulation containing thyme oil at concentration (0.5-3%)	[178]
Triclosan and Chlorhexidine digluconate	SLN, Nanoemulsion	In vitro / In vivo	SLN: Glyceryl behenate, glyceryl palmitostearate NE: Tween80, span80		Eucalyptus oil, Olive oil	Triclosan and chlorhexidine digluconate were formulated as solid lipid nanoparticles (SLNs) and nanoemulsion (NEs) using different types of lipids and oils. The formulations were characterised and optimised according to their physicochemical features and better permeability of skin. The in vitro skin permeation study of triclosan and chlorhexidine was carried out through a synthetic membrane and porcine skin using Franz diffusion cells. The study reported the superiority of penetration of triclosan-SLN using glyceryl palmitostearate as compared to glyceryl behenate. In addition, triclosan-NE was shown to have higher permeability than triclosan-SLN. The permeation of chlorhexidine from NE containing eucalyptus oil was greater ability than formulation containing olive oil.	[62]
Ibuprofen	Cream	In vitro	Cetostearyl alcohol, white petrolatum, methyl paraben, propyl paraben, liquid paraffin, Tween80, TEA, Carbopol 980, glycerin		Olive oil	A 2% ibuprofen cream was developed, characterised, evaluated and optimised as a novel topical preparation. Olive oil was chosen as a penetration enhancer which was incorporated into the optimised formulation. Franz diffusion cells were used for establishing the in vitro release and permeation study. The formulation with olive oil produced a better release and permeation ability of ibuprofen as compared to the formulation without permeation enhancer.	[118]
NaFl	Ultradeformable liposome	In vitro	Phosphatidylcholine, cholesterol, Tween20, PBS		d-limonene, 1,8-cineole, Geraniol	An ultradeformable liposome of NaFl was developed using monoterpenes as penetration enhancers. The formulation was characterised and optimised according to the physicochemical characteristics and in vitro permeation across the skin. The in vitro permeation study was performed across porcine skin using Franz diffusion cells. The study howed an improvement in skin penetration of NaFl from the formulation containing monoterpenes (1,8-cineole, geraniol, d-limonene).	[78]

18-β-Glycyrrhetinic acid, Boswellic acid	Reservoir type transdermal patch, Matrix type transdermal patch	In vitro / In vivo / Ex vivo	Reservoir: ethanol : carbapol934, piperine Matrix: HPMC E50, glycerine, piperine.		Menthol oil	A reservoir and matrix type transdermal patch of 2 phytopharmaceuticals, 18b-glycyrrhetinic acid and boswellic acid, were developed using piperine (as bioenhancer) and menthol (chemical enhancer). The formulations were characterised and optimised for their physicochemical properties and in vitro, ex vivo and in vivo studies. The matrix type patch resulted in 97.8% and 93.2% in vitro and ex vivo drug release, respectively, while the reservoir patch had 95.55% and 91.58% in vitro and ex vivo drug release, respectively. There was no significant difference in the anti-inflammatory activity between the two patch types.	[93]
α-Asarone	Hot-melt, pressure-sensitive adhesive (HMPSA) transdermal patch	In vitro	Styrene-isoprene-styrene, tri-block copolymer, hydrogenate petroleum resin, liquid paraffin, dibutyl phthalate, 2,6-di-tert-butyl-p-cresol	Oleic acid	Menthol oil	A transdermal patch of α-asarone was developed using hot melt pressure-sensitive adhesives, which were shown to be compatible with different kinds of penetration enhancers. The in vitro permeation study was performed through porcine skin. The study wfound a maximum permeation rate of drug from the formulation containing 1% oleic acid and 4% menthol in combination. A replacement of a portion of plasticizer by penetration enhancer was used to optimise the adhesion and effectivity of formulation.	[91]
Losartan	Solution	In vitro	Ethanol: PBS		Tea tree oil, Cumin oil, Rose oil, Aloe vera oil	Four different essential oils (rose, tea tree, aloe vera and cumin oil) were investigated for their effect on the transdermal permeation of losartan potassium. The in vitro skin permeation study was performed using rat skin. The study reported a superior permeation enhancing effect of aloe vera oil followed by rose, cumin and tea tree oil. However, the target permeation required for delivery of therapeutic dose of losartan transdermally was provided by aloe vera oil only. This supported the feasibility of aloe vera oil use in transdermal formulation of losartan.	[138]
Vitamin A	NLC	In vitro / Ex vivo	Emulium, Brij721, lecithin, sodium dehydroacetate		Prickly pear seed oil	A prickly pear seed oil based nanostructured lipid carrier loaded vitamin A was developed using a hot homogenization method. The formulation was characterised for its physicochemical properties. The formulation showed an enhanced in vitro drug release. The ex vivo skin permeation study found a greater deposition of drug in rat skin as compared to solid lipid nanoparticle without prickly pear seed oil. This supported the use of prickly pear seed oil in cosmetology.	[179]

Ketoprofen	Nanoparticles loaded emulgel	In vitro	HPMC, chitosan-chondriotin, Tween80		Argan oil	An argan oil based emulgel was developed and entrapped a nanoparticle of chitosan-chondriotin sulfate loaded ketoprofen. The formulation was characterised with a particle size of 300-500 nm, entrapment efficiency of more than 76% and release rate of 77%. The study showed a significant enhancement of skin permeation of ketoprofen from the optimised formulation as compared to the commercial gel.	[180]
Ubiquinone (CoQ10)	Nanoemulsion	In vivo	Tween80, span80, ethanol, acetate buffer solution		Virgin cocunut oil	A nanoemulsion of ubiquinone (CoQ10) was developed using virgin coconut oil. The optimised formulation was composed of 1% ubiquinone, 18.66% Tween 80, 1.92% Span 80, 3.42% ethanol and virgin coconut oil up to 100%. The formulation was characterised for its physicochemical properties and an in vitro permeation study was performed through rat skin. The study reported a deeper penetration of ubiquinone through the skin from nanoemulsion formulation as compared to emulsion.	[181]
Diclofenac sodium	Gel	In vitro	Carbopol940, TEA, ethanol, glycerol, oleic acid, urea		Karanj oil	The effect of karanj oil on the permeation of diclofenac sodium transdermally was investigated using Franz diffusion cells. The in vitro permeation study fpund an enhancement effect of karanj oil on the drug permeation. Maximum permeation was from the formulation containing ethanol while an additive permeation effect was shown from glycerol containing formulation.	[182]
Olanzapine	Matrix type transdermal patch	In vitro / In vivo	ERL100:ERS100, isopropanol dichloromethane, di-n-butyl phthalate		Corn (maize) oil, Groundnut oil, Jojoba oil	Three natural oils (corn, jojoba and groundnut oil) were incorporated separately into a matrix type transdermal patch of olanzapine in order to investigate their permeation enhancement ability. The in vitro permeation study was carried out through rat skin using Franz diffusion cells. The study showed a higher enhancement of flux by corn oil compared to jojoba and groundnut oil. There was a higher cumulative amount of drug permeated and no irritation was observed on skin.	[26]
Meloxicam	Gel	In vitro	Tween80, oleic acid, Carbopol940, Carbopol934, TEA		sesame oil	A hydrogel formulation of meloxicam was developed using a dispersion method. The optimised formulation was composed of 1% meloxicam, 1% Carbopol 934 and 2% sesame oil as a penetration enhancer. The in vitro permeation study was conducted through pig skin using Keshary-Chein diffusion cells. The study reported that an increase in the concentration of sesame oil was resulted in the highest release rate of drug.	[183]

Tamoxifen citrate	Nanoemulsion	In vitro	Cremophor EL : ethanol		Arachis oil	A nanoemulsion formulation of tamoxifen was developed using arachis oil as an oil phase. The optimised formulation was composed of 5% of tamoxifene, 4.12% of arachis oil, 37.15% of (Cremophor EL:ethanol) and 58.73% of water. The optimised formulation was that with the highest permeation of drug, the lowest globule size and viscosity. Nanoemulsion was suggested as a novel formulation for tamoxifen.	[184]
Pioglitazone	Hydrogel	In vitro / Ex vivo	TEA, ethanol, carboxy polymethylene		Eucalyptus oil, Almond oil	A gel formulation of pioglitazone was developed with penetration enhancer. The physicochemical properties of formulation were evaluated and characterised. The in vitro skin permeation study across the rabbit skin showed the highest drug permeation with the formulation containing the highest concentration of penetration enhancers, i.e. 0.3% almond oil and 2% eucalyptus oil.	[41]
Flurbiprofen	Gel	In vitro / Ex vivo	CPM, TEA, ethanol		Olive oil	A gel formulation of flurbiprofen was developed containing olive oil as a penetration enhancer. The in vitro release study was performed using Franz diffusion cells across an artificial membrane and rabbit skin. The study reported an increase in the enhancement effect of penetration with an increase in the concentration of olive oil in the formulation.	[111]

Abbreviations in summary of characteristics

C_{max}: maximum concentration, CMC: carboxymethyl cellulose, CPM: carboxypolymethylene, DBS: dibutyl sebacate, DMSO: dimethyl sulfoxide, EC: ethylcellulose, EDTA: ethylene diamine tetra acetic acid, ERL100: Eudragit RL100, ERS100: Eudragit RS100, HPC: hydroxypropyl cellulose, HPMC: hydroxypropyl methylcellulose, IPA: isopropyl alcohol, IPM: isopropyl myristate, MCT: medium chain triglyceride, ME: microemulsion, MEG: microemulgel, NLC: nanostructure lipid carrier, PBS: phosphate-buffered saline, PEG: polyethylene glycol, PG: propylene glycol, PLGA: Poly (lactic-co-glycolic acid), PVP: polyvinyl pyrrolidone, SDS: sodium dodecyl sulfate, SLN: solid lipid nanoparticle, SLS: Sodium lauryl sulfate, TEA: trimethylamine, TEC: triethyl citrate, THF: tetrahydrofuran, T_{max}: time taken to reach the maximum concentration.

Table S2. Criteria used for the risk assessment of biasness within included studies in this systematic review [32]

Study area	Description	Reviewer's judgement
Research rationale	Explanation of research rationale including aim and objectives, allowing sufficient knowledge to facilitate the decision-making process.	Was research rationale (hypothesis and/or aim and/or objectives) adequately described?
Description of methodology	Methodology of the experiments are described adequately allowing sufficient knowledge to facilitate the decision-making process and there are probable chances of replication.	Was research methodology adequately/sufficiently described?
Characterization and testing	Characterization and testing techniques are relevant and described in sufficient detail that there are probable chances of replication.	Were research characterization and testing techniques adequately/sufficiently described?
Description of results	Results are described in sufficient detail, allowing sufficient knowledge to facilitate the decision-making process.	Were results adequately/sufficiently described?
Description of discussion	Results are plausibly discussed, allowing sufficient knowledge to facilitate the decision-making process.	Were results discussed adequately/sufficiently described?
Description of conclusions	Conclusions are described in accordance with set hypothesis, allowing sufficient knowledge to facilitate the decision-making process.	Were conclusions adequately/sufficiently described and relevant to rationale?
Other source of bias	Any other important concern not addressed using the described key areas of the present tool.	Was the study free of any unexpected problem?

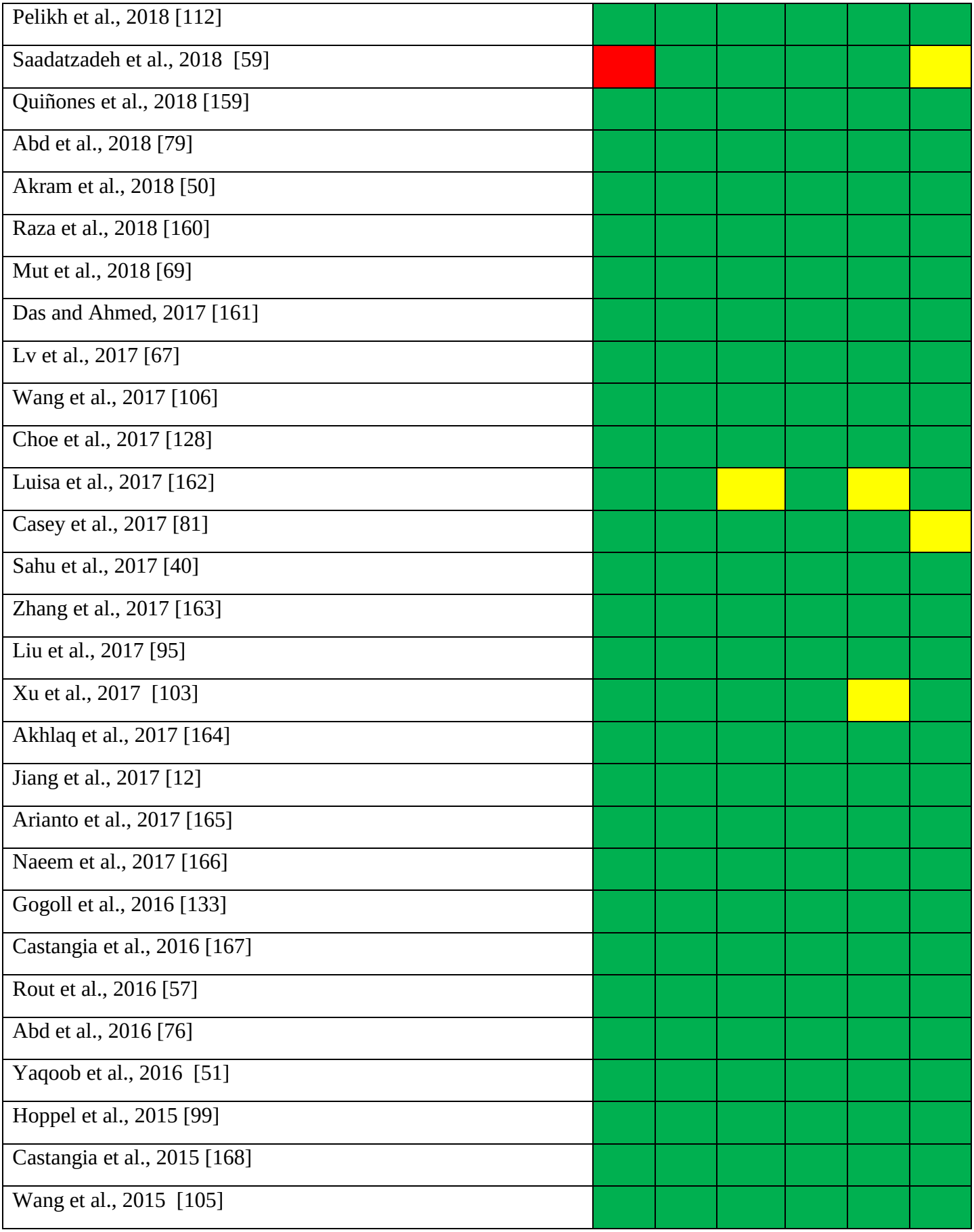
Table S3. The interpretation of risk of bias of studies included in this Systematic Review (within and across study) [32]

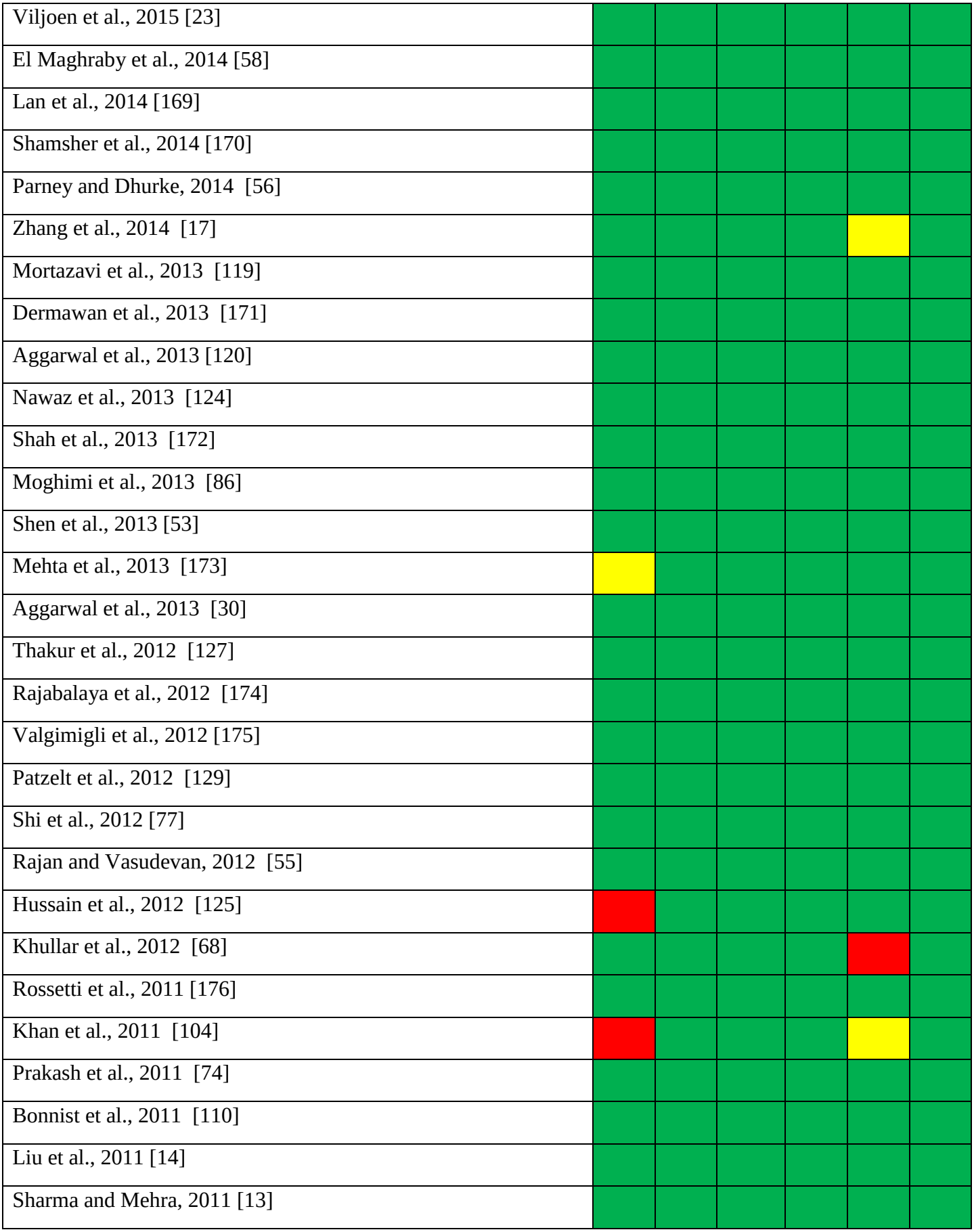
Risk of bias	Interpretation	Within study	Across study
Low (Green)	Probable bias evidence implausible to seriously affect the findings with no impact on confidence	All major areas have low risk of bias	Most of the studies are found to have low risk of bias, not impacting the result interpretation process.
Unclear (Yellow)	Probable bias evidence to raise doubts regarding findings with mild to moderate impact on confidence	One or more area of study has unclear risk of bias.	Most of the studies are found to have low with/or unclear risk of bias, not impacting the result interpretation process.
High (Red)	Probable bias evidence seriously affecting the finings with high impact on confidence	One or more area of study has high risk of bias.	High proportion of studies have high risk of bias, sufficiently impacting the result interpretation process.

Table S4. The risk of biasness assessment of the included literature.

Study ID (Reference)	Risk of biasness parameters					
	Research rationale	Description of methods	Characterization and testing	Description of results	Discussion	Overall conclusion
Madkaikar et al., 2018 [54]						
Quiñones et al., 2018 [143]						
Magdum et al., 2016 [70]						
Hussain et al., 2015 [25]						

Patwardhan et al., 2015 [144]						
El-Nabarawi et al., 2013 [2]						
Nawaz et al., 2012 [145]						
Rani et al., 2012 [146]						
Zeng et al., 2011 [147]						
Hsu et al., 2011 [148]						
Goudanavar et al., 2011 [177]						
Mahmood et al., 2019 [27]						
Vater et al., 2020 [132]						
Aldalaen et al., 2020 [149]						
Alhakamy et al., 2020 [150]						
Hasan et al., 2019 [29]						
Nikolic et al., 2020 [75]						
Dong et al., 2020 [151]						
Amra MS and Momin, 2019 [152]						
Kumar et al., 2019 [126]						
Ruan et al., 2019 [142]						
Chauhan and Saini, 2019 [153]						
Singh et al., 2019 [136]						
Maniyar and Kokare, 2018 [85]						
Ahmed and Das, 2019 [92]						
Limpongsa et al., 2019 [154]						
Eid et al., 2019 [61]						
Akhlaq et al., 2019 [155]						
Shen et al., 2019 [156]						
Wang et al., 2019 [94]						
Arora et al., 2018 [66]						
Kreutz et al., 2018 [157]						
Sahu et al., 2018 [158]						


Pelikh et al., 2018 [112]
Saadatzadeh et al., 2018 [59]
Quiñones et al., 2018 [159]
Abd et al., 2018 [79]
Akram et al., 2018 [50]
Raza et al., 2018 [160]
Mut et al., 2018 [69]
Das and Ahmed, 2017 [161]
Lv et al., 2017 [67]
Wang et al., 2017 [106]
Choe et al., 2017 [128]
Luisa et al., 2017 [162]
Casey et al., 2017 [81]
Sahu et al., 2017 [40]
Zhang et al., 2017 [163]
Liu et al., 2017 [95]
Xu et al., 2017 [103]
Akhlaq et al., 2017 [164]
Jiang et al., 2017 [12]
Arianto et al., 2017 [165]
Naeem et al., 2017 [166]
Gogoll et al., 2016 [133]
Castangia et al., 2016 [167]
Rout et al., 2016 [57]
Abd et al., 2016 [76]
Yaqoob et al., 2016 [51]
Hoppel et al., 2015 [99]
Castangia et al., 2015 [168]
Wang et al., 2015 [105]


Viljoen et al., 2015 [23]
El Maghraby et al., 2014 [58]
Lan et al., 2014 [169]
Shamsher et al., 2014 [170]
Parney and Dhurke, 2014 [56]
Zhang et al., 2014 [17]
Mortazavi et al., 2013 [119]
Dermawan et al., 2013 [171]
Aggarwal et al., 2013 [120]
Nawaz et al., 2013 [124]
Shah et al., 2013 [172]
Moghimi et al., 2013 [86]
Shen et al., 2013 [53]
Mehta et al., 2013 [173]
Aggarwal et al., 2013 [30]
Thakur et al., 2012 [127]
Rajabalaya et al., 2012 [174]
Valgimigli et al., 2012 [175]
Patzelt et al., 2012 [129]
Shi et al., 2012 [77]
Rajan and Vasudevan, 2012 [55]
Hussain et al., 2012 [125]
Khullar et al., 2012 [68]
Rossetti et al., 2011 [176]
Khan et al., 2011 [104]
Prakash et al., 2011 [74]
Bonnist et al., 2011 [110]
Liu et al., 2011 [14]
Sharma and Mehra, 2011 [13]

Shokri and Javar, 2015 [121]						
Ngawhirunpat et al., 2012 [80]						
Nawaz et al., 2011 [28]						
Wattanasri et al., 2016 [100]						
Ngawhirunpat et al., 2014 [98]						
Gul et al., 2019 [178]						
Kakadia, 2016 [62]						
Khan, 2018 [118]						
Subongkot et al., 2012 [78]						
Patel, 2017 [93]						
Yu et al., 2013 [91]						
Vashisth et al., 2014 [138]						
Alzahabi et al., 2019 [179]						
Gul et al., 2018 [180]						
Erawati et al., 2018 [181]						
Rajput et al., 2014 [182]						
Aggarwal et al., 2012 [26]						
Sareen et al., 2011 [183]						
Pathan and Setty, 2011 [184]						
Akhlaq et al., 2019 [41]						
Hussain et al., 2012 [111]						

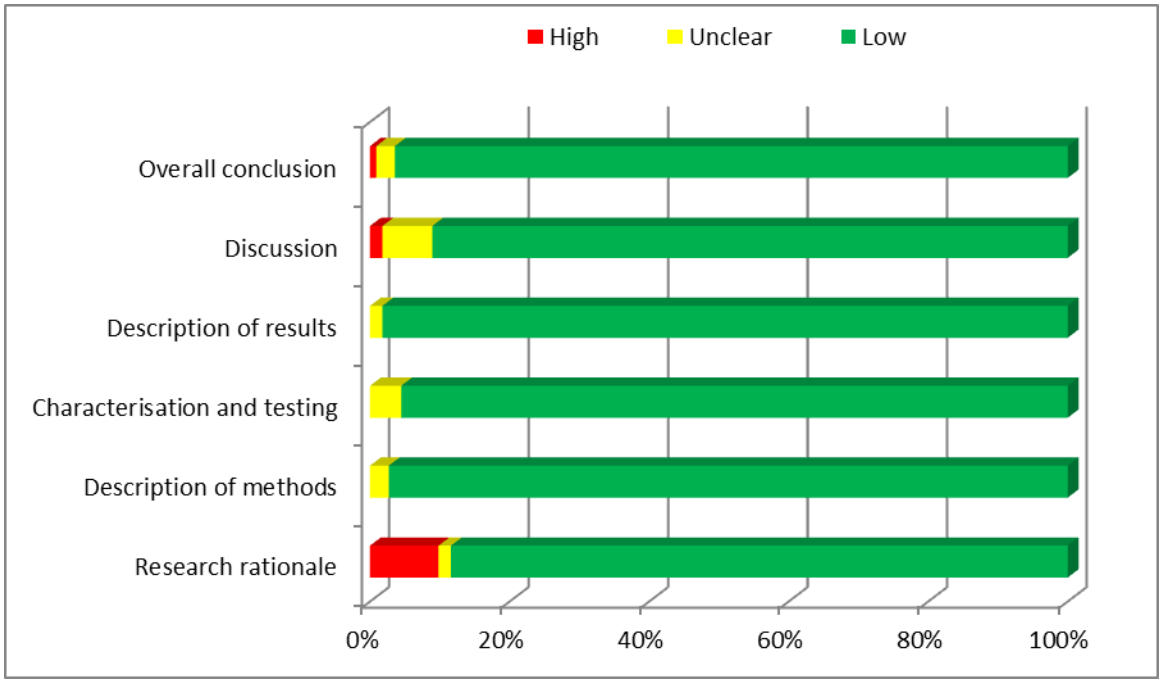


Figure S1. The risk of biasness of eligible articles.

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