REVIEW OF LITURETURE

3.1 Review of literature on topical drug delivery system

Topical delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. acne) or the cutaneous manifestations of a general disease (e.g. psoriasis) with the intent of containing the pharmacological or other effect of the drug to the surface of the skin or within the skin. Semi-solid formulation in all their diversity dominate the system for topical delivery, but foams, spray, medicated powders, solution, and even medicated adhesive systems are in use[14].

3.1.1 Basic principle of permeation[15]

In the initial transient diffusion stage, drugs molecules may penetrate the skin along the hair follicles or sweat ducts and then be absorbed through the follicular epithelium and sebaceous glands. When a steady state has been reached diffusion through stratum corneam becomes the dominant pathway.

The membrane-limited flux (J) under steady condition is described by expression.

$$J = \frac{DAK_{O/W}\, r\, C}{h} \qquad \text{(Equation 1)}$$

Where,

J = Amount of drug passing through the membrane system per unit area, per unit area per unit time.

D= Diffusion coefficient

A= Area of the membrane

C= Concentration gradient

$K_{o/w}$= Membranes / vehicle partition coefficient

h= Thickness of the membrane.

3.1.2 Kinetics of permeation[16-18]

Knowledge of skin permeation is vital to the successful development of topical formulation. Permeation of a drug involves the following steps,

- Sorption by stratum corneum,
- Penetration of drug though viable epidermis,
- Uptake of the drug by the capillary network in the dermal papillary layer.

This permeation can be possible only if the drug possesses certain physicochemical properties. The rate of permeation across the skin (dQ/dt) is given by:

$$\frac{dQ}{dt} = P_s (C_d - C_r) \qquad \text{(Equation 2)}$$

Where,

C_d and C_r = Concentrations of skin penetrant in the donor compartment (e. g. on the surface of stratum corneum) and in the receptor compartment (e.g. body) respectively.

P_s = Overall permeability coefficient of the skin tissues to the penetrant.

This permeability coefficient is given by the relationship:

$$P_s = \frac{K_s \, D_{ss}}{H_s} \qquad \text{(Equation 3)}$$

Where,

K_s = Partition coefficient for the interfacial partitioning of the penetrant molecule form a solution medium on to the stratum corneum,

D_{ss} = Apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues,

h_s = Overall thickness of skin tissues.

As K_s, D_{ss} and hs are constant under given conditions, the permeability coefficient (P_s) for a skin penetrant can be considered to be constant.

From equation 2, it is clear that a constant rate of drug permeation can be obtain when $C_d >> C_r$ i.e., the drug concentration at the surface of the stratum corneam (C_d) is consistently and substantially greater than the drug concentration in the body (C_r). The equation 2 becomes:

$$\frac{dQ}{dt} = P_s C_d \qquad \text{(Equation 4)}$$

The rate of skin permeation (dQ/dt) is constant provide the magnitude of C_d remains fairly constant throughout the course of skin permeation. For keeping C_d constant, the drug should be released from the device at a rate (R_r) that is either constant or greater than the rate of skin uptake (R_a) i.e. $R_r >> R_a$.

3.1.3 Factors affecting topical drug delivery

3.1.3.1 Physiological factors

Age

Structural and functional changes occur as the skin ages. It is not clear whether the changes are because of cumulative environmental damage or inherent ageing processes. It has been determined however that the SC seems to be little affected over the normal lifespan of an individual[19]. Studies have shown that the water content of human skin decreases with age[20]. The extent of skin hydration can have a significant impact on the permeation of a drug molecule hence skin ageing could lead to a change in the drug's ability to diffuse through the skin[19].

With age, dermal blood flow tends to decrease thus resulting in a reduction of transdermal drug flux. This factor however is not of major significance for the current

research work as it applies more to transdermal drug delivery rather than to topical drug delivery[19]. Ageing was found to not have a significant effect on the permeation of water, oestradiol, caffeine, methyl nicotinate and aspirin and thus it is not expected that the permeation of other similar compounds would be significantly affected by ageing[21,22].

Hydration of skin

The level of hydration of the SC can have a significance impact on drug permeation. An increase in hydration is known to increase penetration of the drug molecule through the skin for most drugs[19]. This increased penetration of substances is attributed to the softening and swelling of the skin tissue resulting in a 'sponging' effect where pore size is increased hence allowing greater flux of substances through the skin[23]. The use of occlusive dressing and patches or occlusive dosage forms such as ointments have been shown to increase the hydration of the SC and therefore increase percutaneous absorption of drug molecules[19].

The moisture which results in the hydration of the SC originates either from the underlying epidermal tissue of the skin or from perspiration from occluded appedages. The moisture content in normal SC varies between 10-25% of dry tissue weight but this level of moisture content can change in certain disease states thereby affecting the permeation of the skin[24].

Race

There are limited literature reports concerning the differences or similarities between races when considering topical drug delivery. Studies which have been conducted on the permeation of benzoic acid, nicotine and aspirin between African, Asian and Europeans skin showed no significant difference between transepidermal water loss amongst these different groups[25]. However, there are significance differences in the SC hydration

between races suggesting a potential source for variations in inter-racial percutaneous absorption. Due to the limited data available, generalized conclusions cannot be made concerning variations in topical drug delivery between races[19].

Body site

It is obvious that the skin structure varies at different anatomical sites of the body for example, it is much thicker in regions such as that palms of the hands and the soles of the feet than it is at the lips or eyelids[19]. Variations in skin permeation observed at different sites cannot, however, be simply attributed to differences in skin structure at different areas of the body. This point is supported by studies conducted by Wester and Maibach which showed differences in permeation at different sites of the body which had the same thickness[26].

In addition to differences in skin thickness at different body sites, the density of skin appendages also varies at different areas of the skin and this could further contribute to differences observed in site to site permeation[27]. There are some general trends with site to site permeability. Generally, the genital tissue is the most permeable and the skin of the head and neck is relatively more than that of the arms and legs[19]. The generalized rank order of site permeability is as follow;

Genitalia > head, face and neck> trunk > arm > leg

It is of value to consider variability of permeation at the same site within the same individual. It is estimated that the variation at a body site within the same individual is approximately 30% while variation at the same site in different individuals is estimated at 40%. It is clear then that interregional variations can exceed these figures[28].

The issue of variation in permeation at different sites is a complex one. Different investigators have reported different rank orders with respect to permeability of the skin

at various sites. It has been suggested that skin permeability is a function of the resistance to permeation per unit thickness of the SC at that particular site and the overall skin thickness. For example, the SC thickness at regions such as the palms may be 400-600 µm at other body sites. Regardless of the greater thickness of the SC in the palm regions, it has been found that the SC in these areas is less resistant per unit thickness making permeation of a drug lower in such regions but not as low as would be expected when just considering differences in skin thickness[27].

Integrity of the skin

Intact healthy skin forms a barrier difficult to penetrate for many substances as it should be. The occurrence of disease or any form of abrasion or damage which alters the structure of the skin may lead to a modification in the barrier function of the skin. If the skin is inflamed with loss of SC and altered keratinisation then the ability of this organ to prevent absorption of external molecules is compromised and the permeability of the skin is increased. An example of one such disease is psoriasis which results in a defective SC. It has been found that psoriatic skin may absorb as much as twice the amount of 8-methoxypsoralen that is absorbed by uncompromised skin[27,29].

Skin metabolism

The human skin contains numerous drug-metabolizing enzymes. Histochemical and immunehistochemical studies show that most of these enzymes are located in the epidermis, sebaceous gland and hair follicles. Although the enzymes are present at concentrations considerably lower than in the liver, they have been found to exhibit sufficient metabolic activity which may affect the bioavailability of the topically applied medicament. Most of the metabolic reactions which can occur in the skin are oxidation, reduction, hydrolysis, methylation and glucuronidation reactions. The microorganisms

which are present in the skin such as *staphylococcus epidermis* may also metabolize topically applied drugs[19]. It has been reported that the skin can metabolize up to 5% of some of the drugs available for topical treatment, an example being steroidal hormones[28].

Other factors

Since most molecules pass through the skin by diffusion, changes in temperature at the skin surface could result in changes in the skin penetration of the drug. Increase in temperature results in an increase in the diffusion coefficient of drug molecule ultimately resulting in an increase in the dermal penetration of the drug. The reported temperature of the outer skin surface is approximately 32^0c and increasing the temperature may induce structural changes within the SC which may increase permeation[19].

In theory, alterations in the peripheral blood flow may affect transdermal absorption of drugs. An increased blood flow could increase the concentration gradient across the skin thereby creating sink conditions which may drive the diffusion process from the skin surface into deeper underlying tissue. In the same way, reducing blood flow to the skin could result in a decrease in the clearance rate of topically applied drugs to the skin. However, the issue of blood flow is more relevant when considering transdermal drug delivery and not topical drug delivery[27].

Generally, rubbing of the formulation on the skin will affect the amount of drug absorbed. The longer the period of rubbing and the greater the force used, the greater the absorption of the drug. Another factor that affects percutaneous absorption is the contact period of the formulation. The longer contact period between the formulation and the skin, greater the degree of permeation of the drug through the skin. It is important to note that saturation of the skin, changes in hydration of the skin which occur after application of the formulation and changes in the quality/integrity/state of the formulation itself may

rule out any significant additional permeation of the drug regardless of how long the formulation remains in contact with the skin[23].

3.1.3.2 Pharmaceutical factors

Vehicle composition

Most products applied to the skin for medicinal purposes contain an active drug molecule along with a mixture of inert substances, often called excipients, each with its own unique purpose. Some of these excipients are generally classified as fragrances, co-solvents, preservatives, stabilizers and so on and collectively they are referred to as the vehicle[30]. Absorption of the drugs seems to occur best when the drug is in a vehicle which covers the skin easily and mixed readily with sebum to allow the drug to come into direct contact with tissue cells[23]. The pharmacological effect of the drug molecule is determined in part by the ability of the drug molecule to diffuse out of the vehicle and into the skin[30]. The ability of the drug molecule to move out of the formulation is affected by the solubility of the drug in the vehicle and also by the viscosity of the vehicle itself. Highly viscous vehicles will increase the diffusion coefficient of the drug molecule and consequently result in poor penetration of the medicament.

The solubility of the drug in the vehicle will affect the partitioning of the medicament between the vehicle and the targeted skin surface. If the medicament is highly soluble in the vehicle, it will tend to partition more favorably into the vehicle resulting in poor penetration into the SC. It is thus important for the vehicle to have a suitable balance in terms of solubility which allows for a formulation with suitable solubility to provide aesthetic appeal while at the same time allowing the drug to partition favorably into the SC lipids in order for the drug to reach its target site[31]. Some vehicles have the ability to enhance the hydration of the skin. Oleaginous vehicles occlude the skin surface and thus

prevent evaporation of moisture thereby increasing the water content of the SC. This results in an increase in percutaneous absorption of the molecules in the formulation[30].

Permeation enhancers

Permeation Enhancers have been reported to work in a number of ways. They may increase the solubility of the drug molecule in the SC intercellular lipids by changing the nature of the SC lipids. Some enhancers alter and denature intercellular keratin in the SC thus causing increased hydration[32]. Animal and vegetable oils have been found to facilitate better permeation of drugs than mineral oils as theynpenetrate the skin more readily. Organic solvents such as acetone, benzene and PG have been found to enhance permeation of molecules dissolved in them due to their ability to penetrate the skin[23].

Drug concentration in the formulation

According to Fick's First Law of diffusion, the flux of the drug molecule is directly proportional to the concentration gradient of the molecule across the diffusion path. It follows that the amount of drug absorbed per unit area over a specified time interval increases as the drug concentration in the formulation increases.

Ensuring that the formulation is saturated with the drug will allow for the maximum flux to be achieved in a thermodynamically stable environment. Theoretically, effectively formulated saturated formulations may achieve reproducible percutaneous absorption with drug release kinetics close to zero order kinetics[26,27].

3.1.3.3 Physicochemical properties of drugs

Drug solubility

Percutaneous absorption is affected to a large extent by the solubility of the medicament in lipophilic media. Generally, the more soluble drug is in oil, greater percutaneous absorption. It is, however, important for the drug to possess some degree of solubility in

the aqueous phase to allow the drug to penetrate the deeper more hydrophilic layers of the skin which occur beyond the SC. Drugs which have a good balance between lipophilic and hydrophilic solubility tend to achieve higher concentrations in dermal tissue[23].

Diffusion coefficient (D)

Diffusion coefficient (D) is used as an indicator of the rate of penetration and degree of resistance to penetration of a molecule through the skin. In the skin, the value of D decreases as the penetrant reaches deeper more compact layers of the SC. D is expressed in Fick's First law of diffusion:

$$J = -D \frac{dC}{dX} \qquad \text{(Equation 5)}$$

Where,

J = Rate of transfer per unit area of surface (Flux)

C = Concentration of diffusing substance

X = Space coordinate measured normal to the section

D = Diffusion coefficient

As indicated by the negative sign on the equation, the flux is in the direction of decreasing concentration. The equation shows that an increase in D will result in an increase in the rate of transfer of the drug molecule across the skin and ultimately result in an increase in skin permeation. In biological membranes such as the skin, it is difficult to separate the value of D from that of the partition coefficient[27].

Partition coefficient (K)

The partition coefficient (K) is a measure of the drug's ability to partition out of the formulation into the SC. The value of K is important in establishing the net movement of

drug through the SC. The magnitude of K is especially important when the SC is the rate limiting step in the penetration of a drug molecule across the skin. K values which are too high are often associated with binding of the drug substances to the structures in the SC and poor penetration of the aqueous layers of the epidermis while low K values result in poor partitioning of the drug into the SC. K is affected by factors such as the drug's solubility in vehicle, ionization rate of the drug, the drug concentration in the formulation and the drug's own balance between lipophilic and hydrophilic properties[27].

Protein binding

Generally, the more atoms on a particular molecule, higher the probability of protein binding through the formation of hydrogen bonds. Thus, an ideal drug molecule should have a small number of atoms to minimize hydrogen bonding. In addition to this, the ideal protein binding value required for optimal drug penetration through the skin is 2.6. Higher protein binding values are associated with increased protein binding[33].

Particle size and shape

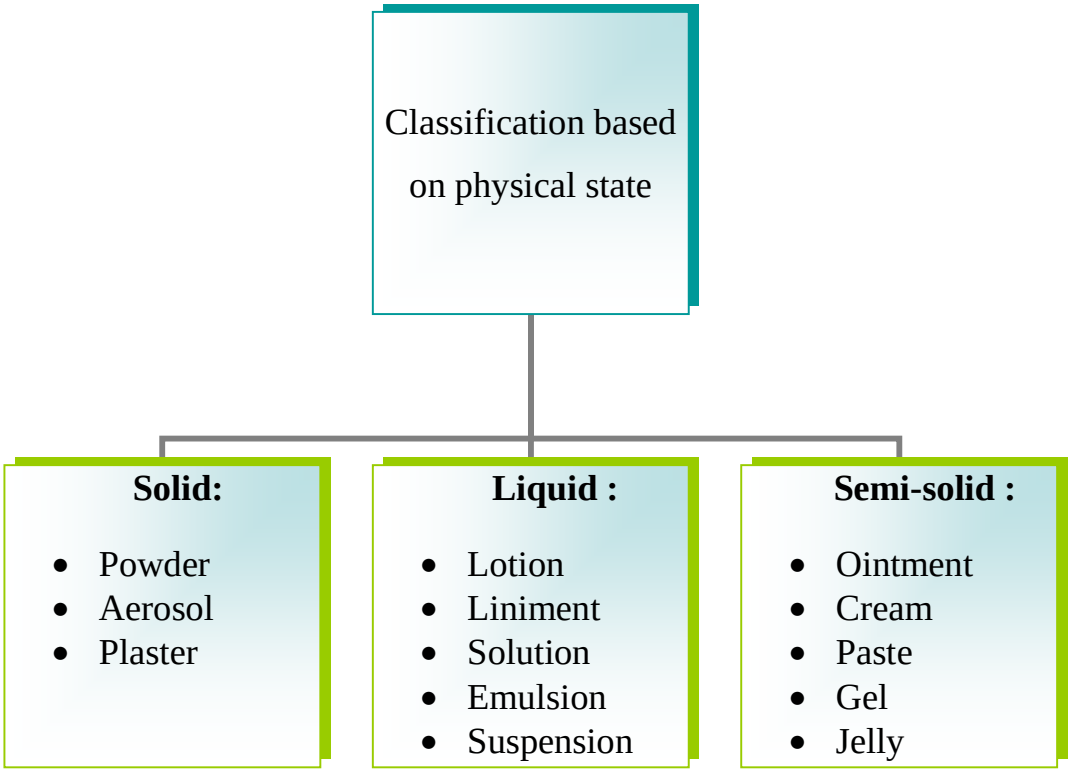
The ideal molecular weight for optimal drug penetration is considered to be less than or equivalent to 500 dalton[34]. The molecular weight of a drug molecule is inversely proportional to the flux of the drug molecule. Smaller the drug particles can penetrate the skin faster and with greater ease than larger particles. It is not easy to assess the effect of the particle shape on drug permeation into the skin[27].

3.1.4 Topical dosage forms

The selection of formulation type for topical drug delivery is usually influenced by the nature of the skin lesion and the opinion of the medical practitioner. To this day a practicing dermatologist would prefer to apply a wet formulation (ranging from simple tap-water to complex emulsion formulations with or without drug) to a wet lesion and a

dry formulation (e.g., petrolactum) to a dry lesion. In modern-day pharmaceutical practice, semisolid formulations are the preferred vehicles for dermatological therapy because they remain in Situ and deliver the drug over extended time periods. The term vehicle is very common for a complex system and implies a differentiation between active and inactive principles, whereby the active principle is embedded into a matrix, the vehicle with the aid of the vehicle the active principle is delivered to the application site or target organ, where the desired effect is achieved[35].

3.1.4.1 Classification of topical dosage form[36]



Gel **[36-39]**

The term "gels" is broad, encompassing semisolids of a wide range of characteristics- from fairly rigid gelatin slabs, to suspensions of colloidal clays, to certain greases. Gels can be looked on as being composed of two interpenetrating phases.

The United State Pharmacopeia (USP) defines gels as semisolids, being either suspension of small inorganic particles or large organic molecules interpenetrated with liquid. It is the interaction between the units of the colloidal phase, inorganic or organic, that sets up the "structural viscosity" immobilizing the liquid continuous phase. Thus gels exhibit characteristics intermediate to those of liquids and solids.

Classification of gel

The classification of gel is undertaken by considering some characteristic of either of the two phases.

Table 2: Classification and description of gel

Class	Description	Example
Inorganic	Usually two phase system	Aluminium hydroxide gel, bentonite magma
Organic	Usually single phase system	carbopol®, tragacanth
Hydrogel	Contains water	Silica, bentonite, pectin, sodium alginate, methyl cellulose, alumina
Organogel	Hydrocarbon type Animal/ Vegetable fats soap base greases Hydrophilic organogel	Petrolatum, mineral Plastibase, oil/polyethylene gel Lard, cocoa butter, Aluminium stearate with heavy mineral oil gel
Hydrogels	Organic hydrogels Natural/synthetic gums Inorganic hydrogels	Pectin paste, tragacanth Jelly Methyl cellulose, Sodium CMC, Puronic® F- 127, Bentonite gel (10% to 25%), Veegum

Advantages of gels

- They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH and enzymatic activity and drug interaction with food and drinks.
- They can substitute for oral administration of medication when that route is unsuitable.
- To avoid the first pass effect, that is, the initial pass of drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding the deactivation by digestive and liver enzyme.
- They are non-invasive and have patient compliance.
- They are less greasy and can be easily removed from the skin.
- Cost effective.
- Reduction of doses as compare to oral dosage forms.
- Localized effect with minimum side effects.

Gel forming substances

A number of polymers are used to provide the structural network that ia the essence of a gel system.

(a) Natural polymer:

Proteins : Collagen, gelatin

Polysaccharides : Pectin, chitosan, amylose.

Natural gums : Guar gum, cassia tora, xanthan gum, gellum gum, acacia, agar, alginate acid, sodium or potassium carageenan, tragacanth.

(b) Semisynthetic polymers:

Cellulose derivatives: Carboxymethyl cellulose, Hydroxypropyl cellulose, Methylcellulose, Hydroxy propyl (methyl cellulose), Hydroxyethyl cellulose.

(c) Synthetic polymers:

- Carbomer: Carbopol 940, Carbopol 934
- Poloxamer 407
- Polyacrylamide
- Polyvinyl alcohol
- Polyethylene and its co-polymers

(d) Inorganic substances:

- Aluminium hydroxide
- Besitonite

(e) Surfactants:

- Cebrotearyl alcohol
- Brij – 96

Creams[23,40,41]

Creams are viscous emulsions of semisolid consistency, intended for external application to the skin or mucous membrane. The typical cream, a soft, emulsified mass of solidified particles in an aqueous, micelle-rich medium, does not form a water-impermeable (occlusive) film on the skin. Nevertheless, creams contain lipids and other moisturizers that replace substances lost from the skin in the course of everyday living. Creams thus make good emollients because, by replenishing lipids and in some instance also polar, hygroscopic substances, they restore the skin's ability to hold onto its own moisture.

There are two types,

(a) Oily creams (water-in-oil creams)

These creams are most useful as water-washable bases whereas creams are emollient and cleansing. Patients often prefer a w/o cream to an ointment because the cream spreads more readily, is less greasy and the evaporating water soothes the inflamed tissue. Oily

creams consist of W/O type emulsifying agents e.g. wool fat, wool alcohol, fatty acid, ester of sorbitol or divalent soap.

Examples of W/O creams: Cold cream, Cleansing cream, Emollient cream

(b) Aqueous creams (oil-in-water creams)

An o/w creams is non-occlusive because it does not deposit a continuous film of water-impervious liquid. However, such a cream can deposit lipids and other moisturizers on and in the stratum corneum and so restore the tissue's hydration ability, i.e. the preparation has emollient properties. When these creams rub into the skin; the continuous phase evaporates and increases the concentration of a water-soluble drug in the adhering film. The concentration gradient for drug across the stratum corneum therefore increases, promoting percutaneous absorption. To minimize drug precipitation a formulator may include a nonvolatile, water-miscible co-solvent such as propylene glycol. Aqueous creams consist of O/W type emulsifying agents e.g. emulsifying wax, monovalent alkali soap, fatty acid ester.

Examples of O/W creams: Vanishing cream, Shaving cream, Hand cream

Due to the presence of water soluble components, aqueous creams are comparatively easier to remove from the skin and cloths, by washing with water. Due to the presence of aqueous phase, creams have a tendency of bacterial and mold growth. Therefore preservatives must be incorporated to the creams. Otherwise, the cream, which is contaminated with microorganisms produce infections, when applied to the broken skin.

If creams consist medically active agents, they are called as "medicated cream". These creams are used for protective, therapeutic, prophylactic purpose.

3.2 Review of literature on Vidang, Embelin and Excipients

3.2.1 Vidang drug profile[42]

Biological source: Drug consists of dried ripe fruits of *Embelia ribes*.

Family: Myrsinaceae.

Geographical sources: The plant is distributed throughout India, Sri Lanka, Malaya and China. It can be found in hilly parts of Maharashtra and Konkan, at an altitude of 1500m.

Synonyms: Sans. : Vidandga, Krimighna, Krimihanta

Beng. : Biranga, Bhai- birrang

Guj. : Vavading

Eng. : False Black Pepper

Hindi : Baberang, Wawrung

Mar. : Karkanie, Vavdinga

Punj. : Babrung

Tam. : Vayu- vilamgam, Vellal

Tel. : Vayu- vilamgam

Macroscopic description: Fruits are small, 3-4 mm in diameter, obovate to subglobular tipped with persistent style; smooth in fresh condition, grayish black when ripe. On drying, the fruits become wrinkled or warty like a peppercorn. In a few fruits, the pedicel (about 1-2 mm long) along with the persistent calyx is present; when not present, at its position a circular scar is seen. Fruits are aromatic, hot and astringent. Pericarp brittle and on its removal a membranous sheath covering the singular, globular to subglobular seed is seen. The outer surface of the seed is brownish black, speckled with yellowish brown spots.

Microscopic description: Epicarp of the pericarp is the outermost layer consisting of one celled epidermis. In surface view the epidermal cells appear rounded with inter cellular spaces. The outer 4-6 layers of mesocarp are parenchymatous with intercellular space and contain tannins. In the central portion of the mesocarp, vascular bundles, encircled by a pericyclic ring of pseudofibres, are seen; xylem vessels show scalariform to spiral thickenings; phloem indistinct. Endocarp is sclerenchymatous consisting of palisade like stone cells, which are much thickened and having prominents pits. Testa consists of 1or 2 layers of rectangular cells with brown pigments. Endosperm has thick hemicellulosic walls. The yellowish brown spots are also seen in the endosperm and contain crystalline masses of embelin. Embryo consists of thin walled rectangular cells with fixed oil and protein.

Ayurvedic properties[43]:

Guna : Laghu (light), Ruksha (dry), Tikashna (sharp)

Rasa : Katu (pungent)

Veerya : Ushna (lukewarm)

Dosha : Balances kapha and vata

Vipaka : Katu

Prabhava: Krimighna

Karma : Jantughna, Kushthaghna, Shirovirechana, Nadibalya, Deepana, Anulomana, Pachna, Krimighna, Mootrajanana, Garbhanirodhaka, Varnya, Rasayana, Raktashodhaka,

Chemical constituents: Major: Embelin – 2.5-3.1 %, an inseparable mixture of 3 components (i) with C9 side chain (homoembelin), (ii) with C11 side chain (embelin) and (iii) with C13 side chain (rapanone).

Others: Vilangin, quercitol, 1% tannins, colouring matter, alkaloid namely christembine.

Plant part used: Fruit, leaf, root[44]

Adulterants / Substitutes: *Embelia tesjeriam-cottam syn., Embelia robusta Clarke, non Roxb*. is used as an adulterant. The two species can however, be distinguished as follows: fruit in *Embelia ribes* are much darker, almost black, somewhat ovate in shape and posses surface reticulations. Fruits in *E. tejseriam-cottam* are reddish brown, almost spherical and have distinct, fine, longitudinal surface striations[45].

Pharmacology: The aqueous extract of the drug acts as a long acting contraceptive by inhibiting endometrial alkaline phosphatase and hence preventing implantation of the fertilized ovum. The drug is a good anthelmintic and very effective in cases infected by *Ascaris lumbricoides.*

Therapeutic category: Anthelminitic.

Indications: The dried fruit is considered anthelmintic, astringent, carminative, alterative and stimulant. It has been used in India since ancient times as an anthelmintic. It is effective in the treatment of ascariasis. The dried fruits are used in decoctions for fevers and for diseases of the chest and skin. The fruit also shows anti-bacterial activity[46].

Clinical Studies: Clinical studies were conducted with alcoholic and aqueous extracts of the berries of *Embelia ribes*, obtained by percolation method, on 40 children infected by ascarides. The alcoholic extract was found very effective in the treatment of 80 per cent of the cases while the aqueous extract cured 55 per cent cases, rendering the stools free from ova. The worms were expelled from the stools. No evidence of toxicity was observed during and after the treatment. There was a slight improvement in the hemoglobin percentage of the blood[47].

Contraindication: In oral dose up to 3 gm/kg body weight Embelin did not show lethal effect in rats and mice. Ten weeks exposure to Embelin (10 mg/kg body weight) showed no significant changes in the histology of heart, liver, kidney and spleen in rodents. The hemograms were also normal[47].

Uses:

Paste: It is being used for mouth wash and avoiding cavities. It is being also used in skin related problems.

Powder: It is being used for wormal infestation, infection in body, indigestion, constipation, paralysis, convulsions, epilepsy etc. it also helps in purifying the blood.

Oil: it is used in skin related problems and wound infections.

Safety aspects: Use of this drug may result in sexual debility.

Dosage: Infusion: 3.75- 15 gm

Powder: 6-12 gm (adult), 2-3 gm (children)

Decoction: 14-28 ml

3.2.2 Excipient profiles

Carbopol

Carbomers were first prepared and patented in 1957. Since then, a number of extended release tablet formulations, which involve carbomer matrices, have been patented[48]. Carbomers readily absorb water, get hydrated and swell. In addition to its hydrophilic nature, its cross-linked structure and it's essentially insolubility in water makes carbopol a potential candidate for use in controlled release drug delivery system[49,50].

Carbopol polymers are polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol. Each particle can be viewed as a network structure of polymer chains interconnected via cross-linking[51].

a) Nonproprietary names

- BP: Carbomers
- PhEur: Carbomera
- USPNF: Carbomer

b) Synonyms

Acritamer; acrylic acid polymer; Carbopol; carboxy polymethylene, polyacrylic acid; carboxyvinyl polymer; Pemulen; Ultrez.

c) Chemical name

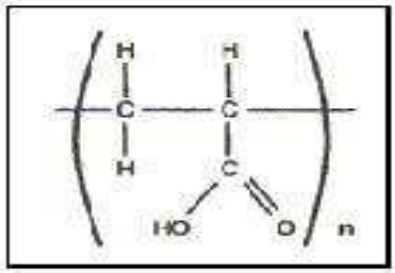
Carbomer

d) Empirical formula and molecular weight

Carbomers are synthetic high-molecular-weight polymers of acrylic acid that are crosslinked with either allyl sucrose or allyl ethers of pentaerythritol. They contain between 56% and 68% of carboxylic acid (COOH) groups calculated on the dry basis. The molecular weight of carbomer resins is theoretically estimated at 7 × 105 to 4 × 109. Molecular weights for Carbopol 940 have been reported 104 400 g/mol.

e) Structural formula

Carbomer polymers are formed from repeating units of acrylic acid. The monomer unit is shown above. The polymer chains are crosslinked with allyl sucrose or allyl pentaerythritol.



Where n is acrylic acid monomer unit in carbomer polymer

f) Description

Carbopols are white-colored, 'fluffy', acidic, hygroscopic powders with a slight characteristic odor[52].

g) Physical and chemical properties[53,54]

The three dimensional nature of these polymers confers some unique characteristics, such as biological inertness, not found in similar linear polymers. The Carbopol resins are hydrophilic substances that are not soluble in water. Rather, these polymers swell when dispersed in water forming a colloidal, mucilage-like dispersion. Carbopol polymers are bearing very good water sorption property. They swell in water up to 1000 times their original volume and 10 times their original diameter to form a gel when exposed to a pH environment above 4.0 to 6.0.

Table 3: Physical and chemical properties of carbopol

Appearance	Fluffy, white, mildly acidic polymer
Bulk Density	Approximately 208 kg/m^3 (13 lbs.ft^3)
Specific gravity	1.41
Moisture content	2.0% maximum
Equilibrium moisture content	8-10% (at 50% relative humidity)
PKa	6.0 ± 0.5
pH of 1.0% water dispersion	2.5-3.0
pH of 0.5% water dispersion	2.7-3.5
Equivalent weight	76 ± 4
Ash content	0.009 ppm (average)
Glass transition temperature	100-105^{0}C (212-221F)

Because the pKa of these polymers is 6.0 to 0.5, the carboxylate moiety on the polymer backbone ionizes, resulting in repulsion between the native charges, which adds to the swelling of the polymer. The glass transition temperature of Carbopol polymers is 105°C (221°F) in powder form. However, glass transition temperature decreases significantly as the polymer comes into contact of water. The polymer chains start gyrating and radius of gyration becomes increasingly larger. Macroscopically, this phenomenon manifests itself as swelling.

h) Rheological properties[55-61]

While the relationships between structure and properties have been of interest both academically and in industry. Different grades of carbopol polymers exhibit different rheological properties, a reflection of the particle size, molecular weight between crosslinks (Mc), distributions of the Mc, and the fraction of the total units, which occur as terminal, i.e. free chain ends.

Table 4: Viscosity range of different carbopol polymers

Polymer	Viscosity range (cps)
Carbopol 934 NF	30500 – 39400
Carbopol 934 P NF	29400 – 39400
Carbopol 71 G NF	4000 – 11000

i) Applications of carbopol polymers[62-80]

The readily water-swellable Carbopol polymers are used in a diverse range of pharmaceutical applications to provide:

- Controlled release in tablets.
- Bioadhesion in buccal, ophthalmic, intestinal, nasal, vaginal and rectal applications.

- Thickening at very low concentrations to produce a wide range of viscosities and flow properties in topical, lotions, creams and gels, oral suspensions.
- Suspensions of insoluble ingredients in oral suspensions and topical.
- Emulsifying topical oil-in-water systems permanently, even at elevated temperatures, with essentially no need for irritating surfactants.

Topical applications

Carbopols are very well suited to aqueous formulations of the topical dosage forms. Many commercial topical products available today have been formulated with these polymers, as they provide the following numerous benefits to topical formulations:

- Safe & Effective: Carbopol polymers have a long history of safe and effective use in topical gels, creams, lotions, and ointments. They are also supported by extensive toxicology studies.
- Non-Sensitizing: Carbopol polymers have been shown to have extremely low irritancy properties and are non-sensitizing with repeat usage.
- No Effect on the Biological Activity of the Drug: Carbopol polymers provide an excellent vehicle for drug delivery. Due to their extremely high molecular weight, they cannot penetrate the skin or affect the activity of the drug.
- Excellent Thickening, Suspending, & Emulsification Properties for Topical Formulations.

Products with a wide range of viscosities and flow properties have been successfully formulated and commercialized. Carbopol polymers are used to permanently suspend the active ingredients in transdermal reservoirs as well as in topical gels and creams. Pemulen polymeric emulsifiers can be used to prepare stable emulsions, such as

turpentine liniment, without the use of surfactants. Carbopol polymers and Pemulen polymeric emulsifiers are often the thickener and emulsifier of choice in topical lotions.

j) Stability and storage conditions

Carbopols are stable, hygroscopic materials that may be heated at temperatures below 104°C for up to 2 hours without affecting their thickening efficiency. However, exposure to excessive temperatures can result in discoloration and reduced stability. Stability to light may be improved by the addition of 0.05–0.1% w/v of a water-soluble UV absorber such as benzophenone-2 or benzophenone-4 in combination with edetic acid. The UV stability of carbomer gels may also be improved by using triethanolamine as the neutralizing base. Carbomer powder should be stored in an airtight, corrosion-resistant container in a cool, dry place. Packaging in aluminum tubes usually requires the formulation to have a pH less than 6.5, and packaging in other metallic tubes or containers necessitates a pH greater than 7.7 to prolong carbomer stability[52].

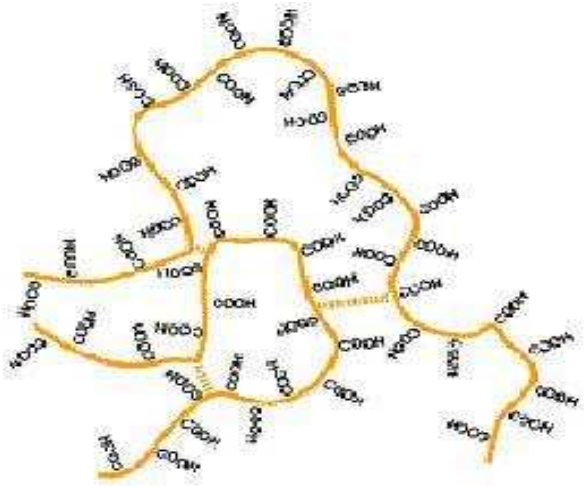
k) Incompatibilities

Carbopol polymers are discolored by resorcinol and are incompatible with phenol, cationic polymers, strong acids, and high levels of electrolytes. Certain antimicrobial adjuvants should also be avoided or used at low levels. Trace levels of iron and other transition metals can catalytically degrade carbopol dispersions. Carbopol also form pH-dependent complexes with certain polymeric excipients[52].

l) Method of manufacture

Carbopol polymers are manufactured by cross-linking process. Depending upon the degree of cross-linking and manufacturing conditions, various grades of Carbopol are available.

Figure 3: Schematic drawing of a molecular segment of a cross-linked polyacrylic acid polymer



Carbopol 934 P is cross-linked with allyl sucrose and is polymerized in solvent benzene. Polycarbophil is cross-linked polymer in divinyl glycol and polymerized in solvent benzene. All the polymers fabricated in ethyl acetate are neutralized by 1-3% potassium hydroxide[52].

m) Safety

Carbopol polymers are used extensively in nonparenteral products, particularly topical liquid and semisolid preparations. They may also be used in oral formulations, although only certain grades can be used. Acute oral toxicity studies in animals indicate that carbopol 934 has a low oral toxicity, with doses up to 8 g/kg being administered to dogs without fatalities occurring. Carbomers are generally regarded as essentially nontoxic and nonirritant materials; there is no evidence in humans of hypersensitivity reactions to carbomers used topically[52].

***Propylene glycol*[52,81]**

a) Nonproprietary names

- BP: Propylene glycol

- JP: Propylene glycol
- PhEur: Propylenglycolum
- USP: Propylene glycol

b) Synonyms

1, 2-Dihydroxypropane; E1520; 2-hydroxypropanol; methyl ethylene glycol; methyl glycol; propane-1, 2-diol.

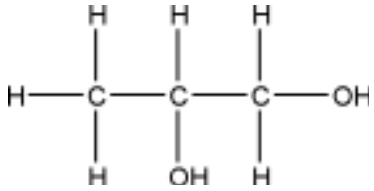
c) Chemical name

1, 2-Propanediol

d) Empirical formula and molecular weight

$C_3H_8O_2$ Mo. Wt. 76.09

e) Structural formula



f) Functional category

Antimicrobial preservative; disinfectant; humectant; plasticizer; solvent; stabilizer for vitamins; water-miscible cosolvent.

g) Applications in pharmaceutical formulation or technology

Propylene glycol has become widely used as a solvent, extractant, and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations. It is a better general solvent than glycerin and dissolves a wide variety of materials, such as corticosteroids, phenols, sulfa drugs, barbiturates, vitamins (A and D), most alkaloids, and many local anesthetics. As an antiseptic it is similar to ethanol, and against molds it is similar to glycerin and only slightly less effective than ethanol.

Propylene glycol is commonly used as a plasticizer in aqueous film-coating formulations. Propylene glycol is also used in cosmetics and food industry as emulsifiers.

Table 5: Use of propylene glycol

Use	Dosage forms	Concentration (%)
Humectant	Topicals	15
Preservative	Solutions, semisolids	15-30
Solvent or cosolvent	Aerosol solutions	10-30
Solvent or cosolvent	Oral solutions	10–25
Solvent or cosolvent	Parenterals	10-60
Solvent or cosolvent	Topicals	5-80

h) Description

Propylene glycol is a clear, colorless, viscous, practically odorless liquid with a sweet, slightly acrid taste resembling that of glycerin.

i) Typical properties

Autoignition temperature: 371°C

Boiling point: 188°C

Density: 1.038 gm/cm^3 at 20°C

Osmolarity: a 2.0% v/v aqueous solution is iso-osmotic with serum.

Solubility: miscible with acetone, chloroform, ethanol (95%), glycerin, and water; soluble at 1 in 6 parts of ether; not miscible with light mineral oil or fixed oils, but will dissolve some essential oils.

Surface tension: 40.1 mN/m (40.1 dynes/cm) at 25°C

Viscosity (dynamic): 58.1 mPa s (58.1 cP) at 20°C

j) Stability and storage conditions

At cool temperatures, propylene glycol is stable in a well-closed container, but at high temperatures, in the open, it tends to oxidize, giving rise to products such as propionaldehyde, lactic acid, pyruvic acid, and acetic acid. Propylene glycol is chemically stable when mixed with ethanol (95%), glycerin, or water; aqueous solutions may be sterilized by autoclaving. Propylene glycol is hygroscopic and should be stored in a well-closed container, protected from light, in a cool, dry place.

k) Incompatibilities

Propylene glycol is incompatible with oxidizing reagents such as potassium permanganate.

l) Method of manufacture

Propylene is converted to chlorohydrin by chlorine water and hydrolyzed to 1, 2-propylene oxide. With further hydrolysis, 1,2-propylene oxide is converted to propylene glycol.

m) Safety

Propylene glycol is generally regarded as a relatively nontoxic material given by oral route. In topical preparations, propylene glycol is regarded as minimally irritant, although it is more irritant than glycerin. Some local irritation is produced upon application to mucous membranes or when it is used under occlusive conditions. Parenteral administration may cause pain or irritation when used in high concentration. Propylene glycol is estimated to be one-third as intoxicating as ethanol, with administration of large volumes being associated with adverse effects most commonly on the central nervous system, especially in neonates and children.

***Stearic Acid*[52]**

a) Nonproprietary names

- BP: Stearic acid
- JP: Stearic acid
- PhEur: Acidum stearicum
- USPNF: Stearic acid

b) Synonyms

Cetylacetic acid; Crodacid; E570; Edenor; Emersol; Hystrene; Industrene; Kortacid 1895;Pearl Steric; Pristerene; stereophanic acid; Tegostearic.

c) Chemical name

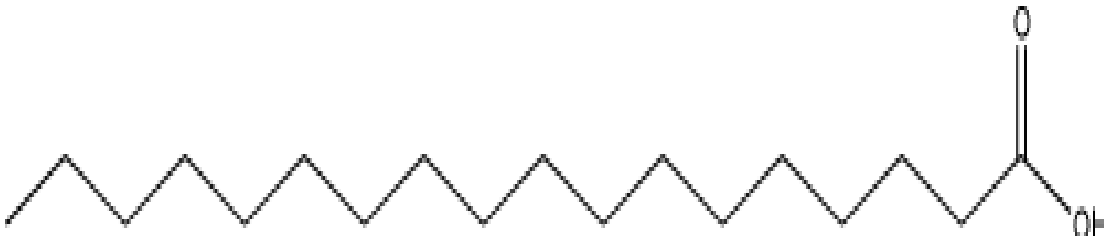
Octadecanoic acid

d) Empirical formula and molecular weight

C18H36O2 284.47

The USPNF 23 describes stearic acid as a mixture of stearic acid (C18H36O2) and palmitic acid (C16H32O2). In the USPNF 23, the content of stearic acid is not less than 40.0% and the sum of the two acids is not less than 90.0%. The USPNF 23 also contains a monograph for purified stearic acid.

e) Structural formula



f) Functional category

Emulsifying agent; solubilizing agent; tablet and capsule lubricant.

g) Applications in pharmaceutical formulation or technology

Stearic acid is widely used in oral and topical pharmaceutical formulations. It is mainly used in oral formulations as a tablet and capsule lubricant although it may also be used as a binder or in combination with shellac as a tablet coating. It has also been suggested that stearic acid may be used as a sustained-release drug carrier. In topical formulations, stearic acid is used as an emulsifying and solubilizing agent. When partially neutralized with alkalis or triethanolamine, stearic acid is used in the preparation of creams. The partially neutralized stearic acid forms a creamy base when mixed with 5-15 times its own weight of aqueous liquid; the appearance and plasticity of the cream being determined by the proportion of alkali used. Stearic acid is used as the hardening agent in glycerin suppositories. Stearic acid is also widely used in cosmetics and food products.

Table 6: Use of stearic acid

Dosage forms	Concentration (%)
Ointments and creams	1-20
Tablet lubricant	1-3

h) Description

Stearic acid is a hard, white or faintly yellow-colored, somewhat glossy, crystalline solid or a white or yellowish white powder. It has a slight odor and taste suggesting tallow.

i) Typical properties

Acid value: 200–212

Density (bulk): 0.537 gm/cm^3

Density (tapped): 0.571 gm/cm^3

Density (true): 0.980 gm/cm^3

Melting point: ≥54°C

Saponification value: 200–220

Solubility: freely soluble in benzene, carbon tetrachloride, chloroform, and ether; soluble in ethanol (95%), hexane, and propylene glycol; practically insoluble in water.

Specific surface area: 0.51–0.53 m^2/gm

j) Stability and Storage Conditions

Stearic acid is a stable material; an antioxidant may also be added to it. The bulk material should be stored in a well-closed container in a cool, dry place.

k) Incompatibilities

Stearic acid is incompatible with most metal hydroxides and may be incompatible with oxidizing agents. Insoluble stearates are formed with many metals; ointment bases made with stearic acid may show evidence of drying out or lumpiness due to such a reaction when compounded with zinc or calcium salts. A number of differential scanning calorimetry studies have investigated the compatibility of stearic acid with drugs. Although such laboratory studies have suggested incompatibilities, e.g. with naproxen, they may not necessarily be applicable to formulated products. Stearic acid has been reported to cause pitting in the film coating of tablets coated using an aqueous film-coating technique; the pitting was found to be a function of the melting point of the stearic acid.

l) Method of Manufacture

Stearic acid is manufactured by hydrolysis of fat by continuous exposure to a countercurrent stream of high-temperature water and fat in a high-pressure chamber. The resultant mixture is purified by vacuum steam distillation and the distillates are then separated using selective solvents. Stearic acid may also be manufactured by the

hydrogenation of cottonseed and other vegetable oils; by the hydrogenation and subsequent saponification of olein followed by recrystallization from alcohol; and from edible fats and oils by boiling with sodium hydroxide, separating any glycerin, and decomposing the resulting soap with sulfuric or hydrochloric acid. The stearic acid is then subsequently separated from any oleic acid by cold expression. Stearic acid is derived from edible fat sources unless it is intended for external use, in which case nonedible fat sources may be used. The USPNF 23 states that stearic acid labeled solely for external use is exempt from the requirement that it be prepared from edible sources. Stearic acid may contain a suitable antioxidant such as 0.005% w/w butylated hydroxytoluene.

m) Safety

Stearic acid is widely used in oral and topical pharmaceutical formulations; it is also used in cosmetics and food products. Stearic acid is generally regarded as a nontoxic and nonirritant material. However, consumption of excessive amounts may be harmful.

3.3 Background of research work

Poulsen BJ et.al.[82] (1968) studied the effect of topical vehicle composition on the *in-vitro* release of flucinolone acetonide and its acetate ester. They have developed a model to test certain concepts regarding the in-vitro release of steroids from topical vehicles. The vehicles selected for the study were propylene glycol-water mixtures gelled with carbopol 934. Isopropyl myristate was used as a receptor phase for the diffusing steroids.

Arellano A et.al.[83] (1998) studied the influence of propylene glycol (PG) on the *in vitro* penetration of diclofenac sodium (DFS) through a synthetic membrane and abdominal rat skin from carbopol gel was investigated using Franz-type diffusion cells. The combined effect of isopropyl myristate (IPM) and PG was also evaluated. It was found that the penetration through the synthetic membrane was well described by the Higuchi model. The gel containing 40% PG showed the highest release rate, indicating that a releasing maximum exists for PG content which provides the fully solubilized drug in the vehicle. When using rat skin as the barrier, the penetration rate was controlled by the membrane. DFS flux decreased with increasing PG content of the gels due to an increase of the drug affinity to the vehicle. A co-solvent action of PG was evident. However, the combination of PG and IPM resulted in a synergistic enhancement of DFS flux. Maximum enhancing activity was obtained from gels containing 40% PG, which yielded an enhancement ratio of about 8. Increasing IPM content from 3 to 5%increased the flux and decreased the lag time taken to reach a steady-state level.

Patel MM et.al.[84] (1993) prepared transdermal gel using 2 % w/w metoprolol tartarate as drug, 0.75 % w/w carbopol as a gelling agent and dimethylformamide (DMF), ethanol, and propylene glycol were selected as absorbance enhancers. The gel formulations were evaluated using the Poulson diffusion cell and human cadaver skin. Cumulative

percentage release (CPR) and corrected cumulative percentage release (CCPR) was calculated for all formulations. All gels were showed zero order release kinetics.

Patel RP et.al.[85] (2009) prepared mometasone furoate semi solid topical gel formulations by using carbopol 940 as a gel forming agent and mixture of ethanol and propylene glycol as a co-solvent system. The concentration of carbopol 940, ethanol and propylene glycol in gel formulation was optimized by Box-Behnken statistical screening design. A marked effect of independent variables (concentration of carbopol 940, ethanol and propylene glycol) on mometasone furoate permeation was observed when it was incorporated in the gel formulations.

Gondaliya DP et.al.[86] (2002) investigated nimesulide clear aqueous gels and emulgel containing Acrypol 940 P.A. 3^2 factorial design was adopted for the optimization of aqueous gel formulation, which produced better penetration though rat skin. Propylene glycol and Polyethylene glycol 400 were chosen as independent variables to study their effect as co-solvents. The % drug diffused through skin in 5 h (Y300) was selected as a dependant variable. The clear aqueous gel formulation containing 15% w/w ethanol, 20 % w/w Propylene glycol and 30 % w/w PEG-400 showed maximum drug penetration (18-68 %) in *in vitro* diffusion study.

Sanghavi NM et.al.[87] (1988) prepared and evaluated several ointments, creams and gel of piroxicam (1% w/w) using different base. The general rank of order of the drug release retardation was found to be: modified gel 934 base > PEG base > simple gel base > alginate gel base > modified gel 940 base > canadian formulary base > modified hydrophilic ointment U.S.P. > oleoginous base > Bellar's ointment base > vanishing cream base.

Patel MM et.al.[88] (1995) prepared the transdermal gel using metoprolol tartarate (2 %) as a drug, carbopol (0.75 %) and triethanolamine. Ethanol and propylene glycol were selected as absorbance enhancers. The gels were evaluated for drug release profile using modified Poulson diffusion cell with human and animal skins. The values of CPR, CCPR and coefficient (r) were obtained. Results showed that rat skin was more permeable than human skin, while guinea pig skin nearly resembles human cadaver skin.

Arul B. et.al.[89] (1998) investigated *in vitro* dissolution characteristic of ketorolac tromethamine in carbopol bases at various concentration and the anti-inflammatory activity was compared with marketed gel. The data showed that the drug release was decreased with increasing carbopol concentration as well as anti-inflammatory activity was better than the marketed gel formulation.

Amin PD et.al.[90] (1998) evaluated ophthalmic gels of Ketorolac tromethamine, a potent NSAID were formulated using polymers carbopol 940, sodium carboxy methylcellulose, hydroxy propyl methylcellulose K-15 M and xanthan gum. The gels were sterilized and subjected to varying stability conditions and assessed for various parameters like pH, viscosity, clarity, extrudability and sterility. Preservative efficacy test B.P.-1988 was performed to evaluate the most suitable preservative for the gels. *In-vitro* release rate was determined using cellophane membrane. Ocular irritation studies were performed on albino rabbits using Draize technique and gels were evaluated for their anti-inflammatory activity on rabbit eyes. Carbopol gels had the maximum *in-vitro* release rate. Benzalkonium chloride was adjudged the most suitable preservative for the gels. Gels exhibited no ocular irritation. All gels of ketorolac exhibited anti-inflammatory activity.

Gaud RS et.al.[91] (1999) formulated insulate gel by employing different gellant such as Carbopol-940, PEG-6000, PEG-4000, HPMC, Sod-CMC and Sodium alginate in

different proportion. These formulations were evaluated for drug content, viscosity, pH, extrudability, homogeneity, spreadability and release pattern through a cellophane membrane using Fites cylindrical tube. *In vitro* release studies of nimesulide from different gels were compared with a marketed nimesulide gel preparation. Carbopol-940 with and without menthol and PEG-6000 with sod-CMC bases of nimesulide gels showed good release pattern compared to other gels.

Chowdary KPR et.al.[92] (1996) prepared & evaluated eight semisolid formulations belonging to anhydrous, cream (O/W and W/O), water soluble and gel categories for their drug release and antibacterial and antifungal activities. Ciprofloxacin release from monophasic systems (anhydrous, PEG base and gels) followed zero order kinetics and from biphasic systems (creams) followed time release order. Overall, PEG and gel formulations gave higher release rate and exhibited higher antibacterial and antifungal activities when compared to cream and anhydrous bases.

Isobel A et.al.[93] (1973) has formulated a lubricant gel of optimal consistency containing a Local anaesthetic lignocaine which can be sterilized by gamma radiation. The authors have used both natural and synthetic polymers tragacanth, methyl celluloses and carbopols as gel forming agents and studied their rheological properties before sterilization and after autoclaving. On gamma radiation, the gel structure was destroyed. Ethanol (5-10%) protected the carbopol formulations. A final formulation was developed consisting of a carbopol gel (1%) neutralized by lignocaine base (2%) and the biological availability of local anaesthetic were assessed using an *in vitro* method.

James N et.al.[94] (1977) has extensively studied the benzoyl peroxide stability in pharmaceutical gel preparations. They have prepared many batches of gels using carbopols as gel forming agents, propylene glycol as humectant, ethanol as organic

solvent and triethaolamine as pH regulator. The storage stability of benzoyl peroxide in the presence of both individual and combined pharmaceutical gel ingredients was investigated. At both 30°C and 40°C storage temperatures, Benzoyl peroxide was destroyed rapidly (within 1 month) in the presence of ethanol and acidic chelating agents. They have concluded that the substitution of acetone for ethanol, the elimination of chelating agents and addition of sodium hydroxide to the gel formulation.

Mayer MC et.al.[95] (1979), in their brilliant research work has studied the rheological properties of carbopol gels. They have reported the effect of physical and chemical variables and consistency of carbopol 940 and carbopol 941 gels by continuous shear rheometry. The have also reported that the continuous shear properties were not greatly effected by centrifuging, milling, temperature cycling, and ageing. Their finding further showed that initially addition of neutralization agent 0 to 6% w/w for 3% gel markedly increased consistency and further addition caused a further increase. Daylight reduced its consistency. Apparent viscosity varied exponentially with concentration. Increase in temperature, gradually decreases apparent viscosity. However, while reporting about solvents, the authors reported that viscosities could not be correlated with solvent viscosity or molecular weight.

Khalil Al-Khamis. et.al.[96] (1987) has studied *in vitro-in vivo* correlations for the percutaneous absorption of salicylates through plastibases, carbopol 940 and polyethylene glycol. They have reported that diffusion of salicylates and their esters within carbopol systems was much faster than PEG system and provides a more rapid attainment of peak plasma level.

Chiang CM et.al.[97] (1989) investigated an *in vitro* technique for evaluating the delivery performance of topical semi-solid formulations which was used to compare

approximately 30 to 45 mg of an oil-in-water cream, a water-in-oil cream or an ointment, each containing a range of concentrations of minoxidil and applied over human cadaver skin within a defined circular area. The rate of permeation of minoxidil from these formulations was reported. Even though all w/o formulations were initially saturated with drug, the flux of minoxidil from these creams increase as the concentration of minoxidil was increased from 0.5% to 2%. In contrast, the delivery rates from the o/w cream and the ointment did not appear to be dependent on the minoxidil concentration applied (0.5 to 2%). If one assumes that the efficacy of a particular formulation is dependent on the ability of the drug to be released from the vehicle and diffuse through the skin, the studies show that the nature of the vehicle can profoundly affect delivery even when excess solid drug is present. They also indicate that reliable in vitro comparisons of drug delivery are possible as long as one performs the studies on skin samples taken from the same section of skin.

Udupa N et.al.[98] (1993) evaluated norfloxacin, a fluroquinolone antibacterial for its percutaneous absorption. The stability, influence of vehicle composition and permeation enhancers on the percutaneous transport of drug across freshly excised mouse skin, was investigated. PEG gel exhibits maximum transdermal flux across mouse skin. *In vitro* studies and pharmacokinetic profile in rats were compared with oral administration. The PEG gel formulation was also evaluated for wound healing.

Chowdary KPR et.al.[99] (1994) prepared various types of semisolid formulations and evaluated for their suitability as drug reservoirs for TDD systems by studying diffusion of diclofenac sodium from these bases through cellulose acetate (CA) membrane and rat abdominal skin alone and in combination. Gel and gel cream bases gave higher release and diffusion rate of diclofenac sodium through CA membrane and were superior to

ointment and cream bases. Zero order diffusion was observed with gel and gel cream bases. Diclofenac sodium was found to diffuse across rat abdominal skin. CA membrane was able to control the transdermal diffusion of diclofenac sodium. A membrane moderated TDD system for diclofenac sodium could be designed employing CA film as rate controlling membrane and sodium alginate and carbopol gels as drug reservoirs.

Gupta GD et.al.[100] (2006) studied that tenoxicam has some side effects when taken orally, viz., epigastric pain, heartburn, nausea, diarrhea, vomiting, peptic ulcer, and hepatic impairment. The aim of this study was to formulate topical gel containing 1% of tenoxicam in 1% carbopol-940 and PEG-4000 and to evaluate it for anti-inflammatory activity using carageenan-induced paw odema in rats. The studies were conducted on wistar rats of either sex (160-180 g). The change in odema volume of the rat hind paw was measured using mercury plethysmometer. The readings were measured in terms of volume displaced in millimeter using a micropipette that has mark to 10 divisions in 1 ml. The carbopol gel formulation of tenoxicam containing 15% of ethanol and 5% of sodium lauryl sulphate was significantly more effective against odema formation than the other formulation of tenoxicam gel and compared to the marketed product of piroxicam gel. Results suggest that the 1% tenoxicam gel in carbopol-940 inhibited 52% of carageenan-induced odema formation as compared with the 44% inhibition obtained with marketed product of piroxicam gel.

Chowdary KPR et.al.[101] (1995) prepared and evaluated eight topical drug delivery systems belonging to anhydrous, cream (o/w and w/o), water soluble and gel categories were prepared and evaluated for drug release and antimicrobial activity of ciprofloxacin. Overall carbopol gel, PEG gel and sodium CMC gel formulations gave higher release rate and exhibited higher anti-microbial activity when compared to cream and anhydrous

bases. A good correlation was observed between release by agar diffusion method and anti-microbial activity by agar cup plate method.

Loganathan V et.al.[102] (2001) studied the effect of polymer and permeation enhance on release of flurbiprofen from gel formulation. Gels have gained more & more importance because the gel based formulations are better percutaneously absorbed than creams and ointment bases. Therefore, flurobiprofen gel formulations were made with different polymers like carbopol 940 (0.6-1.2%) & HPMC (1.0-4.0%) containing various permeation enhancers namely sodium lauryl sulphate SLS (0.25-1.00%) & dimethyl sulfoxide (5-20%) at different proportions having 1% concentration of drug. The formulated gels were evaluated for drug content, pH, Viscosity & in-vivo released through the sigma membrane. Selected formulations were evaluated for its anti-inflammatory activity using the carrageenin-induced paw edema in rats. The physical stability study revealed that the carbopol 940 gels were highly stable & the gels with HPMC were physically unstable. The carbopol with 15% DMSO showed best in-vitro release of flurbiprofen. In vivo study for the selected formulation showed significant (<0.001) anti-inflammatory activity in the carrageenin-induced paw edema in rat.

Patel RP et.al.[103] (2009) developed topical cream formulations of mometasone furoate and studied its permeation through rat skin. Tween 80 as a lipophilic surfactant and Span 80 as a hydrophilic surfactant were used for optimization using 3^2 full factorial designs. The penetration enhancing effect of menthol (0-10% w/w) on the percutaneous flux of mometasone furoate through the excised rat epidermis was also investigated. A marked effect of surfactants (Tween 80 and Span 80) concentration on mometasone furoate permeation was observed when it was incorporated in the cream formulations.

Anil Kumar SJ et.al.[104] (2005) prepared a cream containing extracts of a perennial herb Tridax procumbens linn (family: Compositae), plant Azadirachta indica (family: Meliaceae), and rhizomes Curcuma longa (family: Zingiberaceae). Four optimized cream formulations containing extracts were prepared and out of that AS-4 showed promising physical properties as that of marketed wound healing cream formulations. Hence, AS-4 cream was used as a medicated cream for treatment group, which showed significant wound healing activity in excision wound model. Percentage wound closure, period of complete epithelisation and scar size reduction on complete epithelisation showed P value<0.001. Dead space wound studies also showed significant increase in hydroxyproline content (amino acid present in collagen) indicating promotion of collagen formation and ultimately wound healing activity.

Morteza SK et.al.[105] (2004) studied the species of *Glaucium* have been used in Iranian herbal medicine in the treatment of dermatitis. Due to anti-inflammatory and analgesic activity of *Glaucium grandiflorum* methanolic extract in i.p. administration, these effects in topical administration were studied using carageenan-induced edema and formalin test. Several formulations were prepared and the best cream was chosen for further investigation. Piroxicam gel and methyl salicylates ointment were studied as positive control for anti-inflammatory and analgesic activity, respectively. The edema inhibitions of preparations containing extract at the doses of 1-5% w/w were significantly different from control group. The anti-inflammatory effect of MS4-5% was similar to the effect of piroxicam gel at 3 hrs after carageenan injection. Topical preparation containing *G. grandiflorum* methanolic extract showed analgesic effect in concentrations more than 4% w/w in early phase in formalin test. This activity was observed in concentrations more

than 3% w/w in late phase. The topical analgesic activity of extract was less than the analgesic activity of methyl salicylate ointment.

Feresin GE et.al.[106] (2003) isolated embelin and four alkyl phenols and identified by spectroscopic methods. Embelin presented inhibitory effect on the dermatophytic fungi like *Epidermophyton floccosum, Microsporum canis, Microsporum gypseum, Trichophyton mentagrophytes, Trichophyton rubrum* and methicillin-resistant *Staphylococcus aureus,* and *Escherichia coli* with MICs ranging between 50 to 100μg/ml. Furthermore, embelin was active against *Trypanosoma cruzi* trypomastigotes with 100% lysis at 100μg/ml.

Rao D et.al.[107] (1983) showed antifungal, antibacterial and anthelmintic activities were evaluated for synthesized 6- chloro, 6-bromo and 6-iodo derivative of embelin.

Chitra CS et.al.[108] (1994) studied that the embelin showed significant antibacterial activity. Antibacterial activity was found to be mostly in higher concentration at 100 μg/ml. The inhibition was highly significant against *S. aureus, S. pyogens, S. sonnei, Shigella flesneri* and *P. aeruginosa;* moderately against *S. typhi, S. boydii* and *Proteus mirabilis.*

Namba T et.al.[109] (1985) studied antiplaque activity of embelin. Extract of the fruit of vidang showed antibacterial effect and prevented adherence of viable cells of *Staphylococcus mutans* to smooth surface with 50 % inhibitory concentration of 10-30 μg/ml. It also had antienzymatic action against glucosyltransferase. The active principle was identified as Embelin, which inhibited the bacterial growth at minimum inhibitory concentration of 62.5 μg/ml and glucan synthesis with an IC50 of 125 μg/ml.

Kumara Swamy HM et.al.[110] (2007) studied ethanol extract of the leaves of *Embelia ribes* Burm. (Myrsinaceae) and its isolated quinone compound embelin were screened for

wound healing activity by excision, incision and dead space wound models on Swiss Albino Rats. Significant wound healing activity was observed in both ethanol crude extract (30 mg/ml) and the constituent treated groups. In embelin treated groups (4 mg/ml of 0.2% sodium alginate gel), epithelialization of the incision wound was faster with a high rate of wound contraction. The tensile strength of the incision wound was significantly increased than the ethanol extract. In dead space wound model also the weight of the granulation was increased indicating increase in collagenation. The histological examination of the granulation tissue of embelin treated group showed increased cross-linking of collagen fibers and absence of monocytes. The wound healing effect was comparatively evaluated with the standard skin ointment of framycetin.

Sarin JPS et.al.[111] (1961) studied a simple colorimetric method for the estimation of embelin in *Embelia ribes* has been evolved. The method is based on the colour reaction between embelin and aniline, the colour intensity of which is directly proportional to the concentration and embelin.

Patel RB et.al.[112] (1997) studied a simple colorimetric method using Potassium Hydroxide was developed for embelin determination in *Embelia ribes*. This method was compared with the available method and was found to be more reliable.

Rao B et.al.[113] (1962) studied a new method for gravimetric determination of embelin as vilangin in *Embelia ribes*.

Chauhan SK et.al [114] (1999) showed a simple and reproducible HPTLC method for determination of embelin in *Embelia ribs* was developed and is described. A thin layer chromatographic method with densiometric UV detection has been developed for the quantification of embelin in *Lysimachia punctata.*

Rao VD et.al.[115] (1986) found that only iodo embelin showed enhanced anthelmintic activity compared to embelin. All halo compounds possessed increased antibacterial activity against all organisms tested except *S. typhi.* The acetate of haloembelins was found to be more active than either haloembelin or embelin itself. p-amino benzoate derivative of embelin was also synthesized and studied for biological activity.

Patel RK et.al.[116] (2006) developed a tablet formulation of embelin employing the wet granulation and direct compression techniques. This study was also carried out to design a suitable dissolution medium for embelin. Effect of different diluents like lactose, microcrystalline cellulose, and co-crystallized lactose-microcrystalline cellulose were studied for improving the flow and compressibility. Binders such as starch paste and alcoholic polyvinyl pyrrolidone were used to optimize the crushing strength of the formulation. Solubility study of embelin in different media revealed that embelin has optimum solubility in phosphate buffer of pH 8 and in 2% aqueous sodium lauryl sulfate solution. Incorporation of 10% v/ v ethanol in phosphate buffer of pH 7.4 significantly increased the solubility of embelin. These solutions were also found to be the most suitable media for dissolution of embelin in dissolution studies.

Chitra M et.al.[117] (1994) studied embelin, a plant based benzoquinone derivative, has been found to exhibit significant antitumor activity in methyl cholanthrene induced fibrosarcoma in albino rats besides enhancing their survival time. The drug also has an appreciable action on pain and inflammation. The changes in DNA, RNA and protein levels in various organs in the tumor bearing control and the drug treated animals were also studied.