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AN OVERVIEW OF DANDRUFF AND NOVEL FORMULATIONS AS A TREATMENT STRATEGY

M. Narshana* and P. Ravikumar

Dr. Bhanuben Nanavati College of Pharmacy, Vile Parle (West), Mumbai - 400058, Maharashtra, India.

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Correspondence to Author:

Ms. M. Narshana

M. Pharm,
Dr. Bhanuben Nanavati College of Pharmacy, Gate No.1, Mithibai College Campus, Vaikunthlal Mehta Road, Vile Parle (West), Mumbai - 400056, Maharashtra, India.


E-mail: mnarshana93@gmail.com

ABSTRACT: This review gives an insight of the scalp condition-dandruff which affects more than 50% of the human population. *Malassezia furfur* is reported as the main cause of dandruff. This article aims at investigating other causes of dandruff which include microbial and non - microbial factors. These factors have been explained in this article. It also highlights the various treatment options and newer formulations. Various active agents like anti- fungal agents, keratolytic agents and anti - proliferative agents that are used against dandruff, along with their mechanisms of action are covered in this article. Conventional formulations like Shampoos, creams and lotions have their own set of advantages and limitations. To overcome the disadvantages and prolong the release of actives, novel formulations like Liposomes, Niosomes, Solid lipid nanoparticles, Nanolipid carriers and Silver nanoparticles are being developed. Novel delivery systems have been successfully used for pharmaceutical formulations and they can prove to be a promising delivery system for scalp treatment too.

INTRODUCTION: Scalp is unique among skin areas in human. It is characterized by thick skin layer with high follicular density and abundant sebaceous glands. The pH of scalp is 5.5 and that of a hair shaft is 3.67¹. The presence of these glands along with the dark and warm environment of the scalp makes it more prone to mycotic infections like dandruff, seborrhoeic dermatitis and even parasitic infections like *Pediculosis capitis*. Although scalp disorders are not among those that cause severe physical illness or morbidity, yet are of great social concern. Scalp and hair conditions have more of psychological impact in human societies.

Even minor changes in hair like greying of hair, affects the self-confidence and self- esteem of an individual. Scalp disorders include fungal and bacterial infestations that cause problems like *Tinea capitis* or *Pediculosis capitis*. There are various types of Scalp disorders² some common and some uncommon. These include- (Ref Fig. 1).

1. Alopecia- Hair loss.
2. Seborrheic Dermatitis- inflammation of scalp skin characterized by scaly, itchy, flaky skin.
3. Ring Worm-also known as *Tinea capitis* is a cutaneous fungal infection of scalp, the causative fungi is *Trichophytum rubrum*.
4. Scalp psoriasis- It's a common scalp skin disorder characterized by raised reddish patches that may spread beyond the scalp to forehead or back of the neck or ears.
5. Scalp folliculitis- Inflammation of hair follicle.

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- 6. Head Lice- scientifically termed as *Pediculosis capitis*, is a contagious infection caused by an obligate parasite, called *Pediculus humanus capitis*, resides on human scalp and feeds on human blood.
- 7. Dandruff- It is the shedding of the dead skin cells.

Causes: The cause of dandruff varies among individuals, depending on their susceptibility. Causes can be classified into- a) Microbial and b) Non-microbial.

Microbial Factors:

1. Fungal: *Malassezia furfur* is considered as the leading cause of dandruff. The fungi - *Malassezia* can lead to dandruff by either or both of the following mechanisms-

- *Malassezia* stimulates the enzyme called Lipase on the scalp. The enzyme causes oxidation of triglycerides of sebum to produce unsaturated and saturated fatty acids. Saturated fatty acids are consumed by the fungi for self-proliferation and growth. Unsaturated fatty acids include oleic acid and arachidonic acid. Oleic acid is an irritant for human skin while arachidonic acid is involved in potentiating the inflammatory responses. Hence the result of the degradation of the fatty acids is scalp skin irritation, inflammation and fungal growth. These further cause dry flakes called dandruff. **Fig. 2** represents this mechanism.
- The other mechanism by which this fungi causes dandruff is altering the normal shedding of dead skin cells. Few enzymes on scalp eat up connections between dead skin cells to slough them individually. *Malassezia* modifies this function of enzymes and inhibits cutting of the connections. This leads to aggregation of corneocytes that shed off in clusters, leading to visible white flakes. This mechanism has been explained in the **Fig. 3**.



FIG. 1: DEPICTS THE CLASSIFICATION OF SCALP DISORDERS

Some disorders have a definite cause while some may be idiopathic. Treatment of these disorders is important for personal hygiene.

Dandruff:

Definition: Dandruff is a common scalp disorder, characterized by presence of corneocytes that form clusters due to their high cohesive power, in the form of flaky white to yellowish scales, accompanied by itching³. It has been observed that dandruff occurs mainly between puberty to middle-age, the phase when sebaceous glands are most active.

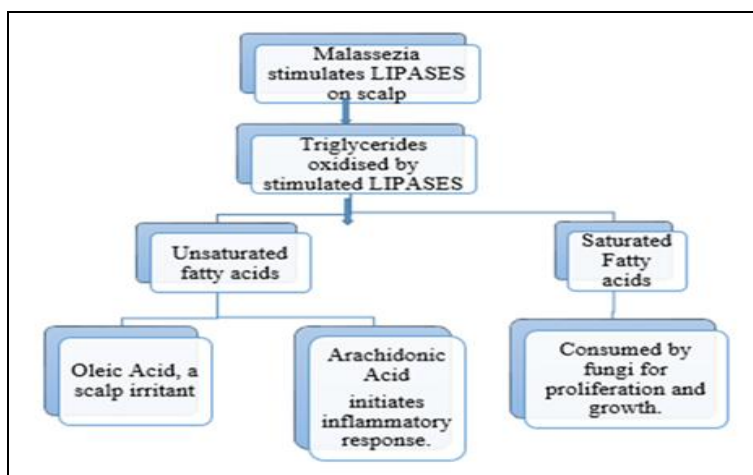


FIG. 2: REPRESENTS THE MECHANISM BY WHICH MALASSEZIA FURFUR CAUSES DANDRUFF

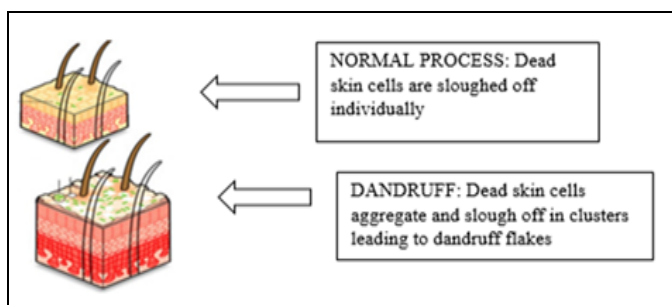


FIG. 3: EXPLAINS ANOTHER MECHANISM BY WHICH DANDRUFF IS CAUSED

2. Bacterial: Disequilibrium in the proportion of the two main bacterial populations found on scalp *Propionibacterium acnes* and *Staphylococcus epidermidis* may also be a cause of dandruff^{4,5}.

b) Non-microbial Factors:

1. Damage to the scalp Stratum corneum⁶.
2. Individual susceptibility to Oleic acid.
3. Dry scalp.

4. Oily or irritated skin.
5. Dirt accumulation due to less frequent shampooing.
6. Sensitivity to hair cosmetics.
7. Other scalp conditions like psoriasis, eczema, etc.

Treatment: Treatment of dandruff can be done by adopting any or all of the following strategies:⁷ Treatment strategies include: (Refer Fig. 4)

1. **Treatment of the Cause:** This primarily includes use of anti-fungal agents like Zinc Pyrithione, Selenium sulphide, Ketoconazole, Climbazole, etc.
2. **Treatment of the Symptoms:** This comprises of employing anti- proliferative like coal tar and keratolytic agents like Salicylic acid.

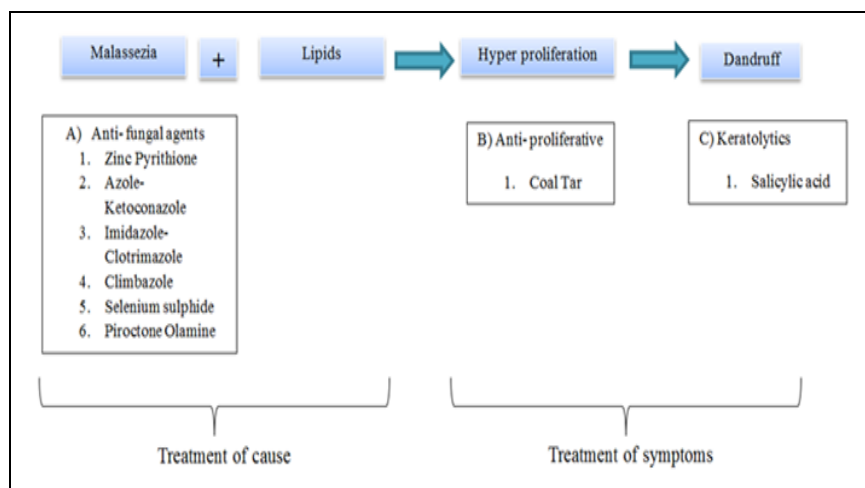
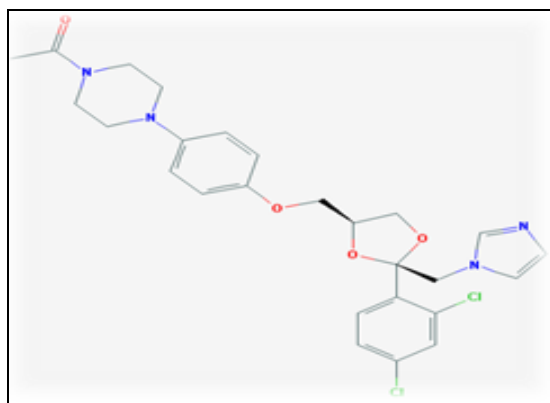


FIG. 4: CLASSIFIES TREATMENT STRATEGIES FOR DANDRUFF

1. Zinc Pyrithione: Most common anti-fungal drug used for dandruff treatment in various formulations.



- Normally 0.5-2% concentration of ZPT is used in shampoos for Anti-fungal activity.
- **Side Effects:** No common side effects. But may be harmful on ingestion. Rare but severe allergic reactions include rash, hives, difficulty in breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue, skin irritation, etc. and these need immediate attention.
- **Mechanism of Action:** (Refer Fig 5a and Fig. 5b)⁹.
- ✓ Zinc Pyrithione increases the intracellular Copper reserves in the fungal cells, which leads to formation of endogeneous CuPT.

- ✓ This then leads to loss of iron-sulphur protein loading activity.
- ✓ This will deactivate the enzyme Aconitase which further leads to cellular toxicity.

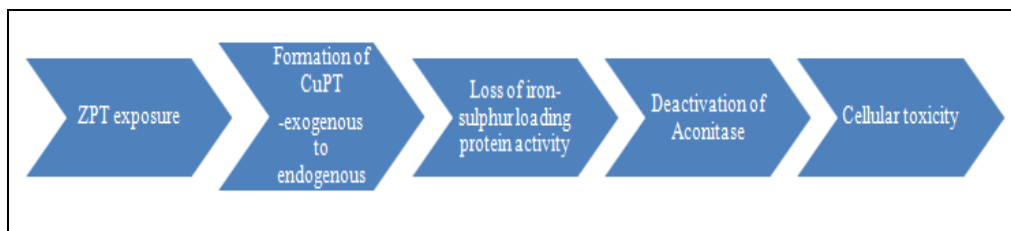


FIG. 5A: MECHANISM OF ACTION OF ZINC PYRITHIONE

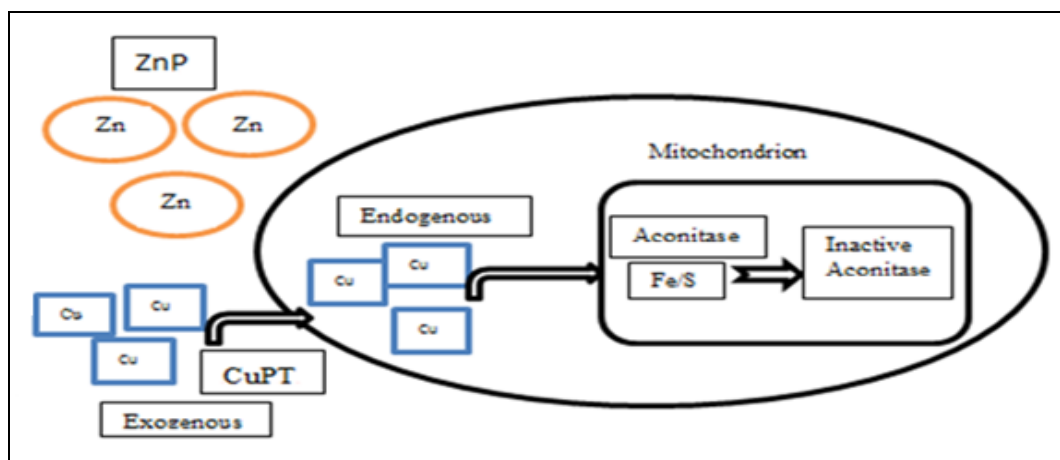
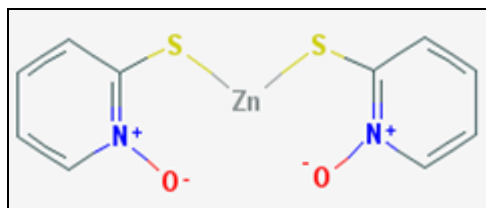


FIG. 5B: CELLULAR MECHANISM OF ZINC PYRITHIONE

2. Ketoconazole: Another commonly used anti-fungal drug.



- Normally 0.25-2% concentration of Ketoconazole is used in shampoos for Anti-fungal activity.
- **Side Effects:** Less serious side effects include: mild skin itching or irritation; dry skin; or headache.

- Consult Doctor in case of effects like severe itching, burning, or irritation where the medicine is applied; oily or dry scalp, mild hair loss; redness, pain, or oozing of treated skin areas; or eye redness, swelling, or irritation.

• **Mechanism of Action:** (Refer Fig. 6).

- ✓ Ketoconazole acts by intervening Ergosterol biosynthesis.
- ✓ It inhibits the Cyp-450 enzyme¹¹ responsible for conversion of Lanosterol to Ergosterol.
- ✓ Inhibition of Ergosterol synthesis disrupts the membrane function and increases the permeability¹².

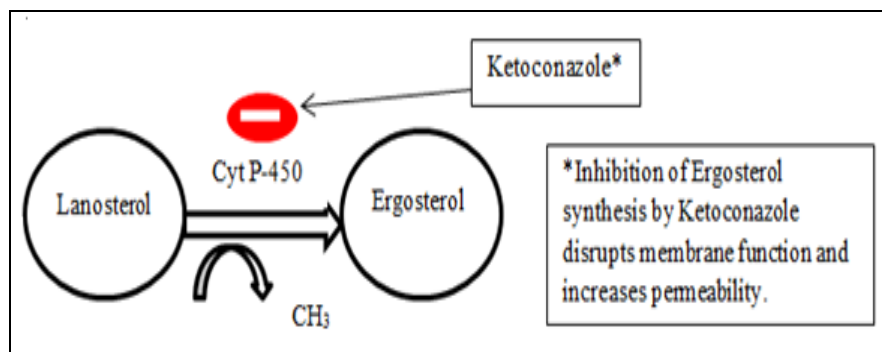
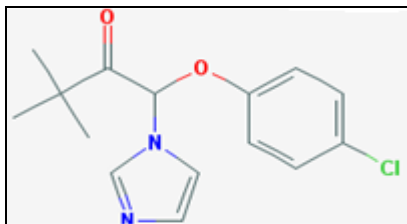


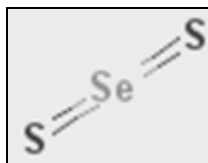
FIG. 6: MECHANISM OF ACTION OF KETOCONAZOLE

3. Climbazole: It is one of the newer anti-fungal drugs used usually in combination or as a monotherapy¹³.



- Normally 0.25 - 2% concentration of Climbazole is used in shampoos for Anti-fungal activity.
- **Side Effects:** Climbazole may cause localized irritation of the skin with symptoms including redness, rashes and itching and allergic reactions.
- But a significant characteristic is that climbazole is ecotoxic¹⁵.
- **Mechanism of Action:**
 - ✓ Climbazole has mechanism of action similar to Ketoconazole as it inhibits Ergosterol biosynthesis.
 - ✓ This affects the normal functioning of the fungal cell membrane further leading to Anti-fungal activity.

4. Selenium Sulphide: Normally 1 - 2.5% concentration of Selenium Sulphide is used in shampoos for its Anti-fungal property.

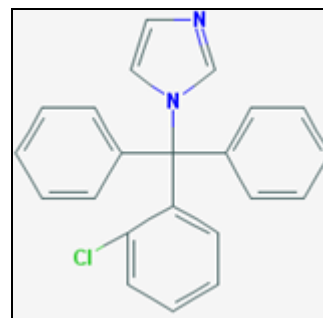


- **Side Effects:** This treatment should not be used if skin or scalp is blistered, raw, or oozing, unless otherwise advised by your doctor. Avoid contact with eyes. Flush eyes thoroughly with water if contact occurs. Some side effects that may occur include: Unusual oiliness or dryness of hair or scalp, Increase in normal hair loss, Scalp discoloration¹⁷.
- **Mechanism of Action:**
 - ✓ It works by treating the excess shedding and irritation that occurs with scalp fungus and also

reduces cellular adhesion in the Stratum corneum.

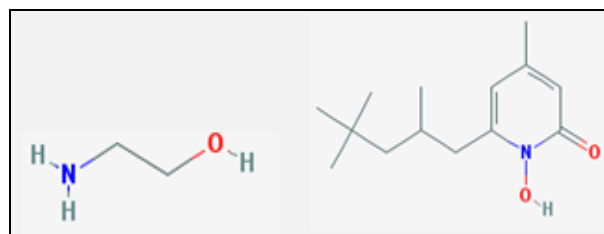
- ✓ It also has local irritant, antibacterial, and mild antifungal activity, which may contribute to its effectiveness.
- ✓ Its anti-mitotic mechanism of action involves decrease in the rate of incorporation of thymidine into DNA of dermal epithelial cells, resulting in a reduction in the turnover of epidermal cells.

5. Clotrimazole:



- Normally 1% concentration is used in formulations.
- **Side Effects:** Symptoms of overdose include erythema, stinging, blistering, urticaria, peeling, edema, pruritus, burning and general irritation of skin and cramps.
- **Mechanism of Action:** Clotrimazole also follows the same mechanism as other azoles. It inhibits biosynthesis of ergosterol and thus disrupts the membrane function and increases the permeability¹⁹.

6. Piroctone Olamine: Normally 0.5 - 1% concentration of Piroctone Olamine is used in shampoos for Anti-fungal activity.



- **Side Effects:** Irritation, swelling, pain, numbness, bleeding, bruising, wrinkling of skin.
- **Mechanism of Action:** (Refer Fig. 7)

- ✓ Piroctoneolamine acts by inhibiting the degradation of sebum triglycerides to Oleic acid and arachidonic acid²¹.
- ✓ As discussed earlier, the degradation of sebum triglycerides to oleic acid and arachidonic acid was the primary mechanism by which the fungi causes dandruff.
- ✓ Thus the inhibition of this mechanism itself helps in treating dandruff.
- ✓ Also, it inhibits energy metabolism in mitochondria of fungal cells. This active agent penetrates into the cell wall to chelate with polyvalent metal ions like iron and aluminium ions²². This complex formation serves as a hindrance for metal- dependent enzymes, resulting in inhibition of energy metabolism in fungal cell, thus leading to fungicidal effects.

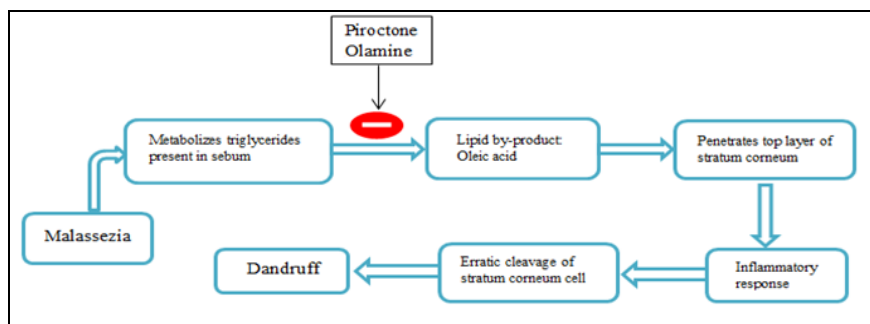
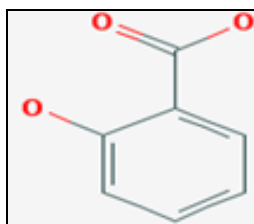


FIG. 7: MECHANISM OF ACTION OF PIROCTONEOLAMINE

A) Keratolytic agent - Salicylic Acid:



- Normally 1.5 - 6% concentration of Salicylic acid is used in shampoos for Keratolytic property^{23, 24}.
- **Side Effects:** Dry, peeling, red, or scaling skin; mild burning or stinging at the application site. A very serious allergic reaction to this drug is rare. However, immediate medical attention required in case of any symptoms of a serious allergic reaction, including: rash, itching /

swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

- **Mechanism of Action:** (Refer Fig. 8).²⁶
- ✓ Salicylic acid, a Keratolytic agent, causes the skin to shed dead cells from its top layer by increasing the amount of moisture in the skin and dissolving the substance that makes the cells clump together.
- ✓ This effect makes it easier to shed the skin cells, softens the top layer of skin, and decreases scaling and dryness.
- ✓ Salicylic acid interacts with the skin protein, called keratin, and forms a complex. This complex formation softens the top layer of the skin, thus eases the shedding of the dead skin cells at the superficial skin layer.

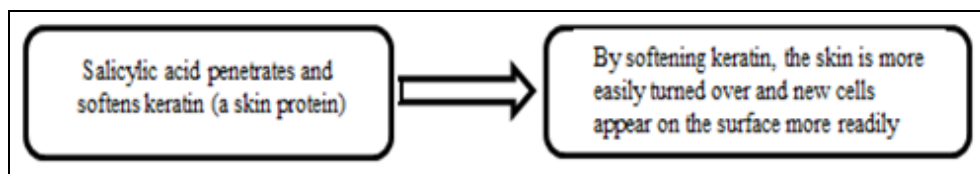


FIG. 8: MECHANISM OF ACTION OF SALICYLIC ACID

B) Anti- Proliferative Agent: Coal Tar:

- Normally 0.5-3% w/w concentration of Coal tar is used in formulations for Anti-proliferative and anti-inflammatory property.

- **Side Effects:** Skin / scalp irritation or staining of skin/hair (especially in patients with blonde, bleached, dyed, or gray hair) may occur.

- (A solution to the problem of staining has been developed *i.e.* novel stain-free lecithinized Coal tar formulation).
 - Coal Tar increases the chance of sunburn and therefore the chance of skin cancer.
 - **Mechanism of Action:**
 - ✓ Coal tar contains as many as 10,000 of chemical compounds, hence its mechanism of action is not well defined.
 - ✓ But it has been observed that coal tar suppresses the hyperplastic* skin.
 - ✓ Coal Tar is said to have anti-proliferative and anti-inflammatory activities. Hence it's useful in Dandruff and Psoriasis (in combination with other drugs).
- * (Hyperplastic = an abnormal increase in the number of cells in an organ or a tissue with consequent enlargement).

TABLE 1: MARKETED PRODUCTS OF ACTIVE INGREDIENTS

Sr. No.	Active Ingredient	Brand Name with Concentration of the active agent
1.	Zinc Pyrithione	Head and shoulders (0.5%, 1%, 2%), Dove shampoo (1%), DHS Zinc Shampoo (2%), Neutrogena- Daily control lotion (1%)
2.	Ketoconazole	Nizoral (1%), Regene (1%), Ketoconazole cream (2%)
3.	Climbazole	Hegor (1.5%) and Neutriderm (1.5%) Shampoos
4.	Selenium sulphide	Selsun (2.5%), Rexall (1%), Perrigo (2.5%) Lotion
5.	Clotrimazole	Clotrimazole 1% Powder, Candid tv suspension (1%)
6.	Piroctone Olamine	Sebamed (1%), Scalpofol anti-dandruff hair lotion (1%)
7.	Salicylic acid	Neutrogena (3%), Giovanni shampoo (2%), Saalex Lotion (6%)
8.	Coal Tar	Denorex shampoo (2.5%), Neutrogena T/Gel Shampoo (4%)

Literature reveals comparative studies data which is compiled as follows:

1) Danby FW *et al.*, reported that Ketoconazole (2%) and Selenium sulphide (2.5%) were equally efficacious but ketoconazole proved to be better tolerated²⁷.

2) Schmidt-Rose T *et al.*, reported in their study that a combination of Piroctone Olamine (0.5%) and Climbazole (0.45%) proved to be equally effective on comparison with Zinc Pyrithione (1%) alone²⁸.

3) Piérard-Franchimont C *et al.*, conducted a comparative study to evaluate the efficacy of a coal tar shampoo with Salicylic acid (2%) and Piroctone Olamine (0.75%). It was concluded in the study that non-coal tar shampoo containing Salicylic acid (2%) and Piroctone Olamine (0.75%) yielded significantly greater reduction in dandruff²⁹.

Various combination products are marketed since they prove to be more efficacious. Some are enlisted in **Table 2**.

TABLE 2: COMBINATION PRODUCTS ALONG WITH THEIR BRAND NAME

Sr. No.	Combination of drugs used	Brand name
1	Zinc Pyrithione and Ciclopiroxolamine (synthetic anti-fungal)	Ducray Kelual DS Treatment Shampoo
2	PiroctoneOlamine and Climbazole	Nivea Anti-dandruff shampoo
3	PiroctoneOlamine and Climbazole	Boderm Oliprox Treatment Cream
4	Climbazole and Ketoconazole	Dandrene (revita)
5	Zinc Pyrithione and Ketoconazole	Shampoo Kezole Plus
6	Coal Tar and Salicylic acid	Protar shampoo / Ointment.
7	PiroctoneOlamine and Salicylic acid	Nutralia shampoo
8	Zinc Pyrithione and Climbazole	Gatsby Hair Cream
9	Climbazole, PiroctoneOlamine and Zinc Pyrithione	D-Free Lotion
10	Climbazole, Zinc Pyrithione, Octopirox and Triclosan	Keto-Z shampoo

Formulations:

Conventional Formulations: The above mentioned drugs can be used in various types of formulations like Shampoos, Lotions / Applications, Creams, Herbal oils and gels.

1. Shampoos: These formulations are used to clean the dirt of scalp and other environmental pollutants, sebum, sweat, desquamated corneocytes and other greasy residues from previously applied hair care products³⁰.



FIG. 9: REPRESENTS A LIST OF INGREDIENTS OF SHAMPOO

Since shampoos contain surfactants as cleansing agents, they may remove excess of sebum which leaves the scalp skin dry and hair become frizzy and unmanageable.

The main aim should be to develop a shampoo which removes only the right amount of sebum while leaving sufficient amount of conditioning agents. The basic ingredients of a shampoo have been listed in **Fig. 9**. Synthetic detergents and conditioners play the role of cleansing and manageability, while all other ingredients are used to aid appearance, stability and marketability.

Surfactants: These are amphiphilic in nature, *i.e.* they have both hydrophilic and lipophilic groups. The lipophilic end is used to bind sebum and oily dirt while the hydrophilic end binds to water, thus allowing removal of sebum with water. There are five types of surfactants depending on their ionic nature. Each type possesses varying properties of cleansing and conditioning³¹.

A compilation of the various types of surfactants along with their chemical classes, charge and their specific characteristics has been given in **Table 4**.

TABLE 4: TYPES OF SURFACTANTS ALONG WITH THEIR CHEMICAL CLASS, CHARGE AND SPECIFIC CHARACTERISTICS

Surfactant type	Charge	Chemical class	Characteristics
Anionic	Negative	Lauryl sulfates, Laureth sulfates	Deep cleansing. Removes sebum and oily dirt. May leave hair harsh and scalp dry
Cationic	Positive	Long chain amino esters, ammonio-esters	Imparts anti-static properties to hair. Softens hair and improves manageability
Non-ionic	No charge	Polyoxyethylene fatty alcohols, polyoxyethylenesorbitan esters alkanolamide	Good detergent properties, wetting agents, emulsifiers and have good foaming properties
Amphoteric	Both positive and Negative charges	Cocamidopropyl betaine and sodium lauraminopropionate	Cationic at lower pH and anionic at higher pH

- Conditioners are ingredients that impart manageability, shine and anti-static properties to hair. Silicones are widely used as conditioning agents, especially in 2 in 1 shampoos (shampoo + conditioner). Also, propylene glycol, animal protein, glycerine and hydrolysed silk have been used as conditioning agents. The protein derived substances help in mending the split ends. The protein binds to the keratin of hair and holds the cortex fragments together thus mending the split ends temporarily.
- Foaming agents are added due to the common myth- "More the foam, more is the cleansing action and thus better cleaning". Sebum inhibits foam formation and thus there is more foam on second shampooing. Cocodiethanolamide,

Cocomonooethanolamide, Lauricmonoethanolamide, are used as foam boosters in shampoos.

- Thickeners and Opacifiers – these aid in enhancing the user- appealing properties of the shampoo which include- physical and optical properties. Opacifiers such as glycerol distearate are added to the formulations to give them pearlescent effect. Sodium chloride and other such thickeners are used to increase the viscosity of the formulation.
- Sequestering agents - Polyphosphates and Ethylene diamine tetra acetic acid are used to chelate with free magnesium or calcium ions (that are present in hard water, if used for cleansing) to avoid formation of scum on the scalp and hair.

- e. pH adjusters- Hair shaft has pH of 3.67 and scalp pH is 5.5. Thus, these are added to adjust the pH of the formulation between 3.67 and 5.5.
- f. Preservatives - Parabens, Quaternium-15, Sodium benzoate, Tetra-sodium EDTA are examples of preservatives used in shampoos.
- g. Special additives - fragrance imparters, chemical sunscreens, Pro-Vitamins, honey and herbal ingredients like tea tree oil are added to the shampoos for additional effects.

Various types of shampoos are available like Normal hair shampoo, Dry hair shampoo, damaged hair shampoo, oily hair shampoo, everyday shampoo, deep cleansing shampoo, baby shampoo, medicated shampoo, two-in-one shampoo and hair dyeing shampoo. Anti-dandruff shampoos are classified under medicated shampoos. Depending on the hair type and compatibility of the active ingredient with excipients, the shampoo formulation can be modified further.

2) Lotions/Creams/Gels:

- Key components of a skin care lotion, cream or gel emulsion (that is mixtures of oil and water) include an emulsifying agent (*e.g.* Glycerylmonostearate / distearate) to prevent separation of the above two phases, the active ingredients, fragrances, glycerol (humectant), petroleum jelly (relieve from dryness), preservatives, proteins (provide additional nutrients to hair follicles).
- The main difference between lotion and cream is that creams are thicker than lotions.

Creams are semi-solid while lotions are thick liquids. Consumers prefer lotions for hair over creams as creams may be greasier. The detailed advantages and disadvantages of the conventional topical dosage forms are discussed in **Fig. 10**.

Comparison of the Topical Dosage Forms: (Refer Fig. 10)

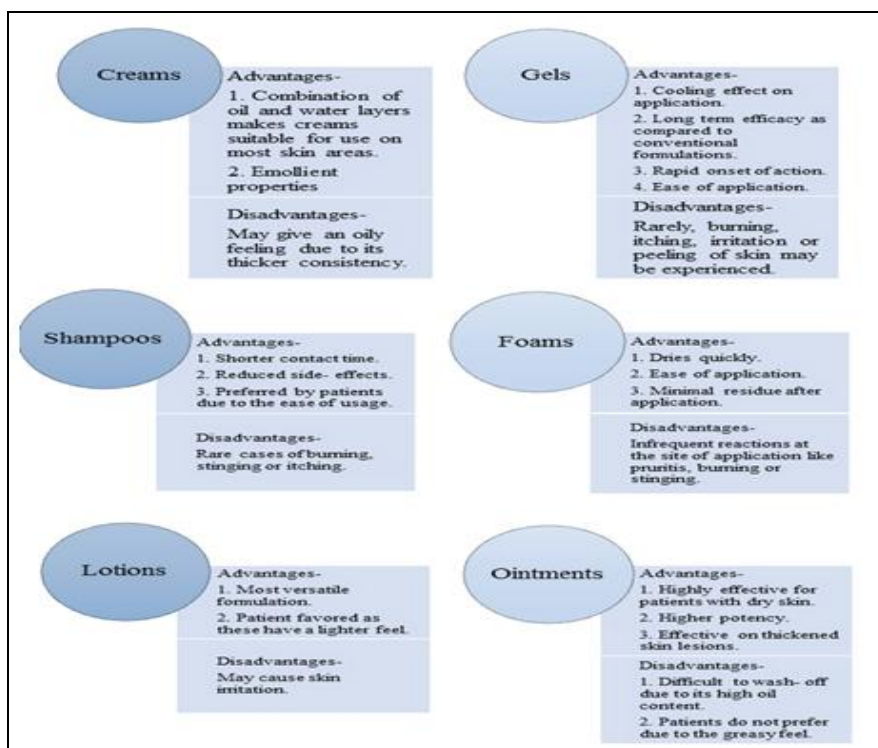


FIG. 10: CLASSIFIES VARIOUS CONVENTIONAL FORMULATIONS ALONG WITH THEIR RESPECTIVE ADVANTAGES AND DISADVANTAGES

4) Herbal oils: Oils as hair care formulations are preferred due to the moisturizing effect they provide on application. Herbal oils are a choice for hair care cosmetics as they have proven efficacy against the fungi *Malassezia* and they avoid the use

of synthetic drugs. Moreover, herbal actives act as hair growth promoters, improve hair smoothness and reduce hair fall³². Some of the herbal oils are given in **Table 5**.

TABLE 5: MARKETED PRODUCTS OF HERBAL OILS

Sr. No.	Herbal oils	Brand name
1	Tea tree oil	FabIndia Tea tree dandruff control oil
2	Tea Tree oil and Rosemary extract	Himalaya Anti Dandruff Hair Oil
3	Rosemary oil and lemon oil	Trichup oil
4	Cedar wood, Patchouli oil, Rosemary and eucalyptus extracts	Aroma Magic Anti-Dandruff hair oil
5	Basil and Neem	Tvam Hair Oil

5) Miscellaneous Formulations: Sedigel Scalp Moisturizing Gel for dry, itchy, flaky scalp. Sedigel is a clear, colorless gel proven to be safe and effective for application on scalp. The prominent characteristic of this gel is that it contains high concentration (10%) of glycerin while it is free from lanolin, steroids and SLS. Glycerin is a common humectant that hydrates and moisturizes the scalp skin³³, beneficial when present in the formulation. This moisturizing effect helps alleviate dryness and the itchy feeling which is associated with dandruff.

Extina Ketoconazole (2%) Foam Formulation:

Extina (ketoconazole foam, 2%) Foam contains 2% ketoconazole in thermolabile hydro-ethanolic foam for topical application³⁴. Hydro-ethanolic foam is made up of ethanol and water. Ethanol is used to solubilize the drug thus increasing the bioavailability of the drug. This formulation is suitable for oily skin areas as well. This does not require the use of any preservatives.

The advantages of foam formulation over creams and ointments include:

- ✓ Quick drying of the formulation.
- ✓ Minimal residues on the skin.
- ✓ Ease of application.
- ✓ No need of fragrance imparters.
- ✓ No difference in cost as compared to creams and ointments.
- ✓ Spreads easily, esp. useful in case of application on larger body surface area.

One disadvantage could be small reactions at the site of application, like burning, stinging, etc.

Novel Formulations: These formulations include Liposomes, Niosomes, Solid lipid nanoparticles and Nano lipid Carriers used for anti- dandruff treatment.

Liposomes: Liposomes are self - assembled vesicular structures that contain one or more lipid

bilayers. These have an aqueous core for solubilizing the hydrophilic drugs and a lipidic bilayer for entrapping the lipophilic drugs. These are often composed of phospholipids to form the bilayer and cholesterol to strengthen the bilayer structure³⁵. They are able to transfer entrapped and non-entrapped drugs into skin³⁶ and can act as carriers controlling the release of active ingredient. The phospholipids help localize the drugs at the site of action due to their interaction with sebum, improve deposition within skin, and reduce systemic absorption and minimizing drug side effects.

➤ Novel Lipotar gels are novel products containing lecithinized coal tar together with pharmaceutically acceptable excipients. Coal tar has been entrapped inside lipid- based self-assembled systems at micro and nano size range. These carrier systems transport the active agent (here, salicylic acid) safely and effectively to the desired site and also produce conducive micro-environment for better drug-receptor interaction. Entrapment of coal tar within these assemblies helps in interaction of phospholipids with the skin as it provides the fully hydrated conditions and larger molecular surface area with enhanced interface. The chemical composition of the system also takes care of the rheological nature of the system. Due to this rheological nature (*i.e.* higher viscosity), coal tar remains confined to the affected area and does not spread to the normal skin surrounding the lesion. This minimizes skin irritation and staining due to coal tar. The carrier system allows the drug to be washed off easily, which otherwise gets strongly absorbed onto the fabric and stains the clothes heavily. Hence this novel formulation seems to be advantageous over the other common formulations^{37, 38}.

➤ Meiyong Ning *et al.*,³⁹ in the article 'Preparation, *in vitro* and *in vivo* Evaluation of

Liposomal / Niosomal Gel delivery systems for Clotrimazole', reported that liposomal / niosomal gels containing Clotrimazole would be useful for effective and convenient treatment of vaginal candidiasis with reduced dosing interval. Also, the liposomal / niosomal gel did not affect the morphology of vagina tissues over 24 hours post dose and hence the formulation would be safe for application. The results of their work proved that the vesical gel systems were stable and provided a sustaining release in simulated vaginal fluid at 37 ± 1 °C for 24 hours. Thus, a liposomal / niosomal gel of Clotrimazole could be formulated and evaluated for anti-dandruff activity as well.

- M. Schaller *et al.*,⁴⁰ compared the effect of two commercially available formulations of Econazole nitrate on uninfected reconstructed human epidermis and on a model of human cutaneous candidosis. The two formulations tested were a conventional cream of Econazole nitrate and a liposomal gel of Econazole nitrate. The cream showed more epidermal barrier damage and irritative toxic effects than Liposomal gel, when applied to the uninfected reconstructed epidermis. Also, on application of the liposomal gel to the modelled human cutaneous candidosis, toxic effects were reduced and no invasion of *Candida albicans* into the stratum corneum was observed, as seen on application of the cream.

Niosomes: Niosomes are non-ionic surfactant based vesicles with microscopic lamellar structure. These can be synthesized using thin film hydration technique with cholesterol and single alkyl chain non- ionic surfactant. Niosomes increase the penetration of active ingredients and serve as a local reservoir of actives. These solubilize hydrophilic and lipophilic drugs, similar to Liposomes. Niosomes contain lesser amount of Cholesterol as compared to liposomes; also the phospholipid content of liposomes renders them less stable than Niosomes. Liposomes are expensive, require special storage and handling conditions, and have drug entrapment efficiency lower than Niosomes^{41, 42}.

- SB Shirsand *et al.*,⁴³ reported that Ketoconazole containing Niosomal gel proved

to give prolonged activity as compared to non-niosomal gel of ketoconazole. Ketoconazole niosomes were prepared by thin film hydration method. Using different ratios of non-ionic surfactants along with Cholesterol. The non-ionic surfactants used by SB Shirsand *et al.*, included Span 40, Span 60 and Tween 60. 1% Carbopol was used as the polymer for gel formation. The formulation was evaluated for size, shape, entrapment efficiency and *in-vitro* drug release. Thus, a niosomal gel formulation of Ketoconazole could be considered for enhanced anti-fungal activity.

- Y. Prem. Kumar *et al.*,⁴⁴ prepared Niosomes of Econazole by thin film hydration method. The Niosomal gel was made by varying the ratios of cholesterol to surfactants. Batches of four different ratios were made and compared for drug release. It was observed that the formula having the highest content of surfactant showed maximum drug entrapment and desired sustained release of the active.

Solid Lipid Nanoparticles: These are sub- micron range colloidal carriers prepared by using physiologically compatible solid lipid or a blend of lipids. These have relatively higher encapsulation efficiencies and improved stability as compared to Liposomes⁴⁵.

Nano Lipid Carriers: These are similar to Solid lipid nanoparticles with the only difference being the presence of liquid lipids along with solid lipids. The solid lipids provide a highly ordered structure to these nanoparticles, while the liquid lipid provides high imperfections in crystal lattice. The imperfections provide higher accommodation of the active agents.

- Sanna V *et al.*,⁴⁶ prepared Solid Lipid Nanoparticles of Econazole Nitrate for topical delivery and evaluated the formulation using *in-vitro*, *in-vivo* and *ex-vivo* tests. They observed that the encapsulation efficiency was nearly 100%. *Ex-vivo* results demonstrated that Solid Lipid Nanoparticles were able to prolong the release of the active in the Stratum corneum and the release rate depended upon the lipid content of the formulation. *In-vivo* tests showed that Solid Lipid Nanoparticles improved the

drug diffusion through deeper layers of skin when compared with the conventional gel formulation. Hence, Solid Lipid Nanoparticles improve the topical delivery of Econazole nitrate.

- Souto EB, Müller RH.⁴⁷ developed a Solid Lipid Nanoparticle based aqueous dispersion of Clotrimazole and compared it with two marketed creams of Clotrimazole. All three formulations contained 1% Clotrimazole. In-vitro studies conducted using Franz diffusion cells with a cellulose acetate membrane showed that the drug released from marketed creams was nearly 50% while that from the Solid Lipid Particle based aqueous dispersion was less than 30%. Thus, Souto EB concluded that Solid lipid nanoparticle formulation prolonged the release of Clotrimazole.

Polymeric Micelle Formulations: Polymeric Micelle Formulations have been investigated due to their potential to solubilize the lipophilic drugs. Spherical polymeric micelles are formed when the block co-polymers self-assemble at a concentration above their Critical Micelle Concentration (CMC). The hydrophobic segments aggregate to form their inner core which accommodates the lipophilic drug and the hydrophilic shell stabilizes the micelles in aqueous solution. Various advantages of polymeric micelles include reduced side effects, selective targeting, stable storage and stability towards dilution.

- Y.G. Bachhav *et al.*,⁴⁸ studied Novel Micelle formulations to increase cutaneous bioavailability ofazole Anti-fungal actives including- Clotrimazole, Econazole nitrate and Fluconazole. Polymeric micelles were investigated due to their stability, size and ability to incorporate significant amounts of hydrophobic drugs in their core. This study included comparison of a formulation of actives encapsulated in hydrophobic MPEG-dihex PLA copolymers with a marketed liposomal formulation. Y.G. Bachhav *et al.*, concluded that the MPEG-dihex PLA micelle formulation lead to significantly higher drug deposition in both porcine and human skin as compared to the marketed liposomal formulation. Also, it was observed that the preparation method like faster

evaporation and addition under sonication, affected micelle properties.

Silver Nanomaterials: Nano-sized metallic particles are unique and depending on their surface to volume ratio, they can change physical, chemical as well as biological properties. Additionally, these particles possess anti-bacterial as well as anti-fungal potency and they also mitigate anti-biotic resistant species. Among the metallic nano-structures, Silver ions have been more extensively explored in the medical sector, including burn and wound dressing for alleviating bacterial infections.

Mechanism of Action of Nanoparticles:

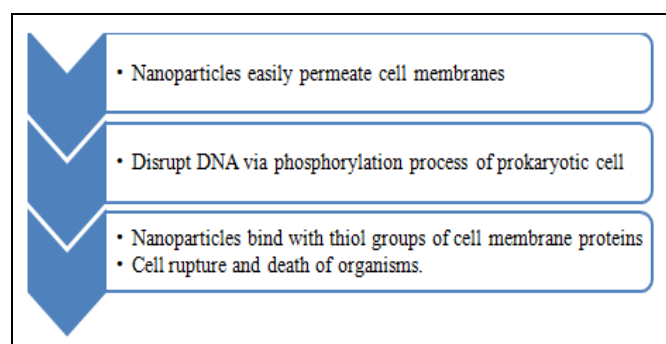


FIG. 11: MECHANISM OF ACTION OF SILVER NANOPARTICLES

- Use of silver spherical nanoparticles in anti-dandruff shampoos has been indicated by Pant *et al.*,⁴⁹ by performing the in- vitro assessment against *Malassezia furfur*. This study was based on green chemistry approach, where *Solanum trilobatum* plant leaf was used for biosynthesis of silver nanoparticles. Silver nanoparticles were proven to be potent against *Malassezia furfur*.
- Satishkumar *et al.*,⁵⁰ concluded in their study that green synthesized silver nanoparticles using *C. sativum* have great potential for use in anti- dandruff treatment.
- Anwar *et al.*,⁵¹ carried out size and shape dependent study of clinical and mycological efficacy of silver nanoparticles on dandruff. In this study, silver nanomaterials in the form of 20nm and 50nm spherical nanoparticles and 50nm nanorods at different concentrations of Ag nanoparticles against known anti- fungal agents like Ketoconazole and Itraconazole. It

was concluded in this study that small sized silver nanoparticles can be used as an important and cost effective anti- fungal agents in formulations for treating scalp problems like dandruff.

Polymeric Nano Capsules: These are nanostructures formed by a polymer shell that encloses a lipophilic or hydrophilic liquid core. These nanocarriers protect the skin from the irritant effects of the active agent and increase its residence time.

- Sara S. Santos *et al.*,⁵² examined the feasibility of developing Clotrimazole loaded cationic nanocapsules using the method of interfacial deposition of preformed polymer. Eudragit RS 100 was used as the polymer and medium chain triglycerides as the oily core. The conclusion of this study was that the polymeric nanocapsules provided adequate physicochemical characteristics and stability along with prolonged release. Thus, Eudragit RS 100 nanocapsules proved to be a promising alternative for prolonged release of the active agent.

Thermophobic Foam: This is a new delivery system which is temperature activated.

This formulation is a mousse which, when applied to the skin, melts rapidly and evaporates at a rate faster than conventional lotions. Evaporation leads to a non- residue, sustained penetration of the active compound.

- G Quadri *et al.*,⁵³ compared the efficacy of a thermophobic foam with 2% Ketoconazole scalp fluid. The thermophobic foam formulation consisted of 1% Ketoconazole, 0.5% Zinc Pyrithione and 2% Salicylic acid as the actives. The foam formulation could enhance the clinical efficacy and the patient's compliance to the treatment. The thermophobic foam breaks down quickly and evaporates when applied to skin, as the solvent evaporates; the active compounds are concentrated on skin. Evaporation of thermophobic foam results in faster and deeper penetration of the active ingredients through scalp. It was concluded in this article that the anti-dandruff foam proves to be an effective and safe option in the treatment of moderate to severe dandruff.

The novel delivery systems have been schematically represented in **Fig. 12**.

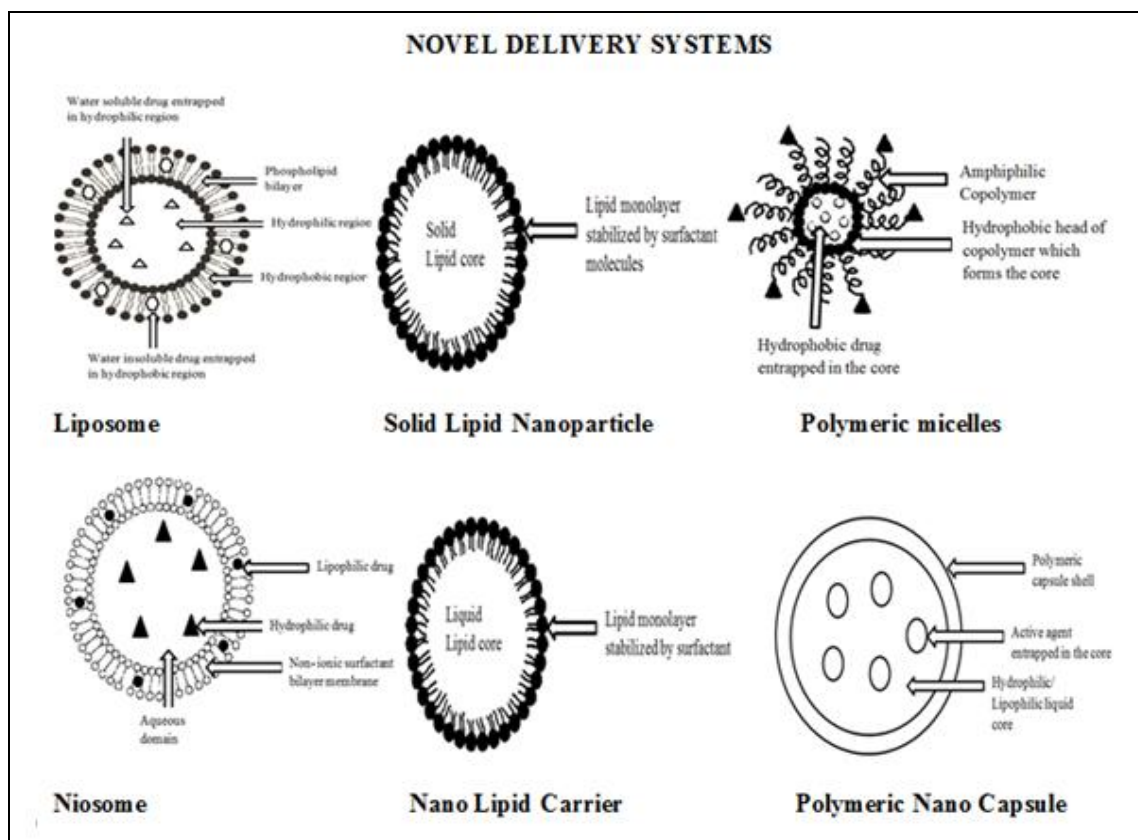


FIG. 12: SCHEMATIC REPRESENTATION OF NOVEL DELIVERY SYSTEMS

CONCLUSION: Dandruff is a scalp condition that affects more than 50% of the human population and affects the social behaviour of the sufferer along with possessing an unhealthy scalp. The cause of dandruff depends on individual susceptibility and hence treatment strategy also varies. Conventional formulations like shampoos, creams and lotions have been used for ages but have not been successful in avoiding recurrence of this condition. Also, these conventional formulations show limited efficacy and duration of action. Herein lays the role of novel delivery systems like Liposomes, Niosomes, and Solid lipid nanoparticles.

These delivery systems could provide high entrapment efficiency and prolonged duration of action since they form a reservoir of the active agents and remain in the scalp even after the clearance of the formulation and these reservoirs release the active agent on a prolonged basis. Novel delivery systems are being widely studied in pharmaceutical formulations and can be beneficial for treatment of dandruff. Novel formulations containing proven anti- dandruff agents with longer contact time at the site of action are the need of the hour and hence can prove to be advantageous in anti-dandruff treatments.

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