

Current Trends in Novel Drug Delivery- An OTC Perspective

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Despite global economic uncertainty, the potential of the OTC market remains noteworthy. The Rx-to-OTC switching and the continuing importance of emerging pharma markets will drive OTC sales growth from 2010 onwards. Novel and advanced therapies will continue to be the key backbone drivers for lifecycle management. This article introduces the global scenario and regulations in the OTC category and highlights the key potential delivery platforms and therapeutic categories in the OTC market.

The field of Novel Drug Delivery Systems (NDDS) is burgeoning at an exponential rate with the insights gained in diversified fields of biotechnology, biomedical engineering, nanotechnology, material science etc with a deeper understanding today of the cellular mechanisms, drug transporters, molecular biology, gene therapy and bioinformatics. This spurt of information has revolutionized and augmented the impetus, synergy and enthusiasm of NDDS.

In this article, the scope and advances in the area of OTC products in the global scenario is discussed.

1. The Global OTC market:

Demographic trends, lifestyles changes and clinical advances are transforming medicine and creating opportunities for therapeutic areas and drug types in OTC pharma. Governments and healthcare providers are promoting self-medication, viewing the process as a tool to help contain healthcare expenditure. It is envisioned that the global OTC Pharmaceutical Market will continue to escalate because of Rx-to-OTC switching and the continuing importance of emerging pharma markets from 2010 onwards. The potential of the OTC market remains significant, despite general economic uncertainty. Figure 1 gives the OTC market estimation and a steady increase is foreseeable. Figure 2 gives the lifecycle of OTC product with and without Rx-to-OTC switch¹.

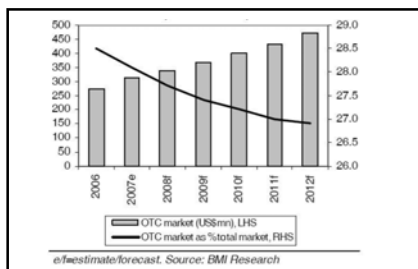


Figure 1 : Potential OTC Global Market

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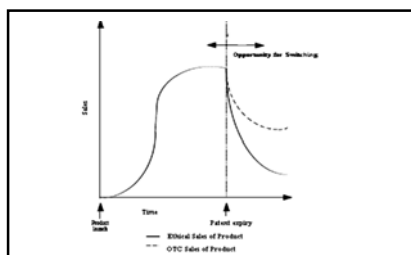


Figure 2 : Lifecycle of OTC product with and without Rx-to-OTC switch.

2. Regulations for OTC drugs

OTC drug products are those drugs that are available to consumers without a prescription. There are more than 80 therapeutic categories of OTC drugs, some of them as listed on the usfda website² include and are not limited to acne and other skin disorders, allergy, antacids, antimicrobial, dandruff, cold and cough remedies, smoking deterrents, nasal decongestants, vaginal products such as contraceptives, otic products, oral healthcare products and vitamins and minerals. As with prescription drugs, CDER oversees OTC drugs to ensure that they are properly labeled and that their benefits outweigh their risks³.

The Durham-Humphrey Amendment [§503; 21 U.S.C. §353], enacted in 1951 established two classes of drugs: prescription and OTC. A catalyst for additional safety regulation was the thalidomide tragedy in the early 1960s which was responsible for a serious birth defect in thousands of infants. Because the FDA had not approved the use of this drug in the United States, the number of birth defects in the US was very low. Despite this fact, in 1962, Congress enacted the Kefauver-Harris Amendment to the 1938 FDCA Act which required, during the New Drug Application (NDA) process, that drugs be proved to be both safe and effective. The procedures for classifying OTC drugs as safe and effective can be found in Section 21 of the Code of Federal Regulations (CFR), Part 330.

A section, (503 (b) (3)), of the Durham-Humphrey Amendment grants the FDA authority to switch prescription drugs to OTC status by regulation. Such a switch may take place when one of the following occurs:

1. The drug manufacturer requests the switch by submitting a supplemental application to its approved NDA
2. The drug manufacturer petitions the FDA.
3. The drug may be switched through the OTC drug review process

The primary mechanism of switching drugs to OTC status is the third--the OTC drug review process. If the FDA agrees, it produces a final report on the OTC and the switch from prescription status to OTC takes place³.

In countries like Canada, Sweden and United Kingdom there is an additional category called "under/behind-the-counter" drugs. Drugs in this category do not require a prescription but neither can they be simply purchased off the shelf. Here, pharmacists would control their access and give counseling. Regulatory changes are underway in the United States.

OTC drugs generally have the following characteristics³:

- Their benefits outweigh their risks
- The potential for misuse and abuse is low
- Consumer can use them for self-diagnosed conditions
- They can be adequately labeled

Often OTC drugs are legally marketed without an application or FDA review by following a regulation called an OTC drug monograph. An OTC drug monograph tells what kind of ingredients may be used to treat certain diseases or conditions without a prescription, and the appropriate dose and instructions for use³.

Differences in Marketing under NDA and OTC monograph are enlisted in Table I.

Table I : Marketing under NDA and OTC monograph

NDA Process	OTC monograph process
Premarket approval needed	No Premarket approval needed
Confidential filing	Public process
Drug product specific	Active ingredient specific
May require a user fee	No user fees
Potential for marketing exclusivity	No marketing exclusivity
May require clinical studies	May require clinical studies
Label comprehension & actual study required	Label comprehension & actual study not required

3 . Novel Drug Delivery

Systems (NDDS) in OTC:

The use of innovative drug delivery technologies has become one of the most attractive tools for extending the lifecycle and value of a drug product line. The OTC as well as generic companies are becoming more and more proactive in developing newer drug delivery platforms of well established compounds to enhance service to increasingly differentiated and demanding patient populations.

Novel Drug delivery would include a wide array of DDS ranging from quick dissolve technologies to extended release products to targeted drug delivery. Any manipulation in the formulation to control the delivery of a drug as a function of time, site or mechanism of release is termed as a controlled drug delivery and the technology is classified as Novel Drug Delivery.

From a technological view point , NDDS in OTC can be primarily categorized into the following dosage route categories:

A. Oral, B. Topical, C. Nasal, D. Vaginal, E. Ophthalmic , F. Transungual

A. Oral

More than 2/3rd of \$200 billion US drug market consists of orally administered drugs and more than 85% of this market segment is in the form of solid oral dosage forms. It is evident that oral drug delivery continues to enjoy its popularity as the most widely utilized route for administration despite the rapid advances and initiative research in the other routes of administration.

Oral OTC formulations can be broadly classified as :

Matrix systems

Here, the drug is embedded in a controlled release polymer. These could be either monolithic, single layer, bilayer, tablet in tablet or in the form of Multiunit particulate system (MUPS).

The Mucinex range of OTC products marketed by Reckitt Benckiser is one of the top brands using matrix technology. Immediate release layer provides instant release of drug for quick relief followed by slow release of drug over the period of 12 hrs through extended release layer(Fig 3). The matrix comprises of hydrophilic polymer like HPMC and a water-insoluble polymer like acrylic resins.

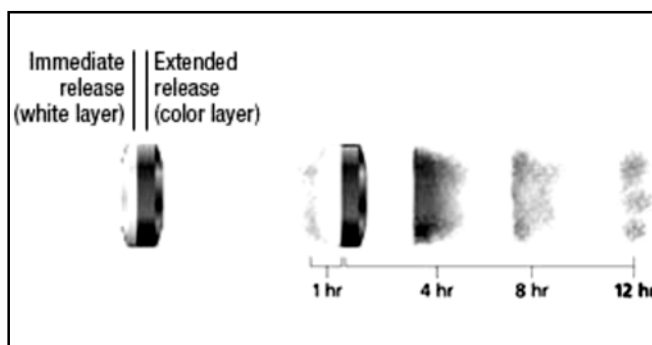


Figure 3 : Depiction of swelling and release of Guaifenesin in Mucinex

Combinations with other drugs such as Dextromethorphan, Diphenhydramine are also marketed⁴.

Multi particulate system(MUPS)⁵

Multiparticulates are composed of pellets, granules and minitabets have numerous advantages over single unit CR dosage forms. Recent trends indicate that MUPS are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. Furthermore they can be easily mixed when either a combination of drugs or various drug release rate at the same site or different site are desired. The mechanism of drug release from multi particulates can occur in the following ways:

Diffusion : On contact with aqueous fluids in the gastrointestinal tract, water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Erosion : Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle.

Osmosis In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.

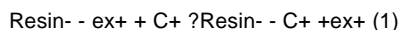
With over 50 million American adults suffering from frequent heartburn, recently Novartis OTC launched Prevacid®24HR (lansoprazole delayed-release capsules 15 mg/acid reducer) for full 24-hour frequent heartburn treatment. The capsule is composed of multiparticulates wherein drug release is controlled by using combination of hydrophilic and hydrophobic polymers. Lansoprazole granules are enteric coated to prevent degradation in acidic pH and regulate drug release in intestine over 24 hrs⁶.

Ion exchange technology: ⁷

Pharmaceuticals complexed using ion exchange resins have shown improved organoleptic performance of pharmaceuticals. They are used to mask the bitter taste, improve processing characters of drug molecules, modify release, disintegration improvement and also confer physicochemical stabilization. Advantages of ion exchange resins include high drug loading ability due to extensive binding sites, chemical inertness, applicability to solid, semisolid and liquid dosage forms, long term physico-chemical stability, freedom from local and systemic side effects and stability to sterilization means they can be formulated in to all sterile dosage forms.

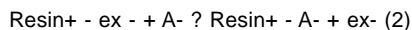
Ion exchange resins are vinyl, divinyl benzene and polystyrene copolymers available as high molecular weight polyelectrolytes having extensive charged functional sites. They are insoluble in nature and exchange their exchangeable ions with same charge ions in the surrounding ionic medium. Mainly, resins are of two types; weak and strong cationic and anionic resins respectively.

The functional group of cation-exchange (Anioinic) resins undergoes reaction (exchange) with the cations in the surrounding medium.



Where, Resin- indicates polymer with SO₃⁻ sites available for bonding with exchangeable cation (ex⁺) and C⁺ indicates cation in the surrounding solution getting exchanged.

Anion exchange (Cationic) resin undergoes reaction (exchange) with the anions in the surrounding medium.



Where, Resin⁺ indicates polymer with N⁺ sites available for bonding with exchangeable anion (ex⁻) and A⁻ indicates cation in the surrounding solution getting exchanged.

The use of ion exchange resins into modified drug delivery systems have been encouraged because of their physico-chemical stability, inert nature, uniform size, spherical shape assisting coating and equilibrium driven reproducible drug release in ionic environment. Resinates of strong cationic drugs are formulated as sustained release suspension, tablets, resinate complex of bromhexine in suspension form has been formulated to control drug release and reduce the frequency of dosage administration⁹. Simultaneously, bioadhesive properties of ion-exchange resins may be useful mucoadhesive systems for local treatment of stomach infections like *H. pylori* for prolonging the gastric residence of amoxicillin and cimetidine¹⁰. Potential superdisintegrant ability of Indion 414 has been reported by Purnima et al¹¹ for mouth dissolve tablets of roxithromycin, montelukast sodium and dicyclomine hydrochloride.. Drugs at molecular level complexed with resin shows more stability due to electrostatic and hydrophobic type nonbonding interactions as seen in Vitamin B12 and carboxylic acid resin complex¹².

Tooth pastes, lacquers, prostheses coming in contact with tooth surface are rendered anti-cariou by incorporating ion exchange resins containing fluorine, phosphate or calcium ions.

Delsym is an American brand of OTC cough medicine based on ion exchange technology owned by Reckitt Benckiser. Each 5 ml of Delsym contains is dextromethorphan polistirex, equivalent to Dextromethorphan(DEX) HBr 30mg. Delsym maintains consistent Plasma Levels of DEX for a 12 hour period (Figure 4). Part of the drug-resin complex in Delsym was coated with Ethylcellulose. The ratio of coated to uncoated drug-resin was approximately 2:1 coated/uncoated. EDTA was added as a chelating agent to reduce degradation of the drug in the drug resin complex. Similar technology is used for Hydrocodone release from TUISSIONEX Pennkinetic Extended-release suspension which combines an ion-exchange polymer matrix with a diffusion rate-limiting permeable coating¹³.

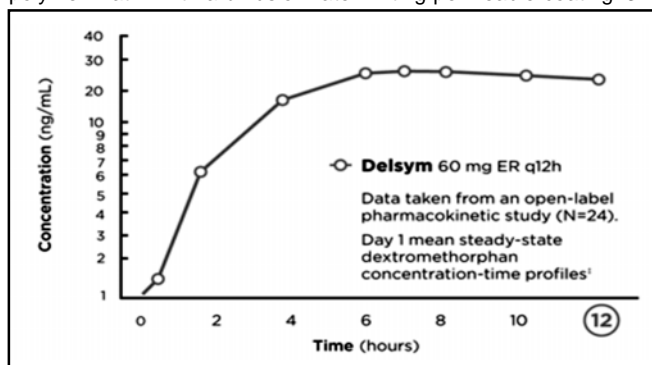


Figure 4 : Release of Dextromethorphan from Delsym

Orally disintegrating tablets (ODTs)

Orally disintegrating tablet technology is one of the widely used technique by pharmaceutical companies as part of the life cycle management. ODTs are solid dosage forms containing medicinal substances which disintegrate rapidly, usually in a matter

of seconds, when placed on the tongue. The main advantage of orally disintegrating tablet (ODT) is patient compliance where the tablet can be taken without water. Some of the brands in OTC include Claritin RediTabs manufacture by Schering plough¹⁴. Each tablet contains 10 mg micronized loratadine, an antihistamine, to be administered orally. The inactive ingredients include citric acid, gelatin, mannitol, and mint flavor. Some of the marketed technologies are given in Table².

Table 2: Technologies for ODTs

Technology	Basis	Patent owner
Quicksolv™	Lyophilization	Janseen Pharmaceutica
Ziplets™	Molding	Eurand
Lyoc™	Lyophilization	Farmlyoc
Flashtab™	Multiparticulate Compressed Tablets	Ethypharm
Orasolv,™/Durasolv	Compressed Tablets	Cima Labs Inc.
RapiTab™	Compressed Tablets	Schwarz Pharma Technologies, Inc
WOWTAB™	Compressed Molded	Yamanouchi Pharma
Fast melt™	Molding	Élan Corp.
FlashDose™	Cotton-candy process	Fuisz Technology Ltd.

Excellent review of ODT is presented by Hirani 15 et al .

Oral Strip technology (OST) 16

The use of thin-film strips is of growing interest in the pharmaceutical sector following the success of Listerine PocketPaks® in the US. The OST continues to be viewed as an alternative for ODT products that would afford a superior barrier to generic entry and product differentiation to over-the-counter brands. OSTs are more robust since the films are flexible they are not as fragile as most of the ODTs. Thus they afford ease of transportation during consumer handling and storage. From the patient point of view OSTs offers ease of administration and improved compliance especially for the pediatric and geriatric patient population. This technology has been used for local action, rapid release products and for buccoadhesive systems that are retained for longer period in the oral cavity to release drug in controlled fashion. OST offers an alternate platform for molecules that undergo first pass metabolism and for delivery of peptides. The manufacturing of this dosage form is cost-effective with affordable end-products. From a clinical aspect, the improved bioavailability can be advantageous in reducing the dose of the formulation leading to a product with minimal side effects.

However disadvantages of OSTs are that not all drugs can be incorporated into this dosage form. Also high dose cannot be incorporated into the strip. Lately, research has proven that the concentration level of active can be improved up to 50% per dose weight. Novartis Consumer Health's Gas-X® thin strip has a loading of 62.5 mg of simethicone per strip.

Formulation aspects

Formulation of OSTs involves the complex application of aesthetic and performance characteristics such as taste masking, fast dissolving, physical appearance, mouth-feel etc.

The buccal mucosa is less permeable than the sublingual mucosa and is thus not able to elicit a rapid onset of absorption and hence an ideal site for sustained release action. To overcome low drug bioavailability, various buccal penetration enhancers have been studied which improve the absorption pattern of the molecules. Tough & fast disintegrating strip forming polymers include pullulan, gelatin & HPMC. Pullulan is preferred because of its low oxygen

permeability and low water content. Mucoadhesive polymers include polycarboxylic, cellulose derivatives like HPMC, poly(acrylic acid) derivatives, NaCMC, HEC, Xanthan gum, locust bean gum, guar gum, carrageenan, and other gums, poly (ortho esters), poly (hydroxyl butyrate), poly(cyano acrylates), polyphosphazenes, poly (vinyl alcohol) etc. Second generation mucoadhesive polymers include thiolated polymers. Plasticizers help to improve the flexibility of the strip and reduces the brittleness of the strip. Glycerol, Propylene glycol, low molecular weight PEGs, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, citrate derivatives, triacetin and castor oil are some of the plasticizers used. Stabilizing and thickening agents are used to improve the viscosity and consistency of dispersion or solution of the strip preparation solution or suspension before casting. Sweeteners typically used are sucrose, dextrose, fructose, glucose, liquid glucose and maltose. Artificial sweeteners such as Acesulfame-K, Sucralose, Neotame and alitame can also be used. Saliva stimulating agents which enhance the rate of production of saliva resulting in the faster disintegration of the rapid dissolving strip formulations can be used. eg Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are used alone or in combination between 2 to 6%w/w.

Ora moist® is a Timed Release oral disk that adheres to the roof of the mouth and has a moisturizing effect for about 4h. It is recommended for dry mouth syndrome (xerostomia). Compeed® is another formulation that is intended to treat cold sore. Other brands of OSTs for cold and cough include Theraflu Thin Strips Long Acting Cough /multisymptom, containing Dextromethorphan, Diphenhydramine, Antigas containing simethicone, Innozen Dextromethorphan and Herbal containing menthol, Chloraseptic Relief Strips Benzocaine; menthol etc.

B. Topical Drug Delivery Systems:

The skin is one of the most extensive and readily accessible organ of the human body (Fig5). Both local and transdermal delivery is receiving increasing attention in the OTC market due to its advantages such as non invasive therapy, reduced side effects and targeting to the actual site of action.

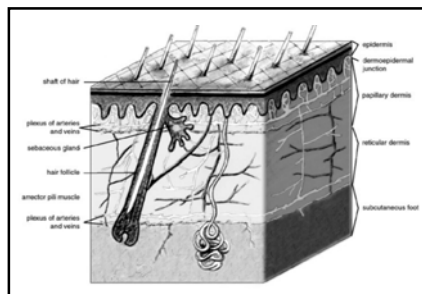


Fig 5: Section of Skin

Acne, the most commonly treated indication by OTC drug therapy is a chronic inflammatory dermatosis of the pilosebaceous unit (PSU) and is characterized by several abnormalities in sebum production, follicular epithelial desquamation, bacterial proliferation, inflammation and immunological host reactions. Acne can be classified as mild, moderate or severe. Topical treatment is the first choice in mild and moderate acne, whereas systemic therapy is used to treat severe and moderate cases. The pathophysiological goal of acne treatment includes the normalization of keratinization, the reduction of interfollicular Propionibacterium acnes, the reduction of inflammation, and the reduction of sebaceous gland activity. The options for the topical treatment of acne consist of agents with a primarily keratolytic action (retinoids and retinoid-like drugs, benzoyl peroxide, salicylic acid and azelaic acid) and antibiotics (clindamycin, erythromycin and erythromycin-zinc complex). Topical retinoids and similar drugs which include tretinoin, adapalene and tazarotene are the most commonly used topical agents. Nevertheless, some of these agents usually produce a high incidence of side effects, such as skin dryness, peeling and skin irritation or bacterial resistance. These symptoms diminish patient compliance, compromising the efficacy of the therapy. The novel delivery systems present the potential to reduce the side effects without reducing the efficacy in comparison to conventional formulations¹⁷.

Large numbers of topical NSAID products exist in the market and an effective long-term treatment of peripheral pain and soreness is still an unmet medical need. Local analgesics normally alleviate pain for merely 1-2 weeks. For a significant and longer lasting therapeutic effect, topical NSAIDs moreover need frequent and abundant applications. Ultradeformable and stable, nanosized drug carriers minimize local drug clearance through the peripheral blood vessels for good therapeutic effect consistent with the results of in-vitro human skin permeation as they cross the skin barrier essentially intact, owing to their stress-dependent adaptation to narrow pores, reach deep tissue below the application site; and release drug molecules slowly in-vitro and at the target site in-vivo. The drug disappearance from subcutaneous peripheral tissue is 2-3 times slower (t1/2,a~4-6 h) after an epicutaneous application of ketoprofen associated with ultradeformable carriers¹⁸.

Microemulsions

"A microemulsion is a system of water, oil, and amphiphilic compounds (surfactant and co-surfactant) which is a transparent, single optically isotropic, and thermodynamically stable liquid"¹⁹. The main difference between emulsions and microemulsions lies in the size and shape

of the particles dispersed in the continuous phase: the magnitude is smaller in the case of microemulsions (10 - 200 nm) than those of conventional emulsions (1 - 20 μ).

Careful and precise choice of surfactants and cosurfactants bring the interfacial tension at the oil/water interface to a very low level which is stable as opposed to conventional emulsions and does not require high input of energy to be formed. As the size of the particles is much smaller than the wavelength of visible light, microemulsions are transparent and their structure cannot be observed through an optical microscope.

Microemulsions have attracted increasing attention as potential drug delivery systems, either as vehicles for topical applications because of their unique solubilization properties or as bioavailability enhancers for poorly water soluble active pharmaceutical ingredients (API). In topical formulations, microemulsions have been proved to increase the cutaneous absorption of both lipophilic and hydrophilic API's when compared to conventional vehicles.

Microemulsion & sub-micron emulsion process & compositions which could be used for sustained topical delivery of steroids have been described by Graziella.²⁰ Transdermal delivery of NSAIDs is an active area of research today as this completely avoids the GI adverse effects. Solvium is a topical Ibuprofen gel marketed by Chefaro (Akzo). In this case, microemulsion has been used to formulate a poorly soluble active at a dose of 5% into a perfectly transparent gel²¹. Flurbiprofen emulsions prepared using using IPM and Ethyl oleate as oil phase, Aerotol OT as surfactant and Sorbitan monooleate as cosurfactant have shown increased skin penetration and more efficacy as investigated by inhibition of carageenan induced rat paw edema test²². Microemulsion based hydrogels of Dexamethasone have been reported for enhanced transdermal delivery of Dexamethasone. Almond oil, olive oil, Linseed oil and nutmeg oil were used along with IPA and lecithin. The system with ME based system based on nutmeg oil was shown to have highest anti-inflammatory potential and demonstrated 74.6% inhibition in rat paw edema²³.

Liposomes

Liposomes are spherical vesicles that are formed of phospholipids of natural, synthetic or semisynthetic origin that have associated themselves spontaneously in a bilayer containing a centralized aqueous cavity. Hydrophilic and lipophilic drugs can be entrapped in the aqueous cavity and phospholipidic bilayer, respectively. Although early studies focused on the parenteral route, Mezei and Gulasekharan²⁴ reported the effectiveness of liposomes for skin delivery. Liposomes are able to

enhance the accumulation of drugs at administration sites, even in the Pilosebaceous unit (PSU)²⁵. Depending on the composition of the phospholipids (saturated or unsaturated) and the presence of co-surfactants (cholesterol, sodium cholate), rigid, fluid or elastic (the high deformable liposomes known as Transfersomes® ; IDEA AG) vesicles can be obtained and dermal or transdermal delivery can be favoured²⁶. Studies have shown the potential of this system for acne treatment. The efficacy of the clindamycin-loaded liposomes was compared with a free clindamycin lotion in a clinical trial in patients with acne (n=30, 4-week treatment). The liposomal clindamycin proved to be much more effective in reducing the total number of comedones, papules and pustules.²⁷ Salicylic acid, a keratolytic agent with comedolytic activity in acne patients, has been efficiently used in the treatment of acne comedones²⁸. Salicylic acid liposomes, when compared with free salicylic acid dispersion, not only prolonged the release of salicylic acid across the porcine skin but also enhanced its retention in the skin (about 10 times). After 12 weeks of storage at refrigeration temperature (4-5°C), the liposomes retained their normal structure and presented only 4.01% of salicylic acid leakage. Benzoyl peroxide has a mild keratolytic as well as bactericidal effect and is one of the most commonly used drugs in the treatment of acne. In a clinical study, liposomal benzoyl peroxide gels showed much less irritation in the first 2 weeks of treatment, when it completely disappeared. No burning was observed throughout the studies. In contrast, the plain benzoyl peroxide gel showed high irritation through the eighth week of treatment and gradually decreased thereafter, whereas high burning was seen throughout the study²⁹.

Self Micro Emulsifying Drug Delivery Systems (SMEDDS)

Further promising development have been brought by SMEDDS patented by Gattefossé in the 90's³⁰. These are "latent" microemulsions in the form of a stable, water-free combination of surfactants, co-surfactants and lipophilic phase, which creates a microemulsion when diluted in water or body fluids. Such systems have the advantages of microemulsions with a water-free formulation protecting sensitive API from chemical degradation they would undergo in an aqueous medium. The performance of SMEDDS has been demonstrated by Gattefossé on Simvastatin, a well known anti-hyperlipidemic drug marketed by Merck (Zocor), which is subject to extensive hepatic first pass metabolism. The use of a SMEDDS formulation has been reported to give a spectacular (four fold) increase in bioavailability in dogs³¹.

Solid lipid nanoparticles (SLNs)

SLNs originally developed for

parenteral application, are particles made from solid lipids with a mean diameter of between approximately 50 and 1000 nm. SLNs can be derived from the emulsions for parenteral nutrition simply by replacing the liquid lipid (oil) of the emulsion droplets with a solid lipid. Compared with vesicular and other particulate systems, SLNs have more advantages for drug delivery, such as good tolerability and biodegradation, high bioavailability, and sustained release due to their solid matrix. Moreover, SLNs are easily scaleable at a low cost and without the use of an organic solvent³². Disadvantages include limited encapsulation efficiency and drug expulsion from the carrier due to lipid polymorphic transformations^{33, 34}. An excellent review on SLNs is presented by Mehnert and coworkers³⁵.

Isotretinoin, a derivative of retinoic acid has been used for the treatment of severe acne but shows serious side effects after oral administration³⁶. Isotretinoin-loaded SLN formulations consisting of 3.0% lipid, 4.0% soybean lecithin, and 4.5% nonionic surfactant significantly increased the drug accumulation/targeting into the skin as compared with tincture³⁷.

Nanostructured Lipid Carriers (NLCs)

NLCs are mixture of solid lipid & liquid lipid and are important for drugs with higher solubility in oils than in solid lipids. Blend of liquid & solid lipid creates a less perfect crystalline structure thereby creating more space for drug. e.g.s of lipids include Tristearin, Tripalmitin, Stearic acid, Palmitic acid, Carnauba wax, Cetyl palmitate, Medium Chain Triglyceride, Isopropyl myristate.

The advantages of NLCs is that epidermal targeting/CR is possible thereby preventing undesired effects of potent glucocorticoids such as skin atrophy, skin sensitization, photosensitivity and also reduce the systemic uptake. NLCs of Fluticasone propionate have been described by Doktorovova et al³⁸ wherein a loading capacity of 0.1% drug was possible. Regular shape particles obtained were 316-408 nm. This technology can also be applied to Triterinoin, Psoralen etc.

Microsponge Delivery Systems

Transdermal delivery systems are efficacious for systemic delivery of drugs but they are not practicable for controlling the drug delivery whose site of action is the skin itself. The Microsponge macroporous Delivery System is a unique technology for the controlled release of topical agents and consists of beads, typically 5-300 microns in diameter depending upon the degree of smoothness or after feel required for the formulation, loaded with active agent. When applied to the skin, the microsponge releases its active ingredient on a time mode and also in response to other stimuli (rubbing, temperature, pH, etc.) They are extremely

small, inert, indestructible spheres that do not pass through the skin. The microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis thereby reduce significantly the irritation of effective drugs without reducing their efficacy³⁹. A review of microsponge delivery system is presented by Chadawar et al⁴⁰. Generally, microspheres are more stable than liposomes. The large-scale production of microspheres, however, is still expensive and the use of organic solvent is a limiting factor. Benzoyl peroxide microsponges characterization, preparation and morphology has been reported by several authors^{41, 42}. Carac® marketed by Sanofi Aventis is the only topical that delivers fluorouracil through a patented Microsponge® system. Carac® is indicated for the topical treatment of multiple actinic or solar keratoses of the face and anterior scalp. It offers once-a-day dosing and 89% of fluorouracil is retained in the skin where it is required⁴³.

C. Nasal delivery:

Nasal Drug administration is an attractive route for OTC products as it offers number of advantages of the parenteral route yet avoids the intervention of a physician and is simple for self medication. Large surface area of the mucosal lining, porous endothelial membrane and high blood flow are key drivers resulting in rapid systemic drug absorption.

A thermosetting nasal gel ; NasalFent® already in Pivotal Phase III clinical Trials using PecSys® Technology using Pectin. Dimenhydrinate gels have been reported for motion sickness (Gellan gum & Carbopol)⁴⁴. Thermoreversible nasal gels of Vitamin B(12) using pluronic PF 127 were aimed to improve absorption and patient compliance. Aqueous PF 127 gels prepared by cold method containing pluronic (20-24%, w/w), vitamin, sorbitol, PEG, and benzalkonium chloride. T(1) decreases and T(2) increased with vitamin and PF concentration⁴⁵. A detailed review of the use of Poloxamer 407 copolymer which shows thermoreversible properties is discussed in optimising drug formulation (fluid state at room temperature facilitating administration and gel state above sol-gel transition temperature at body temperature promoting prolonged release of pharmacological agents)⁴⁶. Amberlite IRP69, cation exchange resin having particle size 10 to 150 microns has been reported for nasal delivery of nicotine. Biphasic, extended drug delivery has been obtained by Cheng et. al for nicotine delivery⁴⁷.

D. Vaginal Delivery

The most commonly treated OTC indication is the vaginal yeast infection, Candidiasis most commonly due to the fungus *Candida albicans*. Most of the OTC medicaments use at least one of the four main types of products following: clotrimazole, tioconazole, miconazole and butoconazole nitrate⁴⁸. Some of the popular

brands being miconazole (Monistat-7, M-Zole), tioconazole (Vagistat Vaginal), butoconazole (Femstat) clotrimazole (Femizole-7, Gyne-Lotrimin).

Nonoxynol-9 (N-9) was formulated into a solid coprecipitate with polyvinylpyrrolidone (with or without iodine to produce solid powders and was formulated as vaginal CR delivery systems in gelatin capsules, bilayer tablets and pellets with immediate and slow releasing components. These systems were non irritating and have the potential to become effective spermicidal products⁴⁹. Itraconazole was formulated in bioadhesive film formulations by solvent evaporation and could be retained in the vagina for prolonged intervals. The films contained solid dispersion of itraconazole, hydroxypropyl cellulose, and polyethylene glycol 400 which was found to be the optimal composition for a novel bioadhesive vaginal formulation, as they showed good peelability, relatively good swelling index, and moderate tensile strength and retained vaginal mucosa up to 8 h.50 Esra et al⁵¹ reported bioadhesive controlled release systems of ornidazole for vaginal delivery . Vaginal tablets of ornidazole were directly compressed with bioadhesive and swellable polymer mixtures as release-controlled agents. Carbopol 934 , pectin , HPMC, Sodium CMC and guar gum were used in different ratios. Bioadhesive properties, swelling capacity, release studies, and histological studies of the formulations were carried out. Detailed reviews of novel vaginal systems such as bioadhesive gels, and other devices have been elaborated by several authors^{52,53}.

Vaginal dryness, which can occur as a result of lowered estrogen production during menopause or as a side effect from medical procedures. Over-the-counter moisturizers developed specifically to treat vaginal dryness include products such as Replens and Lubrin. These lotions mimic the natural vaginal lubricant and can provide moisturizing effects for up to three days following an application. Vaginal moisturizers can help to balance the pH levels inside the vagina to maintain proper acidic levels and avoid infections⁵⁴. This therapeutic indication has a potential to be explored with the novel technologies available today such as in-situ gelling, mucoadhesive polymer applications etc for a more prolonged and effective action.

E. Transungual delivery

Onychomycosis is a fungal infection(Tinea unguium) of the nail plate & bed which results in discoloration/thickening/crumbling of nail. It accounts for approximately 50% of all nail diseases and is the most common disorder in adults. Most of the infections are caused by dermatophytes the rest being yeasts and moulds. Mycotic nail infections rarely resolve spontaneously

and may have a significant effect on the quality of life.

Current treatment modalities include surgery as well as systemic, oral and topical antifungal agents. Earlier surgical avulsion was the only treatment for Onychomycosis but it is largely being replaced by topical therapy as it is very painful and traumatic. Topical nail therapy is important due to its localized effects, minimal adverse systemic effects and possible improved adherence. Indicated for mild to moderate disease and those unwilling to use systemic medication⁵⁵.

Topical therapy is also preferred in elderly patients/patients receiving multiple medications to avoid drug-drug interactions. Conventional topical therapies cannot be readily adapted to nail as they are prone to being washed off or rubbed off. Hence medicated nail lacquers targeted for the disease are important for effective therapy. A detailed review of the current status of and current status of Transungual delivery is elaborated by Elkeeb⁵⁶ and coauthors. Multiple classes of antifungal medications have been utilized; these include: polyenes (e.g. nystatin) which have both fungistatic and fungicidal properties in vitro; imidazoles (e.g. clotrimazole, tioconazole, econazole, ketoconazole, miconazole, sulconazole, and oxiconazole), which have fungistatic properties in-vitro; and allylamines/benzylamines (e.g. naftifine, terbinafine, and butenafine), which have fungistatic and fungicidal properties in-vitro. Susilo et al⁵⁷ conducted in-vivo experiments examining nail patches containing a potent antifungal sertaconazole 3.63 mg; patches were replaced weekly. A nail patch has multiple advantages: constant drug exposure with less frequent application and increased hydration to the dystrophic nail. Penetration of the nail patch was significant, approaching 40-50%; mean sertaconazole concentrations were well above MIC at 2, 4, and 6 weeks.

Currently only one topical therapy has been FDA approved Ciclopirox olamine(broad spectrum antifungal agent) inhibits growth of pathogenic dermatophytes and yeasts is approved by FDA : Ciclopirox nail lacquer 8% solution. Also available in the EU market are Amolorfine (5%) and Ciclopirox nail lacquer 8% solution. Inhibits transport of essential elements to the fungal cell thus disrupting DNA/RNA. Oxaboroles is a new class of antifungals and it has been reported that Oxaborole AN2690 penetrates the nail more effectively than Ciclopirox⁵⁸.

Limited permeability of the nail is a major challenge to transungual delivery as its chemical composition differs significantly from other body membranes: The plate is composed of keratin molecules with many disulphide linkages and has low lipid levels due to which it behaves more like a hydrogel than a lipophilic membrane. Some of the approaches to enhance delivery include use

of penetration enhancers such as Thioglycolic acid(reducing agent) followed by Urea hydrogen peroxide(oxidising agent) to enhance permeability. Hydration of nail also has been found to enhance permeation. Preungual drug delivery systems of Terbenafine HCL have been prepared and characterized by Jan and coauthors⁵⁹.

Conclusion:

With the lifestyle and demographic changes occurring at an exponential rate in today's scenario , the rapid emergence of self-reliant patient populations and support of the knowledge dissemination trajectories, Novel Drug technology in the OTC segment has immense opportunities in the pharmaceutical market. The wide depth of information in various platform technologies today could usher the way of offering newer delivery systems to the ever-demanding consumer population thereby increasing patient compliance and satisfaction.

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