Chinese Journal of Evidence-Based Medicine

HOW FAR HAVE WE PROGRESSED IN ORAL DRUG DELIVERY SYSTEM: AN UPDATE

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ABSTRACT

INTRODUCTION

Drug targeting to specific organs and tissues is the one of the most important part of a treatment, as they help in providing the best treatment outcome whilst maintaining an optimal therapeutic dose and eliminating the side effects/complications associated with it. Herein, our paper provides an insight on the various advancements in local target therapies related to common oral manifestations of microbial infections and immunological diseases associated with oral medicine & therapeutics.

MATERIALS AND METHODS

40 drug delivery system articles associated with oral mucosal lesions and vesiculo-bullous lesions published within the time frame of 2008-2017 were selected which consisted of 5 case reports, 15 research articles & 20 review articles (narrative, meta-analysis and systematic reviews).

CONCLUSIONS

Novel technological advancements in amalgamation with effective formulation helps to overcome these shortcomings, that are observed in the conventional form of drug administration whilst integrating such novel techniques with the current techniques; to improve the patients' quality of life; be it in the systemic or in the topical form.

KEYWORDS

Drug, delivery, therapeutic, dose, sustained, pulsatile, systemic, topical, metabolism

INTRODUCTION

Amongst the plethora of drug administration pathways, the intraoral pathway is the most common and preferred route as it is easy, safe, non-invasiveness, adaptability, patient compliance and acceptability with minimalistic complications during the procedure. Nevertheless, it has its own

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E ISSN: 1672-2531

shortcomings such as the hepatic first pass metabolism and enzymatic degradation in gastrointestinal tract which reduces the drug availability in turn affecting their concentration levels.[1,2]

Alternatively, topical form is advocated (in feasible cases) as they are more convenient and efficacious with immediate outcome in case of localised damage/treatment requirement cases. Even though oral topical applications are same procedure wise, it is not completely the same as the structural aberrations between the skin and the oral mucosa make it difficult in terms of the physical & chemical properties and interactions between the tissues and the drugs administered.[3]

Therefore, advances in this field of drug delivery via use of novel technologies such as bioadhesive mucosal dosage forms like the patches, tablets, films and strips has been continuously advocated due to their superiority with minimalistic complications while rendering patient care.[2]

Newer drug systems have better drug solubility, defend it from external environment like photo-degradation and upholds the essential pH, all of which helps in the release of the drug at the target site.[1,2]

Advantages such as minimal exposure at the non-targeting site with controlled release of the drug at the target site make it more patients compliant. Therefore, this review is focused on assessing the new potential local drug delivery system which is specifically targeted towards the oral mucosal lesions.

MATERIALS & METHODS

A comprehensive literature search was conducted about the various drug delivery system pertaining to oral mucosal lesions, published within the time frame of 2008-2017 in SCIENCEDIRECT.COM, ONLINELIBRARY.WILEY.COM, BMJ.COM, OXFORDJOURNALS.ORG, MEDLINE and PUBMED with the keywords ORAL MUCOSAL LESIONS, TARGET DRUG DELIVERY, NEW DRUG DELIVERY SYSTEM.

Based on level of evidence, critical evaluation was carried out amongst 40 articles, consisting of 5 case reports, 15 research articles & 20 review articles (including systematic reviews, meta-analysis and narrative reviews).

1.CONVENTIONAL DOSAGE FORMS AND SOME EXAMPLES OF COMMERCIALLY AVAILABLE PRODUCTS FOR THE LOCAL THERAPEUTIC EFFECT OF THE ORAL CAVITY[4]

Dosage form	Examples	Use in the oral cavity	Advantages	Limitations
Semisolid dosage forms	Gelclair oral gel, contains sodium hyaluronate and glycyrrhetinic acid	Oral mucositis, pain relief, soothing of oral lesions/ulcers	More acceptable	Poor retention at site of application
	Daktarin oral gel, contains miconazole	Treating oropharyngeal candidiasis	Localized action within oral cavity	Difficulties in accurate drug dosing
	Biotene oral gel,	Dry mouth		

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(gels/creams/ pastes)	contains lubricating polymers	symptom relief		
	Fluoride toothpastes			
	Colgate Orabase paste, contains benzocaine	Local anaesthetic		
Liquid dosage forms (solutions/suspensions)	Fluoride or antiseptics (eucalyptol, menthol, methyl salicylate, thymol, chlorhexidine, cetylpyridinium chloride)	Mouthwashes from various brands	Patient acceptability	Not readily retained at the targeted site of absorption
	Colgate Peroxyl mouth rinse, contains hydrogen peroxide	Oral debriding agent	Ease of administration	Relatively uncontrolled and inconsistent drug delivery
				Palatability
Medicated chewing gum	Fluoride gum under various brand names		Prolonged drug release	Drugs may reach GI tract causing systemic effects
	Vitaflo CHX® containing chlorhexidine		Good patient compliance	
			Patient-controlled dose titration	
Patches /Films	Canker Cover oral patch, contains menthol, a short acting and mild anaesthetic.	Treatment of canker sores	Thin and flexible	Drug delivered to a small area of mucosa, thus limiting the dose delivered
	Listerine, Pocketpaks breath strips, contain menthol, thymol and eucalyptol.	Mouth fresheners killing bad breath germs	Less obtrusive and more acceptable to patient	Thinness may lead to increased susceptibility to over hydration and loss of adhesive

/Strips				properties
			Localized over a specified region, thus less inter- and intra-subject variability	Patches with non-dissolvable backing need to be removed once the drug has been released

Two sites at which mucosal barrier function may occur are

- Basal complex
- Intercellular spaces of the superficial epithelial layers.[5]

Factors influencing permeability of the oral mucosa are primarily the relative thickness and degree of keratinization with in between layers consisting of

- Sublingual mucosa - relatively thin and non-keratinized
- Buccal mucosa - thicker and non-keratinized
- Palatal mucosa - intermediate thickness and keratinized [6]

Most common pathways for transport of substances across the mucosal membrane are[5]

- Passive diffusion
- Carrier-mediated active transport or endocytosis.

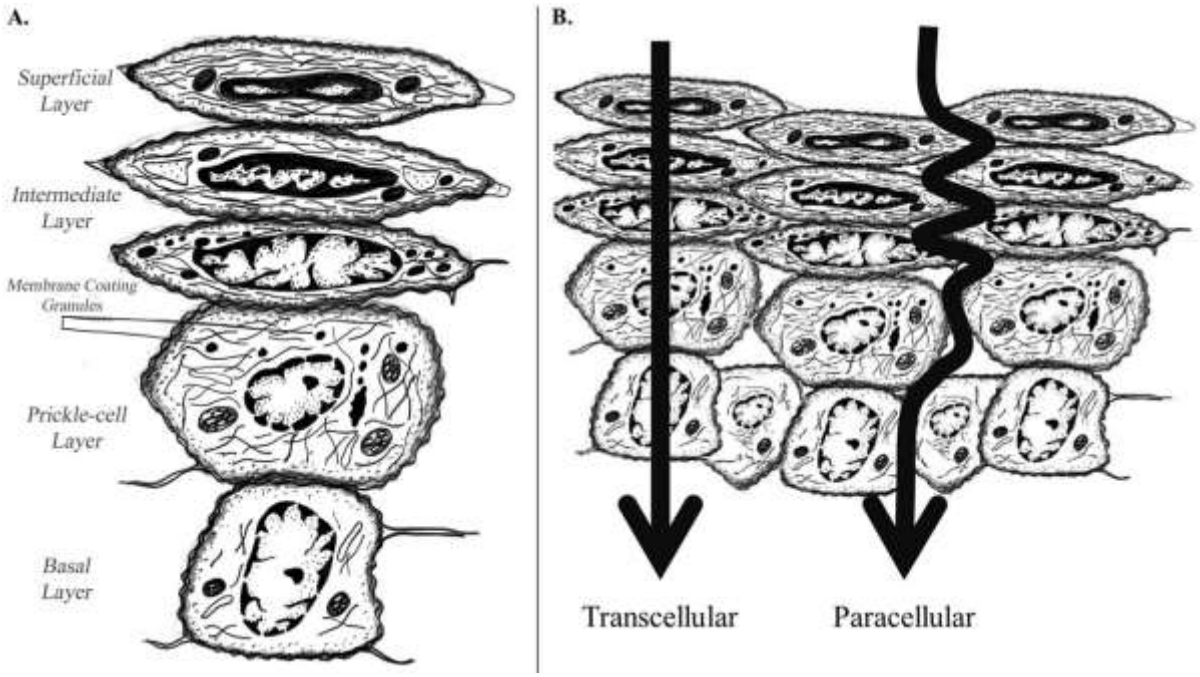

Fig 2

LOCAL ORAL DRUG DELIVERY

Drug delivery via oral mucosa can be accomplished via [1,5,7]

- Keratinized mucosa
- Non-keratinized mucosa

- Sublingual drug delivery (more permeable and thinner) - systemic delivery of drugs across the mucosa lining the floor of mouth, in treating acute disorders, has undesirable taste sensations.
- Buccal drug delivery (less permeable) - via buccal mucosa lining the cheeks, incl. systemic and/or local delivery, comparatively slow rate of absorption.[7]

Keratinized mucosa is still not considered a valid site for the systemic administration of drugs, and instead advocated as useful sites for local (direct) drug delivery.[8]

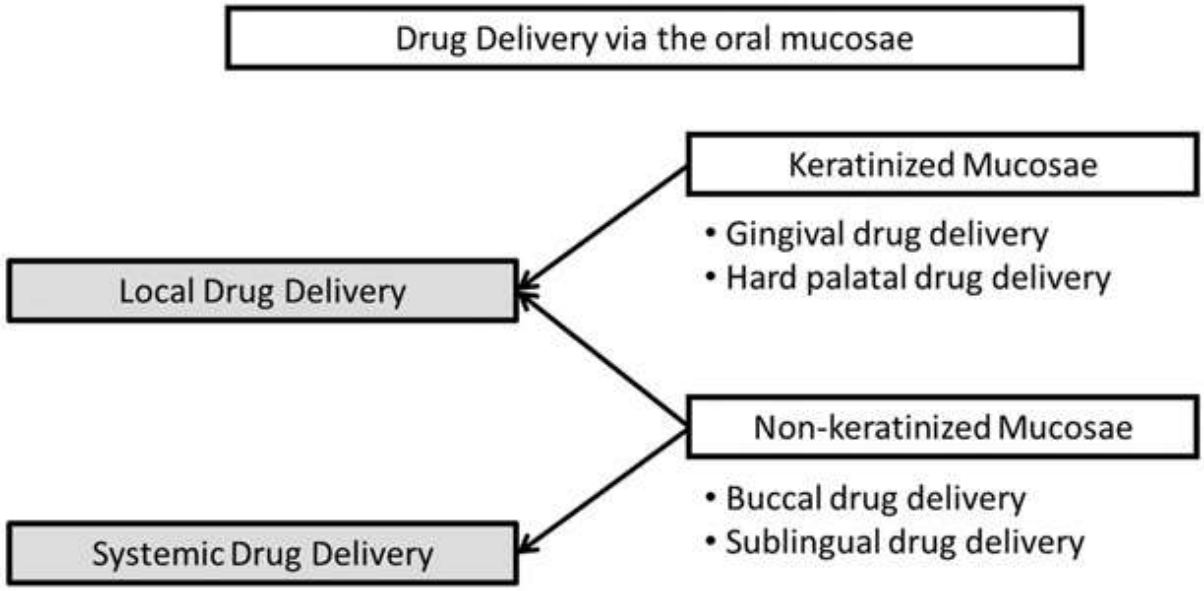

Fig 3

\MUCOADHESIVE DOSAGE FORMS

Carried out in the form of adhesive tablets, adhesive patches, adhesive films or pellicles, adhesive semisolid systems (gels, ointments), and adhesive liquid systems (sprays, mouthwashes).[9]

Mucoadhesion is a complex phenomenon, which is associated with mucoadhesive bond formation with the following procedure protocol

- Spreading, wetting, and dissolution of mucoadhesive polymer at the interface
- Mechanical or physical entanglement between polymer and the tissue surface mucus layer, resulting in an interpenetration layer

All this leads to a series of chemical interactions, such as covalent and ionic bonds, hydrogen bonding, and Van der Waals' interactions which are ultimately responsible for the outcome. [10]

Mechanism of mucoadhesion (as per dosage forms) [11,12]

- A monolithic (or "matrix") type
- Reservoir (or "membrane-controlled") type
- Erodible (degradable) formulations

ADHESIVE TABLETS

Bioadhesive tablet systems have been extensively used in treating oral diseases with the most common type being buccal tablet, which are small, flat & oval with an approx. dia of 5 to 8 mm

& 2 mm thickness with continued slow release of the drug, until it completely gets exhausted with the individual being completely unaware of its presence. However, lack of the physical flexibility of the material due to unwarranted drug release with movements limits its use.

ADHESIVE PATCHES AND FILMS

Laminated patches and films are the most recently developed dosage form for buccal administration which can act as a penetration enhancers or enzyme inhibitors.[13]

These oral patches and films have high flexibility which facilitates a long retention time along with a high level of patient compliance as well as comfort with precise dosing of the drug.[14]

ADHESIVE SEMISOLID SYSTEMS (GELS, OINTMENTS)

Semisolid dosage forms are gels and ointments which can disperse throughout the oral mucosa, but their dosage forms may not be as accurate as that of tablets, patches, or films.[1] As these semisolids have poor retention time (because body fluids, such as saliva, will quickly wash them away), the use of bioadhesive formulations in combination has been advocated.[15,16]

Most commonly it is used for the treatment of periodontitis, recurrent aphthous stomatitis, traumatic ulcers, radiation- or chemotherapy-induced oral mucositis, chronic immunologically mediated oral lesions, hyposalivation, and for the healing of wounds.[1]

ADHESIVE LIQUID SYSTEMS (ORAL RINSE AND SPRAYS)

They produce a very fine mist which coats the entire oral mucosa accumulatively increasing the total surface area for drug absorbption.[17] They are advocated for oral diseases, such as oral lichen planus and other immunologically mediated diseases, aphthous stomatitis, oral mucositis, hyposalivation and potentially malignant disorders, such as leukoplakia and erythroplakia. [18]

CHEWING GUMS

Emulsifiers such as glycerol monostearate, lecithin are added to ease the acceptance of the saliva by gums. In addition, resin esters and poly vinyl acetate are auxiliary to it to avoid the sticking of the gums to the teeth.

It has been also noted that gum formulations with caffeine potrayed rapid release as well as absorption of agent in comparison to capsulated form. Various formulations such as vitamin C, Diphenhydramine, Methadone, Verapamil have been developed. [19]

FAST CAPS

It is a fast dissolving gelatine capsules based drug delivery system with several additives to mend the mechanical and dissolution properties of the capsule shell. Fast disintegrating capsules helps in high drug loading, possible solid and liquid filling, protracted release drug particles/pellets, simple manufacturing, good mechanical properties & stability.[20]

LIPOSOMES

Liposomes have been used in the local delivery of drugs to the oral mucosa in the ulcerated area whilst increasing the local drug concentration & decreasing the systemic concentration (Farshi et al.)[21]

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2.MOST COMMON ORAL MUCOSAL DISEASES AND NOVEL DEVELOPED FORMULATIONS AND THERAPEUTICS (most dosage forms listed are represented by adhesive semisolid or liquid systems) [22]

DRUGS	DOSAGE FORMS	RESULTS
POTENTIALLY MALIGNANT DISORDERS AND ORAL CANCER		
5-FU	Matrix tablets	Matrix tablets containing 5% of 5-FU could be a useful means in topical treatment of OSCC
Acitretin	Mucoadhesive 2-layer tablets	Efficacy in the treatment of oral leukoplakia without side effects
Tretinoin	Patch	The tretinoin patch is safe and effective for such chemoprevention
Ketorolac	Oral rinse	Local delivery of a COX-containing oral rinse was well tolerated but produced no significant reduction in the extent of leukoplakia
Black raspberry anthocyanins	Bioadhesive gel	Reversing or down-grading oral dysplastic lesions
Photosensitizing agents (5-aminolevulinic acid)	Gel	Followed by photodynamic therapy, a complete response was obtained in 10 of 12 treated patients
Idarubicin	Solid lipid nanoparticles	Data confirm nanoparticle internalization by OSCC cells and support the premise that nanoparticle-based delivery provides higher final intracellular levels relative to bolus administration
Engineered adenovirus	Oral rinse	Some complete response, most transient
Imiquimod	Bioadhesive patch	Treatment of neoplastic conditions of the oral cavity and cervix, as well as the vulva.
ORAL MUCOSITIS		
TGF-β3	Oral rinse	TGF-β3 penetrate the epithelium and is detected in the basal cell layer at therapeutically effective

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		concentrations
TGF-β3	Chitosan gel	Improved drug retention, protection against Candida infection; bio-adhesive gel could act as protective barrier to reduce discomfort
Keratinocyte growth factor	Adhesive gel	Tropical prevention and treatment of mucositis. Actually drug is administered systemically
Association of a pool of collagen precursor amino acids with LMW sodium hyaluronate	Spray	Fast reduction of the pain and clinical amelioration of the lesions
Gengigel; Gelclair; MuGard	Mucoadhesive covering agents	Physical coating and protection for thinned or ulcerated oral mucosa
VESICULO-BULLOUS LESIONS		
Clobetasol	Mucoadhesive gel	Mucoadhesive tablet containing 24 _g clobetasol 3 times a day appeared to be effective
Cyclosporin	Mucoadhesive gel	Cyclosporin gel gives stable results
Tacrolimus	Oral rinse	There is need for larger placebo-controlled, randomized studies with carefully selected and standardized outcome measures
Hydroxyapatite	Mucoadhesive gel	Non-effective Topical HA (0.2%) in management of erosive lichen planus
ORAL INFECTIONS		
Metronidazole	Mucoadhesive tablets	Tablets performed 12-h drug sustained release for treatment of periodontal disease
Miconazole	Mucoadhesive buccal slow release tablet	Has shown more efficacy than conventional topical antifungal agents
Clotrimazole	Topical ointment/Lozenges	Antifungal agents

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Nystatin	Mouthwash/Lozenges/Mucoadhesive 2-layer tablets	Antifungal agents
Acyclovir	Suspension/ Ointments	Antiviral agent
Tetracycline	Mucoadhesive patch	Tetracycline and carvacrol showed excellent activity against *Candida albicans*.
SALIVARY HYPOFUNCTION AND XEROSTOMIA		
Physostigmine	Long-lasting gel	Locally applied gel relief in the feeling of dryness
Interferon alpha	Tablets	Enhance salivary secretion in patients with primary Sjögren syndrome
RECURRENT APHTHOUS STOMATITIS		
Amlexanox	Mucoadhesive tablets	Efficacy and safety in reducing aphthous ulcer pain and lesion size
Amlexanox	Adhesive patches (OraDisc)	Efficacy in the prevention and treatment of oral ulcerations
Amlexanox	Oral adhesive pellicles	Better flexibility, higher compliance and patient comfort, but same clinical efficacy in comparison with adhesive tablets
Hydroxyapatite	Mucoadhesive gel	Efficacy and safety in reducing size, number and symptoms of oral ulcers
Doxicycline	Mucoadhesive gel	Faster reduction in pain during than the placebo group
PERICORONITIS		
Chlorhexidine, doxycycline, minocycline, satranidazole or metronidazole	Mucoadhesive gel	Improvement in probing depths and attachment levels
Minocycline	Microspheres	In association to mechanical treatment favour an

		improvement of probing depth in cases of peri-implantitis

SOME DRUGS AVAILABILITY IN INDIA

Drugs are available online & in pharmacies

Drugs available in pharmacy in INDIA

- Hyaluronidase gel - emervel (GALDERMA)
- Miconazole - Bectiderm-m (PRAYAS PHARMACEUTICAL)
- Mouth lubricator - Biotine (GSK)
- 20% benzocaine - Colgate orabase (COLGATE)
- Hydrogen peroxide mouthwash - Colgate peroxyl mouthwash(COLGATE)
- Chlorhexidine chewing gum- vitaflow chx
- Canker cover oral patch- quantum research

Drugs available in e-commerce from merchants delivered at footstep in INDIA (amazon.in, medidart.com, medplusmart.com)

- Gelclair- Hyaluronate
- Daktarin – Salivary substitute
- Biotene – Dry mouth relief
- Pocketpaks – Fresh breathe
- Fluorette – Fluoride
- Quick clot- Haemostatic agent
- Jiffy- Benzocaine drops

RECENT ADVANCES IN DRUG DELIVERY SYSTEM [23]

Iontophoresis

It helps to enhance the infiltration of therapeutic agents from side to side of the skin via electric current with the drug being positioned beneath the electrode of analogous charge drug as that of the drug with a counter electrode placed someplace else in the body.

Drug delivery augmented by 3 mechanisms

- Drug is forced into skin via electronic repugnance of similar charges
- Electric current augments the invasion by impeding the skin's protective barrier function
- Causes water to enter the stratum corneum

Electroporation

Creates transient pores within the lipid bilayer of the skin by application of high voltage (50-1000 volts) pulses, permitting passage of macromolecules from external part of the cell to intercellular space via diffusion as well as electrophoresis.

Sonophoresis

Ultrasonic is used for better skin penetration of active substances by

- Enlarging the radii of skin effective pores
- Creating additional pores

Microporation
Amplifies skin dissemination via drug coated micro needles (projections of solid silicon) sized 10-200 μm in height and 10-15 μm in width by piercing through the stratum corneum

Heat
Heat is known to increase the body fluid circulation, membrane permeability as well as drug solubility, facilitating transfer of drug onto the systemic circulation. Heat, increases the kinetic energy as well as the drug solubility of the drug molecules within the cell membrane, whilst altering the physicochemical properties of the drug formulation.

Needleless injection
A pain free technique of firing of liquid as well as solid particles at an supersonic speed through the stratum corneum.

Radiofrequency
Exposure of skin to a high frequency alternating current of 100 KHz, which generated heat leading to formation of heat-induced micro channels in the cell membrane.

Pressure wave
Intense laser radiation pressure waves of 100 μs -1 μs are generated when applied in a continuous pathway allowing for passage of transport of macromolecules into dermis and epidermis.

Magnetophoresis
Magnetophoresis causes alteration in the structure of skin which acts as an external driving force to enhance drug delivery across the skin.

Chemical enhancement
Water
Hydration of stratum corneum (free water molecules inside the tissue) increases the permeation of hydrophilic as well as lipophilic penetrants leading by swelling of stratum corneum.

Penetration enhancers
Modifies the barrier characteristics of stratum corneum and makes drug penetration easier whilst being non-toxic, non-allergic, pharmacologically inert, tasteless as well as inexpensive; at the same time as being compatible with drug and excipients.

Prodrug
Prodrugs are highly hydrophobic inactive derivatives of therapeutically active drugs which are activated after they undergo metabolic changes

Emulsions
These are biphasic preparations of

- Dispersed phase or internal phase
- Continuous or external phase

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Most of the pharmaceutical emulsions include surfactant (ionic or non-ionic), polymers (non-ionic polymers, biopolymers, or polyelectrolytes), or combination of these.
Transdermal drug delivery systems are defined as self-contained, discrete dosage forms which when applied to intact skin delivers the drug through the skin at controlled rate to systemic circulation.
Advantages are reduced side effects, improved patient compliance, sustained drug delivery as well as elimination of first pass metabolism.

TDDS are classified as follows

- Matrix system
- Matrix dispersion system
- Reservoir system

Topical aerosol

It is a disperse phase system in which very fine solid drug particles or liquid droplets get dispersed in the propellant (gas), which acts as continuous phase.
Dispersed Phase - Solid / Liquid and Continuous phase - Gas /Propellants.

NOVEL TOPICAL DRUG DELIVERY SYSTEMS[24]

- Organogels
- Foams
- Emulgels
- Microsponges
- Mucoadhesive/bioadhesives
- Novel vesicular carriers
  - Liposomes (liposomal gel)
  - Niosomes (Proniosome gel)
  - Transferosomes
  - Ethosomes
- Micelles
- Novasomes
- Hydrogels
- Jellies
- Protein and peptide delivery
- Microemulsion/nanoemulsions

Organogels

It runs as a bi-continuous system with

- Gelators
- A polar solvent

Gelators (< 15 % conc.) may cause physical as well as chemical interactions to form a three-dimensional network structure, which averts the flow of external phase.
Gelators are sterol, lecithin, sorbitan monostearate and cholesteryl anthraquinone derivate.

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Advantages

- Ease of preparation.
- Cost reduction (less ingredients)
- Extensive shelf life
- Thermodynamically as well as chemically stability
- Easy to handle
- Both hydrophilic and lipophilic drugs can be incorporated.
- Easy to maintain structural integrity for longer time periods.
- Better skin permeability
- Heightened transport of the molecules

Applications

- Matrix for transdermal transport of drugs
- Delivery of vaccines

Liposomal gel

These are microscopic spheres with an aqueous core enclosed within one or more external shells entailing of lipids organized in a bilayer arrangement.

Advantages

- Increased safety and therapeutic index.
- Increased stability via encapsulation.
- Site avoidance effect.

Microsponges

Uniform, spherical, porous polymeric microspheres (particle size 5-300 μm), which can store the active drug until its release is triggered by application to the surface of skin such as essential oils, emollients, fragrances, sunscreens and anti-infective, etc.

Release of drug can be controlled via diffusion or other variety of triggers, including moisture, rubbing, pH, friction, or ambient skin temperature.

Advantages

- Enhanced product performance
- Extended drug release
- Improved patient compliance
- Improved flexibility
- Improved thermal, physical, and chemical stability
- Non-irritating/non-allergenic/non-toxic
- Improved bioavailability
- Site specific action on target organ

Niosomes

Consists of 2 components

- Non-ionic surfactants
- Additives

It has higher bioavailability, biocompatibility, biodegradable, controlled in addition to sustained release of drugs.

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Proniosome gel

Entraps a wide range of active compounds with physical stability whilst providing adequate/appropriate transportation, distribution, storage, and dosing making it the most versatile delivery system

Drugs that can be used

- Antifungal agents
- NSAID's
- Anti-acne drugs
- Cosmetics
- Muscle relaxants

Ethosomes

Ethosomes encloses phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water having a size range from 10 nm to microns which are used for the delivery of drugs through transdermal route with enhanced permeation of drug through the stratum corneum barrier.

Applications

- Supply of HIV drugs
- Supply of anti-fungal drugs
- Supply of NSAID's

Transfersomes

An innovative vesicular drug carrier structure composed of phospholipid, surfactant, and water to augment transdermal delivery of both low and high molecular weight drugs. It overcomes the shortcomings such as poor skin perviousness, breach of vesicles, drug leak, accretion and amalgamation of vesicles.

Advantages

- Prolonging half-lives of drugs by aggregating the spell in systemic circulation due to encapsulation.
- Facilitates drug delivery to target organs
- Biodegradable
- Lack of toxicity
- Carrier low/high molecular weight drugs (analgesic, anaesthetic, corticosteroids)
- Used for systemic & topical delivery of drug.

Micelles

Group of surfactant molecules dispersed in a liquid for topical antifungal drug delivery

Microemulsions

Thermo-dynamic mixture of oil & water stabilized by surfactants & co-surfactants

Novasomes

Has 2-7 bilayered membrane composed of amorphous core and amphiphillic molecule, with the capability to encompass a great volume of water immiscible & water soluble drugs.

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Hydrogels

3D cross-linked polymer network responding to fluctuations of the environmental stimuli which are capable of incorporating large quantum of biological fluids & swell for delivery of drugs

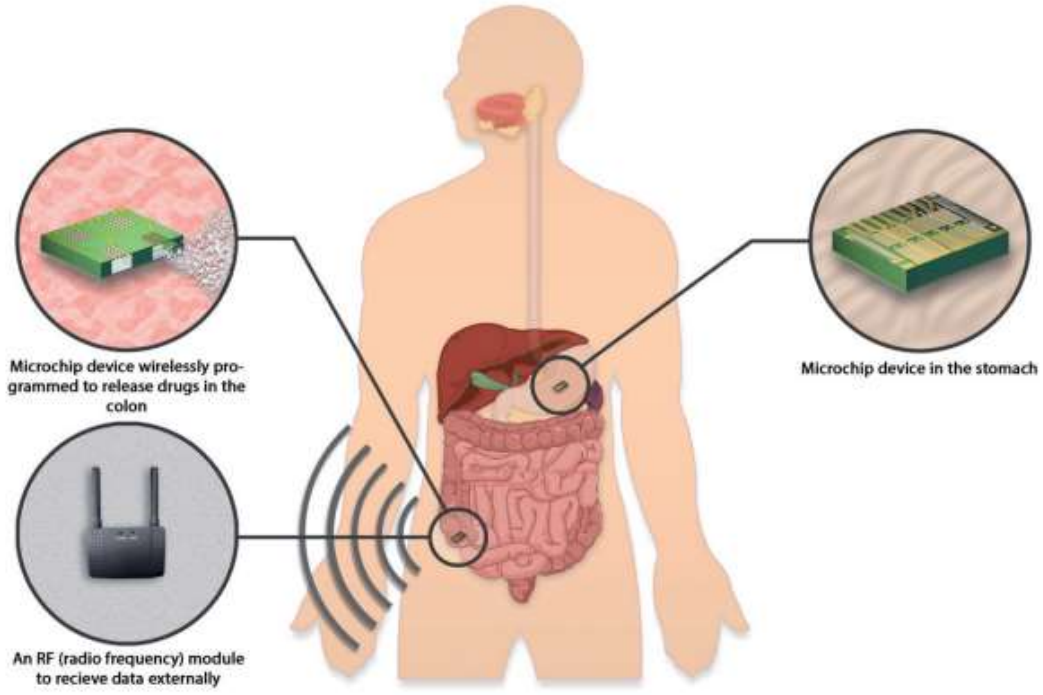
MICROCHIP[25]

Devices used for controlling the release time of a chemical whilst preventing toxicity and better efficacy mimicking the normal endogenous release of substances of the body.

Advantages

- Make best use of the efficacy–dose relationship
- Minimal toxicity
- Fortification of mucosa from exasperating drugs
- Patient compliance and expediency
- Meticulous supervision
- Upkeep of drug concentration

Multiple reservoirs hold chemicals in the solid, liquid and gel form capped with a conductive membrane & wired with the final circuitry, regulated by a microprocessor, reacting as per the applied stimulus



An orally administered drug delivery microchip using wireless transmission of power and data can be activated at a specific time or a specific location in the gastrointestinal tract (Sheppard et al., 2007).

Fig 4

Sustain release

Maintained therapeutic blood or tissue levels of the drug for an extended period

Pulsatile Release

The drug release depends on predetermined time intervals as per a circadian rhythm, designed for chronopharmacotherapy. A single dosage form provides an initial dose of drug followed by one interval, after which second dose of drug is released.

Implantable controlled drug delivery[26]

Implantable controlled drug are alternatives used to deliver medications to those parts of the body wherever consistent modes of drug delivery cannot reach.

3.Name of therapeutic agents that can be delivered by microchip drug delivery system for any oral mucosal or vesiculo-bullous lesions

Therapeutic and prophylactic molecules	Examples	References
Antibiotics	Tetracycline, Erythomycin, and Penicillin	Santini et al. (2005)
Anti-bacterials	Sulfonamides, Sulfadiazine	Santini et al. (2005)
Anti-viral's	Acyclovir, Gancyclovir and interferons	Santini et al. (2005) Gardner (2006)
Anti-inflammatories	Hydrocortisone, Diclofenac, Ibuprofen	Santini et al. (2005) Sharma et al. (2006)
Anti-proliferative agents	Fluouracil, Mitomycin	Santini et al. (2005)
Other drugs	Prostaglandins, Immunomodulatory agent, Antioxidants, Ion channel regulators, Cytotoxic agents, Anaesthetics, Erythropoietin, Metabolites	Santini et al. (2005) Sharma et al. (2006) Staples (2010)

3-D PRINTING AS DRUG DELIVERY SYSTEM[27]

Katstra et al., used 3D extrusion printer to manufacture a polypill, which has instantaneous discharge cubicle for aspirin and hydrochlorothiazide with three sustained release compartments

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containing pravastatin, atenolol, and ramipril. The release rate of the drug was reliant on the geometry, mainly the surface area, with a descending rate order of honeycomb>grid, ring>circle. Weigang et al. invented a programmed release multi-drug implant for bone tuberculosis therapy using 3D printers, which was multi-layered concentric cylinder of four layers from the centre to the periphery with Isoniazid and rifampicin being dispersed independently into the different layers in an explicit arrangement of isoniazid-rifampicin-isoniazid-rifampicin.

4.

Printing technology/Printer type	Dosage forms/Systems	Model drug used
3D powder direct printing technology	Microporous bio ceramics	Tetracycline, Vancomycin and Ofloxacin
Fused-filament 3D printing	Tablets	Fluorescein
3D printer	Tablets	Paracetamol
3D printer	Complex oral dosage forms	Fluorescein
3D extrusion printer	Multi-active solid dosage form (polypill)	Aspirin, Hydrochlorothiazide Pravastatin, Atenolol & Ramipril
Piezoelectric inkjet printer	Micro particles	Paclitaxel
Fused deposition 3D printing	Extended release tablet	Prednisolone
3D printer	Tablet implant	Isoniazid
3D printer	Doughnut-shaped multi-layered drug delivery device	Paracetamol
3D printer	Fast-disintegrating drug delivery device	Paracetamol
Fused deposition 3D printer	Oral pulsatile capsule	Paracetamol

3D printer	**Fast disintegrating tablet**	**Paracetamol**
3D printer	**Oral pulsatile tablet**	**Chlorpheniramine maleate & Diclofenac sodium**
Ink-jet printer	**Solid dispersion**	**Felodipine**
Desktop 3D printer	**Bi-layer matrix tablet**	**Guaifenesin**
Laboratory scale 3-DP™ machine	**Capsule with immediate release core and a release rate regulating shell**	**Pseudoephedrine hydrochloride**
Fused deposition 3D printer	**Modified-release drug loaded tablet**	**5-Aminosalicylic acid & 4-Aminosalicylic acid**
Extrusion-based printer	**Multi-active tablets (Polypill)**	**Captopril, Nifedipine & Glipizide**
3D printer	**Complex matrix tablet with ethyl cellulose gradients**	**Paracetamol**
Inkjet printer	**Implant with lactic acid polymer matrix**	**Levofloxacin**
3D printer	**Multi-layered concentric implant**	**Isoniazid and Rifampicin**
Micro-drop Inkjet 3DP	**Nano suspension**	**Folic Acid**
Thermal Inkjet printer	**Dosing drug Solutions onto oral films**	**Salbutamol sulphate**
Commercial inkjet printer	**Nanocomposite structure**	**Rifampicin and Calcium phosphate**
3D Extrusion printer	**Drug encapsulated film of PLGA and PVA**	**Dexamethasone**
Thermal Inkjet printer	**Oral solid dosage forms**	**Prednisolone**
3D printer	**Microfluidic pump**	**Saline solution**

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Stereolithography printer	**Anti-acne patch**	**Salicylic acid**
3D printer	**Biodegradable patch**	**5-Fluorouracil**
Fused deposition 3D printer	**Immediate release tablets**	***5*-Aminosalicylic acid, Captopril, Theophylline & Prednisolone**
Fused-deposition printer	**T-shaped intrauterine systems and subcutaneous rods**	**Indomethacin**
Electro hydrodynamic atomization technique	**Patterned micron scaled structures**	**Tetracycline hydrochloride**
Fused deposition printer	**Capsules for immediate and modified release**	**Acetaminophen and Furosemide**
3D printer	**Biofilm disk**	**Nitrofurantoin**
Multi-nozzle 3D printer	**Capsule-shaped solid devices**	**Acetaminophen & Caffeine**
Fused-deposition printer	**Capsule-shaped tablets**	**Budesonide**
Stereolithographic 3D printer	**Modified-release tablets**	**4-aminosalicylic acid & Paracetamol**

CONCLUSION

Novel technological advancements in amalgamation with effective formulation help to overcome the shortcomings of the conventional form of drug delivery which is observed at the stratum corneum barrier. These advancements are more efficacious, feasible with a decent shelf life along with patient compliance. Therefore, we recommend the integration of such novel techniques into the current techniques, which is aimed at providing the best treatment outcome in terms of delivering drugs to the patient at an optimal therapeutic dose to improve patients' quality of life; be it in the systemic or in the topical form in either acute subacute, chronic or its refractory phase.

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Vol. 20, No. 1. (2024)
E ISSN: 1672-2531