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A Review on Microsphere Based Topical Drug Delivery

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Abstract

The word "Microsphere" denotes that micrometer in size but the main motto is to deliver the drug and it depends on the routes of administration. Topical delivery of microsphere is one of the most important to deliver the drug into the body. This method has a significant effect on its efficacy. Microsphere can work as a transporter for the drugs in a sustained control release manner. Whereas the topical gel can be used in any part of our body like eyes, vagina, rectum, etc. Microspheres are using as a coating material where the polymeric compounds are incorporate and after that, it is using as a gel for topical administration. Here we can tell the microsphere as a vehicle where it transports the polymers, drugs as well as especially it is transferring the surfactant, co-surfactants, etc as a result it can easy to penetrate our skin and give the proper therapeutic activity. As a result, the slow result in the proper therapeutic efficacy of various diseases can give the suggested a blooming need for a multidisciplinary proposal for the delivery to the target place. As a result, it clears the potential of the effectiveness of active pharmaceutical ingredients through the barrier of skin by the help of penetration property and vehicle technology of microsphere. In this review, some basic and primitive features of microspheres in the form of topical delivery has been discussed.

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INTRODUCTION

The whole thinking about the delivery system of the drug has a great effect on pharmacy. After giving the drug a particular targeted site and getting proper effect as well as also fewer side effects, the patients become very acquiescence (Vyas and Khar, 2004). In recent years, the drug delivery system about the microsphere takes all the focus on it (Guiot and Couvreur, 1986). For getting the highest therapeutic efficacy with lower side effects, it is urgent to deliver the drug to the target region in the optimal amount. In a sustained controlled release fashion, there are various theories to deliver the drug and getting the therapeutic efficacy to the target site. The microsphere is working as a transporter for drugs where is one theory that can be used in a sustained control release fashion. This approach allows the optimum delivery of a small quantity of the potent drugs as well as lowers the drug concentration at the site other than the target site and also give the protection of the compounds which are unstable before and after the administration and before the site of action (Kataria and Middha, 2011).

A topical gel is a localized drug delivery system, intended to administer into eyes, rectum, vagina, or skin. There are various types of semi-solid systems is present and gel is one of the best of them. A gel is a solid and jelly-like substance as well as has an outer solvent phase and it should be present soft and weak to hard and tough. Its solvent part should be water phobic or water philic which should be attenuated

within the space of a three-dimensional networking system. According to the U.S.P. gel is a semisolid dosage form were small or large organic or inorganic compounds are surrounded and permeated by liquid. Gels are present in clear to opaque in appearance. Carbomers are the most common organic polymer present in the preparation of topical gel and as a result, it gives an aesthetically pleasing, clear sparkling appearance to the product as well as it also easily washed off from skin with water (Shelke *et al.*, 2013), (Prateek *et al.*, 2013). There are various types of polymers are used to preparation of gel-like natural, synthetic, and semi-synthetic. The gel has great importance in food, cosmetics, biotechnology, and pharmacy as well as the skin is the main route of topical delivery of drugs which is easy and ready to access the administration (Kaur and Gel, 2013). The skin has to transport different types of diseases like psoriasis, vitiligo, cancer, etc. For this reason, different delivery of drugs required like microsphere, transdermal patch, nano emulsion, microemulsion, etc which are very effective for avoiding the fast pass metabolism without entering the systemic circulation with the help of targeted delivery to the appropriate site of action (Yadav and Nanda, 2014).

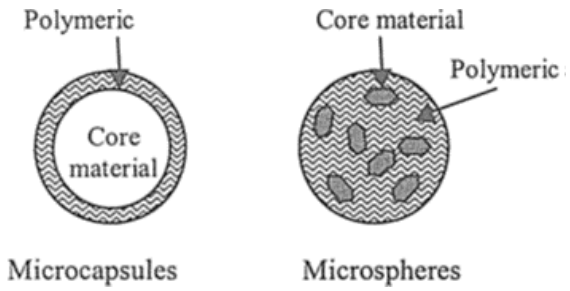

Figure 1: Diagram of microparticles

The microsphere is a solid dosage form and approximately spherical particle-containing disperse drug molecule either in solution or in the crystalline form (Vyas and Khar, 2004). Microspheres are defined as "therapeutic agent distributed throughout the matrix either as a molecular dispersion of particle. There is a small spherical free-flowing particle with a diameter in a range of 1 μm to 1000 μm. This is made up of polymeric waxy or other protective material i.e. biodegradable synthetic polymer and modified natural products like starch, gum, proteins, fats, etc. (Priyanka *et al.*, 2019). Microspheres used usually are polymers. They are classified into two types(a) Synthetic Polymers, (b) Natural polymers. Synthetic polymers are divided into two types. [a] Non-biodegradable polymers e.g. Polymethyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate Epoxy polymers [b]. Biodegradable polymers e.g. Lactides, Glycolides & their copolymers like Poly alkyl cyanoacrylates Poly anhydrides. Natural polymers obtained from different sources like proteins, carbohydrates, and chemically modified carbohydrates (Priyanka *et al.*, 2019). Especially, there are four types of microsphere are present. They are Bioadhesive microsphere, Magnetic microsphere, Floating microsphere, and polymeric microsphere (Yadav and Nanda, 2014). For the bilayer composition, the administration of topical gel is lower level of toxicity than general dosage forms. Specially the preparations which are using for topical delivery, they have proper target to use drug transporters which can confirm the proper localization as well as penetration of drug within or through the skin that can increase the local and lower the systemic effect or to ensure adequate percutaneous absorption. It avoids the GI irritation and drug metabolism as well as it improves the bioavailability and easy to go to site of action (Shelke *et al.*, 2013), (Saroha, 2013).

Merits

1. Microsphere maintains consistency and gives the controlled release of the drug.
2. More patience compliance for lower dosing frequency.
3. They easily penetrate our body by topical gel for spherical and very small size.
4. It improves the bioavailability by proper utilization of drug as well as decrease the untoward effects (Bansal *et al.*, 2011), (Kataria and Middha, 2011).
5. Less amount of energy required. (Walekar *et al.*, 2014).

Demerits

1. Drugs with reasonable partition coefficient and possessing solubility both in oil and water are most ideal, as drug must diffuse through lipophilic stratum - corneum and hydrophilic viable epidermis to reach the systemic circulation. Only drugs, which are effectively absorbed by the percutaneous routes or by using penetration promoters, can be considered.
2. Sensitivity reactions or irritation can occur for using this route.
3. Chances on Loss of drug
4. The route is restricted by the surface area of the delivery system and the dose that needs to be administered in the chronic stage of the disease (Reddy *et al.*, 2010).

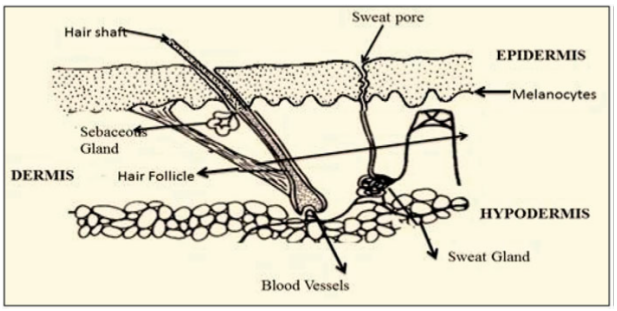

Figure 2: Various Layers of Skin

Properties

1. Whatever the gelling agent used in the preparation should produce a proper solid-like nature during storage that can be easily broken when subjected to shear forces generated by shaking the bottle, squeezing the tube, or during topical application.
2. It has no tackiness.
3. It is safe to use, inert, and not to react with other components in the formulation (Carter, 2000).
4. In comparison with other cosmeceutical ingredients like talc, kaolin, etc, the microsphere has very good oil absorption (w/w) property than them. (Saxena and Nacht, 2005)

Encapsulation of microsphere

Microencapsulation is a process by which very thin coatings of inert natural or synthetic polymeric materials are deposited around micronized particles of solids or droplets of liquids. Products thus formed are known as microparticles, covering two types of forms: microcapsules, micrometric reservoir systems, microspheres, and micrometric matrix systems(Figure 1). These systems consist of two major parts. The inner part is the core material containing one or more active ingredients. These active ingredients may be solidsliquids, or gases. The outer part is the coating material that is usually of a high molecular weight polymer or a combination of such polymers. The coating material can be chosen from a variety of natural and synthetic polymers and must be nonreactive to the core material, preferably biodegradable, and nontoxic. Other components, such as plasticizers and surfactants, may also be added. (Kreuter, 1983)

Microspheres in-vehicle technology

Microsphere has very good transport property, as well as it is using as a very good vehicle. and the design of it is very easy to entrap the active pharmaceutical ingredients as well as it gives the slow release of drugs into the skin. Microsphere has a property to deliver the particular drug into epidermis; as a result, it can make a correlation with the lower potentiality of transdermal penetrability and expose the system. After incorporation of the active ingredients into the microsphere particles, it avoids the epidermal "overload" for the slow release pattern. The progression of topical delivery of active pharmaceutical ingredients into epidermis may occur without any quick production of a concentration gradient of drug which helps in the transcutaneous penetration into the systemic circulation.

When the active ingredient contains microspheres that are getting reduced cutaneous penetration rate, the microsphere vehicles are arising as improve skin tolerability with the least amount of active ingredients. (Smith *et al.*, 2006)

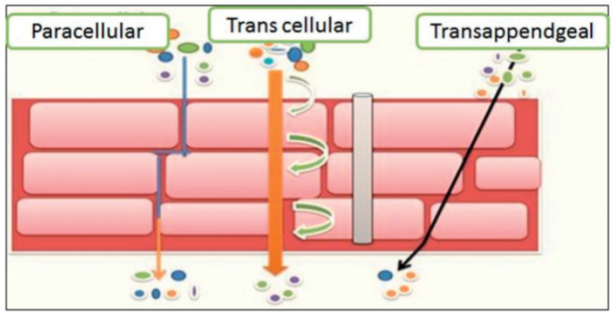

Figure 3: Pathways for penetrating the Skin

Permeation enhancer strategies for topical delivery

The topical administration of the drug gives lots of good effect over the conventional or other techniques. Human skin is the largest part of the body.it mainly works to protect our body from water loss. Human skin is divided into three-part. They are epidermis, dermis, and hypodermis.(Figure 2) (Fukushima *et al.*, 2011).

Our epidermis is divided into five parts and stratum corneum is the outermost layer of the body. It is approximately 10mm thick. Here 79-90% of protein and 5-15% of lipid is present as a result it can make a great barrier in our body. The dermis is the middle layer of the skin with 3-5mm thickness. The hypodermis is the last part which contains the fatty tissue. The drug can penetrate through all three layers and easy to go to the systemic circulation.

The drug cannot penetrate our skin easily; they can go through three pathways to penetrate our skin.[Figure 3] They are transcellular route which can pass the keratinocytes and lipids, next is the paracellular pathway which is very well known and here drug remain in lipid moiety and stay around

keratin and lastly transappendgeal pathway which helps to hinder sweat duct and hair follicle but it is very good for permeation and continuously make a channel to transport the drug. (Marwah *et al.*, 2014)

Components of microspheres for topical delivery

Oil part, surfactant, and co-surfactants are very important components for the preparation of microspheres for using a topical purpose.

Oil components are important and their short-chain oil components easy to penetrate and working than long-chain oils (Ghosh and Murthy, 2006). Unsaturated and saturated fatty acids have a property to easy to penetrate the skin and rupture the jampack lipid layer. If we use an unsaturated alkyl chain with a penetration enhancer, it can give the optimum result but C10-C12 saturated fatty acid can get the proper equilibrium between partition coefficient or solubility. Especially the cis form of the unsaturated fatty acid makes a different form with stratum corneum lipid can be decreased or make resistance in the pathway of stratum corneum. Fatty acid can give this effect particularly for the selective drugs not all like lauric acid and capric acid has no effect on permeation of salicylic acid but they both can increase the permeation of naloxone. Particularly for polar and non-polar drugs, oleic acid is the best unsaturated fatty acid to work as a penetration enhancer. Fatty acid esters and medium-chain triglyceride are also using now as well as semisynthetic oils are hugely using now (Aungst *et al.*, 1986).

Now we can go to the surfactant which very important for microsphere preparation for use as a topical purpose. There is no doubt about skin penetration can be enhanced by surfactants. The lower HLB value surfactants are using in w/o formulation. But when we using the o/w formulations, the HLB value must be greater than 12 and it up to 20, depending upon the drug and polymer quality.

Recently lots of research is going on for reducing their concentration to get well-tolerated surfactants. As well as we can use the non-ionic surfactant also. They are a very good alternative of natural occurring surfactant. There are lots of uses of non-ionic surfactants for topical treatment as a solubilizing agent. Non-ionic surfactant gives the stability, they are not affected by the change of pH easily like Tween which has less toxicity. As well as sorbitan fatty acid ester, polysorbates, poloxamer fatty acid, etc are commonly used (Azeem *et al.*, 2009). If we get a mixture of the same alkyl chain length containing two surfactants can give enhance mutual solubilization oil and water. Tween 20 improve the permeation of 5 FC through the hairless mouse skin, tween 80 can increase the permeation of lidocaine and hydrocortisone. Plurol isostearic has very good tolerability and recently it has huge use in topical purpose into the microsphere (Alvarez-Figueroa and Blanco-Méndez, 2001).

Now we can talk about the co-surfactant which is very important to prepare such type of formulation. Co-surfactant gives the pliability for getting the various flexure of such type of preparation. It can increase the penetration property by increasing the potency of the tail part of hydrocarbon. Hydroxyl group-containing compounds especially alcohols like ethanol is very good and largely using penetration enhancers for the increasing property of drug solubility in the vehicle. as well as it can increase the permeability of drugs. 1 butanol is the best medium-chain alcohol which is used as a penetration enhancer. sometimes a large number of agents in the vehicle system can easily decrease the partition coefficient between skin and vehicle of the drug. As a result, the decreasing transdermal flux can decrease the effect of a drug in a vehicle and upholds the concentration gradient of the formulation (Azeem *et al.*, 2009).

Preparation of formulation

We can prepare the microsphere in different ways like solvent evaporation, emulsification method, quasi emulsion solvent diffusion method, etc. At first, we can prepare the microsphere and for the preparation of it, we can take proper polymer, it should be biodegradable like ethyl cellulose, chitosan, polyvinyl alcohol, etc. As well as we can take the proper solvent media based on the property of the drug. Then the solution should be mix in 700-1200 rpm and then it poured into a continuous phase and mix it in 1500-2000 rpm, crosslinking is done, and then it is filtered and dried. After the preparation of the microsphere, it is poured into such a mixture which should be contained the gelling agents and others (Mandal *et al.*, 2018), (Kreuter, 1983).

Release kinetics

There are two types of system is present. One is matrix type and another is reservoir type.in reservoir type, drug release from the microsphere depends on what type of polymer is present there. Also, it depends on the feature of active pharmaceutical ingredients. Osmotically driven burst method, pore diffusion method, erosion, or degradation of polymer; those three methods are the main method to release the drug. In the biodegradable and non-biodegradable coating, the osmotically driven burst method can diffuse the water. As well as this method depends on the polymer ratio, the particle size of

Table 1: Some marketed microsphere containing topical gels.

Brand Name	Composition	Company
NEXRET gel	Tretinoin (Microsphere) 0.04% w/w	Dr. Reddy's Lab
NEXRET gel	Tretinoin (Microsphere) 0.1% w/w	Dr. Reddy's Lab
NEXRET TC	Tretinoin (Microsphere) 0.04% w/w & Clindamycin 1.0% w/w	Dr. Reddy's Lab
Supatret C	Tretinoin (Microsphere) 0.04% w/w & Clindamycin 1.0% w/w	Sun Pharma
Trunex MS Aqueous Gel	Tretinoin (Microsphere) 0.04% w/w	KLM Laboratories Pvt Ltd
Retino A Micro 0.1% Gel	Tretinoin (Microsphere) 0.1% w/w	Johnson & Johnson Ltd
Supatret 0.04 Aqueous gel	Tretinoin (Microsphere) 0.04% w/w	Sun Pharma

macromolecules and microspheres.

We are using the biodegradable polymer and here the drug release is done by the erosion or diffusion method. In pore, diffusion water is diffused to the core. In polymer erosion, the monomers are accumulated and side by side the polymers are reduced in the release media. The abrasion of polymer compound starts the change in microscopical structure and the carrier penetrates within leading to plasticization of the matrix. The plasticization of the matrix leads to the cleavage of the hydrolytic bond (Ganesan *et al.*, 2014).

The various factors depending on the release of the drug, microsphere, and biological environment. In drugs;

1. Position of microsphere
2. Molecular weight
3. Physicochemical property
4. Concentration
5. Interaction of matrix

In microspheres;

1. Type and amount of matrix
2. Size and density of microsphere
3. Extent of crosslinking
4. Denaturation of polymerization
5. Adjuvants

And lastly in environmental biology

Release from reservoir type system is done by control manner and the drug which is dissolved after portioning through the membrane and diffusion across the stagnant diffusion layer. The release is denoted by Fick's first law of diffusion.

J = -D (dc/dx)

Where J is the flux/ unit area; D is the diffusion coefficient and (dc/dx) is the concentration gradient.

If the diffusion is done through the membrane, it can easily find out the effect of carrier and the cumulative amount of drug that is released through the unit area "Q" at any time.

$$Q_{\mathrm{t}} = \frac{\mathrm{Cs\ KDm\ Dd\ t}}{\mathrm{KDm\ Lm + Dd\ Ld}}$$

Where C is saturation solubility of the drug in the dispersion medium, Lm, Dd is the diffusion coefficient of the drug in static diffusion thickness; Ld, K is partition coefficient of the drug between membrane and reservoir system.

In the matrix type system, the system is depending on the quality of the drug whatever is it dissolve or disperse in the polymer matrix. If the dissolution of the drug is done in the polymer matrix, the release is affected by the nature of the polymer and the amount of drug. If the drug dissolves into a polymer matrix system, the amount of drug should appear in the receptor phase at "t" time. Here it can give two different equation one is to determine the initial 60% of drug release and another show the release profile in later.

$$\frac{\mathrm{dMt}}{\mathrm{dt}} = 2Mx \left(\frac{\mathrm{D}}{\pi \mathrm{L}^2 \mathrm{t}}\right) 1/2$$

$$\frac{\mathrm{dMt}}{\mathrm{dt}} = \frac{8\mathrm{DMx}}{1^2 \exp\pi^2\ \mathrm{Dt/L}^2}$$

Where L is the thickness of the slop of polymer, D is the diffusion coefficient, Mx is the total amount of drug present in matrix and Mt is the amount of drug released in time "t".

When the drug is dispersed through the polymer matrix then the release profile follows the Higuchi equation.

$$\frac{dMt}{dt} = \frac{\frac{A}{2}(2DCs\ Co)\ L/2}{t}$$

Where A is an area of matrix, Cs is the solubility of the drug in matrix and Co represents the total concentration in matrix.

Taking the porosity (ε) and torosity (ε) of the matrix into consideration, the above equation should be written the following way (Ganesan *et al.*, 2014).

$$\frac{dMt}{dt} = \sqrt{\left[\frac{\varepsilon}{\tau} Dm\ (2Co - \varepsilon Cs)\ Cst\right]}$$

Commercially available the topical agents

There is a huge essence of microsphere which is using as topical purpose like various moisturizing facial cream, sunscreen, some "skin rejuvenation" type cosmeceuticals, etc. Especially, the over the counter drugs are hugely using as microsphere as topical purpose. Tretinoin microsphere gel 0.1% and 0.04%, benzoyl peroxide microsphere cream 5.5%, benzoyl peroxide microsphere washes 7%, 5-fluorouracil cream 0.05 % and hydroquinone 4% with retinol cream, etc are hugely using in microsphere as topical delivery (Rosso, 2009).

In India, there are lots of medicaments are preparing for using as a topical gel or others which are contained microsphere. Nexret, supatret c etc medicaments are preparing by the world famous companies like Dr. Reddys, Sun pharma etc (Table 1) (MedlineIndia, 2020).

CONCLUSIONS

This review gives the progression in the ground of topical delivery especially the topical gel of microsphere from the last few decades. It clears the potential of the effectiveness of active pharmaceutical ingredients through the barrier of skin by the help of penetration property and vehicle technology of microsphere. Topical delivery of microsphere shows an impactful future in various pharmaceutical applications in the coming years as they have unique properties like enhanced product performance and elegancy, extended-release, reduced irritation, improved thermal, physical, and chemical stability so flexible to develop novel product forms. Not only it is using in facial moisturizer, sunscreen type cosmetic products but also it is using in anti-inflammatory, anti-fungal, anti-dandruff, etc. The various types of works are going on about it in the research area and they're having lots of hope to overcome various challenges and we will go towards the light.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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