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Importance of advanced topical drug delivery: Emulgel of Nsaids in the treatment of Arthritis and inflammation

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ABSTRACT

Topical formulations are having good patients compliance for many chronic diseases due to its better localised action. Emulgel is one of the most interesting NDDS used topically having characteristics of dual control release i.e. emulsion as well as gel. Emulgel is a combination of gel and emulsion, emulsion either O/W or w/O type, which are gelled by mixing with different gelling agents which allows the formulation to stable by decreasing surface and interfacial tension at the same time increases the viscosity of aqueous phase. In spite of many advantages of gels a major limitation is to deliver the hydrophobic drugs emulgel is proven potential formulation to deliver hydrophobic drugs. Emulgel is used topically because of its characteristic dual control release (i.e.) emulsion as well as gel it demonstrates better drug release as compared to other topical drug delivery system due to excess of oil bases and lack of insoluble excipients. Emulgel are having major advantages on novel vesicular systems as well as on conventional systems considering various aspects. Numerous permeation enhancers can potentiate the effect of decreasing skin barrier resistance on the other hand promoting solubility of the drug in vehicle is also feasible. The use of emulgels can be considered well for NSAIDS in the treatment of chronic inflammation and arthritis

Keywords: Emulgel, NDDS, O/W, W/O, Hydrophobic drugs, Permeation enhancers NSAIDS.

INTRODUCTION

TOPICAL DRUG DELIVERY SYSTEM is used for the localized effect at the site of their application by virtue of drug penetration into the underlying layer of skin or mucous membrane [1]. Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes [2]. The topical drug delivery system is generally used where these systems of drug administration fails or in local skin infection like fungal infection. Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorder [3]. It is al so the largest organ of the

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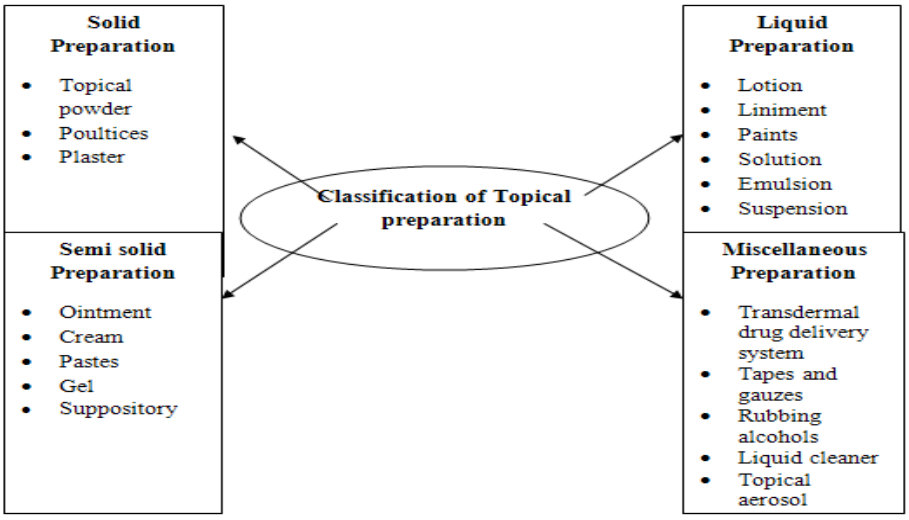
human body, providing around 10% of the body mass of an average person, and it covers an average area of 1.7 m^2. Whilst such a large and easily accessible organ apparently offers ideal and multiple sites to administer therapeutic agents for both local and systemic actions, human skin is a highly efficient self-repairing barrier designed to keep the insides in and the outside out.5

CLASSIFICATION OF TOPICAL DRUG DLIVERY SYSTEM [5]

Topical Delivery Includes Two Basic Types of Products.

- External topical that are spread, sprayed or otherwise dispersed on to cutaneous tissues to cover the affected area such as ointments, creams, liniments, etc.
- Internal topical that are applied to the mucous membrane orally, vaginally or on a rectal tissues for local activity such as emulsions, solutions, suspensions, suppository, etc.

Topical drug delivery system can also be classified on the basis of type of dosage for



Advantages of topical drug delivery system [5]

- Avoidance of first pass metabolism.
- Convenient and easy to apply.
- Avoidance of the risks and inconveniences of intravenous therapy and of varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time. Ability to easily terminate the medications, when needed.
- Ability to deliver drug more selectively to a specific site.
- Avoidance of gastro-intestinal incompatibility.
- Providing utilization of drugs with short biological half-life, narrow the rapeutic window. Improve patient compliance.
- Provide suitability for self-medication.

Disadvantages of topical drug delivery systems

- Skin irritation of contact dermatitis may occur due to the drug and/or excipients. Poor permeability of some drugs through the skin.
- Possibility of allergenic reactions.
- Drugs of larger particle size not easy to absorb through the skin

Anatomy phisology of skin [18]

The skin is the largest organ of the body, accounting for about 15% of the total adult body weight. It performs many vital functions

- Protection against physical, chemical and biological assailants.
- Vital role in thermoregulation.

- Prevention of excess water loss from the body.

The skin consists of three layers i.e. the epidermis, the dermis and the subcutaneous tissue. An average human skin surface is known to contain, on the average 40-70 hair follicles and 200-300 sweat ducts on every cm^2 of the skin.

The pH of the skin varies from 4-5.6 the skin of an average adult body covers a surface area approximately $2m^2$ and receives about one third of the blood circulating through the body.

The skin acts as a two-way barrier to prevent absorption or loss of water and electrolytes.

The epidermis

This is a stratified squamous epithelium layer i.e. composed primarily of two types of cells: keratinocytes and dendrites cells. Epidermis layer harbor a number of other cells such as melanocytes, Langerhans cells and marked cells. But the keratinocytes cells types comprises the majority of the cells by far.

The layers of epithelium are –

- Stratum germinativum (growing layer or basal layer): It contains column-shaped keratinocytes that attach to the basement membrane zone with their long-axis perpendicular to dermis.
- Stratum spinosum (prickly cell layer or squamous cell layer): Its thickness varies from 5-10 cells. Intercellular spaces between spinous cells are bridged by abundant esmosomes (adhering spot) that promote coupling between cells of the epidermis and provide resistance to physical stresses.
- Stratum granulosum (granular layer): It contains living cells, these are responsible for further synthesis and modification of proteins involved in keratinization. It is 1-3 cells layer in thickness.
- Stratum corneum (horny layer): the conrneocytes are rich in protein and low in lipid content (hydrophilic nature) are surrounded by a continuous extracellular lipid matrix.
- Malpighian layer (pigment layer): the layer whose protoplasm has not yet change into horny material.
- Stratum lucidium

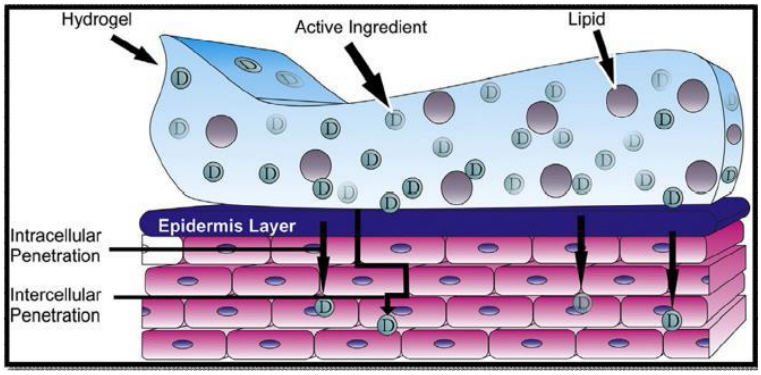


Fig 2: Drug delivery through the skin epidermis by gel formulation

The dermal-epidermal

It act as a support for the epidermis, establishes cell polarity and direction of growth, directs the organization of the cytoskeleton in basal cells, provide developmental signals and function as a semi-permeable barrier between layer.

The dermis

It is on integrated system of fibrous, filamentous and amorphous connective tissue that accommodates stimulus induced entry by nerve, vascular-networks, appendages, fibroblasts, mast cells. Its thickness ranges from 2000- 3000µm. The principal component of the dermis is collagen and represents 70% of the skin's dry weight.

Subcutaneous (connective tissue)

The subcutaneous tissue or hypodermis is not actually considered a true part of the structured connective tissue which is composed of loose

textured, white, fibrous connective tissue containing blood and lymph vessels, secretary pores of the sweat gland and cutaneous nerves. Most investigators consider drug permeating through the skin enter the circulatory

There are three primary mechanisms of topical drug absorption [17]

- Tran cellular
- Intercellular
- Follicular.

Most drugs pass through the torturous path around coenocytes most drugs pass through the torturous path around coenocytes and through the lipid bilayer to viable layers of the skin.

- The next most common (and potentially under recognized in the clinical setting) route of delivery is via the pilo sebaceous route. The barrier resides in the outermost layer of the epidermis, the stratum cornium, as evidenced by approximately equal rates of penetration of chemicals through isolated
- Stratum corneum or whole skin. Creams and gels that are rubbed into the skin have been used for years to deliver pain medication and infection fighting drugs to an affected site of the body.
- These include, among others, gels and creams for vaginal yeast infections, topical creams for skin infections and creams to soothe arthritis pain. New technologies now allow other drugs to be absorbed through the skin (transdermal).
- These can be used to treat not just the affected areas (for example, the skin) but the whole body (systemic).

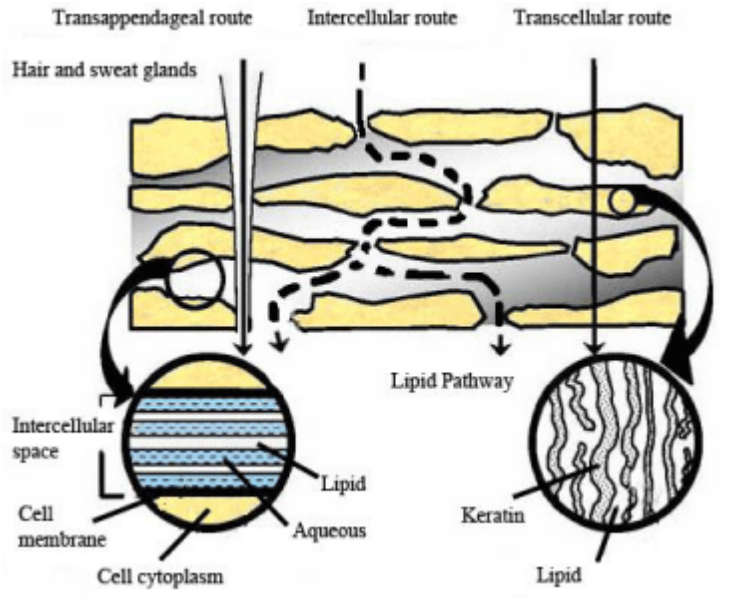


Fig 3: Route of drug absorption through skin

Gels [6]

Definition

Gels are semisolid formulations, which have an external solvent phase, may be hydrophobic or hydrophilic in nature, and are immobilized within the spaces of a three-dimensional network structure. Gel formulations provide better application property and stability in comparison to cream and ointments.

Properties of gels

a. It should be inert, compatible with other additives and non-toxic.
b. It should be convenient in handling and its application
c. It should be stable at storage condition.
d. It should not affect biological nature of drug.
e. Ideally, the gelling agent for pharmaceutical or cosmetic use should be inert, safe, and

should not react with other formulation components.

f. It should possess properties such as thixotrophic, greaseless, emollient, non-staining etc
g. The gelling agent included in the preparation should produce a reasonable 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.
h. It should possess suitable anti-microbial to prevent from microbial attack.
i. The topical gel should not be tacky.

Classification of gel

Gels can be classified based on the basis of colloidal phases, nature of solvent used, physical nature and rheological properties.

RHEOLOGICAL PROPERTIES

Based on colloidal system

Two phase system (Inorganic)

If the particle size of dispersed phase is relatively large and form the three dimensional structure throughout gel such as a system consist of floccules of small particle rather than layer molecule and gel structure in this system is not always stable. E.g. Aluminum Hydroxide Gel

Single phase system (Organic)

These consist of large organic molecule existing on the twisted stands dissolved in continuous phase.
E.g. Carbopol, Tragacanth.

Based on nature of solvent used

Hydro gel

Here they contain water as their continuous liquid phase
E.g. Bentonite magma, Gelatin, cellulose derivatives and poloxamer gel
Organic gel (with a non-aqueous solvent)
These contain a non –aqueous solvent as continuous phase.
E.g. plastibase (low molecular wt. polyethylene dissolved in Mineral oil & short Cooled), Olag (aerosol) gel and dispersion of metallic stearate in oils.

Xerogels

Xerogels are solid gel with low solvent concentration and produced by evaporation of solvent or Freeze drying
E.g. Tragacanth ribbons, acacia tear β-cyclodextrin, dry cellulose and polystyrene.

Based on rheological properties

Usually gels exhibit non-Newtonian flow properties. They are classified into,

Plastic gels

E.g. Bingham bodies, flocculated suspensions of Aluminum hydroxide exhibit a plastic flow and the plot of rheogram gives the yield value of the gels above which the elastic gel distorts and begins to flow.

Pseudo plastic gels

E.g. Liquid dispersion of tragacanth, sodium alginate, Na CMC etc., exhibits pseudo-plastic flow.
The viscosity of these gels decreases with increasing rate of shear, with no yield value.

Thixotrophic gels

The bonds between particles in these gels are very weak and can be broken down by shaking. The resultant solution will revert back to gel due to the particles colliding and linking together again.
E.g. Kaolin, bentonite and agar.

Based on physical nature

Rigid gels

This can be formed from macromolecule in which the framework linked by primary valance bond. E.g. In silica gel, silica acid molecules are held by Si-O-Si-O bond to give a polymer structure possessing a network of pores.

Elastic gels

Gels of agar, pectin, Guar gum and alginates exhibit an elastic behavior.

Methods of preparation of gel[7]

Cold method

In this method the entire ingredient mixed together to form a homogenous mass, under low temperature at about 50C. In this polymer and

penetration enhancer are mixed together to form a solution A, then drug and solvent mixed to form solution B. After that with constant stirring poured solution B into solution A.

Dispersion method

In this method polymer is dispersed over water for 2 hrs till the entire polymer is soaked with water, then addition of remaining ingredients is done with stirring until a homogenous mass is formed.

Chemical reaction

In this method gel is produced by chemical interaction between the solute and solvent.
E.g.: preparation of .silica gel and aluminum hydroxide gel

Temperature effect

With decreased in temperature, solubility of most lipophilic colloid e.g. gelatin, agar is reduced. So that when cool concentrated hot sol gel are produced.

Flocculation

In this method gelatin is produced by adding just sufficient quantity of salt to precipitate to produce age state but insufficient to bring about complete precipitation.

Advantages of gel

- Gels are used to archive optimal cutanious and percutaneous drug delivery.
- They can avoid GI drug absorption difficulties caused by GI Ph.
- Gels having property to avoid enzymatic activity
- They can avoid first pass effect.
- Gels are not deactivated by liver enzymes.

Disadvantages of gel

- Gels have possible of allergic reactions.
- Enzymes in epidermis may denature the drugs of gels.
- Drugs of large particle size do not absorbed through the skin.
- Selection of area can be examine carefully during application of gel
- They may cause skin allergy during application.

NOVEL APPROACHES FOR GEL FORMULATION

- Hydrogel
- Emulgel
- *In situ* gel
- Micro emulsion based gel
- Solid Lipid Nanoparticles based gel
- Ethosomes based gel:
- Liposome based gel
- Microsphere based gel
- Solid Dispersion based gel
- Niosome based gel
- Micro sponge based gel

EMULGELS [8]

Definition: The emulsion and gel are used in the combined dosage form referred as Emulgel having characteristic of dual control release.

Types of Emu gel

The emu gel are classify in to following three categories, which are- Macro-emulsion Gel:

- The particle size of the globules in these emu gels is more than 400 nm. They are apparently obscure. They can be offset using surface element agents.

  Nano – Emulgel:
- These are confined by joining of nano-emulsion in to gel. Nano-emulsions are thermodynamically enduring clear scattering of oil and water offset by proximity of surfactants and co surfactants. These emulgels have a globule size of less than 100 nm.

  Micro Emulsion based Emulgel:
- These emulgels includes joined properties of micro emulsion and gel giving high bioavailability of prescription. The globule size degree from 10-100 nm.

Rational of emulgel [9]

- Many widely used topical agents like ointment, cream, lotion have many disadvantages.
- They have very sticky causing uneasiness to the patient when applied due to some reasons. Moreover they also have lesser spreading coefficient and need to apply with rubbing which may cause dermatitis. And they exhibit

the problem of stability also. Due to all these factors within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations.

- A gel is colloid that is typically 99% wt liquid, which is immobilized by surface tension between it rubbed into the skin have been used for years to deliver pain medication and infection fighting drugs to an affected site of the body. These include others, gels and creams for vaginal yeast infections, topical creams for skin infections and creams to soothe arthritis pain.
- New technologies now allow other drugs to be absorbed through the skin (transdermal). These can be used to treat not just the affected areas (for example, the skin) but the whole body (systemic). these can be applied to hairy skin without any uneasiness caused by other topical formulations.
- In spite of many advantages of gels a major limitation is in the delivery of
- hydrophobic drugs. So, to overcome this limitation an emulsion based approach is being used so that even a hydrophobic therapeutic moiety can be successfully incorporated and delivered through gels.

Advantages of emulgel [10]

Incorporation of hydrophobic drugs

Most of the hydrophobic drugs cannot be incorporated directly into the gel base because solubility act as a barrier and problem arises during the release of the drug. Emulgel helps in the incorporation of hydrophobic drugs into the oil phase and then oily globules are dispersed in aqueous phase resulting in o/w emulsion. And this emulsion can be mixed into gel base. This may be proving better stability and release of drug than simply incorporating drugs into gel base.

Better loading capacity

Other novel approaches like noisome and liposome are of nano size and due to vesicular structures may result in leakage and result in lesser entrapment efficiency. But gels due to vast network have comparatively better loading capacity.

Better stability

Other transdermal preparations are comparatively less stable than emulgels. Like powders are hygroscopic, creams shows phase inversion or breaking and ointment shows rancidity due to oily base.

Production feasibility and low preparation cost

Preparation of emulgels comprises of simpler and short steps which increases the feasibility of the production. There are no specialized instruments needed for the production of emulgels. Moreover materials used are easily available and cheaper. Hence, decreases the production cost of emulgels.

Controlled release

No intensive sonication

Production of vesicular molecules needs intensive sonication which may result in Drug degradation and leakage. But this problem is not seen during the production of emulgels as no sonication is needed.

7 Avoidance of first pass metabolism.
8 Avoidance of gastrointestinal incompatibility.
9 More selective to a specific site.
10 Improve patient compliance and suitability for self medication.
11 Providing utilization of drug with short biological half life and narrow therapeutic window.
12 Ability to easily terminate medication when needed.

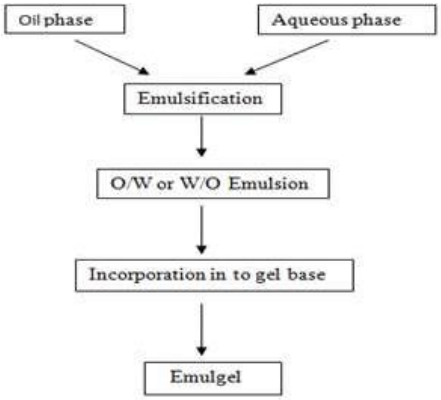
Disadvantages of emulgel [11, 12]

1. Skin irritation of contact dermatitis may occur due to the drug and/or excipients.
2. Poor permeability of some drugs through the skin.
3. Possibility of allergenic reactions.
4. Drugs of larger particle size not easy to absorb through the skin.
5. Enzyme in epidermis may denature the drugs.
7 Bubbles formed during Emulgel formulation.

General method of preparation [13]

STEP1: Formulation of Emulsion either O/W or W/O
STEP2: Formulation of gel base

STEP3: Incorporation of emulsion into gel base with continuous stirring



Important constituents of emulgel preparation [14]

Aqueous material

This forms the aqueous phase of the emulsion. Commonly used agents e.g. water, alcohols.

Oils

These agents from the oily phase. For externally applied emulsions, mineral oils, either alone or combined with soft or hard paraffin's are widely used. In oral preparations non-biodegradable mineral and castor oils that provide a local laxative effect and fish liver oils or various fixed oils of vegetable origin (e.g., a rachis, cottonseed, and maize oils) as nutritional supplements.

Emulsifier

Emulsifying agents are used both to promote emulsification at the time of manufacture and to control stability during a shelf life. e.g. Polyethylene glycol 40 stearate, Sorbitan, mono-oleate (Span 80), Polyoxyethylene sorbitan monooleate (Tween 80), Stearic acid, Sodium stearate.

Preservatives

E.g. Propyl paraben , methyl paraben , Benzalkonium chloride, Benzoic acid, Benzyl alcohol etc.

Antioxidants

E.g. Butylated Hydroxy Toluene (BHT), Ascorbyl palmitate, Butylated Hydroxy anisole (BHA), etc.

Humectants

E.g. Glycerin, Propylene glycol, etc

Gelling agents

These are the agents used to increase the consistency of any dosage form can also be used as thickening agent. e.g. Carbopol 934 , carbopol 940 ,HPMC ,HPMC-2910, sodium CMC .

Permeation enhancer

These are agents that partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability. e.g. Oleic acid ,lecithin , isopropyl myristate , urea , eucalyptus oil , chenopodium oil, Pyrrolidone, laurocapran, dimethyl sulphoxide, linoelic acid, menthol.

LIST OF MARKETED EMULGEL [15]

Table 1: LIST OF MARKETED EMULGEL [15]

Marketed preparations	Product name	Drug manufacturer
Voltaren emulgel	Diclofenac diethyl ammonium	Novartis Pharma
Miconaz-H-emulgel	Miconazole nitrate, Hydrocortison	Medical union Pharmaceuticals

LIST OF PATENTED IN EMULGEL FORMULATION [15]

Table 2: LIST OF PATENTED IN EMULGEL FORMULATION

S.NO	Patent No	Application No	Title of patent	Inventors
1	EP2214642 A1	EP2008084493	Topical composition	Fabienne Caillet-Bois, Isabelle Rault, Michel Steiger
2	EP2019666 A2	EP20070734379	Pharmaceutical preparations for transdermal use	Cristina Cavallari, Barbara Luppi, Pietra Anna Maria Di, Lorenzo Rodirguez
3	2007129162 PCT	IB2007/001061	Pharmaceutical preparations for transdermal use	Cristina Cavallari, Barbara Luppi, Pietra Anna Maria Di, Lorenzo Rodirguez
4	WO2002017905 A2 PCT	EP2001/010041	Treatment of burns	Ancerewicz Jacek, Kienzler Jean-Luc, Sallin Dominique, Schumann Phyllis
5	US 6004566 A	US 08/036, 116	Topical and transdermal delivery system utilizing submicron oil spheres	Doron Friedman, Joeph Schwartz, Haim Aviv
6	5639738x 08	466,778	Topical composition containing hyaluronic acid and NSAIDs	Falk, Rudolf Edgar, Asculai, Samuel Simon
7	US 6113921 A	US 09/006, 446	Topical and transdermal delivery system utilizing submicron oil spheres	Doron Friedman, Joseph Schwartz, Haim Aviv

RHEUMATOID ARTHRITIS [6.15]

Rheumatoid arthritis (RA) is a long lasting autoimmune disorder that primarily affects joints. It typically results in warm, swollen, and painful joints. Pain and stiffness often worsen following rest. Most commonly, the wrist and hands are involved, with the same joints typically involved on both sides of the body.

The disease may also affect other parts of the body. This may result in a low red blood cell count, inflammation around the lungs, and inflammation around the heart. Fever and low energy may also be present.

Often, symptoms come on gradually over weeks to months. While the cause of rheumatoid arthritis is not clear, it is believed underlying bone and cartilage. The diagnosis is made mostly on the basis of a person's signs and symptoms.

X-rays and laboratory testing may support a diagnosis or exclude other diseases with similar symptoms. Other diseases that may present similarly include systemic lupus erythematosus, psoriatic arthritis, and fibromyalgia among others. The goal of treatment is to reduce pain, decrease inflammation, and improve a person's overall functioning. This may be helped by balancing rest and exercise, the use of splints and braces, or the use of assistive devices.

Pain medications, steroids, and NSAIDs are frequently used to help with symptoms. A group of medications called disease modifying anti rheumatic drugs (DMARDs) may be used to try to slow the progression of disease. They include the medications hydroxyl chloroquine and methotrexate. Biological DMARDs may be used when disease does not respond to other treatments.

Signs and symptoms of rheumatoid arthritis

- Tender, warm, swollen joints. Joint inflammation often affecting the wrist and finger joints closest to the hand; other affected joints can include those of the neck, shoulders, elbows, hips, knees, ankles, and feet. Rheumatoid nodules are sometimes present.
- Pain and stiffness lasting for more than 30 minutes in the morning or after a long rest.
- Symmetrical pattern. For example, if one knee is affected, the other one is also.
- Fatigue, occasional fever, a general sense of not feeling well (malaise).
- Symptoms affecting other parts of the body besides the joints.

Etiology

The etiology of RA is not fully understood despite extensive study of metabolic and nutritional factors, the endocrine system, and geographic, psychological, and occupational data. It now appears that an unknown antigen initiates the autoimmune response resulting in RA.

This response supports the suspicion of an infectious origin of the disease process, which includes various bacteria and viruses, but without evidence of precipitating events. Even without this specific knowledge, treatment modalities have been developed that, while not curing the disease, can provide relief from the symptoms of the disease.

Evidence points to a complex interplay between environmental and genetic factors. In monozygotic twins, there is a more than 30 percent concordance rate for rheumatoid arthritis development, and 80 percent of whites with rheumatoid arthritis express the HLA-DR1 or -DR4 subtypes.

These and other regions of the Major His to-compatibility Complex may confer susceptibility to more severe disease by causing a specific arthrogenic peptide to be presented to CD4+ T cells. Scientists are now focusing on the idea that it is a T-cell-mediated autosomal disease precipitated by both genetic and environmental factors.

Pathophysiology

The joint capsule is lined with a type of tissue called synovium, which produces synovial fluid. The synovial fluid secreted by the synovium is thought to serve two main purposes, lubrication of the joint and provision of nutrients to the avascular articular cartilage. The attack on a joint by the disease usually begins with the synovium.

Joint damage in rheumatoid arthritis begins with the proliferation of synovial macrophages and fibroblasts after a triggering incident, either autoimmune or infectious.

White blood cells that are part of the normal immune system travel to the synovium and cause a reaction. This reaction, or inflammation, is called synovitis, and it results in warmth, redness, swelling, and pain that are typical symptoms of RA. Lymphocytes infiltrate the perivascular regions, endothelial cells proliferate and these result in neovascularization. Thus early in the disease, edema begins to be seen in cells in the synovium and multiplication of synovial lining cells occur.

During the inflammation process, the cells of the synovium grow and divide abnormally, making the normally thin synovium thick and resulting in a joint that is swollen and puffy to the touch.

Blood vessels in the affected joint become occluded with small clots or inflammatory cells. As the disease progresses, inflamed synovial tissue begins to grow considerably and irregularly, forming invasive pannus tissue. The pannus is a sheet of inflammatory granulation tissue that spreads from the synovial membrane and invades the joint in rheumatoid arthritis and destroys cartilage and bone ultimately leading to fibrous ankylosis.

Pannus can be considered the most destructive element affecting joints in the patient with rheumatoid arthritis. Pannus can attack articular cartilage and destroy it. Further, pannus can destroy the soft subchondral bone once the protective articular cartilage is gone. There is chronic inflammation with lymphocytes and plasma cells that produce the blue areas beneath the nodular proliferations.

Multiple cytokines, interleukins, proteinases, and growth factors are released, causing further joint destruction and the development of systemic complications In this disease process, an interaction between antibodies and antigens occurs, and causes alterations in the composition of the synovial fluid.

Ultimately, digestants are formed in the fluid that attacks the surrounding tissue. Once the composition of this fluid is altered, it is less able to perform the normal functions noted above, and more likely to become destructive.The changes in the synovium and synovial fluid are responsible for a large amount of joint and soft tissue destruction.

The destruction of bone eventually leads to laxity in tendons and ligaments. Under the strain of daily activities and other forces, these alterations in bone and joint structure result in the deformities frequently seen in patients with rheumatoid arthritis. Considerable destruction of the joint can occur with pannus invading the subchondral bone.

Bone destruction occurs at areas where the hyaline cartilage and the synovial lining do not adequately cover the bone. If the disease progresses to a more advanced stage, the articular cartilage may lose its structure and density resulting in an inability to withstand the normal forces placed on the joint.

In such advanced cases, muscle activity causes the involved ends of the bones to be compressed together causing further bone destruction. Further, the disease can irreversibly change the structure and function of a joint to a degree that other degenerative changes may occur, especially in the weight bearing joints of the body. Thus, joint destruction can progress to the degree that joint motion is significantly limited and joints can become markedly unstable.

While rheumatoid arthritis (RA) primarily affects joints, problems involving other organs of the body are known to occur. Extra-articular (outside the joints) manifestations other than anemia (very common) are clinically evident in about 15–25% of individuals with rheumatoid arthritis.

It is difficult to determine whether disease manifestations are directly caused by the rheumatoid process itself, or from side effects of the medications commonly used to treat it for example, lung fibrosis from methotrexate or osteoporosis from corticosteroids.

Joints

The arthritis of joints known as synovitis is inflammation of the synovial membrane that lines joints and tendon sheaths. Joints become swollen, tender and warm, and stiffness limits their movement. With time, RA nearly always affects multiple joints (polyarthritis), most commonly small joints of the hands, feet and cervical spine, but larger joints like the shoulder and knee can also be involved. Synovitis can lead to tethering of tissue with loss of movement and erosion of the joint surface causing deformity and loss of function.

Rheumatoid arthritis typically manifests with signs of inflammation, with the affected joints being swollen, warm, painful and stiff, particularly early in the morning on waking or following prolonged inactivity.

Increased stiffness early in the morning is often a prominent feature of the disease and typically lasts for more than an hour. Gentle movements may relieve symptoms in early stages of the disease. These signs help distinguish rheumatoid from non-inflammatory problems of the joints, often referred to as osteoarthritis or "wear-and-tear" arthritis. In arthritis of non-inflammatory causes, signs of inflammation and early morning stiffness are less prominent with stiffness typically less than 1 hour, and movements induce pain caused by mechanical arthritis.

In RA, the joints are often affected in a fairly symmetrical fashion, although this is not specific, and the initial presentation may be asymmetrical. As the pathology progresses, inflammatory activity leads to tendon tethering and erosion and destruction of the joint surface, which impairs range of movement and leads to deformity. The fingers may suffer from almost any deformity depending on which joints are most involved, namely ulnar deviation, boutonniere deformity, swan neck deformity and "Z-thumb," (not significant for diagnosis, since they occur in osteoarthritis as well).

Skin

The rheumatoid nodule, which is often subcutaneous, is the cutaneous feature most characteristic of rheumatoid arthritis. The initial pathologic process in nodule formation is unknown

but may be essentially the same as the synovitis, since structural features in both are similar.

The nodule has a central area of fibrinoid necrosis that may be fissured and which corresponds to the fibrin-rich necrotic material found in and around an affected synovial space.

Surrounding the necrosis is a layer of palisading macrophages and fibroblasts, corresponding to the intimal layer in synovium and a cuff of connective tissue containing clusters of lymphocytes and plasma cells, corresponding to the subintimal zone in synovitis.

The typical rheumatoid nodule may be a few millimeters to a few centimeters in diameter and is usually found over bony prominences, such as the olecranon, the calcaneal tuberoses, the metacarpophalangeal joint, or other areas that sustain repeated mechanical stress. Nodules are associated with a positive RF (rheumatoid factor) titer and severe erosive arthritis.

Rarely, these can occur in internal organs or at diverse sites on the body. Several forms of vacuities occur in rheumatoid arthritis. A benign form occurs as micro infarcts around the nail folds. More severe forms include live do reticular is, which is a network (reticulum) of erythematous to purplish discoloration of the skin caused by the presence of an obliterate cutaneous capillaropathy.

Other, rather rare, skin associated symptoms include: pyoderma gangrenous, a necrotizing, ulcerative, noninfectious neutrophilic dermatitis; Sweet's syndrome, a neutrophilic dermatosis usually associated with myeloproliferative disorders; drug reactions; erythema nodosum; lobular panniculitis; atrophy of digital skin; palmar erythema; diffuse thinning (rice paper skin), and skin fragility (often worsened by corticosteroid use).

Lungs

Fibrosis of the lungs is a recognized response to rheumatoid disease. It is also a rare but well recognized consequence of therapy (with methotrexate and leflunomide). Caplan's syndrome describes lung nodules in individuals with rheumatoid arthritis and additional exposure to coal dust. Pleural effusions are also associated with rheumatoid arthritis. Another complication of RA is Rheumatoid Lung Disease. It is estimated that about one quarter of patients with RA develop Rheumatoid Lung Disease.

Kidneys

Renal amyloidosis can occur as a consequence of chronic inflammation.[26] Rheumatoid arthritis may affect the kidney glomerulus directly through a vasculopathy or a mesangial infiltrate but this is less well documented. Treatment with Penicillamine and gold salts are recognized causes of membranous nephropathy. Heart and blood vessels People with rheumatoid arthritis are more prone to atherosclerosis, and risk of myocardial infarction (heart attack) and stroke is markedly increased.

Other possible complications that may arise include

Pericarditis, endocarditis, left ventricular failure, valvulitis and fibrosis. Many people with rheumatoid arthritis do not experience the same chest pain that others feel when they have angina or myocardial infarction. Cardiovascular risk can be reduced by maintaining optimal control of the inflammation caused by rheumatoid arthritis and to use exercise and medications appropriately to reduce other cardiovascular risk factors such as blood lipids and blood pressure.

Psychological factors

There is no evidence that physical and emotional effects or stress could be a trigger for the disease. The many negative findings suggest that either the trigger varies, or that it might in fact be a chance event inherent with the immune response.

Current aims of treatment of ra [19]

- Slow the rate of disease progression.
- Control inflammation and pain; ideally the patients should be as free as possible from pain.
- Design the appropriate treatment regimen for each patient.
- Regular appointments with the clinic and the rheumatologist.
- Regular patient monitoring for adverse effects of treatments.
- Regular blood tests.
- Monitor patient compliance.

Treatment of rheumatoid arthritis with biological drugs [20]

Traditionally, RA was treated symptomatically with non-steroidal and steroidal anti-inflammatory drugs, which still have a place in the management of RA. The use of these drugs is self-limiting through the corrosive effects of nonsteroidal drugs such as aspirin on the gut and the serious effects of steroidal drugs on, for example, water retention and redistribution of body fat.

Paracetamol is an alternative to aspirin for treatment of pain, but has a relatively low therapeutic index. Furthermore these treatments do not slow the progression of tissue damage and loss of hand use and mobility. Several drugs, e.g. methotrexate, penicillamine, gold and azathioprine, commonly known as DMARDs, or disease-modifying anti-rheumatic drugs, have been used for several years. These may provide symptomatic relief and slow the progression of the disease, but are associated with serious adverse effects and are relatively non-specific in their actions.

The biological DMARDs have been developed thanks to the advances made in molecular biology, and especially with regard to the identification of key cellular mediators of inflammation. Essentially, these are monoclonal antibodies (MAbs) directed against chemical mediators of inflammation, notably TNF-a, and interleukins IL-1 and IL-6. These MAbs compete with the endogenous ligands at their receptor sites on cells, e.g. CD20 and CD22, some of which have no identified endogenous ligand (at the time of writing).

CONCLUSION

Oral formulation seems to have adverse effect even topical have adverse effects but intensity is less, even emulsion and gel has a limitations of delivering the hydrophobic drugs So emulgel is most preferred topical delivery of hydrophobic drugs with long duration of action and control release.

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