Formulation and Development of Curcumin Hydrogel for Anti-Inflammatory Activities

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***Abstract*—The aim of the study was to formulate curcumin hydrogel and evaluates its biological activities. The present study aims to increasing the bioavailability of curcumin and increasing the skin penetration.**

Hydrogel are three-dimensional cross-linked polymer network that can respond to the fluctuations of the environmental stimuli. These biomaterials can incorporate large quantum of biological fluids and swell. When swelled, they are soft and rubbery and resemble the living tissue, exhibiting excellent biocompatibility. They are insoluble due to the presence of chemical (tie-points, junctions) and physical cross links such as entanglements and crystallites. The study aims to investigate a hydrogel formulation containing curcumin, which enhance the bioavailability and permeation with the help of polymer which are useful in drug delivery system to Stable, elegant formulations of curcumin gel were successfully prepared, with overcome the problems of bioavailability and in comparison, to other polymer (such as carbopol and sodium alginate) combination of carbopol and HPMC presented higher % of drug diffusion. *In-vitro* release of curcumin from hydrogel was determined by using Franz diffusion cell with a pH of 6.8 at 37ºC. The release profile of the curcumin was also fit into various kinetic models (zero order, first order, Higuchi model, Hixson crowel and Peppus model) and find out the mechanism of drug release.

***Index Terms*—Curcumin, Hydrogel, Carbopol, Franz diffusion cell, *In-vitro* release, Kinetics model, Topical delivery, bioavailability.**

I. INTRODUCTION

SKIN

The human body has two systems that protect it from the harmful organisms existing in the environment. The internal defense system destroys microorganisms and bacteria that have already attacked the body. The external defense system prevents microbial microorganisms to enter the body[1, 2].

ANATOMY OF SKIN

The skin or cutaneous membrane, which covers the external surface of the body, is the largest organ of the body in both surface area and weight[3].

EPIDERMIS

The epidermis is stratified squamous epithelium. The main cells of the epidermis are the keratinocytes, which synthesise the protein keratin[4]. Protein bridges called desmosomes connect the keratinocytes, which are in a constant state of transition from the deeper layers to the superficial [5].

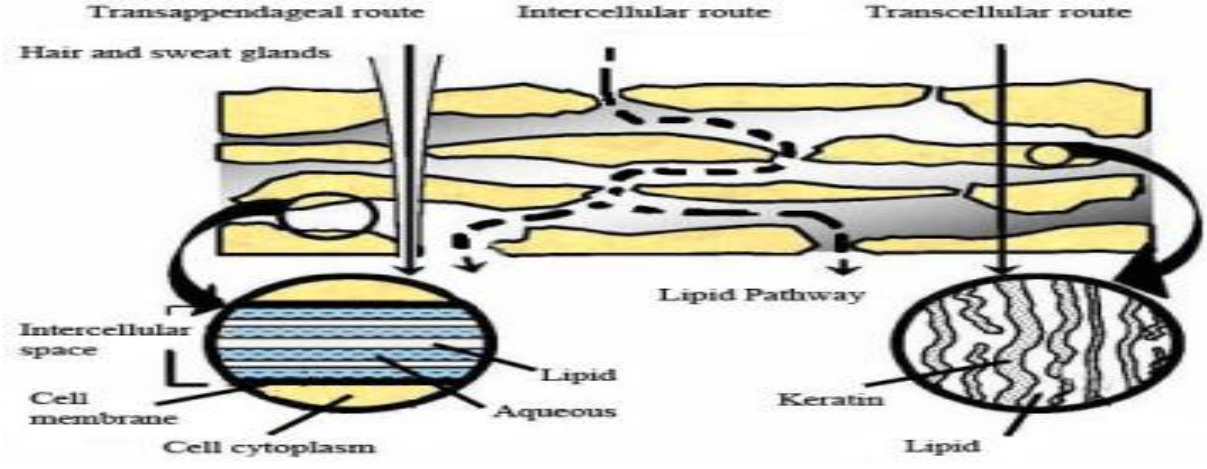

Fig.1 Structure of stratum corneum and penetration pathway[6, 7]

Molecule can basically permeate through skin by two different pathways. The first pathway is called the transappendegeal route. In this route the molecules should permeate through skin by permeation through sweat glands and across the hair follicles. The number of molecules which can penetrate through this pathway is very limited. The second pathway of penetration through skin is the transepidermal pathway. In this pathway molecules should pass through stratum corneum as multilayered barrier. This pathway has two micro pathways; the intracellular micro pathway and the transcellular micro pathway[8].

II. SKIN PENETRATION AND PERMEABILITY

Skin penetration differs from skin permeation. Skin penetration is the former describes the passage of an ingredients into the skin[9]. Skin permeation is the passage of an ingredient through the skin to the circulatory system[10].

Human skin has a low permeability; that is, most foreign substances are unable to penetrate and diffuse through the skin. Skin's outermost layer, the stratum corneum, is an effective barrier to most inorganic nanosized particles[10]. This protects the body from external particles such as toxins by not allowing them to come into contact with internal tissues. However, in some cases it is desirable to allow particles entry to the body through the skin. Potential medical applications of such particle transfer have prompted developments in nanomedicine and biology to increase skin permeability. One application of transcutaneous particle delivery could be to locate and treat cancer. Nanomedical researchers seek to target the epidermis and other layers of active cell division where nanoparticles can interact directly with cells that have lost their growth-control mechanisms (cancer cells). Such direct interaction could be used to more accurately diagnose properties of specific tumors or to treat them by delivering drugs with cellular specificity[11].

The hydrophobicity of the incorporated nanomedicine in hydrogel matrices induced loose cross linking within the hydrophilic network and the permeability of hydrogel matrices improved. Hydrogel permeability is a very important parameter as it characterizes the diffusion and transport of the solutes through the matrix. It depends on a number of parameters including the nature of the solutes, temperature, pH, ionic strength and solute concentration, but mostly on the interconnectivity of pores, pore orientation, pore size and distribution within the hydrogel[12].

III. HYDROGEL

The establishment of the first synthetic Hydrogels by Wichterle and Lim in 1954[13], the hydrogel technologies may be applied to food additives[14], pharmaceuticals[15], biomedical implants[16], tissue engineering and regenerative medicines[17], diagnostics[18], cellular immobility[19], separation of biomolecules or cells[20] and barrier materials to regulate biological adhesions[21], Biosensor and BioMEMs devices and drug carriers[22].

Hydrogels are hydrophilic polymeric network of three-dimensional cross-linked structures that absorb substantial amount of water. Cross linking facilitates insolubility in water because of ionic interaction and hydrogen bonding[23]. It also provides required mechanical strength and physical integrity to the Hydrogels[24].

IV. HYDROGEL-NETWORK DESIGN AND STRUCTURE

Various properties viz. interaction parameters, material properties, kinetic profile and transport mechanisms aids in designing the network of complex hydrogel systems by identifying the determining parameters which decides the rate and extent of drug release[25,26].

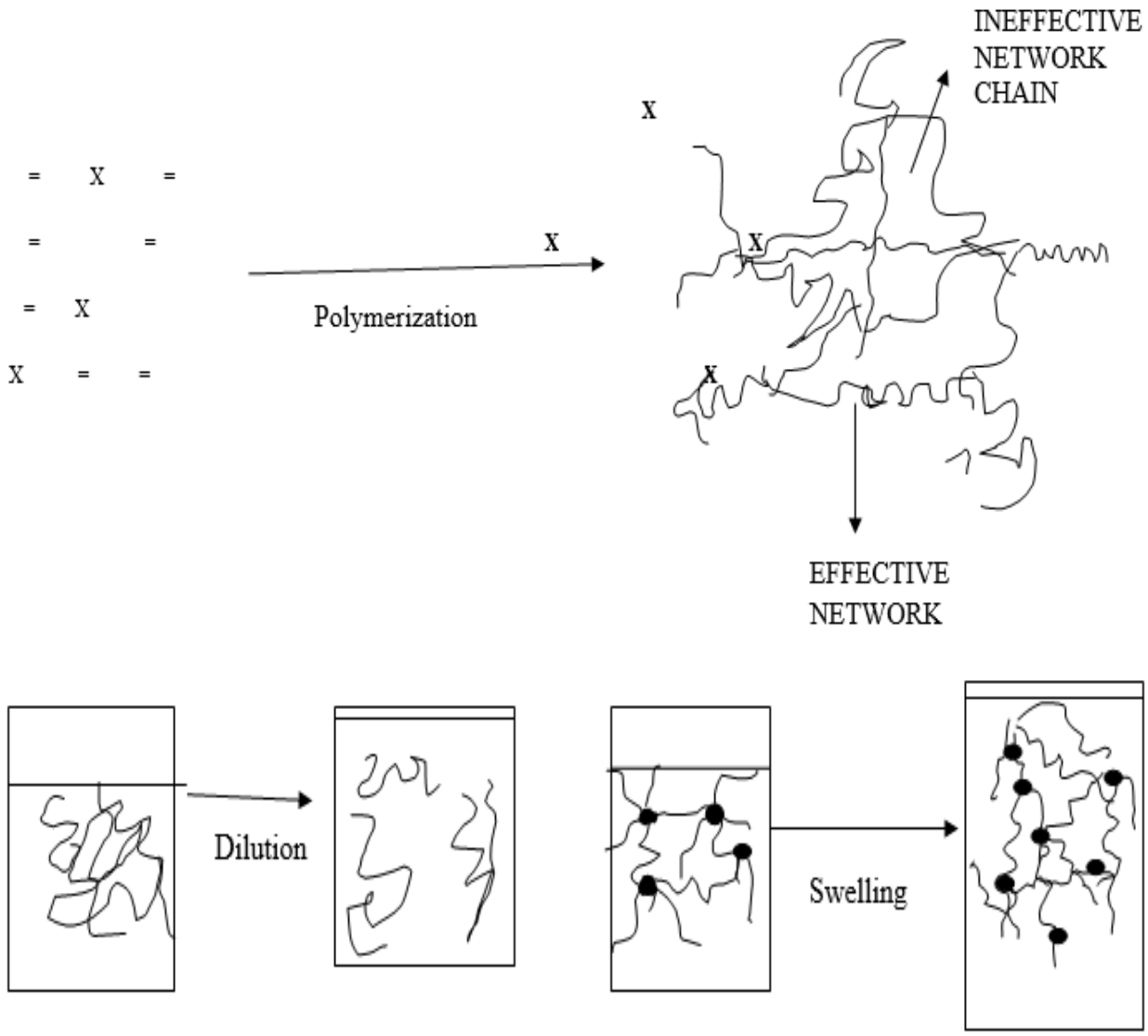

Fig.2 Chemical and physical structure[27]

Networks formed by stitching together monomers in aqueous solutions via cross-linkers that are multifunctional units[27]

1. Draw an example of a crosslinker: bisacrylamide.
2. Networks from hydrophilic vinyl monomers.

V. POLYMER USED IN HYDROGEL

The polymers used for fabrication of these biocompatible hydrogel have expanded from a handful of choices, to several novel materials with tailor-made properties suited to particular applications[28]. Depending upon the application, hydrogel polymers are chosen according to their properties, ease of delivery or encapsulations, as well as cost and availability. One of the most traditional polymers used for drug delivery of proteins is biodegradable PLGA (polymers of lactic and glycolic acid) [29]. However these hydrophobic materials have a tendency to denature protein as well as cause inflammation due to degradation. These problems were overcome when researchers turned towards hydrophilic monomers. Monomers such as acrylic acid, polyethylene glycol, and methacrylic acid are all materials used in therapeutic applications[30].PNIPAAm (poly (N-isopropylacrylamide), PVA (polyvinyl alcohol) are all synthesized by new preparation techniques, for distinct applications[31].

Polymer used in hydrogel

Synthetic polymer	Natural polymers
Polyurethane[32]	Agar[33]
Poly(ethylene glycol) [32]	Carrageenan[34]
Poly(propylene glycol)[32]	Starch[35]
Poly(vinylpyrrolidone)[33]	Acacia[38]
polyethylene glycol[33]	Gum Arabic[40]
poly (vinyl methyl ether)[36]	Collagen[41]
poly (N-isopropyl acrylamide)[36]	Sodium alginate[42]
Eudragit RS100[37]	Gellan gum[43]
Carbopol 934[38]	Hyaluronan[45]
βhairpin peptide[39]	Pectin[70]
Polyacrylic acid[44]	Xanthum gum[70]

VI. CLASSIFICATION OF POLYMER

A) Natural polymers and their derivatives

Anionic polymers: Hyaluronic acid, alginic acid, pectin, carrageenan, chondroitin sulphate, dextran sulphate

Cationic polymers: chitosan, polylysine

Amphipathic polymers: collagen (and gelatin), carboxymethyl chitin, fibrin

Neutral polymers: dextran, agarose, pullulan.

B) Synthetic polymers

Polyesters : PEG-PLA-PEG,PEG-PLGA-PEG,PEG-PCL-PEG,PLA-PEG- PLA,PHB,P(PFCo-EG)6 acrylate end groups, P(PEG/PBO terephthalate)

Other Polymers : PEG-bis-(PLA-acrylate),PEG6CDs,PEG-g-P(AAm coVamine),PAAm,P(NIPAAm-co-AAc),P(NIPAAm-coEMA),PVAc/PVA,PVNP,P(MMA-co-HEMA),P(AN-co-allyl sulfonate),P(GEMA-sulfate),P(biscarboxy-phenoxy-phosphazene)

DRUG USED IN HYDROGEL PREPARATION

Drug	Therapeutic category	Carrier system	Inference	Reference
Insulin	Hypogylcaemic	Hydrogel	Sustain release of insulin	46
Hydrocortisone	Corticosteroids	Hydrogel	Controlled drug delivery system	47
Riboflavin	Water soluble vitamin	Hydrogel	pH sensitivity to localize drug delivery	48
Salicylic acid	Anti-seborrheics	Hydrogel	pH sensitive drug delivery system	49
Terbinafine hydrochloride	Antifungal	Hydrogel	Controlled drug delivery system	50
Propranolol hydrochloride	Antiadrenergic	Hydrogel	electrically modulated drug delivery	51
5-Fluorouracil & Diclofenac sodium	Antimetabolite & AntiInflammatory	Hydrogel	Localized drug delivery	52
Clarithromycin	Anti Helicobacter	Hydrogel	Stomach-specific drug delivery	53
Amoxicillin, metronidazole	Antimicrobial, antiamoebic	Hydrogel	Stomach-specific drug delivery	54

Simvastatin	lipid lowering drug	IPN hydrogel beads	Controlled drug delivery system	55
Methoxsalen	Psoriasis	Micro emulsion hydrogel	Controlled drug delivery system	56
Lornoxicam	Anti-inflammatory	Hydrogel	Localized drug delivery	57
Fluconazole	Antifungal	Micro sponge hydrogel	Localized drug delivery	58
Metronidazole	Periodontitis	Hydrogel	Localized drug delivery	59
Loratadine	Antialergic	Hydrogel	Localized drug delivery	60
Diazepam	Epileptic seizures	Hydrogel	Localized drug delivery	61
Valsartan	AntiInflammatory	Hydrogel	Localized drug delivery	62
Cisplatin	Anticancer	Hydrogel	Controlled drug delivery system	63
Theophylline	Nocturnal asthma	Hydrogel	Controlled drug delivery system	64
Losartan potassium	Antihypertensive	Hydrogel	Controlled drug delivery system	65
Dexamethasone	AntiInflammatory	Hydrogel	Localized drug delivery	66
Clarithromycin	Antibiotic	Hydrogel	Controlled drug delivery system	67
Sliver sulfadiazine	Wound healing	Hydrogel	Localized drug delivery	68
Timolol Maleate	Opthalmic	Hydrogel	Controlled drug delivery system	69
Diltiazem hydrochloride	Antiarrhythmic antianginal	IPN hydrogel beads	Sustain release	70

VII. MECHANISM OF RELEASE OF HYDROGEL

Depending on the composition of hydrogel (type of polymer, type of drug and additives), geometry (size and shape), preparation technique and environmental conditions during drug release, one or more of the following physical and chemical phenomena affect the drug release kinetics[71-73].

The mechanism of release consists of the following phenomena…

1) EXTERIOR DIFFUSION
2) INTERIOR DIFFUSION
3) DESORPTION
4) CHEMICAL REACTIONS

1) EXTERIOR DIFFUSION

The mechanism of release consists of exterior and interior processes of diffusion[74]. Exterior diffusion takes place when drug molecules diffuse from surface of the hydrogel matrix to bulk of the liquid phase. Drug concentration is the highest close to the surface of the hydrogel matrix and it decreases with the length. When the bulk of liquid is well stirred the value of drug concentration is constant. Exterior diffusion can control the rate of drug release only in exceptional cases. In general, the rate of drug release depends on interior phenomena, especially on interior diffusion.

2) INTERIOR DIFFUSION

In general, the rate of drug release is controlled by interior diffusion. Theories which are based on Flick's law of diffusion distinguish two types of systems...

1. Reservoir
2. Monolithic devices

In the reservoir system a polymer membrane surrounds inner bulk of dissolved, suspended drug[75, 76] Diffusion of an encapsulated drug through the membrane is the rate-limiting step in this delivery system. A constant concentration gradient across the

polymer membrane is achieved by saturated concentration of the drug core. Drug is absorbed from inner bulk by the membrane. Then it diffuses through the membrane and is desorbed from the membrane to the fluid which surrounds the reservoir device.

HYDROGELS	DRUG DIFFUSION COEFFICIENTS
Porous Hydrogels- pore size >>> molecular dimensions of drug	Related to porosity
Non- porous Hydrogel Porous gels with pore sizes comparable to the drug molecular size[77, 78].	Decreases due to stearic hindrance from polymer chains with in cross linked networks.

Drug Diffusion Coefficients

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