FORMULATION AND EVALUATION OF DICLOFENAC SOLID DISPERSION INCORPORATED TOPICAL GEL

A Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI

In partial fulfillment of the requirement for the award of the degree of

MASTER OF PHARMACY

(PHARMACEUTICS)

Submitted By

Reg. No: 26104206

Under the guidance of

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CERTIFICATE

This is to certify that the work embodied in this thesis entitled "**PREPARATION AND EVALUATION OF DICLOFENAC SOLID DISPERSION INCORPORATED TOPICAL GEL"** submitted to The Tamil Nadu Dr. M.G.R. Medical University Chennai, was carried out by **(Reg.No.26104206)** in the Department of Pharmaceutics, Nandha College of Pharmacy, Erode-52 in partial fulfillment for the degree of **MASTER OF PHARMACY** in Pharmaceutics under my direct supervision and guidance.

This work is original and has not been submitted in part or full for any other degree or diploma of any university.

Place: Erode **Dr. S. TAMIZHARASI, M. Pharm., Ph.D.**

Date: Research Guide

DECLARATION

The work presented in this thesis entitled "**PREPARATION AND EVALUATION OF DICLOFENAC SOLID DISPERSION INCORPORATED TOPICAL GEL"** was carried out by me in the Department of Pharmaceutics, Nandha College of Pharmacy and Research Institute, Erode, under the direct supervision and guidance of **Dr. S. TAMIZHARASI M. Pharm., Ph.D.,** Nandha College of Pharmacy and Research Institute, Erode -52.

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INDEX

LIST OF ABBREVIATIONS

Mg	Microgram
Mg	Milligram
G	Gram
µm	Micrometer
Ml	Milliliter
Hrs.	Hours
Fig.	Figure
^{o}C	Degree Celsius
PVP	Polyvinyl pyrrolidone
SD	Solid dispersion
HPMC	Hydroxypropyl methyl cellulose
FTIR	Fourier Transform infrared spectroscopy
RPM	Rotations per minute

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INTRODUCTION

The skin is the largest organ of the body, accounting for more than 10% of body mass, and the one that enables the body to interact most intimately with its environment. The skin consists of four layers: the stratum corneum (nonviable epidermis), the remaining layers of the epidermis (viable epidermis), dermis, and subcutaneous tissues. There are also several associated appendages: hair follicles sweat ducts, apocrine glands, and nails. [1]

Many agents are applied to the skin either deliberately or accidentally, with either beneficial or deleterious outcomes and the mechanism was showed in Fig. 1. The use of topical products was evident in ancient times, and there are reports of systemic benefits of topical anti-infective and hormonal agents in the 1940s. Modern transdermal patch technology was introduced in the late 1970s. The main interests in dermal absorption assessment are in the application of compounds to the skin

- For local effects in dermatology (e.g., corticosteroids for dermatitis)
- For transport through the skin for systemic effects (e.g., nicotine patches for smoking cessation)
- For surface effects (e.g., sunscreens, cosmetics, and anti-infective); To target deeper tissues (e.g., Non-steroidal anti-inflammatory agents [NSAIDs] for muscle inflammation)
- Unwanted absorption (e.g., solvents in the workplace, agricultural chemicals, or allergens).

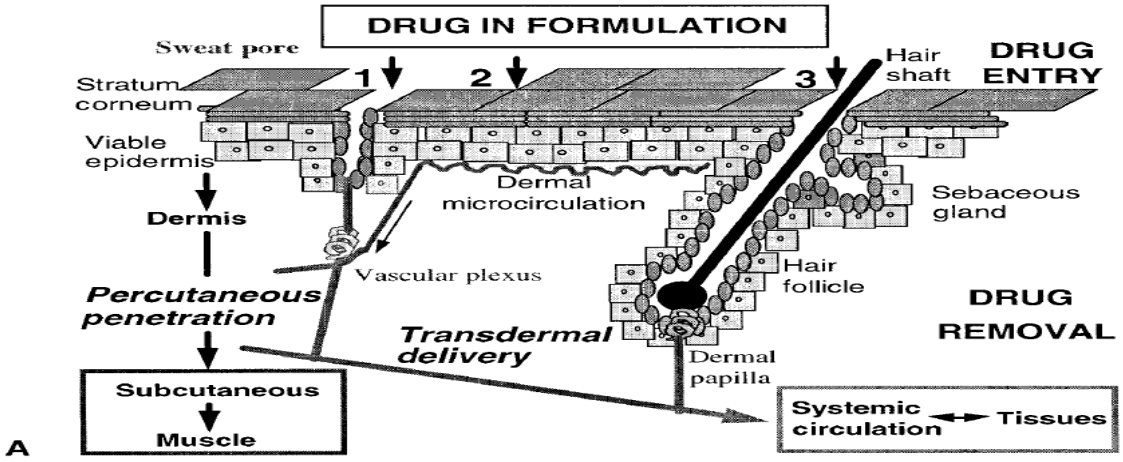


Fig. 1 Mechanism of drug through by transdermal delivery

The skin became popular as a potential site for systemic drug delivery because it was thought to

- Avoid the problems of stomach emptying, pH effects, and enzyme deactivation associated with gastrointestinal passage
- To avoid hepatic first-pass metabolism
- To enable control of input, as exemplified by termination of delivery through removal of the device

Delivery of solutes through the skin is associated with various difficulties, such as

- The variability in percutaneous absorption owing to site, disease, age, and species differences
- The skin's ''first-pass'' metabolic effect
- The reservoir capacity of the skin
- Irritation and other toxicity caused by topical products
- Heterogeneity and indelibility of the skin in both turnover and metabolism
- Inadequate definition of bioequivalence criteria
- An incomplete understanding of the technologies that may be used to facilitate or retard percutaneous absorption.

GROSS STRUCTURE AND FUNCTION OF THE SKIN

It needs to be emphasized that the protection, homeostatic, and sensing functions of the skin are both overlapping and integrated. For instance, barrier properties to a chemical entity involves resistance to its entry (barrier provided by stratum corneum), metabolism for that proportion of entity bypassing the stratum corneum (in viable epidermis), sensing of and attention to damage caused by entry (inflammatory mediator release in epidermis, with involvement of dermis), and removal of entity from site by dermal blood supply and distribution into those body organs specifically responsible for elimination of the entity by metabolism (liver) and excretion (kidney). Heat regulation occurs through the use of the subcutaneous fat pad, physiological regulation of blood flow to affect, for instance, heat loss by vasodilation, and cooling by perspiration.

A. The Epidermis

The epidermis performs a number of functions, as shown in Fig. 2, one of the most important being the generation of the stratum corneum. The stratum corneum is the heterogeneous outermost layer of the epidermis and is approximately 10–20 _m thick. It is nonviable epidermis and consists, in a given cross-section, of 15–25 flattened, stacked, hexagonal, and cornified cells embedded in a mortar of intercellular lipid. Each cell is

approximately 40 mm in diameter and 0.5 mm thick. The thickness varies, however, and may be a magnitude of order larger in areas such as the palms of the hand and soles of the feet, areas of the body associated with frequent direct and substantial physical interaction with the physical environment. Each stratum corneum cell is composed mainly of insoluble bundled keratins (_70%) and lipid (_20%) encased in a cell envelope, accounting for about 5% of the stratum corneum weight. The intercellular region consists mainly of lipids and desmosomes for coenocyte cohesion. The barrier function is further facilitated by the continuous desquamation of this horny layer with a total turnover of the stratum corneum occurring once every 2–3 weeks. The cells of the stratum corneum originate in the viable epidermis and undergo many morphological changes before desquamation. Thus the epidermis consists of several cell strata at varying levels of differentiation. The origins of the cells of the epidermis lie in the basal lamina between the dermis and viable epidermis. In this layer there are melanocytes, Langerhans cells, and two major keratinic cell types: the first functioning as stem cells having the capacity to divide and produce new cells; the second serving to anchor the epidermis to the basement membrane.

The basement membrane is 50–70 nm thick and consists of two layers—the lamina dense and lamina Lucida—which comprise mainly proteins, such as type IV collagen, laminin, nidogen, and fibronectin. Type IV collagen is responsible for the mechanical stability of the basement membrane, whereas laminin and fibronectin are involved with the attachment between the basement membrane and the basal keratinocytes.

B. The Dermis

In Fig. 2 the dermis, a critical component of the body, not only provides the nutritive, immune, and other support systems for the epidermis, through a thin papillary layer adjacent to the epidermis, but also plays a role in temperature, pressure, and pain regulation. The main structural component of the dermis is referred to as a coarse reticular layer. The dermis is about 0.1–0.5 cm thick and consists of collagenous fibers (70%), providing a scaffold of support and cushioning, and elastic connective tissue, providing elasticity, in a semigel matrix of muco-polysaccharides. In general, the dermis has a sparse cell population. The main cells present are the fibroblasts, which produce the connective tissue components of collagen, laminin, fibronectin, and vitronectin; mast cells, which are involved in the immune and inflammatory responses; and melanocytes involved in the production of the pigment melanin. Contained within the dermis is an extensive vascular network providing for the skin nutrition, repair, and immune responses and, for the rest of the body, heat exchange, immune response, and thermal regulation. The blood flow rate to the skin is about 0.05 mL min_1

cc_3 of skin, providing a vascular exchange area equivalent to that of the skin surface area. Skin blood vessels derive from those in the subcutaneous tissues, with an arterial network supplying the papillary layer, the hair follicles, the sweat and apocrine glands, the subcutaneous area, as well as the dermis itself. These arteries feed into arterioles, capillaries, venules, and, thence, into veins. Of particular importance in this vascular network is the presence of arterio venous anastomoses at all levels in the skin.

The lymphatic system is an important component of the skin in regulating its interstitial pressure, mobilization of defense mechanisms, and in waste removal. It exists as a dense, flat meshwork in the papillary layers of the dermis and extends into the deeper regions of the dermis. Also present in the dermis are a number of different types of nerve fibers supplying the skin, including those for pressure, pain, and temperature.

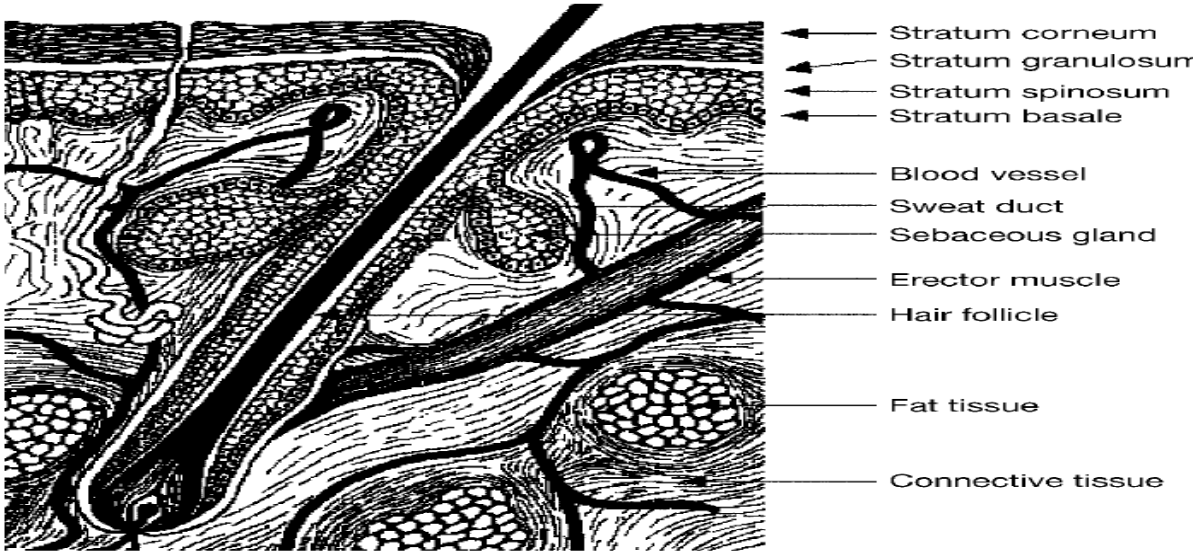


Fig. 2 T.S. of the Skin

C. The Sub-cutis

Fig. 2 shows the deepest layer of the skin is the subcutaneous tissue or hypodermis. The hypodermis acts as a heat insulator, a shock absorber, and an energy storage region. This layer is a network of fat cells arranged in lobules and linked to the dermis by interconnecting collagen and elastin fibers. As well as fat cells (possibly 50% of the body's fat), the other main cells in the hypodermis are fibroblasts and macrophages. One of the major roles of the hypodermis is to carry the vascular and neural systems for the skin. It also anchors the skin to underlying muscle. Fibroblasts and adipocytes can be stimulated by the accumulation of interstitial and lymphatic fluid within the skin and subcutaneous tissue.

D. Skin Appendages

There are four skin appendages: the hair follicles with their associated sebaceous glands, eccrine sweat glands, apocrine sweat glands, and the nails showed in Fig 2. Each appendage has a different function as outlined in Table 1.

Appendages				
Parameter	**Hair follicle and sebaceous gland**	**Eccrine gland**	**Apocrine gland**	**Nails**
Function	Protection (hair) and lubrication (serum)	Cooling	Vestigial secondary sex gland	Protection
Distribution	Most of the body	Most of the body	Axillae, nipples, anogenetal	Ends of fingers and toes
Average/Cm^2	57-100	100-200	Variable	-
Fractional area	2.7×10^3	10^{-4}	Variable	-
Secretions	Sebum	Sweat (dilute saline)	"Milk" protein, lipoproteins, lipid	-
Secretions stimulated By	Heat (minor)	Heat, cholinergic	Heat	-
Biochemical innervation of gland response	-	Cholinergic	Cholinergic	-
Control	Hormonal	Sympathetic nerves	Sympathetic nerves	-

Table 1: Appandages of the Skin

[1, 2] Hydrogels are hydrophilic polymeric network of three dimensional cross linked structures that absorb substantial amount of water5. Cross linking facilitates insolubility in water because of ionic interaction and hydrogen bonding11. It also provides required mechanical strength and physical integrity to the Hydrogels. Thus, hydrogels can imbibe water nearly 10-20 times its molecular weight and hence become swollen. Some examples of Hydrogels include contact lenses, wound dressing, super absorbents.

BENEFITS

- Biocompatible
- Can be injected
- Easy to modify
- Timed release of growth factors and other nutrients to ensure proper tissue growth
- Entrapment of microbial cells within polyurethane hydrogel beads with the advantage of low toxicity
- Environmentally sensitive hydrogels have the ability to sense changes of pH, temperature or the concentration of metabolite and release their load as result of such a change.
- Natural hydrogel materials are being investigated for tissue engineering, which include garose, methylcellulose, hylaronan, and other naturally derived polymers.

LIMITATIONS

- High cost.
- Low mechanical strength
- Difficult to load
- Difficult to sterilize
- Nonadherent
- In contact lenses - lens deposition, hypoxia, dehydration and red eye reactions20-24

CLASSIFICATION

1. On the basis of the nature of the cross linked junctions20

a. Chemically cross-linked networks having permanent junctions.

b. Physical networks have transient junctions arising from polymer chain entanglements or physical interactions

S. No	Characteristics	Natural origin	Synthetic polymers
1	Preparation	By using natural polymer	By chemical polymerization
2	Advantages	-Biocompatible -Biodegradable -Supports cellular activities	-Inherent bioactive properties absent
3	Disadvantages	-Does not possess sufficient mechanical properties -May contain pathogen -Evoke immune and responses	_____
4	Examples	-Properties like collagen and gelatin -Polysaccharides like alginate and agarose	-Acrylic acid -Hydroxy-ethyl-methacrylate (HEMA) -vinyl acetate -Meth acrylic acid (MAA)

Preparation of hydrogels

1. Use of cross linkers

- Copolymerization of monomers using multifunctional co-monomer, which acts as cross linking agent, chemical initiator initiates the polymerization reaction which can be carried out in bulk, solution or suspension.
- Cross linking of linear polymers by irradiation or by chemical compounds. Monomers used here contain an ionizable group that can be ionized or can undergo a substitution reaction after the polymerization is completed. Thus, the hydrogels synthesized may contain weakly acidic groups like carboxylic acids or weakly basic groups like substituted

amines or a strong acidic and basic group like sulfonic acid and quaternary ammonium compounds.

- Cross linkers incorporated are glutaraldehyde, calcium chloride and oxidized konjac lucomannan (DAK). They impart sufficient mechanical strength to the polymers and thus prevent burst release of the medicaments.

2. Isotatic Ultra High Pressure (IUHP)

Suspension of natural biopolymers (e.g.-starch) are subjected to ultra-high pressure of 300-700 MP n for 5 or 20 minutes in a chamber which brings about changes in the morphology of the polymer (i.e. Gelatinization of starch molecules occur).Temperature in the chamber varies from 40 to 52OC30.

3. Use of Nucleophilic substitution reaction

A pH and temperature sensitive hydrogel viz. hydrogel of N-2-dimethylamino-ethyl-methacrylamide (DMAEMA) has been prepared using nucleophilic substitution reaction between methacyloyl chloride and 2-dimethylamino ethylamine31.

4. Use of gelling agent

Gelling agents like glycophosphate1-2propanediol, glycerol, trehalose, mannitol etc. have been used in the preparation of hydrogels. However, presence of negative charged moieties and turbidity are the problems associated with the method.

5. Use of irradiation and freeze thawing

Irradiation method is suitable as well as convenient but the processing is costly along with the poor mechanical strength of the product .Freeze thawing method imparts sufficient mechanical strength and stability to the hydrogels except that they are opaque in appearance with little swelling capacity. However, hydrogels prepared from microwave irradiation are more porous than conventional methods.

6. Synthesis of hydrogel in industry

Formulation of monomer along with initiators and additives lead to polymerization which forms the gel. The gel is dried, sieved and mixed with other additives and post treatment is done if needed.

DESIGN CRITERIA FOR HYDROGELS IN DRUG DELIVERY FORMULATIONS

Nature of material and network fabrication governs the rate and mode of drug release from hydrogel matrices. There are various design criteria for drug that must be evaluated before hydrogel fabrication and drug loading. These criteria play a vital role in Mathematical modeling of drug release. Design criteria for hydrogels in drug delivery formulations are

shown in the **Table 3:** Design criteria for hydrogels Hydrogel formulation even designed with proper physical and transport properties, may still fail to show therapeutic effect when implanted in vivo due to a localized inflammatory response. Fibrous capsule formed around the delivery device gives rise to additional diffusion barriers that may limit drug release rates while increased proteolysis activity may increase rates of matrix and drug degradation. Thus, proper material selection, fabrication process and surface texture are important parameters in designing biocompatible hydrogel formulations for controlled release. Drug incorporation into hydrogel device can be achieved by one of the following methods.

1. Hydrogels Drug Uptake Release Mechanism

Inert hydrogels diffusion and/or gel swelling Hydrogel containing drug –binding ligands drug-polymer interaction and diffusion

2. In-situ Loading

Drug or drug polymer conjugates are mixed with polymer precursor solution and hydrogel network formation and drug encapsulation are achieved simultaneously. Here release of drugs occurs through diffusion, hydrogel swelling, reversible drug-polymer interaction, degradation of labile covalent bonds.

DRUG RELEASE MECHANISMS FROM HYDROGEL DEVICES

Hydrogels imbibe more water than 90% of their weight due to hydrophilicity, thus differing in their release mechanisms from hydrophobic polymers. Various models have been developed to predict the release of an active agent from a hydrogel device as a function of time. These models are based on the rate limiting step for controlled release and are divided into three categories viz.

- Diffusion controlled
- Swelling controlled
- Chemically controlled

DIFFUSION CONTROLLED

It is most widely applicable mechanism relating to drug release. Fick's law of diffusion is commonly used in modeling this release.

S. No	Hydrogels	Drug diffusion coefficients
1	**Porous hydrogels**-pore size >>> molecular dimensions of the drug	Related to porosity
2	**Non- Porous hydrogels-** porous gels with pore sizes comparable to the drug molecular size.[34, 35]	Decreases due to steric hindrance from polymer chains with in cross linked networks.

SWELLING CONTROLLED

It occurs when diffusion of drug is faster than hydrogel swelling. In this condition the modeling of drug involves moving boundary, where molecules are released at the interface of the rubbery and glassy phases of swollen hydrogels. Transition occurs from a glassy state where entrapped molecules remain immobile to a rubbery state where molecules rapidly diffuse. Release of small molecule drugs from HPMC hydrogel tablets are based on this mechanism. For example, Methocel matrices (a combination of methylcellulose and HPMC) from Dow chemical Company prepare swelling controlled drug delivery formulations.

CHEMICALLY CONTROLLED

It characterizes molecule release based on reactions occurring within a delivery matrix. Most commonly occurring reactions are-

- Cleavage of polymer chains via hydrolytic or enzymatic degradation.
- Reversible or irreversible reactions occurring between the polymer network and releasable drug.

It can be categorized on the basis of reactions occurring during drug release.

Purely–kinetic – controlled release

Polymer degradation (bond cleavage) is the rate determining step while diffusion contributes almost negligible to the drug release.

It is of two types viz.

- Pendant chain (prodrugs)
- Surface eroding systems

In pendent chain systems, drugs are covalently linked to the hydrogel network device through cleavable spacers and drug release is controlled by the rate with which spacer bond cleavage occurs. In specific applications where a more targeted delivery approach is desired, it is advantageous to design enzymatically cleavable spacer bonds. In surface eroding systems, drug release is mediated by the rate of surface erosion of the polymer matrix. In hydrophobic polymer networks, surface erosion occurs when the rate of water transport into the polymer is much slower than the rate of bond hydrolysis. Nevertheless due to the inherently high water content of hydrogels, surface erosion occurs slowly in enzymatic degradation systems where the transport of enzyme into the gel is slower than the rate of enzymatic degradation. Models focusing on the release mechanisms are based on hydrolytic degrading polymers.

CHALLENGES OF HYDROGEL DEVICES

There are still many challenges associated with the modeling of drug delivery phenomena and release profiles related to complex hydrogel systems. Fundamental understanding of drug transport processes helps in developing a suitable mathematical model. Mass transport governs the translocation of drug from the interior to the surrounding environment of hydrogel devices. Factors affecting mass transport of encapsulated molecules are as follows.

- Network cross linking density
- Extent of swelling
- Gel degradation
- Size and charge of the encapsulated molecules
- Physical interactions between the encapsulated molecules and the polymer matrix
- Drug – ligand binding present within hydrogel devices.

APPLICATION OF HYDROGELS

Wound Healing – Modified polysaccharide found in cartilage is used in formation of hydrogels to treat cartilage defects. For example, the hydrogel of gelatin and polyvinyl alcohol (PVA) together with blood coagulants are formulated.

1. **Soft Contact Lenses (**silicon hydrogels and polyacrylamides) – The first commercially available silicon hydrogels adopted two different approaches. First approach by Bausch and Lomb was a logical extension of its development of silicon monomers with enhanced compatibility in hydrogel forming monomers. The second by Ciba vision was the development of siloxy monomers containing hydrophilic polyethylene oxide segments and oxygen permeable polysiloxane units.

2. **Industrial Applicability -** Hydrogels are used as absorbents for industrial effluents like methylene blue dye. Another example is adsorption of dioxins by hydrogel beads.
3. **Tissue Engineering –** Micronized hydrogels are used to deliver macromolecules phagosomes) into cytoplasm of antigen-presenting cells. This property is also utilized in cartilage repairing. Natural hydrogel materials used for tissue engineering include agarose, methylcellulose and other naturally derived products.
4. **Drug Delivery in GI Tract –** Hydrogel deliver drugs to specific sites in the GIT. Drugs loaded with colon specific hydrogels show tissue specificity and change in the pH or enzymatic actions cause liberation of drugs. They are designed to be highly swollen or degraded in the presence of micro flora.
5. **Rectal Delivery –** Hydrogels showing bio adhesive properties are used for rectal drug delivery. Miyazaki et al. explored the xyloglucan gel with a thermal gelling property as matrices for drug delivery.
6. **Ocular Delivery –** Chitoni et al. reported silicon rubber hydrogel composite ophthalmic inserts. Cohen et al. developed ***in-situ*** forming gelling system of alginate with high gluconic acid contents for the ophthalmic delivery of pilocarpine.
7. **Transdermal Delivery –** Swollen hydrogels can be used as controlled release devices in the field of wound dressing. Hydrogel based formulations are being explored for transdermal iontophoresis to obtainnicotine.
8. **Subcutaneous Delivery –** Hydrogel formulations for subcutaneous delivery of anticancer drugs are being prepared viz. cross-linked PHEMA was applied to cytarabine (Ara-c).implantable hydrogels are now leading towards the development of biodegradable systems which don't require surgical removal once the drug has been administered.
9. **Novel Hydrogel For Controlled Drug Delivery –** HYPAN is the novel hydrogel having properties useful controlled drug delivery. Physical network of crystalline clusters distinguishes HYPAN hydrogels from others.
10. **Hydrogel For Gene Delivery –** Modification of hydrogel composition leads to effective targeting and delivery of nucleic acids to specific cells for gene therapy. Hydrogel versatility has potential application in the treatment of many genetic and/or acquired diseases and conditions.
11. **Cosmetology –** Hydrogels when implanted into breast accentuate them for aesthetic reasons. These implants have silicon elastomer shell and are filled with hydroxyl propyl cellulose polysaccharide gel.

12. **Tropical Drug Delivery –** Instead of conventional creams, hydrogel formulation are employed to deliver active components like Desonide, a synthetic corticosteroid used as an anti – inflammatory for better patient compliance.
13. **Protein Drug Delivery –** Interleukins conventionally administered as injection are now given as hydrogels which show better compliance and form *in-situ* polymeric network and release proteins slowly.

SOLID DISPERSION

Many potential drug candidates are characterized by a low oral bioavailability. Often poor drug dissolution / solubility rather than limited permeation through the epithelia of the gastrointestinal tract are responsible for low oral bioavailability. Thus aqueous solubility of any therapeutically active substance is a key property as it governs dissolution, absorption and thus the *in-vivo* efficacy. Drugs with low aqueous solubility have low dissolution rates and hence suffer from oral bioavailability problems**3**. Various techniques for the improvement of the dissolution rates of poorly water soluble drugs include micronization, inclusion complexation with cyclodextrins, conversion into amorphous drug and formation of solid dispersions with hydrophilic carriers**2**. Solid dispersion technique is widely used to increase the intrinsic solubility and dissolution and in turns oral bioavailability of poorly water soluble compounds**.** Solid dispersion formulation was developed by Chiou and Riegelman**.** Solid dispersion has traditionally been defined as the "the dispersion of one or more active ingredients in an inert excipient or matrix" where the active ingredients could exist in finely crystalline, solubilized or amorphous states.[3]

It is the most promising method to formulators because of ease of preparation, ease of optimization and reproducibility6. Solid dispersion systems can increase dissolution rate and bioavailability of water insoluble drugs. In solid dispersion systems, a drug may exist as an amorphous form in inert hydrophilic carriers to form solid solutions. When they are exposed to aqueous media, the carriers dissolve, and the drug is released as very fine colloidal particles. This greatly reduces particle size and increases surface area, which results in improved dissolution rates and per oral absorption. Furthermore, no energy is required to break up the crystal lattice of a drug (normally present in a crystalline solid dosage form) during the dissolution process. Drug solubility and wettability may be increased by surrounding hydrophilic carriers**.**

TYPES OF SOLID DISPERSION:

1. **Binary solid dispersion:** It consists of drug and a polymeric carrier.

2. **Ternary solid dispersion:** It consists of drug, a polymeric carrier and a surfactant.

Generally used surfactant is polysorbate 80 which plays an important positive role in dissolution of the solid dispersion both the binary and ternary solid dispersions enhanced the dissolution of poorly water soluble drugs. Moreover, the dissolution of ternary solid dispersion is found faster compared with that of binary solid dispersion 7.This was because of polysorbate 80, which improved the wettability and solubilized the non-molecularly dispersed or crystalline fraction of drug (ex. Ofloxacin)**.**

3. **Surface solid dispersion:** Surface solid dispersion is formulated with polymers such as polyvinyl pyrrolidone, polyethylene glycol and polyvinyl pyrrolidone-vinyl acetate copolymer by fusion technique to improve its solubility. Preparation of surface solid dispersion, a technique that provides deposition of the drug on the surface of certain materials, can alter the dissolution characteristics of drug. Deposition of drug on the surface of an inert carrier leads to reduction in particle size of drug, therapy providing faster rate of dissolution**.**

SUITABLE PROPERTIES OF A CARRIER FOR

SOLID DISPERSIONS

Following criteria should be considered during selection of carriers:

- High water solubility – improves wettability and enhances dissolution
- High glass transition point – improve stability
- Minimal water uptake (reduces TG)
- Soluble in common solvent with drug –solvent evaporation
- Relatively low melting point –melting process
- Capable of forming a solid solution with the drug-similar solubility parameters

First generation carriers

Crystalline carriers: Urea, Sugars, Organic acids.

Second generation carriers

Amorphous carriers: Poly ethylene glycol, Povidone, Poly vinyl acetate, Poly methacrylate, cellulose derivatives

Third generation carriers

Surface active self-emulsifying carriers: Poloxamer 408, Tween 80, Gelucire 44/14.

SOLVENT SELECTION FOR SOLID DISPERSION SYSTEMS

In order to prepare solid dispersion, solvents should be selected on the basis of following criteria:

- Dissolve both drug and carrier.
- Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane
- Ethanol is a less toxic alternative
- Water based systems preferable
- Use of surfactants to create carrier drug solutions but care should be taken as they can reduce the glass transition point.

Class I Solvents (Solvents to be avoided)

Solvents in Class I should not be employed in the manufacture of drug substances, excipients and drug products because of their deleterious environmental effect **Table 1.**

Class II Solvents (Solvents to be limited)

Solvents in **Table 2** should be limited in pharmaceutical products because of their inherent toxicity.

Class III Solvents (Solvents with low toxic potential)

Solvents in class III (**shown in table 3)** may be regarded as less toxic and of lower risk to human health. Class III includes no solvents known as a human health hazard at level normally accepted in pharmaceuticals.

Class IV Solvents (Solvents for which no adequate toxicological data was found)

Some solvents may also be of interest to manufacturers of excipients, drug substances, or drug products for example Petroleum ether, isopropyl ether. However, no adequate toxicological data on which to base a PDE was found.

Table1. List of some Class I Solvents

Solvent	Concentration LIMIT (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazards
1,2-dichloroethane	5	Toxic
1,1-dichloroethane	8	Toxic
1,1,1-trichloroethane	1500	Environmental hazards

Table2. Class II Solvents in pharmaceutical products

Solvent	PDE (mg/day)	Concentration LIMIT (ppm)
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	13.8	380
1,2-dichloroethane	18.7	1870
Ethylene glycol	6.2	620
Methanol	30.0	3000
Pyridine	2.0	200
Toluene	8.9	890

PDE= Permitted Daily Exposure

Table 3. Class III solvents which should be limited by GMP or other quality based requirements

Acetic acid	Heptane
Acetone	Isobutyl acetate
1-Butanol	Isopropyl acetate
2-Butanol	Methyl acetate
Butyl acetate	3-Methyl-1-Butanol
Dimethylsulfoxide	Pentane
Ethanol	1-Pentanol
Ethylacetate	1-Propanol
Ethyl ether	2-Propanol
Formic acid	Propyl acetate

USES OF SOLID DIPERSION:

- Solid dispersion improves dissolvability in water of poorly water soluble drug in a pharmaceutical composition**.**
- Drug is formulated with hydrophilic carrier (ex. poly ethylene glycol) as a solid dispersion to increase its aqueous solubility and dissolution. Then super disintegrant (ex.croscarmellose sodium) is used in tablet formulation to achieve rapid disintegration of tablets prepared by wet granulation method. Thus solid dispersion is used in preparing rapid disintegration oral tablets. These rapidly disintegrating tablets can be used as an alternative to parenteral therapy enabling patient for self-medication even without the aid of water**.**

- Solid dispersion is used as formulation vehicle to facilitate the preclinical safety and early clinical studies on new chemical entities with very low aqueous solubility. A compound with extremely low or negligible aqueous solubility may significantly limit the dose range or exposure of the drug achievable in the preclinical and clinical studies when formulated via traditional means. In these cases, solid dispersion formulations may provide a means to rapidly assess the safety and efficacy profile of the drug substance that may be otherwise difficult to obtain**.**
- In improving immunosuppressive therapy in lung transplant patients, dry powder formulation consisting of a solid dispersion (ex. Cyclosporine A) for inhalation is prepared. It can avoid many problems ex.
    - With dry powder inhalation the use of local anesthesia and irritating solvents can be avoided.
    - The higher deposition efficiency of dry powder inhalation compared with nebulization reduces the need for high metered doses. Solid dispersions are known for their dissolution rate enhancing properties of poorly soluble drugs such as Cyclosporine.

BENEFITS OF SOLID DISPERSION SYSTEM:

Solid dispersion systems can provide numerous additional benefits to oral drug therapy beyond improving bioavailability such as:

- Solid dispersion formulations were demonstrated to accelerate the onset of action for drugs such as Non-steroidal anti-inflammatory drugs where immediacy of action is crucial to relieving acute pain and inflammation.
- For anti-cancer drugs in particular, solid dispersion systems were shown to provide bioavailable oral dosage forms which could be substituted for standard injections to improve patient comfort and compliance.
- Solid dispersion systems were also found to reduce food effect on drug absorption, thus increasing the convenience of drug therapy as the need for some drugs to be taken with food was eliminated.
- It was also demonstrated that a solid dispersion- based dosage form allowed for greater drug loading per dose and improved stability over a soft gelatin capsule formulation which thereby improved the convenience of drug therapy by reducing the dosing regimen and eliminating the need for refrigerated storage.

- Additionally, the improved absorption efficiency demonstrated for solid dispersion systems allows for a reduction in the content of active agent per dose, thus decreasing the cost associated with these drug therapies.
- Finally it was demonstrated the solid dispersion systems can be produced utilizing functional carriers that offer the added benefit of targeting the release of highly soluble forms of poorly water soluble drugs to an optimum site for absorption.
- These benefits demonstrate the current contributions and future potential of solid dispersion systems toward improving drug therapies for a variety of important medical condition whose treatment involves poorly water soluble drugs**.**

METHOD OF PREPARATION:

1. Solvent evaporation method
2. Modified solvent evaporation method
3. Melting method
4. Melt-solvent method
5. Kneading method
6. Co-grinding method
7. Co-precipitation method
8. Co-precipitation with supercritical fluid
9. Spray drying method
10. Gel entrapment technique

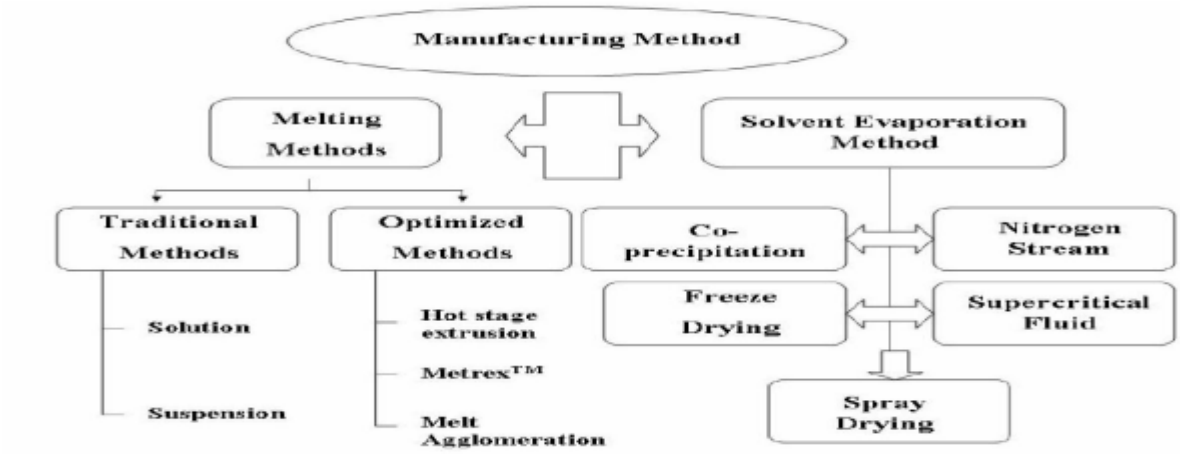


Fig. 4 Methods of preparation of Solid Dispersion

1. **Solvent evaporation method:**

Drug and carrier both are dissolved in organic solvent. After complete dissolution, the solvent is evaporated. The solid mass is ground, sieved and dried.

Ex. Solid dispersion of Ofloxacin with polyethylene glycol was prepared by solvent e vaporation method.

2. **Modified solvent evaporation method:**

Drug is dissolved in organic solvent at its saturation solubility with continued stirring for some time. Polymer is suspended in sufficient amount of water (up to wet mass of polymer). The drug solution is poured at once into polymer suspension. The entire solvent is evaporated. The mass obtained is dried**.**

3. **Melting method:**

Accurately weighed drug and carrier are mixed using glass mortar and pestle. The mixture is heated at or above the melting point of all the components to achieve a homogenous dispersion. It is then cooled to obtain a congealed mass. It is pulverized and sieved.

Ex. Albendazole and urea solid dispersion was prepared this method.

4. **Melt-solvent method:**

Accurately weighed drug is dissolved in organic solvent and the solution is incorporated into the melt of mannitol by pouring into it. It is suddenly cooled. The mass is kept in desiccator for complete drying. The solidified mass is crushed, pulverized and passed through sieve.

5. **Kneading method:**

A mixture of accurately weighed drug and carrier is wetted with solvent and kneaded thoroughly for some time in a glass mortar. The paste formed is dried and sieved.

Ex. furosemide and crospovidone solid dispersion was prepared by this method.

6. **Co-Grinding method:**

Accurately weighed pure drug powder and the carrier are physically mixed for some time using a blender at a specified speed. The mixture is then charged into the chamber of a vibration ball mill. A certain number of steel balls are added. The powder mixture is ground. Then the sample is collected and kept at room temperature in a screw capped glass vial until use.

Ex. chlordiazepoxide and mannitol solid dispersion was prepared by this method.

7. **Co-precipitation method (co-evaporates):**

Accurately weighed carrier is dissolved in water and drug in organic solvent. After complete dissolution, the aqueous solution of carrier is then poured into the organic solution of the drug. The solvents are then heated and evaporated. The dispersion is pulverized with pestle and mortar, sieved and dried.

8. Co-precipitation with supercritical fluid:

Conventional methods for the preparation of solid dispersions include either the fusion or solvent processes, with supercritical fluid processing (SCP) emerging as an alternative solvent- evaporation method for formulating co precipitates of smaller particle size, lower residual organic solvent and better flow ability. A supercritical fluid exists as a single fluid phase above its critical temperature and pressure. Carbon dioxide is currently the most commonly used supercritical fluid because of its low critical temperature of carbon dioxide makes it attractive for processing heat labile pharmaceuticals. In the context of manufacturability, rate of cooling and solvent removal is stringently controlled, resulting in acceptable batch to batch variation.

A precipitation vessel with a nominal capacity of 50ml was loaded with a 7ml solution of pure drug or drug: polymer (carbamazepine: polyethylene glycol) in acetone. The supercritical carbon dioxide was added from the bottom of the chamber and when the liquid phase expanded, the formed particles were retained in the vessel by a suitable filter. During the co-precipitate formation, the pressure was fixed at 70bar and the temperature at 40^{o}C.

9. Spray drying method:

Accurately weighed amount of drug with lipid carrier are dissolved in methanol to obtain a clear solution. This solution is then spray dried using a laboratory scale dryer. The sample is stored over silica gel in a vacuum desiccator.

10. Gel entrapment technique:

Carrier for example hydroxyl propyl methyl cellulose is dissolved in organic solvent (dichloromethane) to form a clear and transparent gel. Then drug for example carbamazepine is dissolved in gel by sonication for few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by glass mortar and sieved**.**

THE UNDERLYING PRINCIPLES FOR IMPROVING THE DISSOLUTION PROPERTIES OF DRUGS BY SOLID DISPERSION TECHNIQUES ARE:

- Reducing particle size.
- Altering the crystalline morphology.
- Intimately mixing the drug with hydrophilic excipients .By altering the bulk drug according to these principles, drug particle surface area is increased, the thermodynamic barrier to dissolution imposed by the crystal lattice is eliminated and the wetting properties of the drug particles are enhanced.

MECHANISMS SUGGESTED BEING RESPONSIBLE FOR THE IMPROVED AQUEOUS SOLUBILITY / DISSOLUTION PROPERTIES OF SOLID DISPERSIONS

INCLUDES:

- Reduction of the particle size of the incorporated drug: In solid dispersions, the particle size of the drugs was reduced, and the wettability and the dispersibility of the drugs were enhanced; therefore, drug dissolution was improved markedly.
- Partial transformation of crystalline drug to the amorphous state.
- Formation of solid solution.
- Formation of complexes.
- Reduction of aggregation and agglomeration.
- Improved wetting of the drug and solubilization of drug by the carrier at the diffusion layer.

EVALUATIONS OF SOLID DISPERSION:

- It is highly acceptable, that often more than one of these phenomena determine the rate and extent of dissolution. Therefore, Bragg-Brentano powder diffractometry, differential scanning calorimetry, infrared spectroscopy, solubility and dissolution experiments are routinely used to study the relationship between dissolution and physicochemical state of solid dispersion.
- Transformation of crystalline drug or semi crystalline polyethylene glycol to the amorphous state and formation of polymorphic drug forms can be detected by Bragg-Brentano powder diffractometry.

- Differential scanning calorimetry offers the possibility to evaluate the crystallinity of both drug and polymer phase and to characterize polymorphic and amorphous phases. Differential scanning calorimetry can be used to study solid dispersion to determine whether the phase is monotectic or eutectic in nature. A monotectic system is one where little or no interaction occurs whereas a eutectic system is one where little or no interaction occurs.
- Infrared spectroscopy reveals crystallographic changes of drug and polymer molecules, such as hydrogen bonds which are indicative of complex formation.
- Equilibrium solubilities of the drug in aqueous polymer solutions of different polymer concentrations reveal the solubilization capacity of the polymer for the drug.
- Micro –Raman spectroscopy with X- Ray Diffraction is used for characterization of the distribution, polymorphism and stability of drug in its solid dispersion in polyethylene glycol**.**

MARKETED PRODUCTS:

Commercial products based on solid solution /dispersion is:

- Gris-PEG, a griseofulvin- PEG fusion method solid dispersion, was manufactured initially by Dorsey / Sandoz and reached the market in the mid- 1970s.Gris-PEG was developed as tablet product, and this led to two USP monographs for griseofulvin tablets. The solid dispersion form is referred to as ultra-micro size griseofulvin tablets USP and offers improved bioavailability and two- thirds reduced dosage compared to griseofulvin tablets USP. The griseofulvin tablets USP are manufactured from micronized drug substance using a conventional tableting approach. Griseofulvin solid dispersion tablets are currently marketed by a number of manufacturers and contain corn starch, lactose, magnesium stearate, PEG, and sodium lauryl sulfate as inactive ingredients.
- Cesamet, a nabilone-PVP solvent method solid dispersion manufactured by Eli Lilly and Co. has been marketed internationally since 1982. Eli Lilly discontinued marketing Cesamet contain PVP and corn starch as inactive ingredients and is presented as a capsule product**.**
- Solid dispersion formulation of Troglitazone (Rezulin) is marketed by Parke-Davis**25**.
- Solid solutions of lopinavir and ritonavir in poly vinyl pyrrolidone-vinyl acetate copolymer successfully enabled a reformulation of "Kaletra" (Abbott Laboratories, Abbott Park, IL). In addition to reducing the dosage burden from six soft gel capsules

to four tablets, tablets made with the solid solutions eliminate the need for refrigeration.

- "Sporanox" (Janssen Pharmaceutical, Titusville, NJ) is a solid dispersion of itraconazole in hypromellose that has been layered onto sugar spheres.
- The most recently approved product is the non-nucleoside reverse transcriptase inhibitor "Intelence" (Tibotec, Yardley, PA) an amorphous, spray-dried solid dispersion of etravirine, hypromellose, and microcrystalline cellulose.

LITERATURE REVIEW

U. D. SHIVHARE *et al.*,[9]developed and evaluated diclofenac sodium gel using water soluble polyacrylamide polymerHigh molecular weights water soluble homopolymer of acrylamide are reported to possess very high viscosity in low concentration, transparency, film forming properties and are useful in formation of gel. The diclofenac sodium gels were prepared by using different concentration of polyacrylamide for topical drug delivery with an objective to increase transparency and spread ability. These preparations were further compared with marketedDiclofenac sodium gel. Spreadability and consistency of polyacrylamide gel containing diclofenac sodium (F9) were 6.5g.cm/sec and 5mm as compared to 5.5g.cm/sec and 10mmrespectively of marketed gel, indicating good spreadability and consistency of the preparedgel (F9). The transparency of prepared batch F9 was good as compared to the marketed gel. The percent drug release was 97.11 and 98.66 from F9 and marketed gel respectively. No irritation was observed by skin irritation test. Stability studies under accelerated condition showed satisfactory results. It can be concluded that polyacrylamide gel containing diclofenac sodium showed good consistency, homogeneity, spreadability and stability and has wider prospect for topical preparations.

M.a.saleem*et al.*,[10]jul-sep.2010formulated and evaluated of meloxicam solid dispersion incorporated topical gels,Solid dispersion complexes of meloxicam were prepared by using cyclodextrins (BCD, HPBCD), PVP and urea by kneading method in different molar and weight ratios. The complexes werecharacterized by DSC and IR, suggested that no chemical interaction between drug and carrier. The solubility,dissolution and permeability of complexes were markedly increased as compared to pure drug. Solidcomplexes were incorporated in 1% carbopol to prepare gels and evaluated for pH, drug content,viscosity, invitro permeability through rat skin. Invitro permeation study reveals that the flux (Jss)and enhancement factor increases with increase in concentration of BCD, HPBCD and decreaseddramatically in case of HPBCD with ratio of 1:2. Similar changes in pattern of permeation wereobserved with urea and PVP complexes .Hence it can be concluded that solid dispersion complexincorporated gel shows highest permeation as compared to plain drug gels.

P.K. LAKSHMI *et al.*,[11]2011 this study aimed to increase the therapeutic effectiveness of ibuprofen by increasing its transdermal permeation, via solid dispersion incorporated in gel. 2- Hydroxy propyl beta cyclodextrins (2-HPβ-CD) and β-cyclodextrin (β-CD) were used as carriers and carbopol 941 was the gelling agent. Eight solid dispersion formulations of

ibuprofen were prepared using different drug: polymer ratios viz. 1:0.5, 1:1, 1:2, and 1:3 for 2-HPβ-CD and β cyclodextrin using the co-evaporation method, and were evaluated for partition coefficient, dissolution studies, and Fourier Transform Infra-Red (FTIR) spectrophotometer. The optimized solid dispersion of ibuprofen was incorporated into gel and was compared with penetration enhancers. The formulations were analyzed to determine their pH, spreadability, viscosity, and in vitro drug release. The absence of extraneous interactions among ingredients was confirmed by FTIR, and differential scanning calorimetry (DSC). The formulation with 1:0.5 SDIB (drug: HPβCD) with a partition coefficient of 1.28 was incorporated in carbopol gel, and produced 98.21% drug release compared to solid dispersion of ibuprofen with menthol (SDIBM5%), which produced 96.5% drug release. In ex vivo studies, SDIB and SDIBM5% formulations gave 94.3% and 92.36% drug release within 24h. The percent inhibitions of the edema formation by the gels were in the range of 18.32% to 67.96%, and the maximum inhibition was shown by the SDIB formulation. Therefore, SDIB formulation incorporated in gel produced better results than other formulations prepared with permeation enhancers. Stability studies conducted for SDIB incorporated gel according to International Conference on Harmonization guidelines showed it to be stable for two months.

Swami N.G.N *et al.*,[12]Formulated and evaluated diclofenac sodium gels using sodium carboxymethyl hydroxypropyl guar and hydroxypropyl methylcellulosein this investigation, Diclofenac sodium gels were formulated employing Sodium carboxymethyl hydroxy propyl guar and Hydroxypropyl methylcellulose as gelling agents. Hydroxypropyl methylcellulose (K4M) was employed at 5 %w/w strength whereas, Sodium carboxymethyl hydroxypropyl guar formed a gel at 2.5 % w/w strength, gels were subjected for various evaluation tests such as pH measurement, assay, stability study, rheological evaluation, and invitro release studies across hairless albino rat skin. Gels formulated using Sodium carboxymethyl hydroxypropyl guar displayed a pH value of 7.48, whereas hydroxypropyl methylcellulose gels revealed a pH value of 7.26. Stability studies revealed good physical stability and assay values did not show much variation from the initial drug content in0 0 both the cases with formulations stored at 25 C, 60% RH and 40 C, 70% RH for six months. Hydroxypropyl methylcellulose at 5% w/w strength revealed shear-thinning property, whereas Sodium carboxymethyl hydroxypropyl guar at 2.5 % w/w strength revealed both pseudo plastic and thixotropic property. The rheological data were fitted into Martin and Co'-worker equation to obtain a linear relationship and from the linear curve fittings, the 'N'- values; the possible flow indices for pseudo plasticity were arrived at. A 'N' value of 4.65 was obtained for Sodium carboxymethyl hydroxypropyl guar gels in contrast to a 'N' value of 1.52 in case of

Hydroxypropyl methylcellulose gels. When subjected to In-vitro release studies across hairless albino rat skin, Sodium carboxymethyl hydroxypropyl guar based gels revealed a % cumulative drug release of 25.66 in contrast to a % cumulative drug release of 20.80 in case of Hydroxypropyl methylcellulose based gels at the end of 6 hours. From the above observations, Sodium carboxymethyl hydroxypropyl guar seems to be a promising pharmaceutical adjuvant in the formulation of Diclofenac sodium gel.

MALAYK.DAS *et al.*,[13]The potential gastrointestinal disorders associated with oral administration of rofecoxib can be avoidedby delivering the drug to the inflammation site at a sustained, concentrated level over an extended period oftime. Hydroxypropyl methylcellulose (HPMC), sodium alginate and Carbopol 940 were used in an attempt todevelop topical gel formulations of rofecoxib. The effects ofpolymer composition on the rate of drug releasefrom the gel formulations were examinedthrough cellulose membrane mounting on a Keshary-Chien diffusioncell. The effects of initial drug concentration and viscosity on the permeation rate of rofecoxib from the gel formulationswere evaluated using rat epidermis at 37 +0.5ºC. The anti-inflammatory activity of the rofecoxib gelformulation was evaluated using the rat hind paw edema model. The gel formulation consisting of 4% w/w sodiumalginate-Carbopol 940 at 3:1 ratio was found to be suitable for topical application based on *in vitro* evaluationand *ex vivo* permeation studies. The drug permeation rate increased with an increase of the initial drug concentrationin gels up to 25 % w/w. An inverse relationship was observed between the *in vitro* drug release rate/*exvivo* permeation rate and viscosity of the gel formulations. The anti-inflammatory activity of 4% w/w sodiumalginate-Carbopol 940 gel containing 25% w/w rofecoxib in the rat hind paw edema model reveals that the drugwas delivered to the inflammation site at a controlled level over a period of 6 h. These results suggest the feasibilityof the topical gel formulation of rofecoxib.

Azmail Khan *et al.*,[14]The present study was investigated the Aceclofenac solid dispersions gel of various compositions were formulated and among these F1; Aceclofenac solid dispersion incorporated gel of HPMC (Hydroxy propyl methyl cellulose) and F2; Aceclofenac solid dispersion incorporated gel of Carbopol 940 subjected for transdermal in vivo efficacy study on rats through abdominal skin. The F1 and F2 were compared with that of control. The F1 found significant increase ($P < 0.05$) in percent inhibition value at 4 h and ($P < 0.01$) at 8 h whereas F2 results obtained significant increase ($P < 0.05$) in percentinhibition value at 8 hours and ($P < 0.01$) at 12 h when compared with control after 1 hour on carrageenan-induced paw edema in rats. The results suggested that solid dispersion

incorporated gels of HPMC are improved transdermal delivery for Aceclofenac than the solid dispersion incorporated gels of Carbopol 940.

Lalit Kumar *et al.*,[15]Nimesulide is a second generation non–steroidal anti–inflammatory agent, which is widely usedin the long term therapy of rheumatoid arthritis, in alleviating pain and inflammation. But its short half-life (only 3–4hrs.), so its causes more fluctuation. After oral administrationNimesulide causes to produces heart burn, nausea, loose motions, pruritus, etc. The present studybased on the preparation of bioadhesive topical gel of Nimesulide, so as to avoid all gastric sideEffects. For the preparation of bioadhesive topical gel natural polymer *angel marmelos* (plantBale) was used. Bioadhesive polymers are the agents which increases the contact between theFormulation and biological membrane, so as to avoid the fluctuation of formulation and behave as a sustained release formulation. In the present study, prepared bioadhesive topical gel was evaluated with the help of different parameters like drug content, spreadability, extrudability, swelling index study, *in–vitro* drug diffusion study, *in-vitro* drug release kinetic study and *ex–Vivo*bio adhesive measurement. On the basis of *in–vitro* drug diffusion study and *ex–vivo*Bioadhesive measurement property of gel, we have concluded that natural polymer *aegelMarmelos*is the best polymer for the preparation of sustained release bioadhesive topical gel.

V.B.Yadav *et al.*,[16]Indomethacin (IM) is one of the most widely used non-steroidal anti-inflammatory active pharmaceutical agents. However, it's limited aqueous solubility and poor flow ability creates bioavailability and formulation related problems. Role of various water-soluble carriers was studied for dissolution enhancement of a poorly soluble model drug, Indomethacin, using solid dispersion approach. Solid dispersions of Indomethacin with lactose monohydrate and different polymers Polyethylene glycol- 6000(PEG), Hydroxy Propyl Methyl Cellulose (HPMC), PolyvinylPyrrolidine (Povidone-30), and Beta Cyclodextrin (BCD) were prepared by kneading method. In the present investigation by keeping the constant amount of lactose monohydrate the effect of different hydrophilic polymers on solubility and dissolution were studied. The prepared solid dispersions were evaluated for content, saturation solubility, and dissolution and flow ability parameters. Powdered solid dispersion with lactose monohydrate and used hydrophilic polymers showed approximately 10-20 fold increases in solubility over the pure drug. The all prepared solid dispersions shows improvement in dissolution profile and flow ability compared to the raw indomethacin. Thus, the bioavailability of this poorly water-soluble drug and their flow ability was greatly enhanced by formulation as solid dispersions with different hydrophilic polymers.

Naresh G *et al.,*.[17] The aim of this study was to prepare and evaluate gels incorporating solid lipid nanoparticles (SLNs) of diclofenac sodium for systemic delivery of the active after topical application. SLNs were prepared using hot homogenization followed by sonication technique and these were incorporated into freshly prepared carbopol gel. Three different gel formulations (DSL1, DSL2 and DSL3) were prepared and characterized for particle size, charge, viscosity, morphology, and drug-lipid compatibility. The gels were evaluated for in vitro drug release, ex vivo permeation studies and in vivo absorption. The gels enriched with SLN sustained the drug release for 24 h both in vitro and in vivo. The results suggest enhancement in systemic delivery of diclofenac sodium with gels incorporating SLNs.

Bazigha K Abdul Rasool *et al.,*.[18]Ibuprofen gel formulations, incorporating various permeation enhancers, were prepared usingChitosan as a gelling agent. The formulations were examined for their in vitro characteristics includingviscosity, pH and drug release as well as in vivo pharmacological activities. Carrageenan-induced ratpaw edema model was used for the evaluation of their analgesic and anti-inflammatory activities. Acommercial ibuprofen gel product (Ibutop®) was used as a reference.The formulations containing 5 % of either menthol or glycerol as permeation enhancers gavedrug release patterns comparable to that of the reference product. Propanol increased the apparentviscosity of the test gels to the same extent as that of the reference. Drug release from the formulationsfitted best to the Higuchi model. A significant in vivo analgesic effect was produced by the testformulations containing 5 % menthol and 20 % propylene glycol and the effect was superior to thatobtained with the reference product. However, no significant anti-inflammatory activity was exerted byany of the test gel formulations ($p > 0.05$).Ibuprofen gel preparations containing 5 % menthol and 20 % propylene glycol, respectively, exhibited pronounced analgesic activity and could be further developed for topical andsystemic delivery of ibuprofen

Sanju Dhawan *et al.,*[19]The treatment for chronic anal fissure (CAF) has undergone a transformation inrecent years from surgical to medical. Both the approaches share the commongoal of reducing the spasm of anal sphincter. Though surgical treatment has ahigh success rate but it can permanently impair fecal continence in largenumber of patients. Smooth muscle relaxation seems to be a novel way bywhich more than 60% of the patients can be cured with the topical use of theagents. In the present investigation, diltiazem hydrochloride gels were preparedusing FDA recommended polymers [hydroxypropylmethyl cellulose (HPMC),methylcellulose (MC) and polyethylene oxide (PEO grade 301 and 303)] fortopical application in CAF. Increasing the concentration of the polymersignificantly

increased the consistency of the gels. All the formulations exhibited pseudoplastic flows with no thixotropic. The values of flow index (n) were found tobe less than one for all the gels confirming the shear thinning behavior of allthe gels. HPMC and MC gels were found to be stable at accelerated stabilityconditions while the bio adhesion of PEO gels was highest. Even after exposureto heat and humidity, no significant change was observed in the contentuniformity, pH, clarity, texture profile analysis and rheological properties of theHPMC and MC gels. The rheograms and various power law equationparameters of these gels were found comparable at various time points in theaccelerated stability study. However, PEO gels failed in accelerated stability studies at one month sample. When four selected gel formulations (HPMCL4,MCL3, P1BL3 and P3BL3.5) were applied topically by six patients each, Gastrointestinal Quality of Life Index (GIQLI) score of each patient wasimproved at the end of 8 weeks. No adverse effects were reported by any of thepatients. Hence 2% DTZ gel was found to be effective in the treatment of analfissures.

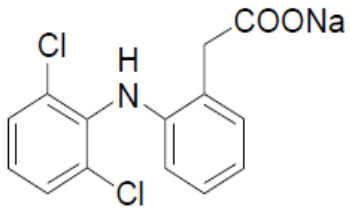
M Najmuddin *et al.*,[20]The Goal of the present investigation was to design and evaluate gels for topical delivery of water insoluble antifungal agent Ketoconazole with an aim to increase its penetration through skin and thereby its flux. Ketoconazole is a broad spectrum imidazole derivative useful in the treatment of superficial and systemic fungalinfections. The solubility of Ketoconazole is increased by complications with ß-cyclodextrin were prepared bysolvent evaporation technique with 1:1 and then incorporated into gels. The complex was characterized byinfrared spectroscopy. There was no interaction between drug and carrier. Gels have gained more and moreimportance because the gel-bases formulations are better percutaneous absorbed than creams and ointmentbases. Therefore, Ketoconazole gel formulations were made with different polymers like carbopol 940, hydroxyl propyl methyl cellulose, methyl cellulose, and sodium carboxymethylcellulose, containing various permeationenhancers namely sodium lauryl sulphate (0.5-1.0%) and dimethyl sulfoxide (5-20%) in different proportions. Theformulated gels were evaluated for various physicochemical parameters like, drug content, pH, viscosity, spreadability, extrudability, in-vitro drug release. The in-vitro drug release study were carried out using pH 7.4phosphate buffer, All the formulated topical preparations showed pH in the range of 6.5 to 7.4, and also showedgood spreadability, extrudability. The carbopol 940 with 15% of dimethyl sulfoxide (KCD3) showed best in-vitrodrug release 98.07% at the end of 6 hrs.

B.Radha Madhavi *et al.*,[21]Zafirlukast is an oral leukotriene receptor antagonist used in the treatment of asthma. Poor solubility in biological fluids is the major problem with this drug which results in poor bioavailability after an oral administration. The rate of absorption and

the extent of bioavailability for such a poor soluble drugs were controlled by rate of dissolution in gastrointestinal fluids. Hence an attempt has been made to enhance the solubility of the drug by preparing its complex with β-cyclodextrin. FT-IR studies were performed. Drug complexing agent interactions were investigated using differential scanning calorimetry (DSC). The study clearly shows that the dissolution rate of zafirlukast may be enhanced to a great extent by solid dispersion technique using kneading method. This is due to the reason that the cyclodextrins increased the aqueous solubility of poorly soluble drug by forming inclusion complexes with heir a polar molecules and functional groups.

DRUG PROFILE [5, 6, 7]

Diclofenac Sodium:



Molecular Formula: $C_{14}H_{11}C_{12}NO_2$

Molecular Weight: 318.10

Chemical Name: 2-[(2, 6-dichlorophenyl) amino] benzene acetic acid, mono potassium salt

Solubility: Freely soluble in methanol; soluble in ethanol (95 per cent); sparingly soluble in water and in glacial acetic acid; practically insoluble in ether, in chloroform and in toluene.

Indications:

- Orally for symptomatic treatment of osteoarthritis, ankylosing spondylitis, primary dysmenorrhea, acute gouty arthritis and for relief of pain, including postoperative (e.g., orthopedic, gynecologic, oral) pain, in adults.
- In combination with misoprostol for the symptomatic treatment of osteoarthritis and rheumatoid arthritis in patients at high risk for developing NSAIDS-induced gastric or duodenal ulcers and in patients at high risk for developing complications from these ulcers.
- Topically (as gel) for the symptomatic treatment of osteoarthritis related joint pain. Used for joints amenable to topical therapy (e.g., hands, knees), has not been evaluated on joints of the spine, hip, or shoulders.
- Orally or topically for symptomatic treatment of infusion-related superficial thrombophlebitis.

Dosage and Administration:

Oral Administration

➢ Diclofenac sodium delayed-release (enteric-coated) and extended-release tablets are not recommended for relief of acute pain or primary dysmenorrhea1 because of slow onset of action.

Topical Administration

Diclofenac Sodium 1% Gel

➢ Apply gel 4 times daily to the affected joint. Use the dosing card from the manufacturer to measure the appropriate dose. Apply the gel within the oblong area of the dosing card up to the appropriate (2- or 4-g of gel) line; then use the dosing card to apply the gel. Gently massage the gel into the skin; ensure gel is applied to the entire affected joint (e.g., foot [including sole, top of foot, and toes], knee, ankle, hand [including palm, back of hand, and fingers], elbow, and wrist).

Diclofenac Epolamine Transdermal System

➢ Apply transdermal system to the most painful area twice daily. Apply to intact skin; do not apply to damaged skin (e.g., wounds, burns, infected areas of skin, areas affected with eczema or exudative dermatitis).

Dosage: Oral

May change dosage to 50 or 75 mg twice daily in patients who do not tolerate usual dosage; however, these dosages may be less effective in preventing NSAIA-induced ulcers.

S.No	Preparation	Dosage
1	Diclofenac potassium conventional tablets	100–150 mg daily, given as 50 mg 2 or 3 times daily
2	Diclofenac sodium delayed-release tablets	100–150 mg daily, given as 50 mg 2 or 3 times daily or 75 mg twice daily
3	Diclofenac sodium extended-release tablets	100 mg once daily
4	Diclofenac sodium (in fixed combination with misoprostol)	50 mg 3 times daily

Topical (gel)

For lower extremity (i.e., knees, ankles, feet) joint pain, massage 4 g of diclofenac sodium 1% gel into the affected joint 4 times daily.

For upper extremity (i.e., elbows, wrists, hands) joint pain, massage 2 g of diclofenac sodium 1% gel into the affected joint 4 times daily.

If multiple joints are treated, total daily dose applied to all joints should be ≤32 g of gel daily.

Rheumatoid Arthritis

Oral

May change dosage to 50 or 75 mg twice daily in patients who do not tolerate usual dosage; however, these dosages may be less effective in preventing NSAIA-induced ulcers.

S.No	Preparation	Dosage
1	Diclofenac potassium conventional tablets	150–200 mg daily, given as 50 mg 3 or 4 times daily
2	Diclofenac sodium delayed-release tablets	150–200 mg daily, given as 50 mg 3 or 4 times daily or 75 mg twice daily
3	Diclofenac sodium extended-release tablets	100 mg once daily; may increase to 100 mg twice daily
4	Diclofenac sodium (in fixed combination with misoprostol)	50 mg 3 or 4 times daily

Warnings/Precautions

Consider potential benefits and risks of diclofenac therapy as well as alternative therapies before initiating therapy with the drug.

Cardiovascular Effects

Selective COX-2 inhibitors have been associated with increased risk of cardiovascular events (e.g., MI, stroke) in certain situations. Several prototypical NSAIAs also have been associated with increased risk of cardiovascular events. Current evidence suggests that use of diclofenac is associated with increased cardiovascular risk.

GI Effects

Serious GI toxicity (e.g., bleeding, ulceration, perforation) can occur with or without warning symptoms; increased risk in those with a history of GI bleeding or ulceration, geriatric patients, smokers, those with alcohol dependence, and those in poor general health.

Renal Effects

Direct renal injury, including renal papillary necrosis, reported in patients receiving long-term NSAIA therapy.

Hypersensitivity Reactions

a) Anaphylactic reactions (e.g., anaphylaxis, angioedema) reported.

b) Immediate medical intervention and discontinuance for anaphylaxis.

c) Avoid in patients with aspirin triad (aspirin sensitivity, asthma, nasal polyps); caution in patients with asthma.

Dermatologic Reactions

Serious skin reactions (e.g., exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis) reported; can occur without warning. Discontinue at first appearance of rash or any other sign of hypersensitivity (e.g., blisters, fever, and pruritus).

General Precautions

Do not use multiple diclofenac-containing preparations concomitantly. Concomitant use of diclofenac sodium 1% gel and oral NSAIAs may increase risk of adverse effects.

Observe the usual cautions, precautions, and contraindications associated with misoprostol therapy when diclofenac is used in fixed combination with misoprostol.

Hepatic Effects

Severe, sometimes fatal, reactions including jaundice, fulminant hepatitis, liver necrosis, and hepatic failure reported rarely with diclofenac.

Other Precautions

Not a substitute for corticosteroid therapy; not effective in the management of adrenal insufficiency.

Obtain CBC and chemistry profile periodically during long-term use.

Specific Populations

Pregnancy

Category C. Avoid use in third trimester because of possible premature closure of the ductus arteriosus.

Category X (in fixed combination with misoprostol).284 Misoprostol exhibits abortifacient activity and can cause serious fetal harm.

Lactation

Distributed into milk; 3 discontinue nursing or the drug.

Pediatric Use

Safety and efficacy not established in children.

Good results with oral diclofenac obtained in a limited number of children 3–16 years of age for the management of juvenile rheumatoid arthritis.

Geriatric Use

Oral diclofenac: Caution advised. Fatal adverse GI effects reported more frequently in geriatric patients than younger adults.

Other Precautions

Not a substitute for corticosteroid therapy; not effective in the management of adrenal insufficiency. It may mask certain signs of infection.

Obtain CBC and chemistry profile periodically during long-term use. Specific Populations

Interactions for Diclofenac Sodium

Protein-bound Drugs

Only minimally displaces other highly protein-bound drugs from binding sites; however, may be displaced from binding sites by other highly protein-bound drugs.51 52 59 61

Specific Drugs

S.No	Drug	Interaction	Comments
1	ACE inhibitors	Reduced BP response to ACE inhibitor. Possible deterioration of renal function in individuals with renal impairment.	Monitor BP.
2	Angiotensin II receptor antagonists	Reduced BP response to angiotensin II receptor antagonist. Possible deterioration of renal function in individuals with renal impairment.	
3	Antacids	Delayed diclofenac absorption.	

	(magnesium- or aluminum-containing)		
4	Anticoagulants (warfarin)	Possible bleeding complications.	Caution advised.
5	Aspirin	Decreased peak plasma concentration and AUC of diclofenac; limited data indicate that diclofenac does not inhibit antiplatelet effect of aspirin. Increased risk of GI ulceration and other complications. No consistent evidence that low-dose aspirin mitigates the increased risk of serious cardiovascular events associated with NSAIDS.	Manufacturer states that concomitant use not recommended.
6	Cyclosporine	Possible increase in nephrotoxic effects of cyclosporine.	Caution advised.
7	Diuretics (furosemide, thiazides)	Reduced natriuretic effects.	Monitor for diuretic efficacy and renal failure.
8	Lithium	Increased plasma lithium concentrations.	Monitor for lithium toxicity.
9	Methotrexate	Severe, sometimes fatal toxicity associated with increased plasma methotrexate concentrations.	Caution advised.
10	Quinolones (ciprofloxacin)	Possible increased risk of seizures.	

Pharmacokinetics

Absorption

Bioavailability

Well absorbed following oral administration. It undergoes first-pass metabolism; only 50–60% of a dose reaches systemic circulation as unchanged drug.

Peak plasma concentration usually attained within about 1 hour (diclofenac potassium conventional tablets), 2 hours (diclofenac sodium delayed-release tablets), or 5.25 hours (diclofenac sodium extended-release tablets). Absorbed into systemic circulation following topical administration as gel or transdermal system; plasma concentrations generally very low compared with oral administration. Following application of a single diclofenac epolamine transdermal system to intact skin on the upper arm, peak plasma concentrations occur in 10–20 hours.

Following topical application of diclofenac sodium 1% gel, peak plasma concentrations occur in about 10–14 hours.

Moderate exercise does not alter systemic absorption of topically applied diclofenac (transdermal system or 1% gel).

Application of a heat patch for 15 minutes before application of the 1% gel did not affect systemic absorption. Not established whether application of heat following gel application affects systemic absorption.

Onset

Single 50- or 100-mg doses of diclofenac potassium provide pain relief within 30 minutes.

Duration

Pain relief lasts up to 8 hours following administration of single 50- or 100-mg doses of diclofenac potassium.

Food

The food delays the time to reach peak plasma concentration but does not affect extent of absorption following administration as conventional, delayed-release, or extended-release tablets.1 302 303

Distribution

Extent widely distributed in animals.

Following oral administration, concentrations in synovial fluid may exceed those in plasma. Plasma Protsein Binding >99%.

Elimination

Metabolism

It metabolized in the liver via hydroxylation and conjugation. Some metabolites may exhibit anti-inflammatory activity.

Elimination Route

It excreted in urine (65%) and in feces via biliary elimination (35%) as metabolites.

Half-life

Oral preparations: 1–2 hours.

Diclofenac epolamine transdermal system: Approximately 12 hours.

Special Populations

In geriatric patients, the pharmacokinetic profile similar to that of younger adults.

In patients with renal impairment, plasma clearance not substantially altered,1, 3, 208, 302, 303 although clearance of metabolites may be decreased.

POLYMER PROFILE [8]

β – CYCLODEXTRIN

1. Nonproprietary Names:

BP: Betadex

PhEur: Betadexum

USPNF: Betadex

2. Synonyms

β-cycloamylose; β-dextrin; Cavamax W7 Pharma; cycloheptaamylose; cycloheptaglucan; cyclomaltoheptose;Kleptose.

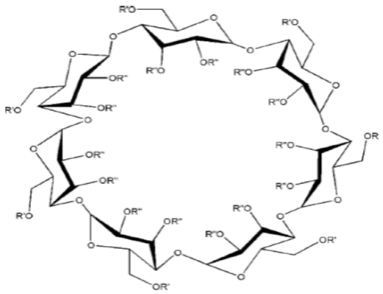
3. Chemical Name and CAS Registry Number

β-Cyclodextrin [7585-39-9]

4. Empirical Formula and Molecular Weight

C42H70O35 - 1135

5. **Structural formula**



6. Functional Category

Solubilizing agent; stabilizing agent.

7. Description

Cyclodextrins are cyclic oligosaccharides containing at least six D-(β)-glucopyranose units attached by a (14) glycoside bonds. The three natural cyclodextrins, a, b, and g, differ in their ring size and solubility. They contain 6, 7, or 8 glucose units, respectively.

Cyclodextrins occur as white, practically odorless, fine crystalline powders, having a slightly sweet taste. Some cyclodextrin derivatives occur as amorphous powders.

8. Typical Properties

Compressibility: 21.0–44.0% for b-cyclodextrin

Density (bulk):0.523 g/cm^3

Density (tapped):0.754 g/cm^3

Melting point: 255–2658C

Moisture content: b-cyclodextrin: 13.0–15.0% w/w;

Particle size distribution: 7.0–45.0 mm

Solubility: b-cyclodextrin: soluble 1 in 200 parts of propylene glycol, 1 in 50 of water at 20^0 C, 1 in 20 at 508C; practically insoluble in acetone, ethanol (95%), and methylene chloride. g-cyclodextrin: soluble 1 in 4.4 parts of water at 20^0C, 1 in 2 at 45^0C.

Specific rotation [a] D25 +162.0

Surface tension (at 258C):71mN/m (71 dynes/cm)

9. Stability and Storage Conditions

β -Cyclodextrin and other cyclodextrins are stable in the solid state if protected from high humidity.

Cyclodextrins should be stored in a tightly sealed container, in a cool, dry place.

10. Applications in Pharmaceutical Formulation or Technology

Cyclodextrin are 'bucket like' or 'cone like' toroid molecules, with a rigid structure and a central cavity, the size of which varies according to the cyclodextrin type. The internal surface of the cavity is hydrophobic and the outside of the torus is hydrophilic; this is due to the arrangement of hydroxyl groups within the molecule. This arrangement permits the cyclodextrin to accommodate a guest molecule within the cavity, forming an inclusion complex.

Cyclodextrins may be used to form inclusion complexes with a variety of drug molecules, resulting primarily in improvements to dissolution and bioavailability owing to enhanced solubility and improved chemical and physical Stability.

Cyclodextrin inclusion complexes have also been used to mask the unpleasant taste of active materials and to convert a liquid substance into a solid material.

B-Cyclodextrin is considered to be nontoxic when administered orally, and is primarily used in tablet and capsule formulations.

In parenteral formulations, cyclodextrins have been used to produce stable and soluble preparations of drugs that would otherwise have been formulated using a non-aqueous solvent.

In eye drop formulations, cyclodextrins form water-soluble complexes with lipophilic drugs such as corticosteroids. They have been shown to increase the water solubility of the drug;

to enhance drug absorption into the eye; to improve aqueous stability; and to reduce local irritation.

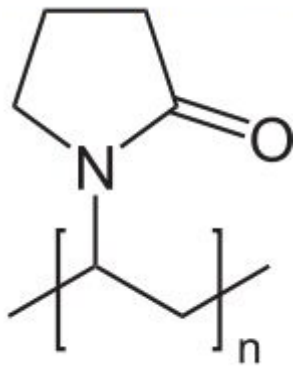
Cyclodextrins have also been used in the formulation of solutions, (9, 10) suppositories, and cosmetics.

11. Safety

When administered parenteral, β-cyclodextrin is not metabolized but accumulates in the kidneys as insoluble cholesterol complexes, resulting in severe nephrotoxicity.

Cyclodextrin administered orally is metabolized by micro flora in the colon, forming the metabolites maltodextrin, maltose, and glucose; which are themselves further metabolized before being finally excreted as carbon dioxide and water.

POLYVINYLPYRROLIDONE



PVP is soluble in water and other polar solvents. When dry it is a light flaky powder, which readily absorbs up to 40% of its weight in atmospheric water. In solution, it has excellent wetting properties and readily forms films. This makes it good as a coating or an additive to coatings. PVP is a branched polymer, that is it structure is more complicated than linear polymer but it too is in a two-dimensional plane. The structure of a polymer greatly depends on its integrity and strength, formed through cross-links and bonds. Firstly, composition of polymers takes place through polymerization of mers, many simple molecules that are repeating structural units called monomers. A single polymer molecule may consist of hundreds to a million monomers and may have a linear, branched, or network structure. Covalent bonds hold the atoms in the polymer molecules together and secondary bonds then hold groups of polymer chains together to form the polymeric material. Copolymers are polymers composed of two or more different types of monomers.

Molecular formula $(C_6H_9NO)_n$

Molar mass 2.500 - 2.5000.000 $g \cdot mol^{-}$

Appearance white to light yellow, hygroscopic, amorphous powder

Density 1.2 g/cm^3

Melting point 150 - 180 °C (glass temperature)

Technical

PVP is also used in many technical applications:

- as an adhesive in glue stick and hot-melt adhesives
- as a special additive for batteries, ceramics, fiberglass, inks, inkjet paper and in the chemical mechanical planarization process
- as an emulsifier and disintegrant for solution polymerization
- as a photoresist for cathode ray tubes (CRT)
- used in aqueous metal quenching
- for production of membranes, such as dialysis and water purification filters
- as a binder and complexation agent in agro applications such as crop protection, seed treatment and coating
- as a thickening agent in tooth whitening gels[7]
- as an aid for increasing the solubility of drugs in liquid and semi-liquid dosage forms (syrups, soft gelatin capsules) and as an inhibitor of recrystallization
- as an additive to Doro's RNA extraction buffer
- as a liquid-phase dispersion enhancing agent in DOSY NMR

Medical

The polymer PVP was used as a blood plasma expander for trauma victims after the 1950's. It is used as a binder in many pharmaceutical tablets;[3] it simply passes through the body when taken orally. However, autopsies have found that crospovidone does contribute to pulmonary vascular injury in substance abusers who have injected pharmaceutical tablets intended for oral consumption.[4] The long-term effects of crospovidone within the lung are unknown. PVP added to iodine forms a complex called povidone-iodine that possesses disinfectant properties.[5] This complex is used in various products like solutions, ointment, pessaries, liquid soaps and surgical scrubs. It is known under the trade name Betadine.

It is used in pleurodesis (fusion of the pleura because of incessant pleural effusions). For this purpose, povidone iodine is equally effective and safe as talc, and may be preferred because of easy availability and low cost.[6]

Safety

The U.S. Food and Drug Administration (FDA) has approved this chemical for many uses,[13] and it is generally considered safe. However, there have been documented cases of allergic reactions to PVP/povidone, particularly regarding subcutaneous (applied under the skin) use and situations where the PVP has come in contact with autologous serum (internal blood

fluids) and mucous membranes. For example, a boy having an anaphylactic response after application of PVP-Iodine for treatment of impetigo was found to be allergic to the PVP component of the solution.[14] A woman, who had previously experienced urticaria (hives) from various hair products, later found to contain PVP, had an anaphylactic response after povidone-iodine solution was applied internally. She was found to be allergic to PVP.[15] In another case, a man experiencing anaphylaxis after taking acetaminophen tablets orally was found to be allergic to PVP.[16]

Povidone is commonly used in conjunction with other chemicals. Some of these, such as iodine, are blamed for allergic responses, although testing results in some patients show no signs of allergy to the suspect chemical. Allergies attributed to these other chemicals may possibly be caused by the PVP instead.

OBJECTIVE AND PLAN OF WORK

Objective of the research work:

Diclofenac is a non-steroidal anti-inflammatory agent (NSAID) with antipyretic and analgesic actions. The anti-inflammatory effects of diclofenac are believed to be due to inhibition of leukocyte migration and the enzyme cyclooxygenase (COX-1 and COX-2), leading to the peripheral inhibition of prostaglandin synthesis. As prostaglandins sensitize pain receptors, inhibition of their synthesis is responsible for the analgesic effects of diclofenac. Antipyretic effects may be due to action on the hypothalamus, resulting in peripheral dilation, increased cutaneous blood flow, and subsequent heat dissipation. The drug shows poor aqueous solubility, low permeability and low bioavailability. Thus development of dosage forms that increases the solubility and dissolution rate will improve the bioavailability of drug.

The rational of present research work is to develop and characterize Solid dispersion incorporated gel of Diclofenac. Diclofenac solid dispersion was prepared by using PVP and β cyclodextrin to increase the solubility, dissolution rate and to improve bioavailability and therapeutic efficacy.

In the present research work an attempt has been made to formulate solid dispersion by kneading and solvent evaporation method using PVP and β cyclodextrin, in different ratio are prepared solid dispersions is incorporated in to Carbopol 934 and Hpmc gel and evaluated for various characterization studies.

PLAN OF WORK

The research work was carried out to formulate, evaluate and compare solid dispersion incorporated solid dispersion gel of PVP and β cyclodextrin in various proportions using carbopol as gelling agent. The following experimental protocol was therefore designed to allow a systemic approach to the study.

- **Procurement of drug and raw materials.**
  - Preparation of standard curve.
  - Preparation of Solid dispersion.
  - Evaluation of Solid dispersion.
  - Saturation solubility.
  - Drug content determination.
  - *In-vitro* drug release studies.
- **Preparation of solid dispersion gel**.
  - Determination of Gel pH.
  - Spread ability test
  - Viscosity.
  - Cloth staining test.
  - *In-vitro* drug release studies
  - *Skin irritation study*
  - *Anti-inflammatory study*
  - Stability studies.

MATERIALS AND INSTRUMENTS

MATERIALS USED:

The following materials that were either AR/LR grade or best possible grade available used for the formulations of solid dispersion gel.

Table No. 01: Materials used for the Research work

S. No	Name	Company Name
1	Diclofenac sodium	Nice chemicals pvt ltd
2	PVP	S.D.fine chemicals ltd
3	β – cyclodextrin	S.D.fine chemicals ltd
4	Carbopol	HI media laboratories
5	TEA	G.S.K Pharmaceuticals
6	Glycerol	Loba chemicals pvt ltd
7	Methyl paraben	HI media laboratories
8	Hpmc	Loba chemicals pvt ltd

Table No. 02: Instruments used for the research work

S. No	Instrument Name	Company Name
1	Electronic digital balance	Shimadzu, Japan.
2	Magnetic stirrer	Genuine Equipment Manufactures, Coimbatore
3	Brook field viscometer	Brook field engineering labs, USA
4	FT-IR	Shimadzu, Japan
5	Dissolution test apparatus	Electro lab, Mumbai, India
6	Double beam UV/VIS Spectrophotometer	ELICO, Mumbai, India

PREFORMULATION STUDIES:

Preformulation study is the first step in the development of dosage forms of a drug substance. It is the study of physical and chemical properties of drug particles alone and combined with different excipients. The study is useful to find out any interaction between drug and excipients and also useful in developing stable and bioavailable dosage forms. The drug samples obtained were examined for its appearance and color and results are recorded.

Appearance of drug:

The drug samples obtained were examined for its appearance and color and results are recorded.

UV Spectroscopy:

Preparation of standard solution

For spectrophotometric method, the standard sample was prepared as follow. Diclofenac sodium standard 50 mg was taken and made the volume 100 ml with 0.01N NaOH. Sonicated for 10 minutes, filtered the solution and took 2 ml of filtered solution and made the volume 100 ml with 0.01 N NaOH. For the spectrophotometric method 2, in the above method for standard preparation, 0.01N NaOH Was replaced with methanol.

FTIR spectroscopy:

The interaction between drug sample used for the formulation and different excipients were studied using FTIR. The FTIR spectrum of pure Diclofenac, polyvinyl pyrrolidone, β-cyclodextrin physical mixture of drug and PVP, physical mixture of drug and β-cyclodextrin were analyzed for compatibility studies.

Preparation of standard curve of diclofenac with 0.1N HCl (pH 1.2):

100 mg of Diclofenac was accurately weighed and dissolved in a small portion of 0.1N HCl in a 100 ml volumetric flask and volume was made to 100 ml. This was primary stock solution contained 1000 µg/ml. From this primary stock solution 10 ml was pipette out and transferred to 100 ml volumetric flask and volume was made up to 100 ml with 0.1 N HCl which contained the concentration of 100 µg/ml. From the second solution 10 ml was pipetted out and diluted to 100ml with 0.1 N HCl. From third stock solution aliquots equivalent to 2-10 µg/ml (2, 4, 6, 8 and 10ml) were pipette out into a series of 10 ml volumetric flask and volume was made up to 10 ml with 0.1 N HCl. The absorbance of this solution is measured at 254 nm using UV-Visible spectrophotometer. The calibration curve was plotted by taking concentration (µg/ml) on X-axis and absorbance on Y- axis.

Preparing diclofenac Solid Dispersion

Initial compatibility studies between Diclofenac and carriers were carried out using Fourier Transform Infra Red (FTIR) spectrophotometer, and compatible excipients were used for final formulations. 1%diclofenac was used for the study. A physical mixture of Diclofenac was prepared by using β cyclodextrin, polyvinyl pyrrolidine carriers in 1:1, 1:2, 1:3 and 1: 1, 1:3, 1:5 ratios respectively. Solid Dispersions (SDs) of diclofenac were prepared using the solvent evaporation, and co-evaporation methods. SD through solvent evaporation was prepared by dissolving the drug and carrier in methanol with 15 minutes of stirring, and then placed in desiccators for 4 days. The resultant solid dispersion was passed through a #120 sieve.

SD through solvent-evaporation was prepared by dissolving the drug in methanol, and the carrier in aqueous media. Subsequently, the organic drug solution was slowly added to the aqueous carrier solution followed by stirring at 300 rpm, using a magnetic stirrer at 37ºC for 24 hrs. The resultant solid dispersion was passed through a #120 sieve.

Table: Different batches of diclofenac Solid dispersion formulation

S. No	**Ingredients**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
1	Diclofenac sodium (%w/w), g	1	1	1	1	1	1
2	Polyvinyl pyrrolidone (%w/w), mg	-	-	-	1:1	1:2	1:3
3	β – Cyclodextrin	1:1	1:3	1:5	-	-	-
4	Water : methanol (1:1)	Qs	Qs	Qs	-	-	-
5	Methanol	-	-	-	10ml	10ml	10ml

Production yield and content determination:

Prepared solid dispersions were weighed after drying, and process yield was calculated. The diclofenac sodium content was determined by UV/Vis spectrophotometer assay method at a wavelength of 283 nm. Prepared solid dispersions (300mg) were powdered, from which powder equivalent to 50 mg diclofenac was weighed and extracted

using three portions of 20mL Phosphate buffer pH 7.2. Each portion was filtered through a Whitman's filter paper and volume was adjusted to 100 ml. After sufficient dilution with Phosphate buffer pH 7.2, samples were analyzed spectrophotometrically at 283 nm. Diclofenac sodium content was calculated by comparison with standard solution.

SATURATION SOLUBILITY STUDIES:

Saturation solubility measurements were assayed through ultraviolet absorbance determination at 283 nm using Shimadzu UV-Visible spectrophotometer. The saturation solubility studies were carried out for both the unprocessed pure drug and different batches of solid dispersion. 10 mg of unprocessed pure drug and diclofenac solid dispersion equivalent to 10 mg of diclofenac were weighed and separately introduced into 25 ml stoppered conical flask containing 10 ml distilled water. The flasks were sealed and placed in rotary shaker for 24 hrs at 37°C and equilibrated for 2 days. The samples were collected after the specified time interval, and it is filtered and analyzed. The diluted samples were analyzed using UV spectrophotometer at 283 nm, the results were analyzed in triplicate and standard deviations are reported.

PERMEATION STUDIES:

Permeation study is carried out for both unprocessed drug and different batches of solid dispersion using cellulose nitrate membrane. The membrane is attached to the diffusion cell and then it is dipped in a beaker containing phosphate buffer pH 7.4. The pure drug sample and equivalent quantity of lyophilized suspension are weighed and placed in the different diffusion cells containing the specified quantity of buffer. The samples were withdrawn at specified time intervals for 1 hr and replaced with fresh buffer solution. Finally the samples are analyzed using UV spectrophotometer at 283 nm.

***IN-VITRO* DRUG RELEASE STUDIES:**

Experimental conditions

Apparatus: USP (type I) dissolution rate test apparatus.

Model : Electro labs, Mumbai.

Dissolution media: Distilled water.

Stirring speed: 50rpm

Temperature: 37±0.5°C

Sampling intervals: 5, 10, 15, 30, 45 and 60.

Sampling intervals: 5ml

Weight of sample: Equivalent to 100mg.

Wavelength: 283nm

Preparing gel formulations

Carbopol:

The formulae used to prepare the diclofenac gel formulations. The formulations were prepared by soaking carbopol 934 in water for 24 hrs. The solid dispersion containing 1% drug was dissolved in ethanol and this solution was added to the above gel with continuous stirring Triethanolamine was also added subsequently. The prepared formulations were filled in lacquered aluminum collapsible tubes and stored in cool place.

S. No	Ingredients	Use	Qty of Gel base
1	Carbopol 934	Gel base	1 g
2	Distilled water	Vehicle	20 ml
3	Triethanolamine	pH adjustment	0.25 ml

Preparation of HPMC:

Weighed quantities of Hpmc socked in 75ml of water for 24hrs and then add glycerin the solid dispersion containing 1% drug was dissolved in ethanol and this dry solution was added to above gel with continouns stirring.

S.no	Ingredients	Use	Qty of gel base
1	Hpmc	Gel base	1gm
2	Distilled water	Vehicle	20ml
3	Triethanolamine	pH adjustment	0.25ml

EVALUATION OF DICLOFENAC SODIUM GELS

The Diclofenac sodium gels were subjected for extensive rheological evaluation, drug content estimation, pH measurement, stability study.

Visual appearance

The prepared gels were visually inspected for clarity, color and transparency. The prepared gels were also evaluated for the presence of any particles. Smears of gels were prepared on glass slide and observed under the microscope for the presence of any particle or grittiness.

Rheological studies: In Brookfield viscometer, analog model was used for the studies. First, the spindle was dipped into the gel till the notch on the spindle touched the gel surface.100 g each of gel I and gel II was used in the study. The spindle no.64 was selected based on the viscosity of the gel for both the formulations. This spindle was rotated at 0.5 rpm, and dial reading was recorded until 2 consecutive similar readings were obtained. Similarly dial readings were recorded at 1.0, 2.5, 5.0, 10.0, 20.0, and 50.0 and up to 100 rpm. As soon the sample was sheared at the highest rate, another set of dial readings were recorded by reducing the spindle rotation in the decreasing order to the pool the data on the down curve. Rheograms were constructed by plotting the dial readings on the X-axis and rpm values along the Y-axis. Rheological data were pooled for

(i) Polymer dispersion in preservative solution (ii) dispersion of polymer and drug in preservative solution

(iii) Dispersion of polymer and humectants in preservative solution (iv) all together.

Drug content estimation: An accurately weighed 1 gm quantity of the gel was transferred into a 250ml stoppered volumetric flask and shaken vigorously with 2x25 ml quantity of methanol to extract the drug. The contents were filtered into a 50 ml volumetric flask and volume was made up to the mark with methanol. From the above solution, 0.5 ml was pipette in to a 25 ml volumetric flask and volume was made up to 25 ml with methanol.

Finally, the UV absorbance of the resulting solution was measured at 283 nm against the blank solution of methanol. Diclofenac Sodium obeys Lambert's beers law in the concentration range of 2 -16 μg/ml. A calibration curve was constructed which revealed a slope value of 0.0421 and intercept value of 0.0025. These values were used in finding the drug content in the formulation after extracting the drug in suitable dilutions and recording the absorbance at 283 nm.

pH measurement: The pH measurement was carried out by using a calibrated digital type pH meter by dipping the glass electrode and the reference electrode completely into the gel system so as to cover the electrodes.

Cloth staining

This study was undertaken to assess the fabric staining property of the gels. Fabrics of different fiber blends ranging from 100% cotton to 100% polyester were procured and stained with 0.5 gm gels of Diclofenac and observed for staining after washing. All sample clothes were cut into 6 sq inch squares and DTZ gels (0.5 g) were applied in the center of each cloth. The stains were air-dried and the clothes left at 50 °C for 48 h to accelerate the drying. After leaving them at room temperature for 5 more days (total 1 week), they were washed with standard detergent Surf® and water. After air-drying the staining on the sample clothes was recorded.

Swelling Index Study of Topical Gel:

Swelling of the polymer depends on the concentration of the polymer, ionic strength and the presence of water. To determine the swelling index of prepared topical gel, 1 gm of gel was taken on porous aluminum foil and then placed separately in a 50 ml beaker containing 10 ml 0.1N NaOH. Then samples were removed from beakers at different time intervals and put it on Dry place for some time after it reweighed. Swelling index was calculated as follows:

$$\text{Swelling Index (SW) \%} = [(Wt - Wo) / Wo] \times 100.$$

Where, (SW) % = Equilibrium percent swelling, Wt = Weight of swollen gel after time t, Wo = Original weight of gel at zero time.

In-vitro release studies: The hairless albino rat skin obtained from the discards of the animal sacrifice at the pharmacology department in the college was used. The 18 skin was soaked in 0.32 N ammonium hydroxide solution for 30 to 35 minutes to remove subcutaneous fat and hair. The skin was rinsed well with saline followed by distilled water. 1 g of the gel was uniformly spread over the rat skin membrane and tied over the donor compartment. The skin was placed with stratum corneum facing the donor compartment and the dermis facing the receptor compartment containg 100ml distilled water. At hourly

intervals, 5ml of sample was withdrawn from the receptor and replaced with fresh 5ml distilled water. The 5 ml withdrawn sample was made up to 25 ml with distilled and the absorbance was recorded at 280nm. The receptor medium was magnetically stirred for uniform distribution and was maintained at a temperature of 37°C ± 0.2°C .

Skin irritation test:

Skin irritation study was carried out on Swiss albino mice weighing 20-30gms. The animal was kept under standard laboratory conditions. The animals were housed in polypropylene cages with access to laboratory diet. A single dose of diclofenac sodium solid dispersion incorporated topical gel was applied once a day for 7days to the left ear of the mice with right ear as a control and the site was observed for any sensitivity and reaction. The development of erythema was monitored for 7 days using the reported method.

In vivo Anti-inflammatory effects:

Procedure and protocol were reviewed by the institutional animal Ethical committee and IAEC guidelines were followed for the studies. Anti –inflammatory effects of the optimized formulations diclofenac solid dispersion incorporated topical gel and marketed gel were evaluated by carrageenan included paw edema method developed in Westar rates by winter et al.Albino rates of Wister strains of either sex between 140-170 grams were selected for the studies. The animals were kept under standard laboratory conditions at a temperature of 25 ± 1^{o}c and relative humidity of 55 ± 5%.the animals were housed in poly propylene cages, with free access to standard laboratory diet.

Group 1: control

Group 2: carrageenan

Group 3: diclofenac sodium solid dispersion incorporated topical gel

Group 4: marketed available gel

25 mg and 50 mg of respective formulation of diclofenac sodium solid dispersion incorporated gel were applied to the right paw half an hour before carrageenan was injected subcutaneously. Paw edema was induced by injecting 0.1% w/v dispersion of carrageenan in distilled water. Paw volume was measured by plethysmometer at different time intervals. The

amount of paw swelling was determined time to time and expressed as percent edema .Percent inhibition of edema produced by each formulation-treated group was calculated against the respective control group. Test was carried out for a period of 12 hours and % inhibition of edema was calculated by using the following formula. Result of these studies were compared using dunnet test of one-way analysis of variance

$$\% \text{ Swelling} = \frac{V-V1}{V1} \times 100$$

Where v = paw volume at 30min interval after the 0.1ml of 1% carrageenan injection.

V1= initial paw volume

The average paw swelling in this drug test group was compared with that of control rats and percentage inhibition was determined using following equation

% of inhibition of edema= [1-vt/vc] ×100

VT= mean inflammation of test group.

VC=mean inflammation of test group.

Stability study

Stability studies for Diclofenac sodium gels were carried out as per ICH guidelines. The gel samples were stored at 25 C, 60% RH and 40 C,70% RH, in stability chambers for a period of 6 months, samples were drawn at regular interval for stability analysis. At the end of 6 months assay was carried out to find out if there is any interaction between the drug and other ingredients of the formulation upon storage.

PREFORMULATION STUDIES:

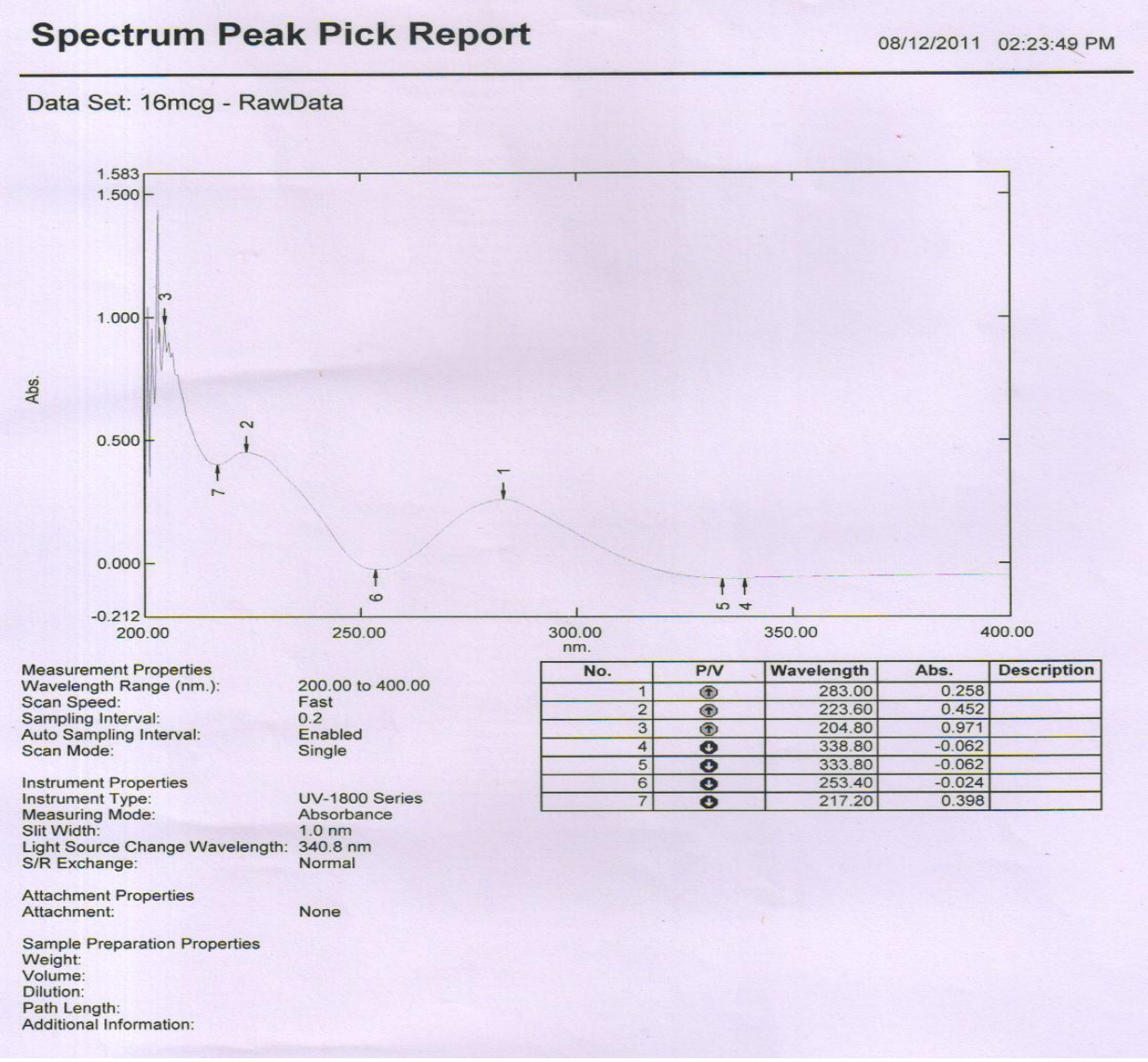
Appearance of drug substance:

The drug sample obtained was appeared as a white to slightly yellowish crystalline powder.

UV-spectroscopy:

The UV spectrum analysis of diclofenac sodium was carried out using methanol as blank and the λ max of diclofenac was found to be 283 nm.

Fig. 1 UV spectrum of Diclofenac



No.	P/V	Wavelength	Abs.	Description
1	↑	283.00	0.258	
2	↑	223.60	0.452	
3	↑	204.80	0.971	
4	↓	338.80	-0.062	
5	↓	333.80	-0.062	
6	↓	253.40	-0.024	
7	↓	217.20	0.398	

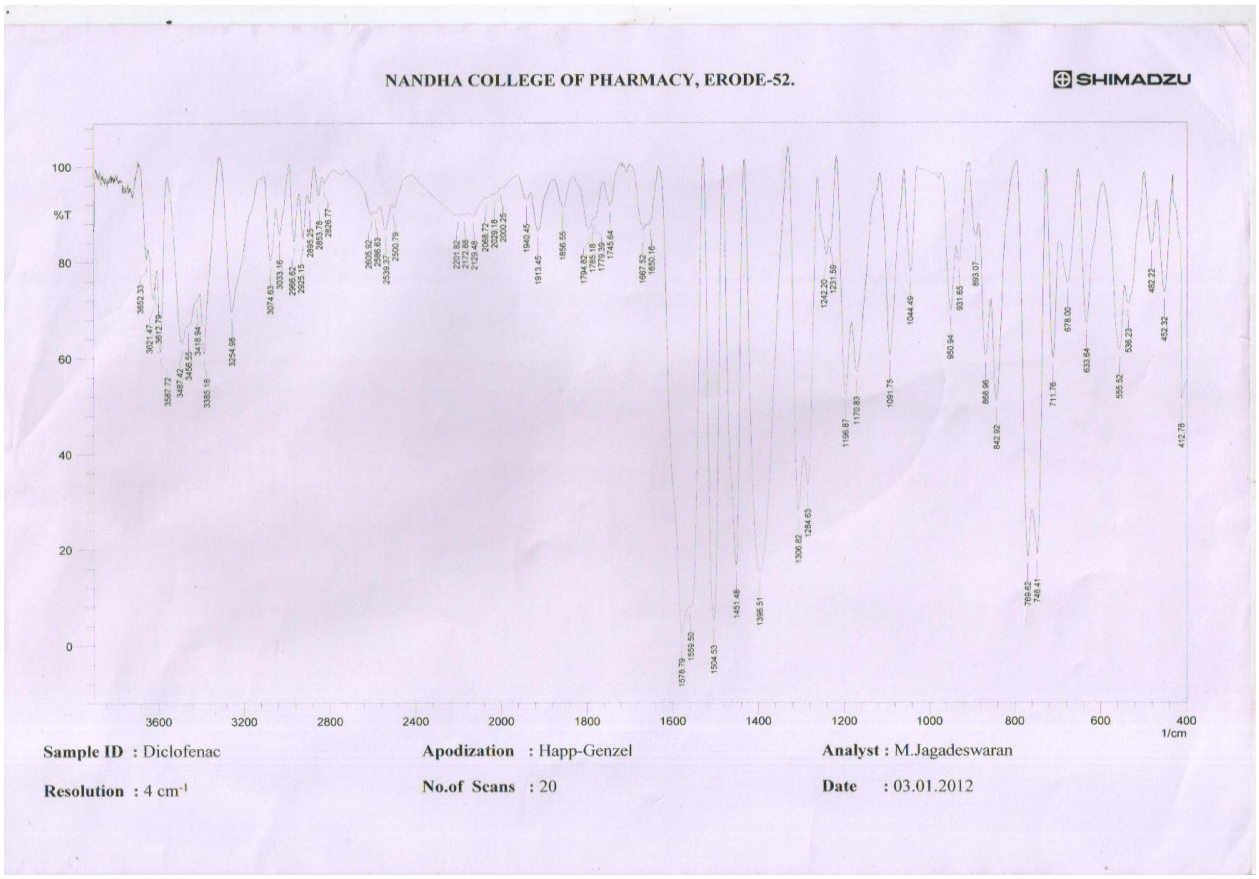
FTIR spectroscopy:

The FTIR spectra of Diclofenac, PVP, β - cyclodextrine, physical mixture 1, physical mixture 2, Formulation is recorded to check any interaction between drug and polymer. The characteristic peak obtained after FTIR indicates that there is no chemical interaction between drug, β-cyclodextrine, and PVP.

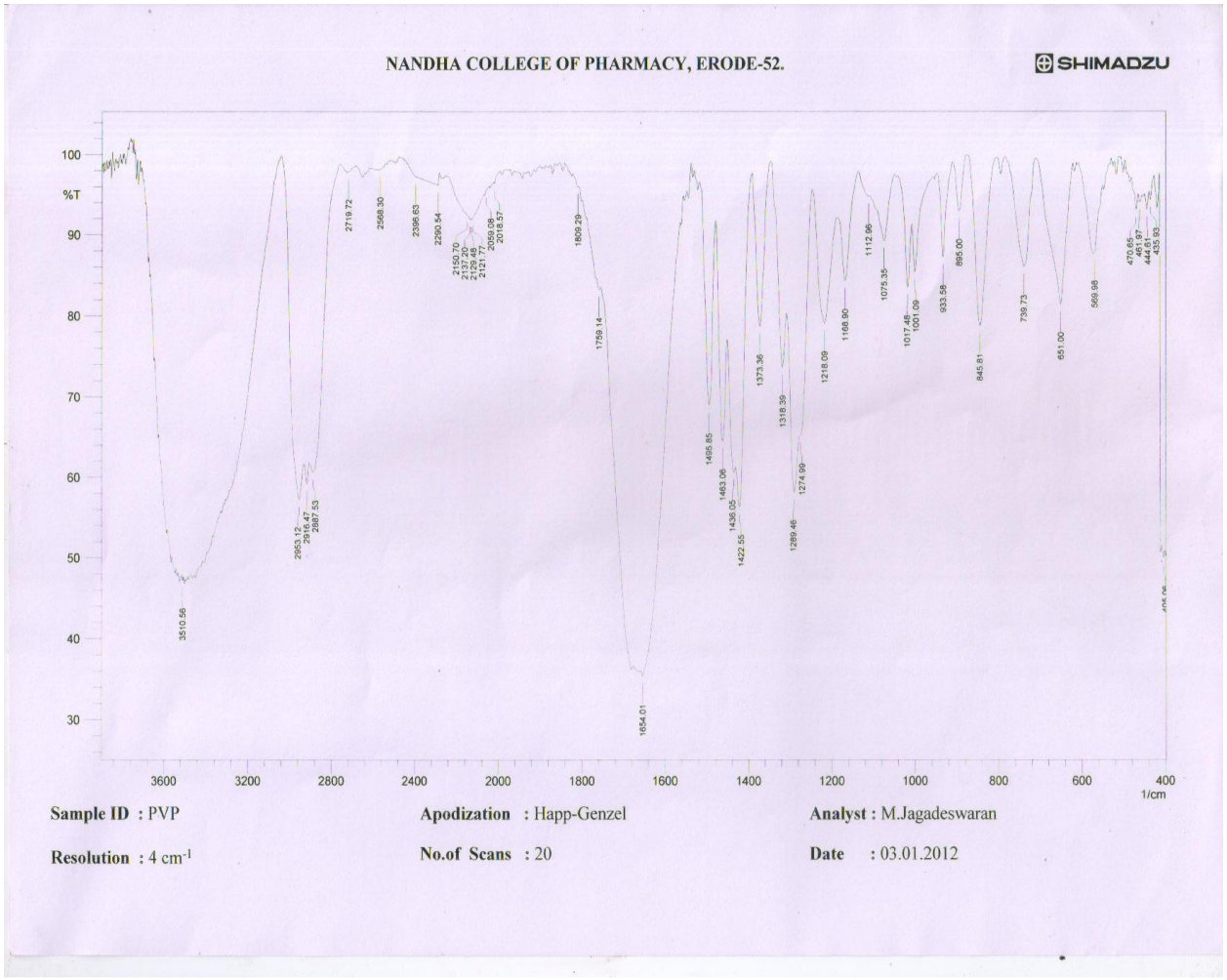
Table No. 05: Interpretation of IR spectrum of Diclofenac

S. No	Type of bond	Standard wave number	Observed wave number		
			Diclofenac	Diclofenac + Cyclodextrin	Diclofenac + PVP
1	O-H	3650-3600	3612.97	3615.69	3588.68
2	N-H (Strec)	3400	3418.94	3387.11	3364.83
3	N-H (Bend)	1640-1550	1504.53	1505.49	1501.63
4	Aromatic	1600 & 1475	1578.79 &1451.48	1576.86 &1451.48	1575.68 &1451.48
5	C-H (Strec)	3000-2850	3035.09	3035.09	3075.60
6	CH3 (Bend)	1450 &1375	1451.48 &1396.51	1451.48 &1398.44	1451,48 &1397.47
7	CH2 (Bend)	1465	1451.48	1451.48	-
8	C-O	1300-1100	1091.75	1083.07	1092.71
9	CONH	1680-1630	-	-	1662.96

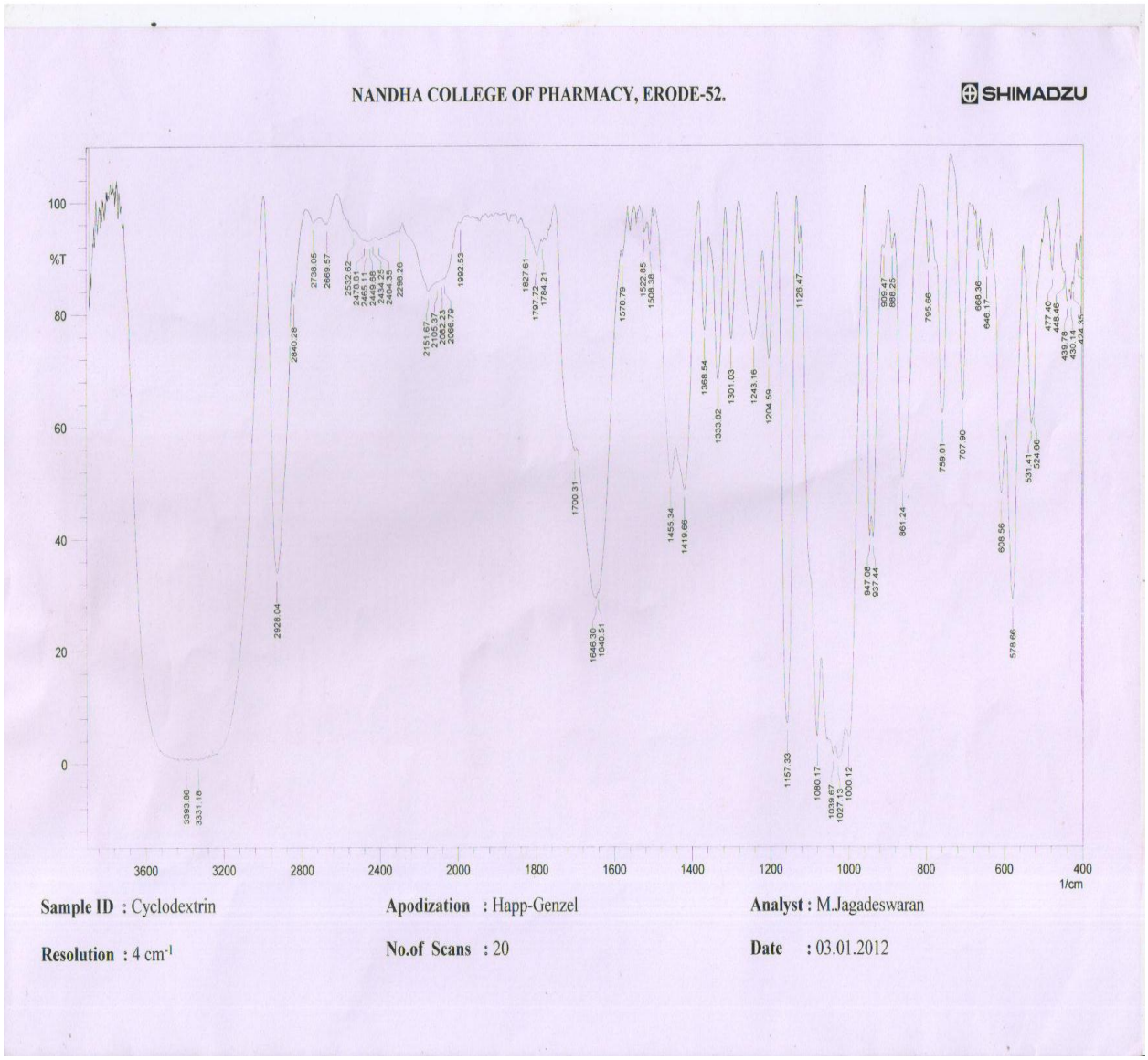
IR Spectrum of Diclofenac
Fig No. 2



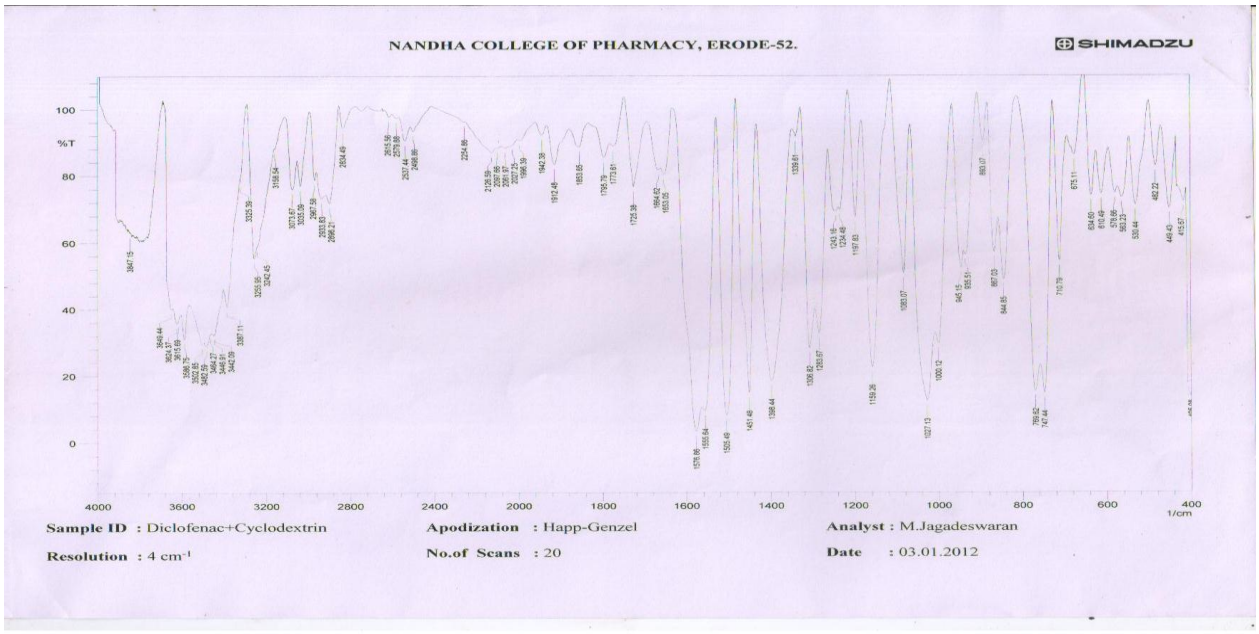
FTIR - Spectrum of PVP
Fig no. 3



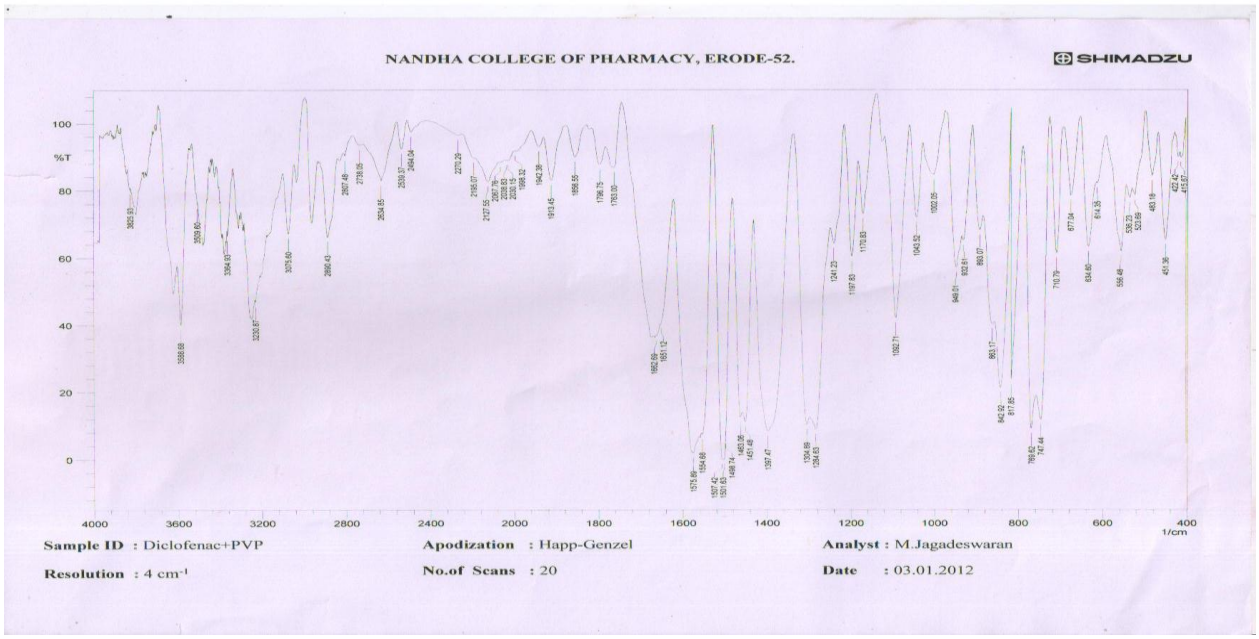
FT-IR Spectrum of β cyclodextrin
Fig no. 4



FT-IR Spectrum of Diclofenac + Cyclodextrin
Fig no.5



FT-IR Spectrum of Diclofenac + PVP
Fig no.6

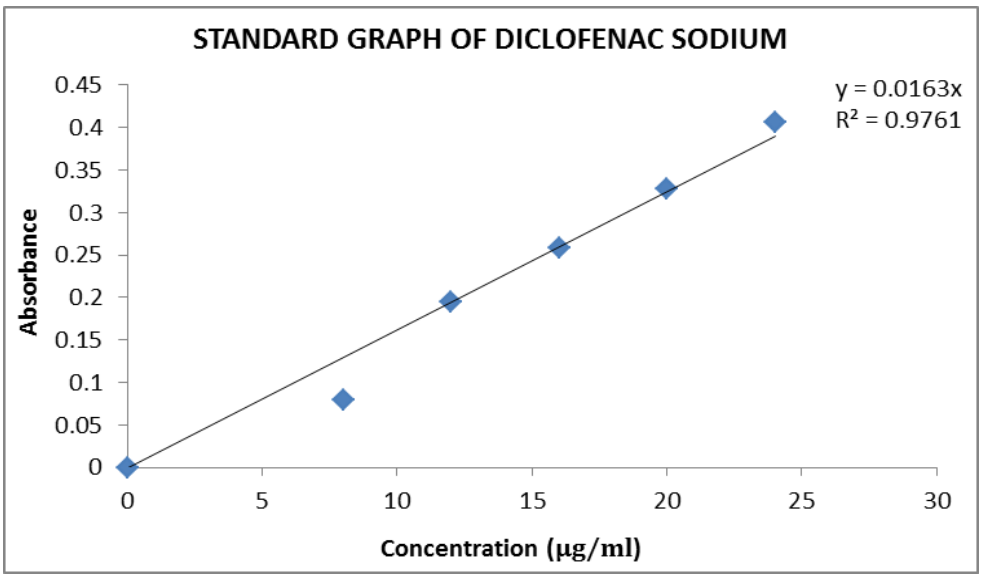


Preparation of Standard Curve:

Table no. 2: Standard curve of Diclofenac sodium 0.1N HCL

S. No	Concentration (µg/ml)	Absorbance at 283
1	8	0.080
2	12	0.195
3	16	0.258
4	20	0.328
5	24	0.406

Fig No.7 Standard curve of Diclofenac Sodium



DRUG CONTENT DETERMINATION

The percentage drug content present in all the formulation was analyzed using UV-spectroscopy. All formulation shows a percentage content between 98.0% to 100% range which is acceptable according to united state pharmacopoeia.

Table No. 03: Estimation of drug content

S. No	Formulation	Percentage Drug content
1	F1	78%
2	F2	80%
3	F3	95%
4	F4	81%
5	F5	93%
6	F6	90%

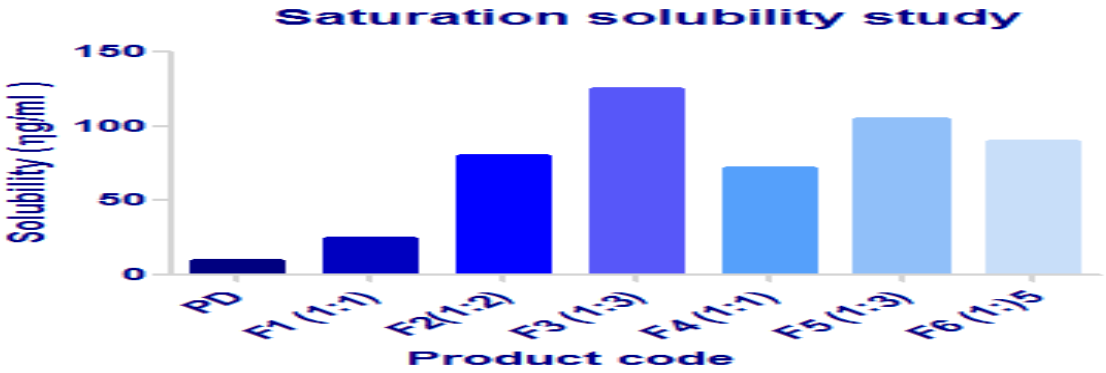
SATURATION SOLUBILITY STUDIES:

The solubility studies are carried out for both unprocessed drug and different batches of solid dispersion. All the formulated solid dispersion shows maximum solubility than the unprocessed drug and the formulation f3 & f5 shows maximum solubility.

Table No. 04: Solubility study data

S. No	Formulation	Solubility (µg/ml)
	Unprocessed drug	9.59
1	**F1**	25
2	**F2**	80
3	**F3**	125
4	**F4**	72
5	**F5**	105
6	**F6**	90

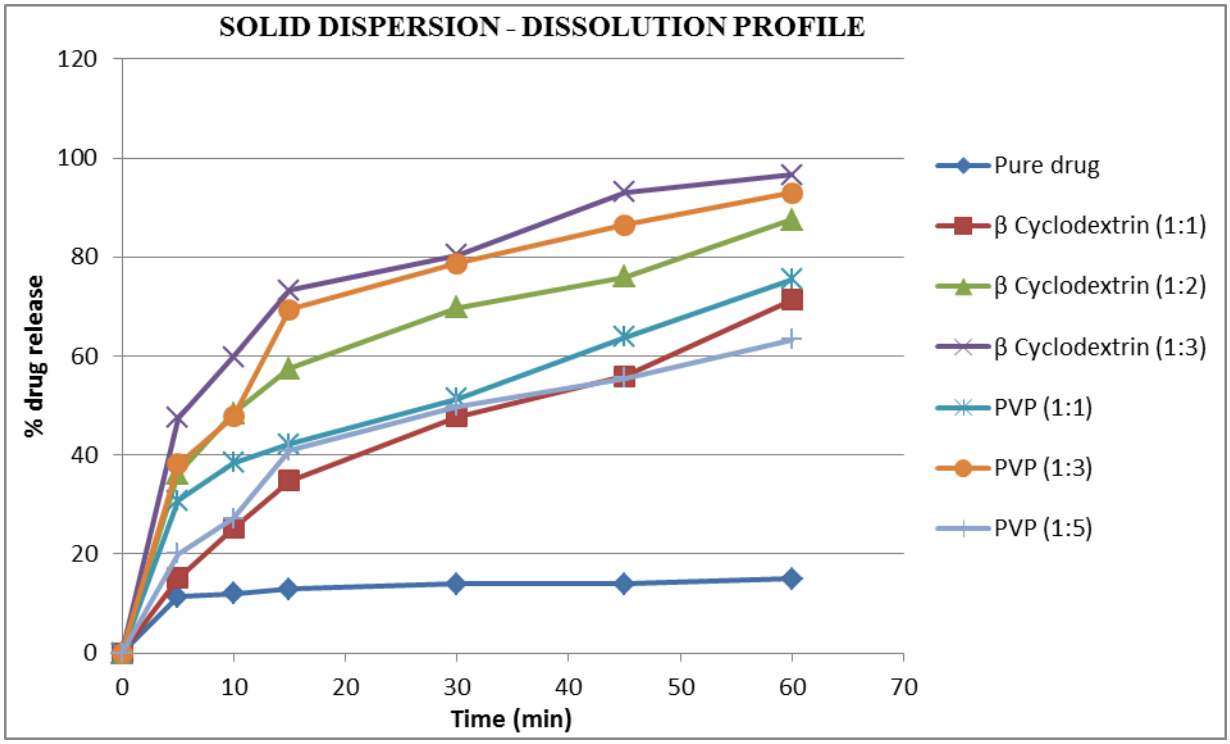
Fig No.8 Solubility study



RELEASE PROFILE FOR SOLID DISPERSION:

Time (mins)	PD (1%W/W)	1:1 (diclo+β-CD)	1:2 (diclo+β-CD)	1:3 (diclo+β-CD)	1:1 (diclo+pvp)	1:3 (diclo+pvp)	1:5 (diclo+pvp)
5	11.32	15.17	36.23	47.48	30.76	38.21	20.03
10	12.02	25.24	48.46	59.84	38.45	47.70	27.14
15	12.89	34.82	57.48	73.28	42.16	69.36	40.85
30	13.90	47.78	69.80	80.39	51.33	78.71	49.77
45	14.01	55.96	75.96	93.12	63.81	86.54	55.52
60	14.93	71.36	87.51	96.59	75.47	92.98	63.29

Fig No.9 Release properties of solid dispersion



EVALUATION OF SOLID DISPERSION INCORPORATED GEL

Spreadability test

Two glass slides of standard dimensions (2cm X 5cm) were selected. The gel formulation of which spread ability has to be determined was placed over one of the slides; the other slide was placed on the top of the gel such that the gel was sandwiched between the two slides.100gm was placed upon the upper slide and the gel between the two slides is pressed uniformly to form thin layer. The two slides in position were fixed to stand (at angle 45º) without any disturbance and in such a way that only the lower slide was held firmly by the clamp following the upper slide to travel the distance at 0.5 cm under the direction of weight was noted. The weight was removed and the excess of gel adhering to the slide was scrapped off. The experiment was repeated and mean time taken for three such determinations was calculated. The results were recorded.

Spreadability calculated using the formula, $S = \frac{MXL}{T}$

Whereas, S = spreadability.

M = weight given to upper slide.

L = distance traveled by glass slide.

T = time taken

Carbopol:

FORMULATION	SPREDABILITY (cm)
F1	6.9
F2	5.6

HPMC:

FORMULATION	SPREDABILITY (cm)
F4	5.4
F4	5.4

Cloth staining:

This study is very important to ascertain the patient compliance of the gels. Patients generally resist gels as they stain clothes. It was observed that all the four gels did not stain any of the fibre blends tested, even after prolonged exposure and accelerated drying. It could be concluded that none of the four gels stained any of the tested fibres.

Swelling Index Study of Topical Gel

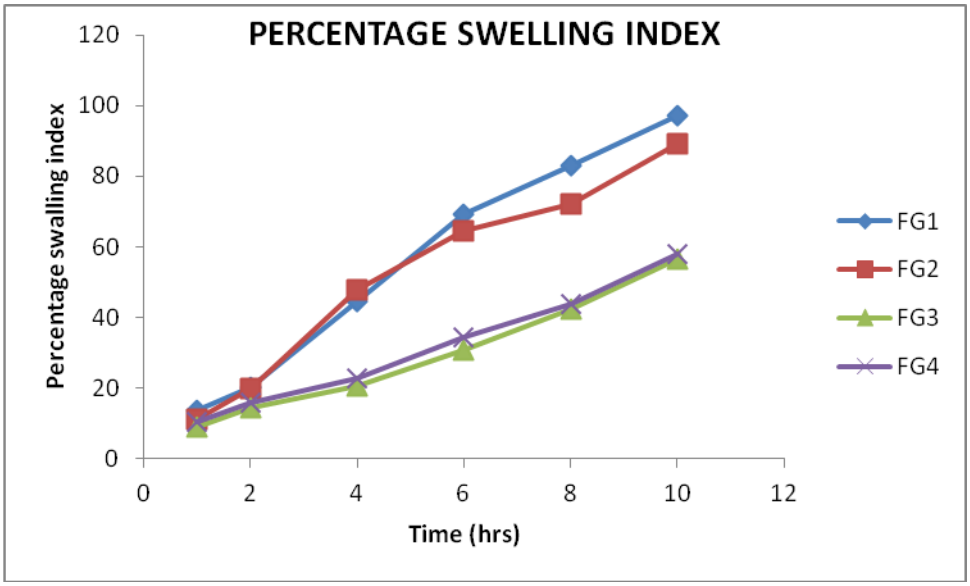
From these data we found, topical gel prepared from carbopol polymer has greater percent swelling index as compare to topical gel prepared from Hydroxy Propyl Methyl Cellulose. Table shows swelling index study data and Fig, shows graphical representation of swelling index study.

Carbapol:

Time (hrs.)	Swelling Index (%Sw)	
	F1	**F2**
1	13.67	11.00
2	20.30	19.98
4	44.66	47.86
6	69.19	64.36
8	83.07	72.12
10	97.33	89.07

HPMC:

Time (hrs.)	Swelling Index (%Sw)	
	F3	**F4**
1	09.02	10.4
2	14.55	15.67
4	20.70	22.56
6	30.91	34.22
8	42.18	43.79
10	56.58	58.01



Homogeneity:

Gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregate.

VISCOSITY MEASUREMENT

FORMULATION	VISCOSITY cp	pH	HOMOGENICITY
F1	**35310**	7.4	Good
F2	**35129**	7.4	Good
F3	**23561**	7.4	Good
F4	**21972**	7.4	Good

***In–vitro* Drug Diffusion Study:**

From these data we have found that the prepared topical gel for carbapol releases 95.69% in in-vitro diffusion study over a period of 24hrs.

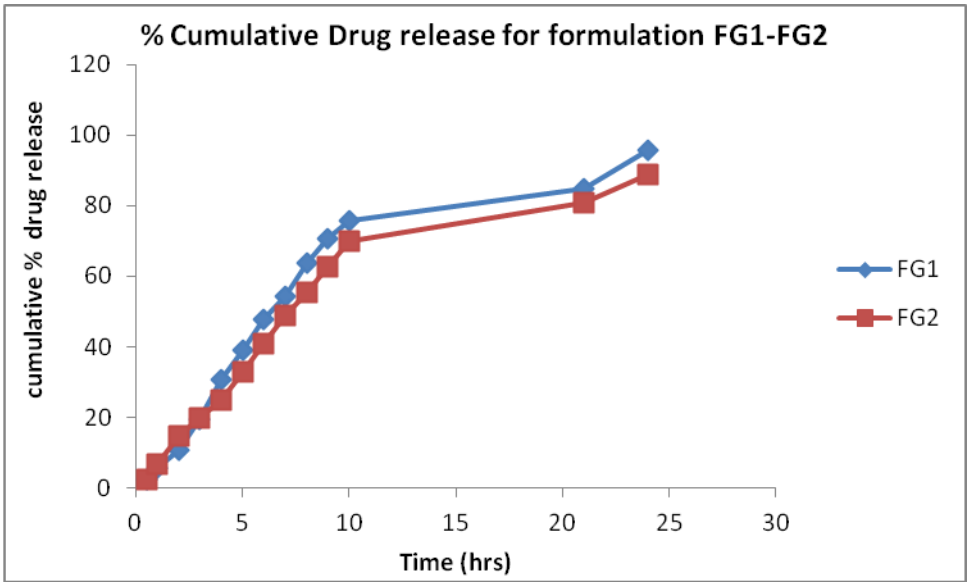
FG 1:

Time in Hrs.	**Absorbance**	**Concentration**	**Amt of drug dissolved in mg/ml**	**Cumulative amt of drug dissolved in 900ml**	**Cumulative %Drug released**
0.5	0.031	0.71	0.0177	15.99	2.45
1	0.078	1.78	0.0447	40.28	5.62
2	0.115	2.63	0.0659	59.47	10.67
3	0.148	3.39	0.0848	76.63	19.41
4	0.201	4.61	0.1152	104.15	30.68
5	0.237	5.43	0.1358	122.96	38.89
6	0.296	6.78	0.1697	153.68	47.92
7	0.354	8.11	0.2029	183.95	54.44
8	0.397	9.10	0.2276	206.54	63.63
9	0.412	9.44	0.2362	214.74	70.53
10	0.523	11.99	0.2998	272.28	75.57
21	0.698	35.558	0.8889	808.43	84.85
24	0.834	42.486	1.0622	956.91	95.69

From these data we have found that the prepared topical gel for carbapol releases 88.81% in in-vitro drug diffusion study over a period of 24hrs.

FG 2:

Time in hrs	Absorbance	Concentration	Amt of drug dissolved in mg/ml	Cumulative amt of drug dissolved in 900ml	Cumulative % drug released
0.5	0.021	1.09	0.0272	24.5287825	2.53
1	0.049	2.49	0.0624	56.2185431	6.89
2	0.093	4.737	0.1184	106.776363	14.7
3	0.169	8.60	0.2152	194.12	19.77
4	0.267	13.60	0.3400	306.88	24.86
5	0.338	17.21	0.4304	388.94	32.83
6	0.416	21.19	0.5298	479.20	40.81
7	0.472	24.04	0.6011	544.45	48.92
8	0.551	28.06	0.7017	636.20	55.56
9	0.61	31.07	0.7768	705.23	62.67
10	0.653	33.26	0.8316	755.74	69.98
21	0.697	35.50	0.8876	808.17	80.82
24	0.774	39.42	0.9857	888.00	88.81



From these data we have found that the prepared topical gel for Hpmc releases 74.52% in in-vitro drug diffusion releases over a period of 24hrs.

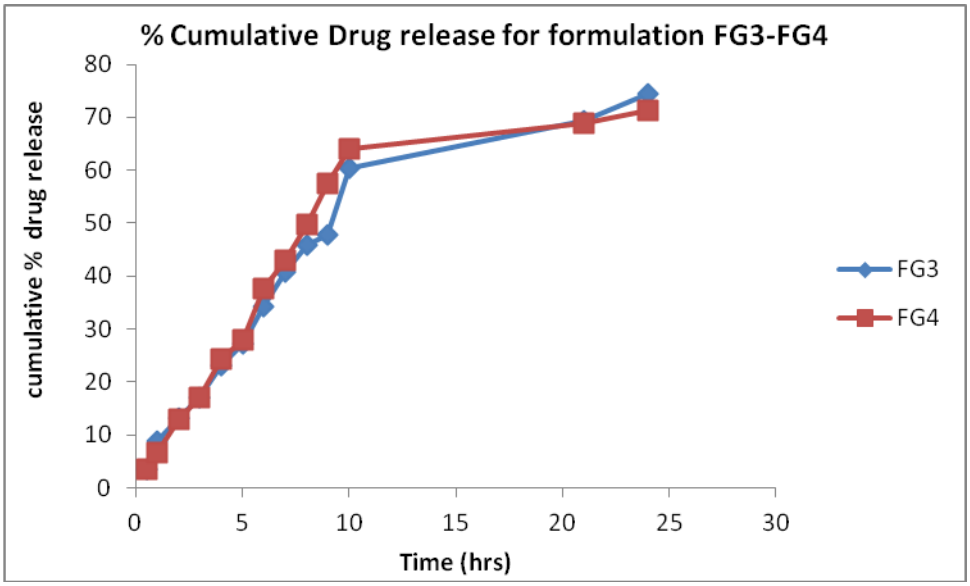
FG 3:

time in Hrs	absorbance	concentration	amt of drug dissolved in mg/ml	Cumulative amt of drug dissolved in 900ml	cumulative % Drug Released
0.5	0.031	0.71	0.0177	15.99	3.55
1	0.078	1.78	0.0447	40.28	8.95
2	0.115	2.63	0.0659	59.47	13.21
3	0.148	3.39	0.0848	76.63	17.02
4	0.201	4.61	0.1152	104.15	23.14
5	0.237	5.43	0.1358	122.96	27.32
6	0.296	6.78	0.1697	153.68	34.15
7	0.354	8.11	0.2029	183.95	40.87
8	0.397	9.10	0.2276	206.54	45.89
9	0.412	9.44	0.2362	214.74	47.72
10	0.523	11.99	0.2998	272.28	60.50
21	0.598	13.71	0.3428	311.80	69.28
24	0.649	14.88	0.372	335.34	74.52

From these data we have found that the prepared topical gel for Hpmc releases 71.19% in in-vitro drug diffusion study over a period of 24hrs.

FG 4:

time in Hrs	Absorbance	concentration	amt of drug dissolved in mg/ml	Cumulative amt of dru dissolved in 900ml	cumulative % Drug Released
0.5	0.03	0.68	0.0172	15.48	3.44
1	0.059	1.35	0.0338	30.48	6.77
2	0.113	2.59	0.0647	58.41	12.98
3	0.149	3.41	0.0854	77.12	17.13
4	0.211	4.83	0.1209	109.29	24.28
5	0.243	5.57	0.1393	126.04	28.01
6	0.326	7.47	0.1869	169.15	37.59
7	0.372	8.53	0.2133	193.26	42.94
8	0.43	9.86	0.2465	223.62	49.69
9	0.498	11.42	0.2855	259.21	57.60
10	0.553	12.68	0.3170	287.97	63.99
21	0.594	13.62	0.3405	309.95	68.87
24	0.62	14.22	0.3555	320.35	71.19



Skin irritation test:

S.no	Group	Score after(days)					Mean score ±SD
		1	2	3	5	7	
1	Gel	2	2	2	2	1	1.8±0.53
2	Mp	3	2	3	3	2	2.6±1.03

Skin irritation study was performed to conform the safety of the optimized diclofenac solid dipersion incorporated gel .van-abbe et al mentioned that valuve between 0and 9.

It indicates that the applied formulation is generally not an irritant to human skin.the mean skin irritation score for optimized diclofenac solid disepersion incorporated gel formulation and marketed gel was found to be 1.8±0.53 and2.6±1.03 respectively optimized diclofenac solid dispersion incorporated gel was shown less irritation profle when compared with marketed product.

Anti-inflammatory effects:

GROUPS	At 0 hr	At 4 hrs	At 8 hrs	At 24 hrs
CONTROL	**4.56±0.081**	**4.56±0.543**	**4.52±0.024**	**4.48±0.109**
STANDARD	**4.97±0.034**	**4.88±0.251****	**4.72±0.018****	**4.67±0.052**
TEST	**5.09±0.100**	**4.91±0.092****	**4.83±0.62****	**3.96± 0.030*****

Stability test:

Month	**0**	**2**	**4**	**6**
Room Tempt (25 ± 1^0C)	100%	99%	98%	98%
Oven Tempt (40 ± 1^0C)	100%	98%	97%	97%

SUMMARY AND CONCLUSION

The diclofenac sodium shows poor aqueous solubility and oral administration causes irritation of gastro intestinal tract, lack of bioavailability. The aim was to investigate the potential of diclofenac loaded solid dispersion based gel for topical delivery in order to improve the solubility, thereby increasing the bioavailability of drug. This alternate topical route eliminates oral side effects, increases patient compliance, avoids high first pass metabolism and maintains the plasma drug level for a longer period of time.

Solid dispersion incorporated diclofenac gel are thermodynamically stable. The solid dispersions are prepared by kneading method (β cyclodextrin) and solvent evaporation technique (PVP), followed by being incorporated into Carbopol 934 and HPMC based gel matrix to form solid dispersion incorporated diclofenac solid dispersion incorporated tropical gel.

Among the solid dispersion, formulation which showed highest release was selected to incorporate with Carbopol 934 and HPMC base to form gel. On the basis of swelling index invitro release studies, spreadability, viscosity, homogenization, saturation solubility study, we selected FG1 formulation which contained the combination of Diclofenac sodium, βcyclodextrin solid dispersion incorporated, carbopol 934 Gel for the use of invitro and in vivo studies. The optimized gel (FG1) was taken for their invitro skin permeation study, in vivo anti-inflammatory, effects and skin irritation study.

The invitro and in vivo study for optimized diclofenac solid dispersion incorporated gel FG1 were compared with Marketed gel, revealed a significant increase in skin permeation profile and anti-inflammatory effects for optimized gel. The percent inhibition value of optimized gel after 12 hours of administration was found to be 5.22% as compared with 5.41% for Marketed gel. From invitro and in vivo data it can be concluded that optimized carbopol gel containing diclofenac solid dispersin have great potential for topical delivery.

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