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Preparation & Characterization of Pharmaceutical Gel Using Model Drug

A Thesis

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بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

وَيَسْأَلُونَكَ عَنِ الرُّوحِ قُلِ الرُّوحُ مِنْ أَمْرِ رَبِّي وَمَا

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صَدَقَ اللَّهُ الْعَظِيمُ

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Supervisor Certificate

I certify that this the **"Preparation and Characterization of Pharmaceutical Gel Using Model Drug"**, was prepared under my supervision at the University of Al-Qadisiyah, College of Pharmacy as a partial fulfillment of the requirements for the degree ofbachelors of Science in Pharmacy.

Signature:

Advisor: ***Dr.*** *Hussein A. Mohammed*

Department:

Date:

Dedication

To whome Allah sent as mercy to the worlds

...

To the prophet Mohammed.....

To my parents...

To my family

To everyone I love.....

Table of contents

Table of contents

Table of contents

List of tables

List of Figures

Abstract

A wide choice of vehicles ranging from solids to semisolids form has been used for skin care and topical treatment of dermatological disease, High molecular weight water soluble polymers of Hydroxypropyl methylcellulose (HPMC), Carbapol 934P, Methyl cellulose that possess very high viscosity, transparency, film forming properties at low concentration, are being used in formation of gel. In the present research Cetirizine Hcl gels were prepared for topical drug delivery by using different concentration of HPMC,Methyl cellulose, Carbapol 934P, with an objective to increase transparency and spreadability. From the study it was concluded that HPMC gel containing Cetirizine Hcl showed good consistency, homogeneity, spreadability and stability and has wider prospect for topical preparations as compared to Methyl cellulose, Carbapol 934P gel containing Cetirizine Hcl.

CHAPTER ONE

INTRODUCTION

1.1. Gels

Gel are define as a Semi rigid systems in which the movement of the dispersing medium is restricted by an interlacing three-dimensional

network of particles or solvated macromolecules of the dispersed phase.

The USP defines gels (sometimes called jellies) as semisolid systems containing either suspensions made up of small inorganic particles,

or large organic molecules interpenetrated by a liquid. Where the gel mass contains a network of small separate particles, the gel is classified as a two-phase system. In a two-phase system, if the particle size of the dispersed phase is relatively large, the gel mass is sometimes called as a magma. Single-phase gels consist of organic macromolecules uniformly circulated throughout a liquid in such a way that no apparent boundaries occur between the dispersed macromolecules and the liquid.[13] [14][15]

In pharmaceutical applications, water and hydroalcoholic solutions are most common. Many polymer gels exhibit reversibility between the gel state and sol, which is the fluid phase containing the dispersed or dissolved macromolecule. However, the formation of some polymer gels is irreversible because their chains are covalently bonded. The three-dimensional networks formed in two-phase gels [17]

1.1.1 Advantages of gel[27][28][29]

1. Gels are used to achieve optimal cutaneous and percutaneous drug delivery.
2. They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH.
3. Gels are having property to avoid enzymatic activity and drug interaction with food and drinks.

4. They can substitute for oral administration of medication when the route is unsuitable.
5. They can avoid the first pass effect, that is, the initial pass of drug substance through the human body.
6. They avoid systemic and portal circulation following gastrointestinal absorption.
7. Gels are not deactivated by liver enzymes because the liver is bypassed.
8. They are non-invasive and have patient compliance.
9. They are applied over skin for slow and prolonged absorption
10. Gels have also been applied in pharmacy to some viscous suspension for oral use for example Aluminium hydroxide gel.
11. They have localized effect with minimum side effects.

1.1.2 Disadvantages [28][30][31]

1. Gels have possibility of allergenic reactions. Enzyme in epidermis may denature the drugs of gels
2. Drugs of larger particle size do not absorb through the skin.
3. They have poor permeability of some drugs through the skin.
4. Selection of area to be examined carefully during application of gels.
5. Gels which are used for the introduction into body cavity or the eyes should be sterilized.
6. They may cause application side reactions.
7. They may cause skin allergy during application.

1.1.3 Delivery through skin

Delivery of drugs to the skin is an effective and targeted therapy for local dermatological disorders. Topical gel formulations provide a suitable delivery system for drugs because they are less greasy and can be easily removed from the skin[32]

Mechanism of Drug Absorption[32]

The principal mechanisms of drug absorption are:

1.Passive diffusion
2.Pore transport
3.Facilitated diffusion
4.Active transport
5.Ionic or electrochemical diffusion
6.Ion-pair transport
7.Endocytosis

Physiological Factors Affecting Skin Penetration[33]:

1. Skin integrity
2. Skin hydration
3. Skin temperature
4. Regional variation
5. Traumatic/pathologic injury to skin
6. Cutaneous drug metabolism

Formulation Factors Affecting Skin Penetration[33][34]

1.Penetration enhancer.
2. Occlusivity
3. Drug concentration
4. pH
5. Solubility
6. Surfactant

1.1.4. Properties of gels: Various Properties of Gels are Following:

A. Physical properties
B. Physiological properties
C. Application properties
D. Hydrophilic properties
E. Rheological properties

Physical Properties[35][36]

1. Smooth texture
2. Elegant in appearance
3. Non dehydrating
4. Transparent and transluscent
5. Non greasy
6. Semi solid in nature

Physiological Properties[34]

1. Non irritating
2. Do not alter membrane / skin functioning
3. Miscible with skin secretion
4. Have low sensitization index

Application Properties[34] :

1. Easily applicable with efficient drug release.
2. High aqueous washability.

Hydrophilic Properties

The water absorbing capacity of oleaginous and water-in-oil bases may be expressed in terms of the water number, defined in 1935 by Casparis and Meyeras the maximum quantity of water that is held (partly emulsified) by 100g of a base at 20^{o} C.

The test consists of adding increments of water to the melted base and triturating until the mixture has cooled. When no more water is absorbed, the product is placed in a refrigerator for several hours, removed, and allowed to come to room temperature. The material is then rubbed on slab until water no larger exudes, and finally, the amount of water remaining in the base is determined.[38]

Rheological Properties

Gels exhibit different rheological properties. Do not flow at low shear stresses but undergo reversible deformation like elastic solids.

When a characteristic shear stress, called the yield value or yield stress, is exceeded, they flow like liquids. Yield stresses usually are caused by structural networks extending throughout an entire system. To break such a network requires stress produce no flow but only elastic deformation. When the yield stress is exceeded, the network is partly ruptured and flow occurs[37].

1.1.5 Composition of gels

Gels consist of a solid three-dimensional network that spans the volume of a liquid medium and ensnares it through surface tension effects. This internal network structure may result from physical bonds (physical gels) or chemical bonds (chemical gels), as well as crystallites or other junctions that remain intact within the extending fluid. Virtually any fluid can be used as an extender including water (hydrogels), oil, and air (aerogel). Both by weight and volume, gels are mostly fluid in composition and thus exhibit densities

similar to those of their constituent liquids. Edible jelly is a common example of a hydrogel and has approximately the density of water

1.1.6 Uses of gels[1]

1. As delivery systems for orally administered drugs.
2. For topical drugs applied directly to the skin, mucous membrane or the eye.
3. As long acting forms of drug injected intramuscularly or implanted into the body.
4. As binders in tablet granulation, protective colloids in suspensions, thickeners in oral liquid and suppository bases.
5. In cosmetics like shampoos, fragrance products, dentifrices and skin and hair care preparations.
6. Lubricant for catheters
7. Bases for patch testing
8. NaCl gel for electrocardiography
9. Sodium fluoride & Phosphoric acid gel for dental care prophylactic

1.1.7 Types of gel

Hydrogels :A hydrogel is a network of polymer chains that are hydrophilic , sometimes found as a colloidal gel in which water is the dispersion medium. Hydrogels are highly absorbent (they can contain over 90% water) natural or synthetic polymeric networks. Hydrogels also possess a degree of flexibility very similar to natural tissue, due to their significant water content. The first appearance of the term 'hydrogel' in the literature was in 1894**.(17)** Common ingredients include polyvinyl alcohol, sodium polyacrylate, acrylate polymers and copolymers with an abundance of hydrophilic groups. Natural hydrogel materials are being investigated for tissue engineering; these materials include agarose, methylcellulose, hyaluronan, and other naturally derived polymers.

Organogels :An organogel is a non-crystalline, non-glassy thermoreversible (thermoplastic) solid material composed of a liquid organic phase entrapped

in a three-dimensionally cross-linked network. The liquid can be, for example, an organic solvent, mineral oil, or vegetable oil. The solubility and particle dimensions of the structurant are important characteristics for the elastic properties and firmness of the organogel. Often, these systems are based on self-assembly of the structurant molecules.[18] .

A xerogel is a solid formed from a gel by drying with unhindered shrinkage. Xerogels usually retain high porosity (15–50%) and enormous surface area (150–900 m^2/g), along with very small pore size (1–10 nm). When solvent removal occurs under supercritical conditions, the network does not shrink and a highly porous, low-density material known as an *aerogel* is produced. Heat treatment of a xerogel at elevated temperature produces viscous sintering (shrinkage of the xerogel due to a small amount of viscous flow) and effectively transforms the porous gel into a dense glass[16][17]..

1.2.Cetirizine [3][4][7][5]

Cetirizine is an antihistamine that reduces the natural chemical histamine in the body. Histamine can produce symptoms of sneezing, itching, water eyes, and runny nose. It is used to treat cold or allergy symptoms such as sneezing, itching, watery eyes, or runny nose.

Cetirizine is also used to treat itching and swelling caused by hives. Cetirizine may also be used for other purposes not listed in this medication guide

Type of medicine	Antihistamine (non-drowsy)
Used for	Allergies, such as hayfever and some allergic skin reactions
Also called	Piriteze® Allergy One a Day; Pollenshield® Hayfever; Pollenshield® Hayfever Relief; Benadryl® Allergy Liquid Release; Benadryl® One a Day Relief; Galpharm Hayfever and Allergy Relief; Lloyds Hayfever and Allergy Relief; Numark Hayfever and Allergy Relief; Zirtek® Allergy
Available as	Capsules, tablets, and oral liquid medicine

1.2.1 Clinical Pharmacology

Mechanism of Actions of Cetirizine, a human metabolite of hydroxyzine, is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H1 receptors [3][4][7] .The antihistaminic activity of Cetirizine has been clearly documented in a variety of animal and human models. *In vivo* and *ex vivo* animal models have shown negligible anticholinergic and antiserotonergic activity. In clinical studies, however, dry mouth was more common with Cetirizine than with placebo. *In vitro* receptor binding studies have shown no measurable affinity for other than H1 receptors. Autoradiographic studies with radiolabeled Cetirizine in the rat have shown negligible penetration into the brain. *Ex vivo*experiments in the mouse have shown that systemically administered Cetirizine does not significantly occupy cerebral H1 receptors**.**[3][5]

1.2.2 Uses for Cetirizine

Allergic Rhinitis: *Self-medication* for symptomatic relief of rhinorrhea, sneezing, lacrimation, itching eyes, and/or oronasopharyngeal itching

associated with seasonal (e.g., hay fever) allergic rhinitis or other upper respiratory allergies.[5][24][23]

Chronic Idiopathic Urticaria :*Self-medication* for symptomatic relief of pruritus associated with chronic idiopathic urticaria (e.g., hives); not for prevention of chronic idiopathic urticaria or allergic skin reactions.[4] .

1.2.3 Contraindications of Cetirizine:

Hypersensitivity to cetirizine hydrochloride, to any of the excipients listed in section 6.1, to hydroxyzine or to any piperazine derivatives.Patients with severe renal impairment at less than 10 ml/min creatinine clearance.Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.**[3]**

1.2.4 Side effects of Cetirizine

side effects have included headache (16%), fatigue (5.6%), and somnolence (5% to 20, dizziness (1.8%), insomnia (1.5%), and nervousness (1.1%).Cetirizine appears to be more sedating than loratadine.also included dry mouth (5.7%) and nausea or vomiting (2.2%) **[8][9]**. Pharyngitis, dyspepsia, and increased appetite have occasionally been reported.And rarely liver function test abnormalities which resolved spontaneously following discontinuation of cetirizine therapy,wheezing, coughing, bronchitis, sinusitis, and asthma.,maculopapular and urticarial eruptions. ,an anaphylactic reaction.[7]

1.2.5 Pharmacokinetics:

Absorption: Cetirizine was rapidly absorbed with a time to maximum concentration (Tmax) of approximately 1 hour following oral administration of tablets or syrup in adults. Comparable bioavailability was found between the tablet and syrup dosage forms. When healthy volunteers were administered multiple doses of Cetirizine (10 mg tablets once daily for 10 days), a mean peak plasma concentration (Cmax) of 311 ng/mL was observed.

No accumulation was observed. Cetirizine pharmacokinetics were linear for oral doses ranging from 5 to 60 mg. Food had no effect on the extent of Cetirizine exposure (AUC) but Tmax was delayed by 1.7 hours and Cmax was decreased by 23% in the presence of food[5].

Distribution: The mean plasma protein binding of Cetirizine is 93%, independent of concentration in the range of 25-1000 ng/mL, which includes the therapeutic plasma levels observed[5][6]

Metabolism: A mass balance study in 6 healthy male volunteers indicated that 70% of the administered radioactivity was recovered in the urine and 10% in the feces. Approximately 50% of the radioactivity was identified in the urine as unchanged drug. Most of the rapid increase in peak plasma radioactivity was associated with parent drug, suggesting a low degree of first-pass metabolism. Cetirizine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity. The enzyme or enzymes responsible for this metabolism have not been identified**.** [5]

Elimination: The mean elimination half-life in 146 healthy volunteers across multiple pharmacokinetic studies was 8.3 hours and the apparent total body clearance for Cetirizine was approximately 53 mL/min**.**[6]

1.2.6 Pharmacodynamics

Cetirizine hydrochloride at doses of 5 and 10 mg strongly inhibited the wheal and flare caused by intradermal injection no tolerance to the antihistaminic (suppression of wheal and flare response) effects of Cetirizine hydrochloride was found that there was a 90% inhibition of histamine-induced (10 mg/mL) cutaneous wheal and 87% inhibition of the flare 12 hours after administration of the last dose. The clinical relevance of this suppression of histamine-induced wheal and flare response on skin testing is unknown.(3) The effects of intradermal injection of various other mediators or histamine releasers were also inhibited by Cetirizine, as was response to a cold challenge in patients with cold-induced urticaria. In mildly asthmatic subjects, Cetirizine

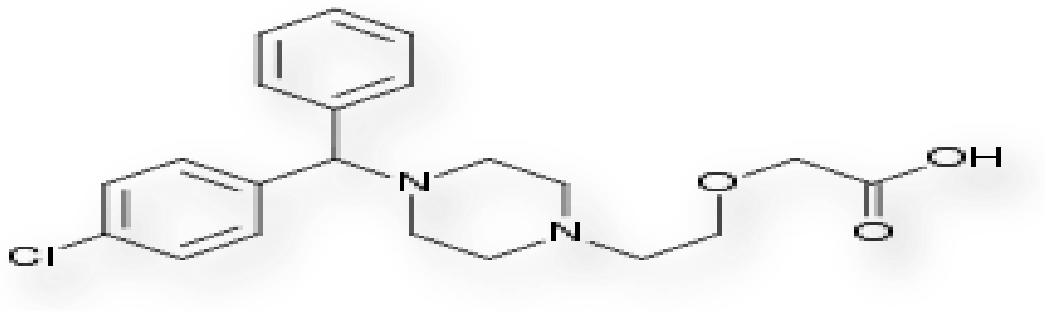
hydrochloride at 5 to 20 mg blocked bronchoconstriction due to nebulized histamine, with virtually total blockade after a 20-mg dose. In studies conducted for up to 12 hours following cutaneous antigen challenge, the late phase recruitment of eosinophils, neutrophils and basophils, components of the allergic inflammatory response, was inhibited by Cetirizine hydrochloride at a dose of 20 mg.[4]

1.2.7 Cetirizine physical properties

Cetirizine itself is a white, crystalline powder, Soluble in water. Cetirizine's melting point is between 110-115 degrees C Cetirizine's water solubility 101 mg/L. It also has a pKa of 3.6. When in tablet form it is a rectangular shape. It is also white and comes in doses of 5 and 10 mg. The chew-able tablets are round purple tablet that come in doses of 5 and 10 m

1.2.8 Cetirizine chemical properties

The ionization and lipophilicity behavior of the antihistamine (H1receptor antagonist) cetirizine was investigated, showing the drug to exist almost exclusively as a zwitterion in the pH region 3.5−7.5. In this pH range, its octanol/water lipophilicity is constant and low compared to cationic antihistamines (log D = log PZ = 1.5), whereas its H-bonding capacity is relatively large (Δlog PZ $\geq$ 3.1). Conformational, electronic, and lipophilicity potential calculations revealed that zwitterionic cetirizine experiences partial intramolecular charge neutralization in folded conformers of lower polarity. Pharmacokinetic investigations have shown the drug to be highly bound to blood proteins, mainly serum albumin, and to have a low brain uptake, explaining its lack of sedative effects. As such, cetirizine does not differ from "second-generation" antihistamines. In contrast, its very low apparent volume of distribution in humans (0.4 L kg-1, smaller than that of exchangeable water) implies a low affinity for lean tissues such as the myocardium and is compatible with the absence of cardiotoxicity of thedrug. The zwitterionic nature and modest lipophilicity of cetirizine may account for this pharmacokinetic behavior [12]



Figure(1) Structure of Cetirizine **C21H25CIN2O3** (Molar Mass **is388.87** grams)

1.2.9 Cetirizine stability

According to the ICH guidelines, the stability of drug substances should be studied in different conditions. There are some reports in the literature about the stability of cetirizine dihydrochloride in different conditions.[39] no degradation was observed for cetirizine in combination with pseudoephedrine under acidic (1 M HCl) or basic (1 M NaOH) conditions at 70°C after 2 h. On the other hand cetirizine was unstable under oxidative conditions. By using 0.1 M HCl, 0.1 M NaOH or 1% H_2O_2 at 80°C for 10 h, it has been concluded that cetirizine dihydrochloride was stable in basic condition but unstable in acidic or oxidative conditions [42] .There is another report regarding the stability of cetirizine dihydrochloride under 0.5 M HCl or 0.5 M HCl at 80°C after 4h[40].Using 1 M HCl or 30% H_2O_2decomposition of cetirizine dihydrochloride was observed after 12 h at 80°C [41] . To the best of our knowledge, these reports are at a descriptive level and there is no research published in the literature in regard to the kinetics of degradation of cetirizine dihydrochloride under acidic, basic or oxidative conditions.

Chapter Two

Aim of study

This study attempt to develop suitable topical gel formulations of Cetirizine using HPMC, Carbopol and methyl cellulose as a gelling agents and glycerin as permeation enhancer and evaluation of the resultant formulations.

Chapter Three

Materials and methods

3.1.Materials

Pure Cetirizine, carbopol 940, methyl cellulose(MC), hydroxypropylmethyl cellulose (HPMC),methyl and propyl paraben, glycerin, propylene glycol, triethanolamine, disodium hydrogen phosphate and sodium dihydrogen phosphate.

Figure(2)sodium dihydrogen phosphate(Acid)

Figure(3)disodium hydrogen phosphate

3.2.Methods Preparation of citerizine topical gels :

cetirizine (1% w/w) was dissolved in glycerin (10% w/w) as moistening agent.(43)Polyacrylic acid polymer (carbopol 940)**,** cellulose polymers (HPMC, MC) gel were prepared by dispersing the calculated amount of polymer in calculated amount of warm water with constant stirring using magnetic stirrer at a moderate speed. Then add the previous mixture containing the drug. The pH of carbopol gel was adjusted using TEA.

Finally methyl and propyl paraben as preservatives were added slowly with continuous stirring until gel formation. The prepared gels were packed in wide mouth glass jar covered with screw capped plastic lid after covering the mouth with an aluminum foil and were kept in dark and cool place.(44)

Figure(4)sensitive palance

Table1: Composition of Cetirizine topical gel(w/w)				
Ingredients (gm)	**F1**	**F2**	**F3**	**F4**
cetirizine	1	1	1	1
Carbopol 940	1	_	_	_
HPMC	_	4	_	_
Methyl Cellulose	_	_	2	4
Glycerin	10	10	10	10
Methyl Paraben	0.03	0.03	0.03	0.03
Propyl Paraben	0.01	0.01	0.01	0.01
Purified water to	100	100	100	100

3.3. Physicochemical Evaluation of Prepared cetirizine Gels

3.3.1. Standard curve preparation

Buffer preparation: add 1g of sodium dihydrogenphosphate in 500ml of distal water .Add 1g of disodium mono hydrogenphosphate in 500 ml of distal water and stir until they well dissolved .Then take 250 ml of the base(Na2HPO4) and mix with 650ml of the acid (NaH2PO4) in a beaker and measure PH by (PH meter) to obtain 6.8 unit PH buffer solution.

Stock solution preparation: weight 10mg of cetirizine and dissolve it in 100ml of buffer prepared solution in volumetric flask. The standard solution of cetirizine was subsequently diluted with Buffer Phosphate "6.8 PH" to obtain a series of dilutions containing 1, 2, 3, 4 and 5 ml of cetirizine in 0.1 mg/ ml solution.

Figure(5)PH meter

Conc. After Dilution:

1. 0.1(mg/ml) × 1 ml = Conc. (mg/ml) × 30 ml => Conc. = 0.0033 mg/ml

2. 0.1(mg/ml) × 2 ml = Conc. (mg/ml) × 30 ml => Conc. = 0.0066 mg/m

3. 0.1(mg/ml) × 3 ml = Conc. (mg/ml) × 30 ml => Conc. = 0.01 mg/ml

4. 0.1(mg/ml) × 4 ml = Conc. (mg/ml) × 30 ml => Conc. = 0.0133 mg/ml

5. 0.1(mg/ml) × 5 ml = Conc. (mg/ml) × 30 ml => Conc. = 0.0166 mg/ml

Figure.(6) UV-spectrophotometric apparatus

The absorbance of these solutions was measured at 230 nm using UV-VIS spectrophotometer against blank .The concentrations of cetirizine and the corresponding absorbance are given in the Table(2). The absorbance were plotted against concentration of cetirizine as shown In Fig.(6)

3.3.2. Visual examination

The prepared gel formulae were inspected visually for their color and syneresis. The developed preparations were much clear and transparent. All

developed gel formulae showed good homogeneity with absence of lumps and syneresis. Results are shown in table(3).

Figure(7)physical appearance of Cetirizine topical gel

3.3.3 pH Determination

The pH of the gel formulations was measured with a pH meter (shown in Fig(4)) using 1 % aqueous solutions of the gels at room temperature.The pH values of all developed formulae was in range from 2.2withmethyl cellulose to5.5with Carbopol 940 shown in table(4)which is considered acceptable to avoid the risk of irritation upon application to the skin.[45][46]

3.3.4 Spreadability

The spreadability is very much important as show the behavior of gel comes out from the tube. The values of spreadability shown below indicate that all the polymers used gave gels spread by small amount of shear. The diameters of the spreaded circles ranged from 6cm to 7.8cm seen in HPMC gel shown in table (4)

3.3.5 Drug Content determination

A specific quantity 1g of developed gel was taken and dissolved in 500ml of phosphate buffer of pH 6.8. The volumetric flask containing gel solution was shaken on mechanical shaker in order to get complete solubility of drug. This solution was filtered using Millipore filter (0.45μm). then take 1ml from the resultant solution and dissolve it in 10ml of buffer and drug absorbance was recorded by using UV- visible spectrophotometer at λ_{max} 230 nm using phosphate buffer (pH 6.8) as blank .Results obtained are shown in table(4)

3.3.6 In Vitro Release Studies

The study was carried out using (Varien dissolution tester, model VK 7010,with an auto sampler unit VK 8000, USA) using dialysis method.A one gram sample of each formulation was accurately weighed and placed on asemi permeable cellophane membrane (previously immersed in phosphate buffer pH 6.8 for24 hours) to occupy a circle of 2.5 cm diameter. The loaded membrane (donor compartment)was firmly stretched over the lower open end of a glass tube of 2.5 cm internal diameter an made watertight by rubber band. The tube was then immersed in a beaker containing 900ml of phosphate buffer pH 6.8 which is the release medium (receptor compartment). The system was maintained for 3hours at 37±0.5ºC in a thermostatic shaking water bath at50rpm. Samples of 5ml were with drawn at intervals of 0.25,0.5,0.75,1,1.5,2,and 3hours. Thevolume of each sample was replaced by the same volume of fresh buffer (kept at the same temperature) to maintain constant volume. Samples were analyzed for cetirizine content spectrophotometrically at λmax 230nm against blank similarly treated.

Figure (8) dissolution tester

The results are shown in table (5) were curved to estimate cetirizine release profile. Shown in Fig(9)

3.3.7Fourier Transfer Infrared spectrophotometer (FTIR)

The FTIR studies were carried for the drug, the polymers and the drug-polymer physical mixture in the ratio 1:1 were mixed separately with IR grade KBr in the ratio of (100:1) and corresponding discs were prepared by applying 5.5 metric ton of pressure in a hydraulic press using FTIR Spectrophotometer (Genesis II, Mattson, England). The disks were scanned over a wave number range (4000 - 400cm).

Chapter four

Result and discussion

4. Result and discussion

4.1.Calibration curve for the estimation of cetirizine in Buffer Phosphate at 6.8 PH:

Construction of calibration curve of cetirizine in phosphate buffer PH 6.8 revealed straight line with high correlation coefficient 0.9951 as shown in figure (6)

Table2 : Calibration curve for the estimation of cetirizine in Buffer Phosphate at 6.8 PH

No. of sample	concentration (mg/ml) cetirizine	Absorbance
1	0	0
2	0.0033	0.114
3	0.0066	0.236
4	0.01	0.326
5	0.0133	0.434
6	0.0166	0.518

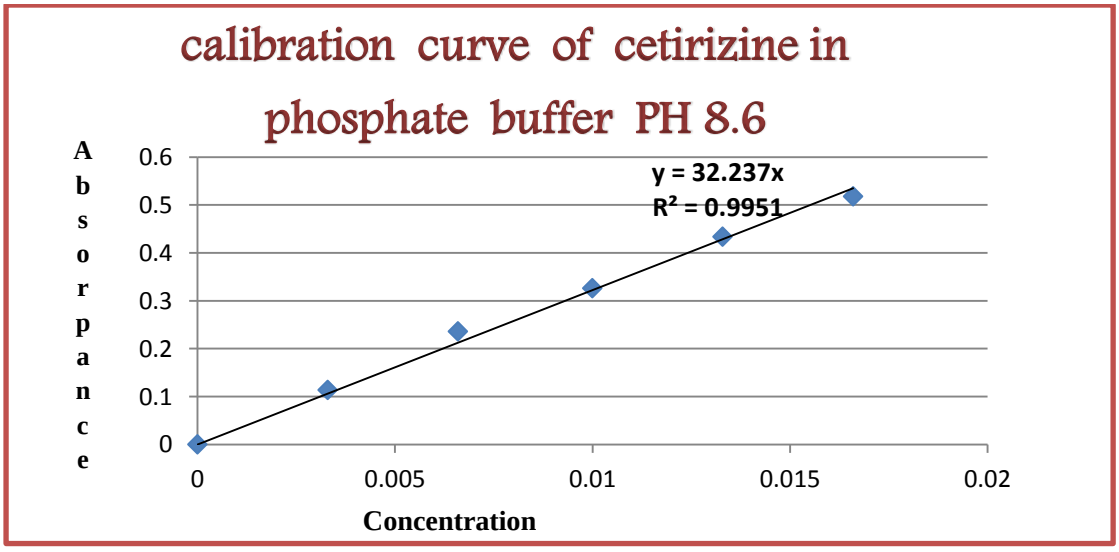


Figure (6) Calibration curve of cetirizine in Buffer Phosphate

4.2.Physical examination:

All developed gel showed good homogeneity with absence of lumps. The formulated F2 preparation was much clear and transparent as compared to F1،F3and F4 formulation as showed in table 3 below . The skin irritation studies of developed gel were carried out on human volunteers and that confirmed the absence of any irritation on the applied surface in all formulations.

Table 3: physical appearance of Cetirizine topical gel

Topical Gels	Clarity	Color	Homogenesity	syneresis
F1(Carbopol 940)	+	White	fair	ve-
F2(HPMC)	+++	transparent	good	ve-
F3(Methyl Cellulose 2g)	+	Opaque transparent	good	ve-
F4(Methyl Cellulose 4g)	+	Opaque transparent	good	-ve

4.3. physiochemical properties of Cetirizine topical gel :

The pH values of all developed (F1, F2,F3, and F4) were 5.5,2.5,2.4 and 2.4 respectively ,this is because the drug(Cetirizine) was acidic.The values of spread ability indicate that the gel is easily spreadable by small amount of shear. Spread ability of formulated gels (F1, F2,F3 and F4) were 2.8 ,7.8 ,7 and 6 g cm/sec. Hence spread ability of F2 formulation was good as compared to other formulations, and we note that F1 (Carbopol 940) is the lowest spreadability because of its high micro-viscosity

Table4:physiochemical properties of Cetirizine topical gel				
Topical Gels	pH	Spreadability (cm)	Drug Content	% Drug content
F1(Carbopol 940)	5.5	2.8	9.7	97%
F2(HPMC)	2.5	7.8	9.9	99%
F3(Methyl Cellulose 2g)	2.2	7	9.81	98.1%
F4(Methyl Cellulose 4g)	2.3	6	9.54	95.4%

The PH values of all developed (F1,F2,F3&F4) were 5.5,2.5,2.4&2.3 respectively ,this is because the drug (Cetirizine) was acidic .The values of spreadability indicate that the gel is spreadable by small amount of shear.Spreadability of formulated gels (F1,F2,F3&F4) were 2.8,7.8,7&6 gcm/sec.Hence spreadability of F2 formulation was good as compared to other formulation ,and noticed that F1 is the lowest spreadability because of its high micro-viscosity.All developed gels showed good homogeneity with absence of lumps.The formulated preparation was much clear and transperant as compared to F1,F3&F4 formulations.The skin irritation studies of developed gels were carried out on human volunteers and that confirmed the absence of any irritation on the applied surface in all formulations.In-vitro permeability study showed that permeation of formulations (F1,F2,F3&F4) was comparable with each other.

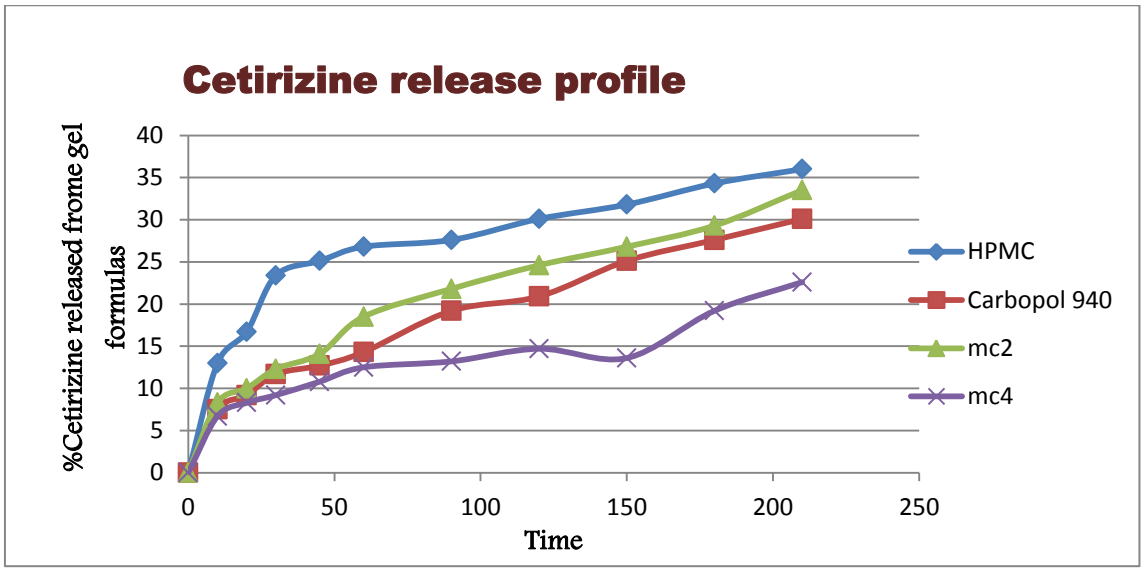
4.4.In Vitro Release Studies

HPMC gels showed higher drug release than methyl cellulose and Carbopol940gels.ThisresultmaybeduetothelowviscosityofHPMCgelsandthe greaterhydrophilicityofHPMC. Cheong et al. [39] reported that the HPMC molecules are giant macromolecules compared to drug and water molecules. They are made up of hundreds of chain segments in random coils held tightly by hydrogen bonding. HPMC being a hydrophilic has a

great affinity for water so when the polymer chain comes in contact with water, polymer-water interaction replaces the polymer-polymer attraction.

The percent of cetirizine released from methyl cellulose gels slightly decreaseuponchangingtheconcentrationofthepolymerfrom2to4%w/wofthein creaseintheviscosity. These results may be explained as the controlled release of drug from methyl cellulose . In general, the inverse relation between polymer concentration and cetirizine released is in agreement with lauffer's molecular diffusion theory of polymer gels (47).The theory states that the diffusion of a solute is inversely proportional to the volume fraction occupied by the gel forming agent. Welin-Berger et al. (48) found that an increase in the macroviscosity may affect the release rate of the active compound inversely.

At three hours, Carbopol gel showed lower drug release than the other polymers except MC4. This indicating that the drug release is influenced by the nature of each individual polymer. The structure of Carbopol plays a role in drug release, the main barrier for drug release from the aqueous Carbopol polymer gels is a mechanical layer formed by the random network of the polymer molecules which bind and entraps the surrounding water, and this aqueous phase may be the region for drug diffusion from the gel but in high concentration of polymer more than 0.5% w/w will increase the crosslink density which increase the tortuosity of the gel from which the drug release occur within the hydrogel network. These findings are in agreement with the data obtained by Songkro etal.[49]



Figure(9) cetirizine release profile from gel formulas

Table (5) %cetirizin released from gel formula				
Time	HPMC	Carbopol	mc2	mc4
0	0	0	0	0
10	13	7.5	8.3	6.7
20	16.7	9.2	10	8.3
30	23.4	11.7	12.3	9.2
45	25.12	12.7	14.1	10.8
60	26.8	14.3	18.5	12.5
90	27.6	19.2	21.8	13.2
120	30.1	20.9	24.6	14.7
150	31.8	25.12	26.8	13.6
180	34.3	27.6	29.3	19.2
210	36	30.1	33.5	22.6

Chapter five

Conclusion

On the basis of the previous findings we can concluded that; Cetirizine was successfully incorporated into the different topical gel preparations .It was observed that(HPMC)gel containing Cetirizine (F2) produced better spread ability and consistency as compared to crabapol 934P gel (F1) and Methyl cellulose gels (F3&4) formulation. The developed F2 gel showed good homogeneity, no skin irritation, good stability, antihistaminic effect and in vitro permeability. The HPMC forms water washable gel because of its water solubility and has wider prospects to be used as a topical drug delivery system. Therefore, it was concluded that our formula could be very promising topical alternative for the treatment of skin disease.

CHAPTER SIX

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