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Effect of Cyclodextrins Inclusion Complex and Gelling Agents on the Release of Ciprofloxacin HCL from Topical Gel Formulations

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Abstract

Background: Topically applied drugs have the advantage of supplying a higher concentration of the drug to the skin than systemically applied medications. The aim of this study was to develop and evaluate a gel formulation of ciprofloxacin hydrochloride (CP-HCL), also to provide a topical treatment for various bacterial skin infections.

Materials and methods: In order to improve the dissolution properties of CP-HCL, the physicochemical properties of CP-HCL:cyclodextrins (CDs) binary systems were studied in both solution and solid states after preparation of the complexes by two methods: simply by physical mixture and kneading methods. CP-HCL:CDs physical mixture and kneaded complexes were prepared and characterized using FTIR ,DSC and SEM comparing with CP-HCL as received. Different gel bases and concentrations of hydroxypropylmethylcellulose (HPMC), sodium carboxymethylcellulose (Na CMC), and sodium alginate (Na Alginate) were used to formulate CP-HCL and its CDs complexes .

Results: The results showed that inclusion complexation occurred for both kneaded and physically mixed CP-HCL with CDs. Almost all of the 19 formulations produced had suitable physicochemical properties, with formula F9, which included a CP-HCL:BCD physical mixture complex and a base consisting of a 10% w/w HPMC gel formulation, providing a good viscosity and drug release properties. Color, consistency, pH, rheological and kinetic properties, skin permeability, and drug release pattern were among the parameters examined. Furthermore, the antibacterial activity of CP-HCL and CP-HCL:CDs complexes, as well as gel formula containing 10% w/w HPMC, was investigated.

Conclusion: Ciprofloxacin and its complexes were successfully incorporated into the various topical gel preparations which showed promising results for the treatment of skin infections.

Key words: Cyclodextrin, Ciprofloxacin, HPMC, Na CMC, Na Alginate, Inclusion complexation.

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INTRODUCTION

Topical drug delivery is a successful way for treating of local conditions or penetrate through the skin's underlying layers, allowing for better absorption and hence the desired pharmacological systemic effect when other routes are ineffective (1).

Dealing with drugs that have limited water solubility, the formulation of suitable dosage forms for oral, parenteral, and topical routes is frequently an issue to be administered in large volume. Commonly, to improve the solubility of poorly-water soluble drugs different methods are used such as prodrug formation, use of non-aqueous co-solvents such as glycols or ethanol, drug solubilization in micelles using surfactants, pH adjustment and complex formation (2) (3).

Interaction of two or more molecules to form a non-bonded system with a well-defined stoichiometry is known as complexation (4). Complexation involves relatively weak forces such as hydrogen bonding, London forces, and hydrophobic interactions. Since there are no involved covalent bonds between them, these are also known as no-bond complexes (5). The formation of host-guest inclusion complexes by weak intermolecular interaction, known as cyclodextrin (CD) inclusion complexation, has been found to be a promising technique for improving the solubility , bioavailability as well as stability of drugs that are poorly water-soluble (6) (7).

Gel for topical application is the most favorable dosage form and could be formulated using gelling agents such as sodium carboxymethylcellulose, hydroxypropylmethylcellulose, and sodium alginate (8).

Ciprofloxacin hydrochloride (CP-HCL)) is a broad spectrum antibiotic, it acts against most bacterial pathogens that cause respiratory, urinary tract, gastrointestinal and skin infections (9). As a salt, CP-HCL is only sparingly soluble in water, very slightly soluble in ethanol, slightly soluble in methanol, and practically insoluble in acetone, ethyl acetate, and methylene

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chloride (10). Like other fluoroquinolone compounds, CP-HCL has a U-shaped pH-solubility profile, with high solubility at pH values below 5 and above 10, and low solubility near its isoelectric point (11) (12). Ciprofloxacin to be BCS Class IV.(13) It is a zwitter ion molecule containing two proton-binding sites values of pKa1 and pKa2 are 6.2 and 8.59, respectively (14).

This study aimed to develop and evaluate a gel formulation of ciprofloxacin hydrochloride (CP-HCL), to be used topically for treatment of various bacterial skin infections.

Materials: β-cyclodextrin and HP- β-cyclodextrin were purchased from Sigma Chemical Company (st. louis.mo), Ciprofloxacin HCl was optained from PiONEER Co. for Pharmaceutical Industries, Hydroxyl propyl methyl cellulose K15M (HPMC) was purchased from Alpha Chemika, India, Sodium alginate was optained from PiONEER Co. for Pharmaceutical Industries, and Sodium carboxy cellulose (SCMC) was purchased from Jiangsu yew al co., ltd (china).

Methods (Experimental Work)

Determination of Ciprofloxacin HCl Melting point

A small amount of the drug powder was placed in a capillary tube to calculate the melting point. The tube was flame-sealed on one side before being placed in Stuart's electric melting point (15).

Preparation of Solid Samples:

The following methods were used to make various CP-HCL/CDs formulations in a 1:1 molar ratio: **(a) Physical mixing method (Phy. Mix. Meth.)** (16): By which CP-HCL and CD were placed in a screw-cap glass vial and mixed for 30 minutes to ensure consistent mixing. **(b) Kneading method (Kn. Meth.):** In this method CDs and CP-HCL were mixed in a mortar and kneaded with the aid of about 1 ml deionized water for 15 minutes, then dried in an oven for 24 hours at 50°C. The resulting dry solid mass was finely powdered, passed through 60 mesh sieve, and placed in a sealed glass vial until used.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 7523 – 7543
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Phase Solubility Study:

In a series of 25ml conical flasks, excess amount of CP-HCL (100 mg) were introduced to either a buffer or β-CD aqueous solutions. The mixtures were shaken for 48 hours at (28°C) in a water bath shaker to reach equilibrium, then 2ml aliquots were taken every 12 hours and filtered via a 0.45μm syringe filter for dilution and CP-HCL concentration was determined by calculating absorbance at its own λmax value (17, 18).

Fourier Transform Infrared Spectroscopy (FTIR)

Samples of CP-HCl , βCD , HP-βCD , physical and kneading complex powders; each sample was pressed in a disk after being combined with potassium bromide. Shimatzu FTIR spectroscopy was used to study the disc (4000-400) cm-1 (19) (20) .

Differential scanning calorimetry (DSC):

With a linseis DSC (STA PT-1000 linseis, Germany), the thermal habits of pure CP-HCL, BCD, HP-BCD, physical, and kneading complex powders were investigated, samples were loaded separately into aluminum crucibles pans and temperature was allowed to raise from 25 to 400 °C at a rate of 10 °C/min under an argon atmosphere (inert conditions) (21, 22).

Scanning electron microscopy (SEM)

The surface morphology of pure CP-HCL, βCD, HP- βCD as well as their physically mixed and kneaded inclusion complexes were examined by a INSPECT F50 scanning electron microscope (FEI, HOLAND) (23) (24).

Preparation of Gel Formulas

Table (1) shows different gel formulations of Phy. Mix. Meth. and Kn.Meth. products using the following gelling agents:

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 7523 – 7543
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Sodium alginate gel

The alginate was dissolved in distilled water and heated to 60°C while stirring. 0.5% w/w CP-HCL or (Phy. Mix. Meth. complex) and (Kn. Meth. complex) were dissolved in the resulting gel after cooling to below 40°C (25).

Hydroxypropylmethylcellulose (HPMC) gel

HPMC was dispersed in hot water (80°C) to make gels. After cooling the dispersions to 25°C, 0.5 % w/w CP-HCL or equal weight in (Phy. Mix. Meth.) or (Kn. Meth.) were added, stored at 4°C for the next 24 hours to allow maximum swelling of the polymer and produce homogenized systems (26).

Sodium carboxymethylcellulose (Na CMC) gel

In a glass mortar, Na CMC was blended with glycerin, and a clear gel was created by adding small amounts of the mixture to a solution of previously warmed deionized water while stirring. This method was used to make the Na CMC gel, and then 0.5 % w/w CP-HCL or equivalent weight of (Phy. Mix. Meth.) or (Kn. Meth.) were applied using a mortar and pestle (27).

Evaluation of the Ciprofloxacin gel

Physical Properties of the gel

The color of the prepared gel formulations was visually evaluated. Homogeneity, consistency, pH, and viscosity were also determined.(28)

Measurement of pH

A gel solution was made by dissolving 1 gram of the gel in 100 mL deionized water and allowing it to sit for 2 hours. After that, a digital pH meter was used to assess the pH of the prepared gel solution at 18 °C. (29)

Viscosity Measurements

A Brookfield viscometer was used to assess the viscosity of various gel formulations at 37°C (Brookfield DV-E Viscometer). The samples were rotated at 3, 5,10,20,30, 50, and 100 rpm using spindles S63 and S64, and the viscosities were measured with a 30 second interval between each rate. (29)

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Table (1) The prepared gel formulas showing the main active and the complexation method.

Formula no.	CP-HCL g%	Sodium Alginate g%	HPMC g%	SCMC g%	Deionized water QS Up to 100 g	Type of drug added
F1	0.5	5			100	Kn. Meth. complex
F2	0.5	5			100	Phy. Mix. complex
F3	0.5	5			100	CP-HCL alone
F4	0.5	10			100	Kn. Meth. complex
F5	0.5	10			100	Phy. Mix. complex
F6	0.5	10			100	CP-HCL alone
F7	0.5		10		100	Kn. Meth. complex
F8	0.5		10		100	CP-HCL alone
F9	0.5		10		100	Phy. Mix. complex
F10	0.5		13		100	CP-HCL alone
F11	0.5		13		100	Phy. Mix. complex
F12	0.5		13		100	Kn. Meth. complex
F13	0.5			4	100	Phy. Mix. complex
F14	0.5			4	100	Kn. Meth. complex
F15	0.5			4	100	CP-HCL alone
F16	0.5			6	100	CP-HCL alone
F17	0.5			6	100	Phy. Mix. complex
F18	0.5			6	100	Kn. Meth. complex
F19	0.5		10		100	Phy. Mix. complex With HP-BCD

In Vitro Release Test

A small funnel with a diameter of 3 cm was adjusted to accommodate 2 gm of each formula containing an equivalent weight of 0.5 % w/w of CP-HCL.

A cellulose membrane was sealed in place with a rubber band over the funnel's mouth. In a 500 mL beaker of the dissolution apparatus, the modified dialysis cell was inverted in phosphate citrate buffer pH 5.5.

After 1, 2, 3, 4, 5, and 12 hours, the buffer solution was pipetted from the collecting medium and replaced with an equivalent amount of fresh buffer solution and the device maintained at 37°C(30). The samples were spectrophotomertircally analyzed for CP-HCL content at its λmax.

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Effect of Different Polymers and β-cyclodextrin as Complexing Agent on the Release of CP-HCL in Phosphate citrate Buffer pH 5.5 at 37°C

In order to choose the appropriate polymer for gel formulation, different polymers (Sod. alginate, HPMC and Na.CMC) were used with CP-HCL or (Phy. Mix.) and (Kn.) complexes by investigating its effect on the release process**.**

Effect of Different Concentration of Polymers on the Release of CP-HCL in Phosphate Citrate Buffer pH 5.5 at 37°C

In order to select the best polymer concentration for formulating of the gel, different concentrations of sodium alginate, HPMC, and Na CMC were used with CP-HCL or (Phy. Mix. Meth.) and (Kn. Meth.) through studying its effect on the release process.

Determinations of the Drug release kinetics and mechanisms

Kinetics of Drug Release

To characterize drug release kinetics and propose a mechanism of drug release, the cumulative amount of (CP-HCL) released from the selected formulas at successive time intervals was fitted to zero order, first order kinetics, Higuchi, and Korsmeyer–Peppas models (31, 32).

Anti-bacterial activity test (33)

Some of the solid formulas and optimal gel formula (9 samples) were clinically tested against different strains of bacteria, then plated on agar media at 37°C for 18-24h. Clinical samples include gram positive bacteria *Streptococcus spp.* and gram negative bacteria *Klebsilla spp*. 100 µl of inoculums (10^8 CFU/ml; 0.5 Mac Farland standard) of each type of bacteria was spread on Mueller Hinton Agar (MHA) plate using cotton swab. The diameter of three wells was punched (6mm). Into each well, 100 microliters of the prepared compounds or formulas in concentration (100µg of CP-HCL in each different formula) were used. CP-

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HCL was used as a standard positve antimicrobial and the buffer solution was used as a negative control (34).

Statistical analysis

The experimental data were presented as mean ± of standard deviation (SD). Three-way ANOVA that include Bonferroni test (pairwise comparisons) was also used for statistical analysis at 95%: significance ($p < 0.05$) and ($p > 0.05$) for non-significance. Statistical calculation was done using Statistical Package for the Social Sciences (SPSS) 25.0 software.

Results and Discussion:

Ciprofloxacin HCL Characterization / Melting Point

The melting point of (CP-HCl) was determined to be 317 °C. This finding is consistent with that stated in references, indicating that the drug powder used in the analysis was pure.(15, 35)

Phase Solubility Study

The total solubility of CP-HCL versus total concentration of βCD is shown in table (2), while Fig. (1) Summarizes the findings of the phase solubility analysis at 28 °C, which were determined by plotting CP-HCL apparent equilibrium concentrations against βCD concentrations. The apparent solubility of CP-HCL at 28 °C increased linearly as a function of βCD concentration, and this linearity was confirmed by these results indicating the formation of water soluble complexes in the solution. The size of the complex stoichiometry was assumed to be 1:1 because the slope of the diagram was less than unity, (0.0029). The apparent stability constant was discovered to be 219 M^{-1}. (17) and the solubility of CP-HCL increased 1.32 fold.

The apparent stability constant (K1:1) for these complexes was determined using phase solubility diagrams and the equation below (36):

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K1:1 = slope/ So (1- slope),

Where, So is intercept, CP-HCL solubility at zero β-CD concentration.

Table (2) Total Solubility of CP-HCL against Total Concentration of βCD

Concentration* 10^{-3} **M of βCD**	**Concentration *10^{-5} M of CP-HCL**
0	0.133
3.5	0.145
7	0.153
10.5	0.161
14	0.176

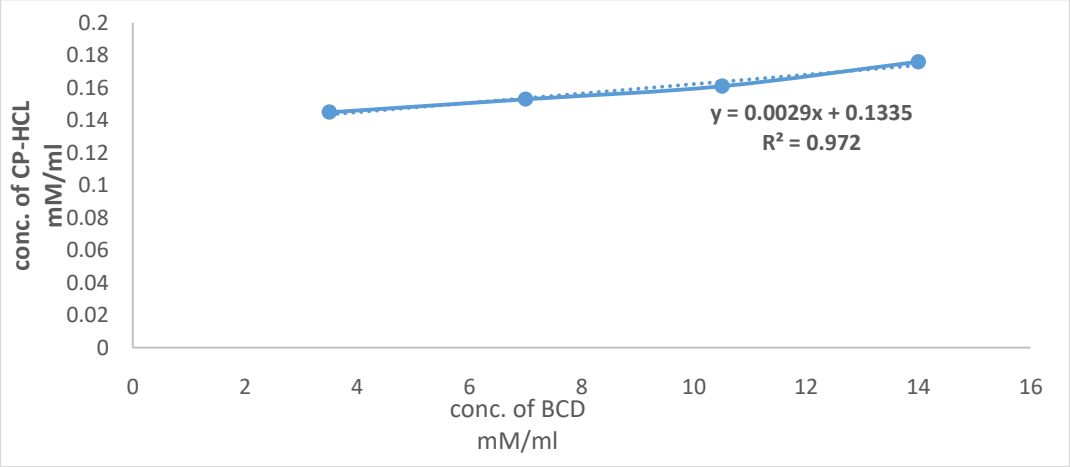

Figure (1) The diagram of Phase solubility for CP-HCL:CD solution.

Study of Fourier Transform Infrared Spectroscopy (FTIR) for solid samples:

The infrared spectra of CP-HCL, βCD, HP-βCD (physical mixture and kneaded samples of CP-HCL with βCD and HP-βCD) samples-CDS complexes are shown in (Fig 2). The absorption intensity of the CN group appearing in 1626 cm-1 was shifted (showed a red shift), and the absorption intensities of CN in all inclusion complexes were weaker than on CP-HCL alone , so it can be assumed that CN from CP-HCL was incorporated into the cavity of CDs (20).

Whereas the spectrum of βCD was characterized by bands at 3363 cm^{-1} of O-H stretching and a broad band due to H-bonding. the spectrum of the complex showed no shift to the band corresponding to OH stretching vibration. (15, 37).

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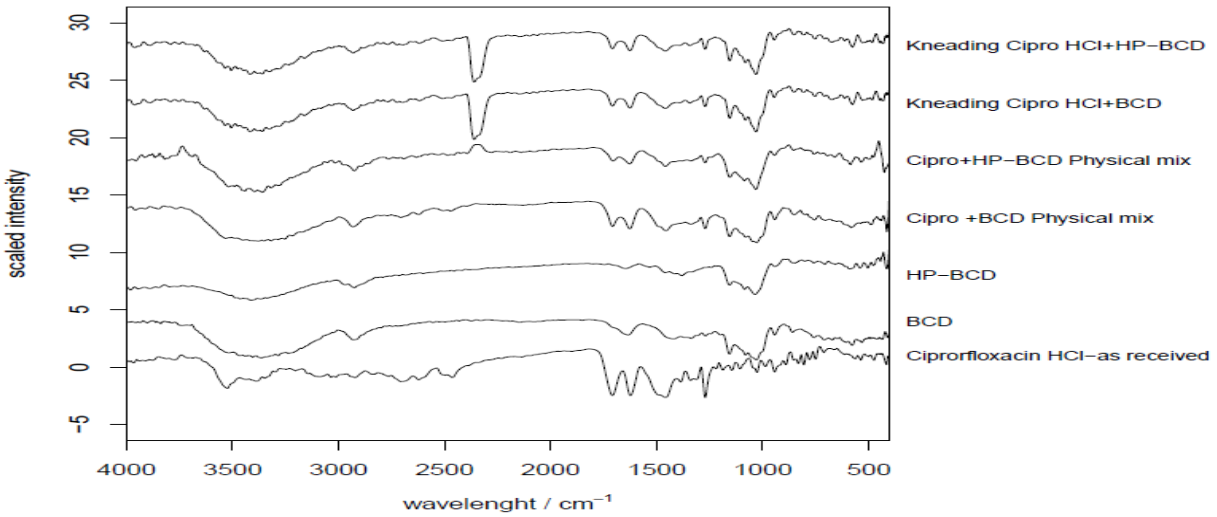

Figure (2) The IR spectra for all solid samples and the prepared solid complexes together by R studio drawing.

Differential Scanning Calorimetry

The DSC results showed endothermic peaks for CP-HCL, βCD, and HP-βCD at 154.1 ℃, 113.9 ℃, and 91.6 ℃, respectively. The disappearance of CP-HCL, βCD, and HP- βCD endothermic peaks, as well as the appearance of another endothermic peak in the range started from 102.3℃ to 149.8℃, could indicate the formation of an inclusion complex between CP-HCL and CDs. The melting points of CP-HCL and inclusion complexes with βCD and HP-βCD were determined to be 317 ℃, and 259 ℃, 252 ℃, respectively (38). As showed in figure (3) below:

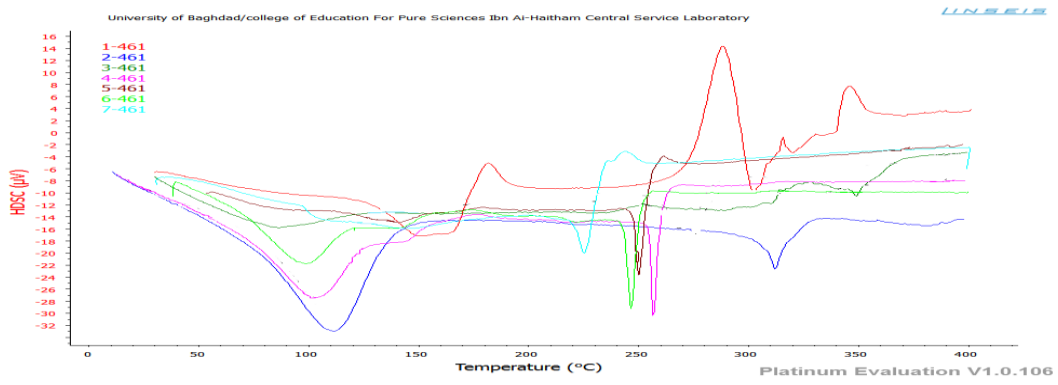

Figure (3) The DSC results for CP-HCL, βCD, and HP-βCD and their physical mixture and kneaded complexes showing the endothermic peaks plotted together.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 7523 – 7543
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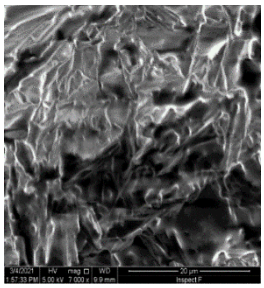
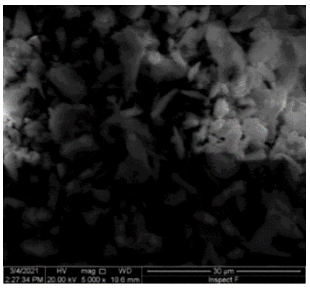
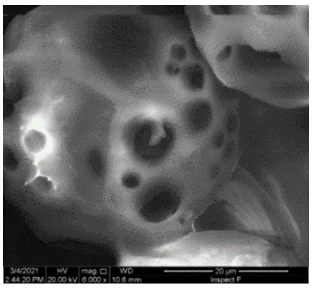
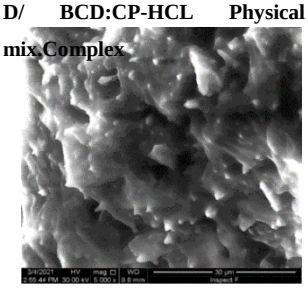
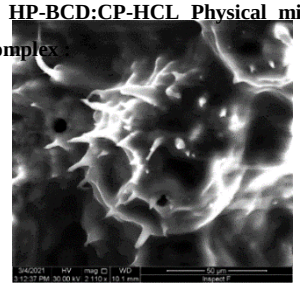
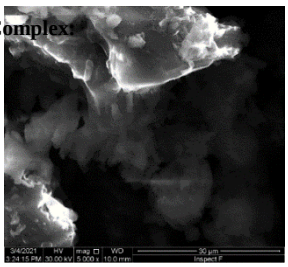
Scanning electron microscopy (SEM) Results:

Figure (4) shows the existence of a crystalline particle of uniform size distinguishes pure CP-HCL. On the other hand, both BCD and HP-BCD appear as crystalline particles with no definable form.

The crystalline structure of both CP-HCL and CDs was visible in the physical inclusion complexes of CP-HCL:CDs. CP-HCL crystals mixed with CDs crystals were observed adhering to their surfaces or within their cavities. For kneaded samples showed the normal morphology of preparations made with this system in general. Where, small particles with a tendency for aggregation, indicating the presence of an amorphous substance with single component in the complex, implying maximum complex formation (17).

Although the SEM technique is incapable of concluding true complex formation, the micrographs obtained support the concept of creating a new specific component. So, in the case of CP-HCL CDs 1:1 M kneaded and physical mixture binary systems, the inclusion complexation can be confirmed using DSC and FTIR data together with this analysis (39).

A / CP-HCL	B/ BCD	C/ HP-BCD
		

D/ BCD:CP-HCL Physical mix.Complex	E/ HP-BCD:CP-HCL Physical mix. Complex	F/ BCD:CP-HCL Kneading Complex
		

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G / HP-BCD:CP-HCL Kneading Complex

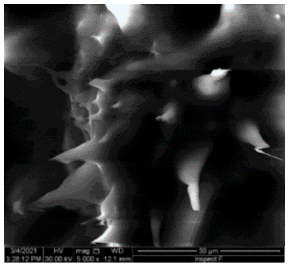

Figure (4) SEM by a INSPECT F50 scanning electron microscope (FEI, HOLAND) for CP-HCL, βCD, HP- βCD, their physically mixed and kneaded inclusion complexes. Size of magnification and sample shot 30 micron/5000X.

Physical properties and pH of the prepared formulations

Ciprofloxacin HCL gel formulas prepared with Na alginate, HPMC, or SCMC were transparent, homogenous, and smooth in appearance, with the exception of the formulas containing Na alginate, which was slightly brown in color. The HPMC base was clearer and stickier than the other formulations (40).The prepared formulas were easily distributed over skin. Their pH values ranged from 5.12 to 7.63, which is considered appropriate to avoid discomfort when applied to the skin, as skin pH is about (5.6). (41). These results were summarized in Table (3):

Table (3) Results of physical properties evaluation of the prepared gel formulations.

Formula No.	**Polymer used**	**Type and Method of Complexation**	**Consistency and Homogeneity**	**Color**	**pH Value** mean ± (SD)
F1	Na Alginate 5%	BCD/Kneading	Excellent	Slightly Clear brawn	7.42±0.120
F2	Na Alginate 5%	BCD/Physical	Excellent	Slightly Clear brawn	7.25±0.110
F3	Na Alginate 5%	CP.HCL Alone	Excellent	Slightly Clear brawn	6.8±0.158
F4	Na Alginate 10%	BCD/Kneading	Excellent	Slightly Clear brawn	7.22±0.086
F5	Na Alginate 10%	BCD/Physical	Excellent	Slightly Clear brawn	7.81±0.295

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F6	Na Alginate 10%	CP.HCL Alone	Excellent	Slightly Clear brawn	7.63±0.092
F7	HPMC 10%	BCD/Kneading	Excellent	Clear yellowish	7.83±0.269
F8	HPMC 10%	CP.HCL Alone	Excellent	Clear yellowish	5.37±0.318
F9	HPMC 10%	BCD/Physical	Excellent	Clear yellowish	5.82±0.088
F10	HPMC 13%	CP.HCL Alone	Excellent	Clear yellowish	5.15±0.136
F11	HPMC 13%	BCD/Physical	Excellent	Clear yellowish	5.12±0.235
F12	HPMC 13%	BCD/Kneading	Excellent	Clear yellowish	5.95±0.075
F13	Na CMC 4%	BCD/Physical	Excellent	Clear white	6.42±0.065
F14	Na CMC 4%	BCD/Kneading	Excellent	Clear white	6.16±0.102
F15	Na CMC 4%	CP.HCL Alone	Excellent	Clear white	6.5±0.081
F16	Na CMC 6%	CP.HCL Alone	Excellent	Clear white	6.62±0.065
F17	Na CMC 6%	BCD/Physical	Excellent	Clear white	6.71±0.237
F18	Na CMC 6%	BCD/Kneading	Excellent	Clear white	6.22±0.080
F19	HPMC 10%	HP-BCD/Kneading	Excellent	Clear yellowish	5.68±0.260

Viscosity Measurements

The viscosity measurement profiles revealed that as the share stress increased, normally arranged molecules aligned their long axes in the direction of flow orientation, lowering the material's internal resistance and decreasing viscosity (42). The findings shows that the viscosity for each kind of polymer increased as the polymer concentration increased. According to many literatures, they have a highly acceptable rheological profile range of 3999 -120000 cps0 (43).

Formulas with HPMC and Na alginate polymers at the highest concentration of the polymer **(group A)** rotated with spindle S63 and the resultant viscosities at different rates were the same for all these formulas; 23990, 12000, and 5999 cps at 5, 10, and 20 speed rotation respectively. Formulas with HPMC and Na alginate polymers at the lowest concentration of the polymer **(group B)** rotated with spindle S63 and the resultant viscosities at different rates were the same for all these formulas; 20000, 9998, and 3999 cps at 5, 10, and 20 speed rotation respectively. While formulas with Na CMC polymer at the highest concentration of the polymer **(group C)** rotated with spindle S64 and the resultant viscosities

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at different rates were the same for all these formulas; 120000, 59990, and 29990 cps at 5, 10, and 20 speed rotation respectively. Formulas with Na CMC polymer at the lowest concentration of the polymer **(group D)** rotated with spindle S64 and the resultant viscosities at different rates were the same for all these formulas; 99980, 49990, and 20000 cps at 5, 10, and 20 speed rotation respectively. These finding are illustrated in the figure (5)

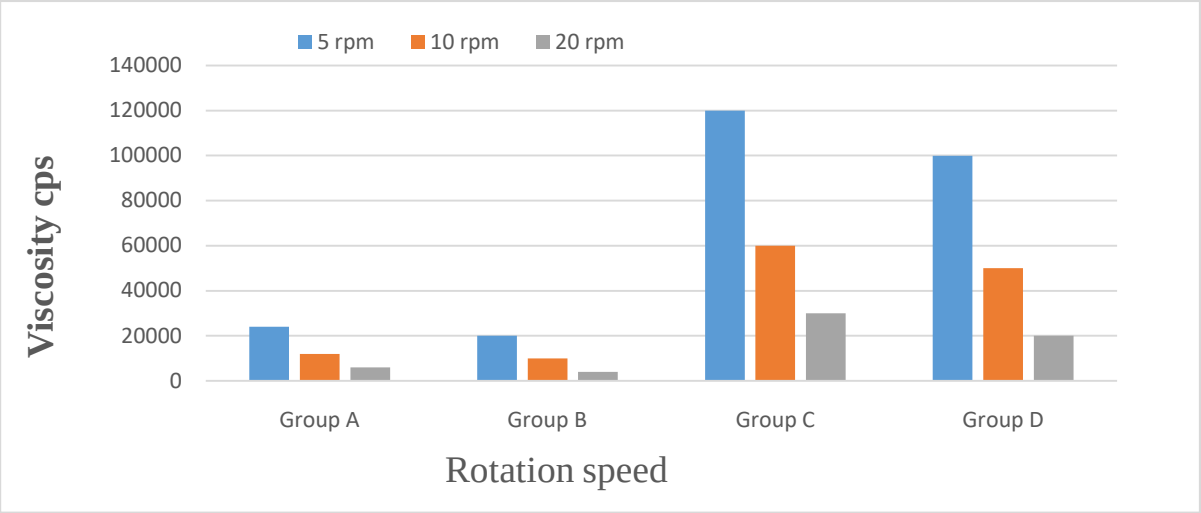

Figure (5) Gel formulas (F1-F19): four group division according to their polymer concentration; viscosity (cps) at 37 °C at different rotation per minute (rpm).

Effect of Different Polymers and Cyclodextrins as Complexing Agent on the Release of CP-HCL in Phosphate Citrate Buffer pH 5.5 at 37 °C

Figure (6) shows the release of CP-HCL as a function of square root of time from various bases containing 0.5 % w/w of the drug to obtain a straight line.
According to the data, the release rate constant (k) reduced in the order shown in table (4): sod. Alginate < sod. CMC < HPMC. This could be explained by the fact that CP-HCL is slightly insoluble in water, so drug partitioning is reduced according to the nature of the base; the highly viscous Na CMC base showed a lower release rate than the HPMC gel (44).

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 7523 – 7543
Received 05 March 2021; Accepted 01 April 2021.

When some types of polymers and cyclodextrins were both present, a significant reduction in the cyclodextrin solubilizing efficiency towards the drug was observed, which was attributed to a possible competition effect between the Na alginate and the drug for the interaction with the macrocycle.(45)

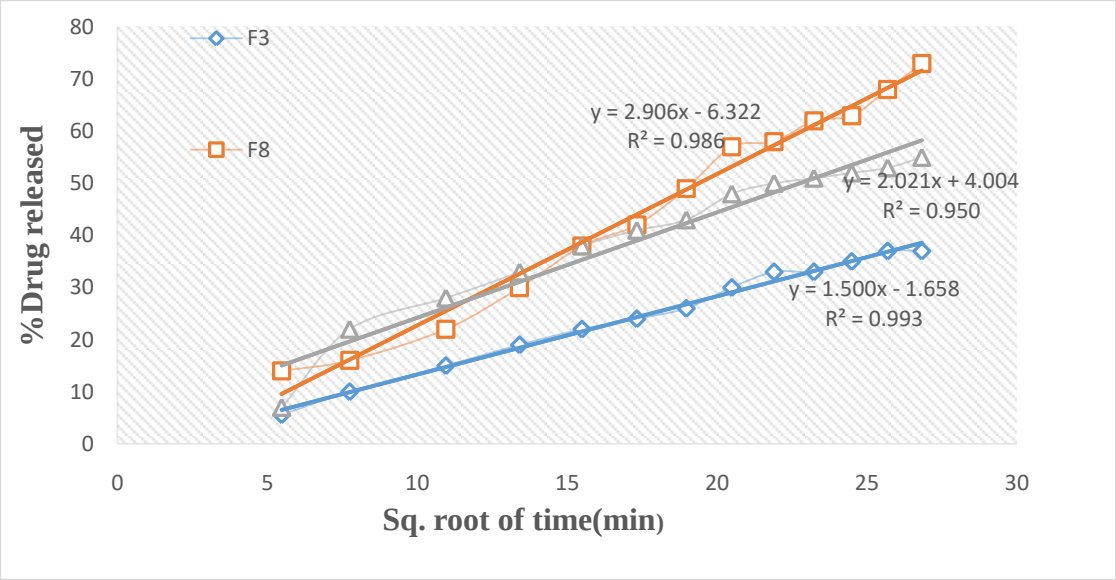

Figure (6) Effect of Different Polymers on the Release of CP-HCL in Phosphate Citrate Buffer pH 5.5 at 37 °C as a function of square root of time in (min)

Table (4) Effect of Different Polymers on the Release Rate Constant (K) of CP-HCL in Phosphate Citrate Buffer pH 5.5 at 37 °C

Type of polymer (base)	**K mg.(min.)-1/2**	**Correlation coefficient (r)**
F3 (Na alginate 5%)	1.50	0.9931
F8 (HPMC 10 %)	2.90	0.9868
F15 (Na CMC 4%)	2.02	0.9508

Effect of Different Concentration of Polymers on the Release of CP-HCL in Phosphate Citrate Buffer pH 5.5 at 37 °C

The effect of various HPMC and sodium CMC concentrations on the CP-HCL release rate as a function of square root of time. The release rate constants are listed in table (5). The result showed that the concentration of the polymer had

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an effect on the release rate constant (k). Increasing in the polymer concentration a decrease the value of (k).

This result's view is in agreement with previous findings, which indicated that a drug's release rate is determined by the physical structure of the polymer network, when the gel is extremely hydrated (low polymer concentration), the drug diffuses through the pores, while when the gel is dehydrated (high polymer concentration), the drug dissolves or remains in the polymer and is transported between its chains, so the hydrophobocity of the gel is increased by cross-linking, which reduces the drug's release rate (3). However, as the impact of increased viscosity on drug release retardation and formula stability becomes more widely recognized, viscosity becomes more significant (46)

Table (5) Effect of sodium CMC and HPMC concentrations on the release rate costant (k) of CP-HCL in phosphate citrate buffer pH 5.5 at 37 °C).

Type of polymer (base)	**K mg.(min.)-1/2**	**Correlation coefficient (r)**
F7 (HPMC 10%) / Kn.meth. complex	3.4405	0.9910
F12 (HPMC 13%) / Kn.meth. complex	2.9556	0.9865
F14 (Na CMC 4%) / Kn.meth. complex	1.6914	0.9401
F18 (Na CMC 6%) / Kn.meth. complex	1.6626	0.9481

Effect of Different types of Cyclodextrins (BCD and HP-BCD) as Complexing Agent on the Release of CP-HCL in Phosphate Citrate Buffer pH 5.5 at 37 °C

According to the the release rate costant (k) of CP-HCL in phosphate citrate buffer pH 5.5 at 37 °C) as shown in table (6), the effect of Different types of CDs as Complexing Agent F9 (with **BCD**) and F19 (with **HP-BCD**); it was found that the F9 was more faster than F19 this may due to **HP-BCD** form

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aggregation that restrict drug release. The statistical analysis showed no significant difference was found if different CDs used.

Table (6) Effect of Different types of Cyclodextrins as Complexing Agent F9 (with **BCD**) and F19 (with **HP-BCD**) on the release rate costant (k) of CP-HCL in phosphate citrate buffer pH 5.5 at 37 °C)

Type of Cyclodextrin	**K mg.(min.)-1/2**	**Correlation coefficient (r)**
F9 (HPMC 10%) / Kn.meth. complex with **BCD**	3.8488	0.9985
F19 (HPMC 10%) / Kn.meth. complex With **HP-BCD**	2.3916	0.8691

Drug Release Mechanisms and Kinetics (Mathematical Analysis)

In order to understand the mechanism of drug release and the release rate from dosage forms, in-vitro release data was fitted to various mathematical models such as Zero order, First order, Higuchi, and Korsmeyer- Peppas models.

The majority of the formulations employ Higuchi kinetics, while a few others had first order, with the following formulas fitting best to a favorable zero order model: (F4,F5,F8,F9,F10,F13,F17,F18,F19), indicated by high regression value (R2).The highest one is **F9**.

The value of the release exponent (n) in the Korsmeyer-Pappas model determines the release mechanism; all formulas with n values between 0.45 and 0.89 indicate anomalous (non–Fickian) transport, which corresponds to a combination of drug diffusion and matrix erosion drug release mechanism. But F4, n values greater than 0.89 indicate super case II transport, in which polymer relaxation and chain disentanglement are involved in drug release.

Anti-bacterial activity test

The antibacterial activity of all compounds was assessed in this study by measuring the inhibition zone (mm), and the effect of CP-HCL alone as a positive control, as well as formula F9 and various prepared complexes and

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polymer composing this formula. It was tested on Klebsilla spp., and was found that **F9** the selected formula zone of inhibition is 34 compared with 30 for CP- HCL alone. Also tested on streptococcus spp., and was found that **F9** the selected formula zone of inhibition is 35 mm compared with 30mm for CP- HCL alone.

CDs improved antibacterial activity against both studied bacteria for solid complexes and selected formula, according to the findings.(47) The increase in antibacterial activity for all forms of CDs complexes alone or in the gel formula may be due to an increase in the nature of water solubility of the drug molecule, which resulted in greater drug diffusivity into the agar medium, resulting in a greater zone of inhibition diameter for CDs complexes .(48)

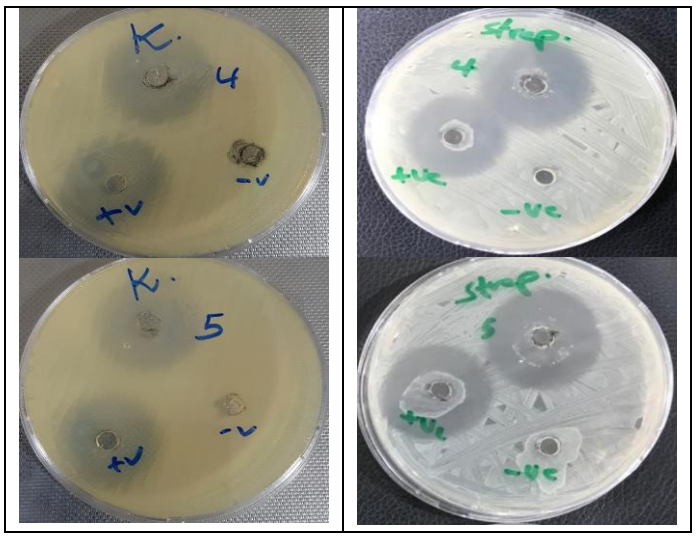

Figure (7) The Zone of Inhibition for the selected formula (F9 containing phy.mix complex) compaired with (F8 containing CP-HCL only).

Conclusion:

Nearly all of the 19 formulations produced had suitable physicochemical properties, with formula F9 containing CP-HCL: BCD physical mixture complex and the base consist of a 10% w/w HPMC gel formulation having the best viscosity and drug release properties. Color, consistency, pH, rheological and kinetic properties, skin permeability, antibacterial activity study and drug release pattern are some of the parameters that were evaluated.

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