

FORMULATION OF AZAPROPAZONE OPHTHALMIC PREPARATIONS USING CYCLODEXTRINS AS COMPLEXING AGENTS

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يتناول البحث دراسة تأثير كل من بيتاسيكلودكسترين وهيدروكسي بروبيل بيتاسيكلودكسترين على ذوبانية الأزابروبازون وكذلك معدل إنطلاقه المعملية من صواعغات متنوعة تستخدم كمستحضرات للعيون. وقد تم التوصل إلى أن ذوبانية العقار في الماء قد زادت بدرجة ملحوظة خاصة مع هيدروكسي بروبيل بيتاسيكلودكسترين ثم بيتاسيكلودكسترين على التوالي كما تناولت الدراسة تحضير صواعغات مختلفة مثل القطرات والمستحضرات الهلامية والرقائق المحتوية على الدواء باستخدام كربوكسي ميثيل سيليلوز الصوديوم والكاربوبول ٩٤١ بتركيزات مختلفة ومناسبة لكل مستحضر. وقد أوضحت النتائج التي تم التوصل إليها أن معدل إنطلاق الدواء من الصواعغات المحضرة والتي تحتوي على معقدات الدواء بنسبة ١:١ مع مشتقات السيكلودكسترينات أعلى من الصواعغات المحضرة والتي تحتوي على معقدات الدواء أعلى من الصواعغات الأخرى والمحتوية على الدواء. وقد أظهرت النتائج أن الإتاحة المعملية للدواء من القطرات أعلى منها في المستحضرات الهلامية والرقائق مما يدل على أن تأثير مشتقات السيكلودكسترين التي تناولتها الدراسة على الزيادة الواضحة في ذوبانية الدواء وتحسين الإتاحة المعملية للدواء من المستحضرات المصاغة.

The effect of cyclodextrins (CyDs), hydroxypropyl beta-cyclodextrin (HP-β-CyD) and beta-cyclodextrin (β-CyD) on the solubility and release characteristics of azapropazone (Az) was investigated. The aqueous solubility of azapropazone was significantly increased by the formation of water soluble (1:1) inclusion complexes with CyDs. Also, the solubility of azapropazone was found to be increased linearly as a function of HP-β-CyD followed by β-CyD. The ophthalmic formulations (drops, gels and ophthalmic inserts) were prepared using aqueous vehicles containing sodium carboxymethyl cellulose and carbopol 941 mixture at different concentrations. The amounts released of azapropazone from eye drops, gels and ophthalmic inserts containing the drug complexes with CyDs in (1:1) molar ratio were significantly higher than formulations containing the drug alone. In addition, the in-vitro availability of the drug from drops was higher than gels or and ophthalmic inserts at different time intervals.

INTRODUCTION

Azapropazone is one of the most potent non-steroidal anti-inflammatory drug.¹ It is used in pre- and post-operative inflammation.² The drug is available as capsule, each contains 300 mg.³ Its oral medication was reported to induce gastrointestinal disorders such as vomiting, ulceration and gastrointestinal hemorrhage.^{4,6} The formulation of such potent drugs in topical preparations will overcome the problems associated with its oral use.⁷

Carbonic anhydrase inhibitors like acetazolamide have been used orally in large

dose to treat glaucoma and this frequently leads to systemic side effects. The topical administration of these drugs directly to the eye could reduce or even abolish these side effects. Acetazolamide is practically insoluble in water and in tear fluid, this is limits its ocular bioavailability. So, one of the attempts used to improve the ocular bioavailability of the topically applied poorly soluble drugs, is the utilization of CyDs.^{8,9}

Also, the topically administered indomethacin as anti-inflammatory has been shown to reduce post-operative inflammation occurring after cataract surgery.¹⁰ The alkylated

and hydroxyalkylated cyclodextrins appear to be more suitable for the formulation of poorly soluble drugs than the non-substituted parent CyDs, because of their increased aqueous solubility, lack of toxicity and ability to alter the phase solubility behavior.¹¹

The use of cyclodextrins in ophthalmic formulations has been receiving some attention.¹² Jansen *et al.* (1990),¹³ demonstrated that, up to 12.5% HP- β -CyD caused no irritation to the corneal tissues. An area where cyclodextrins may have a significant therapeutic benefit, is the solubilization of poorly water soluble drugs intended for the ophthalmic therapy. Some encouraging data has been seen with cyclosporine A and α -cyclodextrin.¹⁴ The best examples of the use of cyclodextrins with poorly water soluble drugs, is the steroids, especially dexamethasone and its acetate ester.^{15,16} Usayapant *et al.* (1991)¹⁵ studied the solubility, chemical stability and improved ophthalmic delivery of dexamethasone and dexamethasone acetate in the presence of HP- β -CyD.

The aim of this study was to investigate the effect of inclusion complexation of azapropazone with HP- β -CyD and β -CyD on the solubility of the drug. Also, the promising drug complexes with CyDs would be formulated in ophthalmic drops, gels and inserts. Then, the release characteristics of the drug from the suggested formulations will be studied.

EXPERIMENTAL

Materials and methods

- HP- β -CyD (an average degree of substitution, 4.8) and β -CyD were supplied by Nippon Shokuhin Kako Co., Tokyo, Japan. The former was used as received, while, the latter was used after recrystallization from water.
- Azapropazone was supplied by Siegfried, Zofingen, Switzerland.
- Carbopol 941, (BF Goodrich Co. Specialty & Chemical Division 6100 Oak Tree Blvd., Cleveland, Ohio 44131, USA).
- Sodium carboxymethyl cellulose and benzalkonium chloride (BDH Chemical Ltd, GB. Liverpool, England).
- Disodium hydrogenphosphate, citric acid and n-octanol (Prolabo, Chemicals, Paris, France).

- Cellophane membrane, Spectrapor: M.W. Cutoff: 12000-14000 (Fischer Sci. Co., Pittsburgh, USA).
- All other chemicals and solvents were of analytical reagent grade and it is used as received.
- Double distilled water was used in all formulations.

Apparatus

- Unicam SP 1800 U.V. Spectrophotometer, (Pye Unicam Ltd Cambridge, England).
- Rotovisco RV3 (Haake Mess-Technik GmbH. U. Co., Germany).
- Beckman pH-meter (Beckman instruments Fullerton, CA 92634, USA).
- Rotating bottle apparatus (Seti, Cairo, Egypt).
- MSE Minor centrifuge (MSE Scientific instruments, Manor Royal, Crawley RH10 2QQ Sussex, England).

Phase solubility study

The solubility measurements were carried out according to the method described by Higuchi & Connors (1965).¹⁷ The screw-capped vials containing azapropazone alone in excess amount (50 mg), and azapropazone (50 mg) with CyDs at various concentrations (2×10^{-3} - 16×10^{-3} M/L) were shaken at $37 \pm 0.5^\circ$. After equilibrium was attained, (12 days), the solutions were properly diluted with water and analyzed spectrophotometrically at 255 nm for total drug content. The experiments were done without drug and served as a blank. The experiments were triplicated and the mean was recorded. Then, apparent stability constants 1:1 for complexes were calculated using the following equation.

$$K_{1:1} = \frac{\text{slope}}{S_o (1 - \text{slope})} \dots \dots \dots \text{Eq. (1)}$$

Where $K_{1:1}$ is the stability constant for the complex and S_o is the solubility of the drug in the absence of CyDs.

Preparation of azapropazone-CyDs complexes

The solid complexes of azapropazone with CyDs (1:1) molar ratio were prepared by the kneading method (Tsuruoka *et al.*, 1981),¹⁸ A

weighed quantity of azapropazone and CyDs were mixed and kneaded in a mortar with an adequate amount of ethanol-water mixture (1:1 v/v) for 45 minutes and kept over night in a dark place. The resulted mass was dried under reduced pressure at room temperature ($25\pm 0.5^\circ$). The products were then sieved and the fractions of particle size of about $125\ \mu\text{m}$ were collected and stored in desiccators, until use.

Determination of partition coefficient

Ten ml of n-octanol was added to an equal volume of distilled water saturated with n-octanol and placed in a screw capped tubes of 50 ml capacity. Azapropazone (20 mg), and an equivalent amount of the drug complexes with HP- β -CyD or β -CyD complexes were added to the partitioning system. The tubes were shaken on thermostatically controlled water bath at $37\pm 0.5^\circ$. When no difference was observed between repetitive sampling, equilibrium was attained. An aqueous phase and n-octanol were separated and assayed for drug content at 255 nm. The experiments were triplicated and the mean was calculated.

Preparation of the ophthalmic inserts

Azapropazone 0.1% or its equivalent weight of HP- β -CyD or β -CyD complexes were dissolved in 5 ml propylene glycol. These solutions were added separately to sodium carboxymethyl cellulose (1.2% W/V) and carbopol 941 (0.5% W/V) in distilled water containing 0.01% benzalkonium chloride, (0.03%) sodium metabisulphite and 0.1% edetate disodium.¹⁹ Equal volumes of the prepared solutions were transferred into polytetrafluorethylene (PTFE) moulds. Each mould was covered with an inverted funnel (stem orifice diameter 6.9 mm) to control solvent evaporation and placed in a laminar flow hood (microflow laminar air flow station) with an air speed of 90-150 feet / min. The solvent was permitted to evaporate for 48 hours at an ambient temperature. The formed film was transferred to a desiccator containing silica gel, where it was stored for another 24 hours before use.²⁰ The prepared ophthalmic inserts (0.4 – 0.5 mm thickness) were cut in the form of circular discs, of one cm diameter, each containing 3.5 mg of azapropazone. Then,

analyzed for azapropazone content spectrophotometrically at 255 nm. The ophthalmic inserts were individually sealed in foil sachets until used.

The surface pH determination of the ophthalmic inserts

The surface pH of the ophthalmic inserts were determined to evaluate the possible irritative effect of the formulations on the eye. The inserts were allowed to swell for one hour in distilled water and after this time, the electrode of the pH meter was brought into contact with the surface of each insert and the pH was measured (Bottenberg *et al.*, 1991).²¹

Drug content uniformity of the ophthalmic inserts

One insert of each preparation was put in a volumetric flask containing 100 ml of Sørensen phosphate buffer (pH 6.8) and stirred until complete dissolution. Samples were filtered and analyzed spectrophotometrically for the drug content at 255 nm using a solution of non-medicated inserts as a blank. The recorded results were the mean of three determinations.

Preparation of azapropazone eye drops

Aqueous solutions of sodium carboxy methylcellulose (0.5% W/V) and carbopol 941 (0.2% W/V) containing 0.01% benzalkonium chloride, 0.03% sodium metabisulphite and 0.1% edetate disodium were prepared.²² Then, azapropazone 0.1% (W/V) or its equivalent weight of HP- β -CyD or β -CyD complexes were dissolved in 5 ml propylene glycol and added to the previous mixture. The solutions were then completed to 100 ml and filled in a clean, dry and sterile glass containers. The sterilization of the prepared solutions was induced by autoclaving at $125\text{-}130^\circ$ for 30 min, then left until cooling. The sterile products were tested for drug content, pH, color change and degradation products using UV scanning and TLC testing.

Preparation of azapropazone eye gels

The calculated amounts of sodium carboxy methylcellulose (2.1% W/V) and carbopol 941 (0.6% W/V) containing 0.01% benzalkonium chloride, 0.03% sodium metabisulphite and 0.1% edetate disodium were prepared. Then,

azapropazone 0.1% (W/V) or its equivalent weight of HP- β -CyD or β -CyD complexes were dissolved in 5 ml propylene glycol and added to the previous mixture. The solutions were completed to 100 ml, then filled in clean, dry and sterile glass containers. The sterilization of the prepared formulations was induced by autoclaving at 125-130° for 30 min, then cooled. The sterile products were tested for drug content, pH, color change and degradation products using U.V. scanning and TLC testing.

Determination of the viscosity of prepared formulations

Suitable samples of the suggested formulations (drops, gels or ophthalmic inserts) were subjected to viscosity determination using Rotovisco. Fifty ml of each polymer solution containing 0.1 % of azapropazone were placed in the cup of the viscometer (MV ST with a diameter of 4.5 cm) and (bob with 4 cm in diameter). The Rotovisco was thermostatically controlled at 37±0.5°. Then, the viscosity values were calculated using the following equation;

$$\eta = \frac{G \times S}{N} \text{ (mPa. s) } \dots \dots \dots \text{ Eq. (2)}$$

where;

η = viscosity (mPa. s)

G = instrumental factor = 1374 (mPa. S/scale grad. Min.).

S = torque (scale grad.)

N = speed (rpm)

1 m. pa. s (milli pascal second) = 1 cp

In-vitro drug release study from different ophthalmic preparations

The *in-vitro* availability of the drug from drops, gels and ophthalmic inserts, in phosphate buffer solution of pH 6.8 was carried out according to the method adopted by Levy & Benita, (1990).²³ An accurate volumes of the test solutions (equivalent to 10.5 mg of Az or it's complexes), an accurate weights of gels (equivalent to 10.5 mg of Az or it's complexes) or three medicated inserts of each formula (equivalent to 10.5 mg of Az or it's complexes), were placed in dialysis glass tube (diameter, 3.5 cm) whose lower end is closed by a semipermeable membrane which is made tight by rubber band and immersed in the dissolution medium. Each tube contains 1.5 ml of the same

sink solution. Hundred ml of phosphate buffer solution (pH 6.8) were placed in a 250 ml beaker, and the temperature of the medium was adjusted at 37±0.5° using thermostatically controlled water bath with magnetic stirrer and placed in dissolution medium. At predetermined time intervals of 5, 10, 20, 30, 60, 120, 180, 240, 300 and 360 min, aliquots of one ml were withdrawn and diluted, then replaced with the same volume of buffer to maintain the dissolution medium constant. The released amounts of azapropazone from each formula were analyzed spectrophotometrically at 255 nm. Blank experiments were carried out using non-medicated formulations and served as control. The experiments were triplicated and the mean was recorded. The obtained data will subjected to kinetic study.

RESULTS AND DISCUSSION

The solubility study

The phase solubility diagrams of azapropazone in aqueous solutions of pH 6.8 containing HP- β -CyD or β -CyD are shown in Fig. 1. The drug solubility increased linearly as a function of CyDs concentration. Thus, the phase solubility diagram of azapropazone is a Higuchi's A_L-type and the formation of a 1:1 complex is thus further evidenced. The solubilizing effect of CyDs towards azapropazone seems to be dependent on the type of CyDs, and found to be in the sequence; HP- β -CyD > β -CyD. The stability constants of the formed complexes were found to be 282 and 181 mol⁻¹ for azapropazone-HP- β -CyD and azapropazone- β -CyD complexes, respectively. This results were in agreement with that of Ammar *et al.*,²⁴ who found that acetazolamide solubility in aqueous eye drops was linearly increased by the complexation with CyDs.

The Partition coefficient and viscosity

The partition coefficient values of azapropazone, azapropazone- β -CyD complex or azapropazone-HP- β -CyD complex using n-octanol / distilled water system were; 33.62, 0.94 and 0.46 respectively. These results indicating a higher extent of azapropazone-HP- β -CyD complex hydrophilicity followed by azapropazone- β -CyD complex, then azapropazone alone.

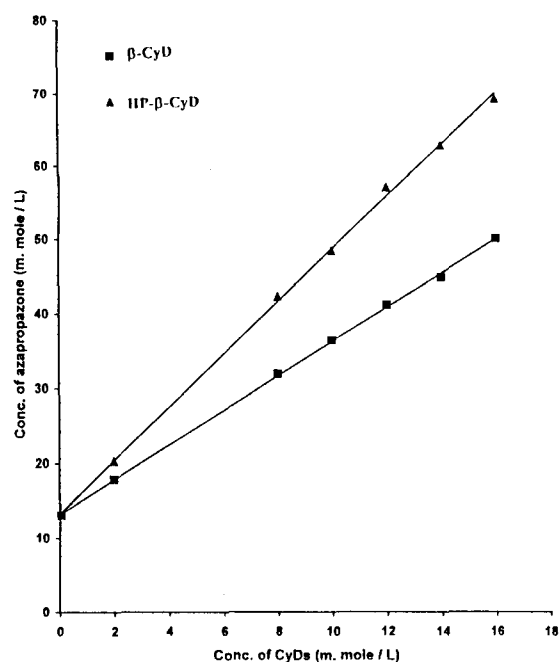


Fig. 1: Solubility phase diagram of azapropazone in the presence of β -CyD and HP- β -CyD in water at 37°.

The viscosity values of ophthalmic drops containing azapropazone, azapropazone-HP- β -CyD complex or azapropazone- β -CyD complex were; 61, 64 and 62 cp respectively. While, the viscosity values of the medicated polymeric solutions used for preparing inserts were; 129, 131 and 129 cp. respectively. In addition, the highest viscosity values obtained were; 240, 242 and 241 cp. for azapropazone, azapropazone-HP- β -CyD complex or azapropazone- β -CyD complex in the form of ophthalmic gels respectively, (Table 1).

In-vitro drug release

Figures (2-4) illustrate the release characteristics of azapropazone from different ophthalmic drops, gels and inserts containing CyDs. The amounts released of the drug was significantly higher from that containing HP- β -CyD followed by β -CyD complexes, then the drug alone. This indicating a higher solubilizing effect of HP- β -CyD than β -CyD for the drug in complex form. The amount released after six hours of the drug complexed with HP- β -CyD from ophthalmic drops, gels and inserts through cellophane membrane were; 7.6, 4.5 and 4.17 mg respectively. While, the amounts of the drug released with β -CyD from the same vehicles respectively were; 4.85, 3.90 and 3.44 mg. In addition, the slowest release rate of the drug was obtained from the formulations containing drug alone. The amounts released were; 1.78, 1.31 and 1.31 mg from the same formulations respectively, Also it is observed that, drops containing azapropazone or it's complexes provided the highest amounts dissolved of the drug followed by the gels, then the ophthalmic inserts. This may be attributed to the higher viscosity of the gels compared to the solutions. While, the lowest amount of the drug released from the inserts could be attributed to the diffusion mechanism of the drug from inserts gradually for long time. These results were in agreement with that obtained by Ibrahim *et al.*,²⁵ who reported that, the percent of clotrimazole released from different solutions depends mainly on their viscosity values. The percent released of the drug from PEG 400 solution in distilled water (86 cp.) was higher than that obtained from PEG 400 solution (96 cp.).²⁵

Table 1: Physical parameters of azapropazone ophthalmic preparations.

Preparation	Parameter	Viscosity (CP)	Thickness (mm)	pH	Drug content (mg)
Az-drops		61	-	5.52	10 ± 0.12 mg/ml
Az- β -CyD drops		62	-	5.54	10 ± 0.16 mg/ml
Az-HP- β -CyD drops		64	-	5.51	10 ± 0.13 mg/ml
Az-gel		240	-	5.57	10 ± 0.22 mg/g
Az- β -CyD gel		241	-	5.53	10 ± 0.18 mg/g
Az-HP- β -CyD gel		242	-	5.49	10 ± 0.17 mg/g
Az-insert		129	0.44 ± 0.015	5.39	3.5 ± 0.07 mg/insert
Az- β -CyD insert		129	0.44 ± 0.13	5.50	3.5 ± 0.09 mg/insert
Az-HP- β -CyD insert		131	0.45 ± 0.010	5.57	3.5 ± 0.11 mg/insert

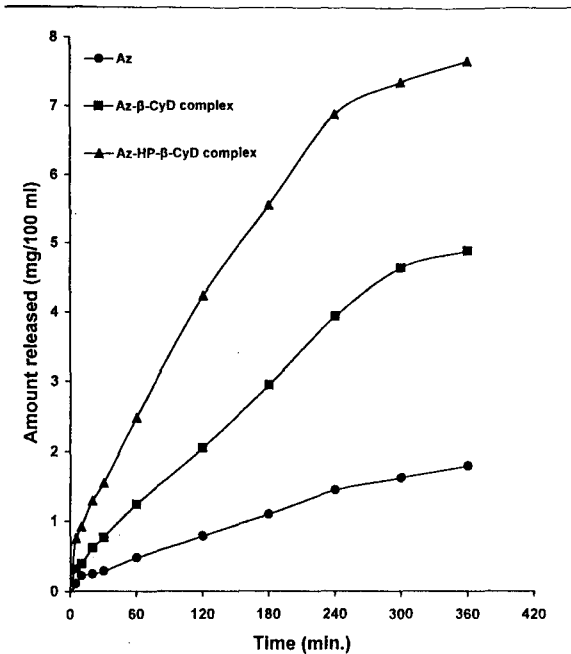


Fig. 2: *In-vitro* release profiles of azapropazone from eye drops.

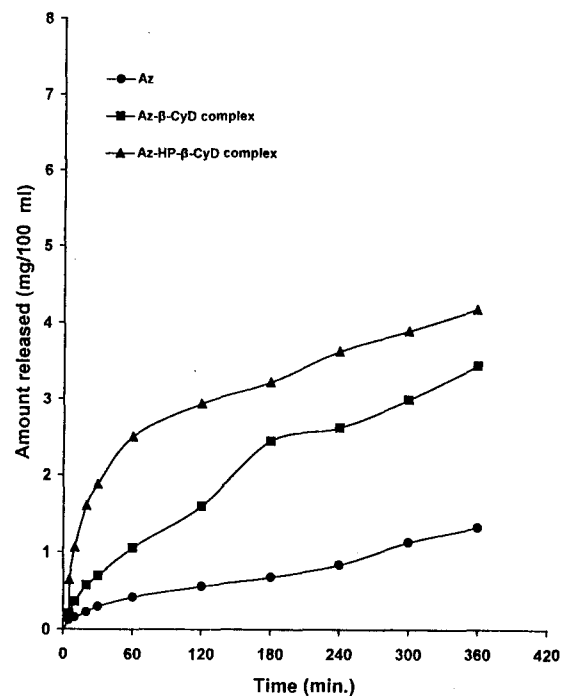


Fig. 4: *In-vitro* release profiles of azapropazone from ophthalmic inserts.

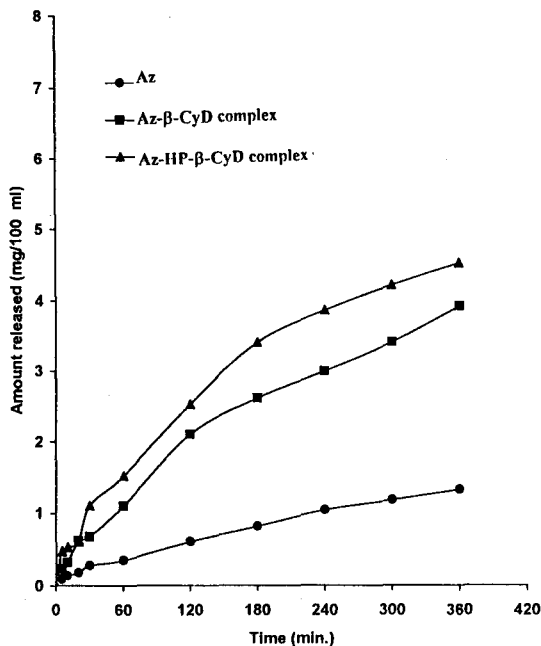


Fig. 3: *In-vitro* release profiles of azapropazone from different gel formulations.

Tables (2&3) and Figures (5&6) summarized the release rate constants (k) and correlation coefficients (r) corresponding to different release mechanisms for azapropazone either alone or in the complexed form with β -CyD or HP- β -CyD from drops, gels and ophthalmic inserts. The r values for different mechanisms were found to be closed to each other and consequently, it seemed that the drug transport did not follow a single mechanism. Also, the obtained results illustrate that the release rate of the drug is directly in favour of fickian and supportive of a zero-order mechanism. The amounts released of the drug from the inserts indicated that the matrix remained intact and the drug diffusion is continued for long time.

The complexation of the drug with CyDs has a clear effect on increasing the relative release rate according to zero-order and Higuchi model. The drug was released from HP- β -CyD and β -CyD complexes in eye drops 4.35 and 2.83 times as the drug alone respectively. Also, the relative release rates of the drug from the

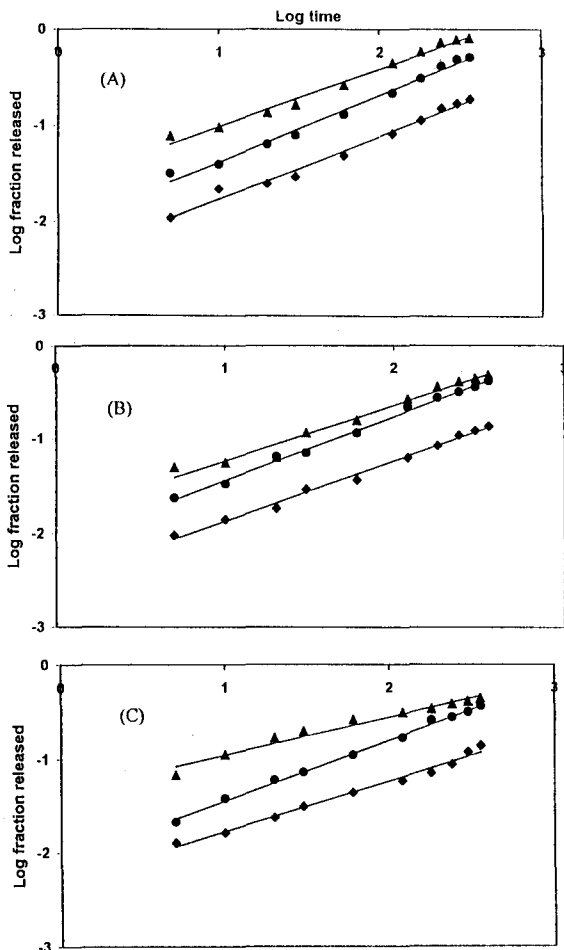


Fig. 5: Diffusion-controlled mechanism of azapropazone from (A): Drops, (B) Gels, (C): Ocuserts.
 ◆ Az ● Az-β-CyD ▲ Az-HP-β-CyD.

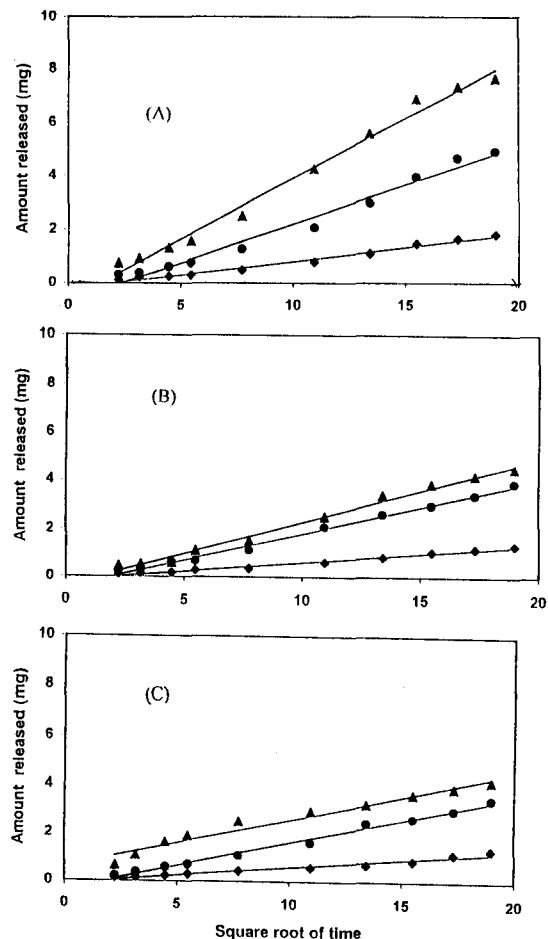


Fig. 6: Release profiles of azapropazone versus square root of time from (A): Drops, (B) Gels, (C): Ocuserts.
 ◆ Az ● Az-β-CyD ▲ Az-HP-β-CyD.

Table 2: Mathematical treatments of the release data according to zero-order, Higuchi and diffusion mechanisms for azapropazone from different ophthalmic preparations.

Mechanism		Zero-order		Higuchi model		Diffusion controlled	
		r	K _Z	r	K _H	r	slope of log Q vs log t
Type of preparation	Az	0.9933	0.0031	0.9791	0.0659	0.9935	0.55
	Az-β-CyD complex	0.9867	0.009	0.9955	0.1930	0.9982	0.65
	Az-HP-β-CyD complex	0.9354	0.0087	0.9830	0.1953	0.9825	0.40
Gels	Az	0.9940	0.0035	0.9936	0.0741	0.9964	0.64
	Az-β-CyD complex	0.9856	0.0104	0.9969	0.2227	0.9974	0.68
	Az-HP-β-CyD complex	0.9768	0.0121	0.9953	0.2620	0.9868	0.59
Drops	Az	0.9945	0.0048	0.9911	0.1023	0.9929	0.65
	Az-β-CyD complex	0.9942	0.0136	0.9891	0.2876	0.9947	0.69
	Az-HP-β-CyD complex	0.9792	0.0209	0.9944	0.4513	0.9936	0.60

Key:

r_Z, r_H, r_D correlation coefficients of zero order, Higuchi and diffusion controlled mechanism.
 K_Z, K_H zero order, Higuchi release rate constants.

Table 3: Relative release rates of azapropazone according to zero-order and Higuchi model from different ophthalmic preparations.

Preparation	Release rate		
	Drug Complex		
		Zero-order	Higuchi model
		R _Z	R _H
Inserts	Az-β-CyD complex	2.9032	2.9240
	Az-HP-β-CyD complex	2.8065	2.9584
Gels	Az-β-CyD complex	2.9714	3.0091
	Az-HP-β-CyD complex	3.4571	3.5403
Drops	Az-β-CyD complex	2.8333	2.8196
	Az-HP-β-CyD complex	4.3542	4.4244

Key:

R_Z, R_H: Relative release rates according to zero-order and Higuchi model.

same complexes in gel preparations were 3.46 and 2.97 times as the drug alone, while, it was 2.8 and 2.9 in the case of ophthalmic inserts respectively. These results were in agreement with that of Shoreibah *et al.*,²⁶ who, stated that, glycyrrhizin patches which are used for treatment of lichen planus were deformed after six hours., while triamcinolone acetone patches only eroded after one week.

In conclusion, the obtained results show that, the solubility of azapropazone had been greatly improved by the complexation with the selected types of CyDs. Also, the drug release from the ophthalmic solutions, gels and inserts containing azapropazone-HP-β-CyD complex, azapropazone-β-CyD complex, was higher than the drug alone. HP-β-CyD has a higher solubilizing effect for the drug than β-CyD. The release rate of the drug from it's complexes from drops is higher than gels followed by ophthalmic inserts. This give an encourage to study the bioavailability of the drug from it's complexes with CyDs using experimental animals in the next work.

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