



## تفريغ فيزيكال 2

محافظة: Complexation

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لجان الرفعات



Cyclo dextrin → CD

Complexation → comp

Solution → Sol

hydrogen bond → H-B

# Complexation and protein binding

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## Complexation and protein binding

### Introduction

عبارت Compound ناتج  
من نوع من ال Rxn بتة 2  
donor-acceptor rxn ←  
acid-base rxn ←  
Chemicals

- Complexes are compounds that result from donor-acceptor mechanisms or Lewis acid-base reaction between two or more chemical species.
- Complexes can be divided broadly into three classes depending the type of the acceptor substance:
  1. Metal ion complexes
  2. Organic molecular complexes
  3. Inclusion complexes
- Intermolecular forces involved in the formation of complexes:
  1. Van der Waals forces
  2. Hydrogen bonds (important in molecular complexes)
  3. Coordinate covalence (important in metal complexes)
  4. Charge transfer
  5. Hydrophobic interaction

ليش الـ Complexation مهم؟؟

Partitioning (3)  
energy absorption and emission of drug (4)

solubility (1) لانه يساعدنا بعد alteration لكثير عن خصائص الدواء مثل  
stability (2)

# Complexation

Physical and chemical properties altered by complexation:

- Solubility
  - enhanced aqueous solubility → e.g., theophylline complexation with ethylenediamine to form aminophylline (making it more suitable for intravenous administration.)
  - optimization of delivery systems (e.g., ion-exchange resins), can help control the release rate of drugs, improving their solubility and bioavailability. This method is used in formulations like cholestyramine resin complexes to improve drug delivery.

hydrophilicity زدت الـ hydrophobic ← theophylline الـ  
⇒ ethylen diamine الـ complexation فيعمل الـ aminophylline (more soluble than theophylline)  
صالح رح يتحول الـ IV بغير اعطيه

- Stability (e.g., inclusion complexes of labile drugs with cyclodextrins)

Labile drugs, which are prone to degradation, can form inclusion complexes with cyclodextrins. This complexation shields the drug from environmental factors like light, heat, and moisture, thereby enhancing its stability. Cyclodextrins are widely used to stabilize compounds such as prostaglandins and volatile oils.  
الـ degradation لسبب اذية بغير الـ stability الـ  
كثير نستخدوم الـ complexation لحتى يحسنوا الـ stability

- Partitioning

Complexation can significantly influence the partition coefficient of a drug. By altering the lipophilicity through complex formation, the distribution of the drug between aqueous and lipid phases can be optimized. This can enhance drug absorption and reduce toxicity.

حطت اتمه الـ drug الـ الـ Partition قبل الـ complexation  
مختلفت عن بعد الـ complexation

- Example: Cyclodextrins reduce toxicity of NSAIDs by limiting direct mucosal contact.
- EDTA binds heavy metals (like lead), reducing metal-induced toxicity.
- The complexation of hydrophobic drugs with hydrophilic carriers can increase their bioavailability by improving their partitioning into biological membranes.

في بعض حالات التسمم من بعض الـ metal فيعطوا الـ EDTA فيعمل الـ complexation مع معدن الـ metal ويخفف الـ toxicity لهم واد الـ availability الـ رح تمل

1,2,3  
عبارة عن اتم ليش تستخدم الـ Partition لخصائص الـ complexation

• هذا الوحيد الذي مش  
therapeutic

## Energy absorption and emission of the drug

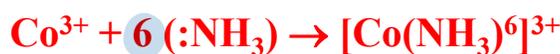
- Complex formation can alter the electronic structure of a drug molecule, leading to changes in its UV-Visible absorption spectra, fluorescence, and phosphorescence properties. These changes can be utilized in analytical chemistry for drug identification and quantification.

رج يفيد عملية ال drug-development  
مش ك therapeutic مثلا رجفت ال compound لما  
يعبر ال Complexation مع رجفت ال drug  
ال metal رج يعبر ال alter ال electronic structure  
ماد drug لما يكون لاجله مثلا ما يكون له UV-vis absorption  
او fluorescence او phosphorescence  
بس مجرد ما اعلم ال Complexation رج تختص  
ال Comp بمساعدة ال determination لعند ال drugs عن طريق ال  
spectroscopy

- **Example:** The complexation of drugs with metal ions often results in a shift in absorption maxima ( $\lambda_{max}$ ) and can enhance or quench fluorescence emission, which is useful in studying drug interactions and stability.

## Metal ion Complexes

- Metal ion complex (coordination complex) consists of a **transition-metal** ion (e.g. cobalt, iron, copper, nickel and zinc) linked or coordinated with one or more counter ions or molecules to form a complex.
- The ions or molecules (e.g.  $Cl^-$ ,  $NH_3$ ,  $H_2O$ ,  $Br^-$ ,  $I^-$ ,  $CN^-$ , etc.) directly bound with the metal are called ligands.
- The interaction between the metal and the ligand represents a **Lewis acid-base reaction** in which the **metal ion (Lewis acid)** combines with a **ligand (Lewis base)** by accepting a pair of electrons from the ligand to form the coordinate covalent or electrostatic forces:



ligand → Lewis base  
metal → Lewis acid  
ولمبعا الرابطة Coordinate

اي لوزم زهرى بالجرود  
الدرى (انزلوا للسلايخ)  
تحت

بناءً على نوع ال bond الون تتكون

لحسب ال orbital الموجود  
حوالته ال metal

ال metal ممكن يعلوا  
ال Complexation مع هذول  
واسم ال ligands

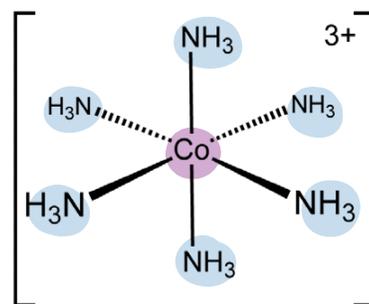
Group	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
Period 1	1																	2	
1	H																		He
2	3	4											5	6	7	8	9	10	
	Li	Be											B	C	N	O	F	Ne	
3	11	12											13	14	15	16	17	18	
	Na	Mg											Al	Si	P	S	Cl	Ar	
4	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	
	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr	
5	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	
	Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe	
6	55	56	57*	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	
	Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn	
7	87	88	89**	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	
	Fr	Ra	Ac	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Cn	Uut	Uuq	Uup	Uuh	Uus	Uuo	

*Lanthanides	58	59	60	61	62	63	64	65	66	67	68	69	70	71
	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
**Actinides	90	91	92	93	94	95	96	97	98	99	100	101	102	103
	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr

## Metal ion Complexes

- The number of ligands bound to the metal ion is defined as **coordination number**. عدد الـ ligand ايكه يرتبط بالـ metal.
- The coordination number of cobalt is six, since it complexed with six  $\text{NH}_3$  groups.
- Compound (e.g.  $\text{NH}_3$ ) which has a single pair of electrons for bonding with the metal ion, is called **unidentate ligand**.



كم يساوي الـ coordination number  
 هوون الـ 6 لانه الـ metal ايكه  
 هو الـ 6 اختلاص يرتبط بـ 6  
 من الـ ligand ايكه هو  $\text{NH}_3$

الـ  $\text{NH}_3$  يرتبط بالـ Co بـ one coordinate bond  
 لانه عندنا 1 pair of electrons  
 الـ ligand ايكه عندنا 1 pair of electrons يسمى unidentate ligand

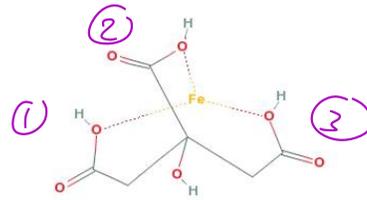
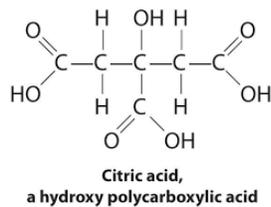
## Metal ion Complexes

- Citric acid forms a complex with  $Fe^{3+}$  attachment (the three carboxylic acid groups bond with  $Fe^{3+}$ ) and is called **tridentate**.

ليجاند الى بعد  
 > Coordinat bond

ال Citric acid بعد 3 Coordinat bond مع  $Fe^{+3}$  عن

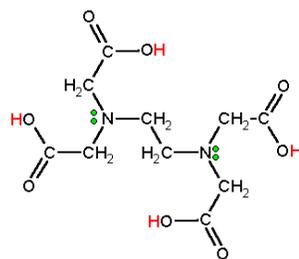
طريقة ال 3 COOH



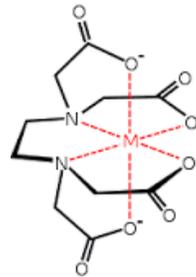
Citric acid-Fe complex

## Metal ion Complexes

- Ethylenediaminetetraacetic acid (EDTA) has six points for attachment (two nitrogen and four oxygen donor groups) and is called hexadentate.

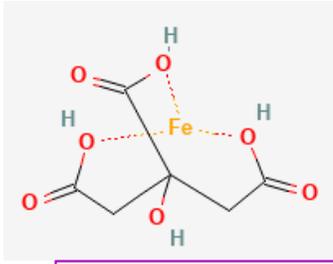


EDTA



EDTA complex

ليجاند الواحد مع ال EDTA بعد 6 Coordinat bond مع ال Meta



- **Formulated iron supplements** often contain iron in the form of ferrous citrate, providing a stable and bioavailable iron source. This prevents iron from precipitating or oxidizing (turning into ferric  $Fe^{3+}$ , which is less soluble).

هون برك احست  
من خستند Iron

لانه رح يتحول من  $Fe^{2+}$  لـ  $Fe^{3+}$  وتعتبر  $Fe^{3+}$  less soluble

- Ferrous citrate = ferrous iron + citric acid
  - ✓ Stays soluble.
  - ✓ Absorbs better.
  - ✓ Less irritation in the stomach compared to some other iron salts.



## Metal ion Complexes

### Chelates

الـ unidentat  
ما يكون chelate

- Chelation is the formation of two or more coordinate bonds between a multidentate ligand (organic compound called chelating agent) and a single central metal atom.
- The bonds in the chelate may be ionic, primary covalent, or coordinate type.
- Important in biological systems, examples:
  - Iron in hemoglobin → Chelation
  - Zinc in alcohol dehydrogenase (ADH)

هذا الشرط لازم  
ليتحقق ليكون  
Chelate في

Metal ion Comp هو النوع الاول اكي هو

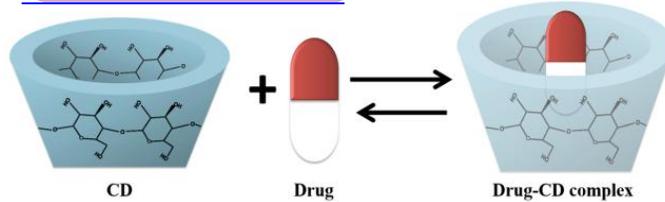
detoxified  
of alcohol

كدهم لاعد

# Inclusion Complexes

- An inclusion compound is a complex in which one chemical compound (the 'host') forms a cavity in which molecules of a second compound ('guest') are entrapped (e.g. Cyclodextrins with drugs).  
*Host صوبك رح يعقل Comp & ال drug رح يحسن خصائصه عاده يكون ال drug ح*

- These complexes generally do not have any adhesive forces working between their molecules and are therefore also known as no-bond complexes.  
*هنا التوي ما يعقل bond رح ال drug ال inclusion comp يكون لما ال drug يدخل حوا ال Host*



# Inclusion Complexes

## Monomolecular Inclusion Compounds: Cyclodextrins

- Monomolecular inclusion complex involves the entrapment of guest molecules into the cage-like structure formed from a single host molecule.  
*اخترنا الليوناروما عنه يكون سكه زيه الصحت والدوا رح يدخل فيه*
- Cyclodextrins are a family of compounds made up of sugar molecules bound together in a ring (cyclic oligosaccharides)
- They consist of 6, 7, and 8 units of glucose referred to as  $\alpha$ ,  $\beta$ , and  $\gamma$  cyclodextrins, respectively.

Cyclodextrin type	Glucose units	Internal diameter	Aqueous solubility	USP name
$\alpha$ -cyclodextrins	6	4.7-5.3 Å <i>اقط</i>	14.5 g/100 mL	Alfadex
$\beta$ -cyclodextrins	7	6.0-6.5 Å	1.85 g/100 mL	Betadex
$\gamma$ -cyclodextrins	8	7.5-8.3 Å	23.2 g/100 mL	Gammadex

*نوع ال Cyclodextrin  
 رح عدد في عدد ال unit*

درد drug ای کے لیے عمل الف drug  
 hydrophobic ← cyclodextrin →

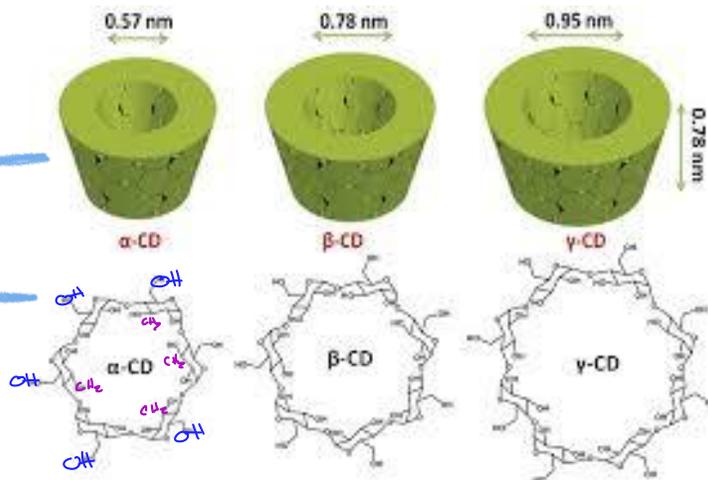
# Inclusion Complexes

## Monomolecular Inclusion Compounds: Cyclodextrins

- Cyclodextrins have truncated cone structure with a hydrophobic interior cavity because of the CH<sub>2</sub> groups, and a hydrophilic exterior due to the presence of hydroxyl group.

من جوا hydrophobic  
 سہولت CH<sub>2</sub> جکونوا من جوا

ومن برا hydrophilic  
 لانہ او OH من برا



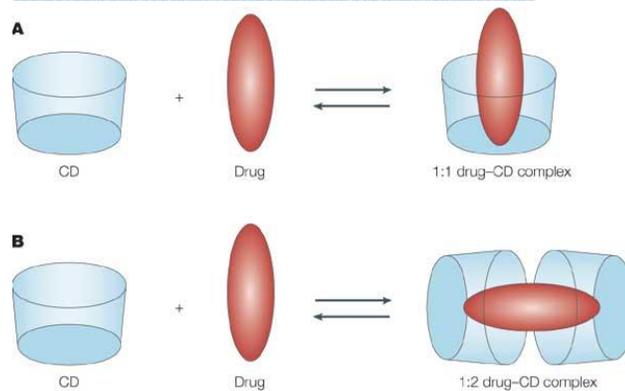
لما ال Units من اد suger  
 ترتب وترتب و بعضا ح  
 بکون او OH برا وال CH  
 جوا

# Inclusion Complexes

## Monomolecular Inclusion Compounds: Cyclodextrins

- Molecules of appropriate size and stereochemistry get entrapped in the cyclodextrin cavity by hydrophobic interaction by squeezing out water from the cavity.

β-CD and γ-CD are the most useful for pharmaceutical technology owing to their larger cavity size.



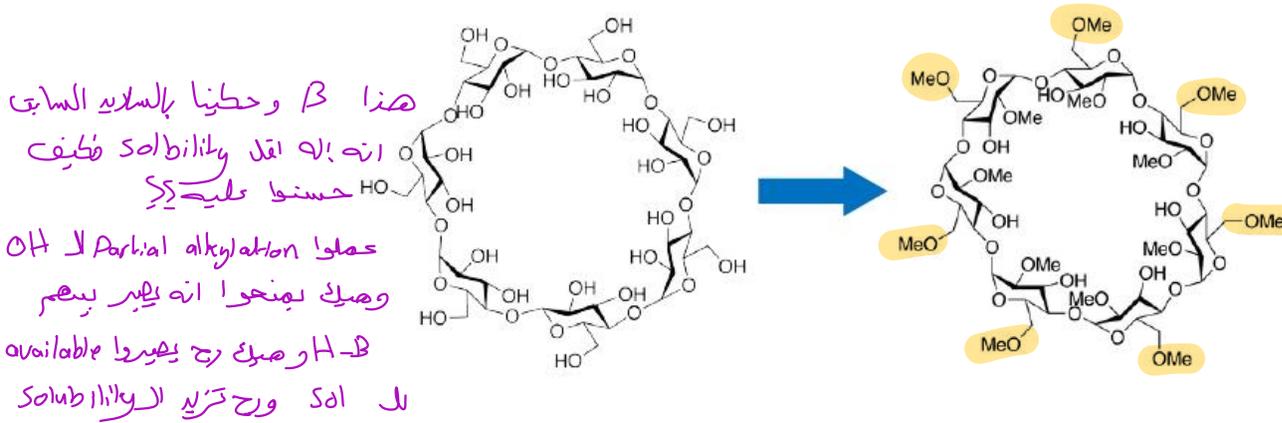
بالسلاوات الجابے لیا  
 اخلی اصی بچوے انه  
 بکون aqueous



# Inclusion Complexes

## Monomolecular Inclusion Compounds: Cyclodextrins

- Derivatives of the natural CDs have been developed to improve aqueous solubility and avoid toxicity.
- Partial alkylation of some of the OH groups in CD reduces the intramolecular hydrogen bonding, leaving some OH groups free to interact with water, thus increasing the aqueous solubility of CD.



# Inclusion Complexes

## Monomolecular Inclusion Compounds: Cyclodextrins

- In addition to hydrophilic derivatives, hydrophobic forms of  $\beta$ CD have been used as sustained release drug carriers.

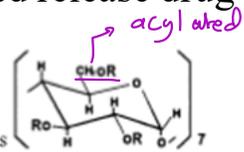
acetylation  
Sustained release

Table 3

Some physicochemical properties of acylated  $\beta$ -CDs

Compound	R	Solubility <sup>b</sup> (mg/dl)
$\beta$ -CD	H	119.0
TA-; peracetyl- $\beta$ -CD	COCH <sub>3</sub>	823.0
TP-; perpropionyl- $\beta$ -CD	COC <sub>2</sub> H <sub>5</sub>	423.5
TB-; perbutyryl- $\beta$ -CD	COC <sub>3</sub> H <sub>7</sub>	219.8
TV-; pervaleryl- $\beta$ -CD	COC <sub>4</sub> H <sub>9</sub>	283.0
TH-; perhexanoyl- $\beta$ -CD	COC <sub>5</sub> H <sub>11</sub>	3.7
TO-; peroctanoyl- $\beta$ -CD	COC <sub>7</sub> H <sub>15</sub>	- <sup>c</sup>
TD-; perdecanyl- $\beta$ -CD	COC <sub>9</sub> H <sub>19</sub>	- <sup>c</sup>
TL-; perlauroyl- $\beta$ -CD	COC <sub>11</sub> H <sub>23</sub>	- <sup>c</sup>

<sup>a</sup>In chloroform at 25°C; <sup>b</sup>In 80% (v/v) ethanol-water at 25°C; <sup>c</sup>Oily substance; <sup>d</sup>In water; <sup>e</sup>Could not be determined because of the low solubility.



كل ما كانت ال R  
المول زادت ال lipophilicity  
وال Solubility رح تقل وصكك  
رح تقدر استخدمه لا  
sustained release  
يشكل انجبر

صالحين للاستخدامات  
 ال Cyclodextrin

# Inclusion Complexes

## Monomolecular Inclusion Compounds: Cyclodextrins

صون لويل رح استخدمه

Property	Drug Examples
① <u>Enhanced aqueous solubility</u>	Prostaglandins; ketoprofen and other nonsteroidal anti-inflammatory drugs (NSAIDs); digoxin and digitoxin; progesterone, testosterone, and other steroid hormones; barbiturates; taxanes; chloramphenicol; sulfonamides; phenytoin; benzodiazepines; coumarin anticoagulants; some diuretics
② <u>Improved stability</u>	Hydrolysis (aspirin, atropine, procaine, digoxin, and prostaglandins), oxidation (chlorpromazine and epinephrine), photodecomposition (phenothiazines, some antibiotics, and vitamins), dehydration (prostaglandin E)
③ <u>Enhanced absorption and bioavailability</u>	Aspirin, phenytoin, digoxin, ketoprofen and other NSAIDs, barbiturates, sulfonamides, and some diuretics
④ <u>Change from liquid to solid</u>	Oil-soluble vitamins (A, D, K), phenols, clofibrate, nitroglycerine, methyl salicylate, and essential oils
⑤ <u>Decreased volatility</u>	Iodine, camphor, menthol, salicylic acid, and chlorobutanol
⑥ <u>Improved taste and odor</u>	Chloral hydrate, prostaglandins, NSAIDs, thymol, and chloramphenicol
⑦ <u>Decreased stomach irritation</u>	Aspirin, indomethacin, and other NSAIDs
⑧ <u>Inhibit red blood cell lysis</u>	Phenothiazines and other basic drugs, fluphenamic acid and other acidic drugs, antibiotics, and menandione
⑨ <u>Prevention of incompatibilities</u>	Vitamins

## Complexes: Methods of analysis

كيف رح اقيس  
 خصائص ال Comp  
 او لادها صار Comp  
 او لا

- A determination of the (1) stoichiometric ratio of ligand to metal (or donor to acceptor) and the (2) stability constant for complex formation are important in the study and application of complexes.
- Several methods for estimation of these parameters have been developed such as:
  - ① Method of continuous variation
  - ② pH Titration method → حسب ال H loss
  - ③ Distribution Method  
 كيف رح مختلف ال Solubility ال drug  
 لهم بعد ال Comp

## Inclusion Complexes

### Monomolecular Inclusion Compounds: Cyclodextrins

- In addition to improving the solubility of compounds, complexation with cyclodextrin has been used to:
  - Improve the stability of many drugs by inclusion of the compound and protecting certain functional groups from degradation.
  - Mask the bitter taste of certain drugs such as fexofenadine.
  - Fixation of very volatile substances
  - Reduction of drug induced irritation

لا تنسوا زميلنا ايهم منا دعائكم