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COMPARATIVE PHYSICOCHEMICAL CORRELATION STUDY OF SYNTHESIZED PRODRUG AND CODRUG OF ASPIRIN+PARACETAMOL AND INDOMETHACIN+PARACETAMOL BY COVALENT AND NON–COVALENT BONDING

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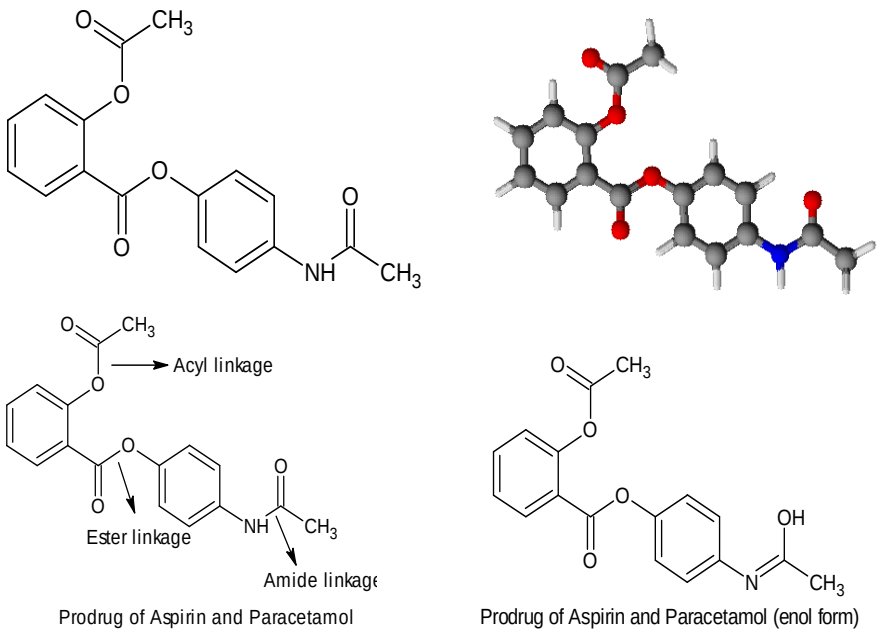
ABSTRACT

The idea of formation of prodrug and codrug of aspirin with paracetamol & indomethacin with paracetamol has been implemented on the structural entity of these NSAIDs. Prodrug of aspirin/indomethacin and paracetamol has been done by converting free carboxylic acid (–COOH) of aspirin/indomethacin into acid chloride (–COCl); by using thionyl chloride and subsequently this acid chloride has been reacted with free phenolic group (–OH) of paracetamol to get the two desired prodrugs, similarly codrug of aspirin/indomethacin and paracetamol has been formed by co–crystallization technique applied on aspirin with paracetamol and indomethacin with paracetamol to get the codrug of two in precipitated crystals. Physicochemical parameter comparison of individual API (Active Pharmaceutical Ingredient) with synthesized prodrug as well as codrug were done for CHN%, solubility profile, melting point, TLC–R_f, UV spectra, IR spectra, Mass spectra, logP and found that the values differ from the API which shows the significance of prodrug and codrug synthesis. Nonpolarity of prodrug and codrug was found as follows: Prodrug–B (3.94) > Codrug–B (3.42) > Prodrug–A (2.15) > Codrug–A (1.55). Codrugs are found always polar than prodrug because prodrug has covalent bonding between two APIs and codrug has non–covalent interactions such as hydrogen bonding, ionic interactions, Van der Waals interactions and π–interactions between two APIs.

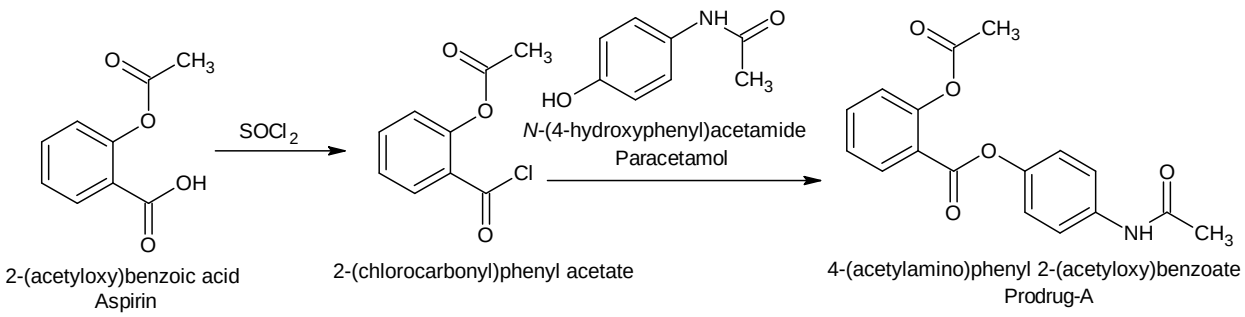
KEYWORDS: API, CHN%, Prodrug, Codrug, Co–crystallization, logP, TLC, UV λ_{max}, IR Spectra, Mass Spectra, Hydrogen bonding, Ionic interactions, Van der Waals interactions, π–interactions.

INTRODUCTION

Prodrugs has been successfully synthesized and has shown different melting points, solubility profile, TLC, UV spectra, IR spectra, Mass spectra from individual parent drugs (Aspirin, Indomethacin and Paracetamol) which indicates the authenticity of fulfillment of Prodrug synthesis through CHN% (carbon, hydrogen, nitrogen percentage) by elemental microanalysis.[1]



Figure–1: Prodrug–A design



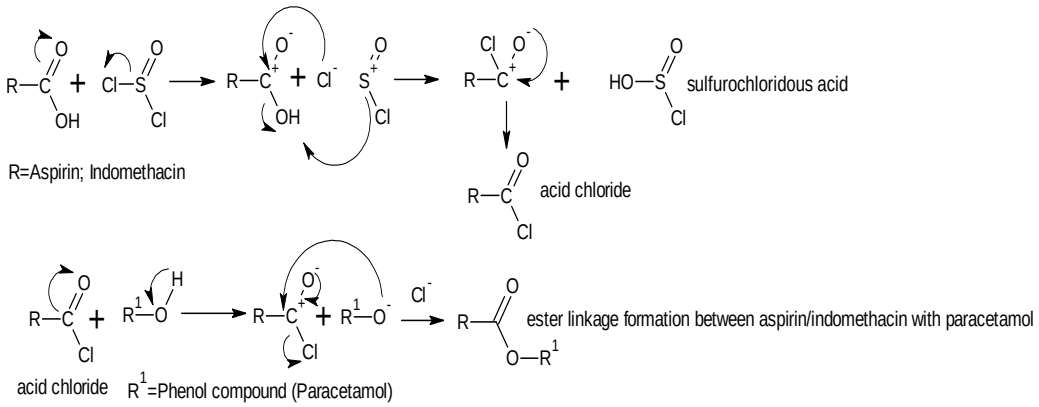
Figure–2: Synthesis of Prodrug–A

Experimental Part

Prodrug–A synthesis

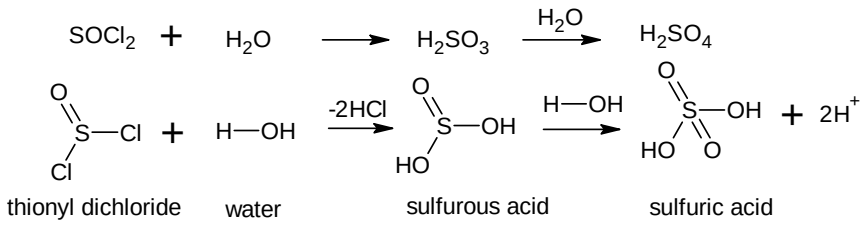
0.01mole (1.80g) of aspirin was treated with 2ml thionyl chloride in moisture free round bottom flask and refluxed on water bath until all the aspirin dissolved [Figure–3 and Figure–5]. It was then heated on water bath to remove excess of thionyl chloride and cooled to get liquid and no solid deposition. Aspirin (2–acetyloxy benzoic acid) is solid but after the

formation of acid chloride 2–(chlorocarbonyl)phenyl acetate which is liquid in nature. It is then reacted with 0.01mole (1.51g) of paracetamol dissolved in dry methanol in room temperature and allowed to react both acid chloride and paracetamol. Phenolic group (–OH) of paracetamol reacted with acid chloride (–COCl) to produce the desired prodrug of aspirin and paracetamol (4–(acetylamino)phenyl 2–(acetyloxy)benzoate) which is then precipitated slowly by addition of cold water with stirring the mixture. [Molecular Formula=$C_{17}H_{15}NO_5$; MW=313.30g]. This prodrug persists three linkages (acyl, ester and amide) which is semipolar in nature produces logP=2.15. It was then filtered washed with cold water and dried to get %yield and m.p. of dried product.[2]



Figure–3: Mechanism of acid chloride formation and ester linkage formation

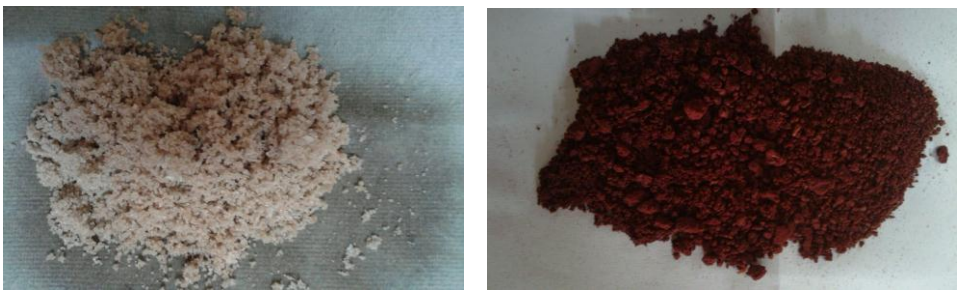
Codrug–A synthesis: 0.01mole (1.80g) of aspirin and 0.01mole (1.51g) of paracetamol were dissolved in methanol separately and mixed slowly with constant stirring. The clear solution was then treated with cold water dropwise with stirring until permanent opalescence appeared. The mixture was then kept in ice for 2–3hours to get the cocrystals of two drugs. [Molecular Formula=$C_{17}H_{17}NO_6$; MW=331.31g]. It was then filtered and dried to get %yield and m.p. of dried product. [Figure–8].



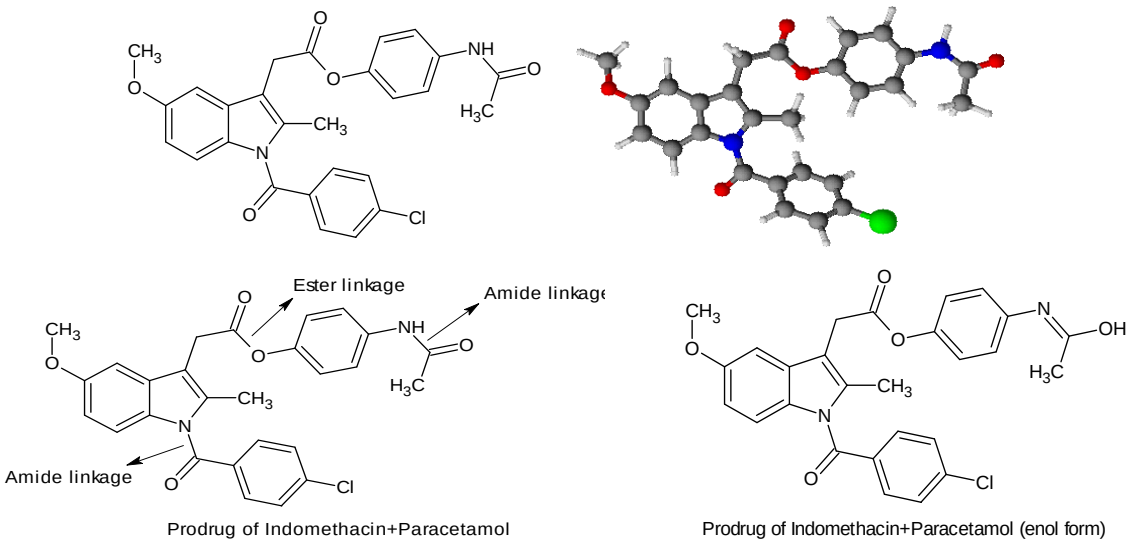
Figure–4: Thionyl chloride is degraded in water to form sulfuric acid with exothermic reaction

Prodrug–B synthesis

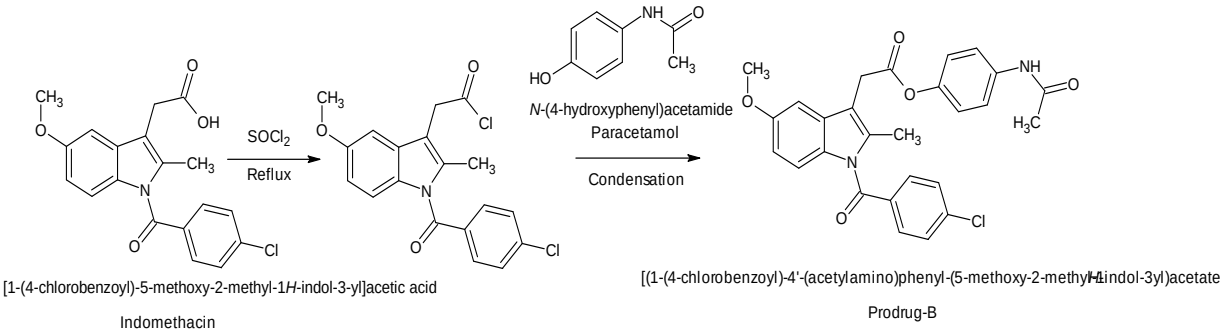
Prodrug of indomethacin and paracetamol has been synthesized by reacting 0.01mole (3.57g) of indomethacin with 5ml of thionyl chloride in moisture free round bottom flask and refluxed on water bath until all the indomethacin has been dissolved [Figure–3 and Figure–5]. It was then heated on water bath to remove excess of thionyl chloride and cooled to get liquid and no solid deposition. Here carboxylic acid group (–COOH) of indomethacin is converted into free acid chloride group (–COCl) to get[1–(4–chlorobenzoyl)–5–methoxy–2–methyl–1*H*–indol–3–yl]acetyl chloride which is then condensed with 0.01mole (1.51g) of paracetamol dissolved in methanol where acid chloride reacts with phenolic group of paracetamol to get the desired prodrug [(1–(4–chlorobenzoyl)–4'–(acetylamino)phenyl–(5–methoxy–2–methyl–1*H*–indol–3–yl)acetate]. (Molecular Formula=$C_{27}H_{23}ClN_2O_5$; MW=490.93g) having both ester and amide linkages. It was then filtered out by getting precipitate by adding water. This prodrug persists three linkages (one ester and two amide) which is nonpolar in nature produces logP=3.94. It was then filtered washed with cold water and dried to get %yield and m.p. of dried product.[3]



Figure–5: Prodrug–A and Prodrug–B



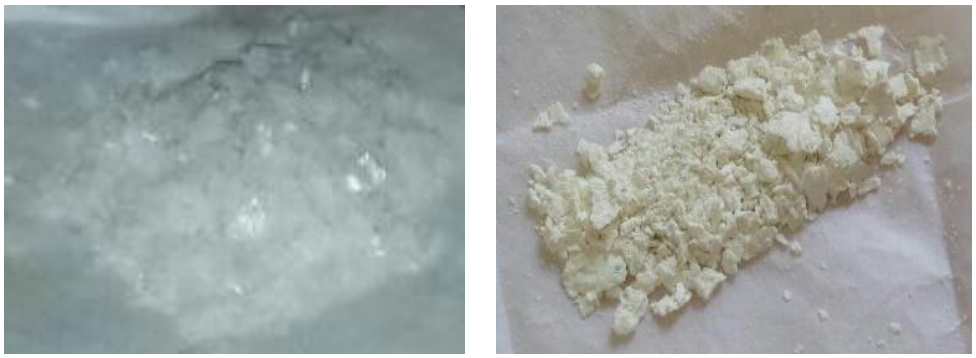
Figure–6: Prodrug–B design



Figure–7: Synthesis of Prodrug–B

Codrug–B synthesis

0.01mole (3.57g) of indomethacin and 0.01mole (1.51g) of paracetamol were dissolved in methanol separately and mixed slowly with constant stirring. The clear solution was then treated with cold water dropwise with stirring until permanent opalescence appeared. The mixture was then kept in ice for 2–3hours to get the cocrystals of two drugs. [Molecular Formula=$C_{27}H_{25}ClN_2O_6$; MW=508.94g]. It was then filtered and dried to get %yield and m.p. of dried product. [Figure–8].



Figure–8: Codrug–A and Codrug–B

Profile

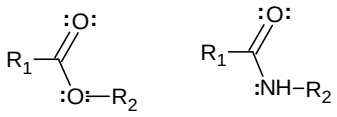
Prodrug–A [$C_{17}H_{15}NO_5$; MW=313.30g], Standard=C (65.17%), H (4.83%), N (4.47%), O (25.53%); Found=C (65.08%), H (4.78%), N (4.26%), O (25.44%), [4–(acetylamino)phenyl 2–(acetyloxy)benzoate]. logP=2.15 (Semipolar), **m.p.=196°C**.

Prodrug–B [$C_{27}H_{23}ClN_2O_5$; MW=490.93g], Standard=C (66.06%), H (4.72%), Cl (7.22%), N (5.71%), O (16.29%); Found=C (65.98%), H (4.35%), Cl (7.03%), N (5.34%), O (16.04%), [(1–(4–chlorobenzoyl)–4'–(acetylamino)phenyl–(5–methoxy–2–methyl–1*H*–indol–3–yl)acetate]. logP=3.94 (Nonpolar), **m.p.=204°C**.

Codrug–A [$C_{17}H_{17}NO_6$; MW=331.31g], Standard=C (61.76%), H (5.13%), N (4.22%), O (28.98%); Found=C (61.34%), H (5.08%), N (4.02%), O (28.74%). logP=1.55 (Semipolar). **m.p.=110°C**.

Codrug–B [$C_{27}H_{25}ClN_2O_6$; MW=508.94g], Standard=C (63.66%), H (4.91%), Cl (6.97%), N (5.50%), O (18.86%); Found=C (63.53%), H (4.88%), Cl (6.85%), N (5.45%), O (18.67%). logP=3.42 (Nonpolar). **m.p.=178°C**.

The rate of precipitation of Codrug–A is found slower than precipitation rate of Codrug–B because logP of Codrug–A (1.55) < Codrug–B (3.42), so the Codrug–A obtained after two days and Codrug–B at once.



Figure–9: Ester: 2+2=4 lone pairs of electrons; Amide: 2+1=3 lone pairs of electrons

Actually acyl [–O–CO–] and ester [–CO–O–] both have same linkages so Prodrug–A have two ester and one amide linkages so logP=2.15 whereas Prodrug–B has one ester [–CO–O–] and two amide [–CO–NH–] linkages so logP=3.94, because the ester and amide both are susceptible for hydrolysis but in amide (–CONH–) three lone pairs of electrons are present [two for oxygen and one for nitrogen] and in ester (–COO–) four lone pairs of electrons are present [four for two oxygens]. So the electron density of ester is greater than amide and electronegativity of oxygen is 3.44 and for nitrogen is 3.04. So total electronegativity of ester (–COO–) is 3.44+3.44=6.88 and for amide (–CONH–) is 3.44+3.04=6.44. Hence ester is more susceptible for hydrolysis compared to amide.

Lone pair profile: Ester>Amide and Electronegativity profile: Ester>Amide. In this case Prodrug–A: two ester & one amide, so lone pair profile: 4×2=6 for ester and 3 for amide; hence 6 (ester electronegativity)>3(amide electronegativity) for Prodrug–A. [Ester is greater than amide so logP is 2.15]. In case of Prodrug–B: one ester and two amide, so lone pair: 4 for ester and 3×2=6 for amide; hence 6 (amide electronegativity)>4 (ester electronegativity) for Prodrug–B. [Amide is greater than ester so logP is 3.94]. Hence Prodrug–B is more nonpolar than Prodrug–A.[4]

Mobile phase of TLC values has been selected after trial and error for all individual NSAIDs (aspirin, indomethacin and paracetamol) according to their logP and R_f values have been determined and after that R_f values have been obtained for Prodrug. The values are as follows:

Table–1: Physicochemical parameters [S=Standard; F=Found]

Samples	Molecular Formula	% yield	Melting Point (°C)	Molecular Weight	λ_{max} (nm)	TLC	logP
Aspirin	$C_9H_8O_4$	API	S=135–136, F=135	180.15g (180=M+)	276	3.7	1.19
Indomethacin	$C_{19}H_{16}ClNO_4$	API	S=162–164, F=163	357.78g (357=M+1)	260	5.2	3.10
Paracetamol	$C_8H_9NO_2$	API	S=169–170, F=169	151.16g (151=M+)	243	2.8	0.34
Prodrug–A	$C_{17}H_{15}NO_5$	34.45	F=196	313.30g (313=M+)	200 and 243	4.8	2.15
Prodrug–B	$C_{27}H_{23}ClN_2O_5$	26.56	F=204	490.93g (491.4=M+1)	248.2 and 203.4	6.2	3.94
Codrug–A	$C_{17}H_{17}NO_6$	42.29	F=110	331.31g (331=M+)	245	4.2	1.55
Codrug–B	$C_{27}H_{25}ClN_2O_6$	23.62	F=178	508.94g (508.9=M+)	270	5.6	3.42

Explanation: Aspirin, Indomethacin and Paracetamol all three have similar bonds (ester: –CO–O–/amide: –CO–NH–) in which O^{16} is bioisoster with NH ($_7N^{14}+_1H^1=14+1=15$) so the λ_{max} came in a range 240–280nm: Aspirin: 276nm, Indomethacin: 260nm and Paracetamol: 243nm. Prodrug–A and Prodrug–B showed two λ_{max}, Prodrug–A: 200nm and 243nm because of presence of two ester and one amide bond whereas and Prodrug–B: 248.2nm and 203.4nm because of presence of one ester and two amide bonds, but in case of Codrug–A (245nm) and Codrug–B (27nm) showed single λ_{max}.

Mobile phase=Ethyl acetate:Methanol=6:4

Polarity profile of compounds is as follows: Nonpolar  Polar Prodrug–B (3.94) > Codrug–B (3.42) > Indomethacin (3.10) > Prodrug–A (2.15) > Codrug–A (1.55) > Aspirin (1.19) > Paracetamol (0.34)

Solubility study of Drugs, Prodrugs & Codrugs

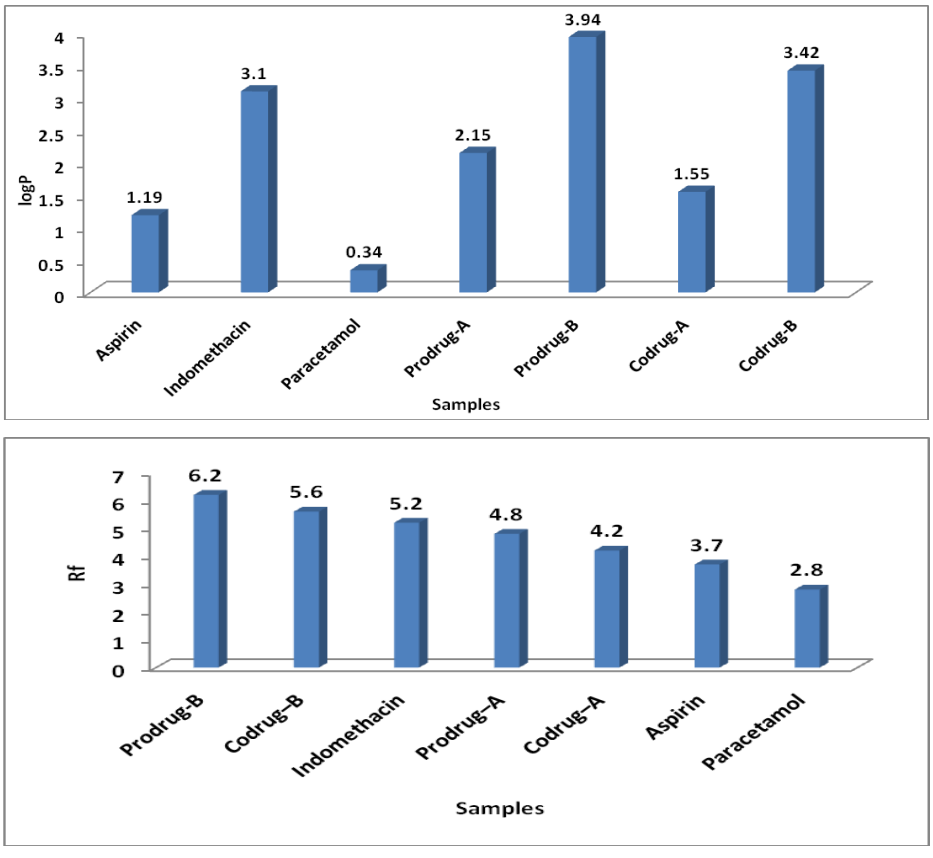
The solubility of Prodrugs was practically determined by taking 100mg of Drugs/Prodrugs/Codrugs in 10ml volumetric flask, adding required quantity of solvent at

room temperature and shaken for few minutes. Solubility data for each study was observed and recorded in Table–2.

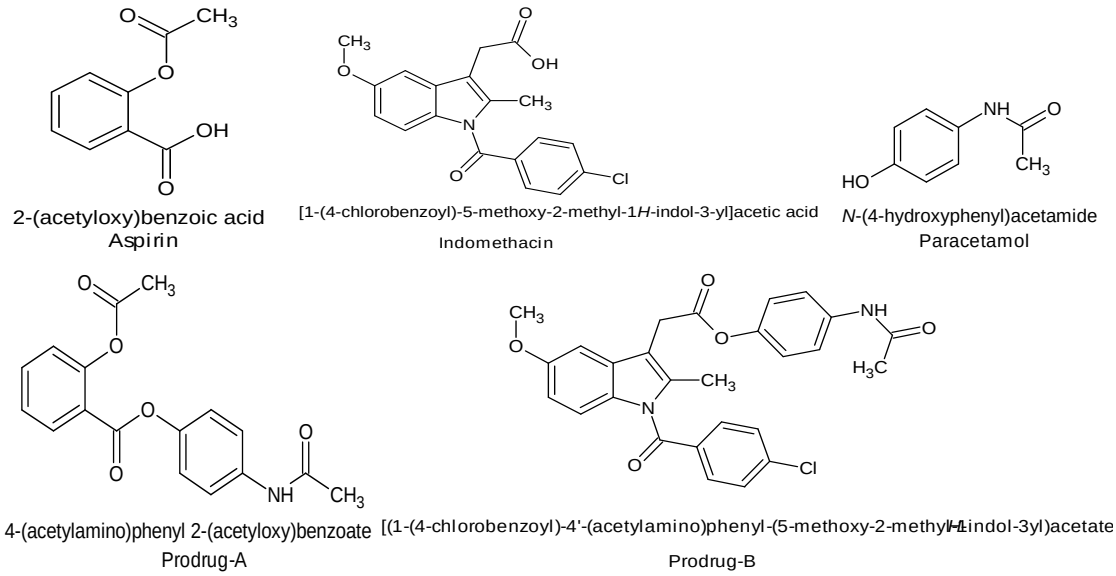
Table–2: Solubility parameters of Drugs, Prodrugs and Codrugs

Samples	Solubility						
	Water	**Acid**	**Base**	**Ether**	**Methanol**	**Ethyl acetate**	**Acetone**
Aspirin	Insoluble	Insoluble	Soluble	Soluble	Soluble	Soluble	Soluble
Indomethacin	Insoluble	Insoluble	Soluble	Insoluble	Soluble	Soluble	Soluble
Paracetamol	Insoluble	Insoluble	Soluble	Insoluble	Soluble	Insoluble	Soluble
Prodrug–A	Insoluble	Insoluble	Soluble	Soluble	Soluble	Soluble	Soluble
Prodrug–B	Insoluble	Insoluble	Soluble	Insoluble	Soluble	Soluble	Soluble
Codrug–A	Insoluble	Insoluble	Soluble	Insoluble	Soluble	Soluble	Soluble
Codrug–B	Insoluble	Insoluble	Soluble	Insoluble	Soluble	Soluble	Soluble

Explanation: Aspirin and Indomethacin both have free –COOH group so it is found soluble in base; similarly Paracetamol has free –OH group so it is also found ***soluble in base*** *and all three are acidic in nature so they are found insoluble in acid. All three are nonpolar in nature so all are found* ***insoluble in water****. Prodrug–A and Prodrug–B are made of covalent bonding interactions forming keto–enol tautomerism (HO–C=N–) from amide linkage (–CO–NH–) so these enols are acidic in nature so these are found* ***soluble in base****.*



Figure–10: Histogram



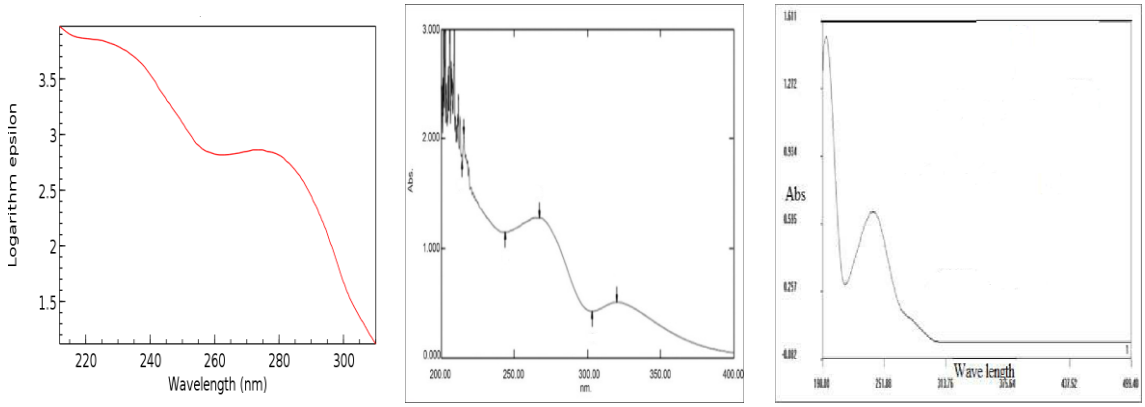
Figure–11: Structural framework

Instrument

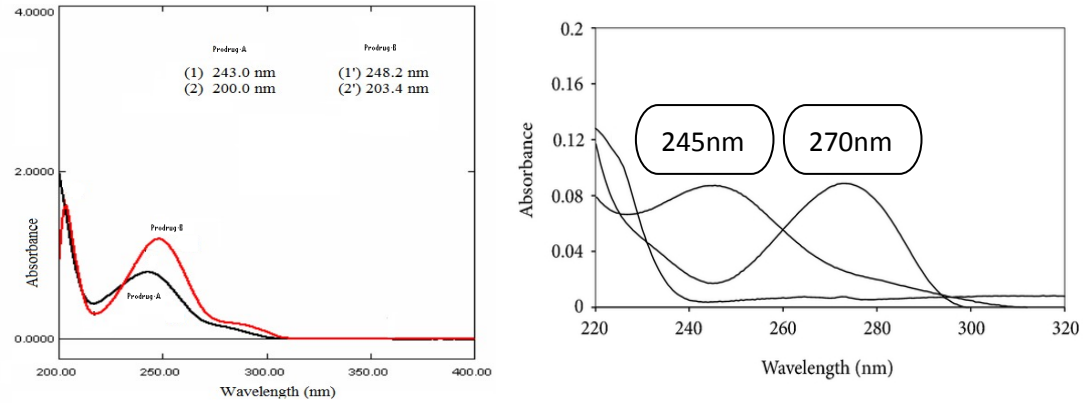
A double beam UV visible spectrophotometer: Manufacturer: Shimadzu. Model: UV–1800, Shimadzu, Japan.

Preparation of Standard solution of Prodrugs and Codrugs: Weighed accurately about 100mg of Prodrug–A, Prodrug–B, Codrug–A and Codrug–B were transferred quantitatively to 100ml volumetric flask. Dissolved in about 70ml of Methanol by sonication and diluted to volume with methanol and mixed. Transferred 0.1ml of this solution to 10ml volumetric flask, diluted to volume with diluents (methanol) and mixed (10µg/ml) and absorption was observed at 276nm.

UV Spectral studies of Drugs, Prodrugs and Codrugs



Drug: Aspirin 276nm **Drug: Indomethacin 260nm** **Drug: Paracetamol 243nm**



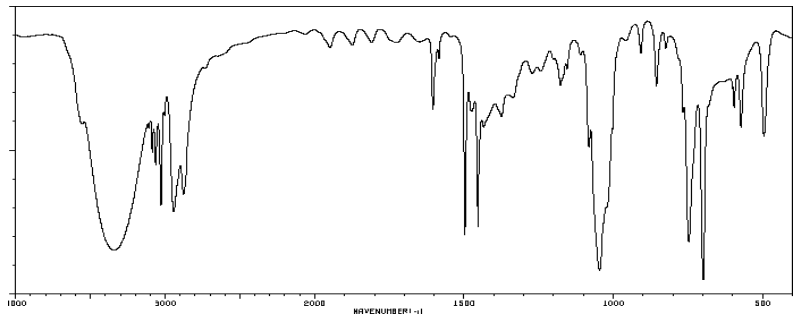
Prodrug–A (200 & 243nm) and Prodrug–B (203.4 & 248.2nm) & Codrug–A (245nm) and Codrug–B (270nm)

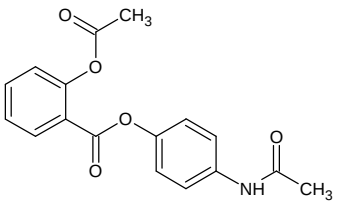
Figure–12: UV Spectra of Drugs, Prodrugs and Codrugs

Explanation: Prodrug–A has two ester and one amide linkages so the λ_{max} shows two values 200 & 243nm and Prodrug–B has one ester and two amide linkages so the λ_{max} shows two values 203.4 & 248.2nm which are higher than Prodrug–A due to covalent bonding interactions, similarly Codrug–A and Codrug–B both are formed by cocrystallization so the λ_{max} shows single values for Codrug–A 245nm and Codrug–B 270nm due to non–covalent interactions such as hydrogen bonding, ionic interactions, Van der Waals interactions and π–interactions. In ester (–COO–) two oxygen atoms are present so the electronegativity of oxygen atom is 3.44 hence for ester total electronegativity is 2×3.44=6.88. In case of amide (–CO–NH–) one nitrogen (3.04) and one oxygen (3.44) atoms are present hence for amide total electronegativity is 3.04+3.44=6.44. In ***Prodrug–A*** *total electroneagitivity is for two ester and one amide [2×6.88+6.44=20.2], for* ***Prodrug–B*** *total electronegativity is for one ester and two amide [6.88+2×6.44=19.76]. Since Prodrug–A has electronegativity 20.2 which is greater than Prodrug–B which is 19.76 so the Prodrug–A shows lower λ_{max} than Prodrug–B. Prodrug–A: 200 & 243nm<Prodrug–B: 203.4 & 248.2nm.*

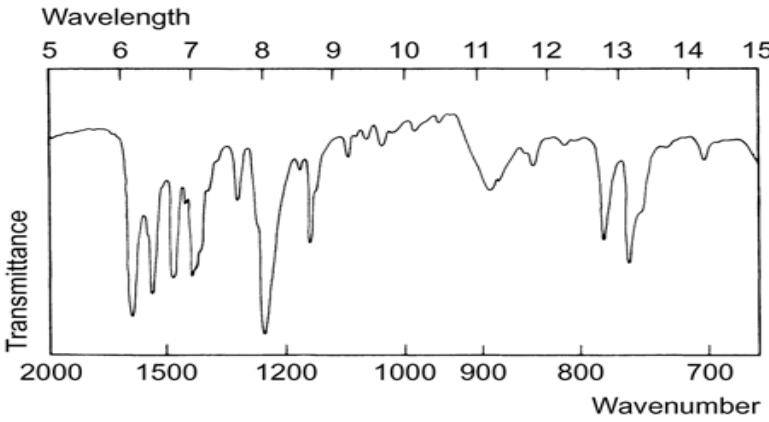
Infra Red Spectral studies of Prodrug–A, Prodrug–B, Codrug–A and Codrug–B

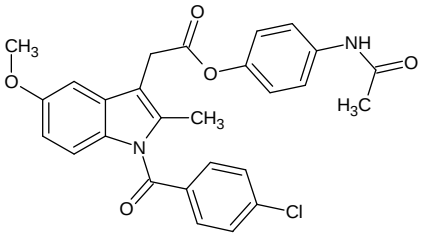
IR spectras of Codrug–A and Codrug–B were measured in KBr pellets in Shimadzu FT–IR spectrophotometer and values in cm^{-1} were obtained for interpretation of structural framework.



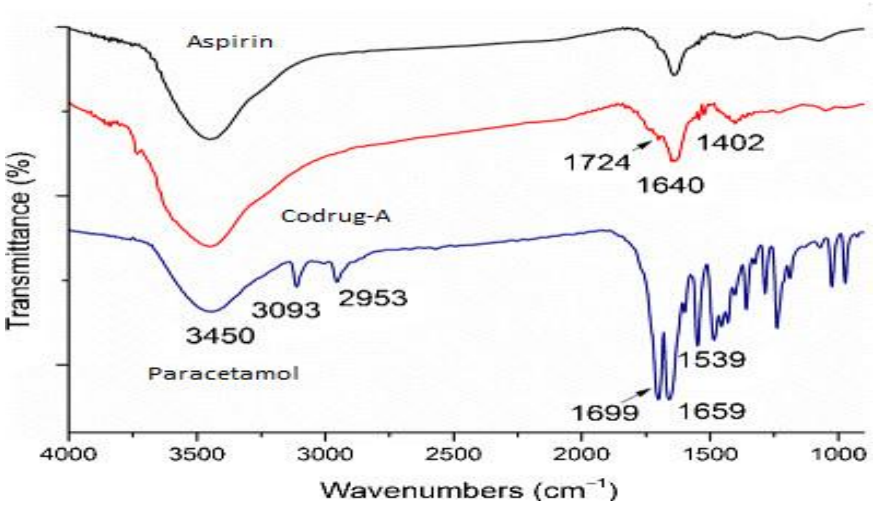


Prodrug–A: IR (cm^{-1}; ν): >C=O stretching: (standard=1735–1750, found=1650), –NH–CO: (standard=1640–1690, found=1650), (standard=3100–3500, found=3100).



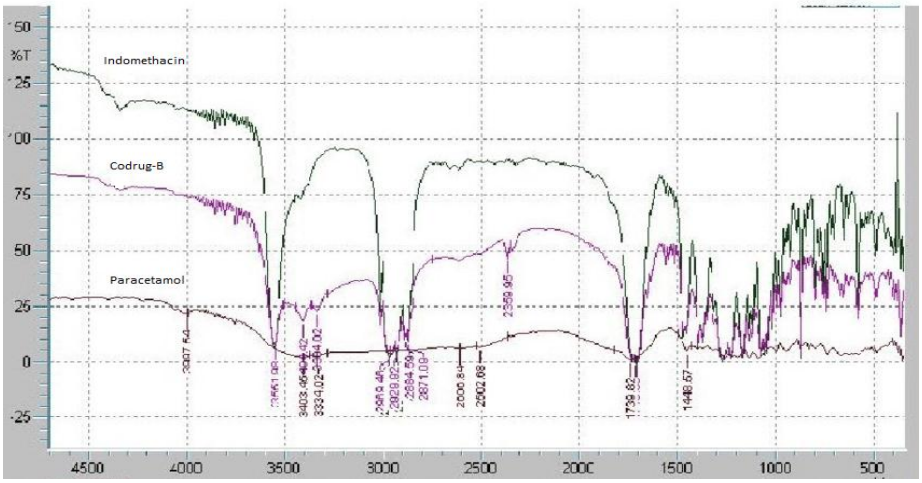


Prodrug–B: IR (cm^{-1}; ν): –C–O– stretching: (standard=1000–1300, found=1170), >C=O stretching: (standard=1735–1750, found=1730), –NH–CO–: (standard=1640–1690, found=1650), Chlorine: (standard=600–800, found=780).



Codrug–A: IR (cm^{-1}; ν): N–H stretching: (standard=3500–3100, found=3093), C–H stretching (aromatic): (standard=3150–3050, found=2953), C=C stretching: (standard=1615–

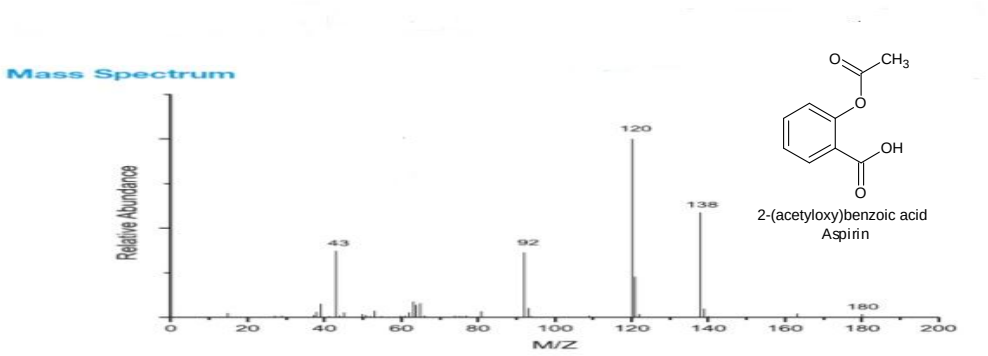
1580, found=1640), >C=O stretching: (standard=1725–1705, found=1724), C–CO–C stretching: (standard=1320–1210, found=1402).



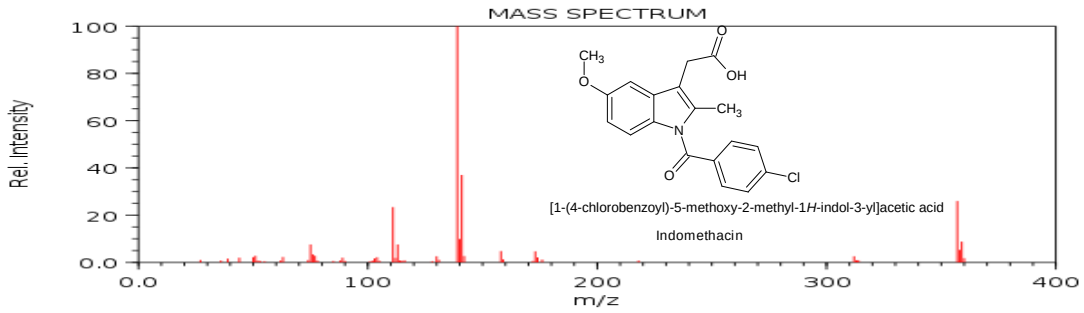
Figure–13: Infra Red Spectroscopy of Prodrug–A, Prodrug–B, Codrug–A and Codrug–B

Codrug—B: IR (cm^{-1}; ν): N–H stretching: (standard=3500–3100, found=3097), C–H stretching (aromatic): (standard=3150–3050, found=3136.36), C=C stretching: (standard=1615–1580, found=1621), C–N stretching: (standard=1650–1550, found=1580), >C=O stretching: (standard=1725–1705, found=1721), C–CO–C stretching: (standard=1320–1210, found=1284.63).

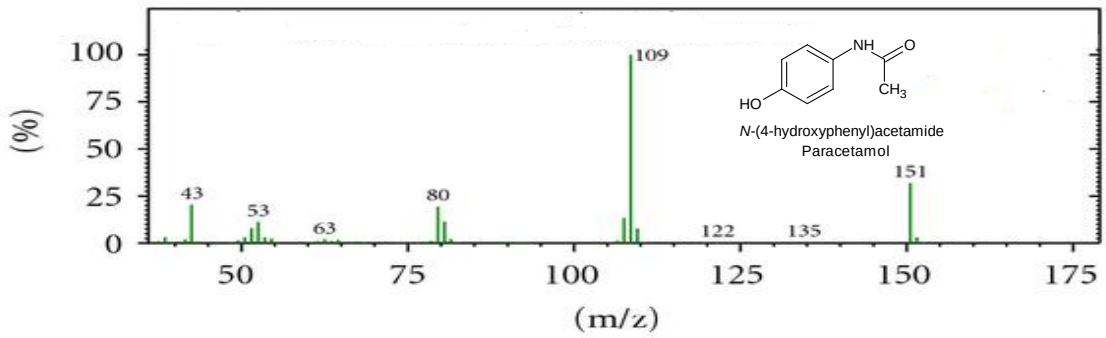
Mass Spectra of all samples



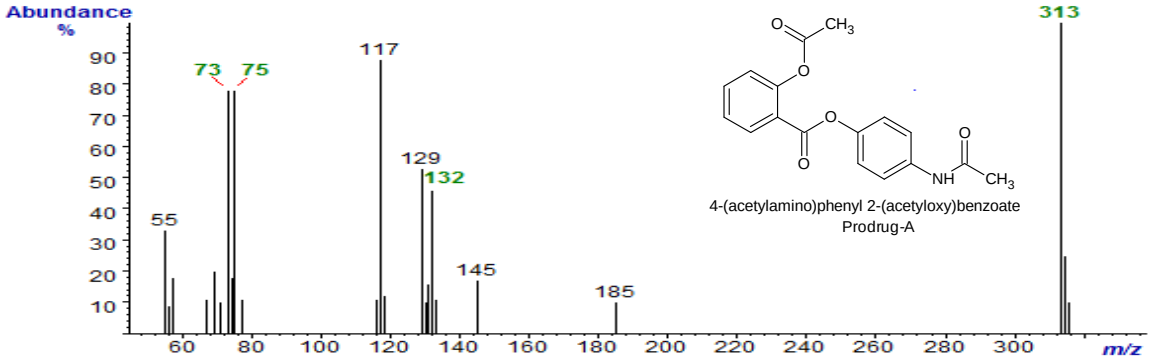
Aspirin Mass Spectra=180 (M+); MW=180.15g



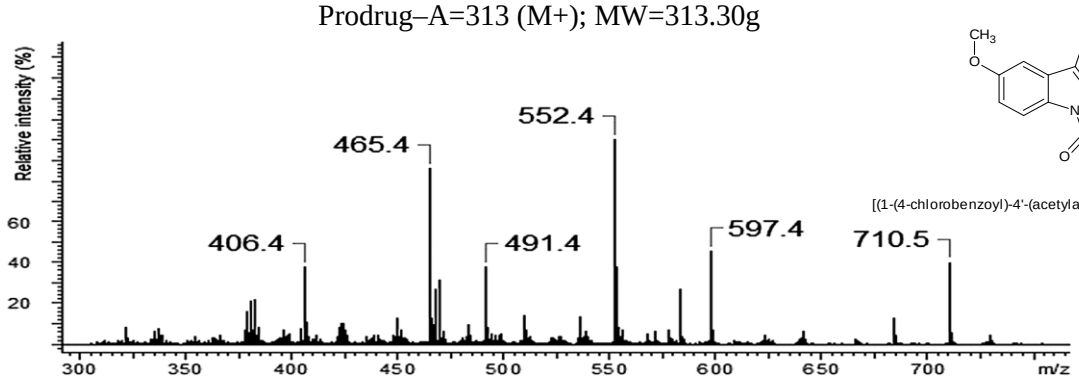
Indomethacin Mass Spectra=357 (M+1); MW=357.78g [M+1 peak is due to Cl atom]



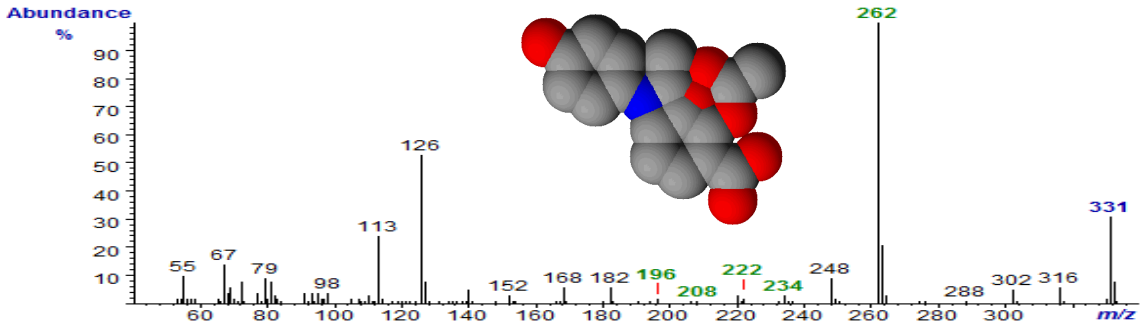
Paracetamol Mass Spectra=151 (M+); MW=151.16g



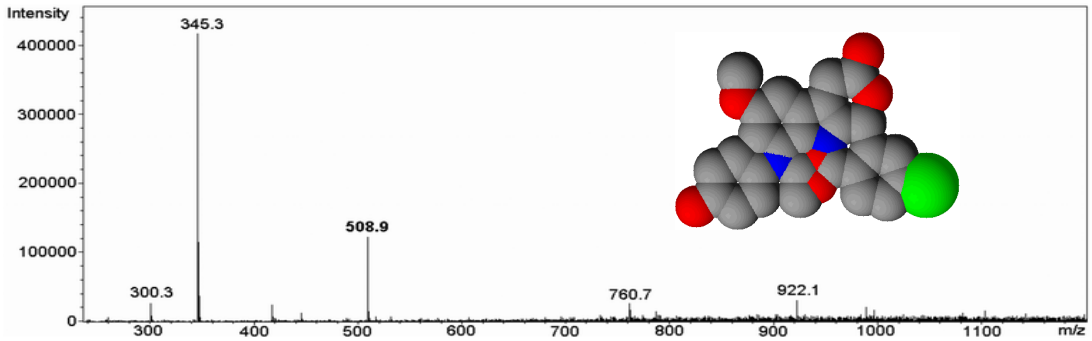
Prodrug–A=313 (M+); MW=313.30g



Prodrug–B=491.4 (M+1); MW=490.93g [M+1 peak is due to Cl atom]



Codrug–A=331 (M+); MW=331.31g



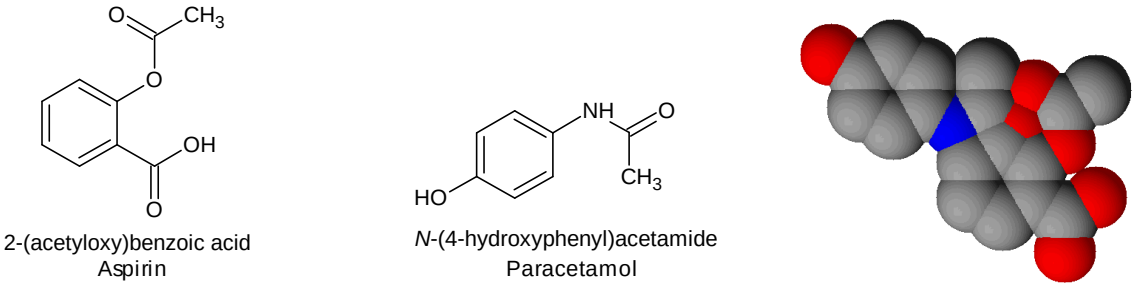
Codrug–B=508.9 (M+); MW=508.94g

Figure–14: Molecular ion peaks (Mass Spectrum)

Prodrug is a substance which after administration is metabolized into a pharmacologically active drug. Actually Prodrug has least medicinal value in *in–vitro/in–vivo* but after biotransformation by metabolism in *in–vivo* it releases the active medicament. A drug is a substance which is a chemical entity, has definite structural skeleton, obtained by natural or synthetic or semisynthetic source, which can fit on bioreceptor platform having controlling capacity to control over the biochemical malfunction. Every drug is xenobiotic because it is coming from outer source (xeno) and active in biological unit (biotic). Prodrug is the precursor of drug which is made by derivatization of the same to enhance the bioavailability by pharmacokinetics, lipid solubility by partition coefficient and increase the physicochemical & biochemical parameters by pharmacodynamics.[5]

Codrug or "mutual prodrug" consists of two synergistic drugs chemically linked together, in order to improve the drug delivery properties of one or both drugs. The constituent drugs are indicated for the same disease, but may exert different therapeutic effects via disparate mechanisms of action.

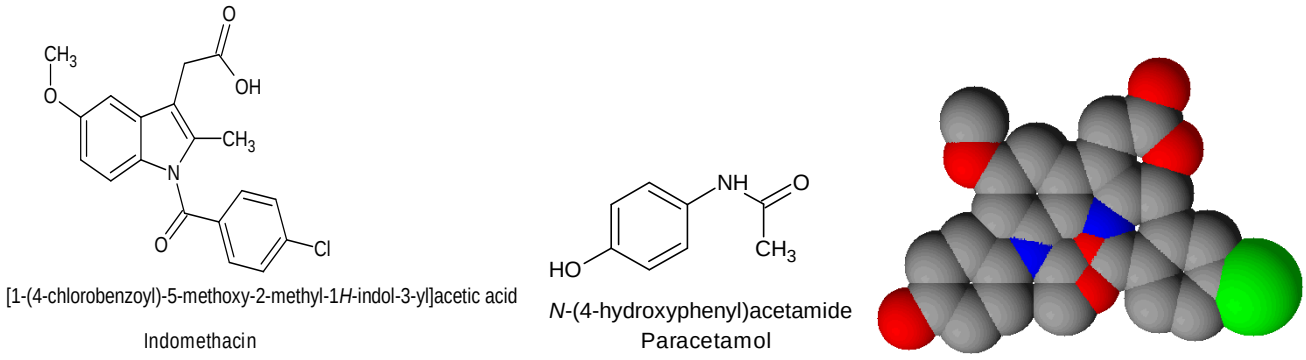
There exists a disagreement on the meaning of the term "cocrystal." One definition states that a cocrystal is a crystalline structure composed of at least two components, where the components may be atoms, ions or molecules. This definition is sometimes extended to specify that the components be solid in their pure forms at ambient conditions. However, it has been argued that this separation based on ambient phase is arbitrary. A more inclusive definition is that cocrystals "consist of two or more components that form a unique crystalline structure having unique properties." Due to variation in the use of the term, structures such as solvates and clathrates may or may not be considered cocrystals in a given situation. It should be noted that the difference between a crystalline salt and a cocrystal lies merely in the transfer of a proton. The transfer of protons from one component to another in a crystal is dependent on the environment. For this reason, crystalline salts and cocrystals may be thought of as two ends of a proton transfer spectrum, where the salt has completed the proton transfer at one end and an absence of proton transfer exists for cocrystals at the other end. Cocrystal structures exhibit long–range order and the components interact via non–covalent interactions such as hydrogen bonding, ionic interactions, Van der Waals interactions and π–interactions. The intermolecular interactions and resulting crystal structures can generate physical and chemical properties that differ from the properties of the individual components. Such properties include melting point, solubility, chemical stability and mechanical properties. Some cocrystals have been observed to exist as polymorphs, which may display different physical properties depending on the form of the crystal. Phase diagrams determined from the "contact method" of thermal microscopy proved valuable in the discovery of new cocrystals. The construction of these phase diagrams is made possible due to the change in melting point upon cocrystallization. Two crystalline substances are deposited on either side of a microscope slide and are sequentially melted and re–solidified. This process creates thin films of each substance with a contact zone in the middle. A melting point phase diagram may be constructed by slow heating of the slide under a microscope and observation of the melting points of the various portions of the slide. For a simple binary phase diagram, if one eutectic point is observed then the substances do not form a cocrystal. If two eutectic points are observed, then the composition between these two points corresponds to the cocrystal.[6]



Figure–15: Co–crystallization of Aspirin and Paracetamol [Codrug–A]

*Explanation: Aspirin has **4** oxygen atoms (red) and Paracetamol has **2** oxygen atoms (red) and **1** nitrogen atom (blue), so the non–covalent interactions such as hydrogen bonding, ionic interactions, Van der Waals interactions and π–interactions, so the total **7** hetero atoms are found in Codrug–A.*

Cocrystal structures exhibit long–range order and the components interact via non–covalent interactions such as hydrogen bonding, ionic interactions, Van der Waals interactions and π–interactions. In case of Aspirin and Paracetamol co–crystal CH_3–CO–O– part of Aspirin is bioisosteres with CH_3–CO–NH– part of Paracetamol because atomic weight of oxygen of –COO– is ($_8O^{16}$) which is close to nitrogen & hydrogen ($_7N^{14}+_1H^1$=14+1=15) of –CONH–. Here π–interactions are quite possible because >C=O group is present in both ester (–COO–) and amide (–CONH–). Here Van der Waals interactions are also quite possible along with the –OH part of carboxylic acid part of Aspirin –COOH with –OH group of Paracetamol.



Figure–16: Co–crystallization of Indomethacin and Paracetamol [Codrug–B]

*Explanation: Indomethacin has **4** oxygen atoms (red), **1** nitrogen atom (blue) and **1** chlorine atom (green) and Paracetamol has **2** oxygen atoms (red) and **1** nitrogen atom (blue), so the non–covalent interactions such as hydrogen bonding, ionic interactions, Van der Waals interactions and π–interactions, so the total **9** hetero atoms are found in Codrug–B.*

In case of Indomethacin and Paracetamol (>N–C=O) linkage is present in both as amide (–CO–NH–) which again shows π–interactions are quite possible because >C=O group (one σ and one π) is present in amide (–CONH–) and –OH group of –COOH of Indomethacin is also present in –OH group of Paracetamol also so here Van der Waals interactions are quite possible because in both cases –OH of –COOH matches with each other and the reason is that –OH of phenolic group of –COOH has two lone pairs of electrons so these lone pairs of electrons produce Van der Waals interactions between the two functional groups to produce co–crystals of Aspirin+Paracetamol and Indomethacin+Paracetamol along with π–interactions. Cocrystals of Aspirin & Paracetamol and Indomethacin & Paracetamol follows as non–covalent interactions such as hydrogen bonding, ionic interactions, Van der Waals interactions and π–interactions.

CONCLUSION

Physicochemical parameter comparison of individual API (Active Pharmaceutical Ingredient) with synthesized prodrug as well as codrug were done for solubility profile, melting point, TLC–R_f, UV spectra, IR spectra, Mass spectra, logP and found that the values differ from the API which shows the significance of prodrug synthesis. Nonpolarity of prodrug and codrug was found as follows: Prodrug–B (3.94) > Codrug–B (3.42) > Prodrug–A (2.15) > Codrug–A (1.55). Codrugs are found always polar than prodrug because prodrug has covalent bonding between two APIs and codrug has non–covalent interactions such as hydrogen bonding, ionic interactions, Van der Waals interactions and π–interactions between two APIs.

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Debojyoti Basu

Divyesh Sharma

Prof. Dr. Dhrubo Jyoti Sen

Comparative physicochemical correlation study of synthesized prodrug and codrug of aspirin+paracetamol and indomethacin+paracetamol by covalent and non–covalent bonding is the outcome of the total efforts and applications of B.Pharm. course contents into practical approach. The authors are thankful to Shri Sarvajanik Pharmacy College, Mehsana for providing drugs and laboratory facilities to perform synthesis of prodrug & codrug with their analytical profiles to fulfill this project with grand success.

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