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Differences in Serum Levels of Polysaccharide among Patients with Hepatitis B Virus, Hepatitis C Virus and Liver Cirrhosis

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Abstract

Bacterial translocation (BT) into the systemic circulation has been documented to be associated with liver dis-ease progression. However, BT has not completely defined in patients with Hepatitis B virus (HBV), Hepatitis C virus (HCV), and Liver cirrhosis. This study aims to study the differences in the lipopolysaccharide (LPS) level as a marker for BT among patients with HBV, HCV, and liver cirrhosis and their effect on disease severity. Across-sectional study was conducted. A total of 89 blood samples was collected from patients with HBV, HCV, and liver cirrhosis. Serum samples was used to measure the level of LPS automatically by ELISA Techniques. SPSS, version 22 software (IBM Corp., NY, and USA), was used to analyze data . Out of all samples analysed pa-tients, 45 (50.56%) patients were infected with HBV, 21 (23.59%) infected with HCV and 23 (25.84%) with liver cirrhosis., The mean age of the patients with HBV, HCV, and Liver cirrhosis were 39.84 ±16.823 years, 42.76 ±15.59 years, and 49.87 ±15.9 years, respectively, Additionally, there were statistically significant difference in the mean age of patients with HBV infection and liver cirrhosis p-value less than 0.05. The mean LPS level was significantly lower in patients with HBV compared to those with HCV and liver cirrhosis. conclusion: The signif-icant positive correlation of LPS with ALP (ALP results was collected from reports of patients) may support the role of this parameter in disease pathogenesis. The highest mean LPS level found in liver cirrhotic patients may reflect the impact of LPS in pathogenesis.

Keywords: Viral hepatitis, HBV, HC, liver cirrhosis, Bacterial translocation, Lipopolysaccharide (LPS)

1. Introduction

Viral hepatitis is an important public health issue [1]. The World Health Organization (WHO) predicteds that in 2019, 296 million individuals would have chronic hepatitis B virus (HBV) infections,

with 1.5 million new cases occurring annually[2] Hepatitis C virus (HCV) infects 1.5 million individuals worldwide each year, and 58 mil-lion people have chronic HCV infection, with a prevalence of 0.8 (0.6-1.0) percent in the general population worldwide [3].Chronic inflammation of liver caused by HBV and HCV can lead to scarring of the tissues (fibro-sis), irreversible scarring (cirrhosis), and hepatocellular carcinoma (HCC) [4] Globally, among individuals with cirrhosis 42% had HBV infection and 21% had HCV infection [5].

The liver plays a critical role as an immunological barrier against pathogens in the circulation [6]. When liver is inflamed or damage due to viral infection, these immune activities of liver become less effective, allowing more gut-derived germs to enter the bloodstream and increasing the risk of developing systemic bacterial infection [7].

An essential factor in the emergence of infection in liver cirrhosis is bacterial translocation (BT). In healthy indi-viduals, the migration and colonization of bacteria and/or bacterial products from the gut to mesenteric lymph nodes is a regulated process.BT occurs through three mechanisms, impaired host defense, bacterial overgrowth, and disruption of the mucosal barrier. Highlight the relationship between bacterial translocation and LPS levels., Impairment of BT in cirrhosis is promoted by increased intestinal permeability, bacterial overgrowth, and defects in the gut-associated lymphatic tissue [8][9][10]. Microbial components like lipopolysaccharide and peptidogly-can are hypothesized to both contribute to and accelerate the progression of liver disease [7]

Increased microbial translocation has been found with HBV and HCV [11] [12]. Understanding the relationship between bacterial translocation and the severity of hepatitis infection may help to understand how translocation affects chronic liver illnesses. This might result in new treatment targets for preventing infections and other cir-rhosis consequences [13]

The aims of current study is to investigate the differences in serum level of LPS among patients with HBV and HCV infections, Study the association of the of LPS level with the disease severity.

2. Materials and Methods

This study was approved by Ethical Committee at College of Applied Medical Science/ University of Kerbala. All subjects involved in this work were informed and agreement was obtained verbally from each one before the collection of samples.

A cross-sectional study was carried out in College of Applied Medical Sciences, University of Kerbala, "from October 2022 to February 2023". 89 Eighty-nine blood samples, were collected from patients with HBV, HCV, liver cirrhosis whom they referred to Karbala health departmental/ AL-

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Hussain Medical city, Women Ob-stetrics and Gynecology Hospital, and Karbala Center for Diseases and surgery of Digestive system and liver. Serum samples were used to measure the level of LPS, by ELISA Techniques .Wells coated with LPS monoclonal antibody bind with LPS in sample. The optical density (OD) is determined spectrophotometrically at a wavelength of 450 nm.

. liver enzymes results(ALT,AST.ALP,ALB, PT,TSB) collected from reports of patients.

2 .1 Statistical Analysis

Data was analyzed using SPSS, version 22 software (IBM Corp., NY, USA). Mean, Standard Deviation, and cross-tabulation, Bivariate correlations, the Least Significant Difference (LSD) test and the Analysis of Variance (ANOVA) test was calculated. To evaluate the categorical variables, the chi-square test was applied. P value <0.05 was used to determine the statistical significance.

3. Results

Eighty-nine patients were enrolled in this study. Out of the 89 patients studied 45 (50.56%) of patients were in-fected with HBV, 21 (23.59%) infected with HCV and 23 (25.84%) with liver cirrhosis, The mean age of the pa-tients with HBV, HCV, and liver cirrhosis were 39.84 ±16.823, 42.76 ±15.59, and 49.87 ±15.9 years, respectively, Additionally, in the mean ages of patients was differ significantly between HBV infection and liver cirrhosis. A higher mean of age was found in cirrhotic liver patients, as shown in Table (1), The distribution of patients ac-cording to age was shown in Table (2).

Table 1. Mean age of patients

Virus types	Mean age (years)	N (%)	SD	Multiple Comparisons LSD			
				(I) virus types	(J) virus types	Mean Difference (I-J)	Sig.
HBV	*39.84*	*45 (50.56)*	*16.823*	*HBV*	*HCV*	*-2.917*	*.500*
					Liver cirrhosis	*-10.025**	*.019*
HCV	*42.76*	*21 (23.5)*	*15.595*	*HCV*	*HBV*	*2.917*	*.500*
					Liver cirrhosis	*-7.108*	*.152*
Liver cirrhosis	*49.87*	*23 (25.8)*	*15.907*	*Liver cirrhosis*	*HBV*	*10.025**	*.019*
					HCV	*7.108*	*.152*
ANOVA test P-value	*0.061*						

*. The mean difference is significant at the 0.05 level;SD: Standard Deviation; LSD: Least Significant Difference

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Table 2 Distribution of Patients According to Age Categories

		Type of Disease N (%)			Total
		HBV	HCV	Liver cirrhosis	
Age Categories	≤40 years	*27(60)*	*11(52.3)*	*6(26.08)*	*44(49.43)*
	>40 years	*18(40)*	*10(47.61)*	*17(73.91)*	*45(50.56)*
Total		*45(100)*	*21(100)*	*23(100)*	*89(100)*
P-value		*0.029*			

.

The Sex distribution of patients were shown in Table (3) with Male/ Female ratio (16/29, 0.5:1), (9/12, 0.75:1), (13/10, .3:1) , For HBV, HCV, and liver cirrhosis, respectively.

Table 3. Distribution of patients with HBV, HCV, and liver cirrhosis according to Sex

	Type of Disease N (%)			
Sex	HBV	HCV	Liver cirrhosis	Total
Male	*16(35.55)*	*9(42.8)*	*13(56.52)*	*38(42.69)*
Female	*29(64.44)*	*12(57.1)*	*10(43.47)*	*51(57.30)*
Total	*45(100)*	*21(100)*	*23(100)*	*89(100)*
P- Value	*0.255*			

The current study revealed the presence of significantly lower mean of LPS in patients with HBV in comparison to HCV and liver cirrhotic patients, as show in table (4).

Table 4. Differences in LPS level among HBV, HCV and Liver cirrhotic patients

	Type of disease	Mean	SD	Min	Max	Post Hoc	Kruskal-Wallis test *P-value*
LPS	HBV	105.89	110.02	2	476	b	.001*
	HCV	232.29	131.03	18	514	a	
	Liver cirrhosis	299.64	133.49	9	619	a	

* Kruskal-Wallis test *Significant at 0.05 level, Similar letter (a) means non-significant differences

This study showed that there was significant positive correlation of LPS with Alkaline phosphatase. No

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significant correlation was found with ALT, AST, TSB, PT, and Albumin, as shown in Table (5).

Table 5. Correlation between LPS Markers of liver damage

		ALT U/L	AST U/L	ALP U/L	TSB mg/dl	PT seconds	Alb mg /dl
LPS U/I	Pearson Correlation	.007	.084	.395**	.173	.125	.028
	Sig. (2-tailed)	.962	.550	.006	.244	.579	.953
	N	55	53	47	47	22	7

AIT (alanine aminotransferase); AST (aspartate aminotransferase); ALP (Alkaline Phosphatase); TSB (Total serum bilirubin); PT (Prothrombin Time); Alb (albumin)

4. Discussion

This study aimed to investigate the importance of serum bacterial LPS presence in patients with HBV, HCV, and liver cirrhosis. Eighty nine patients were included. A significant difference in the mean ages of patients with HBV infection in comparison to cirrhotic liver patients was found. A higher mean was discovered in cirrhotic liver patients as shown in Table (1). This result agrees with previous study (Sajja et al., 2014)[14]. Higher mean found in liver cirrhotic patients might possibly due to life style and accumulated exposure to environmental factors together with drinking alcohol and being exposed to harmful substances, these factors all contribute to the progression of persistent liver inflammation which may result in cirrhosis [15].

Higher frequency of patients with HBV and HCV were found less than 40 years of age whereas higher frequency of patients with liver cirrhosis was above 40 years of age show in Table 2. Similar results were documented in previous studies aged 20–29 and 30–39 years, (18–40-year-old patients) [16] [17] [18]. More than 75 % of patients in this study were suffers from chronic disease. Age is regarded as a major risk factor for hepatitis virus infection. It was documented that infection during the early age of life increases the risk of liver cancer development and the pos-sibility of persistent infection [19]. When HBV or HCV infections are persistent, older age has consistently been reported as an independent risk factor for the development of HCC [20]

In the current study, higher frequency of infection among females was found in case of HBV and HCV infection while lower frequency was found in case of cirrhosis show in Table 3. Higher ratios were recorded in previous studies concerning HBV, HCV, and cirrhosis [21][22].Sex is considered as a risk factor in different types of dis-eases. Actually, there are many differences between female and

male in health and disease status. Women have a longer life expectancy than men, but they are not necessarily healthier. Sex differences in immune response have been documented. The immunological response to viral infections was found to be stronger in females. The course of liver disease appears to differ across the sexes, and numerous clinical trials have demonstrated that postmenopausal women and men with Chronic hepatitis caused by HBV and HCV progresses more quickly to cirrhosis [23].

The presence of significantly lower mean of LPS among HBV infected patients might possibly due to immune response manipulation by the virus show in Table4. It has been documented that during Chronic HBV infection, the virus or its component (HBeAg), manipulate a number of mechanisms that prevent IL-1ß from expressing and having a biological effect. Additionally, it prevents the NLRP3 inflammasome is activated by LPS. the generation of IL-1ß, and the activation of NK-B, all of which may encourage the development of chronic infection [24]. In-terestingly it has been demonstrated that persistent HCV infection causes a considerable elevation in LPS, which is a marker of liver failure. The etiology of the disease and recurrent liver damage are both impacted by the dysbiosis of the gut microbiota in chronic HBV infection [13]

Additionally, dysbiosis of gut microbiome and innate immunological response in the gut are linked to cirrhosis [25]. Pathogen-associated molecular patterns (PAMPs), for instance LPS, are the main cause of systemic in-flammation in cirrhosis and are the result of bacterial translocation [26].

This study showed that there was significant positive correlation of LPS with Alkaline phosphatases (ALP) show in Table 5. ALP is considered as liver disease biomarker and is associated with biliary tract disease[27] .Additionally, ALP has been recognized as a standalone prognostic factor for recurrence in patients with (HCC). There has been evidence of a connection between liver pathology and the digestive system. [28]

(ALP) also has a crucial anti-inflammatory function. ALP cause detoxification of bacterial LPS which decreases its action [29]. ALP, a measure of nodular regenerative hyperplasia, suggests that, even in the absence of viral infection, microbial translocation and LPS-induced monocyte or Kupffer cell activation cause hepatic fibrosis and portal hypertension [11].

5. CONCLUSIONS

Higher mean age of patients with liver cirrhosis and higher frequencies of HBV, HCV infection within the age range of 20 -39 years and the presence of significant difference in the mean age of acute and chronic infection could reflect the impact of age on infection. Higher frequency of infection occurs among female in case of HBV and HCV infection while lower frequency occurs in case of cirrhosis.

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Significant decrease in LPS mean level was seen in patients with HBV infection in comparison to the two other groups which may reflect the role of this virus in manipulating the immune response to achieve persistent infection. Significant positive correlation of LPS with ALP may support the role of these parameter in disease pathogenesis.

This study has the following limitations: Does not Include healthy subjects to compare the LPS level with patient's groups.

Also, study the normal and patients GIT microbiome and study the markers for gram positive bacteria translocation.

Recommendations

Making a Case-Control study to investigate the following :

1. The difference in the mean level of LPS, between patients and control groups
2. The differences in Microbiome of HBV, HCV, Liver cirrhosis patients and compare it with the microbiome of healthy individuals.

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Co-crystallization as a powerful solubilisation approach for Biopharmaceutical Classification System Class II drugs.

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Abstract

In accordance with the Biopharmaceutical Classification System (BCS), drugs that fall into Class II are distinguished by having a lower solubility and a higher permeability. Therefore, co-crystallisation has been developed for the purpose of dissolving medications that are notoriously difficult to dissolve. Active pharmaceutical ingredients (API) and coformers are the components that go into the production of co-crystals. Pharmaceutical co-crystals are a type of nonionic complex that can be utilised to solve a range of physicochemical issues, such as solubility, stability, and bioavailability. An item is said to be a co-crystal if it is comprised of two or more different molecular units and is kept together by weak intermolecular interactions such as hydrogen bonding, super-porous systems, and biodegradable hydrogel systems. Co-crystallisation is frequently considered the most efficient method for improving the quality of medications since it can change the molecular interactions and chemical make-up of medicinal substances. Co-crystals provide an alternative approach for API, regardless of whether the API comprises acidic, basic, or ionizable groups. The reintroduction of compounds that have restricted pharmacological properties due to the fact that their functional groups are not ionizable acts as a complementary approach to approaches that have already been established. Inclusion, preparation, and characterization of the co-crystals, as well as several applied research studies, are all topics that are covered in this review, along with their significance in the recent trend towards improving various physicochemical features of BCS class II medications, such as solubilization, stability, and bioequivalence.

Keywords: co-crystal, soluibility, BCS II, poorly soluble.

1. Introduction

Multiple factors influence the efficacy of medicine. The API's physicochemical properties are one of them. The BCS classifies the solubility and permeability of various pharmaceuticals. The BCS categorises medications based on their permeability and solubility, as shown in Figure 1. These points are crucial because the overwhelming majority of medicines sold around the world are intended for oral consumption. Sixty to seventy percent of the recently discovered novel pharmacological compounds are BCS Class II or Class IV compounds, which have reduced solubility and permeability [1, 2].

Co-crystals are multicomponent crystalline systems formed of ordered proportions of distinct molecular and/or ionic components. To enhance the bioavailability, mechanical characteristics, and solubility of previously insoluble solid medications, scientists have turned to co-crystals [3, 4]. Co-crystals consist of two distinct parts. The API and the coformer make up the two halves of the system. The vast majority of coformers are used in the medical industry as excipients, although some of them also have uses as active pharmaceutical compounds [5]. Coformers also include food additives and preservatives of various kinds. Crystals that are generated from APIs are known as co-crystals [6]. The ideal coformer would be a very small organic acid that could make hydrogen bonds with the API. The coformers of carboxylic acid, amide, and alcohol are encountered frequently. Interactions between these functional groups are prevalent in co-crystal systems [7, 8].

Medications belonging to BCS Class II that are poorly soluble in water but have high levels of permeability [9, 10]. Enhancing a medication's solubility can be accomplished employing hydrotropic, complexation, solid dispersion, salt formation, emulsification, co-crystallisation, and nanocrystal methodologies [11]. The solubility of the medicine and its bioavailability are both improved by inclusion complexation. Cavity structures are characteristic of inclusion complexes, which are formed when one chemical (the host molecule) encircles another. The cavity of the host molecule is occupied by a ringed component known as a guest compound [12].

In this article, we discussed the solubility of BCS Class II medications as well as the role of co-crystallisation in overcoming this undesirable feature of this category. In addition, co-crystallisation, synthesis, and evaluation were discussed in considerable depth (Figure 2). Finally, the application of the co-crystal approach to BCS class II was covered, and some recent studies that confirmed an increase in the solubility of co-crystallised forms of these medications were reviewed.

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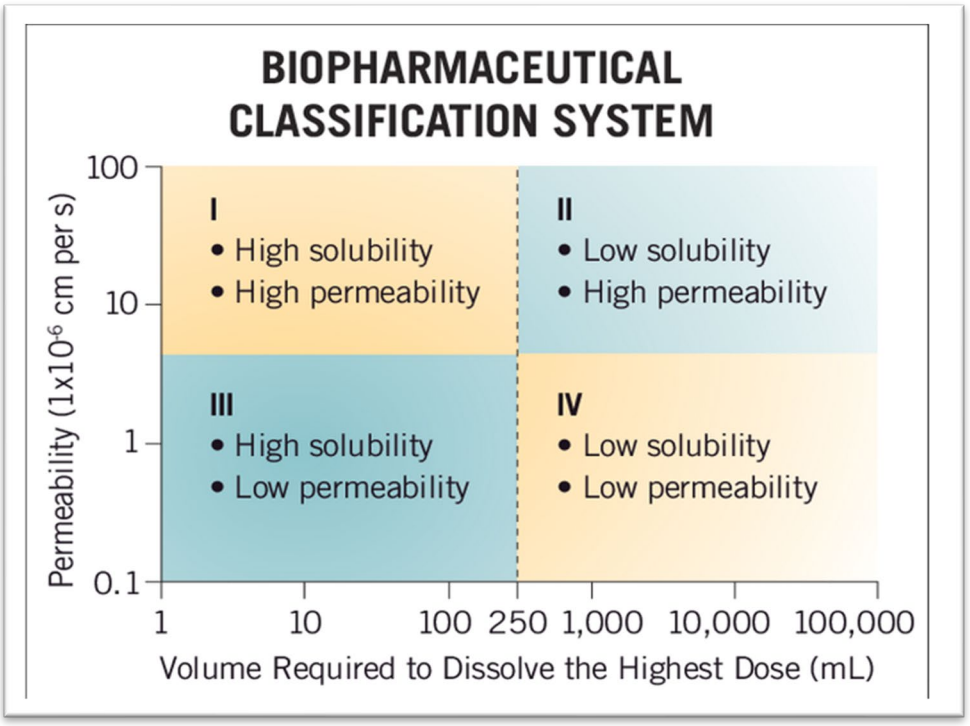

Figure 1: BCS classes of drugs adapted from (Rajadhyax A, Shinde U, Desai H, Mane S. Hot melt extrusion in engineering of drug cocrystals: a review. Asian Journal of Pharmaceutical and Clinical Research. 2021; 14(8): 10-19).

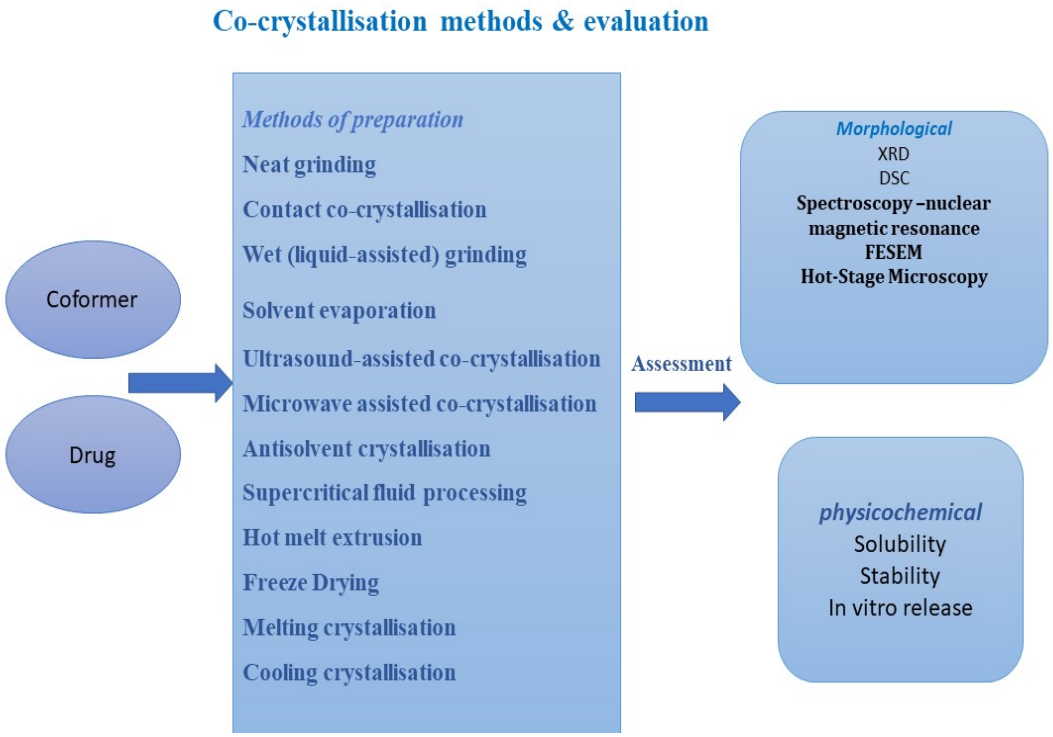

Figure 1: co-crystallisation methods and evaluation.

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2. Co-crystal preparation methods

2.1 Neat grinding

This particular method of grinding creates co-crystals by mixing APIs and coformers while the mixture is subjected to pressure. Blend in a mortar or in a vibrating or ball mill. Controlling the temperature and the amount of time spent mixing can help generate the best possible result. Grinding lasts 30–60 minutes. This method eliminates stability problems by omitting the use of solvents [3].

2.2. Contact co-crystallisation

With the "soft" mixing of raw materials, API-coformer interactions spontaneously occurred [13]. Vapour diffusion of them, moisture sorption, amorphization, and long-range anisotropic molecular motion may explain spontaneous crystallisation by contact [14]. MacFhionnghaile et al. (2020) found that premilling of API and conformer at room temperature and 30% relative humidity produced caffeine-urea co-crystals in three days. They found that caffeine-urea co-crystals formed due to solids' interparticle surface interaction [15]. Moreover, an additional example of spontaneous crystallisation is the isoniazid and benzoic acid co-crystallisation, which showed that moisture promoted the co-crystals' reordering [16]. Premilling the co-crystal physical mixture lowered the nucleation induction time and boosted the composition. Nartowski et al. (2016) showed that moisture addition altered spontaneous co-crystal formation kinetics [17].

2.3. Wet (liquid-assisted) grinding

Solid powders are first catalysed using a variety of solvents, including water, ethanol, and toluene. Only a few drops of the solvent are required. Co-crystal formation can be improved by using a grinding method called solvent drop grinding [18], which binds rather than dissolves the solid particles. This approach results in a co-crystal that has a higher purity than other methods while also being simple, efficient, environmentally friendly, and economical. Wet grinding typically results in higher yields [19].

2.4. Solvent evaporation

This is the most important solvent-based method, including dissolving the API and the coformer in the solvent in order to produce co-crystals [20]. The co-crystal will develop once the solvent has been completely evaporated. While rapid evaporation produces a large number of little co-crystals, slow evaporation results in a smaller number of larger ones. The method of creating co-crystals that is the most reliable is the one in which the solvent is evaporated. In this technique, the drug and the coformer are mixed together in the appropriate proportions before being dissolved in a

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solvent. When a solvent is allowed to evaporate at room temperature, the result is the formation of co-crystals. It is possible to identify a shared solvent by considering the degree to which the drug and the coformer are soluble in the candidate solvent [21]. The bonding between drugs and coformer functional groups results in the formation of co-crystals. The researchers, Mounika and colleagues, used a variety of techniques to synthesise fexofenadine-tartaric acid co-crystals. Mounika et al. (2015) discovered that solvent evaporation is an easy process that increases the medication's stability as well as its solubility [22]. For example, a 1:1 co-crystal of febuxostat and piroxicam that works through a carboxylic group was made by letting acetonitrile slowly evaporate without heat over the course of three to five days. This co-crystal was more soluble and easier to tablet than its individual components [23].

2.5. Ultrasound-assisted co-crystallisation

In order to manufacture co-crystals, this cutting-edge technique makes use of ultrasonic vibrations, which boost nucleation in solution and speed up phase change processes [24]. A solid ultrasonic probe with a temperature controller and a vessel that can be used with the sonicator where the ultrasonic was utilised by Aher et al. (2010) in order to bring about the formation of caffeine-maleic acid co-crystals. This procedure leads to the formation of a co-crystal that is composed of equal parts caffeine and maleic acid [25]. In a glass vial, the particles will first be solubilized in the solvent. Next, the vial will be sonicated at a controlled temperature until the solution is clear. Finally, the co-crystal will be collected by filtering the solution [26]. Rodrigues et al. (2020) made use of ultrasonic baths in order to facilitate the creation of hydrochlorothiazide co-crystals with a range of coformers [27].

2.6. Microwave-assisted co-crystallisation:

By interacting with the revolving dipoles that make up a molecule, microwave radiation stimulates the molecules and makes it easier for them to move about. The heat from the radiation keeps the solvent in a supersaturated state and guarantees that it evaporates quickly [28]. Co-crystallisation is a process that can be carried out using either microwaves found in the home or microwave reactors. In contrast to their domestic counterparts, microwave reactors are capable of accurately controlling both power and pressure [29]. After the APIs and coformer have been solubilized in a solvent based on their solubility behaviours, the mixture is transferred to glass tubes and then microwaved at the appropriate temperature, time, and power. A co-crystal is produced when the solution is filtered [29].

2.7. Antisolvent crystallisation

Antisolvent crystallisation is an additional method that can be utilised for the production of co-crystals of superior quality [30]. During this step of the process, a second liquid is added to the medium

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containing the drug and coformer. This step produces supersaturation. In order for the co-crystal to precipitate, the additional liquid that is being used must be miscible with the solvent [31].

2.8. Supercritical fluid processing

Because of its ability to permeate solids, carbon dioxide (CO2) is the supercritical fluid that is used most frequently in the manufacturing of co-crystals. After dissolving the medication and the coformer in carbon dioxide, they are placed in a tank made of stainless steel. The formation of co-crystals is the end result of a rapid expansion of CO2 due to a gradual decrease in pressure. The drug and the coformer are only partially soluble in the supercritical fluid, which is the primary drawback of this method. Additionally, the clarity of the co-crystals is diminished due to this method [20].

2.9. Hot melt extrusion

It is a process in which a drug is embedded in a melted polymeric matrix with the required characteristics to modify solubility and stability. Thermolabile compounds could be handled at a lower temperature to avoid degradation [24]. Hot melt extrusion may be the best option for the continuous manufacturing of co-crystals, where co-crystals are produced by heating the drug and coformer to a miscible state and then vigorously mixing them together in an extruder [32].

2.10. Freeze Drying

Freeze drying, also known as lyophilization, is another method that could be utilised in the manufacturing of pharmaceutical co-crystals. During the process of freeze drying, moisture is extracted from a substance by first freezing it, then allowing the ice to sublimate straight to vapour at a low partial pressure of water vapour. This removes the moisture from the substance. This is a process that consists of multiple steps that are utilised in food and pharmaceuticals for the goal of preserving products, and this technology is applied in those fields. In more recent times, it has been demonstrated that this method can be effectively utilised to prepare novel solid forms of co-crystal systems [33, 3].

2.11. Melting crystallisation

Melting crystallisation can make pharmaceutical co-crystals greener. Despite the fact that no solvents are employed in this method, the stability of the drug and coformer should be assessed. Melatonin-pimelic acid co-crystals were melted and crystallised by Yan et al. (2015) [34]. Melatonin-pimelic acid co-crystals were formed in the liquid at temperatures between 50 and 70 degrees Celsius. To create the carbamazepine-nicotinamide co-crystal, the drug-coformer mixture was melted at 160 °C before being cooled to room temperature for crystal development, which resulted in a crystal structure with a nicotinamide atom [35]. The crystallisation mechanisms of the carbamazepine-

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nicotinamide from the melt after heating were studied, and the carbamazepine-nicotinamide co-crystal nucleated in a metastable phase and transitioned to the stable form at a slow heating rate (3 °C/min), while at a rate of 10 °C/min, the constituent parts of the co-crystal crystallised separately, were melted, and the stable form grew from the melt [35].

2.12. Cooling crystallization

The cooling crystallisation method is widely utilised for the production of large, pure co-crystals. The distribution size, purity, shape, and polymorphism of these co-crystals are dependent on the localised supersaturation [36]. During the process of crystallisation, the operational region is established according to the stoichiometry of the co-crystal as well as the thermodynamic stabilisation region at both the starting temperature and the finishing temperature. Many investigations have shown that this method is an effective one for increasing the production of co-crystals on a larger scale. These co-crystals had a purity level of 99% and were of uniform particle size. In order to initiate the nucleation of the co-crystals, a seeding slurry with a weight-to-volume ratio of 10% was injected into the crystallizer at a temperature of 10 degrees Celsius for ten seconds [37].

3. 3. Assessment of the co-crystals

3.1. Characterization

3.1.1. X-ray (XRD) investigations

Co-crystal unit cells can be phased using this analytical tool. Crystallography, both single and powder X-rays, has the potential to show co-crystal formations. XRD is utilised to identify co-crystals by detecting differences in the crystal lattice. Crystal sourcing is the primary challenge faced by single-crystal XRD [38].

3.1.2. Differential scanning calorimetry (DSC)

Pharmaceutical co-crystals are usually characterised using the DSC. This method involves heating co-crystals and pure components at a predetermined rate and evaluating the thermogram to determine if co-crystal formation occurred [39]. The eutectic melt generated at mild heating rates recrystallizes to the co-crystal form before melting, regardless of the drug-to-coformer ratio. A DSC-scan thermogram can detect co-crystals. Co-crystal thermograms show an exothermic peak, unlike medications and coformers. Then comes an endothermic peak. It's likely that co-crystal melting and fusion temperatures will vary. Due to physical combinations that cannot form co-crystals, thermograms show just one endothermic peak during eutectic melting [40].

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3.1.3. Spectroscopy: vibrational, nuclear magnetic resonance

In spectroscopy methods, also known as infrared and Raman spectroscopy, the chemical bonds in co-crystals absorb or scatter energy in a manner that is distinct from that of pure substances; this shows the structural behaviour of the co-crystals. Due to the hydrogen bonding presence, the infrared spectra of co-crystals are distinguishable from those of the pure drug and the coformer. Bands of hydrogen-bonded functional groups are distinct from one another. A neutral carboxylic acid group (COOH) has a stronger tension band of C=O at approximately 1700 cm-1 and a lower tension band of C=O at approximately 1200 cm-1, respectively, and a carboxylic anion (COO) has a weak tension band between 1000 and 1400 cm-1 as a result of salt production. Both of these tension bands are caused by the C=O bond. The OH....N H-bonding process produces two significant zones, one at 2450 cm-1 and another at 1950 cm-1. Solid-state nuclear magnetic resonance is used to characterise co-crystals since it can provide information regarding the structures of the co-crystals [41]. This method differentiates between co-crystals and salts by measuring the transit of protons, which is a characteristic of co-crystals. One disadvantage of this method is that the instrument sensitivity is quite low [42].

3.1.4. Field emission scanning electron microscopy (FESEM)

The topography of co-crystals can be investigated using FESEM. Examining the similarities and differences between FESEM components and co-crystal micrographs. The energy utilised by the field emission electron microscope can be described as "cold." Strong electric fields cause the conductor to release electrons into the surrounding space. In cathodes (10–100 nm), tungsten filaments with extremely fine needles are utilized. Both the field emission source and the scanning electron microscope are used to take the micrographs of the co-crystals [43].

3.1.5. Hot-Stage Microscopy

Microscopy and temperature analysis are both utilised in hot-stage microscopy. The physicochemical characteristics of a substance are affected both by temperature and by the passage of time. Under a microscope, it is possible to observe the melting point, melting range, and crystalline transition of a co-crystal sample that has been preserved on a glass slide [44].

4. Physicochemical investigations

4.1. Solubility test

After placing the co-crystal sample and the media in an Erlenmeyer flask or another container of the appropriate size, the mixture is shaken for twenty-four hours in a rotary flask shaker. After 24

hours, the material is subsequently filtered, diluted, and subjected to HPLC analysis [45]. Using the co-crystals approach in conjunction with n-acetylcysteine as a coformer, Paulazzi and colleagues were able to enhance the bioavailability of curcumin [46].

4.2. Stability

Examining how co-crystals and pure active compounds fare in terms of their stability and shelf life 40 degrees Celsius with 75% relative humidity is the standard temperature and humidity utilised [47], while 25 degrees Celsius with 60% relative humidity is the standard for 1, 3, or 6 months [48], evaluating the co-crystal's stability in contrast to the pure API's and its shelf life [49].

4.3. In vitro dissolution:

The formulation's in vivo performance can be predicted based on the release, which can also be employed to measure the percent of medication that accumulates over time. Studies of the co-crystals' release are carried out with the assistance of the dissolving equipment. The co-crystal dissolution research is carried out at various points across the permitted dissolution medium, as outlined in the medication protocol for the mentioned assembly [49]. The samples are collected in the appropriate volumes at the predetermined measure, and they could then be analysed using appropriate methods such as [50].

5. Examples of drugs whose bioavailability is enhanced by co-crystallisation

BCS Class II drugs include many drugs that are required to have rapid action for life-saving purposes, such as antidiabetics and antihypertensives. Recent publications include the results of some experiments that were performed to affect the physical properties of BCS class II medications by using co-crystallisation.

5.1. Antidiabetcs

Many antidiabetic drugs have the property of poor solubility. As a result, improving their solubilization is critical for saving lives. For instance, Srivastava et al. were able to solubilize glibenclamide (GLB) by employing coformer malonic acid, thanks to the assistance of co-crystallization. The co-crystal was subjected to solubility and release tests, as well as DSC, PXRD, and IR spectra, all of which validated the formation of the co-crystal. When GLB was co-crystallised, its solubility and dissolution were both increased by a factor of two [51]. Moreover, Gliclazide (GCZ), Tolbutamide (TOL), and Glipizide, BCS Class II antidiabetic medicines lacking water solubilization, were co-crystallised by Samie et al. Liquid-assisted grinding employing coformers like catechol, resorcinol, p-toluenesulfonic acid, and piperazine (PPZ) yielded GCZ multicomponent solid forms and

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co-crystals. Single crystal, powder, Fourier IR, DSC, thermal gravimetric, and solubility experiments were performed on multicomponent solids. All co-crystals have higher levels of solubility and release than their parent active medicinal ingredients. The solubility of GCZ-PPZ and TOL-PPZ increased by 6.6 and 80 times, respectively [52].

5.2. Antihypertensive

Liquid-assisted grinding and solvent evaporation produced antihypertensive drugs like nebivolol hydrochloride co-crystals, where the parent drug disintegrated much slower than the co-crystals. Nikam & Patil (2020) blend 4-hydroxybenzoic acid and nicotinamide (NA) to make BCS class II antihypertensive nebivolol hydrochloride co-crystals [53]. AMT is licenced to treat pulmonary arterial hypertension. AMT is a BCS II molecule since it is only 0.06 mg/mL in water. Ambrisentan (AMT) and glycylglycine co-crystals develop via hydrogen bonding, and the co-crystal has a higher bioavailability than pure AMT [54].

5.3. Antihistaminics

Setyawan et al. (2021) generated a loratadine-succinic acid co-crystal by employing succinic acid as the conformer. This was accomplished through the application of the solution approach, which involved the use of methanol. The presence of an intermolecular hydrogen link between loratadine and succinic acid may be seen in IR spectra. In the co-crystal phase, the solubility of loratadine was enhanced by interactions between C=O and H-O, resulting in a 1:1 loratadine-succinic acid co-crystal [55].

5.4. Erection - extending enhancers

This category is not for lifesaving, but it is important for a good quality of life, especially for men with problems with erection. Shimpi and colleagues (2018) co-crystallised tadalafil (TDF) with malonic acid (MOA) to increase the drug's solubility. The crystalline structure revealed that the TDF molecules formed hydrogen bonds, indicating that the stoichiometry was 1:1 for the compound, which demonstrates an increase in the rate of disintegration [56].

5.5. Anthelmintics

Yang et al. (2022) solubilize praziquantal by using solvent-assisted grinding (SAG) and solution slow evaporation (SSE). In this particular research, SAG and SSE were used in order to synthesise five different co-crystals of praziquantel (PRA) with polyhydroxyphenolic acids. Co-crystals of PRA-phenolic acids generated by SAG and SSE and their solubility and bioavailability were investigated and found to be increased [57].

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5.6. Anticholestremia

Nanda, A., and Anand, R. (2022) increased the solubility and dissolution of a BCS-class II (Ezetimibe) drug by using co-crystallization with glycine as a coformer and by modifying the chemical structure of the drug. In 90 minutes, co-crystals were able to spread and dissolve more quickly than pure drugs [58].

5.7. Antibiotics

Surampudi et al. (2023) developed BCS class II anti-folate trimethoprim (TMP) co-crystals by using the coformers theophylline-7-acetic acid (T7A), 5-fluorouracil, catechol, and thymine. The system that includes the aminopyrimidinium-carboxylate synthon, which is represented by the notation TMP-T7A, has the highest level of solubility [59].

6. CONCLUSIONS

As a result of the poor solubility of BCS Class II pharmaceuticals, the process of developing a wide variety of medications has become significantly more difficult. Therefore, increasing their solubility will result in a rise in their bioavailability. According to the findings of this review, the process of co-crystallisation has a considerable impact on both the solubility and the bioavailability of BSC Class II medications. Co-crystallisation alters qualities such as solubility, release rate, and chemical and physical stability, resulting in substances having higher-level attributes than those of the pure drug. This review offers a detailed discussion of techniques, cofomers, characterization, and evaluation, as well as many drugs that benefited from co-crystallisation with appropriate coformers and their results, especially lifesaving drugs.

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