1 Introduction and literature review

1.1 Introduction

Oral administration is the most preferred route owing to its several advantages over other route of administration. Patient compliance due to its non-invasive nature and dose accuracy, increased therapeutic efficacy, eradication of potential infections brought on by improper or repeated use of needles, cheaper production are some major advantages of oral drug delivery systems [1–3]. However, poor bioavailability of the drug, which is influenced by three important parameters, namely dissolution, permeability, and solubility is the biggest disadvantage associated with oral drug delivery [4].

Poorly water-soluble compounds continue to be the bottleneck in their transformation into an useful pharmaceutical products. A complex network of physical-chemical, pharmacological, physiological, and anatomical variables that act separately and in unison to limit drugs' bioavailability which is a setback for their effective oral administration [5]. There is a dire need to improve the bioavailability or poorly soluble drug candidates which are causing the discontinuation of product development [6]. It has been demonstrated that drug exposure is increased by other solid-state forms of drug like salts, cocrystals, and amorphous solids, which increase solubility and produce supersaturated drug solutions, particularly for Biopharmaceutics Classification System (BCS) class II drugs, which have high permeability and low solubility [7,8]. These solid-state forms' advantage in bioavailability depends on maintaining supersaturation levels during dissolution, which is accomplished via various techniques depending on the chemistry, structure, and associated solution chemistry [9]. One of the most promising techniques is converting crystalline drug molecules to their amorphous counterparts, with respect to processes with practical limitations like salt formation or simple micronization. It should be emphasised that an amorphous form can enhance the processability of pharmaceuticals in addition to providing a better apparent solubility (and thus higher bioavailability). For instance, by tableting an amorphous drug rather than the crystalline form, one can simplify the formulation by using fewer ingredients in the tablet [10]. This has resulted into several ASD based products in market. Table 1 demonstrates a details and timeline of FDA approved drug products containing an API in the amorphous state.

Table 1.1. List of marketed formulations and their details containing API in amorphous form.

Trade name	**Manufacturer**	**Drug**	**Processing technology**	**Polymer**	**Dosage form**	**Year of approval**	**Ref**
Cesamet®	Valeant	Nabilone	Solvent evaporation	PVP	Tablet	1985	[11]
Isoptin®	Abbott	Verapamil	HME	HPC/HPMC	Tablet	1987	[11]
Sporanox®	Janssen	Itraconazole	Fluid-bed bead layering	HPMC	Capsule	1992	[11]
Prograf®	Fujisawa	Tacrolimus	Solvent evaporation	HPMC	Capsule	1994	[11]
Kaletra®	Abbott	Ritonavir/ Lopinavir	HME	PVP/VA64	Tablet	2000	[11]
Intelence®	Janssen	Etravirine	Spray drying	HPMC	Tablet	2008	[11]
Samsca®	Otsuka	Tolvaptan	Spray drying	HPC	Tablet	2009	[11]
Zortress®	Novartis	Everolimus	Spray drying	HPMC	Tablet	2010	[11]
Norvir®	Abott	Ritonavir	HME	PVP/VA64	Tablet	2010	[11]
Onmel®	Stiefel	Itraconazole	HME	HPMC	Tablet	2010	[11]
Incivek®	Vertex	Telaprevir	Spray drying	HPMCAS	Tablet	2011	[12]
Astagraf XL®	Astellas Pharma	Tacrolimus	Wet granulation	HPMC;EC	Capsule	2013	[11]
Harvoni®	Gilead Sciences	Ledipasvir/Sofosbuvir	Spray drying	PVP/VA64	Tablet	2014	[11]
Epclusa®	Gilead Sciences	Sofosbuvir/Velpatasvir	Spray drying	PVP/VA64	Tablet	2016	[11]
Zepatier®	Merck	Elbasvir/Grazoprevir	Spray drying	PVP/VA64	Tablet	2016	[11]
Vosevi®	Gilead Sciences	Sofosbuvir/Velpatasvir /Voxilaprevir	Spray drying	PVP/VA64	Tablet	2017	[11]
Erleada™	Janssen	Apalutamide	Spray drying	HPMCAS	Tablet	2018	[12]
Braftovi®	Array	Encorafenib	HME	PVP/VA64	Capsule	2018	[11]
Trikafta™	Vertex	Elexacaftor/ivacaftor/tezacaftor	Spray drying	HPMCAS	Tablet	2019	[12]
Tukysa™	Seagen	Tucatinib	Spray drying	PVP/VA64	Tablet	2020	[11]
Delstrigo®	Merck	Doravirine/lamivudine /tenofovir disoproxil fumarate	Spray drying	HPMC AS	Tablet	2018	[12]
Symdeko	Vertex Pharms Inc.	Tezacaftor/ivacaftor and ivacaftor	Spray drying	HPMC AS	Tablet	2018	[12]
Orkambi®	Vertex Pharms Inc.	Lumacaftor and ivacaftor	Spray drying	HPMC AS	Tablet	2015	[12]

Trade name	Manufacturer	Drug	Processing technology	Polymer	Dosage form	Year of approval	Ref
Noxafill®	Merck Sharp Dohme	Posaconazole	HME	HPMC AS	Delayed-Release tablet	2013	[12]
Kalydeco™	Vertex Pharms Inc	Ivacaftor	Spray drying	HPMC AS	Tablet	2012	[12]
Zelboraf™	Hoffmann la roche	Vemurafenib	Solvent/anti-solvent precipitation	HPMC AS	Tablet	2011	[12]
Probuphine®	Titan Pharmaceuticals, Inc.	Buprenorphine hydrochloride	HME	Ethylene-vinyl acetate copolymer	Implant	2016	[13,14]
Implanon™	Merck Sharp Dohme	Etonogestrel	HME	Ethylene-vinyl acetate copolymer	Implant	2001	[13,14]
NuvaRing®	N.V. Organon, Oss	Etonogestrel	HME	ethylene vinylacetate copolymers	Contraceptive vaginal ring	2005	[13,14]
Lynparza®	AstraZeneca Pharmaceuticals LP	Olaparib	HME	Copovidone	Tablet, Capsule	2014	[13,14]
Mavyret®	AbbVie Inc.	Glecaprevir/Pibrentasvir	HME	Copovidone/ PEG	Tablet	2017	[13,14]
Belsomra®	Merck Sharp Dohme	Suvorexant	HME	Copovidone	Tablet	2014	[13,14]
Venclexta®	AbbVie Inc	Venetoclax	HME	Copovidone	Tablet	2016	[13,14]
Viekira Pak	AbbVie Inc.	Ombitasvir/paritaprevir/ ritonavir/dasabuvir	HME	Copovidone	Tablet	2014	[13,14]
Zoladex®	AstraZeneca Pharmaceuticals LP	Goserelin acetate	HME	Polylactic-glycolic acid copolymer	Implant	1989	[13,14]
Ozurdex®	Allergan, Inc.	Dexamethasone	HME	-	Implant	1958	[13,14]
Neupro	UCB, Inc.	Rotigotine	HME	Povidone	Transdermal patch	2007	[13,14]
Fenoglide®	Valeant Pharmaceuticals International, Inc.	Fenofibrate	HME	Polyethylene glycol	Tablet	1993	[13,14]
Gris-PEG®	Novartis Consumer Health Inc.	Griseofulvin	HME	Polyethylene glycol/Povidone	Tablet	2014	[13,14]
Nucynta®	Janssen Ortho, LLC	Tapentadol	HME	PEG/PEO/ HPMC	Tablet	2008	[13,14]
Opana®	Pharmaceuticals Manufacturing Research Services Inc.	Oxymorphone hydrochloride	HME	Hypromellose/ PEO/PEG	Tablet	1959	[13,14]
Annovera™	Mayne Pharma	Segesterone acetate/Ethinyl estradiol	HME	Silicone	Contraceptive vaginal ring	2018	[13,14]
Covera-HS	Pfizer Inc.	Verapamil HCl	HME	PEG/ PEO/Povidone	Tablet	1998	[13,14]

Trade name	**Manufacturer**	**Drug**	**Processing technology**	**Polymer**	**Dosage form**	**Year of approval**	**Ref**
Adalat CC	Merck & Co. Inc.	Nifedipine	HME	PEO/HPMC	Tablet	1993	[13,14]
Rezulin®	Parke Davis Pharmaceuticals, Ltd.	Troglitazone	HME	-	Tablet	1999	[13,14]
Zithromax	Pfizer Inc.	Azithromycin	HME	Pregelatinized starch	Tablet	1991	[13,14]
Palladone	The PF Laboratories Inc.	Hydromorphone HCl	HME	Hydroxypropyl methylcellulose/ ethylcellulose	Capsule	1984	[13,14]
Viekirax	AbbVie Deutschland GmbH & Co. KG	Ombitasvir/paritaprevir/ ritonavir	HME	Copovidone /vitamin e/polyethylene glycolsuccinate	Tablet	2015	[13,15]

1.1.1 The Amorphous state and its stability

The greatest energy state of a solid substance without long-range molecular organisation is called amorphous. Amorphous materials typically exhibit stronger molecular mobility and improved thermodynamic characteristics compared to the crystalline form resulting in better apparent solubility and dissolution rate. This is because of their high internal energy. However, these advantages come at a price and are easily lost because amorphous materials' high internal energy and improved molecular mobility also contribute to their higher chemical reactivity and propensity to crystallise, which can occur during production, storage, or administration [16].

There are a number of reasons for the physical stability of the amorphous form of pharmaceuticals in solid dispersions. The stabilisation of an amorphous drug against crystallisation is typically closely correlated with the miscibility of the drug with the polymer; hence, the drug and polymer should preferable be mixed at the molecular level, generating a glass solution. Polymer-based ASDs have received the most research attention to date. Thus, the use of polymers to stabilise amorphous drug is closely related to the concept of solid dispersion [17].

To realize clinical benefits through the administration of an ASD, it is essential to sustain the supersaturated solution for a duration sufficient for absorption. This necessitates the inhibition of crystal nucleation and growth. Polymers serve this purpose by acting as a 'parachute,' impeding the conversion of a supersaturated solution to a saturated state and facilitating the necessary timeframe for absorption (Figure 1.1).

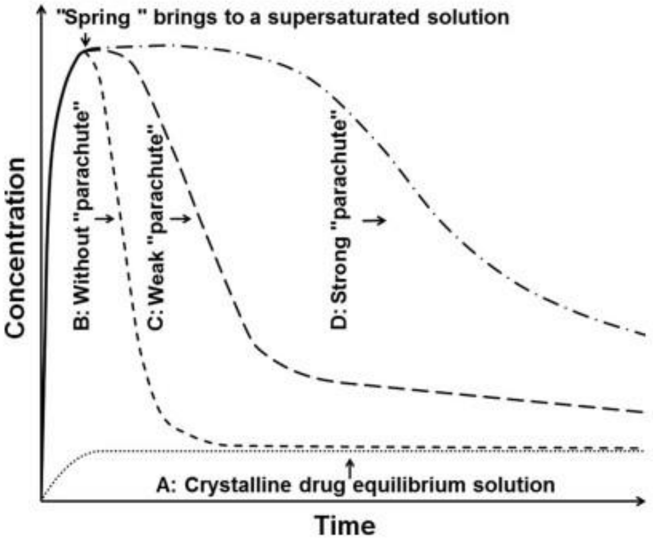


Figure 1.1. Drug profile based on aqueous solubility of amorphous and crystalline form of drug in presence of different polymers acting as parachute to the spring like solubility of amorphous drug[18]; Diagram is not to scale

1.2 Factors affecting physical stability of ASD

The possible mechanisms for the stabilization of an ASD due to the presence of a polymer have been mentioned in Figure 1.2.

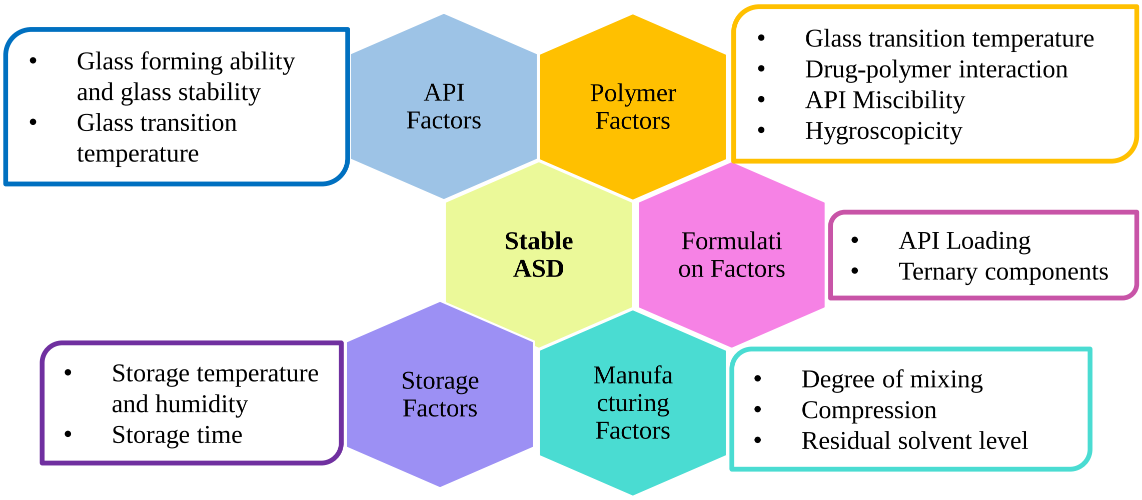


Figure 1.2. Factors effecting the physical stability of ASDs

1.2.1 Glass forming ability and glass stability

The glass-forming ability (GFA) of a drug is defined as its ability to be processed into a glass or amorphous state from a liquid upon cooling. The minimum cooling rate required for this transformation is termed the critical cooling rate, often considered an inverse indicator of GFA. Determination of the critical cooling rate involves the construction of a time-temperature-transformation plot. In practical terms, some APIs may exhibit a critical cooling rate so high that it is unattainable with current technology. The glass stability (GS) of a drug refers to its resistance to recrystallization upon reheating from the amorphous state, above the glass transition temperature, back into the supercooled liquid state. GFA and GS are frequently interconnected; that is, the ease with which an amorphous form is established can serve as a predictor of its likelihood to persist in the amorphous state, although exceptions may exist.

While the GFA and GS play pivotal roles in determining the feasibility of developing an ASD for an API, there was a lack of comprehensive understanding of the factors influencing the varying ease with which different APIs can be amorphized. A noteworthy investigation conducted by the Baird *et al.* in 2010 [19] sought to establish correlations between the physicochemical characteristics of an API and its GFA and GS, employing a dataset comprising 51 drugs. Employing a DSC method involving heating the crystalline drug above its melting temperature, cooling it to -75 °C, and then reheating, they categorized drugs into three classes. Class 1 compounds exhibited crystallization during the cooling cycle, Class 2 during the reheating cycle, and Class 3 showed no crystallization in either cycle. The study revealed that drugs crystallizing during cooling (Class 1) tended to possess lower molecular weight, fewer rotatable bonds, and higher enthalpy and entropy of fusion compared to drugs with favourable GFA/GS (Class 3) [19]. These observations align logically, as high molecular weight and numerous rotatable bonds impede the reorientation necessary for nucleation and crystal growth. Lower entropy and enthalpy of fusion indicate a decreased energy difference between the amorphous and crystalline states, influencing the spontaneity of conversion to the crystalline form. Consistent with these findings, other studies have emphasized the critical roles of molecular weight and free energy difference in an drug's glass-forming ability and stability [20,21] method to categorize GFA and GS, involving heating the drug above its melting temperature and subsequently cooling it below the glass transition temperature. This amorphization approach can be viewed as a scaled-down version of hot melt extrusion, which is a commonly employed method for manufacturing of ASDs. Another prevalent method for ASD preparation is spray drying, a solvent evaporation-based technique. In previous screening studies, spin-coating has been utilized as a miniature counterpart to spray drying [22]. The Eerdenbrugh *et al.* in 2010 [23] amorphized the same set of 51 drugs using a spin-coating method, aiming to determine whether the observed relationship between drug physicochemical properties and amorphization ease remained consistent. Remarkably, in nearly 70% of the drugs examined, the classification of crystallization tendency was consistent, irrespective of the amorphization route [23]. These findings highlighted that the intrinsic physicochemical attributes of the drug, rather than the method of manufacture, serve as the primary determinant of amorphous state formation and stabilization. If the drug does not readily gets converted into the amorphous state, formulators may encounter several challenges in developing an ASD.

1.2.2 Glass transition temperature of drug

An inherent characteristic of amorphous materials lies in the presence of a glass transition temperature (T_g). This temperature related phenomenon becomes evident when plotting the enthalpy or molar volume of a substance against temperature. These parameters exhibit a linear increase until a distinct discontinuity in the temperature-enthalpy/volume relationship occurs, as depicted in Figure 1.3. This critical point is recognized as the T_g of the substance. Below this temperature, the molecular mobility and relaxation processes of the drug occur at a much slower rate compared to temperatures above the T_g [24].

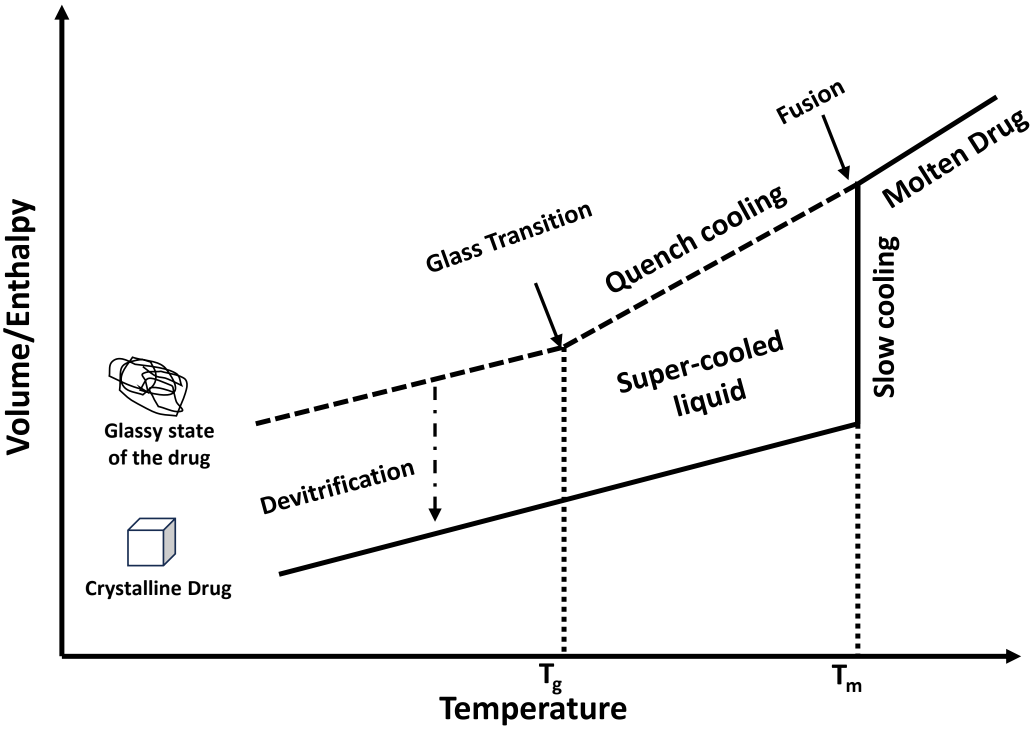


Figure 1.3 Molar volume and enthalpy of different stages of drugs as a function of temperature, Tg and Tm are glass transition temperature and melting temperature respectively; (Figure adapted from Baghel *et al.* 2016)[25] Diagram is not to scale

At T_g, the drug molecules exhibit relatively unhindered rotation, facilitating α-relaxation, also known as global relaxation. This form of relaxation entails coordinated movement among multiple drug molecules. Conversely, below T_g, the rotational freedom of drug molecules diminishes, precluding the possibility of co-operative relaxation. Secondary relaxation processes, commonly denoted as β and γ relaxation, may take place at temperatures below T_g. These secondary relaxation processes involve localized molecular motions, including intramolecular re-orientation [26].

The understanding of the correlation between the speed of molecular relaxation processes and the stability of amorphous solids remains limited. A significant guideline emerged in 1995 when Hancock *et al.* [27] observed exceptionally low molecular mobility in three amorphous materials (PVP, indomethacin, and sucrose) at temperatures 50 °C below their respective T_g, categorizing them as "kinetically frozen” [27]. This temperature is also referred to as the Kauzmann temperature [28]. The researchers concluded that at this critical temperature (T_g-50 °C), molecular motions decelerated to the extent of insignificance over the typical lifespan of a pharmaceutical product. Consequently, a widely accepted consensus emerged, favouring the storage of amorphous materials at temperatures at least 50 °C below their glass transition temperature to ensure physical state stability. Achieving physical state stability for pharmaceutical compounds might require cold chain storage, given that the T_g typically approximates two-thirds of the melting temperature (in degrees Kelvin) [29].

1.2.3 Glass transition temperature of polymer

A useful aspect of employing a polymer to enhance the stability of ASD lies in the high T_g exhibited by many polymers. This characteristic allows them to function as anti-plasticizers in a binary mixture with any drug. Consequently, the glass transition temperature of the molecularly blended binary system of drug and polymer is elevated compared to the drug alone, while it is reduced relative to the T_g of the polymer. Various mathematical models describe the correlation between the glass transition temperature of the binary system (T_g^{mix}) and the individual glass transition temperatures of the API (T_g^1) and the polymer (T_g^2). These models encompass the Fox, Couchman-Karasz, and Kwei equations, among others [25]. However, the Gordon-Taylor equation stands out as the most widely adopted model in this context [30].

$$T_g = \frac{W_1 T_{g1} + K_G W_2 T_{g2}}{W_1 + K_G W_2} \qquad \text{Equation 1.1}$$

Where, T_g is glass transition temperature of the drug-polymer mixture, T_{g1} is the glass transition temperature of drug in amorphous form, T_{g2} is the glass transition temperature of polymer and K_G is the constant defined by equation 1.2.

$$K_G = \frac{\rho_1 T_{g1}}{\rho_2 T_{g2}} \qquad \text{Equation 1.2}$$

Where, ρ1 and ρ2 is the true density value of amorphous drug and polymer respectively.

Most of the commonly used polymers in the preparation of ASDs tend to possess higher T_g. Notable examples include HPMC, HPMCAS, and PVP, all characterized by T_g exceeding 100°C. The T_g of a polymer is influenced by its molecular weight, since higher molecular weights correspond to higher T_g values. This relationship comes from the increased thermal energy required to induce an α relaxation due to increased viscosity in the polymer. In the case of PVP used in ASDs of piroxicam, increasing its molecular weight increased the polymer's efficacy in suppressing crystal growth within the ASD [31]. Nevertheless, it is essential to acknowledge that increasing the molecular weight of the polymer might lead to a decrease in the dissolution rate due to increased viscosity in the boundary layer in aqueous media [32].

1.2.4 Interactions within ASDs

Identification of appropriate drug-polymer interaction occurring in ASDs plays a crucial role in a) understanding their physical stability, b) rationale selection of carrier system, c) scope for customizing factors influencing physical stability, d) getting insights into mechanistic of drug-polymer, e) additional opportunity in drug/polymer designing, f) achieving high drug loaded ASD formulations, g) high thermal stability, and h) higher level of supersaturation [33]. Figure 1.4 represents different types of non-bonding interactions that happen between drug and polymer in any ASD. A summary of various studies highlighting the role of drug-polymer interaction in ASD stabilization with their key findings are mentioned in Table 1.2.

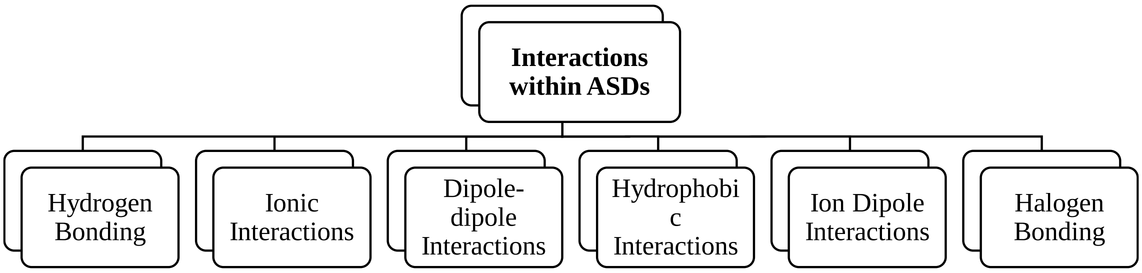


Figure 1.4. Different types of non-bonding interactions responsible for stability of ASDs

Table 1.2. Key findings of studies done on different types of non-bonding interactions

Type of interaction	Findings	Ref
Hydrogen bonding	Observed H-bonding through IR band shifts in nitrofurantoin-PVP ASDs.	[34]
Hydrogen bonding	Proposed adhesive interactions as a key stabilization mechanism in furosemide-PVP ASDs.	[35]
Hydrogen bonding	Demonstrated strong H-bonding in indomethacin-PVP ASDs even at low polymer loadings.	[36]
Hydrogen bonding	Confirmed strong H-bonding as the dominant stabilization mechanism in indomethacin-PVP ASDs.	[37]
Hydrogen bonding	Showed that curcumin's intramolecular H-bonds hindered its stabilization by PVP, while cellulose-based polymers with multiple donor/acceptor groups were more effective.	[38]
Hydrogen bonding	Observed that intramolecular H-bonds in nimesulide reduced its crystallization inhibition by various polymers.	[39]

Type of interaction	Findings	Ref
Hydrogen bonding	Studied the effect of H-bonding on surface composition of spray-dried dispersions and observed phase separation of drug molecules at high drug loadings and with weaker H-bonding.	[40]
Ionic interaction	Major drop in molecular mobility and crystallization propensity was seen in the ASD of ketoconazole, a cationic drug and polyacrylic acid, an anionic polymer due to ionic interaction.	[41]
Ionic interaction	The Tg values of lapatinib with HPMCP was markedly high than their predicted Tg showing strong intermolecular interaction between them based on their pKa values. In accelerated stability studies, two acidic polymers HPMCAS and HPMCP showed crystallization inhibition properties for lapatinib.	[42]
Ionic interaction	The ionic interaction between weakly acidic indomethacin and cationic Eudragit EPO polymer enhance the stability as well as dissolution of indomethacin in simulated gastric fluid.	[43]
Ionic interaction	In the three-month stability samples of indomethacin with Eudragit EPO and itraconazole with HPMCAS-LF, higher supersaturation was found due to electrostatic interactions between drug and their counterionic polymers, which were activated by temperature and moisture.	[44]
Dipole-dipole interaction	Complete miscibility of ketoconazole with PVPs and PVP-VA was attributed to moderate dipole-induced interaction.	[45]
Dipole-dipole interaction	Facilitation of moisture protection and superior dissolution performance due to formation of dipole-induced dipole complex between: • carbonyl and 1,4-dihydropyridine ring present in HPMC AS and felodipine respectively • amide and pyrrole groups of the PVP-VA and ketoconazole respectively • carbonyl and imidazole group of HPMC AS and the ketoconazole respectively	[46]
Hydrophobic interaction	Hydrophobic interactions between nifedipine and efavirenz with HPMC AS resulted in inhibition of drug precipitation in dissolution media hence increasing dissolution rate.	[47]
Hydrophobic interaction	The supersaturation of nimodipine drug in aqueous media was observed due to hydrophobic interactions happening between the drug and polymer PVP.	[48]
Ion-dipole interaction	Increase in crystallization onset temperature (T_c^{onset}) in MK-0591 due to ion-dipole interaction between drug and PVP VA.	[49]

Type of interaction	Findings	Ref
Halogen bonding	Clotrimazole, loratadine, brotrimazole, and Me-DIBF, establish halogen bonds with the amide carbonyl group of the vinylpyrrolidone moiety of copovidone showed enhanced drug solubility.	[50]

1.2.3.1 Hydrogen Bonding

Hydrogen bonding plays a crucial role in stabilizing ASDs by hindering recrystallization. The strength and type of hydrogen bonding depends on the specific donor and acceptor groups present on the drug and polymer combination. However, intramolecular hydrogen bonding within the drug molecule can negatively impact its stabilization by polymers [38]. Controlling hydrogen bonding interactions through careful selection of drug and polymer is crucial for designing stable ASD formulations.

1.2.3.2 Ionic interaction

Drug-polymer salt formation is a promising approach for developing stable and highly bioavailable amorphous solid dispersions. The stronger ionic interactions present in these salts provide significant advantages over conventional formulations, making them a valuable tool for improving drug delivery. Further exploration of basic polymers and optimization of processing techniques hold promising ability for even more effective drug-polymer salt formulations.

1.2.3.3 Dipole dipole interaction

Instances of molecules existing in an isolated state typically exhibit an absence of net charge. However, due to uneven electron sharing among intramolecular atoms, these molecules develop a dipole moment. The propensity for dipole-dipole interactions between molecules is increased in proportion to the magnitude of the dipole moment. Even in cases where drugs and polymers lack hydrogen bond donors or functional groups with the potential for robust interactions in ASD, they can still engage in weak dipole-dipole interactions [33].

1.2.3.4 Hydrophobic interaction

Various pharmaceutical polymers exhibit hydrophilicity, facilitating the formation of hydrogen bonds through interactions with water. Nevertheless, this characteristic has the potential to disrupt cohesive non-covalent interactions within an ASD, causing poorly water-soluble drug molecules to engage in less robust hydrophobic bonding with the polymer or other drug molecules. The influence of water support the hydrophobic interactions, as evidenced by the observation that the interaction energy between two methane molecules in a water environment (-14×10^{-21} J) was approximately six times greater than in free space (-2.5×10^{-21} J). Despite the inherently weak nature of hydrophobic interactions compared to other non-bonding interactions, the presence of water induces increased entropy in the system. This increased entropy, arising from the rearrangement of structured water molecules around the hydrophobic groups of drug/polymer, contributes favourably to the overall free energy of the system. Therefore, while hydrophobic interactions may be comparatively weaker, their inclusion in ASD formulations, particularly those with residual moisture, can enhance the physical stability of the system [33].

1.2.3.5 Ion dipole interaction

Ion-dipole interactions, characterized by electrostatic attraction between dipoles and ions such as Na+, Cl−, etc., surpass the strength of hydrogen bonds. Despite the enhanced solubility advantage exhibited by amorphous drug salts in comparison to their crystalline counterparts, they tend to be less physically stable and prone to rapid salt disproportionation. The enhancement of physical stability in amorphous salts can be achieved through the formation of an ASD, leveraging robust ion-dipole interactions between the drug and the polymer. Although existing research predominantly focuses on salt forms of drugs, it is noteworthy that ion-containing polymers, commonly referred to as ionomers, may offer additional avenues for stabilizing dispersions that include neutral drugs [33].

1.2.3.6 Halogen bonding

Halogen bonds have similarity with hydrogen bonds and forms when there is observable evidence of a net attractive interaction between the electrophilic region linked to a halogen atom within a molecular entity and a nucleophilic region either within the same molecule or in another [33].

1.2.5 Miscibility of drug and polymer

The term "miscibility" in the context of a drug and a polymer typically denotes the solubility of amorphous drug within an amorphous polymer [51]. The extent of miscibility between the polymer and the API is very crucial in the formulation of an ASD. It signifies the maximum achievable drug loading at a specified temperature, defining the amorphous drug-polymer miscibility limit. Enhanced miscibility implies a higher capacity for incorporating amorphous drug into the polymeric matrix before reaching saturation, leading to drug crystallization. In cases of limited miscibility or miscibility only at low drug concentrations, the development of an oral ASD formulation might necessitate high polymer concentrations, potentially resulting in a substantial tablet size.

There are various methods for estimation of drug-polymer miscibility. However, the most utilized and well explained method employs Flory-Huggins theory. This theory was initially given by Flory and Huggins which followed a lattice approach with a mean-field estimate. Originally it was formulated to calculate the free energy of mixing of polymers by calculating the entropy and energy of mixing [52]. Later, Marsac *et al.* in 2009 used this theory to determine the miscibility of amorphous drug into glassy polymers considering all the important aspects [51]. Melting point depression method is used to obtain Flory-Huggins interaction parameter denoted by χ. Equation 1.3 expresses the relationship between the melting point of pure drug (T_m^{pure}), the depressed melting point (T_m^{mix}) with χ.

$$\frac{1}{T_m^{mix}} - \frac{1}{T_m^{pure}} = -\frac{R}{\Delta H_f}\left[\ln \Phi_{drug} + \left(1 - \frac{1}{m}\right)\Phi_{poly} + \chi\Phi_{poly}^2\right] \qquad \text{Equation 1.3}$$

Where, Φ is the volume fraction of the drug and polymer, m is the ratio of the volume of a polymer chain to drug molecular volume and ΔH_f is the heat of fusion of the pure crystalline drug. It is understood that the drug-polymer interaction is stronger than drug-drug-drug or polymer-polymer interaction if the value of χ is negative. However, a positive χ value indicates weaker drug-polymer interactions [53].

1.2.6 Hygroscopicity

The hygroscopic nature of a polymer plays a crucial role in determining the physical stability of an ASD. Water, being a potent plasticizer with a T_g of approximately -137°C, can exert a significant plasticizing effect when integrated at the molecular level within the polymer [27]. This interaction leads to a notable T_g reduction of the polymer, as dictated by the Gordon-Taylor equation. If any moisture introduced during the ASD preparation process is not eliminated, it will lower the T_g of the ASD, compromising its physical stability under ambient conditions.

1.2.7 Drug loading

The thermodynamic stability of ASD is highly dependent upon the drug-polymer miscibility, which also determines the limit of the amount of the drug which can be added in the formulation. Figure 1.5 can be used to understand about this stability. In the figure, equilibrium liquid zone (2, 4, and 6) is separated with non-equilibrium glassy zone (1, 3, and 5) by T_g values of the solid dispersion which can be determined either experimentally of through Gordon-Taylor equation. Zones 1 and 3 characterize thermodynamically stable ASDs and supersaturated ASDs, respectively. In Zone 1 ASDs, there is no inherent thermodynamic force for recrystallization, whereas this force exists in Zone 3 ASDs. Ideally, ASD formulation design should target Zone 1 classification, but achieving this may entail keeping the drug loading at a level that could be too low to develop a practical formulation. However, in zone 3 through kinetic processes like molecular mobility reduction and drug-polymer interaction, stability can be achieved. In zone 5 the stability can be provided kinetically by storing it at very low temperature, but in zone 6 there is no thermodynamic barrier to prevent recrystallization, so this area should be completely avoided [54][55].

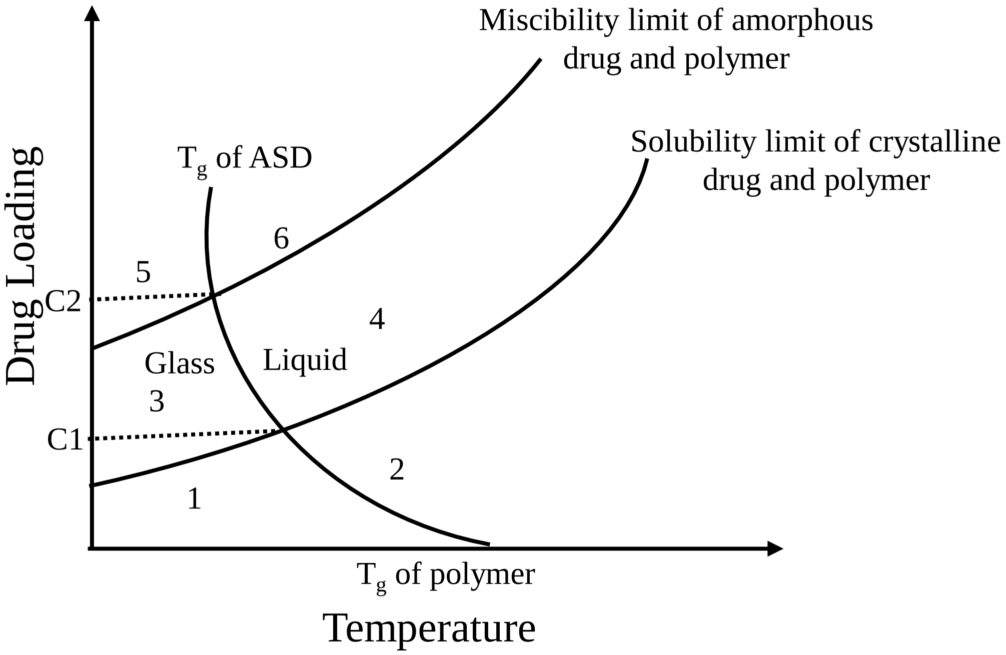


Figure 1.5. Illustration depicting a solid dispersion system with varying drug concentrations and temperatures. The delineation of regions (1–6) is based on factors such as the glass transition (T_g) of the solid dispersion, the limit of crystalline drug–polymer solubility, and the limit of amorphous drug–polymer miscibility. These zones shows: 1) a thermodynamically stable glass, 2) a thermodynamically stable liquid, 3) a

supersaturated glass, 4) a supersaturated liquid, 5) a supersaturated and immiscible glass, and 6) a supersaturated and immiscible liquid. C1 denotes the drug solubility in the polymer at T_g, while C2 represents the miscibility of the drug in the polymer at T_g (Figure adapted from Qian *et al.* 2010)[54]

1.2.8 Ternary excipients

The use of any second polymer for the formulation of a ternary ASD have been now used by formulation scientist for improving the stability of commercial ASD products. The addition of a second polymer is sometimes helpful in achieving higher drug loading. Where one polymer imparts the property of anti plasticization due to its high T_g the other polymer can act as a crystallization inhibitor hence playing a role in providing kinetic and thermodynamic stability respectively. Ternary ASDs can also help in maintaining the supersaturation of drug in the dissolution media [56]. Surfactants like sodium dodecyl sulphate and fillers like microcrystalline cellulose, lactose and mannitol can be used as a second polymer for ternary ASD formation [57,58]. Ternary ASDs and judicious combination of excipients are promising avenues to enhance ASD stability and performance.

1.2.9 Manufacturing factors

1.2.9.1 Particle size/porosity

This property is highly dependent on the manufacturing methods chosen for ASD preparation. High surface area of the particles tends to crystallize the drug faster, since the crystallization process is affected by the surface property rather than the bulk property [59].

1.2.9.2 Drug-polymer mixing

Compared to milling, spray drying allows for a higher drug loading in ASDs. This difference can be attributed to the fact that, in spray drying, the polymer and API are more readily able to interact, as they are already molecularly dispersed in a solution [60]. In contrast, milling requires the mechanical destruction of the crystal lattice of the API before achieving molecular-level mixing with the polymer.

1.2.9.3 Compression

Metastable ASD systems are prone to show phase separation during compression due to compression force [61].

1.2.9.4 Residual solvent

Method of preparation of ASDs which requires solvent, can enhance the blending of the polymer and API, it is imperative to adequately eliminate any remaining solvent. This is essential not only for preserving the physical stability of the ASD but also for meeting regulatory standards. Achieving acceptable residual solvent levels might necessitate an additional drying step, such as tray drying or fluid bed drying.

1.2.10 Environmental factors

The environmental factors have an indirect influence impacting the physical stability of ASDs through its effect of thermodynamic and kinetic factors. Considering ASDs as systems stored within the ambient environment, the environmental variables encompass temperature and humidity [62,63]. Elevated temperatures can result in a significant enhancement of molecular mobility, leading to a considerable acceleration in the rates of phase separation and recrystallization within ASDs. Additionally, humidity exerts an influence on the physical stability of ASDs by facilitating the absorption of water molecules. Moisture uptake, characterized by a plasticizing effect, has the potential to diminish the physical stability of ASDs by disrupting drug-polymer hydrogen bonding [64].

While both factors of temperature and humidity can impact the physical stability of ASDs, the prevailing environmental factor remains undisclosed. The identification of the primary environmental factor crucially influences the determination of optimal storage conditions for ASDs. Studies conducted for the investigation of the impact of temperature and humidity on the physical stability of hot melt extruded cinnarizine and Soluplus® revealed that humidity and temperature exhibited a similar influence on the physical stability of the cinnarizine-Soluplus® system at 20% (w/w) drug loading. Specimens were preserved at 40°C and 60°C in a dry environment and at 25°C under humidity levels of 75% RH and 94% RH, respectively. However, as the drug loading increased, samples stored under high humidity demonstrated diminished physical stability [65]. Another study done on four drugs *viz.* felodipine, carbamazepine, celecoxib and fenofibrate, to formulate ASD with Eudragit® E PO using hot melt extrusion technique revealed that ASDs stored at high humidity conditions of 75% RH and 25 ^{o}C was showing more crystallization than those stored at 0% RH and 40 ^{o}C. These results were found for all four drugs across the drug loading of 10% w/w to 70% w/w. However, the effect of temperature is not completely absent in the first observation [66]. The effect of temperature on the molecular mobility should be considered. Yet it can be said that humidity has more profound effect on the physical stability of ASD. Hence, the storage of ASD is recommended to be moisture proof.

1.3 Method of Preparation of ASDs

1.3.1 Hot Melt Extrusion

Hot melt extrusion (HME) is the most common method of preparation of ASDs which is adapted from plastic industry. Briefly, in HME method, the extruder barrel receives solid raw ingredients, and the screws undertake tasks of conveying, blending, and either softening or melting them [67]. The softened substance is subsequently pushed through a die to give it shape and prepare it for subsequent steps. When dealing with ASDs, the drug is liquefied or rendered soluble within the polymeric medium. Rapid cooling and the polymer's high viscosity then leads to the formation of a thermodynamically or kinetically stable ASD [68]. However, there are a number of obstacles to overcome in this methos, particularly for drugs and polymers that are thermally labile as well as for some pharmaceutical polymer carriers that have viscosity limitations.

The glass transition and melting temperatures, the temperature at which the drug degrades, and its miscibility or solubility in the polymer carrier must all be taken into account when determining the physicochemical parameters of the API [54,69,70]. Only a few numbers of carrier choices are permitted for use in pharmaceutical formulations in this method. As a result, while determining processing conditions, the physicochemical characteristics of the polymer carrier frequently play the most significant role. The degradation temperature and viscoelastic characteristics of the polymer carrier are the two main aspects to take into account when determining an extrusion-processing window [71–73].

1.3.2 Solvent evaporation

These procedures can be categorized into four main groups:

1.3.2.1 Solvent casting

Solvent casting is a fundamental laboratory technique to prepare solid dispersions where drug and polymeric carrier(s) is dissolved the in the same solvent(s). In order to successfully prepare solid dispersions of paracetamol, dimenhydrinate, and resveratrol, the solution is then spread into a petri dish and allowed to evaporate under normal pressure at room temperature, on a hot plate, or in a low temperature oven, followed by cooling in a desiccator and pulverizing the final film [74,75]. For producing very low amount of product as required in the preliminary screening of itraconazole and new chemical entity (NCE) JNJ-25,894,934, miniaturization can be achieved by using low volume glass vials instead of petri dishes [76,77]. The limitation of this method is that only low boiling point solvents such as chloroform, ethanol [78] or a mixture of ethanol and dichloromethane can be used for dissolving drug and polymer. Furthermore, complete removal of solvent is challenging in this method which would ultimately affect its solubility and bioavailability [74].

1.3.2.1 Spray Drying Technique

In spray drying technique the drug and polymer(s) mixture are atomized into a high-temperature airflow, leading to rapid solvent evaporation. This process results in the formation of finely dispersed solid particles, consisting of the drug and polymeric carrier(s), in an amorphous state. This process is relatively easier to scale up from laboratory scale to industrial scale. Process parameters and formulation aspects impacts the performance of the final product. Important process parameters of spray drying techniques are inlet temperature, feed rate humidity and flow rate of drying gas and atomization and drying gas type and flow rate [79]. The ASDs’ particle size, texture, and smoothness are all significantly influenced by the size, type, and size of the spray nozzles [80]. Additionally, the solid content can have an impact on the solution's viscosity, which would then have an impact on drying and the finished product [81]. Formulation factors such feed solid content, solvent type, drug, carrier, and solvent composition, as well as viscosity and surface tension of the drying solution, are important for product properties [22].

1.3.3 Solvent evaporation at reduced pressure

The use of a rotary evaporator, which has recently been used in the development of celecoxib [82], glibenclamide [83], itraconazole [84], nifedipine [85], and zoplicone [86], is one of the most practical laboratory processes for producing solids dispersion. The purpose of this is to remove the solvent(s) under vacuum, allowing for a quicker processing of the sample and/or the use of solvents with a higher boiling point, such as tetrahydrofuran, dimethyl formamide, or dimethyl sulfoxide (DMSO), which could not be utilised in a solvent casting method. The use of solvent casting in a petri dish or vial, followed by evaporation in a low-pressure chamber or oven, is an alternate method. Rotary evaporation is a good choice for discovery, but it has much scale up issues for the development purpose.

1.3.4 Freeze Drying

Freeze-drying or lyophilisation, has recently used in the development of celecoxib [87], diazepam [88], docetaxel [89], nifedipine [85], tadalafil [90] and zoplicone [86] ASDs. This method comprises freezing a solution/suspension of drug and carrier(s) followed by reducing the surrounding pressure to allow water and solvents in the sample to undergo solid-gas transition [91]. Drug and carrier(s) preserve the molecular dispersion structure seen upon dissolution during a freeze-drying procedure [86,89,91]. Laboratory freeze-driers can create lyophilized goods in quantities ranging from a few milligrams to several grams. The molecules are connected during the freeze-drying process as an amorphous solute in a solidified solvent. This technique helps in obtaining a homogeneous dried mixture of drug and polymer without any thermal and mechanical effect which is often a challenge for other techniques [92,93]. Residual solvent and insufficient solubility in the solvent compatible with the drier are frequent issues with solvent evaporation-based technologies. In general, it is preferable to dissolve nearly water insoluble APIs in an organic solvent, which consequently requires removal of the organic solvent in some way, such as by freeze-drying, in order to make ASDs in the lab. However, water is the most utilized media used for freeze-drying [94].

1.3.5 Supercritical Fluids

Preparing solid dispersions is also achievable using supercritical fluids (SCFs). SCFs are gases that exhibit simultaneously gaseous and liquid state features at specific pressures and temperatures [95,96]. The solubilization benefits of liquid qualities outweigh the benefits of gaseous characteristics for drug and carrier(s) diffusion and solvent elimination [96]. Nearly all gases exhibit SCFs properties in adequate condition. However, due to their adequate critical temperature, only a handful can be used in the pharmaceutical industry. Carbon dioxide is the most widely used gas for this process as more than 98% of all applications have been developed using this gas [95]. Low critical temperature (31.18 °C) and pressure (7.4 MPa) are characteristics of carbon dioxide, which is also cheap, non-flammable, non-toxic, recyclable, and environment friendly [96–98]. Trifluoromethane is another example of SCF employed in the pharmaceutical industry and was recently used in the production of simvastatin nanoparticles. The main drawbacks of SCF include the cost of the equipment as well as the challenges in scaling up this process and an entire elimination of organic solvents if applicable [95].

1.4 Applications of Analytical Techniques for the Characterization of ASD

1.4.1 Thermal techniques of analysis

ASDs are characterised using thermal methods. They are carried out according to temperature, making it possible to characterise the thermodynamic characteristics of ASDs. The applications and principles of thermal methods are covered in this section.

1.4.1.1 Thermogravimetric Analysis

Thermogravimetric analysis (TGA) is one of the earliest thermal analytical techniques. With this technique, the weight of a sample in a selected environment (air or nitrogen) is tracked in relation to temperature. TGA is frequently used in ASD characterization to assess the drug's and the polymer's volatile components' thermal stability. In order to prevent thermal degradation during hot-melt extrusion, this information can be used to establish the temperature window [99]. The evaporation profile of feed solutions for spray drying has also been investigated using TGA. According to TGA research, the surface chemistry and particle shape of spray-dried ASDs are significantly impacted by the binary solvent's drying kinetics [100,101]. To enable the chemical identification of volatile compounds released from samples, TGA is frequently integrated with other spectroscopic detection techniques, such as IR or gas chromatography.

1.4.1.2 Calorimetric techniques

Calorimetry is a technique used to assess changes in heat, which are closely linked to variations in temperature between samples during specific processes like chemical reactions or physical shifts. These processes can release heat (exothermic) or absorb heat (endothermic) [102]. Contemporary calorimetric apparatus can examine samples concerning time or temperature with customizable temperature profiles. There are two primary types of calorimeters: heat exchanging and heat compensation [103].

1.4.1.2.1Differential Scanning Calorimetry and Modulated Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) can be categorized into two main types: heat flux DSC and power compensation DSC. Within DSC, a clearly defined heat path is established, involving the placement of two identical thermocouples symmetrically outside the sample pan. This configuration facilitates the accurate quantification of heat flow and the subsequent computation of the area beneath the heat flow curve. Heat flux DSC is known for its superior stability and ease of operation when compared with power compensation DSC [102]. However, the application of power compensation DSC allows for the attainment of significantly higher rates of heating or cooling [104]. Currently, the majority of modern DSC instruments are conceptualized and engineered based on the principles of heat flux.

In pharmaceutical science, there's a focus on phase transitions that occur during the heating or cooling process. Melting, described as a first-order phase transition (Equation 1.4), is particularly significant. In this transition, latent heat is involved, and the system might either absorb or release heat while the temperature stays consistent. Calculating the area under the peak in the heat flow-temperature graph helps determine the heat of fusion, which signifies the energy necessary for the melting process.

$$\frac{\delta \Delta G}{\delta T} = -\Delta S \neq 0 \qquad \text{Equation 1.4}$$

$$\frac{\delta^2 \Delta G}{\Delta T^2} = -\left(\frac{\Delta C_P}{T}\right) \neq 0 \qquad \text{Equation 1.5}$$

Where, G is the Gibbs free energy and S is entropy.

DSC is the most widely used method for directly determining the T_g in pharmaceutical science. T_g is a crucial characteristic of ASDs, indicating the system's mobility. This phenomenon constitutes a second-order phase transition (Equation 1.5), where the sample's heat capacity experiences a sudden change with temperature (essentially, a discontinuous process). Generally, heat capacity represents a substance's sensible energy, involving the kinetic energies of its molecules, including vibrational, rotational, and translational energies. Below the T_g, vibrational motion governs the heat capacity. The transition process is directed by rotation, while above T_g, the change in heat capacity with temperature stems from translational motion. In essence, the glass transition reflects a shift in heat capacity across a narrow temperature range. Both traditional DSC and Modulated DSC (MDSC) can measure this [105].

DSC applies a linear temperature program to measure temperature differences between a sample and a reference, while MDSC introduces periodic temperature perturbations to better analyse complex thermal events. This is particularly beneficial for samples with strong relaxations, where conventional DSC struggles to measure events like glass transitions due to enthalpy recovery peaks [106]. MDSC employs varying heating rates, allowing the separation of heating rate-dependent events (changes in heat capacity) from kinetically hindered events like crystallization and decomposition.

DSC is considered as the “gold standard” in determining the miscibility of drug in polymer [107]. Miscibility of nifedipine, felodipine, ketoconazole, sucrose, and indomethacin with PVP was evaluated by Marsac *et al.* which marked as a starting point of the evaluation of drug-polymer miscibility through DSC [51]. Different protocols like demixing from supersaturated drug-polymer dispersion of indomethacin and PVP was developed by Mahieu *et al.* in 2013 which offered the advantage of faster determination of miscibility since demixing process is faster than mixing process of drug and polymer

[108]. Measurement of equilibrium solubility along with the recrystallization kinetics were ascertained by Askin *et al.* in 2018 where they measured the time dependent heat capacity of the sample by implementing quasi-isothermal modulated temperature DSC [109]. Enthalpy relaxation signifies the degree of freedom as the material is heated, subsequent to being kept at temperatures lower than its T_g [110]. Enthalpy relaxation studies of ASDs are frequently done to study the kinetic stability of drug. Some examples of those studies are carvedilol with PVP [111], celecoxib with PVP and meglumine [112], irbesartan with PVP K30 and HPMC AS [113]. GFA of celecoxib, valdecoxib, rofecoxib and etoricoxib was determined using DSC by determining the critical cooling rate [114], continuous cooling and isothermal transformation diagrams for drugs like carvedilol, dibucaine, felbinac, flurbiprofen, ibuprofen, indomethacin, itraconazole, lidocaine, naproxen, tolbutamide, celecoxib and cinnarizin [115] were made using DSC.

1.4.2 Morphological and Microscopic Techniques

ASDs in its solid-state can be examined using microscopy. Microscopy serves various purposes in pharmaceutical analysis like, investigating the physical and chemical properties of ASDs, such as their glass transition, the compatibility of drug and polymer, crystallization tendencies, level of crystallinity, structure, thermal changes, and dissolution rates [116,117]. Broadly, microscopic techniques fall into three categories: optical, electron-based, and scanning probe microscopy. These encompass methods like polarized light microscopy, scanning electron microscopy, atomic force microscopy, and X-ray diffraction all of which are widely adopted for swift, non-destructive assessments [118]. The details of the studies done on ASDs using various microscopic techniques have been summarized in table 1.3.

Table 1.3. Details of studies done on ASDs using different microscopic techniques

Microscopy technique	**Studies done using microscopic techniques**	**Ref**
Polarised Light Microscopy	Physical stability of nine drugs (celecoxib, naproxen, chloramphenicol, felbinac, sulfanilamide, nifedipine, clotrimazole, indomethacin, and paracetamol) with PVPVA64 were monitored using PLM by examining them at temperature below and above their respective T_gs	[119]
	The effect of ionic interaction on the physical stability between naproxen and meglumine was observed by PLM where recrystallization of naproxen was observed after it was exposed to ambient condition	[120]
Scanning electron microscopy	Effect of method of preparation on the ASDs in case of febuxostat and soluplus was investigated using SEM	[121]
Transmission electron microscopy	Identification of phase separation and formation of microstructure in the drug Evacetrapib and two polymers (HPMC and Kollidone) was done using TEM	[122]
	In the ASD of indomethacin with PVP VA prepared by HME technique TEM was used to detect the crystallinity as low as the order of below 1%	[123]
	Identification of residual crystallinity in felodipine ASD prepared with PVP VA copolymer was done by TEM	[124]
	The mechanism of ASD in the maintenance of supersaturation of nimodipine was explored by TEM	[125]
Atomic force microscopy	Identified the drug and polymer rich domains using AFM-nanoIR imaging	[126]
	To evaluate the phase separation due to presence of water in the organic solvent, evacetrapib–HPMC stock solution were prepared and exposed to different relative humidity conditions and the observed under AFM	[127]
X-Ray Diffraction	Synchrotron XRD and pair distribution function was used to know the chemical stability and ionic interactions occurring between lapatinib and HPMCP and HPMC E3.	[128]
	The effect of crosslinking on molecular mobility and physical stability in ketoconazole ASD was investigated over a wider temperature in the supercooled state using variable temperature XRD	[129]

1.4.2.1 Polarized light microscopy and hot-stage polarized light microscopy

Among various microscopy methods, polarized light microscopy (PLM) is valuable for identifying trace amounts of crystalline substances in ASDs. PLM uses polarized light and crossed polarizers to distinguish between solid forms, particularly amorphous and crystalline materials. Amorphous solids lack long-range molecular order and display no double refraction or interference colours between crossed polarizers. Conversely, crystalline solids possess three-dimensional order and exhibit birefringence-induced interference colours. PLM, combined with other techniques, is sensitive for assessing drug crystallization kinetics, polymorphic transitions, and solid-state or aqueous crystallization. Hot-stage polarized light microscopy (HSPLM) rapidly observes thermal behaviours, aiding formulation studies of ASDs. It reveals drug-polymer interactions, guides optimal mixing temperatures, and validates DSC findings. However, PLM alone can't reliably differentiate all crystalline materials or quantify crystallinity; complementary methods like X-ray diffraction or DSC are recommended for comprehensive analysis [126].

1.4.2.2 Scanning electron microscopy

In scanning electron microscopy (SEM) analysis, a monochromatic electron beam is probed with material’s surface and near-surface at very high resolution. Magnification up to 250000X, large depth field and lateral spatial resolution of 3 nm or higher are some advantages of SEM over traditional light microscope. Change in the morphology of ASD particles after dissolution or stability study can be seen by SEM.

1.4.2.3 Transmission electron microscopy

Transmission electron microscopy (TEM) is a microscopy technique which can produce real-time space image and electron diffraction patterns which can identify the crystalline drug even in nanometre scale.

1.4.2.4 Atomic force microscopy

Atomic force microscopy (AFM) is primarily employed in the investigation of ASDs for the purpose of precisely assessing surface topography at scales finer than a nanometer. In AFM experimentation, a slender probe tip, often prepared from materials such as silicon (Si) or silicon nitride (Si_3N_4), is situated on the lower side of a flexible cantilever. This tip systematically traverses the sample's surface in a grid-like pattern.

1.4.2.5 Powder X-ray Diffraction

Powder X-ray diffraction (PXRD) is often regarded as the most reliable method for analysing the physical properties of pharmaceutical compounds in their solid form. It has demonstrated significant potential for the identification, measurement, and even the simulation of non-crystalline pharmaceutical systems. In PXRD the usual detection limits for crystalline content range from 1% to 5% (w/w), and may vary according on the reflection methods used [126].

1.4.3 Spectroscopic Techniques

Spectroscopic techniques are capable of identifying molecular-level and atomic-level changes occurring in a complex chemical environment. These techniques are used during the product development of ASDs and also for their quality control as they can provide information at macro, micro and nano levels.

1.4.3.1 Infrared spectroscopy and Raman spectroscopy

Infrared and Raman spectroscopy are techniques used for vibrational spectroscopy, wherein they analyse the vibrational movements of molecules. Vibrational patterns in molecules involve repetitive motions towards and away from their centre of gravity, occurring within an energy range of 4000 to 400 cm^{-1}. Infrared-active molecules undergo changes in their dipole moments during vibrational motion, enabling them to absorb infrared radiation. Conversely, Raman-active molecules experience changes in polarizability during vibrational motion. To absorb infrared radiation, a molecule's frequency and energy must match those required for the transition, causing the molecule to transition from its ground state to an excited state. IR spectroscopy leverages this property of molecules to investigate molecular structures and interactions[105].

Molecular structure of indomethacin-PVP ASD was identified and specified by vibrational (Fourier Transform-Raman spectroscopy). The analysis confirmed the formation of hydrogen bond between indomethacin and PVP [37]. Physical solid-state changes and drug-polymer interaction of piroxicam-soluplus ASD was checked using FTIR and Raman spectroscopy. Tres *et al.* in 2014 for the first time utilized Raman spectroscopic imaging in combination with multi-variate curve resolution (MCR) analysis to explore, in a real-time and *in-situ* manner, the dissolution processes that form the basis of ASD [130]. Raman and FT-IR micro-spectroscopy confirmed the existence of interactions between the drug and polymer and the presence of indomethacin in its amorphous form with PVP 12PF, PVP K30 and PVP K90 [131]. Adding more innovation to the analysis, Kapourani *et al.* 2020 used artificial neural networks with ATR-FTIR and Raman spectroscopy to develop a new chemometric model which is capable of identifying percentage of crystalline and neat amorphous drug located in drug-rich amorphous zone in an ASD system [132]. As stated in above examples these vibrational spectroscopic techniques have huge potential in deciphering the drug-polymer interaction in an ASD system which have been used from a very long time. Though these techniques are now being replaced by more modern analytical techniques, yet when combined with other studies these are very useful.

1.4.3.2 Solid-state NMR

Materials such as gases, liquids, gels, and solids can all be characterised using solid state nuclear magnetic resonance (ssNMR). ssNMR is utilised for molecular dynamics, chemical identification, composition measurement, and structural elucidation. This technique is able to detect very tiny changes in the chemical environment of a variety of substances, from small molecules to macromolecules, based on the nuclei's spin as a basis for measurement. As a result, it can provide both quantitatively and qualitatively useful information. The behaviour of nuclei under a magnetic field is used by NMR to determine exact internuclear distances or bond angles of the glasses.

The fundamental characteristics of nuclei are deduced from the analysis and interpretation of the NMR signal. Proton NMR (^{1}H NMR) and ^{13}C NMR are the universal techniques for organic materials, even though many atoms are eligible for NMR research. Due to their dependency on the modulation of internal interactions in time, nuclear relaxation durations offer essential information about the dynamics and mobility of the entire molecule. For nuclei to return to equilibrium, there are two different relaxation durations involved: decay and recovery, or the characteristic time (T_1) and the characteristic time of decay (T_2). They are also known as, spin-lattice relaxation time, or T_1, and the spin-spin relaxation time, or T_2, respectively. In the solid state, a third relaxation time, $T_{1\rho}$, is significant; in the rotating frame, it is referred to as the spin-lattice relaxation time. Internal interactions and molecular movements are particularly sensitive to these three relaxation durations [105]. In the characterization of ASDs, the sharp resonances are indicative of crystalline material while broad Gaussian resonances represents amorphous solids [42].

Song *et al.*in 2015, acquired the ^{13}C and ^{15}N ssNMR spectra measured the ^{1}H relaxation time to gain insights on the interactions between lapatinib and HPMC phthalate [42]. Yuan *et al.* in 2014, determined the miscibility and the molecular mobility of nifedipine-PVP ASD using the ^{1}H T^1 and $T_{1\rho}$ relaxation times in ssNMR [133]. ssNMR technique was used to study the structural details for understanding the nature of the molecular contacts and mechanistic roles in various physicochemical and thermodynamic events in posaconazole ASD in a site-specific manner. For this purpose one- and two-dimensional (2D) solid-state NMR (ssNMR) techniques including spectral editing, heteronuclear ^{1}H–^{13}C, ^{19}F–^{13}C, ^{15}N–^{13}C, and ^{19}F–^{1}H polarization transfer, and spin correlation and ultrafast magic angle spinning, together with the isotopic labelling strategy, were utilized [134]. Quantitative investigation of hydrogen bond in amorphous indomethacin and ASD of indomethacin with PVP and PVP VA, was done using ssNMR. The carbonyl spectrum of indomethacin was analyzed by labelling the carbonyl carbon isotopically with ^{13}C. Then deconvulation revealed that percentages of molecules present in amorphous indomethacin involved in hydrogen bond formation [135]. Formation of ionic bond between protonated clofazimine and HPMCP were identified by various solid state spectroscopic technique including ssNMR. Molecular interaction pattern and the critical bonding structure in clofazipine–HPMCP dispersions were further delineated using ssNMR [136]. In a similar manner, ^{15}N ssNMR was used to identify the bonds between an acidic excipient polystyrene sulfonic acid and two basic drugs *viz.* lapatinib and gefitinib. In the study strong intermolecular interactions were seen between the polymer and model drugs [137]. Along with the drug-polymer interaction, phase behaviour was also investigated in indomethacin-eudragit E using ssNMR [138].

1.5 Polymer matrices for ASD preparation

The design and selection of polymer is very crucial for the preparation of ASD. The performance of ASD totally depends upon its interaction with the drug especially when the drug is a fast crystallizer. The polymer used in drug delivery should be non-toxic, ideally endogenous or dietary, and have the ability to form a molecular dispersion with the drug. The polymer should also have a high glass transition temperature ($T_g \geq 50$ °C above any likely ambient temperature) to restrict drug molecular mobility and retard crystallization [27]. Additionally, the polymer must stabilize the drug against crystallization from supersaturated solutions over the relevant GI tract residence time ($\geq$ ca. 6 h) since ASDs generate supersaturated solutions from which the drug has an inherent propensity to crystallize. Exposure to the polymer will be limited to the GI tract since most polymers will not passively permeate from the GI tract into the bloodstream [139], except for nanoparticle formulations [140]. One potential disadvantage of ASDs is that the metastable amorphous drug may crystallize over time, even trace amounts of crystallinity in the solid dispersions can seed rapid crystal growth, diminishing effectiveness, increasing variability, and shortening the shelf-life of the dosage form. Specific interactions between polymer and drug (e.g. hydrogen bonds) are needed to aid miscibility and avoid phase separation [141].

1.5.1 Physicochemical properties of polymers used in ASD

A variety of polymers have been used in ASD formulations, which can be classified into different groups based on their chemical structures. These groups include polyvinyl lactam polymers, cellulosic polymers, acrylate and methacrylate (co-)polymers, and other types of polymers (Figure 1.6). Tables 1.4 summarize the physicochemical properties of different types and grades of polymers used in ASDs, including solubility, glass transition temperature (T_g), and degradation temperature.

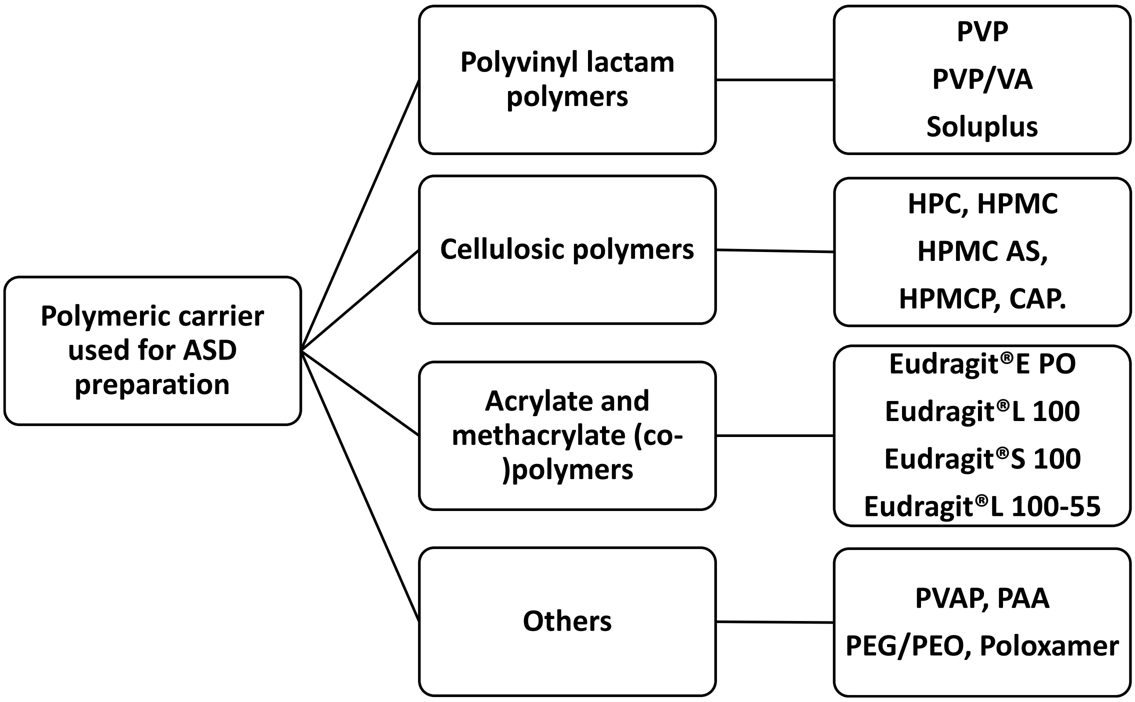


Figure 1.6. Classification of polymeric matrices based on chemical structure

1.5.2 Polyvinyllactam polymers

These polymers comprise of vinylpyrrolidone or vinylcaprolactam monomers. Vinyllactam can be combined with vinyl acetate to create Copovidone (PVP/VA) or without combination as such the homopolymer is known as PVP. Additionally, the formulation of ASDs has been used SoluplusR, a copolymer made of polyvinyl caprolactam, polyvinyl acetate (PVAc), and PEG [142].

1.5.2.1 Copovidone (PVP VA)

PVP VA is a copolymer of vinylpyrrolidone and vinyl acetate, with a widely used ratio of 6:4 of vinylpyrrolidone to vinyl acetate. It is commonly used in the production of ASDs due to its excellent processability and low hygroscopicity. PVP VA64 has a Tg of approximately 100 °C and a degradation temperature above 230 °C. It is widely used for manufacturing ASDs by solvent or melting (fusion) methods due to its excellent stability and processability. Copovidone is another name for PVP VA64, which is a co-polymer of vinyl-pyrrolidone and vinyl-acetate in a ratio of 6:4 [143].

PVP VA is less hygroscopic than PVP due to the vinyl acetate component in the copolymer chain. Weuts *et al.* 2004 reported that PVP VA-based ASDs contained less moisture, and the deviation of T_g between the experimental and calculated values was much smaller than that of PVP-based ASDs. This makes PVP VA a better choice for manufacturing ASDs as it has better stability and processability [144]. In a different study, a TGA analysis revealed that when exposed to high relative humidity, ASDs containing PVP-K30 displayed more water uptake than ASDs containing PVP VA [145]. The drug-polymer interactions were altered by the vinyl acetate in the PVP VA. Using ^{13}C ssNMR spectra, Sarpal *et al.* in 2019 discovered interactions between felodipine and PVP, PVP/VA, and PVAc. The molecular connections' intensities reduced in the prescribed manner. PVAc > PVP > PVP/VA [146]. Kestur *et al.* in 2010 conducted a study to evaluate the impact of polymer type on the crystallization of felodipine. They found that PVP VA was less effective in suppressing the crystallization of felodipine than PVP, which was consistent with the strength of intramolecular interactions [147]. The vinyl acetate content in PVP VA also influenced the drug solubility in polymeric carriers. Sun *et al.* 2010 conducted a study to investigate the solubilities of indomethacin and nifedipine in PVP, PVP VA, and PVAc. Their results showed that the amounts of drugs dissolved in the polymers decreased in the following order PVP > PVP VA > PVAc based on different drug-polymer interactions. It has also been reported that stronger or more extensive drug-polymer hydrogen bonding could translate to a better inhibitory effect on the crystal growth of the drug [148].

1.5.3 Cellulosic polymers

Cellulosic polymers are a category of polymers sourced from naturally occurring cellulose, which happens to be one of the most abundant biopolymers found in nature. Cellulose constitutes the primary structural component in plants and possesses a captivating structure along with numerous intriguing properties. However, cellulose itself exhibits limited solubility in water. Therefore, it undergoes chemical modifications to become cellulose esters or ether derivatives, such as HPC, HPMC, HPMCP, HPMCAS, among others, which are either water-soluble or moderately water-soluble. These cellulose derivatives find widespread use as additives in coatings, film production, and emulsion formulations [11]. Importantly, there have been several FDA-approved ASD products based on these types of cellulose-derived polymers, as indicated in Table 1.5.

1.5.3.1 Hypromellose acetate succinate

Hypromellose acetate succinate (HPMC AS) is derived from HPMC through esterification involving acetic acid anhydride and succinic acid anhydride. Initially, HPMC AS was introduced as an enteric coating material and classified into three grades (L, M, or H) based on the acetyl substituent content [149]. HPMC AS has found extensive use in the formulation of ASDs, offering notable improvements in solubility, physical stability, and manufacturing consistency [11]. One of its advantages is having a relatively low glass T_g while maintaining a high degradation temperature, making it a suitable choice for manufacturing ASDs through the HME method [150]. In comparison to other polymers commonly utilized in ASDs, HPMC AS possesses several benefits, including reduced hygroscopicity, stronger intermolecular interactions between the drug and polymer, and a greater potential for drug supersaturation during dissolution [12]. Additionally, due to its acid group content, HPMCAS has the capability to form robust ionic interactions, particularly with weakly basic drugs [151]. In the following study, ^{1}H–^{19}F correlation experiments were performed to evaluate the drug-polymer interaction in the ASD of Posaconazole with HPMC AS. It was found that hydroxyl group of the polymer and the difluorophenyl group of drug are interacting through two different hydrogen bonds to provide the stability to the ASD system [151].

The quantity of acetate substituents present in HPMC AS can influence the degree of interactions between the drug and polymer in ASDs. HPMC AS showed higher capacity to resist crystallization of felodipine as compared to PVP and HPMC as felodipine ASD prepared with HPMC AS showed less moisture sorption. It confirms the weak hygroscopic property of the polymer under high humidity conditions [152]. In a study done to investigate the effect of polymer on the crystallization and dissolution rate of celecoxib formulated as ASD, HPMC AS was more found to be more effective than PAA in crystallization inhibition [153]. Another study revealed superior property of HPMC AS over PVP VA in maintaining the supersaturation of celecoxib for 8 hours, whereas with PVP the crystallization occurred in the initial 60 mins of the dissolution testing [82].

1.5.4 Acrylate and methacrylate (co-) polymers

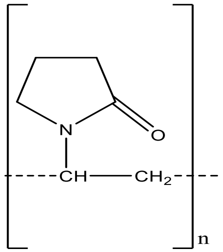
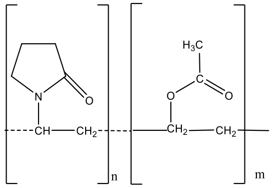
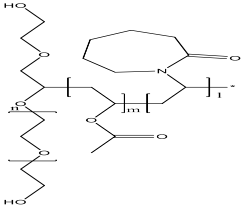
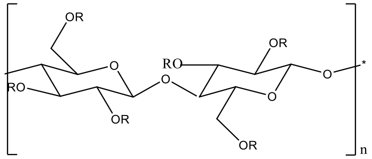
These polymers are called Eudragit with the substituents defining their actual structure and characteristics. These polymers are well known for their functionality as enteric coating, taste masking, barrier to moisture and sustained release of drugs. They are widely used for the preparation of ASDs [11].

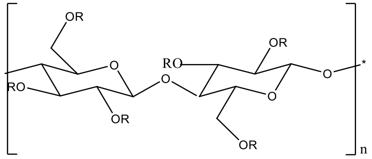
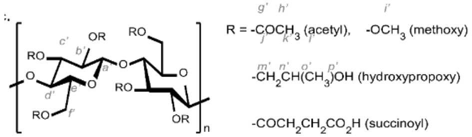
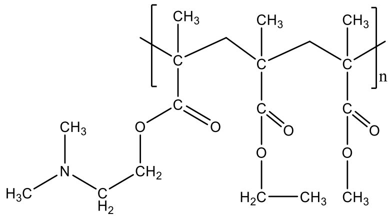
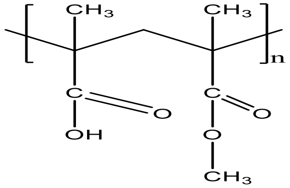
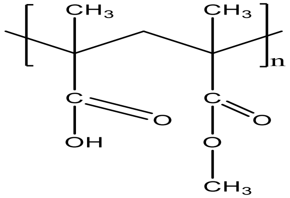
1.5.5 Other Polymers

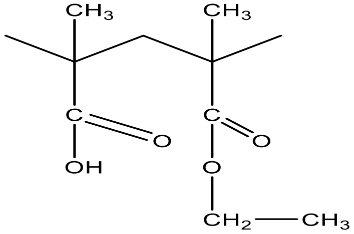
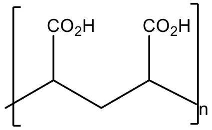
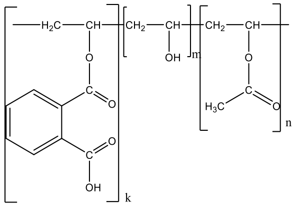
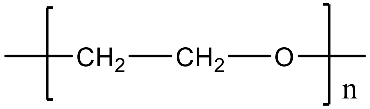
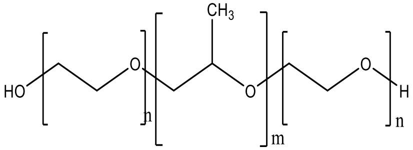
1.5.5.1 Polyacrylic Acid

PAA, which stands for polyacrylic acid, is an acrylic acid polymer characterized by pKa values of around 4.5. PAA possesses numerous carboxylic groups capable of forming amorphous salts when combined with basic drugs. For instance, Gui *et al.* in 2021 developed an amorphous salt of clofazimine and PAA using a straightforward slurry method. Remarkably, the amorphous salt, particularly one with a 75% drug loading, demonstrated robust physical stability even under accelerated conditions. In contrast, an ASD containing PVP crystallized within a week under the same conditions. Additionally, the amorphous CFZ−PAA salt exhibited improved dissolution rates, tablet compressibility, and powder flow characteristics when compared to the crystalline form of the drug [154]. A similar outcome was observed in the case of the ASD involving lumefantrine and PAA, where the formation of an amorphous salt enhanced drug stability and dissolution rates. Notably, there have been reports of an esterification reaction involving PAA and PVA leading to the creation of crosslinked ASDs. These crosslinked ASDs exhibited remarkable stability, even with extremely high drug loadings exceeding 90% [155]

Table 1.4. Different polymers and their properties used in the preparation of ASDs[72,156,157]

Chemical classification	Chemical name	Polymer name	Molecular structure	Molecular weight (AMU)	T_g (°C)	Degradation temperature (°C)
Polyvinyllactam polymers	Polyvinylpyrrolidone	Kollidon 12		2000-3000	102	196
		Kollidon 12 PF		2000-3000	102	196
		Kollidon 17 PF		7000-11000	138	217
		Kollidon 25		28000-34000	165	153
		Kollidon 30		44000 – 54000	171	160
		Kollidon 30 LP		44000 – 54000	171	-
		Kollidon 90 F		900000 – 1200000	177	177
	Polyvinylpyrrolidone vinyl acetate/ Copovidone	Kollidon VA 64		45000-70000	101	220
	Polyvinylcaprolactam–polyvinyl acetate–polyethyelne glycol graft copolymer	Soluplus		~118000	~70	297
Cellulosic polymers	Hydroxypropyl methyl cellulose	Affinisol 15 LV		~95 kDa	135	190
		Affinisol 100 LV		~190 kDa	145	195
		Affinisol 4M	R= H, CH_3,$CH_2CH(OH)CH_3$	~550 kDa	155	200

Chemical classification	Chemical name	Polymer name	Molecular structure	Molecular weight (AMU)	T_g (°C)	Degradation temperature (°C)
	Hydroxypropyl cellulose	Klucel LF	 R= H, $CH_2CH(OH)CH_3$	~95 kDa	-	200
	Hydroxypropyl methyl Cellulose acetate succinate	Aquasolve		18 kDa	117	
Acrylate and methacrylate (co-)polymers	Poly(butyl methacrylate-co-(2-dimethylaminoethyl) methacrylate-comethyl methacrylate) 1:2:1	Eudragit E PO		47,000	52	250
	Hetero block co-polymers of poly(methacrylic acidco-methyl methacrylate)1:1	Eudragit L 100		125,000	195	176
	Hetero block co-polymers of poly(methacrylic acidco-methyl methacrylate)1:2	Eudragit S 100		125,000	173	173

Chemical classification	Chemical name	Polymer name	Molecular structure	Molecular weight (AMU)	T_g (°C)	Degradation temperature (°C)
Others	Poly(methacrylic acid-co-ethyl acrylate) 1:1	Eudragit L 100–55		320,000	111	176
	PAA	-		1,800–450,000	102	200
	PVAP	-		47,000–60,700	42.5	150
	PEG/PEO	-		1,000–7,000,000	55-66	More than 200
	Poloxamer	-		7,600–17,400	52-57	More than 200

1.6 Riluzole

1.6.1 Mechanism of Action of Riluzole

Riluzole (RLZ) is an anticonvulsant Na^+ channel blocker belonging to the benzothiazole class, obtained FDA approval in 1995 for treating amyotrophic lateral sclerosis (ALS). ALS is a progressive neurodegenerative condition marked by degeneration of motoneurons and corticospinal tracts. The established treatment protocol involves administering fixed oral doses of 50 mg twice daily (BID). RLZ is a neuroprotective agent that hinders glutamatergic neurotransmission within the central nervous system (CNS). It impedes the release of glutamic acid in cultured neurons, brain slices, and corticostriatal neurons *in vivo*. These effects are believed to result, at least in part, from the inactivation of voltage-dependent sodium channels on glutamatergic nerve terminals and the initiation of a G-protein-dependent signal transduction process. Furthermore, RLZ exhibits noncompetitive blockade of N-methyl-D-aspartate (NMDA) receptors, thereby blocking certain postsynaptic effects of glutamic acid. In vivo, RLZ demonstrates neuroprotective, anticonvulsant, and sedative properties [158].

1.6.2 Physicochemical Properties of RLZ

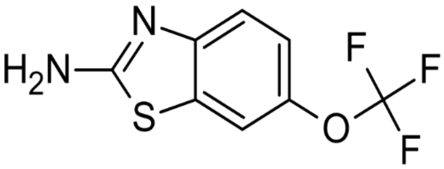


Figure 1.7. Chemical structure of Riluzole

Chemical Name: 2-amino-6-(trifluoromethoxy) benzothiazole.

Molecular weight: 234.2 g/mol

Description: White to slightly yellow coloured powder

Solubility: Highly soluble in dimethylformamide, dimethylsulphoxide, and methanol. Freely soluble in dichloromethane. Sparingly soluble in 0.1N HCl. Very slightly soluble in water and 0.1N NaOH

Melting point: 117-120 ^{o}C

pKa: 3.8

LogP: 3.5

1.6.3 Associated Toxicity with RLZ

RLZ has the potential to trigger acute hepatitis accompanied by hepatocellular damage and microvascular steatosis. Consequently, it is recommended to monitor liver enzymes throughout the course of RLZ treatment. There are evidences of increased level of liver enzymes during RLZ administration. Elevations in enzymes like alanine transferase (ALT), aspartate transaminase (AST), gamma glutamyl transferase (GGT), and bilirubin [159].

1.6.4 Pharmacokinetics of RLZ

Riluzole exhibits an average oral bioavailability of approximately 60%. The ingestion of a high-fat meal results in a reduction of about 45% in peak blood concentrations and 20% in the area under the concentration-time curve. Steady-state plasma concentrations are achieved within 5 days, and the drug shows high plasma protein binding at 96%. Extensive metabolism occurs in the liver through hydroxylation by cytochrome P450 1A2 and glucuronidation. Riluzole produces six major metabolites, along with several minor ones, some of which may possess pharmacological activity. The mean elimination half-life after multiple doses is 12 hours. Following a single dose of [14C]-riluzole, 90% of radioactivity is [160].

1.6.5 Marketed formulations of RLZ

Rilutek is the brand name of RLZ tablet and it has been approved by USFDA in 1995 [161]. Riluzole Zentiva is another brand name of RLZ tablet which is same as Rilutek and is approved by European Medicine Agency [162]. All the approved marketed formulations are available in the strength of 50 mg. The generic tablets of RLZ have been launched by Impax Labs in 2003, Glenmark Pharms Ltd, Mylan Pharms Inc and Sun Pharma Industries Ltd in 2013, Alkem Labs Ltd in 2016 and Kenton in 2019 [163].

1.7 Physiological Based Pharmacokinetic Modelling

Physiologically Based Pharmacokinetic (PBPK) models serve as mechanistic tools commonly utilized in both the pharmaceutical industry and environmental health risk assessment. Regulatory authorities acknowledge the efficacy of these models in forecasting organ concentration-time profiles, pharmacokinetics, and daily intake doses of xenobiotics (drugs/chemicals). The application of the PBPK model contributes to the development of quantitative adverse outcome pathways for various endpoints, including but not limited to developmental neurotoxicity, hepatotoxicity, and cardiotoxicity.

PBPK models are mathematical representations comprising multiple compartments that incorporate physiological, anatomical, biochemical, and physicochemical parameters to elucidate the processes of absorption, distribution, metabolism, and excretion (ADME) of xenobiotics and their metabolites (Figure 1.8) [164]. These models range from empirical and semi-mechanistic to compartmental models, their complexity determined by the nature of the problem at hand. Empirical or semi-mechanistic models encounter challenges in addressing queries such as predicting the concentration-time profile of a compound in a target organ or accurately determining dosing when extrapolating from animal to human. To overcome these challenges, compartmental models have been developed, closely mirroring human anatomy and physiology. Presently, these models enjoy widespread recognition in the region of pharmaceutical and environmental science for their efficacy in predicting the pharmacokinetic behaviour of xenobiotics concerning factors such as dose, route, and species.

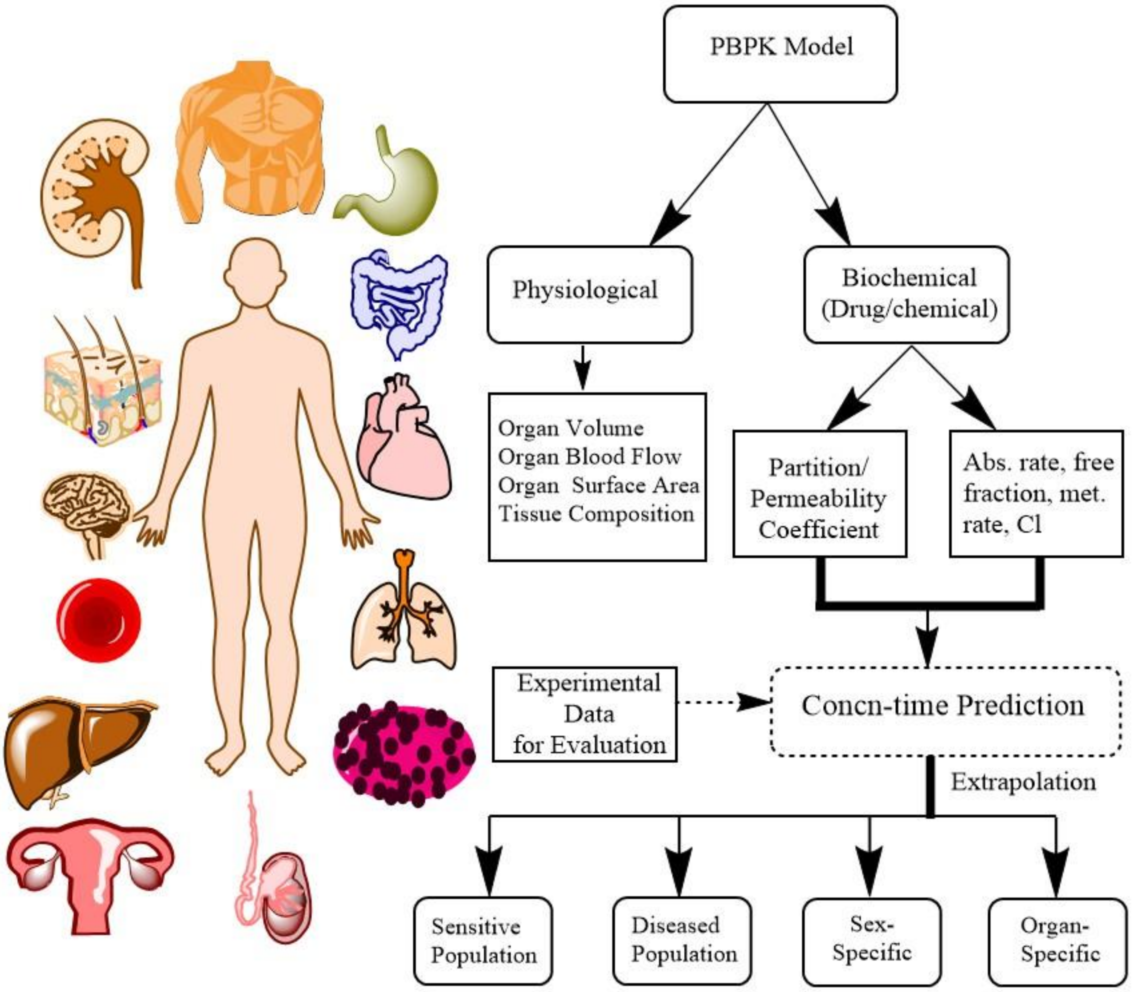


Figure 1.8. Conceptual diagram for the PBPK model, which extrapolates the model for assessing the risk to human health based on physiological and biochemical factors [164]