FUNDAMENTAL ASPECTS OF A THIRD COMPONENT USED IN TERNARY SOLID DISPERSION: A REVIEW

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INTRODUCTION
Solubility, as well as dissolution, is a fundamental principle across every physicochemical science, including biopharmaceutical and pharmacokinetic aspects of any medicine's therapy [1]. In recent decades, novel drugs with extraordinary medicinal benefits generated by various research activities entering the drug development phase are diminishing, due to their non-optimal biopharmaceutical properties [1, 2]. The foremost obstacle in the drug development phase is limited to the solubility/dissolution of the drugs in aqueous media. Since the drug must be bioavailable for the patient to exert its action, at a certain point of time, the drug must be completely dissolved or solubilized within the body fluid, regardless of the route of administration [3]. These complications significantly affect the pharmacokinetic parameter such as absorption, distribution, metabolism and excretion of the drug [4]. The primary objective of improving the solubility/dissolution is to enhance the bioavailability of the drug. The low solubility and dissolution rate of Active Pharmaceutical Ingredient (API) in G. I. T fluid also lead to inadequate bioavailability, increased dosage, and blood concentration variability [5]. Class II and Class IV drugs with low solubility in the Biopharmaceutical Classification System (BCS) suffer from dissolution-related absorption issues. Specific methods to resolve low solubility include chemical and physical alteration of drug candidates [6]. The Noyes-Whitney equation shows that the rate of dissolution of a drug is proportional to both the concentration gradient and the surface area of particles. Increasing the surface area of the substance will, therefore, increase the dissolution rate [7]. Several methods, such as solid dispersion (SD) [8-11], complexation [12, 13], lipid-based systems [14, 15], micronization [16, 17], nanomization [18, 19] and co-crystals [20, 21] were already suggested to increase the solubility of poorly water-soluble drugs. Among them, SD technology, which involves dispersing drugs in different types of polymers, is commonly used to improve solubility and bioavailability [22]. In 1961, the SD principle was introduced by Sekiguchi K and Obi N [23]. Conventional BSD involves dispersing the drug into a single polymer or surfactant or any other additive, thereby enhancing the solubility of the drug [24]. It is known that the solid-state of the product may be either crystalline or amorphous, which varies with the energetical state of solid-packed molecules [25]. The state at which the drug is dispersed in the crystalline or amorphous carrier has a significant impact on solubility and drug release [26]. Although there have been consistent reports of the utilization of SD’s in the pharmaceutical literature, only a few commercial products depend on the SD method [27]. An ideal formulation must be stable, prevent recrystallization, enhance the super saturation and dissolution properties of the drug. BSD may not be adequate for meeting all the criteria listed above [28]. Therefore, BSD can be an efficient technique for combating specific limitations of BSD [29]. TSD was formerly known as a multi-component SD, which involves the addition of a third component other than the drug and a carrier (i.e., API, polymer and an additive) that would further enhance the efficiency of SD [30]. Adding a third component (ternary agent) to produce a TSD system gives improved stability, greater miscibility, stronger intermolecular interactions, significantly higher water-solubility, and synergistic benefit in all of these factors compared to the BSDs [31]. The carrier used in combination with a ternary agent could be a polymer, surfactant or a polymer with surfactant property [32, 33]. Examples of ternary agents comprise surfactant [34], polymer [35], adsorbent [36], pH modulator [37] and hydrotropic agent [38]. Various international publications of the past decade are summarized from the reputed source (Elsevier, Pubmed, NCBI) to emphasize the significance of the key components (ternary agents) particularly, surfactants, polymers, pH modulators, and adsorbents to improve TSD’s reliability in addressing the challenges of formulation associated with the drug solubility and dissolution.

Surface active agents (surfactants)
Surfactants are commonly used in the TSD along with the carrier as it provides multiple benefits. In general, the drug should reside in a supersaturated state to reach the optimum rate of dissolution. The addition of surfactants as a ternary agent results in the formation of complex micelles and promotes supersaturation of the drug [39]. Additionally, it provides improved stability and prevents the precipitation of the drug [40]. In TSD, the surfactant along with the carrier act by reducing the surface tension at the interface thereby alters the nature of the drug and enhances dissolution [41]. The Surfactant acts as a wetting agent [42], plasticizer [43], crystallization inhibitor [44], and stabilizer [45] with respect to dissolution properties [46]. Critical micellar concentration (CMC) and hydrophilic-lipophilic balance (HLB) play a key role in the dissolution of the drug [47]. When the concentration of the surfactant is greater than CMC, it aids in the improved dissolution by forming micelles/inhibiting precipitation and while lesser than CMC acts by reducing the interfacial tension [48-50]. Based on the polarity, surfactants are classified into...
The surfactants recently used in combination with carriers in TSD are poloxamer, PVP, and D-a-TPGS/Vitamin E TPGS. It is reported that the combination of poloxamer 188 and Polyvinyl Pyrrolidone (PVP) K30 showed a beneficial impact on solubility, stability, in vitro dissolution, and bioavailability of Febuxostat [51]. The addition of surfactants could be either intra-granular or extra-granular. When mixed intra-granularly with the API and polymer the surfactants have a beneficial effect on the rate of drug release rather than extra-granularly applied [52]. A study documented the effect of surfactant added internally and externally to indomethacin and PVP. Internally incorporated SLS had a dramatic effect on the release of indomethacin as compared with externally added SLS [49]. Past studies on the Surfactant-carrier combination used in TSD are enlisted in table 1.

### Table 1: Studies on the surfactant-carrier combination used in TSD

| API          | Surfactant | Carrier          | Impact of surfactant on TSD                                                                 | Ref    |
|--------------|------------|------------------|---------------------------------------------------------------------------------------------|--------|
| Domperidone  | Poloxamer 188 | Gelucire 50/13    | Domperidone 188 was found to be an ideal ternary agent than poloxamer 407                   | [53]   |
| Ezetimibe    | Poloxamer 188 | PVP K30          | Melt quenching of Poloxamer 188 with ezetimibe exhibited enhanced solubility as well supersaturation in the bio-relevant media. | [54]   |
| Diacerein    | Pluronic F-68 | PEG 4000         | Pluronic F-68 in TSD enhanced the solubility of diacerein by micellar solubilization and increased steric hindrance. | [55]   |
| Domperidone  | Pluronic F-127 | PVP K30          | The interfacial tension between the drug and the dissolution medium was minimized by surfactant in TSD which resulted in increased wettability and thus enhancing domperidone dissolution. | [56]   |
| LW6          | Poloxamer 407 | Povidone K30     | The presence of poloxamer 407 in TSD resulted in improved solubility by micelle formation and delivering the drug into the core of micelles. | [57]   |
| Manidipine   | TPGS        | Copovidone       | Due to its low CMC, TPGS decreased the interfacial tension and also showed a more porous structure resulting in the improved dissolution of manidipine. | [58]   |
| Valsartan    | TPGS        | Soluplus         | The presence of TPGS as a plasticizer in the TSD resulted in reduced glass transition temperature and also enhanced penetration of the valsartan through the mucosal membrane. | [59]   |
| Lacidipine   | SDS         | Soluplus         | The Ternary system with SDS not only enhanced the solubility and dissolution but also improved the bioavailability of lacidipine up to 3.7 folds when compared to the binary system. | [60]   |
| Felodipine   | SDS         | Soluplus         | By acting as a plasticizer, crystallization inhibitor, a driving force to assist the carrier, SDS offered many advantages and resulted in enhanced dissolution. | [61]   |
| Chlorthalidone | SLS       | Soluplus         | The presence of SLS above the CMC of 2%, significantly enhanced the solubility up to 5.5 times than the pure drug. | [62]   |

### pH Modulators

In general, water-insoluble drugs are weakly acidic or weakly basic compounds in nature. Hence, they mostly dependent upon the pH for their solubility. An approach to modify the release rate of numerous pH-dependent drugs is to modulate the pH of the formulation known as microenvironmental pH [63]. Weakly acidic drugs show greater solubility at neutral or alkaline pH and weakly basic drugs show improved solubility at acidic pH [64]. The dissolution behavior can be closely associated with the microenvironmental pH at the diffusion layer. pH modifying agents act by altering the pH through intermolecular hydrogen bonding with the drug and thereby decreasing the crystallinity of the drug resulting in an enhanced release rate. Alkalizers [66] or Acidifiers [67] are the agents that can be used for altering the microenvironment pH i.e. either by increasing or lowering the pH at which the drug could dissolve easily.

Alkalizers are added to weakly acidic drugs and for weakly basic drugs acidifiers are added. The Conventional BSD technique alone is not sufficient for all pH-dependent drugs as it is restricted to the solubilization capacity [63]. Past studies stated that combining a pH modulator along with a carrier in TSD could effectively enhance the various properties of the drugs [68-70]. A study reported that combining alkalizer with kollidon VA64 and glyceryltric acid (GA), resulted in the enhanced dissolution of GA through the formation of ion complexes by strong electrostatic attraction [71]. Using citric acid (acidifier) along with Amorphous Solid Dispersion (ASD) technology significantly enhanced the absorption of Carvedilol even under elevated gastric pH conditions [72]. Some of the most commonly used alkalizers include Aminoclay, NaOH, Na₂CO₃, Ca(OH)₂, NaHCO₃, and Meglumine. Acidifiers generally used in TSD include citric acid, succinic acid, fumaric acid, and tartaric acid. Past studies on the pH modulator-carrier combination used in TSD are enlisted in table 2.

### Table 2: Studies on pH modulator-carrier combination used in TSD

| API          | pH modulator | Carrier | Impact of pH modulator on TSD                                                                 | Ref    |
|--------------|--------------|---------|---------------------------------------------------------------------------------------------|--------|
| Chrysin      | Aminoclay    | Brij L4 | Chrysin (pKa 6.72) was found to be more soluble in the basic environment. Adding aminoclay increased the SD’s microenvironment pH to the basic state, thus increasing the dissolution. | [73]   |
| Telmisartan  | NaOH         | Soluplu | Among various alkalizer, NaOH (1%) had a beneficial impact on Telmisartan solubility by providing a continuous pH adjustment throughout the dispersion matrix. | [74]   |
| Nateglinide  | Na₂CO₃       | Poloxamer 188 | The presence of Na₂CO₃ deprotonated the nateglinide carbonyl group, resulting in pH-independent solubility in the acid environment, improving the bioavailability of nateglinide by up to four-folds. | [75]   |
| Toltrazuril  | Ca(OH)₂      | PVP     | With the increase in the Ca(OH)₂ ratio, the rate of dissolution of toltrazuril was found to be enhanced, as it facilitates intermolecular interaction with Toltrazuril which is necessary for the maintenance of supersaturation. | [76]   |
| Clarithromycin | NaHCO₃     | HPMC/ PVP | The Clarithromycin would have been degraded by acidic media after 60 min before leaving the tablet if, NaHCO₃ were not added. The alkalizer increased the dissolution and stability of the drug without altering the crystallinity of the drug. | [77]   |
Solid and solution phases is vital. The polymer prevents crystal dissolution [86]. Retaining a drug in the amorphous state in both the solid-state or else during dissolution is impaired by their low thermodynamic stability and their solubility and dissolution properties of many poorly water-soluble drugs [89]. Thus, the Amorphous Ternary Solid Dispersion (ATSD) has gained more attention in enhancing the solubility and dissolution of celecoxib compared to the SD prepared with PVP or HPMC alone. The combination of PVP K30 and HPMC K100 had a synergistic impact on the solid state property and crystallization inhibition. PVP K30 and Soluplus had a synergistic impact on the solid state property and crystallization inhibition. By acting as an anti-plasticizer, HPMC HP55 increased stability and kollidon VA64 increased the wettability resulting in a rapid release of dipyridamole. Though surrounded by enteric polymer, electrostatic interaction between tartaric acid and dipyridamole resulted in a change of microenvironment pH facilitating a rapid dissolution of dipyridamole.

### Table 3: Studies on the polymer-polymer combination used in TSD

| API            | Polymer/polymer TSD                                                                 | Impact of polymers on TSD                                                                 | Ref       |
|----------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|-----------|
| Indomethacin   | PVP K30 and HPMC K100                                                             | The SD was stabilized by Eudragit E100 and the supersaturation was retained by PVP K30 and the mixture of both had a synergistic effect on the indomethacin dissolution. Pre-dissolved HPMC as a powder extended the supersaturation by inhibiting growth over the dissolution period by maintaining the particle size. | [89]      |
| Celecoxib      | Polyvinyl alcohol and HPMC, prepared by hot-melt extrusion                         | By acting as an anti-plasticizer, HPMC HP55 increased stability and kollidon VA64 improved the dissolution rate by increasing API wettability. Soluplus as a major component inhibited the crystal growth and a minor component VA64 increased the wettability resulting in a rapid release of griseofulvin. | [92, 93]  |
| Ibuprofen      | Kollidon and VA64                                                                  | The combination of PVP-HPMC prevented recrystallization and considerably improved the dissolution of celecoxib compared to the SD prepared with PVP or HPMC alone. | [97]      |
| Griseofulvin   | PVP K30 and HPMC K100                                                             | The PD of griseofulvin is enhanced by the additional benefits of polymer blends.         | [98]      |

### Adsorbents

Despite several advantages, TSD has certain drawbacks due to its handling and stability issues. TSD formulation often results in a waxy yield, and this is due to the carrier’s nature. As a result, they tend to have a poor flow, poor compressibility, and hard to pulverize [99, 100]. To resolve these problems, inert material with good flow and compressibility should be used to absorb the dispersion on its surface [101]. Moreover, adsorption carriers not only prevent the crystal growth due to confined space within the pores of carriers but also stabilize the drug in the TSD by various chemical interactions [102]. Previous research has suggested that the adsorption carriers (sylsyila 350) can be used as a ternary agent in addition to their anti-plasticizing effect in the ATSD of itraconazole [103]. Another study stated that using neusilin US2, as an adsorbent effectively tuned viscous semisolid substance into a free-flowing powder so that it can be compressed into a tablet or filled into the capsule as powders [104]. The presence of neusilin US2 not only resolved the issue of TPSGs’s stickiness but also enhanced the ticagrelor flow property and the study revealed that the use of neusilin US2 in TSD preparation would improve industrial processes [105]. Some of the adsorbent widely used are sylsyila 350 [106, 107], neusilin [108, 109], Aerosil [110, 111], Lactose [112, 113], Florite [114]. Past studies on the adsorbent-carrier combination used in TSD are enlisted in table 4.
The polymer-polymer combination aids in maintaining the superrecrystallization, it is vital to maintain them in the amorphous state. ATSDs are thermodynamically unstable and more liable to its crystalline counterpart owing to its high free energy. Since the amorphous form of the drug offers improved apparent solubility than stability without altering the nature of the formulation. The interaction with the drug. Additionally, pH modulators improved easily.

modulating the microenvironment pH at which the drug dissolves solubility and dissolution of weakly acidic/weakly basic drugs by the appropriate choice of excipients. Alkalizers/acidifiers aids in drugs that depend on the pH for their solubility, pH modulators are variables to be considered when selecting a surfactant for the study. recrystallization, maintenance of supersaturation and also improves example, surfactants along with the carrier act by distinct

Table 4: Studies on adsorbent-carrier combination used in TSD

| API          | Adsorbent | Carrier          | Impact of adsorbents on TSD                                                                 | Ref       |
|--------------|-----------|------------------|---------------------------------------------------------------------------------------------|-----------|
| Valsartan    | Lactose   | Gelucire 50/13   | Increased quantity of lactose addition resulted in free-flowing powder with reproducible dissolution characteristics. | [100]     |
| Bosentan     | Sylsia 350| Poloxamer 188    | The inclusion of Sylsia 350 turned the waxy SD into a free-flowing powder with adequate compressibility and also expanded the surface area, resulting in rapid drug description. | [101]     |
| Cefuroxime axetil | Sylsia 350 | Gelucire 50/13 | The benefits of adding sylsia 350 are better yield, inhibition of recrystallization, flowability, an increase in the effective surface area, and amorphous state preservation. | [106]     |
| Celecoxib    | Neusil US2 | Phosphatidylcholine (PC) | As the PC-based SD exhibited a lipidic consistency, it was challenging to formulate it into an oral dosage form. The flowability of the SD was improved by adding an adsorbent. | [107]     |
| Carbamazepine | Neusil UFL2 | Kollidon VA64 | Together with the carrier, Neusil UFL2 improved the dissolution by increasing the surface area and carbamazepine flowability. | [108]     |
| Curcumin     | Aerosil   | Gelucire 50/13   | Due to the hydrogen bonding between the drug and the carrier and its surface adsorption onto the aerosil, the TSD was found to be stable for around 9 mo. The absence of adsorbent resulted in a gelatious mass, while free-flowing powder was observed along with a significant increase in dissolution in the presence of Aerosil 200. | [109]     |
| Nifedipine   | Aerosil 200 | Eudragit E | Complete desorption of glidazide resulted in rapid dissolution by the combined effect of adsorption and reduction of agglomeration. | [111]     |
| Gliclazide   | Lactose   | Poloxamer/PEG | Florate prevented the transformation of an amorphous form to a crystalline and increased the stability of the amorphous state. | [112]     |
| Lurasidone hydrochloride | Florte | Poloxamer 188 |                                                                                             |           |

CONCLUSION

Various additives are used as a third component to overcome the limitations associated with BSD. These additives improve the efficiency of TSD as a formulation through several strategies. For example, surfactants along with the carrier act by distinct mechanisms such as reducing the surface tension, preventing recrystallization, maintenance of supersaturation and also improves the physical stability of the drug. CMC and HLB are the important variables to be considered when selecting a surfactant for the study. Therefore, care must be taken in choosing suitable surfactants. For drugs that depend on the pH for their solubility, pH modulators are the appropriate choice of excipients. Alkalizers/acidifiers aids in solubility and dissolution of weakly acidic/weakly basic drugs by modulating the microenvironment pH at which the drug dissolves easily.

They also assist in supersaturation by establishing an intermolecular interaction with the drug. Additionally, pH modulators improved stability without altering the nature of the formulation. The amorphous form of the drug offers improved apparent solubility than its crystalline counterpart owing to its high free energy. Since the ATSDs are thermodynamically unstable and more liable to recrystallization, it is vital to maintain them in the amorphous state. The polymer-polymer combination aids in maintaining the super saturation, inhibiting the crystal growth, and improved the stability of the ATSD. Despite enormous benefits, the commercial use of SD is limited due to the complexity of handling and scale-up. To overcome these obstacles, adsorbents are added to the TSD as a third component. These adsorbents convert the waxy SD into a free-flowing powder so that it can be compressed into a tablet or powder that can be filled into the capsule. Every excipient has both benefits and drawbacks, so caution should be given to selecting the appropriate excipient for the research. It is therefore concluded that the addition of different additives as a third component improves TSD’s efficacy in enhancing the solubility, dissolution, and bioavailability of poorly water-soluble drugs.

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CONFLICTS OF INTERESTS
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