REVIEW ON IN-VIVO AND IN-VITRO PERFORMANCE OF CO-AMORPHOUS SYSTEM, POLYMER-BASED, AND MESOPOROUS SILICA-BASED AMORPHOUS SYSTEM

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ABSTRACT:

Majority of newly developed drugs are associated with solubility problems; this problem should be fixed by enhancing solubility through various techniques. This review aims to combine recent studies related to solid dispersion methods, amorphous solid dispersion, mainly polymeric amorphous solid dispersion & mesoporous-based solid dispersion, and finally about the co-amorphous system and their formulation aspects. The importance of these techniques for the improvement of solubility of main drugs of BCS class II & class IV drugs has been described, as it also corresponds to the bioavailability of drugs. In-vitro and In-vivo effectiveness of these systems has been tallied to provide a improved comprehension of these systems.

KEYWORDS: Solid dispersion, Amorphous solid dispersion, Polymer amorphous solid dispersion, Mesoporous silica-based solid dispersion, In-vitro & in-vivo performance.

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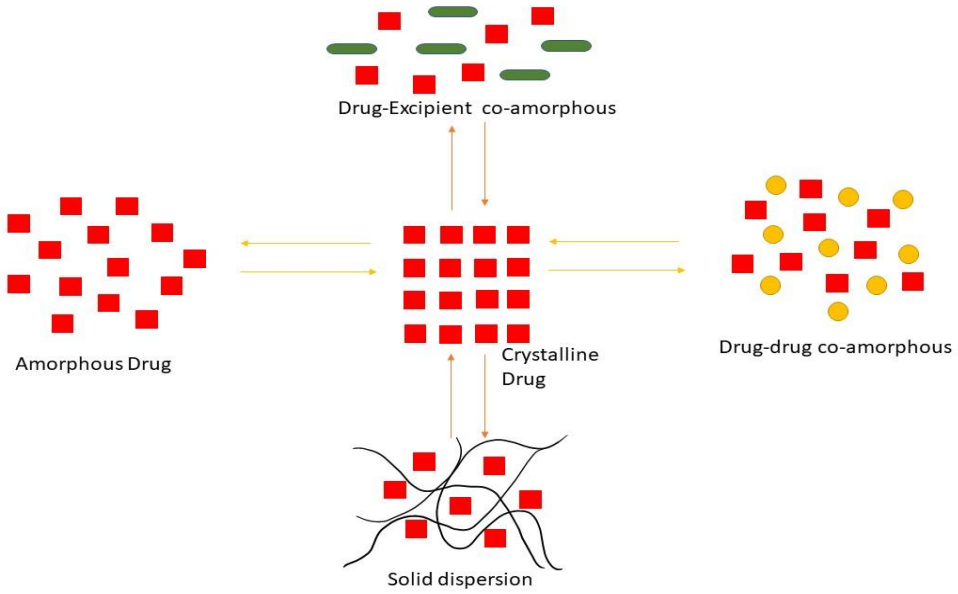
INTRODUCTION:

High-throughput screening technology has resulted in the identification of numerous novel active pharmaceutical ingredients (APIs). As the structural complexity of drug candidates has been increasing, 75% of new drug candidates have demonstrated poor aqueous solubility and low bioavailability, which significantly negatively impacts clinical efficacy.[1]

Prospective NCEs are typically only absorbed in the upper small intestine, with absorption dramatically decreasing after the ileum, indicating a narrow absorption window regardless of permeability. However, if these drugs are not entirely released in the gastrointestinal region, their bioavailability will be poor.[2] Therefore, one of the primary concerns in the

pharmaceutical industry is linked with the methods used to boost the drugs water and the bioavailability.[2]



Crystalline drugs to be transformed into various forms to improve solubility and bioavailability. [3][4]

Drug release is a critical and constricting phase in the bioavailability process for oral drugs which has limited GIT solubility and more permeability. By modifying drug release profile, the bioavailability can be increased. [3],[4]. One of the most successful strategies established in the market is solid dispersion, which are the methods that can be used to improve the solubility of insoluble substances and thereby their release. [2]The generation of a solid-state dispersion of one or even more hydrophobic active ingredients in a hydrophilic inert carrier through the melting (fusion), solvent, melting solvent technique is the definition of solid dispersion. In the finished product, a hydrophilic matrix and hydrophobic drugs are present.[5]

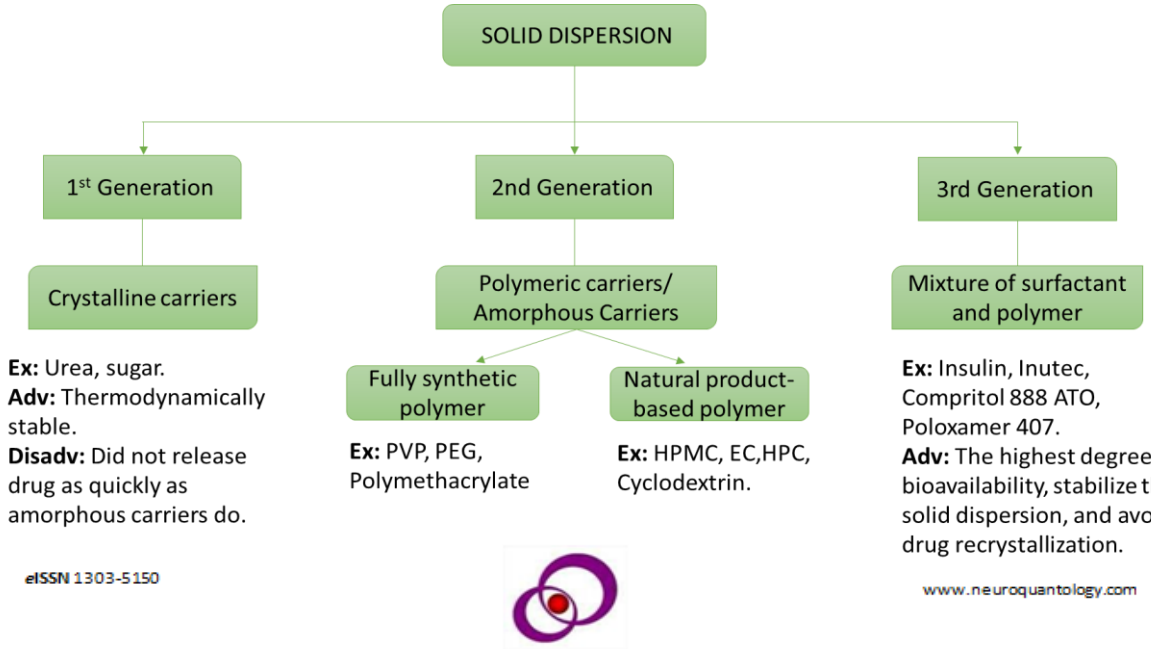


TABLE 1: Solid dispersion recent advancements classification - [6]

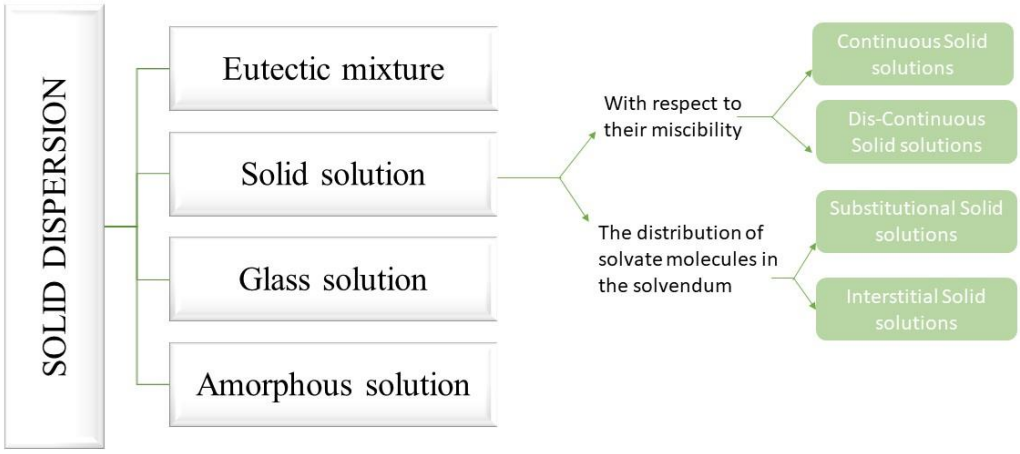


TABLE 2: Solid dispersion molecular arrangement classification -[6]

There are many non-conventional platforms available to effectively expose patients in clinical trials. The usage of ASDs, however, has established as the preferred platform to deliver low-soluble APIs among the non-conventional platforms that are accessible. [7]-

Two essential qualities are necessary for an amorphous solid dispersion system (ASD) to be successfully designed, to increase bioavailability, a drug must have the following properties:

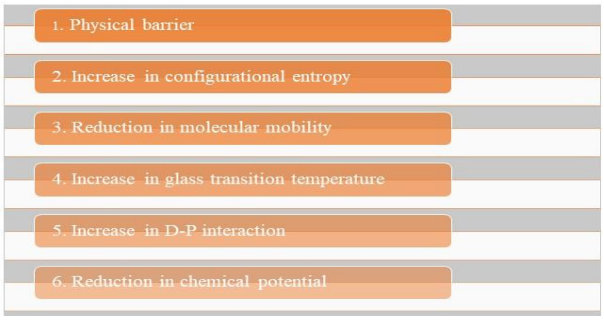
1) Physical stability should be optimum during downstream processing and storage; and
2) Good dissolving performance when administered intravenously.

Researchers from academia and business have worked to address the critical problem of ASDs' low in vivo performance predictability during the production of ASD in the pharma industry. The advancement of the field's expertise has resulted from initiatives like the creation of bio- medium and others. These initiatives will undoubtedly help to improve predictions of in-vivo effectiveness of ASDs and the development of a approach to improve ASD design. - [8]

The in vivo performance of Amorphous Solid Dispersion can be predicted by-

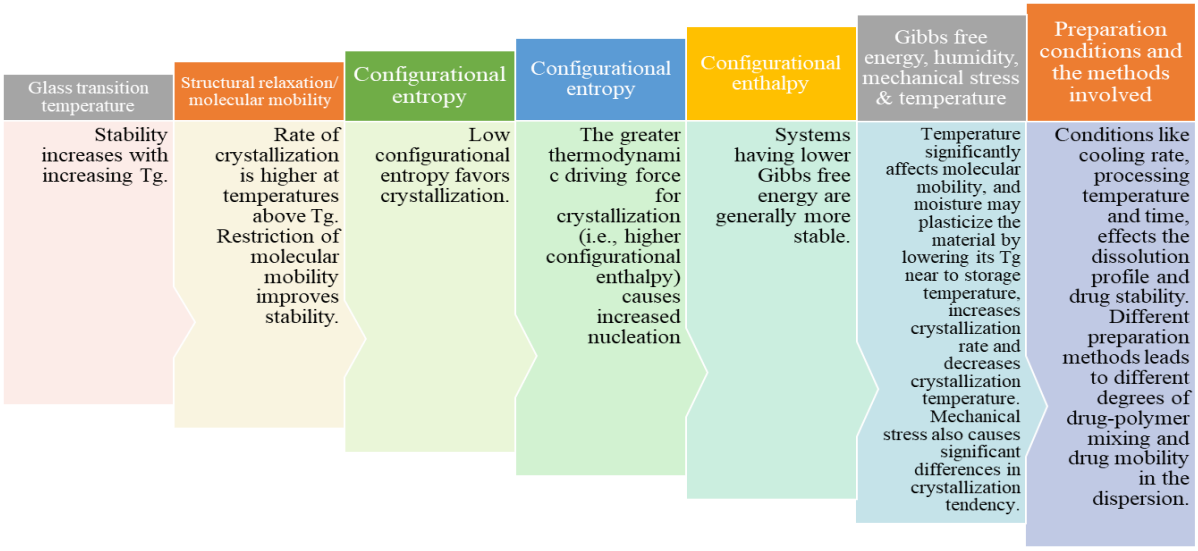
- During the early stages of drug development, ASDs can be utilised to obtain basic information about bio-availability and exposure using various formulations.
- Because the polymer helps to prevent API recrystallization in solution or in vivo, the results of animal safety studies and human clinical trials show improved exposure.- [7]

ASD systems contain amorphous active pharmaceutical ingredient (API) with superior physical stability and the capability to preserve supersaturation in the in vivo environment, as supported by a polymer that prevents crystallisation under elevated temperature and relative humidity. The stabilization also occurs, if there is reduction in molecular mobility and extension in glass transition temperature (Tg). – [7] [9]



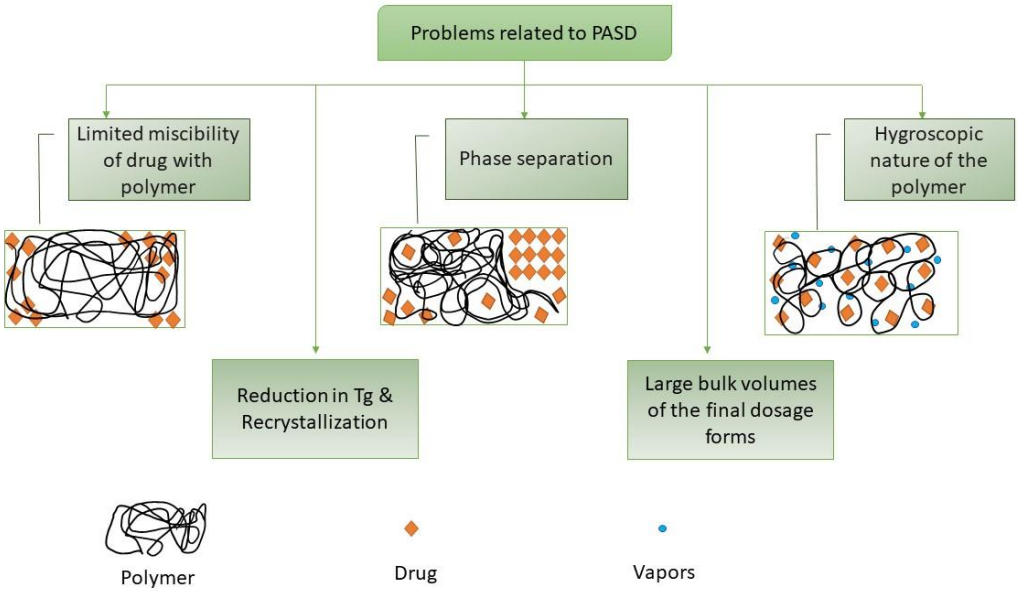
The approaches for stabilizing Amorphous Solid Dispersion that helps to prevent the devitrification and plasticization. [10]

The stabilization of the drug in its amorphous form is difficult to succeed, their high free energy, thermo- dynamically unstable character and have a ability to form nuclei and then eventually devitrify into a stable crystal form that is only slightly soluble in water. Recrystallization of drug can change the drug's solid-state properties as well as dissolution performance, which can have influence on clinical performance, thus the dug can get removed from market. [11] The significant obstacle of ASD is their high hygroscopicity which subsequently increases molecular mobility of the API and their typically high polymer to API mass ratios results into downstream formulation problems.[12]



Factors responsible for affecting the stability of ASD- [10]

To integrate a drug into ASDs, however, substantial quantities of polymers would be required because drugs are not well miscible with polymeric carriers. This might lead to a high ratio of polymer to drug in the final dosage forms, as well as a large volume relative to their mass. In addition, the majority of the water-soluble polymers that are utilised in the production of ASDs have the capability of rapidly absorbing moisture, which contributes to the recrystallization of the amorphous component. To resolve the problems, other or alternative approaches are therefore required. [13][14] The most widely accepted technological approaches for stabilising amorphous drug forms are inclusion complexation with a cyclodextrin[15] in this, the incorporation of drug into hydrophobic environment of cyclodextrin results into inclusion complex, molecular solid dispersion in a polymer[10], in this drug is either anti-plasticized or is dissolved in a polymer below saturation solubility, co-amorphization with another small molecule [3] This explains the utilisation of a combination of low molecular weight molecules and adsorption to a mesoporous substrate to stabilise amorphous substances. [16] Mesoporous carriers have small pores that help to accommodate amorphous drugs and a large surface area for drug adsorption. [11]



Disadvantage of PASD [4]

This review will provide some overview regarding CAMS, PASD, Mesoporous silica-based ASD, few formulation aspects of the above-mentioned system and finally briefly about the in vivo and in-vitro performance of CAMS, polymer based and mesoporous-based ASD to improve solubility, stability and bioavailability.

POLYMERIC AMORPHOUS SOLID DISPERSION:

Polymeric ASD have been regarded as a significant accomplishment to overcome oral absorption problems and inadequate water solubility and the polymer based ASDs plays major role in the domain of ASDs, and extensive recent studies has resulted in a variety of commercially available products. [17] The main flaw in this strategy is during storage recrystallization occurs which can negatively impact the stability. Also, many PASD are

hygroscopic and consequently absorb moisture, which makes the preparation unstable. [18] Therefore, the generation of stable amorphous formulations necessitates a significant amount of up-front development.[10]

The so-called "spring and parachute" theory serves as the general solubilization process for PASDs. The drug and the soluble polymer matrix have been dissolved or mixed together, resulted into supersaturated solution (spring) and then the concentration of drug in the media declines because of either absorption or precipitation (parachute). The steps for drug incorporation into a polymer matrix vary according to the PASD formation method..[19] With the help of drug-polymer interaction, polymer delays supersaturation by preventing crystallisation, either by disrupting the nucleation process or by preventing the development of crystals.[10]

For changing the physicochemical properties of a drug requires careful consideration of which polymer to use.

(i) It needs to be able to keep the drug in its amorphous state throughout the whole process, from production to storage to shipment.

(ii) It must sustain the supersaturated solution state required for drug absorption and be easily soluble in GI circumstances.

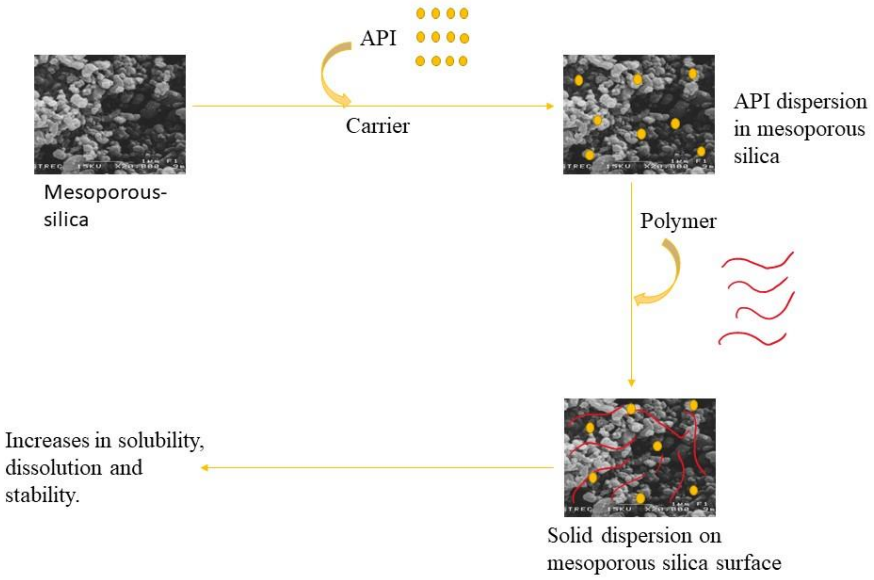
(iii) Further, it should improve the drug's bioavailability by facilitating its transport through the gastrointestinal (GI) membrane. [9]

In order to create effective amorphous polymeric solid dispersion systems, it is essential to characterise and correlate the physicochemical properties of both drug and polymer at infancy of development. To select a suitable polymeric carrier, multiple requirements must be met. Therefore, the thermodynamic miscibility of the drug- polymer, the glass transition temperature of polymers, viscosity, etc. at the necessary condition, play primary role in the formation of stable phases. As any fluctuations can produce phase separation of the single phase system.[20]

MESOPOROUS SILICA-BASED ASD:

Recently, there has also been a surge in interest in mesoporous silicon and silica for drug-delivery systems. The utilization of porous media or adsorbents as an alternative to drug/polymer systems has been investigated, and stable drug delivery systems for amorphous drugs have been studied. These materials support controlled and rapid drug release by having a wide surface area and nanoscale capillaries that can accommodate substantial drug loading.[16]. A Mesoporous silica is categorized into two types: ordered mesoporous silica, which is a porous material with a pattern of uniform mesopores that contain a high specific surface area, and pore volume and hence have high porosity, and non-ordered MS such as Syloid, Sylysia, and aerosol. The dissolving qualities are improved by the use of this. In this, the deposited molecules must be adsorbed to the surface, and the pores must be very small (on the order of a molecular diameter or less) , thus inhibitsrecrystallization[21] These mesoporous carriers facilitate better drug solubilization and intestinal membrane permeability.[11] The most well-known MSMs are Mobile Composition of Matter-41 [MCM-41], Santa Barbara

Amorphous-15 [SBA-15], and MCM-48, all of which have a cubic arrangement of their mesopores.[22] Amorphous drugs based on mesoporous silica nanoparticles (MSNs) have had their glass transition temperature (Tg) and glass dynamics characterised, with the results showing that drug molecules forming an amorphous monolayer on the surfaces of MSNs have a Tg but no Tg despite their limited mobility; any excess drug confined in the MPS pores had the same properties as the pure amorphous drug..[23]



Mesoporous silica dispersion.[24]

For mesoporous drug delivery systems consist two main components are required, poorly soluble drug and a mesoporous carrier. Numerous no. of loading methods is available, out of which solvent evaporation i.e., impregnation and immersion are the most convenient technique be used, as it is effective, simple and no special instrument are required. The main factor to be considered in this is flowability as these are hygroscopic in nature. In a comparative study of melt loading and spray drying results as melt loading SBA-15 with ibuprofen improved flow properties over co-spray drying. [25] When compared to a formulation without a precipitation inhibitor, bioavailability is increased and supersaturated concentrations are maintained in vitro for several hours when the drug is co-loaded into a mesoporous carrier. [25] For example, In a study done by O'Shea et al, shows Fenofibrate-loaded mesoporous silica [FF-SLC], with HPMCAS, act as precipitation inhibitor, displayed significant improvements in dissolution.[26] In another study, the drug itraconazole has been loaded by SBA-15 which is a MCN and conjugated with combined precipitation inhibitors hydroxy-propyl- methylcellulose [HPMC] and hydroxy-pro- pyl-methylcellulose acetate succinate [HPMCAS], shows enhance invivo performance and dissolution.[27] In many studies combination of two different polymer excipients is utilised as precipitation inhibitors, been conjugated with mesoporous silica nanoparticles to improve the solubility, bioavailability and

gastrointestinal oral absorption. For instance, hydroxypropyl methylcellulose (HPMC) and Kollicoat [IR] utilised as precipitation inhibitors [PIs]—conjugated with mesoporous silica nanoparticles (MSNs) as carriers incorporated in indomethacin by solvent evaporation method. It resulted in approximately three-fold increase of dissolution rates as compared to the pure indomethacin.[28]

The mesoporous drug carriers have been used in many cancers' treatment and gene delivery, and in several biomedical studies, also used for targeted drug delivery for specific targeting and attenuately reduction in side effects i.e., tumour targeting. [25][29] For instance, there is a study concluded that, quercetin-loaded MSN tagged with folic acid is an effective breast cancer treatment. Quercetin-loaded MSN tagged with folic acid induces apoptosis and limits breast cancer cell migration without harming normal cells. [30] Coating CNFs with mesoporous silica can reduce their toxicity and make them biomedical-ready.[31] Another study demonstrates that in response to oxidative stress in periodontitis, ceria oxide (CeO2) loaded on the surface of mesoporous silica [MSN@Ce] and then modified with polyethylene glycol (PEG) [MSN@Ce@PEG] for better dispersion and biocompatibility can simultaneously regulate intracellular reactive oxygen species [ROS] and promote osteogenic differentiation of periodontal ligament stem cells [PDLSCs].[32]

Amorphous or nanocrystalline forms of poorly soluble drugs loaded in mesopores have higher apparent solubility and a larger surface area than crystalline drug microparticles, enhancing their dissolution rate. In a study, Huang et al explained that, Apigenin was prepared as a 1:1 weight-ratio SD of mesoporous silica nanoparticles [AP-MSN] using a physical absorption technique. The [AP-MSN] SD showed superior invitro, invivo, and cumulative release behaviour compared to the raw AP..[33] SBA-15 may serve as robust platform to improve the RLZ oral bioavailability, by improving the rate of dissolution of riluzole via amalgamation or immersion-rotavapor method.[34] One more study attempted to improve CARBA solubility by stabilising it and by integrating it into the mesoporous silica material SBA-15 and changing its crystalline structure to an amorphous one. Therefore, the solubility and physical stability of carbamazepine were improved by mixing SBA-15 with CARBA..[35] Co-spray drying of drug particles with ordered mesoporous silica, SBA-15, led to an increase in the bioavailability of artemisinin [ART], by increasing solubility.[36]

Two common mesoporous carriers used to create amorphous solid dispersions—silica and magnesium aluminosilicate—were the focus of another study that sought to compare and contrast them. Both the ethanolate and amorphous silica supports improve darunavir solubility. Amorphous sample preparation with the chosen carriers was evaluated using hot melt extrusion, solvent wetting, and spray drying, the major typical procedures for preparing solid dispersions. And the result was, both ethanolate and amorphous silica supports improve darunavir dissolution which was achieved through spray drying technique.[37]

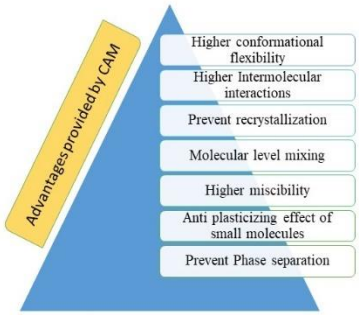
Mesoporous silica carriers are conjugated with polymeric compounds incorporated into the drugs for the delivery of supersaturated drug loading systems. For example, in a study cilostazol are co-loaded with Syloid®-244FP and Kolliphor®-P188 provides synergistic effect.

Bioavailability has been evaluated of three formulations in beagle dogs [CLT], [CLT-SD,] osmotic-pump tablets) result shows that [CLT-SD] has higher bioavailability among all.[38] In a study done by Antonino et al, monolayer loading capacity of the drugs in mesoporous silica of the drugs by utilising theoretical density functional theory [DFT] and ab initio Molecular Dynamics [AIMD]. An analysis of the monolayer's physical stability contrasted with that of the confined amorphous drugs above the MLC, found to be thermodynamically unstable and, as a result, to be diffusing out of the pores in order to crystallise.[39] Drugs with strong glass-forming ability in mesoporous silica [MS] were studied, and the results showed that the monomolecular loading capacity could be estimated quickly and accurately using the differential scanning calorimetry (DSC) method.[40]

There are few studies in which comparative studies have been performed between two different formulation strategies. For example in a study Zhang et al, concluded that mesoporous silica based formulation is superior compared to spray dried SDs, as out of Fenofibrate- loaded mesoporous silica and spray-dried SD, Fenofibrate- loaded mesoporous silica performed better as it maintained accelerated stability for up to 3 months at 40 °C/75% Relative Humidity in open dish and shows better flowability, and also the invitro dissolution release is well controlled contrasted to Spray dried solid dispersions.[41] The mesoporous delivery system improves dissolution without drug-carrier chemical interactions. Therefore, these delivery system works with most drug-carrier combinations.[25]

CO-AMORPHOUS DRUG DELIVERY SYSTEMS:

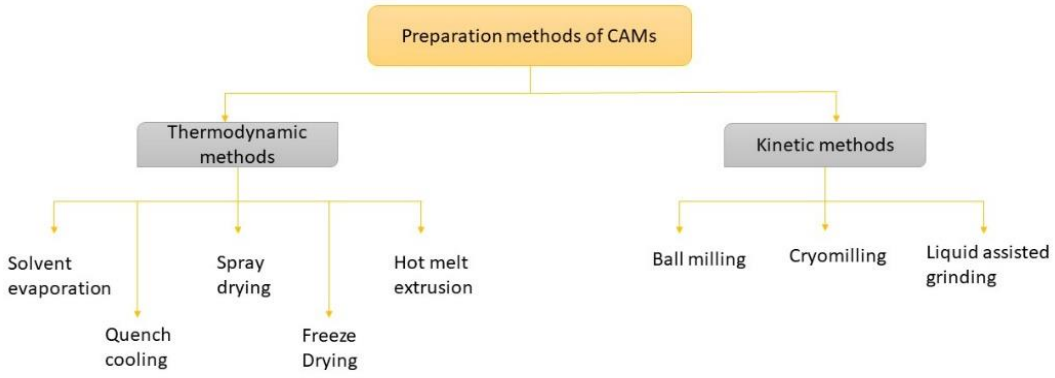
Co-amorphous drug delivery systems have generated a lot of interest recently as a means of overcoming ASD's drawbacks. Drug and co-former (such as a lower m.w. excipient or another drug) are amorphized together to generate a one phase, amorphous systems during preparation of the co-amorphous system (CAM).[13][14]



Advantages provided by CAMs [4]

Co-amorphous designates as the interaction of lower molecular weight molecules to generate a homogenous amorphous single-phase system. Because of their capacity to stabilize the

drug's amorphous state, co-amorphous structures are believed to boost the dissolution rate of drugs. Also, these co-amorphous solids have good Tg values, which may promote the thermodynamic stability and prevent crystalline solids from recrystallizing during formulation. -[42][16]



Preparation methods for CAMs.[14][13]

Co-formers involved in CAMs:

The selection of a relevant co-former can determine the three CQA i.e., co-formability, physical stability, and dissolution performance, which are essential for the preparation of a desired co-amorphous drug delivery system**.** [17][43] There are various methods for co-former selection in CAMS which are, experimentally detected single glass transition (Tg) implies drug-polymer miscibility. Other techniques for determining miscibility in drug-polymer solid dispersions include estimating solubility parameters, using partition coefficients, rheological methods, measuring melting point depression, and computational methods based on X-ray powder diffraction (XRPD) data. Ibuprofen and ibuprofen lysinate solubility in tiny sugar molecule carriers were estimated using these characteristics.. [17][44] Furthermore, lattice-based solution models like the Flory-Huggins theory can be used to evaluate miscibility in drug-polymer blends**.**[45] For rapid screening of a huge drug and co-former set, Flory-Huggins interaction parameters considered as good indicator.[17][46] Through various stabilisation mechanisms, such as chemical interactions or hydrogen bonds, pi-pi interactions, molecular mixing and salt formation, the co-former physically stabilises the drug's amorphous state.,.[43][49][17] Co-formers involved in the CAMS are of two broad types, drug-drug CAMs and drug-excipient CAMs [13]

Drug-drug combinations:

Drug-drug combinations which are the ideal choices for combination therapy, drug-AA combinations, and drugs combined with other inactive molecules, such as organic acids[50] like citric acid, benzoic acid or saccharin, weak bases, like meglumine, flavonoids, such as quercetin

have been introduced [16][3]. The Selection criteria for these mixtures can include things such pharmacological significance (to some extent), considering the chemical properties of the molecules that are being employed in the formulations..[16] One of the drugs functions as an amorphous stabiliser in these binary amorphous systems.[14] Drug-drug CAMs categorized into two:

1. Drugs contain similar pharmacological effects.
2. Drugs contain different but synergistic pharmacological effects.

Some investigations were performed recently shows the improvement of solubility of a drug in its co-amorphous system.

Table 3: Few examples of Drug-drug CAMs from recent years.

S.No.	Co-amorphous System	Co-former	Component under study	Results	Reference
1.	Platensimycin-berberine chloride	Berberine [BCL]	Platensimycin [PTM]	-Good physicochemical stability at room temperature at room temperature & 40℃, -$t_{1/2}$ 2-3-fold longer in rats than amorphous and crystalline PTM.	[51]
2.	Indomethacin-paracetamol & Indomethacin-Nicotinamide	Paracetamol [PAR] & Nicotinamide [NCT]	Indomethacin [IND]	PAR & NCT, increases solubility, dissolution and supersaturation, of IND under FaSSIF &FaSSIF blank.	[52]
3.	Apigenin-Oxymatrine	Oxymatrine [OMT]	Apigenin [APG]	Solubility and dissolution Increases, therefore, bioavailability also increases than pure APG	[53]
4.	Ciprofloxacin-Quercetin	Quercetin	Ciprofloxacin	Different molar ratio of 2:1, 1:1, 1:2 compared with	[54]

				amorphous drugs, result shows aerosol performance is visible in 1:1 molar ratio and stability also improves.	
5.	Telmisartan-Hydrochloro-thiazide	Hydrochloro-Thiazide [HCT]	Temlisartan [TEM]	Different molar ratio 1:1, 2:3, 1:2, 1:3 is used, out of which 1:3 showed 79 and 10-fold improvement in solubility and dissolution and $AUC_{0\text{-}48h}$ also increased.	[55]
6.	Tolbutamide-Tromethanine	Tromethanine [TRIS]	Tolbutamide [TBM]	Physical stability demonstrates that at 25°C, it maintains an amorphous state for up to 90 days, with 2.5 times the solubility of crystalline medication.	[56]
7.	Fexofenadine-Naringin	Naringin	Fexofenadine	Permeability is determined in exerted gut sac, which shows increased in permeability by 5-fold & 3.5-fold.	[57]
8.	Sinomenine-Indomethacin, Sinomenine-Naproxen and Sinomenine-Sulindac	Indomethacin [IND], Naproxen, & Sulindac.	Sinomenine	Sustained release rates increased and no crystallization is found after 4 months at 25℃ &	[58]

				75% RH.	
9.	Simvastatin-Epigallo-catechin-3-gallate & Nifedipine - Epigallo-catechin-3-gallate	Epi-gallocatechin-3-gallate [EGCG]	Simvastatin [SIM] & Nifedipine [NIF]	-Each drug is extremely stable at 75% RH, 40°C, and 25°C. - Both [SIM-EGCG] and [NIF-EGCG] have enhanced Cmax by 1.81 and 5.69 times, respectively. Additionally, the AUC 0-24h increases by 1.62-4.57-fold.	[59]

The research on co-amorphous drug-drug combinations has provided a basic understanding of these mixtures' physicochemical characteristics as well as their mechanism for amorphous stabilisation, drug dissolution, permeability and also bioavailability. [60]

Drug-excipients CAMs:

In case of Drug-excipients CAMs, they are classified into - drug - organic acids CAMs, drug amino acids drug saccharides.[13] Some of the examples as per recent studies performed are –

Table 4: Few Examples for Drug-excipient CAMs from recent years.

S.No.	Co-amorphous System	Co-former	Component under study	Results	Reference
1.	Olanzapine-Sulfonic Acid	Sulfonic Acid-Saccharin, Cyclanic Acid, Acesulfame	Olanzapine	These CAMs are stable for upto 24 weeks, at 11-75% RH and also solubility increases by 145 times.	[61]

2.	Quercetin-Different Amino Acid	Amino Acid-Arginine, Glutamic Acid, Aspartic Acid, Tryptophan, Glycine	Quercetin	QCT: ARG, F1 formulation is best, as it shows high solubility, bioavailability, and stability than the pure drug.	[62]
3.	Carbamazepine-Tannic Acid & Indomethacin-Tannic Acid	Tannic Acid (TA)	Carbamazepine (CBZ) & Indomethacin (IND)	CBZ-TA system shows stability upto 6 months at 40℃, 60% RH upto 1 month at 20℃ whereas, IND-TA found stable upto 6 months at 4℃ & 60% RH upto 1 month at 20℃.	[63]
4.	Carvedilol-Organic Acids	Organic Acids-Benzoic Acid, Malic Acid, Citric Acid	Carvedilol	Compared to other, carvedilol-benzoic acid shows increase in dissolution, bioavailability, and also permits a higher drug loading.	[50]
5.	Mebendazole- 5 dipeptides	Dipeptides-Tryptophan-phenylalanine, Phenylalanine-tryptophan, Aspartic acid-tyrosine, Histidine-Glycine, Proline-tryptophan	Mebendazole	Dissolution rate & physical stability of mebendazole is increased than crystalline and amorphous drugs.	[64]

6.	Drug-saccharides CAMs	Saccharides- Low m.w. saccharides, Lactose, Sucrose, Mannitol, Trehalose, Chitosan oligosaccharide	Drug	Solubility and safety increases	[13]

A unique class of excipients AA, have been used in co-amorphous formulations on the theory that their propensity for molecular interactions (specifically, AA in drug receptors) would result in the solid state development of stable co-amorphous structures and can be the cause of the prominent aqueous solubility/dissolution of drugs and amino acids CAMs.. [65][66][13]

Below is a summary of the three broad guidelines for selecting co-formers for drug-amino acid CAMs, based on the probability that CAMs will form as well as their physicochemical characteristics, including physical stability and dissolution rate:

i. The best option for drugs that are both acidic and basic is co-amorphous salt formation.
ii. Non-polar Aliphatic AA like leucine, isoleucine, and valine are poor co-formers and should be avoided if at all feasible,
iii. Whereas, non-polar aromatic amino acids produce better co-formers..[13]

The first CAMS were reported before the year 2000 was binary amorphous systems. And then eventually, some ternary systems were described in the literature. To improve the CQA of CAMS, a third element—which might be a polymer, surfactant, or other small molecule—is included in this ternary system or added to the binary system. Additionally, a 3rd excipient, introduced to a CAMs formulation to improve production and perhaps obtain performance advantages through tableting and coating. [17] Few examples of recent studies are:

Table 5: Few examples of Ternary CAMs from recent years.

S.No.	Binary CAMs	Component added in Binary CAMs	Results	References
1.	Flutamide [FL]-Bicalutamide [BIC]	Poly - (methyl methacrylate-co-ethyl acrylate [MMA/EA] Or Polyvinyl Pyrrolidone [PVP]	Solubility of ternary systems was increased compared to crystalline drug.	[67]

2.	Indole- 2-Carboxamide derivative [North 2], Curcumin	Polyvinyl-Pyrrolidone Eudragit EPO Hydroxy-propyl Methylcellulose [HPMC]	Out of all EPO, solubility was increased by more than 55 times times for both, [North 2] and [CUR] than that of binary system.	[68]
3.	Quercetin-Hydroxyl propyl methyl cellulose acetate succinate [HPMCAS] & L-lysine (Lys)	Lysine	Dissolution effect of ternary system increases than the binary system.	[69]
4.	Lacidipine [LCDP]-Soluplus	Sodium dodecyl Sulfate	Solubility increased, also C_{max} & AUC increases by 3.3 & 3.7- fold.	[70]
5.	Griseofulvin-Hypromellose Phthalate [HP]	Erythritol	Solubility increases and maintain supersaturated concentration, compared to crystalline drugs.	[71]
6.	Andrographolide-Oxymatrine [AP-OMT]	Transcinnamic acid [CA], P-hydroxycinnamic acid (Ph-ca), Ferulic acid [FA]	Solubility increases and no recrystallization is visible. Stability is seen for upto 18 months.	[64]
7.	Carvedilol-Tryptophan	Polymer	Solubility increases, Physical stability at room temperature at room temperature for 6 months.	[72]

Therefore, the preparation of co-amorphous small-molecule combinations are suggested as viable ways to improve the stability as well as dissolution and bioavailability of amorphous pharmaceuticals.[16]

IN-VITRO & IN-VIVO PERFORMANCE:

The amorphous form of a poorly soluble in water. API possess higher internal energy, shows greater solubility and a faster rate of dissolution than the crystalline counterpart part. The "spring" is a higher energy amorphous API that, when dissolved with other drugs or excipients, helps drugs dissolve and supersaturate. The "parachute" is the co-former that lingers amorphous API crystallisation and nucleation in order to sustain or extend the supersaturation for the allotted duration.[3]

CAMS are considered for their good amorphous stability, but ultimately to increase drug dissolution, solubility, and bioavailability, their in vitro and in vivo effectiveness is crucial to determine. The dissolution rate, apparent drug solubility, supersaturation ability, and maintenance can be examined. However, it is well known that in vitro dissolution efficacy

S.No.	Common Drugs	Co-amorphous drug delivery system		Mesoporous -silica based system		Polymeric Amorphous Solid Dispersion	
		Co-formers	In-vivo & in-vitro study	Carriers	In-vivo & in-vitro study	Polymers	In-vivo & in-vitro study
1.	Curcumin (CUR)	Piperine (PIP)	CUR membrane permeability in the gastrointestinal tract increased in a CaCO2 model, and CUR glucuronidation was blocked in a rat intestinal microsome in vitro investigation. In crystalline and amorphous CUR, the CUR AUC increased 2.16 and 1.92-fold, respectively. [73]	Solutol® HS15	SD (1:10) improved curcumin dissolution in pH 6.8 buffer by 90% in 1 h. The solid dispersion formulation had better bioavailability than pure curcumin in rat pharmacokinetic studies. SD with 1:10 drug/Solutol® HS15 had 5 times higher AUC0–12 h.[74]	Cellulose acetate	Formulations formed Cur more soluble than pure drug. Cur release from solid dispersions was optimally controlled in vitro for 12 h. In rats, the optimised formulation had a higher PK- parameter (C max=187.0 ng/ml, t_{max}=2h) than pure drug (Cmax=87.0, t_{max}=0.7 h).[75]
2.	Atorvastatin (ATV)	Naringin (NRG)	co-amorphous formulations of atorvastatin (ATV) and naringin (NRG) were generated by three techniques,	SBA-15 and MSF	SBA-15, and MSF were confirmed to significantly improve the release profile of atorvastatin calcium. Additionally, in enzyme-free simulated gastric fluid, MSF	HPMC, PVP K-30 or PVP VA-64	The improved super-saturation and dissolution properties of the PVP VA-64 SD significantly increased the oral absorption of

			quench cooling, solvent evaporation, and ball milling, out of three methods, ATV solubility increases by 56-fold in SE, drug is released by 97% whereas AUC and Cmax increases by 4.5-fold and 7-fold respectively. [76]		showed a faster release rate of AC than SBA-15 (pH 1.2).[77]		atorvastatin in rats. Supersaturation was activated by HPMC, PVP K30, and PVP VA64 SD, which increased absorption of atorvastatin in rats, orally.[78]
3.	Ritonavir (RTV)	Indomethacin (IND)	Co-amorphous samples in the molar ratios RTV:IND were created by solvent evaporation (2:1, 1:1, 1:1). (1:2). Tg values were above 40 °C for all three systems, with RTV: IND (2:1) having the highest value at 51.88 °C. RTV and IND	Syloid®244 FP	At 25°C, 70%, 32%, and 20% saturated ritonavir ethanol solutions were used. Ritonavir was loaded into silica 1:1, 1:2, and 1:3. All ritonavir-Syloid®244 FP systems had non-crystalline ritonavir.[80]	PEG-4000	Amorphous ritonavir dissolving 10-fold faster than crystalline. Beagles are tested. In vivo, 10–30% amorphous solid dispersions had higher AUC and Cmax than crystalline drug. 10% amorphous dispersion

			were almost three times more soluble in amorphous form than in crystalline form. [79]				increased AUC 22-fold and Cmax 13.7-fold.[81]
4.	Olanzapine (OLZ)	carboxylic acid (CA)	OL-ascorbic acid co-amorphizatio n via H-bonding. In co-amorphous dispersions with a 1:2 molar ratio, OL solubility rose more than 600-fold. When compared to commercially available references, in vivo studies demonstrated high bioavailability (145ng/mL) and maximal plasma levels (14.3 ng/mL). [82]	NLCs	Mesoporous lica increased lanzapine ioavailability in ano-structured oid carriers (NLCs). he optimised ystem utperformed drug uspension by 2.0 h ?< 0.05). hysiologically MRT 3.47 h), higher C_{max} 2.12±0.40 ng/ml), and T_{max}. The biological performance was assessed in albino abbits.[83]	Metho-cel® K100 LV-CR and Etho-cel® standard 7FP premium.	CR tablets optimised Cmax and extended Tmax ($P<0.05$). Drug absorption in-vivo and drug release in vitro correlated well ($R2=0.9082$). The test tablet had 94% bioavailability. [84]
5.	Naproxen (NAP)	Cimetidine (CIM)	There were two molar ratios used 1:1 & 1:2, out of which 1:1 Has more physical	(N-ANI), modified mesoporou s silica nanoparticl e & β-	The carrier is used to formulate pH responsive drug delivery system of drug 5-Fluorouracil (5-	PVP-K25	The miscibility, dissolution and physical stability increases.[87]

			stability. No crystallization was visible. Intrinsic dissolution rate was also improved compared to crystalline[85]	cyclodextrin	FU) & naproxen (NAP). The drug was released by 88.5% & 98.75 respectively. [86]		
6.	Loratidine (LOR)	Carboxylic acid (CA)	1:1 molar ratio co-amorphous show increase in T_g compared to amorphous drug. Dissolution rate was increased. Three months of physical stability at 25°C with 0% and 60% Relative Humidity.[88]	NA	NA	PVP-K30	Water solubility and bioavailability increases.[89]
7.	Docetaxel (DOC)	Natural p-gp inhibitor (MYR)	Increases dissolution rate and physical stability, maintains super-saturation. C_{max} and AUC increases to 3.9-fold 3.1-fold, respectively. [90]	NA	NA	Sodium acetate	Dissolution rate was increased[91]

8.	Fenofibrate (FF)	NA	NA	FF-SLC	FF-SLC incorporated by HPMCAS, resulted as increases in dissolution rate, In-vivo determination shows bioavailability is increased in capsule by 86.69 ± 35.37% and in suspension by 19.92 ±9.89% [26]	1.COP 2.PVCL-PVA-PEG 3.HPMC	Dissolution rate increases, and supersaturation maintains 7.6-12.1h, no recrystallisation was visible after 26 weeks for fenofibrate-COP.[92]
9.	Valsartan (VAL)	Nifedipine (NIF)	Physically stable for 1 month at 40±2℃ & 75±5% RH. Dissolution rate increases by 5.66-fold & 1.61- fold, C_{max} increases by 3.63- fold and 2.19-folds.[93]	HPMC Or 3-D ordered macro-porous carbon monoliths (OMCMs)	In rat, PK study was performed and observed that HPMC base shows improvement in bioavailability by 2.4-fold and also dissolution rate was also increased.[94]	1.Eudragit ® 2.Soluplus 3.PVP-K25	Eudragit ® polymer improves Cmax, AUC and dissolution, thus improving bioavailability. [95]

Table 6: Overview of in-vitro & in-vivo study reports performed on common drugs by Co-amorphous system, mesoporous- silica based system and polymeric solid dispersion.
HPCM- Hierarchical porous carbon monolith, SBA-15- Santa Barbara Amorphous-15, MSF- Meso-cellular siliceous foam, HPMC- Hydroxy propyl methyl cellulose, PVP-K30- Polyvinylpyrrolidone, PEG- Polyethylene glycol, NLC- Nano structural lipid carriers, (N-ANI)- N-propyl Aniline, COP- Co-povidone, (PVC-PVA-PEG) – Polyvinyl Caprolactam-polyvinyl acetate- polyethylene glycol co-polymer, HPMC- Hypromellose 2910/5

doesn't always correlate with in-vivo performance of a drug delivery system.[17] Pharmaceutical formulation bio-performance is best assessed in-vivo. In vivo performance of co-amorphous formulations has been less studied than in-vitro. For drugs that operate as

glycoprotein (P-gp) substrates, maintaining the supersaturation of co-amorphous formulations in the gastrointestinal tract has been suggested as an effective method for boosting in vivo bioavailability. Therefore, the factors like degradation, metabolism and efflux transportation also effects the in-vivo performance of co-amorphous systems.[3][13] It was also proven that drugs of BCS IV with efflux transporter and metabolism inhibitors may improve in vitro and in vivo performance. The comparisons can be made between the co-amorphous formulations and the amorphous drugs, as well as other systems like polymer- and mesoporous silica-based solid dispersions to determine which system is better to improve the bioavailability is important.[1] Further we have discussed about the research performed by using Co-amorphous system, mesoporous silica-based system and polymeric amorphous solid dispersion system, which has been undergone recently, to determine in-vivo-in-vitro data's regarding the common drugs.

CONCLUSION:

The new drug discovery in pharmaceutical industry focuses mainly on the lipophilic dugs, thus majority of drugs have solubility issues, as they are poorly water-soluble, which makes the formulation scientist to face many obstacles to formulate these products. Therefore, to fix these issue, amorphous solid dispersion system came into the market, which helps to improve the solubility, and bioavailability of the product. In PASD, polymer plays an important role, to stabilize the amorphous form of drug through different mechanism. Because of some problem related to PASD, two alternative approaches have been developed. Firstly,due to their low molecular weight, co-amorphous systems, which combine two drugs or drugs and excipients, are advantageous for high dosage. But these is a very challenging approach because during storage recrystallization might occur, which results in dissolution failure. Secondly, Mesoporous carrier system, which is a recently trending research topic helps to increase the solubility of drug by dispersing the drug into mesoporous silica carrier phase. In this review, limited research publication has been considered to briefly explain about three types of system and to provide basic understanding regarding the in-vivo and in-vitro study of these systems, so that in future the comparison can be made against amorphous drugs and other systems such as polymer based solid dispersion and mesoporous silica based Solid dispersion.

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