



Various techniques involved in solubility enhancement: An overview

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Abstract

Solvency is the phenomenon of disintegration of solid in fluid stage to give a homogenous framework. Solvency is one of the significant parameter to accomplish wanted convergence of medication in fundamental flow for pharmacological reaction to be appeared. Severely water dissolvable medications regularly require high dosages so as to arrive at restorative plasma concentrations after oral organization. Low watery solvency is the serious issue experienced with definition advancement of new compound substances. Any medication to be assimilated must be available as a fluid arrangement at the site of retention. Water is the dissolvable of alternative for fluid pharmaceutical definitions. The greater part of medications unfortunately acidic and feebly essential with terrible fluid solvency. Subsequently different process are utilized for the improvement of the solvency of gravely water-dissolvable medications incorporate micronization, substance modification, pH change, strong scattering, complexation, co-solvency, micellar solubilization, hydrotropy and so forth. The rationale of this survey article is to depict the process of solubilization for the accomplishment of viable ingestion and improved bioavailability.

Keywords: Solubility, solubility enhancement, co-solvent, pH, emulsions

Introduction

Various processes can be adjusted to improve solubilization of terrible water solvent medication and further to improve its bioavailability. The process for the most part utilized for solubilization of medication incorporates micronization, concoction alteration, pH modification, strong scattering, complexation, co-solvency, micellar solubilization, hydrotropy and so forth. Solubilization of gravely dissolvable medications is an as often as possible experienced test in screening investigations of new compound elements just as in definition structure and advancement. Any medication to be assimilated must be available as a watery arrangement at the site of ingestion. As Solvency and vulnerable is the central factor for the in-vivo retention of the medication, these can be adjusted or altered by upgrade process like. The term 'dissolvability' is

characterized as most extreme measure of solute that can be disintegrated in a given measure of dissolvable. It can be characterized quantitatively just as subjectively. Quantitatively it is characterized as the convergence of the solute in an immersed arrangement at a specific temperature. In subjective terms, solvency might be characterized as the unconstrained communication of at least two substances to frame a homogenous atomic scattering. A soaked arrangement is one in which the solute is in harmony with the dissolvable. The solvency of a medication is spoken to through different fixation articulation, for example, parts, rate, molarity, molality, volume division, mole portion.

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This audit along these lines starts with conversation in regard to the customary ways to deal with sedate solubilisation incorporate pH alteration, cosolvency and molecule size decrease. While microemulsion and self-emulsifying frameworks are novel methodologies. The various methodologies of dissolvability improvement are talked about beneath.¹

Various techniques have been used in attempt to improve solubility and dissolution rates of poorly water soluble drugs which include as following:

1. Particle Size Reduction
2. Co solvency
3. Hydrotropy
4. pH Adjustment
5. Supercritical Fluid (SCF) Process
6. Micellar Solubilization
7. Ball milled product

pH Adjustment

Seriously water solvent medications with parts of the particle that can be protonated (base) or deprotonated (corrosive) may possibly be broken down in water by applying a pH change. pH modification can on a basic level be utilized for both oral and parenteral organization. Upon intravenous organization the gravely dissolvable medication might be hasten in light of the fact that blood is a solid support with pH between 7.2 – 7.4. To survey the reasonableness of the methodology, the cushion limit and mediocrity of the chose pH are imperative to consider. In the stomach the pH is around 1 to 2 and in the duodenum the pH is between 5-7.5, so upon oral organization the level of dissolvability is additionally likely be influence as the medication goes through the digestion tracts. Ionizable aggravates that are steady and dissolvable after pH modification are most appropriate. The compound kinds might be acids or bases or zwitterionic. It can be applied to crystalline just as lipophilic gravely solvent mixes. Solubilized excipients that expansion ecological pH inside a measurements structure, for example, a tablet or case, to a range higher than pKa of pitifully acidic medications builds the dissolvability of that tranquilize, those excipients which go about as alkalizing operators may expand the solvency of feebly fundamental medications. The solvency of the gravely solvent medication is expanded contrasted with water alone, so if mixes can

penetrate through the epithelium orally, the part of orally ingested medication might be extended. pH alteration is additionally as often as possible joined with co-solvents to additionally expand the dissolvability of the seriously dissolvable medication. The precipitation upon weakening is fine or indistinct, bioavailability can be extended because of a broadened fixation slope and upgraded surface territory for disintegration. In circumstances where the medication encourages into severely dissolvable particles that require disintegration and don't fastly dissolve, bioavailability may not be adequately extended²⁻³. This methodology is utilized much of the time in Overview as pre-clinically pH modification is a decent procedure to survey the viability of seriously solvent medications because of its all-inclusiveness and relative effortlessness. Be that as it may, if precipitation of the severely dissolvable medication happens wildly after contact with a pH at which the medication is significantly less solvent (oral just as parenteral), the understanding of the outcomes might be deceiving.

Co-Solvency

The dissolvability of a seriously water dissolvable medication can be extended as often as possible by the expansion of a water miscible dissolvable in which the medication has great dissolvability known as cosolvents. Co-solvents are blends of water and at least one water miscible solvents used to make an answer with improved dissolvability for gravely dissolvable mixes. Generally, this is one of the most broadly utilized process in light of the fact that it is easy to deliver and assess. Instances of solvents utilized in co-dissolvable blends are PEG 300, propylene glycol or ethanol. Co-dissolvable plans of gravely solvent medications can be directed orally and parenterally. Parenteral definitions may require the expansion of water or a weakening advance with a watery media to bring down the dissolvable focus earlier to administration. The pharmaceutical structure is consistently fluid. Gravely dissolvable mixes which are lipophilic or profoundly crystalline that have a high dissolvability in the dissolvable blend might be fit to a co-dissolvable methodology. CoSolvents can build the dissolvability of severely solvent exacerbates a few thousand times contrasted with the watery

dissolvability of the medication alone. Extremely high medication centralizations of seriously solvent mixes can be broken down contrasted with other solubilization draws near. Nonetheless, the bioavailability may not be drastically expanded on the grounds that the seriously solvent medication will regularly wildly crash out upon weakening into a crystalline or undefined accelerate. For this situation, disintegration of this hasten is required for oral ingestion. Co-solvents might be joined with other solubilization process and pH change in accordance with further increment dissolvability of seriously dissolvable mixes. The utilization of co-solvents is a profoundly viable procedure to improve the dissolvability of badlysoluble drugs. The most regularly utilized low poisonousness cosolvents for parenteral use are propylene glycol⁴, ethanol, glycerin, and polyethylene glycol. Dimethylsulfoxide (DMSO) and dimethylacetamide (DMA) have been generally utilized as cosolvents as a result of their huge solubilization limit with regards to seriously solvent medications and their moderately low harmfulness.

Particle size reduction

The bioavailability characteristically identified with medicate molecule size. By limit molecule size, extended surface territory improves the disintegration properties. Molecule size decrease, it is finished by processing process utilizing plane plant, rotor stator colloid factories and so on. Not reasonable for drugs having a high portion number since it doesn't change the immersion solvency of the medication.

These days Molecule size decrease can be accomplished by micronisation and nanosuspension. Each procedure uses distinctive contraption for decrease of the molecule size. In micronization the solvency of medication is regularly characteristically identified with sedate molecule size. By limit the molecule size, the amplified surface region improves the disintegration properties of the medication. Micronization of medications is finished by processing process utilizing plane factory, rotor stator colloid plants and so on. Micronization isn't appropriate for drugs having a high portion number since it doesn't change the immersion solvency of the medication. Nanosuspension is another procedure which is sub-micron colloidal

scattering of unadulterated particles of medication, which are settled by surfactants. The nanosuspension approach has been utilized for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquon. The preferences offered by nanosuspension is augmented disintegration rate is because of bigger surface territory uncovered, while nonappearance of Ostwald aging is because of the uniform and thin molecule size range got, which disposes of the focus inclination factor. Nanosuspensions are delivered by homogenization and wet processing process⁵⁻⁶.

Ball milled product

This procedure is broadly utilized in nonpharmaceutical applications especially in beautifying agents to get refined particles for sun square. Instances of pharmaceutical items incorporate rapamycin .

Microemulsion

Microemulsions have been utilized to expand the solvency of numerous medications that are basically insoluble in water, alongside consolidation of proteins for oral, parenteral, just as percutaneous/transdermal use³. A microemulsion is an optically clear pre-concentrate containing a blend of oil, hydrophilic surfactant and hydrophilic dissolvable which breaks up a severely water solvent medication. Upon contact with water, the plans immediately scatter (or 'self emulsifies') to shape an away from of exceedingly little and uniform oil beads containing the solubilized gravely solvent medication. Microemulsions are isotropic, thermodynamically stable straightforward (or translucent) frameworks of oil, water and surfactant, much of the time in blend with a co-surfactant with a bead size for the most part in the scope of 20-200 nm. These homogeneous frameworks, which can be set up over a wide scope of surfactant fixation and oil to water proportion, are on the whole liquids of low consistency. A selfmicroemulsifying drug conveyance framework (SMEDDS) is an anhydrous arrangement of microemulsions. It has likewise been alluded to as microemulsion pre-concentrate by certain specialists. It is made out of oil, surfactant and cosurfactant and can shape o/w microemulsion when scattered in fluid stage under delicate disturbance. The fomentation required for

the self-emulsification originates from stomach and intestinal motility. The surfactant can be non-ionic like polyoxyethylene surfactants for example Brij or sugar esters like sorbitanmonooleate (Range 80), cationic, or anionic like alkyltrimethylammonium bromide and sodium dodecyl sulfate, or zwitterionic, for example, phospholipids like lecithin (phosphatidylcholine) monetarily accessible from soybean and eggs. Lecithin is exceptionally well known in light of the fact that it displays astounding biocompatibility. Blends of ionic and non-ionic surfactants are additionally seen as compelling. The significant impediment of microemulsions is their high grouping of surfactant/cosurfactant, making them inadmissible for IV organization. Weakening of microemulsions underneath the basic micelle centralization of the surfactants could cause precipitation of the medication; in any case, the fine molecule size of the subsequent encourage would even now upgrade assimilation. Contrasted with macroemulsion pre-concentrates, microemulsionpreconcentrates remain optically clear after weakening and generally contain a higher measure of water dissolvable surfactant and a higher substance of a hydrophilic dissolvable. These definitions are just directed orally because of the idea of the excipients. Solubilization utilizing microemulsion pre-concentrates is fit to seriously solvent lipophilic aggravates that have high dissolvability in the oil and surfactants blends. Most self-emulsifying frameworks are constrained to organization in lipid-filled delicate or hard-shelled gelatin cases because of the fluid idea of the item⁷. Association between the container shell and the emulsion ought to be thought of in order to keep the hygroscopic substance from getting dried out or moving into the case shell. Emulsion bead size is a central point affecting bioavailability of medications from emulsionformulations, with little bead radii improving the plasma levels of medications, partially because of direct lymphatic take-up. Since SMEDDS contain high convergence of surfactants, they ought to be restricted to oral applications and may not be fitting for long haul use because of the capability of causing the runs.

Microemulsion product

Instances of seriously solvent exacerbates that utilization miniaturized scale emulsion pre-concentrates are the HIV protease inhibitor tipranavir (Aptivus® cases, Boehringer IngelheimGmbH) and the classification characterizing immunosuppressant cyclosporine A, USP altered (Neoral® containers, Novartis AG)⁸.

Micellar solubilization

The utilization of surfactants to improve the disintegration execution of severely solvent medication items has likewise been effectively utilized. Surfactants can bring down surface pressure and improve the disintegration of lipophilic medications in watery mediumThey can likewise be utilized to balance out medication suspensions. At the point when the grouping of surfactants surpasses their basic micelle fixation (CMC, which is in the scope of 0.05-0.10% for most surfactants), micelle development happens, entangling the medications inside the micelles. This procedure is known as micellisation and by and large outcomes in upgraded solvency of seriously solvent medications. Regularly utilized non-ionic surfactants incorporate polysorbates, polyoxy ethylated castor oil, polyoxyethylated glycerides, lauroylmacroglycerides and mono-and di-unsaturated fat esters of low atomic weight polyethylene glycols. Surfactants are likewise frequently used to balance out microemulsions and suspensions into which medications are dissolved. Micellar solubilization is a generally utilized option for the disintegration of seriously solvent medications.⁹

Complexation

Complexation of medications with cyclodextrins has been utilized to improve fluid dissolvability and medication steadiness. Cyclodextrins of pharmaceutical importance contain 6, 7 or 8 dextrose atoms (α , β , γ -cyclodextrin) bound in a 1,4-setup to frame rings of different distances across. The ring has a hydrophilic outside and lipophilic centre in which properly measured natural atoms can shape noncovalent incorporation edifices bringing about amplified watery solvency and concoction stability.⁵⁶ Subordinates of β -cyclodextrin with expanded water dissolvability (for example hydroxypropyl- β -cyclodextrin HP- β -Compact disc) are most

ordinarily utilized in pharmaceutical definition. Cyclodextrin edifices have been appeared to expand the solidness, wettability and disintegration of the lipophilic creepy crawly repellent N, N-diethyl-m-toluamide (DEET) and the soundness and photostability of sunscreens¹⁰. Cyclodextrins are huge particles, with sub-atomic loads more prominent than 1000Da, in this way it would be normal that they would not promptly saturate the skin. Complexation with cyclodextrins has been differently answered to both increment and lessening skin penetration. In an ongoing audit of the accessible information, Loftsson and Masson inferred that the impact on skin infiltration might be identified with cyclodextrin focus, with diminished transition commonly saw at generally high cyclodextrin fixations, while low cyclodextrin focuses bringing about expanded motion. As motion is relative to the free medication fixation, where the cyclodextrin focus is adequate to complex just the medication which is in abundance of its solvency, an expansion in motion may be normal. In any case, at higher cyclodextrin focus, the abundance cyclodextrin would be relied upon to complex free medication and henceforth diminish transition. Skin infiltration upgrade has additionally been credited to extraction of layer corneum lipids by cyclodextrins. Given that most analyses that have announced cyclodextrin interceded transition improvement have utilized rat model films in which lipid extraction is impressively simpler than human skin, the infiltration upgrade of cyclodextrin complexation might be an overestimate. Shaker and partners as of late inferred that complexation with HP- β -Cd had no impact on the motion of cortisone through smooth mouse skin by both of the proposed mechanisms¹¹.

Lipophilic medication cyclodextrin buildings, regularly known as consideration edifices, can be framed just by gathering the medication and excipient into a single unit, bringing about improved medication solubilization. Cyclodextrins (Album) are a gathering of basically related cyclic oligosaccharides that have a polar pit and hydrophilic outer surface. Cyclodextrins comprising of 6, 7 and 8 D-glycopyranosyl units associated with α - 1, 4

glycosidic linkages are known as α , β , γ , cyclodextrins⁶⁹, respectively. Hydrophilic cyclodextrins are nontoxic in ordinary portions while lipophilic ones might be poisonous; thus, methyl, hydroxypropyl, sulfoalkylated and sulfated subsidiaries of characteristic cyclodextrins that have improved fluid dissolvability are favored for pharmaceutical use. The solvency upgrade application, CDs can likewise be utilized as film vulnerable enhancer and balancing out operators. The vulnerable through natural layer is improved by the nearness of cyclodextrins. Masson announced about the penetration improvement property of severely water dissolvable medications in nearness of the CDs. These goes about as pervasion enhancers via bringing the medication through the watery obstruction which exists before the lipophilic surface of natural layers. This can likewise be accomplished through the twofold qualities of the CDs, subsequently present character a lot of lipophilic as hydrophilic. Albums can likewise be utilized as nasal pervasion enhancers acting by communication with nasal epithelium by altering tight intersection and lipid and protein substance of the layer, which upgrades the penetration of the film. CDs can likewise be used as penetration enhancer in pneumatic medication conveyance frameworks. Rifampicin is an alleged focus subordinate anti-toxin, the rate and degree of bacterial murder is identified with the fulfilment of high greatest fixation comparative with the negligible inhibitory fixation. The rifampicin-CDc consideration compound can improve the lung transport of medication when nebulized with good aspiratory affidavit and accomplish required centralization of medication in broncho-alveolar epithelium lining-liquid when regulated as aerosolized arrangement. The powers driving complexation were credited to (I) the prohibition of high vitality water from the cavity, (ii) the arrival of ring strain especially on account of α - Album, (iii) Vander dividers collaborations, and (iv) hydrogen and hydrophobic bindings. Solubilization by complexation is accomplished through explicit association as opposed to changes in the mass dissolvable properties as in other solubilizing framework, for example, cosolvents, emulsion and pH modifications. The separation is extremely

quick, quantitative and accordingly unsurprising. Another noteworthy favourable position of complexation process is that some ordinarily utilized complexing operators, for example, hydroxy propyl beta cyclodextrin and sulfobutyl beta cyclodextrin are less harmful contrasted with other solubilizing specialists, for example, surfactant and cosolvents. Since most edifices shaped is 1:1 buildings of the AL type, the weakening of edifices won't bring about arrangement which is very immersed concerning substrate. This can be significant for insoluble intensifies that may encourage upon infusion when solubilized by other framework, for example, cosolvents. In spite of all the alluring bit of leeway of complexation, there are detriments. Most importantly the compound must have the option to frame edifices with chose ligand. For mixes with restricted dissolvability to begin with, solvency improvement can be extremely constrained. The subsequent confinement is the buildings of Ap type, weakening of framework may at present outcome in precipitation. This is additionally valid for solubilization by means of joined procedure, for example, complexation with pH change. In conclusion the potential harmfulness issue, administrative and quality control issue identified with nearness of ligand may add entanglement and cost to the improvement procedure.

Supercritical fluid (SCF) process

The quantity of uses and innovations including supercritical liquids has additionally developed violently. It has been known for over a century that supercritical liquids (SCFs) can disintegrate non-volatile solvents, with the basic purpose of carbon dioxide, the most broadly utilized supercritical liquid. It is protected, naturally agreeable, and prudent. The low working conditions (temperature and weight) make SCFs alluring for pharmaceutical research (MarkkuRantakyla *et al.*, 2004). A SCF exists as a solitary stage over its basic temperature (T_c) and weight (P_c). SCFs have properties valuable to item handling since they are middle between those of unadulterated fluid and gas (i.e., fluid like thickness, gas-like compressibility and consistency and higher diffusivity than fluids). In addition, the thickness, transport properties, (for example, consistency and diffusivity), and other

physical properties, (for example, dielectric steady and extremity) fluctuate impressively with little changes in working temperature, pressure, or both around the basic points. Hence, it is conceivable to adjust a special mix of properties important for an ideal application. These extraordinary handling abilities of SCFs, since quite a while ago perceived and applied in the food business, have as of late been adjusted to pharmaceutical applications. Regularly utilized supercritical solvents incorporate carbon dioxide, nitrous oxide, ethylene, propylene, propane, pentane, ethanol, smelling salts, and water. When the medication particles are solubilised inside SCF, they might be recrystallised at enormously decreased molecule sizes. The adaptability and exactness offered by SCF forms permits micronisation of medication particles inside limited scopes of molecule size, frequently to sub-micron levels. Current SCF forms have exhibited the capacity to make nanosuspensions of particles 5-2,000nm in distance across. A few pharmaceutical organizations, for example, Nektar Therapeutics and Lavipharm, are spend significant time in molecule designing by means of SCF innovations for molecule size decrease and dissolvability improvement¹⁴. A few process of SCF handling have been created to address singular parts of these weaknesses, for example, precipitation with packed antisolvents process (PCA), Quick Extension of Supercritical Arrangements, Gas Antisolvent Recrystallisation, Precipitation with Compacted Liquid Antisolvent, Impregnation or imbue of polymers with bioactive materials, Arrangement improved Scattering by Supercritical Liquid, arrangement upgraded scattering by SCF (SEDS), supercritical antisolvents forms (SAS) and airborne supercritical extraction framework (ASES).

Solid dispersion

SCF process can be applied to the readiness of dissolvable free strong scattering measurement structures to improve the solubility of severely solvent mixes. Conventional process experience the ill effects of the utilization of mechanical powers and overabundance natural solvents. In this procedure, a severely solvent medication is scattered in an exceptionally dissolvable strong hydrophilic network, which improves the disintegration of the medication. Strong scattering

process can yield eutectic (non sub-atomic level blending) or strong arrangement (sub-atomic level blending) items. A strong scattering of carbamazepine in polyethylene glycol 4000 (PEG-4000) amplified the rate and degree of disintegration of carbamazepine. In this procedure, a precipitation vessel was stacked with arrangement of carbamazepine and PEG4000 in CH₃)₂CO, which was extended with supercritical CO₂ from the base of the vessel to acquire dissolvable free particles. Strong scatterings are set up by utilizing a few process, for example, the combination (liquefy) process and the dissolvable procedure. A strong scattering of griseofulvin and polyethylene glycol 8000 (Gris-PEG®) is financially accessible. Notwithstanding the promising parts of disintegration upgrade and straightforwardness of idea, the strong scattering process has neglected to pick up prominence because of assembling, dependability and scale-up issues.¹⁵

Hydrotrophy

Hydrotrophy is a solubilisation procedure whereby expansion of a lot of second solute brings about an increment in the fluid dissolvability of another solute. Solute comprises of soluble base metal salts of different natural acids. Hydrotropic operators are ionic natural salts. Added substances or salts that expansion dissolvability in given dissolvable are said to "salt in" the solute and those salts that decline solvency "salt out" the solute. A few salts with huge anions or cations that are themselves dissolvable in water bring about "salting in" of non-electrolytes called "hydrotropic salts" a marvel known as "hydrotropism". Hydrotropic arrangements don't show colloidal properties and include a frail collaboration between the hydrotropic specialist and solute. Hydrotrophy assign the expansion in solvency in water because of the nearness of enormous measure of added substances. The system by which it improves dissolvability is all the more firmly identified with complexation including a powerless cooperation between the hydrotropic specialists like sodium benzoate, sodium acetic acid derivation, sodium alginate, urea and the seriously solvent medications.

The hydrotropes are known to self-gather in solution. The order of hydrotropes based on atomic structure is troublesome, since a wide

assortment of mixes have been accounted for to show hydrotropic conduct. Explicit models may incorporate ethanol, fragrant alcohols like resorcinol, pyrogallol, catechol, and b-naphthol's and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulfate) and dodecylatedoxybenzone. The sweet-smelling hydrotropes with anionic head bunches are for the most part examined mixes. They are huge in number in view of isomerism and their viable hydrotrope activity might be because of the accessibility of intuitive orbitals. Hydrotropes with cationic hydrophilic gathering are uncommon, for example salts of fragrant amines, for example, procaine hydrochloride. Other than improving the solubilization of mixes in water, they are known to show effects on surfactant collection prompting micelle arrangement, stage indication of multicomponent frameworks regarding nanodispersions and conductance permeation, blurring of surfactants and polymers, and so forth. Different process that upgrade the dissolvability of seriously water dissolvable medications incorporate salt development, change in dielectric consistent of dissolvable, Substance adjustment of the medication, utilization of hydrates or solvates, utilization of Solvent prodrug, Use of ultrasonic waves, circular crystallization¹⁶.

Conclusion

By this article we reason that, solvency of the medication is the most significant factor that controls the detailing of the medication just as remedial viability of the medication, consequently the most basic factor in the definition improvement. Disintegration of medication is the rate deciding advance for oral assimilation of the severely water dissolvable medications and dissolvability is likewise the essential prerequisite for the plan and improvement of various dose type of various medications. The different process portrayed above alone or in mix can be utilized to upgrade the dissolvability of the medication. Solvency can be upgraded by numerous process and number of folds increment in dissolvability. As a result of solvency issue of numerous medications, the bioavailability of them gets influenced and henceforth dissolvability upgrade gets essential. It is currently conceivable that to

expand the solvency of gravely dissolvable medications with the assistance of different process as referenced previously.

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