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RECENT DEVELOPMENT AND ACHIEVEMENTS IN SOLUBILITY AND DISSOLUTION ENHANCEMENT OF ITRACONAZOLE: A REVIEW

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Itraconazole, solubility, solid dispersion, hot melt extrusion, cocrystals, Nanosuspensions

Abbreviations
ITRA: Itraconazole; **CO_2:** Carbon dioxide; **HPMC:** Hydroxypropyl methylcellulose; **CAP:** Cellulose acetate phthalate

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ABSTRACT: A drug should be available in accessible in disintegrated state before producing its therapeutic effect however; in current market more than 40%, drugs are poorly soluble in water. In view of their low aqueous solubility, those new chemical entities fail to reach market in spite of revealing potential pharmacodynamics activities. Poorly aqueous soluble drugs are connected with moderate drug absorption leading inevitably to insufficient and variable bioavailability. Consequently, different methodologies have been grasped for solubility and dissolution enhancement of poorly water-soluble drugs thus bioavailability. Solubility assumes a paramount part in attaining the desired plasma drug concentration. In this review article, different techniques like solid dispersion using hot stage extrusion, freeze-drying, spray drying, and hot melt extrusion also nano suspensions, dried emulsions were discussed for solubility and dissolution rate improvement of BCS class II antifungal drug Itraconazole. Amongst various method described in this review, solid dispersion was found to be most preferred technique by researcher as it provide ease in preparation and efficiency in terms of resolving the solubility and dissolution problems associated with Itraconazole.

INTRODUCTION: New chemical entities (NCEs) are novel drugs or active pharmaceutical ingredients (APIs) entering the drug discovery pipeline due to technological innovation and pressure of competition. NCEs were initiated in the mid-1990s by a combination of combinatorial chemistry and high throughput screening rather than wet chemistry [1-4].

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Oral bioavailability of drugs is contingent on its solubility and/or dissolution rate, hence major problems allied with these drugs was its very low solubility in biological fluids, which results into poor bioavailability after oral administration [5-9].

Poorly water-soluble drugs are associated with slow drug absorption leading ultimately to insufficient and variable bioavailability. Up to 50% of orally administered drugs suffer from formulation problems allied to their high lipophilicity [10]. Because of their low aqueous solubility, up to 40% of new chemical entities fail to reach market despite revealing potential pharmacodynamics activities.

Poor aqueous solubility of drugs is an industry wide bigger challenge in front of pharmaceutical scientists [11-14]. Consequently, lots of efforts partake to increase dissolution of drug. Different approaches to enhance the dissolution rate of poorly soluble drugs include, particle size reduction, inclusion complexation with cyclodextrins, chemical modification, pH adjustment, solid dispersion, [15-16] complexation, co-solvency, salt formation, micellar solubilization and Hydrotrophy [17-19].

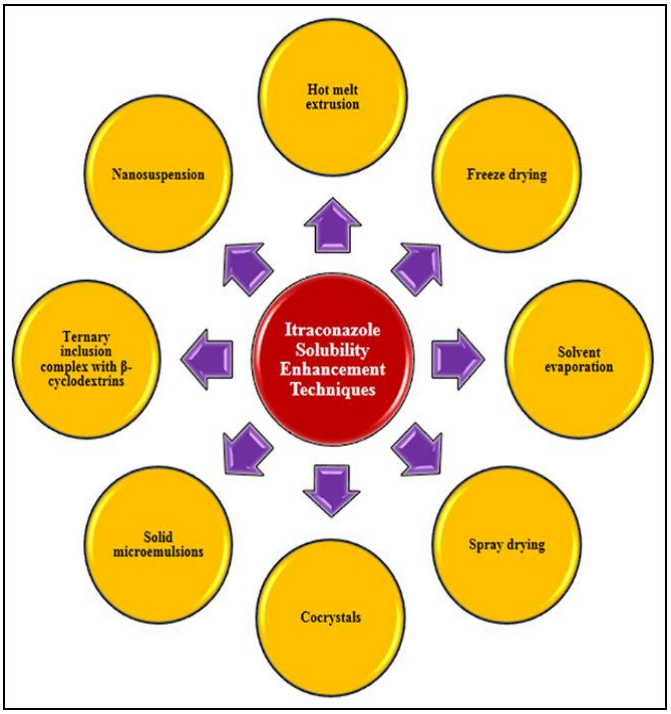

FIGURE 1: ITRA SOLUBILITY ENHANCEMENT TECHNIQUES

This review has been readied to give a concise thought regarding different strategies embraced for solubility and dissolution improvisation of Itraconazole and finally development of an appropriate oral dosage forms.

Itraconazole (ITRA) is a potent broad-spectrum triazole antifungal drug with activity against blastomycosis, histoplasmosis and onchomycosis. It is a weakly basic compound (pKa=3.7) which can only be ionized at low pH such as in gastric juice with a very poor aqueous solubility. It is also very lipophilic with an octanol/water log partition coefficient of 5.66 at a pH of 8.1. The drug has a pH dependent dissolution resulting in low and variable oral absorption.

Based on the biopharmaceuticals classification system, ITRA is thus an extreme example of class II compounds meaning that its oral bioavailability was determined by dissolution rate in the GI tract. In addition, the drug undergoes extensive hepatic metabolism. The factors resulted in a low and variable oral bioavailability [20, 21]. ITRA is a synthetic antifungal agent and a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs), each possessing three chiral centers. It has a molecular formula of $C_{35}H_{38}C_{12}N_8O_4$ and a molecular weight of 705.64. The solubility of ITRA in water is less than 1 µg/ml. It is a white to slightly yellowish powder, practically insoluble in water, very slight soluble in alcohols and freely soluble in dichloromethane (239 mg/ml) [22].

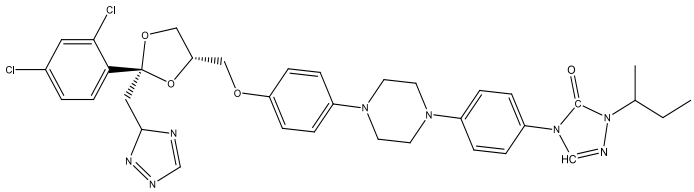

FIGURE 2: CHEMICAL STRUCTURE OF ITRACONAZOLE

This review escapes examination of fundamental insights about solubility such as definition and various methods used for solubility enhancement. We have directly concentrated on methods and results achieved by several scientists who worked in the area of solubility and dissolution rate enhancement thereby bioavailability of ITRA in last few years.

Solid Dispersion:

Hot Stage Extrusion: Verreck *et al* prepared solid dispersions of ITRA and polyvinylpyrrolidone-co-vinyl acetate 64 (PVP-VA 64) by consolidating pressurized CO_2 with hot stage extrusion and assessed the capacity of the pressurized gas to go about as an interim plasticizer and additionally to handle a frothed extrudates. The physical mixture was breastfed with a K-Tron loss-in weight feeder framework. Pressurized carbon dioxide was injected through Leistritz Micro 18 intermeshing co-rotating twin-screw melt extruder using an ISCO 260D-syringe pump. The physicochemical attributes of the extrudates with and without infusion of CO_2 with reference to the morphology of the strong scattering and disintegration conduct

and molecule properties were assessed. CO_2 acted as plasticizer for ITRA / PVP-VA 64, reducing the processing temperature throughout the hot stage extrusion process. Amorphous dispersion was obtained and the CO_2 did not influence the solid dispersion. The dissolution was evaluated utilizing simulated gastric fluid without pepsin (SGF) at 37ºc in dissolution apparatus with a paddle rotating at 100 rpm (USP II apparatus).The parameters as temperature and pressure during the hot stage extrusion process controlled the dissolution of ITRA.

The extrudates readied with Co_2 infusion uncovered a more level introductory disintegration in the initial 5 min because of molecule agglomeration. After 5–10 min, dissolution rate was tantamount for extrudates with and without CO_2 injection. The macroscopic morphology found changed to a foam-like structure due to expansion of the CO_2 at the extrusion die, which prompt in an expanded particular surface range, porosity, and hygroscopicity. This is leeway, since further down-stream handling was improved, that is processing of the extrudates was enhanced [23].

Janssens *et al* reported Kollicoat IR® as a carrier in solid dispersions of Itraconazole. The glassy Itraconazole was prepared by melting crystalline ITRA at 180ºC in an oven emulated by prompt cooling to room temperature. The product was subsequently milled and sieved (< 355µm), this was further used in preparation of solid dispersion by hot stage extrusion. The miscibility of the medication and the transporter had done by adjusted temperature differential examining calorimetry and X-beam powder diffraction innovation.

In the X-ray diffractograms, no ITRA peaks were visible; the polymer, on the other hand, appeared to be semi-crystalline. Modulated temperature differential scanning calorimetry analysis showed that the drug and the polymer formed a two-phase system. Divide bunches of glassy ITRA were present for drug loads of 40% or higher, representing further phase separation. The USP 24 method II (paddle method) dissolution apparatus used for the study of pharmaceutical execution. Dissolution test performed in triplicate using simulated gastric fluid without pepsin (SGFsp). Dissolution measurements confirmed a significantly increased dissolution rate for the solid dispersions compared to physical mixtures. Astoundingly, the physical mixture made up of glassy ITRA and Kollicoat IR® (20/80, w/w) uncovered a dissolution rate and most extreme that was much higher than that of the physical mixture made up of crystalline ITRA and that of immaculate glassy ITRA. The result of their study shows that Kollicoat IR® is a guaranteeing excipient for the formulation of solid dispersions of ITRA prepared by hot stage extrusion [24].

Verreck *et al* prepared solid dispersions of ITRA and ethylcellulose 20 cps (EC 20 cps) by combining pressurized CO_2 with hot stage extrusion. Physical mixtures of ITRA and EC 20 cps in a ratio 10 and 40% (w/w) ITRA respectively were readied by mixing both components in a planetary blender for 10 min at a mixing speed of 20 rpm. The physical mixture was fed with a K-Tron loss-in-weight feeder system. CO_2 was pressurized and injected into the extruder using an ISCO 260 D syringe pump, operating at a constant pressure. They have utilized CO_2 as liquid from a gas cylinder with a dip tube and cooled to 1.5ºc with a spiral tube in a cooling bath.

Prior to analysis, a lab scale mill was used for milling of melt-extruded samples for 30 sec; the fraction beneath1000µm was characterized further. The capability of the pressurized gas to go about as a reversible plasticizer and to process a frothed extrudate was checked. The evaluation the physicochemical characteristics of the extrudates with and without injection of CO_2 with reference to the morphology of the solid dispersion, release characteristics of the drug, and particle properties.

The modulated differential scanning calorimetry (MDSC) was performed using a TA Instruments modulated DSC Q1000 differential scanning calorimeter and thermal analysis controller to determine the thermal properties of the extrudates before and after injection of CO_2. Drug content was analyzed using HPLC dissection. UV detection at a wavelength of 224 nm used for concentration determination. The dissolution testing using simulated gastric fluid without pepsin (SGF) at 37ºC in dissolution apparatus with a paddle rotating at 100 rpm (USP II apparatus).

The Leica MZ6 modular stereomicroscope used for macroscopic morphology of the extrudates. It was revealed that the macroscopic morphology changed to a foam-like structure due to expansion of the CO_2 at the extrusion die. This was lead to in improved specific surface area and porosity and consequently milling efficiency found improved [25].

Solvent evaporation and freeze-drying: Engers *et al* depicted solid-state approach to increase bioavailability of ITRA by preparing solid dispersions. ITRA used as a model crystalline compound displaying poor aqueous solubility and low bioavailability. Solid dispersions were prepared with different polymers (PVP K-12, K29/32, K90; PVP VA S-630; HPMC-P 55; and HPMC-AS HG) at varied concentrations (1:5, 1:2, 2:1, 5:1 by weight) using two preparation methods (solvent evaporation and freeze drying). Physical characterization and stability data gathered to examine recommended storage, handling, and manufacturing conditions.

Based on generated data they have selected a 1:2 (w/w) ITRA / HPMC-P dispersion selected for further characterization, testing, and scale-up. Thermal data and computational analysis suggest that it is a possible solid nanosuspension. The dispersion was successfully scaled using spray drying, with the materials exhibiting similar physical properties as the screening samples. The contrasted crystalline ITRA in a capsule with simple formulation of 1:2 (w/w) ITRA / HPMC-P dispersion in a capsule in a dog bioavailability study, with the dispersion being significantly more bioavailable. Their study demonstrated the utility of utilizing a nebulous strong structure with attractive physical legitimate ties significantly build bioavailability and gives a reasonable method to assessing early drug applicants [26].

Solvent evaporation: Maghraby *et al* adopted solvent evaporation method for ITRA solid dispersion preparation. The impact of joining of Pluronic F68 as a ternary segment in solid dispersions of ITRA with hydroxypropyl-methylcellulose (HPMC) on the dissolution rate of ITRA was studied. They have dissolved ITRA and the HPMC in methylene chloride/ethanol (8:2) and the organic solvent removed at ambient temperature, under reduced pressure. Then, lessened the resulting powder through a 355µm sieve. Binary solid dispersions with HPMC, reduced the drug crystallinity, increased the equilibrium solubility but showed slow dissolution. Binary dispersions with Pluronic produced eutectic systems but the increment in solubility and dissolution was lower than that of HPMC systems. The drug content was determined to evaluate the homogeneity of dissemination of the drug in the binary and ternary solid dispersion. The results revealed drug content values in the range of 95.8 to 104 % w/w indicating homogenous distribution of the drug in the prepared mixtures.

The dissolution experiments carried on the binary and ternary dispersions and the corresponding physical mixtures. The tests employed the USP XXIV method II (paddle method) dissolution apparatus. The dissolution medium was 0.1 N HCl (pH 1.2) maintained at a temperature of 37°c with a paddle speed of 100 rpm. The comparison of the results of formulation to the dissolution data of the marketed formulation (Sporanox capsule) had done. The study presented a surfactant containing ternary system, which showed synergistic effect on the dissolution of ITRA with a potential of improving the bioavailability of the drug by enhancing its dissolution with a possible reduction in the presystemic disposition.

Ternary system comprising optimum proportions of drug with Pluronic and HPMC enhanced the dissolution rate demonstrating dissolution efficiency comparable to that obtained with the marketed product of ITRA. Their study hence introduced a framework equipped for expanding the dissolution rate of ITRA with a potential for increased oral bioavailability by inhibiting its pre-systemic metabolism as well [21].

Spray drying and film casting: Janssens *et al* planned solid dispersion of ITRA and Eudragit E100 via spray drying and film casting to assess the impact the influence of the solvent drying rate. The drug / polymer experimental miscibility level studied using XRPD, MDSC, FT-IR, HPLC and TGA. The evaluation of solubility and miscibility had done using the Flory-Huggins mixing theory and experimental drug in monomer solubility data, and the same value compared with the theoretical crystalline drug solubility in the amorphous

polymer and the miscibility of the amorphous drug in the amorphous polymer. The experimental miscibility level found to be 27.5% w/w for spray-dried and 15% for film casted solid dispersions. FT-IR estimations affirmed the unlucky deficiency of saturable connections like hydrogen bonds, and investigation of the blended glass move temperatures prescribed low grip drives in the amorphous mixture. The solubility analysis rendered a positive FH interaction parameter, a crystalline solubility of approximately 0.012% w/w and an amorphous drug-polymer miscibility of roughly 7.07% w/w. The solid dispersions found significantly supersaturated as for both crystalline solubility and amorphous miscibility demonstrating the influence of manufacturing methodology [27].

Freeze-drying: Dinunzio *et al* reported utilization of cellulose acetate phthalate (CAP) and polyvinyl acetate phthalate (PVAP) as a potential concentration enhancing polymer for preparation of solid dispersion of ITRA using ultra-freeze drying technique. The samples of engineered particles prepared using a thin film freeing technique. Measured quantities of ITRA and enteric polymer (CAP or PVAP) were dissolved in 1, 4-dioxane to produce a 1% w/v solution and then slowly fed as discrete droplets on top of an ice-cold rotating drum maintained at approximately -60°c. A scrubber razor sharp edge, collected, and dried using a lyophilizer took the frozen material from the drum.

X-ray diffraction analyses of engineered particle compositions showing amorphous nature. Modulated DSC demonstrated that ITRA: CAP engineered particle compositions exhibited a strong correlation with the Gordon-Taylor relationship while ITRA: PVAP formulations exhibited positive deviations from predicted values attributed to hydrogen bonding interactions between the drug and polymer.

SEM imaging of the particles confirmed that the material occurred in two general forms, discrete particles of approximately 5 μm and larger aggregates in excess of 30 μm, with engineered particle compositions devising approximately 15 times higher measured specific surfaces areas compared to micronized ITRA.

The supersaturated dissolution testing based on the USP *XXIX* method A enteric dissolution test using a VK 7010 dissolution apparatus operating at 50 rpm paddle speed and VK 8000 auto sampler 0.1 N HCl used as dissolution media. In vitro supersaturated dissolution results revealed that all compositions provided show lower levels of super saturation in acidic media and greater extents of super saturation in neutral media compared to Sporanox pellets. They have used 1:2 (ITRA:CAP) engineered particle compositions because that presented superior *in vitro* performance compared to all other and it was selected for *in vivo* testing.

The experimental data showed the stabilization mechanism was due to interactions between the drug and polymer, predominantly attributed to steric hindrance resulting from the molecular weight of the polymer chain and chemical composition of the polymer backbone relative to position of hydrogen bonding sites. The *in vivo* testing in Sprague-Dawley rats (n=6) demonstrated a significant improvement in oral bioavailability from the 1:2 ITRA: CAP (AUC) 4,516 ±1,949 ng. h/mL) compared to the Sporanox pellets (AUC) 2,132 ± 1,273 ng.h/mL).

Moreover, the more rapid onset of action indicated superior targeting of the upper small intestines, and the prolonged half-life suggested the utility of CAP to retain supersaturated concentrations, *in vivo*. Their results demonstrated that amorphous compositions of ITRA and enteric concentration enhancing polymers provided improved bioavailability due to better intestinal targeting and amplified durations of supersaturation [28].

Cocrystals: Ober *et al* prepared cocrystals of ITRA, by dissolving ITRA (250 mg) and L-malic acid (250 mg) in 10 mL THF using adequate stirring and heat. The filtered the solution through a 0.2μm size nylon filter to remove any undissolved material. Further N-heptane (50 mL) was added drop wise to the solution, with continuous stirring, to induce cocrystal precipitation. The suspension centrifuged and the supernatant discarded. The same process carried out for an additional three times to ensure full removal of the THF. The THF was then removed and the cocrystals dried by flushing with excess supercritical CO_2. The cocrystals dried overnight.

The ITRA / L-malic acid cocrystals prepared by GAS cocrystallization were compared to those produced using a traditional liquid antisolvent, n-heptane, for crystallinity, thermal behavior, size and surface morphology, composition, and dissolution rate. X-ray diffraction and differential scanning calorimetry analyses showed that an ITRA / L-malic acid cocrystal could be produced using either CO_2 as an antisolvent in the GAS technique or a traditional liquid antisolvent, n-heptane, but with some content of uncocrystallized amorphous material also being present. The cocrystal powder produced by GAS cocrystallization had slightly larger particles than those precipitated with n-heptane, their microporous structure and amorphous content allowed for enhanced dissolution.

Their results indicated cocrystallization of ITRA with L-malic acid using CO_2 as an antisolvent is a feasible means of increasing ITRA dissolution while reducing solvent use in favour of environmentally benign CO_2. The amount of ITRA in solution measured at pressures of 0, 21, 41, 62, 83, and 103 bar and in the presence of L-malic acid. Both cocrystals exhibit improved dissolution compared to the supplier ITRA due to both the presence of amorphous ITRA and the intimate association of ITRA with the water-soluble former, L-malic acid, to form a cocrystal structure. Despite the cocrystals produced by GAS cocrystallization being slightly larger than those were produce from n-heptane, they had improved dissolution attributed to their microporous structure [29].

Solid solution: Kapsi *et al* reported solid solutions of ITRA by melting polyethylene glycol (PEG) in a beaker upto 60-70ºc and then temperature was raised to 120°c. ITRA further added in small quantities until it dissolved with the formation of a clear solution. This hot solution then rapidly cooled by dipping the beaker in ice-cold water, prominent to rapid solidification of PEG, formed a solid solution. The cooled, solid solution was then grind into granules of different sizes. This solid solution shows improved dissolution and improved bioavailability. Influence of processing factors on drug and carrier properties in solid solution and consequently on drug dissolution behaviour also studied.

The comparison had done for optimized solid solution formulation with marketed product in healthy human subjects under fasted and fed conditions for bioequivalency. Solid solutions of lower drug concentration dissolved at a faster rate, and drug dissolution improved significantly with increasing molecular weight of PEG. Initial treatment of ITRA with the wetting agent/cosolvent glycerol prior to making ITRA into solid solution improved drug dissolution also reduced the PEG amount required to dissolve drug to form solid solution.

Addition of a polymer such as HPMC to the solid solution eliminated precipitation of drug following dissolution. As the granule size of the solid solution reduces, precipitation of drug during dissolution became prominent. Branched PEG 20000 resulted in a faster drug dissolution rate than from linear PEG 20000.The bioavailability comparison of solid solution formulation with marketed product in human volunteers showed these two products to be not bioequivalent [30].

Solid Microemulsions: Choi *et al* worked on solubility and bioavailability enhancement of ITRA by a combined use of membrane emulsification and spray drying solidification technique. The shirasu-porous-glass (SPG) membrane with a mean pore size of 2.5µm to produce monodispersed microemulsions of ITRA consisting of methylene chloride as the dispersed phase, a mixture of Transcutol HP and Span 20 as a stabilizer, and dextran as solid carrier dissolved in water as the continuous phase.

The dispersed phase permeated through the SPG membrane into the continuous phase at an agitator speed of 150 rpm, a feed pressure of 15 kPa and a continuous phase temperature of 25ºc. The resultant emulsion was solidified using spray-drying, the liquid emulsion pre-warmed to 60ºc was delivered to the nozzle (0.7 mm diameter) at a flow rate of 5 ml/min using a peristaltic pump and spray-dried at 130ºc inlet temperature and 75–80ºc outlet temperature. Solid-state characterizations of the solid emulsion showed that the crystal state of ITRA in solid emulsion found conversion from crystalline to amorphous form. The dissolution profiles of ITRA powder and ITRA -loaded solid emulsion in water.

The accurately weighed samples equivalent to 100 mg of ITRA were filled in size 0 gelatin capsules. The dissolution test performed at 36.5ºc using the basket method at 100 rpm with 900 ml water as the dissolution medium. The solid emulsion of ITRA displayed a significant increase in the dissolution rate than that of pure ITRA. Furthermore, the solid emulsion after oral administration give about eight-fold higher AUC and about ten-fold higher C_{max} in rats than pure ITRA powder ($p < 0.05$), indicating this formulation greatly improved the oral bioavailability of drug in rats. Thus, their results demonstrated that a promising technique to develop solid formulation of ITRA with enhanced solubility and bioavailability by the SPG membrane emulsification system combined with spray-drying technique [31].

Ternary inclusion complex with β-cyclodextrins: Taupitz *et al* prepared binary inclusion complexes of ITRA with 2-Hydroxypropyl-β-cyclodextrin (HP-β-CD) and sulfobuthyl-ether- β -cyclodextrin sodium (SBE-β-CD) which is commonly used cyclodextrin derivatives and a recently announced hydroxybutenyl-β cyclodextrin (HBen-β-CD). They have used optimal ITRA / cyclodextrin ratio is 1:2 for all β–CD derivatives used in their study. Ternary complexes were made by combining Soluplus® with the with the CD complexes. The molar ratio for preparing the ternary complexes was 1:2:0.005, (ITRA / CD derivative / Soluplus®). They compared solubility and dissolution behaviour with that of the pure drug and the marketed formulation Sporanox. Ternary complexes were prepared by addition of Soluplus®, a new highly water-soluble polymer, during the formation of the ITRA / CD complex.

The solid dispersion made of ITRA and Soluplus® for the study as a control. Solid-state analysis performed for all formulations and for pure ITRA using powder X-ray diffraction (pX-RD) and differential scanning calorimetry (DSC). They have carried out dissolution tests with simulated gastric fluid without pepsin (SGFsp) pH 1.2 and acetate buffer pH 5.0 to simulate pH conditions of a healthy and a hypoacidic stomach, respectively. Solubility tests indicated that with all formulation approaches, the aqueous solubility of itraconazole formed with hydroxypropyl-β-cyclodextrin (HP-β-CD) or hydroxybutenyl-β-cyclodextrin (HBen-β-CD) and Soluplus® proved to be the most favorable formulation approaches. Though the marketed formulation and the pure drug showed very poor dissolution, both of these ternary inclusion complexes resulted in fast and extensive release of ITRA in all test media, which they have evaluated. Using the results of the dissolution experiments, a newly developed physiologically based pharmacokinetic (PBPK) *in silico* model applied to compare the *in vivo* performance of Sporanox® with the predicted performance of the most promising ternary complexes from the in vitro studies.

The PBPK modelling predicted that the bioavailability of ITRA found increased after oral administration of ternary complex formulations, especially when ITRA is formulated as a ternary complex comprising HP-β-CD or HBen- β -CD and Soluplus® [32].

Hot melt extrusion:

Extruded films: Trey *et al* reported hot-melt extruded hydroxypropylcellulose (HPC) based films containing anti-fungal drug ITRA and α-tocopherol for the topical treatment for onychomycosis. The films were prepared from a blend of the components: 5wt. % α-tocopherol (vitamin E), 10wt. % ITRA, and 85 wt. % HPC. The screw speed was controlled to afford films with a size of 45 mm in width by 0.1 mm in thickness. XRD analysis of the powders and films done in order to determine the relative crystallinity. DSC and X-ray measurements did not show a crystalline ITRA phase indicating the drug is present in the amorphous state.

The drug quantification performed using a HPLC system consisting of a Waters 600 pump and a dual wavelength Waters 2487 UV detector. The drug release studies had done using a Hanson dissolution test system according to USP XXVIII Apparatus 5, paddle over disk method. 900 ml aqueous solution containing 0.5–1.0% SLS at 37°c used as dissolution media and the paddle rotation speed was 75 rpm. The rate of ITRA release trended directly with the degree of film hydration and inversely to the HPC molecular weight.

This results from a higher degree of crystallinity of the HPC films, which also changes the release kinetics from first order to zero order. Data from their studies indicated that the matrices produced via HME utilizing various Klucel® HPC grades can used for the controlled-release of poorly water-soluble drugs [33].

Solid dispersion: Dinunzio *et al* investigated KinetiSol® Dispersing (KSD) is a novel high energy manufacturing process for the production of pharmaceutical solid dispersions. They prepared solid dispersions of ITRA and hypromellose by KSD and compared to identical formulations produced by hot melt extrusion. The ITRA and hypromellose quantities were exactly weighed and premixed by hand in a polypropylene bag for 2 min. Materials were charged into the compounder at room temperatures and processed by both KSD and HME process to obtained solid dispersions. They have measured powder true densities by helium Pycnometry.

The material characterization done for solid-state properties by modulated differential scanning calorimetry and X-ray diffraction. Supersaturated dissolution testing performed based on the USP XXIX Apparatus II dissolution test using a VK 7010 dissolution apparatus. Dissolution behaviour studied under supersaturated conditions. Increased dissolution rates for compositions manufactured by KSD observed compared to HME processed material. Their Results showed that KSD was able to produce amorphous solid dispersions in fewer than 15s while production by HME required over 300s.

Dispersions produced by KSD exhibited single phase solid state behaviour indicated by a single glass transition temperature (Tg) whereas compositions produced by HME exhibited two Tgs. Near complete supersaturation was observed for solid dispersions produced by either manufacturing processes. Oral bioavailability was determined using a Sprague–Dawley rat model. Oral bioavailability from both processes showed enhanced AUC compared to crystalline ITRA. Based on the results presented from their studies, KSD shown to be a viable manufacturing process for the production of pharmaceutical solid dispersions, providing benefits over conventional techniques including enhanced mixing for improved homogeneity and reduced processing times [34].

Solid dispersion and Nanosuspension: Zhang *et al* investigated solid dispersion of soluplus-based carrier loading ITRA, prepared by HME and the ITRA nanosuspension prepared by wet milling. They have used a nano circulation-grinding machine. Before milling, 20 g ITRA dispersed in 200 ml 5% W/V HPC-L aqueous solution under magnetic stirring to form a coarse suspension. Then, the suspension was poured into the milling bowl and milled for 2 h with the rpm of 3500.

A high shear force generated during the milling process by the grinding media of yttrium-stabilized zirconium oxide beads (0.6–0.8 mm). For further characterization of the ITRA nanocrystals, the nanosuspension solidified by freeze-drying. The HME with twin-screw extruder TE-20 used for preparation of solid dispersion, with varying drug concentration in dispersion from 15%, 20%, 30%, 45% and 60% w/w. Their experiments proved truly to form nanocrystalline and amorphous ITRA characterized by differential scanning calorimetry (DSC), X-ray powder diffraction (XRD) analysis, Fourier transform infrared spectrum (FTIR), transmission electron microscope (TEM), and scanning electron microscope (SEM).

The release of ITRA / Soluplus solid dispersions with amorphous ITRA was almost complete while only 40% release obtained with ITRA nanocrystals. In the *in vivo* assay, the AUC (0–t) and C^{max} of ITRA / Soluplus were 6.9 and 11.6 time higher than those of pure ITRA. The formulation of the extrudate had an AUC (0–t) and C^{max} similar to those of ITRA also OH- ITRA compared with the commercial capsule (Sporanox®). The results of their study showed increased dissolution and bioavailability of the solid dispersion of soluplus-based carrier loading ITRA prepared by HME compared with the ITRA nanosuspension prepared by wet milling [35].

Solid dispersion: Verreck *et al* prepared solid dispersion using HME technology using ITRA and HPMC as a carrier. The solvent casting method used for selecting optimal ratio of ITRA and HPMC.

The physical mixture of ITRA and HPMC in a ratio 40:60 w/w was prepared by mixing both components in a planetary blender for 30 min. The hot melt extrusion performed with a corotating twin-screw extruder (APV MP19) and the design of experiments (DOE) approach used for HME process report. All parameter settings resulted in the formation of an amorphous solid dispersion whereby HPMC 2910 5mPa s prevents re-crystallization of the drug during cooling. Dissolution studies performed using a paddle rotating at 100 rpm (USP II apparatus).

Simulated gastric fluid (without pepsin) used as dissolution media at 37ºc. The concentration of ITRA quantified with UV at the maximum wavelength of 254 nm. Dissolution measurements demonstrated that a significantly increased dissolution rate obtained with the amorphous solid dispersion compared to the physical mixture. The outcome of DOE further indicated that melt extrusion is very robust with regard to the ITRA / HPMC melt extrudate characteristics. Stability studies demonstrated that the ITRA / HPMC 40/60 w/w milled melt extrudate formulation is chemically and physically stable for periods in excess of 6 months as indicated by the absence of degradation products or re-crystallization of the drug. Based on their results they have proposed to select the ITRA / HPMC 40:60 w/w milled melt extrudate for further development as an alternative for the currently marketed Sporanox® oral capsule [36].

Nanosuspension: Rundfeldt *et al* explored a wet-milling process using a pearl mill to generate a stable nanosuspension of ITRA for inhalation purpose. The microcrystalline ITRA was pre-suspended in distilled water at a concentration of 5–20% by weight with addition of a suitable stabilizer using a high shear mixer. They have tested suspension stabilizers poloxamer 188, Solutol® HS 15 and polysorbate 80 at concentrations of 14–100% relative to the ITRA concentration. They have milled all suspensions in a temperature controlled pearl mill with a horizontal milling chamber filled with grinding media. A peristaltic pump circulated the suspension during the process, and the milling time varied to identify the optimal milling time (60 min to 4 h). The grinding media used was polystyrene and polycarbonate organic media as well as zirconium oxide beads. The particle size was measured repetitively during the milling process by dynamic light scattering of dilutes samples. The polydispersity index (PDI) was evaluated for the particle size distribution. The suspension was stable if stored at 8ºC for 3 months without particle growth and could be nebulized using standard nebulizer technologies including mesh technology and pressured air nebulizers. A 10% suspension found well tolerated upon repeated dose inhalation once daily for 7 days at a predicted dose of 45 mg/kg in rats.

A single dose inhalation at a predicted dose of 22.5 mg/kg resulted in maximum lung tissue concentration of 21.4 lg/g tissue with a terminal half-life of 25.4 h. Serum concentrations were lower, with a maximum concentration of 104 ng/ml at 4 h after dosing and a terminal half-life of 10.5 h. High and long lasting lung tissue concentrations well above the minimal inhibitory concentration of *Aspergillus* species enable once daily administration with minimal systemic exposure. Their result data indicate that ITRA nanosuspension represents an interesting formulation for inhaled administration in Cystic Fibrosis patients suffering from allergic Broncho pulmonary aspergillosis [37].

CONCLUSION: It has been observed that amongst various techniques available for solubility enhancement of poor soluble drug, solid dispersion preparation hot stage extrusion found best given 99.21% improved dissolution efficiency. Solid dispersion also produced by different techniques like spray drying, freeze drying, hot melt extrusion by most of the researcher for solubility and bioavailability purpose.

Solid dispersion can be a good approach for solubility enhancement due to its ease preparation and good in efficiency. Beside solid dispersion, other approaches like cocrystals, solid microemulsions, nanosuspensions, ternary inclusion complex with β - cyclodextrins formulation can also employed for solubility and bioavailability improvement of ITRA.

Conflict of the Interest: None.

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