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An Investigational Study For Screening Of Different Polymers For The Solubility Enhancement Of Pazopanib Hydrochloride Via Formulation Of Third-Generation Solid Dispersion.

Ramendu Mishra[1]*, Anjana Devi[1], Swati Suman[2]

[1]*School of Pharmaceutical and Health sciences, Career Point University, Hamirpur-176041, Himachal Pradesh, India*
[2] *Research and Development centre, Sun Pharmaceuticals Industries Limited, Gurugram, Haryana, India*

***Corresponding Author**: Ramendu Mishra*
**E-mail: rmjphm@gmail.com*

Abstract

In the conducted research study, solubility investigation was performed to elucidate the dissolution rate and behaviour of a drug incorporated within a solid dispersion matrix. The foremost objective was to appraise the impact of formulation parameters on the improvement of drug's solubility, the list of factors influencing the bioavailability. To this end, a systematic series of experiments were undertaken, wherein the drug was co-precipitated with a hydrophilic polymer carrier using various solvent systems and ratios. The resulting solid dispersions were meticulously characterized, employing state-of-the-art analytical techniques. Subsequently, solubility profiles were generated through equilibrium solubility studies, encompassing a range of pH conditions and temperatures, to comprehensively evaluate the dissolution behaviour of the drug. Based on study, it was concluded that the solubility of Pazopanib Hydrochloride (Pazopanib base) is significantly increased from 0.001 mg/ml to ~8.000 mg/ml. the same was confirmed from the analytical tools. Analytical tools also confirm the conversion of crystalline form to amorphous form. The outcomes of these investigations provide essential insights into the potential utility of solid dispersion systems as a viable strategy for enhancing the solubility and, consequently, the therapeutic efficacy of the drug in question.

Keywords: Pazopanib Hydrochloride (PZPH), Solid dispersion, Solubility enhancement, solvent evaporation, hydrophilic polymer, and Amorphous solid dispersion.

Introduction:

Drug solubility is one of the most prominent hurdles for the formulators and researchers during development and designing of a formulation. Most of the drugs and NCE in the pipelines are having low or limited solubility(1). The drugs in the development phase with solubility as a challenge are difficult to develop. Most of the generic formulations in their development phase were dropped due to challenges originated due to solubility such as meeting the BE studies, failures on stability and so on(2,3). Pazopanib Hydrochloride

(PZPH) is a medication used in first line treatment of renal cell carcinoma(4,5). It is also used in the treatment of soft tissue carcinoma that has already been treated with other anti-cancer medication. The mechanism of action of pazopanib can be described as reduction in blood supply to the cancer cells leading to slow growth of tumour(6). The chemical name of Pazopanib is 5-[4-{(2,3-dimethylindazol-6-yl)-methyl amino} pyrimidin-2-yl] amino]-2-methylbenzenesulfonamide. Molecular formula of pazopanib is $C_{21}H_{23}N_7O_2S.HCl$ with a molecular weight of 473.991(7). Pazopanib is a BCS class II drug, having low solubility and high permeability with an oral bioavailability in humans ranging from 14% to 39%(8). Many BCS Class II and class IV drugs having lower solubility and low permeability are the prime area of research in the pharmaceutical industry(9–12).

Material and method

Pazopanib was provided by Sun Pharmaceuticals Industries Limited. Kollidon VA 64 was obtained from BASF, Navi Mumbai, Maharashtra, India. Hypromellose (HPMC), Kollidon K30 (PVP K30) and Kollidon K90 (PVP K90) was obtained from Dow Chemicals, USA. Polyvinyl caprolactam polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®), PEG 6000, Poloxamer 188 [Kolliphor® P188] (P188), and Poloxamer 407 [Kolliphor® P 407] (P407), and sodium lauryl sulphate (SLS) were kindly gifted by BASF, India. Apinovex was gifted from Lubrizol, USA. Lauryl Polyoxyl-32 glycerides [Gelucire® 44/14] (GEL) were kindly gifted by Gattefosse (France). Tween® 80 (T80) was purchased from Croda, Spain. Other excipients used in study were such as but not limited to DMSO, Ethanol, Methanol, DCM and all other solvents and ingredients used were of analytical grade.

Preliminary Solubility studies

Sample was added to 10 ml of solubility media gradually with constant stirring up to the point when no more solid dissolves, to achieve a saturated solution. The saturated solution was kept at bio-shaker for a specific duration. The samples were taken off the bio-shaker and filtered using a 0.45-micron filter. The filtered solution was diluted accordingly and analysed using UV-Spectrophotometer. Solubility study of drug was performed in 0.1N HCl, pH 4.50 acetate buffer and pH 6.8 phosphate buffer. The results are reported accordingly by using validated UV-visual spectrophotometric method(13,14).

Formulation design and development:

For formulation development of Pazopanib Hydrochloride which has pH dependent solubility and is a BCS class II molecule, solid dispersion is selected as one of the techniques for improvement in rate of solubility which ultimately improves the drug release(15,16).

Selection of Polymer:

While selection of polymer is one of the most critical and primary excipient selection process. A study was planned initially on the basis of development experience, literature search and behaviour of the polymer. For screening of polymer from the already selected polymers. A study was planned for understanding the basic behaviour and characteristics of the polymer with drug. Pre-mixture of drug with polymer was prepared in 1:1 and solubility study were performed in pH 4.5 acetate buffer. Pre-mixture of below mentioned polymers were prepared.

Table 1: Selection of polymer

S. No.	Polymer used
1.	HPMC AS
2.	Kollidon VA 64
3.	Kollidon K30
4.	Kollidon K90
5.	Polyethylene glycol
6.	Soluplus
7.	HPMC E5

Selection of Surfactant:

For selection of surfactant same approach was used and a solubility screening was performed with drug in ratio 1:0.1 and solubility was determined in pH 4.5 acetate buffer. A third-generation solid dispersion contains a polymer and a surfactant which adds to the solubility enhancement of any drug candidate. In addition to selection of polymer, surfactants were screened alongside to prepare a third-generation amorphous solid dispersion. Initially surfactants were chosen based on existing literature for the selection process. The polymers used in the research are sodium Lauryl Sulphate, Kolliphor P188, Kolliphor P 407 and Tween 80 (Polysorbate 80) with the drug in a ratio of 1:0.1.

Table 2: Selection of surfactant

S. No.	Surfactants used
1.	Sodium Lauryl Sulphate (SLS)
2.	Kolliphor P 188 (P188)
3.	Kolliphor P 407 (P 407)
4.	Tween 80 (polysorbate 80) (T80)

Selection of process:

Based on experience in formulation development, literature search and process feasibility, solvent evaporation was selected for formulating solid dispersion of PZPH(16,17). A robust and rugged formulation comes from a rugged and robust process. Keeping process feasibility, easy commercialization, and process robustness in mind. Solvent evaporation method was selected and developed(18,19).

Selection of Solvent

The method selected for preparation of solid dispersion was solvent evaporation. The less time requirement of the process and ease of availability of various solvents made the solvent evaporation process the choice of methodology. The solvents screened in the process were DMSO: Water (in a ratio of 1:1), Methanol: DCM (in a ratio of 1:1) and acidify Methanol: DCM (in a ratio of 1:1)

Process optimization

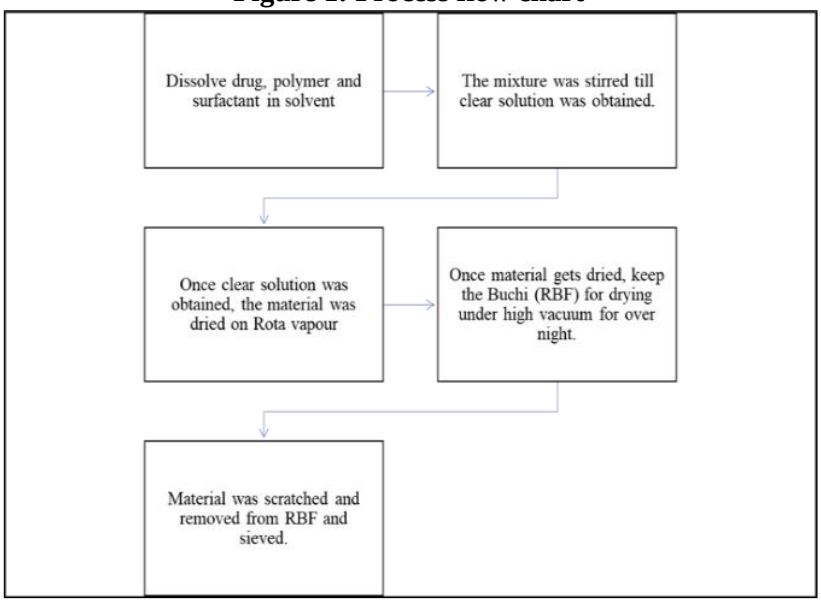
Based on evaluation of the polymer, surfactant and process feasibility below mentioned polymers, surfactant and solvent was selected for further study and optimization.
For process optimization below mentioned parameters were selected and evaluated based on results.

- Polymer ratio → Polymer ratio was screened with respect to drug
- Drying method→ Drying on rota vapour, Vacuum tray dryer and tray dryer were evaluated.
- Solvent selection→ Solvent selection as solvent system.
- Drying temperature→ drying temperature
- Final screened surfactant→ from screening.

Preparation of Solid Dispersion

For preparation of screening batches for finalisation of polymer, surfactant, solvent, and process- below mentioned procedure was used.

Figure 1: Process flow chart



Screening of polymer, polymer ratio, surfactant, and process parameters:

Design of Experiment

Design of Experiment is a statistical tool used to screen out the best possible polymer, surfactant, solvent system for formulating solid dispersion. Where drug and polymer is in 1:1 ratio and surfactant is 10% of polymer.

Table 3: Details of screening batches

S. No.	Formulation	Polymer	Surfactant	Solvent
1	Formulation 1	Kollidon VA 64	SLS	DMSO: Water (in a ratio of 1:1)
2	Formulation 2	Kollidon K 30	P188	DMSO: Water (in a ratio of 1:1)
3	Formulation 3	Kollidon VA 64	SLS	Methanol: DCM (in a ratio of 1:1)
4	Formulation 4	Kollidon K 30	P188	Methanol: DCM (in a ratio of 1:1)
5	Formulation 5	Kollidon VA 64	SLS	Methanol: DCM (in a ratio of 1:1)
6	Formulation 6	Soluplus	SLS	Methanol: DCM (in a ratio of 1:1)
7	Formulation 7	PEG 4000	SLS	Acidify Methanol: DCM (in a ratio of 1:1)
8	Formulation 8	PEG 4000	T80	Methanol: DCM (in a ratio of 1:1)
9	Formulation 9	Soluplus	P407	Methanol: DCM (in a ratio of 1:1)
10	Formulation 10	HPMC E5	P188	Acidify Methanol: DCM (in a ratio of 1:1)
11	Formulation 11	HPMC E5	P407	Acidify Methanol: DCM (in a ratio of 1:1)
12	Formulation 12	Kollidon VA 64	T80	Acidify Methanol: DCM (in a ratio of 1:1)

Final optimised solid dispersion

For final optimised formulation with screened polymers, surfactant, and their ratio in the formulation with final process parameters were established. The finalization of polymer, polymer ratio, surfactant and process were done based on screening and optimization studies for formulation and process. After different trial batches for process optimization and polymer optimisation below mentioned batches were executed and characterisation was done. For formulating the third-generation solid dispersion of Pazopanib HCl different polymers were used (refer below table).

Table 4: Final batches details

S. No.	Formulation	Polymer	Drug to polymer Ratio	Surfactant	Solvent system
1	Formulation A	Soluplus	1:5	SLS (10% of Polymer)	DCM: Methanol (1:1)
2	Formulation B	Soluplus	1:2		
3	Formulation E	Soluplus: Kollidon VA 64	1:3:3		
4	Formulation F	Kollidon VA 64	1:10		
5	Formulation G	Soluplus	1:10		

Evaluation of Solid dispersion

Solubility: To understand the rate of solubility of the prepared solid dispersion. Solubility studies were plan accordingly and pH 4.5 acetate buffer was selected as solubility media for evaluation. Sample was added to 10 ml of solubility media which is pH 4.5 acetate buffer gradually with constant stirring up to the point when no more solid dissolves, to achieve a saturated solution. The saturated solution was kept at bio-shaker for a specific duration. The samples were taken off the bio-shaker and filtered using a 0.45-micron filter. The filtered solution was diluted accordingly and analysed using UV-Spectrophotometer.

In-Vitro dissolution test: The in-vitro dissolution of prepared SDs were performed and compared to the PZPH. The dissolution media was selected to maintain non sink conditions which can mimic the in-vivo environment more as compared to that of sink conditions. This can lead to the super saturated solution. As the subjected drug is BCS class II with low solubility and high permeability. For molecules belongs to this class the rate limiting step is solubility. Hence presence of sufficient amount of drug substance for permeability can lead to better bio availability.
For evaluating drug release profile below mentioned parameters were used for dissolution.
USP-II (Paddle)/75 rpm/900ml/37℃±0.5℃. For analysis of solubility and dissolution samples UV-Visible spectrophotometer was used at 269nm wavelength. A validated method as per ICH guidelines was used for the analysis.

Characterization of solid dispersion

X-Ray diffraction: The optimised solid dispersions were characterised through x-ray diffraction. The developed SD were evaluated for the crystallinity of the solid dispersion. The XRD was generated and interpreted to put a conclusive statement.

Results and discussion

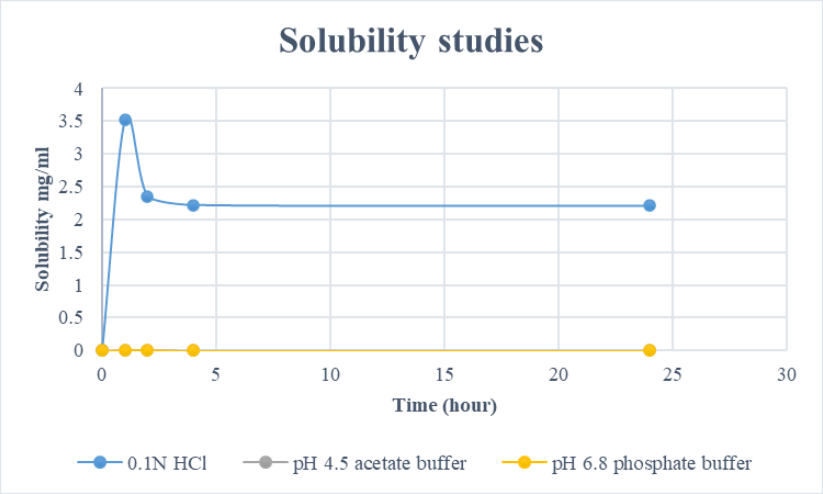
The solubility of PZPH was evaluated in different solubility medias such as 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. The solubility was conducted for 24 hrs but also performed for 1 hr, 2hrs and 4 hrs.

Table 5: Solubility results of drug in different medias.

Solubility of PZPH at different time points in mg/ml				
S. No.	**Media**	**1 hr**	**2 hrs**	**4 hrs**
1	0.1N HCl	3.517	2.355	2.223
2	pH 4.5 acetate buffer	0.002	0.002	0.001
3	pH 6.8 phosphate buffer	0.001	0.001	0.000

From the above solubility studies, it was concluded that the drug is getting precipitated out after once getting solubilized. At the point of saturation, the drug again starting precipitate and present in un-solubilised form.

Figure 2: Graphical representations of solubility studies



From the above reported results, we can conclude that the drug has a pH dependent solubility and at lower pH the drug is more readily soluble when compared to higher pH.

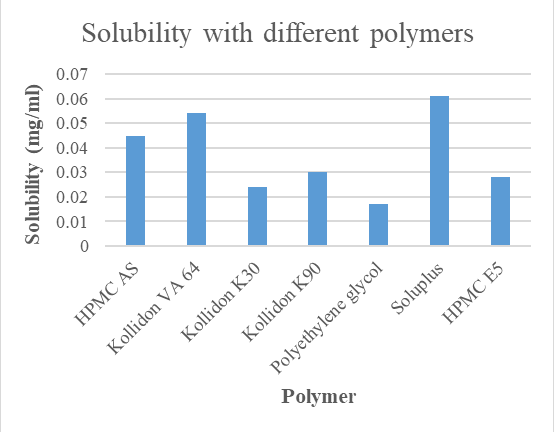
Selection of Polymers

For selection of polymers, premix of drug with polymer in defined ratio were mixed and saturated solubility was performed for specific time duration. Based on the results of the saturated solubility studies, the polymers were selected for further screening.

Table 6: Solubility results of premix of drug with polymer (1:1) in pH 4.5 acetate buffer.

Media: pH 4.50 acetate buffer		
S. No.	**Polymer used**	**Solubility at 1 hr (mg/ml)**
1.	HPMC AS	0.045
2.	Kollidon VA 64	0.054
3.	Kollidon K30	0.024
4.	Kollidon K90	0.030
5.	Polyethylene glycol	0.017
6.	Soluplus	0.061
7.	HPMC E5	0.028

Figure 3: Solubility study representation



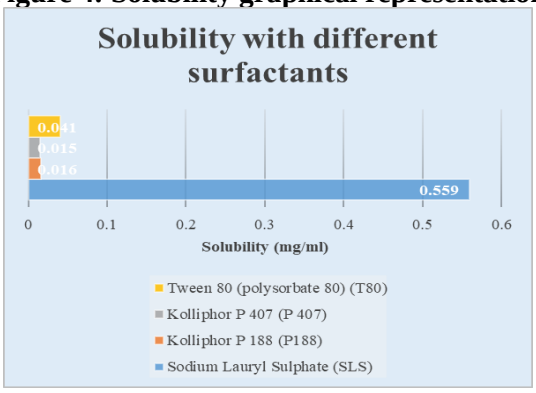
Selection of Surfactant

For screening of surfactants. Solubility study was done and results are summarised below.

Table 7: Solubility results of premix of drug with surfactant (1:1) in pH 4.5 acetate buffer.

Media pH 4.50 acetate buffer		
S. No.	**Polymer used**	**Solubility at 1 hr (mg/ml)**
1.	Sodium Lauryl Sulphate (SLS)	0.559
2.	Kolliphor P 188 (P188)	0.016
3.	Kolliphor P 407 (P 407)	0.015
4.	Tween 80 (polysorbate 80) (T80)	0.041

Figure 4: Solubility graphical representation



Selection of solvents

From the pre-screened solvent system used for the preparation of SD, only few solvents were selected and were screened for the formulation of SD on the basis of process feasibility.

Selection of process

The process selected for preparation of solid dispersion was solvent evaporation and optimisation was done. Keeping in mind about the scale-up challenges and feasibility of process. A simple, robust, and rugged process was developed.

Design of Experiment

Different experiments were planned in order to finalise the polymer, surfactant, process, and polymer-surfactant ratio with drug for the preparation of the solid dispersion. Custom design was selected to list out the experiments and trials planned for final screening.

Characterization of Solid Dispersion

The prepared solid dispersion was subjected to characterization to evaluate various parameters such as solubility, X-ray diffraction, DSC, and in-vitro dissolution. These results help in evaluation of prepared formulation in terms of their change in molecular form or change in their crystallinity. In-vitro dissolution study was also performed to evaluate the impact on dissolution with change in solubility of the prepared drug formulation. The final solid dispersion was evaluated for the in-vitro dissolution study.
After evaluating the screening batches for XRD, solubility final optimised formulation was prepared and evaluated.

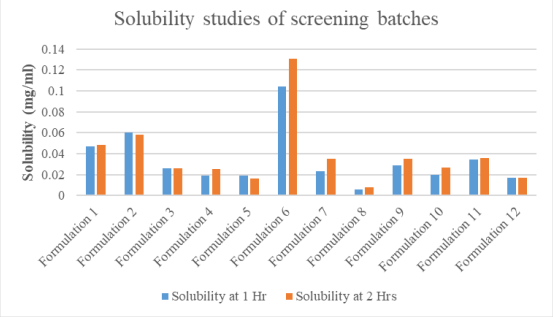
Solubility Studies

The prepared solid dispersion was added to 10 ml of pH 4.5 Acetate buffer gradually with constant stirring up to the point when no more solid dissolves, to achieve a saturated solution. The saturated solution was kept at bio-shaker for a specific duration. The samples were taken off the bio-shaker and filtered using a 0.45-micron filter using a syringe. The filtered solution was then diluted accordingly and analysed using UV-Spectrophotometer. Solubility study of drug was performed in pH 4.50 acetate buffer and the results of the study is compiled in the below table.

Table 8: Solubility results of solid dispersion in pH 4.5 acetate buffer.

Media pH 4.50 acetate buffer			
S. No.	**Formulation**	**Solubility at 1 hr (mg/ml)**	**Solubility at 2 hr (mg/ml)**
1.	Formulation 1	0.047	0.048
2.	Formulation 2	0.060	0.058
3.	Formulation 3	0.026	0.026
4.	Formulation 4	0.019	0.025
5.	Formulation 5	0.019	0.016
6.	Formulation 6	0.104	0.131
7.	Formulation 7	0.023	0.035
8.	Formulation 8	0.006	0.008
9.	Formulation 9	0.029	0.035
10.	Formulation 10	0.020	0.027
11.	Formulation 11	0.034	0.036
12.	Formulation 12	0.017	0.017

Figure 5: Solubility studies graphical presentation



The results of the screened batches were compiled and based on them it was concluded that for further optimization trials Soluplus and Kollidon VA 64 were selected as polymer, SLS was selected as surfactant after final screening batches, DCM: Methanol was selected as solvent system used for the preparation of solvent dispersion.

Other experiments were planned to finalise the process and the same was finalized after conducting different experiments.

- Polymer and polymer ratio → Kollidon VA 64 and Soluplus were selected
- Drying method→ Drying on rota vapour with Vacuum tray was selected.
- Solvent selection→DCM: Methanol in 1:1 ratio as solvent system.
- Drying temperature→ 60°C was finalised for solvent evaporation and drying.
- Final screened surfactant→ SLS was selected as final surfactant.

Final solid dispersion

The final batches were prepared and evaluated. Solubility, XRD and in-vitro dissolution characteristics were studied with respect to the drug for the selection of the final solid dispersion.
The solubility studies were performed and the results were reported below:

Table 9: Details and solubility data of final batches

S. No.	Formulation	Polymer and drug to polymer ratio	Solubility in pH 4.5 acetate buffer at 1 hr (mg/ml)
1	Formulation A	Soluplus (1:5)	7.980
2	Formulation B	Soluplus (1:2)	2.950
3	Formulation E	Soluplus: Kollidon VA 64 (1:3:3)	4.864
4	Formulation F	Kollidon VA 64 (1:10)	3.428
5	Formulation G	Soluplus (1:10)	8.138

The solubility of the optimised batches were significantly increased as compared to the drug and on the basis of the solubility data the in-vitro dissolution was planned.

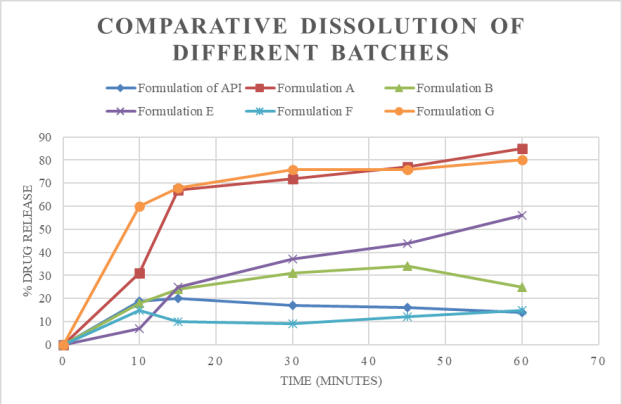
In-vitro dissolution study

The dissolution was conducted for the drug release profiling of the prepared formulation in comparison to the drug release profile of the drug formulation.
The media selected for the dissolution was pH 4.5 acetate buffer/USP-II/75rpm/900ml.

Table 10: In-vitro drug release profile of final batches

S. No.	Formulation	% drug release (%w/w) in minutes				
		10	15	30	45	60
1	Formulation of API	19	20	17	16	14
2	Formulation A	31	67	72	77	85
3	Formulation B	18	24	31	34	25
4	Formulation E	7	25	37	44	56
5	Formulation F	15	10	9	12	15
6	Formulation G	60	68	76	76	80

Figure 6: Graphical representation of drug release profile



As per the above data the solubility of has direct impact on the drug release profile and based on solubility data formulation A and formulation G are both considerable for the final formulation development.

X-ray Diffraction

The XRD of the optimised batches were conducted and compared with the API for drafting a conclusion.

Figure 7: XRD of model drug

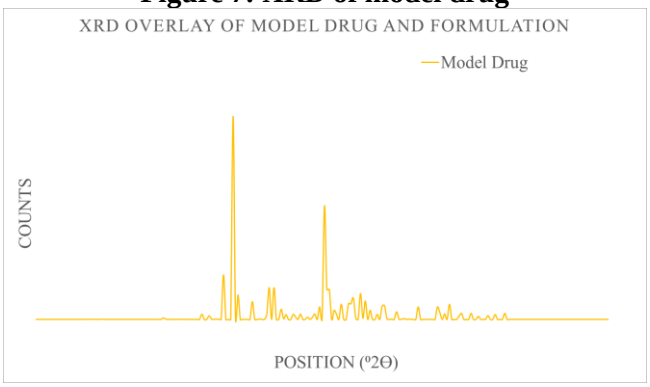


Figure 8: Overlay XRD of model drug and formulation A

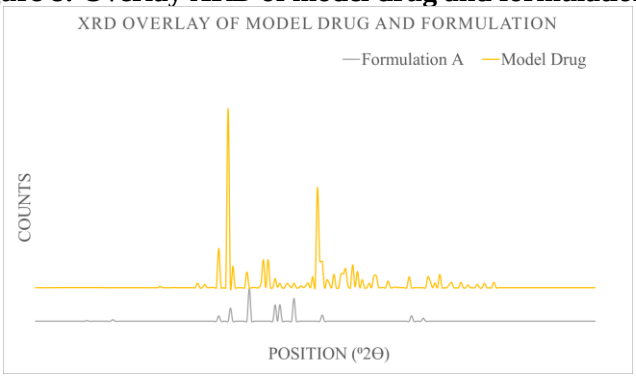


Figure 9: Overlay XRD of model drug and formulation B

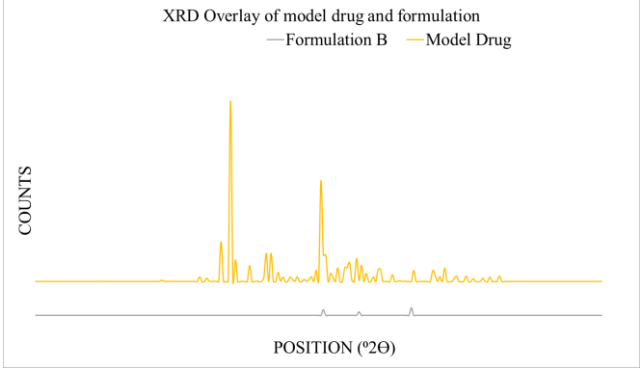


Figure 10: Overlay XRD of model drug and formulation E

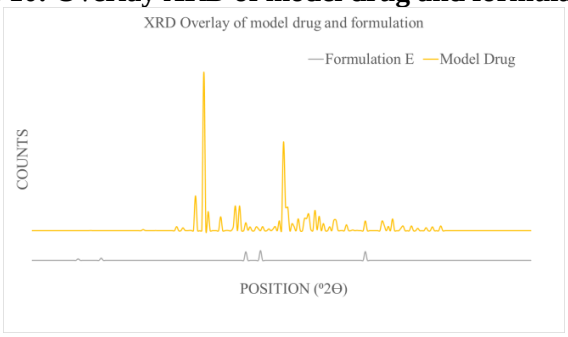


Figure 11: Overlay XRD of model drug and formulation F

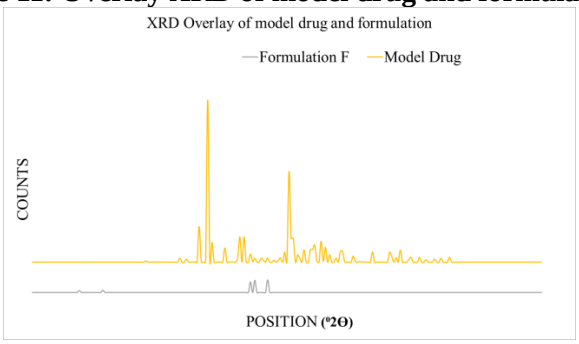


Figure 12: Overlay XRD of model drug and formulation G

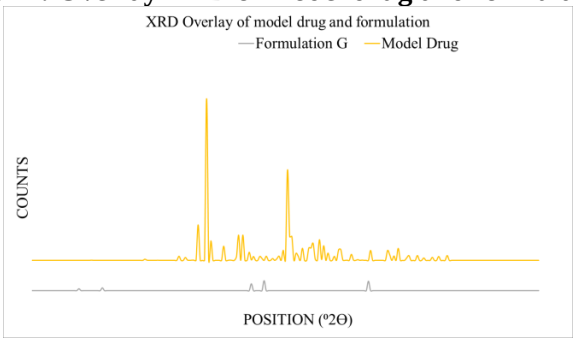


Table 11: Details of final formulation for amorphous and crystalline.

S. No.	Formulation	Crystalline or Amorphous
1	API	Crystalline
2	Formulation A	More amorphous, less crystalline
3	Formulation B	More amorphous, less crystalline
4	Formulation E	More amorphous, less crystalline
5	Formulation F	More amorphous, less crystalline
6	Formulation G	More amorphous, less crystalline

From the above XRD data it can be concluded that the characteristic peaks of PZPH which were at 5.6±0.2° 2 theta, 15.6±0.2° 2 theta, 16.4±0.2° 2 theta , 18.0±0.2° 2 theta and 24.0±0.2°2 theta are not in formulation E, formulation F and formulation G. In formulation B only one characterstic peak present. But in formulation A most of the characterstic peaks are present. Hence formulation G, formulation F and formulation E can be considered with formulation B.

Conclusion:

According to the study conducted it was clear that the solubility of the model drug is significantly impacted. From the given solubility, in-vitro dissolution and XRD data we can conclude that significant amount of drug is converted into the amprphous form from crystalline which leads to the increase in the solubility and dissolution profile of the model drug. Formulation G has significant increase in solubility which further leads

to better drug release profile. Keeping XRD data in consideration we can select formulation G for further study and investigation.

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