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Original Article

Modification in the Approach of Developing Solid Dispersed Particles for Enhanced Dissolution

Rahul Gupta*, Ashwani Kumar Mishra, Anupam Kumar Pathak

Department of Pharmacy, Barkatullah University Bhopal, Madhya Pradesh, INDIA.

ABSTRACT

Objective: To use tween 80 with a novel approach of applying a layer over the outer surface of solid dispersion particles for the improvement of the poor results of solubility enhancement by solid dispersion produced by the conventional technique of using surfactant in the matrix form. **Methods:** The solid dispersed particles of Repaglinide and Polyvinylpyrrolidone K_{30} were formulated using solvent evaporation method. The surfactant tween 80 was added as matrix forming agent during the solid dispersion and the prepared solid dispersed particles were also allowed to coat with tween 80 just by applying over the surface of container in which solvent was allowed to evaporate. **Key findings:** It was inferred that tween 80 coated particles were formulated with maximum solubility enhancement of 1982 µg/ml as compared to 103 µg/ml of non coated solid dispersed particles and to 3.82 µg/ml of Repaglinide. The conversion of the crystalline form of drug into an amorphous form was confirmed by DSC, X-RD, FT-IR studies and SEM images. The dissolution study showed that 90% of drug released within 30 min of dissolution. **Conclusion:** The solubility estimation data confirmed the efficiency of novel approach used for the formulation of particles as the best technique for solubility enhancement over conventional techniques.

Key words: Solubility Enhancement, Solid Dispersion, Repaglinide, Pvp K30, pH Solubility Studies, Amorphous Powder.

Correspondence:
Rahul Gupta
H.No: 49, Alpha -1, Millennium Village, Greater noida, Uttar Pradesh, INDIA.
Phone no: 9718399054

E-mail: rahul191sb@gmail.com
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INTRODUCTION

Solid dispersion for poorly water soluble drugs was considered to be the most common and an efficient method of solubility enhancement[1] but the extent of enhancement always created a doubt due to poor results. The dissolution of solid dispersion particles usually involves a series of steps such as wetting, solvent penetration, disintegration, swelling and transport of components and all these steps are generally affected by the interaction between penetrating solvent, polymer and drug.[2] Amongst various steps, wetting of particles is the first and most important step for dissolution. This wetting increases with the presence of hydrophilic groups from the layer of the hydrophilic carrier at the outer surface of solid dispersion particles. The formulation of solid dispersion particles usually involves the use of non-aqueous solvent which results in the matrix formation of hydrophobic drug and hydrophilic carrier thus aids in the decrease in wetting. In matrix formation the substance with greater affinity for the liquid/air interface tend to dominate the outer surface of solid dispersion particles and hydrophobic drug molecules are mostly active for this as they easily solubilized into the non-aqueous solvent in contrast of formation of slightly viscous solution with the hydrophilic carrier in non-aqueous solvent. The degree of dominance is so high that even increase in the concentration of the hydrophilic carrier would not result in the effective decrease in hydrophobicity. Thus, formation of solid dispersion particles using this technique results in the minimal solubility enhancement or comparably no enhancement.[3]

The presence of surfactant at the solid / liquid interface was considered to be best for decreasing the hydrophobicity.[4] The literature studies confirmed that surfactant was usually added in the form of a matrix which does not result in its presence as a layer of the solid / liquid interface and this was the reason of poor enhancement of solubility with an addition of surfactant. This addition of surfactant in the form of matrix basically aids in the decrease of the viscosity of the solution and increase of the homogeneity of the drug within the carrier.[5] So, in this research the procedure of an addition of surfactant within the formulation for obtaining maximum solubility enhancement was mainly focused.

The addition of surfactant within the formulation be such, as it forms a layer of surfactant at particle surface. The layer on an outer surface when comes in contact with water shows micellization.[6] This micelle formation exhibits the anisotropic water distribution of higher water concentration at the surface while lower at the hydrophobic core and such spatial position allows the solubilization of poorly soluble drugs and formation of thermodynamically stable isotropic solution.[7] The micellization depends upon the concentration of surfactant which needs to be above the critical micelle concentration.[8] From the pharmacological point of view, the surfactants with low *cmc* value form stable missiles, which do not precipitate within the blood.[9] The increase in solubility by micellization increases bioavailability and also these micelles even act as a drug carrier and drug carrying capacity of micelles is usually higher as compared to the other carrier systems such as soluble polymers and liposome.[10] The quantitative estimation of solubilization efficiency of the surfactant is mainly done by determining the molar solubilization capacity and micelle-water partition coefficient. The non-ionic surfactant (Tween-80) due to their low *cmc* value generally shows higher solubilization efficiency by comparing with other ionic surfactants and mixtures of ionic + non-ionic surfactants.[11,12] The surface spreading coefficient of surfactant over moderately as well as highly hydrophobic materials was also considered to be higher for non-ionic surfactant as compared to ionic surfactant.[13] The micelle forming systems on contact with aqueous media results in supersaturated conditions[14] which may lead to catastrophic precipitation of the drug *in vivo*.[15] This precipitation of drug can hinder by the addition of a precipitation inhibitor,[16] polyvinylpyrrolidone and tween were considered as precipitation inhibitor.[17] The usual hypothesis for this precipitation inhibition was that these excipients aids in a decrease in degree of supersaturation via solubilization.[14] Considering the points of higher solubilization obtained by micellization, the need of the presence of a layer of a surfactant at particle surface was focused on this research and this need was fulfilled by allowing the adsorption of surfactant at an outer surface of solid dispersion particles.

Considering an approach of maximum solubility enhancement, the poorly water soluble drug Repaglinide was chosen for this research. Repaglinide was the first meglitinide analogue approved by FDA in 1997 for treating type 2 diabetes mellitus.[18] The Preprandial administration of Repaglinide ensures the gastrointestinal specific target action, but poor bioavailability range 56 to 63%[19] reduces the effectiveness of conventional dosage form. The poor bioavailability is due to the rate limited dissolution profile of BCS class II repaglinide[20] with higher lipophilicity (3.97) and lower water solubility (34 µg/ml). Repaglinide drug molecules generally show pH dependent U shape solubility profile.[21] Therefore, the design of a formulation for Repaglinide is a challenging task as its physicochemical parameters do not permit the formulation design without considering the solubility enhancement of the drug. To our conception, solid dispersion is one of the best methods of an increasing the solubility of Repaglinide and there were various research studies which were published regarding this, but an extension of enhancement in all studies was not so impressive as must be. So, in this research an approach of allowing an adsorption of surfactant at an outer surface of solid dispersion particles was considered for improving the results generally obtained by a solid dispersion method. In various studies, it was determined that amongst various hydrophilic carriers such as Polyvinylpyrrolidone K_{30} (PVP K_{30}), Poloxamer 188 and Crospovidone and Polyethylene glycol 6000 (PEG 6000), PVP K_{30} was the only polymer which showed the maximum increase in solubility.[22,23] The selection of hydrophilic carrier and surfactant was mainly done by considering the various points such as solubility enhancement, micelle formation and stability of supersaturation.

MATERIALS AND METHODS

Materials

Repaglinide was obtained as a gift sample from East West Pharma (Uttarakhand, India). PVP K_{30} and Tween 80 were purchased from Chemical Drug House (New Delhi, India). All other reagents and solvents used were of analytical grade.

Methods

pH Solubility Study[21-24]

The study was performed for determining the solubility of pure drug Repaglinide in different pH buffer media solution at 37°C. Phosphate buffer solutions for pH 1.5, 3, 4.5, 6, 7.5 and 9 were made. 10mg of Repaglinide was allowed to dissolve into each volumetric flask containing 50ml of the different buffer solutions with continuous stirring up to 24 h. Aliquots were withdrawn and filtered using Whatman filter paper and analyzed at 211nm wavelength using a UV spectrophotometer.

Sample preparation[22]

The solid dispersion particles were formulated using the solvent evaporation method. Initially the five batches (S1, S2, S3, S4, S5 and S6) were prepared containing Repaglinide and polymer PVP K_{30} in different 1:4, 1:8, 1:12, 1:16 and 1:20 w/w ratios respectively (Table 1). For each batch, the polymer PVP K_{30} in the required quantity was dissolved in ethanol at 4% w/v solution and to this ethanolic solution, the drug was added in the required quantity as per the ratio optimized. The solution was then continuously stirred at a moderate speed using magnetic stirrer till the complete dissolution of the drug and polymer occurred and then in each batch Tween 80 was added to 2% w/v of the ethanolic solution. The solution was then poured into a petri plate whose inner surface was previously coated thoroughly with a 1 ml of Tween 80 and the evaporation of solvent was then allowed at a room temperature. After the evaporation of solvent the particle were then scrapped out using the spatula and in this way tween 80 applied to the surface of petri plate was adsorbed over an outer surface of the solid dispersion particles. The particles were then dried for 24 h in an oven at 37°C. The dried particles were then triturated using mortar pestle and allowed to pass through different sieves No.120 and 140 respectively, and it was observed that particles were passed through sieve no. 120 but not through the sieve no. 140. Similarly, five more formulations (Sa, Sb, Sc, Sd and Se) with the same composition and procedure were formulated, except that the tween 80 was not allowed to adsorb over final particles.

Table 1: Formulation of Solid dispersion particles of Repaglinide

Batch No.	Ratio of Drug and PVP K30	Ethanolic solution of Drug and PVP K30 (%w/v)	Tween 80 in ethanolic solution (%w/v)
S1	1:4	4	2
S2	1:8	4	2
S3	1:12	4	2
S4	1:16	4	2
S5	1:20	4	2
Sa	1:4	4	2
Sb	1:8	4	2
Sc	1:12	4	2
Sd	1:16	4	2
Se	1:20	4	2

Evaluation of solid dispersion drug particles

Percent Yield[22]

The percent yield of the prepared solid dispersion drug particles for each batch was calculated using following formula:

$$\%yield = \frac{Observed\ weight\ in\ mg}{Theoretical\ weight\ in\ mg} x\ 100$$

Drug entrapment efficiency[25]

Solid dispersion drug particles equivalent to 10 mg of drug were taken and dissolved in 10 ml of ethanol. The solution was then assayed for the drug content at 211 nm wavelength.

Solubility estimation[22-24]

Solid dispersion particles equivalent to 10 mg of drug were taken and allowed to dissolve in pH 5 Citro phosphate buffer with continuous stirring for 20 to 25 min after that the solution was centrifuged at 20,000 RPM for 5 min. The supernatant obtained was finally filtered to separate an undissolved particle. The filtered solution was further diluted with distilled water and analyzed at 211 nm using a UV spectrophotometer.

Differential Scanning Calorimetry analysis

The thermogram study was performed for pure drug Repaglinide, PVP K_{30} and best-optimized formulation of solid dispersion particles. The samples were evaluated on an instrument Jade DSC (Pyris 6 DSC). Samples in the quantity of 4-5 mg were heated from 35°C to 300°C at 10°C/min.

Fourier transform infrared (FT-IR)

The spectra of FT-IR (Shimadzu FT-IR Spectrometer) for determining the interaction between drug and polymer was obtained using the potassium bromide disk method in the range of 450-4000 cm^{-1} at a scan period of 4 cm^{-1}.

XRD measurements

Powder X-ray diffraction measurements of the solid dispersion particles were determined on Rigaku X-ray generator over the 2θ range of 10-70^{0}C.

Scanning Electron Microscopy

The SEM images of the best-optimized batch of solid dispersion particles were obtained at different resolution using Gemini SEM (ZEISS).

In vitro Dissolution[26]

Dissolution study of the best-optimized batch, which showed the maximum increase in solubility was determined using dissolution testing apparatus (USP Type-II Paddle type, Jyoti Scientific, Gwalior India). The weighed quantity

of solid dispersion particles equivalent to the calculated dose of drug repaglinide was added into the hard gelatin capsule and dissolution test was performed by using 900 ml of pH 5 Citro-phosphate buffer at 37 ± 0.5^{o}C and 75 rpm for one hour. A sample of 5 ml of the aliquot was withdrawn from at an interval of 5 min and fresh volume of dissolution media was also added to replenish the dissolution media. The aliquot was filtered by using filter paper and finally analyzed using UV–Spectrophotometer at 211nm.

Stability studies[22]

The stability study of the best optimized formulation which showed a maximum increase in solubility was carried out at 40^{0}C ± 2^{0}C/60% RH for 45 days. Samples were withdrawn periodically to estimate the drug content.

RESULTS AND DISCUSSION

pH Solubility Study

Repaglinide is an ampholitic compound with two proton binding sites, the two pKa values 6.2 and 3.96 respectively make it very difficult to determine the pH at which drug ionizes or shows maximum solubility. So such compounds are usually analyzed for solubility at different pH values so that a perfect range of pH value can be obtained at which compound shows maximum solubility. The solubility of such ampholitic compounds at any pH is the sum of the concentrations of each different species in saturated solution.[19] The solubility profile of Repaglinide as obtained in Figure 1 showed a U-shaped graph with maximum solubility at extreme basic (pH 7 – pH 9) and extreme acidic (pH 2.5 – pH 3). The solubility at basic pH is greater as compared to an acidic pH. The least solubility was obtained at pH 4 – pH 6. So, it could be inferred that Repaglinide ionizes at the maximum at basic pH 9 but as per one study the drug usually unstabilized at such higher pH values[21] and even the value of solubility obtained was so low that further solubility enhancement techniques needed to be pursued. Thus, finally, the optimal pH value selected for solubility estimation of a solid dispersion particle was pH 5 at which Repaglinide showed the least solubility.

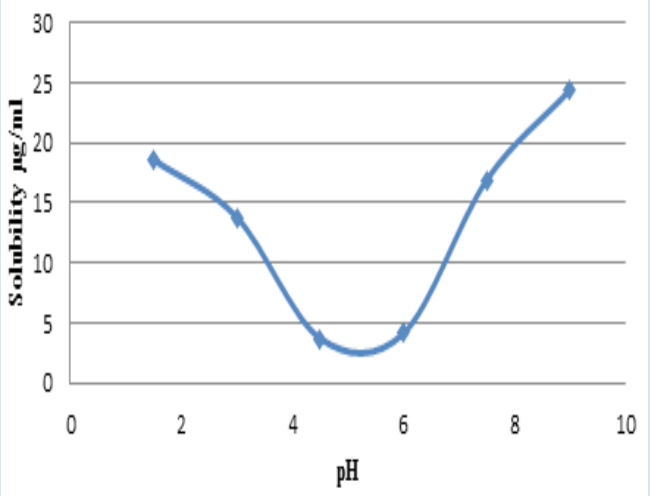

Figure 1: Solubility profile of Repaglinide (µg/ml) at different pH values.

Percent Yield

The different batches of solid dispersion particles were formulated with an approach to increase the concentration of PVP K_{30} with a constant drug concentration. The percent yield obtained in the case of tween 80 adsorbed particles (S1 – S5) were in the range of (84.20 – 91.20%) Table 2 with maximum value was obtained for batch no S5 and it was inferred that as the concentration of PVP K_{30} increases the yield increases. In case of other batches (Sa - Se) to which tween 80 was not allowed to adsorb on an outer surface, (39.41 – 49.39%) range of percent yield was obtained. The possible reason for such low percent yield was that the presence of tween 80 over the surface of particles reduces the friction of the particles which in turn aids in an easy recovery of the dried particles from the container.

Table 2: Percent Yield and Drug entrapment efficiency of different batches of solid dispersion drug particles

Batch No.	% Practical yield	Drug Entrapment efficiency
S1	84.20%	89.62%
S2	87.23%	93.10%
S3	90.74%	93.06%
S4	91.19%	92.77%
S5	91.20%	91.88%
Sa	39.41%	88.73%
Sb	41.82%	92.54%
Sc	44.31%	90.92%
Sd	47.58%	89.86%
Se	49.39%	87.46%

Table 3: Solubility estimation of pure drug Repaglinide and different batches of solid dispersion drug particles

Batch No.	Solubility µg/ml In pH 5 Citro-phosphate buffer
Drug	3.82
S1	162
S2	330
S3	683
S4	1914
S5	1982
Sa	5.1
Sb	11.6
Sc	62.4
Sd	101
Se	103

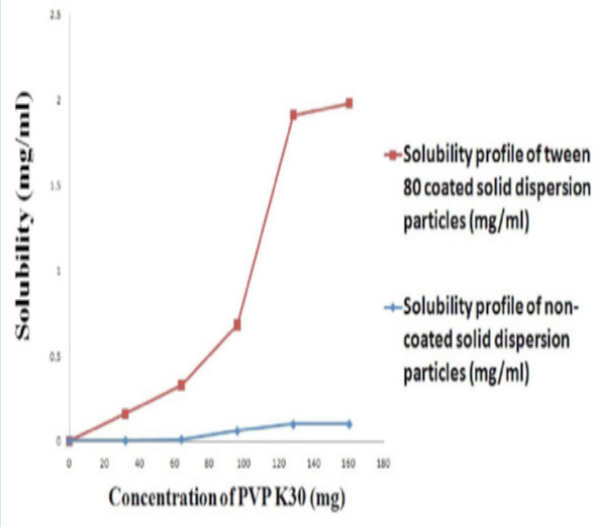

Figure 2: Effect of Tween 80 on the solubility of drug products compared with non-coated particles.

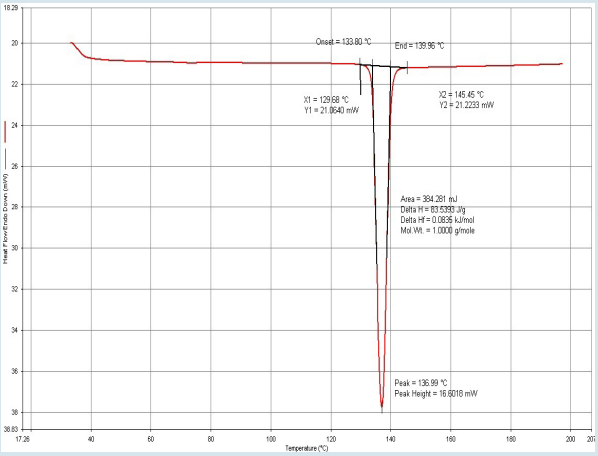

Figure 3: DSC Thermogram of Repaglinide.

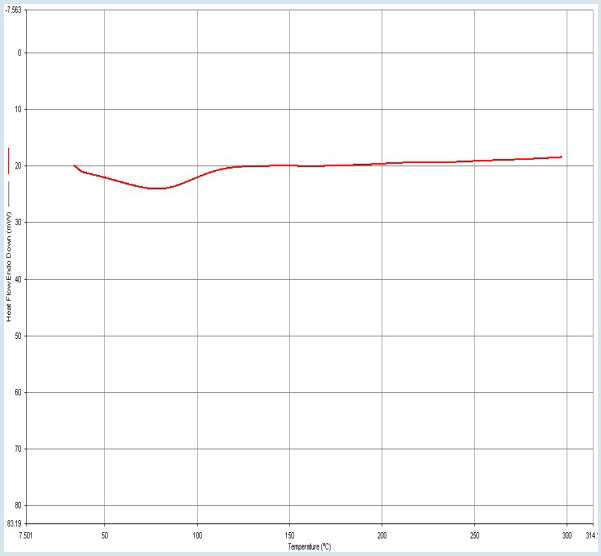

Figure 4: DSC Thermogram of PVP K30.

Drug Entrapment efficiency

The entrapment efficiency of different batches S1- S5 were in the range of (89.62 – 93.10%) Table 2. The maximum drug entrapment efficiency was shown by Batch no. S2. From this result, it was inferred that after a particular limit as the concentration of the polymer increases the drug entrapment efficiency of formulation decreases. The drug entrapment efficiency of Sa – Se were in the range of (87.46 – 92.54%) Table 2. The high drug entrapment efficiency obtained by a different section of batches was due to the presence of tween 80 within the matrix formulation as it allows the homogeneity of drugs within the carrier.[5]

Solubility estimation

The solubility profile of pure drug showed minimum solubility in the range of pH 4 to pH 6. So, pH 5 Citro phosphate buffer was used for the solubility estimation. Results from the Table 3 showed an extensive increase in the solubility when solid dispersion particles were allowed for an adsorption by surfactant tween 80 (S1- S6) on compared to solubility profiles of pure drug Repaglinide and solid dispersion particles (Sa – Se) which were not allowed for an adsorption by surfactant. Although the tween 80 was added in the form of matrix in all the batches, but the result obtained proved that mere presence of the tween 80 in the form of the matrix was not sufficient for enhancing the solubility. So, the presence of surfactant at an outer surface of particles is the main reason for its extensive enhancement in solubility due to micellization. The concentration of surfactant to be adsorbed over an outer surface of the solid dispersion particles was also very much important as a slight increase in surfactant would lead to stickiness in particles as determined in placebo formulation.

The effect of supersaturation was also noticed in the case of batch S5 and S4 having the highest and just similar solubility estimation with the different concentration of the carrier as 20 times the drug and 16 times the drug respectively as showed in Figure 2. This supersaturation showed that the concentration of the carrier in batch S5, be the last limit to be added to the solid dispersion as beyond such concentration the recrystallization of particles may occur. The selection of the carrier was also done by considering the factor of supersaturation as PVP K_{30} was considered as an efficient carrier inhibiting precipitation.[14] The factor of drug dosage size is also a limiting factor for further increasing the carrier concentration. Thus the best optimized batch S5 with maximum percent yield and solubility enhancement was selected for determining the further evaluation parameters.

Differential Scanning Calorimetry studies

The DSC thermograms of Repaglinide, PVP K_{30} and the sample of batch S5 were illustrated in Figure 2, 3 and 4 respectively. The sharp endothermic peak of Repaglinide at 136.9°C in Figure 3 showed the melting point of the drug. The broad endotherm between 45°C to 100°C obtained in Figure 4 depicts the glass transition temperature of an amorphous powder. The absence of an endothermic peak in Figure 5 depicted the loss of crystallinity of the drug in the presence of an amorphous polymer. Thus, solid dispersion particles produced from above technique allowed the formation of amorphous matrix of amorphous drug and polymer which is possible when the drug is molecularly but irregularly dispersed within the amorphous carrier. Such amorphous solid dispersion exhibits a disordered state having higher free energy and when such particles come in contact with water, shows an enhancement in apparent solubility and dissolution rate.[25]

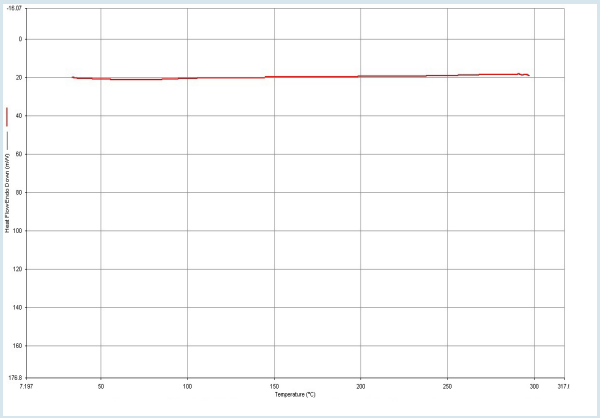

Figure 5: DSC Thermogram of final optimized formulation.

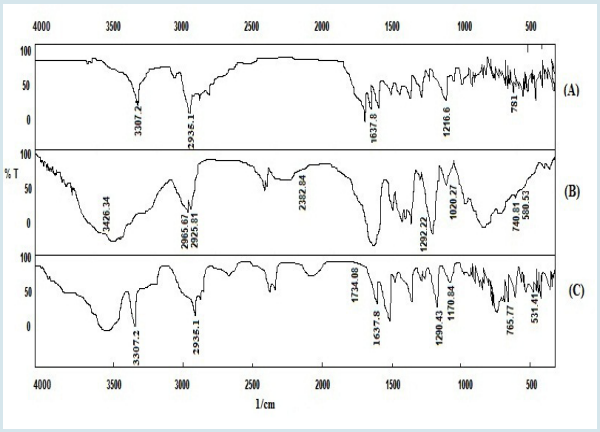

Figure 6: FT-IR Spectra (A) Repaglinide, (B) PVP K30, (C) Solid Dispersion.

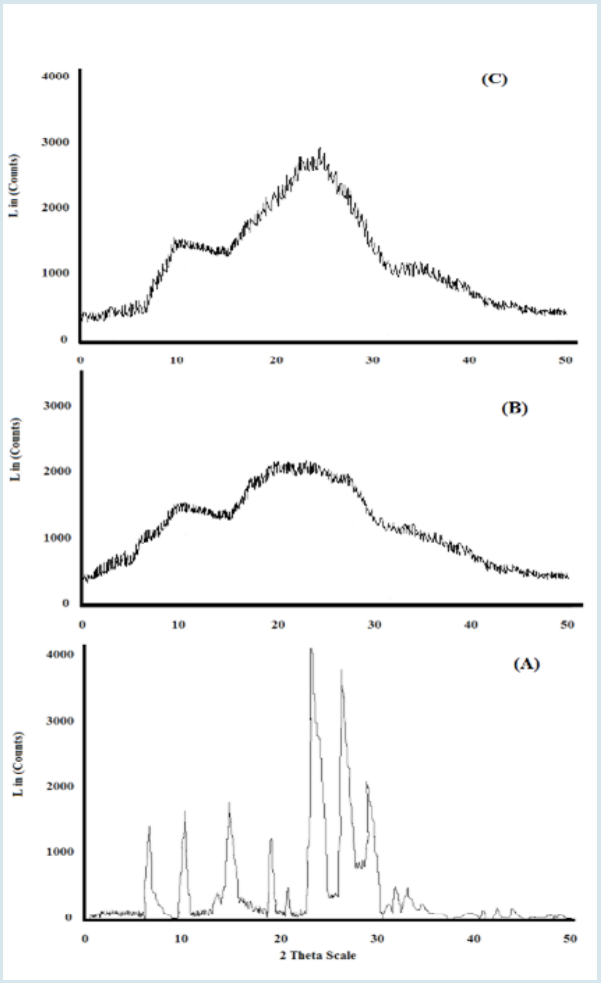

Figure 7: XRD spectra of (A) Repaglinide, (B) PVP K30, (C) Solid dispersion.

FT-IR studies

Drug-excipients compatibility study is an important characteristic of determining the identity of the product as well as its reproducibility with ensured therapeutic efficiency.[25] The identification of any sort of interaction between repaglinide and PVP K_{30} was determined by using this method. The spectra of drug repaglinide, PVP K_{30} and solid dispersion particles were illustrated in Figure 6. The characteristic absorption peak of pure drug repaglinide (A) was obtained at 3307.2, 2935.1, 1216.6 and 781cm^{-1}. The interaction between drug and polymer was determined by comparing the IR spectra of drug and polymer with spectra of solid dispersion. The spectra of solid dispersion (C) show all of the characteristic peaks of drug and polymer at the same wave number except the O-H stretching vibration absorption peak of the drug. This absence may be attributed to the formation of hydrogen bonding between drug and polymer.[27] The formation of hydrogen bonding mainly results in the alteration of crystalline structure of drug,[28] proving the result obtained by DSC.

X-RD measurements

The powder X-ray diffraction study of pure drug, polymer and solid dispersion was shown in Figure 7. The presence of numerous peaks in the spectrum of drug repaglinide (A) depicted the crystalline nature of the drug. Absence of any peak in the spectrum of polymer (B) depicted its amorphous nature. Similarly, the absence of any characteristic peak of drug in the spectrum of solid dispersion showed the conversion of crystalline drug in its amorphous form which occurs due to its molecular dispersion within the amorphous carrier.[29] This result obtained through X-RD spectrum supports the DSC and FT-IR studies.

Scanning Electron Microscopy

The SEM image of repaglinide showed the crystalline structure while at different magnification and particle size of 10 µm and 20 µm respectively the surface of a solid dispersed particle of formulation S5 appeared to be amorphous, heterogeneous and porous in nature Figure 8. This appearance of amorphous form confirmed the loss of crystallinity of drug particles. The rough, coarser and porous surface of solid dispersion may offer enhanced bioadhesion.[30]

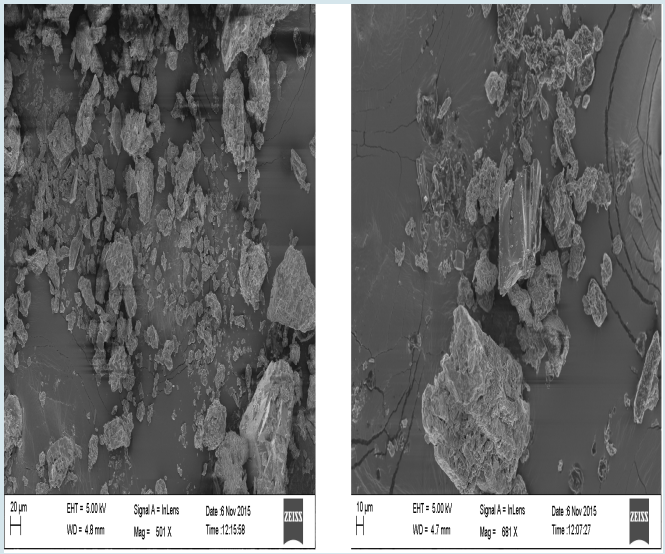

Figure 8: SEM Images of Solid dispersion formulation.

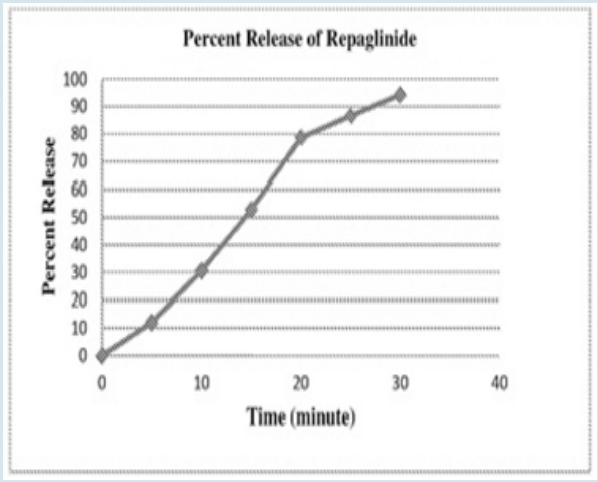

Figure 9: Percent drug release of Repaglinide form solid dispersion formulation.

Table 4: Stability study testing of final optimized formulation

Formulation Code	Percentage drug content				
S5	0 day	7th day	15th day	30th day	45th day
	91.88	91.82	91.78	91.84	91.79

In vitro Dissolution

The release of 90% of drug Repaglinide from standard dosage form within 30 min confirmed the enhanced dissolution of solid dispersion drug particles. The percent release of Repaglinide was illustrated in Figure 9.

Stability studies

The result obtained showed that there were no significant changes in the drug content of the dosage form (Table 4).

CONCLUSION

The dissolution capacity generally depends upon the contact angle at the liquid / air interface which can be decreased by focusing on the use of surfactant with a new approach of applying a layer over the final solid dispersed particles of poorly soluble drug. In this study, the solubility of poorly soluble Repaglinide was easily increased by formulating its solid dispersion particles with PVP K_{30} and surfactant Tween 80 and maximum solubility enhancement was achieved at a 1:20 w/w ratio of drug to PVP K_{30} containing tween 80 at 2% w/v. The importance of hydrophilic carrier PVP K_{30} was to allow easy dissolution of drug particles for which its presence at the surface was essential, but due to competition between drug and polymer to dominate the outer liquid/air interface their leads to decrease in solubility of the drug. Thus, the presence of Tween 80 at the external surface becomes essential, but the excess quantity on the outer surface could lead to stickiness within the particles or lump formation.

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CONFLICT OF INTEREST

None

ABBREVIATIONS USED

DSC: Differential Scanning Calorimetry; FT-IR: Fourier Transform Infrared; X-RD: X-ray Diffraction; SEM: Scanning Electron Microscopy; PVP K_{30}: Polyvinylpyrollidone; BCS: Biopharmaceutical Classification Systems.

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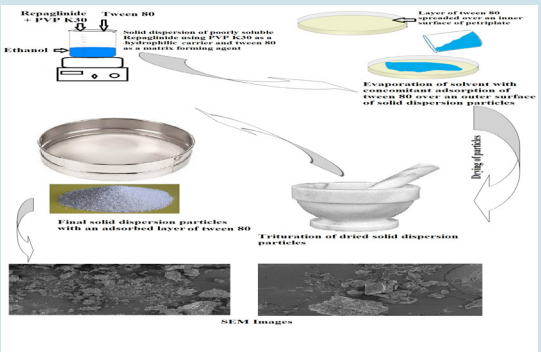
PICTORIAL ABSTRACT



SUMMARY

- The drawbacks of conventional technique were overcome by new approach.
- Application of the layer of tween 80 over the solid dispersed particles.
- Reducing contact angle and increasing wetting.
- Reducing size and allowing hydrophobic particles to remain suspended with poor settling.
- Suspended nanoparticles in turn enhanced dissolution.

ABOUT AUTHORS

Rahul Gupta: At the time of doing Research on the above topic. Project Scholar at Department of Pharmacy, Barkatullah University, Bhopal, Madhya Pradesh, India. Currently working as Assistant Professor, Department of Pharmacy, SMAS, Galgotias University, Greater Noida, U.P, INDIA.

Dr. A.K. Mishra: Assistant Professor, Department of Pharmacy, Barkatullah University, Bhopal, Madhya Pradesh, INDIA.

Dr. A.K. Pathak: Head Department of Pharmacy, Barkatullah University, Bhopal, Madhya Pradesh, INDIA.