Review Article

Solid dispersions: A boon for solubility enhancement

Tejvir Kaur

Department of Pharmacy, Government Medical College, Patiala, Punjab, India

Correspondence:
Dr. Tejvir Kaur, Department of Pharmacy, Government Medical College, Patiala, Punjab, India.
E-mail: tejvirkaur07@gmail.com

How to cite this article:
Kaur T. Solid dispersions: A boon for solubility enhancement. Innov Pharm Pharmacother 2020;8(4):121-127.

Source of Support: Nil.
Conflicts of Interest: None declared.

ABSTRACT

The rate-limiting step in oral absorption of Biopharmaceutical Classification System (BCS) Class II poorly water-soluble drugs is the dissolution process; thus, finding a simple and feasible means to improve this aspect is desirable. The most attractive and simplest approach to enhance the dissolution of poorly water-soluble drug is by increasing its solubility and/or available surface area for dissolution. Various techniques are used for solubility enhancement of poorly water soluble drugs. Formulation approaches include solubilization and particle size reduction techniques. Solid dispersions are more acceptable to patients than solubilization products, since they give rise to solid oral dosage forms instead of liquid as solubilization products usually do. Milling or micronization for particle size reduction is commonly performed as approaches to improve solubility, on the basis of the increase in surface area. Solid dispersions are more efficient than these particle size reduction techniques, since the latter have a particle size reduction limit around 2–5 mm which frequently is not enough to improve considerably the drug solubility or drug release in the small intestine and, consequently, to improve the bioavailability. Hence, solid dispersions prove a boon for the BCS Class II drugs as these results in enhancement of bioavailability.

Keywords: Bioavailability, Poorly water-soluble, Solid dispersions

Introduction

With the arrival of high-throughput screening of potential therapeutic agents and combinatorial chemistry, the number of poorly water-soluble drug candidates has climbed significantly.[1,2] Consequently, the formation of these compounds for oral delivery systems presents an increasing challenge in drug development in the pharmaceutical industry. Although many poorly water-soluble drugs fall into the Biopharmaceutical Classification System (BCS) Class II category, that is, high permeability and low solubility,[3,4] poorly water-soluble drugs in general exhibit less than desired oral bioavailability from solid dosage forms due to one or more of the four factors:[5] Low solubility and/or dissolution rate in the gastrointestinal tract, low membrane permeability, interactions with components of the gastrointestinal tract leading to the complex formation, metabolism in the liver, the gastrointestinal lumen or in the gastrointestinal mucosa.

The rate-limiting step in oral absorption of BCS Class II poorly water-soluble drugs is the dissolution process; thus, finding a simple and feasible means to improve this aspect is desirable.

Access this article online	
Website: www.innpharmacotherapy.com	**e-ISSN:** 2321-323X
Doi: 10.31690/ipp.2020.v08i04.003	**p-ISSN:** 2395-0781

The Noyes-Whitney Eq[6] provides a useful insight into parameters affecting the dissolution rate:

$$\frac{dc}{dt} = \frac{Ac(C_s - C)}{h} \quad (1)$$

Eq 1: Noyes-Whitney Equation

where dc/dt is the rate of dissolution, A is the surface area of the drug, D is the drug diffusion coefficient, C_s is the concentration of the drug at the drug particle surface (drug solubility), C is the concentration of the drug in the bulk dissolution medium at time t, and h is the diffusion boundary layer thickness.

Based on Eq 1, it is apparent that the dissolution rate can be enhanced by several means. The boundary layer thickness can be decreased, available surface area can be increased, sink conditions can be ensured during dissolution, and apparent solubility of the drug can be enhanced. Of the possible changes, altering boundary layer thickness, maintaining sink conditions, and changing the diffusion coefficient are difficult to achieve *in vivo*. The boundary layer thickness is a function of hydrodynamics which is a complex property to control *in vivo*.[7] The diffusion coefficient cannot be significantly increased without making large modifications to the drug molecule. Furthermore, preservation of sink condition depends on several factors including

drug permeability through the gastrointestinal mucosa.[8] However, permeation enhancement through the gastrointestinal tract cannot easily be achieved without damaging the gastrointestinal mucosal membrane.[9] Consequently, the most attractive and simplest approach to enhance the dissolution of poorly water-soluble drug is by increasing its solubility and/or available surface area for dissolution.

Factors Affecting Aqueous Solubility of Drug[10]

a. The entropy of mixing which favors complete miscibility of all components
b. The difference between the sum of drug-drug (DD) and water-water (WW) interactions in one hand and the drug-water (DW) interactions on the other. This difference is related to the activity coefficient of the drug in water γ_w by

$$RT \ln \gamma_{w} = DD + WW - 2DW \quad (2)$$

$$\text{If, } DD + WW - 2DW > 0 \quad (3)$$

as is usually the case for nonelectrolytes in water, there will be less than complete mixing and the drug will have a finite solubility in water. The greater the difference between the adhesive and cohesive interactions, the lower the solubility.

c. The additional DD interactions that are associated with the lattice energy of crystalline drugs (DD). This effect is measured as the ideal solubility of a crystalline solute X_i^C. The ideal solubility will be shown to be dependent upon the melting point and other thermodynamic properties of fusion. The ideal solubility of a solute represents the solubility of a solute in a perfect solvent, that is, a solvent for which the activity coefficient is equal to unity.

Mathematically, the observed solubility of a solute X_w is related to the ideal solubility and the activity coefficient by

$$\text{Log } X_w = \log X_i - \log \gamma_w \quad (4)$$

Both crystalline structure effects as reflected by X_i and solution interactions as reflected by γ_w can contribute to the insolubility of a solute.

Physical and Chemical Approaches Used to Improve Solubility

Various physical and chemical approaches used to achieve improvement to solubility and surface area are given in Table 1.[7]

Solid dispersion method provides a means for both improving the solubility and dissolution of poorly water-soluble drugs.

Solid dispersions

The term "solid dispersion" has been utilized to describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix, usually with a view to enhance oral bioavailability.[11] More specifically, these systems are defined as the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting-solvent method.[12]

Table 1: Methods for improving drug solubility and/or surface area for dissolution

Method	Limitations
Physical modifications	
Particle size reduction	Aggregation, agglomeration Poor wettability Handling difficulties
Modification to crystal structure (polymorphs, pseudopolymorphs)	Stability issues
Complexation and/or solubilization	Toxicity issues
Drug solid dispersions in carriers	Scale up and stability issues
Chemical modifications	
Salt formations	Not feasible for neutral compounds
Prodrugs	Limited application

Solid Dispersions Can Be Classified Into Three Categories

First generation solid dispersions

The first description of solid dispersions was from Sekiguchi and Obi in 1961. They noted that the formulation of eutectic mixtures improve the rate of drug release and, consequently, the bioavailability of poorly water-soluble drugs.[13] In the same decade, several solid dispersions were described using poorly water soluble drugs, such as sulfathiazole[14] and chloramphenicol[13] using urea as high water-soluble carrier. These solid dispersions produced faster release and higher bioavailability than conventional formulations of the same drugs. The small particle size and the better wettability of the drug were the main reasons for the observed improvements in bioavailability. Later, Levy[15] and Kanig[16] developed solid dispersion systems, containing mannitol as carrier, by preparing solid solutions through molecular dispersions instead of using eutectic mixtures.[8] The observed improvements were attributed to faster carrier dissolution, releasing microcrystals or particles of drug.[17] These solid dispersions, which could be designed as first generation solid dispersions [Figure 1], were prepared using crystalline carriers. Crystalline carriers include urea[13,14,17] and sugars,[16] which were the first carriers to be employed in solid dispersions. They have the disadvantage of forming crystalline solid dispersions, which were more thermodynamically stable and did not release the drug as quickly as amorphous ones.

Second generation solid dispersions

In the late sixties,[18] it was observed that solid dispersions, where the drug was maintained in the crystalline state, might not be as effective as the amorphous, because the former were more thermodynamically stable.[18-20] Therefore, a second generation of solid dispersions appeared, containing amorphous carriers instead of crystalline. Indeed, the most common solid dispersions do not use crystalline

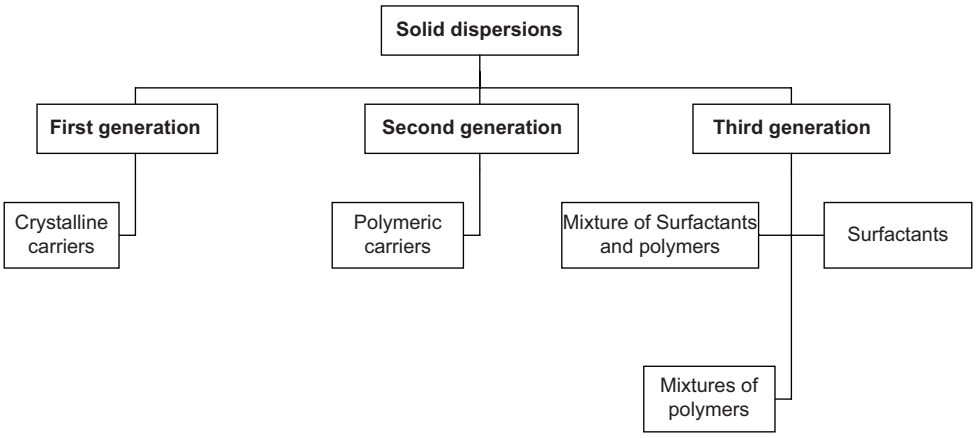

Figure 1: Classification of solid dispersions

carriers but amorphous. In the later, the drugs are molecularly dispersed in an irregular form within an amorphous carrier, which are usually polymers.[21] Polymeric carriers have been the most successful for solid dispersions, because they are able to originate amorphous solid dispersions. They are divided into fully synthetic polymers and natural product-based polymers. Fully synthetic polymers include povidone (PVP),[18,22-24] polyethylene glycols (PEG),[20,25-27] and polymethacrylates.[36] Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxypropylmethyl cellulose (HPMC),[28-30] ethylcellulose[30,34,35] or hydroxypropyl cellulose[31,32] or starch derivates, like cyclo dex- trins.[33]

In second-generation solid dispersions, the drug is in its supersaturated state because of forced solubilization in the carrier.[20,21,32] These systems are able to reduce the drug particle size to nearly a molecular level, to solubilize or codissolve the drug by the water soluble carrier, to provide better wettability and dispersibility of the drug by the carrier material, and to produce amorphous forms of the drug and carriers.[37] In these solid dispersions, the carrier dissolution (or mixtures of carriers) dictates the drug release profile.[8,30]

Third-generation solid dispersions

Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self-emulsifying properties; therefore, third-generation solid dispersions appeared. These contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. These third-generation solid dispersions are intended to achieve the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion avoiding drug recrystallization. The use of surfactants such as inulin,[22] Inutec SP1,[38] Compritol 888 ATO,[39] gelucire 44/14,[40,41] and poloxamer 407[15] as carriers was shown to be effective in originating high polymorphic purity and enhanced *in vivo* bioavailability. The association of amorphous polymers and surfactants has also been reported. For instance, the dissolution rate and bioavailability of LAB68, a poor water-soluble drug, were improved after being dispersed in a mixture of PEG and polysorbate 80. The bioavailability of this solid dispersion was ten-fold higher compared to the dry blend of micronized drug. In addition, the solid dispersion system was physically and chemically stable for at least 16 months.[42] HPMC was also associated with poloxamer and polyoxyethylene hydrogenated castor oil to prepare an amorphous felodipine solid dispersion.[28] The inclusion of surfactants in the formulation containing a polymeric carrier may help to prevent precipitation and/or protect a fine crystalline precipitate from agglomeration into much larger hydrophobic particles.[43]

Mechanism of Drug Release from Solid Dispersion

There are two sets of observations with regard to the mechanism of drug release from solid dispersions.

Carrier-controlled release

Corrigan provided a very valuable contribution by not only measuring the dissolution rate of the incorporated drug but also assessing that of the polymer itself, in this case PEG. He found that the dissolution rate of the drug in the polymer and the polymer alone were in fact equivalent, leading to the suggestion of carrier-controlled dissolution whereby the dissolution rate of the drug is controlled by that of the inert carrier.[44] This finding was supported by the work of Dubois and Ford who noted that the dissolution rates of a range of drugs in a single carrier, prepared under comparable conditions, were identical in most cases.[45]

In this instance the particles dissolve into the polymer-rich diffusion layer at a sufficiently rapid rate that there is insufficient time for the particles to be released intact into the medium. Consequently, the drug is molecularly dispersed within this concentrated layer.[11]

Drug-controlled release

Sjokvist and Nystrom measured the particle size of the griseofulvin particles released from the dispersions and produced strong evidence that dissolution rate enhancement was a direct function of the size of the released particles.[46] In an attempt to reconcile these contradictions Sjo¨ kvist-Saers and Craig used an homologous series of drugs (para-aminobenzoates) in PEG 6000 in an attempt to interrelate the solid state structure, drug solubility, and dissolution rate.[47]

These authors noted that there was a linear relationship between the intrinsic dissolution rate of the model drugs in the dispersions and the drug solubility, clearly linking the properties of the drug (and not the polymer) to the dissolution rate; it may be helpful at this stage to refer to such behavior as drug-controlled dissolution as opposed to carrier-controlled dissolution.[46,47]

Here, the dissolution into the polymer diffusion layer is comparatively slow and the drug is released as solid particles. Consequently, the dissolution will not be associated with the polymer but will instead be dominated by the properties (size, physical form, etc.) of the drug itself.

Advantageous Properties of Solid Dispersions

Increase in dissolution rate of poorly water soluble drugs by solid dispersion is achieved due to the properties of solid dispersions. These properties include:

Reduction in particle size

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers.[8] A high surface area is formed, resulting in an increased dissolution rate and, consequently, and improved bioavailability.[48,49]

Improvement in wettability

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions.[50] It was observed that even carriers without any surface activity, such as urea[13] improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts, when used, can significantly increase the wettability properties of drugs. Moreover, carriers can influence the drug dissolution profile by direct dissolution or cosolvent effects.[8,43,51] Recently, the inclusion of surfactants[38,52] in the third-generation solid dispersions reinforced the importance of this property.

Particle with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity.[53] The increase in porosity also depends on the carrier properties, for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate.[54] The increased porosity of solid dispersion particles also hastens the drug release profile.[53,54]

Changes in crystal form

Poorly water-soluble crystalline drugs, when in the amorphous state tend to have higher solubility.[55,56] The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process.[57] In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form.[8,38,50] For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them.[19]

Reduction in aggregation and agglomeration of hydrophobic drugs

Presence of carriers reduces aggregation and agglomeration of drug particles which will further increase the surface area available for dissolution.[58,59]

Factors Affecting Release Rate of Drugs from Solid Dispersions

Influence of nature of carriers on drug release

Release rate of drug from solid dispersion depends on the nature of carrier whether it is hydrophilic or hydrophobic.[60,61] Thus, incorporation of water-soluble drug with inert slightly water-soluble carrier leads to retardation of drug release from matrix.

Influence of drug carrier ratio

The dissolution rate increases with increase in proportion of carrier.[62] However, after certain limit dissolution rate decreases, for example, 38-fold increase in dissolution rate was reported with piroxicam:PVP[63] ratio as 1:4 than of the pure drug. However, further increase of PVP concentration; the dissolution rate decreases. It has been suggested that leaching out of the carrier during dissolution might cause this decrease in dissolution rate with increase in carrier proportion. This leached out carrier then can form concentrated layer of solution around the drug particles resulting in slowing down of migration of released drug particles.

Synergistic effect of two carriers used

This has been exemplified in ibuprofen solid dispersion using PEG; talc and PEG-talc as dispersion carriers. It was reported that in 9.1% drug loading, the ibuprofen amount dissolved was about 66% from ibuprofen-talc dispersion, 73% from ibuprofen-PEG dispersion, and 93% from ibuprofen PEG-talc dispersion at the end of 120 min. The synergistic effect was explained by the partial replacement of PEG with talc. This would cause improved wettability of ibuprofen and enhanced solubility of drug by overlapping the diffusion layers between PEG and ibuprofen.[65]

Influence of method of preparation

Solid dispersion prepared by melting method generally shows faster dissolution rate than solvent evaporation method.[65] For example,

solid dispersion of 10 and 20% griseofulvin-PEG 6000 prepared by solvent evaporation is much slower than those prepared by melting method.[66,67] The average mean particle size for the melting method ranges between 1.8 and 2.1 μm in low concentration of Griseofulvin-PEG 3000 solid dispersion and which is smaller than that for the corresponding dispersion prepared by solvent method.[66] Further, white cloudy system was obtained after evaporation of solvent indicating coarser particulate dispersion. In case of melting method, higher temperature combined with rapid cooling gives smaller particle size. Furthermore, in case of solvent evaporation method of griseofulvin-PEG 3000 solid dispersion, the solubility increase was 9.6 mg/ml irrespective of drug concentration.[62] Solid dispersion prepared by melting method with low concentration of griseofulvin (1%, 2%, and 4% w/w) gave an average solubility close to 11 mg/l and for higher concentration of griseofulvin (10% and 20% w/w) solubility increases to 12 mg/l.

Influence of cooling conditions of solid dispersion

In melting technique for preparation of solid dispersion, the dispersion is formed by incorporating the drug in a melted carrier; followed by cooling. The method of cooling whether slow or flash cooling affects the rate of dissolution. For instance, PEG 6000-Tolbutamide (2:1) dispersion,[68] the melt is cooled by two processes. First process involved flash cooling by placing melt on aluminum dish and then in a bath of dry ice and acetone. Second process involves slow cooling in oil bath under ambient conditions. The percent drug release after 6 min was reported 36.9 ± 5.39 (Process 1) and 29.7 ± 2.6 (Process II). This 15% more drug release in case of flash cooled dispersion was due to the difference in particle size; as flash cooled dispersion gives smaller particle size and low crystallinity.

Effect of vehicle amphiphilicity

It has been reported that as the proportion of amphiphilic vehicle increases; the dissolution rate and amount dissolved also increases. It is due to the fact that the amphiphilic proportion of vehicle emulsifiers the drug in aqueous media. As a result of this effect, the dissolution and dispersibility of the drug in simulated gastric fluid and water, respectively, are complete.

Various examples of types of physicochemical structures of solid dispersions are shown in Table 2.

Table 2: Examples of various physicochemical structures of solid dispersions

Type	Drug	Carrier
Eutectics[60,89]	Phenobarbitone	Urea
	Acetaminophen	Urea
	Primidone	Citric acid
	Chloramphenicol	Urea
	Khellin	Urea
	Tolbutamide	Mannitol, PEG 2000
Solid solutions[60]	Sulfathiazine	Urea
	Indomethacin	PEG
	Griseofulvin	Pentaerythritol
	Digitoxin	PEG
	Hydrocortisone acetate	PEG
Glass formation	Griseofulvin	Citric acid
	Phenobarbital	Citric acid
Complexation	Flurbiprofen[60]	Cyclodextrin
	Benzodiazepines[61]	Cyclodextrin
	Spironolactone[62]	Cyclodextrin
	Cinnamic and derivatives[63]	Cyclodextrin
	Indomethacin/Griseofulvin[64]	α, β, and γ Cyclodextrin

Conclusion

Improving drug bioavailability by changing their water solubility has been possible by chemical or formulation approaches.

Chemical approaches to improve bioavailability without changing the active target can be achieved by salt formation or by incorporating polar or ionizable groups in the main drug structure, resulting in the formation of a pro-drug. Solid dispersions appear to be a better approach to improve drug solubility than these techniques, because they are easier to produce and more applicable.

References

1. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Del Rev 1997;23:3-25.
2. Khandurina J, Guttman A. Microchip-based high-throughput screening analysis of combinatorial libraries. Curr Opin Chem Biol 2002;6:359-66.
3. Amidon LG, Lennernas H, Shah VP, Crison JR. A Theretical basis for a biopharmaceutic drug classification: The correlation of *in vivo* drug product dissolution and *in vivo* bioavailability. Pharm Res 1995;12:413-20.
4. Lobenberg R, Amidon GL. Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards. Eur J Pharm Biopharm 2000;50:3-12.
5. Mooter GV, Brande JV, Augustijns P, Kinget R. Glass forming properties of benzodiazepines and Co-evaporate system with poly(Hydroxyethyl methacrylate). J Therm Anal Calorim 1999;57:493-507.
6. Noyes AA, Whitney WR. The rate of solutions of solid substances in their own solutions. J Am Chem Soc 1897;19:930-4.
7. Sethia S, Squillante E. Solid dispersions: Revival with greater possibilities and applications in oral drug delivery. Crit Rev Ther Drug Carrier Syst 2003;20:215-47.
8. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersion. Eur J Pharm Biopharm 2000;50:47-60.
9. Aungst BJ. Intestinal permeation enhancers. J Pharm Sci 2000;89:429-42.
10. Yalkowsky SH. Techniques of Solubilization of Drugs. New York, Basel: Marcel Dekker, Inc.; 1981. p. 2-3.
11. Craig DQ. The mechanism of drug release from solid dispersions in water-soluble polymers. Int J Pharm 2002;231:131-44.
12. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci 1971;60:1281-302.
13. Sekiguchi K, Obi N, Ueda Y. Studies on absorption of eutectics mixure. II. absorption of fused conglomerates of chloramphenicol and urea in rabbits. Chem Pharm Bull 1964;12:134-44.
14. Sekiguchi K, Obi N. Studies on absorption of eutectics mixtures. I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man. Chem Pharm Bull 1961;9:866-72.
15. Levy G. Effect of particle size on dissolution and gastrointestinal absorption rates of pharmaceuticals. Am J Pharm Sci 1963;135:78-92.

16. Kanig JL. Properties of fused mannitol in compressed tablets. J Pharm Sci 1964;53:188-92.
17. Goldberg AH, Gibaldi M, Kanig JL, Mayersohn M. Increased dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures. IV. Chloramphenicol-urea system. J Pharm Sci 1966;55:581-3.
18. Simonelli AP, Mehta SC, Higuchi WI. Dissolution rates of high energy polyvinylpyrrolidone(PVP)-sulfathiazole coprecipitates. J Pharm Sci 1969;58:538-49.
19. Vippagunta SR, Wang Z, Horhung S, Krill SL. Factors effecting the formation of eutectic solid dispersions and their dissolution behavior. J Pharm Sci 2007;96:294-304.
20. Urbanetz NA. Stabilization of solid dispersions of nimodipine and polyethylene glycol 2000. Eur J Pharm Sci 2006;28:67-76.
21. Vilhelmsen T, Eliasen H, Schaefer T. Effect of a melt agglomeration process on agglomerates containing solid dispersions. Int J Pharm 2005;303:132-42.
22. Van Drooge DJ, Hinrichs WL, Visser MR, Frijlink HW. Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques. Int J Pharm 2006;310:220-9.
23. Karavas E, Georgarakis E, Bikiaris D. Application of PVP/HPMC miscible blends with enhanced mucoadhesive properties for adjusting drug release in predictable pulsatile chronotherapeutics. Eur J Pharm Biopharm 2006;64:115-26.
24. Hasegawa S, Hamaura T, Furuyama N, Kusai A, Yonemochi E, Terada K. Effects of water content in physical mixture and heating temperature on crystallinity of troglitazone-PVP K30 solid dispersions prepared by closed melting method. Int J Pharm 2005;302:103-12.
25. Prabhu S, Ortega M, Chan M. Novel lipid-based formulations enhancing the *in vitro* dissolution and permeability characteristics of a poorly water-soluble model drug, piroxicam. Int J Pharm 2005;301:209-16.
26. Guyot M, Fawaz F, Bildet J, Boninin F, Lagueny AM. Physicochemical characterization and dissolution of norfloxacin/cyclodextrin inclusion compounds and PEG solid dispersions. Int J Pharm 1995;123:53-63.
27. Chiou WL, Riegelman S. Oral absorption of griseofulvin in dogs: Increased absorption via solid dispersion in polyethylene glycol 6000. J Pharm Sci 1970;59:937-42.
28. Won DH, Kim MS, Lee S, Park JS, Hwang SJ. Improved physicochemical characterization of felodipine solid dispersion particles by supercritical anti-solvent precipitation process. Int J Pharm 2005;301:199-208.
29. Kono H, Taylor LS. Influence of different polymers on the crystallization tendency of molecularly dispersed amorphous felodipine. J Pharm Sci 2006;95:2692-705.
30. Ohara T, Kitamura S, Kitagawa T, Terada K. Dissolution mechanism of poorly water-soluble drug from extended release solid dispersion system with ethylcellulose and hydroxypropylmethylcellulose. Int J Pharm 2005;302:95-102.
31. Tanaka N, Imai K, Okimoto K, Ueda S, Tokunaga Y, Ibuki R, *et al*. Development of novel sustained-release system, disintegration-controlled matrix tablet (DCMT) with solid dispersion granules of nilvadipine (II): *In vivo* evaluation. J Control Release 2006;112:51-6.
32. Tanaka N, Imai K, Okimoto K, Ueda S, Tokunaga Y, Ohike A, *et al*. Development of novel sustained-release system, disintegration-controlled matrix tablet (DCMT) with solid dispersion granules of nilvadipine. J Control Release 2005;108:386-95.
33. Rodier E, Lochard H, Sauceau M, Letourneau JJ, Freiss B, Fages J. A three step supercritical process to improve the dissolution rate of eflucimibe. Eur J Pharm Sci 2005;26:184-93.
34. Desai J, Alexander K, Riga A. Characterization of polymeric dispersions of dimenhydrinate in ethyl cellulose for controlled release. Int J Pharm 2006;308:115-23.
35. Verreck G, Decorte A, Heymans K, Adriaensen J, Liu D, Tomasko D, *et al*. Hot stage extrusion of p-amino salicylic acid with EC using CO_2 as a temporary plasticizer. Int J Pharm 2006;327:45-50.
36. Haung J, Wigent RJ, Bentzley CM, Schwartz JB. Nifedipine solid dispersion in microparticles of ammonio methacrylate copolymer and ethylcellulose binary blend for controlled drug delivery: Effect of drug loading on release kinetics. Int J Pharm 2006;319:44-54.
37. Damian F, Blaton N, Naesens L, Balzarini J, Kinget R, Augustijns P, *et al*. Physicochemical characterization of solid dispersions of the antiviral agent UC-781 with polyethylene glycol 6000 and gelucire 44/14. Eur J Pharm Sci 2000;10:311-22.
38. Mooter Van Den G, Weuts I, Ridder TD, Blaton N. Evaluation of inutec SPI as a new carrier in the formulation of solid dispersions for poorly soluble drugs. Int J Pharm 2006;316:1-6.
39. Li FQ, Hu JH, Deng JX, Su H, Xu S, Liu JY. *In vitro* controlled release of sodium ferulate from compritol 888 ATO-based matrix tablets. Int J Pharm 2006;324:152-7.
40. Chauhan B, Shimpi S, Paradkar A. Preparation and evaluation of glibenclamide-polyglycolized glucerides solid dispersions with silicon dioxide by spray drying technique. Eur J Pharm Sci 2005;26:219-30.
41. Yuksel N, Karatas A, Ozkan Y, Savaser A, Ozkan SA. Baykara T. Enhanced bioavailability of piroxicam using gelucire 44/14 and labrasol: *In vitro* and *in vivo* evaluation. Eur J Pharm Biopharm 2003;56:453-9.
42. Dannenfelser RM, He H, Joshi Y, Bateman S, Serajuddin AT. Development of clinical dosage forms for a poorly water-soluble drug I: Application of polyethylene glycol-polysorbate 80 solid dispersion carrier system. J Pharm Sci 2004;93:1165-75.
43. Pouton CW. Formulation of poorly water-soluble drugs for oral administration: Physicochemical and physiological issues and the lipid formulation classification system. Eur J Pharm Sci 2006;29:278-87.
44. Corrigan OI. Retardation of polymeric carrier dissolution by dispersed drugs: Factors influencing the dissolution of solid dispersions containing polyethylene glycol. Drug Dev Ind Pharm 1986;12:1777-93.
45. Dubois JL, Ford JL. Similarities in the release rates of different drugs from polyethylene glycol 6000 dispersions. J Pharm Pharmacol 1985;37:494-5.
46. Sjokvist E, Nystrom C. Physicochemical aspects of drug release VI. Drug dissolution from solid particulate dispersions and the importance of carrier and dug particle properties. Int J Pharm 1991;69:53-62.
47. Sjokvist-Saers E, Craig DQ. An investigation into the mechanism of dissolution of alkyl p-aminobenzoates from polyethylene glycol solid dispersions. Int J Pharm 1992;83:211-9.
48. Torrado S, Torrado S, Torrado JJ, Cadorniga R. Preparation, dissolution and characterization of albendazole solid dispersions. Int J Pharm 1996;140:247-50.
49. Bikiaris D, Papageorgiou GZ, Stergiou A, Pavlidou E, Karavas E, Kanaze F, *et al*. Physicochemical studies on solid dispersions of poorly water-soluble drugs: Evaluation of capabilities and limitations of thermal analysis techniques. Thermochim Acta 2005;439:58-67.
50. Karavas E, Ktistis G, Xenakis A, Georgarakis E. Effect of hydrogen bonding interactions on the release mechanism of felodipine from nanodispersions with polyvinylpyrrolidone. Eur J Pharm Biopharm 2006;63:103-14.
51. Kang BK, Lee JS, Chon SK, Jeong SY, Yuk SH, Khang G, *et al*. Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. Int J Pharm 2004;274:65-73.
52. Ghebremeskel AN, Vemavarapu C, Lodaya M. Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: Selection of polymer-surfactant combinations using solubility parameters and testing the processability. Int J Pharm 2007;328:119-29.
53. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today 2007;12:1068-75.
54. Ghaderi R, Artursson P, Carlfors J. Preparation of biodegradable microparticles using solution-enhanced dispersion by supercritical fluids (SEDS). Pharm Res 1999;16:676-81.
55. Pokharkar VB, Mandpe LP, Padamwar MN, Ambike AA, Mahadik KR, Paradkar A. Development, characterization and stabilization of amorphous form of a low T_g drug. Powder Technol 2006;167:20-5.

56. Lloyd GR, Craig DQ, Smith A. A calorimetric investigation into the interaction between paracetamol and polyethylene glycol 4000 in physical mixes and solid dispersions. Eur J Pharm Biopharm 1999;48:59-65.
57. Taylor LS, Zografi G. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. Pharm Res 1997;14:1691-8.
58. Mummaneni V, Vasavada RC. Solubilization and dissolution of famotidine from solid glass dispersions of xylitol. Int J Pharm 1990;66:71-7.
59. Craig DQ, Newton JM. The dissolution of nortriptyline HCL from polyethylene glycol solid dispersions. Int J Pharm 1992;78:175-82.
60. Bloch DW, Speiser PP. Solid dispersions-fundamentals and examples. Pharm Acta Helv 1987;62:23-7.
61. Serajuddin AT, Sheen PC, Mufson D, Bernstein DF, Augustine MA. Effect of vehicle amphiphilicity on the dissolution and bioavailability of a poorly water-soluble drug from solid dispersions. J Pharm Sci 1988;77:414-7.
62. Rabasco AM, Gines JM, Arevalo MF, Holgado MA. Dissolution rate of diazepam from polyethylene glycol 6000 solid dispersions. Int J Pharm 1991;67:201-5.
63. Tantishaiyakul V, Kaewnopparat N, Ingkatawornwong S. Properties of solid dispersions of piroxicam in polyvinylpyrrolidone K-30. Int J Pharm 1996;143:59-66.
64. Fernandez M, Margarit MV, Rodriguez IC, Cerezo A. Dissolution kinetics of piroxicam in solid dispersions with polyethylene glycol 4000. Int J pharm 1993;98:29-35.
65. Khan GM, Jiabi Z. Preparation, characterization, and dissolution studies of ibuprofen solid dispersions using polyethylene glycol (PEG), Talc, and PEG-Talc as dispersion carriers. Drug Dev Ind Pharm 1998;24:455-62.
66. Chiou WL, Reigelman S. Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. J Pharm Sci 1969;58:1505-10.
67. Sjokvist E, Nystrom C. Physicochemical aspects of drug release. VI. drug dissolution rate from solid particulate dispersions and the importance of carrier and drug particle properties. Int J Pharm 1988;47:51-66.
68. McGinity JW, Maincent P, Steinfink H. Crystallinity and dissolution rate of tolbutamide solid dispersions prepared by the melt method. J Pharm Sci 1984;73:1441-4.