" Enhancement of Solubility of poorly water soluble drug by solid dispersion technique"

V.R.Tagalpallewar[1*], M.A.Ughade, Dr.N.H.Indurwade, P.G.Kubare, A.A.Chintawar

(1*) Asst.Lecturer, Ishwar Deshmukh institute of pharmacy, Digras- 445203

ABSTRACT:

Atovaquone and Satrinidazole has poor solubility resulting in low oral absorption hence low oral bioavailability. Hence to improve the solubility of poorly Atovaquone and Satrinidazole , hydrophilic polymers were used to enhance the dissolution by solid dispersion technique. Polyehylene Glycol 4000 and PVP k30 used to enhance the dissolution of both the drug by Solubilisation. Many alternative techniques have been used to improve such bioavailability; this study thus employed the simple solid dispersion technique and incorporated excipients which can increase the bioavailability of these drugs directly enhancing the dissolution rate of the drug and indirectly by reducing particle size.The aim of present work is to enhance the dissolution of poorly water soluble drug by using solid dispersion technique. To improve the dissolution rate, by using the various concentration of carrier or matrix with drug and hence ,improve the bioavailability of poorly water soluble drug by formulating solid dispersion.To enhance the solubility of poorly water soluble drug ,by means of solubilising agent. In case of poorly water soluble drug , dissolution may be the rate limiting step in the process of absorption. In such case ,we can improve their solubility and dissolution rate.To study the effect of surfactant on the solid dispersion of poorly water soluble drug.

Keywords: Solubilisation, solid dispersion, Polyehylene Glycol, bioavailability, dissolution rate etc.

INTRODUCTION:

Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems associated with these drugs was its very low solubility in biological fluids, which results into poor bioavailability after oral administration[1,3,5]. A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption[6]. Therefore, pharmaceutical researchers, focuses on two areas for improving the oral bioavailability of drugs include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs [7]. It has been estimated that 40% of new chemical entities currently being discovered are poorly water soluble[8,9]. Unfortunately, many of these potential drugs are abandoned in the early stages of development due to the solubility problems. It is therefore important to realize the solubility problems of these drugs and methods for overcoming the solubility limitations are identified and applied commercially so that potential therapeutic benefits of these active Solid dispersion (SD) is one of such methods and involves a dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method[2,11]. The formulation of drugs having low aqueous solubility using solid dispersion technology has been an active area of research since 1960[12].Among the various approaches to improve solubility, the solid dispersion (SD) technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble drugs because it is simple, economic, and advantageous [13]. Solid dispersion means a group of solid products consisting of at least two different components, generally a hydrophilic inert carrier or matrix and a hydrophobic drug. The carrier can be either crystalline or amorphous in nature. Most commonly used carriers for the preparation of SDs are different grade of polyethylene glycols (PEGs) and polyvinylpyrollidine (PVPs), sugar etc.

1.1.Advantages of Solid Dispersion[10, 12]

1.Preparation of solid dispersions results in particles with reduced particle size and thus the surface area is improved and increased dissolution rate is attained. The ultimate result is improved bioavailability.

2.Wettability is improved during solid dispersion production. Improved wettability results in increased solubility. Here the carriers play the major role to improve the wettability of the particles.

3.Particles in solid dispersions have been found to have a higher degree of porosity. The increased porosity of solid dispersion particles accelerates the drug release profile. Increased porosity also depends on the carrier properties.

4.In solid dispersions drugs are presented as supersaturated solutions which are considered to be metastable polymorphic form. Thus presenting drugs in amorphous form increase the solubility of the particles.

5.Rapid dissolution rates that result in an increase in the rate and extent of the absorption of the drug, and a reduction in presystemic both can lead to the need for lower doses of the drug.

1.2. Disadvantages of Solid Dispersion[12]

1.2.1 The major disadvantages of solid dispersion are related to their instability. Several systems have shown changes in crystalline and a decrease in dissolution rate with aging. The crystallization of Ritonavir from the supersaturated solution in a soliddispersion system was responsible for the withdrawal of the Ritonavir capsule (Norvir, Abboft) from the market.

1.2.2 Moisture and temperature have more of a deterioratingeffect on solid dispersions than on physical mixtures. Some solid dispersion may not lend them to easy handling because of tackiness

1.3. LIMITATIONS OF SOLID DISPERSIONS[3]

Although a great research interest in solid dispersion in the past four decades, the commercial utilization is very limited. Problems of solid dispersion involve

1) The physical and chemical stability of drugs and vehicles,
2) Method of preparation, Reproducibility of its physicochemical properties
3) Formulation of solid dispersion into dosage forms, and
4) Scale-up of manufacturing processes[17].

1.4 Classification of Solid dispersion,

1.4.1. On the basis of carrier used

1.4.1.1. First generation

First generation solid dispersions were prepared using crystalline carriers such as urea and sugar,which were the first carriers to be employed in solid dispersion. They have the disadvantage of forming crystalline solid dispersion, which were thermodynamically more stable and did not release the drug as quickly as amorphous ones.

1.4.1.2. Second generation

Second generation solid dispersions include amorphous carriers instead of crystalline carriers which are usually polymers. These polymers include synthetic polymers such as povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates as well as natural product based polymers such as hydroxylpropylmethyl-cellulose (HPMC), ethyl cellulose, and hydroxypropoylcellulose or starch derivates like cyclodextrins.

1.4.1.3. Third generation

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. The use of surfactant such as inulin, inutec SP1, compritol 888 ATO, and poloxamer 407 as carriers was shown to be effective in originating high polymorphic purity and enhanced

in vivo bioavailability[6].

1.4.2. On the basis of solid state structure1.4.2.1. Drug and polymer exhibiting immiscibility in fluid state

If a drug and polymer are immiscible in their fluid state, it is expected that they would not exhibit miscibility on solidification of the fluid mixture. Such systems may be regarded as similar to their corresponding physical mixtures and any enhancement in dissolution performance may be owing to modification in morphology of drug and/or polymer due to physical transformation (i.e.,

solid to liquid state and back), intimate drug–polymer mixing, and/or enhanced surface area.Formation of crystalline or amorphous soliddispersions can be biased by the rate of solidification of mixture and the rate of crystallization of drug and/or polymer [9].

1.4.2.2. Drug and polymer exhibiting miscibility in fluid state

If the drug and polymer are miscible in their fluid state, then the mixture may or may not undergo phase separation during solidification, thereby influencing the structure of solid dispersion[9].

1.4.2.3. Eutectic Mixtures

Eutectic mixture was first described as solid dispersions in 1961 by Sekiguchi & Obi. Eutectic mixtures are formed when the drug and polymer are miscible in their molten state, but on cooling, they crystallize as two distinct components with negligible miscibility. When a drug (A) and a carrier (B) are co-melted at their eutectic composition defined by point ‘e’, as shown schematically in

Figure1, the melting point of the mixture is lower than the melting point of either drug or carrier alone. At the eutectic composition (e), both drug and carrier exist in finely divided state, which results in higher surface area and enhanced dissolution rate of drug. This was first reported for sulfathiazole-urea[10,11]. Other examples of

eutectic mixture include acetominophen-urea[12] and the dispersion of griseofulvin and tolbutamide in polyethylene glycol (PEG)-2000[13].

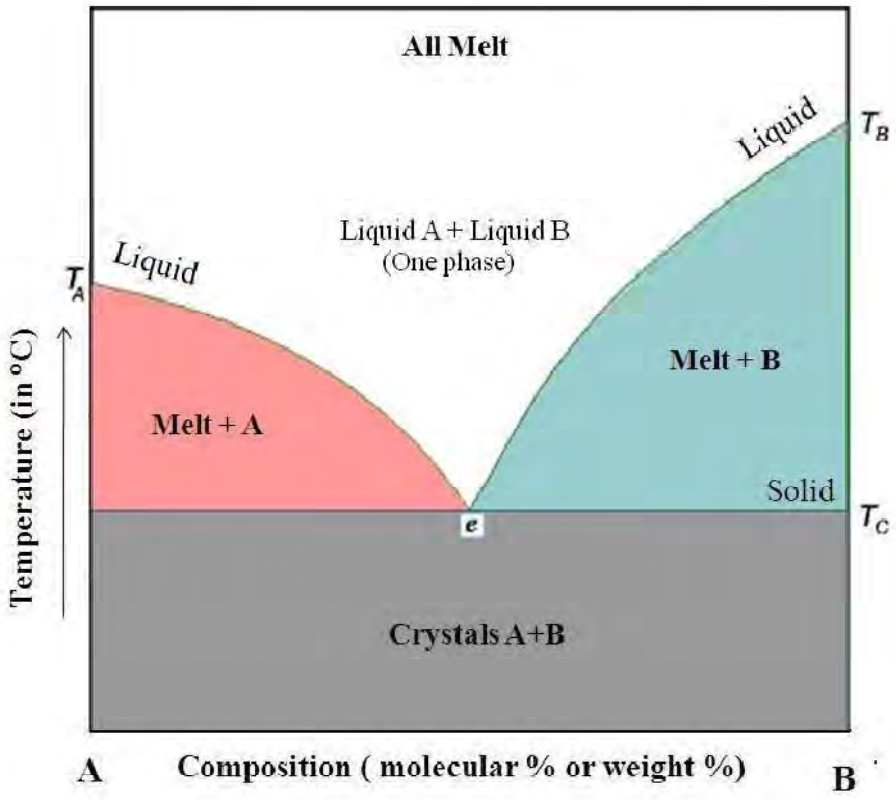

Figure 1: Phase diagram of a eutectic mixture

1.4.2.4. Crystalline Solid Dispersion

A crystalline solid dispersion (or suspension) is formed when the rate at which drug crystallizes from drug–polymer miscible mixture is greater than the rate at which drug–polymer fluid mixture solidifies [9].

1.4.2.5. Amorphous Solid Dispersion

If the drug–polymer fluid mixture is cooled at a rate that does not allow for drug crystallization, then drug is kinetically trapped in its amorphous or a

"solidified-liquid" state. These types of dispersions have the risk of potential for conversion to a more stable and less soluble crystalline form[9].

1.4.2.6. Solid Solution

Solid solution is a solid dispersion that is miscible in its fluid as well as solid state. These solid solutions may be either of amorphous or crystalline type. In

amorphous solid solutions as the drug is molecularly dispersed in the carrier matrix, its effective surface area is significantly higher and hence the dissolution rate is increased. Amorphous solid solutions have improved physical stability of

amorphous drugs by inhibiting drug crystallization by minimizing molecular mobility[14]. Crystalline solid solution may result when a crystalline drug is

trapped within a crystalline polymeric carrier. Poorly soluble drugs have been incorporated in carrier molecules using crystal inclusion and crystal

doping techniques [15], although the usage of such technologies has not yet gained widespread application in pharmaceutical product development. According to extent of miscibility of the two components, solid solutions are continuous or discontinuous type. In continuous solid solutions, the two components are miscible in the solid state in all proportions. The components that are immiscible at intermediate composition, but miscible at extremes of composition are referred to as discontinuous solid solutions. According to the criterion of molecular size of the two components, the solid solutions are classified as substitutional and interstitial [16]. In the substitutional solid solution, the solute molecule substitutes for the solvent molecule in the crystal lattice as shown in Figure 2. In this case, the molecular size of the two components should not differ by more than 15%. An interstitial solid solution is obtained when the solute (guest)molecule occupies the interstitial space in the

solvent (host) lattice. For this to occur, the solute molecule diameter should be less than 0.59 than that of solvent molecule[16]. Therefore, the volume of the solute molecule(s) should be less than 20% of the solvent molecule(s). Examples include solid solutions of digitoxin,methyltestosterone, predinsolone acetate and hydrocortisone acetate in the matrix of PEG 6000. They all exhibit faster rate of dissolution.

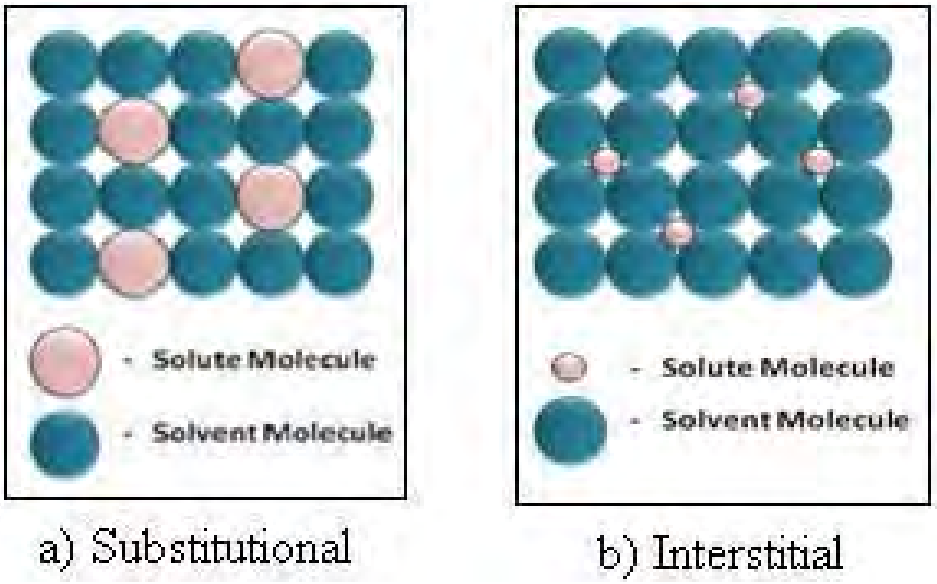

Figure 2: Schematic representation of substitutional and interstitial solid solutions

Goldberg et al., 1965 discussed the theoretical and practical advantageous of solid solution over eutectic mixtures. The reason for the improvement in dissolution rate is that drug has no crystal structure in solid solution. Therefore, the energy normally required to break up the crystalline structure of the drug before it can dissolved is not a limitation to the release of the drug from a solid solution. A further way in which a solid solution could enhance dissolution is through improvement of the wettability of the drug. Even carriers that are not surface active, e.g. urea and citric acid, can improve wetting characteristics. If carriers with surface activity such as cholic acid, bile salts, lecithine, are used the improvement in wetting can be much greater.

MATERIALS AND METHOD:

Materials

The drug, excipients, chemicals/reagents used for various experiments are enlisted as follows. All other chemicals and regents used were of analytical regent (AR) grade.

Table 1: List of materials used

Sr. No.	Name of materials	Manufacturer/Supplier
1	Atovaquone	Macleods pharmaceuticals,India
2	Satrinidazole	Macleods pharmaceuticals,India
3	Polyvinylprovidone K30 (PVP K30)	Macleods pharmaceuticals,India
4	Poly ethylene glycol 4000	Macleods pharmaceuticals
5	Methanol	Macleods pharmaceuticals
6	Ethanol	Macleods pharmaceuticals
7	Concentration Hydrochloric acid	Macleods pharmaceuticals

Equipments

Table 2: List of apparatus/ equipments/ instruments used

Sr. no.	Equipments/ Instruments	Source
1	UV –Visible Double Beam Spectrophotometer	Macleods pharmaceuticals
2	Fourier Transform Infra-Red Spectrophotometer	Macleods pharmaceuticals
3	Hot-air Oven	Macleods pharmaceuticals
4	Dissolution Test Apparatus USP XXII (Type-II)	Macleods pharmaceuticals
5	Electronic Weighing Balance (single pan)	Macleods pharmaceuticals
6	Digital pH Meter	Macleods pharmaceuticals
7	Differential Scanning Calorimeter	Macleods pharmaceuticals
8	X-Ray Differactometer	Macleods pharmaceuticals

RESULTS AND DISCUSSION

RESULTS

1. Preformulation study

Physical characters of Atovaquone were found as

Table 3: Physical characters of Atovaquone drug

Sr.no.	Characters	Inference
1	Nature	crystalline powder
2	Colour	Dark Yellow
3	Odor	Odorless
4	Taste	Slightly Bitter
5	Melting point	219-221^{o}C
6	Solubility- In methanol In water In ethanol	 Soluble Practically insoluble Freely soluble
7	Bulk density	0.217 gm/cm^3
8	Tapped density	0.385 gm/cm^3

Physical characters of Satrinidazole drug were found as

Table 4: Physical characters of Satrinidazole drug

Sr.no.	Characters	Inference
1	Nature	Crystalline powder
2	Color	Buff yellow
3	Odor	Odorless
4	Taste	Bitter
5	Melting point	201-204^{o}C
6	Solubility- In methanol In water In ethanol	 Soluble Poorly water soluble Freely soluble
7	Bulk density	0.313 gm/cm^3
8	Tapped density	0.357 gm/cm^3

Preparation of solid dispersion:

The solid dispersions of Atovaquone and Satrinidazole were prepared by solvent evaporation method.

Characterization of solid dispersion of Atovaquone and Satrinidazole:

The solid dispersions were characterized by

1. Micrometrics studies
2. Percentage yield of solid dispersion
3. Drug content
4. Solubility study
5. *In-vitro* dissolution study
6. DSC
7. SEM
8. XRD

Micromeritics studies

The results of micromeritics properties of solid dispersion formulations were as below

Table 5:Micrometrics studies of pure drugs and solid dispersion formulations

Parameters / Formulation code	Bulk density (g/cm^3)*	Tapped density (g/cm^3)*	Percentage Compressibility index	Hausner's ratio	Angle of repose
A1	0.217	0.385	43.48	1.77	46°25'
B1	0.323	0.327	9.68	1.1	27°15'
C1	0.333	0.37	10	1.11	30°14'
A2	0.313	0.357	12.5	1.14	31°47'
B2	0.294	0.334	11.76	1.13	30°46'
C2	0.334	0.385	13.33	1.15	28°18'

Percentage yield

The results of percentage yield of binary solid dispersion formulations were as below

Table 6: Percentage yield of solid dispersion formulations

Sr. no.	Formulation code	Percentage yield*
1	B1	79.91
2	C1	75.44
3	B2	75.16
4	C2	71.85

Drug content

The results of drug content of pure drug and their solid dispersion formulations were as below

Table 7: Percent drug content of solid dispersion formulations

Sr. no.	Formulation code	Percent drug content
1	B1	96.83
2	C1	89.46
3	B2	98.45
4	C2	96.55

Solubility study

The results of solubility study of binary solid dispersion formulations were as below

Table 8: Solubility (µg/ml) of pure drug and solid dispersion formulations

Sr. no.	Formulation code	Solubility (µg/ml)
1	A1	12.657
2	B1	40.880
3	C1	22.789
4	A2	12.75
5	B2	43.815
6	C2	16.151

***In-vitro* dissolution studies of solid dispersion formulations**

Table 9: Percent Drug release of pure drugs and solid dispersion formulations

Time (min)	Percentage of drug release (%)					
	A1	B1	C1	A2	B2	C2
0	0	0	0	0	0	0
5	0.740	9.68	1.35	15.43	19.01	1.43
10	4.08	14.86	23.23	38.53	29.96	25.57
15	8.97	21.31	40.54	46.85	33.82	27.60
20	18.72	29.79	35.41	43.73	38.75	31.02
30	20.01	33.83	49.22	51.06	42.78	32.69
45	24.96	43.16	45.44	61.92	43.94	37.69
60	26.43	54.48	49.49	65.80	51.33	48.96

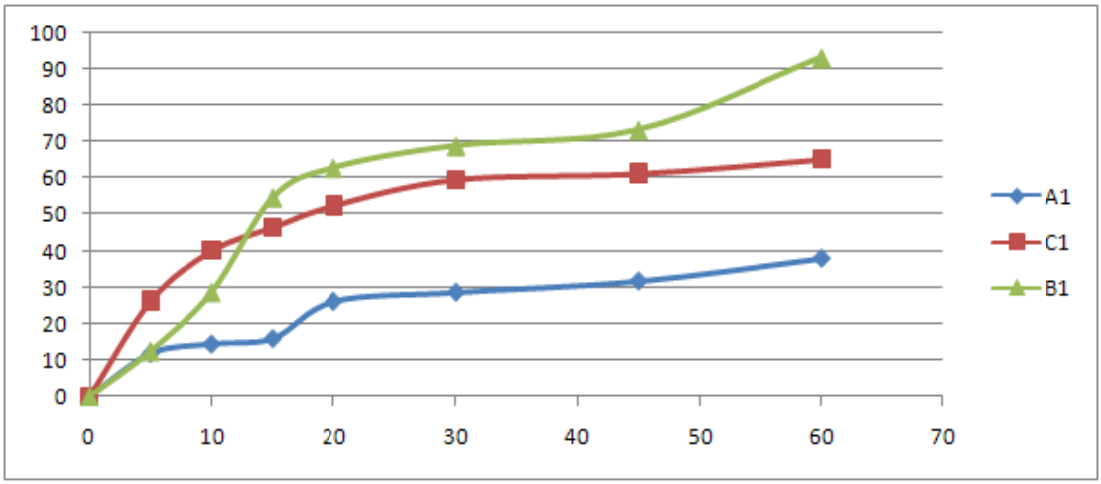

Figure 3: *In-vitro* dissolution profile of Atovaquone pure drug and its solid dispersion formulations

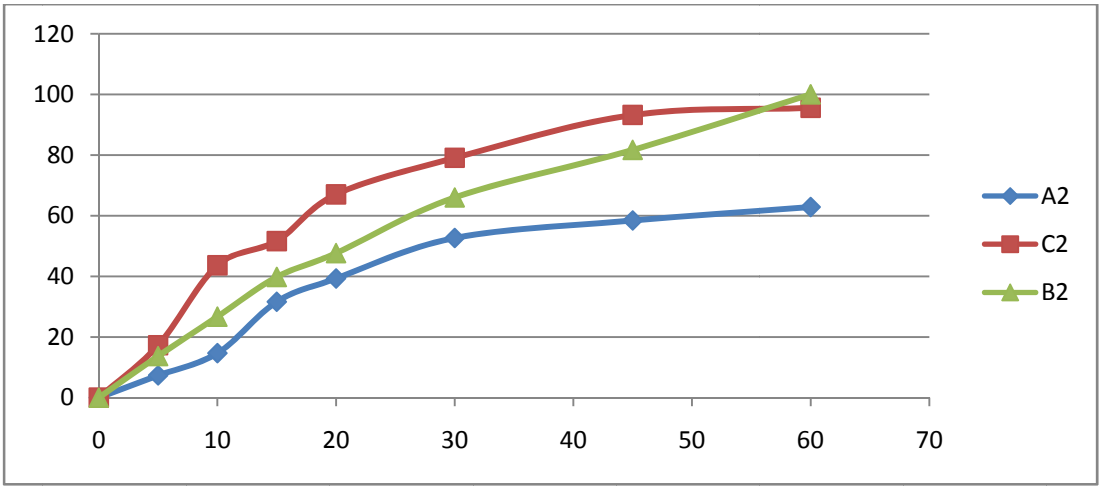

Figure 4: *In-vitro* dissolution profile of Satrinidazole pure drug and its solid dispersion formulations

SUMMARY AND CONCLUSION

Dissolution of drug is rate determining step for oral absorption of poorly water soluble drugs, which subsequently affect the *in-vivo* absorption of drug Solubility is the key parameter for the oral bioavailability of poorly water soluble drugs. Atovaquone and Satrinidazole are poorly soluble drugs and it also has poor bioavailability. Therefore many strategies have been worked out to improve its aqueous solubility as well as its release rate from various solid dosage forms and also improve the flow property for easily compression more are under constant investigation.In the present study, solid dispersion technique was evaluated for enhancement of solubility and the dissolution rate. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules.The products obtained by all these means were appropriately characterized and evaluated for enhancement of solubility and for their *in-vitro* dissolution

Atovaquone and Satrinidazole are potent antiprotozoal agent having high lipophilicity and poor aqueous solubility. It shows slow and variable absorption when administered orally. Thus the objective of the study was to formulate solid dispersion of both the drug ,in order to achieve a better dissolution rate which would further help in enhancing its oral bioavailability. Solid dispersion prepared with hydrophilic polymer showed a higher enhancement in solubility rate with PEG4000 i.e. 2-3 fold as compared to1.2 fold for that prepared with PVPk30. Further analysis was done on formulation prepared with Lipoid S100. DSC data indicated a depression in melting temperature and enthalpy for the formulation.XRD results indicated no change in crystal structure of drug in formulation. Lack of chemical interaction between drug and carrier was confirmed by the FT-IR spectra. The *in vitro* dissolution studies showed a significant increase in the dissolution rate of solid dispersions of Atovaquone and Satrinidazole as compared with pure drug, and physical mixtures of satranidazole with PEG 4000 and PVP K30.

Thus from the various studies conducted it may be concluded that solid dispersions of the poorly water soluble drug satranidazole and Atovaquone were successfully prepared by solvent evaporation method using hydrophilic polymers PEG 4000 and PVP K30.Therefore, it can be concluded that the solubility and the dissolution rate of poorly water soluble drug Atovaquone and satranidazole can be significantly enhanced by preparation of solid dispersions using hydrophilic polymers by solvent evaporation method.

REFERENCES:

[1] Chawla G, Bansal AK. Improved dissolution of a poorly water soluble drug in solid dispersion with polymeric and nonpolymeric hydrophillic additives. Acta Pharma. 2008; 58:257-274.

[2] Dabbagh S, Taghipour B. Investigation of solid dispersion technique in improvement of physiochemical characteristics of ibuprofen powder. Iranian Journal of Pharmaceutical Sciences. 2007; 3:69-76.

[3] Pathak D, Dahiya S, Phatak K. Solid dispersion of meloxicam factorial design dosages form for gastric population. Acta Pharm. 2008; 58:99-110.

[4] Karanth H, Shenoy VS, Murthy RR. Industrially feasible alternative approaches in the manufacture of solid dispersion; A technical report. AAPS Pharmscitech. 2006; 7:E1-E8.

[5] Chiou WL, Riegelman S. Pharmaceutical application of solid dispersion. J Pharm Sci. 1971; 60:1281-1302.

[6] Vasconcelos T, Sarmanto B, Costa P. Solid dispersion as strategy to improve oral bioavailability of poorly water soluble drugs. J Pharm Sci. 2007; 12:1068-1075.

[7] Serajuddin A, Sheen PC, Agustine MA. Improved dissolution of a poorly water soluble drug from solid dispersion in polyethylene glycol; polysorbate 80 mixtures. J Pharm Sci. 1990; 79:463-464.

[8] Heo MY, Piao ZP, Kim TW, Cao QR, Kim A, Lee BJ. Effect of solubilizing and microemulsifying excipient in polyethyleneglycol 6000 solid dispersion on enhanced dissolution and bioavailability of ketoconazole. Arch Pharm Res. 2005; 28:604- 611.

[9] Liu R. Water-Insoluble drug formulation. New York: CRC Press. 2nd ed. 2008; 522.

[10] Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm. 2000; 50:47–60.

[11] Sekiguchi K, Obi N. Studies on absorption of eutectic mixtures, I. A comparison of the behavior of eutectic mixtures of sulphathiozole and that of ordinary sulphathiozole in man. Chem Pharm Bull. 1961; 9:866-872.

[12] Goldberg AH, Gibaldi M, Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drug via solid solutions and eutectic mixture II-experimental evaluation of a eutectic mixture; urea-acetominophen system. J Pharm Sci. 1966; 55:482-487.

[13] Kaur R, Grant DJW, Eaves T. Comparision of poly (ethylene glycol) and polyoxy ethylene sterate as excipients for solid dispersions system of griseofulvin and tolbutamide II: Disslution and solubility studies. J Pharm Sci. 1980; 69:1321-1326.

[14] Yoshioka MB, Hancock C, Zogra G. Inhibition of indomethacin crystallization in poly (vinylpyrrolidone) coprecipitates. J Pharm Sci. 1995; 84:983–986.

[15] Vishweshwar R, JA Mahon, JA Bis, MJ Zaworotko. Pharmaceutical co-crystals. J Pharm Sci. 2006; 95:499–514.

[16] Vadnere MK. Co-precipitates and Melts. In: Swarbrick J, Boylan JC, editors. Encyclopedia of pharmaceutical technology. New York: Marcel Dekker Inc; 1990.

[17] Craig DQM. The mechanism of drug release from solid dispersion in water soluble polymers. Int J Pharm. 2002; 231:131-144.

[18] Arise MJ, Gines JM, Moyano JR, Perez M. Influence of preparation method of solid dispersions their dissolution rate; Study of triamterene d-mannitol system. Int J Pharm. 1995; 123:25-31.

[19] Chiou WL, Riegelman S. Preparation and dissolution characteristics of several fastrelease solid dispersion of griseofulvin. J Pharm Sci. 1969; 55:1505-1510.

[20] Kanig JL. Properties of fused mannitol in compressed tablets. J Pharm Sci. 1964;53:188-192.

[21] Walker SE, Gangley JA, Bedford K, Eaves T. The filling of molten and thyrotrophic formulations into hard gelatin capsule. J Pharm Pharmacol. 1980; 32:389-393.

[22] Dressman J, Leunne C. Improving drug solubility for oral delivery using solid dispersions. Review article. Eur J Pharm Biopharm. 2000; 50:47-60.

[23] Sharma DK, Joshi SB. Solubility enhancement strategies for poorly water soluble drug in solid dispersion: A Review. Asian Journal of Pharmaceutics. 2007; 1:9-19.

[24] Ambike AA, Mahadik KR, Paradkar A. Spray dried amorphous solid dispersions of simvastatin, a low Tg drug: In vitro and in vivo evaluations. Pharm Res. 2005; 22:990– 998.
[25] Takayama K, Nambu N, Nakai T. Factor affecting the dissolution of ketoprofen from solid disoersion in various water soluble polymers. Chem Pharm Bull. 1982; 30:673- 677.
[26] Subramanian B, Rajewski RA, Snavely K. Pharmaceutical processing with supercritical carbon dioxide. J Pharm Sci. 1997; 86:885–890.
[27] Palakodaty S, York P. Phase behavioural effects on particle formation process using supercritical fluids. Pharm Res. 1999; 16:976–985. [28] Sethia SE, Squillante. Physicochemical characterization of solid dispersions of carbamazepine formulated by supercritical carbon dioxide and conventional solvent evaporation method. J Pharm Sci. 2002; 91:1948–1957.
[28] Vemavarapu C, Mollan MJ, Needham TE. Crystal doping aided by rapid expansion of supercritical solutions. AAPS Pharm Sci Tec. 2002; 13:1–15.
[29] Muhrer GU, Meier F, Fusaro S, Mazzotti M. Use of compressed gas precipitation to enhance the dissolution behavior of a poorly water-soluble drug: Generation of drug microparticles and drug-polymer solid dispersion. Int J Pham. 2006; 308:69-83.
[30] [31] Jarmer DJ, Lengsfeld CS, Anseth KS, Randolph TW. Supercritical fluid crystallization of griseofulvin: Crystal habit modification with a selective growth inhibitor. Pharm Sci. 2005; 94:2688–2702.
[31] Edwards AD, Shekunov BY, Kordikowski A, Forbes RT, York P. Crystallization of pure anhydrous polymorphs of carbamezapine by
[32] solution enhanced dispersion with supercritical fluids (SEDS). J Pharm Sci. 2001; 90:1115–1124.
[33] Morita M, Hisrota S. Correlation studies between thermal and dissolution rate constant of cimitidine drug and tablet. Chem Pharm Bull. 1985; 33:2091.
[34] Shine SC, Oh IJ, Lee YB, Choi HK, Choi JS. Enhancement dissolution of furosemide by co-precipitating or co-grinding with corsprovidone. Int J Pharm. 1998; 175:17-24.
[35] Breitenbach J. Melt extrusion: Fromprocess to drug delivery technology. Pharm Biopharm. 2002; 54:107–117.
[36] Choksi R, Zia H. Hot-melt extrusion technique: A review. J Pharm Res 2004; 3:107–117.
[37] Breitenbach JW, Confocal J. Raman spectroscopy: Analytical approach to solid dispersion and mapping of drug. Pharm Res. 1999; 16:1109–1113.
[38] Verreck G, Six K, Van G, Mooter L, Baert J, Brewster ME. Characterization of solid dispersions of itraconazole and hydroxypropylmethylcellulose prepared by melt extrusion. Int J Pharm. 2003; 251:165–174.
[39] Breitenbach J, Soliq A. Melt extrusion: from process to drug delivery technology. Eur J Pharm. 2002; 54:107-117.
[40] Sushama R, Desai MS, Loyd V, Robert B, Greenwood ML. Effervescent solid dispersions of prednisone, griseofulvin and primidone. Drug Dev Ind Pharm. 1989;15:671-677.
[41] Ho HO, Shu HL, Tsai T, Sheu MT. The preparation and characterization of solid dispersions on pellets using a fluidized bed system. Int J Pharm. 1996; 139:223-229.
[42] Yamamoto K, Nakamo M, Arita T, Nakai Y. Preparation and thermal characterization of poly (ethyl oxide)/ griseofulvin solid dispersions for biomedical application. J Pharmaco Biopharm. 1974; 2:487-495.
[43] Tantishaiyakul V, Kaewnopparat N, Ingkatawornwong S. Properties of solid dispersions of piroxicam in poly (vinylprollidine) K-30. Int J Pharm. 1996; 143:59-66.
[44] Batra. V, Shirolkar VS, Mahaparale PR, Kature PV, Deshpande AD. Solubility and dissolution enhancement of glipizide by solid dispersion technique. Ind J Pharm Edu Res. 2008; 42:371-376.
[45] Rabasco AM, Gines JM, Holgado MA. Enhanced dissolution of ibuprofen using with PEG-6000 solid dispersion. Int J Pharm. 1991; 67:201-205.
[46] McGinity JW, Maincent P, Steinfink H. Crystallinity and dissolution rate of tolbutamide solid dispersions prepared by melt method. J Pharm Sci. 1984; 73:1441-1444.
[47] Beckett AH, Stenlake JB. Analysis of drugs in solid state in practical pharmaceutical chemistry 1970; 3:64-66.
[48] Vidyadhara S, Babu PS, Swapnasundari P, Rani MT. Solid Dispersion: An approach to improve sold formulation development. Pharma Bioworld 2004; 70-76.
[49] Ahuja S, Scypinski S. Handbook of modern pharmaceutical analysis. Academic press2005; 247.
[50] Raymond C Rowe, Paul J Sheskey, Marian E Quinn, Handbook of Pharmaceutical Excipients sixth edition, 315, 506, 326
[51] Indian pharmacopeia, Published by The Indian Pharmacopoeia Commission, Ghaziabad, vol.3, 2007, 954-956
[52] Aulton M E. Pharmaceutics "The Science of Dosage Form Design". 2nd Edition Published by Livingstone C. Elsevier science Ltd. 2002, 200-208.
[53] Martin A. N., Swarbrick J., Commarata A., "Physical Pharmacy", 3rd edition, Lea and Febiger, Philadelphia, 1983, 423-425.
[54] V. Tantishaiyakul*, N. kaewnopparat, S. Ingkatawornwong, Properties of solid dispersions of Piroxicam in polyvinylpyrrolidone K30, International journal of pharmaceutics 143 (1996) 59-66.
[55] Indian pharmacopeia, Published by The Indian Pharmacopoeia Commission, Ghaziabad, vol.1, 2007, 145-148.
[56] Indian pharmacopeia, Published by The Indian Pharmacopoeia Commission, Ghaziabad, vol.1, 2007, 152-153.
[57] Indian pharmacopeia, Published by The Indian Pharmacopoeia Commission, Ghaziabad, vol.1, 2007, 144-145.
[58] Chandrakant D.S*, Lingaraj S.Danki, Abdul Sayeed, Mallikarjun B. Kinagi., Preparation and evaluation of inclusion complexes of water insoluble drug, International Journal of Research in Pharmaceutical and Biomedical Sciences, Vol. 2(4) Oct - Dec 2011, 1599-1616.
[59] Mahmoud, El-Badry., Feith, G., Mohamed, Fathy., 2009. Improvement of solubility and dissolution rate of indomethacin by solid dispersions in Gelucire 50/13 and PEG 4000 Saudi. Journal of Pharmaceutics, 17, 217-225.
[60] Ahuja,N., Katare, O.P., Singh, B. 2007. Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water-soluble carriers. European Journal of Pharmaceutics and Biopharmaceutics, 65, 26- 38.
[61] Lachman, L., Liberman, H.A., Kanig, J .L., The theory and practice of Industrial pharmacy. 3rd edition. Varghese publication house, Bombay, 62-73.
[62] Desai J., Alexander K., Riga A. (2006) Characterization of polymeric dispersions of dimenhydrinate in ethyl cellulose for controlled release. Int. J. Pharm. 308,115-123.