ASIAN JOURNAL OF BIOMEDICAL & PHARMACEUTICAL SCIENCES

e-ISSN: 2249-622X

RESEARCH ARTICLE

Formulation and Characterization of Novel Solid Dispersions of Hydrochlorothiazide by Solvent Evaporation Technique

Abhay N. Padalkar [1]*, Sadhana R. Shahi [1], Abhijit G. Kale [2], Mahesh Thube [1], Varsha A .Padalkar [1],

[1] Govt. College of Pharmacy, Aurangabad. (M.S.)

[2] School of Pharmacy, SRTM University, Nanded (M.S.)

Received:
30th July 2012
Received in revised form:
18th Aug 2012
Accepted:
30st Aug 2012
Available online:
10th Sept 2012

OPEN ACCESS

Online ISSN 2249–622X
http://www.jbiopharm.com

ABSTRACT

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug**.** In addition to bioavailability enhancement, much recent research on solid dispersion systems was directed towards the development of extended-release dosage forms. Knowledge about behavior of solid dispersions during preparation, storage and dissolution can help to tackle these problems. A thorough understanding of processes that occurs place on the molecular level is a prerequisite for rational and more efficient design of solid dispersions. However, development of solid dispersions has often been a trial-and-error approach. Solid dispersion prepared by solvent evaporation method were subjected to x ray diffraction study, dissolution study, In the present study, a 3^2 full factorial design was employed containing 2 factors evaluated at 3 levels and experimental trials were performed at all 9 possible combinations. Two independent variables selected were HPMC E5 and PVP K30. The objective achieved and these findings suggested that the above-mentioned technique can be employed successfully for improvement of solubility profile and stability of Solid dispersions of poorly water soluble drugs.

Key words: hydrochlorothiazide, solid dispersion, extended –release, solubility, solvent evaporation technique

1. INTRODUCTION

Solubility enhancement of poorly water soluble drugs can be achived by using solid dispersion formulation. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.

The number of commercial products marketed as solid dispersions still remains rather limited due to its limited use for the sustained release preparations. The use of solid dispersion in sustained release preparations could be a different strategy which is interesting to carefully evaluate the preparative aspects of these formulations and to suggest variations to the proposed methods with a view of promoting their practical and commercial applications.

In addition to bioavailability enhancement, much recent research on solid dispersion systems was directed towards the development of extended-release dosage forms. It may be pointed out that this area of research has been reinvigorated by the availability of surface-active and self-emulsifying carriers and the development of new capsule filling processes. Because the formulation of solid dispersion for bioavailability enhancement and extended release of drugs may employ essentially similar processes, except for the use of slower dissolving carriers for the later use, it is expected that the research in these two areas will progress simultaneously and be complementary to each other.

Unmet Needs and Challenges:

In spite of almost thirty years of research on solid dispersions, their commercial application is limited. Only a few products have been marketed so far. Amongst these are:

*Corresponding author: Abhay Padalkar , | Mobile: 09860335566| Email: abhaypadalkar1@gmail.com

1) Gris-PEG (Novartis), Griseofulvin in PEG
2) Cesamet (Lily), Nabilone in PVP
3) Sporanox (Janssen Pharmaceutica/J&J), Itraconazole in HPMC and PEG 20,000 sprayed on sugar spheres

Ritonavir capsules (Norvir, Abbott) has been withdrawn temporarily from the market because of crystallization. The rare occurrence of solid dispersion based pharmaceutical dosage forms in the clinic are due to problems in scale-up of preparation methods, difficulties in dosage form development and poor and irreproducible physical and chemical stability of drug and matrix .

Knowledge about behavior of solid dispersions during preparation, storage and dissolution can help to tackle these problems. A thorough understanding of processes that occurs place on the molecular level is a prerequisite for rational and more efficient design of solid dispersions. However, development of solid dispersions has often been a trial-and-error approach. Unfortunately, most reports deal with a case, in which the authors used a specific matrix to accelerate the dissolution of a specific drug in-vitro or to show increased bioavailability. These studies prove the potential of solid dispersions, but for successful industrialization and clinical application, the following challenges have to be faced first.

The main objective of the work was solubility enhancement of hydrochlorothiazide, by the solvent evaporation technique. In this context attention was focused on the elucidation of the mechanism of drug release from solid dispersion, the prediction of drug carrier miscibility in case of solvent evaporation technique, and thermodynamic stability of the techniques. The objective to be achieved is so mentioned below,

1) To develop a formulation for improving solubility of a poorly water-soluble drug.
2) To optimize the Solvent evaporation technique for solubility enhancement of a poorly soluble drug and to prove the applicability of the technique for different carriers and drugs.
3) In-vitro evaluation of solid dispersions prepared by solvent evaporation technique.

2. MATERIAL AND METHOD:

MATERIALS

Hydrochlorothiazide was procured as a gift sample from Cipla Pharmaceuticals Verna Estate Goa. All the Ingredients used are of Analytical grade with high purity.

Preparation of solid dispersion of Hydrochlorothiazide by solvent evaporation technique:

In this method solid dispersion is prepared by dissolving a physical mixture of two solid components in a common solvent, followed by evaporation of the solvent. Many investigators studied solid dispersion of Meloxicam, Naproxen, Nimesulide, Carbamezipine and Celecoxib using solvent evaporation technique. These findings suggested that the above-mentioned technique can be employed successfully for improvement and stability of Solid dispersions of poorly water soluble drugs.

The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of organic solvents. However, some disadvantages associated with this method are the higher cost of preparation, the difficulty in completely removing liquid solvent, the possible adverse effect of the supposedly negligible amount of the solvent on the, chemical stability of the drug, the selection of a common volatile solvent, and the difficulty of reproducing crystal forms. It must be emphasized that the suitability of the solvent method to prepare simple eutectics or partial solid solutions remains to be studied further because their final physical properties may be quite different from those obtained by the melting method.

Preliminary Formulations

The goal of the experiment was to produce solid dispersions of a poorly water-soluble drug via solvent evaporation technique in order to improve the solubility. The carrier selected was PVP K-30 and HPMC E-5 .The compatibility study showed compatibility of PVP K-30 and HPMC E-5 with hydrochlorothiazide. Based on the literature review the solid dispersion has been developed with the composition, Table-6.

Method of Preparation of Preliminary Formulations

To develop a binary solid dispersion (SD) for solubility enhancement, PVP K-30 and HPMC E-5 were selected and the Solid dispersion prepared using ethanol and dichloromethane (DCM) as solvent, in the ratio of 1:1. Weighed quantity of HCTZ/PVP and HCTZ/HPMC E-5 in different ratios was dissolved in ethanol, DCM mixture. The solvent was evaporated under reduced pressure in a vacuum chamber. The mass was stored at room temperature for 24 hr. and then pulverized using a glass mortar and pestle. The pulverized mass was sifted through a #120 sieve, weighed, and transferred to amber-colored Type-I glass vials, stored at 30ºC ± 1ºC.

© Asian Journal of Biomedical and Pharmaceutical Sciences, all rights reserved.

Sr. No	Formulation Code	HCTZ (g)	PVP K-30 (g)	HPMC E-5 (g)	Solvent (Ethanol &DCM)*
1	SEP-1	10	5	NA	Q.S
2	SEP-2	10	6.6	NA	Q.S
3	SEP-3	10	10	NA	Q.S
4	SEP-4	10	NA	5	Q.S
5	SEP-5	10	NA	6.6	Q.S
6	SEP-6	10	NA	10	Q.S
7	SEP-7	10	4.95	1.65	Q.S
8	SEP-8	10	1.65	1.65	Q.S
9	SEP-9	10	2.47	0.73	Q.S
10	SEP-10	10	3.3	3.3	Q.S
11	SEP-11	10	1.65	4.95	Q.S

*- Does not remain in final product, SEP-Solvent Evaporation technique preliminary formulations

Table 1: Preliminary formulations of HCTZ solid dispersion by solvent evaporation technique

The release profile of an entrapped drug predicts how a delivery system might function and gives valuable insight into its in-vivo behavior. In-vitro release profile for each solid dispersion as well as pure drug were performed using USP XXII type 2 dissolution apparatus (TDP-06P, Electro lab, Mumbai, India).Solid dispersion equivalent to 50 mg was exposed for 90 min to 0.1 N HCl, the dissolution medium. Samples (5ml sample volume) were withdrawn from the dissolution medium at predetermined intervals (10, 20, 30, 40, 50, 60, 75, and 90 min) and an equivalent amount of fresh medium was added to maintain a constant dissolution volume. The samples were filtered through a 0.45 µm Millipore syringe filter and suitably diluted with 0.1N HCl solution and the drug concentration was determined spectrophotometrically at 272 nm using UV/VIS double beam Spectrophotometer (V-600, Jasco Corporation, Japan).

S.No	Formulation Code	Cumulative % Drug Release	
		30 min*	90 min*
1	Plain HCTZ	24.36±3.9	49.49±6.9
2	SEP-1	28.56±5.5	59.65±6.3
3	SEP-2	22.50±6.5	51.68±5.1
4	SEP-3	36.12±6.6	60.03±5.6
5	SEP-4	57.37±4.6	84.70±5.3
6	SEP-5	65.33±3.9	86.02±5.4
7	SEP-6	71.32±5.6	85.25±6.3
8	SEP-7	74.25±5.3	102.3±5.4
9	SEP-8	40.82±5.3	82.52±3.9
10	SEP-9	59.92±2.9	92.36±3.6
11	SEP-10	31.52±3.9	59.36±2.6
12	SEP-11	44.05±2.6	76.46±3.6

1*-Average of three readings, SEP-Preliminary formulations of Solvent Evaporation technique

Table 2: Dissolution profile of the preliminary formulations of HCTZ solid dispersion prepared by solvent evaporation technique.

S.No	Formulation	PVP K-30 (g)	HPMC E-5 (g)	HCTZ (g)	Solvent(Ethanol & DCM)*
1	SEF-1	1.65	1.65	10	Q.S
2	SEF-2	0	1.65	10	Q.S
3	SEF-3	4.95	1.65	10	Q.S
4	SEF-4	1.65	0	10	Q.S
5	SEF-5	0	0	10	Q.S
6	SEF-6	4.95	0	10	Q.S
7	SEF-7	1.65	4.95	10	Q.S
8	SEF-8	0	4.95	10	Q.S
9	SEF-9	4.95	4.95	10	Q.S

Table 3: Composition of final formulations of HCTZ Solid dispersion prepared by solvent evaporation technique.

© Asian Journal of Biomedical and Pharmaceutical Sciences, all rights reserved.

***In-Vitro* evaluation parameters of final formulations**

The solid dispersions prepared by the solvent evaporation were evaluated for angle of repose, bulk density, percentage yield, drug content as per the method mentioned in section. The results are shown in Table-4.

Solubility Study

Solubility measurements were performed according to method reported by Higuchi and Connors, An excess amount of the drug was added to 10 ml volumetric flask containing 10%, 20%, 30% and 40% aqueous solution of carrier. The samples were shaken for 48 hr. at 25±1°C. The solutions were filtered through Syringe filter (0.45 µ). After 48 hr., the hydrochlorothiazide concentration was determined spectrophotometrically at 272 nm. The results are shown in Table5.

Sr. No	Solvent	Temp (°C)	pH	Solubility of HCTZ (g/100 ml)	Solubility of SD of HCTZ (g/100 ml)*
1	Water	37	7.2	108×10^{-3}	140×10^{-3}
2	0.1M HCl	25	1	60.8×10^{-3}	119×10^{-3}
3	0.067 M Phosphate buffer	25	7.4	61.6×10^{-3}	134×10^{-3}
4	0.05 M Borate buffer	25	9	103×10^{-3}	98×10^{-3}
5	1.0 M Ammonia	25	11.6	2.2×10^{-3}	86×10^{-3}
6	0.1M NaOH	25	10.2	1.79×10^{-3}	65×10^{-3}
7	Simulated Gastric Fluid	37	1.1	108×10^{-3}	199×10^{-3}
8	Simulated Intestinal Fluid	37	7.5	109×10^{-3}	188×10^{-3}

Table 4: Physicochemical characterization of HCTZ Solid dispersions prepared by solvent evaporation technique

Sr. No	Solvent	Temp (°C)	pH	Solubility of HCTZ (g/100 ml)	Solubility of SD of HCTZ (g/100 ml)*
1	Water	37	7.2	108×10^{-3}	140×10^{-3}
2	0.1M HCl	25	1	60.8×10^{-3}	119×10^{-3}
3	0.067 M Phosphate buffer	25	7.4	61.6×10^{-3}	134×10^{-3}
4	0.05 M Borate buffer	25	9	103×10^{-3}	98×10^{-3}
5	1.0 M Ammonia	25	11.6	2.2×10^{-3}	86×10^{-3}
6	0.1M NaOH	25	10.2	1.79×10^{-3}	65×10^{-3}
7	Simulated Gastric Fluid	37	1.1	108×10^{-3}	199×10^{-3}
8	Simulated Intestinal Fluid	37	7.5	109×10^{-3}	188×10^{-3}

*-Average of three readings.

Table 5: Solubility study of plain HCTZ and Solid dispersion prepared by Solvent Evaporation technique at different pH solutions

© Asian Journal of Biomedical and Pharmaceutical Sciences, all rights reserved.

3. RESULT AND DISCUSSION:

Dissolution Profile

The solid dispersions prepared by solvent evaporation technique were evaluated for dissolution as per the method mentioned in section 4.1.2 and reported in Table 6.

S.No	Formulation Code	Cumulative % Drug Release	
		30 min*	90 min*
1	SEF-1	74.25±6.3	107.6±5.5
2	SEF-2	70.05±6.6	99.1±5.4
3	SEF-3	65.34±3.6	88.90±6.9
4	SEF-4	59.92±3.5	87.44±6.3
5	SEF-5	57.38±3.9	81.27±5.3
6	SEF-6	47.44±5.3	76.46±5.5
7	SEF-7	44.01±7.5	74.17±3.7
8	SEF-8	40.82±9.6	64.62±4.8
9	SEF-9	31.53±6.3	54.81±4.9

B.D- Bulk density, SEF-Final formulations of Solvent Evaporation technique,

*-Average of three readings

Table 6: Dissolution profile of solid dispersions formulations of HCTZ prepared by solvent evaporation technique.

Infrared Spectroscopy

The Inclusion complex or physical mixture was thoroughly mixed with potassium bromide at a ratio of 1:99 in a mortar. This dispersion was then loaded in the sample cell and the FTIR spectrum was recorded using an FTIR–4100 spectrophotometer (IR 200 spectrometer, Thermo electron Corporation). The wavelength ranged from 600 to 4000 cm^{-1} with a resolution of 4 cm^{-1}. The spectra obtained were studied comparatively, Figure-1.

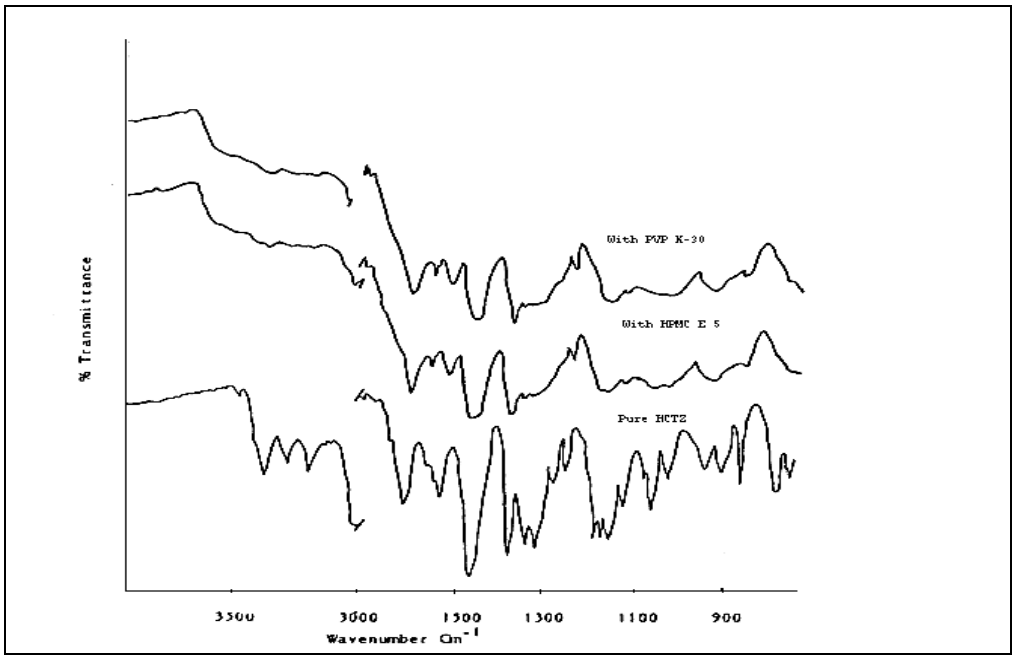

Figure 1 IR spectrum of pure HCTZ with HPMC E 5 & PVP K30

© Asian Journal of Biomedical and Pharmaceutical Sciences, all rights reserved.

X-Ray Diffraction

Powder X-ray diffraction analysis is used to judge any changes in crystallinity of the drug which precipitated in an amorphous form, when formulated into a Solid dispersion, which could be one of the mechanisms responsible for improved dissolution. The different SD powders were scanned in increments of 0.02° from 0° to 40° (diffraction angle 2θ) with scanning speed of 50 per min, using a standard sample holder. PXRD patterns were obtained with a D5005 diffractometer (Bruker, Germany) using Cu-K-α1 radiation at a voltage of 40 kV and a current of 40 mA.

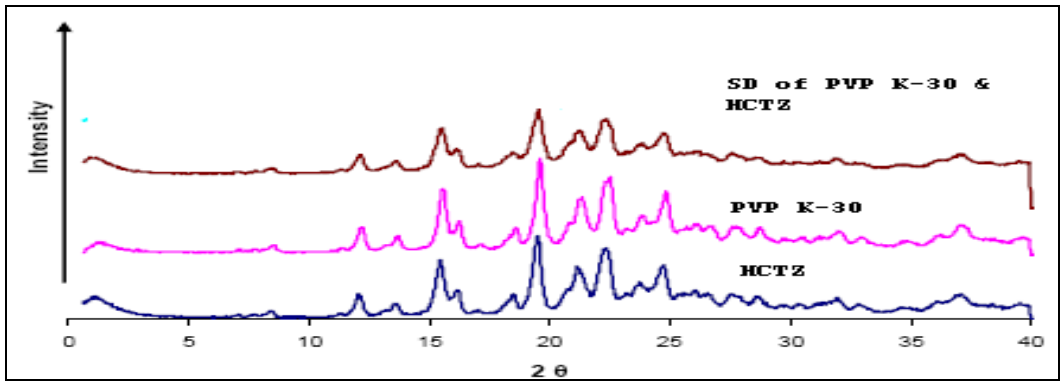

Figure 2 X-Ray Diffractogram of pure HCTZ, PVP K-30 and Solid dispersion of HCTZ and PVP K-30.

Analysis of Data by Design Expert Software

Traditional designing of the pharmaceutical formulations are based on time consuming **approach** of changing one variable at time which does not take into consideration the joint effect of independent variables. Thus, factorial design can serve as an essential tool to understand the complexity of the pharmaceutical formulations. The results can be expressed either as simple linear or second order polynomial equation to statistically evaluate the responses obtained after experiments. In the present study, a 3^2 full factorial design was employed containing 2 factors evaluated at 3 levels and experimental trials were performed at all 9 possible combinations. The formulation variables and their ranges were chosen from the knowledge acquired from the preliminary studies and the Literature Survey. Two independent variables selected were HPMC E5 and PVP K30 and nine formulations formulated as per Table 7.

Sr. No	Formulation Code	PVP K-30 (g) (A)	HPMC E-5 (g) (B)	Q_{30}	Q_{90}
1	SEF-1	-1	-1	74.25	107.06
2	SEF-2	0	-1	70.05	99.10
3	SEF-3	1	-1	65.34	88.90
4	SEF-4	-1	0	59.92	87.44
5	SEF-5	0	0	57.38	81.70
6	SEF-6	1	0	47.44	76.46
7	SEF-7	-1	1	44.01	74.17
8	SEF-8	0	1	40.82	64.62
9	SEF-9	1	1	31.53	54.81

Q_{30}- Drug release in 30 minutes.Q_{90}- Drug release in 90 minutes.

Table 7 Factorial design formulations with dependable and independent variables for the HCTZ Solid dispersions prepared by solvent evaporation technique.

© Asian Journal of Biomedical and Pharmaceutical Sciences, all rights reserved.

Response: Q_{90}

ANOVA Study Q_{90}

ANOVA and multiple regression analysis were done using Stat-Ease Design Expert 7.1.4 software. The coefficients of A and B were found to be significant at p <0.05, hence confirmed the significant effect of both the variables on the selected responses. Overall both the variables caused significant change in the responses.

The Model F-value of 60.60 implies the model is significant. There is only a 0.0033% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. The "Pred R-Squared" of 0.8812 is in reasonable agreement with the "Adj R-Squared" of 0.9739."Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 23.207 indicates an adequate signal. This model can be used to navigate the design space.

Final Equation in Terms of Coded Factors:

$Q90 = 82.09 - 8.08A - 16.91B - 0.29AB - 0.33A^2 - 0.42B^2$

Final Equation in Terms of Actual Factors:

$Q90 = 82.09 - 8.08A - 16.91B - 0.29AB - 0.33A^2 - 0.42B^2$

Response Curve Q_{90}

The response surface plot was generated using Design Expert 7.1.4 software presented in Figure-3 to observe the effects of independent variables on the response.

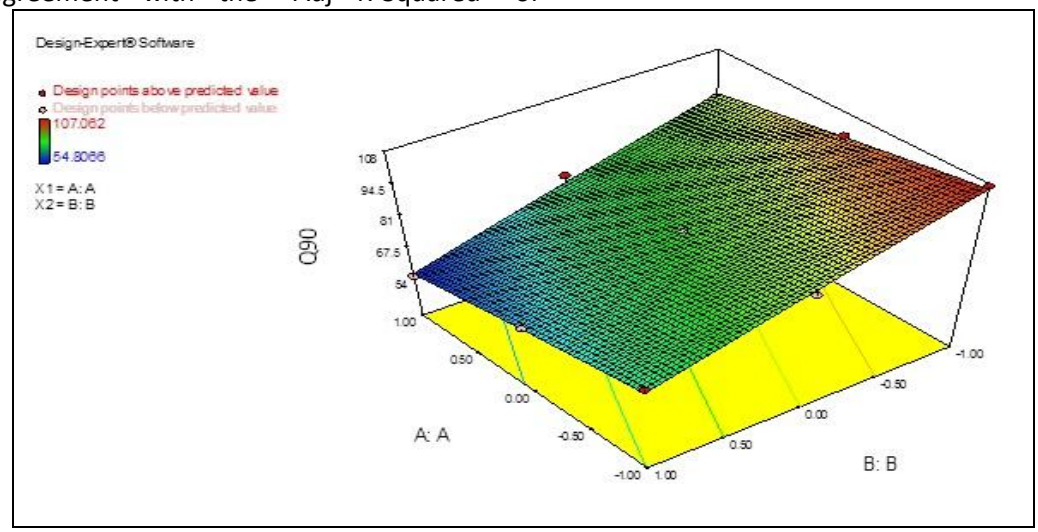

Figure 3 - Topograph of response curve of Q_{90}

The causal factor and response variables were related using polynomial equation with statistical analysis through Design-Expert® software. The contour plots illustrating the simultaneous effect of the causal factors on individual and combined response variable are represented in Figures-5. This expression gives an insight into the effect of the different independent variables (response). A positive sign of coefficient indicates a synergistic effect while a negative term indicates an antagonistic effect upon the response.

4. CONCLUSION:

The solid dispersions of a poorly water-soluble drug via solvent evaporation technique were produced in order to improve the solubility. The carrier selected was PVP K-30 and HPMC E-5 .The compatibility study showed compatibility of PVP K-30 and HPMC E-5 with hydrochlorothiazide. Solid dispersion prepared shows good dissolution profile and release characteristics.

The objective achieved and these findings suggested that the above-mentioned technique can be employed successfully for improvement of solubility profile and stability of solid dispersions of poorly water soluble drugs.

© Asian Journal of Biomedical and Pharmaceutical Sciences, all rights reserved.

5. REFERENCE:

1. Sekiguchi K and Obi N (1961).Studies on Absorption of Eutectic Mixture. I. A comparison of the behaviour of eutectic mixture of sulfathiazole and
3. Karmarkar A.B. Poloxamers and their applications.www.pharmainfo.net November 27, 2008.
4. Lachmann. L., Lieberman H. A, Kanig J. L, Theory a nd Practice of Industrial Pharmacy, Varg-hese Publishing House: Bombay, 1991, 315-316.
5. Dua K, Ramana M V, Sara UVS, Himaja M, Garg V, Agrawal A. Dissolution enhancement of aceclofenac through solid dispersions. Indian pharmacist 2006, 70-72.
6. Daisy Sharma, Mohit Soni, Sandeep Kumar and GD Gupta, Solubility Enhancement – Eminent Role in Poorly Soluble Drugs. Research J. Pharm. and Tech. 2009,2(2).
7. Kaushal AM, Gupta P and Bansal AK (2004). Amorphous drug delivery systems: molecular aspects, design, and performance. Crit. Rev. Ther. Drug Carrier Syst.,21(3): 133-193.
8. Kerc J and Srcic S (1995). Thermal analysis of glassy pharmaceuticals. Thermochim. Acta., 248: 81-95.
9. Kushida I, Ichikawa M and Asakawa N (2002).Improvement of dissolution and oral absorption of ER- 34122, a poorly water-soluble dual 5-lipoxygenase/cyclooxygenase inhibitor with anti-inflammatory activity by preparing solid dispersion. J. Pharm. Sci.,91(1): 258-266.
10. Langer M, Höltje M, Urbanetz NA, Brandt B, Höltje HD and Lippold BC (2003). Investigations on the predictability of the formation of glassy solid solutions of drugs in sugar alcohols. Int. J. Pharm., 252(1-2): 167-179.
11. Law SL, Lo WY, Lin FM and Chaing CH (1992).Dissolution and absorption of nifedipine in poly (ethylene glycol) solid dispersion containing phosphatidylcholine. Int. J. Pharm., 84: 161-166.
12. Hu J, Johnston KP and Williams RO (2004). Rapid dissolving high potency danazol powders produced by spray freezing into liquid process. Int. J. Pharm., 271(1-2): 145-154.
13. Ignatious F, Baldoni JM and inventors (2001). Smithkline Beecham Corp. Electrospun pharmaceutical compositions. World patent 0 154 667. August 2.
14. Kang BK JS Lee, SK Chon, SY Jeong, SH Yuk, G (2004). Development of self-microemulsifying drugdelivery systems (SMEDDS) for oral that of ordinary sulfathiazole in man. Chem. Pharm. Bull., 9: 866-872.
2. ASF – Expertise in health and nutrition No. 3 1999. bioavailability enhancement of simvastatin in beagle dogs. Int. J. Pharm., 274: 65-73.

Conflict of Interest: None Declared

© Asian Journal of Biomedical and Pharmaceutical Sciences, all rights reserved.