INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

PREPARATION AND COMPARATIVE EVALUATION OF LORATADINE SOLID DISPERSIONS WITH VARIOUS BINDERS BY SPRAY DRYING TECHNIQUE

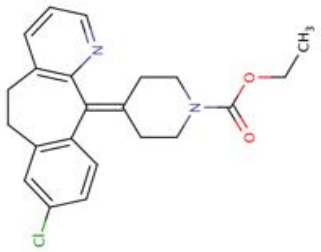
A. Sathyaraj* and M. Palraja

Department of Pharmacy, Krishna University, Machilipatnam, Andhra Pradesh, India.

ABSTRACT

The objective of the present work was to preparation and evaluation of Spray dried compositions of loratadine. This study was improvement of dissolution rate of poorly soluble drug of loratadine by solid dispersion containing with enteric polymers as a carrier. Solid dispersion was prepared by spray drying method. The morphological characteristics of amorphous or crystalline nature of the SDD were investigated by Differential scanning calorimetry. And it was employed to study the physical and chemical properties. Invitro release was studied using a USP II baddle method. The dissolution rates of loratadine from solid dispersions were carried out in comparison with corresponding Spray Dried Dispersion and drug alone. The Spray dried samples containing loratadine were stored at under different conditions (25Cand 60% RH, 30C and 65% RH, 40C and 75% RH) to investigate their stability as a function of time. The dissolution properties deteriorate upon storage at high temperature and relative humidity.

INTRODUCTION



LORATADINE

Loratadine second-generation histamine H1 receptor antagonist used in the treatment of allergic rhinitis and urticaria. Unlike most classical antihistamines (histamine H1 antagonists) it lacks central nervous system depressing effects such as drowsiness. It's like other H_1-blockers, loratadine competes with free histamine for binding at H_1-receptors in the GI tract, uterus, large blood vessels, and bronchial muscle. Loratadine also has a weak affinity for acetylcholine and alpha-adrenergic receptors.

The poorly water-soluble drugs often show an erratic dissolution profile in gastrointestinal fluids, which consequently results in variable oral bioavailability. To improve the dissolution and bioavailability of poorly soluble drugs, researchers have employed various techniques, such as micronization, solubilization, salt formation, complexation with polymers, and change in physical form, use of prodrug and drug derivatization, alteration in pH, addition of surfactants[7].

SPRAY DRYING TECHNOLOGY

Many products are preferentially used in solid form. This simplifies storage and metering, and it may be essential for the application for which the compound is to be used. Spray drying is a speedy, time- saving and gentle method of obtaining even the smallest quantities of substances in powder form. The advantages compared with freeze drying are the greater throughout rate and the short process times. The very short residence times and the cooling effect resulting from evaporation make it possible to process even temperature-sensitive products in a gentle manner. If the use of organic solvents is

involved, the thermal load is reduced to a minimum.

Spray drying is the most widely used industrial process for particle formation and drying. It is well suited to continuous production of dry solids in powder, granulate or agglomerate particle form from liquid feed stocks. Feedstock's can include solutions, emulsions and pump able suspensions. The technology is ideal when the end-product must comply with precise quality standards. This regards particle size distribution, residual moisture content, bulk density and particle morphology.

EXPREMENTAL WORK

MATERIALS AND METHOD

Materials used

DRUG-crystalline loratadine (purity more than 99%, melting temperature133.49 ºC) was kindly donated by Cadila pharmaceuticals (Angles war India)

Procedure of Spray Drying

Based on the DSC film studies, the suitable drug-polymer combinations that can be taken up for spray drying. The selected polymer and drug was dissolved in methanol, according to the ratio.This formulation used to Spray Dried in preparation of Spray Dried composition of poorly soluble drug. The following Spray Dried formulation batches with the parameters.

Parameters -Spray drying
Table 1

S. No.	Temperature°C			Inert Loop°C		Process Gas Pressure (N2) (mbar) Flow	Feed rate (3.0ml/min)	
	Set Inlet	Inlet	Outlet	Set	Actual		Solvent	Solution
1	140	139	80	-20	-11	+	+	-
2	140	140	78	-20	-15	+	+	-
3	140	141	85	-20	-16	+	+	-
4	140	140	75	-20	-16	+	-	+
5	140	139	76	-20	-17	+	-	+
6	140	140	79	-20	-18	+	-	+
7	140	143	80	-20	-19	+	-	+
8	140	142	73	-20	-19	+	-	+
9	140	140	75	-20	-18	+	-	+
10	140	140	81	-20	-20	+	-	+

+ = Flow, - = Flow is stopped

EVALUATION

Differential scanning calorimetry

As the temperature increases, an amorphous solid will become less viscous. At some point the molecules may obtain enough freedom of motion to spontaneously arrange themselves into a crystalline form. This is known as the crystallization temperature (Tc). This transition from amorphous solid to crystalline solid is an exothermic process, and results in a peak in the DSC signal.Differential scanning calorimetry can be used to measure a number of characteristic properties of a sample. Using this technique it is possible to observe fusion and crystallization events as well as glass transition temperatures (Tg). DSC can also be used to study oxidation, as well as other chemical reactions.

DSC analysis of spray dried formulation

SDD formulation powder weighing 2-3 mg was kept on the aluminum pan and was enclosed with aluminum lid with the help of crimper. Then the DSC analysis was done.

DSC of Spray Dried Dispersion of loratadine + Plasdone (PVP) K29/32 at 1:3 Ratios, and Following SDD's DSC was respectively is shown in the Fig No.5

- loratadine + Plasdone(PVP)S-630 at 1:3
- loratadine + Ethyl Cellulose at 1:1 ratio
- loratadine +HP55 at 1:1 ratio
- loratadine +HPMC 603 at 1:1 ratio
- loratadine +HPMC 606 at 1:1 ratio
- loratadine +HPMC AS MF at 1:1 ratio

Flow properties

The spray dried product was evaluated for its physical properties as well as the properties pertaining to the drug content and release of the drug from the formulation.

Apparent Bulk Density; (ρ1)

It is the ratio of the weight of powder to the volume it occupies. Volume occupied by the powder includes, volume of the solid portion of the particles and voids between the particles. It is expressed in g/cc. Bulk density is important in determining the size of the equipment needed for handling and processing.

It is obtained by dividing the weight of the SDD powder sample by the bulk volume of the same SDD powder sample in a measuring cylinder.

Apparent Bulk Density (ρ1) =W1/ V1

Tapped density (ρ2)

Tapped density refers to density of the substance, excluding the entire pore volume larger than the spacing f molecular or atomic dimension that exists in the crystal lattice of the solid it is expressed in g/cc. In this method SDD powder is filled in measuring cylinder. After that it is mechanically tapped on device.

Tapped density (ρ2) = W1/ Vf

Compressibility Index

Compressibility is indirectly related to the relative flow rate, cohesiveness and particle size distribution of the powder. Tapped (ρ2) and Apparent (ρ1) Bulk density measurements can be used to estimate the compressibility of a material. For the determination of the flow of SDD powder value were placed in below

Carr's Compressibility Index (%) = (ρ2-ρ1)/ (ρ2) X 100

Preparation of standard cure of Loratadine

Loratadine (100mg) was transferred to a 100 ml standard volumetric flask, to this flask methanol was added. The Loratadine was dissolved in methanol and the volume was making up to the mark with water. From this solution 10ml was diluted up to 100ml .it gave standard stock solution of the strength 100µg /ml. from the stock solution required quantity of Loratadine were transferred to 10ml volumetric flask and were diluted with water up to mark to obtain Loratadine concentration of 2,4,8,16,20, µg /ml respectively.

Absorbance of each solution was measured at 247nm using UV/visible spectrophotometer using water as a reference solution. Same procedure performed to SGF medium also. This statistical analysis of the data was done and fig.5 shows the standard curve obtain.

Assay

Determination of Loratadine content in each batch was carried at by spectrophotometer analysis. In this processes, spray Dried sample from each batch was individually taken and analysis to find the % of loratadine in each batch. The weight taken of the SD sample was equivalent to 10mg of pure loratadine. After that SDD powder were transferred to 500 ml standard volumetric flask. The SDD powder was dissolved in methanol and the volume was made up to the mark with distilled water. To obtain the loratadine concentration 20mg / ml.

After obtaining the concentration value there absorbance were taken at 247 nm. Through this absorbance value corresponding assay value was calculated.

$$\text{Loratadine} = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \times 100$$

Assay value of each respective SDD batch is shown in table no. 2

S. No.	Sample	Concentration(ppm)	Absorbance at 247nm	Percentage of Loratadine
1.	Pure loratadine	20	0.6030	100%
2.	PVP K29/32	20	0.6616	109%
3.	PVP S -630	20	0.5875	97%
4.	Ethyl Cellulose	20	0.6276	104%
5.	HP55	20	0.6553	108%
6.	HPMC 603	20	0.6081	101%
7.	HPMC AS MF	20	0.6522	108%

DISSOLUTION

Dissolution testing of dosage forms is considered to be one of the most important quality control tools while assessing the efficacy of the product in vitro. The process of dissolution of an active ingredient from solid pharmaceutical dosage forms. Involves several intermediate physicochemical steps such as wetting, swelling, capillary action solubility and diffusion among most significant factor that control the process of dissolution are the type nature of the dissolution from with in which the active ingredient is contained .

Although in vitro dissolution methodology will never replace bioavailability testing the parameter obtained from this test can give relative assurance that a drug in vitro will be liberated in a suitable fashion from its dosage form and afterward absorbed. Amorphous nature of loratadine was prepared by spray drying technique were subjected to this in vitro dissolution study. The study helps in understanding the release profile of this SDD. This study was amide out using USP II dissolution tester.

COMPARISON OF DISSOLUTION PROFILE BETWEEN SDD SAMPLES AND PURE CRYSTALLINE DRUG

Comparison between SDD formulation and pure crystalline drug are shown in fig.6 respectively.

RESULT AND DISCUSSION

Table 3: Solubility Polymers

S. No.	Polymers	Solubility in Methanol (mg/ml)
1.	Plasdone (PVP) K29/32	875
2.	Plasdone (PVP)K12	1550
3.	Plasdone (PVP)K90	525
4.	Plasdone (PVP)S630	1025
5.	HPMC 603	415
6.	HPC	295
7.	HP 55	535
8.	HP55-S	475
9.	HPMC 606	315
10.	ETHYL CELLULOSE	475
11	HPMC AS MF	385
12.	HPMC AS HF	385
13.	HPMC AS LF	385

From the Table No.3 It was seen that Polymers show high solubility in Methanol.
Hence methanol was consider as a solvent in Spray dried dispersion because in spray dried dispersion, solvent which ever used should show high solubility for the test.

DIFFERENTIAL SCANNING CALORIMETER (DSC)

DSC of pure loratadine at Various Ramp rates

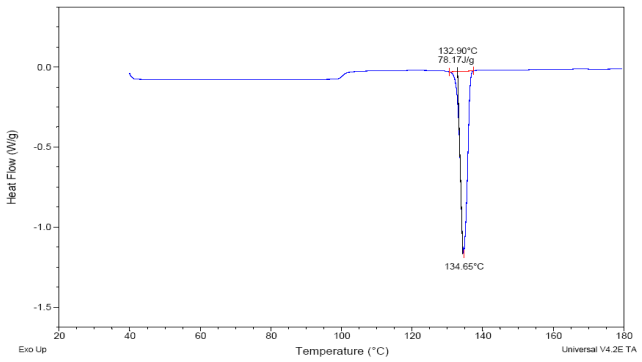


Fig. 1: DSC – Ramp rate 2ºC/min

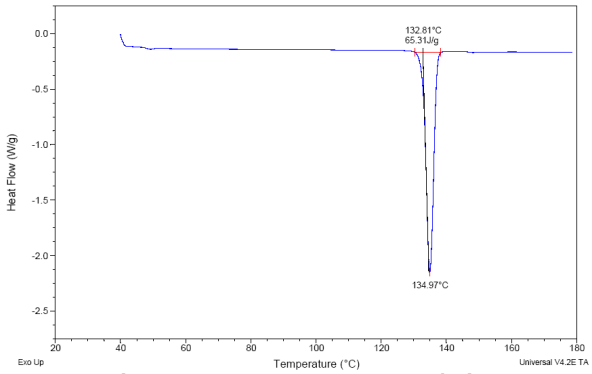


Fig. 2: DSC – Ramp rate 5ºC/min

MODULATED DIFFERENTIAL SCANNING CALORIMETERY (MDSC)

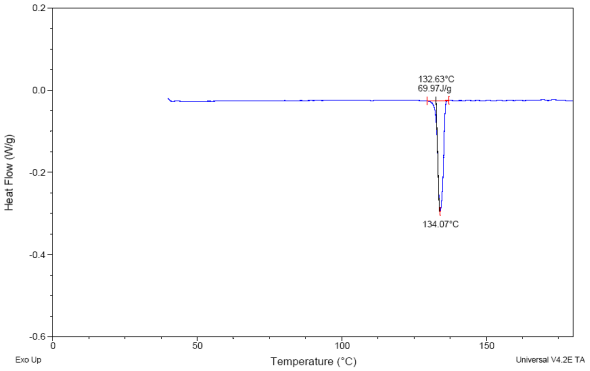


Fig. 3: MDSC -Ramp rate at 0.5 ºC/min

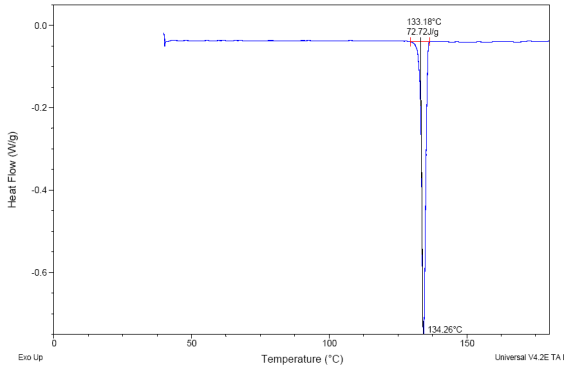


Fig. 4: MDSC -Ramp rate at 1 ºC/min

DISCUSSION

From the fig 1, 2, 3 and 4, it was found that as the ramp rate was increase the corresponding melting point of the loratadine was also increase. It can be seen from the table 4

Table 4

S. No.	Ramp rate	Endothermic Energy required to melt the Loratadine
1.	2ºC/min	132.90 ºC
2.	5ºC/min	132.81 ºC
3.	10ºC/min	133.77 ºC

Above the Formulation Process was used to prepare the Spray dried Loratadine. This had shown Amorphous Nature during drug and polymer interaction by Spray dried dispersion technique in following ratios of the SDD.
The Following Spray Dried formulation was preparation Batches with their Parameters.

EVALUATION

Differential Scanning Calorimeter (DSC)

DSC thermogram of spray dried dispersion of Loratadine + polymers with pure drug are as follows;

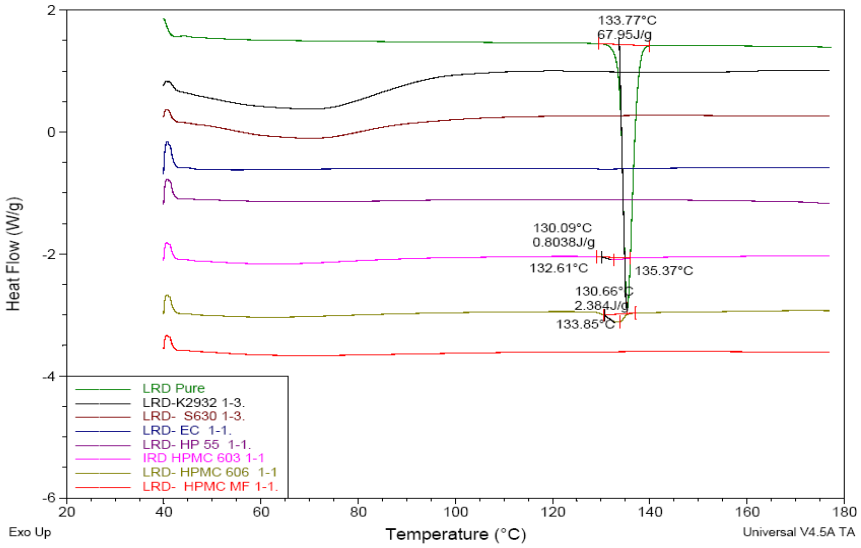


Fig. 5

Table 5

S. No.	Sample Name	Melting Temperature And J/g Value	Powder Characteristics
1.	Loratadine:K2932	No Endothermic Peak	Amorphous
2.	Loratadine:S-630	No Endothermic Peak	Amorphous
3.	Loratadine:Ethyl cellulose	No Endothermic Peak	Amorphous
4.	Loratadine:HP55	No Endothermic Peak	Amorphous
5.	Loratadine:HPMC603	0.8308 J/g	Amorphous
6.	Loratadine:HPMC606	2.384 J/g	Crystalline
7.	Loratadine:HPMC AS MF	No Endothermic Peak	Amorphous

From the table no. 5. It was observed That Spray dried dispersion of Loratadine and Respective Polymer had shown amorphous or Crystalline Nature.

Evaluation of physical properties of spray dried dispersion of powders

Physical Parameters of Loratadine SDD
Table 6

S. No.	Drug : Polymer System Ratio	Bulk Density	Tapped Density	Hausner's Ratio	Carr's Index (%)	% of LOD	% of Yield
1.	Loratadine: PVP K2932 1:3	0.1658	0.2014	1.21	17.67	1.22	60%
2.	Loratadine: PVP S630 1:3	0.1865	0.2136	1.14	12.68	0.98	85%
3.	Loratadine: Ethyl Cellulose1:1	0.1724	0.2023	1.17	14.78	0.88	56%
4.	Loratadine: HP 55 1:1	0.1843	0.2091	1.13	14.29	0.72	72%
5.	Loratadine: HPMC 603 1:1	0.1696	0.1965	1.15	13.68	0.73	64%
6.	Loratadine: HPMC AS MF	0.1382	0.1522	1.10	10.13	0.78	69%

DISCUSSION

This result shown in the Table 6 for all the spray dried formulations are according to limits given in the British Pharmacopoeia for the flow properties of powder, which is good enough to be compressed in to a tablet.

ASSAY

The drug content in all SDD formulations was determined by the method discussed in the result has been described in Table No.7

Table 7

S. No.	Sample	Concentration(ppm)	Absorbance at 247nm	% of Loratadine
1.	Pure loratadine	20	0.6030	100%
2.	PVP K29/32	20	0.6616	109%
3.	PVP S -630	20	0.5875	97%
4.	Ethyl Cellulose	20	0.6276	104%
5.	HP55	20	0.6553	108%
6.	HPMC 603	20	0.6081	101%
7.	HPMC AS MF	20	0.6522	108%

The drug content in the SDD formulations complies with the pharmacopeial limit of content uniformity (90%-110%)

DISSOLUTION

Comparison of Dissolution profile between SDD formulation and pure Loratadine in SGF (simulated Gastric Fluid) medium. (Drug: polymer) Table no.8

SGF without Enzyme							
TIME	Pure	K29/32 1:3	HP 55 1:1	HPMC 603 1:1.	HPMC MF 1:1	S630 1:3	EC1:1
0	0	0	0	0	0	0	0
5	47	19	61	13	43	12	30
10	69	44	79	34	74	39	90
15	81	67	87	60	92	54	97
30	100	94	96	98	105	96	101
45	101	95	99	103	106	96	101
60	101	95	100	103	107	96	101

Invitro Release Study of Spray Dried Dispersion of Loratadine in SGF Medium

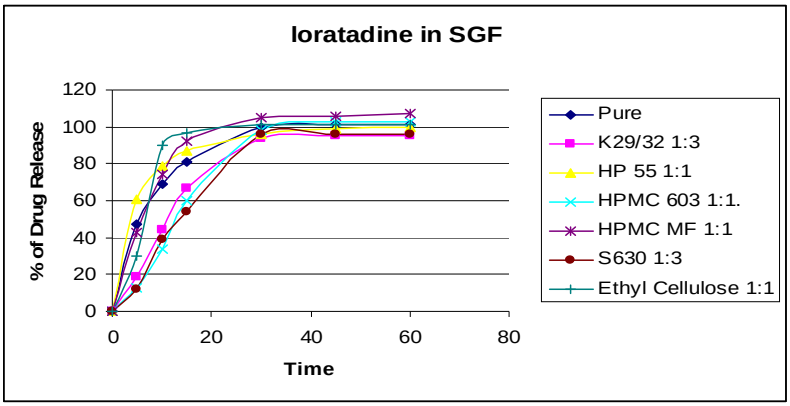


Fig. 6

Discussion

From Table No. (8) And Fig No. (6) It was found that Formulation Shown the following percentage of release of Loratadine in SGF Medium after 45 Minutes

1. Pure Crystalline Drug 101 % Release
2. HPMC 603 103 % Release
3. HPMC AS MF 107 % Release

Stability studies

The Stability Spray Dried samples was carried for three months at different temperature and humidity condition such as Long term 25C ± 2C / 60RH ± 5%, Intermediate 30C ± 2C/65RH ± 5%, Accelerated 40C± 2C/75RH ± 5%. The Stability Spray Dried samples are evaluated by DSC analysis & dissolution Studies .whether the SDD's Stable or unstable were calculated. **T**he dissolution profile of the above storage conditions Spray Dried Samples are follows:

Table 9: Dissolution profile of "Day 90" Stability Spray Dried Composition

Sample name	25˚C /60RH	30˚C /65RH	40˚C /75RH
Loratadine:K29/32	52 %	45%	27%
Loratadine:S-630	39 %	27 %	29 %
Loratadine:HP 55	41 %	40 %	38 %
Loratadine: Ethyl cellulose	18 %	17 %	18 %
Loratadine:HPMC603	21 %	23 %	30 %
Loratadine:HPMC AS MF	19 %	22 %	23 %

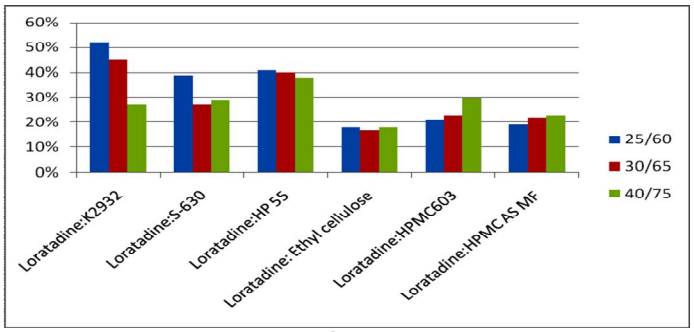


Fig. 7

Discussion

From Table No. (9) It was found that Stability SDD Formulation Shown the Percentage of release of Loratadine: HP 55 was the better dissolution release of all storage condition compared with pure crystalline drug.

SUMMARY AND CONCLUSION

The conclusion of this study, all the SDD formulations, powder evaluation, DSC analysis and Invitro release studies were performed. It was found that following batches complying with the specifications for the spray dried product namely, PVP K29/32 PVPS-630,. Ethyl Cellulose, HP55, HPMC 603, HPMC AS MF. The result shows that in Spray dried composition is improved the wetting of the drug increased the intrinsic solubility, and thus improved intrinsic dissolution rate of the drug. The stability studies suggested that in the Spray dried dispersion with respective polymers, the drug retains its crystalline form and showed identical dissolution profiles after storing at high temperature and humidity conditions.

The loratadine HP 55 Spray dried formulation was amorphous nature in all three stability condition, It was Evaluated by DSC analysis. & this was high dissolution rate, compared with pure crystalline drug. However, after storage at accelerated conditions, the dissolution rates of solid dispersions were lower due to partial reversion to crystalline form.

REFERENCES

1. Ainley Wade and J. Paul. Wedder Eds. Handbook of Pharmaceutical excipients, 2nd Ed; 1994.
2. Andersson M, Nolte H, C Baumgarten and Pipkorn U. Suppressive effect of loratadine on allergen-induced histamine release in the nose. Allergy. 1991;46(7):540-546.
3. Armbusters S and Werner K. spray drying II. Chem Ztg Chem App. 1999;93(13):493-504.
4. Bhaskar Chauhan, Shyam Shimpi and Anant Paradkar. Preparation and evaluation of glibenclamide-polyglycolized glycerides solid dispersions with silicon dioxide by spray drying technique. European Journal of Pharmaceutical Sciences. 2005;26:219–230.
5. Broadhead J and EdmondRouan SK. Spray drying technique for preparing

agglomerated powders II. Drug Dev Ind pharm. 1992;18:1169-1206.
6. Beuter W and Steiger K. Influence of particle size in spray drying. Pharm Acta Helv. 1996;31:543-54.
7. BASF Technical Literature, Kollidone-Polyvinylpyrrolidone for pharmaceutical industry, BASF Aktiengesellschaft, Fine Chemicals, D-67056, Ludwigshafen; March 1998 (4th edition).
8. R. Bruce Cassel, Market Specialist. Enhanced DSC Instrumentation Design and Characterization of Adhesives. TA Instruments, and New Castle, Del. January 31, 2002.
9. Chokshi RJ, Zia H, Sandhu HK, Shah NH and Malick WA. Improving the dissolution rate of poorly water soluble drug by solid dispersion and solid solution: pros and cons. Drug Deliv. 2007;14(1):33-45.
10. Chen R, Tagawa M, Hoshi N, Ogura T, Okamoto H and Danjo K. Improved dissolution of an insoluble drug using a 4-fluid nozzle spray-drying technique. Chem Pharm Bull (Tokyo). 2004;52(9):1066-70.
11. Dangprasirt P and Ritthidej GC. Development of Diclofenac sodium Controlled Release solid dispersion by spray Drying using Optimization Strategy Powder Formulation. Drug Development and Industrial pharmacy. 1995;21(20):2323-2337.
12. Edmond Rouan and Rhodes CT. Spray drying of pharmaceutical drug development and industrial pharmacy, 1992;18(11&12):1169-1206.
13. Greiff L, Persson CG, Svensson C and Enander I. Loratadine reduces allergen-induced mucosal output of alpha 2-macroglobulin and tryptase in allergic rhinitis. Allergy Clin Immunology. 1995;96(1):97-103.
14. Guy Van den Mooter A, Ilse Weuts A, Thomas De Ridder A and Norbert Blaton. Evaluation of Inutec SP1 as a new carrier in the formulation of solid dispersions for poorly soluble drugs. International Journal of Pharmaceutics. 2006;316:1–6.
15. Harpreet K. Sandhu, Navnit H. Shah, and Waseem A. Malick. Improving the Dissolution Rate of Poorly Water Soluble Drug by Solid Dispersion and Solid Solution. Pros and Cons Drug Delivery.2007;14:33–45.
16. Hirofumi Takeuchi, Shinsuke Nagira, Hiromitsu Yamamoto and Yoshiaki awashima. Solid dispersion particles of amorphous indomethacin with fine porous silica particles by using spray-drying method. International Journal of Pharmaceutics. 2005;293:155–164.
17. Ilse Weuts, Dieter Kempen, Geert Verreck and Annelies. Study of the physicochemical properties and stability of solid dispersions of loperamide and PEG6000 prepared by spray drying. European Journal of Pharmaceutics and Biopharmaceutics. 2005;59(1):119 -126.
18. ICH Harmonized Tripartite Guideline on Stability Testing For New Drug substances And Products QIC Nov 1996.