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SOLUBILITY ENHANCEMENT STUDY OF POORLY ABSORBABLE DRUGS

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ABSTRACT

The solubility behavior of drugs is one of the most challenging aspects in formulation development. Most of the newly invented or naturally occurring phytochemical entities are poorly water soluble. As a result formulating them as oral solid dosage forms is a major hurdle to the specialists. Thus a greater understanding of dissolution & absorption behavior of drug with low aqueous solubility is required to successfully formulate them into more soluble and hence bioavailable drug product. Therefore different approaches are being explored to enhance the solubility of poorly water soluble drugs; one of such approach is using Solid dispersion technique . In this study, we are trying to increase the solubility of two synthetic drugs i.e. Meloxicam [chemically designated as 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide] is a member of the enolic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs) and hydrochlorothiazide (6-chloro-1,1-dioxo-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide) which is diuretic and used in the management of hypertension. According to BCS classification meloxicam and hydrochlorothiazide is a class four drug having low aqueous solubility and low permeability. Major reasons contributing to the low plasma and tissue levels of meloxicam and hydrochlorothiazide appear to be due to poor absorption, rapid metabolism, and rapid systemic elimination. For this solvent evaporation and spray drying technique has been applied to improve the solubility and thus dissolution of poorly soluble and absorbable class IV drugs.

KEYWORDS: Solubility, Dissolution, Solid dispersion, Spray Drying Technique.

INTRODUCTION

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability rather than the limited permeation through the epithelial and the formulation of poorly soluble drugs for oral delivery now presents one of the major challenges to formulation scientists in the industries. A review of new monograph (1992-1995) in European pharmacopoeia shows that more than 40% of the drug substances have aqueous solubility below 1mg/ml and the 32% have an aqueous solubility below 0.1mg/ml.[1] The oral route of drug administration is the most common and preferred method of delivery. Drug absorption from the gastrointestinal tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and or poor membrane permeability of the drug molecule. When delivery an active agent orally, it must first dissolve in the gastric and or intestinal fluids before it can then permeate the membranes of the GI tract to reach systemic circulation. Therefore a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption. [2] And a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Therefore, pharmaceutical companies are focusing on finding a method or technology by which they can enhance the aqueous solubility and bioavailability of the drug. To date, various methods for modification of active pharmaceutical ingredients have included physical, chemical and controlled solid state methods. Each of the methods given above has their own drawbacks which restrain their use to modify the active pharmaceutical ingredient to improve its aqueous solubility and bioavailability. Some other conventional methods used to improve aqueous solubility and bioavailability includes: the use of surfactants; pH modification; solid dispersion technique; co-solvent and hydrotrope formation; co-crystallization techniques; and many more. [3] The application of solid dispersion is a promising approach to increase the dissolution rate of these drugs. A solid dispersion is generally composed of a drug incorporated in a (hydrophilic) carrier or matrix. The drug can be present in the amorphous state and/or as small crystals. An increased dissolution rate of the drugs incorporated in the solid dispersion is attributed to an increased surface area available for dissolution, an increased saturation concentration of the drug, a decreased thickness of the diffusion layer and an increased wettability of the drug. Two essential factors that strongly influence the dissolution behavior of solid dispersions are their composition and the method used to produce them. Many new drug substances can be classified according to the Biopharmaceutical Classification System (BCS) as class II drugs. These drugs show a poor aqueous solubility but once dissolved they are rapidly absorbed over the gastro-

intestinal. The next to the BCS class II drugs BCS class IV drugs may also benefit from the use of solid dispersions. The bioavailability of class IV drugs is limited because of both a poor solubility as well as a poor permeability. Although in general the improved dissolution rate will not improve the poor permeability, the overall bioavailability of these drugs may increase due to the improved dissolution behavior provided by the solid dispersions Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include: [4]

(1) Enhancing solubility and dissolution rate of poorly water soluble drugs and

(2) Enhancing permeability of poorly permeable drugs. The use of solid dispersion technique is used to improve the dissolution characteristics of poorly water soluble drugs and in turn their oral bioavailability.

MATERIALS AND METHODS

The materials and equipments used in the study are summarized in Table No. 1

Table No. 1: List of materials used

Sr.No	Materials/Chemicals	Source
1	Meloxicam	Gift sample from Ramdev Chemicals, Boisar,Thane
2	Hydrochlorothiazide	Gift sample from Abott Laboratories
3	Plasdone S-630	Ashland (Thailand)
4	Potassium dihydrogen phosphate	Loba Chemicals Pvt Ltd. Mumbai
5	Sodium hydroxide	Molychem
6	Chloroform	Molychem
7	Ethyl acetate	Molychem
8	Hydrochloric acid	Molychem
9	Acetone	SD Fine Chemicals Ltd. Mumbai
10	Methanol	SD Fine Chemicals Ltd. Mumbai

Table No. 2 : List of equipments used

Sr.No	Equipment Name	Source
1	Dissolution apparatus	USP Type II apparatus, TDT -08L, Electrolab
2	Electronic balance	Shimadzu BL 2200H(L)
3	Water bath	Water bath thermo static
4	pH meter	Equiptronics (EQ-610)
5	Bulk density apparatus	Innovative instruments Ltd
6	Mechanical shaker	Remi motors Ltd, Mumbai
7	Stability chamber	Aditi enterprises, Mumbai
8	UV/VIS Spectrophotometer	Shimadzu 1800
9	Fourier transform infrared spectroscopy	Shimadzu IR affinity 1
10	Spray dryer	Jay instrument and systems Pvt Ltd
11	Differential Scanning Calorimetry	SII Nanotechnology (SIECKO)

Preformulation Studies On Solid Dispersion

Solubility Of Polymers[53,54]

Polyethylene glycol (PEG 6000), Plasdone S630 in distilled water and various solvents such as methanol, ethanol, dichloromethane ,dimethylformamide were carried out.

Accurately weight amount of polymers (5 mg) were added in the test tubes containing 10 mL of distilled water, methanol, ethanol, dichloromethane ,dimethylformamide until, even after vigorous and prolonged stirring, some of that polymers does not dissolve. Such a solution is said to be saturated because it contains as much solute as possible at that temperature. In this saturated solution, the amount of solute is the solubility of that substance at that temperature in that solvent. At the time of saturation the total amount of polymers added was noted.

Preformulation Studies Of Solid Dispersion

Solvent Evaporation Method: PEG 6000 and Plasdone S630 were used for this technique and dimethylformamide were used for formulating solid dispersion.

Best solvent was selected based on the dryness of the granules and free flowing, and safety of solvent on humans.

Spray Drying: PEG 6000 and Plasdone S630 combination were used as hydrophilic polymers for solid dispersions and dimethylformamide for meloxicam and hydrochlorothiazide was used as solvent as it is the cheapest, easily available and safe.

Various parameters were evaluated for the formation of solid dispersion by spray drying such as feed rate, flow properties, infrared,differential scanning calorimetry were carried out.

Formulation Strategy.

Preparation And Evaluation Of Solid Dispersion

Formulation Of Meloxicam And Hydrochlorothiazide Solid Dispersions

Polyethylene glycol (PEG 6000) and Plasdone S630 were selected as carriers and evaluated for their use in their preparation of meloxicam and hydrochlorothiazide solid dispersion and for their efficiency in increasing solubility of meloxicam and hydrochlorothiazide.

Preparation Of Solid Dispersion Of Meloxicam And Hydrochlorothiazide With PEG6000 And Plasdone S630 By Solvent Evaporation Method[5,10]

PEG 6000 and Plasdone S630 were selected as carriers and evaluated for their use in their preparation of meloxicam and hydrochlorothiazide solid dispersion and for their efficiency in increasing solubility of meloxicam and hydrochlorothiazide.

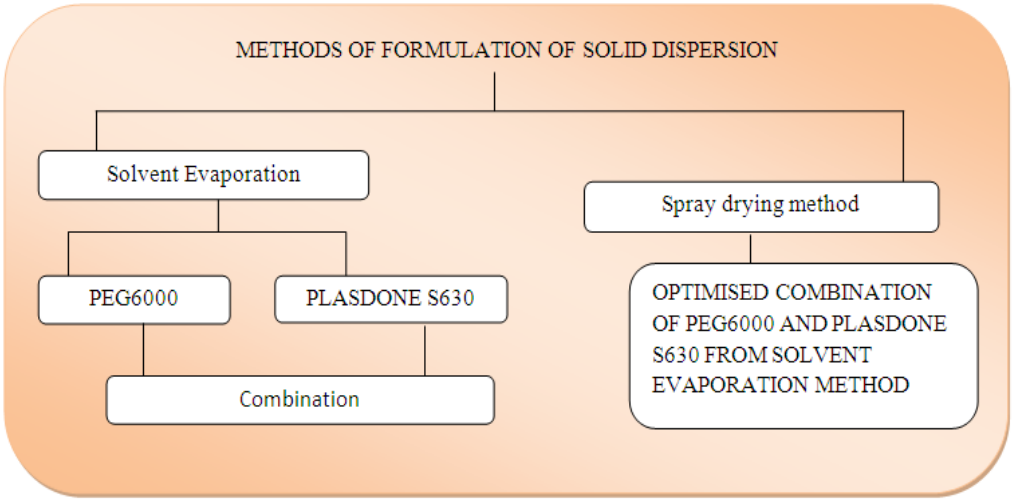

Figure No.1: Summary Of Solid Dispersion Formulation

Solid dispersions (SD) of different drug:polymer ratios were prepared by solvent evaporation method. The required amounts of meloxicam and hydrochlorothiazide and carriers were dissolved in few ml of N,N^1-dimethylformamide and allowed to stand overnight. The solvent was removed at 60^0 C under vaccum until the solid dispersion was dry. The dried mass was pulverized, passed through 60-mesh sieve and stored in a desiccator until used for further studies. This mass was hand filled into zero-size hard gelatin capsules just before the dissolution studies.

Preparation Of Solid Dispersion Of Meloxicam And Hydrochlorothiazide Using PEG6000 And Plasdone S630 (COMBINATION) By Solvent Evaporation Method

Solid dispersions(SD) of different drug :polymer ratios were prepared by solvent evaporation method. The required amounts of meloxicam and hydrochlorothiazide and carriers(in combination) were dissolved in few ml of N, N-dimethyl formamide and allowed to stand overnight. The solvent was removed at 60^0 c under vaccum until the solid dispersion was dry. The dried mass was pulverized, passed through 60-mesh sieve and stored in a desiccator until used for further studies. This mass was hand filled into hard gelatin capsules just before the dissolution studies.

Optimisation Of Selected Ratio Of Solid Dispersion (Selected Through Solvent Evaporation Method) Using Spray Drying Technique[8]

Selected ratios of meloxicam and hydrochlorothiazide by solvent evaporation technique were taken and dissolved in sufficient quantity of N,N-Dimethylformamide .The solution wa spray dried at constant aspiration speed of 1450, Inlet temperature =160^0, Outlet temperature =100^0, and at different feed rates i.e.at 20rpm, 25rpm, 30rpm, 35rpm. Dissolution studies were performed at each feed rate to select the optimized batch.

EVALUATION OF POWDERS

Bulk Density (ρb) (g/cc)

The bulk density of a powder is the ratio of mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume. Hence, the bulk density depends on both the density of powder particles and the spatial arrangement of particles in the powder bed. Bulk Density was determined by pouring the blend in a 50 mL measuring cylinder and recording the weight (W) and volume (Vb).

$$\text{Bulk Density(gm/cc)} = \frac{\text{Weight of samples in grams}}{\text{Volume occupied by the samples}}$$

Tapped Density (ρt) (g/cc)

Tap Density is measured by tapping the blend in a 50 mL measuring cylinder till a constant level is reached. The weight (W) and the tap volume (Vt) reached is determined. In this case, a total of 100 taps were given and it was calculated using the following formula.

$$\text{Tapped Density(gm/cc)} = \frac{\text{Weight of samples in grams}}{\text{Volume occupied by the sample after tapping}}$$

Angle Of Repose

Angle of repose was determined using funnel method. The blend was poured through a funnel and the cone height (h) was measured. The radius of the heap (r) was measured and angle of repose was calculated.

$$\text{Tan } \theta = \frac{h}{r}$$

Table No : 4: Relationship Between Angle Of Repose And Flow Ability

Angle of repose	Type of flow
25-30	Excellent
31-35	Good
36-40	Fair
41-45	Passable
46-55	Poor
56-65	Very Poor
>66	Extremely Poor

Hausner's Ratio

Hausner's Ratio is an ease of index of powder flow. It is calculated by using the following formula:

$$HR = \frac{\text{Tapped density } (\rho t)}{\text{Bulk density } (\rho b)}$$

Table No. 5: Hausner's Ratio Values And Its Significance

Hausner's ratio	Type of flow
1-1.1	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very Poor
>1.6	Extremely Poor

Carr's Index (Compressibility Index)

Based on the bulk density and the tapped density, the percentage of compressibility of the sample was calculated by using the following formula.

$$I = \frac{(\rho t - \rho b)}{\rho t} X\ 100$$

: % Compressibility values and its significance

Table No. 6: % Compressibility Values And Its Significance

Compressibility Index	Type of flow
1-10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very Poor
>38	Extremely Poor

Content Uniformity

Content Uniformity (Drug Content) Of Meloxicam[5]

Weigh accurately a quantity of powder containing about 15mg of meloxicam and dissolved in small volume of methanol and further diluted with phosphate buffer 6.8 .Drug content of meloxicam was determined at 362.6nm using UV -visible spectrophotometer.

Content Uniformity (Drug Content) Of Hydrochlorothiazide[4]

Weigh accurately a quantity of powder containing about 20mg of hydrochlorothiazide ,add 50.0ml of 0.1 M NaOH ,shake for 20 mins and dilute to 100ml 0.1M sodium Hydroxide. Mix, filter,dilute 5.0ml of filtrate to 100ml with water .Calculate the content of hydrochlorothiazide taking 520 as specific absorbance at 274.0 nm.

Phase Solubility Studies[10,100]

Phase Solubility Study Of Meloxicam

Excess drug were added in buffer and water and were shaken in a constant temperature shaker water bath held at 25 + 0.5^{o}C. The solutions are filtered after attaining equilibrium (72 h) using filters and meloxicam content was estimated using *UV*- visible spectrophotometer .Same procedure is followed with different drug:Polymer physical mixtures and solid dispersions.

Phase Solubility Study Of Hydrochlorothiazide

Solubility measurements were performed according to method reported by Higuchi and Connors, An excess amount of the drug was added in buffer and water. The samples were shaken for 48 hr. at 25±1°C. The solutions were filtered . After 48 hrs, the hydrochlorothiazide concentration was determined spectrophotometrically at 271 nm. Same procedure is followed with different drug:Polymer physical mixtures and solid dispersions.

***In Vitro* Dissolution[4,5]**

***In Vitro* Dissolution Of Meloxicam**

All *in-vitro* dissolution studies were carried out using 900 mL of phosphate buffer (pH 6.8) at 37 ± 0.5˚C as the dissolution medium in a USP Type II apparatus (TDT -08L, Electrolab) at a stirring speed of 50 rpm. Accurately weighed pure drug,solid dispersions and physical mixtures containing 15 mg of meloxicam were used and filled in capsules. 5 ml samples of dissolution medium were withdrawn at predetermined intervals (0, 10, 20, 30, 45, 60, 90,120 mins) and immediately replaced with an equal volume of the dissolution medium (maintained

at 37 ± 0.5˚C) in order to maintain constant volume of dissolution medium. Cumulative percentage (%CR) of meloxicam dissolved was calculated. The amount of meloxicam removed in each sample was compensated in the calculations. All experiments were performed in triplicate.

In Vitro Dissolution Of Hydrochlorothiazide

All *in-vitro* dissolution studies were carried out using 900 mL of 0.1MHCl (pH 1.2) at 37 ± 0.5˚C as the dissolution medium in a USP Type II apparatus (TDT -08L, Electrolab) at a stirring speed of 100 rpm. Accurately weighed pure drug, solid dispersions and physical mixtures containing 20 mg of hydrochlorothiazide were used and filled in capsules. 5 ml samples of dissolution medium were withdrawn at predetermined intervals (0, 10, 20, 30, 45, 60 mins) and immediately replaced with an equal volume of the dissolution medium (maintained at 37 ± 0.5˚C) in order to maintain constant volume of dissolution medium. Cumulative percentage (%CR) of meloxicam dissolved was calculated. The amount of hydrochlorothiazide removed in each sample was compensated in the calculations. All experiments were performed in triplicate.

Physical Characterization

Differential Scanning Calorimetry (DSC)[6]

Samples of 5 mg pure meloxicam, hydrochlorothiazide and its solid dispersions optimized with spray dried were hermetically sealed in flat bottomed aluminium pans and heated in the DSC instrument. The heating rate was 5 ^{0}C/min in a temperature range of 25–300 ^{0}C. The DSC thermograms were recorded.

Fourier Transform Infrared Spectroscopy (FTIR)[10]

The potassium bromide discs were prepared by mixing a small amount of the sample with potassium bromide and powder mixture was compressed to form the disc. It is then scanned over a frequency range of 4000–500 $cm^{-1.}$

Stability Studies[5,59]

Stability study for selected preparations of meloxicam and hydrochlorothiazide was carried out by storing dispersions in an amber colored screw capped bottle at different temperatures and relative humidity for a period of 3 months. The dispersions were visually examined for any physical change and drug content was estimated at the end of 3 months. Representative formulations were tested for stability with respect to physical appearance, drug content and

dissolution, at controlled room temperature (25^0 c / 60% RH) conditions for 3 months in amber coloured glass containers with 1 gm silica gel desiccant. The results indicated the formulations were stable under the tested conditions of storage.

RESULTS AND DISCUSSIONS

Fourier Transmission Infrared (FT-IR) Spectroscopy

Fourier Transmission Infrared (FT-IR) Spectroscopy Of Meloxicam

The identity of drug was confirmed by comparing IR spectrum of drug with reported spectrum of meloxicam as shown in Figure and its structure in Figure No.2 . Table No. 9 gives the functional groups that absorb IR wavelengths.

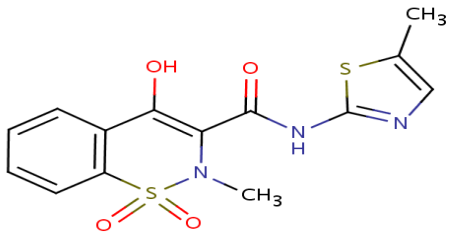

Figure No. 2: Structure Of Meloxicam

Table No. 7: IR Values Of Meloxicam

FUNCTIONAL GROUP	Wave number (cm^{-1})	
	Range	Pure Drug
(–NH) stretching	3500-3100	3285
C-O Stretching of amide	1670-1640	1618
C-C Stretching of aromatic ring	1600 an 1475	1452
Two S=O STRETCING OF Vibration	1375-1140	1345 and 1159
Ar-O stretching vibrations	1300-1100	1282.66

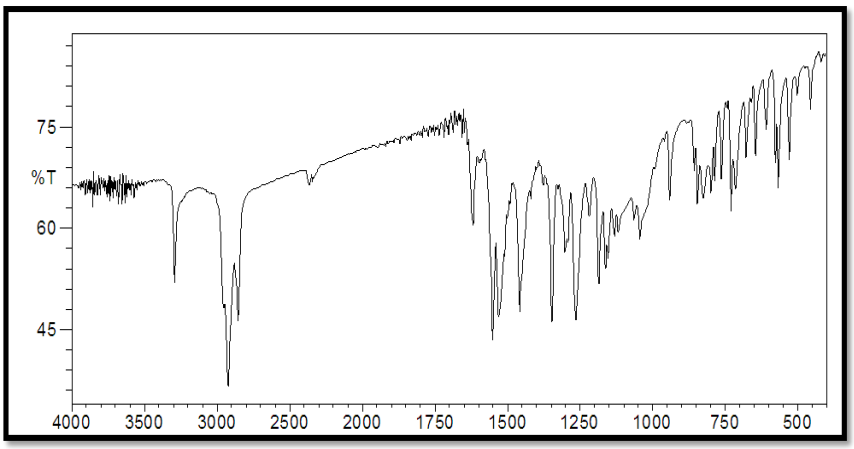

Figure No.3 : IR Spectra Of Meloxicam

Fourier Transmission Infrared (FT-IR) Spectroscopy Of Hydrochlorothiazide

The identity of drug was confirmed by comparing IR spectrum of drug with reported spectrum of hydrochlorothiazide as shown in Figure and its structure in Figure No. 4. Table No.10 gives the functional groups that absorb IR wavelengths.

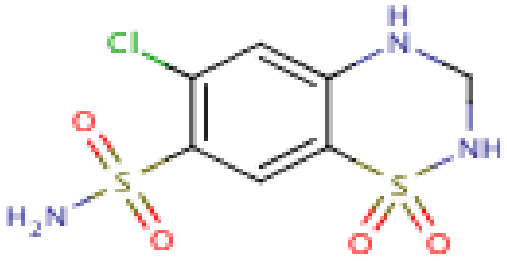

Figure No.4: Structure Of Hydrochlorothiazide

Table No. 8: IR Values Of Hydrochlorothiazide

FUNCTIONAL GROUP	Wave number (cm^{-1})	
	Range	Pure Drug
(–NH) stretching	3500-3100	3361.93 cm^{-1}
C=C Stretching	1680-1600	1604.77cm^{-1}
C-N Stretching	1350-1000	1319.31cm^{-1}
Two S=O STRETCING OF Vibration	1375-1140	1345 and 1159 cm^{-1}

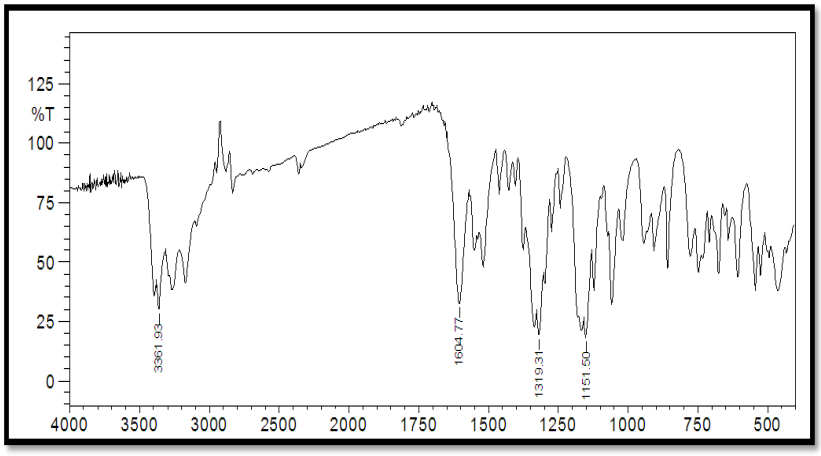

Figure No .5 : IR Spectra Of Hydrochlorothiazide

Differential Scanning Calorimetry (DSC):

DSC analysis of pure drug and prepared solid dispersion of optimized batch were accurately weighed (5mg) in aluminum pans, sealed and thermograms were obtained at the heating rate of 5˚C per min up to a temperature of 300˚C. Alumina was used as a reference standard.

Differential Scanning Calorimetry (DSC) Of Pure Meloxicam

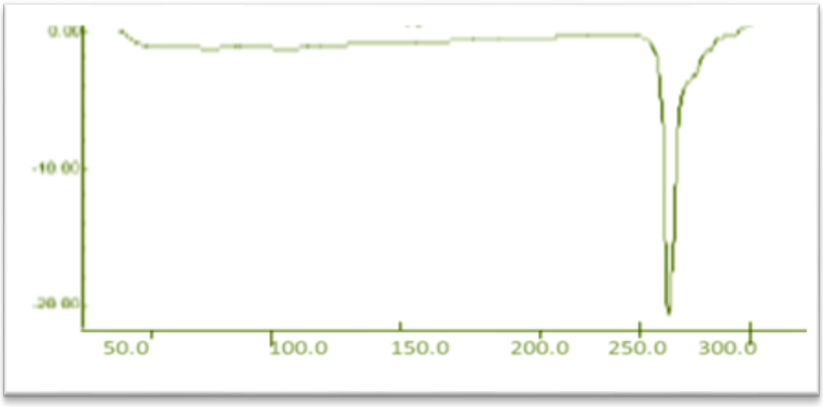

Figure No.6: DSC Thermogram Of Meloxicam

The DSC curve of pure Meloxicam showed a single sharp endothermic peak at 253.0°C corresponding to the melting of meloxicam as shown in the Figure No.6 . The reported melting point in the literature was in the range of 242-260^{0}C. Thus the given sample complied with the standard.

Differential Scanning Calorimetry (Dsc) Of Pure Hydrochlorothiazide

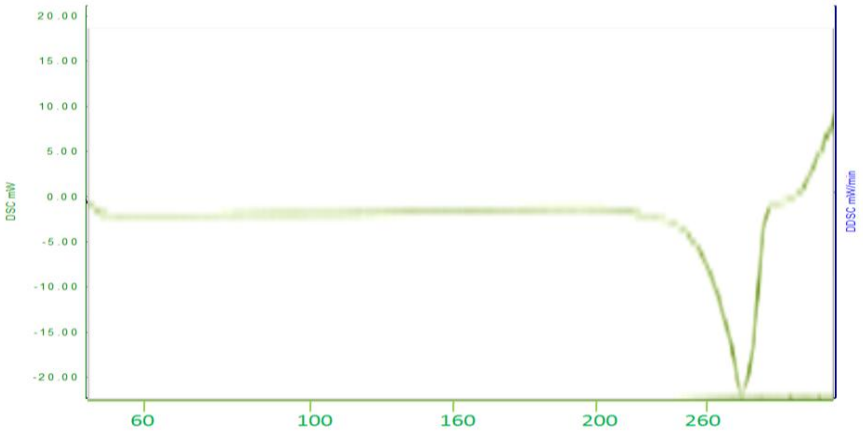

Figure No.7: DSC Thermogram Of Hydrochlorothiazide

The DSC curve of pure Hydrochlorothiazide showed a single sharp endothermic peak at 265.0°C corresponding to the melting of hydrochlorothiazide as shown in the Figure No.7. The reported melting point in the literature was in the range of 264-269^{0}C. Thus the given sample complied with the standard.

Determination Of Solubility

Determination Of Solubility Of Meloxicam

Meloxicam is practically insoluble in water at acidic and neutral pH, also insoluble in phosphate buffer (pH 6.8) and in 0.1N HCl. The solubility of meloxicam was found to be in the order of 6.8 > Distilled Water > 0.1NHCl as shown in Figure No.8.

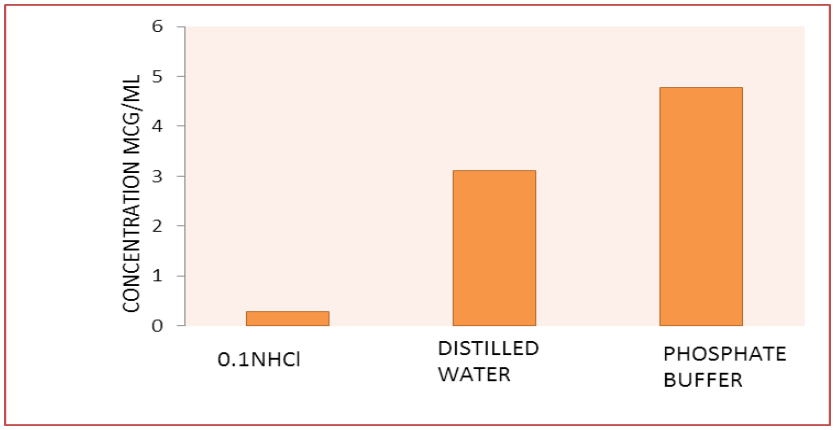

Figure No. 8: Solubility Of Meloxicam

Determination Of Solubility Of Hydrochlorothiazide

Hydrochlorothiazide is practically insoluble in water at acidic and neutral pH, also insoluble in phosphate buffer (pH 6.8) and in 0.1N HCl. The solubility of hydrochlorothiazide was found to be in the order of 6.8 > Distilled Water > 0.1NHCl as shown in Figure No.9.

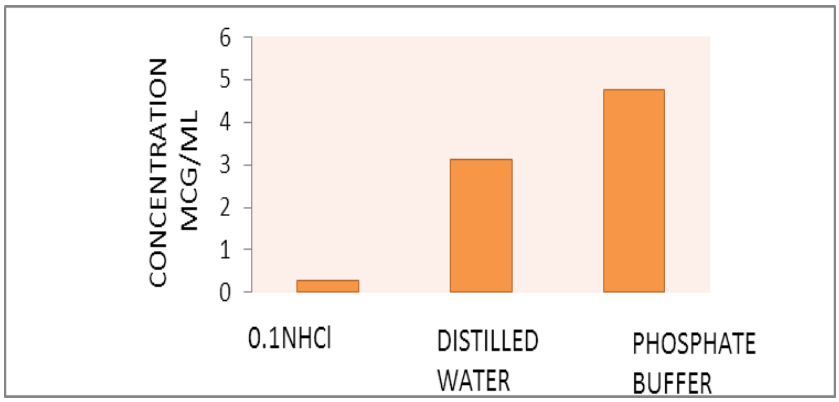

Figure No. 9: Solubility Of Hydrochlorothiazide

Physical Properties

Physical Properties Of Meloxicam And Hydrochlorothiazide

The Bulk density, Tapped density, Angle of repose, Hausner's ratio and Carr's index values of the meloxicam and hydrochlorothiazide are represented in Table No. 9. The bulk density

was found to be 0.47 ± 0.31 g/cc,tapped density of 0.51 ± 0.27, Hausner's ratio of 1.08 indicating good flowability, Carr's index was found to be 8.5 suggesting it can't be compressed directly. The good flowability of the solid dispersion was also evidenced with angle of repose within range of 43.6 ± 0.15°C indicating poor flowability, still needs the incorporation of glidants during formulation of solid dosage form.

Table No.9: Physical Properties Of Meloxicam And Hydrochlorothiazide

Drug	Bulk density (g/cc) (X±SD) (n=3)	Tapped density (g/cc) (X±SD) (n=3)	Carr's index (%)	Hausner's ratio	Angle of repose (0) (X±SD) (n=3)
Meloxicam and Hydrochlorothiazide	0.47 ± 0.31	0.51 ± 0.27	8.5	1.08	43.6± 0.15

Preformulation Studies On Solid Dispersion:

Solubility Of Polymers

Both PEG 6000 and Plasdone S630 were found to be highly soluble in water, phosphate buffer, 0.1N HCl,Dichloromethane, Ethanol, Dimethylformamide And Partially Soluble In Chloroform And Acetone.

Table No.10: Data Showing The Solubility Of Polymers In Buffers And Different Solvents.

Polymers	Medium	Amount of polymers added	Observation	Remark
PEG 6000	Distilled water	5mg/10ml	Clear solution	Soluble
	Phosphate buffer	5 mg/10ml	Clear solution	Soluble
	0.1NHCl	5 mg/10ml	Clear solution	Soluble
	Dichloromethane	20 mg/10ml	Clear solution	Soluble
	Ethanol	20 mg/10ml	Clear solution	Soluble
	Dimethylformamide	30 mg/10ml	Clear solution	Soluble
	Chloroform	20 mg/10ml	Clear solution	Soluble
	Acetone	5 mg/10ml	Does not dissolves	Insoluble
Plasdone S630	Distilled water	5 mg/10ml	Clear solution	Soluble
	Phosphate buffer	5 mg/10ml	Clear solution	Soluble
	0.1NHCl	5 mg/10ml	Clear solution	Soluble
	Dichloromethane	20 mg/10ml	Clear solution	Soluble
	Ethanol	20 mg/10ml	Clear solution	Soluble
	Dimethylformamide	30 mg/10ml	Clear solution	Soluble
	Chloroform	20 mg/10ml	Clear solution	Soluble
	Acetone	5 mg/10ml	Does not dissolves	Insoluble

Formulation

Solvent Evaporation Method

It can be concluded that combination of Plasdone S630 and PEG6000 was suitable for solvent evaporation as compared to individual polymers. Since some amount of solvent residue always remains in the PEG resulting in sticky mass not suitable for formulation. From the above data dimethylformamide is used for formulating solid dispersion by solvent evaporation method for both the drugs.

Table No. 11: ***Preformulation Studies For Formulating Solid Dispersion By Solvent Evaporation Method***

Sr. no	Drug (mg)	Polymer (mg)	Solvents (mL)	Temp (^{0}C)	Observation	Remark
1	Meloxicam and hydrochlorothiazide	PEG 6000 / PlasdoneS630	Dichloromethane	40^0	Dry powders	Selected
2	Meloxicam and hydrochlorothiazide	PEG 6000 / PlasdoneS630	Ethanol	90^0	Film formation	Not selected
3	Meloxicam and hydrochlorothiazide	PEG 6000 / PlasdoneS630	Dimethylformamide	60^0	Dry powders	Selected
4	Meloxicam and hydrochlorothiazide	PEG 6000 / PlasdoneS630	Chloroform	40^0	Film formation	Not selected

Spray Drying Method

Batches were prepared in dimethylformamide because as compared to dichloromethane solvent requirement is less and temperature was maintained at 160^0C. The product obtained is completely dry and free flowing.

Formulation Studies

Phase Solubility Studies

The solubility of meloxicam was determined at 37˚C±0.5^{0}C in purified water as well as in phosphate buffer solution of pH 6.8.Similarly, the solubility of hydrochlorothiazide was determined at 37˚C±0.5^{0}C in purified water as well as in hydrochloric acid solution of pH 1.2.The solubility of meloxicam in purified water at 37˚C was 3.1058±0.01 µg/ml and pH 6.8 was 4.7654±0.01 µg/ml, very similar to the solubility in purified water and that of hydrochlorothiazide was found to be 1.737±0.01 µg/ml and pH 1.2 was 0.28±0.01 µg/ml . A significant increase in its solubility was observed as the concentration of the polymers was increased. It was suggested that both the polymers might form the soluble complex with meloxicam and hydrochlorothiazide.

The solubility increased linearly, though marginally in the PEG 6000 suggesting very weak interactions with the polymer. Solutions of Plasdone S630 exhibited linear and significantly greater increase in the solubility of meloxicam and hydrochlorothiazide as the concentration of polymers was increased signifying approximately 2-fold greater,but after certain concentration of polymers , in both the case of drugs ,there is decrease in solubility of drug in both water and buffers.

From the equilibrium solubility data it if found that the combination of polymers (Meloxicam: PEG 6000: Plasdone S630, 1:4) and (hydrochlorothiazide: PEG 6000: Plasdone S630, 1:5) shows the highest solubility of meloxicam and hydrochlorothiazide as compared to others. Both the polymers have additive properties in the solubility enhancement. Further the mechanism behind this is the decrease in the particle size of the meloxicam and hydrochlorothiazide results in the diffusion of the meloxicam and hydrochlorothiazide from the matrix of the polymers. Also the viscosity of the combined polymers may be the reason for enhancement of solubility of drug.

The viscosity may have been decrease or may not been hampered due to combination of these to different polymers. This may be the reason that the drug easily gets diffuse from the matrix of the polymers and since more particle size reduction causing more drugs to get solubilized. After getting the optimized batch from solvent evaporation, the optimized ratios were spray dried at different feed rates.

The following are the parameters set for meloxicam and hydrochlorothiazide:
Feed rate:20,25,30,35(RPM)
Aspiration speed:1450 m/s
Inlet temperature:160^0C
Outlet temperature:100^0C.

The solubility of meloxicam at all RPm's was found to be 124.081µg/ml in phosphate buffer (pH 6.8) and 112.298 µg/ml in distilled water.Similarly,the solubility of hydrochlorothiazide at all RPM's was found to be 82814.465 µg/ml in 0.1N HCL and 128632 µg/ml in distilled water.

Drug Content, Flow Properties And Dissolution Properties Of Meloxicam And Hydrochlorothiazide Formulations By Two Techniques.

The content uniformity test is used to ensure that every formulation contains the amount of drug substance intended with little variation among tablets within a batch. Mainly it is used for testing the consistency of

1) Bulk powders before or after compression
2) Liquid orals before filling
3) Also during filling of powders into capsules or liquids into vials or ampoules
4) Amount of active pharmaceutical ingredient within individual units of tablets or capsules.

The dissolution profile of pure drug, physical mixtures and solid dispersions are studied. Both physical mixtures and solid dispersions showed enhanced dissolution rate as compared with pure drug. Solid dispersion increased the solubility and maximizing the surface area of the drug that came in contact with the dissolution medium as the carrier dissolved. In all cases, the dissolution rates of meloxicam and hydrochlorothiazide solid dispersions were remarkably enhanced compared to their corresponding physical mixtures and pure meloxicam and hydrochlorothiazide.

Several mechanisms have been proposed to account for the increase in the dissolution kinetic of drug from solid dispersions. These mechanisms include the reduction of drug crystallite size, a solubilization effect of carrier, an absence of drug aggregation and agglomeration, an improvement in drug wettability, the conversion of drug to the amorphous state.

The increased in meloxicam and hydrochlorothiazide dissolution from these solid dispersions can thus be contributed by several factors such as an excellent wettability, which could be observed clearly from the solid dispersion since it rapidly left the surface and was dispersed in the bulk of the dissolution medium, a markedly increase in meloxicam and hydrochlorothiazide solubility, the solubilizing effect of the carrier, an absence of aggregation and agglomeration and the formation of high energy amorphous state as confirmed by DSC, FTIR.

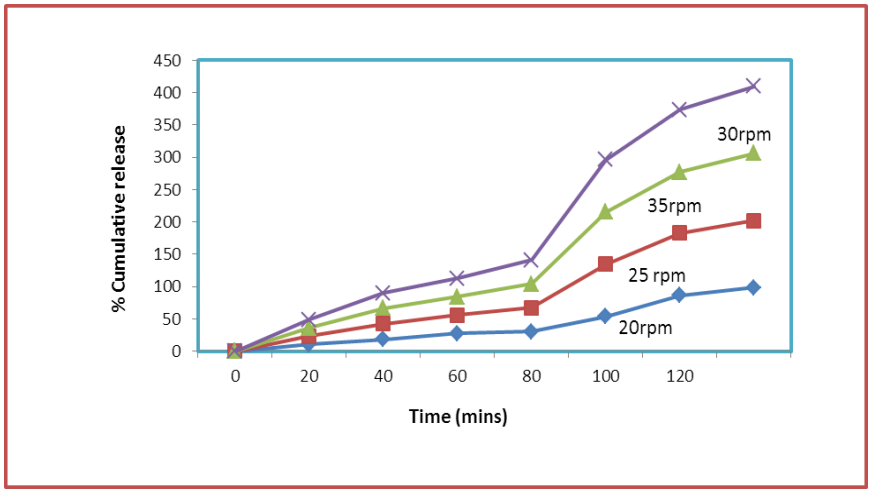

Figure No.10: Dissolution Profile Of Meloxicam At Different Rpm's

It is found that using spray drying technique the amount of drug release after 120 mins has increased to 15.187 mg at 30 rpm as compared to other feed rates. This ensures the complete conversion of crystalline drug into the amorphous form leading to increase in dissolution rate.

The dissolution of pure hydrochlorothiazide was just 4.4727mg from 20.0mg even after 60 mins. Addition of 5 parts combined polymers(PEG 6000+Plasdone S630{1:1}) physically along with the API increased the release from 4.4727mg to 8.30982 mg and by using same amount of combination of polymers the solid dispersion prepared by solvent evaporation method release has increased a little bit as compared to the physical mixture i.e.11.766 mg. Hence, using the same ratios of drug:polymer ,the further optimization of formulation were carried out using spray drying technique.

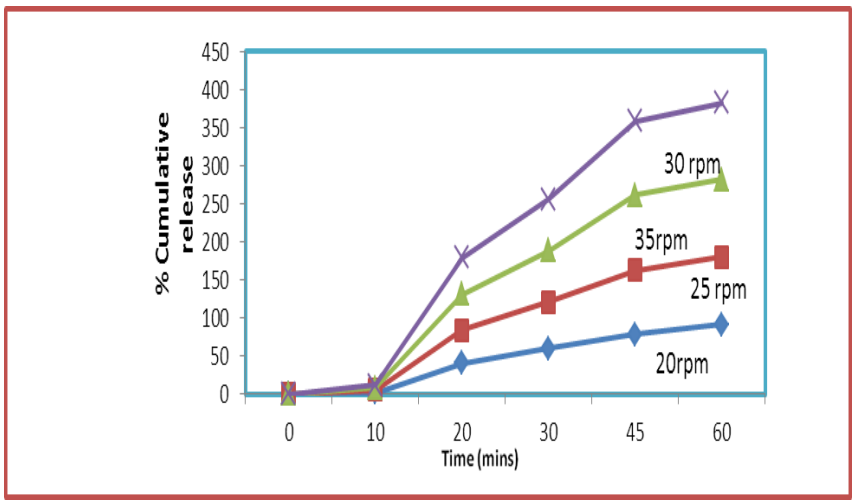

Figure No.11: Dissolution Profile Of Hydrochlorothiazide At Different Rpm's

It is found that using spray drying technique the amount of drug release after 60 mins has increased to almost 19.99 mg at 30 rpm as compared to other feed rates.This ensures the complete conversion of crystalline drug into the amorphous form leading to increase in dissolution rate.

Table No. 12: Flow Properties, Drug Content Of Solid Dispersion Of Batch Prepared By Solvent Evaporation Method And Spray Drying Technique.

Formulations	Bulk density (g/ml) (X±SD)	Tapped density (g/ml) (X±SD)	Carr's index (%)	Hausner's ratio	Angle of repose (0) (X±SD)	Drug content (%) (X±SD)
Meloxicam solvent evaporation	0.3778± 0.000611	0.611± 0.00057735	38.298± 0.0023094	1.62± 0.0057735	40.25± 1.125093	93.33± 0.335112
Meloxicam spray dried	0.2437± 0.000404	0.2902± 0.000153	16.02± 0.0057735	1.19± 0.0057735	29.473± 0.515854	98.613± 0.105548
Hydrochlorothiazide solvent evapotion	0.3778± 0.000611	0.611± 0.00057735	38.298± 0.0023094	1.62± 0.0057735	42.6± 1.628906	85.88± 1.328947
Hydrochlorothiazide spray dried	0.2437± 0.000404	0.2902± 0.000153	16.02± 0.0057735	1.19± 0.0057735	29.67± 2.501926	97.86± 0.410731

The drug content was found to be 98.613% for meloxicam and 97.86% for hydrochlorothiazide using spray drying technique indicating uniform drug distribution in the prepared solid dispersion batch. Similarly, the drug content was found to be 93.33% for meloxicam and 85.88% for hydrochlorothiazide using solvent evaporation technique indicating non uniform drug distribution in the prepared solid dispersion batch .The bulk density, tapped density, angle of repose, Hausner's ratio and Carr's index values of the formulations are represented in Table by both the techniques.. The above results indicate that the there is good flowability of powder using spray drying technique as compared to solvent evaporation technique.

Physical Characterization

Differential Scanning Calorimetry (Dsc)

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*. 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. As the temperature increases the sample eventually reaches its melting temperature (*Tm*). The melting process results in an endothermic peak in the DSC curve. The ability to determine transition temperatures and enthalpies makes DSC a valuable tool in producing phase diagrams for various chemical systems. The DSC measures the melting point of the meloxicam , hydrochlorothiazide and based on that it is possible to measure whether the meloxicam , hydrochlorothiazide is in the crystalline state or in amorphous state in the prepared solid dispersion and based on that the mechanism of increased in the solubility can be confirmed.

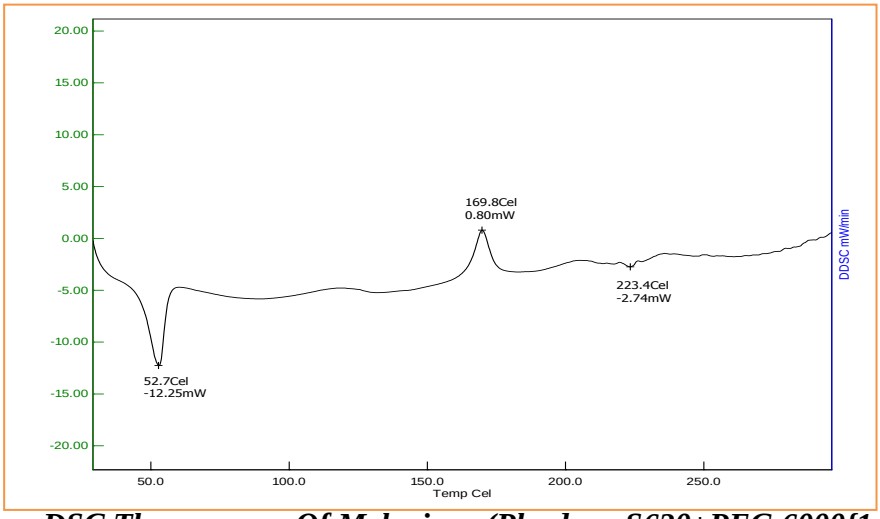

Figure No.12. : DSC Thermogram Of Meloxicam(Plasdone S630+PEG 6000{1:4} [30rpm] Using Spray Drying Technique

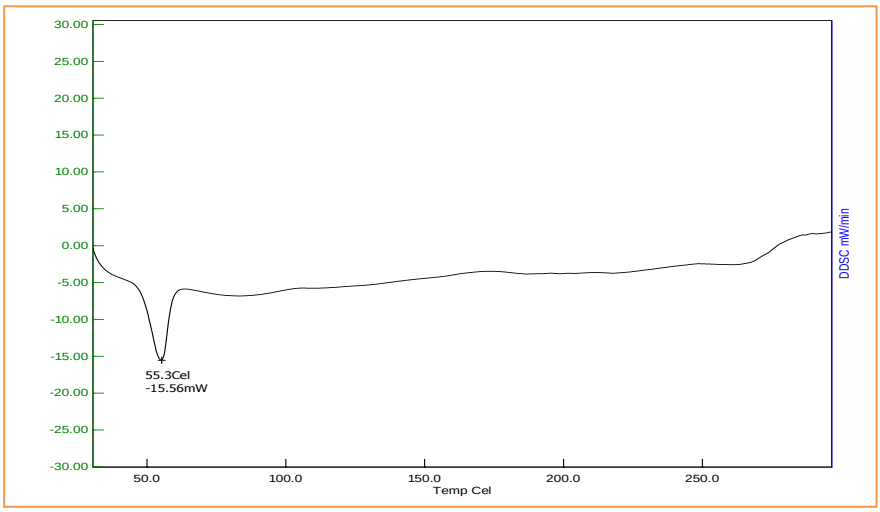

Figure No.13 : DSC thermogram of Hydrochlorothiazide(plasdone S630+PEG 6000{1:5} [30rpm] using spray drying technique

Fourier Transform Infrared Spectroscopy

The FTIR spectroscopy of the solid dispersion preparations of drugs are as follows.

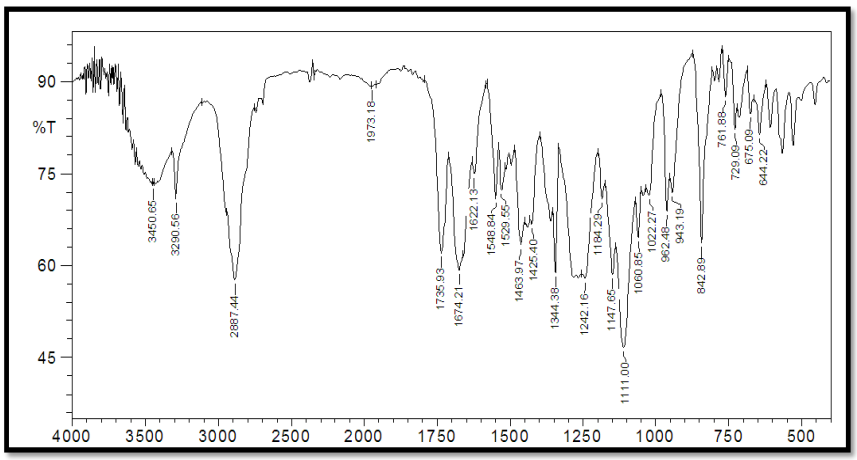

Figure No. 14: IR Spectroscopy Of Meloxicam Solid Dispersion By Solvent Evaporation

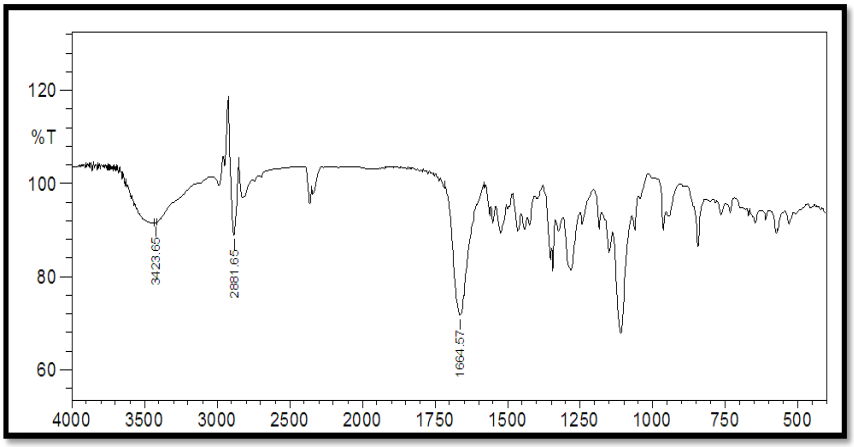

Figure No. 15: IR Spectroscopy Of Meloxicam Solid Dispersion By Spray Drying Technique

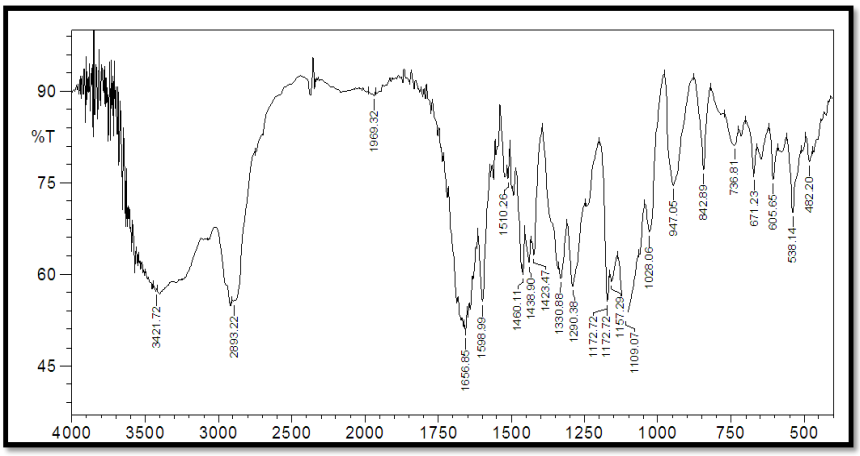

Figure No.16 : IR Spectroscopy Of Hydrochlorothiazide Solid Dispersion By Solvent Evaporation Technique

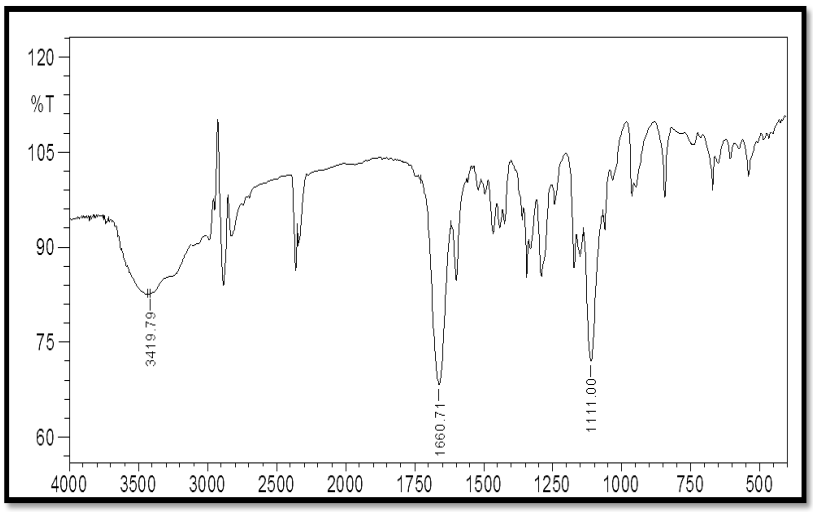

Figure No. 17:IR Spectroscopy Of Hydrochlorothiazide Solid Dispersion By Spray Drying Technique

FTIR spectroscopy was carried out to further elucidate the interaction in meloxicam and hydrochlorothiazide with polymers in the solid state. The FTIR spectrum of pure meloxicam and hydrochlorothiazide showed an absorption band at 3423.66 and 3306.109cm^{-1} respectively assigned to the phenolic O-H stretching vibration. The FTIR spectra of all physical mixtures were similar to the synthetic spectra producing by the addition of meloxicam and hydrochlorothiazide and both the polymers.

This indicates no interaction between meloxicam and hydrochlorothiazide and Polymers causing meloxicam and hydrochlorothiazide to remain in its crystalline state. In particular, the O-H stretching vibration at 3500 cm^{-1} of all solid dispersions showed significant broadening of peaks in the region 3600–3400 cm−1. It may be attributed to intermolecular hydrogen bonding. This interaction caused to change meloxicam and hydrochlorothiazide crystalline structure to amorphous form resulting in the increased in the dissolution of the drug and its solubility.

STABILITY

The stability of the samples(spray dried) was carried out at 25 ± 2°C/60 RH ± 5% RH as per the ICH guidelines. The granules were sampled at 1 month and 3 month

Table No. 13: Stability Data Of Solid Dispersion.

Parameters	Initial		1 Month		3 Months	
	Meloxicam	Hydrochlorothiazde	Meloxicam	Hydrochlorothiazde	Meloxicam	Hydrochlorothiazde
Bulk density (g/ml)	0.2437	0.2437	0.2437	0.2437	0.25	0.25
Tapped density (g/ml)	0.2902	0.2902	0.2902	0.2902	0.28	0.28
Carr's index (%)	16.02	16.02	16.02	16.02	10.714	10.714
Hausner's ratio	1.19	1.19	1.19	1.19	1.12	1.12
Angle of repose (^{0})	29.473	29.67	29.473	29.67	29.473	29.67
Drug content (%)	98.613%	97.86%	100.632%	100.41%	97.103%	94.564%
Dissolution studies	104.44%	100.671%	102.853%	100.760%	103.10%	100.32%

CONCLUSION

The combination of PlasdoneS630 and PEG 6000 was found to be better as compared to their single use in the solid dispersion. Drug: Polymer ratio of 1:4 for meloxicam and drug ratio 1:5 for hydrochlorothiazide was found to be better as compared to other ratios by solvent evaporation technique which is further optimized using spray drying technique by performing dissolution studies of the product obtained at different feed rates where it is found that both the drugs were showing same increased in solubility compared to solvent evaporation technique irrespective of the feed rates but increase in the % cumulative release at 30 rpm compared to other feed rates.

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