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Preparation, Characterization, and Evaluation of Physical Mixtures of Ibuprofen for Solubility Enhancement

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ABSTRACT

The aqueous solubility of a therapeutically active substance is an important property as it controls the action of dissolution, absorption and thus the efficacy *in-vivo*. Poor aqueous solubility is the major problem for various drugs. There are lots of techniques are already reported for increasing the solubility of such important drugs. The objective of the present investigation was to prepare physical mixtures to investigate the enhancement of the aqueous solubility and dissolution of ibuprofen(a poorly soluble, weakly acidic, NSAID) using some selected hydrophilic carriers with the different ratio. The prepared ibuprofen physical mixtures were characterized by using Differential scanning calorimetry, FT-IR studies, drug solubility and *in-vitro* drug dissolution and compared these data with a pure drug which showed remarkable improvement in solubility and drug dissolution of these new ibuprofen physical mixtures. This study concluded that the improved solubility, as well as drug dissolution of these new ibuprofen physical mixtures using PVP K 30-PEG 6000 combination or other PVP K 30 /Hydrophillic carrier combination, may be attributed to improved wettability, and reduction in drug crystallinity, which can be modulated by appropriate level of hydrophilic carriers.

INTRODUCTION:

Aqueous solubility is a key property as it governs dissolution, absorption and thus the efficacy *in vivo*. Solubilization may be defined as the preparation of a thermodynamically stable solution of a substance that is normally insoluble or very slightly soluble in a given solvent by the introduction of one or more amphiphilic compound.[1-3]Solubilization of poorly soluble drugs is a challenge in screening studies of new chemical entities as well as in formulation design and development. In the case of poorly water-soluble drugs, dissolution is the rate-limiting step in the process of drug absorption. The solubility depends on the nature and composition of the solvent medium, the physical form of the solid as well as temperature and pressure of the system. There are various techniques available to improve the solubility of poorly soluble drugs like pH adjustment, Micro-emulsion, Self-emulsifying drug delivery systems, Particle size reduction, Supercritical fluid (SCF) process, Inclusion complexes/complexation, Solid Dispersions, Nano-suspension, Nano-crystallization etc[4-6,8].

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) and used to relieve the pain, tenderness, inflammation, and stiffness caused by arthritis and gout[9,10]. It is also used to reduce fever and to relieve headaches, muscle aches, menstrual pain, aches and pains from the common cold, backache, and pain after surgery or dental work. Ibuprofen is a core medicine in the World Health Organization's "Essential Drugs List", that means it is in the list of minimum medical needs for a basic health care system[11].

MATERIALS AND METHODS:

MATERIALS:

The standard sample of Ibuprofen, Ethanol, PEG4000, PEG6000, HPMC, sorbitol, Lactose, Mannitol, PVP, Sodium hydroxide, Potassium dihydrogen phosphate were obtained from Merck specialistpvt Ltd. Shiv Sagar Estate, Mumbai-400018. Methanol was obtained from Changshu Yangyuan chemical, China.

METHODS:

For optimizing drug to carrier ratio, the physical mixture of ibuprofen was prepared with a different hydrophilic carrier in different ratios.

Preparation of Physical mixtures:

Physical mixtures of ibuprofen were prepared by mixing ibuprofen with different polymeric carrier (i.e.-PVP, mannitol, lactose, sorbitol, HPMC, PEG 4000, PEG6000, carbopol) in combination and individually in a glass mortar by trituration for 15 minutes in different ratio (1:1; 1:2)(Table-5).

Characterization of prepared physical mixtures:

Determination of percent yield-

The percent yield of ibuprofen solid dispersions can be determined by using the following expression:

Percent yield = (weight of prepared solid dispersion/weight of drug + carriers) x 100

Determination of percent drug content:

Weight amount of physical mixtures and solid dispersions, each sample equivalent to 25 mg of ibuprofen were separately taken and added to 50 ml of methanol in Stoppard conical flasks. The sealed flasks were agitated on a rotary shaker for 1 hour. The solution was dilutedwith methanol and was assayed by a UV-VIS spectrophotometer for drug content at 221 nm using the following expression:

Percent drug content = (practical drug content in solid dispersions / theoretical drug content In solid dispersions) x 100

Dissolution studies:

Dissolution studies were performed in phosphate buffer (pH 7.2, 900 ml) at 37 ± 0.5 °C, using USP XXIII apparatus with a paddle rotating at 50 rpm. The samples equivalent to 100 mg ibuprofen were kept in a capsule shell (size #00#) and subjected to dissolution. At fixed time intervals, samples (5 ml) were withdrawn and the equal amount of fresh dissolution medium was added. Withdrawn samples were filtered through 0.45 µm membrane filter and spectrophotometrically assayed for drug content at 221 nm wavelengths using a UV-VIS spectrophotometer.

RESULT AND DISCUSSION:

Preformulation study of Ibuprofen:

Organoleptic properties:- The following organoleptic properties were found-

1. Nature	A white powder
2. Color	white
3. Odor	characteristic.
4. Taste	Slightly Bitter taste
5. Solubility-	
In water	Sparingly soluble
In methanol	Freely Soluble.
In ethanol	Freely Soluble
In acetone	Freely soluble
In phosphate buffer	Soluble.

From the solubility study of the drug, it has been seen that the drug is soluble in the organic solvent so it can be concluded that the drug is nonpolar.

Melting point determination:

The melting point of the drug sample was found to be 76ºC, which matched the melting point as reported in official pharmacopoeia (B.P). This reveals that drug sample is retaining the desired property of purity.

FT-Infrared spectroscopy study:

The principle absorption peaks of ibuprofen appear at 2990.82 cm^{-1}(C-H stretching of the aromatic group) and at 1120.65 cm^{-1}(C-C stretching). However, a sharp peak at 1683.53 cm^{-1}(C=O stretching of carbonyl group) and at 3089.41 cm^{-1}(O-H stretching of the alcoholic group). The identical peaks of C-H stretching, C-C stretching also appeared in the spectra of ibuprofen

physical mixtures prepared by using different hydrophilic carriers. These observations indicated that no chemical interactions between the drug and the polymers used.

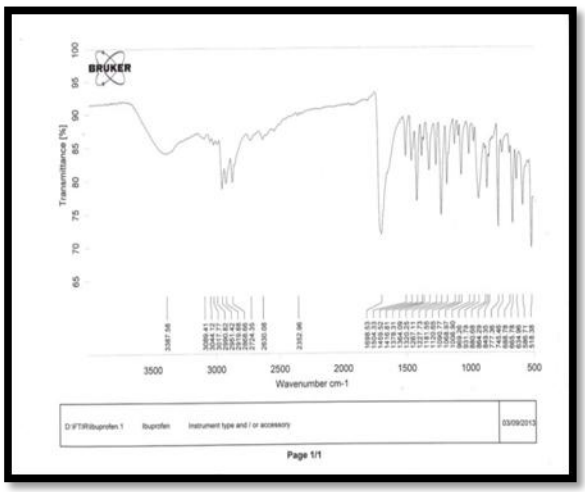

Fig 1.- IR Spectrum of Ibuprofen

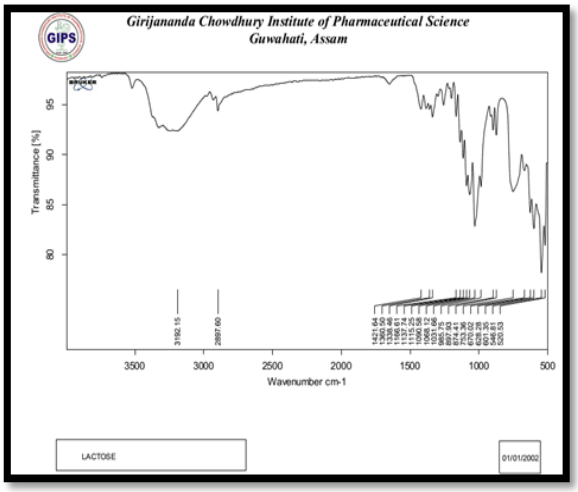

Fig 2 – IR Spectrum of lactose

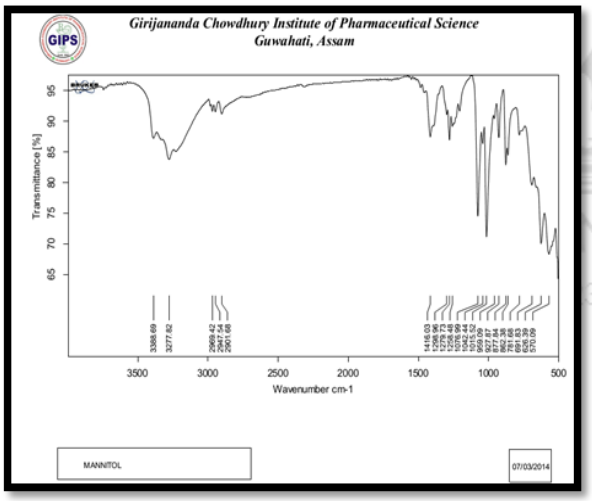

Fig 3 – IR Spectrum of Mannitol

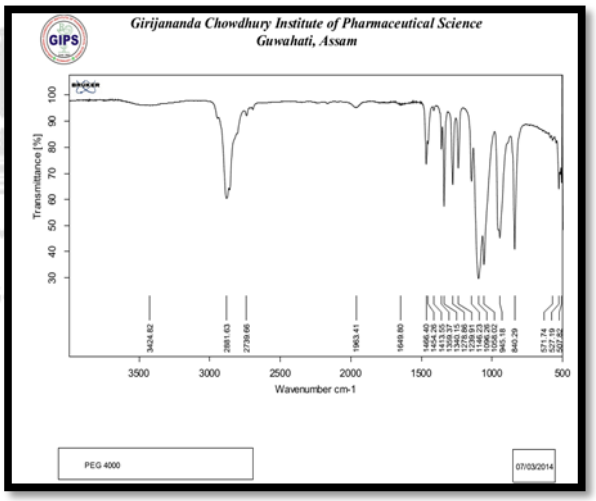

Fig 4 – IR Spectrum of PEG4000

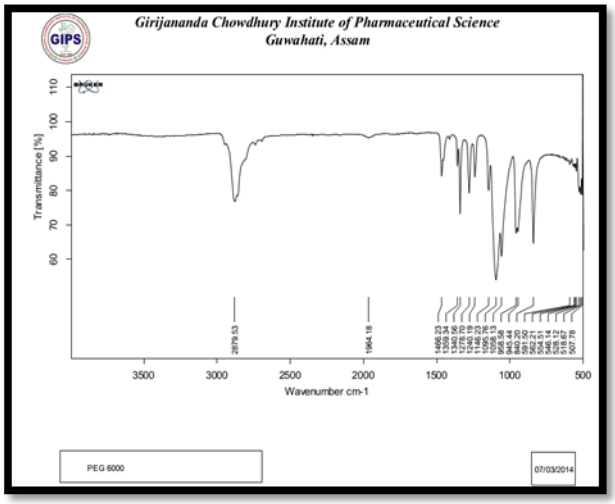

Fig 5- IR Spectrum of PEG6000

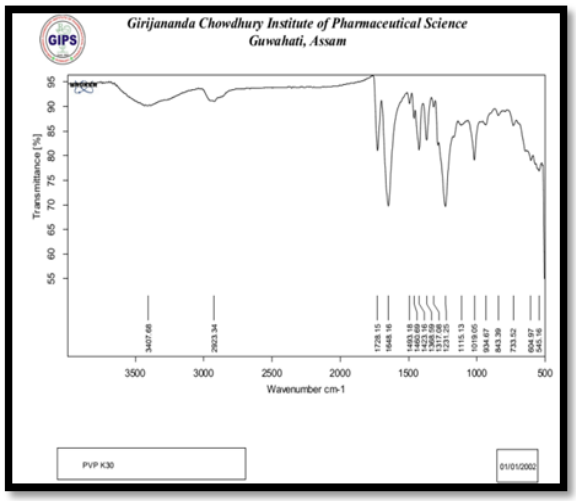

Fig 6- IR Spectrum of PVP K30

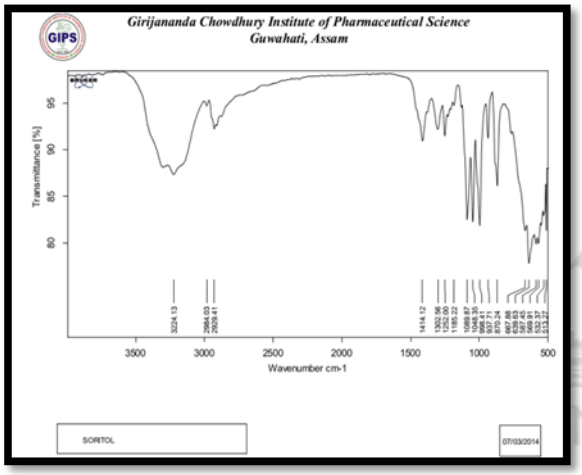

Fig 7- IR Spectrum of Sorbitol

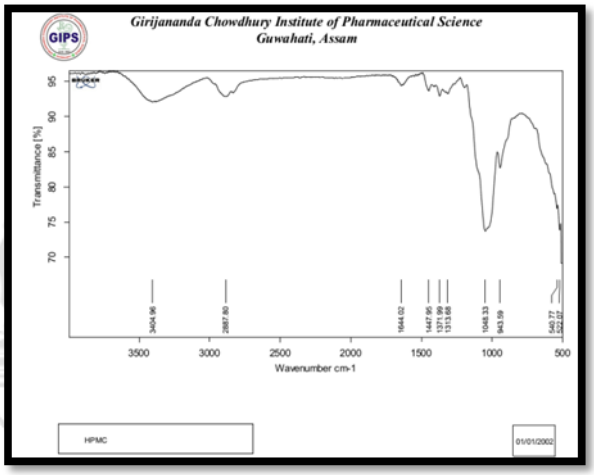

Fig 8- IR Spectrum of HPMC

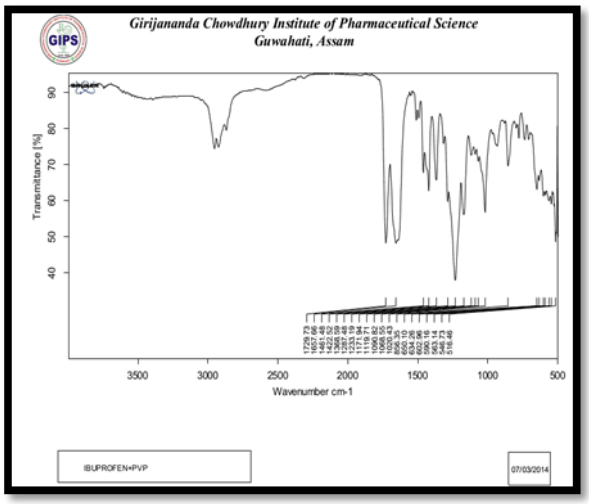

Fig 9 – IR Spectrum of physical mixer Ibuprofen and PVP K30

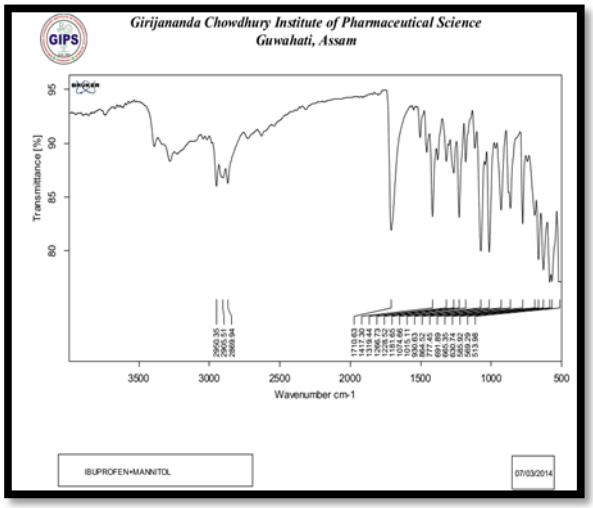

Fig 10- IR Spectrum of physical mixer of Ibuprofen and Mannitol

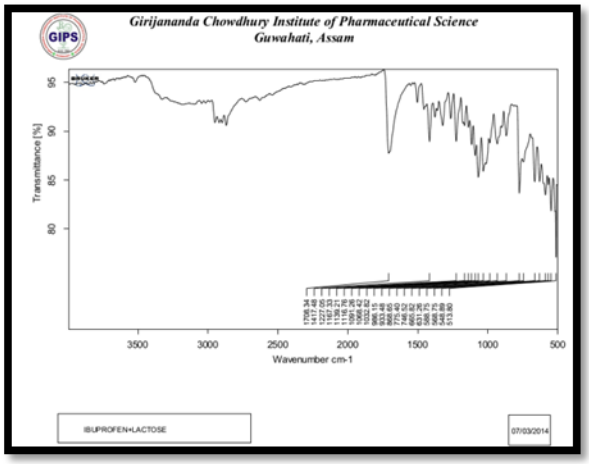

Fig 11– IR Spectrum of physical mixer of Ibuprofen and Lactose

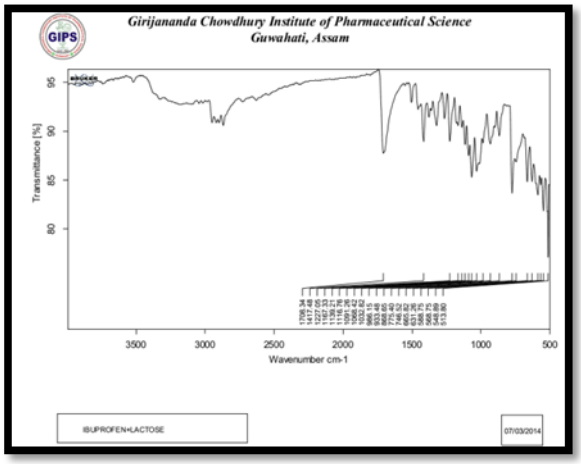

Fig 12– IR Spectrum of physical mixer of Ibuprofen and PEG4000

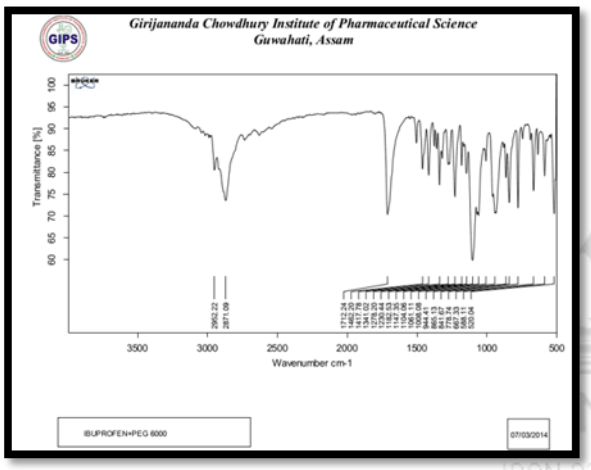

Fig 13- IR Spectrum of physical mixer of Ibuprofen and PEG6000

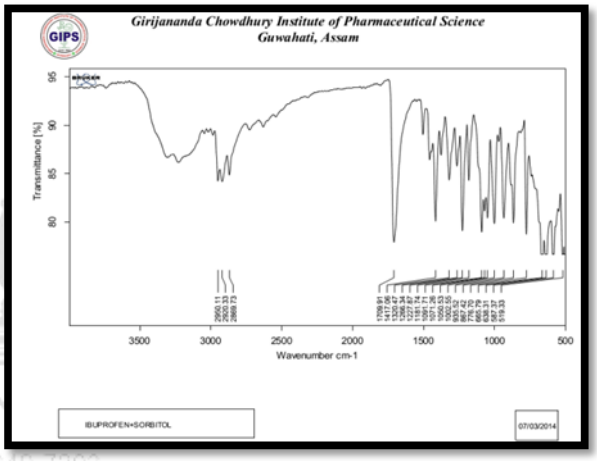

Fig 14- IR Spectrum of physical mixer of of Ibuprofen and Sorbitol

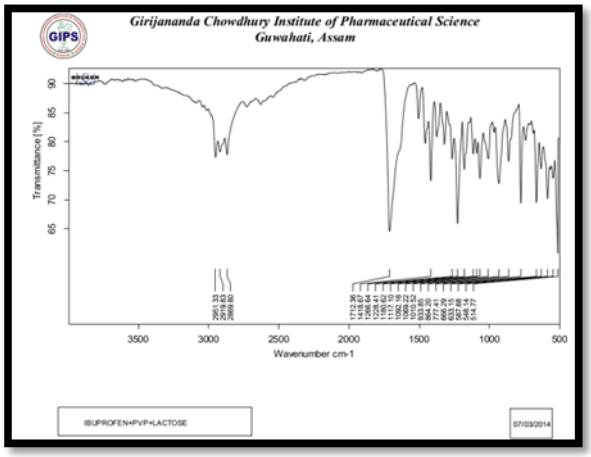

Fig 15– IR Spectrum of physical mixer of Ibuprofen, PVP K30 and Lactose

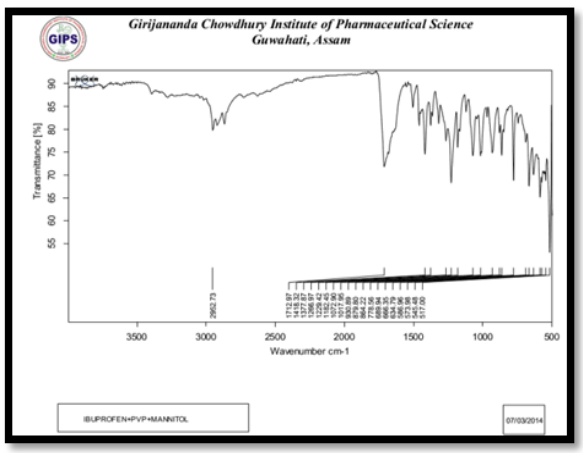

Fig 16– IR Spectrum of physical mixer of Ibuprofen, PVPK30 and Mannitol

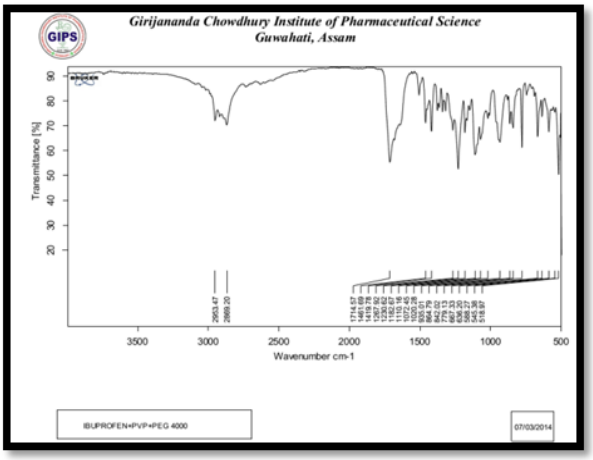

Fig 17– IR Spectrum of physical mixer Ibuprofen, PVPK30, and PEG4000

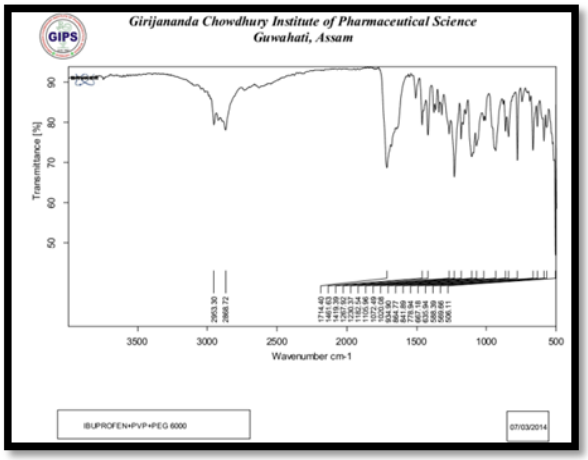

Fig 18 – IR Spectrum of physical mixer of of Ibuprofen, PVPK30 and PEG6000

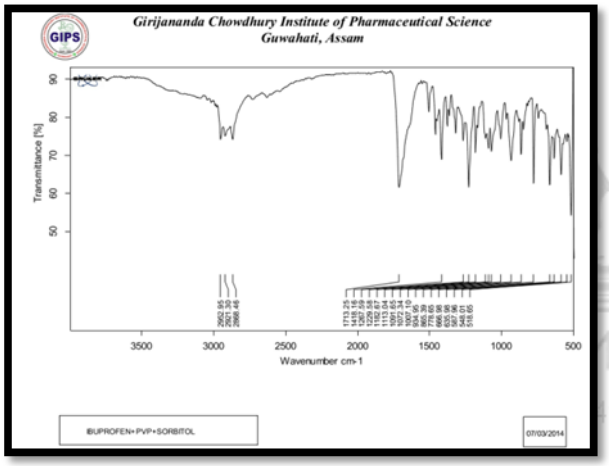

Fig19– IR Spectrum of physical mixer of Ibuprofen, PVPK30, and Sorbitol

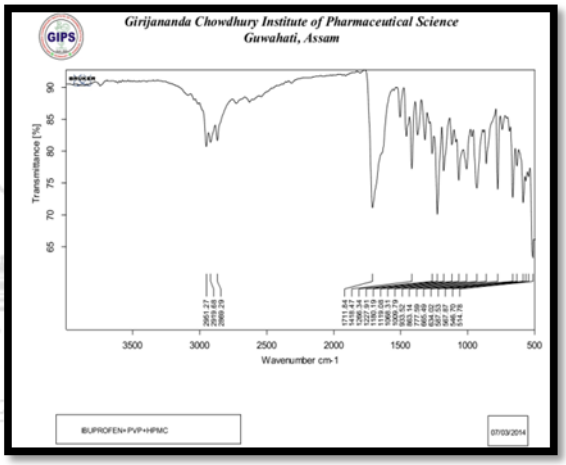

Fig 20 – IR Spectrum of physical mixer of Ibuprofen, PVPK30 and HPMC

UV ANALYSIS OF DRUG

Determination of U V maximum:

The UV maximum (λmax) of drug Ibuprofen was found to be 221 nm.

Saturation solubility:

The saturation solubility of the drug sample was determined in the various solvent like phosphate buffer pH 6.8, phosphate buffer pH 7.2, and phosphate buffer pH 7.4 and from the

UV spectrometer data the saturation solubility was calculated using the standard calibration curve of drug Ibuprofen in respective solvents.

Sr. No.	Solvent used	Absorbance	Saturation solubility(mg/ml)
1	Phosphate buffer pH 6.8	0.1871	0.433
2	Phosphate buffer pH 7.2	0.1637	3.590
3	Phosphate buffer pH 7.4	0.2168	0.524

From the calculations, the saturation solubility of Ibuprofen was found to be 0.433 mg/ml, 3.590 mg/ml, and 0.524 mg/ml respectively.

Differential scanning calorimetry (DSC) analysis:

Differential scanning calorimetric (DSC) studies of pure ibuprofen and their physical mixtures were conducted to investigate the crystallinity and drugs carrier interaction. The DSC thermogram of pure Ibuprofen shows a sharp endothermic peak at 83.36 ^{0} c .which corresponds to its melting point. The DSC thermograms of Ibuprofen-PVP-PEG6000, Ibuprofen-PVP-PEG4000, Ibuprofen-PVP-Mannitol, Ibuprofen-PVP-Lactose, Ibuprofen-PVP-HPMC physical mixtures endothermic peak was observed at temperature 121.77 ^{0} C, 124.66 ^{0} C, 75.66 ^{0} C, 76.02 ^{0} C, 120.60 ^{0} C with some changes in the characteristics of the peaks (except PEG 4000, PEG 6000 and HPMC physical mixers). It showed that no possible interaction was found between drug and carrier but the loss of peaks sharpness may be due to conversion from crystalline form to amorphous form of the drug

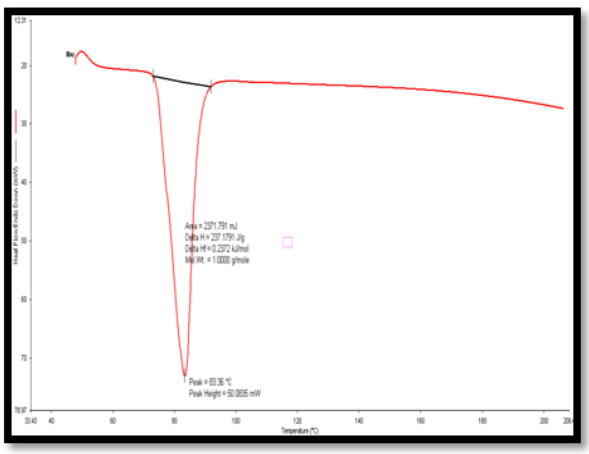

Fig 39– DSC of Ibuprofen

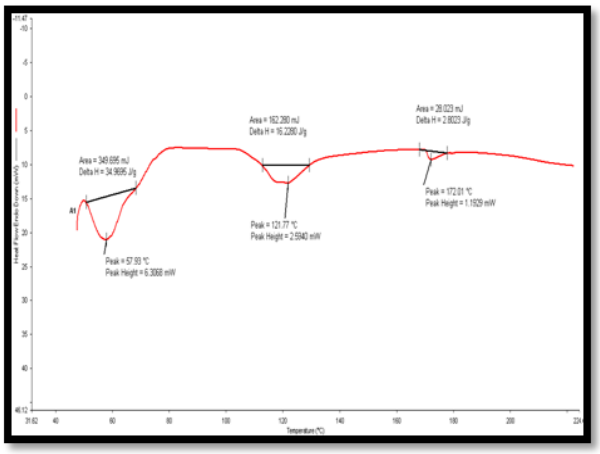

Fig 40– DSC of physical mixer of Ibuprofen, PVP and PEG6000

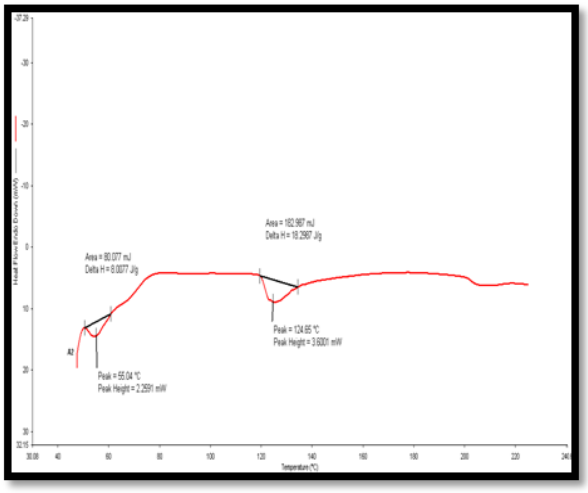

Fig 41– DSC of physical mixer of Ibuprofen, PVP and PEG 4000

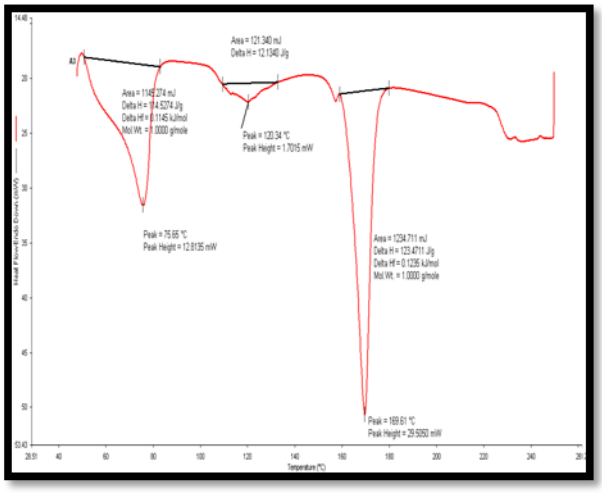

Fig 42– DSC of physical mixer of Ibuprofen PVP and Mannitol

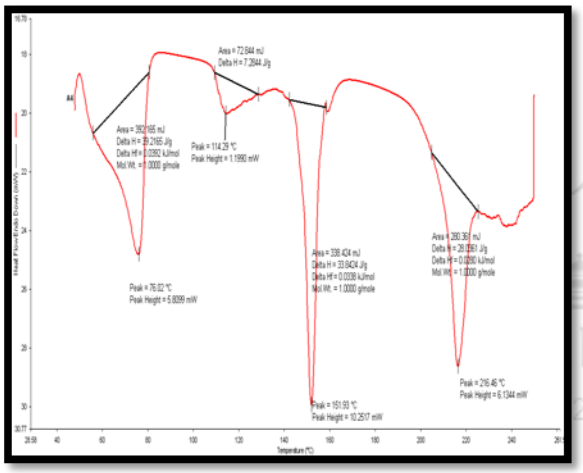

Fig 43– DSC of physical mixer of Ibuprofen, PVP and Lactose

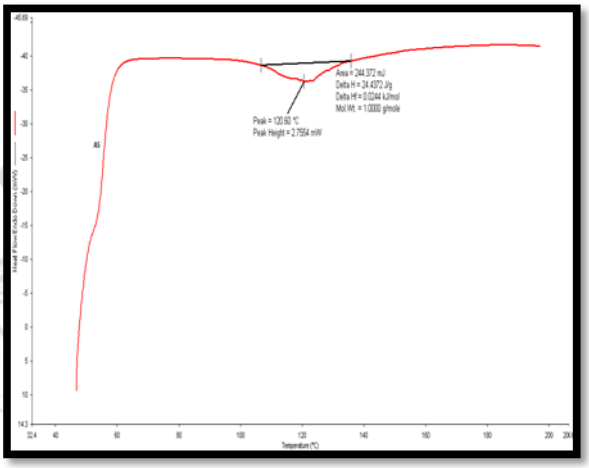

Fig 44– DSC of physical mixer of Ibuprofen, PVP and HPMC

Preparation of ibuprofen physical mixtures:

For the sake of comparison, physical mixtures were prepared by simply triturating the drugs and the polymers in a glass mortar for 15 min. The mixtures were then sieved with a 40 mesh screen and stored in an airtight container. Formulations were shown in table 9.

Table 9: Preparation of drug-polymer physical mixer

Formulation	Drug	Carrier	Ratio	Solubility (mg/ml)	% Solubility
---	Ibuprofen	-------	---	0.195	19.5
P1	Ibuprofen	PVPK30	1:1	0.245	24.5
P2	Ibuprofen	Mannitol	1:1	0.284	28.4
P3	Ibuprofen	Lactose	1:1	0.260	26.0
P4	Ibuprofen	Sorbitol	1:1	0.303	30.0
P5	Ibuprofen	PEG4000	1:1	0.285	28.5
P6	Ibuprofen	PEG6000	1:1	0.289	28.9
P7	Ibuprofen	HPMC	1:1	0.218	21.8
P8	Ibuprofen	PVPK30	1:2	0.326	32.6
P9	Ibuprofen	Mannitol	1:2	0.357	35.7
P10	Ibuprofen	Lactose	1:2	0.338	33.8
P11	Ibuprofen	Sorbitol	1:2	0.385	38.5
P12	Ibuprofen	PEG4000	1:2	0.369	36.9
P13	Ibuprofen	PEG6000	1:2	0.376	37.6
P14	Ibuprofen	HPMC	1:2	0.318	31.8
P15	Ibuprofen	PVPK30 + Mannitol	1:1	0.309	30.9
P16	Ibuprofen	PVPK30 +Lactose	1:1	0.299	29.9
P17	Ibuprofen	PVPK30 + Sorbitol	1:1	0.358	35.8
P18	Ibuprofen	PVPK30 + PEG4000	1:1	0.344	34.4
P19	Ibuprofen	PVPK30 + PEG6000	1:1	0.350	35.0
P20	Ibuprofen		1:1	0.293	29.3
P21	Ibuprofen		1:2	0.357	35.7

P22	Ibuprofen	PVPK30	1:2	0.343	34.3
P23	Ibuprofen	+HPMC	1:2	0.405	40.5
P24	Ibuprofen	PVPK30 + Mannitol	1:2	0.398	39.8
P25	Ibuprofen	PVPK30	1:2	0.400	40.0
P26	Ibuprofen	+Lactose	1:2	0.321	32.1
		PVPK30 + Sorbitol			
		PVPK30 + PEG4000			
		PVPK30 + PEG6000			
		PVPK30 +HPMC			

EVALUATION:

a) Determination of % yield:

The percent yield of ibuprofen physical mixer and ibuprofen solid dispersions can be determined by using the following expression:

Percent yield = (weight of prepared solid dispersion/weight of drug + carriers) x 100

b) Determination of percent drug content:

The % DrugContent of Ibuprofen physical mixer and Ibuprofen solid dispersion can be determined by the following expression:

Percentdrug content = (practical drug content in solid dispersions / theoretical drug Content in solid dispersions) x 100

Table 13: % Yield and % drug content of ibuprofen physical mixture

Formulation	Code	Ratio	% Yield	% Drug Content
Ibuprofen: PVP K30	P1	1:1	92.0	98.85
Ibuprofen: Mannitol	P2	1:1	95.0	98.89
Ibuprofen: Lactose	P3	1:1	93.4	98.78
Ibuprofen: Sorbitol	P4	1:1	97.4	98.71
Ibuprofen: PEG4000	P5	1:1	95.3	98.82
Ibuprofen: PEG6000	P6	1:1	98.0	98.75
Ibuprofen: HPMC	P7	1:1	96.6	98.60
Ibuprofen: PVPK30	P8	1:2	92.6	98.82
Ibuprofen: Mannitol	P9	1:2	95.4	98.85
Ibuprofen: Lactose	P10	1:2	93.8	98.75
Ibuprofen: Sorbitol	P11	1:2	97.6	98.71
Ibuprofen: PEG4000	P12	1:2	95.2	98.78
Ibuprofen: PEG6000	P13	1:2	98.2	98.71
Ibuprofen: HPMC	P14	1:2	96.4	98.60
Ibuprofen: PVPK30: Mannitol	P15	1:1	88.8	98.78
Ibuprofen: PVPK30: Lactose	P16	1:1	88.2	98.82
Ibuprofen: PVPK30: Sorbitol	P17	1:1	89.4	98.71
Ibuprofen: PVPK30: PEG4000	P18	1:1	89.2	98.67
Ibuprofen: PVPK30: PEG6000	P19	1:1	90.0	98.75
Ibuprofen: PVPK30: HPMC	P20	1:1	88.6	98.57

Ibuprofen: PVPK30: Mannitol	P21	1:2	89.2	98.75
Ibuprofen: PVPK30: Lactose	P22	1:2	88.4	98.78
Ibuprofen: PVPK30: Sorbitol	P23	1:2	88.6	98.67
Ibuprofen: PVPK30: PEG4000	P24	1:2	90.2	98.60
Ibuprofen: PVPK30: PEG6000	P25	1:2	89.4	98.71
Ibuprofen: PVPK30: HPMC	P26	1:2	89.2	98.53

In table 13 the % yield and the % drug content of physical mixer were shown. From the data, it has been found that the % yield of Ibuprofen –polymer physical mixer were in the range of 88.2-98.2 and % drug content were in the range of 98.53- 98.89.

c) Dissolution behavior of pure drug/physical mixtures and solid dispersions:

The dissolution study was carried out in phosphate buffer (pH 7.2) at 37+ 0.5°C and it was found that the rate of dissolution was increased in physical mixers as compared to pure drug. The dissolution rate is slightly increased to the pure drug when dissolution profile is compared between the combination of single polymer with drug and combination of two different polymers with the drug then it was found that dissolution rate is increased in a combination of two different polymers with the drug. Among all the solid dispersion the drug shows more drug release in combination with PVP & lactose, PVP & mannitol, and PVP & sorbitol.

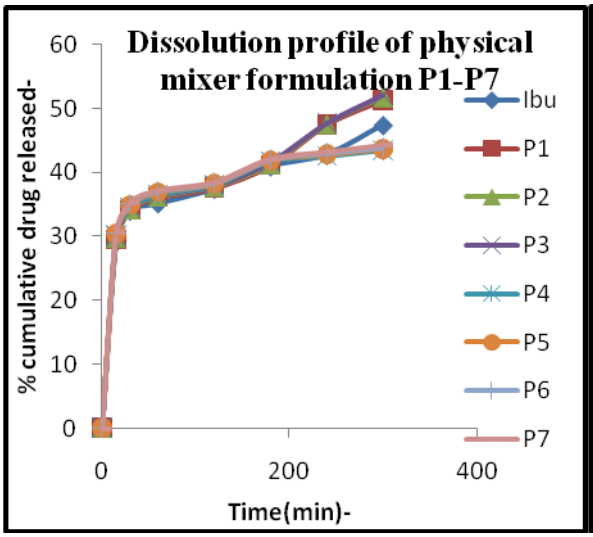

Fig 51- Dissolution profile of physical mixture formulations P1-P7

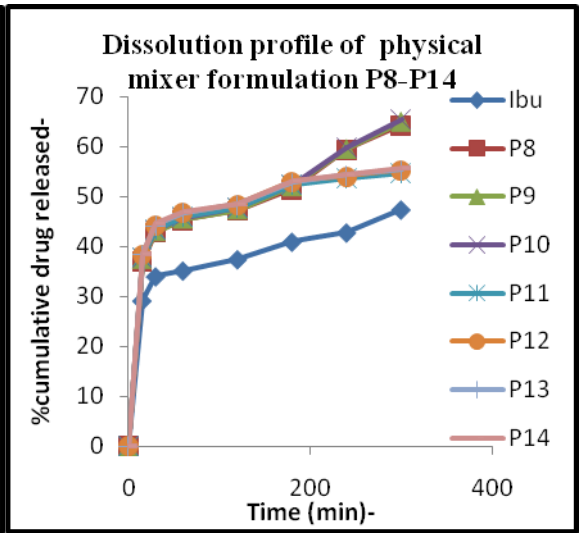

Fig 52- Dissolution profile of physical mixture formulation P8-P14

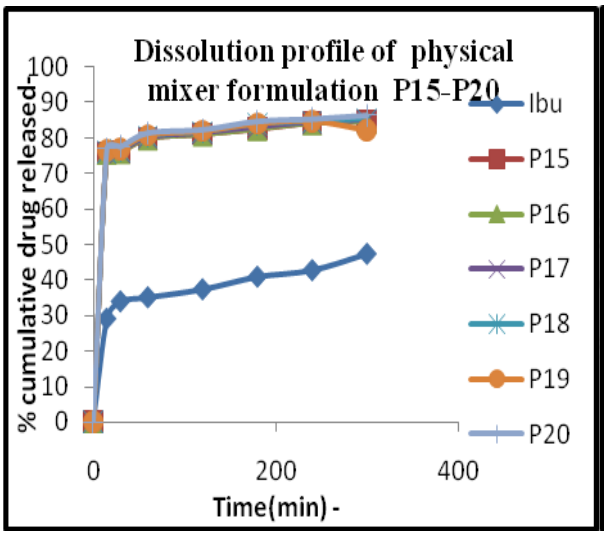

Fig 53- Dissolution profile of physical mixer formulation P15-P20

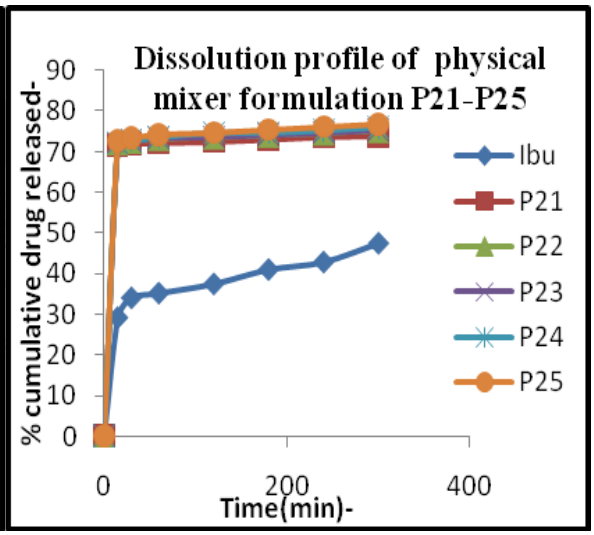

Fig 54 Dissolution profile of physical mixer formulation P21-P25

CONCLUSION:

The solid dispersion method is one of the effective approaches to achieve the goal of solubility enhancement of poorly water-soluble drugs. Ibuprofen physical mixtures were prepared with the objective of solubility and dissolution improvement using the selected hydrophilic carrier with either PEG 6000 or PVP K 30 combination. The saturation solubility and *in-vitro* dissolution studies showed remarkable improvement in solubility and drug dissolution of these new ibuprofen physical mixtures over pure ibuprofen. DSC studies

indicated the transformation of crystalline ibuprofen (in the pure drug) to amorphous ibuprofen with PEG 6000-PVP K 30 combination or PVP K 30 with other hydrophilic carrier combinations.

All of the physical mixtures showed the improved dissolution of ibuprofen over that of pure ibuprofen. The improved dissolution of ibuprofen is mainly attributed to increased wettability and accordingly solubility due to the higher level of hydrophilicity by the use of polymeric carriers.

This study concluded that the improved solubility, as well as drug dissolution of these new ibuprofen physical mixture using PVP K 30-PEG 6000 combination or other PVP K30 /Hydrophillic carrier combination, may be attributed to improved wettability and reduction in drug crystallinity, which can be modulated by appropriate level of hydrophilic carriers.

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