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PREPARATION AND EVALUATION OF IBUPROFEN MICROCRYSTALS

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ABSTRACT

Crystallization, a technique that had proved to be a new era in the growth of pharmaceutical industry. Crystal's preparation by different methods solved the problem of solubility to a large extent. Furtherly, size reduction to micron level and even lesser had accelerated the solubility of major drugs. The main objective of this study is to prepare and evaluate the micro crystals of ibuprofen (class II drug according to BCS classification) and to investigate the solubility profile of the prepared micro crystals. The micro crystals of ibuprofen are prepared by antisolvent method by taking two different polymers, poly vinyl pyrrollidine and poly ethylene glycol- 300 (PEG- 300). The prepared micro crystals are evaluated from FTIR, solubility, dissolution, microscopic studies. From the data obtained from the above research work it was observed that the treated micro crystals has shown increased solubility and dissolution rate when compared to that of the pure drug.

Key Words:- Micro crystals, Crystallization, Ibuprofen, Size reduction, Poly vinyl pyrolidine, Poly ethylene glycol- 300.

INTRODUCTION

Ibuprofen is Non-steriodal anti-inflammatory drug that is used for analgesic, antipyretic, and anti-inflammatory purposes. (Ulbrich H *et al*., 2002; DAVIES NM, 1998) Ibuprofen being the class II drug according to the BCS classification, it generally has low solubility with high permeability rate where solubility acts as a rate limiting factor for the drug absorption ie., the bioavailability of the drug (Kasim NA *et al*., 2004; CPMP, 2001).

BCS class II drugs are to be improved in their rate of dissolution by increasing its solubility rate. The bioavailability of poorly water-soluble drug substances (like many newly developed pharmaceutically active molecules) is a well known difficulty to be coped with during the development of new drug substances. An enhancement in dissolution rate is important to attain suitable blood-levels of these drugs. Several methods are existent to achieve a higher solubility or a higher dissolution rate of a drug (Varun Raj Vemula, 2010). If the drug substance molecule shows a basic or acid property, water soluble salts can be formed. Because of the precipitation of the hydrophobic molecule from the solution previously formed during the passage of the GI-tract, the bioavailability of these salts can be lowered. Another chemical modification is the formation of prodrugs.

Solubility enhancement includes both conventional techniques as particle size reduction, inclusion complexation, solid dispersions, salt formation etc. as well as relatively newer techniques such as self-emulsifying systems, micro emulsion, nanosizing and supercritical fluid processing have been tried and tested successfully, and the search for more advanced techniques rolls on (Varun Raj Vemula, 2010). A significant requirement during early stage development, solubility enhancement also offers the possibility to reformulate approved drugs.

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In general the enhancement of solubility can be achieved easily by means of micronization (size reduction to micron range). By reducing the particle size, the increased surface area improves the dissolution properties of the drug. Conventional methods of particle size reduction, such as communition and spray drying, rely upon mechanical stress to disaggregate the active compound. The micronisation is used to increased surface area for dissolution. Micronisation increases the dissolution rate of drugs through increased surface area; it does not increase equilibrium solubility. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug (Chaumeil JC, 1998).

The technique of crystallization and then reduction of size shows enhancement of solubility with stability (Blagden N *et al*., 2007). Crystals are prepared by various methods where anti solvent method is used to crystals with different excipients. The solvent change precipitation procedure was optimized in order to obtain stable and homogeneous particles with a small particle size, high yield and fast dissolution rate. The thermal and crystallographic analysis showed no polymorphic change in the microcrystals and microscopy confirmed a significant reduction in particle size. A marked improvement in the drug dissolution rate was observed for micronized particles (Keraliy *et al*., 2010).

A previous author has reviewed on hydrophobic drugs that had failed to reach market due to their poor aqueous solubility. For orally administered drugs solubility is one of the rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist, which can be solved by different technological approaches during the pharmaceutical product development. Solid dispersion, Micronization, Salt formation, are some of the vital approaches routinely employed to enhance the solubility of poorly soluble drugs but each approach has some limitation and advantages. The solubility behavior of drugs remains one of the most challenging aspects in formulation development. The present review is devoted to various traditional and novel techniques for enhancing drug solubility to reduce the percentage of poorly soluble drug candidates eliminated from the development (Keraliy RA *et al*., 2010).

Nokhodchi A. *et al* (Nokhodchi A *et al*., 2010) had investigated on the Physico-mechanical and dissolution behaviors of ibuprofen crystals crystallized in the presence of various additives (Bolourtchian N *et al*., 2009). Ibuprofen is poorly compatible drug with a high tendency of capping. The aim of the present investigation was to employ crystallization technique in order to improve the physico-chemical properties of the drug. The experimental methods involved the preparation of ibuprofen crystals by solvent change technique. Ibuprofen was dissolved in ethanol and crystallized out with water in the absence or presence of various hydrophilic additives (PEG 6000, 8000, Brij 98P and polyvinyl alcohol 22000, PVA 22000) with different concentrations. The physico-mechanical properties of the ibuprofen crystals were studied in terms of flow, density, tensile strength and dissolution behavior. Morphology of ibuprofen crystals was studied by scanning electron microscopic (SEM). Solid state of the recrystallized particles was also investigated using differential scanning calorimeter (DSC) and FT-IR (Nokhodchi A *et al*., 2010).

Tapan Kumar Giri and Hemant Badwaik (2010) had presented a regular article on solubility enhancement of ibuprofen in the presence of hydrophilic polymer and surfactant. It reveals Solid dispersions of ibuprofen preparation by solvent evaporation method using polyvinyl pyrrolidone (PVP) and/or sodium lauryl sulphate (SLS). Physicochemical properties of the various solid dispersion systems were determined by differential scanning calorimetry (DSC) and X-ray diffraction (XRD) analysis. The results from dissolution studies indicated that ternary solid dispersion systems were more efficacious than the corresponding binary ones. The increase in the dissolution rate of ibuprofen from its solid dispersions with the PVP and/or SLS used in this study could be attributed to several factors such as improved wettability, local solubilisation, and drug particle size reduction (Tapan Kumar Giri and Hemant Badwaik, 2010).

The main aim of this study is to prepare the microcrystals by solvent change (anti-solvent) technique and to evaluate the physic-chemical parameters of drug majorly to improve the solubility under the influence of excipients like Poly vinyl pyrrollidine (PVP) and Poly ethylene glycol- 300 (PEG-300).

MATERIALS AND METHODS

Materials

Ibuprofen (RS)-2-(4-(2-methylpropyl)phenyl) propanoic acid was provided by cipla as a gift sample. Poly vinyl pyrrollidine (PVP) and Poly ethylene glycol-300 (PEG-300) was purchased from Merck limited (Germany). Ethanol was purchased from S.D.Fine Chem. Ltd.All other chemicals used were of analytical grade. Double distilled water was used throughout the experiments.

METHODS

Preparation of Ibuprofen Microcrystals

The micro crystals of ibuprofen are prepared by anti-solvent method. The drug is dissolved in solvent and to this mixture water is added slowly that acting as anti-solvent forming precipitate. During the process of precipitation probably nucleation it is put for agitation under the mechanical agitator for 15-20 min to reduce the size to microns. The crystals prepared are collected by filtration (using watt man filter paper) and dried at normal room temperature and are preserved properly. Different polymers of concentration of 0.5% i.e., PEG-300 and PVP are dissolved in distilled water and this solution is used as an anti-solvent to prepare crystals. They are collected separately and preserved for further studies.

Table 1a. The micro crystals of ibuprofen are prepared by anti-solvent method

S.No	Drug	Solvent	Aq. Solution used as anti- solvent	
			PEG-300	PVP
1	Ibuprofen	Ethanol	0.5%	0.5%

CHARACTERIZATION OF CRYSTALS

Fourier Transform Infrared (FT-IR) Studies

Fourier Transform Infrared (FT-IR) spectra for ibuprofen and prepared crystals were recorded in a Thermo-IR 200 FTIR spectrophotometer. Potassium bromide pellet method was employed and background spectrum was collected under identical conditions. Each spectrum was derived from 16 single average scans collected in the scanning range of 400-4000 cm^{-1} at the spectral resolution of 2 cm^{-1}.

Photographic Studies

A pinch of ibuprofen was taken on glass slide which is mounted in mineral oil and cover slip was placed on the slide. Observe in microscope at 45X magnifications. Photographs were taken.

Solubility Studies

Excess amount of ibuprofen was taken in test tube containing 5ml distilled water; 0.1N HCl and phosphate buffer 6.8 pH. Then the test tube was shaken frequently and kept in thermostatically controlled shaker. Temperature was maintained at $30^0 \pm 1^0$C. After 24 hr the samples were collected, filtered and diluted suitably. The absorbance was checked with UV-VIS spectrophotometer (shimadzu, UV-1700) using distilled water as blank at 226 nm as λ_{max}. The same procedure was followed for 0.1 N HCl (at 220.5 nm as λ_{max}), phosphate buffer P^H 6.8 (at 222 nm as $\lambda_{max)}$ and absorbance was noted.

Invitro Dissolution Studies

Dissolution studies of ibuprofen and its crystals (Et. treated, treated with PVP and PEG-300) weight equivalent to 50 mg were performed using USP XXII apparatus at the stirring speed of 50 rpm and temperature maintained at 37 ± 0.5^0C with distilled water, 0.1N HCl, phosphate buffer 6.8 pH as dissolution mediums separately. The samples of 5ml were withdrawn at regular intervals of 15, 30, 45, 60 min. Every time the samples are replaced with 5ml of the fresh dissolution medium. The filtrates of the samples were analyzed at 226 nm, 220.5 nm and 222 nm as λ_{max} respectively.

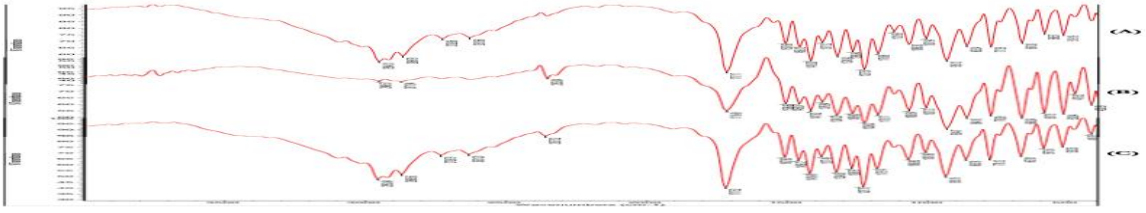
Percentage drug release and other parameters of the samples were calculated by using Disso software PCP Disso V3 software.

Release Kinetics

The drug release data were fitted to various models like Higuchi's model (cumulative percent release against square root to time), Zero order model (cumulative percent release against time), First order model (log cumulative percent release against time) Higuchi model (cumulative percent release against square of time) Korsmeyer'speppas model (log cumulative percent release against log time) Hixson-Crowell model (cubth root of % drug remained against time) kinetics to know the release mechanism. The model fitting for the drug release for the samples were calculated by using Disso software PCP Disso V3 software and Microsoft Excel.

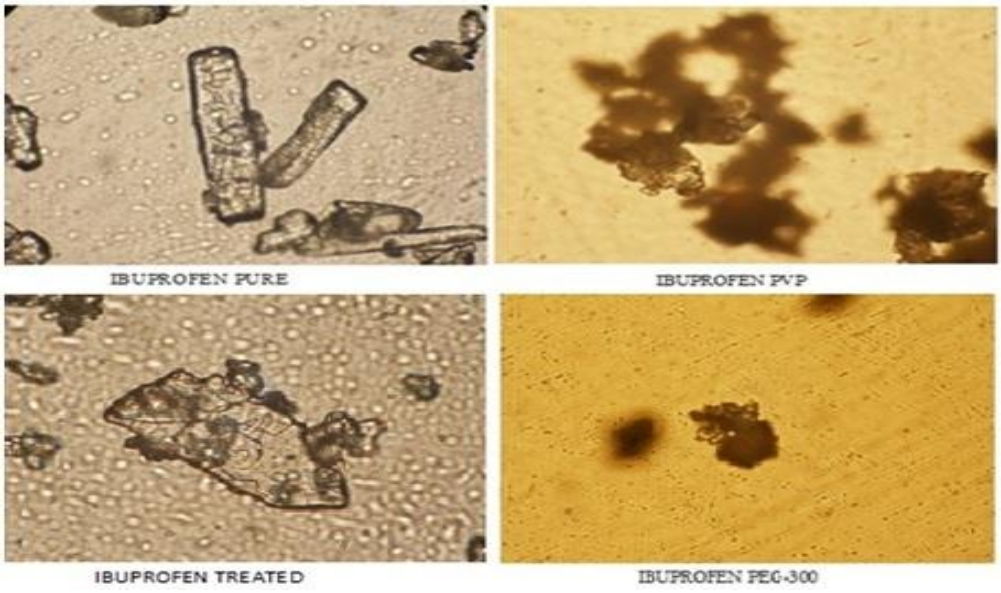
RESULTS AND DISCUSSION

Fig 1. Comparitive FTIR spectrum of Ibuprofen (A), PVP treated crystal (B), PEG- 300 treated crystal (C)



Photographic Studies

Fig 2. Microscopic Photographs of Ibuprofen and Ibuprofen Crystals



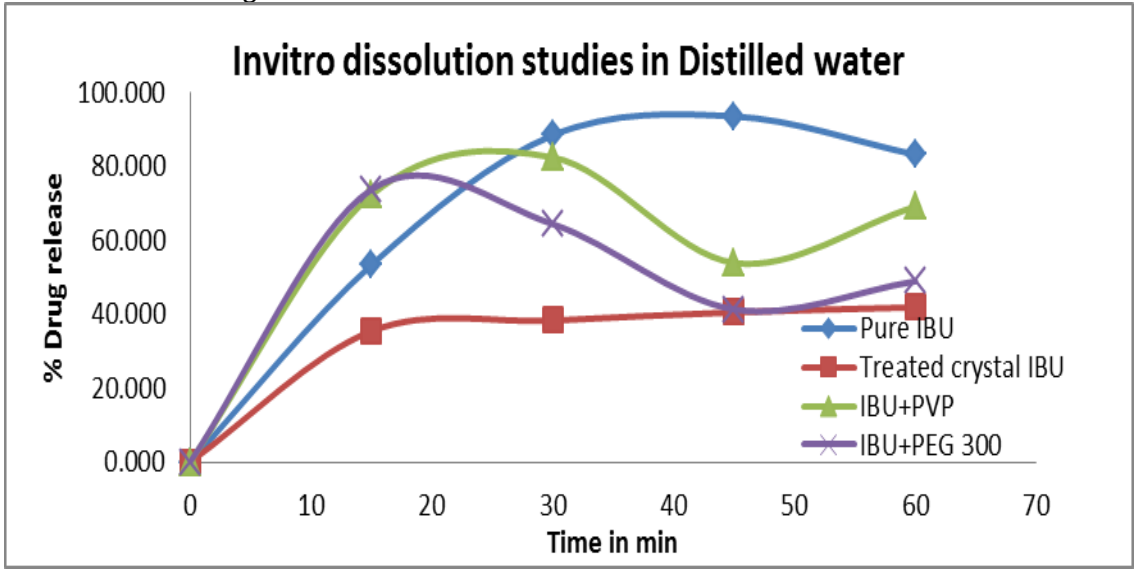
Solubility Studies

Table 1b. Solubility of Ibuprofen and Ibuprofen crystals

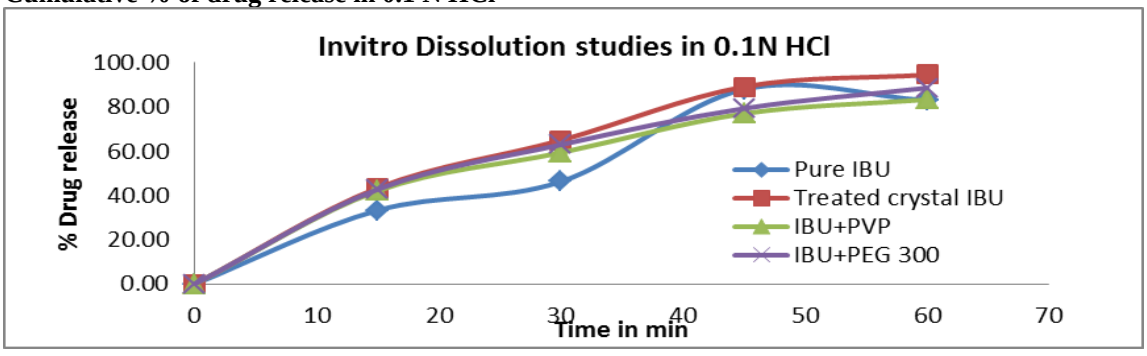
SNO	Medium	Solubility (mg/ml) of			
		IBU	Et. Treated IBU crystals	PVP treated IBU crystals	PEG-300 treated IBU crystals
1	Distilled Water	0.116	0.153	0.147	0.134
2	0.1 N HCl	0.187	0.234	0.188	0.199
3	pH6.8 Phosphate Buffer	2.91	3.00	2.29	2.52

Dissolution Studies

Graph 1. Cumulative % of drug release in distilled water



Graph 2. Cumulative % of drug release in 0.1 N HCl



Graph 3. Cumulative % of drug release in phosphate buffer pH 6.8

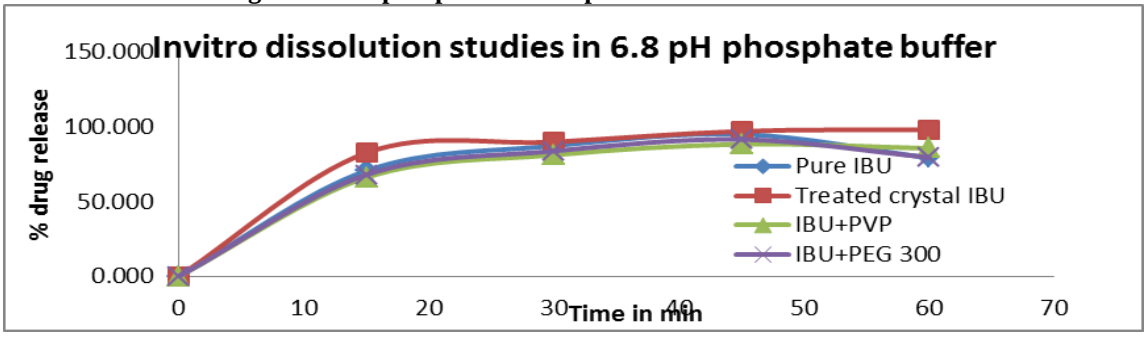


Table 2. Release kinetics of pure Ibuprofen

		Zero order model	First order model	Higuchi model	Krosemeyer model	Hixson-Crowell model
0.1 N HCl	**R^2**	0.914	0.825	0.914	0.898	0.746
	M	1.471	-0.015	11.52	0.739	0.066
	C	2.448	1.424	2.179	0.638	1.064
Distilled water	**R^2**	0.705	0.635	0.898	0.684	0.601
	M	1.376	-0.016	12.16	0.353	0.063
	C	4.728	1.354	2.393	1.163	1.233
pH 6.8 Phosphate buffer	**R^2**	0.572	0.500	0.828	0.353	0.601
	M	1.215	-0.014	0.063	0.126	0.063
	C	5.455	1.321	3.417	1.311	1.233

Table 3. Release kinetics of Et. treated Ibuprofen

		Zero order model	First order model	Higuchi model	Krosemeyer model	Hixson-Crowell model
0.1 N HCl	**R^2**	0.929	0.954	0.989	0.982	0.703
	M	1.620	-0.028	13.09	0.588	0.067
	C	3.44	0.976	1.362	0.990	0.083
Distilled water	**R^2**	0.635	0.673	0.876	0.998	0.546
	M	0.612	-0.003	5.638	0.121	0.047
	C	3.730	1.387	2.336	0.191	0.073
pH 6.8 Phosphate buffer	**R^2**	0.629	0.976	0.873	0.981	0.544
	M	1.422	-0.045	13.12	0.12	0.063
	C	5.714	1.420	3.583	1.337	1.317

Table 4. Release kinetics of PVP treated Ibuprofen crystals

		Zero order model	First order model	Higuchi model	Krosemeyer model	Hixson-Crowell model
0.1 N HCl	**R^2**	0.910	0.994	0.996	0.990	0.680
	M	1.428	-0.015	11.71	0,509	0.064
	C	3.581	1.413	0.002	0.102	1.151
Distilled water	**R^2**	0.336	0.173	0.598	0.159	0.449
	M	0.849	-0.005	8.874	-0.118	0.053
	C	5.788	1.296	4.092	1.428	1.322
pH 6.8 Phosphate buffer	**R^2**	0.685	0.831	0.911	0.876	0.568
	M	1.366	-0.018	12.33	0.202	0.062
	C	5.206	1.350	3.057	1.081	1.277

Table 5. Release kinetics of PEG-300 treated Ibuprofen crystals

		Zero order model	First order model	Higuchi model	Krosemeyer model	Hixson-Crowell model
0.1 N HCl	**R^2**	0.921	0.962	0.998	0.996	0.688
	M	1.550	-0.023	12.64	0.534	0.066
	C	3.612	1.442	0.079	1.010	1.157
Distilled water	**R^2**	0.131	0.016	0.359	0.736	0.358
	M	0.474	-0.001	6.141	-0.374	0.045
	C	5.953	1.295	4.518	1.532	1.340
pH 6.8 Phosphate buffer	**R^2**	0.606	0.436	0.854	0.517	0.543
	M	1.320	-0.021	12.28	0.149	0.061
	C	5.515	1.315	3.397	1.308	1.300

CONCLUSION

The micro crystals of ibuprofen (Et. Treated, PVP, PEG- 300 treated) have been recrystallized and characterized by FT-IR, microscopic, solubility and dissolution studies. The drug release from all the crystalline forms was observed. The crystalline forms have shown enhancement in the solubility when compared to that of the pure drug. From the current research performed it can be concluded that the polymer (PVP, PEG- 300) crystals of ibuprofen had an increase in the solubility and dissolution, compared to that of the pure drug.

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