ISSN: 2279 - 0594

Journal of Biomedical and Pharmaceutical Research 1 (2) 2012, 38-45

RESEARCH ARTICLE

Formulation and Characterization of Novel Solid Dispersions of Hydrochlorothiazide by Hot Melt Extrusion Technique

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

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

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

ABSTRACT

The preparation method of Hot melt extrusion involves the treatment of temperature to get the desired properties of the Solid Dispersion. No significant changes has been observed in the physical nature of the both the rochlorothiazide and the carrier. The carrier concentration plays a determining role for in improving solubility of the Hydrochlorothiazide without altering the physical and chemical properties. The carrier selected for the present study was Poloxamer 188 which is very soluble in water and having the capacity to modify the solubility when used along with Hydrochlorothiazide. The preliminary formulations were planned for varying concentration of the Poloxamer 188. The results of the preliminary formulations were promising mainly in drug release pattern and other parameters. The Solid Dispersion of the Hydrochlorothiazide prepared by Hot melt extrusion method using Poloxamer 188 as carrier showed maximum solubility enhancement of Hydrochlorothiazide. The optimum release was found in concentration range of 55%-75%, and was considered for further studies. The final formulations of Solid Dispersion prepared by Hot melt extrusion method were simple and frangible enough to be ground easily. This is indicative of good material handling properties of prepared Solid Dispersion and from the industrial point of view because pulverization of Solid Dispersions is one of the major problems.

KEYWORDS: - Hydrochlorothiazide, Hot-melt extrusion, solid dipsersions

INTRODUCTION:

SOLID DISPERSIONS FOR SOLUBILITY ENHANCEMENT:

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. The number of commercial products marketed as solid dispersions still remains rather limited due to its limited use for the sustained release preparations. The use of solid dispersion in sustained release preparations could be a different strategy which is interesting to carefully evaluate the preparative aspects of these formulations and to suggest variations to the proposed methods with a view of promoting their practical and commercial applications. In addition to bioavailability enhancement, much recent research on solid dispersion systems was directed towards the development of extended-release dosage forms. It may be pointed out that this area of research has been reinvigorated by the availability of surface-active and self-emulsifying carriers and the development of new capsule filling processes. Because the formulation of solid dispersion for bioavailability enhancement and extended release of drugs may employ essentially similar processes, except for the use of slower dissolving carriers for the later use, it is expected that the research in these two areas will progress simultaneously and be complementary to each other.

UNMET NEEDS AND CHALLENGES:

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

1) Gris-PEG (Novartis), Griseofulvin in PEG

2) Cesamet (Lily), Nabilone in PVP

3) Sporanox (Janssen Pharmaceutica/J&J), Itraconazole in HPMC and PEG 20,000 sprayed on sugar spheres Ritonavir capsules (Norvir, Abbott) has been withdrawn temporarily from the market becauseof crystallization. The rare occurrence of solid dispersion based pharmaceutical dosage forms in the clinic are due to problems in scale-up of preparation methods, difficulties in dosage form development and poor and irreproducible physical and chemical stability of drug and matrix . Knowledge about behavior of solid dispersions during preparation, storage and dissolution can help to tackle these problems. A thorough understanding of processes that occur place on the molecular level is a prerequisite for rational and more efficient design of solid dispersions. However, development of solid dispersions has often been a trial-and-error approach. Unfortunately, most reports deal with a case, in which the authors used a specific matrix to accelerate the dissolution of a specific drug *in-vitro* or to

* ***Corresponding author:*** Abhay N. Padalkar **/** ***Email:*** abhaypadalkar1@gmail.com

show increased bioavailability. These studies prove the potential of solid dispersions, but for successful industrialization and clinical application, the following challenges have to be faced first.

OUTLINE AND OBJECTIVE OF WORK:

The main objective of the work was solubility enhancement of hydrochlorothiazide, by the selected method hot-melt extrusion technique. In this context attention was focused on the elucidation of the mechanism of drug release from solid dispersion, the physico-chemical processes taking place during Hot-melt extrusion, and thermodynamical stability of the technique. The objective to be achieved is so mentioned below

1. To develop a formulation for improving solubility of a poorly water-soluble drug

2. To optimize the hot-melt extrusion technique for solubility enhancement of a poorly soluble drug and to prove the applicability of the technique for different carriers and drugs

3. *In-vitro* evaluation of solid dispersions prepared by hot-melt extrusion technique.

PREPARATION OF SOLID DISPERSION BY HOT MELT EXTRUSION TECHNIQUE:

The melting or fusion technique, first proposed by Sekiguchi and Obi involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melts. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. However many substances, either drugs or carriers, may decompose during the fusion process which employs high temperature. It may also cause evaporation of volatile drug or volatile carrier during the fusion process at high temperature. Some of the means to overcome these problems could be heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier.The poloxamers are a group of surface active compounds widely used in the pharmaceutical industry. poloxamers are described as block polymers of the type aba, consisting of a central, hydrophobic block of polypropylene oxide, which is edged by two hydrophilic blocks of polyethylene oxide. The poloxamers are readily soluble in aqueous, polar and non-polar organic solvents and due to this fact they have established themselves as a preferred molecule in the formulation techniques.

PRELIMINARY FORMULATIONS OF HOT MELT EXTRUSION TECHNIQUE:

The goal of the experiment was to produce solid dispersions of a poorly water-soluble drug via hot-melt extrusion technique in order to improve the solubility and bioavailability. The carrier selected was poloxamer 188.The compatibility study showed compatibility of poloxamer 188 with hydrochlorothiazide. Based on the literature review the solid dispersion has been developed with the composition, Table-1.

Sr. No	Formulation Code	HCTZ (gm)	Poloxamer 188 (gm)
1	HMP-1	10	10
2	HMP-2	10	20
3	HMP-3	10	30
4	HMP-4	10	40
5	HMP-5	10	50
6	HMP-6	10	60
7	HMP-7	10	70
8	HMP-8	10	80
9	HMP-9	10	90

Table No. 1: Composition of preliminary formulations of solid dispersions of HCTZ prepared by hot melt extrusion technique

HMP-Hot melt preliminary formulations

METHOD OF PREPARATION OF PRELIMINARY FORMULATIONS:

Hydrochlorothiazide was heated at a temperature of 55°C ± 0.5°C using a thermostatically controlled water bath (Labtronik, Ahmadabad, India). Poloxamer 188 was used in 1:2, 1:3, 1:4, 1:5, 1:6, 1:7 1:8, and 1:9 drug-to-polymer ratio. The drug was dispersed in the melted polymer. The resultant mixture was immediately cooled to 25ºC and was maintained at the specified temperature for a period of 2 hrs. The mass was stored at room temperature for 24 hrs and then pulverized using a glass mortar and pestle. The pulverized mass was sifted through a #120 sieve, weighed, and transferred to amber-colored Type-I glass vials, stored at 30ºC ± 1°C.

DISSOLUTION PROFILE OF PRELIMINARY FORMULATIONS:

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

Sr. No	Formulation Code	Cumulative % Drug Release	
		30 min*	90 min*
1	Plain HCTZ	24.36±6.3	49.49±5.3
2	HMP-1	42.54±5.3	64.61±6.5
3	HMP-2	36.34±3.7	54.80±5.5
4	HMP-3	47.44±3.9	68.63±5.4
5	HMP-4	57.37±5.4	81.70±2.9
6	HMP-5	65.33±2.3	87.44±2.7
7	HMP-6	71.32±5.3	99.89±4.9
8	HMP-7	74.25±6.3	107.0±6.5
9	HMP-8	40.82±5.8	74.16±5.6
10	HMP-9	59.92±3.8	88.89±5.3

Table No. 2: Release profile of preliminary formulations of HCTZ solid dispersions prepared by hot melt extrusion technique

HMP-Hot melt preliminary formulations, *-Average of three readings

RESULTS AND DISCUSSION:

An increased solubility and improved dissolution profile of hydrochlorothiazide was achieved by the selected hot melt extrusion technique. The release profiles were compared to the dissolution profile of the plain hydrochlorothiazide. The study revealed higher dissolution rate with formulation ratio 1:6 and 1:7. Further increase in the concentration of poloxamer 188 did not show increase in dissolution rate. The optimum range of poloxamer 188 was selected 55 to 75 gm for final formulations. The technique is highly useful for preparation of solid dispersions and solubility enhancement.

FINAL FORMULATIONS OF HOT MELT EXTRUSION TECHNIQUE:

COMPOSITION OF FINAL FORMULATIONS:

The study of preliminary formulations revealed the composition of poloxamer 188 in the range of 55 gm to 75 gm and 10 gm of HCTZ. The composition of optimized formulations is depicted in Table-3.

Sr. No.	Formulation code	HCTZ (gm)	Poloxamer 188(gm)
1.	HMF-1	10	55.0
2.	HMF-2	10	57.5
3.	HMF-3	10	60.0
4.	HMF-4	10	62.5
5.	HMF-5	10	65.0
6.	HMF-6	10	67.5
7.	HMF-7	10	70.0
8.	HMF-8	10	72.5
9.	HMF-9	10	75.0

Table No. 3: Composition of final formulations of HCTZ solid dispersions prepared by hot melt extrusion technique.

HMF-Hot melt technique final formulations

METHOD OF PREPARATION OF FINAL FORMULATIONS:

The solid dispersions of HCTZ-poloxamer 188 were prepared by the hot melt extrusion technique as mentioned in section 7.2.2.2.

***IN-VITRO* EVALUATION OF FINAL FORMULATIONS:**

The prepared Solid Dispersions formulations were evaluated for the series of parameters and the observations are summarized in Table 4.

ANGLE OF REPOSE:

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for the granules of each formulation was determined by the funnel method. The granules mass was allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. The pile forms an angle of granules on the paper. The angle of repose was calculated by substituting the values of the base radius 'R' and pile height 'H' in the following equation,

$$\tan \theta = H / R$$

$$\theta = \tan^{-1} (H / R)$$

BULK DENSITY:

Apparent bulk density (BD) was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of the powder (M) was determined. The bulk density (BD) was calculated using following procedure. The sample of about 50 cm^3 of powder, previously been passed through a standard sieve no.20, was carefully introduced into a 100 ml graduated cylinder. The cylinder was tapped at 2 second intervals on a hard wood surface three times from a height of 1 inch. The bulk density was calculated using the equation:

$$BD = M / V_p$$

Where, V_p = final volumes of granules in cm^3

PERCENTAGE YIELD:

The prepared Solid Dispersions was accurately weighed and the percentage yield was calculated using the following equation,

% yield = (Weight of SD/Total weight of ingredients taken) × 100

DRUG CONTENT:

Solid dispersions equivalent to 50 mg of hydrochlorothiazide was weighed accurately and dissolved in the 10 ml of 0.1 N HCl. The solution was filtered, diluted suitably and the drug content was analyzed at 272 nm by UV spectrophotometer.The Drug Content was calculated using the following equation

$$\% \text{ Drug Content} : \frac{\text{Actual amount of Drug in Solid Dispersion}}{\text{The Theoretical amount of drug in Solid Dispersion}}$$

SOLUBILITY STUDY:

Solubility measurements were performed according to method reported by Higuchi and Connors, An excess amount of the drug was added to 10 ml volumetric flask containing 10%, 20%, 30% and 40% aqueous solution of carrier. The samples were shaken for 48 hrs at 25±1°C. The solutions were filtered through Syrilnge filter (0.45 µ). After 48 hrs, the hydrochlorothiazide concentration was determined spectrophotometrically at 272 nm. Table-5.

Sr. No	Formulation Code	Evaluation Parameters				
		Angle of Repose (θ)	B.D (g/cm^3)	Yield (%)	Drug content* (%)	Dissolution* (%)
1	HMF-1	52°60'	0.49	85.52	98.2 ±0.51	88.2 ±0.51
2	HMF-2	58°60'	0.46	89.36	98.6 ±0.67	91.6 ±0.67
3	HMF-3	56.°60'	0.47	87.69	98.7 ±0.61	98.7 ±0.61
4	HMF-4	54°60'	0.42	89.52	98.1 ±0.71	98.1 ±0.71
5	HMF-5	51°60'	0.42	95.56	99.4 ±0.81	99.4 ±0.81
6	HMF-6	58°60'	0.43	92.58	99.7 ±0.66	99.7 ±0.66
7	HMF-7	56°60'	0.45	89.26	96.7 ±0.89	99.2 ±0.89
8	HMF-8	53°60'	0.49	87.23	98.00±0.81	91.00±0.81
9	HMF-9	55°60'	0.48	92.28	98.53±0.59	94.53±0.59

Table No.4: Physicochemical characterization of final formulations of hctz solid dispersions prepared by hot melt extrusion technique
HMF-Hot melt final formulations, B.D-Bulk Density,*- Average of three readings.

Solvent	Temp (°C)	pH	Solubility of HCTZ (g/100ml)	Solubility of SD of HCTZ (g/100 ml)*
Water	37	7.2	108×10^{-3}	114×10^{-3}
0.1N HCl	25	1	60.8×10^{-3}	210×10^{-3}
0.067M Phosphate buffer	25	7.4	61.6×10^{-3}	119×10^{-3}
0.05M Borate buffer	25	9	103×10^{-3}	103×10^{-3}
1.0 M Ammonia	25	11.6	2.2×10^{-3}	95×10^{-3}
0.1M NaOH	25	10.2	1.79×10^{-3}	85×10^{-3}
Simulated Gastric Fluid	37	1.1	108×10^{-3}	265×10^{-3}
Simulated Intestinal Fluid	37	7.5	109×10^{-3}	109×10^{-3}

Table No.5: Solubility study of plain hctz and solid dispersion formulations prepared by hot melt extrusion technique at different pH solutions
*- Average of three readings

DISSOLUTION PROFILE:

The dissolution of the prepared solid dispersions was done same as per the procedure mentioned in section 4.1.2.

INFRARED SPECTROSCOPY:

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

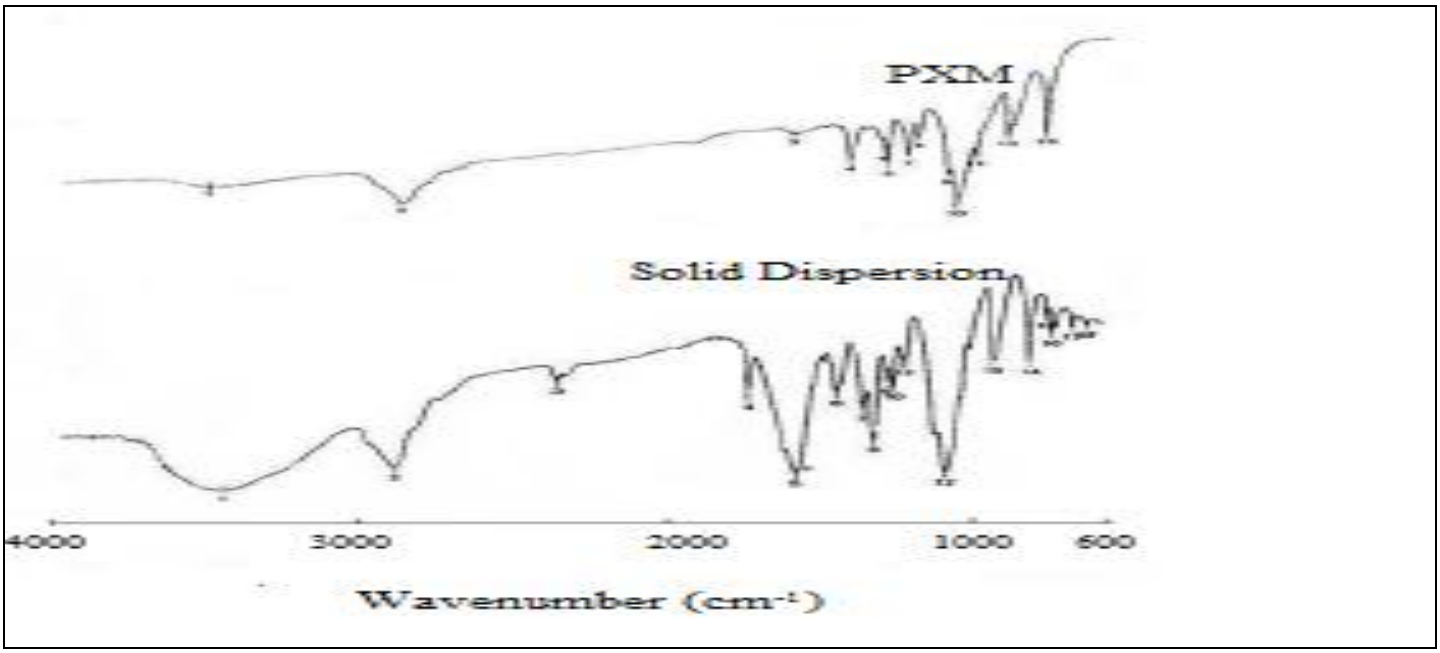

Figure No. 1: Infrared spectrum of hctz solid dispersion obtained from hot melt extrusion technique

X-RAY DIFFRACTION:

POWDER X- RAY DIFFRACTION STUDIES:

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

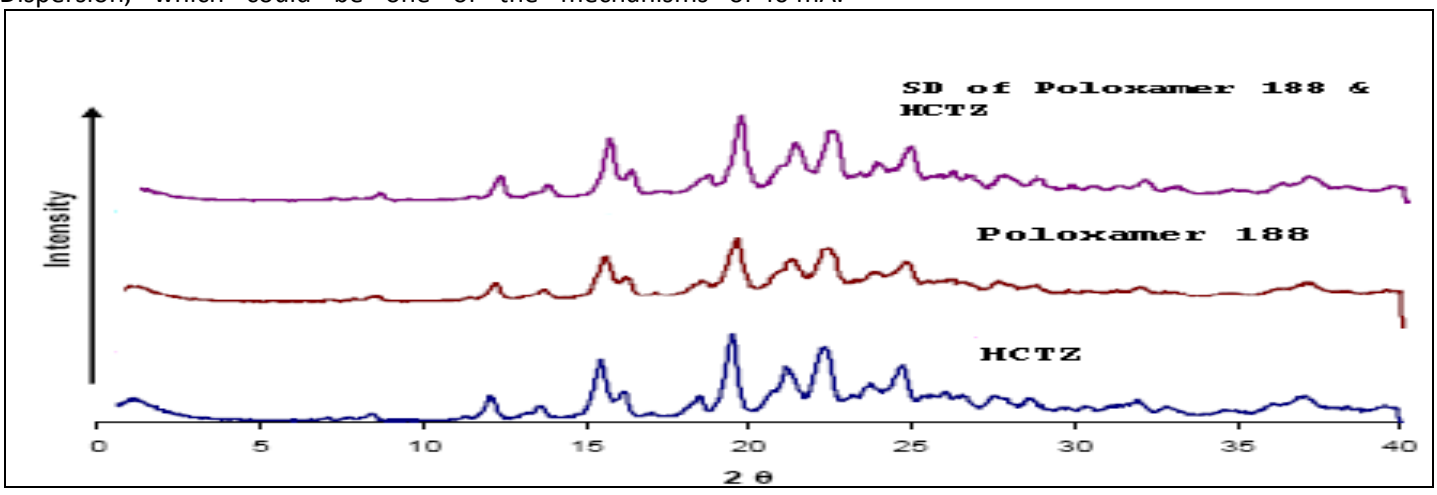

Figure No. 2: Powder x-ray diffraction pattern of hctz, poloxamer 188 and solid dispersion of hctz and poloxamer 188.

RESULTS AND DISCUSSION:

The preliminary formulations for the hot melt extrusion technique were taken based on the concentration of the drug, its therapeutic need and mainly the carrier concentration.The preparation method of hot melt extrusion involves the treatment of temperature to get the desired properties of the solid dispersion. No significant changes has been observed in the physical nature of the both the Hydrochlorothiazide and the carrier. The carrier concentration plays a determining role for in improving solubility of the hydrochlorothiazide without altering the physical and chemical properties. The carrier selected for the present study was poloxamer 188 which is very soluble in water and having the capacity to modify the solubility when used along with Hydrochlorothiazide. The preliminary formulations were planned for varying concentration of the Poloxamer 188. The results of the preliminary formulations were promising mainly in drug release pattern and other parameters. The solid dispersion of the Hydrochlorothiazide prepared by hot melt extrusion method using poloxamer 188 as carrier showed maximum solubility enhancement of hydrochlorothiazide. The optimum release was found in concentration range of 55%-75%, and was considered for further studies. The final formulations of Solid Dispersion prepared by hot melt extrusion method were simple and frangible enough to be ground easily. This is indicative of good material handling properties of prepared solid dispersion and from the industrial point of view because pulverization of solid dispersions is one of the major problem. The method was feasible because of low melting points of poloxamer 188 and Hydrochlorothiazide; which facilitate better control over process variables such as temperature, shearing rate and time required for preparation. In addition the results were reproducible with relatively higher percentage yields. The drug content and the higher yield showed relatively lower process loss. The solubility study of the plain hydrochlorothiazide and solid dispersion prepared by hot melt technique of the hydrochlorothiazide revealed there is significant increment of the solubility between pure drug and SDs. The angle of repose values indicates the poor flow of the powder this is because of polymer and HCTZ interactions. Enhancement in the solubility and dissolution of the hydrochlorothiazide could be correlated to the chemical structure of highly water soluble poloxamer 188. Arrangement of ethylene oxide (EO) and propylene oxide (PO) blocks in poloxamer 188 results in an amphiphilic nature, which has the properties to self assemble into micelles in aqueous solution; the hydrophobic core (PO block) can act as reservoir for the HCTZ, while the hydrophilic portion (EO block) acts as interface between the aqueous medium and the HCTZ . At lower concentrations, approximating those at which more conventional nonionic detergents forms micelles, the poloxamer monomers are thought to form monomolecular micelles by a change in configuration in solution. At higher concentration, these monomolecular micelles associate to form aggregates of varying size, which have the ability to solubilize the HCTZ and to increase the stability of solubilizing agents. Solubilization might have occurred by one of the following mechanism. In the dry state, the particles are in close contact or adhered to the polymer particles as a result of mixing. When the mixture comes in contact with water, the polymer particles are hydrated rapidly into polymer solution solubilizing the adjacent HCTZ particles and subsequently releasing the HCTZ into the medium. This could also possibly explain the higher solubility of the HCTZ in phase solubility study where the hydrochlorothiazide particles were already dispersed in the aqueous polymer solutions And may be due to surface active property and critical micelle concentration of Poloxamer 188 which is a polyoxyethylene-polypropylene block copolymer non-ionic surfactant with a hydrophilic-lipophilic balance value of 18-23 and used as emulsifier and solubilizer in pharmaceutical preparations. The poloxamer 188 is reported to prevent the mobility of the HCTZ molecules to reunite and recrystallize during formation of solid dispersion. Hydrogen bonding may be possible when the HCTZ is molecularly dispersed in the carrier (solid solution). Along with this, improvement in the wettability may be the possible reason for solubility as well as the dissolution enhancement. Wettability and the solubilization of the HCTZ are improved due to presence of diffusion layer of high carrier concentration around the HCTZ particles. The solubilized HCTZ diffuses to and gets diluted in the bulk of dissolution medium. As the solubilizing effect of the poloxamer 188 is very high, a concentrated HCTZ solution would be formed in the diffusion layer, which would retard the HCTZ precipitation in both the diffusion layer and bulk dissolution medium. Such a potential difference in the kinetics of HCTZ precipitation in the diffusion layer might be a possible reason for finer particles and satisfactory dissolution along with the possibility of HCTZ particle size reduction of the dispersed HCTZ. The results of the FTIR studies, XPRD indicated reduction in crystallinity of the HCTZ in the solid dispersion; this increased the solubility and dissolution of the hydrochlorothiazide from the solid dispersions. Thus, solubility of the hydrochlorothiazide was enhanced by combined and synergistic effect of the poloxamer 188. The

solubility of the prepared solid dispersion was compared with plain HCTZ and significant increment in the solubility was observed. The HCTZ-polymer interaction, drug entrapment, other physico chemical parameters were evaluated for the Hot melt extrusion method and were found satisfactory.

REFERENCE

1. Sekiguchi K and Obi N (1961).Studies on Absorption of Eutectic Mixture. I. A .comparison of the behaviour of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem. Pharm. Bull., 9: 866-872.

2. ASF-Expertise in health and nutrition No.3 1999.

3. Karmarkar A.B. Poloxamers and their applications.www.pharmainfo.net Nov 27, 2008.

4. Lachmann. L., Lieberman H. A, Kanig J. L, Theory and Practi ce of Industrial Pharmacy,Varg-hese Publishing House: Bombay, 1991, 315-316.

5. Dua K, Ramana M V, Sara UVS, Himaja M, Garg V, Agrawal A., Dissolution enhancement of aceclofenace through solid dispersions Indian pharmacist 2006, 70-72.