CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1188902

Available online at: http://www.iajps.com Research Article

ENHANCEMENT OF SOLUBILITY OF POORLY WATER SOLUBLE LOVASTATIN DRUG BY SOLID DISPERSION METHOD

Dr. N. Sandeepthi[1*] and N. Jhancy laxmi bai[2]

[1] Associate Professor,Department of Pharmaceutics, Omega College of Pharmacy, Edulabad, Ghatkesar, Hyderabad,Telangana 501301

[2] Assistant Professor, Department of Pharmaceutics, Omega College of Pharmacy, Edulabad, Ghatkesar, Hyderabad,Telangana 501301

Abstract:

Solid dispersions are one of the most promising strategies to improve the oral bioavailability of poorly water soluble drugs. By reducing drug particle size to the absolute minimum, and hence improving drug wettability, solubility increases hence bioavailability may be significantly improved. They are usually presented as amorphous products, mainly obtained by two major different methods, melting and solvent evaporation

KeyWords: *Hot melt extrusion, Hyperlipidemia, Povidone, Eudragit RL, Eudragit RS, polyethylene glycol (PEG), degree of porosity, Renex, Texafor AIP*

Corresponding author:

Dr. N. Sandeepthi,

Associate Professor,

Department of Pharmaceutics,

Omega College of Pharmacy, Edulabad,

Ghatkesar, Hyderabad,Telangana 501301

E-Mail: sandeepthi06@gmail.com

QR code

Please cite this article in press as N. Sandeepthi and N.Jhancy laxmi bai., ***Enhancement of Solubility of Poorly Water Soluble Lovastatin Drug By Solid Dispersion Method,*** *Indo Am. J. P. Sci, 2018; 05(02).*

INTRODUCTION:

Cholesterol is a fatty substance known as a lipid. It is mostly made by the liver from the fatty foods we eat and is vital for the normal functioning of the body. Having an excessively high level of lipids in your blood (hyperlipidemia) can have a serious effect on your health as it increases your risk of having a heart attack or stroke. Cholesterol is needed in the body to: make up the structure of the membrane (outer layer) of every cell in the body, insulate nerve fibres, make hormones, such as sex hormones and steroid hormones, and make bile acids, which are needed for the digestion and absorption of fats. Cholesterol cannot travel around the body on its own because it does not dissolve in water. Instead, it is carried in your blood by molecules called lipoproteins. Blood cholesterol is measured in units called millimoles per litre of blood, often shortened to mmol/L. It is recommended that cholesterol levels should be less than 5mmol/L. In the Ireland, half of all adults have a total cholesterol level of 5mmol/L or above.

SYMPTOMS

High cholesterol is not a disease but increases your risk of serious conditions such as:

- coronary heart disease, caused by atherosclerosis (narrowing of the arteries),
- stroke, and
- Mini-stroke (transient ischaemic attack or TIA).

Coronary heart disease

A high level of cholesterol in your blood, together with a high level of triglycerides, can increase your risk of developing coronary heart disease. Coronary heart disease is caused by narrowing of the arteries that supply the heart with blood. This narrowing is called atherosclerosis. Cholesterol and other substances build up in the inner lining of an artery. This build-up, known as plaque, usually affects small- and medium-sized arteries. The flow of blood through the arteries is restricted as the space inside the artery is reduced. Blood clots, which often happen in the coronary arteries (leading to the heart) during a heart attack, are more likely to develop when artery walls become rough due to the build-up of fatty deposits.

Symptoms of atherosclerosis can include:

- Angina (pain in the chest or neighbouring parts of the body), caused by narrowed arteries going to the heart.
- Leg pain when exercising, caused by narrowed arteries going to the lower limbs.
- Blood clots and ruptured blood vessels, which can result in a stroke or mini-stroke
- Ruptured plaques, which can lead to a blood clot forming in one of the arteries delivering blood to the heart (coronary thrombosis). If a significant amount of heart muscle is damaged, this may lead to heart attack, heart failure and death.
- Cholesterol deposits around the eyes, in the skin or in the tendons. Yellowish deposits can form in the skin of the eyelids and white rings can form around the edge of the iris. In rare cases, hard white deposits of cholesterol form in the tendons, particularly around the knuckles or in the Achilles tendons (the back of the heel). These deposits may be seen in people with inherited high cholesterol (familial hypercholesterolemia).

Stroke and mini-stroke

A stroke or mini-stroke, also called a TIA, occurs when the blood supply to your brain is disturbed. In the case of TIA, this goes back to normal within 24 hours.

Symptoms vary from person to person, but may include your face falling on one side, arm weakness or slurred speech. The symptoms of a mini-stroke usually get better very quickly.TREATING

Cholesterol-lowering medication

There are several different types of cholesterol-lowering medication which work in different ways.

Statins

Statins block the enzyme (a type of chemical) in your liver that is needed to make cholesterol, and reduce your blood cholesterol level.

Aspirin

Low-dose aspirin can prevent blood clots from forming. .

Niacin

Niacin is a B vitamin that is found in foods and multivitamin supplements. In high doses (available by prescription), niacin lowers LDL and triglycerides and raises HDL. However, it can cause side effects, particularly flushing (turning red in the face), so is not commonly used.

Other medications

Ezetimibe is a medication that blocks the absorption of cholesterol from food and bile juices in your intestines into your blood. It is generally not as effective as statins, but is well tolerated.

INTRODUCTION TO SOLID DISPERSIONS

Solid dispersions are one of the most promising strategies to improve the oral bioavailability of poorly water soluble drugs. By reducing drug particle size to the absolute minimum, and hence improving drug wettability, solubility increases hence bioavailability may be significantly improved. They are usually presented as amorphous products, mainly obtained by two major different methods, melting and solvent evaporation

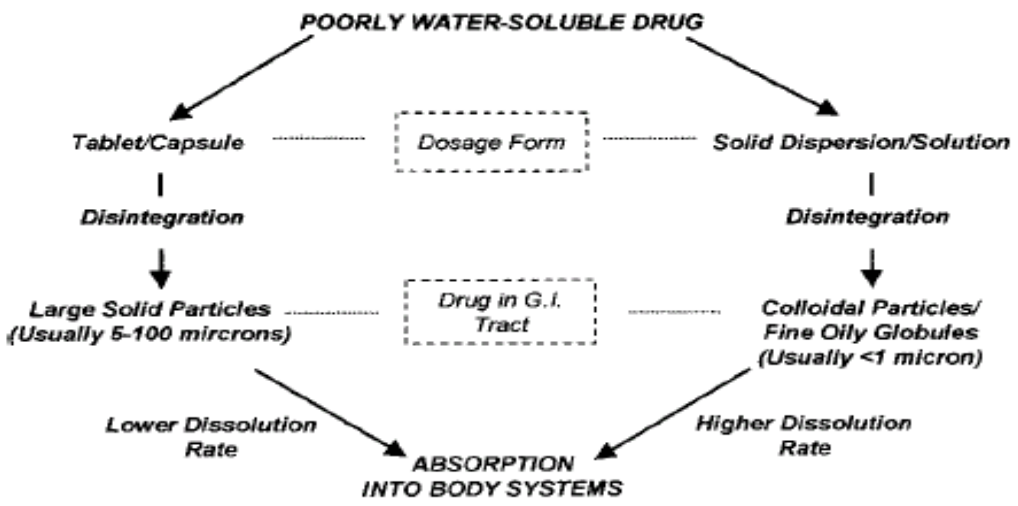


Fig. 1: A schematic representation of the bioavailability enhancement of a poorly soluble drug by solid dispersion compared with conventional tablet or capsule

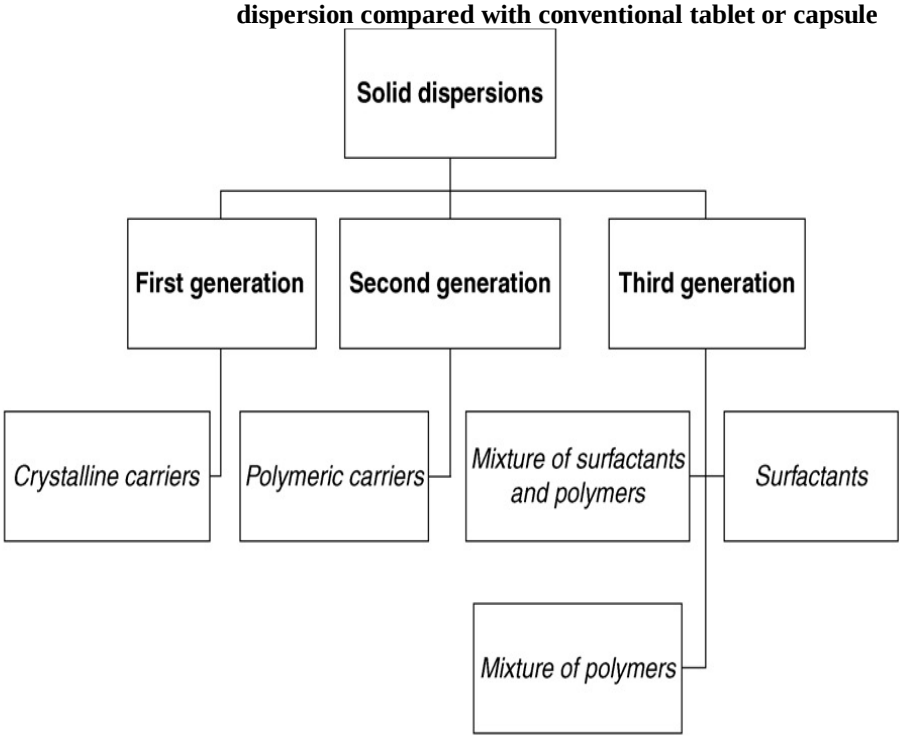


Fig. 2: The classification of solid dispersions

Table 1: Types of solid dispersions

Solid Dispersion Type		Matrix	Drug	No. of Phases
I	Eutectics	Crystalline	Crystalline particles	2
II	Amorphous Precipitations in crystalline matrix	Crystalline	Amorphous clusters	2
III	**Solid solutions**			
	Continuous solid solutions	Crystalline	Molecularly dispersed	1
	Discontinuous solid solutions	Crystalline	Molecularly dispersed	2
	Substitutional solid solutions	Crystalline	Molecularly dispersed	1 or 2
	Interstitial solid solutions	Crystalline	Molecularly dispersed	2
IV	Glass suspension	Amorphous	Crystalline particles	2
V	Glass suspension	Amorphous	Amorphous clusters	2
VI	Glass solution	Amorphous	Molecularly dispersed	1

Advantages of solid dispersion

1. Particles with reduced particle size

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers, a high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability [1].

2. Particles with improved wettability

A strong contribution to the enhancement of drug solubility is related to the improvement of drug wettability of solid dispersions [2].

3. Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity [3]. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate [4]. The increased porosity of solid dispersion particles also hastens the drug release profile.

4. Drugs in amorphous state

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility [(5,6)]. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process [7]. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form [(1,2)] For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them [(8)].

Table 2: Materials used as carriers for Solid Dispersions

Materials	Examples
Sugars	Dextrose, Sucrose, Galactose, Sorbitol, Maltose, Mannitol, Xylitol, Lactose.
Acids	Citric acid, succinic acid
Polymeric materials	Povidone (PVP), (Poly ethylene glycol) (PEG), Hydroxy propyl methyl cellulose, methyl cellulose, Hydroxy ethyl cellulose, cyclodextrins, Hydroxy propyl cellulose, Pectin, Gal.
Insoluble or enteric polymers	Hydroxy propyl -methyl cellulose phthalate, Eudragit L- 100, Eudragit S- 100, Eudragit RL, Eudragit RS.
Surfactants	Polyoxyethylene stearate, Renex, Poloxamer 188, Texafor AIP, Deoxycholic acid, Tweens, Spans.
Miscellaneous	Pentaerythritol, Pentaerythrityl tetra acetate, urea, urethane, Hydroxyalkylxanthins.

METHODS OF PREPARATION OF SOLID DISPERSIONS

Various preparation methods for solid dispersions have been reported in literature.

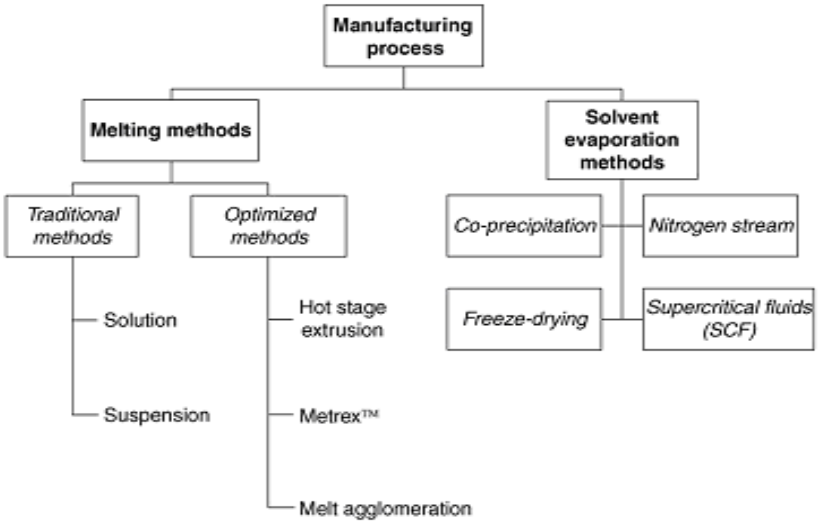


Fig. 3: Manufacturing processes used to produce solid dispersions

1. HOT MELT EXTRUSION MTHOD:

A "hot-melt" is any material that undergoes a transition from a solid or semi-solid state at a lower temperature, to a liquid or semi-liquid state at a higher temperature[9].

Hot-melt extrusion (HME) is the process of pumping raw materials with a rotating screw under elevated temperature through a die into a product of uniform shape. It is a process used to disperse or dissolve a drug in a molten polymer, has become increasingly important in pharmaceuticals due to the possibility of dissolving poorly soluble drugs in a solid solution.

It is a process that involves forcing a raw material or blend through a die or orifice under set conditions such as temperature, pressure, rate of mixing and feed-rate, for the purpose of producing a stable product of uniform shape and density.

The product stability and dissolution are similar, when compared to melting in a vessel, but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms. Solubility parameters are investigated to predict the solid state miscibility and to select matrices suitable for melt extrusion. High shear forces resulting in high local temperatures in the extruder, which can be a problem for heat sensitive materials[10]. However, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding.The drug/carrier mix is typically processed with a twin-screw extruder. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermo labile to be processed.It is composed of active ingredient and carrier, and prepare by hot-stage extrusion using a co-rotating twin-screw extruder. The concentration of drug in the dispersions is always 40% (w/w). The screw-configuration consist of two mixing zones and three transport zones distribute over the entire barrel length, the feeding rate is fix at 1 kg/h and the screw rate is set at 300 rpm. The five temperature zones are set at 100, 130, 170, 180, and 185C from feeder to die. The extrudates are collect after cooling at ambient temperature on a conveyer belt. Samples are milled for 1 min with a laboratory-cutting mill and sieve to exclude particles >355µm. Melt extrusion technology includes softening of the blend using the solvent mixture of water soluble polyethylene glycol, using methanol and passing of softened mass through the extruder machine or syringe to get a the product into a cylindrical segments using heated blade to form tablets.

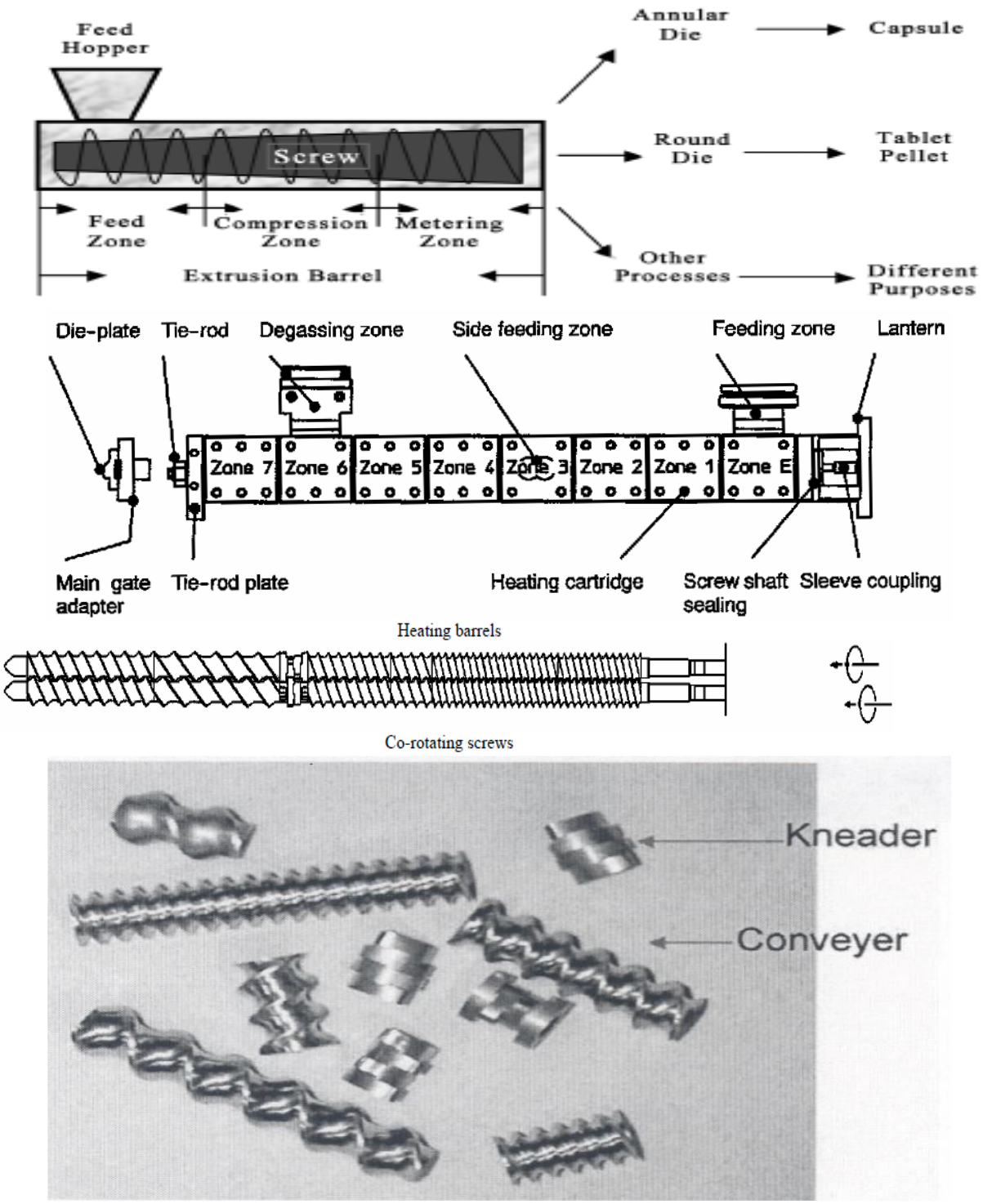


Fig 4: Different Parts of Hot Melt Extruder Equipment

Melt extrusion is commonly used to prepare solid dispersions by:

1. Softening the polymer and any desired adjuvants in a twin screw extruder
2. Adding the API to the molten mixture and mixing it into the system as it flows through the extruder
3. Rapidly cooling the extrudate to form strands of polymeric glass with embedded API and
4. Milling the glass strands into a powder suitable for subsequent finished formulation.

In the hot melt extrusion process, the formulation is processed above the glass transition temperature of

the polymer/API/ adjuvant system to mix the active ingredient with the polymer on a molecular level. When carried out in a twin screw extruder,

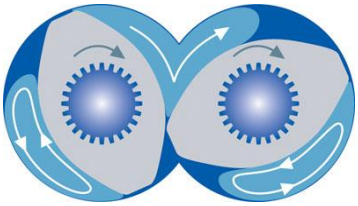


Fig 5: Working principle of co-rotating twin screw extruder

Because of their excellent mixing behavior and degassing possibilities, co-rotating twin-screws are particularly suitable for hot melt extrusion. Individual steps, such as melting, dispersive mixing, distributive mixing, degassing and pressure build-up, can be controlled very selectively and very effectively.The key factor in preparing solid dispersions through melt extrusion is the use of an individually developed screw configuration and zone temperature profile for optimal intake of individual formulation components (polymer, API, etc.), melting the polymer, mixing in the API, removal of any volatiles and discharging the end product.

It is mandatory that each zone has its own heating and cooling circuit and that the temperature adjustment of the individual process steps be well-controlled.

The main task in pharmaceutical hot melt extrusion is to control the process such that the required softening temperature of the polymer is exceeded, but the degradation temperature of the API is not reached. In the case of semi-crystalline polymers, the temperature of the melting zone is normally set a few degrees higher than the melting point. In the case of amorphous polymers, the temperature of the melting zone should be above the polymer glass transition temperature.

For many APIs, the delta in temperature between the softening point of the polymer and the degradation temperature of the API is very narrow and therefore offers only a very small operating window. Thus, tight process control is critical.

Key factors to control the process within these tight limits are the heating and cooling device in the process zone where the API is dispersed into the polymer. Modern extruders provide the ability to cool the barrel in the mixing zone where high levels of shear can contribute to local heating effects. Over the entire process section a combination of dispersive or distributive kneading or mixing elements as well as back-conveying elements are used to mix the API into the polymer. These elements also create shear energy that can increase the product temperature. In combination with the heating and cooling device of each individual barrel section and relaxation zones between the high-shear areas, a gentle and sensitive temperature profile can be achieved. This continuous process offers numerous **advantages** over other melt processing methods, including:

- A short residence time at elevated temperatures thus a thermolabile drug can also be processed.
- A high reproducibility
- Intensive mixing (dispersive or distributive mixing) thus improved content uniformity
- High throughput rates
- A self-wiping effect from the closely inter-meshing screws
- It is non-solvent technology
- Good method of granulation of poorly soluble drugs and poorly compressible powders.
- Uniform dispersion of fine particles occurs
- Good stability at varying pH and moisture levels
- Fewer processing steps needed thus time consuming drying steps eliminated
- Applicable in formulation of matrix tablets and Hard gelatine capsules.
- Cost effective
- The hot melt extrusion process and hot melt extrusion equipment are readily scalable, from lab- to pilot plant-scale, through to commercial production

Applications of hot-melt technique

- Improving dissolution rate and Bioavailability of drug.
- Controlling or modifying drug release.
- Masking the bitter taste of active drug.

Disadvantages of melting methods

1) This method is not suitable for the drug or carrier unstable at fusion temperature or evaporates at higher temperature.

2) Solidification temperature may affect crystallization rate and hardness of the dispersion.

3) Irregular crystallization owing to the presence of a miscibility gap on the phase diagram for a given drug-carrier system.

In 1961, Sekiguchi and Obi formed eutectic mixtures of drugs with water-soluble carriers by melting their physical mixtures. This was a significant advance in the development of solid dispersion systems.

Mechanism of drug release from solid dispersion:

Solid dispersion is a molecular dispersion of a compound, particularly a drug substance, within a carrier matrix. Formation of a molecular dispersion (solid solutions) of such a compound provides a means of reducing the particle size of the compound to nearly molecular levels (i.e. there are no particles). As the carrier dissolves, the compound is exposed to

the dissolution media as fine particles that are amorphous, which can dissolve and be absorbed more rapidly than larger particles. The solid dispersion compositions has been used to enhance the

TECHNIQUES TO EXPLORE MOLECULAR INTERACTIONS AND BEHAVIOR

Drug –carrier miscibility

- Hot stage microscopy
- DSC (Conventional modulated)
- pXRD (Conventional and variable temp)
- NMR 1H Spin lattice relaxation time

Drug carrier interactions

- FT-IR spectroscopy
- Raman spectroscopy
- Solid state NMR

Physical Structure

- Scanning electron microscopy
- Surface area analysis

Surface properties

- Dynamic vapor sorption
- Inverse gas chromatography
- Atomic force microscopy
- Raman microscopy

Amorphous content

- Polarized light optical microscopy
- Hot stage microscopy
- Humidity stage microscopy
- DSC (MTDSC)
- ITC
- PXRD

Stability

- Humidity studies
- Isothermal calorimetry
- DSC (Tg, Temperature recrystallization)
- Dynamic vapor sorption
- Saturated solubility studies

Dissolution enhancement

- Dissolution
- Intrinsic dissolution
- Dynamic solubility
- Dissolution in bio-relevant media

RESULTS AND DICUSSION:

Preformulation studies: API Characterization:

Organoleptic properties:

Table 3: Organoleptic properties of drug

Sr. No.	Properties	Observation
1	Description	Amorphous powder
2	Colour	Cream
3	Taste	Tasteless
4	Odour	Odourless

Flow properties of API

Table 4: Flow properties of model drug

Test	Observations
Bulk density	2.05gm/cm^3
Tapped density	2.37gm/cm^3
Carr's index	13.15%
Hausner's ratio	1.15

Inference: From the recorded observations it was found that Carr's index and Hausner's ratio indicate that the flow of model drug has very poor flow properties. The values of carr's index and Hausner's ratio categorize the drug with very poor flow properties.

Particle size distribution data of model

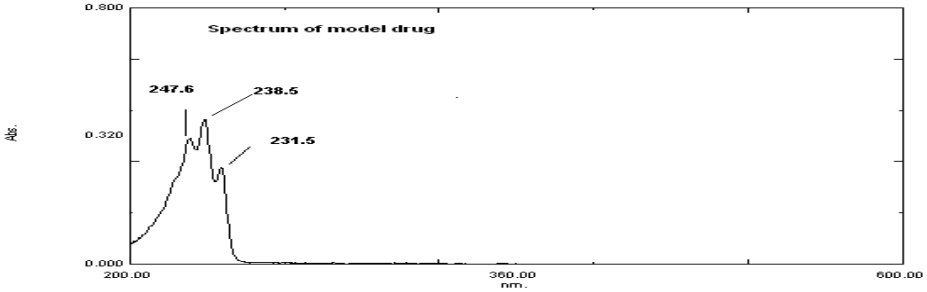
Table 5: Particle size determination of model drug

Sieve Mesh Number	Sieve Size Opening(µm)	Mass of Sample Retained on Each Sieve(g)	Percentage of Sample Retained on Each Sieve (%)	Cumulative Percentage of Sample Retained on Each Sieve (%)
20	841	0.64	12.8	12.8
40	420	0.87	17.4	30.2
60	250	2.03	40.6	70.8
80	177	0.77	15.4	86.2
100	149	0.29	5.8	92.0
120	125	0.25	5.0	97.0
Pan	-	0.10	2.0	99.0

Inference: From the particle size distribution data, it was observed that the model drug has12.8 % of particles were around 841 microns and 30.2 % of particles were found to be around 420 microns, 92 % of API particles were found to be around 149 microns in size

Analytical Method Results

A) Determination of λmax



No.	P/V	Wavelength in nm.	Abs.
1.		383.50	0.002
2		377.50	0.002
3.		374.50	0.003
4.		365.50	0.003
5.		357.50	0.004
6.		353.50	0.005
7.		351.50	0.005
8.		344.50	0.004
9.		342.50	0.003
10.		330.00	0.004
11.		305.00	0.002
12.		286.00	0.003
13.		277.50	0.004
14.		263.50	0.005
15.		259.00	0.008
16.		247.6	0.137
17.		238.5	0.189
18.		231.5	0.106
19.		198.5	0.012

B) Standard Calibration Curves:

Table 6: Preparation of standard plot of model drug in 0.1 N HCl (pH 1.2)

Concentration(mcg/ml)	Absorbance at 238.5 nm
0	0
5	0.139
10	0.252
15	0.421
20	0.581
25	0.715

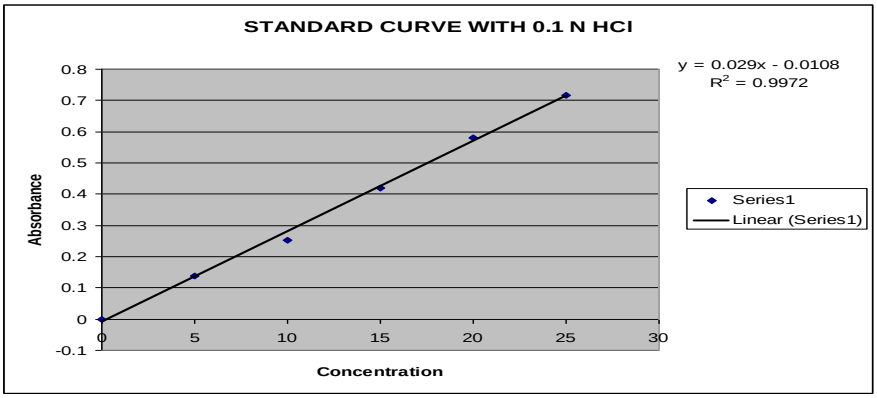


Fig. 6: Standard plot of model drug in 0.1N HCl

Table 7: Preparation of standard plot of model drug in acetate buffer (pH 4.5)

concentration in (mcg/ml)	Absorbance at 238.5 nm
0	0
5	0.161
10	0.349
15	0.483
20	0.629
25	0.761

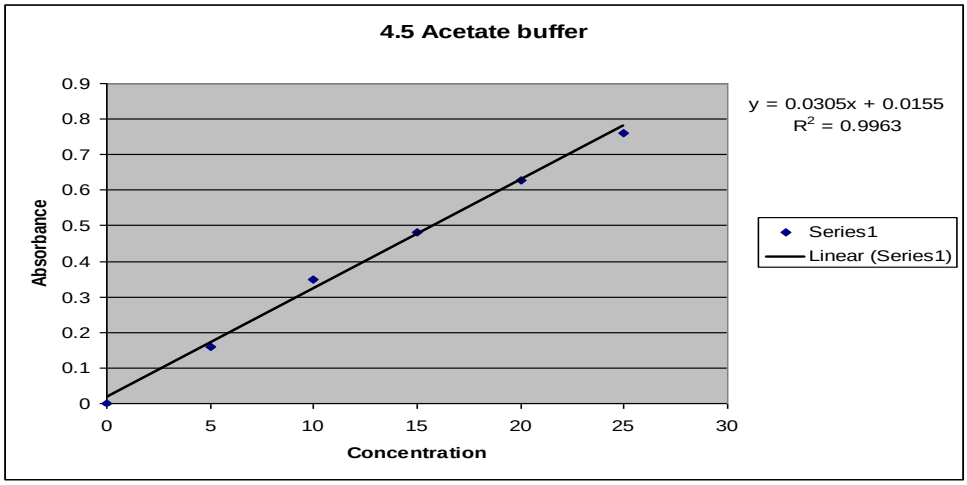


Fig.7: Standard plot of model drug in 4.5 acetate buffer

Table 8: Preparation of standard plot of model drug in phosphate buffer (pH.8)

concentration in mcg/ml	Absorbance at 238.5 nm
0	0
5	0.17
10	0.370
15	0.543
20	0.698
25	0.874

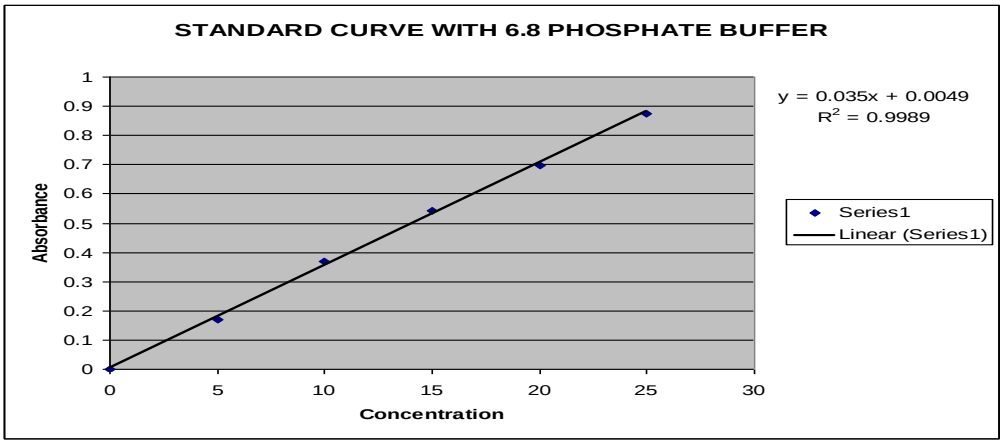


Fig. 8: standard plot of model drug in phosphate buffer (pH 6.8)

Table 9: Preparation of standard plot of model drug in water (pH 7.2)

Concentration(mcg/ml)	Absorbance at 238.5 nm
0	0
5	0.083
10	0.171
15	0.255
20	0.343
25	0.409

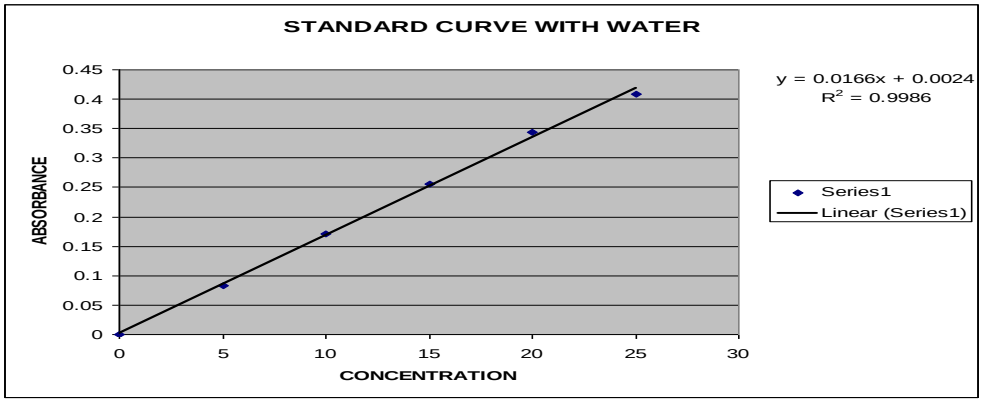


Fig.9: Standard plot of model drug in water

Table 10 : Preparation of standard graph of model drug in phosphate buffer (pH 7.4)

concentration(mcg/mL)	Absorbance at 238.5 nm
0	0
5	0.211
10	0.41
15	0.604
20	0.804
25	0.969

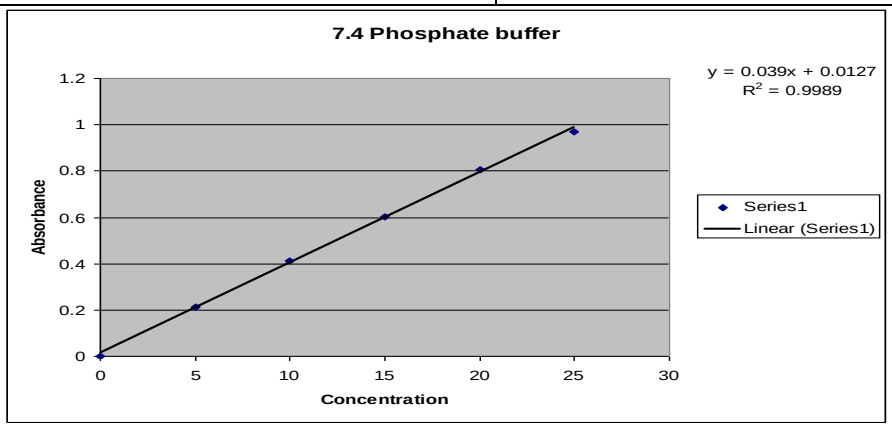


Fig. 10: Standard plot of Model drug in phosphate buffer (pH 6.8)

Drug-Excipient Compatibility Study:

After 4 weeks of study, physical appearance of these compositions was compared with the initial observations. The observations were recorded in the following table:

Table 11: Visual observation for Drug-Excipient Ratios for Compatibility Study

Physical Appearance					
Composition Code	**Initial**	**I Week, 40°C/75% RH**	**II Weeks, 40°C/75% RH**	**III Weeks, 40°C/75% RH**	**IV Weeks, 40°C/75% RH**
Drug	Cream powder	Cream powder	Cream powder	Cream powder	Cream powder
Drug+ Soluplus	Cream powder	Cream powder	Cream powder	Cream powder	Cream powder
Drug+β-cyclodextrin	White powder	White powder	White powder	White powder	White powder
Drug+ Avicel pH 101	White powder	White powder	White powder	White powder	White powder
Drug+ Mannitol SD 100	White powder	White powder	White powder	White powder	White powder
Drug+Cross carmellose sodium	White powder	White powder	White powder	White powder	White powder
Drug+Magnesium stearate	White powder	White powder	White powder	White powder	White powder

Inference: Physical mixture of model drug and other excipients after storage period of 4 weeks at 40°C / 75% RH showed no physical changes like color change, caking, odour etc indicating the compatibility of excipients with model drug. Hence the said excipients were proposed for formulation development

Evaluation of Tablets:

Table 12: Evaluation properties of powder blend of different batches

Formulation Code	Tapped Density (gm/cm^3)	bulk density (gm/cm^3)	Compressibility Index (CI) (%)	Hausner ratio (HR)	PSD (in µ)
F1	3.6	3.3	9.09	1.09	175-185
F2	3.7	3.4	8.11	1.09	173-184
F3	3.9	3.5	10.25	1.11	168-184
F4	3.6	3.2	11.11	1.13	177-178
F5	3.4	3.1	8.82	1.10	178-189
F6	3.6	3.2	13.88	1.16	173-177
F7	3.8	3.3	13.16	1.15	175-177
F8	3.5	3.2	8.57	1.09	171-179
F9	3.5	3.2	8.57	1.09	173-185
F10	3.3	3.0	9.09	1.1	172-186
F11	3.4	3.1	13.88	1.16	173-185
F12	3.6	3.3	11.11	1.13	177-178

Inference: Compressibility indices, Hausner ratio, angle of repose of 12 trial batches were computed and found that all blends possess good flow properties hence suitable for direct compression of blends into tablets.

Post compression parameters

Table 13: Physical characterization of tablets

Formulation	Average weight of Tablet(mg)	Average thickness (mm)	Average hardness (kp)	Friability (%)	Disintegration Time (min)
F1	500-502	3.6	7.5-8	0.52	10min
F2	500-501	3.5	9.7-10	0.67	6min
F3	500-502	3.7	7.8-8	0.64	12min
F4	499-501	3.5	9-10	0.65	9 min
F5	500-502	3.5	7.5-8	0.56	13min
F6	500-503	3.7	8.2-9	0.54	10 min
F7	220-222	2.3	5-7	0.57	10min
F8	220-221	2.0	5-8	0.56	5min
F9	220-222	2.1	5-6	0.58	11min
F10	220-221	2.1	4-7	0.69	9min
F11	220-222	2.2	4-8	0.58	13min
F12	221-223	2.0	4-6	0.51	11min

Inference: Physicochemical properties (thickness, hardness,friability, disintegration time,) of 12 formulations of trial batches were performed and the results were within USP limits.

Excipients also have an impact on disintegration time. DT of SD tablets of formulations F2 and F8 are comparatively less than that of F1, F2, F4, F5, F6, F7, F9, F10,F11,F12. So in vitro dissolution studies were performed for F2 and F8 (optimized formulations).

Rate of Disintegration: CCS> SSG > Crospovidone

Drug Excipient compatibility studies using DSC

DSC Thermogram of Pure API:

Table 14: Compatibility of model drug with different excipients with aid of DSC

Sample	Apperarance of new peaks	Fade of existing peaks	Shifting of peaks > 15°C
Drug + Soluplus	No	No	No
Drug + β-Cyclodextrin	No	No	No
Drug + Microcrystalline cellulose (Avicel pH 101)	No	No	No
Drug + Mannitol (Pearlitol SD 100)	No	No	No
Drug + Cross carmellose sodium	No	No	No
Drug + Magnesium stearate	No	No	No

In vitro Dissolution studies:

Table 15: In vitro dissolution studies of F2, F8 in 0.1 N HCl

Time (min)	% drug release of F8	% drug release of F2
0	0	0
5	17.35	34.23
10	19.44	46.56
15	22.56	59.65
30	26.97	68.69
45	31.53	92.24
60	39.37	98.81

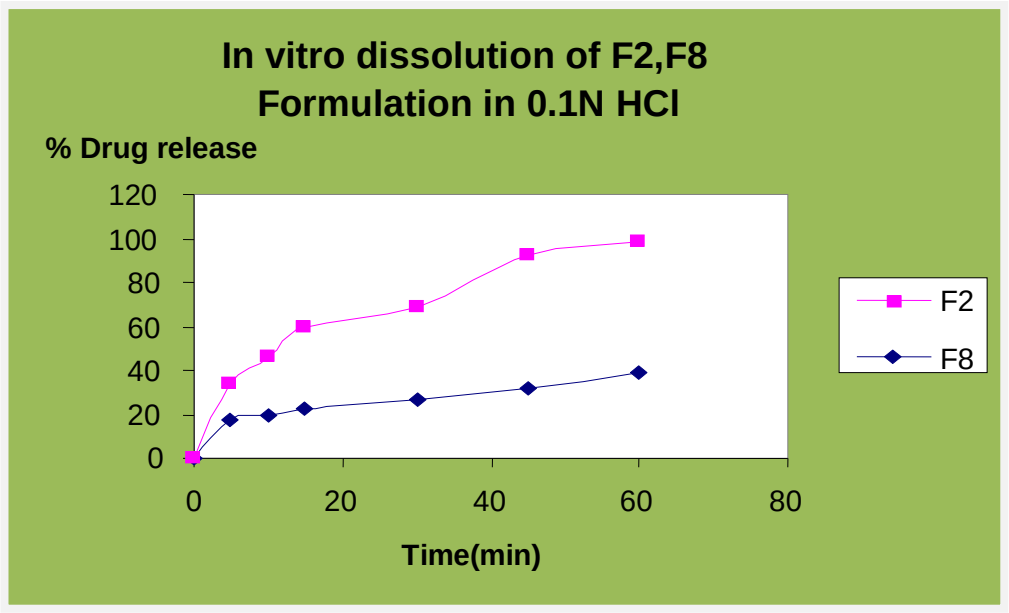


Fig.11: Comparison of in vitro dissolution profiles of formulations F2, F8

Inference: In vitro dissolution profiles of F2 and F8 in 0.1N HCl were compared and found that F2 has shown 98.81 % drug release within 60 min, whereas F8 has shown 39.37% drug release within 60 min. The study infers that solid dispersion tablet has shown improved dissolution of drug

Table 16: *In vitro* dissolution studies of F2, F8 in 6.8 phosphate bufferbfggyg

Time (min)	% drug release of F8	% drug release of F2
0	0	0
5	18.25	30.13
10	22.85	42.56
15	25.62	49.65
30	29.98	58.69
45	35.58	89.24
60	43.35	98.73

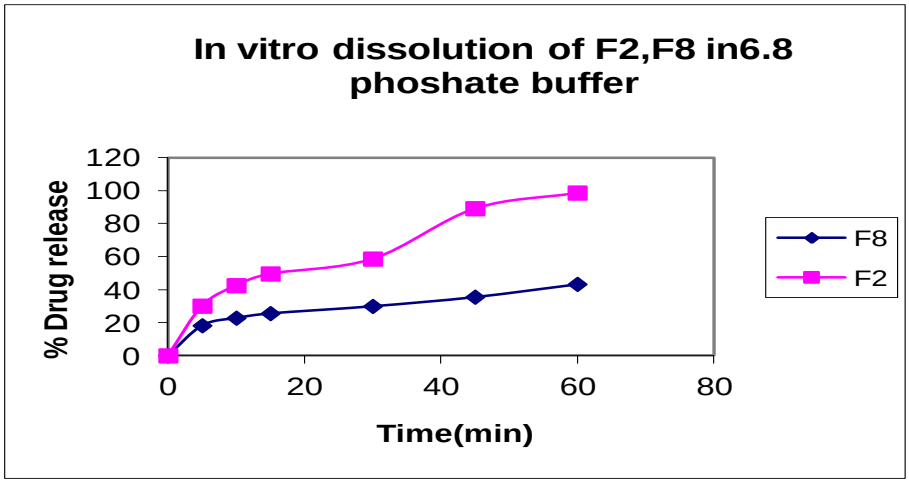


Fig. 12: Comparison of in vitro dissolution profiles of formulations F2, F8.

Inference: In vitro dissolution profiles of F2 and F8 were compared and found that F2 has shown 98.73 % drug release within 60 min, whereas F8 has shown 43.35% drug release within 60 min. The study infers that solid dispersion tablet has shown improved dissolution of drug.

SUMMARY AND CONCLUSION:

Dissolution and absorption of poorly water soluble drugs is the main challenge in pharmaceutical industry. Solid dispersion of poorly water soluble drugs may enhance the solubility, absorption and bioavailability.

The main objective of this study was to enhance the aqueous solubility of poorly water soluble drugs and its dissolution rate using hot-melt extrusion technique.

Solid dispersion technique can be combined with traditional dosage forms such as tablets, capsules and pellets. Solid dispersion will be of interest in development of oral and non-oral dosage forms.

Model drug was antihyperlipidemic agent, which is used for the treatment of hyperlipidemia.

The model drug was poorly soluble in water, so there was need to make it soluble through Solid dispersion technique.

In present study, Solid dispersion of poorly soluble drug was prepared by Hot-melt extrusion technique to enhance its solubility.

The results of drug excipients compatibility studies suggest that there was no change in the physical appearance of mixtures when stored at 40°C ± 2°C / 75% ± 5% RH for 1 month indicating that the selected excipients may be compatible with the selected drug.

The Solid dispersion of model drug was prepared by using Hot-melt extruder.

Different batches were taken in order to convert the crystalline form of drug to the amorphous form with different concentration of Soluplus and Kollidon VA 64 in the ratios of 1:2, 1:3, and 1:4 respectively and Soluplus, Kollidon VA 64 and β-cyclodextrin in the ratios of 1:4:1,1:4:2 . All the batches were found to be the best and all the trials showing conversion from crystalline form of drug to the amorphous form which is indicated by the PXRD studies .Batch no. SD8 (Solid dispersion) was further mixed with extra granular material and compressed as immediate release tablets.

Excipients also have an impact on disintegration time. DT of SD tablets of formulations F2 and F8

are comparatively less than that of F1, F2, F4, F5, F6, F7, F9, F10,F11,F12. So in vitro dissolution studies were performed for F2 and F8 (optimized formulations).In vitro dissolution profiles of F2 and F8 were compared and found that F2 has shown 98.81 % in 0.1 N HCl ,98.83% in 6.8 phosphate buffer drug release within 60 min, whereas F8 has shown 39.37% in 0.1 N HCl,43.35% in 6.8 phosphate buffer drug release within 60 min. The study infers that solid dispersion tablet has shown improved dissolution of drug

Stability study results of batch no. SD3 at 40°C/75% RH for 1 month were found to be satisfactory.

So, it can be concluded that by Solid dispersion using Hot-melt extrusion technique, enhanced solubility and dissolution rate of the drug is achieved and hence bioavailability may also be enhanced which is to be explored further.

REFERENCES:

1. Recommendations of the Advisory Committee on Immunization Practices: Use of vaccines and immune globulins in persons with altered immunocompetence. MMWR 1993;42(RR-4):1-18.

2.Ingle U.S. et al; A Review on Solid Dispersion: A Dissolution Enhancement Technique; International Journal of Research in Ayurveda & Pharmacy, 2(3), 2011, 751- 757.

3.Karanth, H., Shenoy, V.S., Murthy, R.R., 2006. Industrially feasible alternative approaches in the manufacture in the solid dispersion: A technical report. AAPS PharmSciTech, 7 (4) article 87

4.Pokharkar et al; (2006). Development, characterization and stabilization of amorphous form of a low Tg drug. *Powder Technol.*, 167: (8) 20-25.

5.Ahuja, N. et al; Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water-soluble carriers; 2007, Eur. J. Pharm. Biopharm. 65, (10) 26–38.

6.Dandagi P.M. et al developed mouth disintegrating tablets of Ofloxacin using aspartame as sweetener, sodium starch glycolate disintegrant and isopropyle alcohol as granulating agent and by mass extrusion technique using eudragit E100 as taste masking agent along with avicel 102 and ethanol.

7.Rapidly disintegrating domperidone tablets were formulated by Dandagi P.M.using two methods as mass extrusion technique and treated agar. In mass extrusion formulations sodium starch glycolate, eudragit E-100, low substituted hydroxyl propyl cellulose, lactose and in treated agar formulations mannitol, treated agar, lactose, aspartame were used as excipients.

8.Mayersohn M, Gibaldi M. New method of solid-state dispersion for increasing dissolution rates. J Pharm Sci. 1966;55:1323–4. [PubMed]