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Solubility Enhancement of Glybenclamide by Solid Dispersion

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ABSTRACT

Glibenclamide is a highly lipophilic drug therefore it faces challenges in solubility and absorption patterns. This study aims to improve the solubility and dissolution characteristics of Glibenclamide by preparing solid dispersion using solvent evaporation technique and to study the effect of particle size and different dissolution media on drug release property. The carrier used was Soluplus as a solubilizer. The solid dispersions were prepared in drug: carrier ratios 1:0.5, 1:1, 1:2 1:3, 1:4, 1:6 and 1:8 by solvent evaporation method. The resultant solid dispersions were evaluated for solubility studies at different pH conditions. The release rate of drug from the capsule formulation was studied. Solid state characterization of solid dispersion has been carried out by DSC, FTIR. Solid dispersions were subjected to accelerated stability studies and were characterized by DSC. Our results describe an effective solid dispersion of glibenclamide with improved solubility and dissolution which results in the improved bioavailability.

Keywords: Glibenclamide, soluplus, DSC, FTIR, Mottler Toledo.

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INTRODUCTION

Solid oral drug delivery is the simplest and easiest way of administering drugs. These dosage forms have many advantages over other types of oral dosage forms. It is estimated that 40% of new chemical entities identified in combinatorial screening programs are poorly water soluble [1] The rate and extent of absorption of class II & class IV compounds is highly dependent on the bioavailability which ultimately depends on solubility. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs.

Process of solubilization: The process of solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute[2], the separation of the molecules of the solvent to provide space in the solvent for the solute followed by interaction between the solvent & the solute molecule or ion.

Factors effecting solubility: The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature & pressure of system[3].

1. ***Particle Size:*** The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent. The effect of particle size on solubility can be described by equation.

$$\text{Log } S / S_0 = 2\ \gamma\ V / 2.303\ R\ T\ r$$

2. ***Temperature:*** Generally, an increase in the temperature of the solution increases the solubility of a solid solute.

3. ***Molecular size:*** The larger the molecule or the higher its molecular weight the less soluble the substance. In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent.

4. ***Polarity:*** Polarity of the solute and solvent molecules will affect the solubility. Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction.

5. ***Polymorphs:*** The capacity for a substance to crystallize in more than one crystalline form is polymorphism. It is possible that all crystals can crystallize in different forms or polymorphs. If the change from one polymorph to another is reversible, the process is called Enantiotropic. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubility's. Generally the range of solubility differences between different polymorphs is only 2-3 folds due to relatively small differences in free energy.

Approaches to increase solubility: This focuses on the technologies that have arisen to meet the challenge posed by insoluble compounds and the ways in which these technologies have made a difference[2,4]. The techniques that are used to overcome poor drug solubility are discussed under following major headings.

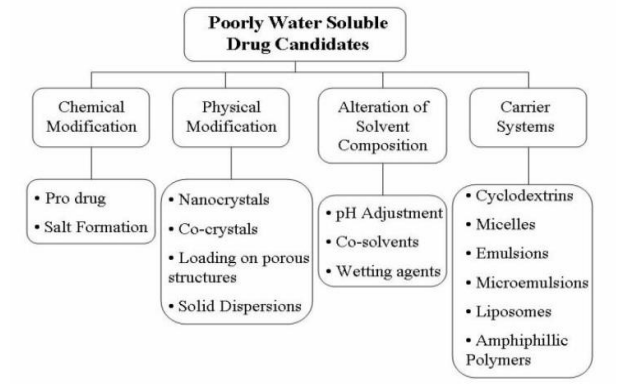

Fig1. Approaches to increase solubility/dissolution

Poorly water-soluble drugs present many difficulties in the development of pharmaceutical dosage forms due to their limited water solubility, slow dissolution rate and low bioavailability. Solid dispersions (SDs) have been widely reported as an effective method for enhancing the dissolution rate and bioavailability of poorly water-soluble drugs. SD refers to the dispersion of one or more drugs in inert and solid water soluble carriers, either molecularly or as fine particles.

Mechanisms to improve the solubility and dissolution properties of SDs include change of the drug crystal structure into an amorphous structure, reduction of aggregation and increased wetting and solubilization of drugs by the carriers. As soluble carriers dissolve, poorly water-soluble drugs are exposed to dissolution media as very fine particles or dispersions that enhance their dissolution and absorption.

One of most widely used carriers in the preparation of SDs is solid-type polyethylene glycols (PEGs), such as PEG 4000, 6000, and 8000. PEG-based SD are commonly prepared using the fusion (or melting) method, due to its convenience, ease and pulverization over a shorter period, without the use of organic solvents. However, due to the limited solubilizing capability of carriers, various pharmaceutical excipients, such as solubilizers, surfactants, oils and fatty acids, or in the form of mixtures, can be added into the SDs to further improve the drug solubility and dissolution rate.

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

Solvent evaporation [5,6]
This method involves dissolving the drug and carrier in a common organic solvent, and then removing the solvent by evaporation.

The melting method
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.

Direct melt filling[7]
In 1978, Francois and Jones further developed the solid dispersion method by directly filling hard gelatin capsules with semisolid materials as a melt, which solidified at room temperature. Chatham reported the possibility of preparing PEG-based solid dispersions by filling drug--PEG melts into hard gelatin capsules.

Melt extrusion[8]
Melt extrusion is a new method for producing solid dispersions. Special equipment is needed to develop the dosage form from solid dispersions, which limits the use of the extrusion method. Forster et al. report the use of melt extrusion to prepare glass solutions of poorly water-soluble drugs with hydrophilic excipients. It is claimed that the method is an improvement to existing formulation methods such as spray-drying and co-melting because it uses smaller quantities of drug, reduces particle size and speeds up the formulation process.

Dropping method [9]
The dropping method, developed by Ulrich et al. to facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions. This technique may overcome some of the difficulties inherent in the other methods.

Alternative strategies

Spraying on sugar beads using a fluidized bed coating system
The approach involves a fluidized bed coating system, wherein a drug-carrier solution is sprayed onto the granular surface of excipients or sugar spheres to produce either granules ready for table ting or drug-coated pellets for encapsulation in one step. The method has been applied for both controlled- and immediate-release solid dispersions.[10,11]

Hot-melt extrusion
Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971. Since the turn of the century, many studies have been conducted on this process for the preparation of solid dispersion. It has been reported that melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component leads to amorphous drug dispersed in crystalline excipient. The process has been useful in the preparation of solid dispersions in a single step. Hot-melt extrusion method is used in the preparation of various dosage forms in the pharmaceutical industry such as preparation of sustained-release pellets.

Direct capsule filling
The filling of semisolid materials into hard gelatin capsules as melts, which solidify at room temperature, was first done in 1978. It was not until much later that the potential application of the technique for solid dispersions was fully realized. Laboratory-scale semiautomatic equipment and large-scale manufacturing equipment for direct capsule filling are commercially available. Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug.

Surface-active carriers
A surface-active carrier may be preferable in almost all cases for the solid dispersion of poorly

water-soluble drugs. The surface-active and self-emulsifying carriers for solid dispersion of poorly water-soluble drugs have been of great interest in recent years.

Two of the important surface-active carriers are Gelucire 44/14 and Vitamin E R-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS). Gelucire 44/14 (Gattefosse´ Corp, Gennevilliers, France) has commonly been used in solid dispersion for the bioavailability enhancement of drugs.

A commonly used surfactant, Polysorbate 80, when mixed with solid PEG, has also been reported to be an alternative surface-active carrier. Polysorbate 80 is liquid at room temperature; it forms a solid matrix when it is mixed with a PEG because it incorporates within the amorphous regions of PEG solid structure.

Initial formulation development studies can be conducted by filling hot solutions or dispersions into hard-gelatin capsule shells manually by using pipettes or by using laboratory-scale semiautomatic equipment.

MATERIALS AND METHODS

Glibenclamide was a kind gift from Matrix laboratories, Hyderabad. Soluplus was a kind gift from OBASF chemical company. Lactose monohydrate, Microcrystallincellulose, croscarmellose sodium, Magnesium stearate, Aerosil is purchased from Ranbaxy Fine Chemicals. All other chemicals and solvents of analytical reagent grade were used.

Preparation Methods: Solid dispersion using the Soluplus was prepared by the solvent evaporation method. Initially the drug and the carrier were dissolved in dimethyl formamide in 1: 3 ratio. Then the polymer solution was added to the drug solution with continuous stirring after complete evaporation of the solvent, solid dispersion was dried at 58^0C-60^0C in an oven until thin flakes are formed.Then that solid dispersion was collected, milled and passed through 40 # mesh size. Diluent (avicel), glident (Aerosil 200M), disintegrant (croscarmellose sodium) were sifted through mesh # 30 and added to solid dispersion and blended together in a blender for 10 minutes **,**Lubricant (Magnesium stearate) was sifted through mesh # 40 and blended with mass for 5 minutes and capsules are filled.

Evaluation Methods

Drug content estimation: 20mg of pure drug was taken and dissolved in approximately 25 mL of ethanol. The solution was filtered and the volume of solution was made up with phosphate buffer pH 7.5, suitably diluted with buffer and drug content was analyzed against blank by UV spectrophotometer at 226 nm. Solid dispersions equivalent to 20 mg of drug was transferred to a separate volumetric flask and dissolved in ethanol, mixed and filtered through 0.45 micron filter. Required amount of phosphate buffer was added to the filtrate, suitably diluted with buffer and drug content was analyzed against blank by UV spectrophotometer at 226 nm. The percentage of drug present in the solid dispersion was calculated.

Disintegration time: Disintegration time was observed with the help of disintegration test apparatus consisting of a basket rack assembly with 1000 ml beaker, a thermostatic arrangement for heating the beaker between 35^0and39^0 C and a device for raising and lowering the basket in the immersion fluid at a constant rate between 29 and 32 cycles per min.

Solubility tests: Solubility studies were performed by taking physical mixture, solid dispersions of drug/ carrier ratios (1:0.5, 1:1, 1:2, 1:3, 1:4, 1:6 and 1:8) in 25 mL of 0.1 N HCL, water, pH.4.5 acetate buffer, pH.6.8 phosphate buffer, pH.7.5 phosphate buffer medium and subjected to mechanical shaking at 200 rpm for 24 hrs. The resultant dispersions were collected and filtered through 0.45 µ filters and the concentration of drug was determined from absorbance at 226 nm. The solubility was performed at various pH conditions pH 1.2, pH 4.5, pH 6.8, water and pH 7.5. Solubility studies were performed by taking solid dispersions of drug/ carrier ratios (1:0.5, 1:1, 1:2, 1:3, 1:4, 1:6 and 1:8) in 25 mL of buffer and subjected to mechanical shaking at 200 rpm for 24 hrs.

Dissolution test

Dissolution test protocol: Dissolution study was conducted for API and Solid dispersions using USP type-II apparatus (ELECTROLAB). The dissolution test was performed using 900 mL of phosphate buffer (pH 7.5) as the dissolution medium at 50 rpm and at a temperature of 37 ^{0}C ± 0.5 ^{0}C. Five milliliters of aliquots were periodically withdrawn at 5, 10, 15, 30, 45, 60, 90, 120,150 and 180 mins and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were diluted and analyzed spectrophotometrically at 226 nm.

Characterization of Solid dispersions: To elucidate the enhanced dissolution and bioavailability, the physical state of the drug crystals in the soluplus -based SD (1:3) was

investigated using instrumental analysis. Studies such as DSC, FTIR are performed for the characterization of solid dispersions

RESULTS AND DISCUSSION

The solid dispersions were taken in an pierced aluminium crucible with a capacity of 40µL and evaluated in Metller Toledo equipment using eStar software (version 9.10) in a temperature range of 30-300º C at a heating rate of 10 º C/min under a stream of nitrogen. The thermograms were recorded. Polymorphic studies were performed by DSC for Glyburide and carrier. The melting range of Glyburide was found to be 172.74-177.02 º C and for Soluplus 63.66-114.49 º C. The sharp peak in the thermogram of Glyburide indicates crystalline nature of drug. Pure drug exhibits a sharp melting endotherm at 174.49ºC. Soluplus exhibited a single sharp melting endotherm at 87.44º C .Melting point of both soluplus and drug are decreased after preparation of solid dispersion, suggesting the formation of eutectic. Soluplus along with drug exhibits sharp endotherm at 68.11º C. No endotherm corresponding to the melting point of the pure crystalline API was observed. These results suggest that heating in DSC, the drug progressively dissolves in soluplus and melts completely below the melting point of the drug. The drug in F5 formulation shows characteristic peaks at 1306 cm^{-1} and 1458 cm^{-1}. Soluplus shows characteristic peaks at 3461.37cm^{-1}, 1245.64 cm^{-1}, and 1633.72 cm^{-1}.The absence of any other new peak in the solid dispersion indicates that drug is not undergoing any polymorphic change during their preparation. Furthermore the presence of shifts in the wave numbers of the FTIR peaks of the solid dispersions indicates significant interactions between the drug and the soluplus in the solid dispersions which resulted in improved solubility of Glibenclamide.

Percent drug content for pure drug, F1, F2, F3, F4, F5, F6, F7 and F8 formulations were found to be 99, 97.1, 98.2, 97.4, 98.09, 98.98, 98.01, 98.67 and 98.5 respectively. Solubility of solid dispersions has shown higher in pH 7.5 buffer compared to other pH conditions. Solubility of solid dispersions was in the order of:F8>F7> F6> F5> F4> F3> F2> F1>PD. The order of % drug release of various formulations is F8 < F7 < F6 < F5 > F4 > F3 > F2 > F1 > PD. The study shows that up to the optimum concentration i.e. at 1:3 ratio (F5) of drug to soluplus ratio, soluplus will increase the drug release. After that concentration it will retard the drug release. Below the optimum concentration it will not solubilize the drug. This study showed that dissolution of pure drug was incomplete. Soluplus® dispersion showed a significant dissolution enhancement of drug compared to crystalline drug alone and Physical mixture of drug, Soluplus. So Soluplus® appears to be an acceptable polymer for formation of solid dispersions using solvent evaporation. The percentage release of F5 formulation was found to be higher in 7.5 buffers. So increase in the pH of the dissolution media increases the solubility of solid dispersion.

Stability studies showed that there is no change in Glyburide endotherm in DSC after 1 month 40°c / 75% RH- open exposure show that there is no physicochemical change after exposure studies. The organoleptic properties were as per the standards set previously for the formulation. The release patterns were desirable and the dissolution patterns within the desired ranges. The stability studies for 40^0C/75% RH proved the formulation to be stable for the specified period. Capsule formulation was found to be stable physically and chemically under storage conditions studied for one month. No change in drug content also confirmed chemical stability.

CONCLUSION

Solid dispersion technology is a promising approach to enhance the solubility of poorly water soluble drugs. The carrier concentration plays an important role in the enhancement of solubility and dissolution parameters. Increase in carrier concentration upto the optimum i.e. at 1:3 ratio showed an improved solubility of drug because of hydrophilicity, porosity and wetting properties of carrier and amorphous nature of solid dispersion.The result indicates that the dissolution rate of the poorly soluble Glibenclamide can be increased significantly via the solvent evaporation method using an amphiphilic carrier soluplus at different drug: carrier ratios.From the dissolution analysis it was observed that the drug release from F5 formulation was released above 50% within 5min than that of physical mixture of drug, soluplus and then of pure drug.In F5 formulation the particle size of solid dispersion with 250 micron . Stability studies at 40 $\pm$ 2º C/ 75$\pm$ 5% RH over a 1 month period revealed that solid dispersions prepared using Glyburide: soluplus (1:3) has shown amorphous nature of drug and found to be stable compared to other solid dispersions.

Table1: Composition of Formulations

Formulation Code	Drug (mg)	Soluplus (mg)	Avicel PH 102(mg)	Croscaramellose sodium(mg)	Aerosil 200 pharma (mg)	Magnesium stearate (mg)	Total capsule content(mg)
PD	5	-	95	-	-	-	100
F1	5	5	90	-	-	-	100
F2	5	2.5	85.5	5	1	1	100
F3	5	5	83	5	1	1	100
F4	5	10	78	5	1	1	100
F5	5	15	73	5	1	1	100
F6	5	20	68	5	1	1	100
F7	5	30	58	5	1	1	100
F8	5	40	48	5	1	1	100

PD=Pure Drug; F1=physical mixture of drug, polymer; From F2 to F8 are the solid dispersions having drug, polymer ratios of F2=1:0.5, F3=1:1, F4=1:2, F5=1:3, F6=1:4, F7=1:6 and F8=1:8.

Table 2: Drug content in solid dispersions

Drug/solid dispersions	% drug content
PD	99
F1	97.1
F2	98.2
F3	97.4
F4	98.09
F5	98.98
F6	98.01
F7	98.67
F8	98.5

Table 3: Solubility Data of different formulations

	Solubility in mcg/Ml								
Ph	**PD**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
1.2	0.6	2.9	4.52	5.8	6.96	9.79	13.25	15.45	15.9
4.5	2.09	10.47	13.52	14.61	17.2	19.84	16.68	21.29	24.8
6.8	3.58	49.4	67.9	89.48	100	122.86	139.49	140.91	169.78
Water	3.97	79.6	99.8	112.25	138.04	147.6	166.81	170.1	190.8
7.5	8.35	101.3	112.25	117	190.62	170.91	170.91	220.2	239.01

Table 4*: In vitro* drug release profile of different solid dispersions

Time(mins)	Cumulative % drug release								
	PD	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5	4.5	7.9	12.73	19.98	28.33	69.87	15.14	13.08	9.637
10	4.8	15.6	19.96	21.68	27.53	75.8	19.62	22.03	19.99
15	6.4	17.5	26.85	28.57	35.45	80.67	24.44	30.29	23.4
30	10.1	18.9	33.73	39.92	63.33	82.8	30.63	30.29	25.47
45	12.7	23.7	46.81	59.2	69.18	89.55	40.27	37.17	32.35
60	13.5	25.5	41.64	66.77	78.81	92.58	43.02	38.2	32.35
90	13.8	26.7	40.96	72.94	86.04	94.4	57.13	38.89	32.7

120	13.9	27.8	48.87	80.01	93.96	97.8	60.23	43.71	33.38
150	14.6	27.8	55.76	87.07	94.65	97.2	62.98	43.02	36.14
180	14.6	35.1	55.76	98.18	98.8	99.8	67.46	49.56	37.17

Table 5. *In vitro* release profile of F5 formulation in different dissolution media

Time(mins)	**cumulative % drug release**				
	pH 1.2 buffer	**pH 4.5 acetate buffer**	**pH 6.8 phosphate buffer**	**water**	**pH 7.5 phosphate buffer**
0	0	0	0	0	0
5	28.3	46.2	54	59.3	69.8
10	27.5	58.5	60	67.4	75.8
15	35.5	61.9	64.6	70.2	80.6
30	63.3	63.5	68.9	86.9	82.8
45	69.2	69.2	72.6	90.2	89.5
60	78.8	78.5	76.5	92.2	92.58
90	82.9	82.6	85.5	95.7	94.4
120	83.1	83.1	89.2	96.8	97.8
150	83.1	87.07	90.3	97.8	97.2
180	85	90.5	94.1	97.9	99.8

Table 6:Invitro release of capsules after stability

Time(min)	**Initial**	**After stability**
0	65.82	0
5	77.8	69
10	84.4	82.6
15	90.58	91.0
30	93.3	91.4
45	96.9	94.2
60	97.74	94.6
90	98.11	96.0
120	98.27	98.2
150	99.8	99.7
180	100.5	100.1

Table 7: Physical parameters after stability

S.No.	**Parameters**	**Capsule formulation**
1	DT (min.sec)	5.15
2	Assay (%) initial	98.98
	Assay (%) after stability	97.81

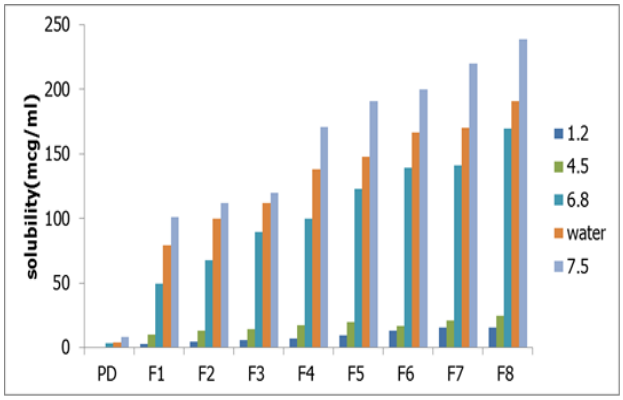

Figure 1. Solubility Data of different solid dispersions

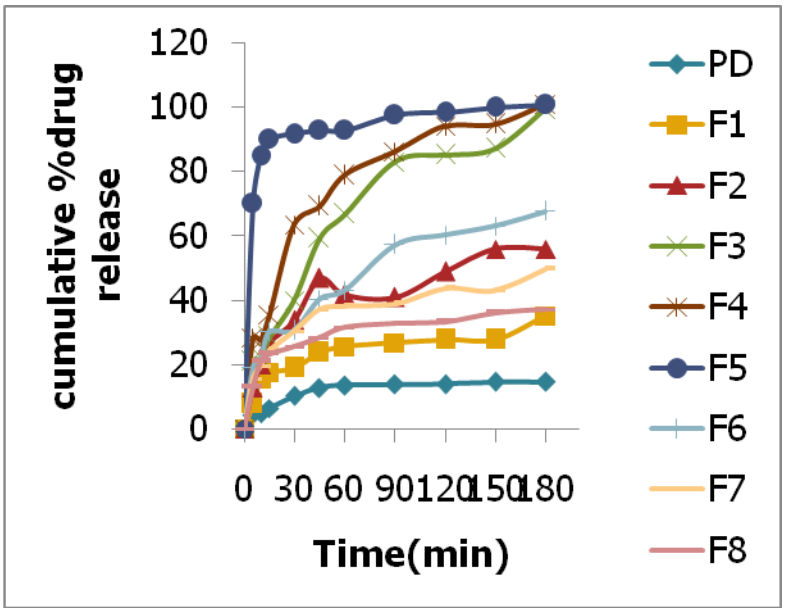

Figure 2. Graph of % drug release of various solid dispersions

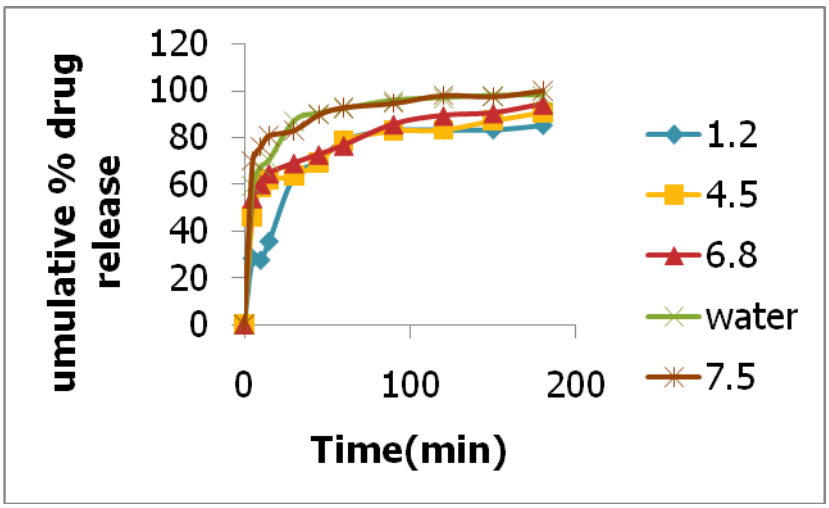

Figure 3. % drug release of F5 formulation in different dissolution media

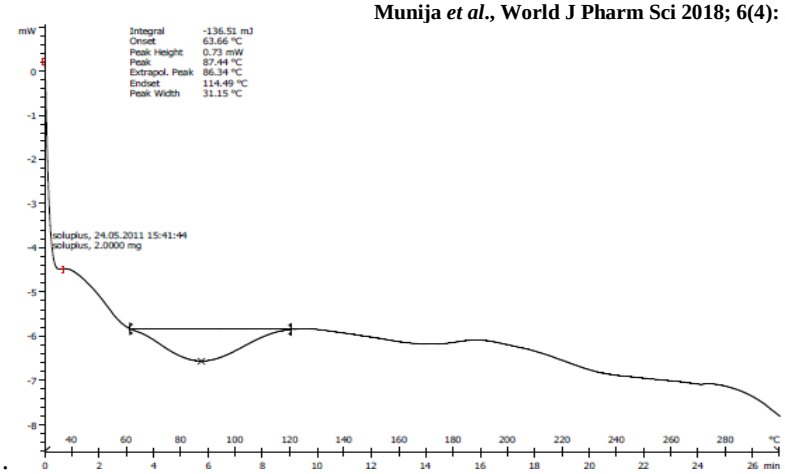

Figure 4: Thermogram of (a) Glyburide and (b) Soluplus

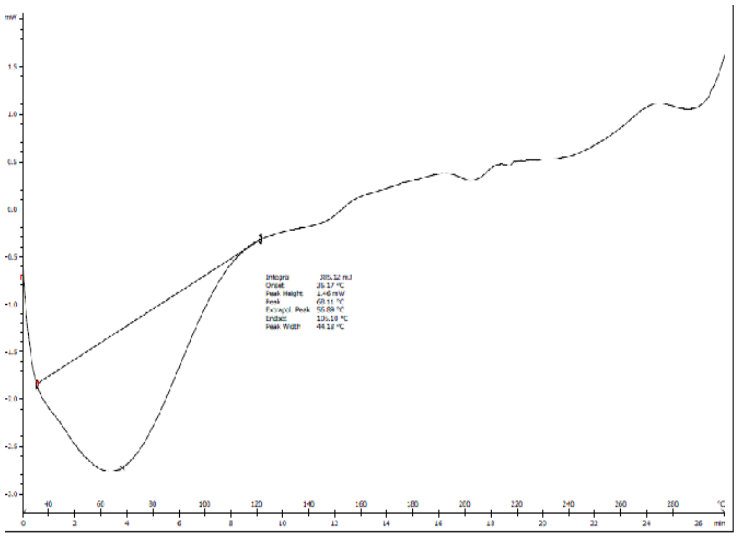

Figure 5: Thermogram of F5 formulation

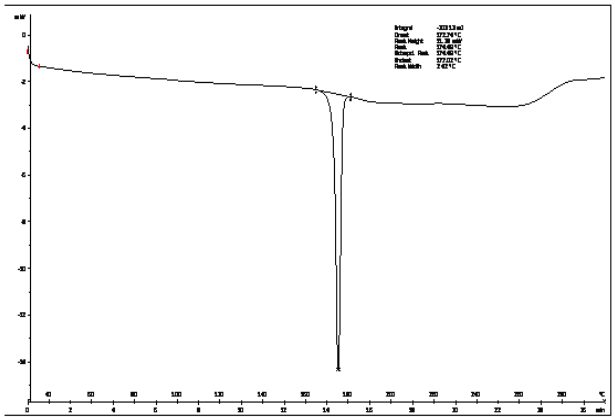

Figure 6. DSC of Glyburide at 1month 40^0C/75% RH open exposure

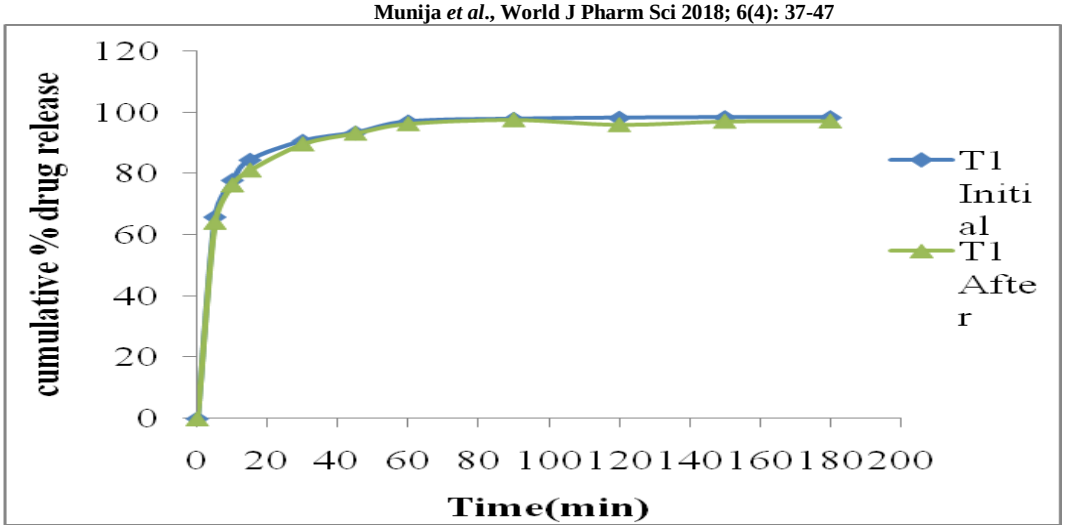

Figure 7. *In-vitro* release of capsules after stability

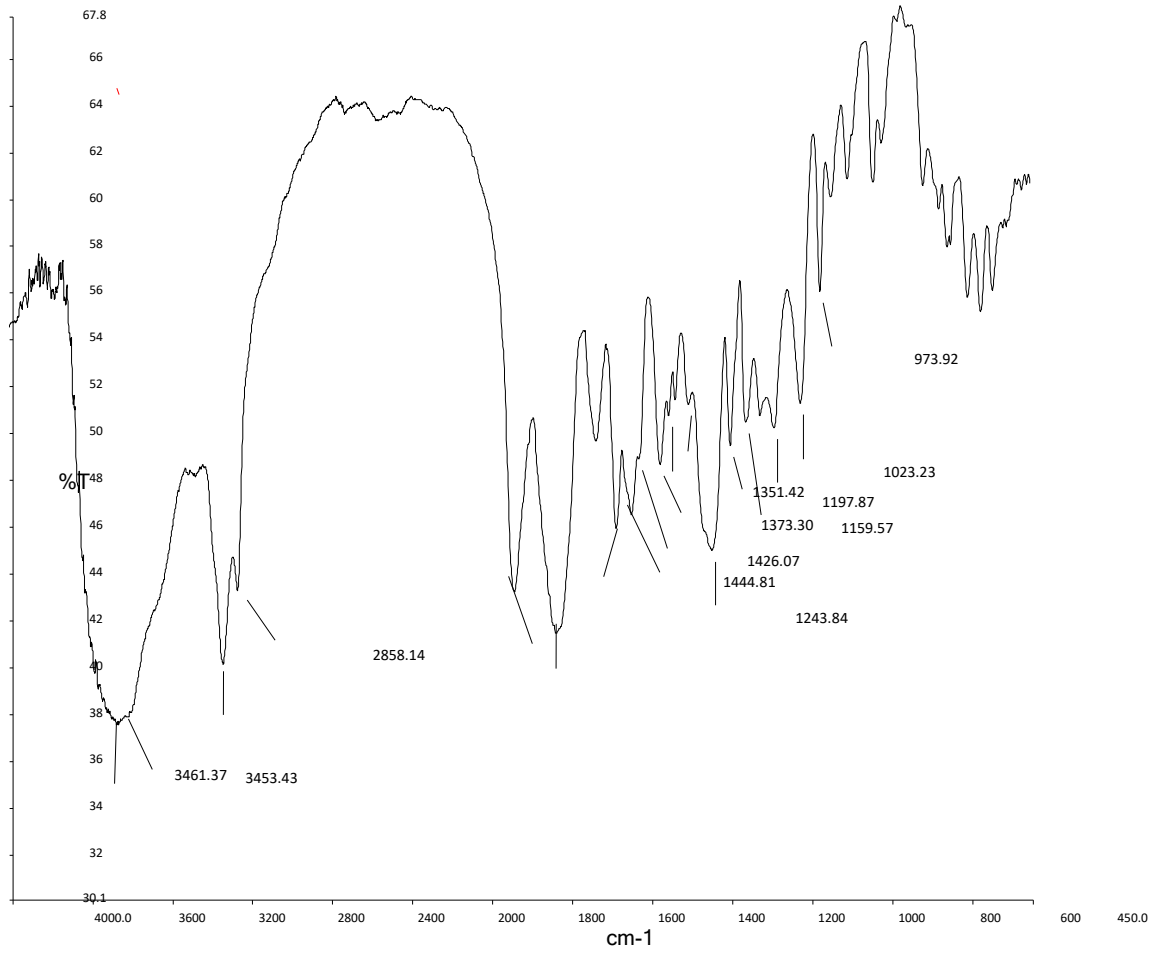

Figure 8: FT-IR of F5 formulation

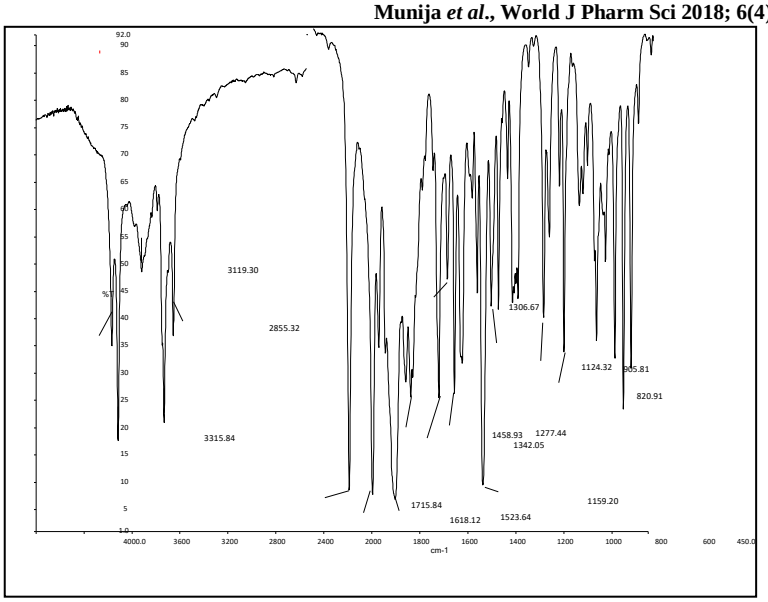

Figure 9: FTIR of Glyburide after 1month 40^0C/75% RH open exposure

REFERENCES

1. Chaudhari P.D., Current trend in solid dispersion techniques, www.pharmainfo.net,2-12,2006.
2. Swarbrick J, Encyclopedia of Pharmaceutical Technology, 3rd Edition, Pg no. (3314-3316-3318-3322-3326-3328.), 2006
3. Shinde A, Solublization of poorly water soluble drugs, *Pharminfo.net*, vol 5 issue 6, 2007
4. Perrett s, Venkatesh G, Enhancing the bioavailability of insoluble drug Compound. http://www.eurand.com/pdf/EURX_Article_technology_2006.pdf
5. W.L. Chiou and S. Riegelman, "Preparation and Dissolution Characteristics of Several Fast-Release Solid Dispersions of Griseofulvin," *J. Pharm. Sci*. 58, 1505-1509 (1969).
6. M. Fernandez et al., "Characterization of Solid Dispersions of Piroxicam/poly-(ethylene glycol) 4000," *Int. J. Pharm*. 84, 197-202 (1992).
7. K. Sekiguchi and N. Obi, "Studies on Absorption of Eutectic Mixture. A Comparison of the Behavior of Eutectic Mixture of Sulfathiazole and that of Ordinary Sulfathiazole in Man," *Chem. Pharm. Bull*. 9, 866-872 (1961).
8. A. Foster, T. Rades and J. Hempenstall, "Selection of Suitable Drug and Excipient Candidates to Prepare Glass Solutions by Melt Extrusion for Immediate Release Oral Formulations," *Pharm. Technol. Eur*. 14(10), 27-37 (2002).
9. H.C. Bulau and J. Ulrich, "Parameters Influencing the Properties of Drop-Formed Pastilles," in J. Ulrich, Ed., CGOM4 (Shaker Verlag, Aachen, Germany, 1997) 123-130
10. Beten DB, Amighi K, Moes AJ. Preparation of controlled-release coevaporates of Dipyridamole by loading neutral pellets in a fluidized-bed coating system. *Pharm Res*. 1995; 12:1269-1272.
11. Ho HO, Shu HL, Tsai T, Sheu MT. The preparation and characterization of solid dispersions on pellets using a fluidized bed system. *Int J Pharm*. 1996; 139: 223-229.19/14.