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Preparation and Evaluation of Fast Release Surface Solid Dispersion of Glibenclamide

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ABSTRACT

Solid Dispersions were prepared by solvent evaporation technique using microcrystalline cellulose, PEG 4000, PEG 6000, PVP-K30 and Gelucire 50/13. Further objective of the project was to develop fast release surface solid dispersion of glibenclamide and compressed at low pressure to form fast-melting pharmaceutical tablet. In this study, we used sodium starch glycolate for mouth dissolving nature. The inherent hygroscopic nature of PEG could decrease the affinity for moisture of effervescent mixtures and can provide a stabilizing effect. The formulations using sodium starch glycolate and surface solid dispersion with Gelucire 50/13, PEG 4000 and 6000 were found to have better release properties. Fast Release tablet of glibenclamide might aid in dissolution due to increase in microenvironmental pH around the granules and saliva.

Keywords: Surface solid dispersion, Glibenclamide, PEG, Gelucire 50/13

BACKGROUND

Fast dissolving surface solid dispersions are disintegrating or dissolve rapidly in the saliva without the need for water. Fast dissolving surface solid dispersions are useful in patients such as pediatric, geriatric, Bedridden or developmentally disabled who face difficulty in the swallowing of conventional tablet or capsules and liquid orals leading to ineffective therapy(Bhowmik *et al*,2009).

Glibenclamide is a popular anti-diabetic drug, belonging to class of sulfonylureas. Glibenclamide is widely used for treating type II diabetes. So, in the present work an attempt was made to formulate the fast dissolving surface solid dispersions using superdisintegrants adopting direct compression technique(Jyoti *et al* ,2010)

Rationale behind the selection of drug

- Glibenclamide belongs to class II drug in BCS classification i.e. low solubility and high permeability.

- One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration.
- The solubility of Glibenclamide in aqueous medium is very low i.e. 4 mg/l in water.
- Biological half-life of the Glibenclamide 1.4-1.8 hours (unchanged drug only); 10 hours (metabolites included), results into poor bioavailability after oral administration and duration of effect is 12-24 hours.
- Conjugation of Glibenclamide with the different types of carriers is used to increase its solubility and dissolution rate.

Criteria for fast dissolving drug delivery system: Process involved to improve the solubility of poorly soluble drugs (Glibenclamide) (Figure 1).

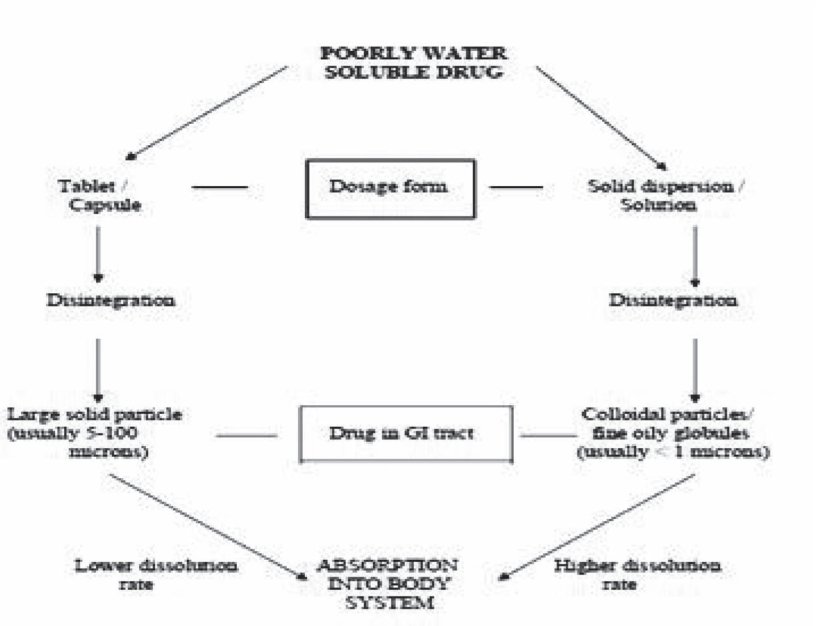

Figure 1: Comparison of absorption enhancement of poorly soluble drug by solid dispersion with conventional tablet dosage form

Solid dispersion

Solid dispersion technique has been used for a wide variety of poorly aqueous soluble drugs such as nimesulide, ketoprofen, aceclofenac, glibenclamide etc using various hydrophillic carriers like microcrystalline cellulose (avicel PH102), polyethylene glycol, polyvinylpyrrolidone, hydroxypropylmethyl cellulose, sugar, mannitol etc.

Solid Dispersion is dispersion of one or more active ingredients in an inert carrier or matrix at a solid state prepared by solvent evaporation method. (Figure 2)

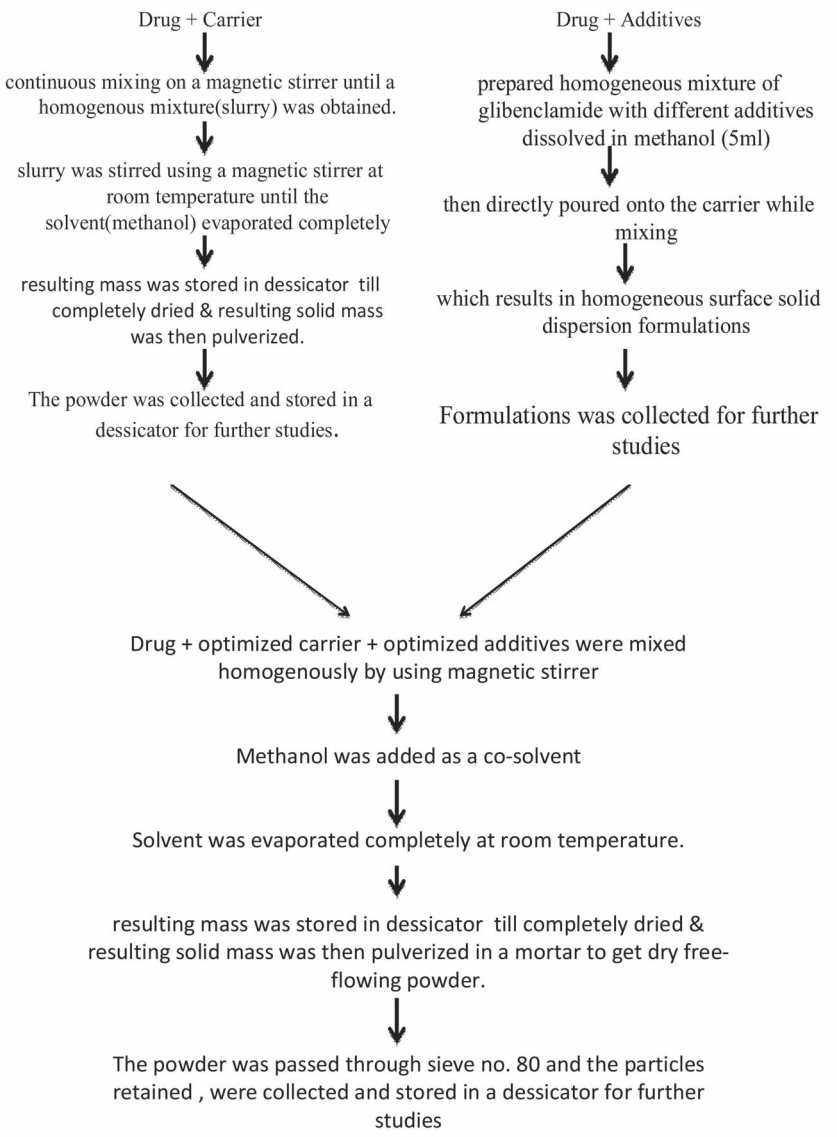

Figure 2: Flow chart to process solid dispersion technique

Advantages of solid dispersion

- Solid dispersion is more acceptable technique for improving solubility than other techniques due to its applicability, effectiveness and ease of production.
- Transformation of the liquid form of the drug into a solid from. For e.g: Clofibrate and benzylbenzoate can be incorporated into PEG 6000 to give a solid.

- Salt formation technique is only applicable for solubility enhancement of weakly acidic or basic drugs and not effective for neutral drugs.
- Solubilization technique is more indicative for preparation of liquid formulation but not the solid dosage forms so lack patient acceptability.

Disadvantages of solid dispersion

- During storage, there can be a change in its state from amorphous state to crystalline and the moisture can also enhance drug crystallinity by decreasing drug mobility.
- By absorbing moisture, phase separation, crystal growth or a change from metastable crystalline form to stable form can take place which can lead to reduction in drug solubility.

Problem Statement

- One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Hence Conjugation of Glibenclamide with the different types of carriers is used to increase its solubility and dissolution rate.
- This drug has been incorporated in the fast dissolving Surface solid dispersion with help of SD and then delivered to oral route.
- From the above points, it could be stated that Glibenclamide is suitable drug to formulate into fast dissolving Surface solid dispersion and may provide a better therapeutic profile than that of conventional dosage form

The Surface Solid Dispersions Should

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasant mouth feel.
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.
- Allow the manufacture of the Surface solid dispersion using conventional processing and packaging equipments at low cost.

Limitations of Fast Dissolving Surface solid dispersions

- The Surface solid dispersions usually have insufficient mechanical strength. Hence, careful handling is required.

- The Surface solid dispersions may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

The basic approach in development of fast release tablet(Gupta *et al*,2010) is the use of superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel, explotab), polyvinylpyrollidone (polyplasdone) etc, which provide instantaneous disintegration of surface solid dispersion after putting on tongue, their by release the drug in saliva(EIbary *et al*,2011) The main possibilities for improving dissolution according to this analysis are to increase the surface area available for dissolution by decreasing the particle size of the solid compound(Deshmukh *et al*,2011).

Objective: The objective of the current study is to design oral fast-release of a poorly soluble drug and to optimize the drug dissolution profile by modifying the carrier concentration. Fast release Surface solid dispersions will be prepared by using direct compression method by varying the concentrations of drug, polymers and super-disintegrants. The dissolution rate of the drug from the dosage form can be markedly enhanced by altering the polymer and superdisintegrant concentrations. Sodium starch glycollate together with crosscarmellose sodium will be used as superdisintegrants. The formulations will be evaluated for Disintegration time, wetting time, hardness, friability, Carr's index, Haussner's ratio and in vitro

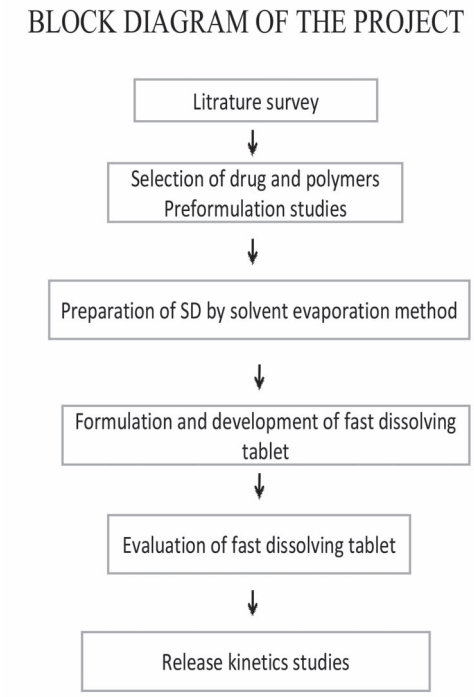

Figure 3: Block diagram of process done to complete project

dissolution test as per USP. (Figure 3)

MATERIALS AND METHODS

Glibenclamide was procured as gift sample from Prudence Pharma Chem (Ankleshwar-393002, India). Gelucire 50/13 was procured as gift sample from Gattefosse (St.Priest, Cedex, France). All Chemical were of analytical grade and Purchased from CDH, Delhi, India.

1. Preparation of Solid Dispersions

The solid dispersions of glibenclamide were prepared by common solvent evaporation method (Vallori *et al*,2004). Microcrystalline cellulose, lactose, and starch were selected as carriers on the basis of their properties for the preparation of solid dispersions as inTable 1. The release of drug from the carrier material depends on hydrophilicity, particle size, porosity and effective surface area of the carrier, so that the surface area available for the surface adsorption of the drug enhances resulting into better release rate for the drug.

Table 1: Formula of drug–carrier (1:19) ratio and their dissolution efficiency (%) of SDs:

Formula No.	Drug : carrier(1:19)	Dissolution efficiency(DE%)
Pure GLB	-	13.78+0.07
SD_1	Microcrystalline cellulose(MCC)	53.82+1.26
SD_2	LACTOSE	45.07+0.86
SD_3	STARCH	49.12+0.48

Preparation steps

- The SDs of Glibenclamide in different carriers like microcrystalline cellulose (Avicel PH102), lactose, starch was prepared in a 1:19 drug to carrier ratio using solvent evaporation technique.
- The calculated amount of drug (5 mg) was dissolved in methanol (5 ml). This solution was added to each carrier with continuous mixing on a magnetic stirrer until a homogenous mixture (slurry) was obtained.
- The obtained slurry was stirred using a magnetic stirrer at room temperature until the solvent (methanol) evaporated completely.
- The resulting mass was stored in dessicator containing $CaCl_2$ and till completely dry. The resulting solid mass was then pulverized in a mortar to get dry free-flowing powder.
- The powder was passed through a sieve no. 60 (50 µm) to sieve no. 80 (180 µm) and the particles retained on a sieve no. 80 (180 µm) was collected and stored in a dessicator for further studies.

2. Preparation of surface solid dispersions of Glibenclamide with different excipients

Based on the dissolution parameters listed in Table-1, microcrystalline cellulose was selected as a optimized carrier due to its maximum dissolution efficiency for glibenclamide in comparision to other carriers. From this optimized solid dispersion various surface solid dispersion were made with different additives.

Now, the surface solid dispersions were prepared that were used to reduce the agglomeration of the drug by increasing its surface area in a way that can help in increasing the dissolution rate. Polymers used for the preparation of surface solid dispersions were PEG 4000(Larson *et al*,2009) PEG 6000(Marzia *et al*, 2007), PVP K-30 and Gelucire-50/13(Upadhyay and Pandit,2012) in the ratio of 1:1, 1:2 and 1:4 w/w respectively (Table 2 and 3).

Table 2: Different ratio of Surface Solid Dispersions with Different Excipients

Batch	Carrier	Excipients	D:E Ratio
A	GLB: MCC (1:19)	PEG 4000	1:1 1:2 1:4
B	GLB: MCC (1:19)	PEG 6000	1:1 1:2 1:4
C	GLB: MCC (1:19)	PVP K-30	1:1 1:2 1:4
D	GLB: MCC (1:19)	G-50	1:1 1:2 1:4
E	GLB: MCC (1:19)	i)PEG 6000:G-5050 ii)PEG 4000: G-50 iii)PVP K-30:G-	1:2:10 1:2:10 1:2:10

Preparation steps

- The additives used were mainly polyethylene glycols (PEG4000 and PEG 6000), polyvinyl pyrrolidones (PVP K-30), and Gelucire 50/13.
- Each additive was first homogeneously mixed with the drug in ratios of 1:1, 1:2, and 1:4 w/w, respectively.
- The prepared homogeneous mixture of glibenclamide with different additives was individually dissolved in methanol (5ml) and then directly poured onto the carrier while mixing which results in 12 homogeneous surface solid dispersion formulations.

Table 3: Composition of different formulations (SSDs) with different polymers:

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	V1	V2	V3
Glibenclamide	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
(PEG 4000)	5	10	20											10	
(PEG 6000)				5	10	20							10		
(PVP K-30)							5	10	20						10
Gellucire50/13										5	10	20	50	50	50
MCC	95	95	95	95	95	95	95	95	95	95	95	95	95	95	95

Preparation of fast dissolving tablet by Direct compression method

The formulation optimised were FDTf2, FDTf6, FDTf9 and FDTv3 further formulated by direct compression method on single punch tablet machine as fast dissolving tablet (Table 5) in Industrial laboratory of Department of Pharmaceutics, IFTM.

RESULTS AND DISCUSSION

In-vitro drug release study

From the table 1, based on the dissolution parameters measured, MCC was found to be most effective as carrier in enhancing the dissolution rate of Glibenclamide having the maximum dissolution efficiency (%DE) of 53.82 as compared to others (lactose and starch). So it was selected as the carrier of choice for further studies.

From the Release kinetic data of formulation (Table 4), the regression correlation (r^2 values) in various kinetic models such as zero order, first order, Higuchi and Korsmeyer peppa's model, the best dissolution profile was of $FDT_{F-2,}$ $FDT_{F-6,}$ $FDT_{F-9,}$ and FDT_{v-3} as in Table 4, it was observed that % drug release were found to be 78.99, 76.40, 55.68 and 89.35% respectively. Fig 4a and 4b respectively. It was observed that formulation FDT_{v-3} containing MCC, Gelucire 50/13, PVP K-30 having more % drug release as compare to other combinations (MCC-PEG-4000 and MCC-PEG-6000). This may be due to more supporting capacity of MCC with G-50 and PVP K-30, to disintegration and dissolution as compared to others.

Table 4: Release Kinetic data for different formulations:

Formulation Code	Zero-order	First-order	Higuchi	Korsmeyer peppa's
F1	0.927	0.976	0.988	0.961
F2	0.938	0.860	0.995	0.958
F3	0.970	0.988	0.895	0.865
F4	0.983	0.971	0.822	0.964
F5	0.991	0.979	0.914	0.998
F6	0.993	0.848	0.915	0.994
F7	0.982	0.910	0.843	0.991
F8	0.989	0.980	0.903	0.764
F9	0.984	0.898	0.917	0.988
F10	0.988	0.979	0.876	0.822
F11	0.992	0.978	0.880	0.835
F12	0.993	0.930	0.940	0.667
V1	0.994	0.956	0.894	0.958
V2	0.987	0.956	0.829	0.850
V3	0.990	0.989	0.947	0.686

In the present work an attempt was made to prepare a fast dissolving surface solid dispersion of Glibenclamide using microcrystalline cellulose (avicel PH 102) alone

Table 5: Formula of the fast dissolving tablet (FDT) of surface solid dispersion (in mg):

Formulation composition	FDT_{f-2}	FDT_{f-6}	FDT_{f-9}	FDT_{v-3}
Glibenclamide	05	05	05	05
MCC	95	95	95	95
Gellucire 50/13[14]	-	-	50	50
PVP K-30	-	-	20	10
PEG 4000	10	-	-	-
PEG 6000[15]	-	20	-	-
Sodium Starch Glycolate [20]	14	13	14	13
Talc	05	05	05	05
Magnesium stearate	05	03	03	03
Sodium saccharin	1.5	1.5	1.5	1.5

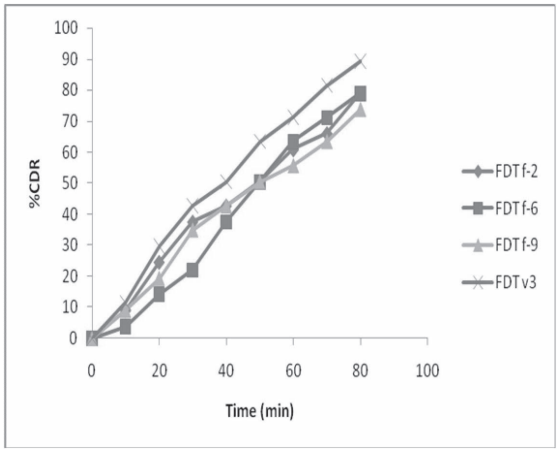

Figure 4 (a): *in vitro* release profile of optimized batches of surface solid dispersion formulation

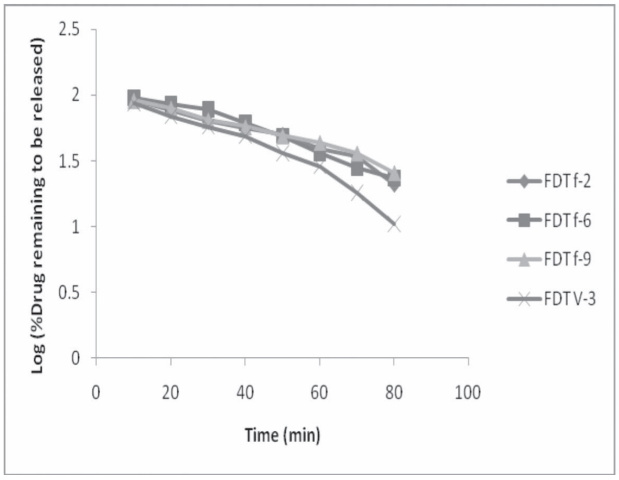

Figure 4 (b): First order *in vitro* release profile of optimized surface solid dispersions

Table 6: Evaluation parameters of FDTs prepared by direct compression:

Formulation code	Disintegration time (sec)	Wetting time (sec)	Hardness (kg/cm2)	Friability (% w/w)	Carr's index	Haussner's ratio	Dissolution test USP
FDT f-2	56±2.5	48±3.0	3.56±0.230	0.6522	9.66	1.10	H" 79%
FDT f-6	58±3.5	52±4.5	2.98±0.210	0.6431	11.71	1.13	H" 76%
FDT f-9	58±2.5	52±4.5	3.36±0.174	0.7411	10.93	1.12	H" 75%
FDT v-3	49±3.0	42±2.5	2.38±0.135	0.4858	13.76	1.15	H" 88%

and in combination with polyethylene glycol 4000 (PEG 4000), Polyethylene glycol 6000 (PEG 6000), polyvinylpyrrolidone K-30 (PVP K-30) and gelucire 50/13 as copolymers by solid dispersion technique (an approach for improving the solubility and bioavailability of drug) and various evaluation parameters were assessed, with a view to obtain fast release for oral delivery. From the dissolution data of all formulations developed, solubility of Glibenclamide (a poorly water soluble drug) was enhanced by the surface solid dispersion technique using MCC as a carrier with PVP K-30, and gelucire 50/13 by the solvent evaporation method. This effect may be due to fine particle size of Glibenclamide adsorbed over MCC, resulting in a higher surface area of drug exposed to the dissolution media and improved wettability of drug particles(Janssens *et al*, 2007). The fast dissolving surface solid dispersions of Glibenclamide were developed by using solid dispersions of Glibenclamide with MCC as a carrier, PVP K-30 and gelucire along with superdisintegrant(Chaulang *et al* ,2009). Sodium starch glycolate(Shah *et al* 2010) was used successfully to prepare fast dissolving tablet by direct compression method having ideal characteristics of DT and % drug release. Thus on the basis of above parameters we can conclude that the formulation FDT_{v-3} is the best formulation that fulfills our objective of formulating fast dissolving surface solid dispersion of Glibenclamide.

CONCLUSION

Fast dissolving surface solid dispersions of glibenclamide based on solvent evaporation technique were successfully prepared and optimized preparation was further successfully formulated as fast dissolving tablet by direct compression technique.

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REFERENCES

Bhowmik Debjit *et al*, 2009. Fast Dissolving Tablet: An Overview, *Journal of Chemical and Pharmaceutical Research,* **1**(1):163-177.

Chaulang Ganesh *et al*, 2009. Formulation and Evaluation of Solid Dispersions of Furosemide in Sodium Starch Glycolate, *Tropical Journal of Pharmaceutical Research*, February **8**(1): 43-51.

Christian Leuner., Jennifer Dressmann., 2000. Improving drug solubility for oral delivery using solid dispersions. *European Journal of Pharmaceutics and Biopharmaceutics,* **50:**47-48.

Deshmukh Keshav Ram *et al*, 2011. A review on mouth dissolving tablet techniques, *International Journal Of Research In Ayurveda & Pharmacy*, **2**(1): 66-74.

Devarajan, Padma V and Gore S.P. 2000. Melt-in-mouth Tablets- innovative oral drug delivery systems. *Express Pharma Pulse*. **7**(1):16-18.

Elbary Abd A.A. *et.al*,2011. In vitro and in vivo Evaluation of Glibenclamide using Surface

Solid Dispersion (SSD) Approach, *British Journal of Pharmacology and Toxicology*, **2**(1): 51-62.

Gare Kani., H.A., Sadeghi., F., Badiee., A., Mostafa, S.A. and Rajabisiahboomi, A.R. 2001. Crystal habit modifications of Ibuprofen and their Physicochemical Characteristics, *Drug Development and Industrial Pharmacy,* **27**(8):803-809.

Gupta A. *et al*, 2010. Recent Trends of Fast Dissolving tablet - An Overview of Formulation Technology, *International Journal of Pharmaceutical & Biological Archives*, **1**(1):1–10.

Janssens Sandrien *et al*, 2007. The use of a new hydrophilic polymer, Kollicoat IR®, in the formulation of solid dispersions of Itraconazole, *European Journal Of Pharmaceutical Sciences,* **30:**288–294.

Jyothi Jeevana. B *et al*, 2010. Development of Fast Dissolving Tablet of Glibenclamide Using Crospovidone and its Kneading Mixture, *Indian J.Pharm. Educ.* Res. **44**(4).

Larson, A., Unga,J., Tajarobi,F., Norder O. and Frenning G.,. 2009. Relating solubility data of parabens in liquid PEG 400 to the behaviour of PEG 4000- parabens solid dispersions. *Eur J. Pharm Biopharm*., **78**: 260–268.

Marzia Cirri , Francesca Maestrelli ,Giovanna Corti, Paola Mura and Maurizio Valleri,2007. Fast-Dissolving tablet of Glyburide Based on Ternary Solid Dispersions with PEG 6000 and Surfactants, *Drug Delivery*, **14** (4) : 247 – 255.

Mudgal S.S. et al., Formulation of glibenclamide solid dispersions by solvent evaporation technique, *Journal of Chemical and Pharmaceutical Research*, 2012, 4(1); 353-359.

Owusu-Ababio G, Ebube N.K, Reams R and Habib M., 1998. Comparative dissolution studies for mefenamic acid-polyethylene glycol solid dispersion systems and tablet; *Pharm Dev Technol*., **3**(3):405-12.

Park Kinam *et al*, 2008. Material properties for making fast dissolving tablet by a compression method, *Journal of Materials Chemistry*, **18:**3527–3535.

Shah Dhiren P. *et al*, 2010. Influence of various excipients on quality control parameters of aceclofenac tablet containing sodium starch glycolate (SSG), *An International Journal of Pharmaceutical Sciences*, **1(**1): 113-121.

Tiwari Ruchi *et al*,2009. Solid Dispersions: An Overview To Modify Bioavailability Of Poorly Water Soluble Drugs, *International Journal of PharmTech Research*, **1**(4): 1338-1349.

Upadhyay Prashant and Pandit, Jayanta Kumar, 2012.Formulation of Fast-Release Gastroretentive Solid Dispersion of Glibenclamide with Gelucire 50/13, *Tropical Journal of Pharmaceutical Research*, **13**(3):361-369

Vallori M, Mura P, Maestrelli F, Cirri M and Ballerini R.,2004. Development and evaluation of glyburide fast dissolving tablet using solid dispersion technique; *Drug Dev Ind Pharm.*, 30(5): 525-34.

Verma M.M and Pandit J.K., Dissolution , 2005. Solubility, XRD and DSC studies on Flurbiprofen-Nicotinamide Solid Dispersions, *Drug Development and Industrial Pharmacy*; **31**: 417-423.