IJPSR (2012), Vol. 3, Issue 12 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 25 August, 2012; received in revised form 05 November, 2012; accepted 19 November, 2012

FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLET OF GLIPIZIDE BY SOLID DISPERSION

Yogesh L. Jadhav* and Parashar Bharat

Department of Pharmaceutics, Manav Bharti University , Solan, Himachal Pradesh, India

Keywords:
Glipizide, CCS, solid dispersion, Superdisintegrants, Mouth dissolving tablet

Correspondence to Author:

Yogesh L. Jadhav

Department of Pharmaceutics, Manav Bharti University, Solan, Himachal Pradesh, India

E-mail: jadhav.yogesh530@gmail.com

ABSTRACT

The aim of the present research work was to enhance the solubility of Glipizide by solid dispersion method and to formulate a mouth dissolving tablet. Drugs are more frequently taken by oral administration. The solubility of Glipizide enhanced with different ratios of CCS by the kneading method .In-vitro release profile of solid dispersion obtained in Ph 6.8 phosphate buffer indicate that 100% drug release found within 20 min. These solid dispersions were directly compressed into tablets using sodium starch glycolate, crosspovidone and pregelatinised starch in different concentrations as a superdisintegrants. The prepared tablets containing the solid dispersion of Glipizide had sufficient strength of 1.5-2 kg/cm^2. The disintegrated in the oral cavity within 21 sec. contain crosspovidone (5%) as superdisintegrant.

INTRODUCTION: An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desire therapeutics concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment. Drugs are more frequently taken by oral administration. It is considered most natural, uncomplicated, convenient, safe means of administering drugs, greater flexibility in dosage form design, ease of production and low cost.

Since the introduction of mouth dissolving tablet (MDT) in 1980s, it has become one of the fastest growing segments of oral drug delivery. About one-third of the world's population mainly the geriatric and pediatric patient have swallowing difficulties and for such a group, MDT is emerged as an attractive alternative. Mouth dissolving tablets are characterized by hydrophilic matrix which allows rapid disintegration of the tablets when comes in contact with saliva and disintegrates/dissolves/disperses in saliva within few seconds, without the need of water, so, alleviating the problem of swallowing or chewing.

Techniques that have commonly been used to improve dissolution and bioavailability of poorly water-soluble drugs, in general, include micronization, the use of surfactant and the formation of solid dispersion (SD) [1].

The SD approach has been widely and successfully applied to improve the solubility, dissolution rates, and consequently, the bioavailability of poorly water soluble drugs.

A number of drugs have been shown to improve their dissolution character, which converted to SDs. To date, some reports on the formulation of these systems have appeared [2-5].

QUICK RESPONSE CODE

IJPSR: ICV (2011)- 5.07

Website: www.ijpsr.com

An obstacle of SD technology in pharmaceutical product development is that a large amount of carrier, *i.e.*, more than 50 to 80% wt/wt, was required to achieve the desired dissolution.

This high percentage of carrier causes consistency of product performance at the time of manufacturing. This is a major consideration in that the number of market products arising from this approach has been less than expected.[6-9]

With regard to carriers for SD formulations, many carriers such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), hydroxypropylmethyl cellulose (HPMC), hydroxypropylcellulose, hydroxy propyl methylcellulose phthalate (HPMCP), Gelucires, Eudragits® and chitosans have been reported to improve the solubility and bioavailability of poorly water soluble drugs [10-12].

Among the various carriers used in the formation PEG is most commonly used. CCS are semicrystalline polymers that have been used extensively in the SDs preparation for their solubilizing and surface active properties [13-14]. Reported enhancement of solubility, dissolution and bioavailability of Glipizide (GLP) in SD systems using CCS as a hydrophilic polymer carrier. The non-ionic surfactant Tween 80 was used as the third component in the ternary SD system [15].

Mouth dissolving tablets of itraconazole [16], valdecoxib [17], diazepam [18], glyburide [19], clonazepam [20] and rofecoxib [15] were prepared using SD technique. Glipizide is a class-II antidiabetic drug which is purely insoluble in water. Rate of bioavailability of GLP is highly variable due to their low aqueous solubility.

One of the major problems with drug is its very low solubility in biological fluids and its short biological half-life of 2 h [21]. Thus, these two factors act as the rate determining step or the barrier to rapid onset of action upon oral ingestion of GLP.

The aim of the present study was to prepare and evaluate the SD formulation of GLP. Moreover, it was also attempted for the incorporation of optimized SD formulation for the development of mouth dissolving tablets of GLP.

MATERIALS AND METHODS: Glipizide was obtained as gift sample from JCPL PHARMA, Jalgaon. PEG, β-Cyclodextrin and Cross carmellose sodium (CCS) was procured from JCPL PHARMA. All other chemicals used were of analytical grade.

Construction of Standard Calibration Curve: Glipizide can be estimated spectrophotometrically at 275.0 nm as it obeys Beer-Lambert's law. 10 ml of stock solution was made to 100 ml with pH 6.8 phosphate buffer, thus giving a concentration of 100 µg/ml. Aliquot of standard drug solution ranging from 0.2 to 1 ml were transferred in to 10 ml volumetric flask and were diluted up to the mark with pH 6.8 phosphate buffer. Thus the final concentration ranges from 2-10 µg/ml. Absorbance of each solution was measured at 276 nm against pH 6.8 phosphate buffer as a blank. A plot of concentrations of drug versus absorbance was plotted. The linear regression analysis was done on absorbance data points and given in **Figure 1.**

Solubility Determination: The apparent solubility of Glipizide was determined in distilled water and buffer of pH 6.8 at 37 °C. Each preparation equivalent to 10 mg was added to 10 ml of solvent in glass vials with rubber closers. Then the vials were kept on a shaker incubator maintained at 37±0.5°C for 24 h.

After shaking, the vials were kept in an incubator at 37±0.5°C for equilibrium for 12 hr. The solution was then filtered through 0.45 µm millipore filter and the filtrate was assayed spectrophotometrically at 275 nm. The results are given in **Table 1 & 2.**

Solid Dispersions Formulation by Kneading Method [22]: In this method weighed quantity of Glipizide CCS was placed in a mortar and then the mixture was kneaded with 1.5 times their amount of either ethanol 70 % v/v or water for 20 minutes. The kneaded mixture was dried in oven at 40°C until it reached uniform weight and then pulverized and screened through 100 meshes. Solid dispersion formulation given in **table 3**.

Evaluation of Solid Dispersions:

Fourier Transform Infra Red Spectroscopy (FTIR): The solid dispersions were subjected to fourier transform infra red (FTIR) studies to check drug polymer interaction using FTIR (Shimadzu 8400 S).

The potassium bromide (KBr) disk method was used for preparation of sample. **Figure 2, 3 and 4** shows the infrared spectra of Glipizide, CCS, and Glipizide-CCS SD respectively. The spectrum was compared with the infrared spectra of plain drug and polymer and checked for the drug-polymer interaction.

***In vitro* Dissolution Rate Study** [23]**:** Dissolution rates from different solid dispersions were determined in 900 ml of pH 6.8 buffer containing 2 % SLS at 37 °C with a stirrer rotation speed of 50 rpm using the USP dissolution test apparatus employing a paddle stirrer (method – II). A 5 ml aliquot of dissolution medium was withdrawn at 5, 10, 15, 30, 45, 60, 90, 105, 120 min with a pipette. The samples were suitably diluted and assayed spectrophotometrically at 275 nm. Each dissolution rate test was repeated 3 times. Results are reported in **Table 4, Figure 5** shows the dissolution profiles of solid dispersions.

Tablet Formulation: Mouth Dissolving Tablets of Glipizide:CCS solid dispersions were prepared using direct compression method after incorporating different disintegrants like crosspovidone, SSG, Pre-gelatinized starch and microcrystalline cellulose (MCC) in different concentrations.09 batches of tablets were prepared for Glipizide:CCS solid dispersions. The methods of preparation, amount of solid dispersions equivalent to drug, and other tabletting excipients were kept constant to avoid the influence of these on the results.

Solid dispersions and mannitol were mixed thoroughly in a glass mortar using a pestle. Disintegrants were mixed in the powder mixture, finally the talc and magnesium stearate were added as lubricants. Tablets of Glipizide: CCS were prepared using 1mm round flat-faced punch of rotary tablet machine (Cadmach, Ahmadabad India). Compression force was kept constant for all formulations. The composition of the tablet is as shown in **Table 5**.

Precompression parameter:

a) Angle of Repose [25]**:** The angle of repose was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of a funnel was adjusted in such a way that its tip just touches the apex of the heap of the powder. The powder was allowed to flow through funnel freely on to the surface. The diameter of the powder heap was measured and angle of repose was calculated using following equation.

$$\tan(\theta) = h/r ;$$

h = Height of powder heap, r = Radius of powder heap

Results of angle of repose are given in **Table 6**.

b) Moisture Sorption Capacity [25]**:** Moisture sorption study was performed using programmable environmental test chamber (Remi Labs, Mumbai) One gram of powdered blend was taken in a petri dish and spread uniformly. Then it was kept in programmable environmental test chamber 37 ± 1 °C and 100 % relative humidity for two days. The moisture sorption was calculated by recording weight difference of the sample before and after exposure to programmable environmental test chamber.

c) Hydration Capacity (H.C.) [25]**:** Powdered blend was taken in the 15 ml tarred centrifuge tube. Then 10 ml of distilled water was added to it and allowed to centrifuge for 10 minutes. After the centrifugation process the tarred centrifuge tube was taken out and inverted to remove the supernatant. The decanted tube then weighed on digital balance (shimadzu) and the hydration capacity was calculated using following equation.

H.C. = Weight of hydrate sample/ Weight of dry sample.

d) Density [24]**:** The loose bulk density (LBD) and tapped bulk density (TBD) of powder blend were determined. Powdered (2 gm) was poured into calibrated measuring cylinder (10 ml) and noted initial volume. Then the cylinder was allowed to fall under its own weight onto the hard surface from the height of 2.5 cm at 2 second intervals. The tapping was then continued until no further change in volume was noted. LBD and TBD were calculated using following equation.

LBD = Weight of the powder/ Volume of the packing.

TBD = Weight of the powder / Tapped volume of the packing.

e) Compressibility: Compressibility Index (Carr's Index) was determined by using following equation.

Carr's Index (%) = [(TBD-LBD) X 100]/ TBD

Results of compressibility index are given in **Table 6.**

Evaluation of the Formulated Tablets:

Weight Variation, Drug Content, Friability And Hardness: Tablet weight variation, drug content uniformity, and friability were measured using the USP methods and criteria. Drug content was analyzed using a UV spectrophotometer (Shimadzu, UV-1700) at λ_{max} 275 nm. Tablet friability was measured using friability tester (Roche friabilator). Hardness of tablet was measured by Monsanto hardness tester. Weight variation, drug content and hardness of tablet were representing as mean ± SD. The data is shown in **Table 7**.

Wetting Time [24]**:** The method reported by Mutasem was followed to measure tablet-wetting time. A piece of tissue paper folded twice was placed in a small petri dish (ID 6.5cm) containing 6ml of pH 6.8 buffer (simulated saliva fluid). A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each were performed.

In Vivo **Disintegration Time** [26]**:** Disintegration test was performed using USP apparatus. pH 6.8 buffer was used as media. Time required for complete disintegration of tablet was recorded.

In Vitro **Release Profile of Formulated Tablets:** Dissolution test of tablets was performed using buffer pH 6.8 and with USP dissolution type II apparatus at 50 rpm and 37 ± 0.5 °C temperatures. Test sample (5 ml) was withdrawn at particular time interval and replaced with fresh dissolution media maintained at 37±0.5 °C. The test sample was filtered (membrane filter, 0.45 µm) and analyzed using UV spectrophotometer at λ_{max} 275 nm for Glipizide Mouth Dissolving tablets. The data is shown in Table 8

RESULT AND DISCUSSION:

Solubility Determination:

TABLE 1: SOLUBILITY PROFILE OF GLIPIZIDE & ITS DISPERSION IN WATER

Batch code	Absorbance	Concentration (µg/ml)
GLP	0.518	4.46
PEG 1	1.379	11.88
PEG 2	1.385	11.93
PEG 3	1.469	12.66
PEG 4	1.598	13.51
B – CD 1	2.332	20.10
B – CD 2	2.302	19.84
B – CD 3	2.274	19.60
B – CD 4	2.215	19.09
CCS 1	2.378	20.5
CCS 2	2.378	20.5
CCS 3	1.410	9.82
CCS 4	1.514	13.05

TABLE 2: SOLUBILITY PROFILE OF GLIPIZIDE & ITS DISPERSION IN PHOSPHATE BUFFER (pH 6.8)

Batch code	Absorbance	Concentration (µg/ml)
GLP	1.175	10.12
PEG 1	1.402	12.08
PEG 2	1.194	10.29
PEG 3	2.306	19.87
PEG 4	2.317	19.97
B – CD 1	2.470	21.29
B – CD 2	2.470	21.29
B – CD 3	2.154	18.66
B – CD 4	2.198	18.94
CCS 1	**2.496**	**21.51**
CCS 2	2.470	21.29
CCS 3	2.238	19.29
CCS 4	2.189	18.94

Solid Dispersions Formulation By Kneading Method:

TABLE 3: SOLID DISPERSIONS FORMULATION

Formulations	Method of Preparation	Content (mg)			
		Drug	CCS	PEG 4000	β – CD
C1	**Kneading method**	**100**	**100**	-	-
C2	Kneading method	100	200	-	-
C3	Kneading method	100	300	-	-
C4	Kneading method	100	400	-	-
P1	Kneading method	100	-	100	-
P2	Kneading method	100	-	200	-
P3	Kneading method	100		300	
P4	Kneading method	100		400	
B1	Kneading method	100	-	-	100
B2	Kneading method	100	-	-	200
B3	Kneading method	100			300
B4	Kneading method	100			400

Evaluation of Solid Dispersions:

In vitro Dissolution Rate Study:

TABLE 4: *IN VITRO* RELEASE OF GLIPIZIDE FROM SOLID DISPERSIONS

	% Cumulative release			
	In Dist. Water		In phosphate buffer pH 6.8	
Time	GLIPIZIDE	GLIPIZIDE: CCS (1:1)	GLIPIZIDE	GLIPIZIDE: CCS (1:1)
0	0	0	0	0
5	39.75	48.97	59.3	61.70
15	50.9	54.56	67.6	73.8
30	59.8	61.16	75.4	78.4
60	66.2	68.02	82.6	87.4
120	74.0	80.9	88.5	90.64

Tablet Formulation:

TABLE 5: FORMULATION OF MOUTH DISSOLVING TABLETS

Ingredients	Batches								
	M1	M2	M3	M4	M5	M6	M7	M8	M9
Drug dispersion (eq. to 5 mg of Glipizide)	10	10	10	10	10	10	10	10	10
Mannitol	70	68	66	70	68	66	70	68	66
MCC PH- 102 (Avicel)	40	40	40	40	40	40	40	40	40
Sodium starch glycollate	2	4	6	-	-	-	-	-	-
Pregeletenised starch	-	-	-	2	4	6	-	-	-
Crosspovidone	-	-	-	-	-	-	2	4	6
Aspartame	1	1	1	1	1	1	1	1	1
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4
Aerosil (Colloidal Silicon dioxide)	1	1	1	1	1	1	1	1	1
Total weight	130	130	130	130	130	130	130	130	130

Precompression parameter:

TABLE 6: PRECOMPRESSION PARAMETERS OF MOUTH DISSOLVING TABLET

Batch	Angle of Repose	LBD (g/mL)	TBD (g/mL)	Carr's Index (%)	Hausner's Ratio
M1	33.23	0.52	0.64	18.40	1.23
M2	32.58	0.47	0.53	11.32	1.12
M3	31.71	0.52	0.60	13.33	1.15
M4	34.47	0.49	0.57	14.03	1.16
M5	33.21	0.57	0.64	10.93	1.12
M6	32.68	0.53	0.62	14.51	1.16
M7	30.33	0.48	0.55	12.72	1.14
M8	32.51	0.51	0.59	14.87	1.19
M9	33.16	0.49	0.62	16.90	1.15

Evaluation of the Formulated Tablets:

TABLE 7: EVALUATION OF MOUTH DISSOLVING TABLET

Properties	M1	M2	M3	M4	M5	M6	M7	M8	M9
Weight (mg) Mean	130±1.3	127±0.8	126±0.6	129±1.4	128±1.2	127±0.9	131±0.7	132±0.8	133±0.9
Hardness (kg/cm^2)	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2
Thickness (mm) Mean	1.98±0.2	2.05±0.2	2.01±0.2	2.06±0.2	1.96±0.2	1.86±0.2	2.02± 0.0.2	2.04±0.2	2.03±0.2
Friability (%)	0.58	0.54	0.68	0.62	0.68	0.70	0.74	0.69	0.66
Drug content (%) Mean ± SD	98.6±0.8	99.2±1.3	102±0.8	100.4±1.4	99.8±1.8	101.5±0.7	99.2±1.2	99.5±1.5	98.4±1.2
Disintegration time (Sec)	20 ± 23	17 ± 31	12 ± 16	44 ± 23	36 ± 28	28 ± 15	42 ± 24	35±15	31±22
Wetting time (seconds)	630 ± 24	580 ± 62	732 ± 27	431 ± 42	362 ± 51	482 ± 48	320 ± 63	342± 25	329±31

In Vitro Release Profile of Formulated Tablets:

TABLE 8: DISSOLUTION PROFILE OF MOUTH DISSOLVING TABLETS

Time (min)	% Cumulative release								
	M1	M2	M3	M4	M5	M6	M7	M8	M9
0	0	0	0	0	0	0	0	0	0
5	78.32	80.18	85.89	75.41	76.31	77.21	85.64	85.31	88.73
10	80.14	86.13	89.17	78.23	79.51	79.95	89.51	86.64	90.86
15	85.53	89.75	93.15	81.15	82.43	82.81	90.96	88.98	93.52
20	90.46	92.17	96.40	85.74	86.12	87.65	92.43	92.43	96.09
30	92.15	95.71	97.09	88.90	89.99	90.62	95.87	97.71	98.90

Construction of Standard Calibration Curve:

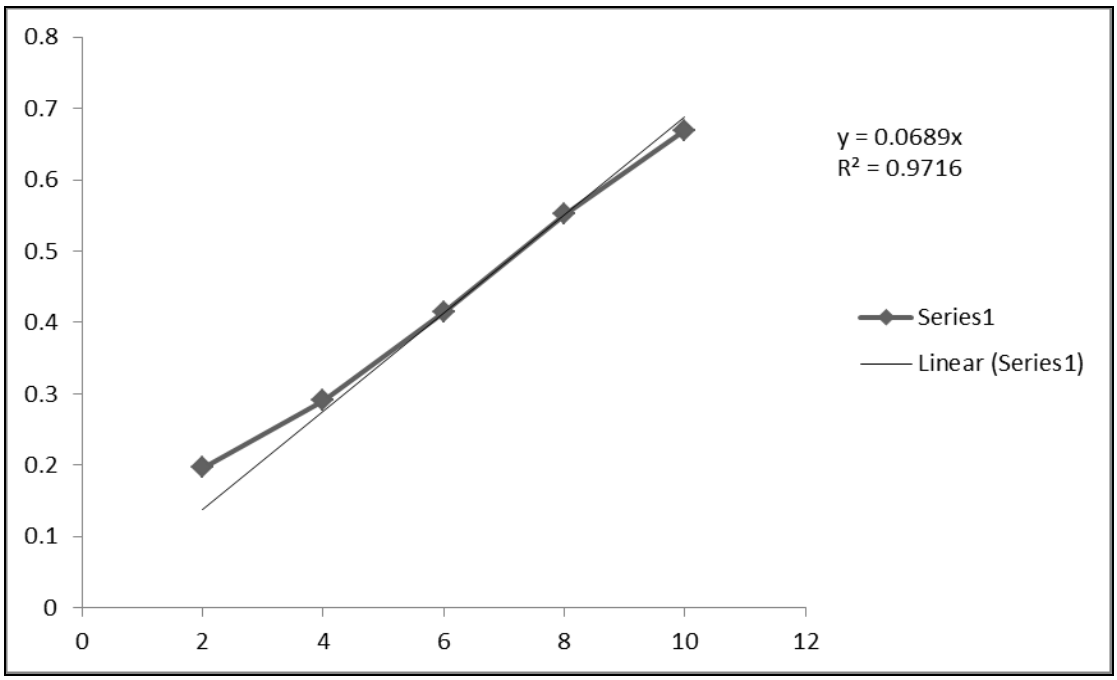

FIG. 1: STANDERD CALIBRATION CURVE OF GLIPIZIDE

Evaluation of Solid Dispersions:

Fourier Transform Infra red Spectroscopy (FTIR):

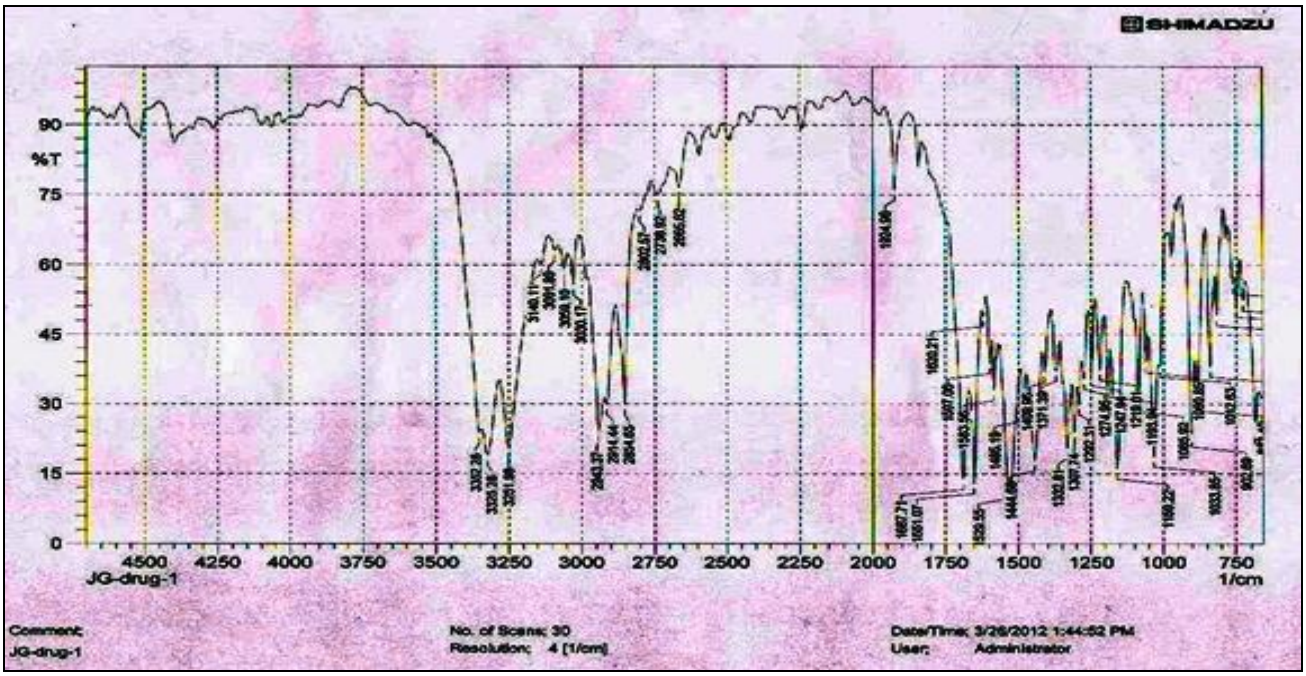

FIG. 2: FTIR OF GLIPIZIDE

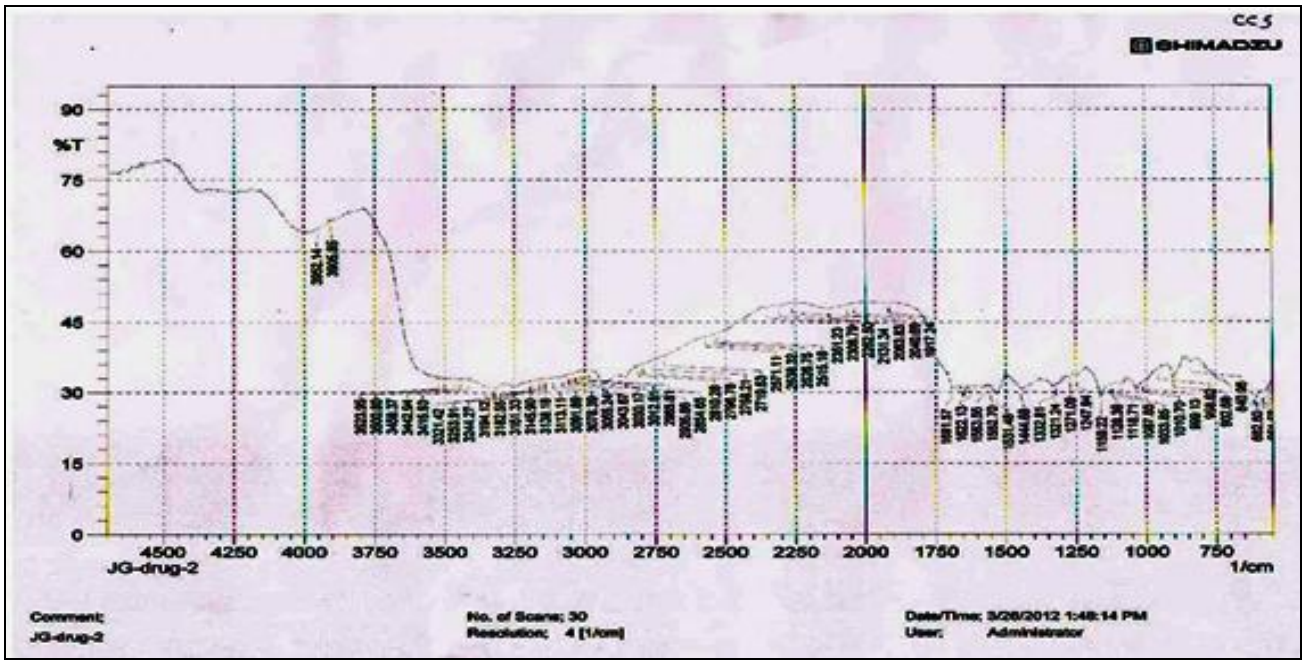

FIG. 3: FTIR OF CCS

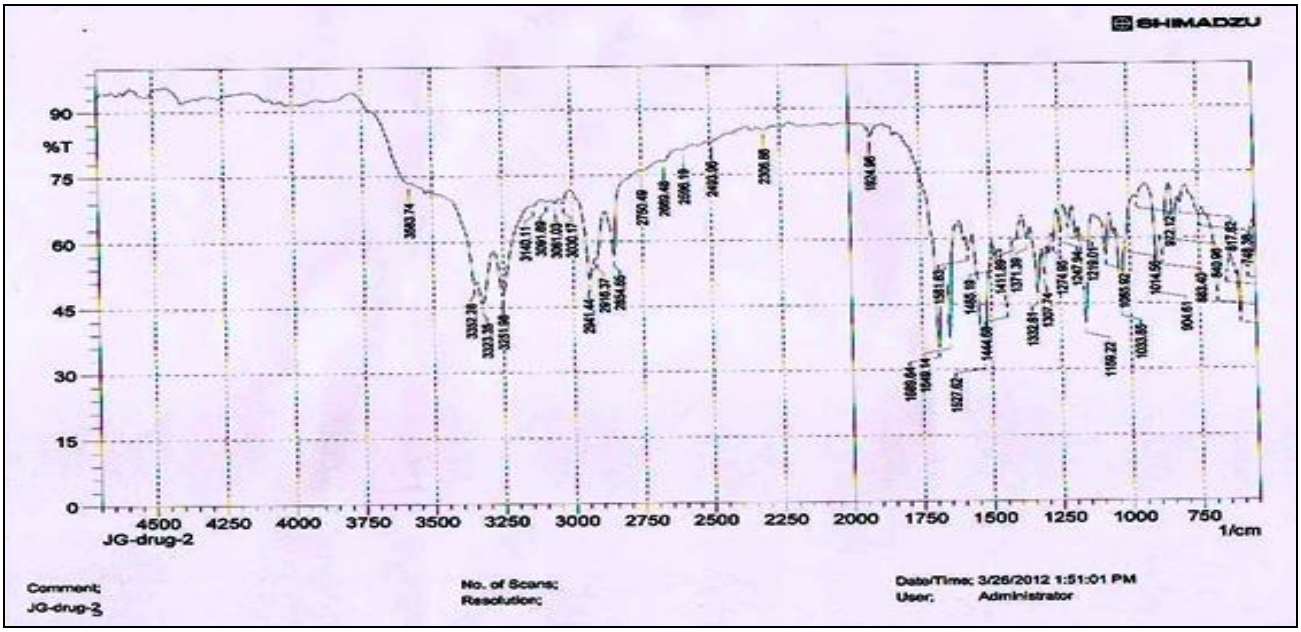

FIG. 4: FTIR OF PHYSICAL MIXTURE

***In vitro* Dissolution Rate Study:**

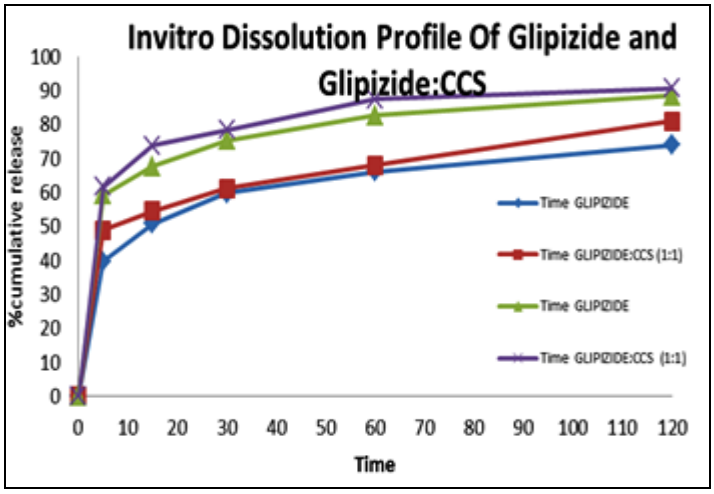

FIG. 5: DISSOLUTION GRAPH OF SOLID DISPERSION

***In vitro* Release Profile of Formulated Tablets:**

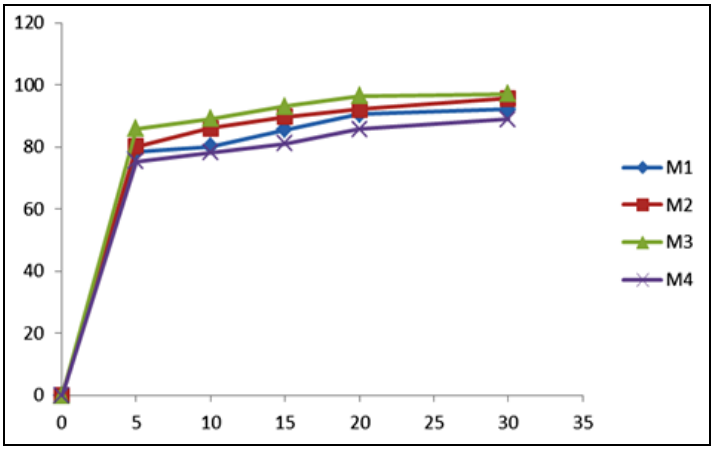

FIG. 6: DISSOLUTION GRAPH OF TABLET(M1-M4)

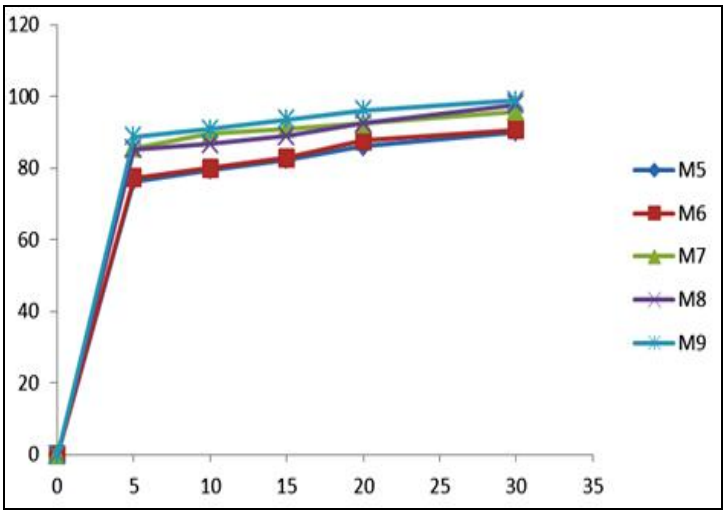

FIG. 7: DISSOLUTION GRAPH OF TABLET(M5-M9)

CONCLUSION: The aim of improving drug dissolution and bioavailability of poorly soluble glipizide was achieved successfully because of increased wettability and increased surface area available for dissolution.

Therefore, consequently solubility of drug was increased. So, the SD is promising technique for solubility enhancement of glipizide.

ACKNOWLEDGEMENT: We express our sincere thanks and gratitude to Dr. Bharat Parashar, HOD, Pharmacy Department Manav Bharti University, Solan, Himachal Pradesh, India, for providing departmental infrastructural facilities.

REFERENCES:

1. Van den Mooter G., Wuyts M., Blaton N., Busson R., Grobet P., Augustijns P., Kinget R., *Eur. J. Pharm. Sci.*, 12, 261—269 (2001).
2. Ford J. L., *Pharm. Acta Helv.*, 58, 101—08 (1983).
3. Szente L., Apostol L., Gerloczy A., Szejtli J., *Pharmazie*, 40, 406—407 (1985).
4. Patel D. M., Shah R. R., Jogani P. D., *Ind. J. Pharm. Sci.*, 66, 49—55(2004).
5. Madhusudhan B., Rambhau D., Gudsoorkar V. R., Shete J. S., Apte S.S., *Ind. J. Pharm. Sci.*, 64, 233—238 (2002).
6. Okonogi S., Puttipipatkhachorn S., *AAPS PharmSciTech*, 7, Article 52(2006).
7. Owusu-Ababio G., Ebube N. K., Reams R., Habib M., *Pharm. Dev.Technol.*, 3, 405— 412 (1998).
8. Schachter D. M., Xiong J., *Int. J. Pharm.*, 281, 89—101 (2004).
9. Sethia S., Squillante E., *Int. J. Pharm.*, 272, 1—10 (2004).
10. Okimoto K., Miyake M., Ibuki R., Yasumura M., Ohnishi N., Nakai T., *Int. J. Pharm.*, 159, 85—93 (1997).
11. Damian F., Blaton N., Kinget R., Van der Mooter G., *Int. J. Pharm.*,244, 87—98 (2002).
12. Nakamichi K., Nakano T., Yasuura H., Izumi S., Kawashima Y., *Int. J.Pharm.*, 241, 203—211 (2002).
13. Craig D. Q. M., *Drug Dev. Ind. Pharm.*, 16, 2501—2506 (1990).
14. Newa M., Bhandari K. H., Kin J. O., Im J. S., Kim J. A., Yoo B. K.,Woo J. S., Choi H. G., Yong C. S., *Chem. Pharm. Bull.*, 56, 569—574(2008).
15. Sammour O. A., Hammad M. A., Megrab N. A., Zidan A. S., *AAPS PharmSciTech*, 7,Article 55 (2006).
16. Oshima T., Sonoda R., Ohkuma M., Sunada H., *Chem. Pharm. Bull.*,55, 1557—1562 (2007).
17. Patel M. M., Patel D. M., *Ind. J. Pharm. Sci.*, 68, 222—226 (2006).
18. Giri T. K., Jana P., Sa B., *J. Sci. Ind. Res.*, 67, 436—439 (2008).
19. Valleri M., Mura P., Maestrelli M., Cirri M., Ballerini R., *Drug Dev.Ind. Pharm.*, 30, 525—534 (2004).
20. Bhalerao A. V., Deshkar S. S., Shirolkar S. V., Gharge V. G., Deshpande A. D., *Res. J. Pharm. Tech.*, 2, 375—377 (2009).
21. Brunton L. L., Parker K. L., Blumenthal D. K., Buxton I. L. O.,"Goodman & Gillman's Manual of Pharmacology & Therapeutics,"McGraw-Hill Medical Publishing Division, U.S.A., 2008, pp. 452—453
22. Modi, A. and Tayade, P., 2006. Enhancement of dissolution profile by solid dispersion (kneading) technique. *Aaps pharm. Sci. Tech.,* 7(3), e1-e6.
23. Murali Mohan Babu G.V., Prasad, Ch. D.S., Raman Murthy, K.V., 2002. Evaluation of modified gum karaya as carrier for the dissolution enhancement of poorly water soluble drug nimodipine, *Int. J. Pharm.* 234, 1-17.
24. Mutasem, M., Rawas, Q., 2006. Fast-disintegrating sublingual tablets: effect of epinephrine load on tablet characteristics. *AAPS pharmscitech*, 7(2), E1-E7.
25. Ohwavworhu, F., Adelakun, T., 2004. Phosphoric acid-mediated depolymerization and decrystallization of α-Cellulose obtained from corn cob: preparation of low crystallinity cellulose and some physicochemical properties. *Trop. J. Pharm. Res.*, 4, 509-516.
26. Kimura, S., Imai, T., Ueno, M., Otagiri, M., 1992. Pharmaceutical evaluation of ibuprofen syrup containing low molecular weight gelatin. *J. Pharm.Sci.* 81, 141-144.

How to cite this article:
Jadhav YL and Parashar B: Formulation and Evaluation of Mouth Dissolving Tablet of Glipizide by Solid Dispersion. *Int J Pharm Sci Res*. 3(12); 4929-4937.