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Research Article

FORMULATION AND CHARACTERIZATION OF FAST DISINTEGRATING TABLET OF GLICLAZIDE BY HYDROTROPY TECHNIQUE

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ABSTRACT

The purpose of this research study was to formulate and evaluate fast disintegrating tablet of Gliclazide by hydrotropic solid dispersion technique. The pharmacological response of drug mainly depends on its absorption rate, which in turn depends on drug's solubility which is an important parameter. Gliclazide is an oral anti hyperglycemic agent useful in lowering the blood glucose level in normal subjects with type 2 diabetics, has poor aqueous solubility. The poor aqueous solubility of medicament results in decreased bioavailability and insufficient therapeutic effect. In the present investigation, an attempt was made to improve the solubility and dissolution rate of a poorly soluble drug Gliclazide by mixed hydrotropy technique using hydrotropic solutes, such as sodium citrate, sodium salicylate and sodium benzoate. Different ratios of hydrotrops were prepared by solid dispersion technique and optimized was selected for final tablet formulation. To increase the disintegration of the tablet formulation some super disintegrants are used such as crospovidone and sodium starch glycolate. Preparation of tablet by direct compression and evaluation were done. This study revealed the influence of hydrotropic agents in the improvement of solubility of Gliclazide. Compatibility between drug and excipient examined by FTIR and DSC study.

Keywords: Pharmacological, Anti hyperglycemic, Hydrotropy, Bioavailability, Disintegrants.

INTRODUCTION

In pharmaceutical research among all the newly developed drug molecules, maximum is lipophilic in nature due to this the solubility is poor. It is often noted that the low solubility and dissolution rate of poorly soluble drugs in gastrointestinal fluids often causes insufficient bioavailability. This poor aqueous solubility is the main complication targeted by the formulators in order to design dosage form for newly developed drugs. Techniques which are generally hired for enhancing the solubility are nanonisation, supercritical fluid re-crystallization, solvent deposition, precipitation, alteration of pH, molecular encapsulation, solid dispersion, hydrotropy etc.[1]

Hydrotropic Solubilization technique is useful for improving the dissolution of poorly water soluble drugs by overcoming crystal lattice energy, as it concomitantly decreases the size of medicament theoretically to the colloidal and even to the molecular level. When solid dispersions are exposed to the fluids of the gastrointestinal tract, the carrier is dissolved leaving the drug in molecular state, which causes enhancement of drug dissolution. The 'hydrotropes' are the compounds that have ability to increase aqueous solubility. A number of hydrotropic agents are available like sodium citrate, catechol, sodium benzoate, sodium cumin sulphonate, sodium gluconate, urea, sodium ascorbate, pheniramine, sodium acetate and sodium cinnamate, etc. which are utilized in hydrotropy technique. For the systemic use and oral administration, capsules and tablets are prepared because of easy handling and self administration. Other therapeutic situations which include motion sickness, nausea and vomiting, etc; also affect dosage form design. Fast Disintegrating Tablets are the one which dissolve very fast in the saliva without any requirement of water. Mainly fast dissolving tablet are designed for bedridden patients, geriatrics and pediatrics.[2-4]

Gliclazide is an oral anti hyperglycemic agent useful in lowering the blood glucose level in normal subjects with type 2 diabetics not in type 1 diabetics. Gliclazide shows low solubility in gastrointestinal medium which result in low bioavailability which offers it best candidate for fast dissolving tablet formulation. The present investigation deals with the development of an effective and stable FDT of Gliclazide having adequate hardness, low disintegration time and pleasant taste.[5]

MATERIALS AND METHODS

Gliclazide was obtained as a gift sample from Chandra Labs, Hyderabad, India. Microcrystalline cellulose and other ingredients were obtained as a gift sample from Fine Chem Industries, Mumbai. Crospovidone was purchased from Cortex Laboratories, Hyderabad. All the other raw materials were of pharmacopoeial grade.

Pre-formulation study

Standardization of the drug was carried out using phosphate buffer pH 6.8 by UV spectrophotometer (UV-160A, SHIMADZU). Solubility analysis of drug in various solvents including water, phosphate buffer pH 6.8 and organic solvents like methanol was carried out.

Formulation of Hydrotropes

Screening of Hydrotropes with Gliclazide

The foremost step was to screen different hydrotropic agents with Gliclazide. In this step we screened different hydrotropic agents with the drug Gliclazide for the final selection of the hydrotropic agents for development of different hydrotropes of drug by mixed hydrotrophy solid dispersion technique. The lists of different hydrotropic agents used for screening with drug are specified in Table 1.

Preparation of Hydrotropes

The hydrotropes of Gliclazide were prepared by mixed hydrotropy solid dispersion method after the selection of suitable hydrotropic agents, in different ratios. The hydrotropes of Gliclazide with different ratios of suitable hydrotropic agents were prepared.[6]

Evaluation of the Hydrotropes

Particle Size Analysis

Optical microscopy method was used to analyze the particle size of prepared hydrotrops, where a number of particles were observed. In this technique ocular and stage micrometer were first calibrated by fixing the stage micrometer on stage micrometer and eye piece.

Solubility Analysis

In solubility analysis a weighed quantity of hydrotrope equivalent to 40 mg of Gliclazide of different drug: hydrotropic agent ratio was conveyed to a volumetric flask having 10 ml of distilled water. These hydrotrophs containing flasks were kept for 24 h. Next morning all the samples were analyzed in UV-spectrophotometer at λ_{max} 228 nm. (Table 4)

Drug Content Estimation

In drug content estimation a measured quantity of hydrotrope equivalent to 40 mg of Gliclazide was dissolved with methanol in volumetric flask of 100 ml, the volume was marked up to 100 ml mark and assayed for drug content was analyzed spectrophotometrically at 228 nm and similarly drug content of other hydrotropes was estimated.

Drug – Carrier Interaction Study

Fourier Transformed Infrared Spectroscopy

Fourier Transformed Infrared Spectroscopy of samples, selected hydrotropes and Pure drug i.e. Gliclazide were attained using FTIR spectrophotometer (Table 6).

Differential Scanning Calorimetry

Differential Scanning Calorimetry of the selected formulation was obtained to the study of drug- excipient interaction. DSC profile of Gliclazide and selected hydrotropes are shown in Figure 4-6.

***In Vitro* Dissolution Study of hydrotropes**

Dissolution Study of hydrotropes was done by using USP basket type apparatus for 2 h. The basket rpm was set at 100 rpm, 0.1N HCl was used as a dissolution medium (900 ml), temperature was controlled at 37 ± 1^0C, hydrotropes equivalent to 40 mg of Gliclazide was used for dissolution studies, at different time intervals sample are withdrawn and analyzed by UV-spectrophotometer at 228 nm (Table 5).[7]

Formulation of Tablet

Hydrotropic solid dispersions so prepared were then finally formulated into FDT by using super disintegrants. Fast disintegrating tablet of so prepared hydrotrophic solid dispersion contain a quantity equivalent to 40 mg of drug (Gliclazide) additionally by incorporating super disintegrants such as crospovidone or sodium starch glycolate are added, as an effervescent agent, sodium bicarbonate and citric acid are supplemented, magnesium stearate and talc are used as a lubricant, to minimize the tablet defects like capping, etc.; and to mask the bitter taste of tablet mannitol is used as a sweetening agent.

Weight variation

From each formulation twenty tablets were randomly selected and determined their average weight. Then individual tablet was weighed and was compared with average weight.

Friability

Friability test apparatus was used to examine the friability of tablet. Initially weighed tablet ($W_{initial}$) were placed in friabilator. The percentage friability was determined by following formulae. (Table 7)

$$F = W_{initial} - W_{final} \times 100 / W_{final}$$

Hardness

Pfizer Hardness tester was used to examine the hardness of tablet. It is expressed in kg/cm^2. (Table 7)

Disintegration Test

Disintegration test apparatus was used to examine the disintegration time of fast dissolving tablet (Table 7)

Wetting time

Wetting time was examined by a simple method in which five petriplate with a diameter of 10 cm are taken and five circular tissue papers with same diameter were placed in it. Now in the petriplate 10 ml of water was poured. Then a tablet was introduced on the surface of tissue paper. (Table 7)

***In-vitro* dissolution study**

In-vitro dissolution study was done using USP type II apparatus or paddle type apparatus which was rotated at 60 rpm.[8,9]

RESULTS AND DISCUSSION

Maximum solubility of drug was found in the batch no. 3, 5, 7. This increase was directly related to increase in solubility of Gliclazide (Table 4).

***In-Vitro* Dissolution Study of the Prepared Hydrotropes**

On the basis of the solubility analysis the three batches (3, 5, 7) were optimized for further work. From the dissolution studies it was resulted that only 14 % of drug was released in 45 minutes

from the pure drug, whereas 18 %, 44 % and 48 % of drug was released in 45 minutes from the prepared hydrotropes respectively, which indicates that there is a rapid release of drug from the hydrotropes. (Table 5)

Drug – Carrier Interaction Study

FTIR Study

It was found that there is no considerable change in the peak of the prepared hydrotropes was observed when compared to pure Gliclazide. FTIR spectra of the prepared hydrotropes show that no change occurred in chemical structure. Thus it can be concluded, FTIR studies revealed that there is no physico-chemical interaction between Gliclazide and the prepared hydrotropes. (Figure 2,3)

DSC Study

1. 176.19 ºC is the melting temperature of Gliclazide (pure drug)
2. The melting points of the two hydrotropes so prepared were found to be 168.79 and 169.90 ºC respectively.
3. In the formulation prepared the absence of the melting thermo gram peak of the drug at 176.19ºC indicated that the drug has been converted by the hydrotropic agents into a molecularly dispersed state and in such cases the solubility of the drug is markedly increases. This shows that the hydrotropic formulation was prepared. (Figure 4,5)

Post Compression Studies of Tablet

The results of the physico-chemical evaluation of the prepared tablets are shown in Table 7.

***In-Vitro* Drug Release Study of Different Formulations**

The dissolution of various tablet formulations revealed that gliclazide release from all the prepared tablets formulations was very rapid. Tablets containing crospovidone 100 mg and sodium bicarbonate 22 mg along with prepared hydrotropes of batch no.5 i.e. F_{11} formulation showed the fast initial drug dissolution. (Figure 7-10)

Table 1: List of Hydrotropic agents used

S. No.	Hydrotropic agent Used
1	Sodium benzoate
2	Sodium salicylate
3	Sodium citrate
4	Sodium acetate
5	Sodium chloride
6	Potassium citrate
7	Urea

Table 2: Composition of Various Hydrotropes

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Batch No.	Drug (mg)	Sodium Salicylate (mg)	Sodium Benzoate (mg)	Sodium Citrate (mg)
1	200	100	100	100
2	200	200	100	100
3	200	100	200	100
4	200	100	100	200
5	200	200	200	100
6	200	200	100	200
7	200	100	200	200
8	200	200	200	200

Table 3: Formulations for the Fast Disintegrating Tablets using Optimized Hydrotropes

Ingredient (mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
Hydrotrope (3)	120	-	-	120	-	-	120	-	-	-	-	-
Hydrotrope (5)	-	140	-	-	140	-	-	140	-	140	140	140
Hydrotrope (7)	-	-	140	-	-	140	-	-	140			
Sodium Starch Glycolate	-	-	-	80	80	80	-	-	-	-	-	95
Crospovidone	70	70	70	-	-	-	90	90	90	95	100	95
Microcrystalline Cellulose	179	159	159	169	149	149	159	139	129	124	117	124
Sodium Bicarbonate	10	10	10	10	10	10	10	10	20	20	22	20
Citric Acid	10	10	10	10	10	10	10	10	10	10	10	10
Magnesium Stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Mannitol	4	4	4	4	4	4	4	4	4	4	4	4

Table 4: Solubility Analysis of the Prepared Hydrotropes

Batch No.	Conc. (µg/ml)	Amount (mg/ml)	Solubility enhancement
1	8.31	83.1	23.74
2	8.27	82.7	23.62
3	9.14	91.4	26.11
4	6.95	69.5	19.85
5	9.89	98.9	28.25
6	8.43	84.3	24.08
7	8.85	88.5	25.28

Table 5: *In Vitro* Dissolution Data for Pure Drug and Different Batches of Hydrotropes

S. No.	Time (minutes)	% Drug Release (Pure Drug)	% Drug Release (Batch No. 1)	% Drug Release (Batch No.2)	% Drug Release (Batch No.6)
1	5	9.723215	10.84822	17.4375	16.79464
2	15	10.85902	12.22634	21.47473	27.98295
3	30	12.22634	13.75464	29.67563	36.67393
4	45	13.43321	18.97955	44.63116	48.41571
5	60	14.07741	25.49429	46.57634	53.25018
6	90	15.68527	35.30509	54.85527	59.84482
7	120	17.93705	46.56598	56.39125	73.4325

Table 6: Reported and Observed FTIR Frequencies of Gliclazide

Functional Group	Reported Frequencies (in cm^{-1})
C –H	1500-1300
N –H	3700-3000
S=O	1140-1325
C=O	1900-1600

Table 7: Characteristics of Tablets of the Prepared Formulations

Evaluation Parameter	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
Hardness (kg/cm^3)	3.1	3.3	3.2	2.9	3.1	2.8	3.0	3.1	2.92	2.87	3.01	3.2
Drug Content	99.1	102.4	93.35	101.1	99.7	102.2	98.65	94.85	99.55	99.25	100.4	99.4
Friability	1.07	0.70	0.78	1.04	0.77	0.69	1.14	1.06	0.85	0.89	1.01	0.61
Disintegration Time	4 Sec.	3 Sec.	4.4 Sec.	4.5 Sec.	5 Sec.	4 Sec.	6 Sec.	8 Sec.	5 Sec.	7 Sec.	6 Sec.	4 Sec.
Wetting Time	12 Sec.	14 Sec.	10 Sec.	11 Sec.	13 Sec.	15 Sec.	10 Sec.	12 Sec.	14 Sec.	17 Sec.	15 Sec.	13 Sec.

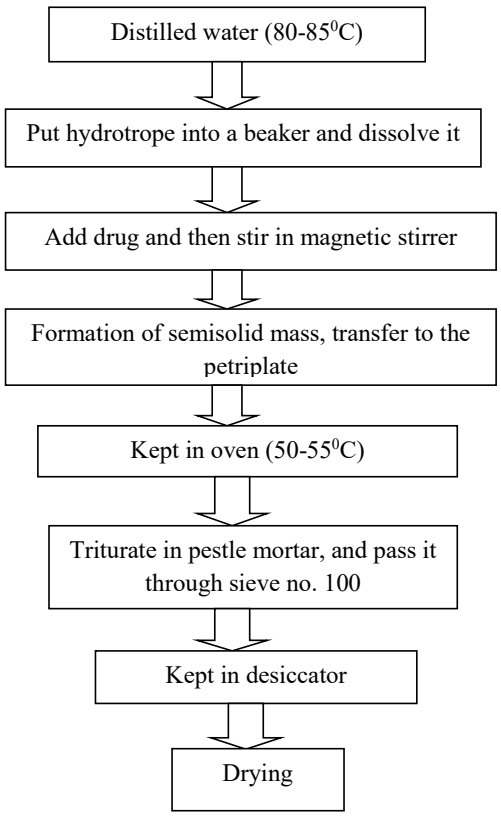

Figure 1: Flow Chart for hydrotropes preparation

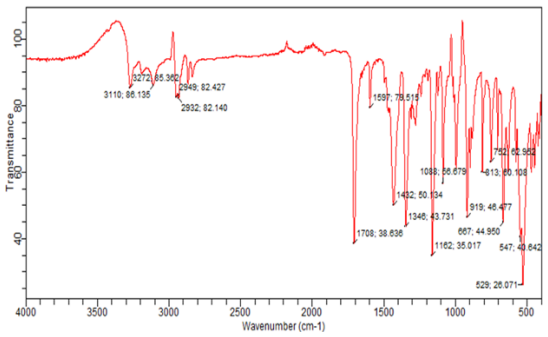

Figure 2: FTIR of Drug Gliclazide

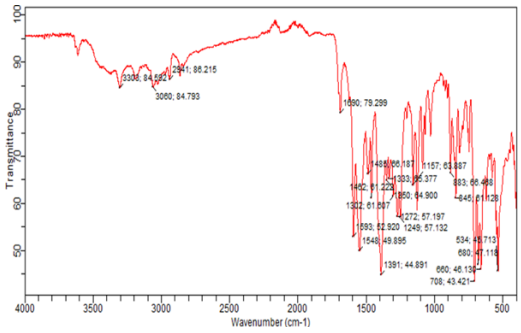

Figure 3: FTIR of Prepared Hydrotrope of Gliclazide

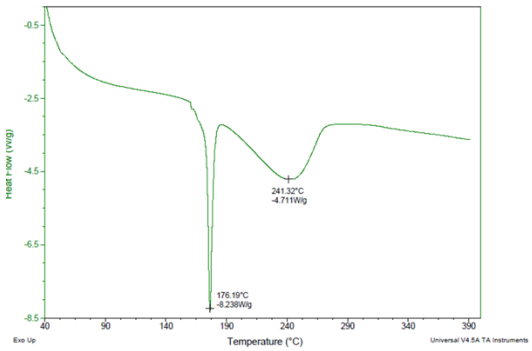

Figure 4: DSC of Gliclazide

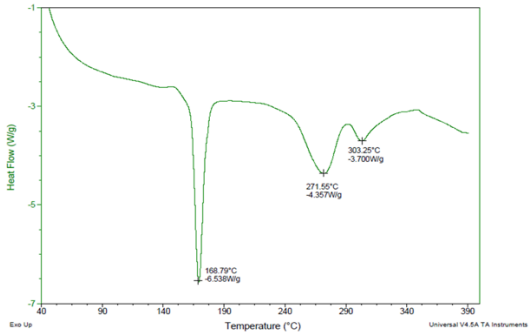

Figure 5: DSC of Prepared Hydrotrope no. 5

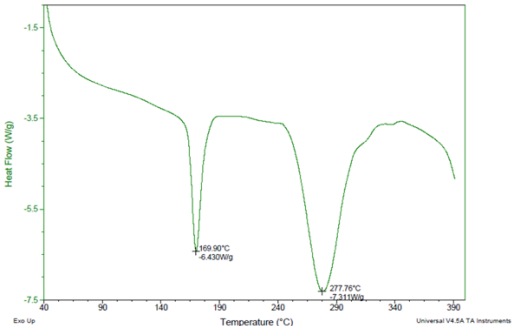

Figure 6: DSC of Prepared Hydrotrope no. 7

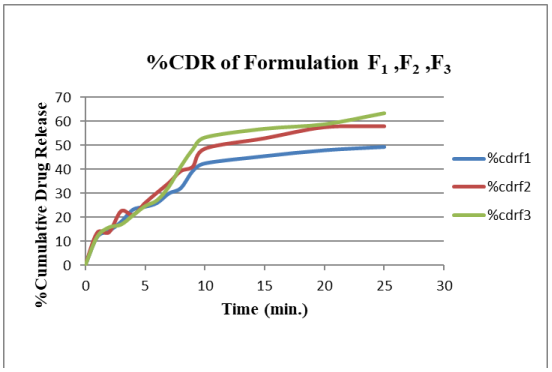

Figure 7: Comparison of % cumulative drug released from the formulation varying in different batches of tablets prepared

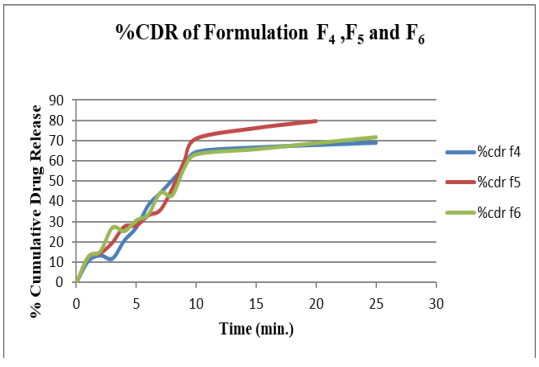

Figure 8: Comparison of % cumulative drug released from the formulation varying in different batches of tablets prepared.

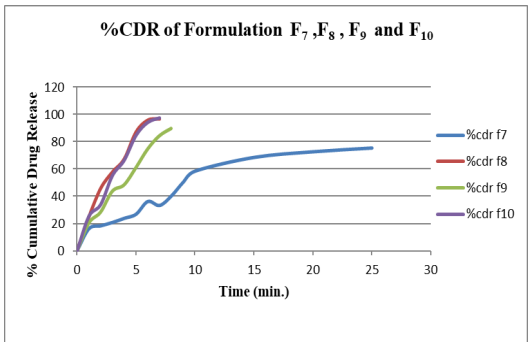

Figure 9: Comparison of % cumulative drug released from the formulation varying in different batches of tablets prepared

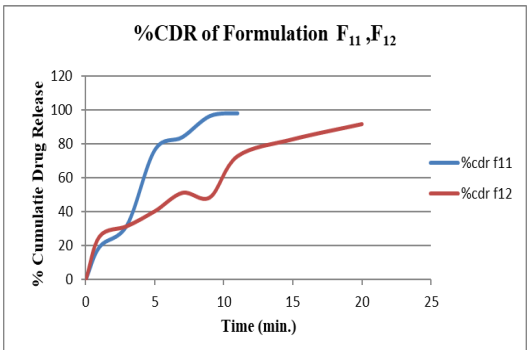

Figure 10: Comparison of % cumulative drug released from the formulation varying in the amount of F_{11} (use of crospovidone) and F_{12} (use of sodium starch glycolate)

CONCLUSION

Based on the observation it was concluded that the hydrotropic agents Sodium Benzoate, Sodium Salicylate and Sodium Citrate have the ability to enhance the solubility of the drug more than 20 times of its original solubility. The hydroptrops so selected after analysis were formulated into fast disintegrating tablet and the evaluation of different formulation revealed excellent drug release profile as compared to conventional dosage form.

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