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Formulation and Evaluation of Glibenclamide Solid Dispersion Using Different Methods

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Abstract: The oral route is widely acceptable route for delivery of drug. Poor soluble drug show poor dissolution characteristics via oral route hence the solubility is the important characteristic to ascertain the dissolution of drug. The present study is related to preparation and evaluation of solid dispersions of Glibenclamide to improve the aqueous solubility and dissolution rate in order to enhance bioavailability. Glibenclamide is oral hypoglycemic agent which comes under BCS class II drug. In this study solid dispersions of Glibenclamide using HPMC as water soluble carriers were prepared by kneading and dropping methods. The formulations were further characterized for percentage yield, drug content, *in vitro* release study and solubility study. *In vitro* release studies revealed that the solid dispersions prepared by kneading method showed better dissolution characteristics compare to solid dispersion prepared bydropping method. It was also concluded that among different ratio of solid dispersion the 1: 2 ratio of drug carrier was found as the best formulation.

Key words: Solid Dispersion · Dissolution · Kneading Method · Dropping Method

INTRODUCTION

Oral drug delivery is the widely acceptable and simplest way of administering drugs. If the drug does not completely release in the gastrointestinal tract have poor bioavailability. Dissolution characteristic of drug is the important property for ascertain its bioavailability. The dissolution of drug via oral routedepends at a large extent on its solubility [1-3]. Enhancement in the dissolution rate for poorly water soluble drug is one of the most important concerning aspects of the pharmaceutical industries [4, 5]. Thus, an attempt is required to increase the solubility of drugs [6]. Now a day there are various research is going on to enhancement of solubility of poorly water soluble drugs.

Glibenclamide or glyburide is known as5-chloro-*N*-(4-[*N*-(cyclohexylcarbamoyl) sulfamoyl]phenethyl)-2-methoxybenzamide chemically, is oral hypoglycaemic drug (sulphonyl urea's-second generation). It acts by inhibiting ATP-sensitive potassium channels in pancreatic beta cells [7]. This inhibition causes cell membrane depolarisation, which cause voltage dependent calcium channels to open, which causes an increase in intracellular calcium in the beta cell, which stimulates insulin release [8].

It has been widely used in treatment of type 2 diabetic patients after well establishing that this compound acts by increasing insulin release from the beta cells in the pancreas [9]. It is used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM).

According to biopharmaceutical classification system (BCS) Glibenclamide is classified under class II. The solubility of drug depends on pH. Glibenclamide exhibits very poor solubility at 37°C (<0.004 mg/ml) in acidic and neutral aqueous media, at pH > 7, solubility of drug is slightly increases to 0.02 mg/ml. This poor solubility may lead to poor dissolution and unpredictable bioavailability [10-12].

MATERIALS AND METHODS

Glibenclamide pure drug was purchased from Lark laboratories (India) Ltd, Bhiwadi, with 99.9% w/w assay value. HPMC were purchased from CDH ltd, New Delhi (India). All other excipients and solvents were of analytical grade.

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Table 1: Different formulation of Solid Dispersion with batch code

Batch Code	Drug (mg)	Polymer(mg)	Method Use
F1	900	900	KneadingMethod
F2	900	1800	
F3	900	2700	
F4	1800	900	
F5	900	900	DroppingMethod
F6	900	1800	
F7	900	2700	
F8	1800	900	

Preparation and Evaluation of Solid Dispersions: The different batch of Solid dispersion of the Glibenclamide was prepared by kneading method (F1 to F4) and dropping method(F5 to F8) as follow:

- By kneading Method:A mixture of GLB and HPMCas shown in table 1 were wetted with sufficient volume of methanol and kneaded thoroughly for 30 minutes in a glass mortar. The paste formed was dried under vacuum and kept for 24 hours. Dried powder was scrapped, crushed, pulverized and passed through sieve No. 60 and stored in a desiccator [13].
- By Dropping Method: The dropping method facilitates the crystallization of different chemicals and produces round particles from melted solid dispersions.In this method GLB solid dispersion was prepared by wetting a melted GLB and HPMCwith methanolas shown in table 1 andthe melted GLB-HPMC mixture was pipetted and placed into an adjustable heating device to keep the temperature constant. The melted drug-carrier mixture was dropped onto a plate, where it solidifies into round particles. The mixture was dried, scrapped, crushed, pulverized and passed through sieve No. 60 and stored indesiccators [14].

Evaluation of Prepared Solid Dispersions: The following parameters were evaluated for prepared solid dispersions.

Drug Excipient Compatibility Studies: Drug excipients compatibility studies give the information about any possible interaction between drug and polymer which can reduce the efficiency of final formulation.The drug-excipient compatibility study is generally carried out by infrared Spectroscopy or Differential Scanning Calorimetry.

Determination of Percentage Yield: The percentage yield is useful to determine the efficiency of a preparation technique. The percentage yield was calculated by using following equation:

$$\text{Percentage Yield} = \frac{\text{Practically Obtained Weighted of Product}}{\text{Theoretically Weight of formation}} \times 100$$

Determination of Drug Content: The determination of drug content is helpful in the administering the accurate dose of the formulation. For calculating the drug content in the present study a accurately weighed quantity of prepared solid dispersion was dissolved in minimum quantity of methanolwith continuous shaking to make a homogeneous solution and volume was made upto 10 ml using 0.1 N HCl. The solution was then filtered and the absorbance was measured at 300 nm. The % drug content was calculated as follow:

$$\text{\% Drug Content} = \frac{\text{Practically Obtained Weighted of Product}}{\text{Theorectical amount of glibenclamide in solid dispersion}} \times 100$$

Solubility Studies of Solid Dispersions: The solubility study for the formulation is carried out to determine release strategies of the drug from its formulation. For performing the solubility study in the present work the prepared solid dispersions equivalent to 5 mg of Glibenclamide drug wasadded to 10 ml of 0.1 N HCl.The solutions were stirred in a magnetic stirrer at37ºC for 24 hrs. The solutions werethen filtered and theabsorbance of the prepared dilutions was measured at 300 nmusing UV-Visible spectrophotometer [16].

Dissolution Studies: The dissolution studies give the information about amount of drug available at a particular time interval. In the present study the dissolution rate of pure glibenclamide and solid dispersion systems were carried out using the basket method (USP Type-I) at 37°C in 900 ml of 0.1N HCl at 100 rpm. Samples equivalent to 5 mg of glibenclamide were subjected to the testing. At a different time intervals the 5 ml samples of dissolution medium were withdrawn, filtered andanalyses at 300 nm using UV Spectrophotometer. At each time of withdrawal, 5 ml of fresh 0.1 N HCl was added in the dissolution flask [17].

RESULTS AND DISCUSSION

Drug-Excipients Compatibility Study: The Drug-excipients compatibility study was carried out by IR Spectroscopy. The IR spectra of Glibenclamide, HPMC and its binary systems with HPMC are

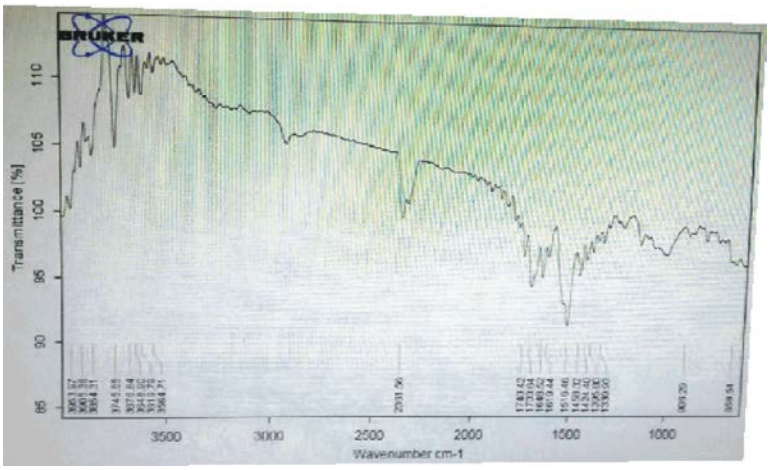

Fig. 1: FTIR spectra of pure Glibenclamide

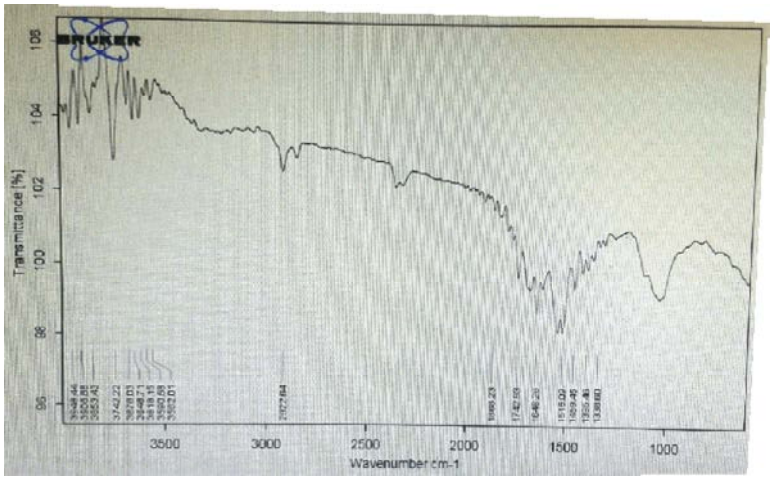

Fig. 2: FTIR spectra of HPMC Polymer

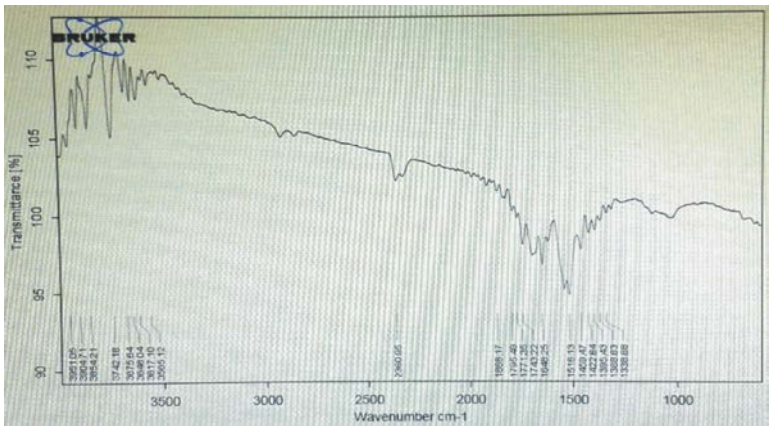

Fig. 3: FTIR Spectrum of solid dispersion of Glibenclamide and HPMC

present in figures 1, 2, 3. Pure Glibenclamide spectra showed sharp characteristicpeaks at 2361.58, 1516.46, 1339.93 cm^{-1}. All the above characteristic peaks appear in thespectra of all binary systems and are within the same wave number indicating no modification or interaction between drug and carrier. The interpretation of IR spectra also given in Tables 2,3, 4.

Table 2: Interpretation ofInfrared spectra of Glibenclamide

Sr. No.	Frequency(cm^{-1})	Vibration Mode
1.	2361.58	S=O (cm^{-1})
2.	1743.42	C=O (cm^{-1})
3.	1516.46	C=C (cm^{-1})
4.	1339.93	C-N Amines (cm^{-1})

Table 3: Interpretation ofInfrared spectra of HPMC

Sr. No.	Frequency(cm^{-1})	Vibration Mode
1	3648.71	O-H (cm^{-1})
2	2922.64	C-H Alkenes (cm^{-1})
3	1648.26	C=C (cm^{-1})
4	1459.45	C-H bend (cm^{-1})
5	1338.60	C-N Amines (cm^{-1})

Table 4: Infrared spectral assignment of Glibenclamide and HPMC

Sr. No.	Frequency(cm^{-1})	Vibration Mode
1	3648.04	O-H (cm^{-1})
2	2360.95	S=O (cm^{-1})
3	1516.13	N-O Nitro (cm^{-1})
4	1338.60	C-N Amines (cm^{-1})

Table 5: Drug Content of solid dispersion

Batches	Percentage yield	Drug Content (%)
F1	86.66	88.38
F2	92.77	99.30
F3	92.41	96.02
F4	93.55	92.75
F5	83.33	85.39
F6	91.11	97.93
F7	90.83	94.93
F8	94.55	91.66

Table 6: Solubility data of glibenclamide and solid dispersions batches

Sr. No	Formulation Code	Solubility (µg/ml)
1.	Glibenclamide Drug	12.93
2.	F1	64.59
3.	F2	91.86
4.	F3	82.77
5.	F4	77.77
6.	F5	61.40
7.	F6	88.68
8.	F7	78.22
9.	F8	74.59

Table 7: Drug release of different batches of Glibenclamide

	Cumulative drug release (%)							
Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
15	18.24±0.72	26.640.19	28.87±0.15	23.56± 0.41	17.89±0.32	23.32 ±0.55	19.03±0.58	20.61± 0.22
30	22.16±0.81	31.68±0.38	33.60±0.41	36.48±0.59	20.43± 0.21	33.57±0.22	27.78±0.41	31.44±0.46
45	31.24±0.67	38.19±0.57	38.56±0.26	39.27±0.46	37.92±0.12	39.33±0.46	35.05±0.15	37.13±0.26
60	41.33±0.36	45.16±0.44	41.16±0.46	48.96±0.77	39.14±0.54	42.88±0.93	39.21±0.28	42.93±0.98
75	46.59±0.22	52.28±0.62	51.10±0.48	55.89±0.74	51.67±0.52	54.92±0.58	53.66±0.73	47.32±0.53
90	58.65±0.24	63.54±0.35	57.95±0.39	63.71±0.51	54.48±0.96	61.11±0.95	56.73±0.61	59.99±0.36
105	62.50±0.43	73.04±0.24	65.76±0.32	68.83±0.55	59.07±0.52	69.87±0.36	61.48±0.42	63.45±0.64
120	68.23±0.73	81.91±0.38	74.98±0.71	72.98±0.28	63.76±0.85	75.54±0.78	71.94±0.39	69.97±0.95

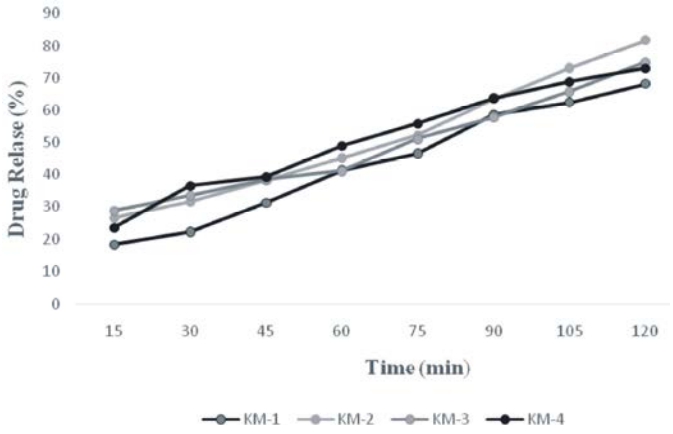

Fig. 4: Figure showing cumulative percent drug released versus time for batchF1 to F4.

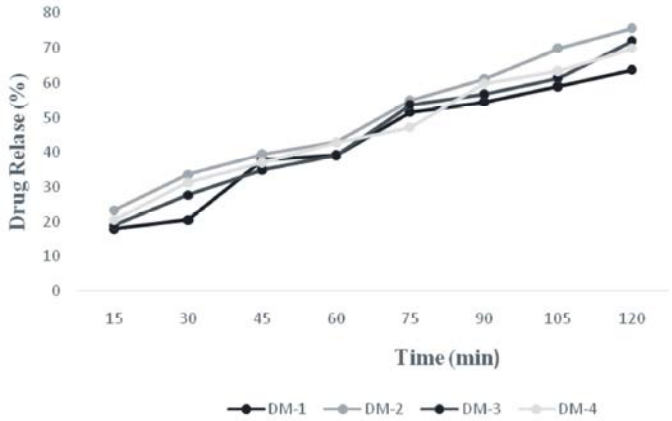

Fig. 5: Figure showing cumulative percent drug released versus time F5 to F8

Drug Content: The drug content for prepared formulation was obtained as showed in the Table 5.

From the data given in the table it was found that the maximum drug content among all formulation was 99.30% (batch F2) and minimum % drug content from the all formulation was 85.39% (batch F5)

Solubility study: From the data obtained as given in table 2 it was found that increase in solubility of the drug was observed with the increasing concentration of polymers, but it was up to a certain limit. After that, the increases in concentration of polymers lead to a no more change in solubility of the pure drug.The solubility of formulation code F2 was 91.86 µg/ml and that of F6 was 88.68 µg/ml.

***In-vitro* Release Studies:** The *in vitro* release studies were carried out for the Glibenclamidesolid dispersions prepared by two methods, namely kneading and dropping methods. The results of in-vitro release studies are given in table 7 and the graph for percentage cumulative release are given in Figures 4,5.

In kneading method, it was observed that F2 (1: 2 ratio) exhibited maximum release of 81.71% and it was rated as the best formulation in kneading method using HPMC. In case of dropping method, it was observed that F6 (1: 2 ratio) exhibited maximum release of 75.54%.From the above results it can be concluded that the Kneading method give best result compare to dropping method formulated at the same extent.

CONCLUSION

In the present studysolid dispersion of Glibenclamide by using the water soluble carrier HPMC was prepared for 1:1, 1:2, 1:3, 2:1 ratios by kneading and dropping method. Among all of these formulations the 1: 2 ratio prepared by Kneading method (Batch F2) provide best release of drug (81.71% released in 120 min.). So it can be concluded that the kneading and dropping methods are very useful methods for the successful enhancement of solubility of poor water soluble drug. Among all the formulationsit can also be concluded that the kneading method give better results compare to dropping method for all the formulations. So we conclude that the ratio 1:2 of drug and carrier can be effectively used to enhance the solubility and dissolution rate of Glibenclamide.

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