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FORMULATION AND EVALUATION OF ORAL SOFT JELLY CONTAINING GLIBENCLAMIDE

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Abstract:
Convenience of administration and patient compliance are gaining significant importance in the design of dosage forms. Glibenclamide is an orally administered antihyperglycemic agent, used in the management of non-insulin-dependant (type-2) diabetes mellitus. Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly and pediatrics. Persons suffering from dysphagia may get choked when they consume liquid formulations, thus to alleviate such problem liquid formulation of high viscosity were prepared. Formulation of oral soft gel (batches of Glibenclamide) were prepared by using hydrophilic polymer guar gum at concentration ranging from 0.3-0.5% w/v and pectin at two different concentrations (0.2% and 0.3% w/v). The batch with 0.5% w/v guar gum and 0.2%w/v pectin not only showed 85% drug release after 1h. The prepared batches were evaluated for appearance, viscosity, pH, drug content, syneresis and in vitro drug release. The optimized batch showed substantial stability when subjected to short term stability study (0-8°C and at room temperature). The problem of dose measurement by patients was outweighed as oral medicated gels are to be packed in unit dose container.

Keywords: *Diabetes mellitus, Jelly, Dysphagia, Glibenclamide.*

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INTRODUCTION:

Glibenclamide is 1-[4-[2-(chloro-2-methoxy benzamido) ethyl]-benzenesulphonyl]-3cyclohexylurea, 5-chloro-N- [2-[4[[[(cyclohexyl (amino) carbonyl]-amino] sulphonyl] phenyl] ethyl]-2-methoxy benzamid. It is a white solid crystalline compound, having molecular formula C23H28ClN3O5S, with molecular weight 494. Glibenclamide is a sulphonylurea derivative used for the treatment of Type-2 Diabetes mellitus. It is practically insoluble in water and so possesses poor solubility and subsequent poor gastrointestinal absorption and bioavailability. It causes hypoglycemia by stimulating release of insulin from pancreatic β-cells and by increasing the sensitivity of peripheral tissue to insulin. It has a history of low bioavailability, which is attributed to poor dissolution. Several attempts for increasing dissolution and bioavailability of glibenclamide have been made, such as micronization, molecular dispersion, incorporation of surfactants inclusion complexation with cyclodextrin crystal modification glass formation and co-precipitation.

Type-2 diabetes is a progressive illness and most patients will eventually need more than two oral agents to maintain adequate glucose control. Switching from one drug to another in a patient with poorly controlled glycemia or maximizing the dosage of an existing drug is rarely achieved. Adding medications from different groups to the existing regimen often provides more effective glycemic control. Several of the available oral agents have been studied in combination and have been shown to further improve glycemic control when compared with monotherapy [1, 2].

Unfortunately, a high percentage of patients suffering from type-2 diabetes are elderly people showing dysphagia. The above problem becomes even more severe since the medication has to be taken lifelong everyday and the tablets are quite big due to the high therapeutic dose. The patients with dysphagia can be choked by water while consuming liquid formulation which can be eliminated by administering liquid formulations with high viscosity. Thus, jelly formulation containing Glibenclamide combination was prepared.

The gel dosage form not only overcomes the disadvantages of liquid dosage form, but also of solid dosage forms. The problem of dose measurement by patients is outweighed as oral medicated gels are to be packed in unit dose container [3, 4].

The aim of the present study was to improve patient compliance by development of jelly preparation of an orally administered oral hyperglycemic agent (Glibenclamide) used in treatment of non insulin dependent (type-2) diabetes mellitus and reducing the condition of dysphagia. Apart from that jelly preparation also helps to control over harshness and bitterness of drug. So we can say it as patient friendly dosage form.

MATERIAL AND METHODS:

Materials

Glibenclamide was received as a gift sample from Wilcure Remedies Pvt. Ltd., Indore (M.P.). All other chemical like guar gum, pectin, mannitol, citric acid, sodium citrate, methyl paraben, stevia purchased were of analytical grade.

Preparation of oral soft jelly

All the required ingredients of the formulation were weighed accurately. Dry guar gum powder and pectin were dispersed in 50 ml of distilled water maintained at 95°C. The dispersion was stirred at 95°C for 20 min using a magnetic stirrer (Remi magnetic stirrer Mumbai, India) to facilitate hydration of guar gum. The required amount of mannitol was added to the gelling agent solution with continuous stirring and the temperature was maintained about 80-85°C. Glibenclamide was added with stirring. Then stevia, citric acid, and preservatives (methylparaben) were added with stirring. Finally, required amount of sodium citrate and sodium citrate was dissolved in 10 ml of distilled water and added to the mixture. At last flavor was added. The weight of the gel was monitored continuously during manufacturing and finally it was adjusted to the 100 g with distilled water. The jelly was packed in polyethylene mould with airtight seal. The mixture was allowed to cool up to room temperature to form jelly. The gels were prepared using three different concentrations of guar gum (0.3, 0.4 and 0.5% w/v), each with two different pectin concentrations (0.2 and 0.3% w/v).

Evaluation of oral soft gel

Following studies were carried out for evaluation of oral gellan gum soft gel of Glibenclamide.

General appearance

Texture and clarity of the soft gel was evaluated in terms of stickiness and grittiness by mildly rubbing the gel between two fingers. Consistency and odour were also evaluated by physical observation.

Rheological measurement

Viscosity of the all the batches of soft gels were measured using Brookfield DV-II+ Pro viscometer. The Glibenclamide containing soft jelly was squeezed out from the polyethylene plastic bag by making a cut of uniform size on the bag and viscosity was measured using spindle number LV4 at the rotation of 50 rpm at room temperature. The viscosity measurements were made in triplicate using fresh sample each time [5].

pH of the soft jelly

The pH of the final gel has a great influence not only on stability, but also on the taste. The pH of glibenclamide containing soft jelly was measured using Electroquip Digital pH meter at room temperature [6].

Syneresis

Syneresis is one of the major problems associated with low acylated gellan gum gels. Syneresis means contraction of gel upon standing and separation of water from the gel. Syneresis is more pronounced in the gels where lower concentration of gelling agent is used. Gels were kept under scrutiny for signs of syneresis. The gels showing signs of syneresis were rejected and not considered for further studies [7].

Drug content

Take 10 jellies from jelly mould in a beaker and there average weight was determined. They were breaked into gel consistency. Then gel equivalent 5.0 mg of glibenclamide was taken in 100 mL volumetric flask and dissolved in 70 ml of methanol with vigorous shaking for 5-10 min. Finally the volume was made up to the mark with methanol. Finally it was analyzed in HPLC after proper dilution and filtration [4].

***In vitro* drug release**

In vitro drug release studies was carried out using USP dissolution apparatus 2 using paddle at a speed of 50 rpm using 900 ml of 0.1N HCl as dissolution media containing 0.1% sodium lauryl sulphate at 37±2°C. The ready to use soft jelly (2.5 gm) containing 5.0 mg of glibenclamide was used in the dissolution test. 5 ml of sample was withdrawn at the interval of every 5 min and the drug solution was replaced with the same volume of 0.1N HCl (pH 1.2) maintained at 37±2°C. 1 ml of the filtered sample was diluted up to 50 ml with methanol and absorbance was measured at 255 nm using HPLC [8, 9].

Evaluation of taste masking

5 ml of pH 6.8 phosphate buffer (to simulate salivary pH and volume) was used to study the taste masking efficiency of jelly preparation. One jelly equivalent to 5.0 mg of glibenclamide selected from batch F5 was placed in 50 ml beaker. 5 ml of the buffer solution was then added and the bottles were allowed to stand for 60 sec and 120 sec, respectively. After the specified time, the suspensions were filtered using 0.45µ nylon filters. The filtrates were analyzed for drug content. The test was performed in triplicate [10, 11].

Stability studies of soft gel

A physically stable oral gel retains its viscosity, color, clarity, taste, and odor throughout its shelf-life. Gels were checked for syneresis during storage. A freshly made sample should serve as a reference standard for subjective evaluations.

The samples were kept at different temperatures (0-8°C and at room temperature) for 3 months. The samples of soft gel were observed for pH, viscosity and appearance at the interval of one month. All the measurements were performed after allowing the samples to be equilibrated at 25°C for 2 h [4].

HPLC Method

Chromatographic condition:

Column: C8 column (phenominex) (250×4.6mm, 5µm particle size)

Mobile Phase: Phosphate buffer of pH 6.8: methanol (75:25)

Detector: UV detection at 253nm

Loop size: 20 µl

Stock standard solutions of Glibenclamide were freshly prepared in Methanol as 1g/ml. Calibration curve for each of analytes after appropriate dilution of stock solution to obtain final concentrations of 2, 4, 6, 8, 10 µg/ml for Glibenclamide (Fig. 1). The calibration curve was prepared taking the peak area of the analytes (Glibenclamide) versus the concentration (µg/ml) using a linear least squares regression as the mathematical model. The regression equation of the calibration curve was then used to calculate the drug content, and *in vitro* drug release [12].

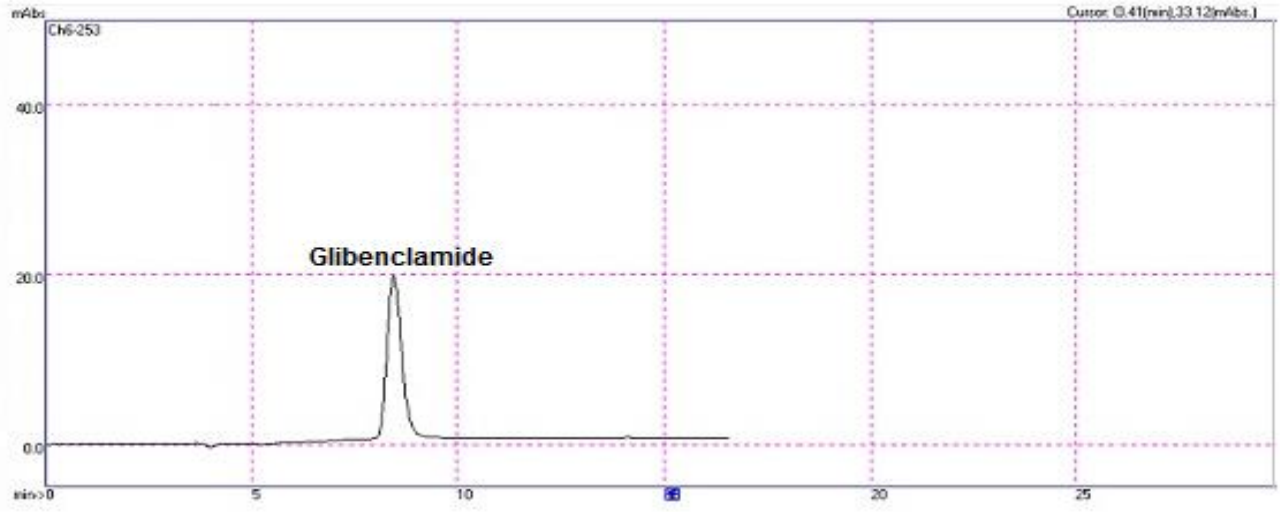

Fig 1: RP-HPLC chromatogram of Glibenclamide

RESULT AND DICSUSSION:

General appearance

The results of evaluation of Glibenclamide soft gel batches are shown in Table 1.

Table 1: Composition of various jelly formulations

S.NO.	INGREDIENTS (%)	BATCH CODE					
		F1	F2	F3	F4	F5	F6
1.	Glibencamide	0.5	0.5	0.5	0.5	0.5	0.5
2.	Citric Acid	0.1	0.1	0.1	0.1	0.1	0.1
3.	Sodium citrate	0.5	0.5	0.5	0.5	0.5	0.5
4.	Guar gum	0.3	0.3	0.4	0.4	0.5	0.5
5.	Pectin	0.3	0.4	0.3	0.4	0.3	0.4
6.	Stevia	0.3	0.3	0.3	0.3	0.3	0.3
7.	Mannitol	20.0	25.0	20.0	25.0	20.0	25.0
8.	Methyl paraben	0.1	0.1	0.1	0.1	0.1	0.1
9.	Colour	q.s	q.s	q.s	q.s	q.s	q.s
10.	Flavour	q.s	q.s	q.s	q.s	q.s	q.s
11.	Distilled water up to	100.0	100.0	100.0	100.0	100.0	100.0

All the batches of soft gels were transparent in appearance. The gel of batches F3, F4, and F5 were non-sticky and non-gritty while the gel of batch F6 was gritty. The non-gritty nature of the batches F3 to F5 may be due to the lower concentration of guar gum and pectin but F6 was gritty due to higher concentration of both guar gum and pectin.

Viscosity

Viscosity is the one important parameter which provides vital information during the optimization of the soft gel. The results of evaluation of glibenclamide soft jelly batches F1-F6 are provided in Table 2.

Table 2: Physio-chemical properties of oral soft jelly

Test parameter	Batch Code					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Clearity	T	T	T	T	T	T
Consistency	F*	L F	L F	A	A	A
Texture	NS &NG	NS & NG	NS & NG	NS & NG	NS & NG	S & NG
Odour	P & F	P & F	P & F	P & F	P & F	P & F
pH(n=3)	6.63±0.37	6.78 ±0.05	6.74 ±0.08	6.94 ± 0.08	6.98 ± 0.04	6.10 ± 0.06
Viscosity (n=3)	1868 ± 30	2578 ± 52	4325 ± 32	5790 ± 35	6548 ± 20	8161 ± 20
Syneresis at R.T	+++	++	++	+	-	-
Drug Content (n=3)	98.23 ± 0.15	98.26 ± 0.09	98.22±0.15	98.23±0.16	98.58±0.05	98.22±0.12

T: Transparent; A: Acceptable; NS: Non Sticky; NG: Non Gritty; S: Sticky; P: Pleasant; F: Fruity; LF: Fluid; SD: Standard Deviation (N=3)

The viscosity of the batches (as shown in Fig.2), F1 and F2 were low because of its fluid like consistency while the viscosity of the batches F5 and F6 were high because they were very thick in consistency.

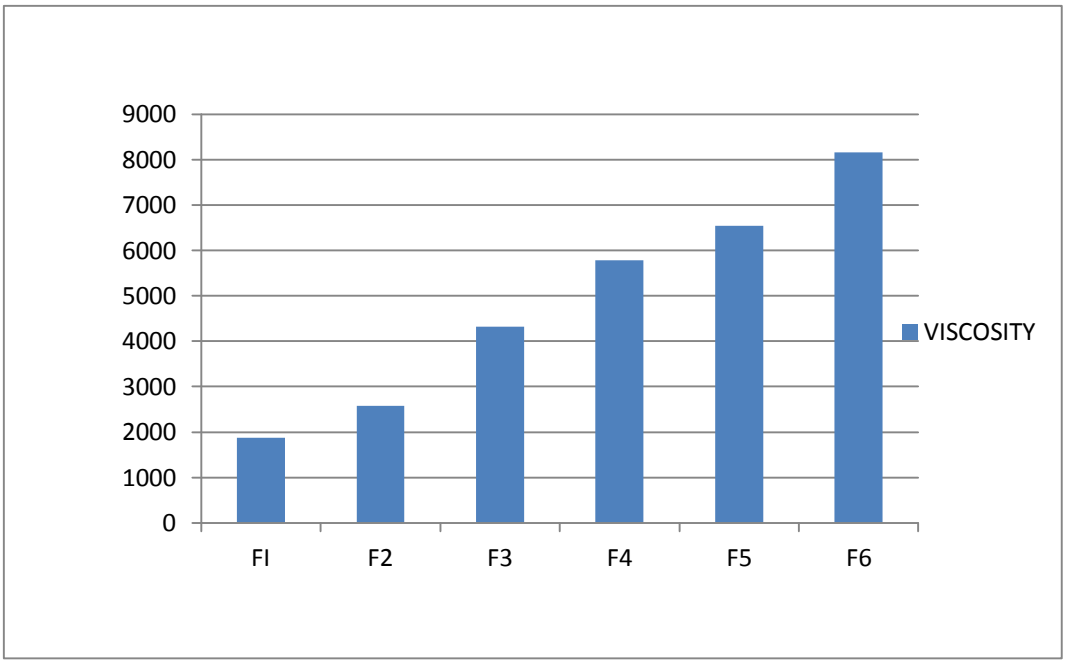

Fig 2: Viscosity of different soft jelly batches F1 to F6

But, viscosity of batch F5 was near to in house specification. Thus, it was considered for evaluation along with F3 and F4. As the jellies of batch F6 were thick in consistency, sticky and gritty, they may failed to give good mouth feel. The viscosity of the batches F4 and F5 were of acceptable consistency. The consistency and viscosity of the soft gels are co-related to each other because both are dependent on concentration of guar gum, pectin sodium citrate, and co-solute.

pH

The pH of the jelly preparation in the form of solution just before gelation is adjusted preferably to 4.0 or more up to 7.0. This is because when pH is below 4 jelly preparation liable to cause syneresis and stability of the preparation deteriorates in some cases. When the pH is 6 or more (close to neutrality), the jelly preparation is far more excellent in stability. Therefore, the pH of the formulated gels were adjusted and maintained in between 5 and 7 with the help of buffering agents such as citric acid and sodium citrate.

Syneresis

Syneresis is more pronounced in the gels where lower concentration of gelling agent is used. Syneresis was not noticed at room temperature probably due to binding of free water by co-solute. The batch F3 showed slight syneresis on standing, thus it was not considered for further studies. F5 and F6 showed very less degree of syneresis at room temperature and in refrigerator (2-8°C). Syneresis was observed after 24 h of jelly preparation.

Drug content

The drug content of all the batches were in between 98.3 ±1.0 for glibenclamide which is well within acceptable limits.

***In vitro* dissolution studies**

The results shown in reveals that jelly of the batches F5 exhibited acceptable consistency and viscosity. Thus, it was subjected to dissolution study to draw any conclusion and their percentage drug release at different time intervals has been shown in Fig.3.

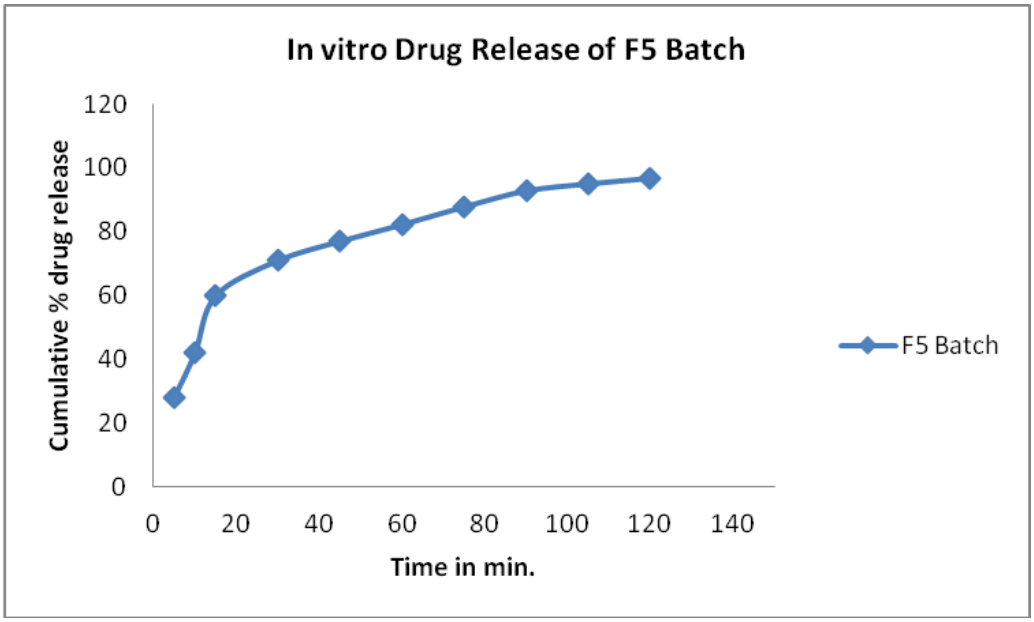

Fig 3: Release of Glibenclamide containing jelly batch F5 in 0.1N HCl

Table 3: Stability study of oral soft jelly batch F5

S. No.	Storage condition	Months	General appearance	Syneresis	pH	Viscosity	Drug content
1.	2-8°C	Initial	Non Gritty	+	6.80	6540	98.44
		1	No change	+	6.74	6572	98.00
		3	No change	++	6.68	6592	97.12
2.	25 ± 5 °C	Initial	Non Gritty	+	6.80	6540	98.44
		1	No change	+	6.70	6549	97.86
		3	No change	+	6.45	6511	97.50

Stability studies

The results of short-term stability studies, shown in Table No.3 indicated insignificant changes in pH, viscosity and appearance in the optimized formulation with time.

Precipitation of drugs in the soft gels was not observed in any of the gels. Also, insignificant syneresis was not observed in any of the samples at both temperatures. Therefore, it is recommended that soft gel should be stored at about 25°C.

Discussions

From Table No. 2 and Table No.3 it was found that the optimized soft jelly batch F5 was substantially stable at both room temperature and also at low temperature, thus storage at room temperature is possible. Also, Fig.2 showed F5 was able to release 85% of drug before 2 h, thus meets in house specification. Finally, it was found out that batch F5 meets all laid in house specifications thus is the optimized batch.

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