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Formulation and evaluation of glibenclamide loaded mouth dissolving films with xanthan gum as film forming polymer

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Abstract

Glibenclamide is a BCS class II oral hypoglycemic agent that is widely indicated for the management of type 2 diabetes mellitus and has the ability to pass through the gastrointestinal mucosa. The need to rapidly maintain glucose levels in the body is subject to design systems that can release drugs into the systemic circulation in a very short time. The present study attempts to prepare glibenclamide loaded mouth dissolving films (GMDFs) using xanthan gum, as it forms polymers for rapid absorption of the drug in systemic circulation. The solvent casting method was used to produce oral disruptive film containing glibenclamide. All formulations exhibited instant release drug release, rapid dissolution and optimal mechanical strength. The GMDF3 formulation exhibited the highest drug content (96.1±5.89) and all aggregates were found to decompose within 40 seconds. The GMDF1, GMDF2 and GMDF3 formulas were able to release 97, 96 and 98% 10 drugs at the end of 10 minutes, respectively, while GMDF4 and GMDF5 were able to release 94 and 90%, respectively. The results of rapid stability studies have shown that all aggregates are stable under extreme conditions.

Key words

Mouth dissolving films, glibenclamide, folding endurance, stability, hypoglycemic, xanthan gum

1. Introduction

Various pharmacologically active ingredients have been researched for absorption through the mucous membrane[1] like nitroglycerine.The Formulation of fast dissolving films is rapidly gaining attraction among the pharmaceutical researcher as delivery system for systemic delivery of drugs through the oral mucosa. The primary advantage of these systems is that they do not need to be swallowed or chewed, yet they break down within a minute in the oral cavity [2]. The ability to manage without swallowing makes these systems particularly beneficial for children,

the elderly and non-assisted patients. The large capillary network beneath the oral mucosa is rapidly absorbed and increases the bioavailability of drugs. It is also beneficial as it bypasses the first proximal liver metabolism that occurs on oral administration using conventional dosage forms[3]. Some natural polymers, such as polyvinyl alcohol, polyvinyl pyrrolidone, hydroxypropylene methyl cellosos, chitosan and polymer, have been researched for manufacturing of MDFs4. MDF has been researched for rapid release[5] and continuous release of drug particles[6]. Glibenclamide is a widely prescribed oral hypoglycemic agent for the management of type 2 diabetes mellitus. It belongs to the second generation sulfonyl urea and increases the sensitivity of peripheral insulin receptors by stimulating insulin release from pancreatic cells. It is the most lipophilic drug of Class II (BCS Class II)[7] of the biopharmaceutical classification scheme. In oral administration it undergoes hepatic first pass metabolism and only 40-50% of the drug is absorbed. The need to rapidly maintain glucose levels in the body is subject to design systems that can release drugs into the systemic circulation in a very short time. To overcome the above problem many researchers have researched MDFs or fast soluble tablets containing glybenclamide [6,8-11]. These tablets or films are made using synthetic polymers with excellent results. The present study attempts to prepare glibenclamide-containing MDF using xanthan gum, as it forms polymers for rapid absorption of the drug in systemic circulation.

2. Materials and methods

Glibenclamide was obtained as a gift sample from Flamingo Pharmaceuticals, Mumbai, Xanthan Gum, Sucrose, Sodium Starch Glycolate and citric acid was extracted from Oxford Lab Fine Chemicals in Mumbai. Polyethylene Glycol (PEG 400) was procured from Merck India Limited. Acetone, methanol, ethanol, hydrochloric acid, sodium hydroxide, potassium di hydrogen phosphate, sodium chloride and all the other chemicals required were purchased from Oxford Lab Fine Chemicals LLP, Maharashtra. Distilled water prepared using a glass distillation unit was used throughout the study.

3. Preparation of GMDFs[12]

Solvent casting techniques are the most widely used methods to create smooth films. MDFs of gliben clamide were prepared using solvent casting method. The aqueous solution of the polymer was dissolved in xanthan gum taken in 5ml distilled water and set aside to remove trapped air bubbles. The drug is dissolved in a very small amount in a suitable solvent and in a polymer solution. All other components such as plasticizers, sweeteners, salivary agents, etc are soluble in distilled water. The solution was stirred at 1000 rpm for 10 min with constant stirring into the polymer solution. The resulting mixture is poured on a petri dish in the form of a film and dried in a hot air oven at 50°C for 24 hours. After 24 hours the films are carefully removed from the petri dish and any defects are noticed. The films were wrapped in butter paper or aluminum foil and stored in desiccators until further use. The composition of MDFs is shown in Table 1

4. Evaluation of MDFs[13]

Prepared MDFs were analyzed for physical parameters such as thickness, weight variation, folding endurance and appearance. The drug content, *in vitro* disintegration time, *in vitro* drug release and rapid stability were also studied.

4.1 Weight variation

The films are largely subjected to mass variation by weighing randomly selected films. These decisions were made for each formulation.

4.2 Thickness

The thickness of each film is measured using a vernier calliper at different positions of the film and the average thickness is calculated.

4.3 Folding endurance

Folding endurance is determined by bending repeatedly until a patch breaks. The value of folding endurance is given by the number of times the film can be folded without breaking / cracking.

4.4 Drug content test

The Films enriched with 1% sodium lauryl sulfate, dissolved in100ml phosphate buffer pH 6.8. After the film was completely dissolved, the amount of glibenchlamide was estimated using UV spectrophotometry by measuring the absorption at 292 nm.

4.5 Moisture content

Films of 4 cm^2 region were cut and properly weighed and stored in a desiccator containing fused anhydrous calcium chloride. After 24 hours, the films were removed and weighed again. The moisture content of the film is calculated by the following formula

% Moisture content = (Initial weight – Final weight)/Initial weight x 100

4.6 Moisture uptake

The pre-weighing Films uncovered for three days using a saturated solution of sodium chloride at relative humidity 84% at 28°C. After 3 days the films were removed from the desiccators and weighed. The moisture absorbed by the films was calculated using the following formula

% Moisture uptake = (Final weight – Initial weight)/Initial weight x 100

***4.7 In-vitro* Disintegration time**

To determine the disintegration time, films were placed on glass petri dish containing 10 mL of distilled water. The time required to break the film is recorded as the *in vitro* disintegration time of the film.

***4.8 In vitro* dissolution study**

A film of 4 cm^2 was placed on a glass petri dish and 25 mL of soluble medium (phosphate buffer pH 6.8) was added to it. The solution was stirred at 100 rpm throughout the study. Sections of 2.5 mL were withdrawn and filled with fresh buffer in equal amounts of medium over a period of

1, 2, 3, 4, 5 and 10 min. The collected samples were filtered and the concentration of glibenclamide in each sample was measured at 292 nm using a UV spectrophotometer.

4.9 Stability study

Formulations were prepared according to the guidelines of the International Conference on Harmonization (ICH) were subjected to stability studies. The films were packed in aluminum foil and stored for 3 months at 40°C/75% RH under rapid test conditions and their physical appearance, drug content, *in vitro* disintegration time, drug release at 1 month intervals of time and results were reported.

5. Results and discussion

5.1 Physical parameters of films

The different physical properties of the prepared films were analyzed according to the reported methods and the results obtained were reported in Table 2 and Figure 1. The thickness of the films was measured at five different locations to ensure the uniformity of the results. The weight variation was calculated as deviation from the average weight and is reported as the percentage weight variation obtained from the 10 films. Folding tolerance and thickness are found to be related to the film-forming polymer aggregate in the formulation with the exception of GMDF5, where, in contrast to reduced folding endurance, the polymer is unable to retain moisture during high volume manufacturing and hence a low mechanical strength.

5.2 Drug Content estimation in films

The drug content in the film formulations prepared according to the method reported by Velmurugan et al[14]. The results are described in Table 3 and Figure 2. Results show that the highest drug content of formulation GMDF3 (96%) and all the formulations shows drug content within the limit 85-110%. The amount of drug loading in the films initially increased with increasing polymer ratio, but decreased GMDF4 and GMDF5, indicating that high swelling of the polymer was detrimental to the hydrophobic drug that exceeded the polymer matrix.

5.3 In vitro disintegration of MDFs

In vitro disintegration of films was performed using the Petri dish method to ensure that the films provide a faster release of glibenlamide. The results obtained for the film disintegration studies are shown in Table 4.

The disintegration time of all the aggregates is less than 40 seconds, which indicates that the aggregates are dissolving rapidly and can release drug in a short time.

5.4 In vitro release study

The release of glibenclamide from prepared films using different concentrations of Xanthan gum is shown in Table 5. All formulations were found to decompose within 40 seconds, which paved the way for the rapid release of glibenclamide from the films. It was found that the ratio of polymer content did not play a significant role during the disintegration of the films.

The results show that the drug was able to release the entire volume in about 10 minutes. GMDF3 (98%) released the maximum amount of drug. This indicates that the cross-linked

matrix of the polymer increases the ratio as a polymer beyond the optimum value for drug entrapment. The release data were subjected to various mathematical models to determine the dynamics of the release and the regression value of each was calculated. The results of the mathematical modeling of the data are presented in Table 6.

From the table 6 it can be ascertained that the formulation follow mixed order kinetics. The best-fitting model (Higuchi's model) exhibits a fickian diffusion in which the drug release is proportional to the release time.

5.5 Stability studies

Stability study of all films has been studied for a short time. The films were stored at 40 ° C at 75% relative humidity and tested at the end of 1 and 3 months. The results obtained were found to be within the allowable range and are shown in Tables 7 and 8. No significant difference was found in the parameters tested at the end of the study.

6. Conclusion

The aim of the present study is to formulate fast dissolving film of glibenclamide to rapidly release the substance that helps maintain the glycemic level in the serum. This study was able to justify the use of films to quick release medicine using natural polymer xanthan gum as a film matrix and PEG-400 as a plasticizer. From the film release drug studies suggest that this film is a good approach to improve the bioavailability of glibenamide and to improve patient adherence to the prescribed diet due to ease of film administration.

7. References

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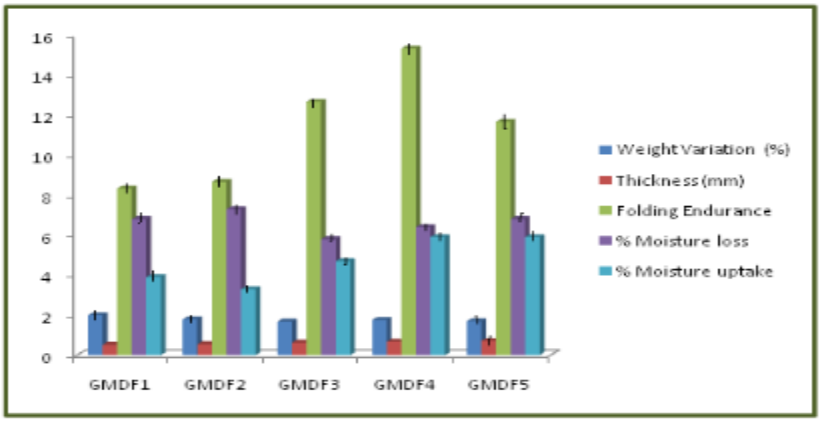

Figure 1:- Physical parameters of the prepared films

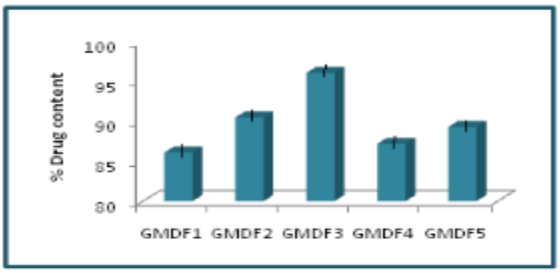

Figure 2:- Drug content analysis of MDFs

Table 1:- Composition of GMDF

S. No	Formulation	GMDF 1	GMDF 2	GMDF 3	GMDF 4	GMDF 5
1	Glibenclamide (mg)	98.175	98.175	98.175	98.175	98.175
2	Xanthan gum (mg)	100	150	200	250	300
3	Poly ethylene glycol (mg)	0.4	0.4	0.4	0.4	0.4
4	Sodium starch glycolate (mg)	10	10	10	10	10
5	Citric acid (mg)	5	5	5	5	5
6	Sucrose (mg)	5	5	5	5	5
7	Vanillin (mg)	5	5	5	5	5
8	Water (mL)	8	8	8	8	8

GMDF:- Glibenclamide Mouth Dissolving Film

Table 2:- Physiochemical Parameters of films

Formulation	Weight Variation (%)	Thickness (mm)	Folding Endurance	% Moisture loss	% Moisture uptake
GMDF1	1.996±0.104	0.51±0.07	8.33±.15	6.8±1.28	3.9±1.21
GMDF2	1.794±0.279	0.54±0.03	8.66±1.52	7.3±0.89	3.3±1.36
GMDF3	1.674±0.386	0.62±0.06	12.66±1.52	5.8±1.26	4.7±0.87
GMDF4	1.757±0.131	0.67±0.04	15.33±1.15	6.4±1.75	5.9±0.95
GMDF5	1.698±0.213	0.71±0.08	11.66±1.15	6.8±1.45	5.9±0.79

Values are mean ± SD of 3 replicates

Table 3:- Drug content in the MDFs

Formulation	% Drug Content
GMDF1	86.1±3.18
GMDF2	90.5±2.31
GMDF3	96.1±5.89
GMDF4	87.2±4.42
GMDF5	89.3±7.26

Table 4:- Disintegration time of the MDFs

Formulation	Disintegration time (sec)
GMDF1	36
GMDF2	34
GMDF3	37
GMDF4	35
GMDF5	36

Table 5:- *In vitro* drug release of formulations

Time (minutes)	% Drug Released				
	GMDF1	GMDF2	GMDF3	GMDF4	GMDF5
0	0	0	0	0	0
1	32±0.3	29±0.1	26±0.1	23±0.1	19±0.1
2	42±0.2	35±0.2	32±0.1	31±0.2	32±0.1
3	55±0.1	38±0.1	34±0.2	35±0.2	32±0.2
4	59±0.2	47±0.1	47±0.3	41±0.3	43±0.3
5	68±0.1	61±0.2	59±0.4	54±0.3	51±0.4
10	97±0.3	96±0.4	98±0.5	94±0.4	90±0.6

Table 6:- Drug release kinetics

Formulation Code	Zero order R^2	First order R^2	Higuchi's model R^2	Peppas model R^2
GMDF1	0.8831	0.9504	0.9977	0.6948
GMDF2	0.9468	0.9179	0.9581	0.6404
GMDF3	0.9655	0.8865	0.9415	0.6087
GMDF4	0.9719	0.9110	0.9380	0.6343
GMDF5	0.9726	0.9389	0.9448	0.6793

Table 7:- Results of stability study (1 month)

Parameter	GMDF1		GMDF2		GMDF3		GMDF4		GMDF5	
	Initial	Final	Initial	Final	Initial	Final	Initial	Final	Initial	Final
Thickness (mm)	0.51	0.51	0.54	0.54	0.62	0.62	0.67	0.67	0.71	0.71
Folding endurance	8.33	8.33	8.66	7.66	12.66	11.66	15.33	14.66	11.66	11.66
In vitro disintegration time (sec)	36	36	34	35	37	37	35	35	36	37
Drug content (%)	86.1	85.8	90.5	90.1	96.1	95.9	87.2	86.5	89.3	89.1

Table 8:- Results of stability study (3 month)

Parameter	GMDF1		GMDF2		GMDF3		GMDF4		GMDF5	
	Initial	Final	Initial	Final	Initial	Final	Initial	Final	Initial	Final
Thickness (mm)	0.51	0.51	0.54	0.54	0.62	0.62	0.67	0.67	0.71	0.71
Folding endurance	8.33	8.33	8.66	7.66	12.66	11.66	15.33	14.66	11.66	11.33
In vitro disintegration time (sec)	36	37	34	35	37	38	35	36	36	37
Drug content (%)	86.1	85.6	90.5	89.9	96.1	95.7	87.2	86.2	89.3	89