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Research Article

FORMULATION AND EVALUATION OF ORAL SOFT GEL OF METFORMIN: A PATIENT FRIENDLY DOSAGE FORM

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ABSTRACT

Convenience of administration and patient compliance are gaining significant importance in the design of dosage forms. Metformin hydrochloride is an orally administered antihyperglycemic agent, used in the management of non-insulin-dependent (Type-2) diabetes mellitus. Dysphagia (difficulty in swallowing) is common among all age group, especially in elderly and pediatrics. Unfortunately, a high percentage of patients suffering from Type 2 diabetes are elderly people showing dysphagia. Formulation of batches oral soft gel of metformin was carried out using hydrophilic polymer Gellan gum at concentrations ranging from 0.2-0.4 % w/v and sodium citrate at two different concentrations (0.3 % and 0.5%). The prepared batches were evaluated for appearance, viscosity, pH, drug content, syneresis, *in vitro* drug release and taste masking. The batch with 0.4% w/v gellan gum and 0.5% sodium citrate showed 85% drug release at 15 minutes and all the desired organoleptic properties. The taste masking was carried out using nonnutritive sugar and flavors. The optimized batch showed substantial stability when subjected to short term stability study (0-8 °C and room temperature). The unit dose packing overcame the problem of dosing error.

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INTRODUCTION

Convenience of administration and patient compliance are gaining significant importance in the design of dosage forms. More emphasis is now given to the development of organoleptically elegant and patient friendly drug delivery system for pediatric and geriatric patients (1, 2).

Elderly people, critically ill persons, persons with dysphagia find it difficult to swallow the tablets and hard gelatin capsules and thus do not comply with the prescription, leading to ineffective therapy.

Unfortunately, a high percentage of patients suffering from Type 2 diabetes are elderly people with dysphagia. The situation becomes worse as the antidiabetic medication has to be taken lifelong every day and the high dose makes the tablets big. A tablet comprising 1000 mg of metformin hydrochloride would need to have a size of 19 mm×10.5 mm (Glucophage® 1000mg tablets) or more as functional excipients are needed to modify release of drug from the dosage form and would be very difficult to swallow [3,4]. The only available alternative for patients with dysphagia is metformin hydrochloride oral solution RIOMET®(500 mg/5 mL)**.** This composition is only available in the United States, and it has well known disadvantages of all kind of syrup formulations (3).

The patients with dysphagia can get choked while consuming liquid formulation which can be eliminated by administering liquid formulations with high viscosity which ae easy to swallow (4-7). Thus, oral gel formulation of metformin was prepared.

The gel dosage form overcomes the disadvantages of liquid dosage form and solid dosage forms. The problem of dose measurement by patients is overcome as oral medicated gels are to be packed in unit dose packs.

EXPERIMENTAL MATERIALS AND METHODS

Metformin hydrochloride (Intas Pharma, Ahmedabad), Gellan Gum, Sucralose (Parsh Pharm. Chem., Vapi, India.), Methyl paraben, Propyl paraben (Apex Pharma, Mumbai., India) strawberry flavor (Dewang Corporation, Baroda, India) were obtained as gift samples. All other chemicals like Citric acid, Sodium citrate, Mannitol, purchased were of analytical grade.

Preparation of oral soft gel

All the required ingredients of the formulation were weighed accurately. Dry gellan gum powder was dispersed in 50 mL of distilled water maintained at 95 ºC. The dispersion was stirred at 95 ºC for 20 min

using a magnetic stirrer (Remi Magnetic Stirrer, Mumbai, India) to facilitate hydration of gellan gum. The required amount of mannitol was added to the gellan gum solution with continuous stirring and the temperature was maintained above 80 ºC. Then sucralose, citric acid, and preservatives (methyl paraben, propyl paraben) were added with stirring. At last, required amount of sodium citrate was dissolved into 10 mL of distilled water and added to the mixture. Continuously the weight of the gel was monitored during manufacturing and finally adjusted to 100 g with distilled water. The mixture containing gellan gum, metformin and other additives was packed in polyethylene bag with airtight seal. The mixture was cooled to room temperature for forming gel. The gels were prepared using four different concentrations of gellan gum (0.2, 0.3, 0.4 and 0.5%), each with two different sodium citrate concentrations (0.3 and 0.5%).

The formulations of metformin soft gel are shown in Table 1.

Evaluation of oral soft gel

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

Texture evaluation

Texture of the soft gel was evaluated in terms of stickiness and grittiness by mildly rubbing the gel between two fingers.

Table 1: Formulation of batches of Metformin oral soft gel

INGREDIENTS % w/v	BATCH CODE							
	OG 1	OG 2	OG 3	OG 4	OG 5	OG 6	OG 7	OG 8
Metformin	5	5	5	5	5	5	5	5
Gellan gum	0.2	0.2	0.3	0.3	0.4	0.4	0.5	0.5
Mannitol	20	20	20	20	20	20	20	20
Citric acid	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Sodium citrate	0.3	0.5	0.3	0.5	0.3	0.5	0.3	0.5
Sucralose	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Methylparaben	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
Propylparaben	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Raspberry flavor	2	2	2	2	2	2	2	2
Water, %, up to	100	100	100	100	100	100	100	100

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Rheological measurement

Viscosity of the all the batches of soft gels was measured using Brookfield DV-II+Pro viscometer. The viscosity of metformin soft gel was measured using spindle number LV4 at the rotation of 50 rpm at room temperature. The viscosity measurements were made in triplicate using fresh samples each time.

pH of the soft gel.

The pH of the final gel has got impact on stability & taste. The pH of metformin soft gel was measured using Electrolab Digital pH meter at room temperature.

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 not considered for further studies.

Drug content

About 5g of metformin soft gel was accurately weighed on an electronic balance and then transferred to 1000 mL volumetric flask. Then 900 mL of phosphate buffer (pH 6.8) was added to dissolve the gel. From that, 1 mL of the sample was withdrawn and diluted up to 50 mL with phosphate buffer pH 6.8. Samples were analyzed spectrophotometrically at 233 nm by UV spectrophotometer (Pharmaspec 1700, shimadzu) after filtering the sample through 0.45 µ filters. The gels comply with the test if not more than one of values thus obtained is outside the limits of 85-115 % of the average value and none is outside the limits 75 -125 %.

***In vitro* drug release** (8)

In vitro drug release studies were carried out using USP dissolution apparatus 2 using paddle at a speed of 100 rpm using 900 mL of pH 6.8 phosphate buffer as dissolution media at 37± 0.5 °c. The ready to use soft gel (5g) containing 250 mg of metformin was used in the dissolution test. Each time 5 mL samples were withdrawn at the interval of every five minutes and replaced with the same volume of phosphate buffer (pH 6.8) maintained at 37± 0.5 ºC. One ml of the filtered sample was diluted up to 50 mL with phosphate buffer pH 6.8 and absorbance was measured at 233 nm using UV Spectrophotometer.

Table 3: Comparison of dissolution profile of OG6 and OG7

TIME (MIN)	CCPR	
	OG6	OG7
0	0	0
5	55.616	48.609
10	75.939	67.945
15	91.187	79.920
20	96.414	94.237
25	99.276	99.318

CCPR: Corrected Cumulative Percentage Release

Evaluation of taste masking

Amount of five gram of optimized formulation containing 250 mg metformin was given to taste panel experts and they were told to keep the gel in mouth for 5 sec. The volunteers were instructed not to swallow the gel. The volunteers were asked to comment on the bitterness, aftertaste, sweetness and flavor of the gel. Mouth feel in terms of grittiness was also checked. Bitterness and aftertaste were graded from non-bitter and nonsaline (-) to slightly saline and bitter (+) to bitter and saline (++) to very bitter and strong saline (+++). Sweetness was graded from less sweet (+) to sweet (++) to very sweet (+++). Flavor and mouth feel were assessed from less (+) to moderate (++) to good (+++).

Table 4: Taste evaluation of Metformin gellan gum soft gel (batch OG6)

Parameters	Volunteers									
	1	2	3	4	5	6	7	8	9	10
Bitterness and saline taste	-	-	-	-	-	-	-	-	-	-
Aftertaste	-	-	-	+	-	-	-	-	-	-
Sweetness	+++	+++	+++	+++	+++	+++	+++	+++	++	+++
Flavor	++	+++	+++	++	+++	++	+++	+++	+++	++
Mouth feel	+++	+++	+++	++	+++	+++	+++	++	++	++

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.

Table 5: Stability studies of the Gellan gum Soft Gel (batch OG6)

	Gellan gum soft gel batch OG6			
Temperature	0-8° C			
Weeks	1st	2nd	3rd	4th
Viscosity (cps)	7135	7143	7148	7154
pH	5.78	5.82	5.84	5.86
Temperature	Room.Temperature. (25°C)			
Weeks	1st	2nd	3rd	4th
Viscosity (cps)	7145	7157	7162	7159
pH	5.79	5.80	5.78	5.79

The samples were kept at different temperatures i.e., 0-8 ºC and room temperature for four weeks. The samples of soft gel were observed for pH, viscosity and appearance at the interval of one week. All the measurements were performed after allowing the samples to be equilibrated at 25°C for two hours.

RESULTS AND DISCUSSION

Appearance

The results of evaluation of metformin soft gel batches are shown in Table 2. All the batches of soft gels were transparent in appearance. The gel of batches OG5, OG6 and OG7 were non-sticky and non-gritty while the gel of batch OG8 was gritty. The nongritty and nature of the batches OG5 to OG7 was due to the optimized concentration of gellan gum and sodium citrate but OG8 was gritty due higher concentration of both gellan gum and sodium citrate.

Consistency

Gellan gum has a good gelling power hence it can produce gels at low concentration. Table 2 shows, batches OG1 and OG2 exhibited fluid like consistency while the gels of batches OG7 and OG8 were thick in consistency, as consistency of gels depends on the concentration of the polymer. Batches OG5, OG6 and OG7 had acceptable in consistency. These visual inspection results are supported by the viscosity measurements.

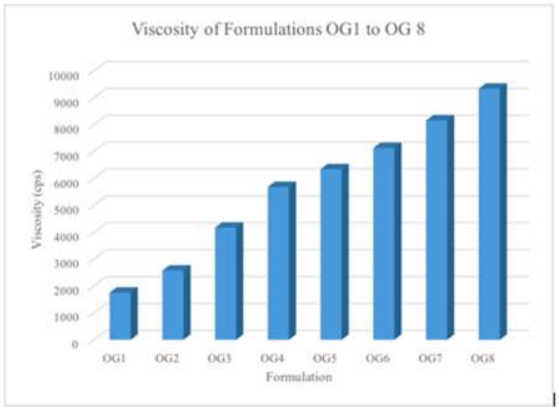
Viscosity

Viscosity is the one important parameter which provides important information during the optimization of the soft gel. The results of evaluation of metformin gellan gum soft gel batches OG1 – OG8 are shown in Table 2 and Figure 1.

Table 2: Evaluation of gellan gum soft gel batches OG1 – OG8

Test Parameters	Results							
	OG1	OG2	OG3	OG4	OG5	OG6	OG7	OG8
Clarity	T	T	T	T	T	T	T	T
Consistency	Fluid	Fluid	Less fluid	Less fluid	Acceptable	acceptable	Slightly thick	Very thick
Texture	NS and NG	NS and NG	NS and NG	NS and NG	NS and NG	NS and NG	Non-sticky and slightly gritty	Sticky And gritty
pH of the gel	5.67	5.75	5.72	5.82	5.70	5.79	5.65	5.77
Viscosity (cps)	1756	2578	4175	5690	6348	7135	8162	9345

T –Transparent, NS- Nonsticky, NG- Nongritty, cps- centipoise



The viscosity of the batches OG1 and OG2 were low because of its fluid like consistency while the viscosity of the batches OG7 and OG8 were high because they were very thick in consistency. But viscosity of batch OG7 was near to in house specification. Thus, it was considered for evaluation along with OG5 and OG6. As batches OG7 and OG8 were thick in consistency, sticky and gritty, they failed to give good mouth feel. The viscosity of the batches OG6 and OG7 were acceptable, supported by their acceptable consistency. The consistency and viscosity of the soft gels are related to each other because both are dependent on concentration of gellan gum, sodium citrate and co-solute.

Effect of concentration of co-solute (mannitol and sucralose) on the viscosity and consistency of all the batches of the soft gel was same because it was constant in all the batches. It is clearly evident from the Table 2 that changes in the viscosity and consistency of soft gel is greatly because of change in

concentration of gellan gum and slightly because of change in concentration of sodium citrate. Free carboxylate groups are present in the structure of gellan gum; therefore, gellan gum is anionic in nature and thus it would undergo ionic gelation in the presence of both divalent and monovalent cations such as Ca^{++}, Mg^{++},K^{+}, Na^{+} and H^{+} from acid (9). However, its affinity for divalent cations such as Ca^{2+} and Mg^{2+} is much stronger than monovalents such as Na^{+} and K^{+} (10).

Therefore, gels of batch OG6 and OG7 were selected for further studies under drug content and in-vitro dissolution studies.

pH

The pH of the maximum stability of metformin in aqueous phase is in between 4 to 9 [7]. It is also reported that the apparent viscosity of gellan gum dispersion can be markedly increased by increase in both pH and cation concentration (11, 12). Therefore, the pH of the formulated gels was adjusted and maintained in between 5 to 7 with help of buffering agents such as citric acid and sodium citrate. The amount of citric acid was kept minimum, i.e. just to adjust the required pH. Sodium citrate was selected as a salt to contribute cation because it also act as sequestrant, buffering agent and helps in maintaining mechanical property of the gel(13). The pH of gels of batches OG1 – OG8 are shown in Table 2.

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. Syneresis was not noticed at room temperature probably due to binding of free water by co-solute (14)**.** The batch OG5 showed slight syneresis on standing thus it was not considered for further studies.

Drug content

The drug content of the batch OG6 and batch OG7 were 99.6±1.56% and 99.1±1.48% respectively which is well within the acceptable limit.

***In vitro* dissolution studies**

The results shown in Table 2 reveal that gels of the batches OG6 and OG7 exhibited acceptable consistency and viscosity. Thus, they were subjected to dissolution study to draw further conclusion.

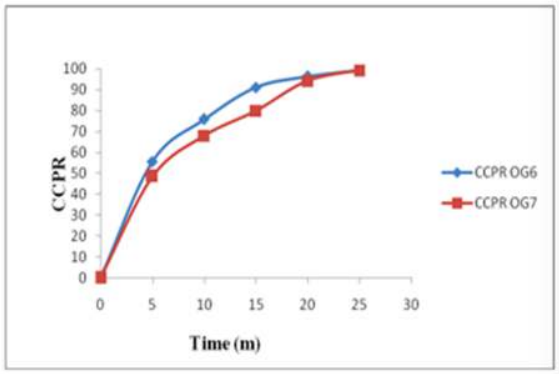


Figure 2: Comparison of dissolution profile of OG6 and OG7

Figure 2 shows, batch OG6 took 15 mins to release 85% of drug where as it took 20 min in case of batch OG7. There was no significant difference between release profiles of the OG 6 and OG7 but release profile of batch OG7 does not meet the in-house specification as batch. Also, viscosity of the Batch OG7 was out of in house specification, also it shows slightly gritty structure which may decrease the mouth feel thus Batch OG6 is the optimized batch.

Taste evaluation

The results of taste evaluation of the batch OG6 Metformin gellan gum gel are shown in Table 4. All the ten volunteers perceived the soft gel as non-bitter. The probable reason is that the gelling agents can lower diffusion of bitter substances from the gel to the taste buds. However, the volunteers reported that a slight bitter after taste. Mannitol was selected as a sweetener in soft gel to mask the taste of Metformin. As it is an antidiabetic formulation sucralose was selected as an auxiliary sweetener because it is non-nutritive and 300-1000 times sweeter than the sucrose (14) Raspberry flavor was selected because to certain extent it helps in masking the bitter taste of drug also improves patient acceptance.

Short term stability studies

The results of short term stability studies, shown in Table 5**,** indicated insignificant changes in pH, viscosity and appearance in the optimized formulation with time. Precipitation of Metformin in the soft gels was not observed in any of the gels. Also, syneresis was not observed in any of the samples at both temperatures. Therefore, it is recommended that soft gel should be stored at about 25º C.

Conclusions

From Table 4 and 5it was found that the optimized soft gel batch OG6 was substantially stable at both room temp and also at low temp thus storage at room temp can be used. Also, the gel showed good taste masking with acceptable mouth feel. Figure 2showed OG6 was able to release 85% of drug before 15 min thus meets in house specification. Finally, it was found out that batch OG6 meets all laid in-house

specifications thus is the optimized batch.

Thus, batch OG6 was the optimized batch.

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