RESEARCH ARTICLE

Formulation, development and evaluation of patient friendly dosage forms of metformin, Part-II: Oral soft gel

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Dionvenience 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-dependant (type-2) diabetes mellitus. Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly and pediatrics. Unfortunately, a high percentage of patients suffering from type-2 diabetes are elderly people showing dysphagia. Persons suffering from dysphagia may get choked when they consume liquid formulation, thus to alleviate such problem liquid formulation of high viscosity was prepared. Formulation of oral soft gel batches 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 not only showed 85% drug release at 15 min, but 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 problem of dose measurement by patients was outweighed as oral medicated gels are to be packed in unit dose container.

Key words: *Gellan gum, metformin hydrochloride, oral soft gel*

INTRODUCTION

Convenience of administration and patient compliance are gaining significant importance in the design of dosage forms. Recently, more stress is laid down on the development of organoleptically elegant and patient friendly drug delivery system for pediatric and geriatric patients.[1,2]

Many patients, elderly people and person with dysphagia find it difficult to swallow the tablets and hard gelatin capsules and thus do not comply with prescription, which results in high incidence of noncompliance and ineffective therapy.

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. A tablet comprising 1000 mg of metformin hydrochloride would need to have a size of 19 mm × 10.5 mm (Glucophage® 1000 mg 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 such patients is the above mentioned 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 compositions.[3]

The patients with dysphagia can be choked by water while consuming liquid formulation which can be eliminated by administering liquid formulations with high viscosity.[5-7] Thus, gel formulation of metformin 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.

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EXPERIMENTAL MATERIALS AND METHODS

Metformin hydrochloride (Intas pharma, Ahmedabad) and gellan gum, sucralose (Parsh Pharm. Chem., Vapi, India). Methyl paraben, propyl paraben (Apex Pharma, Mumbai, India) strawberry flavor (Dewang Corporation, Baroda, India). 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°C. The dispersion was stirred at 95°C for 20 min using a magnetic stirrer (Remi magnetic stirrer 2MLH, 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°C. Metformin was added with stirring. Then sucralose, citric acid, and preservatives (methylparaben, propylparaben) were added with stirring. Finally, required amount of sodium citrate was dissolved in 10 ml of distilled water and added to the mixture. At last raspberry flavor was added. The weight of the gel was monitored continuously during manufacturing and finally it was adjusted to the 100 gm with distilled water. The mixture containing gellan gum, metformin, and other additives was packed in polyethylene bag with airtight seal. The mixture was allowed to cool to room temperature to form 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%).

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.

Rheological measurement

Viscosity of the all the batches of soft gels was measured using Brookfield DV-II+Pro viscometer. The metformin soft gel 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 samples each time.

pH of the soft gel

The pH of the final gel has got influence not only on stability, but also on the taste. The pH of metformin soft gel was measured using Electroquip 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 rejected and not considered for further studies.

Drug content

Five grams 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 of 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 was 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 ± 2°C. The ready to use soft gel (5 gm) containing 250 mg of metformin was used in the dissolution test. Five milliliters of sample was withdrawn at the interval of every five minutes and the drug solution was replaced with the same volume of phosphate buffer (pH 6.8) maintained at 37 ± 2°C. One milliliter 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-Pharmaspec 1700 Spectrophotometer.

Evaluation of taste masking

Five grams 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 s. The volunteers were instructed not to swallow the gel. They 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 (+ + +).

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 1: Formulation of batches of metformin oral soft gel

Ingredients	Batch code							
% w/v	MG1	MG2	MG3	MG4	MG5	MG6	MG7	MG8
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

Table 2: Evaluation of gellan gum soft gel batches MG1–MG8

Test parameters	Results							
	MG1	MG2	MG3	MG4	MG5	MG6	MG7	MG8
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: centipoises

The samples were kept at different temperatures (0-8°C 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 1. All the batches of soft gels were transparent in appearance. The gel of batches MG5, MG6, and MG7 were non-sticky and non-gritty while the gel of batch MG8 was gritty. The non-gritty nature of the batches MG5 to MG7 may be due to the suitable concentration of gellan gum and sodium citrate but MG8 was gritty due to 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 MG1 and MG2 exhibited fluid like consistency while the gels of batches MG7 and MG8 were thick in consistency. As the consistency of gels depends on the concentration of the polymer, batches MG5, MG6, and MG7 had acceptable consistency. These visual inspection results are supported by the viscosity measurements.

Viscosity

Viscosity is the one important parameter which provides vital information during the optimization of the soft gel. The results of evaluation of metformin gellan gum soft gel batches MG1–MG8 are shown in Table 2. The viscosity of the batches (as shown in Figure 1) MG1 and MG2 were low because of its fluid like consistency while the viscosity of the batches MG7 and MG8 were high because they were very thick in consistency. But, viscosity of batch MG7 was near to in house specification. Thus, it was considered for evaluation along with MG5 and MG6. As batches MG7 and MG8 were thick in consistency, sticky and gritty, they failed to give good mouth feel. The viscosity of the batches MG6 and MG7 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

Table 3: Comparison of dissolution profile of MG6 and MG7

Time (min)	CCPR	
	MG6	MG7
0	0	0
5	55.62587	48.60942
10	75.94935	67.96512
15	91.19197	79.82049
20	96.51478	94.33727
25	99.17619	99.41814

CCPR: Corrected cumulative percentage release

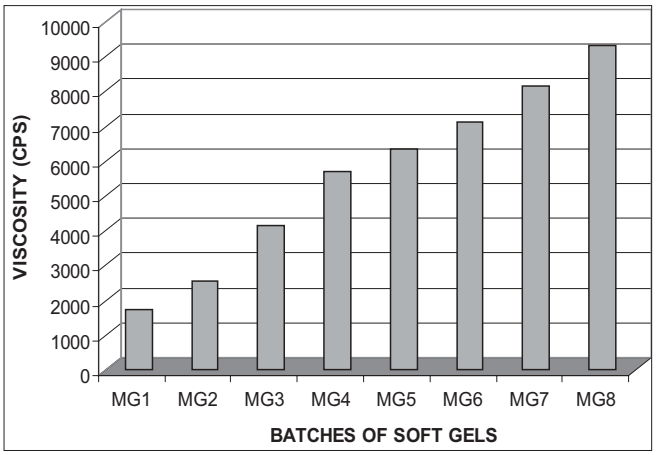

Figure 1: Comparison of viscosity of gellan gum soft gels batches MG1–MG8.

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 Ca2+ and Mg2+ is much stronger than monovalents such as Na+ and K+.[10]

Therefore, gels of batch PG6 and PG7 were selected for further studies under drug content and in vitro dissolution studies.

pH

The pH of the most stable metformin in aqueous phase is in between 4 and 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 and 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 PG1–PG8 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 MG5 showed slight syneresis on standing, thus it was not considered for further studies.

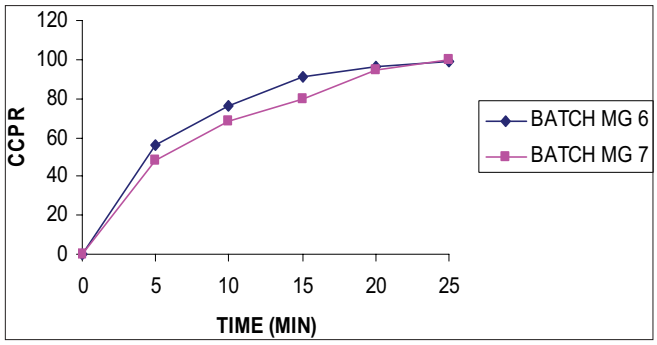

Figure 2: Comparison of dissolution profile of MG6 and MG7.

Drug content

The drug content of the batches PG6 and PG7 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 PG6 and PG7 exhibited acceptable consistency and viscosity. Thus, they were subjected to dissolution study to draw any conclusion and their percentage drug release at different time intervals has been shown in Table 3.

Figure 2 shows that 85% of drug release from batch MG6 took 15 min where as it took 20 min in case of batch MG7. There was no significant difference between release profiles of the MG6 and MG7, but release profile of batch MG7 does not meet the in house specification. Also, viscosity of the batch MG7 exceeded in house specification and it showed slightly gritty structure which may decrease the mouth feel, thus batch MG6 was choosen as the optimized batch.

Taste evaluation

The results of taste evaluation of the batch MG6 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 a slight bitter aftertaste. 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 and 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

Table 4: Taste evaluation of metformin gellan gum soft gel (batch PG6)

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

Table 5: Stability studies of the gellan gum soft gel (batch MG6)

	Gellan gum soft gel batch MG6			
Weeks	**1st**	**2nd**	**3rd**	**4th**
Temperature: 0-8°C				
Viscosity (cps)	7135	7143	7148	7154
pH	5.78	5.82	5.84	5.86
Temperature: Room temperature*				
Viscosity (cps)	7145	7157	7162	7159
pH	5.79	5.80	5.78	5.79

*around 35˚C

at both temperatures. Therefore, it is recommended that soft gel should be stored at about 25°C.

CONCLUSIONS

From Tables 4 and 5 it was found that the optimized soft gel batch MG6 was substantially stable at both room temperature and also at low temperature, thus storage at room temperature is possible. Also, the gel showed good taste masking with acceptable mouth feel. Figure 2 showed MG6 was able to release 85% of drug before 15 min thus meets in house specification. Finally, it was found out that batch MG6 meets all laid in house specifications thus is the optimized batch.

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