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Extraction of FSM and Formulation of Metformin Sustained Release Matrix Tablets

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ABSTRACT

Objective: Now days as very few anti diabetic drugs are coming out of research and development and some existing drugs are showing several side effects when administered orally, multiple times in a day, hence change in the operation is a suitable and optimized way to make some drug more effective by slight alteration in the drug delivery. Herbs and gums are extracted from many seeds, plants and fruits, such as fenugreek gum *Trigonella foenum graecum* L., also known as fenugreek seed or methi in Hindi. It is a herbaceous plant of the *Fabaceae* family. Seeds of *Trigonella foenum graecum* L.

Methods: A various metformin formulations containing hydrophillic and hydrophobic carrier, which is prepared by factorial design. Formulation technique of metformin hydrochloride is wet granulation employing both Xanthan Gum and Hydroxy Propyl Methyl Cellulose (HPMC K4M) as a rate controlling polymer and direct compression method is evaluated. This carrier and polymer influenced the method of preparation on metformin release *in-vitro* as well as other physiochemical were studied from the formulation.

Results: The development of oral sustained release systems has been a challenge to formulation scientists due to their inability to restrain and localize the system at targeted areas of the gastrointestinal tract. From all the formulation trial batches, formulation F7 shows the best results. It has been observed that HPMC K4M alone cannot give satisfactory drug release profile but the blend of HPMC K4M and Xanthan gum together give the best drug release kinetics.

Conclusion: The use of a hydrophobic carrier along with a hydrophilic polymer effectively controls the initial rapid release of a highly water soluble drug such as metformin HCl. Thus, sustained release matrix tablets of metformin hydrochloride can be expected to reduce the frequency of administration and decrease the dose dependent side effects.

Keywords: Metformin hydrochloride, Matrix tablets, Diffusion rate, Anti-diabetic.

INTRODUCTION

Diabetes is one of the biggest causes of death and disability in the world. Diabetes is a long-term disease that affects the way our body converts food into energy. When you have diabetes, your body does not produce enough insulin, which leads to serious health problems such as heart disease, vision loss, and kidney disease. Diabetes is divided into two main types. First is type I or juvenile diabetes which is also called as insulin dependent diabetes and second type is type I or non-insulin dependent diabetes mellitus, this type II diabetes is most common type of diabetes. Oral drug delivery is the most widely utilized route of

administration among all the routes (nasal, ophthalmic, rectal, transdermal and parenteral routes) that have been explored for systemic delivery of drugs *via* pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe, due to its cease of administration, patient acceptance and cost-effective manufacturing process [1].

New drug delivery systems are designed to achieve sustained drug delivery with predictable and reproducible kinetics over long periods of time in the bloodstream. Potential benefits of this concept include minimization of medication-related side effects due to controlled therapeutic blood levels rather than variation in blood levels, improved patient compliance due to lower dosing frequency and reduction of the total dose of medication administered. Thus, the combination of both slow release and controlled properties in a delivery system would further enhance therapeutic efficacy [2].

Controlled drug delivery systems have been developed that can regulate the rate of drug release, maintain the duration of therapeutic effect, and/or direct drug delivery to the tissue. Controlled drug delivery or modified drug delivery system. A controlled drug delivery system is usually designed to deliver the drug at a fixed rate. Safe and effective blood levels are maintained as long as the system continues to deliver the drug. Controlled drug administration typically results in essentially constant blood levels of the active ingredient, compared to the uncontrolled fluctuations seen when multiple doses of immediate-release conventional formulations are administered to a patient. Metformin hydrochloride is the best drug as a slow-release drug, because with one dose of metformin we perceive the therapeutic effect in our body for up to 12 hours. Metformin is a hypoglycemic drug that improves glucose tolerance in patients with type 2 diabetes by lowering plasma glucose at baseline and postprandial. Its pharmacological mechanisms of action differ from other oral hypoglycemic agents. Metformin reduces hepatic glucose production, reduces intestinal glucose absorption and improves insulin sensitivity by increasing peripheral glucose absorption and utilization. Unlike sulfonylureas, metformin does not cause hypoglycemia or hyper insulinemia in patients with type 2 diabetes or in normal subjects [3].

In our research article, we developed an extended formulation of metformin using both xanthan gum and hydroxypropylmethylcellulose (HPMC K4M) as rate controlling polymers. Xanthan gum is a natural polymer that has been used as a rate-controlling agent to reduce the drug release pattern in solution [4].

MATERIALS AND METHODS

Metformin chloride was purchased from aarti drugs, polyvinylpyrrolidone (PVP K-30), microcrystalline cellulose (PH101), xanthan gum was purchased from Loba Chemie, and hydroxypropylmethylcellulose was purchased from Anhui Sunhere Pharmaceutical Excipients Co. Ltd. Talk and Chemie Magnets, Talk and Chemie. All other chemicals, solvents and reagents used were of analytical grade.

Methods

Drug excipient compatibility study: Understanding the physicochemical properties of the Active Pharmaceutical Ingredient (API), which is metformin hydrochloride, and studying the compatibility of inactive pharmaceutical excipients is a very important process before designing a prototype formulation. Infrared spectra of pure drug and drug and polymers were recorded using a Fourier-Transform Infra-Red spectrophotometer available at Bengal Institute of Technology, Sugandha, and Hooghly. The plate method was used to investigate potential drug-polymer interactions. The infrared spectrum was taken by scanning the sample with a KBr plate (IR grade) and the produced powder pellets were analyzed at a wavenumber range of 4000-400 cm^{-1}. Transmission spectra were recorded [5].

Preparation of matrix tablets using drug substance, polymers and other excipients: Metformin hydrochloride matrix tablets were prepared by wet granulation method using Polyvinylpyrrolidone (PVPK30) as granulating agent. Different formula was designed using varying proportions of hydrophilic polymer alone and in combination. The composition of matrix tablet is given in Table 1. Following steps were followed for preparation of granules:

- **Step 1 Sifting:** Metformin hydrochloride was accurately weighed by composition and sieved through 60 #, microcrystalline cellulose (PH101), xanthan gum, hydroxypropyl methylcellulose (HPMC K4M) was accurately weighed by composition and sieved through 40 #. of.

- **Step 2 Dry mixing:** The above examined materials were collected in a polybag and mixed for 30 minutes to obtain a complete homogeneous mixture of drug and excipients. Here, powder samples were collected after mixing to check the

LOD of the dry mixture as well as the homogeneity of the mixture.

- **Step 3 Preparation of binder solution:** According to the composition, the necessary amount of purified water was taken in a beaker. Polyvinyl pyrrolidone (PVP K30) was accurately weighed and added to this beaker with slow stirring and continue to stir until it completely dissolves in the purified water and forms a clear translucent binding solution.

- **Step 4 Wet mixing:** The binder solution slowly added to the dry mixture is then continuously mixed until a uniform wet mass is obtained. The end point of granulation was determined by continuous visual monitoring of granule formation.

- **Step 5 Wet sifting:** Wet mass sifted through 10# to get uniform size particles.

- **Step 6 Drying:** After wet sieving, the pellets were air-dried for 10 minutes and then stored in a tumble dryer at 50°C until the target LOD was reached.

- **Step 7 Dry screening:** Dried granules sifted through 20# and collected in double polythene lined container.

- **Step 8 Lubrication:** Talc and magnesium stearate was weighed as per requirement and added to the above granules and mixed in a blender to get a lubricated blend.

- **Step 9 Compression:** Tablets were compressed in a 10-station single rotary tablet punch, having break-line on one side and plain on other side. A constant compression force required to produce hardness of tablets about 5-7 kg/cm^2. All physical parameters were checked and tablets were stored in airtight containers for further use (Table 1).

Ingredients per tablets (mg)	**Composition (mg/s) of the prepared formulation**						
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Metformin HCl	500	500	500	500	500	500	500
Microcrystalline cellulose (PH 101)	150	140	120	115	115	115	110
Hydroxypropyl methyl cellulose (HPMC K4M)	180	180	200	200	100	100	100
Xanthan Gum	-	-	-	-	100	110	110
Polyvinylpyrrolidone (PVP K30)	10	20	20	25	25	25	25
Purified water	qs	qs	qs	qs	qs	qs	qs
Talc	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	10
Total weight	850	850	850	850	850	850	850

Table 1: Composition of matrix tablets of metformin hydrochloride.

Pre-compressional evaluation

Angle of repose: The angle of repose helps determine the effect of the friction force of the loose powder and the cohesion of the particles. It is defined as the largest possible angle between the surface of the powder pile and the horizontal plane. The static angle of repose was determined using the solid funnel or solid cone method. The angle of repose was calculated using the following equation [6].

$\tan \theta = h/r$

Where θ=angle of repose, h=height of pile, r=radius of pile base

Compressibility index: Powder flow property can be measured by compressibility index also known as Carr's Index. So, it is defined by the equation.

Where, bulk density is the ratio of mass of powder to the bulk volume and tapped density is the ratio of mass of powder to the tapped volume.

Concentration (µg/ml)	Absorbance
0	0
1	0.079
2	0.165
3	0.246
4	0.323
5	0.407
6	0.48
7	0.562
8	0.65

Table 2: Concentration v/s absorbance of metformin hydrochloride at 6.8 phosphate buffer evaluation of matrix tablets.

Extraction of fenugreek seed mucilage: Fenugreek seed mucilage was collected by the market and proceed into following two steps:

Step: 1 Extraction of mucilage: This seed were used for isolation of mucilage. The seeds was washed and dried at room temperature for required temperature, dried seeds were boiled in water then release of mucilage in water. After releasing squeezed using muslin cloth, then filtrate keep refrigerator for cooling.

Step: 2 Isolation of mucilage:

- Add ethyl alcohol into filtrate
- Then precipitate of mucilage
- Separation of mucilage using muslin cloth
- Dried in oven (50°C)
- Crushed into powder

Uniformity of drug content: Ten tablets of each formulation were weighed and ground into a fine powder in a mortar. The powder, corresponding to 500 mg of metformin hydrochloride, was extracted with 100 ml of phosphate buffer pH 6.8 and then the liquid was filtered with Whatman filter paper. Using a Simadzu UV 1800 UV-visible spectrophotometer, drug concentration was determined by measuring absorbance at 233 nm after the filtrate was properly diluted with phosphate buffer pH 6.8. Drug concentration was determined using a standard calibration curve.

In vitro dissolution study

The *in vitro* dissolution study of metformin hydrochloride matrix tablets was performed using a USP type II dissolution apparatus (LABINDIA) at a rotation speed of 50 rpm. The tablets were placed in different dissolution media to simulate the gastrointestinal environment. The dissolution medium used was 900 ml of 0.1 (N) HCl acid buffer pH 1.2 for the first two hours and then phosphate buffer pH 6.8 for the next ten hours. The dissolution medium was maintained at 37 ± 0.5°C. At predetermined time intervals, 5 mL of the sample solution was removed from the solvent and the samples were replaced with fresh solvent medium to maintain absorption conditions. The collected samples were filtered through a 0.45 µm membrane filter and the drug content of each sample was analyzed by measuring the absorbance at 233 nm with a UV spectrophotometer (SHIMADZU UV 1800) after appropriate dilution. Cumulative percentage of drug release was calculated using the equation obtained from the calibration curve.

RESULTS AND DISCUSSION

Extraction of FSM

Trionella foenum L. and *Linum usitatissimum* were separated by hot water extraction method and then identified. Mucus smear was performed if it was negative for gums and flavonoids. the isolated mucilage also contained carbohydrates and the remaining phytoconstituents such as tannins and fat were absent. These results were considered as proof of the purity of the isolated plants.

Characterization of powder

The bulk density, tap density, compressibility index, Hausner ratio and angle of repose of the lubricated mixture were evaluated for all compositions and their values are shown in Table 2. The bulk densities and thread densities were 0.77 ± 0.01-0.80 ± 0.03. g/cm^3 and 0.87 ± 0.02 to 0.95 ± 0.01 g/cm^3. The powder mixture initially showed acceptable flow characteristics and then improves after increasing the lubricant concentration. Angle of repose values range from 27.65°C to 38.29°C. The Carr compressible index range of all formulations was found to be 11.49-16.13%, indicating that the powder mixture has good flowability. The Hausner ratio was also calculated, the dose varying between 1.12 and 1.23.

Evaluation of physical parameters

The bulk density, tap density, compressibility index, Hausner ratio and angle of repose of the lubricated mixture were evaluated for all compositions and their values are shown in Table 2. The bulk densities and thread densities were 0.77 ± 0.01-0.80 ± 0.03. g/cm^3 and 0, 87 ± 0.02 to 0.95 ± 0.01 g/cm^3. The powder mixture initially showed acceptable flow characteristics and then improves after increasing the lubricant concentration. Angle of repose values range from 27.65°C to 38.29°C. The Carr compressible index range of all formulations was found to be 11.49-16.13%, indicating that the powder mixture has good flowability. The Hausner ratio was also calculated, the dose varying between 1.12 and 1.23 (Tables 3 and 4).

Formulation	Bulk density (g/cm^3)*	Tapped density (g/cm^3)*	Compressibility index (%)	Hausner's ratio	Angle of repose (°C)
F1	0.78 ± 0.02	0.93 ± 0.01	16.13	1.19	36.86
F2	0.79 ± 0.01	0.90 ± 0.03	12.22	1.23	38.29
F3	0.78 ± 0.02	0.90 ± 0.02	13.33	1.15	34.99
F4	0.80 ± 0.03	0.95 ± 0.01	15.79	1.19	35.94
F5	0.78 ± 0.01	0.90 ± 0.02	13.33	1.15	33.02
F6	0.78 ± 0.02	0.92 ± 0.01	15.22	1.17	32
F7	0.77 ± 0.01	0.87 ± 0.02	11.49	1.12	27.65
Note: *All values are expressed as mean ± SD (Standard deviation), n=3					

Table 3: Micromeritic properties of lubricated blend of all formulations.

Formulation	Weight variation ± SD (mg)	Hardness ± SD (kg/cm^2)	Friability (%)	Content uniformity (%)
F1	850.52 ± 2.58	5.65 ± 0.43	0.78	98.96
F2	850.35 ± 2.47	6.32 ± 0.46	0.65	99.02
F3	849.79 ± 2.32	6.45 ± 0.42	0.62	99.56
F4	850.30 ± 1.97	6.59 ± 0.37	0.54	100.56
F5	850.36 ± 1.03	5.90 ± 0.58	0.81	99.98
F6	850.86 ± 2.52	6.00 ± 0.59	0.89	101.23
F7	850.44 ± 0.76	6.55 ± 0.35	0.48	100.05

Table 4: Physical properties of metformin hydrochloride sustained release matrix tablets of all formulation.

CONCLUSION

Sustained release metformin hydrochloride matrix tablets were prepared using HPMCK4M alone and in combination with xanthan gum by wet granulation method. The results of this study show that HPMC K4M alone could not effectively control the release of metformin hydrochloride within 12 h, while it was combined with xanthan gum and could control the release of metformin hydrochloride from its matrices. It was concluded that the formulation containing xanthan gum and HPMCK4 (F5, F6 and F7) achieved sustained release of metformin chloride for 12 hours. Of these three formulations, F7 shows the best results. Both physical parameters and drug release kinetics showed satisfactory results for formulation F7. The mechanism of drug release from matrix tablets follows Fickian diffusion. The comparative dissolution profile shows satisfactory results for the similarity and difference factor of the test product with the reference sample. Thus, metformin hydrochloride extended-release matrix tablets can be expected to reduce the dose frequency and dose-dependent side effects associated with repeated administration of conventional metformin hydrochloride tablets. In order to study the in vivo correlation of the study sample, an in vivo study of the study product must be conducted in the future.

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