Formulation Development, Optimization and *in Vitro* Evaluation of Gas Based Gastroretentive Drug Delivery System of Anti Diabetic Drug

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Abstract

Oral route is most convenient route of drug administration. Objective of this study was to develop a gas generating drug delivery system of MH with the help of different viscosity grades of hydroxyl propyl methyl cellulose to obtain continuous release and provide buoyancy in the stomach. HPMC K15, HPMC K100M, HPMC K100LVCR were use as release controlling polymer. Citric acid, Sodium bicarbonate was use gas forming compounds. Design of experiment (DoE) is applied by using JMP software and formulate 17 batches obtain through DoE. In vitro characterization was performed for all the formulation. Precompression parameters were found to be 0.41±0.121 gm/cc bulk density, 0.608±0.179 gm/cc tapped density and good flow properties. Post compression parameters were 15.0±0.009 kp hardness, 7.23±0.005 mm thickness, and 95.29±0.021% drug content. Swelling index was 135.64±3.2% at 6 hrs. In vitro drug release was 95.95±1.89% at 24 Hrs. F1 value was 7.63 and F2 value was 56.33. Formulation was stable in given stability condition. Formulation obtained after optimization was compared with marketed formulation so we can say that gas generating formulation of MH was having good characteristics over the marketed formulation.

Keywords: GRDDS • Metformin Hydrochloride (MH) • Floating lag time (FLT) • Total Floating Time (TFT)

Introduction

Oral route is easiest route for administration of various drugs. Those system having properties of single dose for prolonged action and deliver the drug directly to target site called ideal drug delivery system. Purpose of developing controlled release drug delivery system is to improve safety of drug and extended duration of action of a single dose [1]. Those drug having sparingly solubility and insoluble properties are best candidate for gas based delivery system. Gastro retentive dosage form increase gastro retention time so its gives high local effect e.g. drug use for gastro intestinal tract problems [2].

Controlled release drug delivery system having various advantage over other formulation. It gives reduction in dosing frequency due to long duration of action. So it's directly shows effect on patient's convenience and compliance. Controlled release of drug from formulation through gastro retention process improve first pass metabolism and decrease side effect at colon region. Gas based drug delivery system can used for target therapy of upper portion of GI tract [3].

GRRDS is best option for that type of drugs having short absorption window (e.g. Metformin Hydrochloride) [4]. In the gas based drug delivery system carbonate or bicarbonate react with acid release CO_2 and this gas entrapped in jelly like structure and decrease specific gravity of dosage form and provide buoyancy to formulation.

Retention of tablet formulation in the stomach varies on various factors. Male have less gastro retention as compare to female due to variation in physical parameter like weight, height and surface area. Age is also one factor because older people having more gastro retention as compare to younger people. Density of dosage form, shape of dosage form also alters the gastro retention. During fasting condition GI motility shows stronger action as compare to fed condition because food require appropriate digestion time in the stomach. Those foods are rich in protein and fat shows long gastro retention time [4-7].

Materials and Methods

Materials

MH was obtained from Sun Pharmaceutical Industries, HPMC K100MCR and HPMC K15M was supplied by Dow Chemical USA. Polyvinyl Pyrrolidone and polyplasdone XL10 was supplied by Ashland. Isopropyl alcohol was supplied by Deepak fertilizers Ltd. Citric acid and $NaHCO_3$ was supplied by Merck Pharmaceutical India. Colloidal silicon dioxide was supplied by Wacker Chemie. And magnesium stearate was supplied by M/s Mallinckordt, St Louis USA. Marketed formulation was in house tablet of Sun Pharmaceutical Industries. All experimental work was performed in the lab of Sun Pharmaceutical Industries – Product Development Research (PDR) department.

Methods

Reformulations Studies

DVS study was performed for measurement of MH hygroscopicity. Study was performed at 25 °C. Metformin Hydrochloride (50mg) was taken for DVS study. It was kept for 3hrs time period for each condition.

Solubility of MH was determined in different pH condition as well as aq. Condition. Different pH range was pH 1.2, 4.5, 6.8 and 7.4.a saturated solution was prepared in all pH condition and DM water and each solution were kept in in incubator shaker for 48hrs at 37±0.5 °C at 50RPM. Now all samples solution was filtered using syringe filter and diluted. Now scanned at 233nm by using UV Spectrophotometer and determine concentration of MH.

Drug excipients compatibility studies was performed. MH was taken with all excipients in 1:1 ratio in glass vial (close lid). Condition was maintained 40°C ± 2°C / 75% RH ± 5% RH. After 30 days physical observation was observed and chemical observation was observed by using IR spectroscopy [8].

Preparation of Tablet

All ingredients were weighed as per formula. Shifting of HPMC K15M, HPMC K100M, HPMC K100LVCR and PVP K30 were performed using #30ASTM and citric acid, sodium bicarbonate by using #60ASTM. Now extra granular material (PPXL, Aerosil, Magnesium stearate) was shifted by using #60ASTM. Appropriate amount of Isopropyl Alcohol in a beaker was taken and mix PVP K30 and stirred well. Now pre shifted polymer blend were taken in a stainless steel pot and add PVP K30 suspension slowly, after dough formation granules were dry by using hot air oven at 45 °C for appropriate time till achieving < 2% LOD. And dried granules were shifted by using #18 ASTM and add effervescent agent. Add extra granular material and mix and compressed lubricated blend by using multi station compression machine [9].

Experimental Design

A full factorial design was applied using JMP Software 16.1. Measure

responses of all possible combination of factors and its level (Table 1).

Pre-compression Parameters

Pre-compression parameter was studies as follows:

Angle of Repose

Funnel was used for determination of angle of repose of tablet blend. A fix amount was weighed of tablet blend (same for every experiment). The height of funnel was adjusted like tip of funnel just touch to the apex of the heap of the powder. Now free the powder to flow through the funnel. The diameter of pass powder was measured and height of heap (h) [9].

Then put the value in the following formula and calculate angle of repose Θ.

$\tan \Theta = h / r$

Bulk Density

It is the ratio of weight of the powder and bulk volume of tablet blend. 50gm of tablet blend was taken and poured in to measurement cylinder and note the volume [9].

Bulk density (ρ_b) = weight of the powder / volume of the powder bed

Tapped Density

Tapped density is defined as; it is the ratio of weight of the powder and tapped volume of blend. 50gm of powder was taken in measuring cylinder and load in the tapped density apparatus. Finally determine tapped volume and put in to the formula [9].

Tapped density (ρ_t) = weight of the powder / tapped volume of the powder bed

Compressibility Index (CI)

CI was determined by using following formula [9]:

Compressibility Index (%) = [(Tapped density – Bulk density) x 100] / Tapped Density

Hausner's Ratio

It is the ratio of tapped density (**ρt) and** bulk density (**ρb**)[9].

$H = \rho t / \rho b$

Loss on drying

Loss on drying was calculated by using Carbolite Gero instruments. This instrument was generated 105 °C for 10 min [9].

Post-compression Parameters

Physical appearance

All the tablets should free from all tablet defects like cracks, pinholes, depressions etc. color of the surface of the tablet should be uniform and surface of tablet should be smooth [9].

Thickness

Thickness of tablet was measured with the help of using vernier caliper [9].

Uniformity of weight

Weight variation is evaluation parameter of tablet finished product. So selected 20 tablets randomly and calculate avg. weight. Now avg. weights of tablet were compared with individual weight of tablet. Percentage deviation was measured by using following formula [9]:

Table 1: Tablet Characterization.

Factors	Level (mg)	
HPMC K15M	100	260
HPMC K100M	100	260
Citric Acid	60	120
Sodium Bicarbonate	60	120

% Deviation = {(individual weight - average weight) / average weight} x 100

Hardness

Hardness of tablet was measured by using Dr Schleuniger Pharmatron 6D instrument. Unit of hardness was kp (kilo pound) [9].

Friability

Friability is defined as loss of surface of tablet material due to friction of tablet and nearby surface. 10 tablets were randomly selected and load in to the Roche Fribilator. Instruments were rotate for 100 rotations and determine percentage friability by using following formula [9].

% friability = $[(W1 - W_2) / W_1] \times 100$

Uniformity of Drug Content

20 tablets were randomly selected and crushed in to the mortar pestle. And weight 500mg Metformin Hydrochloride equivalent tablet blend. Blend was dissolved in to the 0.1N HCl solution and diluted the solution by using pH 6.8 Phosphate buffer [9].

Swelling studies

Swelling studies were performed basis on swelling index, TFT and floating lag time. TFT means time when formulation remain floating in the medium and lag time means time required for starting of floating character by the formulation. Every experiment carried out in the pH 1.2 0.1N HCl buffer, type 2 dissolution apparatus at 50RPM. Swelling index was determined at different time interval by weighing the tablet [9].

In *Vitro* Dissolution Studies

In *vitro* release of MH was performed in USP Type II (Rotating Paddle) dissolution apparatus. 0.1N HCl was taken as dissolution medium. 37 °C ± 0.5 °C temperature and 50 RPM was maintained throughout experiment. 5 ml of samples were withdrawal at 05, 0.5, 1, 3, 6, 10, 12 and end point 24 hours. All samples solution were filtered by the application of syringe filter and diluted by using pH 6.8 phosphate buffers. Diluted sample were analyze at 233 nm by using UV spectrophotometer. F1 and F2 value was also determined by using MS Office 2019 as tool [9].

Model dependent kinetics

Release kinetics of for all batches was studies by using MS Office 2019 as tool. First order, zero order, Higuchi Model, Krosmeyer – Papas Model and Hixon - Crowell Model R^2 value was determined [10].

Stability Studies

Purpose of stability study is to provide evidence that formulation will remain stable in given condition. So prevention of delayed procedure accelerated stability study was performed by using stability chamber. Guidelines of ICH Q1A for stability study were followed [11-15].

Result and Discussion

Result

Pre-formulations study

The study claimed that as% RH increased in DVS chamber, the drug tends to be absorbed more moisture and gain more weight. Thus we can say that Metformin Hydrochloride is not a hygroscopic as the difference in weight gain was insignificant and can be formulated at any humidity condition.

Experimental design

17 formulation batches were prepared obtained through full factorial design (2^4) of experiment (JMP 16.1). All the 17 experiment obtained from design space was formulate and evaluated. Four responses are considered for validation batch drug release at 1 hour, drug release at 3 hours, drug release at 10 hours and floating lag time.

Optimized formulation

Optimized formulation was obtained by using JMP design space based on desired response and expected response (Table 2).

Table 2: Formulation of Optimized Batch.

Sr No	Ingredients	Quantity (mg/tablet)
1	Metformin Hydrochloride	500
2	HPMC K15M CR	139
3	HPMC K100M CR	220
4	$NaHCO_3$	90
5	Citric Acid	115
6	IPA	Qs
7	PVP K30	50
8	PPXL 10	50
9	Mg Stearate	12
10	Aerosil	5
	Total	1181

Pre-compression parameters

Pre compression evaluation of tablet blend were performed and was found to 0.41 ± 0.121 gm/cc bulk density (BD) and tapped density (TD) was found to be 0.608 ± 0.179 gm/cc. Hausner's ratio and Carr's index was found to be 1.48 ± 0.009 and 32.56 ± 0287 respectively. Angle of repose of tablet blend of optimized formulation was 57 ± 1.49 degree. Moisture content was also present within range.

Post-compression parameters

All the tablet of optimized batch was passed weight variation test and Hardness of optimized formula was found to be 15.0 ± 0.009 kp. Thickness of optimized batch was 7.23±0.005 mm. friability was obtained 0.65±0.007%. Drug content in optimized batch was 95.29±0.021%. Floating character of optimized batch was found to be 18±0.126 second as FLT and >12 hrs. as total floating time (TFT).

Swelling studies

Swelling studies was performed using dissolution apparatus. Swelling index of Optimized formula was found to be 73.49±4.98 at 1 hr, 97.89±4.39 at 2hrs, 116.06±4.55 at 3hrs, 125.36±.36 at 4hrs, 132.64±7.53 at 5hrs, and 135.64±3.22 at 6hrs. time point (Figure 1).

In *Vitro* release studies

In *Vitro* dissolution profile of optimized formulation was carried out at 0.5, 1, 3, 6, 10, 12 and 24 hrs. Time point and found to be 21.6±1.69, 32.67±1.07, 52.83±1.98, 72.23±2.14, 90.72±1.89, and 94.85±1.47 and 98.95±1.89 percentage drug release respectively (Figure 2).

Model dependent kinetics

Release kinetics of optimized batch was studied on different kinetic models. R^2 value of at different kinetics was studied and found to be 0.8486, 0.9937, 0.9481, 0.9693, 0.9144 of Zero order, first order, Higuchi, Krosmeyer Pappas and Hixon model respectively. T90 and T50 Was also studied, T50 was 8.567, 2.667, 3.970, 2.404, 3.520 of Zero order, first order, Higuchi, Krosmeyer Pappas and Hixon model respectively. T90 was 15.421, 8.892, 12.885, 13.288 and 9.144 for Zero order, first order, Higuchi, Krosmeyer Pappas and Hixon model respectively.

Stability studies

Accelerated stability experiment was performed on the optimized formula by using stability chamber at 40±2ºC and 75±5% RH for 180 months. After complete sample out period all samples were observed for change in physical parameters. Hardness which was slightly decreased, (15.0 ± 0.009 kp to 14.7 ± 0.015 kp) thickness was constant for whole stability period and friability was slightly increasing (0.65 ± 0.007% to 0.74 ± 0.009%), Insignificant change in drug content, floating lag time was slightly increase (18 ± 1.26 Sec. to 21 ± 1.11 Sec.) And total floating was more than 12 hours. We found that there was no such different in both drug release character and release pattern was also similar. Multi agitation effect on drug dissolution and swelling properties was studied and it was satisfactory.

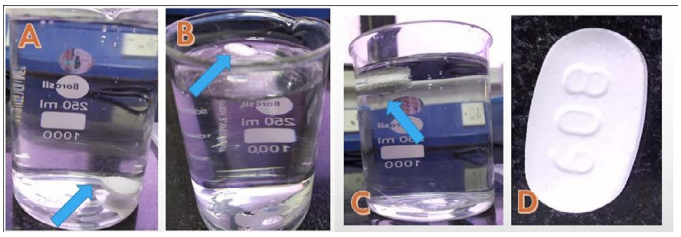

Figure 1: Tablet at 0 times (A) and after 18 second (B) and tablet at 12 hr. (C) and at 0 time (D).

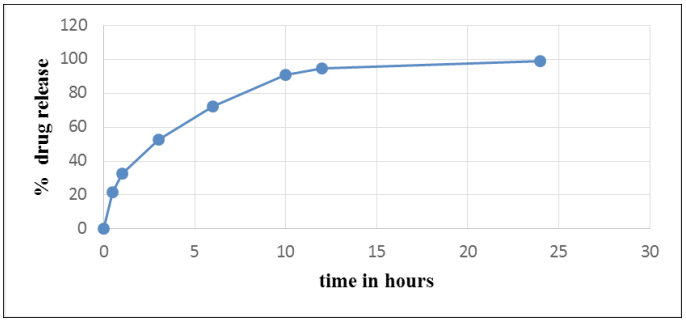

Figure 2: In Vitro Release studies.

Comparison of marketed and optimized formulation

Marketed formulation was in house product of Sun Pharmaceutical Industries Ltd. It was Sustained Release formulation. Optimized formula was compare with post compression parameter, floating properties, release kinetics and In *Vitro* dissolution release profile. Drug content in optimized formulation and marketed formulation was 95.29±0021 and 94.45±0.102 respectively. In *Vitro* drug release at 3hr. through optimized formulation and marketed formulation was 52.83±1.98, 48.26±2.01 at 24hr was 98.95±1.89%, 99.89±1.99% respectively. Optimized and marketed formulation follow first order release kinetics and was showing 0.9937 and 0.9396 R^2 value respectively. F1 value was found to be 7.63 and F2 value was 56.33.

Discussion

Floating tablet of Metformin Hydrochloride gas based system was formulated by wet granulation tableting method. Various grades of HPMC polymer e.g. HPMC K15M, HPMC K100M and HPMC K100LVCR were used. In which HPMC K100LVCR was showing tablet matrix distraction due to low viscosity. Screening batches were formulated by the combination of carpool-974 and HPMC different grades polymers. HPMC polymer was used as release controlled polymer, granulation was perform with combination PVP K30 and Isopropyl Alcohol. Extra granular material was added to provide positive floatability to the formulation because PPXL 10 normally acts as disintegrants but in this formulation act as swelling index enhancer. After that full factorial design (2^4) was applied for optimization of formulation. Optimized formulation was characterized based on pre-compression parameters, post compression parameters, swelling character and comparative in-vitro dissolution. Optimized formulation was showing first order release kinetics and R^2 value was 0.9937. Stability study of optimized batch was performing based on stability guidelines ICH-Q1A. Post stability period, optimized formulation was characterized. Changes in formulation were negligible hence formulation was stable. Optimized formulation and Marketed formulation was compared. Similarity factor (F2) and difference factor (F1) was calculated, and was found to be 7.63 and 56.33.

Conclusion

Metformin Hydrochloride is an anti-diabetic drug widely used for treatment of Type II diabetes. Metformin Hydrochloride is reported to be absorbed mainly upper part of GIT. The bioavailability of Metformin Hydrochloride is 50 – 60% and biological half-life is approx. 1.5-3 hr. Metformin Hydrochloride having narrow absorption window and high water solubility and by approach gas

based drug delivery system it would be beneficial to retain the drug in the GI tract for long period of time so its achieve maximum absorption and maximum bioavailability.

In this study, we were started with carpool-974 as release controlling polymer but carpool was not having acid pH stability so formulation matrix was disintegrate in 0.1 N Hydrochloric acid so change the study, we were used HPMC of different viscosity (K15M , K100M CR and K100 LVCR) as release controlling polymer but K100 LVCR having low viscosity so tablet matrix were disintegrate and formulation was not stable .So we used combination of HPMC-K100M and HPMC-K15M as release controlling polymer.

Therefore, the present study proves that gastro retentive drug delivery system of Metformin Hydrochloride can be design by using different viscosity grades of HPMC, cellulose (HPMC K15M and HPMC K100M) .which give first order release kinetics and prolong the drug release. This system remains buoyant in the stomach, so this would enhance the oral bioavailability of Metformin Hydrochloride (anti-diabetic drug).

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