Development and formulation of metformin (*Antidiabetic*) effervescent *Granules*: To increase patient compliance and its stability study

Saeed Ur Rashid Nazir[1], Ghazala Ambreen[1], Hafiz Muhammad Irfan[1*], Sajid Bashir[1] and Asim Rauf[2]

[1]Faculty of Pharmacy, University of Sargodha, Sargodha, Pakistan
[2]Drugs Control Authority, Pakistan

Abstract: Convenience of administration and patient compliance are gaining importance in the formulation of dosage forms. Many patients, like elderly people and person with dysphagia find difficulty to swallow the tablets and thus do not comply with prescriptions. So the present study was conducted to develop and formulate metformin effervescent granules. The stability study was carried out for 24 weeks (168 days) at temperatures of 4˚C, Room temperature, 40˚C & 60˚C and at the end, the %age of drug remaining in the formulation was determined. The results showed that the formulation of metformin effervescent granules were remained best stable at 4˚C in refrigerator, as the %age of drug remaining is not decreased more than 5% and the formulation stored at room temperature, was also found to be very close to the standard at the end of 24 weeks. It is concluded from the study that granules may be another dosage form to use as antidiabetic pharmaceutical product.

Keywords: Stability, Metformin, effervescent granules, development.

INTRODUCTION

Effervescent granules and tablets are now become more and more popular dosage form as they are readily soluble and easy to consume just by drinking glass of water. Metformin is now believed to become the most widely prescribed anti-diabetic drug in the world and about 42 million prescriptions are being generated in United States on regular basis (Bailey and Day, 2004). Moreover, the percentage of patients suffering from type 2 diabetes is elderly people, showing dysphagia. The problem becomes even more severe due to big tablets (high dose 500-1000mg) having a size of 19mm × 10.5mm and need for daily intake of drug. The only alternative for such patients is Effervescent Formulation (Hausler *et al;* 2007). Recently, more stress is laid down on the development of organoleptically elegant and patient friendly drug delivery system for pediatric and geriatric patients (Bhusan *et al;* 2000) and (Wadhwani *et al;* 2004).

MATERIALS AND METHODS

Preparation of metformin HCl effervescent granules

Metformin Effervescent granules were prepared by making various modifications, which involves use of Ultrasonic Bath (Elmasonic E30H), addition of some excipients (PVP K-30, color, and flavor) and altering order and concentration of excipients involved, in method described by Ashtosh, Rajesh and Mukesh (Mohapatra *et al;* 2008). Metformin Effervescent Granules were prepared by ingredients listed in the table 1.

All the ingredients (Metformin, Mannitol, Saccharin Na, Aspartame, Erythritol, Citric acid, Tartaric acid and Sodium bicarbonate) were passed through sieve no. 40. Required quantity for each formulation table 1 and all the above mentioned ingredients were co ground in pestle and motor. PVP K-30 and isopropyl alcohol were used as binder to prepare granules. PVP K-30 and both colors (Tartrazine yellow and Sunset Lake) in a ratio of 2:1 were dissolved in isopropyl alcohol separately by using ultrasonic bath. After complete mixing of color and PVP K-30, both solutions were mixed and used to wet above mentioned dry mixture. The wet mass was screened through sieve no. 60 and dried in oven (Daihan Labtech Co) at a temperature not exceeding 50˚C. The dried granules were sieved through sieve no.40 and then mixed with orange flavor and then subjected for evaluation of granules.

Method of analysis of metformin effervescent granules

The assay of metformin Effervescent Granules was carried out on Spectrophotometer UV 1700 (Shimadzu). The absorbance was measured at 236nm (Anthony C Moffat, 2004).

Preparation of standard solution

50/mg of Metformin HCl (99.86%) was carefully measured on an analytical balance (Sartorius GC1603S-OCE) and then dissolved in 100ml of absolute methyl alcohol (Lab Scan Asia Co., Ltd.) to give a clear, transparent solution then diluted it further to prepare E1% solution.

Preparation of sample solution

The granules from single unit dosage form were crushed

**Corresponding author:* e-mail: irfan_pharmacist06@yahoo.com

to make a fine, homogenous powder. Then took the weight of powder equivalent to 50/mg of standard (Metformin) and dissolved in 100ml of methyl alcohol. This solution was then filtered. Then took sample from aliquot and diluted it further to prepare E1% solution.

Table 1: Composition of effervescent granules

Name of Ingredients	Quantity Given (%)
Metformin HCL 99.86% purity	8.5
Mannitol (Merck Germany)	57
Saccharin (BDH Laboratory chemicals: Poole England)	0.5
Aspartame (Uni-chem Laboratory, Germany)	1.6
Erythritol(BDH Laboratory chemicals: Poole England)	16.5
Citric acid (anhydrous) (BDH Laboratory chemicals: Poole England)	7.5
Tartaric Acid (Merck Germany)	2.5
Sodium Bicarbonate (Merck Germany)	3.3
Polyvinyl pynolidone k 30 (Merck Germany)	1.3
Tartrazine yellow color (Tyfransco Canada)	q.s.
Instant orange flavor (Tyfransco Canada)	0.82
Sunset lake color (Tyfransco Canada)	q.s
Isopropyl aloohol (Labscan Asia Co., Ltd)	q.s

Metformin formulations designed for taste acceptability using different sweetening agents

Following six formulations of metformin Effervescent Granules were made with different concentrations of low calorie sweetening agents (Srisagul, 2004) as shown in table 2.

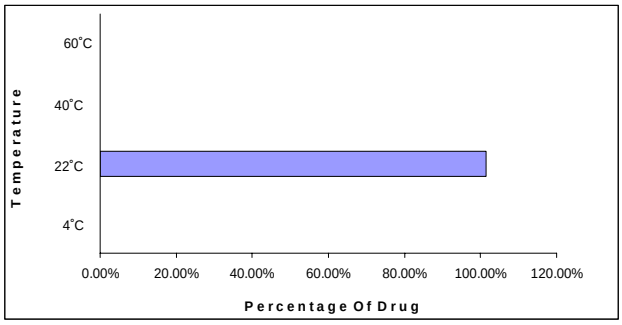

Fig. 1: Graphical representation of remaining drug concentration at zero time (at room temperature).

Evaluation of taste acceptability of metformin effervescent granules

Taste Acceptability of metformin Effervescent Granules was checked by using Flavor panel. The panel was consisted of the volunteers from the members of Faculty of Pharmacy, students from the Department of Pharmacy, University of Sargodha and the members of Envoy Pharmaceuticals (Pvt.) Ltd. Each of formulation was evaluated by 20 volunteers (Takagi and Toka, 1998).

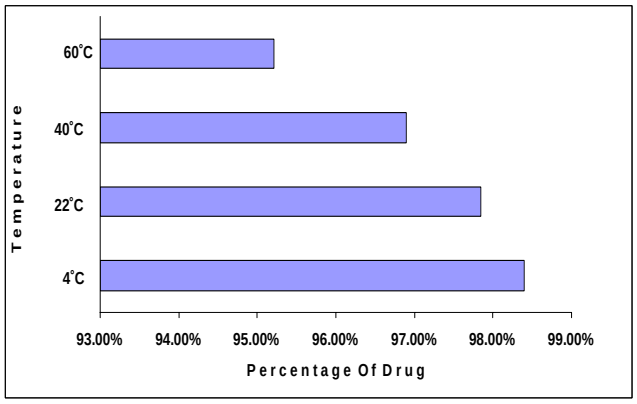

Fig. 2: Graphical representation of remaining drug concentration after 24 weeks.

In-vitro stability studies of metformin effervescent granules (Stability Chamber: Curio SC-0709)

Stability study was carried out by packing the effervescent granules properly in aluminium foil in the form of sachets. These sachets were divided in four sets; one set was placed at 4˚C in refrigerator, Room temperature (22±5˚C), 40˚C and 60˚C. The effervescent granules were analyzed by UV spectrophotometer, immediately after preparation (at zero time), after 2 hours, 6 hours, 12 hours, 24 hours, 48 hours, at 7 day and thereafter, at the end of every week until 24 weeks (Alexandar and Thyangarajapuram, 2003).

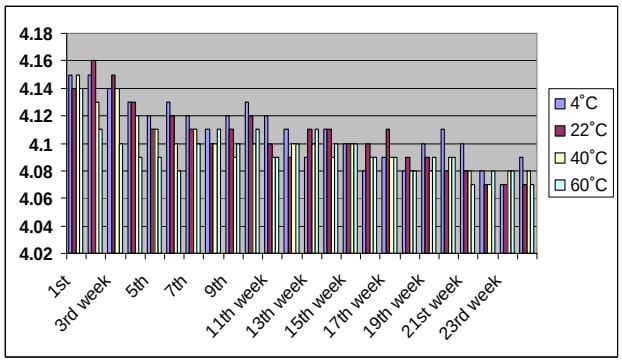

Fig. 3: Graphical representation of pH at different temperatures.

The active content in Effervescent granule formulation was checked by measuring the absorbance of sample solutions on UV spectrophotometer at 236nm wavelength at abovementioned time intervals and by calculating the %age remaining of active content by following formulae: (USP, 2003).

Remaining %age of active contents in sample = [As/Ao] × [Cs/ Co] × %age purity of Std.

A_S=Absorbance of sample, A_O=Absorbance of standard, Cs=Concentration of sample and Co =Concentration of standard.

Table 2: Percentage of metformin at zero time (at room temperature)

Absorption of standard	Absorption of Sample	% age of drug in sample	Mean	S.D
1.086	1.081	101.50%	1.082333	0.000943

Table 3: Percentage of metformin HCl after 24 weeks

	A 4˚C	B Room Temp	C 40˚C	D 60˚C
Absorption of Samples	1.048	1.042	1.032	1.014
% of drug In Samples	98.40%	97.84%	96.90%	95.21%
Mean	1.05833	1.05367	1.04633	1.032667
S.D	0.00732	0.00826	0.01014	0.013199

Table 4: Evaluation of different parameters of effervescent granules (EG)

Test Parameters	EG1	EG2	EG3	EG4	EG5	EG6
Angle of Repose	58	52	43	27	35	55
Bulk Density (g/cm3)	0.42	0.40	0.40	0.42	0.41	0.42
Tapped Density (g/cm3)	0.53	0.50	0.52	0.48	0.54	0.54
Flow Property	Fair	Fair	poor	Good	Poor	Fair
In-vitro effervescence Time*	110s	1.5min	1min	75s	90s	120s

RESULTS

Accelerated stability testing was done using temperatures of 4˚C, Room temperature, Accelerated 40˚C and 60˚C. metformin granules were evaluated for physical parameters at the time of preparation and later at the end of every week until 24 week as shown in tables 2 & 3 (figs. 1 & 2). The different batches of test formulation were evaluated for different physical parameters and these parameters were given below in table 4. The pH of formulation was checked at zero time, immediately after formulation and later at end of every week until 24 weeks as shown in fig. 3.

DISCUSSION

It is evident from the results that the formulation of metformin remained best stable at 4˚C, as the %age of drug remaining is not decreased more than 5% (David B Troy, 2000) and the formulation stored at room temp (22±5˚C) was also found to be very close to the standard at the end of 24 weeks. The shelf life of metformin effervescent granules was 510 days at 4˚C and at room temperature 425 days. There was no change in visual appearance and odor at all four different temperatures. The pH values were surprisingly not found different at all temperatures for a period of six months as shown in fig. 3. It is also observed that the density of Metformin Effervescent granules after constitution remains same at the end of six months. The most acceptable angle of repose of Effervescent Granules formulation 4 (EG4) was 27 (Angle of repose ≤30: free flowing property) and In-vitro effervescent time was 75s.

CONCLUSION

It is concluded from the study that metformin effervescent granules were best stable when they were stored at 4˚C and the most acceptable shelf life was 510 days at 4˚C and at room temperature 425 days. Moreover, among the different formulations of Effervescent Granules, the EG4 formulation disintegrate rapidly in aqueous solution and also has angle of repose less than 30, indicating good flowing property. So granules may be another dosage form to use as antidiabetic pharmaceutical product.

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