IJPT
Available Online through
www.ijptonline.com
ISSN: 0975-766X
Research Article

FORMULATION OF METFORMIN HYDROCHLORIDE MATRIX TABLETS BY SINTERING TECHNIQUE AND ITS EVALUATION

Flowerlet Mathew [1*], K.R.Anoop[2], Shoma Jose[2], Asha Jose[3].
[1]Nirmala College of Pharmacy, Muvattupuzha, Kerala, India.
[2]Amrita School of Pharmacy, Amrita Viswa Vidyapeetam, AIMS, Kochi, Kerala, India- 682041.
[3]Karpagam college of Pharmacy, Ottakal mandapam, Coimbatore, Tamilnadu, India- 641032.
Email: *ssnvij@yahoo.co.in*

Received on 27-03-2010 ***Accepted on 19-04-2010***

ABSTRACT

Metformin hydrochloride is a biguanide, which is used as an oral hypoglycemic agent. It is a white crystalline hygroscopic drug used as an antidiabetic agent specifically for type-2 diabetes mellitus. When given, a divided dose of 0.5-3 gm daily, it increases the hepatic glucose production thereby increasing the peripheral glucose uptake and utilization and shows a significant bioavailability about 50-60%. Since metformin hydrochloride is widely chosen as the first line drug in the treatment of type2 DM, because of its minimal risk and maximum efficacy, the formulation of metformin hydrochloride matrix tablet was taken in to consideration. Matrix tablets reduce the frequency of dose administration, and are found to have increased patient compliance. A relatively recent technique called sintering technique is involved in the formulation which aims to extend the release of metformin hydrochloride from the matrix tablets. After formulation the tablets where subjected to preformulation studies, micromeritic studies, stability studies and other tablet evaluation methods. In the present world diabetes is a haunting threat for life and so, the development of metformin hydrochloride matrix tablets paves the way to increase the quality of life.

KEYWORDS: Metformin hydrochloride, Matrix tablets, Sintering technique, In vitro dissolution, HPLC, Stability test.

INTRODUCTION

The concept of formulation of controlled release drug delivery has become a milestone in the treatment of diseases. Currently, the increased awareness in the community and the importance of safe use of drugs prompted to develop novel drug delivery system .In the present study, an attempt was made to extend the release of Metformin hydrochloride from matrix tablets by sintering technique. This has been an evolving one in the study of effect of heating on mechanical properties of pharmaceutical powders that is used in the formulation of sustained release matrix tablet. Matrix tablets are considered the commercially feasible sustained action dosage forms that involve the least processing variables, utilize the conventional facilities and accommodate large doses of drug (Y.S.R Krishanaiah, et al 2003)Diabetes is a major public health concern where more and more people are falling prey to the disease in both the developed and developing world. Metformin is a hyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Clinical studies proved a significant reduction in the risk of myocardial infarction and overall mortality in overweight patients with type 2 diabetes treated with Metformin hydrochloride which made the drug a cornerstone in the treatment of patients with type 2 diabetes. Metformin - controlled release was developed with the intention of decreasing the dosing interval of Metformin, and of improving its gastro-intestinal tolerability and convenience.[1]

MATERIALS AND METHODS

Metformin hydrochloride is the drug used, Eudragit RL 100 and Eudragit RS 100 are the polymers used. Sodium starch glycolate and aerosols were the other excipients used in its formulation. Fused

Calcium Chloride, acetone, Potassium dihydrogen o-phosphate and Sodium hydroxide were the reagents used. (Jens T. Cartensen 1997) Instruments like Hardness tester, Friablator, Single punch tablet compression machine, Dissolution apparatus, UV Visible spectrophotometer, HPLC, FTIR and Vacuum desiccators were used.

SINTERING

Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat. Conventional sintering involves the heating of a compact at a temperature below the melting point of the solid constituents in a controlled environment under atmospheric pressure. The changes in the hardness and disintegration time of tablets stored at elevated temperatures were described as a result of sintering. The sintering process has been used for the fabrication of sustained release matrix tablets for the stabilization and retardation of the drug release.[2]

Procedure:

The punched tablets were subjected to sintering process. The lower chamber of the dessicator was filled with acetone, closed and kept aside for saturation. After saturation the compressed tablets were taken in petry dishes and placed over a wire-mesh which is kept above the lower chamber of the dessicator containing acetone. The dessicator is made airtight by closing the lid with the help of wax. The acetone vapours in the saturated dessicator enter the pores of tablets, solubilize the surface of the polymer particles which results in the fusion of particles, thus bringing about sintering. 90 tablets of each formulation were divided into three batches and exposed to three different durations of sintering (1.5, 3.0 and 4.5 hours) as shown in Table No.3 & 4.

Table No. 3: Metformin hydrochloride-Eudragit RS100 matrix tablets sintered for different durations of time.

FORMULATION	1.5 hours	3.0 hours	4.5 hours
$D\text{-}RS_1$	$D\text{-}RS_1$ (1.5)	$D\text{-}RS_1$ (3.0)	$D\text{-}RS_1$ (4.5)
$D\text{-}RS_2$	$D\text{-}RS_2$ (1.5)	$D\text{-}RS_2$ (3.0)	$D\text{-}RS_2$ (4.5)
$D\text{-}RS_3$	$D\text{-}RS_3$ (1.5)	$D\text{-}RS_3$ (3.0)	$D\text{-}RS_3$ (4.5)
$D\text{-}RS_4$	$D\text{-}RS_4$ (1.5)	$D\text{-}RS_4$ (3.0)	$D\text{-}RS_4$ (4.5)

Table No. 4: Metformin hydrochloride-Eudragit RL100 matrix tablets sintered for different durations of time

FORMULATION	1.5 hours	3.0 hours	4.5 hours
$D\text{-}RL_1$	$D\text{-}RL_1$ (1.5)	$D\text{-}RL_1$ (3.0)	$D\text{-}RL_1$ (4.5)
$D\text{-}RL_2$	$D\text{-}RL_2$ (1.5)	$D\text{-}RL_2$ (3.0)	$D\text{-}RL_2$ (4.5)
$D\text{-}RL_3$	$D\text{-}RL_3$ (1.5)	$D\text{-}RL_3$ (3.0)	$D\text{-}RL_3$ (4.5)
$D\text{-}RL_4$	$D\text{-}RL_4$ (1.5)	$D\text{-}RL_4$ (3.0)	$D\text{-}RL_4$ (4.5)

FORMULATION OF METFORMIN HYDROCHLORIDE MATRIX TABLETS

To study the influence of different polymers, polymer concentrations and time period of sintering on the physicochemical and in-vitro release behaviour of matrix tablets the following steps were conducted.

- Formulation of drug polymer mixture for direct compression.
- Compression of formulated powder mixture into tablets
- Sintering of compressed tablets
- Comparison of formulated Eudragit matrix tablets with marketed sustained release tablet
- Ageing studies

Matrix tablets of Metformin hydrochloride were prepared by direct compression method. Two different polymers i.e., Eudragit RS100 and Eudragit RL100 were taken in four different ratios each, with drug and other excipients as shown in the Tables 1& 2.

Table No. 1: Composition of Metformin hydrochloride-Eudragit RS100 matrix tablets

Ingredients	**D-RS$_1$ (mg)**	**D-RS$_2$ (mg)**	**D-RS$_3$ (mg)**	**D-RS$_4$ (mg)**
Metformin Hydrochloride	500	500	500	500
Eudragit RS100	100	150	200	250
Sodium Starch Glycolate	25	25	25	25
Aerosil	1.5	1.5	1.5	1.5

Table No. 2: Composition of Metformin hydrochloride-Eudragit RL100 matrix tablets

Ingredients	**D-RL$_1$ (mg)**	**D-RL$_2$ (mg)**	**D-RL$_3$ (mg)**	**D-RL$_4$ (mg)**
Metformin Hydrochloride	500	500	500	500
Eudragit RL100	100	150	200	250
Sodium Starch Glycol	25	25	25	25
Aerosil	1.5	1.5	1.5	1.5

Quantity of drug, polymer and other excipients in the form of fine powder sufficient for a batch size of 120 tablets of each formulation were taken in a plastic container and mixed thoroughly to ensure complete mixing and obtain a uniform blend. The powder blends of all the formulation were dried in an oven at 40°C before compression. As the transition temperature of Eudragit RS and Eudragit RL polymers are 50°C and 55°C respectively, the blends should not be exposed to temperature above 45°C during drying. Tablets containing 500 mg of Metformin hydrochloride were compressed using a flat round 12mm single stroke Cadmac punching machine.

Preformulation Studies:

This involves the investigation of physical and chemical properties of drug substance alone when combined with the excipients. The sample vials were kept in different temperature and humidity conditions for a period of two month. The bulk density, tap density, compressibility index, angle of repose, organoleptic properties and drug content were analyzed.

Analytical methods:

Calibration curve in Phosphater Buffer pH6.8 was plotted and absorbance was measured at 233nm.

In-vitro Dissolution Studies

The in-vitro dissolution studies of the tablets were carried out by using USP-dissolution apparatus type-II, using 900 ml of phosphate buffer pH 6.8 as medium maintained at 37 ± 1° C at 100 rpm for 8 hour.

Samples of 5 ml volume were withdrawn at predetermined time intervals, which were later filtered diluted and assayed spectrophotometrically at 233 nm. (Parikh P.P.2005.) An equal volume of fresh medium was immediately replaced to maintain the dissolution volume constant. The amount of Metformin hydrochloride release at each time interval was calculated from the absorbance of the samples. Dissolution studies were performed in three-sets and mean values were reported. The

percentage drug release was then graphed against time and the release profiles were studied. Three different pharmacokinetic models, i.e. Higuchi's, Zero-order, and First-order models were studied using non-linear regression analysis remove performed. Marketed product Glycomet SR (500 mg) was also evaluated for its dissolution profile and compared with the fabricated formulations.The regression coefficients of Higuchi and Zero-order models for the marketed samples are 0.96148 and 0.9909 respectively. The fabricated formulation D-$RS_{40\%}$ 4.5 which show similar release profile to marketed formulation has regression values of 0.9824 and 0.9961 for Higuchi and Zero-order models respectively.[4]

Stability studies of the tablets:

Stability of a formulation can be defined as the time from date on manufacture of the formulation until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time. Under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf lives.[9]

Method

The selected formulations were packed in amber-colored bottles, which were tightly plugged with cotton and capped. They were then stored at 25°C/60% RH and 40°C/75% RH for 8 weeks and evaluated for their physical appearance and drug content at specified intervals of time. The drug solutions were further scanned to observe any possible spectral changes. T_{80} was also calculated by using dissolution studies. [5, 6, 7]

RESULT AND DISCUSSION

CHARACTRIZATION OF THE MATRIX TABLETS

Angle of repose:

It is necessary to characterize the flow properties of powders in order to estimate their suitability for employing them as direct compression excipients. Angle of repose is considered as an indirect measurement of powder flowability. Compressibility index also indirectly measures the flow ability of powder mass. The CI value of Eudragit powder was measured and found to be high, which indicated that Eudragit has poor flow property. Hence Aerosil was added to improve the flow characteristics of these mixtures for compression. The formulations D-RS2, D-RS3, D-RS4, and D-RL3 showed poor flow.

Hardness

The hardness of the tablets was determined by Monsanto hardness tester. There is a significant difference between the hardness of the un-sintered and sintered matrix tablets which may be attributed to the bridge formation between the polymer particles during sintering which strengthens the tablet. The hardness of the tablets was found to increase with an increase in both the polymer concentration and sintering time. This may be due to more number of bridges and formation of thicker bridges respectively. The formulation D-RL4 was found to have maximum hardness (8.5) at 4.5hrs.

WEIGHT VARIATION

The weight variation of the tablets was determined and reported. The individual weight variation of twenty tablets was calculated. All the batches of tablets complied with the weight variation limits as per Indian Pharmacopoeia i.e., The percentage weight variation of the individual tablets remained within 5% and not more than 2 tablets in a batch of 20 deviated from ±5% weight variation. All the formulations passed the test for weight variation.

THICKNESS:

Thickness of the tablets was determined using Vernier-Calipers. Thickness was found to remain in the limits of ± 5% of the size .The formulation D-RS4 and D-RL4 showed the maximum average thickness of 0.693 and 0.690 cm.

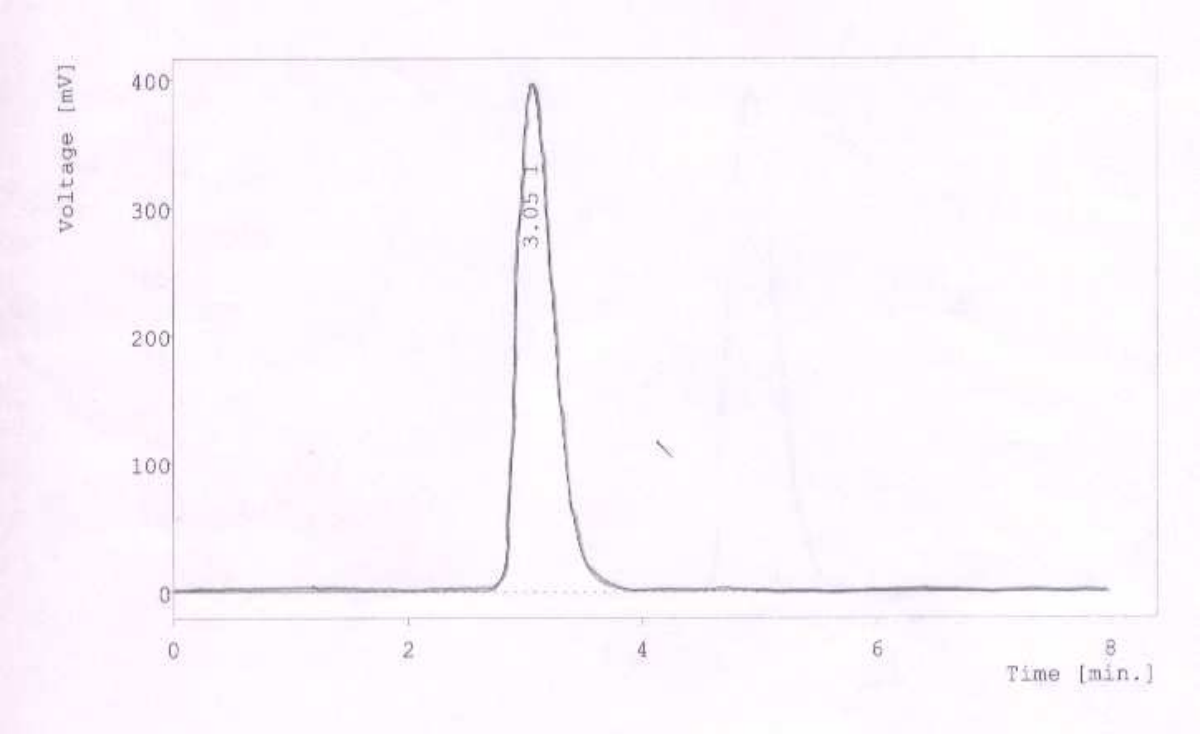
FRIABILITY

The friability test of all batches of tablets was done. The exceptionally low friability of the matrix tablets may be attributed to inter-particulate bridges formed during sintering which holds the drug and excipients particles between them very strongly. Some batches that are having higher polymer concentration and subject to longer sintering duration showed no friability which may be because of thicker bridges formed during sintering time as the depth to which the polymer particle is solubilized is more, and more such bridges formed due to higher polymer proportion in the matrix.

HPLC STUDIES:

The pure drug and powdered matrix tablets were subjected to HPLC studies using acetonitrile: buffer (1:1) as mobile phase. Chromatogram of pure drug was served as control. HPLC studies was employed to check whether there was any interaction between the drug, Metformin Hydrochloride and the polymeric material, when it was exposed to acetone vapour for different time periods. The batches which were exposed to the maximum sintering time of 4.5 hour and the maximum concentration was only subjected for the study, since the interactions, if any, present can be detected at these highest concentration and sintering time.[3]The chromatograms and surface area of the peak of each and every formulation were almost similar to that of pure drug.The chromatogram is shown in figure 1.

Chromatogram of HPLC



Peak No.	Reten. Time	Area (mV. s)	Height (mV)
1	3.053	8709.4358	396.4231

INVITRO DISSOLUTION STUDIES

Dissolution test was performed on three tablets from each formulation.

The cumulative drug release of all the formulations at the end of 12 hours was calculated. In case of Eudragit RS 100 matrices, the least retardation was achieved by D-$RS_{20\%}$ 1.5 with 92.62 % in 8 hours, while the highest retardation was achieved by D-$RS_{50\%}$ 4.5 with only 52.63 % drug release in 8 hours. In case of the Eudragit RL 100 matrices the least drug release retardation was achieved by D-$RL_{20\%}$ 1.5 with as much as 99.93 % drug release in 8 hours, while the highest retardation was offered by D-

$RL_{50\%}$ 4.5 with only 81.03 % drug release in 8 hours. (Reddy KR et al 2003) Similarly for a particular sintering time, the release rate decreased with increasing polymer concentration. For 1.5, 3.0, and 4.5 hours sintering durations the least retardation is offered by least polymer concentration of 100 mg for both Eudragit RS 100 and RL 100 matrices. The highest retardation was offered by matrices with highest polymer concentration.

The cumulative drug release of all formulations at the end of 12hours is given in the following table no: 5.The samples were compared with that of the marketed product Glycomet SR (500mg).

Table No. 5: Cumulative % drug release at end of 12 hours

Formulation	**% Drug Release**	
	Eudragit RS100	**Eudragit RL100**
D – Polymer 20% 1.5 hr	92.62	99.93
D – Polymer 20 % 3hr	79.23	90.03
D – Polymer 20% 4.5 hr	73.63	84.04
D – Polymer 30% 1.5 hr	82.62	99.9
D – Polymer 30 % 3hr	75.43	89.57
D – Polymer 30% 4.5 hr	63.24	83.04
D – Polymer 40% 1.5 hr	83.01	98.25
D – Polymer 40 % 3hr	62.03	85.4
D – Polymer 40% 4.5 hr	57.61	81.73
D – Polymer 50% 1.5 hr	80.01	97.05
D – Polymer 50 % 3hr	62.63	80.91
D – Polymer 50% 4.5 hr	52.63	81.03
Marketed Sample	66.57	

STABILITY STUDIES:

Formulation and the development of a pharmaceutical product is not complete without proper stability analysis, carried out on it to assess the physical and chemical stability and the safety. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time. Under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf lives.

Stability studies were carried out by placing the samples at different temperature (25^0C and 40^OC) and different relative humidity conditions (60% RH and 75% RH). There is no significant change in release characteristics and physicochemical properties of the tablets used in the release study. Based on the results it can be concluded that the formulated matrix tablets were stable at room temperature at different relative humidities over a period of 60 days. Even though its stability is assured for two months, further studies at different temperatures and humidity conditions are needed to establish its shelf-life.

CONCLUSION

This thesis deals with the objective of developing oral controlled release formulations through matrix tablets for the widely used antidiabetic drug Metformin hydrochloride using plastic polymers such as Eudragit RS100 and Eudragit RL 100 by sintering technique in varying concentration and sintering time and comparative evaluation of their controlled release potential were also investigated.

In conclusion, among the different strategies employed for the design of a controlled release dosage forms, sintering technique for the preparation of polymer matrices for controlled release of Metformin hydrochloride appears to be an alternative technique. This new method for controlling the release rate of Metformin hydrochloride has been developed using Eudragit and was tested. At room temperature

when exposed to acetone vapors, Eudragit – RL 100 and Eudragit RS 100 powder particles fused or welded to each other due to coming in contact with other particles were the particles get contacted. The extend of fusion was depends on concentration of polymer and sintering time. This type of system provides a significant and convenient method for achieving controlled release in oral dosage forms. The release of the drug form un-sintered matrix tablets containing 100mg polymer was 100% within 90minutes. This clearly shows that Eudragit RS100 and Eudragit RL100 polymers do not have drug release retardant properties when employed as matrix materials by direct compression.

REFERENCE

1. Lawrence Blonde, George E. Dailey, Serge A, Jabbour, Charles A, Reasner and Donna J. Mills. Gastrointestinal tolerability of extended release Metformin tablets compared to immediate – release Metformin tablets : results of a retrospective cohort study. Current Medical Research and Opinion. Vol 20, No.4 2004; 565 – 572.
2. Cohen J, siegel RA, Langer R. Sintering technique for the preparation of polymer matrices for the controlled release of Macromolecules. J Pharm Sci 1984 Aug; 73(8): 1034-1037.
3. Kale V.V, Kusliwal R.H and Avari J.G. Effect of matrix geometry on drug release from guar gum matrix tablet. Indian Drugs. 42(2). Feb; 2005. 84 – 86.
4. Kalpana Swain, Satyanarayan Pattnaik, K.A Chowday, P. Suresh. Design and evaluation of controlled release hydrodynamically balanced system of theophylline with HPMC $K_{100}M$ using sintering technique. 55th IPC Article Pharmaceutical Technology (21).
5. Sreenivasa Rao B, Seshasayana A, Himasankar K, Prasanna Raju Y and Ramana Murthy KV. Design and evaluation of ethylene- vinyl acetate sintered matrix tablets. Indian J Pharm Sci.2003; 65(5): 496-502.

6. S.K. Ghosal, K. Ruckmani, B. Agul, B. Jaykar. Sustained release of Nifedipine from eudraget matrix tablets. The Eastern Pharmacist. Nov; 1995. 137 – 139.
7. Y.S.R Krishanaiah, K. Latha, L. Nageswara Rao. Development of colon targeted oral guargum matrix tablets of albendazole for the treatment of helminthiasis. Indian J.Pharam. Sci 2003.;65(4) 378 – 384.
8. Mutalik Srinivas, Hiremath Doddayya. Formulation and evaluation of chitosan matrix tablets of nifedipine. The Eastern pharmicist. 2000 Feb; 109-111.
9. Jens T. Cartensen, pharmaceutics of solid and solid dosage forms, Hohn wiley and Sons, Inc (1997) 248.
10. Indian pharmacopoeia 1996 Vol II Page 460 – 470.
11. Sunil A. Kanvinde, Stability of oral solid dosage forms – a global perspective. Pharma Times Vol 37 No. 5 May 2005 9 - 15 Carr RL. Development of Metformin HCl (500 mg) slow release formulation using method: hydrophilic matrices.
12. Guyton, Text Book of Medical Physiology

***Corresponding Author Address:**

Flowerlet Mathew*,
Nirmala College of Pharmacy,
Muvattupuzha, Kerala, India.