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FORMULATION AND EVALUATION OF SINTERED MATRIX TABLETS OF METFORMIN HYDROCLORIDE

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ABSTRACT

Metformin hydrochloride, a water soluble drug,has a short half life of 4 to 5 hours and a limited window of absorption .This necessitates the formulation of this drug as a controlled release tablets .so the present work was aimed to extend the release of metformin hydrochloride from matrix tablets by sintering technique .For this purpose polymers like eudragit L 10055and H P M C K 4M were used .These polymers were added to the active ingredient and other excipients. The formulation was then punched into tablets and kept in a dessicator for 1.5 hrs ,3 hrs, 4.5 hrs for sintering.The dessicator must be previously saturated with acetone vapours for 24 hrs .After sintering the tablets were removed from the dessicator , and dried at room temperature for 24 hrs to evaporate the adhering acetone and were finally dried in a vaccum dessicator at 30ºC over fused calcium chloride for 24 hrs to remove the residual acetone from the tablets and stored in dessicator for further studies .The tablets were subjects to all evaluation tests of tablets .The results proved that tablets sintered for 4.5 hrs were harder and released drug at slower rate than those sintered for 3 hrs also eudragit L 100 55 was found to be better rate controlling polymer than HPMC K4M.

KEYWORDS: Sintering technique,Metformin hydrochloride,Eudragit L 10055, H P M C K 4M, matrix tablets.

INTRODUCTION

Metformin hydrochloride a water soluble drug having shorter half life of 4-5hrs and limited window of absorption which necessitates the formulation of drug as a controlled release tablet.The controlled release dosage form ensures safety and it improves the efficacy of the drug as well as patient compliance.Matrix tablets are considered the commercially feasible sustained actions dosage forms that involves the least processing variables, utilize the conventional facilities and accommodate large doses of drug[1].So the present work was aimed to extend the release of an anti-diabetic drug Metformin hydrochloride from the matrix tablets by sintering technique.

Diabetic is a major public health concern more and more people are taking prey to the disease in both the developed and developing worlds. Diabetes mellitus result, from diminished secretion of insulin by the beta cell of the islets of Langerhans. Heredity plays a major role in determining in whom diabetics will develop and in whom it will not develop[2].

Sintering[3]:

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.

Exploration of the sintering concept in the pharmaceutical sciences is relatively recent and research interests relating to this process have been growing. The concept of sintering was applied in the investigation of the effect of heating on the mechanical properties of pharmaceutical powders. The formation of solid bonds within a powder bed during tablet compression was also studied in terms of sintering. The change in the hardness and disintegration time of tablets stored at elevated temperature was described as a result of sintering. Furthermore, the sintered process has been used for the fabrication of sustained release matrix tablets for the stabilization and retardation of the drug release.

FORMULATION OF METFORMIN HYDROCHLORIDE MATRIX TABLETS

Metformin hydrochloride Matrix tablets were prepared by direct compression method. Eudragit L100 55 and HPMC K4M were taken in same ratios each, with drug and other excipients as shown in the Table 1.

TABLE NO. 1 Composition of Metformin hydrochloride matrix tablets

Ingredients	**E** (mg)	**H** (mg)
Metformin hydrochloride	500	500
Eudragit L100-55	100	-
HPMC K_4M	-	100
Sodium Starch Glycolate	13	13
Aerosil	6.5	6.5
Magnesium Sterate	6.5	6.5

H and **E** (Weight of each tablet – 626mg)

Quality of drug, polymer and other expicients 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 40^0C before compression. Tablets containing 500 mg of

Metformin hydrochloride were compressed using a flat round 12mm single stroke Cadmac punching machine.

Steps in the manufacturing of sintered matrix tablets of Metformin hydrochloride

All the ingredients were added as per the formula (table 1) in geometric dilutions after making sure that all the particles are in a uniform size range.The formulation was then made into tablets each weighing 626mg by direct compression.The lower chamber of a desicator was filled with acetone, closed and kept aside for saturation (24 hrs). after saturation the compressed tablets were taken in petri dishes and placed over a wire-mesh which was kept above the lower chamber of the desiccator containing acetone.The desicators was made airtight by closing the lid with the help of wax.The acetone vapours in the saturated desicators enter the pores of tablets and solubilize the surface of the polymer particles which results in the fusion of particles, thus bringing about sintering[25].After sintering, the tablets were removed from the desicator, and dried at room temperature for 24 hours to evaporate the adhering acetone and were finally dried in a vacuum desicator at 30^0C over fused calcium chloride for 24 hours to remove the residual acetone from the tablets and stored in desicator for further studies.

ANALYTICAL METHOD

Standard Curve in Phosphate Buffer

8gm of sodium hydroxide was dissolved in distilled water and volume was adjusted to 1000 ml with distilled water.

Preparation of 0.2M Potassium Dihydrogen Phosphate

27.218 gm of potassium dihydrogen phosphate was dissolved in distilled water and volume was adjusted to 1000 ml with distilled water.

Preparation of Phosphate Buffer of pH 6.8

250ml of 0.2M potassium dihydrogen phosphate was placed in a 1000 ml volumetric flask. 112.5 ml of 0.2M sodium hydroxide was added to the flask and volume was adjusted with distilled water.

Calibration curve in Phosphate Buffer pH 6.8

100 mg of Metformin hydrochloride was dissolved in phosphate buffer pH 6.8 and volume was made up to 100 ml in a volumetric flask. From the above stock solution. 10 ml was transferred into a 100 ml volumetric flask and volume was adjusted. This corresponds to 100 ug/ml of the drug. From the above solution different aliquots of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 & 1.0 ml were transferred to 10 ml volumetric flasks. Volume was adjusted with phosphate buffer pH

6.8 which gives a concentration of 1,2,3,4,5,6,7,8,9,10 ug/ml and absorbance was measured at 233nm. Calibration data is given in table no.2.

TABLE NO.2:Calibration Data of Metformin Hydrochloride in Phosphate Buffer pH 6.8 at 233nm

Concentration (µg/ml)	Absorbance*
1	0.091±0.0048
2	0.179±0.0068
3	0.258±0.0170
4	0.347±0.0113
5	0.438±0.0098
6	0.517±0.0073
7	0.611±0.0056
8	0.698±0.0031
9	0.782±0.0081
10	0.866±0.0041

*** Mean of 6 replication**

Calibration curve of metformin hydrochloride in phosphatebuffer pH 6.

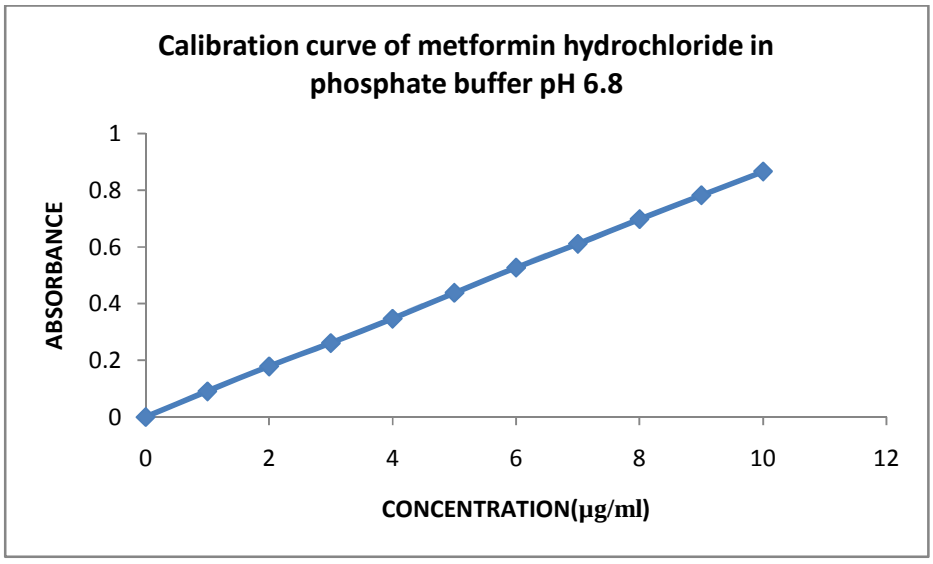

Figure no.1

COMPATIBILITY STUDIES

Infrared spectra matching approach was used for the detection of any possible chemical reaction between the drug and the polymer. A physical mixture (1:1) of the drug and polymer was prepared and mixed with suitable quantity of potassium bromide. About 100 mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 10 tons pressure. It was scanned from 4000 to 400 cm^{-1} in a shimadzu FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and polymers and matching was done to detect any appearance or disappearance of peaks[4].

POWDER PROPERTIES

Direct compression is defined as a process by which tablets are compressed directly from powder blends of the active ingredients and suitable excipients which will flow uniformly into a die cavity and form into a firm compact. No pretreatment of the powder blend by wet of dry granulation procedures is necessary. Before employing direct compression as a method of preparation of tablets the powder properties of the ingredients should be assessed to ascertain their suitability for direct compression. The evaluation of powder properties of drug and polymers were taken up as they from the bulk of tablet. The powders of polymer and drug are characterized by bulk density, tapped density, carr's consolidation index and angle of repose. The flow properties of solids have great impact on tableting and encapsulation processes for dosage form manufacturing which require the flow of materials from a storage container to filling stations.

Flow Properties

The flow properties of the solids also have a great influence on mixing and demixing of powders which take place before tableting or encapsulation. Different flow properties are required at different stages of processing and should be carefully taken into consideration during formulation and process validation. Characterization of the powders is essential to quality control of raw materials, active or expicients, in order to maintain product uniformity[5].

Compressibility index (carr's consolidation index)

Another indirect method of measuring powder flow from bulk density was developed by carr's. The percentage compressibility of a powder is a direct measure of the potential powder arch or bridge strength and stability and is calculated according to the following equation.

$$\% \text{ Compressibility} = \frac{\text{tap density} - \text{bulk density}}{\text{Tap density}} \times 100$$

TABLE NO.3 Relationship between powder flow property and percentage compressibility

Percentage Compressibility	Flow description
5-15	Excellent(free flowing granules)
12-16	GOOD(free flowing powdered granules)
18-21	FAIR(powdered granules)
23-28	POOR(very fluid powder)
28-38	VERY POOR(fluid cohesive powder)
>40	EXTREMELY POOR(cohesive powder)

Angle of repose

A funnel with its bottom closed is fixed to a stand and a weighed quantity of powder (6gms) is placed in it. The bottom of the funnel is opened and the powder is allowed to fall on a paper and form a pile. The angle of the pile makes with the horizontal and the diameter of the pile are used to calculate the angle of repose[6].

CHARACTERIZATION OF THE TABLET

The prepared tablets were subject for various quality control tests in order to characterize them.

Weight Variation

The weight variation test of the tablets was done as per the guidelines of Indian Parmacopoeia. Weight of twenty tablets selected at random and its individual weight was noted and calculated the mean weight also. Percentage deviation of each tablet from the mean was calculated and tabulated as shown in Table 7. Not more than two of the individual weights deviate from the average weight by more than 5% and none deviation by more than twice that percentage[5].

Thickness

Once the tablet size and shape have been established, tablet thickness remains the only overall dimensional variable. Thickness should be controlled with in 5% or less of an established standard value. Excessive variation in tablet thickness can result in problems with packaging as

well as consumer acceptance. Variation in tablet thickness can also indicate formulation or processing problems such as change in die fill, and compressive force. The thickness of the individual tablet was measured with vernier calipers and average thickness is reported in Table 8.

Hardness

Tablet requires a certain amount of mechanical strength to withstand the shock of handling in its manufacture, packaging, shipping and dispensing. It may be especially important to monitor the tablet hardness for sustained release drug products or other products that possess real or potential bioavailability problems or are sensitive to variations in drug release profile. The crushing strength that just causes the tablet to break is recorded by means of Monsanto hardness tester. The tablet is placed vertically in between the lower and upper plungers. The lower plunger was placed in contact with the tablet and the four reading was taken. The upper plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed, a point moves along a gauge in the barrel to indicate pressure. The position of the pointer at the time of fracture was noted and the difference between the initial and the final readings was taken as the hardness of the tablet.

Friability

Friability is the measure of a tablet's ability to with stand both shock and abrasion without crumbling during the handling of manufacturing, packing, shipping and consumer use. Tablets that tend to powder, chip, and fragment when handled lack elegance, and hence, consumer acceptance. The weight of 10 tablets was noted and placed them in Roche type friabilator. The device subjects the tablets to the combined effect of shock and abrasion by utilizing a plastic chamber which revolves at 25rpm, dropping the tablets a distance of 6 inches with the revolution. The pre-weighed tablet sample is removed after 100 revolutions, dusted and reweighed. Tablets that loose less than 0.5 to 1 percent in weight are generally considered acceptable[5].

Drug Content Estimation

From each batch 5 tablets were triturated to form fine powder after knowing the individual weight of each tablet. The powder equivalent to 100 mg of Metformin hydrochloride was weighed and transferred into a 100 ml volumetric flask and was dissolved in phosphate buffer of pH 6.8 and made up the volume to get 1 mg/ml. 1ml of this stock solution was taken in 100 ml volumetric flask and made up with phosphate buffer of pH 6.8 to get a concentration of 10 ug/ml. The absorbance of this solution was measured at 233 nm by using UV Visible spectrophotometer. The drug content was estimated by using calibration curve. Metformin

hydrochloride tablets contain not less than 95% and not more than 105% of the labeled amount of Metformin hydrochloride.

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 ± 1^0C 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. 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.

RESULTS AND DISCUSSION

METFORMIN HCL +EUDRAGIT L100 55

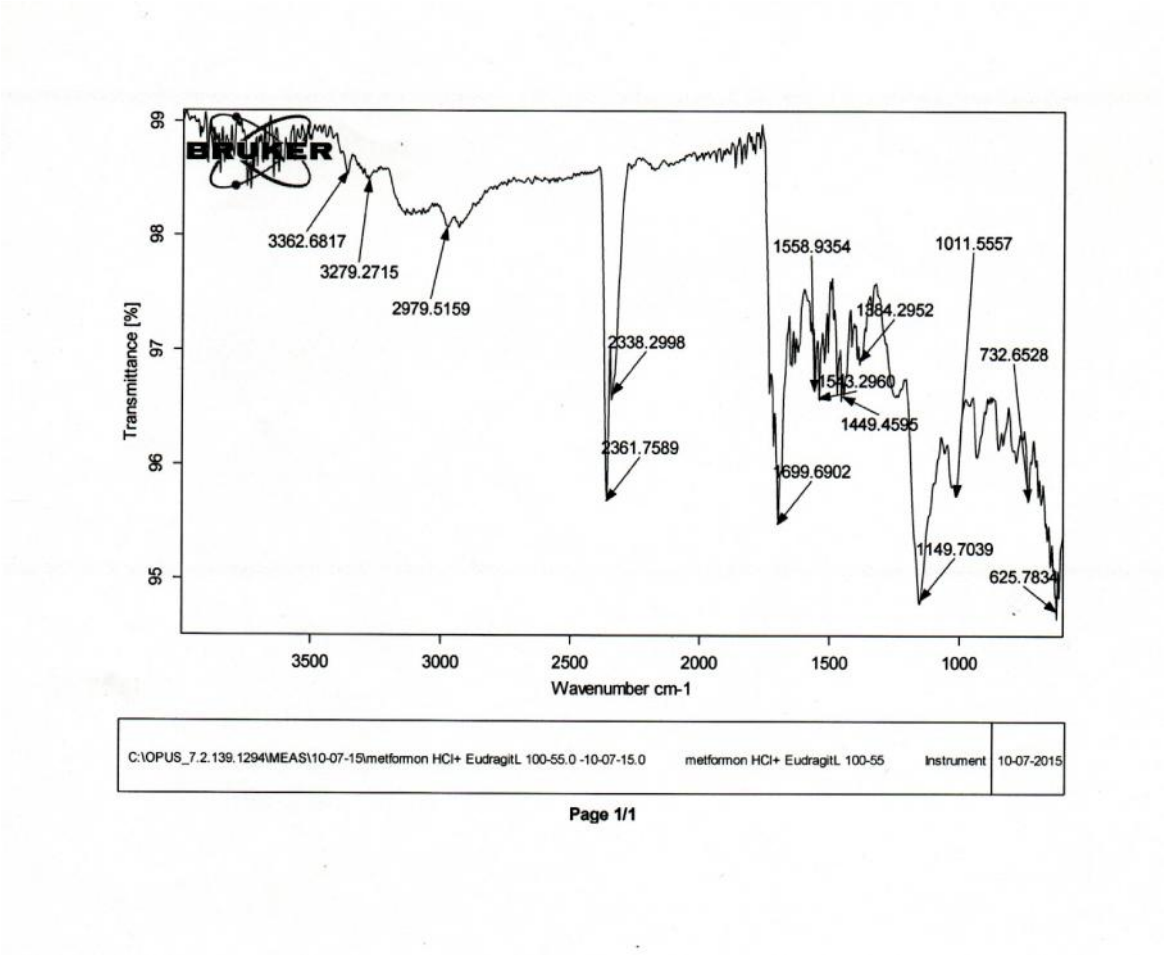

Figure no.2

METFORMIN HCL+HPMC K4M

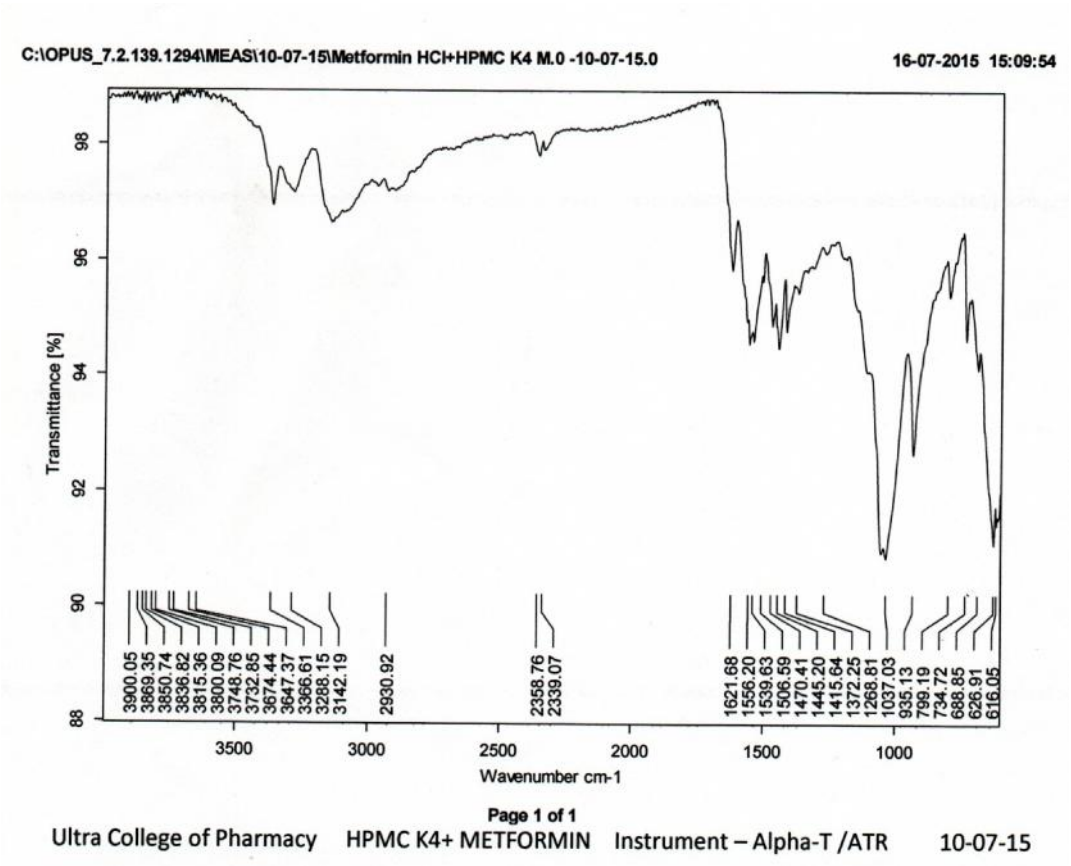

Figure no.3

The compatibility between the drug and the polymer Eudragit L100 55 polymer were evaluated using FTIR peak matching method. The IR spectra of pure drug, polymers and the physical mixtures are shown in figures there was no appearance or disappearance of peaks in the polymer drug mixture, which confirmed the absence of any chemical interaction between the drug and the polymers.

POWDER PROPERTIES

FLOW PROPERTIES

It is necessary to characterize the flow properties of powders in order to estimate their suitability for employing them as direct compression excipients. Here angle of repose and compressibility index (CI) were employed to characterize the flow properties of the power. In the development laboratory, these tests could be used to characterize bulk solids routinely before compression. So, better optimization of flow properties can be achieved in experimental formulations.

Angle of repose is considered as an indirect measurement of powder flowability. Compressibility index also indirectly measures the flowability of powder mass. The CI value of Eudragit powder was measured and found to be high, which indicated the Eudragit has poor flow property. Hence Aerosil was added to improve the flow characteristics of these mixtures for compression.

TABLE NO.4Compressibility Index of Metformin-Eudragit & Metformin-HPMC Powders

S.NO	FORMULATION	BULK DENSITY ($g/cm^{3)}$	TAPPED DENSITY (g/cm^3)	COMPRESSIBILITY INDEX(%)
1	E	0.562	0.690	18.55
4	H	0.583	0.74	21.62

TABLE NO.5: Angle of Repose of Metformin-Eudragit & Metformin-HPMC Powders

S.NO	FORMULATION	ANGLE OF REPOSE(^{0}) $O = \tan^{-1} H/R$
1	E	28.43
4	H	17.79

CHARACTERIZATION OF THE MATRIX TABLETS:

HARDNESS:

The hardness of the tablets was determined by Monsanto hardness tester as described in the previous chapter and is reported in the table.

TABLE NO.6Hardness of matrix tablets with different sintering times:

FORMULATION	HARDNESS ($kg\ cm^2$)		
	1.5hr	3hrs	4.5hrs
E_1	3.5	4	5.5
E_2	4.5	5.5	6
E_3	5	5.5	6.5
H_1	1.5	2	2
H_2	2	2.5	3
H_3	2.5	3	3.5

The comparatively low hardness of the unsintered matrix tablets indicates that the main forces holding the particles together are probably Vander walls and mechanical forces due to interlocking of the irregularities on the surface of particles. Mild sintering may have occurred due to heat generated during compression, because of the low transition temperature of the polymers.

There is a significant difference between the hardness of the unsintered 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 with an increase in both the polymer concentration and sintering time. The increase in hardness with increase in the sintering time was more pronounced than the increase in hardness with increase in the polymer concentration. The increase in the hardness with an increase in the sintering time may be due to the formation of thicker bridges and the increase in hardness with an increase in polymer concentration may be due to more number of bridges as more polymer particles are involved in bridge formation.

WEIGHT VARIATION

The weight variation of the tablets was determined and reported in table. 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.

TABLE NO.7: Weight variation of Metformin-Eudragit & Metformin- HPMC matrix tablets

S.NO	FORMULATION	WEIGHT VARIATION
1	E_1	Pass
2	E_2	Pass
3	E_3	Pass
4	H_1	Pass
5	H_2	Pass
6	H_3	Pass

THICKNESS

Thickness of the tablets was determined using Vernier-Calipers and is reported in the table. Thickness of the tablets was found to remain in the limits of + 5% of the size.

TABLE NO.8: Thickness of Metformin-Eudragit & Metformin-HPMC matrix tablets

FORMULATION	AVERAGE THICKNESS (cm)
E_1	4.50
E_2	4.51
E_3	4.52
H_1	4.49
H_2	4.49
H_3	4.50

FRIABILITY

The friability test of all batches of tablets were carried out and the result are shown in table. The exceptionally low friability of the matrix tablets may be attributed to inter-particulate bridges formed during sintering which holds the drug and excipient 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.

TABLE NO.9: Friability of Metformin-Eudragit & Metformin-HPMC matrix tablets:

Formulation	Weight of tablets before friability (w_1)	Weight of tablets after friability (w_2)	W_1-W_2=W	Percentage friability
E_1	0.626	0.620	0.006	0.96
E_2	0.626	0.622	0.004	0.64
E_3	0.626	0.624	0.002	0.32
H_1	0.626	0.620	0.006	0.96
H_2	0.626	0.620	0.006	0.80
H_3	0.626	0.622	0.004	0.64

TABLE NO.10: IN-VITRO RELEASE PROFILE OF METFORMIN FROM HPMC K4M AND EUDRAGIT L100 55 (UNSINTERED TABLET)

TIME (MINS)	% DRUG RELEASE	
	H (HPMC K4M)	E (EUDRAGIT L100 55)
15	62.59	55.927
30	89.39	83.73
60	102.927	94.91
90		101.02

IN-VITRO RELEASE PROFILE OF METFORMIN FROM HPMC K4M AND EUDRAGIT L100 55 (UNSINTERED TABLET)

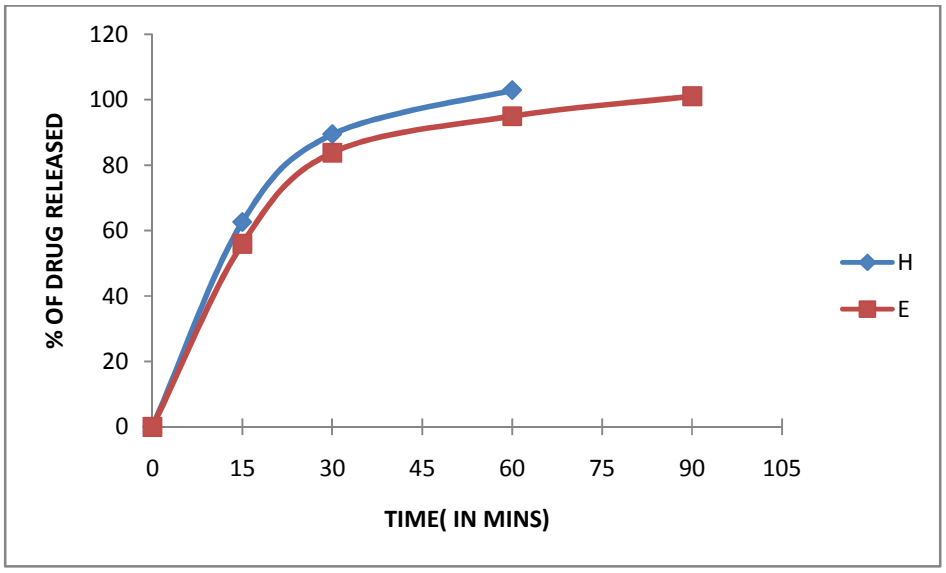

Figure no.4

TABLE NO.11: IN-VITRO RELEASE PROFILE OF METFORMIN FROM HPMC K4M SUBJECTED TO DIFFERENT DURATION OF SINTERING

TIME (hours)	% DRUG RELEASE		
	H_1 (ST=1.5 hr)	H_2 (ST=3 hrs)	H_3 (ST=4.5 hrs)
0.5	5.31	3.2	1.53
1	14.85	12.09	10.04
2	23.18	19.95	17.99
3	30.29	27.03	24.07
4	37.96	34.43	30.19
5	45.61	38.91	35.20
6	56.12	46.93	43.12
7	69.07	61.12	56.95
8	89.65	86.27	79.98

INVITRO RELEASE PROFILE OF METFORMIN HYDROCHLORIDE FROM HPMC K4M SUBJECTED TO DIFFERENT DURATION OF SINTERING

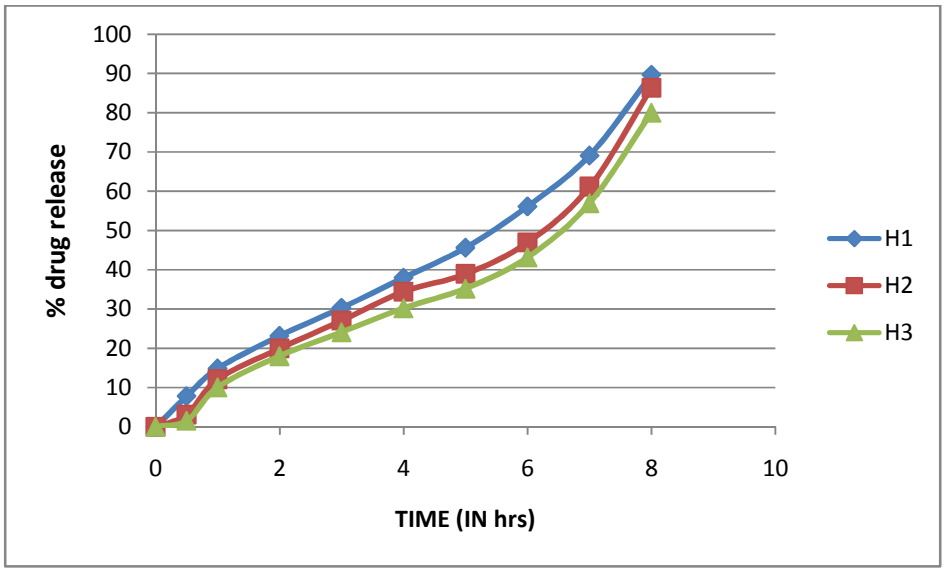

Figure no.5

TABLE NO.12: IN-VITRO RELEASE PROFILE OF METFORMIN FROM EUDRAGIT L100 55 SUBJECTED TO DIFFERENT DURATION OF SINTERING

TIME (hours)	% DRUG RELEASE		
	E_1 (ST=1.5 hr)	E_2 (ST=3 hrs)	E_3 (ST=4.5 hrs)
0.5	18.25	13.84	9.91
1	22.42	16.85	12.83
2	29.59	24.01	16.89
3	35.5	28.98	26.10
4	45.7	35.55	30.11
5	53.9	41.42	36.64

6	63.13	48.73	42.13
7	72.01	54.44	49.93
8	82.94	72.22	63.98

INVITRO RELEASE PROFILE OF METFORMIN HYDROCHLORIDE FROM EUDRAGIT L100 55 SUBJECTED TO DIFFERENT DURATION OF SINTERING

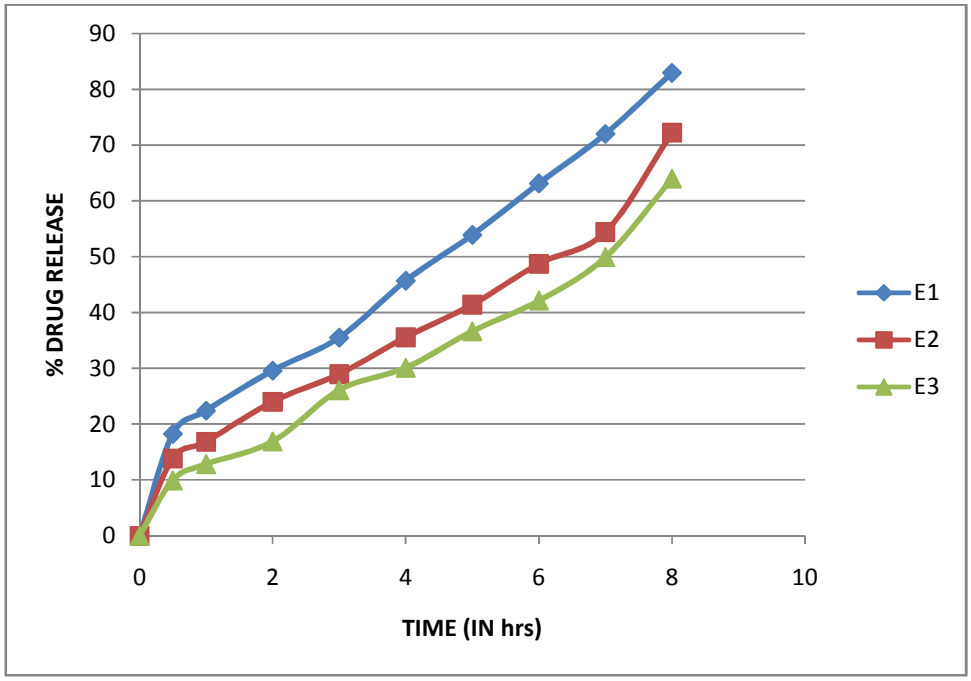

Figure no.6

Sintering in conventional method is achieved by heating the powder at elevated temperaturess depending on transition temperature of the material to be sintered. Sintering can also be achieved by exposing the material to the vapours of the liquid in which it has high solubility.

In this case acetone is selected as solvent for sintering as the polymer is highly soluble, while the drug and other excipients are completely insoluble in it. More over acetone being highly volatile can saturate the dessicator with its vapours at room temperature without the requirement of heating.

During sintering, the acetone vapours enters the pores of the fluffy matrices, come in contact with the polymer particles and solubilize their outer surfaces. As a result, the polymer particles fuse and come in intimate contact with each other. After the stipulated period, the matrices were dried at room temperature which removes the acetone from matrices. Placing them in vacuum dessicator over fused calcium chloride removes the residual acetone, there by strengthening the inter-particulate bridges.

The release of the drug from unsintered matrix tablets containing 100mg Eudragit polymer was 100% within 90 minutes and HPMC K4M polymer was 100% within 55 minutes. This clearly shows that Eudragit L100 55 and HPMC K4M polymer does not have drug release retardant properties, when employed as matrix materials by direct compression. The tablets distintegrated completely during the dissolution and finally settled at the bottom of the dissolution container as fine powder after the complete release of the drug.

When compared to unsintered matrix tablets, the sintered matrix tablets markedly retarded the release of Metformin Hcl due to micro structural changes brought about by sintering phenomenon. In the present investigation of SR matrix tablets of metformin Hcl were prepared by using Eudragit L100 55 polymer and HPMC K4M polymer. The higher retardation was achieved by E_3 (Sintering Time 4.5) only 63.98% drug release in 8 hours.

The unsintered formulation were compared to sintered formulations with respect to dissolution data. The cumulative % release of the 8^{th} hour for the formulation E_1, E_2, E_3 and H_1, H_2, H_3 are E_1 82.94%, E_2 72.22%, E_3 63.98% and H_1 89.65%, H_2 86.27%, H_3 79.98%. This data shows that the polymer concentration and duration of sintering were varied, the release profiles of the drug also varied. The release of the drug from the matrix can be controlled by altering the polymer concentration or sintering time or both.

It was the evident from the table n0. 11 and 12 that at a particular drug : polymer ratio and sintering time, the releas rate and cumulative amount of drug release is more from EUDRAGIT L100 55 matrices than HPMC K4M matrices. This may be due to difference in permeability of water into the polymers.

From among the sintered formulation E_1, E_2, E_3 and H_1, H_2, H_3 the formulation E_3 possessing good release retardant ability has fulfilled the objectives of our studies. The highest retardation was achieved by E_3 formulation sintering time 4.5 hours showed 63.98% drug release in 8 hours. The very low retardation offered by un-sintered matrix tablets might be due to the weaker inter-particulate bridges that were formed between the polymer particles. The highest retardation was offered by matrices with highest polymer concentration.

The drug release profiles of Metformin hydrochloride from Eudragit L 100 55 and HPMC K4M matrices were summarized in figures8 to 10.

CONCLUSION

Among the tablets prepared, sintered formulations exhibited better retardation in the release rate of the drug than the unsintered formulations.This thesis deals with the objective of developing oral controlled release formulations through matrix tablets for the widely used antidiabetic drug Metformin hydrochloride using polymers such as Eudragit L100 55 and HPMC K4M by sintering technique with varying sintering time and comparative evaluation of their controlled release potential were also investigated. By employing sintering technology, friability was found to decrease and the hardness also increased with increasing sintering time. Thus, sintering technique proved to be effective than the unsintering technique in retarding the release rate of the drug.They are cost effective with a predictable release behavior than the conventional multi-unit pellet preparation method.Sintering technique is an alternative technology for the manufacture of sustained release formulations.

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