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Research Article

FORMULATION AND EVALUATION OF SINTERED MATRIX TABLETS OF METFORMIN HYDROCHLORIDE AND ITS COMPARISION OVER UNSINTERED MATRIX TABLETS

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INTRODUCTION

Metformin is a biguanide, and Oral hypoglycaemic agent treated for type-II Diabetes mellitus. It is widely chosen and half life is 3hrs and given in divided doses daily(0.5-3gms). Matrix tablets are preferred to sustain drug activity and reduce frequency of administration. So, the new technique called sintering technique is followed here to obtain sustained release matrix tablets for better patient compliance. Diabetes is a haunting threat for life. so, metformin hcl matrix tablets paves the way to increase the quality of life.

The term sintering means fusion of particles or formation of welded bonds between particles of polymer. The SR oral dosage forms can be developed by sintering the polymer matrix by exposing to temperature above glass transition point of the polymer or exposing these matrix systems to solvent vapours. As the temperature treatment method may be a limiting factor for many drugs that get degraded at elevated temperature, therefore, in the present investigation, solvent casting method was followed in which the above mentioned problems were eliminated.

MATERIALS AND METHODS

Metformin was kindly obtained from, Xanthan gum and Guar gum was obtained from Rexer pharma, Hyd. Hydroxyl Propyl Methyl Cellulose (Methocel-K4M), Ethyl cellulose (Ethocel), Polyvinyl pyrollidine-K30, Iso propyl alcohol, Magnesium Stearate were of analytical grade .

PRECOMPRESSION STUDIES

The prepared granules of various batches were evaluated for their Bulk density, Tapped density, Angle of repose, Hausner's ratio, compressibility index,

Evaluation of granules

Angle of repose

The angle of repose was determined by the funnel method. The accurately weighed powder blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder blend. The blends were allowed to flow freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan^{-1} \theta = h/r$$

Where h and r are the height and radius of the powder cone.

Compressibility index

To calculate the Carr's compressibility both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerate formed, was introduced into a 10ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD was calculated and used to calculate the Carr's index and hausner's ratio.

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

The compressibility index of the powder blend was determined by Carr's compressibility index.

Carr's index (%) = [(TBD-LBD) x 100]/TBD

Hausner's ratio
This value was calculated by making use of bulk and tap densities of powder samples.

Hausner's ratio = TBD/LBD

PREPARATION OF METFORMIN MATRIX TABLETS
A non- aqueous procedure was performed for preparation of matrix tablets. Granules were prepared as follows. Proportion of excipients with drug was as given in Table 1. All ingredients were sifted through sieve no: 40. Polymer of various proportions were mixed with metformin manually and the obtained blend were mixed with Micro crystalline cellulose to form final blend. PVP K-30 was dissolved in IPA (5% w/v) and used for wet granulation of the final blend. The wet mass was passed through sieve no.10 and wet granules dried at 50°C in an oven for 30 minutes. Dried granules were sized by passing it through sieve no. 22 and mixed with magnesium stearate for 1 minute and compressed into tablets. Tablet weight was (200mg) kept constant as shown in Table 1.

Table 1: Composition of metformin matrix tablets by various polymers

S. No	Ingredients	FI	FII	FIII	FIV	FV	FVI	FVII	FVIII
1.	Metformin	50	50	50	50	50	50	50	50
2.	HPMC	30	60	-	-	-	-	-	-
3.	Ethyl cellulose	-	-	30	60	-	-	-	-
4.	Xanthan gum	-	-	-	-	30	60	-	-
5.	Guar gum	-	-	-	-	-	-	30	60
6.	MCC	110	80	110	80	110	80	110	80
7.	PVP-K 30	5%	5%	5%	5%	5%	5%	5%	5%
8.	IPA	1%	1%	1%	1%	1%	1%	1%	1%
9.	Magnesium stearate	1%	1%	1%	1%	1%	1%	1%	1%
10.	Total weight	200	200	200	200	200	200	200	200

SINTERING OF TABLETS
Sintering technique is a new technique and is applied to some tablets of prepared formulations. This is done by taking acetone in a vacuum controlled desiccator and these tablets were placed on a wire mesh and kept in the desiccator for a period of 3hours(S-I to S-VII) and 6hours(S-a to S-h) and this desiccator is wax sealed. These sintered tablets were also evaluated and compared with un-sintered matrix tablets.

EVALUATION OF VARIOUS BATCHES OF FORMULATED TABLETS
All prepared matrix tablets and sintered tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods. The **weight variation** was determined by taking 20 tablets using an electronic balance. Tablet **hardness** was determined for 10 tablets using a Monsanto tablet hardness tester. **Friability** was determined by testing 10 tablets in a friability tester for 4 minutes at 25 rpm.

Drug content
Five tablets were powdered in a mortar. An accurately weighed quantity of powdered tablets (100 mg) was extracted with pH 6.8 buffer and the solution was filtered through 0.45 µ membranes. The absorbance was measured at 233.5 nm after suitable dilution.

In vitro release study
The in vitro dissolution studies were carried out using USP I Dissolution apparatus at 50 rpm. For the first 2 hr the dissolution medium was 0.1 N hydrochloric acid and phosphate buffer pH 6.8 from 3-12 hr (900 ml), maintained at 37˚C±0.50˚C. At each time point 5 ml of sample was withdrawn and it was replaced with 5 ml of fresh medium. The drug release at different time interval was measured by UV-visible spectrophotometer at 233.5nm. The release studies were conducted in triplicate, and the mean values were plotted versus time.

RESULTS AND DISCUSSSIONS

Pre compression studies

Formulation code	Angle of repose	Bulk density	Tapped density	Compressibility Index	Hausner's Ratio
F-I(HPMC15%)	16.12	0.44	0.47	6.38	1.06
F-II(HPMC30%)	19.10	0.38	0.41	7.31	1.07
F-III(Ethyl cellulose15%)	17.64	0.45	0.48	6.25	1.06
F-IV(Ethyl cellulose30%)	16.53	0.45	0.48	6.25	1.06
F-V(Xanthan gum15%)	17.85	0.44	0.47	6.38	1.06
F-VI(Xanthan gum30%)	19.27	0.43	0.46	6.52	1.06
F-VII(Guar gum15%)	19.70	0.44	0.47	6.38	1.06
F-VIII(Guar gum30%)	18.85	0.41	0.43	4.65	1.04

From the above pre-compression studies, it is clear that the prepared granules have excellent flow properties.

Post compression studies

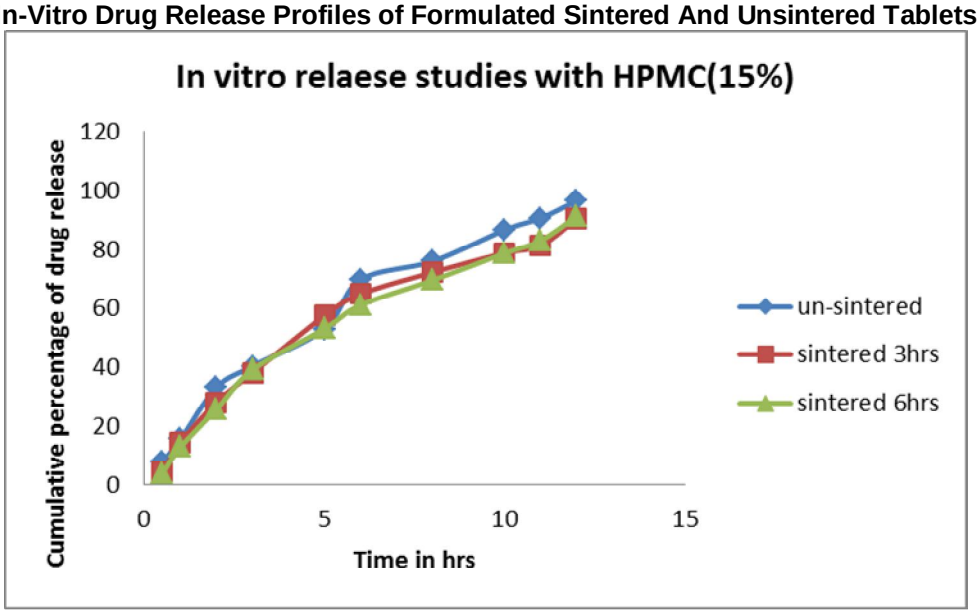
Formulation	Average weight variation	Friability (%)	Hardness(kg/cm^2)	Drug content (%)
F-I(HPMC15%)	201.5±0.45	1.0±0.2	5.03±0.11	98.5
F-II(HPMC30%)	201±0.32	0.8±0.2	4.06±0.16	97.2
F-III(Ethyl cellulose15%)	204.7±0.56	0.9±0.2	5.0±0.20	100.5
F-IV(Ethyl cellulose30%)	200.75±0.33	0.9±0.2	4.0±0.12	98.4
F-V(Xanthan gum15%)	201.9±0.12	0.8±0.2	5.5±0.18	99.8
F-VI(Xanthan gum30%)	201.1±0.16	0.8±0.2	4.5±0.14	99.56
F-VII(Guar gum15%)	200.85±0.23	0.8±0.2	4.2±0.37	97.2
F-VIII(Guar gum30%)	202.05±0.45	0.8±0.2	4.5±0.28	97.9

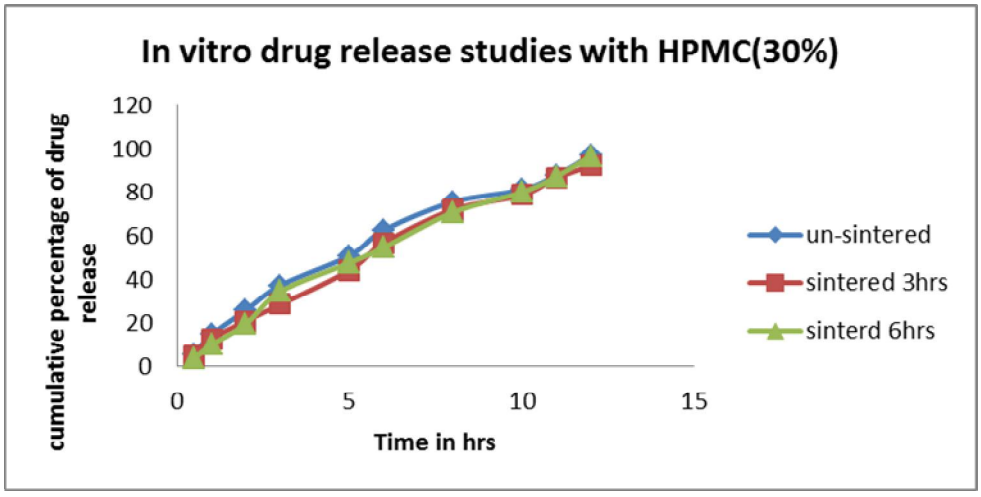
EVALUATION OF FORMULATED TABLETS AFTER SINTERING FOR 3 Hrs AND 6Hrs

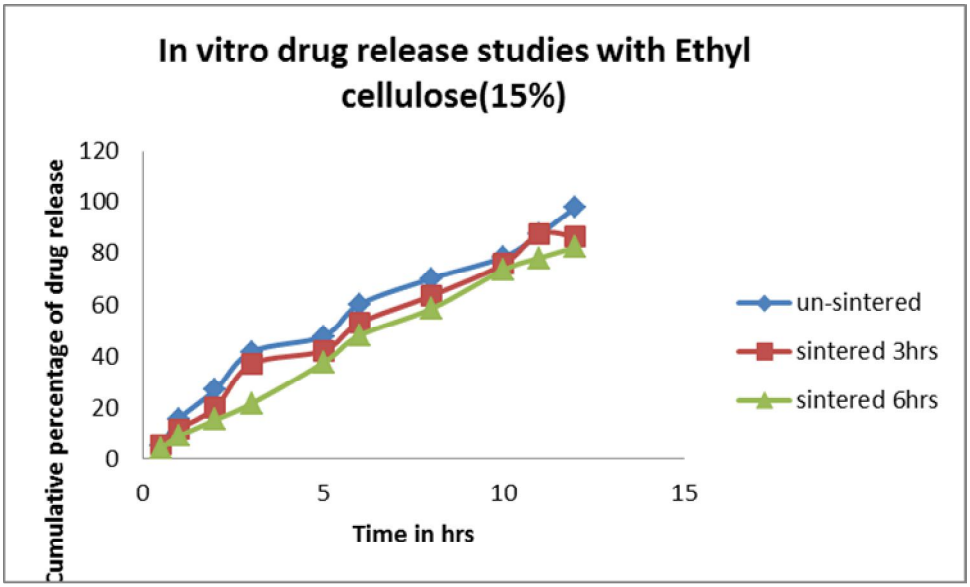
Formulation	Hardness (kg/cm^2)	Friability (%)	Formulation	Hardness (kg/cm^2)	Friability (%)
S-I	5.5±0.19	0.6±0.2	S-a	6.0±0.20	0.6±0.2
S-II	6.0±0.24	0.6±0.2	S-b	6.0±0.28	0.5±0.2
S-III	5.5±0.14	0.5±0.2	S-c	6.0±0.12	0.5±0.2
S-IV	6.0±0.10	0.6±0.2	S-d	5.5±0.28	0.6±0.2
S-V	6.5±0.28	0.7±0.2	S-e	6.5±0.35	0.7±0.2
S-VI	6.0±0.15	0.6±0.2	S-f	6.0±0.16	0.6±0.2
S-VII	6.5±0.29	0.6±0.2	S-g	6.5±0.16	0.5±0.2
S-VIII	6.5±0.30	0.6±0.2	S-h	6.5±0.27	0.5±0.2

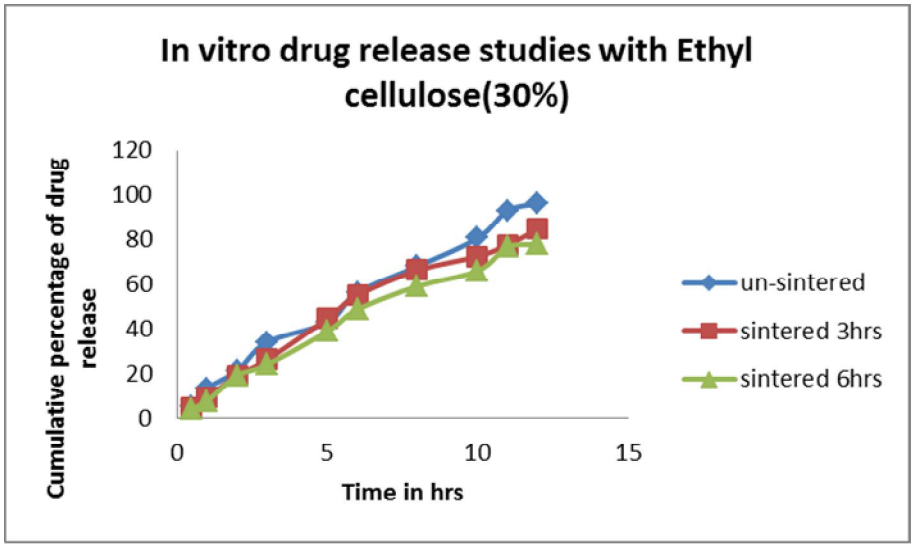
S-I to S-VIII ---- Matrix tablets sintered for 3 hours
S-a to S-h ------ Matrix tablets sintered for 6 hours

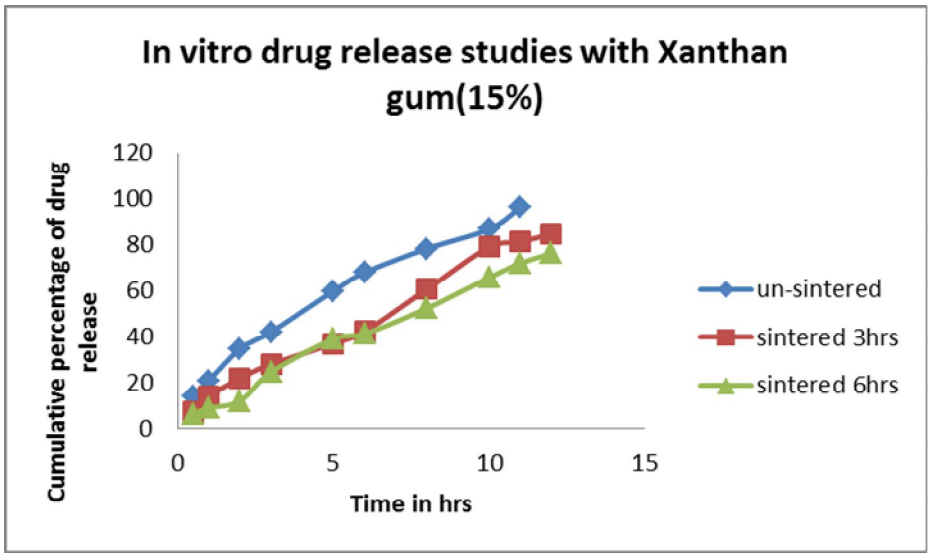
In-Vitro Drug Release Profiles of Formulated Sintered And Unsintered Tablets

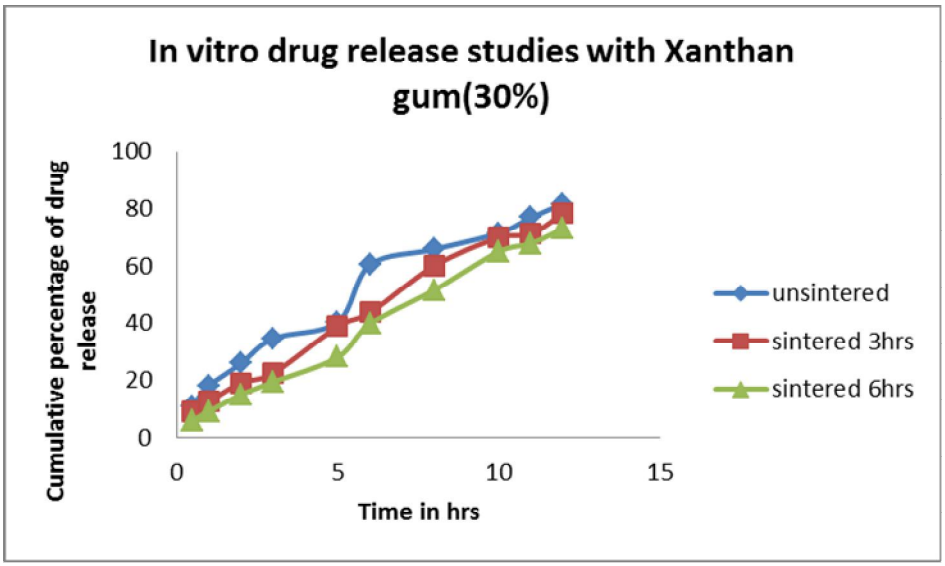


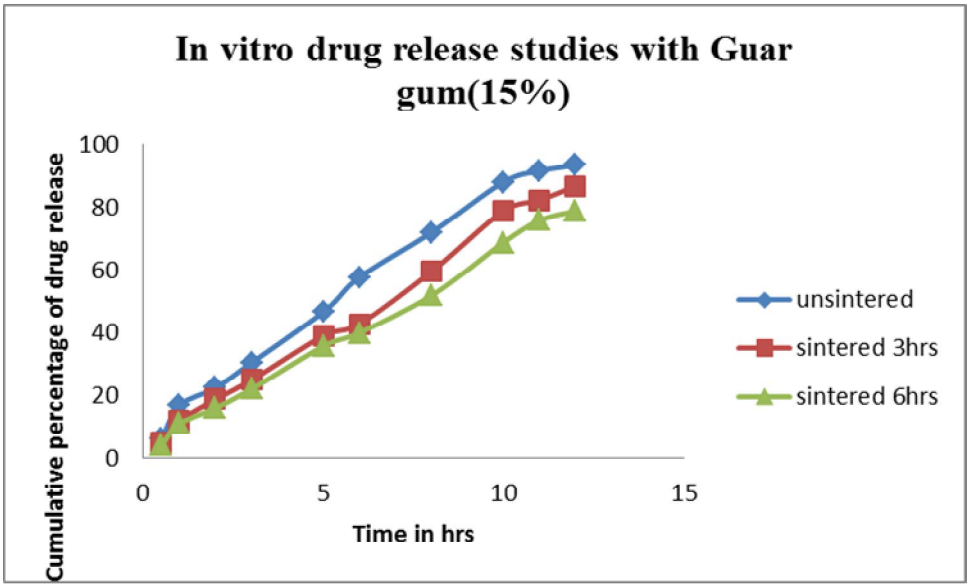


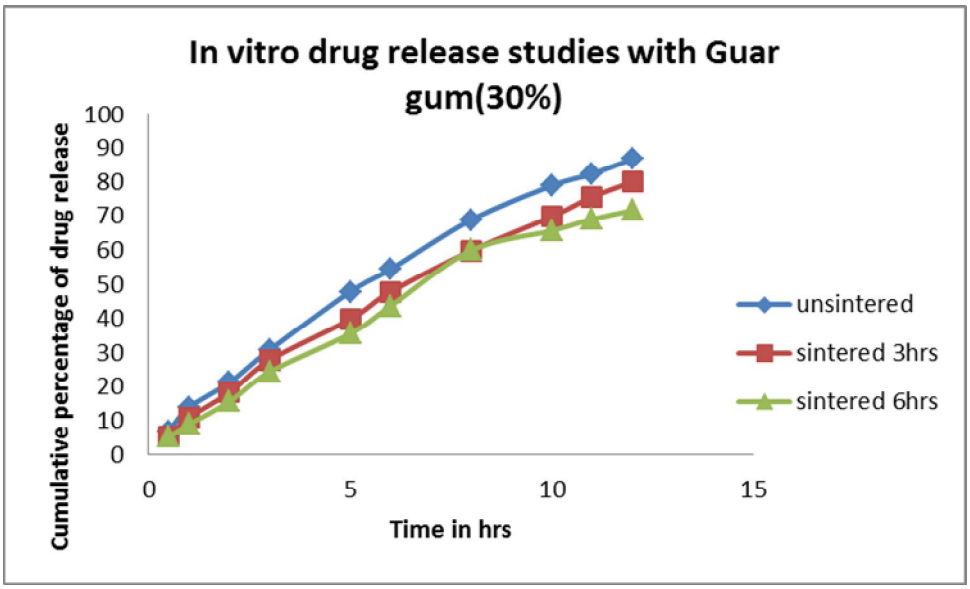



In vitro drug release studies with Ethyl cellulose(30%)
Cumulative percentage of drug release
120
100
80
60
40
20
0
0
5
10
15
Time in hrs
un-sintered
sintered 3hrs
sintered 6hrs


In vitro drug release studies with Xanthan gum(15%)
Cumulative percentage of drug release
120
100
80
60
40
20
0
0
5
10
15
Time in hrs
un-sintered
sintered 3hrs
sintered 6hrs

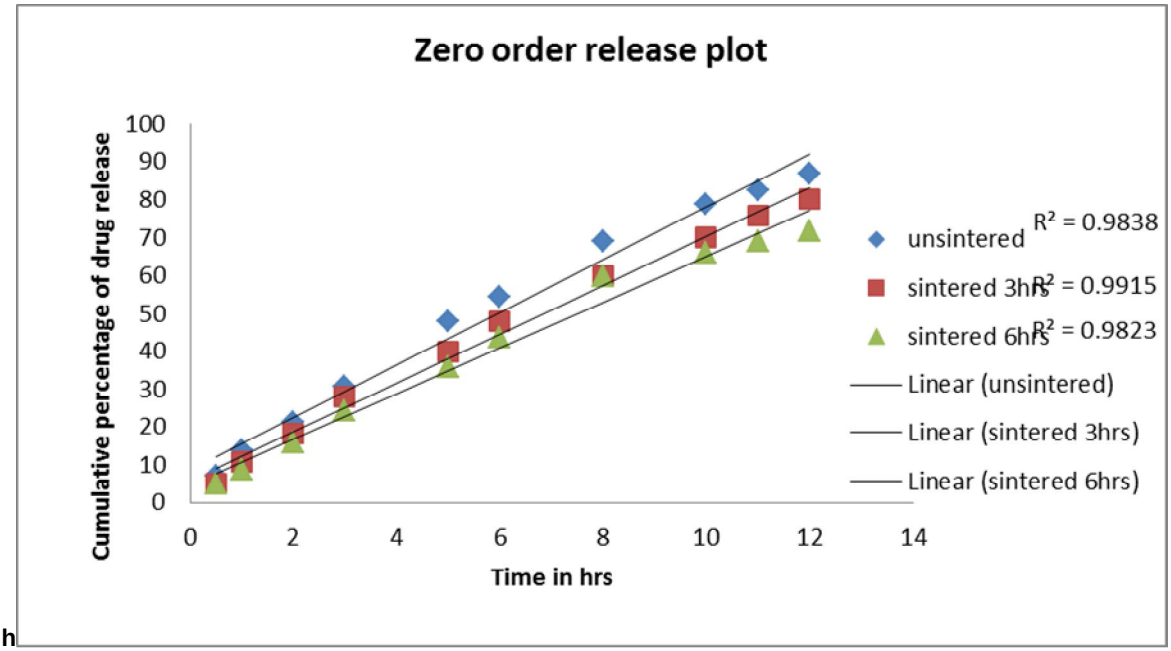

In vitro drug release studies with Xanthan gum(30%)
Cumulative percentage of drug release
100
80
60
40
20
0
0
5
10
15
Time in hrs
unsintered
sintered 3hrs
sintered 6hrs





S. No.	Formulation	Zero order	Higuchi	Formulation (3hrs sintered)	Zero order	Higuchi	Formulation (6hrs sintered)	Zero order	Higuchi
1.	FI	0.9597	0.9933	S-I	0.9690	0.9903	S-a	0.9609	0.9968
2.	FII	0.9733	0.9954	S-II	0.9874	0.9936	S-b	0.9865	0.9920
3.	FIII	0.9718	0.9879	S-III	0.9803	0.9864	S-c	0.9953	0.9958
4.	FIV	0.9919	0.9819	S-IV	0.9847	0.9939	S-d	0.9861	0.9937
5.	FV	0.9750	0.9968	S-V	0.9901	0.9783	S-e	0.9926	0.9936
6.	FVI	0.9640	0.9795	S-VI	0.9927	0.9936	S-f	0.9943	0.9896
7.	FVII	0.9886	0.9851	S-VII	0.9950	0.9823	S-g	0.9965	0.9823
8.	FVIII	0.9838	0.9992	S-VIII	0.9915	0.9993	S-h	0.9823	0.9917

Drug release kinetics plots for best formulation (metformin: guar gum(30%) after sintering 6 hrs.-S-



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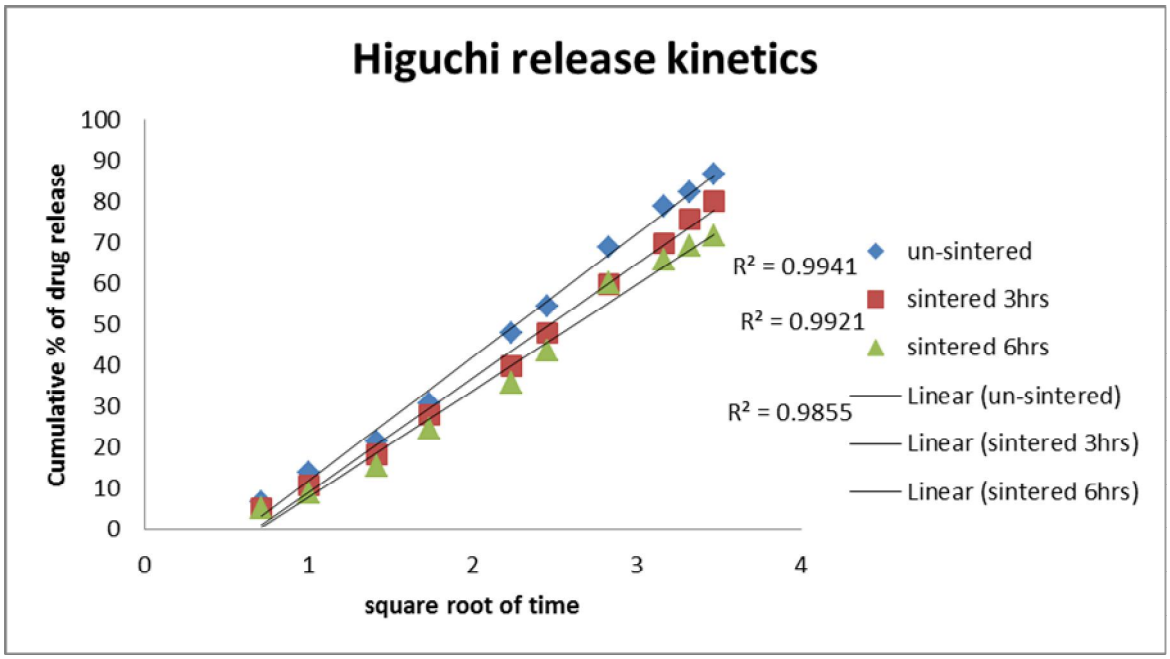

CONCLUSION AND SUMMARY

Among the different strategies employed for the design of controlled release dosage forms, sintering technique is one of them. In the pharmaceutical science, sintering has been described as the mechanism for the strengthening of the mechanical properties of consolidated pharmaceutical powders at elevated temperatures, for solid-bond formation during tablet compression, and for thermal curing of polymer-latex film coatings. However, sintering has not experienced a broad application in pharmaceutical manufacturing. From the viewpoint of economy, a conventional high-temperature sintering process or chemical sintering is much less efficient than a tableting process for powder consolidation because of the long time

required for sintering. Furthermore, the prolonged exposure of some drug molecules to higher temperatures may cause thermal decomposition. However, a better understanding of the theoretical and technical aspects of the sintering process may allow the identification of its specific needs for pharmaceutical manufacturing such as the fabrication of controlled-release polymeric matrix or sustained release matrix forms systems. More importantly, an understanding of the ever-growing advancements in new technologies relating to sintering as used in other technical fields may lead to new applications of modern sintering processes to pharmaceutical system.

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