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FORMULATION AND EVALUATION OF METFORMIN HCL ORAL DISPERSIBLE TABLETS BY SUBLIMATION METHOD

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ABSTRACT

Metformin HCL is a biguanide antihypoglcemic agent used for treating non-insulin-dependent diabetes mellitus (NIDDM). It improves glycemic control by decreasing hepatic glucose production, decreasing glucose absorption and increasing insulin mediated glucose uptake. Fast dissolving tablets of Metformin HCL were prepared by sublimation method with a view to enhance patient compliance. Tablets were prepared by direct compression method. The objective of present research work was to prepare fast dissolving tablets of Metformin HCL using varying concentrations of three different sublimating agents to improve the dissolution rate. Six formulations were prepared containing different concentrations of Camphor, as sublimating agent along with Sodium Starch Glycolate and Crosscarmallose Sodium as a superdisintegrant. The blend was evaluated for Angle of repose, Bulk density, Tapped density, Compressibility index and Hausners ratio. The tablets were examined for hardness, friability, disintegration time, dissolution rate, drug content.

KEYWORDS

Oral dispersible tablets, Metformin HCL, Sodium Starch Glycolate, Crosscarmallose Sodium, Camphor and Sublimation method.

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INTRODUCTON

We often experience inconvenience in swallowing conventional tablets where water is not available. Dysphagia is a common problem encountered in all age groups in concern to solid dosage forms, which results in high incidence of non-compliance and ineffective therapy[1]. Recent advances in novel drug delivery systems (NDDS) mainly focused on safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance i.e., one, which can rapidly disintegrate in the mouth without need

of water (fast dissolving tablet). Advantages of this drug delivery system may include administration without water, anywhere, anytime, accuracy of dosage, easy portability, alternative to liquid dosage forms, ideal for pediatric and geriatric patients, rapid onset of action, more bioavailability and good stability make these tablets popular as a dosage form of choice in the current market[2-4]. Fast dissolving tablets are the tablets, which dissolve easily in patient's mouth within a few seconds without the need of water, or chewing, providing best remedy for the patient suffering from dysphasia. Some drugs easily absorbed from the mouth, pharynx and esophagus as the saliva passes down the stomach. In such cases the bioavailability is greater than those observed for conventional dosage form. The advantages of Oral dispersible dosage form are increasingly being recognized in both industry and academia[5,6]. Orally disintegrating tablets are also called as Orodispersible (ODT), quick disintegrating, fast dissolving, rapid dissolving, porous, and rapimelts tablets[7]. In sublimation technology, the high porosity necessary for fast disintegration is achieved by using volatile materials. Inert solid ingredients, such as urea, ammonium carbonate, ammonium bicarbonate, hexamethylene tetramine, and camphor, can volatilize readily. When these volatile materials are compressed into tablets, they can be removed via sublimation, which generates porous structures. In addition, several solvents (e.g., cyclohexane, benzene) can also be used as pore forming agents[8,9].

Criteria for Selection of Drug to Develop Oral Dispersible Tablets

An ODT may have varying degrees of pregastric absorption of drugs and thus, the pharmacokinetic profiles of drugs will vary, therefore, the ODTs will not be bioequivalent to the conventional dosage forms.

The ideal characteristics of a drug to develop as an ODT include:

No bitter taste

Small to moderate molecular weight.

Good stability in water and saliva.

Partially non-ionized at the oral cavities pH.

Ability to permeate oral mucosal tissue.

Dose should be low as possible

Unsuitable drug characteristic for MDTs

Short half-life and frequent dosing.

Required controlled or sustained release[10-12].

Selection of super disintegrants

Super disintegrants not only affect the rate of disintegration, but when used at higher concentrations they also affect mouth feel, tablet hardness and friability (Rakesh *et al*, 2010)[13].

MATERIAL AND METHODS

Materials

Metformin HCL, was Purchased from Yarrow Chem Products, Mumbai. Croscaramellose sodium and Sodium starch glycolate were obtained from SD fine chemicals limited, Mumbai India. All other ingredients used in the present study were of analytical grade and were used as received.

Methods

Estimation of Metformin HCL

Standard calibration curve of Metformin HCL was obtained by plotting absorbance vs concentration using UV Spectroscopy. The λ_{max} of Metformin HCL in pH 6.8 Phosphate buffer was determined to be 236nm. The curve found to linear in the range between 2-20µg/ml.

Fourier transform infra-red spectroscopy (FTIR)

FTIR spectra of pure Metformin HCL and formulation were recorded on Bruker model, directly placing on probe analyzing for functional groups. Spectrum was derived from single average scan collected in the region 400-4000cm-1 at spectral resolution of $2cm^{-2}$. The obtained spectrum is allowed for peak picking[14-16].

Preparation of fast dissolving tablets of Metformin Hydrochloride

Tablets containing 250mg of Metformin Hydrochloride were prepared by sublimation method. The various formulations used in the study are shown in the Table No.1. The drug, diluents, super disintegrants, camphor and mannitol were passed through sieve #40. All the above ingredients were properly mixed together. Talc and Magnesium Stearate were passed through sieve #80, mixed and blended with initial mixture in a poly bag. The

powder blend was compressed into tablets on tablet machine (16 Station punching machine) using 8mm concave punch set. Compressed tablets were subjected to the process of sublimation in Hot air oven (at 60ºC for 6hrs).

Evaluation of powder blend

Angle of repose

Funnel method was used for determining angle of repose. Funnel with 10mm inner diameter of stem was fixed at a height of 2 cm over a platform. Then powder blend was poured into the funnel[17]. A cone of height (h) was formed having radius (r).

Tan ɵ = h/r,

Where

ɵ=angle of repose,

h=height of cone,

r=radius of the cone base.

Bulk density and tapped density

Cylinder method was used for determining bulk density. Powder after weighing was poured into the cylinder and volume was marked. After that mass of the powder was divided by the volume occupied by the powder in the cylinder[18]. Tapped density of the formulations containing drug was also be determined by using cylindrical method. Weighed amount of powder blend was poured into the graduated cylinder and the cylinder subjected to a given number of tappings. Volume occupied by the sample after tappings were recorded.

Carr's index

Compressibility is the ability of powder to decrease volume under pressure. An One of the simplest and well known methods for determining the compressibility is Carr's compressibility index.

Hausner's ratio

It is measured by the ratio of tapped density to the bulk density. It indirectly measures the index of flow of powders. If Hausner's ratio value may be below 1.25 it shows powder has better flow properties. On the other hand, if its value is greater than 1.25 it represents poor flow properties[19].

Total porosity

It was determined by measuring the volume occupied by the blend and true volume of the blend. Intramolecular/intraparticle spaces remain small as compared to the volume occupied by the whole blend.

Post compression Evaluation of Oral Dispersible Tablets

Hardness

It was measured to ensure integrity and shape maintenance of tablets so that tablets might be able to bear transportation effects[18]. Monsanto hardness tester was used to find out tablet hardness in kg/cm^2. Average of three values was determined.

Tablet thickness and weight variation

Verneir caliper was used to determine tablet thickness. Tablet was placed in between two arms of the caliper. Average of three values was calculated[6]. Weight variation is determined by taking twenty tablets and weighing them on electronic weighing balance to determine the average weight. At the end, the individual weight was compared with average weight[18].

Friability

Friability of tablets was calculated by using Roche Friabilator (Pharma Test, Germany). Tablets were weighed and placed in the drum of the friabilator and speed was adjusted at 25rpm. The tablets were allowed to revolve, fall from height of six inches for 4 min. Then tablets were de-dusted using muslin cloth and re-weighed[18].

Tablet disintegration

Tablet disintegration apparatus was used. Tablets were taken and placed individually in tubes and properly covered. The temperature of medium was maintained at 37 ± 2°C and timely noted by thermometer. The time taken by the tablet to disintegrate completely was noted[20].

Uniformity of content

Ten tablets were taken randomly. Tablets were crushed separately to a fine powder and each tablet analysed individually for drug content. Powder of each tablet was taken into a volumetric flask. 50ml of 0.1N HCL was added, shaken for 30 min and was made to volume with 0.1N HCL and filtered. 1ml of the filtrate was taken into 10ml volumetric flask and volume were made up to mark with 0.1N HCL. The absorbance was measured at 303 nm using UV spectrophotometer. Each tablet should contain not

less than 85% and not more than 115% of the labelled claim[21].

***In vitro* disintegration time**

Disintegration time of FDT's was determined by following the procedure described by Gohel *et al.* Briefly, 10ml of water at room temperature was taken in a petridish of 10 cm in diameter. The tablet was then carefully placed in the centre of petridish and the time required for the tablet to completely disintegrate into fine particles was noted. Measurements were carried out in triplicate[22].

***In-vitro* dissolution study**

In-vitro dissolution study was carried out USP XXII dissolution test apparatus type II. The dissolution medium used was 900ml of 7.4 pH which was maintained at 37 ± 0.5°C. The paddle was able to rotatate at the speed of 50 rpm throughout the study. 5 ml of sample was withdrawn at every 5 minutes interval and diluted to 10ml. Then 5ml of fresh dissolution media maintained at the same temperature was replaced. The samples were analyzed spectrophotometrically at 236nm 6.8 pH using as blank. The dissolution data was analyzed for calculating the amount of drug released and percentage cumulative drug released at different time intervals.

RESULTS AND DISCUSSION

Solubility studies

Solubility study for Metformin Hydrochloride

The selection of the medium was made on the basis of solubility data of Metformin Hydrochloride in different solvents or buffer medium at 25 ± 10ºC. The saturation solubility of drug Metformin Hydrochloride was found to be in Phosphate buffer 6.8 PH and the results were given in Table No.2.

Construction of Calibration Curve for Metformin HCL

Standard calibration curve of Metformin Hydrochloride was obtained by plotting absorbance vs concentration using UV spectroscopy. The λ max of Metformin Hydrochloride in pH 6.8 Phosphate buffer was determined to be 236 nm. The standard calibration curve shows r^2 of 0.998. The curve found to be linear in the Beer's range between 2 – 10µg/ml. (Table No.3).

Fourier transform infrared (FTIR) spectroscopy studies

FT IR studies revealed that there was no physicochemical interaction between Metformin Hydrochloride and other excipients (Figure No.2 and No.3). The pure drug Metformin Hydrochloride showed characteristic absorption peak at 3365.77cm^{-1} due to N-H stretching, 1624.03 cm^{-1} due to C = N stretching . All peaks were remained un altered in the IR spectrum of physical mixture of drug and excipients. IR spectra revealed that there was no chemical interaction of drug with other excipients.

Powder characterization

In the present investigation oral dispersible tablets of Metformin HCL were prepared by using Camphor as subliming agent, Sodium starch glycolate and Croscarmellose sodium as superdisintegrants. The tablets prepared by sublimation method. The data obtained from pre-compressional parameters such as Angle of repose, Bulk density, Tapped density, Carr's index, Friability and Hausner ratio were found to be within acceptable pharmacopoeia range as shown in (Table No.2).

Post compression parameters

The results of the weight variation, hardness, thickness, friability, and drug content of Metformin HCL oral dispersible tablets by sublimation method were given in Table No.5. All the tablets of different batches matched with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 3 to 4 kg/cm^2 and the friability values were less than 1% indicating that the tablets were compact and hard. The thickness of the tablets ranged between 2 to 3 mm. All the formulations satisfied the content of the drug as they contained 98-100% of Metformin HCL and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control limits.

***In vitro* Dissolution Studies**

In vitro drug release studies for prepared Metformin Hydrochloride tablets were conducted for a period of 40 minutes using USP type II dissolution

apparatus. The percentage drug release of Metformin Hydrochloride FDT'S is as shown in Table No.4 and Figure No.4. The formulation containing 2%, 4%, 6% Sodium starch glycolate showed a % release 95.9 ± 0.002 % in (30 min), 99.9 ± 0.007 in (15 min), 98.9 ± 0.004 in (35 min) respectively. The formulation containing 2%, 4%, 6% Croscarmellose sodium showed a % release 98.2 ± 0.009 % in (40 min), 99.3 ± 0.002 in (20 min), 98.9 ± 0.006 in (25 min) respectively.

This showed that dissolution capacity of formulation increased with increased in the concentration of super disintegrant, whereas dissolution capacity of formulation containing Sodium Starch Glycolate increased initially but decreased with further increased in a concentration.

Table No.1: Formulae of Orodispersible tablets of Metformin HCL

S.No	Quantity per tablet (mg) in batch No: FDT in (mg)						
	Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
1	Metformin HCL	250	250	250	250	250	250
2	Sodium Starch Glycolate	10	29	30	-	-	-
3	Crosscarrmellose sodium	-	-	-	10	20	30
4	Magnesium stearate	4	4	4	4	4	4
5	Mannitol	30	30	30	30	30	30
6	Micro crystalline cellulose	206	196	186	206	196	186
7	TOTAL WEIGHT (in mg)	500	500	500	500	500	500

Table No.2: Solubility studies of Metformin Hydrochloride

S.No	Medium	Solubility (mg / ml)
1	Water	0.263
2	pH 7.4 Phosphate buffer	0.258
3	0.1 N HCL	0.185
4	P H 6.8 Phosphate buffer	0.671

Table No.3: Calibration Curve of Metformin HCL with Phosphate buffer of p H 6.8

S.No	Concentration(µg/ml)	Absorbance(236nm)
1	0	0
2	2	0.241 ± 0.007
3	4	0.516 ± 0.002
4	6	0.728 ± 0.005
5	8	0.999 ± 0.008

*All values represent mean standard deviation (SD) n=3

Table No.4: Powder characterization of formulation blends

S.No	Formulation code	Angle of repose (θ)	Bulkdensity (gm/cc)	Tapped Density (gm/c)	Carr's index (%)	Hausner's ratio
1	F1	26.92±0.13	0.650 ±0.045	0.768 ±0.036	17.23 ±0.18	1.140 ±0.32
2	F2	25.01±0.11	0.741 ±0.072	0.232 ±0.028	16.99 ± 0.11	1.161 ±0.28
3	F3	26.95±0.17	0.617 ±0.036	0.781 ±0.034	17.54 ±0.86	1.116 ±0.34
4	F4	26.73±0.11	0.540 ±0.081	0.697 ±0.076	22.54 ±0.19	1.217 ±0.32
5	F5	25.09±0.5	0.560 ±0.002	0.691 ±0.072	21.56±0.18	1.263 ±0.27
6	F6	28.20±0.13	0.342 ±0.05	0.690 ±0.033	21.36±0.033	1.136 ±29

Table No.5: Evaluation of post compression parameters of sublimation tablets

S.No	Formulation code	Average Weight (mg)	Thickness (mm)	Hardness (kg/cm2)	Friability	Disintegration time (sec)	Content uniformity (%)
1	F1	502.2±1.92	2.4±0.11	3.9±0.25	0.45	21±0.25	98.78±0.97
2	F2	498.9±2.10	3.1±0.12	4.2±0.27	0.55	17.5±0.11	99.99±0.98
3	F3	496.3±2.19	2.7±0.14	3.5±0.34	0.43	33.5±0.21	98.35±0.45
4	F4	497.9±1.43	3.2±0.15	3.2±0.77	0.46	27±0.19	99.73±98
5	F5	402.8±1.67	3.3±0.19	3.0±0.99	0.50	25±0.18	99.87±0.85
6	F6	499.1±1.99	2.4±0.13	4.1±0.54	0.62	18.5±0.19	99.94±1.21

Table No.6: Dissolution profile of Metformin Hydrochloride FDT'S

S.No	Time (min)	% Drug release from Metformin Hydrochloride tablets mean ± SD					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	00	0	0
2	5	35.7±0.005	79.6±0.005	63.1±0.005	59.1±0.002	65.1±0.006	64.4±0.007
3	10	45.4±0.005	89.9±0.003	75.2±0.002	67.2±0.003	78.4±0.002	79.4±0.003
4	15	57.5±0.001	99.9±0.007	84.1±0.003	78.5±0.006	89.6±0.002	86.9±0.004
5	20	72.9±0.002	---	89.4±0.004	82.5±0.003	99.3±0.002	90.9±0.005
6	25	89.9±0.002	---	95.1±0.002	89.9±0.001	---	98.9±0.006
7	30	95.9±0.002	---	97.5±0.003	92.5±0.004	---	---
8	35	---	---	98.9±0.004	95.5±0.003	---	---
9	40	---	---	---	98.2±0.009	---	---
10	45	---	---	---	---	---	---

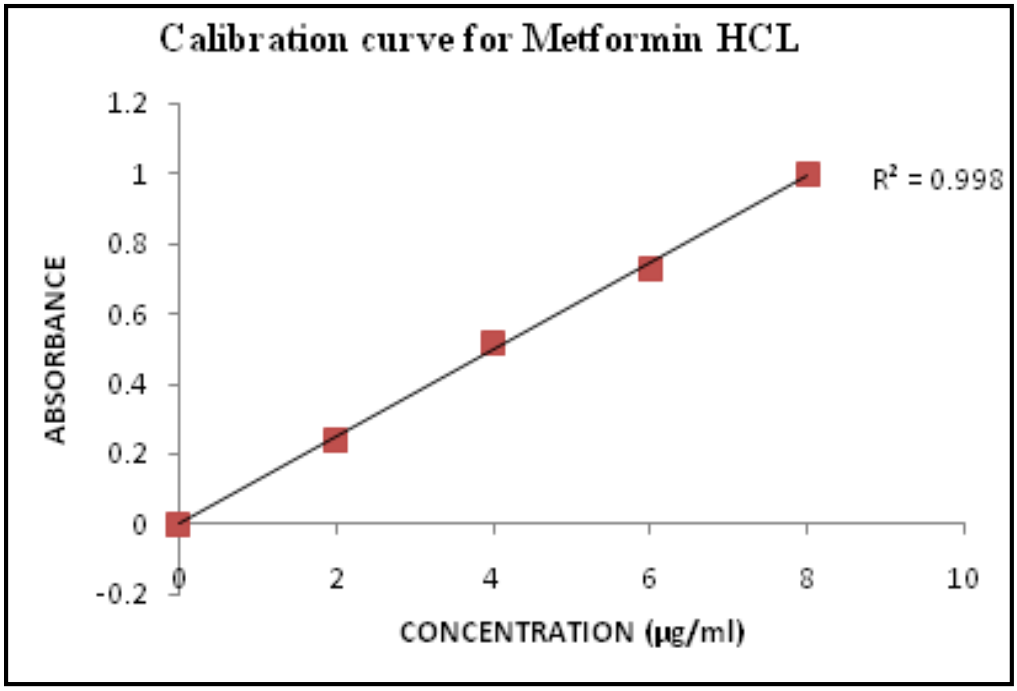

Figure No.1: Calibration curve of Metformin Hydrochloride in phosphate buffer pH 6.8

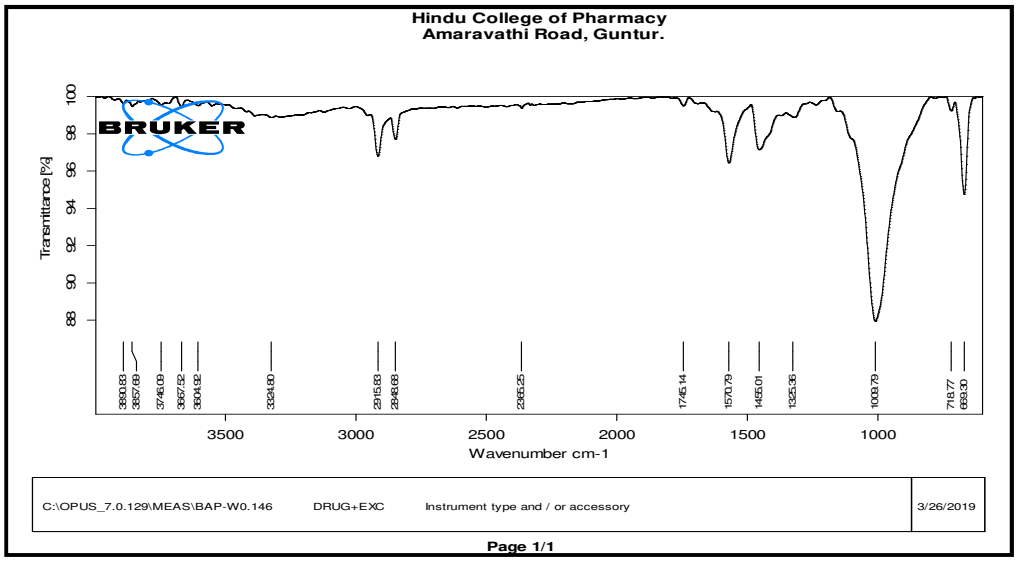

Figure No.2: FTIR graph of Pure drug (Metformin Hydrochloride)

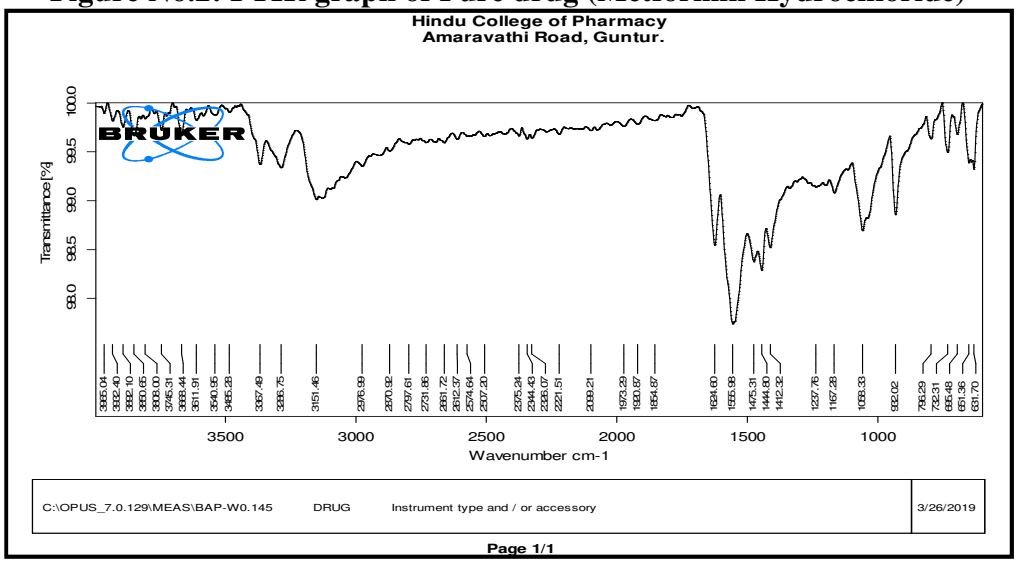

Figure No.3: FTIR graph for Metformin Hydrochloride and excipients

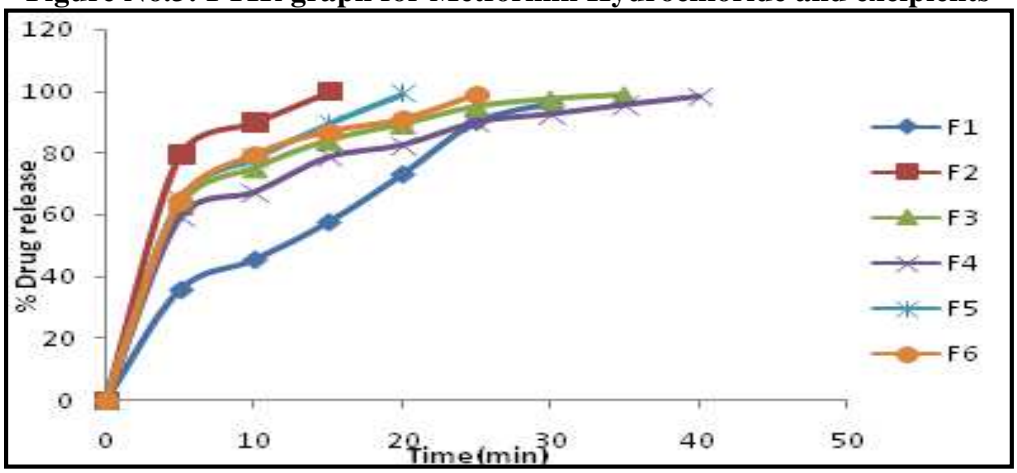

Figure No.4: Release profile of Metformin HCL Oral dispersible Tablets by sublimation method (n=3)

CONCLUSION

An attempt was made to develop the Oral Dispersible tablets of Metformin hydrochloride by sublimation method to improve the dissolution rate. Metformin hydrochloride fast dissolving tablets were successfully formulated and evaluated for different parameters, which were found in the acceptable range. From the dissolution studies of all formulations, F2 formulation showed rapid disintegration time as well as fast dissolution rate. The percent drug release in 30 min and for formulation F3 was 99.9±0.007%. In conclusion, development of fast dissolving tablets using sublimation method is able to enhance the dissolution rate of Metformin hydrochloride.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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