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PREFORMULATION STUDY OF METFORMIN HYDROCHLORIDE (ANTIDIABETIC DRUG)

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ABSTRACT

In the present study we have discussed about the preformulation of Metformin hydrochloride (1, 1-dimethyl biguanide hydrochloride) for the various parameters like solubility, melting point, pH, bulk density, tapped density, car's index, partition coefficient and drawn the calibration curve in the different solvent system in acidic and alkaline medium using ultraviolet spectroscopy. Infra-red spectroscopy also included in the preformulation study for the better identification of the drug and compared with the standard.

KEYWORDS

Metformin hydrochloride (1, 1-dimethyl biguanide hydrochloride), Solubility, Melting point, pH, Bulk density, Tapped density and Car's index.

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INTRODUCTION

Metformin's main effect is to decrease liver glucose production[1]. It also increases insulin sensitivity, which increases peripheral glucose uptake[2]. Metformin decreases high blood sugar, primarily by suppressing liver glucose production (hepatic gluconeogenesis)[1]. The average patient with type 2 diabetes has three times the normal rate of gluconeogenesis; metformin treatment reduces this by over one-third[3]. The molecular mechanism of metformin is incompletely understood: inhibition of the mitochondrial respiratory chain(complex I), activation of AMP-activated protein kinase

(AMPK), inhibition of glucagon-induced elevation of cyclic adenosine monophosphate (cAMP) with reduced activation of protein kinase A (PKA), inhibition of mitochondrial glycerophosphate dehydrogenase, and an effect on gut microbiota have been proposed as potential mechanisms[4-6]. Activation of AMPK was required for metformin's inhibitory effect on liver glucose production[7]. AMPK is an enzyme that plays an important role in insulin signaling, whole body energy balance and the metabolism of glucose and fats[8]. AMPK Activation was required for an increase in the expression of small heterodimer partner, which in turn inhibited the expression of the hepatic gluconeogenic genes phosphoenolpyruvate carboxykinase and glucose 6-phosphatase[9]. Metformin is frequently used in research along with AICA ribonucleotide as an AMPK agonist. Mouse models in which the genes for AMPK α1 and α2 catalytic subunits or LKB1, an upstream kinase of AMPK, had been knocked out in hepatocytes, have raised doubts over the role of AMPK, since the effect of metformin was not abolished by loss of AMPK function The mechanism by which biguanides increase the activity of AMPK remains uncertain; however, metformin increases the concentration of cytosolic adenosine monophosphate (AMP) (as opposed to a change in total AMP or total AMP/adenosine triphosphate)[10]. Increased cellular AMP has been proposed to explain the inhibition of glucagon-induced increase in cAMP and activation of PKA.

MATERIAL AND METHODS

Metformin hydrochloride obtained from hetero labs limited, Baddi India. Hydroxypropyl methylcellulose obtained from S D fine-Chem limited, Mumbai, India. Ethyl cellulose obtained from Kemphasol, Mumbai, India. Dichloromethane and polyethylene glycol 400 obtained from S D fine-Chem limited, Mumbai, India. Propylene glycol obtained from thermo fisher scientific India Pvt Ltd, Mumbai. Ethanol obtained from S D fine-Chem Limited Mumbai.

Preformulation

Concept of preformulation

Preceeding to the development of this formulation, it is necessary that certain fundamental physicochemical properties of potential drug molecules and other derived properties of the drug powder are determined. This information dictates many of the subsequent events and approaches in formulation development. This first learning phase is known as preformulation. The meaning of the word is quite literal in that it defines the steps to be undertaken before formulation proper. It is normal for preformulation to be performed on potential active drugs (at this stage often referred to as new chemical entities (NCES) or new drug candidates). In case of the generic formulation of existing drugs, sufficient information is usually known prior to formulation. Preformulation will give pointers to the feasibility of the various possible dosage forms and to any potential problems of instability and poor in vivo dissolution, and thus bioavailability. It should also give some guidance to the suitability of potential excipients to be used in subsequent formulation[11].

Melting point

The determination of melting point during preformulation studies is important since it is a simple test requiring only small amounts of material that can yield much valuable information regarding the thermal properties of the material. It can also assist at this stage in making predictions about the potential stability of the NCE. There is, for example, and possibly somewhat surprisingly, a link between melting point and solubility. This is discussed later in this section.

Techniques

The melting point of a drug can be measured using these techniques.

1. Capillary melting
2. Hot stage microscopy
3. Differential Scanning Calorimetry or Thermal Analysis.

Capillary Melting

Capillary melting (the observation of melting in a capillary tube in a heated metal block) gives

information about the melting range but it is difficult to assign an accurate melting point using this technique.

Hot Stage Microscopy

This is visually observed under a microscope equipped with a heated and lagged sample stage. The heating rate is controllable and other transitions can be observed and recorded. It is more precise since the phase transitions (first melt, 50% melt and completion) can be registered on a recorder as the melting proceeds and, by virtue of high magnification, the values are more accurate.

Differential Scanning Calorimetry and Differential Thermal Analysis

Neither of the previous methods is as versatile as either differential thermal analysis (DTA) or differential scanning calorimetry (DSC). An additional advantage is that the sample size required for these is only 2-5mg. Differential thermal analysis measures the temperature difference between the sample and a reference as a function of temperature or time when heating at a constant rate. Differential scanning calorimetry is similar to Differential thermal analysis, except that the instrument measures the amount of energy required to keep the sample at the same temperature as the reference, i.e. It measures the enthalpy of transition. When no physical or chemical change occurs within the sample then there is neither a temperature change nor input energy to maintain as isotherm however, when phase changes occur then latent heat suppresses a temperature change and the isothermal energy required registers as an electrical signal generated by thermocouples. Crystalline transitions, fusion, evaporation and sublimation are changes in state which can be quantified[12].

Procedure

The melting point of drug was estimated with the help of melting point apparatus and compared with values given in literature[13].

First powder the crystalline substance.

Then take a capillary tube and close one end by sealing by the application of heat.

Then fill the capillary tube with the active drug powder. To fill the tube, make a load of the powdered drug on the porous laminate. Set in motion one end of the capillary tube into the load. Some of the powdered drug will enter the capillary tube.

Now tap the sealed end of the capillary tube on the porous plate gently. Fill the capillary tube with powdered drug upto 2-3mm.

Put together the capillary tube to a thermometer by means of a thread.

Take liquid paraffin in a beaker and place it over a piece of wire gauze placed over a tripod stand.

Hold tightly the thermometer carrying the test tube to the iron stand and dip them in the bath of liquid paraffin. The surface active agent of the bath liquid is sufficient to hold the capillary tube into the position.

Warm the beaker gradually while frequently stirring the contents using a stirrer to maintain a uniform temperature throughout the medium.

After the temperature is within 15^{o} C of the melting point of the pure powder substance, the flame is abridged. Then the temperature rises gradually.

When the drug substance starts melting then note down the temperature (T_1).

When the drug substance has completely melted then again note down the temperature (T_2).

Correct melting point is calculated by the average of the two readings of the drug substance.

Solubility

Solubility is an important phenomenon in pharmaceutical sciences. It plays very effective and prominent role in the formulations of dosage forms. Solubility of a compound in a particular solvent is defined as the concentration of the solute (compound) in a saturated solution at a certain temperature. In another term, it may be defined as the continuous interaction of two or more compound to form homogenous molecular dispersion[14]. The approximate solubilities of the articles of the pharmacopoeia are given here primarily as information, they are not meant to be applied as tests for identifying materials. However, they may indirectly help in the preliminary evaluation of the integrity of an article. They have been indicated by descriptive terms in the

accompanying table and have the following significance with reference to a temperature of 15º to 30ºC[15].

Partition coefficient

The oil water partition coefficient is a measurement of a lipophilic character of the molecule, its preference for the water hating or water loving phase. If a solute is added to a mixture of two immiscible liquids, it will distribute between the two phases and rech an equilibrium at a constant temperature. The distribution of the solute (unaggregated and undissociated) between the two immiscible layers can be described thus[16]:

$K=C_U/C_L$

Where

K= is the distribution constant or partition constant

C_U= drug concentration at the upper phase

C_L= drug concentration at the lower phase

Procedure

N-octanol and distilled water pre saturated with each for at least 24 hours before the experiment. To the pre-equilibrated water (10ml), known quantity of drug is dissolved. Then 10ml of octanol was added to equal volume of aqueous solution of a drug in a separating funnel. The system was kept for 24 hours with intermittent shaking. Finally, the aqueous layer was separated for 24 hours with intermittent shaking. Finally, the aqueous layer was separated, clarified by centrifugation and assayed spectrophotometrically[17-19].

FTIR STUDY OF DRUG

The physicochemical compatibility between metformin HCL and polymers used in the films was studied by using Fourier transform-infrared (FT-IR, Shimadzu Co., Japan) spectroscopy. KBr pellet method is used for the pellatization. The FT-IR spectra were recorded in the wavelength region between 4000 and 400cm^{-1}. The spectra obtained for metformin hydrochloride and mixtures of metformin hydrochloride with excipient were compared.

Ultra-violet spectroscopy

Preparation of stock solution in water

Metformin hydrochloride were accurately weighed 10mg and transferred to 10ml volumetric flask. Drug was dissolved in 5ml of water shaken manually for 10 minute and volume was made up to the mark with the same solvent. This was the standard mother solution containing 1mg/ml (1000µg/ml). 1ml of this prepared solution was pipette out and transferred to the 10 ml volumetric flask, and volume made up to 10ml with same solvent to obtained final concentration 0.1mg/ml (100µg/ml i.e. stock solution). 2.5ml solution is pipette out from stock solution and transferred to 25ml volumetric flask. This concentration found to 10µg/ml solution.

Spectrophotometric scanning of metformin hydrochloride in water

An appropriate portion of 1, 2, 3, 4, and 5ml of metformin hydrochloride stock solution in water was pipette out and transferred to separate 10ml volumetric flask and then volume made up to 10ml with water to obtain concentration 1, 2, 3, 4 and 5µg/ml. the solution were scanned separately between 200nm to 400nm. The spectrum of drug was recorded. Wavelength 232nm was selected for further study.

Preparation of calibration curve of metformin hydrochloride in water

Taken a series of concentration of ranging between 1-5µg/ml. Absorbance was measured using spectrophotometer at 232nm against water as blank. Standard calibration curve was plotted as absorbance against concentration. Beer's law obey the concentration range between 1-5µg/ml.

Preparation of saline pH 7.4 phosphate buffer

Dissolve 2.38 g of disodium hydrogen phosphate, 0.19g of potassium dihydrogen phosphate and 8.0 g of sodium chloride in sufficient water to produce 1000ml.

Preparation of stock solution in phosphate buffer pH 7.4

Metformin hydrochloride were accurately weighed 10mg and transferred to 10ml volumetric flask. Drug was dissolved in 5 ml of phosphate buffer pH

7.4, shaken manually for 10 minute and volume was made up to the mark with the same solvent. This was the standard mother solution containing 1mg/ml (1000µg/ml). 1ml of this prepared solution was pipette out and transferred to the 10 ml volumetric flask, and volume made up to 10ml with same solvent to obtained final concentration 0.1mg/ml (100µg/ml i.e. stock solution). 2.5 ml solution is pipette out from stock solution and transferred to 25 ml volumetric flask. This concentration found to 10µg/ml solution.

Spectrophotometric scanning of metformin hydrochloride in phosphate buffer pH 7.4

An appropriate portion of 1, 2, 3, 4, and 5ml of metformin hydrochloride stock solution in phosphate buffer pH 7.4 was pipette out and transferred to separate 10ml volumetric flask and then volume made up to 10ml with phosphate buffer pH 7.4 to obtain concentration 1, 2, 3, 4 and 5µg/ml. The scanning of solution was separately done between 200nm to 400nm. The spectrum of drug was recorded. Wavelength 232nm was selected for further study.

Preparation of calibration curve of metformin hydrochloride in phosphate buffer pH 7.4

Taken a series of concentration of ranging between 1-5µg/ml. absorbance was measured using spectrophotometer at 232nm against phosphate buffer as blank. Standard calibration curve was plotted as absorbance against concentration.

Preparation of calibration curve of metformin hydrochloride in plasma using HPLC method

The HPLC method reported by Abolghasem Jouyban *et al*, (2011) was followed for estimation of metformin hydrochloride in biological sample.

Equipment

The High Performance Liquid Chromatography was performed with a modular system consisting of a variable wavelength UV visible detector and auto sampler.

Mobile phase

Mobile phase consist of a methanol: water mixture (75:25).

Preparation of stock solution and standard curve

Accurately weight quantity of drug (10mg) was taken in 10ml volumetric flask, dissolved in 3 drops of methanol, made upto 10ml with sufficient quantity of HPLC grade water, this gave a stock solution of 1mg/ml.

Aliquots were prepared by transferring 0.1, 0.2, up to 0.5ml to a series of 10ml volumetric flasks and mixed with 0.2ml of rat plasma homogenate and the volume was made up to 10ml then all aliquots were filtered by whattman filter paper. The 200µl solution was then injected in the loop attached to the pump, the mobile phase was run at the rate of 1ml/min. Detection were done at 232nm sample concentration were calculated by measuring covered area and plotting against standard concentration.

MICROMERITICS

Micromeritics is the science of small particle, a particle is any unit of matter having defined physical dimensions it is important to study particles because most drug dosage forms are solids, solids are not static systems, the physical state of particles can be altered by physical manipulation, and particle characteristics can alter therapeutic effectiveness micromeritics is the study of a number of characteristics, including particle size and size distribution, shape, angle of repose, porosity, true volume, bulk volume, apparent density, and bulkiness[20].

Bulk density (Db)

It is calculated by the total mass of powder divided by the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and initial weight was noted down. This initial volume is called the bulk volume. Bulk density is calculated by the formula given below. It is expressed in g/ml and is given by,

$D_b = M/Vb$

Where M (mass of powdered drug), Vb (bulk volume of the powdered drug).

Tapped density (Dt)

It is calculated by total mass of the powder divided by the tapped volume of the powder. Volume was

measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volume is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2% (in a bulk density apparatus). It is expressed in g/ml and given by,

$D_t = M/Vt$

Where, M (mass of powdered drug), Vt (tapped volume of the powdered drug).

Carr's index or % compressibility

It indicates powder flow properties. It is expressed in percentage and is give

$I = Dt-Db/Dt \times 100$

Where, Dt tapped density of the powdered drug and Db (bulk density of the powdered drug).

Hausner's ratio

Hausner's ratio is an tortuous index of easiness of powder flow. It is calculated by the following formula.

Hausner's ratio = tapped density/bulk density

Lower Hausner's ratio (<1.25) indicates better flow properties and higher Hausner's ratio (>1.25) indicates poor flow properties[22].

Angle of repose

The angle of repose is a comparatively effortless technique for estimating the flow properties of a powder. It can easily be determined by allowing a powder to flow through a funnel nd fall freely onto a surface, the height and diameter of the resulting cone are measured and the angle of repose calculated from this equation.

$$\tan\Theta = h/r$$

Where

h = is the height of the powder cone

r = is the radius of the powder cone[23]

Fixed funnel method

In this method a funnel is fixed at a particular height weighed amount of the sample is allowed to flow through the funnel. The height of the cone formed and the circumference is determined. The radius can be calculated from the diameter or the area. Angle of repose is given as $\Theta = \tan^{-1} h/r$[25].

RESULTS AND DISCUSSION

Preformulation Study

Melting point analysis

Melting point determined by using capillary melting point method, melting point of metformin hydrochloride was found to be 222ºC. This was matching to the literature value 222-226ºC indicating the identity and purity of drug sample.

Solubility study of metformin hydrochloride

Partition coefficient

$K = C_{U//}/C_L$

Where

K is the distribution constant or partition constant,

C_U is the concentration of the drug in the upper phase, and

C_L (concentration of the powdered drug in the lower phase).

Result: The partition coefficient of metformin hydrochloride is found to be 0.383.

FT-IR study

The preformulation studies were carried out to study the compatibility of pure drug (metformin HCL) with polymers for preparation of transdermal patch of metformin hydrochloride. The individual spectra of pur drug and polymers as combination spectra of drugs and polymers shown in fig. which indicates no interaction between metformin HCL and polymers when compared with spectra of pure drug as all functional group frequencies were present(CDRI-317-1-1).

Spectrophotometric methods for estimation of metformin hydrochloride by UV

Spectrophotometric scanning of metformin hydrochloride in water and phosphate buffer pH 7.4

The solutions containing metformin hydrochloride (µg/ml) were prepared in water and phosphate buffer pH 7.4 and prepared solutions were scanned for absorption maxima in range of 200-400nm. The λ max obtained was recorded (table).

Calibration curve for the estimation of metformin hydrochloride in water

Calibration curves of metformin hydrochloride were prepared according to the method described in section methodology. The absorbance values of the

dilutions, given in table below prepared in the concentration range of 1-5 µg/ml in water. The data were plotted without standard deviation and the calibration curves obtained followed Beer's-lambert law.

Calibration curve for the estimation of metformin hydrochloride in phosphate buffer pH 7.4

Calibration curve of metformin hydrochloride were prepared according to the method described in section methodology. The absorbance values of the dilutions, given in table below prepared in the concentration range of 1-5µg/ml in phosphate buffer pH 7.4. The data were plotted without standard deviation and the calibration curves obtained followed Beer's-Lambert law.

Calibration curve for the estimation of metformin hydrochloride in biological sample

Calibration curve of metformin hydrochloride were prepared according to the method described in section methodology. The absorbance values of the dilutions, given in table below prepared in the concentration range of 1-5µg/ml in phosphate buffer pH 7.4.

Micromeritics properties

Bulk density

Observation

Weight of powder = M

Bulk volume of powder = V

Calculation

Bulk density = [mass of powder/bulk volume of powder]

Result

Bulk density of powdered drug was found to be $0.4094 g/cm^3$.

Tapped density

Observation-

Weight of powder=5g

No. of tapping= 100.

Calculation

Tapped density = [mass of powder/tapped volume of powder]

Result

Tapped density of powder was found to be $0.6018 g/cm^3$.

Carr's index or % compressibility

$I = D_t - D_b/D_t \times 100$

Where

D_t (tapped density of the powdered drug) and D_b (bulk density of the powdered drug).

Calculation

Result

The compressibility index was found to be 31.71%. Hence the type of flow of powder is poor.

Hausner's ratio

Hausner's ratio = tapped density-bulk density

Lower hausner's ratio (<1.25) indicates better flow properties (>1.25) indicates poor flow properties.

Calculation

Result

Hasuner's ratio was found to be 1.48%, therefore it indicates poor flow.

Angle of repose

$\tan\Theta = h/r$

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

Calculation

Radius = 3.15, height = 4

Radius = 3.5, height = 5

Radius = 3.6, height = 5

Result- the angle of repose was found to be 53.49º, hence the flow property is very poor.

Table No.1: Solubility parameter for drug

S.No	Descriptive term	Parts of solvent required for part of solute
1	Very soluble	Less than 1
2	Freely soluble	From 1 to 10
3	Soluble	From 10 to 30
4	Sparingly soluble	From 30 to 100
5	Slightly soluble	From 100 to 1000
6	Very slightly soluble	From 1000 to 10,000
7	Practically insoluble, or insoluble	10,000 or more

Table No.2: Relationship between % compressibility and flow ability[21]

S.No	% Compressibility	Flow ability
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair passable
4	23-35	Poor
5	33-38	Very poor
6	<40	Very very poor

Table No.3: Angle of repose as an indication of powder flow properties[24]

S.No	Angle of repose (degrees)	Type of flow
1	<20	Excellent
2	20-30	Good
3	30-34	Passable*
4	>40	Very poor

Table No.4: Solubility study of metformin hydrochloride in different solvent

S.No	Solvent	Drug solubility
1	Water	Soluble
2	Ethanol	Slightly soluble
3	Acetone	Practically insoluble
4	Methanol	Practically insoluble
5	Petroleum ether	Practically insoluble

Table No.5: Partition coefficient

S.No	Absorbance of upper layer	Concentration of upper layer(C_U) (µg/ml)	Absorbance of lower layer	Concentration of lower layer (C_L) (µg/ml)	$K=C_U/C_L$	mean
1	0.317	1.396	0.826	3.638	0.383	0.383
2	0.316	1.392	0.825	3.634	0.383	
3	0.317	1.396	0.826	3.638	0.383	

Table No.6: Peak table results of metformin hydrochloride

Peak Name	X	Y
6	466.65	22.56
5	666.77	43.84
4	758.73	20.6
3	1215.41	35.12
2	1567.63	39.9
1	3020.73	39.87

Table No.7: Peak table results of metformin hydrochloride and HPMC

Peak Name	X	Y
16	458.93	19.13
15	668.61	35.92
14	759.57	5.01
13	935.16	47.67
12	1070.76	20.57
11	1118.67	23.45
10	1216.01	10.38
9	1376.36	38.97
8	1451.01	34.95
7	1568.11	35.1
6	1630.03	35.05
5	2401.77	49.84
4	2932.91	31.25
3	3019.01	20.29
2	3160.04	38.24
1	3372.15	30.37

Table No.8: Peak table results of metformin hydrochloride and ethyl cellulose

Peak Name	X	Y
17	471.86	33.81
16	668.28	39.46
15	760.71	20.23
14	881.19	55.67
13	926.38	48.38
12	1109.78	26.36
11	1215.96	22.45
10	1377.24	33.23
9	1445.41	35.69
8	1531.16	37.9
7	1630.07	38.33
6	2401.94	43.09
5	2878.19	27.67
4	2978.79	25.85
3	3018.48	24.75
2	3372.28	39.27
1	3681.76	54.29

Table No.9: Peak table results of metformin hydrochloride and HPMC and ethyl cellulose

Peak Name	X	Y
17	464.72	23.11
16	626.81	62.87
15	668.73	27.89
14	757.34	1.78
13	930.45	46.67
12	1074.65	12.08
11	1215.82	6.78
10	1376.69	31.65
9	1416.71	36.61
8	1448.47	34.43
7	1532.1	40.8
6	1630.85	39.49
5	2401.89	48.7
4	2884.06	24.13
3	2980.32	22.64
2	3017.96	15.09
1	3374.44	30.54

Table No.10: Spectrophotometric determination metformin hydrochloride

S.No	Media	Experimental λ max
1	Water	232nm
2	Phosphate buffer pH 7.4	232nm

Table No.11: Data of calibration curve of metformin hydrochloride in water.

S.No	Calibration curve for	Metformin hydrochloride
1	solvent	Water
2	λ max	232nm
3	Unit of concentration	µg/ml
4	Slope of calibration curve	0.227
5	Constant of calibration curve	0.012
6	Coefficient correlation of calibration curve	0.982

Table No.12: Absorbance of metformin hydrochloride in water

S.No	Concentration	Absorbance
1	0	0.0
2	1µg/ml	0.290
3	2µg/ml	0.480
4	3µg/ml	0.644
5	4µg/ml	0.850
6	5µg/ml	1.224

Table No.13: Data of calibration curve in phosphate buffer pH 7.4

S.No		
1	**Calibration curve for**	**Metformin hydrochloride**
2	Solvent	Phosphate buffer pH 7.4
3	λ max	232 nm
4	Unit of concentration	µg/ml
5	Slope of calibration curve	0.641
6	Constant of calibration curve	0.185
7	Coefficient correlation of calibration curve	0.988

Table No.14: Absorbance of metformin hydrochloride in phosphate buffer pH 7.4

S.No	Concentration	Absorbance
1	0	0.0
2	1µg/ml	0.928
3	2µg/ml	1.569
4	3µg/ml	2.209
5	4µg/ml	2.762
6	5µg/ml	3.259

Table No.15: Data of calibration curve in biological sample

S.No	Calibration curve for	Metformin hydrochloride
1	Solvent	Phosphate buffer pH 7.4
2	Λmax	232nm
3	Unit of concentration	µg/ml
4	Slope of calibration curve	0.184
5	Constant of calibration curve	0.144
6	Coefficient correlation of calibration curve	0.865

Table No.16: Absorbance of metformin hydrochloride in biological sample

S.No	Concentration	Absorbance
1	0	0.0
2	1µg/ml	0.543
3	2µg/ml	0.552
4	3µg/ml	0.629
5	4µg/ml	0.764
6	5µg/ml	1.140

Table No.17: Bulk density

S.No	Mass of powder[M]	Volume of powder[V]	Bulk density	Average bulk density
1	5	11	0.4545	0.4094±0.049098g/cm^3
2	5	12	0.4166	
3	5	14	0.3571	

Table No.18: Tapped density

S.No	Mass of powder[M]	Volume of powder[V]	Tapped density	Average tapped density
1	5	8	0.625	0.6018±0.040126g/cm^3
2	5	9	0.5555	
3	5	8	0.625	

Table No.19: Carr's index or % compressibility

S.No	Tapped density	Bulk density	Tapped density-bulk density	Tapped density-bulk density/tapped density	Tapped density-bulk density/tapped density×100	Average Carr's index
1	0.625	0.4545	0.1705	0.2728	27.28	31.71±9.720377%
2	0.5555	0.4166	0.1389	0.2500	25.00	
3	0.625	0.3571	0.2679	0.4286	42.86	

Table No.20: Relation between % compressibility and flow ability

S.No	% compressibility	Flow ability
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair passable
4	23-35	Poor
5	33-38	Very poor
6	<40	Very very poor

Table No.21: Hausner's ratio

S.No	Tapped density	Bulk density	Tapped density/bulk density	Average Hausner's ratio
1	0.625	0.4545	1.37	1.48±0.231805
2	0.5555	0.4166	1.33	
3	0.625	0.3571	1.75	

Table No.22: Angle of repose

S.No	Height(h)	Radius(r)	tanϴ=h/r	ϴ	mean
1	4	3.15	1.26	51.56	53.49±1.715197
2	5	3.5	1.42	54.84	
3	5	3.6	1.38	54.07	

Table No.23: Angle of repose as an indication of powder flow properties

S.No	Angle of repose(degrees)	Type of flow
1	<20	Excellent
2	20-30	Good
3	30-34	Passable
4	>40	Very poor

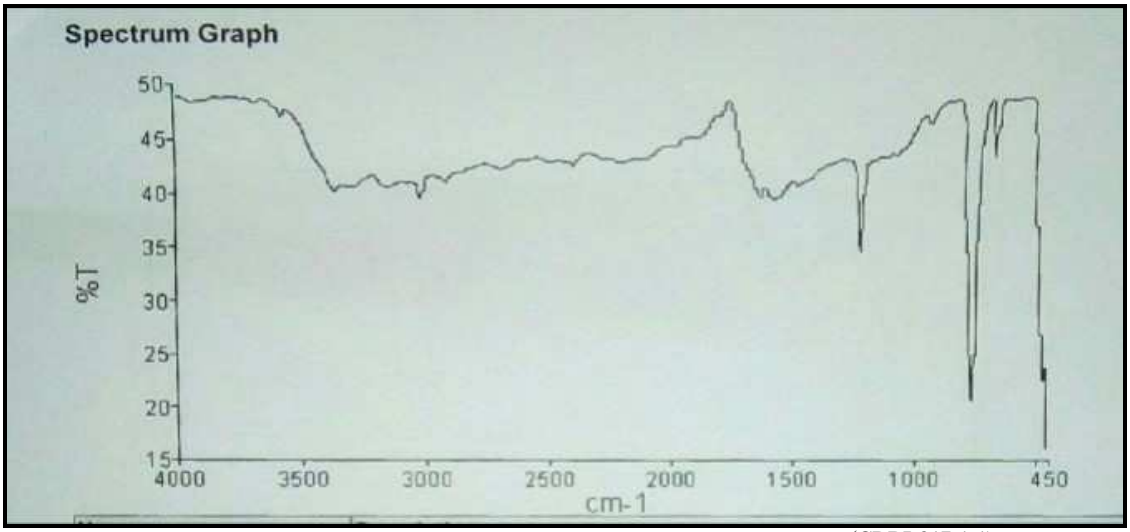

Figure No.1: IR spectra of metformin hydrochloride(CDRI-317-1-1)

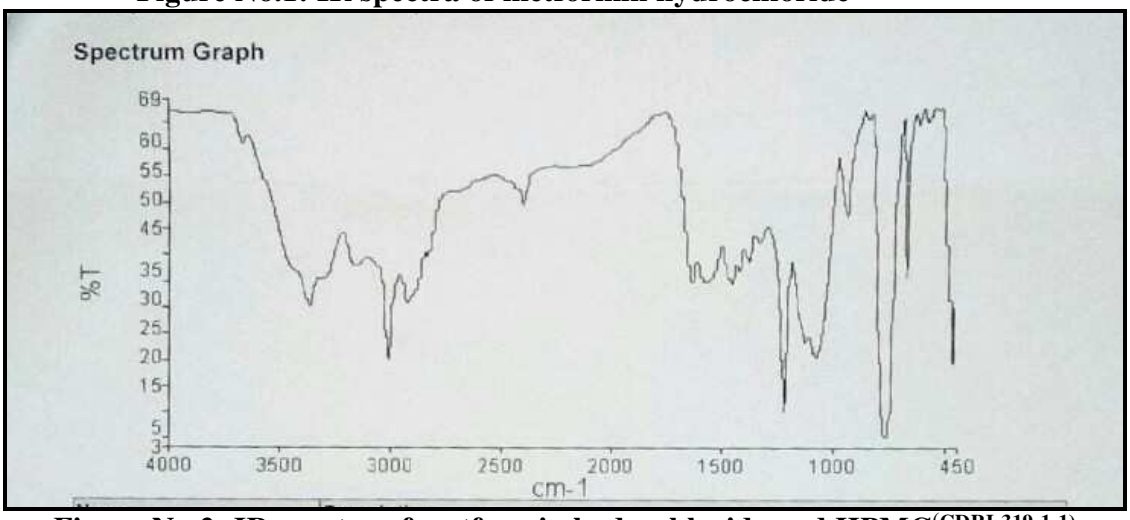

Figure No.2: IR spectra of metformin hydrochloride and HPMC(CDRI-319-1-1)

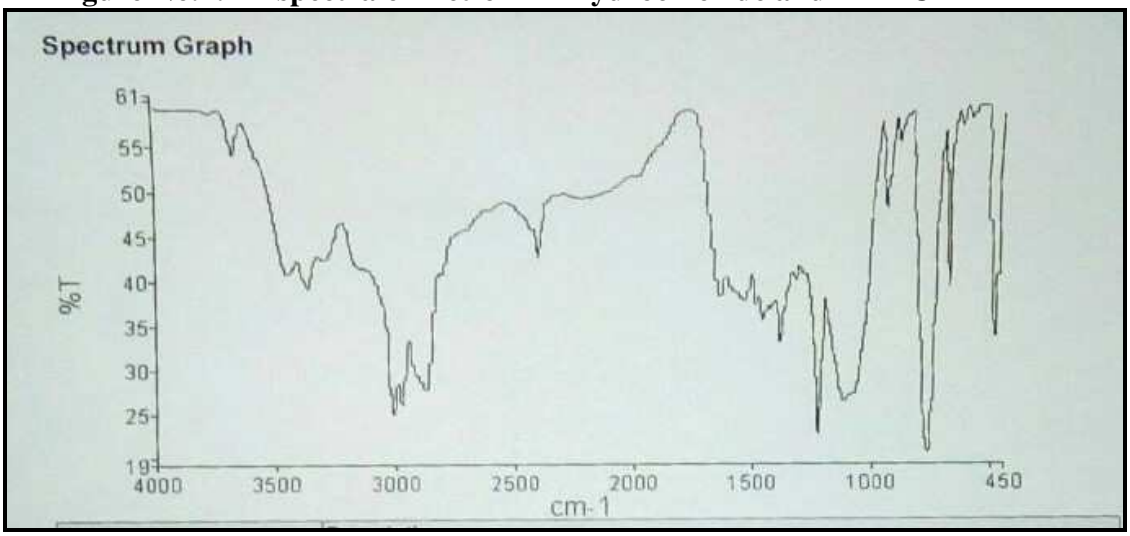

Figure No.3: IR spectra of metformin hydrochloride and ethyl cellulose(CDRI-320-1-1)

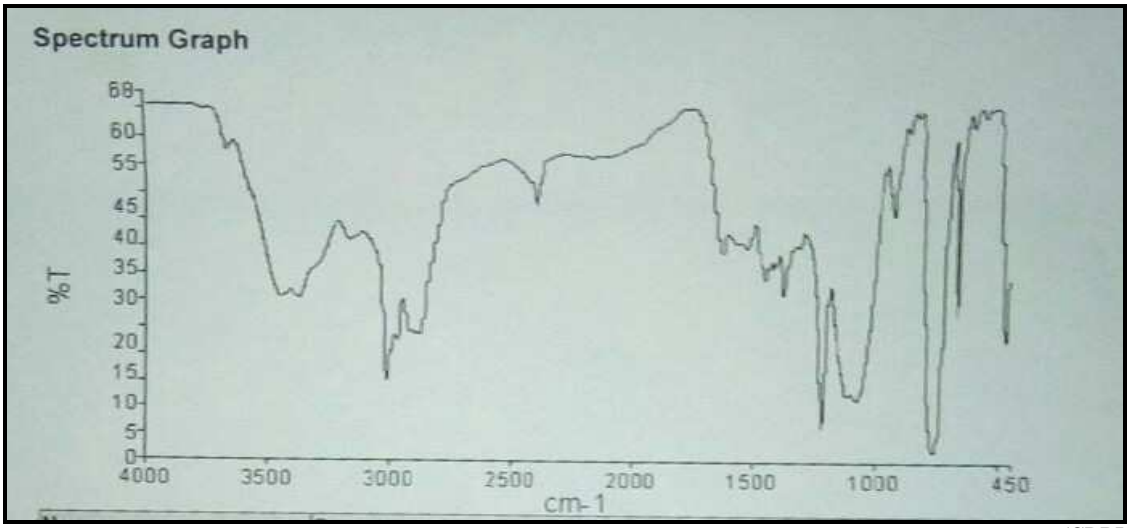

Figure No.4: IR spectra of metformin hydrochloride and HPMC and ethyl cellulose(CDRI-318-1-1)

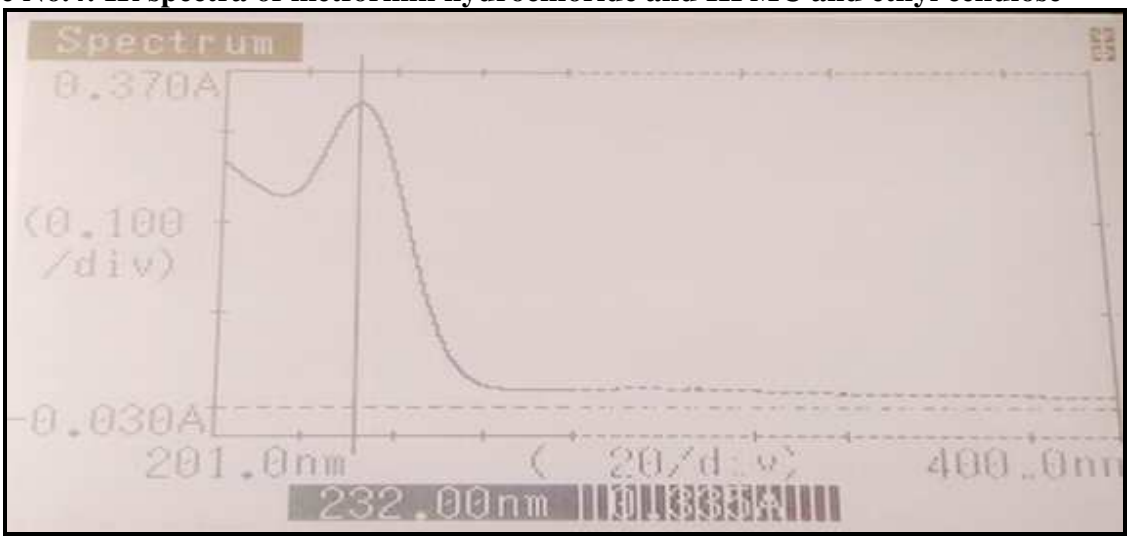

Figure No.5: Spectra of metformin hydrochloride

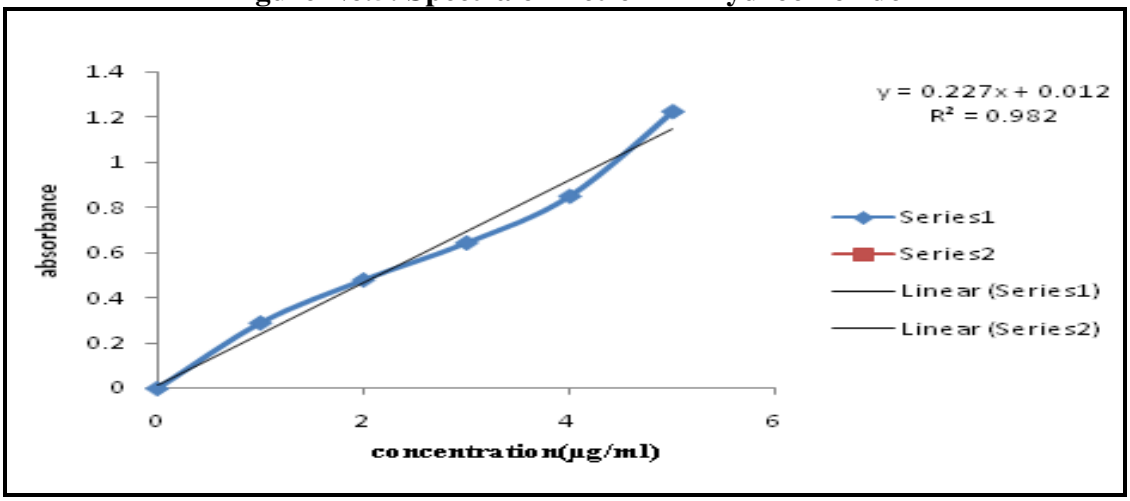

Figure No.6: Calibration curve of metformin hydrochloride in water

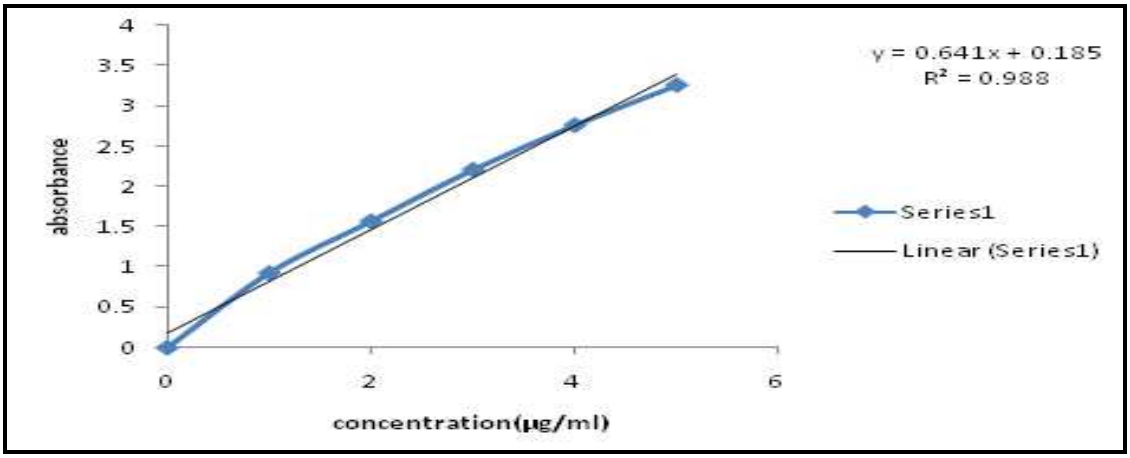

Figure No.7: Calibration curve of metformin hydrochloride in phosphate buffer pH 7.4

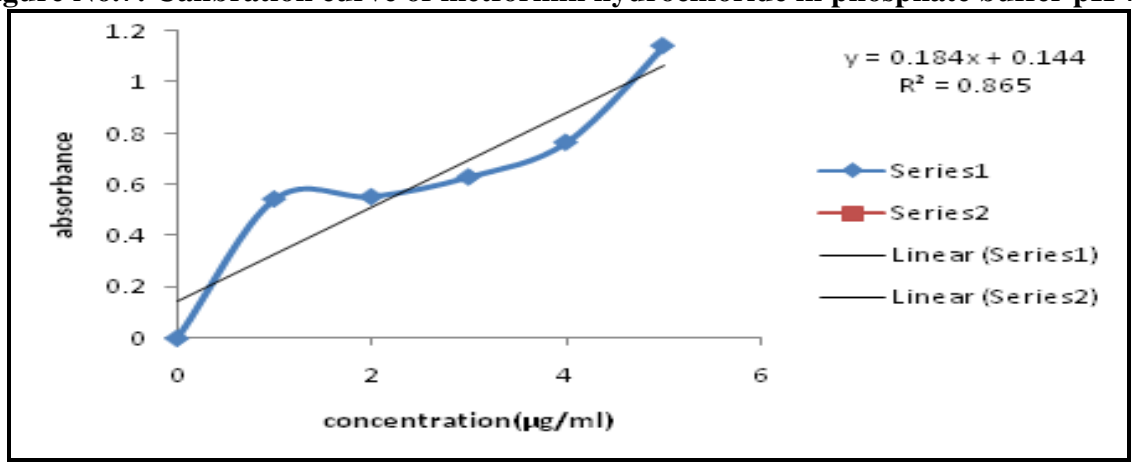

Figure No.8: Calibration curve of metformin hydrochloride in biological sample

CONCLUSION

Metformin hydrochloride (1, 1-dimethyl biguanide hydrochloride) is used in the treatment of diabetes mellitus with dose of 1.5 to 3g of metformin hydrochloride daily. Gastrointestinal irritation (GIT irritation), including diarrhea, cramps, nausea, vomiting, and increased flatulence are the main adverse effect of metformin is considered. Metformin hydrochloride is more commonly associated with GIT effects than other antidiabetic drugs. Lactic acidosis is the most serious potential side effect of metformin, this obstacle is very rare, and the immeasurable majority of these cases appear to be related to co morbid situation, such as impaired liver or kidney function, rather than to the metformin itself.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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