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Research Article

FORMULATION AND IN-VITRO EVALUATION OF METFORMIN HYDROCHLORIDE LOADED MICROSPHERES FOR ORAL CONTROLLED RELEASE

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ABSTRACT

Biodegradable microspheres may develop improved drug delivery system to gastrointestinal tract, for treatment of Diabetes. Metformin hydrochloride have the ability to produce thus effect for extended period.The Objective of this Work to prepare metformin hydrochloride microspheres by using ethyl cellulose and polyvinyl alcohol as the retardant material with entrapment efficiency and extended release using solvent evaporation techniques.Also, the microspheres were prepared by the double emulsification technique with a yield (40%) are characterized . The Characterization was included : Optical microscopy, Scanning electron microscopy (SEM), Study the compatibility between the selected polymer and metformin hydrochloride by using IR and study the interaction between drug and polymer as well as the microspheres-drug polymer thermal behaviour and crystallinity by using DSC and XRD respectively.Drug release studies were conducted using the dissolution apparatus, the dissolution medium was phosphate buffer at pH 6.8. However the release of loaded metformin hydrochloride in microspheres occurred gradually of 30% up to 8 hours compared to the control which completely released within two hours.

Key wards: Metformin, Ethyl cellulose, Polyvinyl alcohol, SEM, Evaporation techniques, DSC, XRD..

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by a high blood glucose concentration (hyperglycemia) which due to insulin deficiency or insulin disorder. Metformin hydrochloride is used in the treatment of noninsulin-dependent diabetes mellitus. It's biological half-life is 2.5 to 3 hours. Due to its short biological half-life and narrow absorption window, it is incompletely absorbed in the small intestine. It is a strong base (pKa = 11.5), protonated depending on the physiological pH of the human body. It is also poorly absorbed in the colon. However, reduction of gastrointestinal motility enhances the drug absorption. Most of the drug is excreted unchanged in urine while accumulation in the body causes toxicity. Bioavailability is 50 to 60 % due to its site specific absorption in the body [1].

Administration of the conventional dosage forms does not usually provide rate-controlled release or target specificity. It is observed in many cases, the conventional drug delivery provides sharp increases of drug concentration at potentially toxic levels. Following a relatively short period at the therapeutic level, drug concentration eventually drops off until re-administration. Today new methods of drug delivery are possible, desired drug release can be provided by rate-controlling membranes.

Its disadvantages are that it delivers the drug to systemic circulation without controlling its release behavior, short gastric residence time as well as fluctuation in the plasma drug concentration [2]. Sustained release formulation is modulated to reduce the gastric motility time, increase the gastric residence time and thus the bioavailability of the drug [3, 4].The release rates of microspheres are dependent on many factors. The polymers used and the processing conditions during microsphere preparation determine the properties of microspheres formed and also influence the distribution and release behavior of the drug. Hence, polymers those are biocompatible, biodegradable, easily available, having good mucoadhesive properties were used in the study.

Administration of a drug by microspheres has been studied from last many years. Microspheres as a drug carrier has many advantages which include, they can be injected as well as ingested, can be modified for desired drug release, organ targeted drug delivery is possible, avoids variance of gastric emptying and different transit rates, releases the drug in a more predictable way, rapid and easy to scale up [5, 6, 7 & 8]. Metformin hydrochloride being a water soluble drug, it is difficult to control the release of water soluble drugs over the time period desirable to achieve better plasma concentration using spray-drying method for the preparation of microparticles [9].

Microspheres made from the naturally occurring biodegradable polymers have attracted considerable attention for several years in sustained drug delivery (Figure: 1). Recently, dosage forms that can precisely control the release rates and target drugs to a specific body site have made an enormous impact in the formulation and development of novel drug delivery systems. Microspheres form an important part of such novel drug delivery systems. They have varied applications and are prepared using assorted polymers. In context of the above principles, a strong need was felt to develop a dosage form that delivered metformin in small intestine and would increase the efficiency of the drug, providing sustained action. Thus, an attempt was made in the present investigation to use Ethyl cellulose and polyvinyl alcohol by using double emulsification technique [10, 11]. Hence, metformin hydrochloride microspheres could reduce the dosing frequency and improve patient compliance [12].

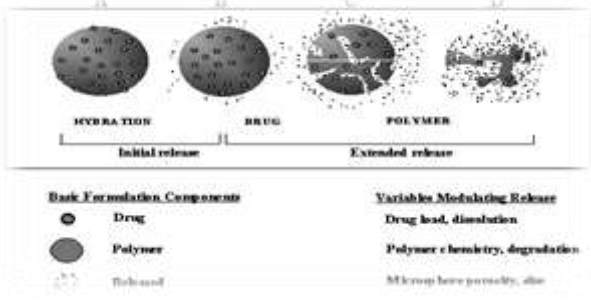

Fig. 1: Diagram explains the sustained release of drug from metformin hydrochloride loaded microspheres.

MATERIALS AND METHODS

Materials & Instruments

Metformin hydrochloride Asia pharmaceutical industries, India. Ethyl cellulose: Riedel-de haen, Germany. Polyvinyl alcohol (PVA) : BDH Chemicals Ltd Poole- England.

Instruments : Infra-red spectrophotometer. Scanning electron microscope-LEO-England. Differential scanning Colorimetry-Mettler Toledo, UK. X-ray Diffraction (XRD), PHILIPS-Holland. Ultra Turrax, IKA-WERKE, Germany. Spectrophotometer JENWAY, U.K.

Methods

Preparation of metformin hydrochloride loaded microspheres

Preparation of microspheres containing metformin as a core material were prepared by a non-aqueous solvent evaporation method, metformin in water and ethyl cellulose in chloroform were mixed with various ratios 1:2 respectively. 1% of PVA was added to previous mixture, the mixture was mixed by a homogenizer at rate 11,000 rpm for 10 minutes using Ultra Turrax, IKA.

The stirring was continued using magnetic stirrer (50 rpm) for 4 hours until the microspheres were produced (i.e the chloroform had evaporated). The microspheres were isolated by filtration and dried. The collected microspheres were examined under light microscope.

Characterization of micro-spherical matrices of Metformin hydrochloride

Optical microscopy

A sample of microspheres suspension was mounted between a slide and cover slip, and one drop of immersion oil was placed on the top of cover slip. An immersion lens on a micro system 40, Leica, Microsystem was used to achieve a x200 magnification.

Scanning electron microscopy

Scanning electron microscopy (SEM) was used to evaluate the shape and surface characteristics of particles. Scanning was carried out using the LEO-1430 vp,. Prior to examination, the sample was fixed on a brass stub and coated with a gold palladium layer under argon atmosphere by using a gold sputter module in a high vacuum evaporator.

Infrared Spectrophotometry

IR Spectroscopy is used for recording spectra in the region of 4000-650 cm-1 (2.5-15.4 μm) or in some cases down to 200 cm-1 (50 μm).

METHOD FOR PREPARATION OF SAMPLE (DISC METHOD)

Triturate 1-2 mg of the substance to be examined with 300-400 mg of finely powdered and dried potassium bromide R . These quantities are usually sufficient to give a disc of 10-15 mm diameter and a spectrum of suitable intensity . Carefully grind the mixture, spread it uniformly in a suitable die, and submit it to a pressure of about 800 MPa (8 t•cm-2).

Differential Scanning Colorimetry (DSC)

Differential Scanning Colorimetry (DSC) Mettler, Toledo was used to determine the thermal behaviour of metformin hydrochloride alone and micro-capsulated metformin. An appropriate amount was directly weighed into an aluminium volatile pan and crimp sealed. An empty aluminium volatile pan was used as reference. The samples were run at different cooling rates (1, 5 and 10°C/min) under a constant nitrogen pure gas, over the temperature range between 40°C to 300°C. The melting point and enthalpy of fusion for melting point events observed were calculated by DSC soft wares.

X-ray diffraction (XRD)

The X-ray diffraction was carried out by using the PW1800 X-ray Diffractometer, Obtain a defined weight of the material, as pure as possible, grind the sample to a fine powder, the Powder less than ~10 μm (or 200-mesh) in size is preferred. The sample was mounted on to the diffractometer and ciliated the X‑rays on to the powdered sample to get the diffraction peak of certain intensities and recorded. Typically the substrate is amorphous to avoid interference.

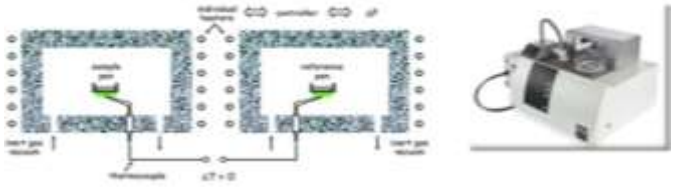

Fig. 2: Diagram of Differential Scanning Colorimetry (DSC) Mettler, Toledo.

Metformin hydrochloride drug content

To determine the metformin contents of prepared microspheres, in separated funnel 100 mg of metformin loaded microspheres were dissolved in 50 ml of distilled water and then added 50 ml of chloroform at room temperature, by gentle shaking of the funnel, the solution were separated into two layers, one was the aqueous layer (metformin water layer) and the other was oily Layer (polymer chloroform layer), the aqueous layer was then separated and measured by UV spectrophotometer at wavelength 233 nm .

In vitro drug release profiles of metformin hydrochloride loaded microspheres.

Drug release studies were conducted using the dissolution apparatus, basket-type, at a rotational speed of 100 rpm at 37±0.5°C. The dissolution media used were 900 mL phosphate buffer at pH 6.8 as a dissolution medium . Samples (10 ml) were withdrawn at regular intervals and the same volume of pre-warmed (37±0.5°C) fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered through a 0.45-μ membrane filter, and the drug content in each sample was analyzed after suitable dilution with a UV spectrophotometer (Shimadzu UV-1700; Shimadzu) at 233 nm. As shown in (figure 3).

Fig. 3: Study the in vitro release of metformin hydrochloride loaded Microspheres, by dissolution apparatus.

Results

Table 1: Characterization of micro-spherical matrices loaded with metformin hydrochloride.

Size of microsphere	Shape of microsphere	Crystanility	Porosity	Melting point
100 µm in diameter	Spherical	Amorphous	porous	155.7 ºC

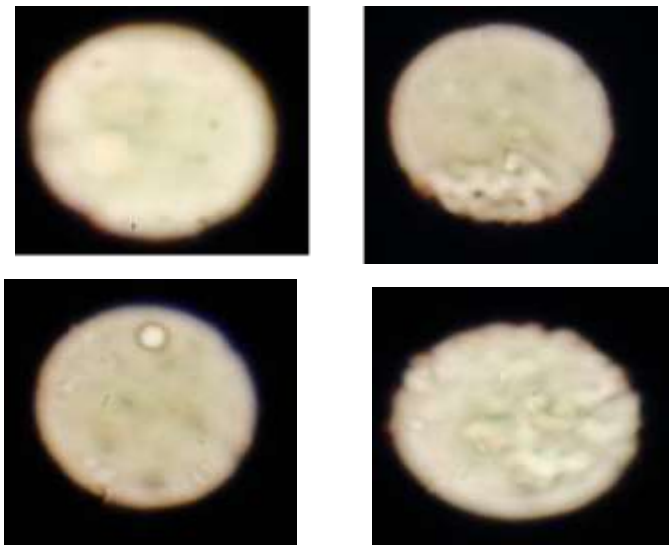

Fig. 4: Microscopically photographs of metformin microspheres prepared using solvent evaporation method

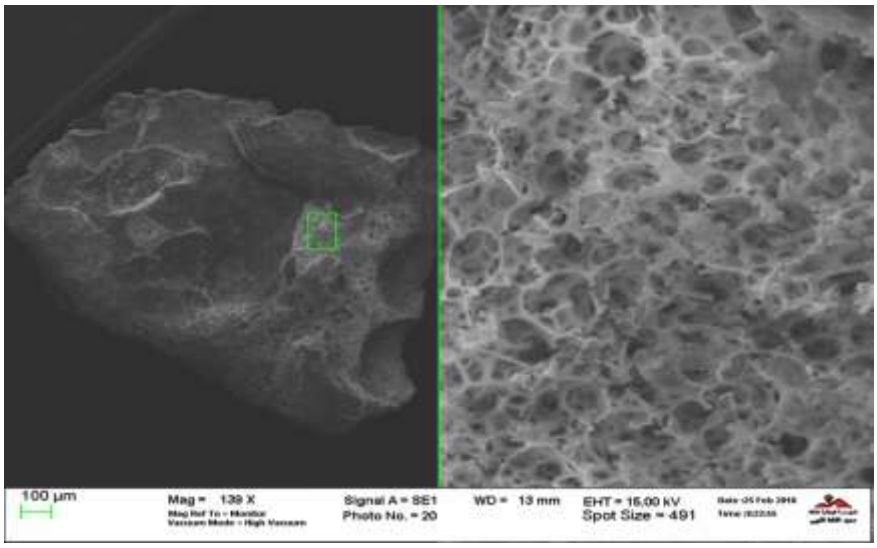

Fig. 5: SEM microphotographs of metformin microspheres prepared by using solvent evaporation method.

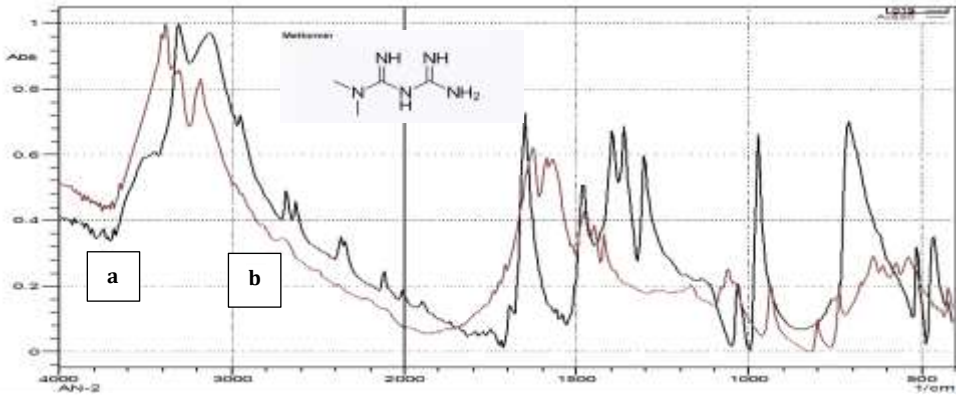

Fig. 6: Overlay of IR spectra, (a) Control Metformin Hcl (b) Microspherical matrices of metformin hydrochloride.

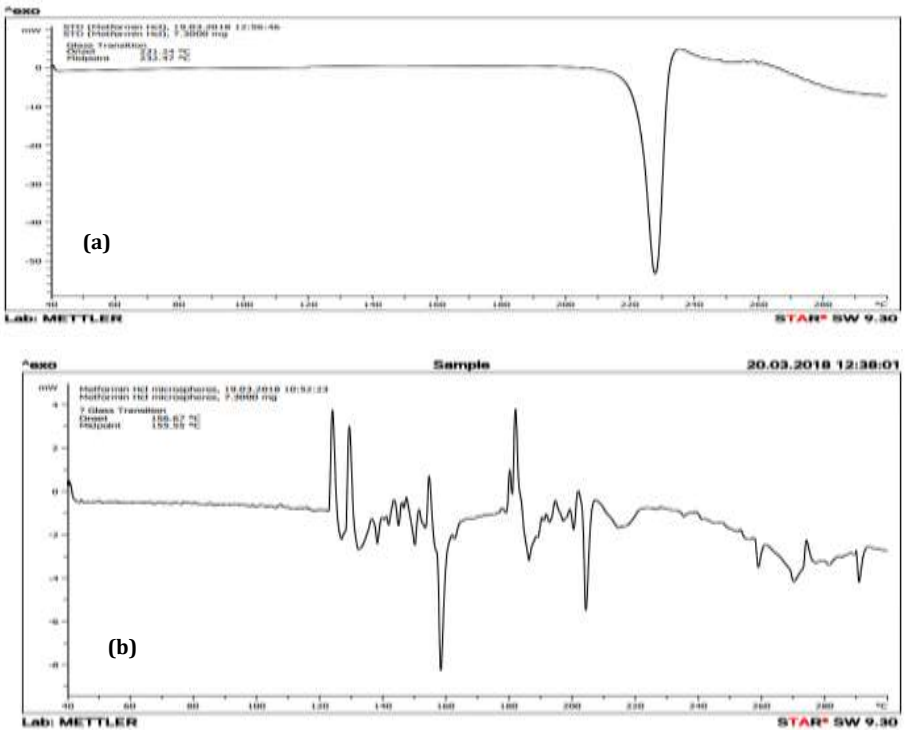

Fig. 7: Differential scanning Colorimetry (DSC) of (a) Metformin hydrochloride and (b) Microspheres containing Metformin hydrochloride.

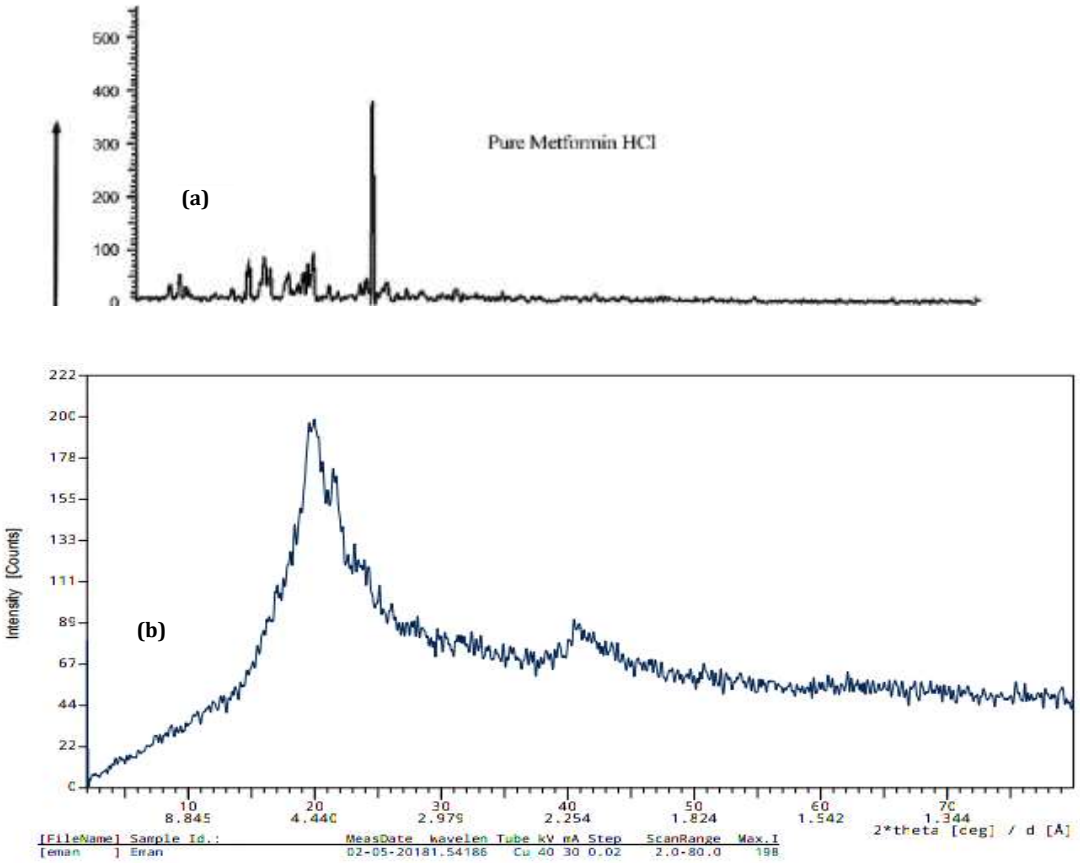

Fig. 8: X-ray diffraction (XRD) of (a) metformin hydrochloride and (b) microspheres loaded with metformin hydrochloride.

Table 2: In vitro drug release profile of metformin hydrochloride alone (STD) and metformin hydrochloride loaded microspheres.

Time (Hours)	Absorbance (nm) Of STD drug	% Relesae Of STD drug	Absorbance (nm) of encapsulated drug	% Release of encapsulated drug
1	0.044	45	0.010	14
2	0.049	46	0.011	15
4	0	0	0.014	19
6	0	0	0.018	25
8	0	0	0.022	30

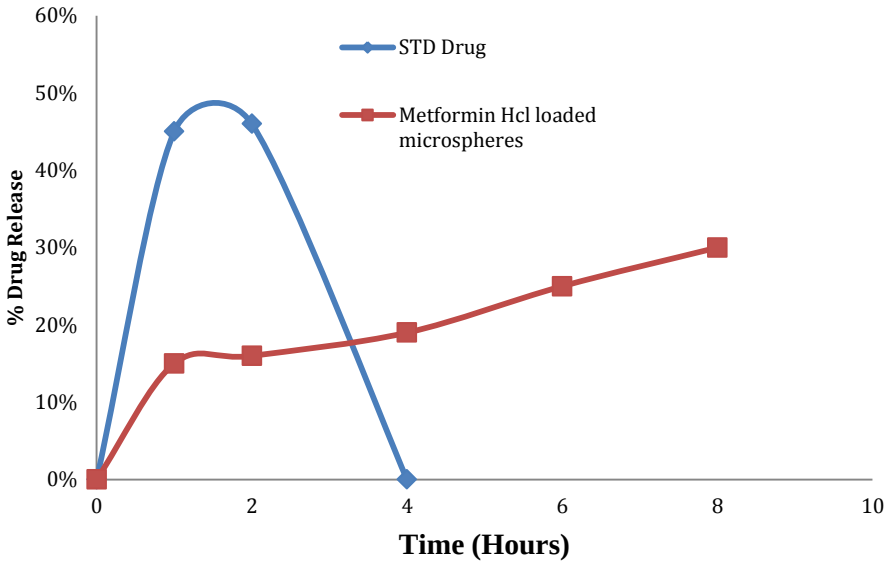

Fig. 9: In vitro drug release profile of metformin hydrochloride loaded Microspheres.

DISCUSSION

The oral drug delivery was potentially enhancing the bioavailability of water soluble drugs such as metformin by using ethyl cellulose polymer & PVA. The resultant 100 µm in diameter of spherical matrix and porous structure of spheres as demonstrated by SEM, also low entrapment efficiency (10 %) as shown in table1 & figure 4 &5 .

The IR spectra (Figure 6 (a-b)) revealed that there was no such interaction between metformin hydrochloride and the polymer, ethyl cellulose. The principal absorption peaks of metformin hydrochloride appear at 3169 cm−1 due to the N-H stretching of the primary amine group (-NH2) and at 1063 cm−1 due to C-N stretching. A peak at 1584 cm−1 occurs due to N-H bending vibrations of the primary amine group. The identical peaks (N-H stretching, C-N stretching, and N-H bending vibrations) were also appeared in the spectra of ethyl cellulose microparticles containing metformin hydrochloride, as shown in figure 6 (b).

The DSC curve of pure metformin exhibited an initially flat profile, followed by a single sharp endothermic peak representing the melting of the substance in the range 223–237°C (T onset = 231.2, T peak = 233.33 and ΔH fusion = -313.51 J/g). The thermal curve of microspheres prepared by Ethyl cellulose and 1% PVA containing metformin, corresponded to the superimposition of those of the single components, indicating the absence of solid state interactions and allowing assessment of drug–polymers compatibility. Thus, no definite solid–solid interaction could be concluded for examination of all the DSC thermograms, as shown in figure 7.

XRD studies proved that, there was retention of the crystalline nature of the drug in solid dispersion ruling out any probability of drug and polymer interaction or complex formation, as shown in figure 8.

Initial in vitro experiments were under taken to examine the release profiles of metformin hydrochloride from microspheres in phosphate buffer at 37°C, pH 6.8, the process is continued for to 8 hrs by when the of particles mass was eroded, however the release of metformin hydrochloride was gradually sustained compared to the control of metformin hydrochloride that was completely immediately released. The metformin hydrochloride release effectively for 8 hrs was not more than 30% of drug content of the matrix, as well as the microsphere was not more than degradation showed 27 % of polymer degradation, as shown in table 2 and figure 9.

CONCLUSION

The findings of the present study demonstrated that the hydrophobic matrix of ethyl cellulose alone could delay the Metformin hydrochloride release for up to 8 hours with only delay 30% of drug released from their matrix, as well as the degradation only was up to 27 % of polymer degradation, therefore this polymer can be successfully employed for formulating SR matrix tablets. Diffusion coupled with erosion might be the mechanism for the drug release, which can be expected to reduce the frequency of administration and decrease the dose-dependent side-effects associated with repeated administration of conventional metformin hydrochloride tablets.

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