ISSN 0975-6299

Vol 2/Issue 2/Apr-Jun 2011

International Journal of Pharma and Bio Sciences

RESEARCH ARTICLE

PHARMACOGNOSY

DETECTION OF METFORMIN HYDROCHLORIDE IN A TRADITIONALLY USED INDIAN HERBAL DRUG FOR ANTIDIABETIC: A CASE REPORT

MANISH KUMAR, VIVEKANANDA MANDAL AND S. HEMALATHA*

Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi-221005, India.

S. HEMALATHA
Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi-221005, India.

ABSTRACT

In the presented case, we got an herbal medicine in the form of a set of different color pills from local herbal medicinal practitioner. According to the advertisements on monograph, the product contains only herbal ingredients without any adequate declaration of the ingredients and was declared as anti-diabetic formulation. For identification of the ingredients, the pills were analyzed by UV, IR and HPLC spectroscopy. One major ingredient was detected in the herbal pills and was identified as metformin hydrochloride. Quantification by UV spectroscopy yielded 93.1 mg of metformin base, Dissolution study states that 85% of the drug release in 240 min from pills while the Indian Pharmacopoeia reveals that uncoated metformin hydrochloride tablets should release 85 % drug within 45 minutes. This study demonstrates a common problem with herbal medicines, where adulterations with synthetic therapeutic substances can lead to severe side effects and/or potentially fatal interactions with conventional medicines.

ISSN 0975-6299 Vol 2/Issue 2/Apr-Jun 2011

KEYWORDS

Anti-diabetic, Herbal pills, Metformin HCl.

INTRODUCTION

The use of herbal medicinal products (HMPs) has recently increased, thereby enhancing the market for herbal products worldwide because of their low risk factor [1, 2]. In India's more than 70% populations still using these non-allopathic systems of medicine. A survey conducted in 2005 found that 71% of Canadians were using HMPs along with vitamins and minerals [3]. In the United States, about 19% of the adult populations were using HMPs as of 2002 [4]. About 36% of pregnant women in Norway use herbs [5]. But there has been more recognition of the potential risks associated with this type of product as the use of HMPs increases. Potential harm can occur via plant misidentification, as well as from contamination, heavy metal toxicity, interactions with other herbal products or pharmaceutical drugs, inherent toxicity of herbs, and adulteration with undeclared synthetic drugs or by mixing the analogues of prescription drugs that are created by replacing or adding functional groups to the original chemical of products. There are number of cases reported, in which synthetic drugs like corticosteroids present in the HMP have shown some serious side effects in patients.

Herbal medicines are marketed in pharmacies, drugstores and directly by local practitioners, with advertising either in the printed media or, increasingly, from international internet suppliers, with direct delivery [6-9]. Many products are delivered as different formulations, without any adequate declaration of the ingredients, or information on the recommended dosages or side effects. Translations of product information are often missing from foreign products [10-12]. One of the greatest risks to human health related to HMPs arises from economically motivated adulteration. Such adulteration can occur through the addition of undeclared pharmaceutical drugs or, in illicit attempts to evade detection of adulteration, their analogues [12-14]. Examples of HMP types commonly adulterated include sleeping aids that have been adulterated with benzodiazepines such as estazolam or clonazepam [15], weight loss products adulterated with sibutramine or fenfluramine [16-18], erectile dysfunction or sexual enhancement products adulterated with sildenafil, tadalafil, vardenafil, or their analogues [19, 20], remedies for diabetes adulterated with glibenclamide [21] and bodybuilding products adulterated with androgenic steroids [22]. The work presented in this paper brings into light use of synthetic antidiabetic drug metformin admixed with some traditionally used herbal pills for diabetes.

MATERIALS AND METHODS

Samples :

Samples of herbal pills that were under suspicion of adulteration with undeclared synthetic drugs were purchased from local herbal medicinal practitioner. According to the advertisements on the monograph, the product contains herbal ingredients and was declared as anti-diabetic formulation. These products were mainly from tribal areas of India.

Sample preparation:

10 Pills were weighed and crushed it to made coarse powder then dissolved in 95% (v/v) ethanol with slight warming on water bath then filtered and left for natural evaporation. On natural evaporation white needle shaped crystals appeared in the ethanol soluble portion which was separated from mother liquor and further recrystalized, dried to get in pure form.

Characterization of crystals by:

IR-Spectroscopy:

The crystals so obtained were finally subjected to IR spectroscopy using FTIR (8400S, Shimadzu, Japan). We compared the spectra of crystal with all the synthetic anti-diabetic drugs present in Indian Pharmacopoeia, 1996 [23] and the results revealed that measured peaks of compound were very much closer to the IR peaks of metformin hydrochloride and further confirmation was done by matching the IR spectra of pure metformin hydrochloride and sample (Fig. 1).

HPLC analysis:

A waters high performance liquid chromatography (HPLC) systems USA with PDA detector was used for analysis. The solvents used for preparation of mobile phase were of HPLC grade. HPLC of standard metformin hydrochloride and the crystals obtained from herbal pills was done as per the method described by Kar et al., 2009 [24], using cosmosil C_{18} column (5 µ) 150 mm x 4.6 mm column, mobile phase selected for this method contains acetonitrile: phosphate buffer (65:35) pH adjusted to 5.75 with o-phosphoric acid which was filtered through 0.2 µ membrane filter. Flow rate employed was 1.0 ml/ min. Detection of eluent was carried out at 233.0 nm. Column was saturated with mobile phase for about an hour at above specified condition.

Analysis of metformin tablets:

Tablets equivalent to 20 mg of metformin hydrochloride was dissolved in 20 ml ethanol and then after filtration was evaporated to dryness on water bath. The residue was then dried at 105 °C for 1 hour. Finally IR Spectrum was taken. After overlapping the IR-Spectra of pure metformin hydrochloride with the spectra of crystals obtained from pills, it was confirmed that the compound was metformin hydrochloride (Fig. 1).

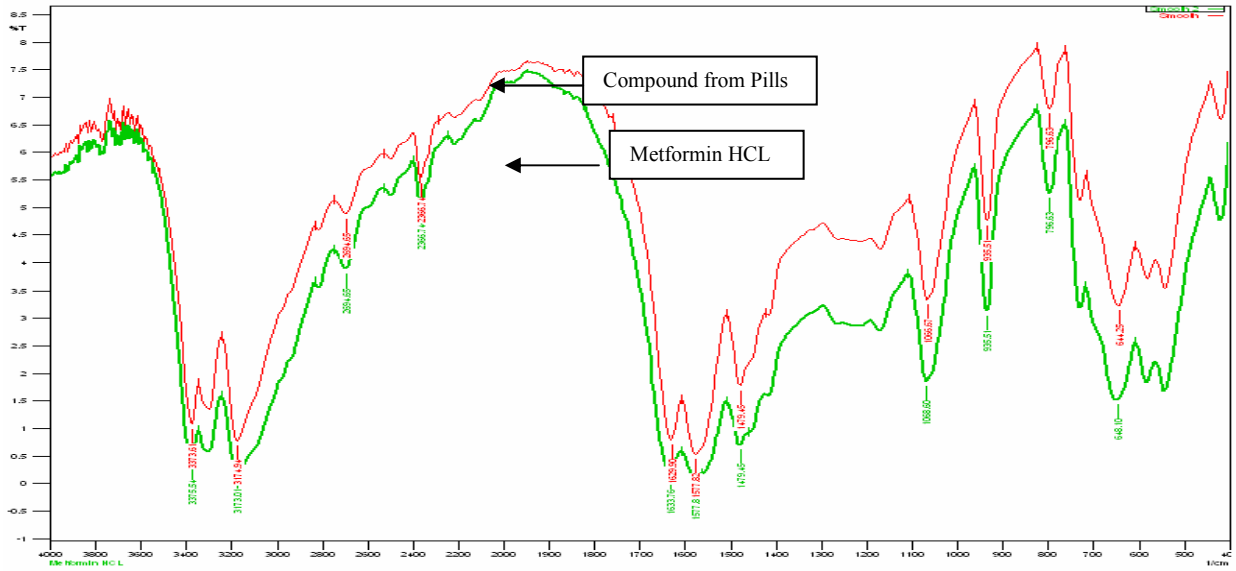

Figure 1

Overlapped IR-Spectra of Pure metformin hydrochloride and the crystals obtained from herbal pills.

Assay for herbal pills:

Weigh accurately a quantity of the powder equivalent to 0.1 gm of metformin hydrochloride, shake with 70 ml of water for 15 minutes, dilute to 100 ml with water and filter. Dilute 10 ml of the filtrate to 100 ml with water further dilute 10

ml to 100 ml with water and measure the absorbance of resulting solution at λ_{max} 232 nm (IP, 1996) [25] (Fig. 2, Table 1).

Identification test for metformin hydrochloride:

Dissolve 10 mg in 10 ml of water and add 10 ml of a solution by mixing equal volume of a 10% w/v solution of sodium nitroprusside, a 10% w/v solution of potassium ferricyanide and a 10% w/v solution of NaOH and allowing to stand for 20 minutes a wine red color develops within 3 minutes (IP, 1996)[25].

Dissolution studies:

The *in vitro* release of metformin hydrochloride from pills was examined using paddle type dissolution apparatus (USP-Type II). The phosphate buffer (pH-6.8) 900 ml was used as dissolution medium at controlled 37 ^{o} C using rotation speed of 100 rpm. An aliquot of 5 ml of the solution was withdrawn at different time intervals and replaced by 5 ml of fresh dissolution medium. The samples were assayed through spectrophotometer (Pharma sec, UV-1700, Shimadzu, Japan) at λ_{max}233 nm. The experiments were performed in triplicate.

RESULTS

One major ingredient was detected in the herbal pills and was identified as metformin hydrochloride (Fig. 1). Quantification by UV spectroscopy for metformin tablet states that 100 mg of powder contains 97.1 mg of metformin and for herbal pills 100 mg of Powder contains 93.1 mg of metformin (Fig. 2, Table 1). The figure-3 depicts the release of metformin hydrochloride from the herbal pills in buffer media; it was observed that more than 45 % and 85% of the drug release took place in 30 minutes and 240 min. The Indian Pharmacopoeia reveals that uncoated metformin hydrochloride tablets should release 85 % drug within 45 minutes. Hence, it was found the release of drug from the pills under controlled manner took place upto 6 hours which doesn't comply. Chromatogram matching through HPLC studies also confirmed the fact that crystals obtained from the pills were none other than metformin.

Tabel 1
Observation table

	O.D-I	O.D-II	O.D-III	Mean O.D.
Metformin Tablet	0.696	0.698	0.702	0.699
Pink Pills	0.668	0.672	0.673	0.671

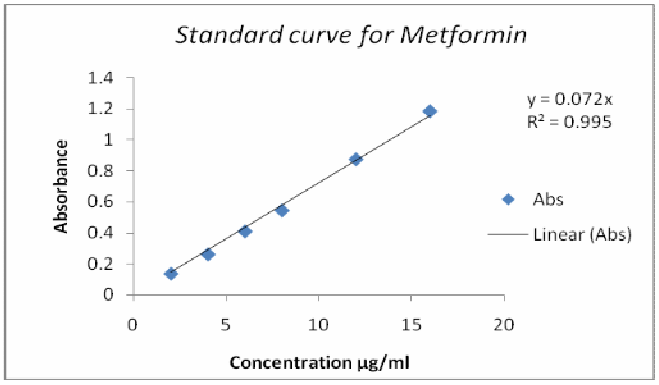

Figure 2
Standard curve for Metformin hydrochloride

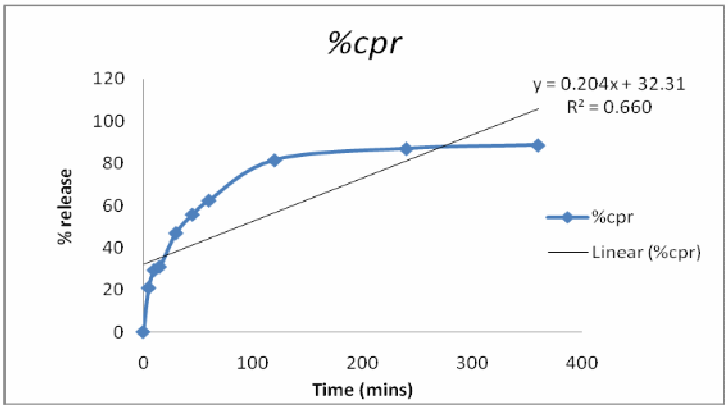

Figure 3
Shows % release of herbal pills

DISCUSSION

Many herbal medicines and synthetic drugs are useful at therapeutic doses but toxic at high concentrations. Co-administration of herbs and drugs can enhance or decrease the pharmacological or toxicological effects of drugs. Synergistic therapeutic effects may also complicate long-term medication. Prescribing these types of herbal drugs without knowing the history of a patient may lead to serious side effects due to overdosing and co-administration with other synthetic medicines [26]. Metformin hydrochloride is an oral anti-hyperglycemic drug used in the management of type 2 diabetes. It improves glucose tolerance in patients with type 2 diabetes (NIDDM), lowering both basal and postprandial plasma glucose. Quantification yielded 93.1 mg of metformin base per pills. The dissolution study states that 85% of the drug release in 240 min from pills while the Indian Pharmacopoeia reveals that uncoated metformin hydrochloride tablets should release 85 % drug within 45 minutes.

The use of metformin is contraindicated in patients with renal and hepatic impairment. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL (males), ≥ 1.4 mg/dL (females) or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicaemia. Moreover, it may cause severe interaction with drugs like nifedipine by increasing plasma metformin C_{max} and AUC by 20% and 9% respectively, with thiazide diuretics it decreases insulin sensitivity thereby leading to glucose intolerance and hyperglycemia, thus leading to a loss of diabetic control, cationic drugs (amiloride, cimetidine, digoxin, morphine, procainamide, quinidine, ranitidine) may increase the risk of lactic acidosis. Concomitant administration of angiotensin enzyme inhibitors (captopril,enalapril), other antidiabetic drugs (insulin, acarbose), beta-blockers, fluconozole, histamine (H2) receptor antagonist, monoamine oxidase inhibitors (MAOIs), sulphonamides and non-steroidal anti-inflamatory agents increases sensitivity to insulin and potentiation of blood glucose lowering effect and thus, in some instances, hypoglycemia may occur.

CONCLUSION

The conclusion of present study is that, products available without a prescription whose contents are claimed to be purely herbal may nonetheless contain synthetic substances in concentrations far above the therapeutic range and may lead to severe side effects or potentially fatal interactions with conventional drugs. Therefore, stronger regulations on the control of traditional herbal medicines are required, including licensing, labeling rules and

quality control mechanisms to verify ingredients. When taking the history of a patient possibly suffering from intoxication, the physician should ask specifically about drugs, dietary supplements, and so-called lifestyle products that were obtained without a prescription. It would be desirable for the contents of all such products to be declared, as required by law, so that their suitability for the market can be checked.

REFERENCES

1. Bodeker G and Kronenberg F, Public health agenda for traditional, complementary and alternative medicine. Am J Publ Health, 92: 1582-1591, (2002).
2. Zollman C and Vickers A, ABC of complementary medicine: what is complementary medicine? Br. Med. J, 319: 693-696, (1999).
3. IPSOS Reid. Health Canada Baseline Natural Health Products Survey Among Consumers. c2005 Available from http://www.hc-sc.gc. (accessed September 22, 2009).
4. Kennedy J, Herb and supplement use in the US adult population. Clin Ther, 27: 1847-1858, (2005).
5. Nordeng H and Havnen GC, Use of herbal drugs in pregnancy: a survey among 400 Norwegian women. Pharmacoepidemiol Drug Saf, 13: 371-380, (2004).
6. Morris CA and Avorn J, Internet marketing of herbal products. JAMA, 290: 1505-1509, (2003).
7. Eisenberg DM, Davis RB and Ettner SL, Trends in alternative medicine use in the United States 1990-1997: results of a follow-up national survey. JAMA, 280: 1569-75, (1998).
8. Tindle HA, Davis RB, Phillips RS and Eisenberg DM, Trends in use of complementary and alternative medicine by US adults: 1997-2002. Altern Ther Health Med, 11: 42-49, (2005).
9. De-Smet PA, Health risks of herbal remedies: an update. Clin Pharmacol Ther, 76: 1-17, (2004).
10. Routledge PA, The European Herbal Medicines Directive: could it have saved the lives of Romeo and Juliet? Drug Saf, 3: 416-418, (2008).
11. Foster BC, Arnason JT and Briggs CJ, Natural health products and drug deposition. Annu Rev Pharmacol Toxicol, 45: 203-26, (2005).
12. Ernst E, Adulteration of Chinese herbal medicines with synthetic drugs: a systematic review. J Intern Med, 252: 107-113, (2002).
13. Elvin-Lewis M, Safety issues associated with herbal ingredients. Adv Food Nutr Res, 50: 219-313, (2005).
14. Huang WF, Wen KC and Hsiao ML, Adulteration by synthetic therapeutic substances of traditional Chinese medicines in Taiwan. J Clin Pharmacol, 37: 344-350, (1997).
15. Health Canada Sleep Supplement Found to Contain Habit-Forming Drug. c2007. Available from http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2007/2007_89-eng.php. (accessed Oct. 3, 2009).
16. Corns C and Metcalfe K, Risks associated with herbal slimming remedies. J R Soc Promot Health, 122: 213-219, (2002).
17. Jung J, Hermanns CM and Weinmann W, Anorectic sibutramine detected in a Chinese herbal drug for weight loss. Forensic Sci Int, 161: 221-222, (2006).
18. Yuen YP, Lai CK, Poon WT, Ng SW, Chan AYW and Mak TWL, Adulteration of over-the-counter slimming products with pharmaceutical analogues-an emerging threat. Hong Kong Med J, 13: 216-220, (2007).
19. Li L, Low MY, Aliwarga F, et al. Isolation and identification of hydroxyl thiohomosildenafil in herbal dietary supplements sold as sexual performance

enhancement products. Food Addit Contam - Part A Chemistry, Analysis, Control, Exposure and Risk Assessment, 26: 145-151, (2009).
20. Singh S, Prasad B, Savaliya AA, Shah RP, Gohil VM and Kaur A, Strategies for characterizing sildenafil, vardenafil, tadalafil and their analogues in herbal dietary supplements, and detecting counterfeit products containing these drugs. Trends Anal Chem, 28: 13-28, (2009).
21. Padinjakara RNK, Ashawesh K, Butt S, Nair R and Patel V, Herbal remedy for diabetes: two case reports. Exp Clin Endocrinol Diabetes, 117: 3-5, (2009).
22. U.S. FDA. Warns Consumers Not to Use Body Building Products Marketed as Containing Steroids or Steroid-Like Substances. c2009d. Available from http://www.fda.gov/ (accessed Oct. 6, 2009).
23. Infra-red reference spectra. In: Indian Pharmacopoeia, Vol 2, Published by the controller of publications, Delhi, Ed. 1996, pp. S-59.
24. Kar M and Choudhury PK, HPLC method for estimation of metformin hydrochloride in formulated microspheres and tablet dosages form. Indian J Pharm Sci, 71(3): 318-320, (2009).
25. Metformin hydrochloride tablet. In: Indian Pharmacopoeia, Vol 1, Published by the controller of publications, Delhi, Ed. 1996, pp. 470.
26. Kua YR, Li YC, Li KH and Jer HL, Analysis of synthetic antidiabetic drugs in adulterated traditional Chinese medicines by high-performance capillary electrophoresis. Journal of Pharmaceutical and Biomedical Analysis, 33: 329-334, (2003).