ORIGINAL ARTICLE

# Assessment of quality control parameters of multi-sourced metformin HCl sustained released tablets marketed in Nepal

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## ABSTRACT

**Background:** Availability of numerous brands of metformin hydrochloride tablets places health practitioners, pharmacists and patients in a dilemma of generic substitution. Variable clinical responses to drugs and brand-to-brand inconsistencies have been reported due to counterfeiting. The objective of the study was to evaluate quality control parameters to compare the quality, safety and efficacy of nine brands of Metformin tablets available in the Nepalese market.

**Methods:** It was a cross-sectional study. Nine brands of Metformin HCL were collected from various retailers and were assessed for their shape, size, weight and colour and they were tested for their physicochemical equivalence through the evaluation of both official and non-official standards according to the established methods. The *in-vitro* release kinetics of drugs were studied by using Zero order, First order, Higuchi, Hixson-Crowell and Korsemeyer-Peppas models based on the correlation coefficient ($r^2$) value. Descriptive statistics were calculated.

**Results:** Most of the metformin tablets were deviated by less than ±5% from the mean value except for brand I that showed a deviation greater than 7.51%. All brands showed the permissible deviation of ±5% except for brand F which showed a deviation of ±5.50. The amount of active ingredient in the solution for the metformin HCL tablets was within the acceptable range of USP limit of 65-85% for all brands except Brand B that showed slightly lower values of 63.28±1.69% after 6hrs. The cumulative amount of metformin release from the product at different time intervals were best fitted to First order and Hixson-Crowell models. Similarity factor analysis between the tablets for the release of Metformin HCL showed a f2 factor greater than 50 for all brands except brand H which showed f1 values 17.32, and f2 value 48.20.

**Conclusion:** The study showed that all the nine brands of the metformin hydrochloride sustained release tablet tested showed satisfactory results for the test employed and are pharmaceutical equivalent, except brand H as it showed dissimilar dissolution profiles to that of innovator product. As eight brands conformed to the established standards, they could be used interchangeably in clinical practice even though there was slight variation in their pharmaceutical equivalences.

**KEYWORDS:** Quality assessment, Metformin Hydrochloride 500mg, Sustained Release, Nepalese market

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## INTRODUCTION

Metformin HCL is the first-line drug of choice for type 2 diabetes mellitus.[1] It acts by decreasing intestinal absorption of glucose, reducing hepatic glucose production. It improves insulin sensitivity by increasing peripheral glucose uptake and utilization.[2] Metformin HCL is a hydrophilic drug which slowly and incompletely absorbed from the gastrointestinal tract. It has been reported that the absolute bioavailability of Metformin HCL, when given orally, is 50-60% only because of its narrow absorption window. It has a relatively short biological half-life of 1.5-6.2 hours.[3] The sustained release (SR) form of Metformin is thus designed to achieve a prolonged therapeutic effect by continuously releasing the drug over an extended period of time after administration.[4,5] It prolongs the duration of action and patient compliance is also improved.[6,7]

The extensive use of Metformin HCL SR tablets in clinical practice creates the need to monitor and ensure the quality of the various brands commercially available in the market. It will also help to know their interchangeability so that the patients can safely switch from one brand to another. The prediction of the *in-vivo* bioavailability of most oral drugs depends on the *in-vitro* dissolution studies.[8] The assessment of quality control is useful in monitoring the production consistency of batch to batch product release of each brand Metformin HCL and in comparing the quality characteristics of different brands in the market.[8] Therefore, the present study aimed to evaluate bio-pharmaceutical and physicochemical equivalence of different brands of Metformin HCL SR tablets available in the Nepalese market.

## MATERIALS AND METHODS

**Study design and setting:** A cross-sectional study was conducted in the Department of Pharmacy, Shree Medical and Technical College, Bharatpur, Chitwan, Nepal. It was ethically approved by the institutional ethical review committee (SMTC-IRC-20190812).

**Reagents and Chemicals:** All reagents used were of analytical grade. Necessary chemicals and Metformin SR tablets of various brands were purchased from the local market. Freshly prepared distilled water was used throughout the work. Monobasic Potassium Phosphate and Sodium Hydroxide were obtained from Qualikeme Fine Chem Pvt. Ltd and Thermo Fisher Scientific India Pvt Ltd respectively. Metformin HCl reference standard powder was obtained from Time Pharmaceutical Laboratory Pvt. Ltd., Mukundapur, Nawalparasi, Nepal as a gift sample for the research work. Nine different brands of metformin HCL sustained-release tablets, having label strength of 500mg were selected and purchased from registered retail pharmacies. The products were coded as A, B, C, D, E, F, G, H, and I (**Table 1**).

**Table 1: List of the metformin HCL tablets used in the study**

| Code of product | Brand name | Batch no. | MFG Date | EXP Date | Manufacturer |
|---|---|---|---|---|---|
| A | Melmet | MEBD 0200 | June 2014 | Nov 2016 | Microlab Ltd, H.P., India |
| B | Metfor | 072014 | Dec 2014 | Nov 2016 | Quest Pharma. Pvt Ltd, Bara, Birgunj, Nepal |
| C | Glycomet | 28010395 | Feb 2015 | Jan 2017 | USV Ltd, India, H.P., Baddi, Solan, India |
| D | Effimet | EET 1801 | Mar 2015 | Nov 2017 | Deurali Janta Pharmaceutcal Pvt Ltd, Dhapasi, Kathmandu, Nepal |
| E | Bigomet | M286L023 | Nov 2013 | Oct 2015 | Aristo Pharmaceuticals Pvt Ltd, India |
| F | Glyfall | 031008 | Dec 2014 | Nov 2016 | Vega Pharma Pvt Ltd, Lalitpur, Nepal |
| G | Netformin | NOTE 14008 | Aug 2014 | Jul 2016 | National Healthcare Pvt Ltd, Chhatapipra, Birgunj, Nepal |
| H | Reform | EZ14007 | Oct 2014 | Sep 2016 | Magnus Pharma Pvt Ltd, Rampur, Tokani, Bara |
| I | Formin | LPN-71061 | Oct 2014 | Sep 2016 | Nepal Pharma Laboratory Pvt Ltd, Jeetpur, Birgunj, Nepal |

The different brands of metformin HCL SR tablets were subjected to the following assessments to assess their biopharmaceutical equivalence.[6-8, 9]

**(i) Physical Inspection:** The shape, size and color of these brands of tablets were examined visually. The diameter and thickness of 5 tablets from each brand were measured using Vernier Caliper.

**(ii) Uniformity of weight:** Sample tablets (20) of each brand were weighed individually using a digital analytical balance. The average weight was determined and then the percentage (%) deviation of each tablet was calculated using the formula below:

$$\%\ \text{deviation} = \frac{[\text{individual weight of a tablet} - \text{average weight of 20 tablets}]}{\text{average weight of 20 tablets}} \times 100$$

**(iii) Hardness:** The crushing strength of the tablets was determined individually using the Monsanto hardness tester. Samples of 5 tablets of each brand were taken. Each tablet was placed between the anvils until the tablets break and the pressure required to break the tablet was then read off the machine and recorded. The average tablet hardness and standard deviations were calculated.

**(iv) Friability Test:** Twenty sample tablets of each brand were taken and then weighed. They were then subjected to abrasion using a Roche friabilator at 25 revolutions per minute. After 100 revolutions, tablets were de-dusted and re-weighed. The friability of the tablets was then calculated as the percentage (%) weight lost using the following expression;

$$\%\ \text{friability} = \frac{[\text{Initial weight} - \text{Final weight}]}{\text{Initial weight}} \times 100$$

**(v) Assay (percent drug content):** Initially twenty tablets of metformin hydrochloride SR tablet were weighed and the average weight was taken. Tablets were then powdered using mortar and pestle. Powder equivalent to 0.1g (100mg) of Metformin HCL was then stirred with 70ml of distilled water for 15 minutes using a magnetic stirrer. The resultant solution was diluted to 100ml with distilled water and filtered. The 10ml of the filtrate was pipette out and then diluted to 100ml with distilled water and 10ml of the resulting solution to 100ml with distilled water. The absorbance of the final solution was measured by a UV-Visible spectrophotometer at a wavelength of maximum absorption of 232nm. The content of metformin hydrochloride was then calculated using the calibration curve.

**(vi) In-vitro Dissolution Rate Determination:** This test was carried out using a USP dissolution apparatus–II (paddle type). The dissolution medium of 1000 ml phosphate buffer (pH 6.8) maintained at 37±0.5ºC was rotated with a fixed speed of 100 rpm. Six tablets of each brand were put in each of the six compartments and the machine operated at the intervals of 1, 2, 6 and 10hrs. To draw the dissolution profile, 5 ml of dissolution samples were withdrawn at specified intervals and replaced with the same volume of pre-warmed fresh dissolution medium to maintain a constant dissolution volume. Each withdrawn sample was filtered and the dilution was carried out up to 10ml with the same phosphate buffer and absorbance was measured at 232nm using a UV visible spectrophotometer. The concentration of each sample was then determined from the calibration curve.

**(vii) Preparation of Calibration Curve:** UV-visible Spectrophotometric method of analysis at $\lambda_{max}$ 232nm was developed with the help of calibration curve. First of all, a stock solution of concentration 10µg/ml was prepared in a phosphate buffer of pH 6.8. From this solution, other solutions of concentration (2, 3, 4, 5, 6, and 10) µg/ml were prepared with appropriate dilutions. Finally, absorbance of these solutions was determined by UV spectrophotometry at the $\lambda_{max}$ 232nm. A calibration curve showing the relationship between concentration and absorbance was plotted.[10]

**Statistical analysis:** Descriptive statistics mean, standard deviation, frequency and percentage were calculated using Microsoft Excel 2016. The data were presented as tables and graphs.

## RESULTS

The standard calibration curve was obtained by plotting the values of the concentration versus respective absorbance for each concentration from 2µg/ml to 10µg/ml of metformin HCL. The analysis for linearity showed that the solvents used in the estimation of Metformin HCL and *in-vitro* drug release were suitable and have no interference while taking absorbance in a UV-Visible Spectrophotometer. From the calibration curve, the correlation coefficient ($R^2$) values and regression equation of metformin HCL standard in phosphate buffer pH was found to be 0.997. The plotted calibration curve of SR Metformin HCL is given in figure 1.

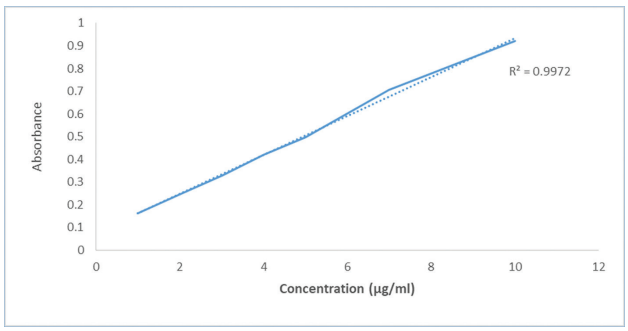


**Figure 1: Standard calibration curve of Metformin HCl tablets in 6.8 pH phosphate buffer**

**Physiochemical parameters**: Physiochemical Parameters of Metformin HCL tablets are shown in Table 2. On physical inspection, all tablets were white in color and oval in shape. Thickness assessment of the tablets showed that Brand I was thicker with thickness values of 0.931mm±0.011mm and Brand E had a smaller thickness value of 0.541mm±0.021mm. Brand C was the smallest and Brand D was the largest in size.

The weight of the tablets is given in the table 2 and it showed that most of the metformin tablets were deviated by less than ±5% from the mean value except for brand I as it showed a deviation greater than 7.51%.

Brand H of metformin HCL tablet had a minimum hardness of 4.5±0.59 Kg/cm$^2$ while brand F showed higher hardness values of 11.4±0.59 Kg/cm$^2$ (**Table 2**). All brands of the tablets had friability values less than 1%. Brand B had a maximum friability value of 0.43% and at the same time, Brand F showed minimum values of 0.14%. (**Table 2**).

**Uniformity test:** The assessment of the percentage content of active ingredient of Metformin HCL tablets is shown in **Figure 2**. All brands showed the permissible deviation of ±5% except for brand F which showed a deviation of ±5.50.

**Table 2: Physiochemical Parameters of different brands of Metformin HCl tablets (n=20)**

| Brand Name | Thickness (mm) | Length (mm) | Weight (mg) | Hardness (Kg/cm$^2$) | Friability (%) | Assay (%) |
|---|---|---|---|---|---|---|
| A | 0.86±0.054 | 1.66 | 748.1±3.69 | 6.0±0.79 | 0.33 | 98.35±1.57 |
| B | 0.91±0.011 | 1.77 | 936.4±3.201 | 9.2±0.75 | 0.43 | 95.76±1.97 |
| C | 0.63±0.015 | 1.58 | 714.65±2.39 | 9.9±0.41 | 0.19 | 104.78±4.65 |
| D | 0.66±0.016 | 1.61 | 716.95±2.37 | 10.6±0.65 | 0.27 | 104.41±3.45 |
| E | 0.54±0.021 | 1.97 | 834.1±2.67 | 9.5±0.22 | 0.28 | 103.74±3.09 |
| F | 0.66±0.015 | 1.69 | 696.3±5.601 | 11.4±0.41 | 0.14 | 96.85±5.50 |
| G | 0.63±0.015 | 1.67 | 845.15±2.62 | 9.5±0.62 | 0.24 | 93.05±4.57 |
| H | 0.66±0.010 | 1.59 | 899.05±3.67 | 4.5±0.59 | 0.33 | 99.67±2.22 |
| I | 0.94±0.011 | 1.95 | 911.7±7.51 | 6.5±0.70 | 0.15 | 94.98±3.07 |

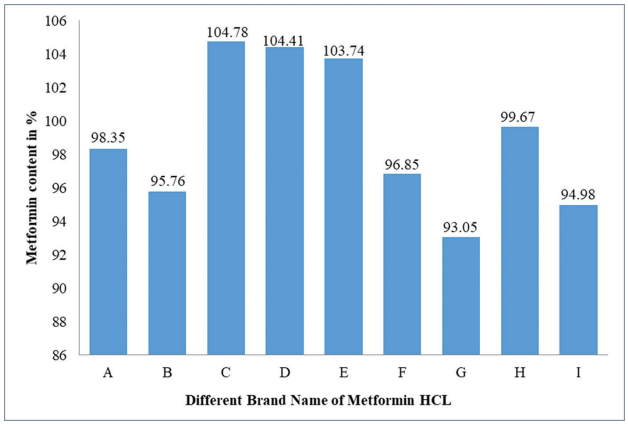


**Figure 2: Drug release profile of different brands of Metformin HCL tablets**

**Dissolution tests:** The amount of active ingredient in the solution for the metformin HCL tablets was within the acceptable range of USP limit of 65-85% for all brands except Brand B that showed slightly lower values of 63.28±1.69% after 6hrs (**Figure 3**).

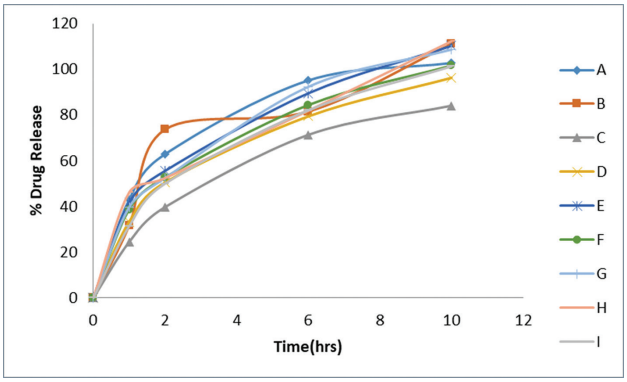


**Figure 3: Dissolution profile of the different brands of Metformin HCL tablets**

**Drug Release kinetics:** The cumulative amount of metformin release from the product at different time intervals were best fitted to First order and Hixson-Crowell models. The release mechanism exponent "n" value for different metformin products ranged from 0.3815 to 0.5401 (**Table 4**).

**Table 4: Release kinetics of different brands of metformin HCL tablets**

| Brand Name | $R^2$ | | | | | |
|---|---|---|---|---|---|---|
| | Zero-order | First-order | Higuchi | Hixson Crowell | Peppas | n Value |
| A | 0.8844 | 0.9993 | 0.9526 | 0.9759 | 0.9722 | 0.3815 |
| B | 0.8088 | 0.6894 | 0.8486 | 0.8525 | 0.8245 | 0.4687 |
| C | 0.9398 | 0.9988 | 0.9854 | 0.9826 | 0.9870 | 0.5401 |
| D | 0.9542 | 0.9968 | 0.9915 | 0.9962 | 0.9909 | 0.4544 |
| E | 0.9765 | 0.9983 | 0.9992 | 0.9999 | 0.9993 | 0.4249 |
| F | 0.9660 | 0.9999 | 0.9966 | 0.9197 | 0.9990 | 0.4217 |
| G | 0.9569 | 0.9929 | 0.9908 | 0.9952 | 0.9431 | 0.4528 |
| H | 0.9996 | 0.9926 | 0.9789 | 0.8659 | 0.9664 | 0.3869 |
| I | 0.9577 | 0.9987 | 0.9930 | 0.9198 | 0.9899 | 0.5014 |

Similarity factor analysis between the tablets for the release of Metformin HCL showed a $f_2$ factor greater than 50 for all brands except brand H which showed $f_1$ values 17.32, and $f_2$ value 48.20 (**Table 5**).

**Table 5: Calculated similarity and difference factors for different brands of metformin HCL tablets**

| Brand name | Similarity factor ($f_2$) | Difference factor ($f_1$) |
|---|---|---|
| A | 69.28 | 10.23 |
| B | 72.34 | 9.73 |
| C | 82.93 | 6.61 |
| D | 58.48 | 13.39 |
| E | 59.04 | 13.12 |
| F | 68.38 | 11.01 |
| G | 81.21 | 6.02 |
| H | 48.20 | 17.32 |
| I | 53.80 | 14.2 |

## DISCUSSION

The weight uniformity tests result of the nine brands of the metformin tablets gave the values that complied with the United States Pharmacopoeia (USP) specifications with a deviation less than ±5% from the mean value except for brand I as it showed a deviation greater than the permissible limit i.e. ± 7.51%. Hence, only eight brands of metformin tablets conformed to the specifications. Our study also revealed that Brand H had a minimum hardness of 4.5±0.59 Kg/cm$^2$ while brand F showed higher hardness values of 11.4±0.59 Kg/cm$^2$. The hardness could be more because of the amount of binder, compression force and method of granulation.[11] A friability value of less than 1% is desirable for the good quality of the tablet.[12] The results of the tablet friability test showed that virtually all the brands tested had impressive friability values as it was found to be less than 1%. Therefore, all brands of metformin tablets were mechanically stable as all met the USP standard. The assessment of the percentage content of active ingredient of Metformin HCL tablets revealed that all the brands had the values within the monograph specification of the USP.[13] Eight brands of the tablets also showed the permissible deviation of ±5% except for brand F which showed a deviation of ±5.50 which is slightly higher than the desired value.[13]

Our study showed that only eight brands of metformin HCL tablets passed the USP general specifications standard for the dissolution rate test and only one brand (code B) failed to pass the desirable limit of 65-85% after 6hrs as it showed slightly lower values of 63.28±1.69% after 6hrs. The cumulative amount of metformin release from the product at different time intervals i.e. dissolution data (from the values of 1st, 2nd, 6th and 10th hour) i.e. according to the USP specification of all brands of metformin hydrochloride sustained release tablets were best fitted to First-order and Hixson-Crowell models. For all nine brands, first order and Hixson Crowell release kinetics were predominant than the other release kinetics. From these in-vitro release kinetics mechanism studies, it might be revealed that the drug release of those brands followed concentration-dependent and describes drug release from polymeric systems in which the release deviates from Fickian diffusion. The release mechanism exponent "n" value for different metformin products ranged from 0.3815 to 0.5401 indicating fickian diffusion along with non-fickian or anomalous diffusion.

The model-independent approach of similarity, and difference factor was used to ascertain the interchangeability of the different brands of metformin HCL tablets. The similarity factor should be 50–100, and the difference factor should be less than 15 to be interchangeable.[13] Accordingly, only eight brands of the tablet can be used interchangeably with the innovator product as they had a similarity factor of >50 and difference factor of <15 and brand H (Reform) was found to be non-interchangeable.

## CONCLUSION

The results of the study demonstrated that all the products have satisfactory results although there existed slight variations in terms of weight uniformity, hardness and dissolution parameters of nine brands of metformin HCL tablets marketed in Nepal when compared with USP requirements. Only eight brands of metformin HCL tablets were bio-pharmaceutically and chemically equivalent and therefore they can be substituted with the innovator product in clinical practice; however, one brand (Reform) was found to be bio-pharmaceutically and chemically non-equivalent. Further in-vivo correlation studies could be performed on the selected brands since the drug release

performance obtained in-vitro is a likely prediction but does not necessarily mean that formulations will perform similarly in-vivo.

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