SIGNIFICANCE OF RECONSTITUTION TIME AND OTHER PHYSICAL PARAMETERS FOR EVALUATION OF DRY POWDER INJECTABLES

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ABSTRACT

Objective: The objective of the study was to compare marketed Generic and Innovator product of Meropenem for injectionnearing theshelf life.

Method: The marketed samples of Generic and Innovator Company were tested for pH, Clarity, Appearance of the product and Reconstitution time. All the samples were reconstituted and pH was determined using calibrated pH meter.

Results: No phenomenal differences in Innovator and Generic samples were observed with respect to pH and clarity,whereas phenomenal differences were seen in reconstitution time and appearance of the product. Innovator product showed fast and good reconstitution time, clarity and appearance complying with referenced pharmacopoeias.

Conclusion: The increase in reconstitution time of generic product may be due to sourcing of raw material from less regulated markets (economic source) or a different method of manufacturing employed by raw material manufacturer.

Keywords: Meropenem, Reconstitution time, Clarity and Appearance of the product.

INTRODUCTION

Meropenem is an ultra-broad spectrum Carbapenem that exerts its antibacterial activity by inhibiting bacterial cell wall synthesis through binding to penicillin binding proteins [1].Meropenem (Fig.1) is used to treat infections such as septicaemia, febrile neutropenia, pneumonias, meningitis, urinary tract infections, abdominal infections, etc. and it has least resistance potential.
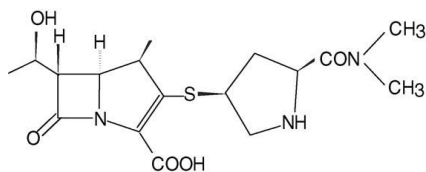

Fig. 1: Chemical structure of Meropenem

Chemically, Meropenem is (-)- (4R,5S,6S)-3-[[(3S,5S)-5-(Dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1 azabicyclo [3.2.0]hept-2-ene-2-carboxylic acid trihydrate.[1].

Meropenem is white to off white crystalline powder and pKa values are 2.9 and 7.4.It has limited aqueous solubility.It has a beta lactam ring making it susceptible to hydrolytic degradation thus necessitating its formulation as powder for injection. Meropenem for injection (powder for injection) is available as a 0.5g or 1g sterile lyophilized powder for either intravenous (IV) injection or intramuscular (IM) injection after reconstitution with appropriate infusion solutions[4].The stability of Meropenemis an important consideration if continuous infusion administration is to be used. From the manufacturer's guidelines, Meropenemis stable at room temperature for 8hours when the drug is reconstituted in saline solution. The stability of Meropenemreconstituted in solution is influenced by the following factors:

a. **Storage temperature:** The drug is stable for longer time in solutions stored at 4° to 5°C than in solutions stored at 21° to 26°C.

b. **Type of fluid for reconstitution:** The drug reconstituted in normal saline solution is stable for a longer time than the drug reconstituted in 5% dextrose in water.[6].

Most of the raw material for manufacture of Meropenem for injection is imported from less regulated countries since they are cost effective.

The raw material is imported only when the manufacturing company follows current Good Manufacturing Practice standards set by the federal agencies. From India, DCGI (Drug Controller General of India) inspects the facility of the importer periodically before giving approval to a pharmaceutical manufacturing facility and then approves for the import of the raw material.

Meropenem powder for injection has to be reconstituted just before use with sterile water for injection or saline solution for administration as I.V bolus or infusion. Complete reconstitution within short period of time is very important whereas incomplete reconstitution of the product indicates the stability issue of the product which will have direct implications on patient'shealth and safety.The stability of the product can be assessed by evaluating various parameters like Reconstitution time (In House test), pH of the reconstituted solution, clarity, discoloration of product, water content etc. The objective of present study was comparative evaluation of various parameters like Appearance, pH, Clarity & Reconstitution time between generic and innovator products of Meropenem for injection 1g. This comparison is done before the expiry date of the product (i.e.,products nearing expiry date) to find out the efficiency and quality of product till the end of the shelf life. For this study, near expiry samples were randomly procured from retail pharmacy.

MATERIALS AND METHODS

Materials

Generic & Innovator finished product

Five formulations of Meropenem for injection marketed by generic and Innovator Company were procured from retail pharmacy.

Other requirements

pH meter (EUTECH pH 510), magnifying lens, black and white background, syringes, water for injection, standard buffer solutions, virgin white paper for inspection, Proper illumination for inspection.

Methods

Method of reconstitution

Reconstitution was carried out using 20mL of sterile water for injection for 1g Meropenem powder for injection. Before reconstitution, vial has to be checked with respect to flip off seal integrity and any other observations. After removing the flip off, 20mL of water for injection was injected into the vial through the rubber

stopper using a sterile syringe. The vial was then shaken vigorously until all the powder had dissolved and no particles were present.The criteria used to attain consistent end point to define full reconstitution was no apparent particulate matter and clear solution [3]. The time taken for complete reconstitution was noted and this test was performed randomly using 5 generic and 5 innovator samples.

Determination of pH

The pH of reconstituted solution was determined potentiometrically by means of a glass electrodeand a reference electrode using a pH meter. The pH meter was calibrated using standard buffer solutions before measuring the pH of reconstituted solutions.

Determination of clarity

Samples were reconstituted as per the directions stated on the label or pack insert leaflet. Clarity of reconstituted solutions was observed against a visual inspection board with a black and white background under sufficient illumination. Presence of black particles can be seen using white background whereas any white particles and fibers present can be observed against black background.

RESULTS AND DISCUSSION

The United States Pharmacopoeia (USP) 2006 [2]., defines completeness of reconstitution as the state where the solid dissolves completely, leaving no visible residue as un-dissolved matter or the constituted solution is not significantly less clear than an equal volume of the diluent or purified water present in a similar vessel and examined under similar conditions.

Reconstitution time of both Innovator and Generic product was depicted in the given Table 1.

Table 1: Reconstitution time and pH of Innovator and Generic product

Vial No.	Reconstitution time (seconds)		pH of Reconstituted solutions	
	Innovator Product	Generic product	Innovator Product	Generic product
1	20	170	7.78	7.81
2	21	181	7.80	7.80
3	25	215	7.79	7.74
4	22	165	7.81	8.10
5	23	210	7.81	7.95

Innovator product dissolved very quickly in sterile water for injection showing a reconstitution time of 20seconds.Reconstitution time of the generic product ranged from the 160 to 210 seconds.

This comparison of reconstitution time between innovator and generic product can be clearly understood with the help of graphical representation Fig.2.
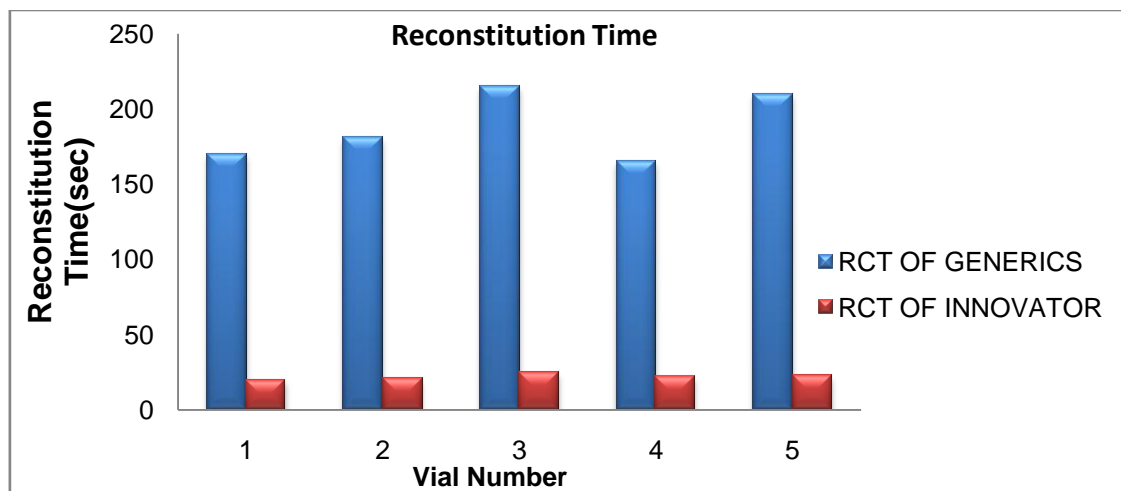

Fig. 2: Comparison of Reconstitution time of Generic and Innovator product

According to the Indian Pharmacopoeia (I.P) 2007 [5],the pH range of reconstituted solution of Meropenem for injection should be in the range of 7.3 – 8.3.If the pH is out of this range it indicates the changes in chemical properties of the drug or any other degradation or contamination which is threat to the patient. The pH values of both generic and innovator products are comparable and all the values are within the range as prescribed in I.P (Table 1).Innovator product shows a pH range of 7.78 to 7.81 whereas the generic products show a pH range of 7.74 to 8.10.Phenomenal variations in pH are observed in case of generic products Fig.3.

Meropenem powder for injection exists in the form of crystalline powder.This crystalline form of the drug affects properties like aqueous solubility, reconstitution time and chemical stability. The color of the product mainly indicates chemical stability. According to I.P, the product should be white to off white crystalline powder.

Innovator product is white crystalline powder whereas generic product is off white in color(Table 2).The color development of the reconstituted solution indicates formation of degradation products and itaffects the stability of product after reconstitution(Table 2).The reconstituted solutions are pale yellowish in color and the color of the generic product reconstituted solution is more yellowish when compared to innovator product.This observation was more prominent in generic product than in innovator product.

Clarity of the reconstituted solution is determined to observe whether the solid had dissolved completely without leaving any visible residue in solution. It also helps to determine the presence of any foreign particles or other contaminants like fibers and charred black particles. Innovator product is very clear when compared to generic product however both innovator and generic product did not contain any foreign particles or contaminants.

Packaging quality of finished product is determined by visual inspection. USP specifies that "containers, including the closures for dry powder solids intended for parenteral use,do not interact physically or chemically with the preparation in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale and use." The packaging quality differences seen between Innovator and Generic product are shown in Table 3.From the table it is clear that overall packaging quality of innovator product is very good when compared to generic product.
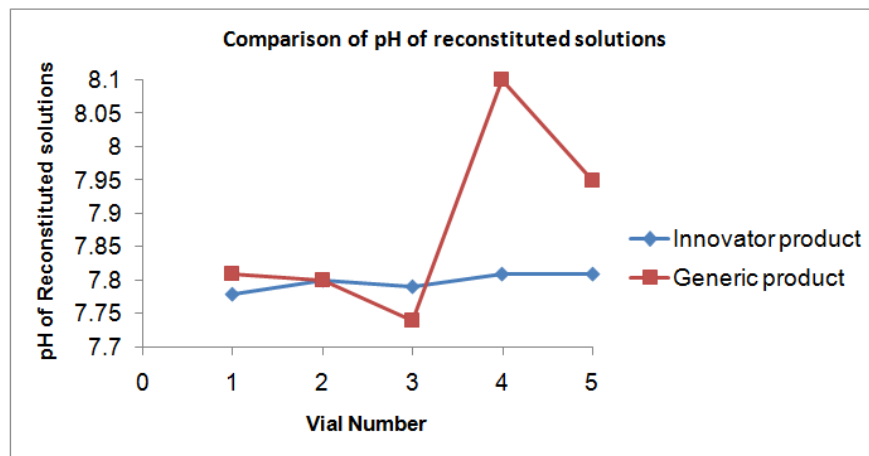

Fig. 3: Comparison of pH of Reconstituted solutions of Innovator and Generic product

Table 2: Appearance of dry powder for injection and color of Reconstituted solutions of Innovator and Generic product

Vial No.	Appearance of the product		Color of reconstituted solution*	
	Innovator product	Generic product	Innovator product	Generic product
1	White	Off-White	Pale yellow	Yellow
2	White	Off-White	Pale yellow	Pale yellow
3	White	Off-White	Pale yellow	Yellow
4	White	Off-White	Pale yellow	Pale yellow
5	White	Off-White	Pale yellow	Yellow

*Reported only for information purpose

Table 3: Comparison of finished product package of Innovator and Generic Product

S. No.	Innovator product	Generic product
1	Uniform spreading and adhesion of label quality is good	Wrinkles and uneven adhesion of label is observed
2	Quality of batch coding on the label is acceptable and good	Smudging of print with respect to batch over coding detail is observed
3	Flip off seal contains "flip off" imprinting	Flip off seal contains "logo and name" of generic company
4	Meropenem powder is not adhered to the inner side walls of the vial and the powder is free flowing	Meropenem powder is adhered to the inner side walls of the vial and the powder is not free flowing
5	Shelf life – 4 years	Shelf life – 2 years

CONCLUSION

From the results, it is evident that phenomenal difference between generic and innovator product is observed in terms of reconstitution time and appearance. Reconstitution time for generic product is very high when compared to innovator product. This implies that generic product is not efficient and user friendly as that of innovator product. The difference may be because of variations in the physico-chemical properties of input raw material obtained by the generic company which is usually imported from less regulated markets as they are cost effective and economic. Finally to conclude, establishing proper limits for input sterile raw material will help in controlling the reconstitution time of generic product throughout its shelf life.

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