

Heavy Water Board to Scale New Heights in “Non-Nuclear Applications of Deuterium/Heavy Water”

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Abstract

This article offers an overview of the developmental activities taken up by Heavy Water Board (HWB) on non-nuclear applications of heavy water/deuterium/deuterium depleted water. It also includes recent in-house projects, collaboration with industries, collaboration with academics, marketing prospects of heavy water, way forward etc.

Keywords: *Non-Nuclear Applications, Deuterium, Heavy water*

1. Background

Heavy Water Board (HWB), an industrial unit of Department of Atomic Energy (DAE), is engaged in the production of heavy water and specialty materials required by DAE. HWB through its four operating plants has ensured self-sufficiency in availability of heavy water for the country's nuclear power programme based on Pressurized Heavy Water Reactors (PHWRs) being set up by Nuclear Power Corporation of India Ltd (NPCIL). HWB has also executed several orders for export of heavy water. After meeting the requirement of heavy water, the mandate of HWB has been enlarged with production of specialty materials for DAE. This includes development of synthesis route/technology for production of solvents required for closed nuclear fuel cycle activities, development and deployment of technology on industrial scale for production of special materials, such as nuclear grade sodium, enriched boron compounds, boron carbide pellets for Fast Breeder Reactors (FBR) in the second phase of Indian Nuclear Power Programme (INPP). Development and deployment of new processes, technologies, systems and equipment in frontier areas of relevance to DAE *viz.* recovery of value metals like cobalt, gallium, rare earth material *etc.*, from the secondary resources is yet another objective of HWBs enlarged mandate.

HWBs mandate includes develop and deployment of spin-offs, allied and separation technologies on industrial scale for lighter molecules in particular, like production of oxygen-18 enriched water, hydrogen, helium etc; identifying and promoting non-nuclear uses of heavy water/deuterium, as deuterium labeled compounds for industrial and medical applications.

Way back during 2002-2004, HWB took the initiative to validate the published data on thermostabilization of Oral Polio Vaccine (OPV) in heavy water medium, in collaboration with Enterovirus Research Centre (ERC) - Mumbai. Though, it was successfully demonstrated that OPV in heavy water medium can retain its potency at much higher temperature compare to that in normal water medium, this benefit could not be potentially exploited for actual application due to other issues. However that was not the end, as it triggered the beginning of our journey towards-Developmental work on non-nuclear applications of heavy water and deuterium.

Deuterium exhibits a subtle but distinct difference in behaviour when substituted in place of hydrogen in various compounds, primarily due to the kinetic isotope effect [1]. The Deuterium Isotope Effect (DIE), is due to difference in zero-point energy between a bond with D and the corresponding bond with H. The higher mass of the deuterium atom gives rise to stronger bonds. The isotope effect modifies the kinetics of chemical/bio-chemical reactions, which leads to many gainful applications in bio-science and advanced technologies. These applications are called in a broader term as 'Non-Nuclear Applications' (other than nuclear application of heavy water in pressurized heavy water reactors).

The applications include metabolism studies, NMR solvents, deuterated drugs/Active Pharmaceutical Ingredients (APIs), optical fiber, semiconductors etc.

Non-nuclear applications of heavy water picked up momentum in recent years as was clear from the increased number of inquiries received by HWB for supply of heavy water in bulk quantity to private industries for a wide range of applications *viz.* in NMR solvents, in medicinal chemistry, in optical fiber etc.

2. Development of deuterated compounds by HWB

HWB as a part of its diversification programme has taken up development of D-labeled compounds including NMR solvents. Presently all the compounds are being imported in the country. It was felt prudent to have development of these compounds in order to exploit the demand and also to keep the country in the forefront of such technologies. HeavyWaterPlant (HWP), Baroda laboratory took up the activity of setting up the facility for in-house



Figure 1: Deuterated Products by HWB marketed by BRIT

developments of methods for deuterium labeling of hydrogen bearing compounds like CDCl_3 , DMSO-d_6 , acetone- d_6 , acetonitrile- d_3 , benzene- d_6 , etc. (Fig. 1) under the DAE approved XII Plan R&D project of BARC. HWB successfully executed the project. Hands on experience in process selection, process optimization, quality control for development of deuterated compounds has been achieved through this project [2]. Till now this facility (Fig. 2) is being utilized for synthesis of deuterated NMR solvents under applied R&D and products are being marketed through Board of Radiation & Isotope Technology (BRIT), DAE.



Figure 2: Set up for Deuterium Compounds synthesis

3. New Projects of HWB

Recently DAE has approved the project titled “Development of Deuterated APIs and therapeutic use of Deuterium Depleted Water”. This project envisages in-house deuterium depleted water generation facility, with various concentrations of deuterium depleted water and off-grade heavy water up-gradation facility. This project includes few collaborative sub-projects with research Institutes viz. MS University Baroda, Advanced Centre for Treatment, Research, Education in Cancer (ACTREC), Kharghar.

In process of exploiting the potential of non-nuclear application of deuterium and heavy water, it is understood that Deuterium Depleted Water (DDW) can also demonstrate its usefulness in medical application [3]. Accordingly, HWB persuaded ACTREC to take-up the R&D work on application of DDW in cancer treatment. HWB took the responsibility of supplying the DDW of varying concentration required for the study. Phase-I study has shown the possibility of its therapeutic effectiveness on certain breast and lung cancer cell lines.

In the phase-I study, it was reported by ACTREC that, exposure to altered deuterium concentrations in water (both lower or higher deuterium strength) have shown altered cell proliferation, survival, colony formation ability or migration ability. The effect was found to be more favorable and consistent for breast and lung cancer cell lines, tested. However, wide variation in cell line to cell line, with respect to the above mentioned cancer cell properties signify cell type specific effect.

The encouraging results of phase-I instigated us to take up phase-II activities. The new project with ACTREC is expected to identify key changes in terms of cancer properties for a wide variety of breast cancer cell lines. This project is likely to establish the anti-cancer potential of DDW, if any. There are various experiments planned to assess if DDW adds any value as an additive, during standard cancer treatment procedures. This study is expected to benefit in defining a simplified therapy for breast and lung cancer patients in future. These study will reflect on the possibility to design clinical protocols in future.

A deuterated compound can have significantly different metabolic stability and/or pharmacokinetics compared to its non-deuterated version of the compound [4]. Deuterium modification affects the biological fate of certain drugs that are metabolized by pathways involving hydrogen-carbon bond scission.

Cancer chemotherapy has been one of the major medical advances in the last few decades. Many drugs used for this therapy have a narrow therapeutic index. In the recent past, deuteration has become an efficient tool in drug design. It is expected that experimentation with strategic introduction of deuterium into the structures of organic compounds will enable future development of a variety of novel drugs and chemical tools. In selective cases, deuterium incorporation into an API will have certain merits of lower dose, improved safety profile and unparalleled predictability of its effects.

Envisaging the potential benefits of deuterium incorporation in medicinal chemistry, a project titled “Synthesis and Biological Evaluation of Deuterated Analogs of some Antineoplastic drugs” has been taken up with Department of Pharmacy, MS University Baroda. Scope of the project includes identification and designing of the deuterated analogs of certain antineoplastic drug, development of protocol for the synthesis of the desired compounds, characterizations and biological evaluation etc.

Another New project titled “Augmentation of production of Deuterated compounds at HWP-Baroda” is also going to be initiated. This project is for augmentation of in-house production of deuterated NMR solvents/reagents. This will facilitate reduction or stoppage of imports of such chemicals and make the same available in the country. This project envisages units for production of chloroform-d, DMSO-d₆, acetone-d₆, acetonitrile-d₃.

4. Collaborative agreement with Indian Private Parties

HWB has entered into collaborative agreement with two Indian Parties, M/s Clearsynth, Hyderabad and M/s SyNMR, Bangalore for development of deuterated NMR solvents, reagents, APIs and other value added products. Both the parties have made good progress in the intended work, using heavy water supplied by HWB. Both the parties have developed many deuterated products which have been sold out by the parties generating revenue during last year and as per the agreement 5% of revenue is being paid to HWB as royalty.

5. Collaborative developmental work

To promote applications of deuterium in medicinal chemistry, HWB took initiative to identify and take up project through existing Department of Atomic Energy (DAE)-Institute of Chemical Technology (ICT) Centre.

Subsequently few sub-projects have been taken up with ICT, Mumbai viz. Modified Deuterated Polyphenols as Chemotherapeutic & Anti-microbial agents, Bio enhanced & targeted Drug Delivery System of Deuterated Mitocurcumin etc. Notable progress has been



Figure 3: Signing of collaborative agreement with M/s SyNMR

made by ICT in these projects and HWB has supplied deuterated precursors required for the project.

Under this project, several polyphenols with reported therapeutic activities of interest (anti-cancer/anti-bacterial) have been identified for modification. This novel mito-polyphenols have been purified and structure have been elucidated by spectroscopic methods. Biological evaluation has been carried out for few of the synthesized polyphenols. Deuteration of several phenolic compounds has been attempted using different synthetic methods. Deuterated vanillin and deuteratedmito-vanillin were synthesized and structures have been characterized by spectroscopic methods. Metabolic studies of these compounds are ongoing.

Process optimization has been done to the existing method for synthesis of mitocurcumin. Process for synthesis of deuterated curcumin and deuterated mitocurcumin has been established. Various analytical methods for characterizing the synthesized compounds have been developed.

Initial experiments for metabolic stability of curcumin, deuterated curcumin, mitocurcumin and deuterated mitocurcumin have been carried out and development of new techniques for biological evaluation are under progress.

6. Supply of D₂ Gas

Under government initiative of National Optical Fibre Network (NOFN) project “BharatNet”, it is expected to connect all gram panchayats in the country and have an information super highway, through creation of a robust infrastructure. As a result, there has been announcement of capacity expansion in the optical fibre industry and the requirement of deuterium-nitrogen gas mixtures is expected to go up. HWB has also ventured into information technology by supporting optical fiber industry by supplying deuterium gas enhancing signal transmission characteristics, with reduced loss of intensity and better transmission efficiency.

HWP-Baroda is having the bench scale facility for production (Fig. 4) and filling of deuterium gas in cylinders at high pressure. HWB executed many orders for supply of D_2 gas/ D_2 - N_2 gas mixture to the leading companies viz. M/s Air Liquide, M/s Sterlite Technologies Ltd, M/s Six Sigma Gases India Pvt Ltd etc. for application in Optical Fibre Industry. HWB also supplies D_2 gas to academic institutes/private industries for research purpose.



Figure 4: Deuterium gas generation facility at HWP Baroda

7. Marketing of Heavy Water

HWB is promoting research and commercial activities by supplying heavy water within the country. During last 2 years, substantial quantity of heavy water has been supplied to various users viz. M/s Sigma Aldrich, M/s SynZeal, National Center for Biological Sciences-Bangalore, IIT-Bombay, IIT Roorkee etc. Demand of heavy water for non-nuclear applications is consistently increasing and number of users in the country has also been on the rise.

8. Export Opportunity

In the recent past HWB has exported heavy water to countries like USA, France for non-nuclear applications. Recently M/s Iwatani, Japan, M/s Linde Electronics and Specialty Gases, USA, M/s Dupont, USA etc. approached HWB for supply of heavy water. Deuterium market play a vital role in chemicals/materials industry. There is a growing demand for high quality heavy water to boost the research and developmental activities in non-nuclear applications world-over.

9. Regulatory aspects of Heavy Water and Safeguarding

The issue and utilization of deuterium/heavy water necessitates appropriate licensing and compliance to the Atomic Energy rules and regulations. Appropriate end user certificate is mandatory and HWB audits the use of the same. Any bulk supply requires thorough evaluation of the work of the users, by team of HWB/DAE regarding facilities and expertise available with the users.

10. Deuterium Depleted Water

Deuterium Depleted Water (DDW) is another field that is gaining prominence due to reported benefits for its application in therapeutic uses mainly in cancer treatment as adjuvant therapy. DDW with various deuterium content is available in international markets. HWB being

the largest producer of heavy water has the capability of producing large quantities of deuterium depleted water and supply the same at various concentrations ranging between 30 ppm to 120 ppm for societal purpose.

There exist a huge market for DDW both in India and abroad. HWB is receiving frequent enquiries (including export) for supply of bulk quantities of DDW for commercial products development, mainly as potable water. Recently HWB supplied substantial quantity of DDW to various users in India for processing it into value added potable deuterium depleted water. HWB has geared up to tap the market for commercial activities with DDW.

11. Way Forward

Applications of deuterium in non-nuclear field are diversified at large. To reach out to the society, HWB is putting efforts to enter in to new horizons by taking up various research projects on developmental work on applications of deuterium in medicinal chemistry/biological field in collaboration with academics/research institutes/industries,utilizing the deuterium resources as well as knowledge base available in the country.

Non-nuclear applications of deuterium have already taken a shape, which is becoming more tangible day by day. Indian industry as well as academics has unique opportunity to grow in this field. It is possible to accelerate the research and industrial scale activities in this field with collaborative efforts. HWB takes a lead to catalyze the research and development in this direction.

Field of deuterium applications has broad spectrum and it is difficult for a single organization to cover all the field of applications. HWB is therefore, putting effort to transplant idea to the expert organization through collaboration to get the best outcome on the subject.

As per data available, there are only few countries who are presently into manufacturing of deuterium oxide. Number of global sources for heavy water is reducing with heavy water plants in other countries near in entering shut down. There is a huge scope for HWB to play a key role in the global market of heavy water in near future by tapping the benefits of changing market trends for this market. HWB has demonstrated its core competence in field of heavy water production technology and is widening its horizon in line with the HWBs enlarged mandate of identification and promoting non-nuclear uses of heavy water/deuterium as deuterium labeled compounds for industrial and medical applications.

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