

# Some Suggestions on Conduct of Sellable Drug Delivery Research in Academia

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## Abstract

Despite that huge amount of drug delivery research is being carried out by academia in India, the faculty and students tend to miss out on essentials for making their technology sellable. Hence, there are no takers of their research output and efforts. This note provides some suggestions for bridging the gap.

**Keywords:** Academia, Drug Delivery Research, Sellability, Elements, Success

## Introduction

It is said that academia is powerhouse of innovation and it can contribute significantly to Industrial product launches. That is very true, in particular, of drug delivery systems. Majority of faculty in almost every institution in our country is into it, pursuing the same as a key area of research. The issue is whether the research done on drug delivery systems in the four walls of our institutions is sellable? Equally big question is whether local or global industry is showing interest in research output from Indian academia and picking the same to launch innovative products?

In practical, the same is negligible, considering the total research effort being made, and actual translation of academic research into commercial products. In fact, sporadic news of academic successes appears in the newspapers from time to time, but that is it, without actual success in the practice.

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So why drug delivery research from Indian academic institutes is not sellable? Where is the gap? This write-up attempts to provide certain suggestions that can help fill the space to some extent.

## Types of drug delivery research carried out in academia

Based on training and experience, faculty members in academia usually opt to carry out research in one or more of the following areas related to drug delivery systems:

- i) Systematic investigation of phenomena
- ii) Exploration of the use of new materials
- iii) Investigation of utility of existing technology for a drug where no previous report exists
- iv) Modification of existing technology for improved functionality
- v) Development of new drug delivery technology (platform technology), etc.

The issue is whether all these types constitute sellable research. Yes, except the first, the industry may be interested in the remaining.

Also, there is long list of drug delivery areas where one can work upon, but maximum interest of industry remains in injectable, transmucosal, targeted and delayed release systems (Fig. 1) [1].

### **A typical example of a sellable drug delivery research**

A typical example is an oral insulin delivery system, which is an urgent unmet need, but success has been eluding till this time. In India, M/S Biocon, Bangalore jumped into it, is still on the job [2], and even in the middle it picked up M/S Bristol Myers Squibb as a partner [3], but the good news is yet awaited, due to delay in the project [4]. World over, the effort is being done, both in academia and industry, and too many research papers and reviews also have been published. But patients are still eagerly waiting when they would be freed from the cycle of painful subcutaneous injections. The difficulty is to make sure that the drug reaches the bloodstream intact, which by no means is an impossible hurdle.

A review entitled 'oral insulin delivery: how far are we?' by Fonte et al. [5] summarizes the effort as follows: *'Oral delivery of insulin may significantly improve the quality of life of diabetes patients who routinely receive insulin by the subcutaneous route. In fact, compared with this administration route, oral delivery of insulin in diabetes treatment offers many advantages: higher patient compliance, rapid hepatic insulinization, and avoidance of peripheral hyperinsulinemia and other adverse effects such as possible hypoglycemia and weight gain. However, the oral delivery of insulin remains a challenge because its oral absorption is limited. The main barriers faced by insulin in the gastrointestinal tract are degradation by proteolytic enzymes and lack of transport across the intestinal epithelium. Several strategies to deliver insulin orally have been proposed, but without much clinical or commercial success. Protein encapsulation into nanoparticles is regarded as a promising alternative to administer insulin orally because they have the ability to promote insulin paracellular or transcellular transport across the intestinal mucosa.'* The review covered

different delivery systems intended to increase the oral bioavailability of insulin, with a special focus on nanoparticulate carrier systems, as well as the efforts that pharmaceutical companies were making to bring to the market the first oral delivery system of insulin. The toxicological and safety data of delivery systems, the clinical value and progress of oral insulin delivery, and the future prospects in this research field were also scrutinized.

So any researcher who is successful to contribute innovatively in any aspect of oral insulin delivery research has huge scope of making a big kill. However, to take such promising research to a higher level, one needs to be cautious from the very start.

### **The essentials for development of a sellable drug delivery system**

#### 1. Identification of the unmet need

The above example of insulin oral delivery is a pinnacle unmet therapeutic need for development of a novel drug delivery system. Yet there may be many more disease areas and drugs, where a delivery system might be a significant therapeutic necessity. The researcher has to pick up the thread, by first understanding the disease mechanism and then mechanism(s) by which the drug acts against the disease. The exact necessity shall be identified: whether to alter the pharmacokinetics, pharmaco-dynamics, requirement for targeting like in anti-cancer drugs, reduction of drug dose and alteration of dosage frequency, and/or improved stability. Of course, one has to find a very strong reason to select a particular type of drug delivery system, which is most suitable for achieving the expectation. Eventually, a justified and convincing research project with a commercial appeal has to be proposed.

The success of the project would require building up of knowledge space with respect to the unmet need and possible mode of

fulfillment. For it, one must carry out complete survey of the literature and of the patent resources, have full understanding of physicochemical properties of the drugs and proposed materials, and gain knowledge of all aspects related to the possible drug delivery system. Among the possibilities, one can use novel materials, employ existing technology with and without modification (of course must be non-infringing with respect to the proposed system), or involve development of new platform technology. The latter is always an attractive proposition for industry [6].

## 2. Planning for experiments and procuring of materials

A critical planning is required for preparation of the delivery system at laboratory scale and its subsequent evaluation. For the same, all key materials must be procured along with their Certificates of Analysis (COAs). Preferably, these shall be of the quality that may be available eventually at industrial scale. Before initiating experiments, one must organize all facilities for quality assessment, functionality tests, and all in vitro and in vivo studies.

## 3. Requirement for documentation of all activities

The COAs shall be systematically filed. It is important that all study plans are duly documented before start of the experiments. Also, Standard operating protocols, standard testing protocols, etc. shall be prepared and followed, as applicable. The experiments need to be properly recorded in a laboratory note-book, whose format must be standard, with each page numbered and signed by the student and supervisor. There is a definite trend towards use of e-note books [7], and if facility is available, the same shall be preferred. All details of experiments shall be entered on the date they were conducted. Instruments with print-out facility, even in case of the simple equipment

like balances, pH meter, etc. shall be preferred. Recording of all instrument outputs shall be done systematically by duly pasting them as a part of Results in the laboratory notebook. A fool-proof system of archival of records needs to be developed in the laboratory.

## 4. Training of team members

In an academic environment, usually research faculty handles multiple projects at a time, based on the number of students being guided. He/she always likes to be in tune with the time, but might not be personally trained in every research project area. So it is left to the student to plan and execute his/her research. Herein lies the problem. The student might not also be trained, and as a learner, may not be immaculate with respect to requirements of sellable research. So the leader of the group must clearly explain objectives, share the approach in clear terms, and insist on building knowledge to the maximum, including search of patents. The students need to be explained how to fill laboratory notebook and make entries as per the standard procedure. All necessary precautions need to be explained before-hand. If the training on certain experiments is not available in-house, external training shall be arranged for critical experiments.

## 5. Considerations important with respect to the formulation

Carrying out sellable drug delivery research means developing of a novel formulation, which shall be non-infringing to existing technologies. Other important considerations are whether the drug is a small molecule or a biomolecule; and whether the proposed formulation type would be solid (lyophilized) or liquid. The quality of drug used is an added consideration here, e.g., insulin purchased from Sigma Aldrich and sources from product manufacturer may differ in activity due to differential purity. The next aspect is correct strength of drug in formulation. In normal way,

drug delivery systems tend to reduce the dose, but surprisingly studies exist where insulin dose for oral delivery had been taken ten times than the injected dose, which is irrational. Such delivery system may become unaffordable for patients, whenever it is commercialized. A related issue is with respect to the entrapment efficiency, for which the targeted ideal value shall be pre-established, or the value minimally acceptable shall be defined. Here important is to check the reproducibility, by carrying out multiple experiments. It is recommended that the polymers and other formulation excipients preferably shall be from United States Food and Drug Administration's Generally Regarded As Safe (GRAS) list [8], otherwise for any new excipient, there would be need to 'self affirm' the safety, which means subjecting it to extensive safety studies. Also, one shall target in advance on acceptable drug release behavior from the formulation and its mechanism, keeping in view the expected pharmacodynamics and optimal action at the target site.

#### 6. Considerations with respect to process involved in developing the formulation

While finalizing plan for the formulation development, one has to envisage that the process involved is industrially viable. The focus also should be on process optimization, and the final yield, whether it is sufficient to take the formulation forward. In true sense, the process shall have minimal number of steps. The acceptability of the delivery system by industry enhances if the conversion and scale-up is possible with the already available equipment. This calls for critical scalability assessment. In the present era of Quality by Design (QbD) requirements, one shall also plan formulation development involving critical elements of QbD, as enshrined in International Conference on Harmonisation (ICH) guidelines Q8-12 [9].

#### 7. Stability of drug and formulation integrity

While the formulation development is taking place, it is prudent to look into drug's inherent stability, and its degradation profile. This is important for establishing stability of the drug in the formulation environment. Also, important is basic integrity of the formulation itself. One must verify that there is no chance of drug release before actual delivery at the site, which may be the cause of failure during in vivo studies.

#### 8. Analytical methods for quality evaluation of the formulation

Multiple methods of analysis are needed at various stages of drug delivery system development. The first is for assay of the drug, which can be simple and may find application in the determination of entrapment efficiency and drug release. More complex procedure may be required for determination of the drug from the formulation. Therein, an effective sample preparation procedure is important. The same shall allow extraction of the drug to the maximum. Due to variety of drug delivery systems, the analytical method and sample preparation protocol developed for one may not be extendable to others. So here ingenuity is required during analytical method development. Of course, one must have documented evidence that the developed methods did pass the test of validation, as enshrined in regulatory and/or compendial guidelines.

During stability studies on the developed formulation, the additional expectation from an analytical method is an assurance that it is also stability-indicating in nature, which means that the degradation products are well separated from the drug and among themselves. This is a still bigger challenge as the extraction procedure involved in sample preparation shall focus not only on quantitative recovery of the drug, but also on the degradation products, likely to be formed during stability testing.

There should be fitting method(s) available for assessment of other quality parameters of drug delivery systems, like particle size and aggregation.

In industry, the comparison of developmental formulation with a reference listed drug or product is given due importance. If the developmental formulation is a non-infringing generic formulation, then choice of reference listed product must be done as per industry norms.

#### 9. Practical issues concerning in vivo animal studies

In vivo studies on developmental formulation in academia are usually limited to animal models. Here it is important that most fitting animal species is selected for the study. While making project proposal for the animal ethics committee, it might be required to justify the animal species selected, choice of male or female animals, and the number of animals required per group. Some disease models, like cancer, are associated with high mortality of animals; or there might be failure in development of diabetes in multiple animals per group, and hence at the end, only limited number of animals might be available for testing of the formulation. Such restricted study might lead to incorrect result analysis and may call for redoing the same. Also, there are some studies, where samples are taken from the same set of animals at multiple time points, but some other type of study models require separate group of animals at different time points. Decision also shall be taken on whether to use fast or fed animals, the time period at which food is to be given post start of the study, and

whether animals need to be provided with low or high fat diet. Some evaluations may require genetically modified animals, so they might be needed to be procured on time. Another key issue is decision on the end point, whether to look for drug bioavailability in the blood (e.g., analysis of insulin in the blood), activity (e.g., glucose lowering) or both. Hence all these aspects must be critically considered, while planning for in vivo studies. Ethics committee approval of animal study protocol must be obtained and shall be available on record. Revalidation studies must be done in restricted manner, based on the outcome of previous study. It must be kept in mind that superfluous studies are strongly objected by animal ethics committees.

#### 10. Revalidation studies

The supervisor should not have absolute confidence on single study done by a student. So it is best is to go for a check on reproducibility of the results for sellable research/technology. The same shall include both in vitro and in vivo experiments. The revalidation must be done by including students/personnel from inside and outside the group.

#### 11. Considerations with respect to costing

While developing a sellable drug delivery system, one must not ignore the cost aspect of the formulation under development. The tentative cost of the formulation to the patient shall be assessed after taking all kinds of expenses, including drug and excipients, conversion and packaging costs, patent filing/maintenance costs, etc.

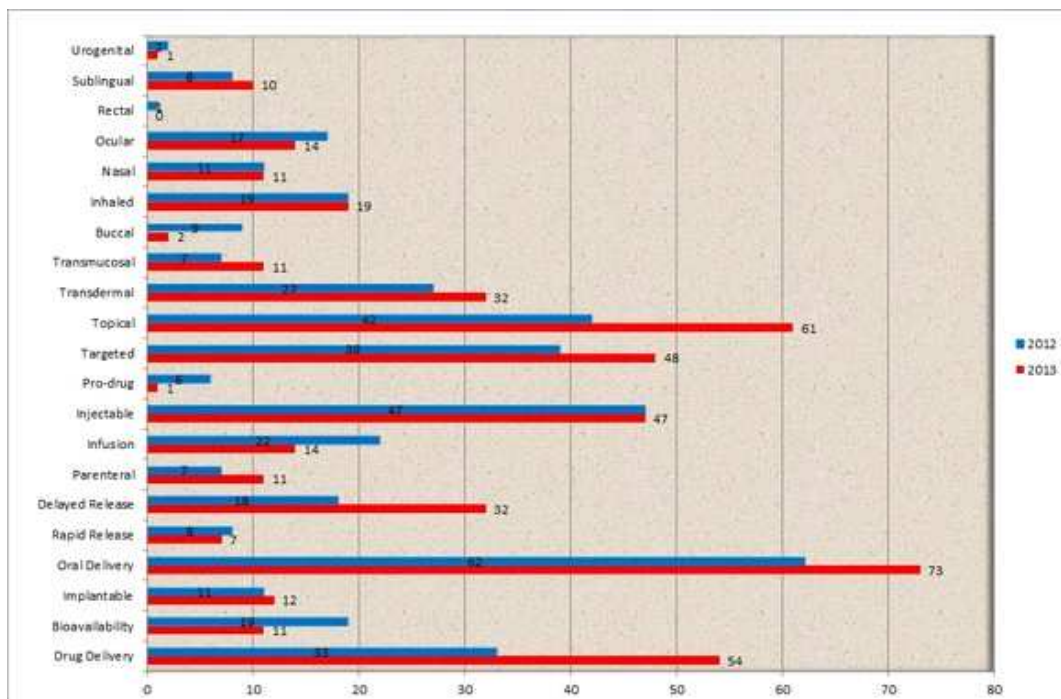


Figure 1. Number of deals made by healthcare industry in different drug delivery areas in 2012 and 2013 [Sourced from Reference 1].

The same shall be compared with the conventional dosage form.

## 12. Other essentials

One shall never shy from taking expert opinion at any stage. Also, the supervisor must be vigilant at each step of research conducted by the student. Equally important is timing of patent filing, and contacting with clients.

### Transition of drug delivery systems from academia to industry

Table 1 summarizes the academia to industry transition of drug delivery research. Once the delivery system is developed and characterized by the academia, and industry shows interest in it and takes it over, then the latter is bound to re-develop the same through its own approach. When the same is found to be promising, only

then the technology is transferred for scale-up. As discussed above, the first preference of industry is towards platform technology developed by academia. The industry then will like to use it, and transform the same into product for delivering different drugs. Generally the development time for a mature platform technology in academia shall take 3-5 years, while industry with its multiple Research and development teams acts more quickly and reaches the technology transfer stage within 2-4 years. Due to richer experience of industry in commercializing the products, the chance of success in hands of industry is higher as compared to the academia. In general, the academia shall protect its research through Patent Cooperation Treaty (PCT) application, while the interest of industry always is to file regional applications to protect specific markets.

Table 1. Roles of academia and industry in drug delivery research [Courtesy Dr S. Arora, Ex-President R&D, Ranbaxy Laboratories Limited, Gurgaon].

	<b>Academia</b>	<b>Industry</b>
<b>Scope</b>	Development and characterization	Development and technology transfer
<b>Innovation</b>	Platform technology	Product specific
<b>Development time*</b>	3 – 5 years	2 – 4 Years
<b>Success potential</b>	Medium	High
<b>IP Rights</b>	World wide	Market specific
<b>Royalty</b>	2-5%, 7 Years	10-15%, 15 Years
<b>Future Potential</b>	Long term	One time

\*Clinical trials and regulatory approval time not included.

The academia, by selling the patent to industry, can enjoy royalty between 2-5% for up to 7 years. And as academic research is a continuous activity, and if the research is innovative, then there is endless scope of its commercialization. The industry always looks for short-term gains and hence might be restricted in its overall approach, unlike the free intellectual inputs possible in academia.

### Conclusion

There is ample scope for academia to develop and transfer drug delivery technologies to industry [10]. However, the academia must understand industry and regulatory requirements, and shall take care of them from the very start of the identified research project. It is hoped that the elements discussed above, though not absolute, might help in some way to improve the sellability of drug delivery research done in academic laboratories.

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