International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

A Study of the Process of Identifying New Dugs and Enabling Ways

Dr. Suryadevara Ramakrishna

Vice -President, Sarvani Labs Pvt Ltd

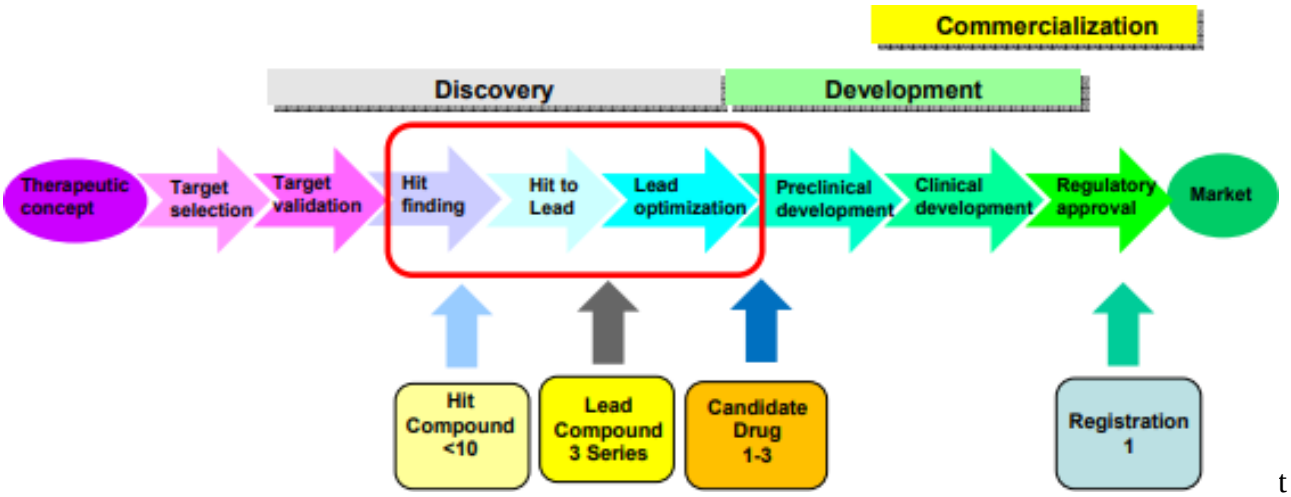
ABSTRACT

The selection of clinical candidates, their synthesis, and characterization for therapeutic efficacy are all steps in the drug discovery process. This method underwent tremendous development over the past 50 years, beginning with a chemistry-centric approach and progressing through a more biological one to one that is more disease-specific. The development of molecular biology, along with improvements in screening and synthetic chemistry techniques, has made it possible to combine random screening with knowledge of the biological target. Although a strategic need drove this change, the astounding technological developments in chemistry and biology made it possible. The features of the new molecular entities will be refined during the course of numerous iterative screening runs required for this process, and the best balanced compounds will then move on to in vitro and in vivo testing in the selected disease model. 100 hits are thought to be found out of every 100,000 compounds tested. Only one of these 100 hits moves on to the lead compound stage. Most of these lead compounds—between 40% and 60%—fail ADMET testing. Despite the fact that the human genome project has revealed numerous unique and clinically verified targets in recent years, fewer new drugs are being launched, and the overall costs associated with developing a medicine are dramatically growing.

KEYWORDS: Drug, Medicine, Human, Compound

INTRODUCTION

High-throughput screening (HTS) and/or computational drug design are typically used to complete the "Hit finding" step of the process of discovering a new treatment for a specific disease through the interaction with a selected target (Figure 1). In order to uncover novel chemical entities with a relatively high probability, HTS is conducted on libraries that are sufficiently broad and diverse. Finding a molecule that will interact solely with the specified target and not with other related targets is the main objective of HTS, and it serves this purpose by demonstrating how selective the compounds are for the selected targe



t

Figure 1 shows how drugs are discovered in the third millennium.

Hits are evaluated and studies are run to weed out non-specific hits during the hit validation stage. To define the develop ability profile for promising hits and to identify SARs (Structure- Activity Relationships), it is crucial to screen related molecules. Following their validation, the "hit to lead" campaign can begin, with a specific set of requirements that must be completed in order to launch a lead optimization project. This contains a variety of ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) qualities to be optimized in addition to activity criteria.

Pharmaceutical and biotechnology businesses are under intense pressure to consistently create novel, distinctive medicines that are less expensive to research and develop. Drug development is still a time-consuming, expensive, challenging, and ineffective process with a low rate of new therapeutic discoveries, in spite of technological advancements and improvements in our knowledge of biological systems. Currently, it takes 10–14 years to develop and sell a medicine, and each novel molecular entity (NME) costs about US$1.8 billion to produce.

Compounds can now be produced at a higher rate thanks to new and innovative technologies for synthesis, work-up, and isolation. The so-called "Enabling Techniques" 1 evolved over the previous ten years and have received much academic study. Both the hit validation and lead optimization processes can now use them. These methods compile numerous conventional and cutting-edge approaches that have been created to quicken synthetic transformations and, more crucially, to simplify the workup and product isolation.

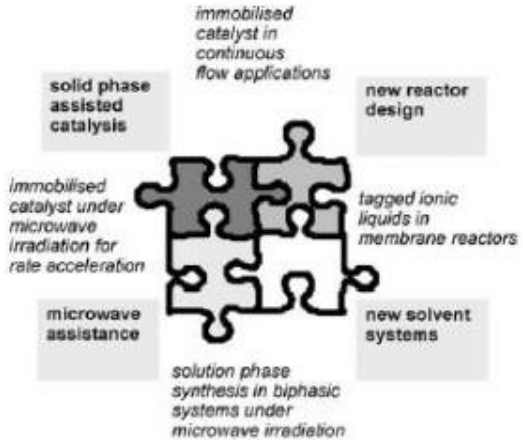


Figure 2 Facilitating Methods

When it comes to the most important technical advancements, polymer-assisted solution-phase synthesis (PASPS), microwave assisted organic synthesis (MAOS), and, more recently, continuous-flow techniques have had the biggest impact. The literature has given these technologies a lot of attention, and they have shown that they have the potential to increase productivity in organic synthesis and medicinal chemistry.

Process of discovering new drugs and enabling methods

Solid-supported reagents and scavengers have recently gained popularity in research chemistry (starting in the second half of the 1980s) because they allow for the simplification of both synthetic processes and isolation or purification steps, while avoiding the drawbacks of solid- phase synthesis. The work-up activities are greatly simplified and reduced to straightforward filtering when using PASPS as opposed to conventional synthesis, which is the most notable change. This eliminates the need for further purification processes and allows for the use of a significant excess of reagents, which are frequently required to push reactions to completion. Immobilization of toxic, noxious, or hazardous chemicals and their by-products prevents their release into the solution, enhancing their general acceptability and safety profile. It is conceivable to combine species that are incompatible in solution to perform one-pot transformations that are not feasible under conventional homogeneous conditions because of the site isolation of reagents on the resin bead.

MAOS, or microwave-assisted organic synthesis has emerged as a leading tool for the efficient synthesis of new chemical entities, the quick optimization of processes, and the identification and investigation of novel chemical reactivity. The primary technology behind MAOS is the

Microwave dielectric heating effect, which effectively warms materials. The use of microwave irradiation has many benefits, including: higher reaction temperatures through the use of microwave heating in conjunction with sealed vessels; quicker reactions, higher yields, and cleaner reaction profiles; the use of lower boiling point solvents under pressure in sealed vessels; the targeted heating of strongly microwave-absorbing metal catalysts; more repeatable experimental conditions through precise control of temperature and pressure professional.

The rate of many organic reactions is drastically accelerated by MAOS (from days to hours and from hours to min), which generally increases the yields of the final products. This has been demonstrated to significantly increase productivity4. A wide range of reactions have benefited from MAOS, and organic reactivity with microwaves has been thoroughly investigated. This has all started with early reports of microwave-promoted Suzuki coupling. In fact, high-speed microwave-assisted chemistry has been used to successfully conduct a wide range of organic reactions, including cycloaddition reactions, heterocyclic synthesis, processes utilizing transition metal catalysts, solvent-free reactions, and nearly all chemical transformations requiring heating. Because traditional procedures for work-up and purification of reaction products slow down the overall process, increasing reaction rates frequently did not boost productivity. Anyhow, MAOS may be advantageously coupled to inorganic-supported solvent- free conditions, which would ease work-up operations (in many situations, the pure expected products might be obtained straight by simple extraction, distillation, or sublimation), as well as waste disposal. Similar to this, MAOS and PASPS, or solid-supported organic synthesis, can be used together. In order to achieve high conversions, the synthetic processes requiring polymeric supports typically necessitate more runs and longer reaction durations than the corresponding solution-phase methods. Once more, microwave heating enables faster reaction times and better loading of Because traditional procedures for

work-up and purification of reaction products slow down the overall process, increasing reaction rates frequently did not boost productivity. Anyhow, MAOS may be advantageously coupled to inorganic-supported solvent-free conditions, which would ease work-up operations (in many situations, the pure expected products might be obtained straight by simple extraction, distillation, or sublimation), as well as waste disposal. Similar to this, MAOS and PASPS, or solid-supported organic synthesis, can be used together. In order to achieve high conversions, the synthetic processes requiring polymeric supports typically necessitate more runs and longer reaction durations than the corresponding solution-phase methods. Using not just conventional polystyrene supports but also soluble polymers and fluorous phase synthesis, the functionalized solid support.

Continuous flow organic synthesis is one of the "Enabling techniques" that is attracting attention and shifting from a purely academic level to a larger research and development exploitation. This evolution is seen in the rise in the number of reactions that have been successfully carried out using this method and documented in the literature. Pharmaceutical companies are embracing flow methodology in drug discovery programmes more lately, thanks to the development of commercially available micro/meso flow reactors, drawn by its potential advantages over the pre-existing batch methodologies. Many typical organic transformations, spanning from liquid-liquid to solid-liquid-gas systems, have been shown to benefit theoretically and practically from being performed under micro/meso continuous flow. Because the reaction conditions established in a micro reactor can be directly transferred to production scale without the need for re-optimization, either by running the flow-reactor for an extended period of time or by using multi-channel parallel reactors, continuous-flow processes, in particular for pharma companies, are very appealing.

In flow chemistry, a chemical reaction is carried out in a stream of fluid that is continuously flowing through a system of interconnected channels. Where the channels converge, the fluids come into contact, and the reaction occurs. The following basic elements are typically found in flow reactors: one or more fluid control devices, which load the solutions of various reactants into the reactor section, the reactor, which can typically be heated or cooled, allowing reactions to take place under precise temperature and pressure control, and suitable reservoirs to collect the resulting mixture (Figure 3).

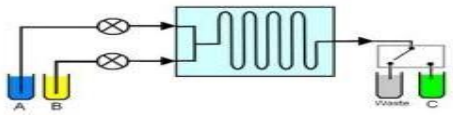


Figure 3 shows the general layout of a flow reactor.

On the basis of channel size and volume, laboratory sized flow reactors may generally be split into two major classes: micro- and meso-flow reactors. Micro-flow reactors have channels with a diameter of 10 to 1000 m, whereas meso-flow reactors have bigger channels with a diameter of up to 1000 m, however this distinction is not always clear-cut.The fundamental distinction between these two types of machinery has to do with the reactors' shapes and production methods.

DISCUSSION

In particular, photolithography and micro-patterning techniques from the semiconductor microelectronics industry are used to design and manufacture micro-flow reactors, which are typically planar objects the size of a small plate, or "chips." A number of different microreactors have been

created recently, and some of them are being sold commercially. A microreactor's applicability is determined by its size, the chemical and physical characteristics
of the material used to build it, and the method employed to introduce reagents and solvents into the system. Figure 4 presents a few different microreactors to show the variety of miniaturised reaction devices that have been documented thus far. There have been a variety of materials employed, including glass, silicon, stainless steel, metals, and polymers.

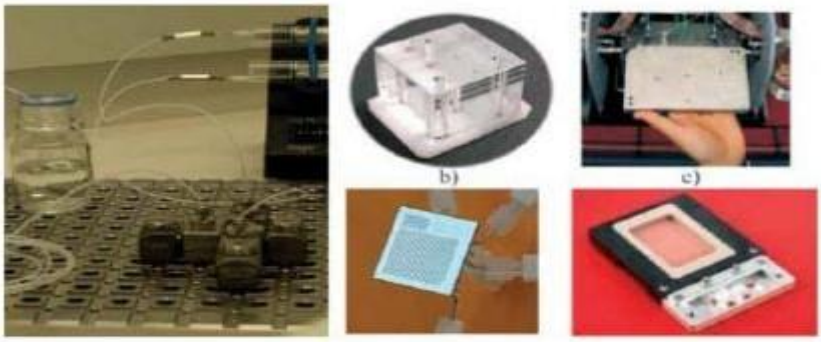


Figure 4 shows silicon-based microreactors, glass microreactors, and stainless steel microreactors in order of appearance

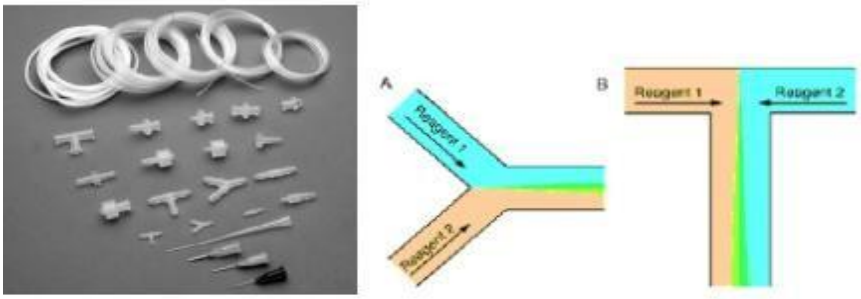


Figure 5: T- or Y-shaped connectors in meso-flow reactors made of PTFE

As all the properties listed apply to both categories of micro- and meso-flow reactors, the name "microreactor" (MR) will be used to refer to both types of reactors. In microreactors, the fluid behavior is primarily non-convective, with "laminar flow" and mixing determined only by diffusion. All flow reactors require precise fluid control, which is accomplished using one of two major methods: hydrodynamic flow or electrokinetic flow. The former, also known as pressure-driven flow, is frequently related to peristaltic or syringe pumps that impart a positive pressure to the system's input. These devices' extensive compatibility with any solvent and any building material is their key benefit. Hydrodynamic flow has a parabolic shape, which can
cause non-homogeneous residence times since the flow is quicker in the channel's center and slower towards the sides (Figure 6).

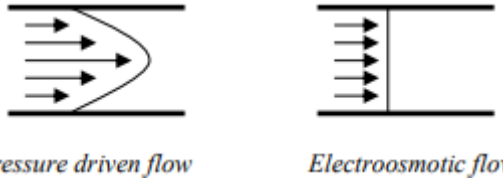


Figure 6 shows the velocity profiles for electroosmotic and pressure-driven flow.

The application of a potential difference at the system's ends is related to the alternate electrokinetic

flow. The immediate migration of ions in solution towards the electrode with the opposite charge is the initial effect of this. Electroosmotic flow, the second element of electrokinetic flow, results from the electrical double layer that develops on channels with charged surfaces. Glass and silica surfaces have a negative charge at neutral to basic pH due to the partial ionisation of surface hydroxyl groups. Positive species in the solution create a second layer close to the channel's surface in reaction to the negative surface charge. Viscous friction between the moving ions and the remaining solution generates net flow of the fluid towards the negative electrode when an electric potential is provided between the channel ends, causing the mobile positive ions to migrate towards the negative electrode.

Precision in fluid handling is made possible by the linear relationship between the velocity of electroosmotic flow and the applied voltage. When compared to hydrodynamic flow, the velocity profile in this example is essentially flat across the channel, considerably reducing reagent dispersion. Unfortunately, only polar solvents like water, methanol, acetonitrile, dimethylformamide, and tetrahydrofuran and device materials like silicon, glass, and treated PDMS (Polydimethylsiloxane) may be used with electroosmotic flow.

CONCLUSION

A sizable number of laboratory scale gadgets were commercialised in recent years. Although the majority of the fundamental characteristics listed in this paragraph are present in all instances, producers added additional features to give the end user the widest possible range of applications. These additional features include the ability to use solid catalyst or polymer- supported reagents, gaseous reagents (for example, for hydrogenations and carbonylations), and more reactors in parallel or in series. The use of more complicated devices, combining two or more distinct approaches to take use of their unique advantages, was described in certain examples in the literature. Examples of microwave flow reactors and photochemical flow reactors stand out in this regard.

REFERENCES

1. C. A. Hone and C. O. Kappe, Chem. Methods, 2021, 1, 454– 467
2. J. Britton and T. F. Jamison, Nat. Protoc., 2017, 12, 2423– 2446
3. N. J. W. Straathof, Y. Su, V. Hessel and T. No¨el, Nat. Protoc., 2016, 11, 10–21
4. C. R. Sagandira, M. Siyawamwaya and P. Watts, Arab. J. Chem., 2020, 13, 7886–7908 5 G. R. D. Prabhu and P. L. Urban, Chem. Rev., 2020, 120, 9482–9553
5. K. P. L. Kuijpers, W. M. A. Weggemans, C. J. A. Verwijlen and T. No¨el, J. Flow Chem., 2021, 11, 7–12.
6. B. König, P. Kreitmeier, P. Hilgers and T. Wirth, J. Chem. Educ., 2013, 90, 934–936
7. M. B. Plutschack, B. Pieber, K. Gilmore and P. H. Seeberger, Chem. Rev., 2017, 117, 11796–11893.
8. S. Han, M. A. Kash□pour, M. Ramezani and M. Abolhasani, Chem. Commun., 2020, 56,10593–10606
9. G. Laudadio, Y. Deng, K. van der Wal, D. Ravelli, M. Nuño, M. Fagnoni, D. Guthrie, Y. Sun and T. No¨el, Science, 2020, 369, 92–96
10. D. Ravelli, S. Protti and M. Fagnoni, Acc. Chem. Res., 2016, 49, 2232–2242 12 L. Capaldo, D. Ravelli and M. Fagnoni, Chem. Rev., 2022, 122, 1875–1924
11. 13 F. Raymenants, T. Masson, J. S. J. Orduna and T. No¨el, Chemrxiv, 2023, DOI: 10.26434/chemrxiv-2023-jbjh2