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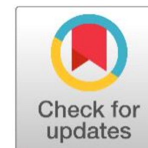
Review Article:

Cell line culture in pharmaceutical development and application: A review



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Abstract

Background: The involvement of conventional animal testing to determine how medications affect a biological system comes with many challenges. In the past few decades, A number of methods have emerged to accomplish these objectives, one of which is cell line creation technology which has dramatically increased the usefulness and efficiency of drug discovery research. Cell culture is the term used to describe the removal of cells from an animal or plant and their subsequent cultivation in a lab setting. The Caco-2 model is commonly used in the early stages of drug discovery to make decisions about permeability, absorption or both of tested chemicals. It is evident that novel 3D cell culture models offer enormous potential for disease modeling, medication's efficacy and safety assessment. However, the challenges provided by the inherent traits of Caco-2 cell variants and inter-laboratory methods have led to the development of irreducible data. **Conclusion:** These restrictions affect the extrapolation of findings from preclinical research to clinical investigations on drug-drug and herbal-drug interactions.

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1. Introduction

1. Permeation and Transport mechanism

The small intestine of humans is specially designed to carry out tasks like initial and selective barrier activity, nutrient absorption, host-microbiome interactions, and control of the gut, host, and immunological responses. Anatomy and physiology of the gastrointestinal tract (e.g., pH environment), in addition to physico-chemical characteristics of the drug and the type of dosage form (such as capsules, solution, emulsion, tablets), determine the oral intake of natural and artificial compounds (1,2), which ultimately affects their bioavailability. Many researches and reports highlight that 90% of orally administered drugs have low bioavailability due to inefficient gut absorption, hampering their ultimate therapeutic efficacy (3).

Once a new drug has been identified and characterized, the determination and validation of an appropriate biological response, the study of pharmacokinetic parameters (absorption, distribution, metabolism and elimination of drug molecules) is one of the most important steps in discovery and development (4). The ability of the material to be absorbed in the intestine is subject to two primary limitations., these are:

- Ability to penetrate the epithelial mucosa
- Gastrointestinal passage, since the gastrointestinal passage can only be evaluated in vivo, all *In vitro* systems can only determine mucosal permeability.

The primary obstacle to absorption of compounds is the intestinal epithelium, and there are numerous ways to

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penetrate this wall. Solute molecules travel through the cytoplasm and across the apical membrane using the passive transcellular pathway (**Figure 1**), and it is the primary route for hydrophobic chemicals to transport through the basolateral membrane (5).

The close connection of enterocytes forms the paracellular route, another passive pathway. Small hydrophilic molecules are primarily transported via the paracellular route. The intestinal mucosa also expresses a large variety of transporters, which may help with either intestinal absorption (influx) or the ejection of molecules from cell cytoplasm. Impulse transporters boost intestinal absorption, whereas efflux transporters have the opposite effect(6).

According to FDA strategies, numerous methods can be employed to determine a drug's gastrointestinal tract permeability. These include: human pharmacokinetic studies; *In vivo* human gut perfusion studies, intestinal perfusion research conducted in living or in situ using the proper animal models; *In vitro* permeation studies using dissected human or animal intestinal tissue; or *In vitro* permeability studies through a monolayer of cultured epithelial cells, such as Caco-2 cells (7). In addition to human pharmacokinetic studies, the harmonized ICH guidance document currently only recommends Caco-2 permeability studies.

This review mainly summarized the transport and absorption mechanisms, the challenges and limitations of the Caco-2 cell models and the general applications of these models.

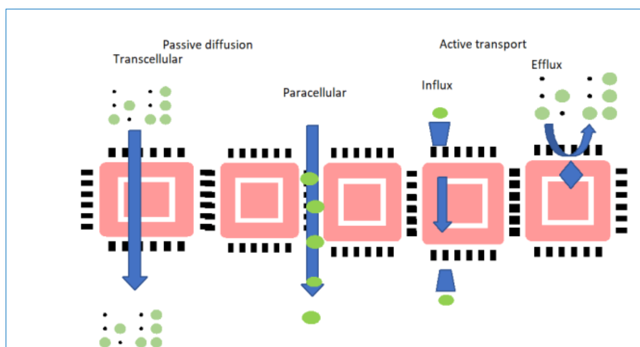

Figure 1. A visual representation of the various intestinal drug transport mechanisms

2. Cell line models

Many monolayer cell types that mimic the human intestinal epithelium have been established and are gaining admiration. These simulations employ rapidly expanding immortalized cells in confluent monolayers and differentiate spontaneously. Therefore, these monolayer models represent an ideal system to study drug absorption from the gut. Quite a lot of cell lines have been used to model uptake in humans, including Madin Darby Canine Kidney (MDCK), TC-7 (Cac-2 Clone), Human Colorectal Adenocarcinoma Cell line (HT29-MTX), Intestinal Epithelial Cell line (IEC) and the most popular, Caco-2 cells (8).

From cancer of the cervix, the first human cell lineage, HeLa, was established in 1951. In the 1960s, human diploid cells were developed for the production of vaccines; despite the absence of suggestive phenotypic characteristics, concerns regarding a latent oncogenic agent delayed their acceptance. Numerous viral vaccines are currently made with human diploid cells. However, animal cells have persisted the preferred substrate for the production of recombinant proteins and, monoclonal antibodies (mAbs) this is due to their quick development, high protein production, and systemic investment (9).

Particular human respiratory and nasal epithelial cell culture systems, like the (EpiAirway) and (MucilAir) systems, have recently been created to assess human nasal permeability in vivo.

These systems are available for use and display three-dimensional simulations of goblet cell, mucociliary tissue and healthy human bronchial and tracheal epithelial tissue (10).

Co-culture systems are another form of these commercial systems that can be used to estimate the toxicity, virus infection, and other factors like human nasal permeability. Particularly, the *In vivo* phenotypes of barriers, mucociliary responses, infection, toxicity responses, and disease are adequately represented by these systems (11).

Therefore, these systems can be utilized in a variety of experiments and are useful tools for studies of nasal absorption. However, these culture systems are difficult to use due to limitations such as cost and time lag especially, the manufacturer of EpiAirway says that the product can be stored for up to three days at 4 °C, including the delivery time of tissues, and the longer storage times are not suggested unless absolutely necessary (12).

To evaluate the gut permeability of herbal medicines and dietary supplements, researchers and pharmaceutical companies use cellular assays like Caco-2 cells and (MDCK); lipid-based artificial systems, such as the Parallel Artificial Membrane Permeability Assay (PAMPA) (13), and the Caco-2 cell line, created from human colon cancer, is regarded to be the most widely used in vitro model for studying and predicting drug absorption in the gut (14) .

In 1989, the Madin-Darby Model Dog Kidney (MDCK), a cell culture model meant to take the place of Caco-2 cells, was initially identified. Particularly for medications that absorb passive ions, the Caco-2 model and MDCK monolayer cell models are closely similar (15).

2.1 Characterization of Caco-2 cells

Since MDCK cells are produced from canine kidney cells, as opposed to Caco-2 cells, which are derived from human colon cancer cells, the expression levels of various transporters may vary between the two cell lines. Indeed, MDCK cells derived from sources other than humans and nuclear cells can be deemed dysfunctional. Compared to Caco- 2 cells, they express fewer transport proteins and have lower metabolic rates (16). These variations in substrate activity might be brought on by variations in the relative expression levels of total P-gp in Caco-2 and MDCK cells, as well as variations in how substrates are distributed throughout cell membrane bilayers (17).

Enterocytes that have undergone the naturally occurring differentiation into polarized cells with apical and basolateral surfaces and stably anchored tight connections

with appropriate culture. The expression of certain cytochromes (CYPs), isoenzymes, and phase II enzymes, as well as brush border enzymes and other functions unique to normal enterocytes, are all seen in polarized cells (18).

The model is additionally used to identify drug transporter substrates and/or inhibitors, in addition drug-drug interactions involving both novel and well-established chemical entities are also investigated using the Caco-2 cell line, and for investigation the pharmacological interactions between current and novel chemical entities, the Caco-2 cell line is utilized. The routine uses of the Caco-2 cell in the assessment of biopharmaceutical properties of some drugs, such as herbal remedies, in dedicated research laboratories, however, requires dependable processes in order to yield consistent results (19).

Cell lines can be employed as primary cells since they are extracted directly from tissues and organs and share the same genetic makeup, shape, and patterns of protein expression as in vivo cells. They have a fixed lifespan, which means they can only survive a specific number of passages, and they are extremely sensitive to anything that occurs during cultivation. Secondary cell lines have some form of immortalization, suggesting that they might be immortal (20).

One of its limitations is the requirement that cells from cell culture models be grown on filters for a number of weeks before being used in drug transportation tests. For example, Caco-2 must normally be cultured on filters for three weeks without the best growing circumstances before it can be employed for transport medication trials (21).

2.2 Metabolic enzymes in Caco-2 cell lines

Caco-2 cell lines, which exhibit the morphological and biochemical characteristics of differentiated adult enterocytes and goblet cells, are helpful in examining the development and function of intestinal epithelial cells. The well-known Caco-2 cell monolayer technique can be used to directly assess the drug fluxes that go through an epithelium (22).

Metabolic enzymes and P-gp are also recommended for predicting the absorption of oral drugs. Sulfotransferases, UDP-glucuronosyltransferase, and glutathione S-transferases are among the metabolic enzymes found in the Caco-2 monolayer (23). Cytochrome P450 3A4 (CYP3A4) is either completely absent or modestly expressed in Caco-2 cells. However, the CYP3A4 gene can be transfected or the active vitamin D metabolite 1,25-dihydroxyvitamin D3 can be added to the cells to increase CYP3A4 levels (24). These cells have also been used to examine the rates of CYP3A4-mediated metabolism and modify P-gp activity in order to study the interaction between transporters and enzymes.

2.3 Uses for Caco-2 cell monolayer

2.3.1. Drug permeability screening

Because of how well the Caco-2 cell monolayer matches the human intestinal barrier in terms of morphology, polarity, and the expression patterns of transporters and enzymes, it is commonly used to estimate drug permeability in the intestine and the percentage of the dosage absorbed (Fa) (25).

Studies of in vitro Caco-2 permeability for drugs that are passively absorbed correspond well with measurements of human intestinal permeability, while this correlation is significantly weaker for drugs that are delivered in part by carrier-mediated pathways. When compared to passively absorbed compounds under those conditions, permeability measurements for carrier-mediated drugs were shown to be significantly higher in humans than in Caco-2 due to the lack of P-glycoproteins (P-gp) and multi-drug resistant (MDR) proteins (26).

Caco-2 cells were used as a permeation model to study passive diffusion, active transport and efflux, and paracellular permeability of Dronedarone Hydrochloride-Loaded Proliposomes (27).

2.3.2. Recognizing the mechanics of transfer

The Caco-2 cell monolayer contains the majority of the known intestinal transporters in a rank order or pattern that is similar to that of the small intestine, making it valuable for research into the mechanism of intestinal drug absorption and drug-drug interactions (DDI) (28).

An *in vitro* cell-line-based intestinal barrier model would be very helpful for more in-depth study into the molecular and cellular mechanisms of engineered nanoparticle (ENP) absorption and transepithelial transport, as well as for animal-free higher throughput screening (29).

When examining the transport method for various materials using cellular-based models, the transepithelial resistance (TEER) is generally utilized to address the integrity of the monolayer (such as Caco-2 monolayers). A change in tight junctions, which is connected to paracellular transport, is shown by a change in TEER. Studies that reject paracellular modes in favor of transcellular modes generally use TEER and other paracellular permeability markers (30).

Caco-2 cells were used to study the absorption mechanism of a polysaccharide, which was obtained from Curcubita monistha, that could improve the type 2 diabetes partly associated with pancreas and liver of inflammation by the mean of urinary metabolomics (31).

2.3.3. Gene expression upon exposure to drugs or substances that mimic drugs

Gene expression has been widely utilized to discover metabolizing enzymes in the human intestine, despite the fact that it is commonly known that results do not necessarily quantitatively correlate with protein and activity. It was discovered that mRNA for CYP2E1, CYP3A4, and the mucosa of the stomach, duodenum, colon, and rectal all expressed CYP3A5. It has been observed that Caco-2 cells express low amounts of CYP3A4, a critical enzyme involved in the metabolism of gastrointestinal drugs. Subcloning, transfection of CYP3A4 or nuclear receptors, or the addition of CYP3A4 inducers to the culture media can all help to further improve this (32).

Caco-2 cells are regarded as a crucial in vitro experimental system for the assessment of oral drug permeability and P-gp-mediated efflux, but not for enteric drug metabolism, due to their absence of indigenous drug metabolizing enzyme activity (33).

1,25-Dihydroxyvitamin D3, the vitamin D receptor's natural ligand, activates the receptor to encourage its

translocation into the nucleus for the formation of the VDR-RXR (retinoid X receptor) heterodimer. This heterodimer can bind to the vitamin D response element located within the regulatory region of the target gene and change the target gene's transcription. In Caco-2 cells, VDR is expressed in large amounts. One great model for studying CYP3A4 gene induction in response to VDR is Caco-2 (34).

A study was searched about how 1,25-Dihydroxyvitamin D3 and verapamil affected the transport and metabolism of adefovir dipivoxil in a Caco-2 cell monolayer (35).

2.3.4. In Vitro Systems for Toxicity Screening

If new medications are examined for toxicity in the proper *in vitro* cell lines, only a few animal model toxicity tests are necessary. Toxicology studies on cell lines can be assessed by testing the substance on a number of cell types for which cell lines are accessible. The outcomes of this cell line toxicity testing could point to potential pharmacological treatments for the type of cancer under investigation. Cytotoxicity assays are extensively used in the pharmaceutical industry to test substances for biosafety and to evaluate the possible antitumoral effect of chemotherapy medicines (36).

In vitro toxicity assessment at the normal cellular level can now be expanded using enhanced epithelial cell culture and normal cells from human induced pluripotent stem cells (hiPSC).

Neuronal cells, cardiomyocytes, endothelial cells, hepatocytes, and cardiomyocytes produced from hiPSC are all in demand. These techniques will be used in the future to assess heart and liver cells and reduce toxicity in whole animals (37). Caco-2 cells are widely used to predict intestinal drug absorption in vitro. The toxicity of excipients and formulations used, on the other hand, can artificially increase drug permeation by damaging cell monolayers, resulting in different results (38). Caco-2 cells were used to investigate the cell toxicity and biocompatibility of betamethasone micro- and nanoparticles (39).

2.3.5. Using cancer cell lines for drug screening

It is helpful to test cancer drugs on cancer cell lines since they are comparable to the original tumor. They can be simply replaced and serve as an inexhaustible source of auto-replication for studies. Cancer cell lines are used in drug development to get consistent experimental outcomes.

One of its shortcomings is that they can be cross-contaminated with Hela cells. During study, they may lose genetic stability and homogeneity and become contaminated with bacteria and mycoplasma. Additional challenges are presented by long-term cancer cell line proliferation (40).

The majority of human cell lines are derived from cancerous tissues as well as healthy adult or embryonic tissues and normal epithelium-derived cell lines are immortalized by virus transformation or recombinant DNA constructs (41).

Cell culture system models can be distinguished from two- and three-dimensional (2D and 3D) cell cultures. Drug discovery has historically relied heavily on and accepted 2D models. Adherent 2D culture cells develop as a monolayer in a specialized culture flask or a Petri dish attached to a plastic surface (42).

The fundamental appeal of 2D cultures is their simplicity, rapid culture creation, and minimal maintenance costs. Despite this, 2D cultures face many difficulties; for example, adhesive culture cannot express the interactions between cells and their extracellular environments, which are crucial for cancer research, and it cannot replicate the organic structure of tumors.

Under 2D culture conditions, cells lose their diverse phenotypic and their morphology changes, which has an impact on their activities and cell signaling and limits the ability to replicate cellular architecture and cell-to-cell and cell-to-matrix connections (43).

Three-dimensional (3D) cultures provide a more realistic model of in vitro cancer cell cultures.

They are either scaffold-based models (in which cells interact with a substrate) or scaffold-free models (in which cells are unable to attach to a surface, forcing cell aggregation and spheroid formation) (44).

Comparatively, 3D cultures more closely resemble the in vivo communication network, allowing for improved toxicity screening and medication response and efficacy evaluation. Another benefit of the 3D model is that it eliminates the ambiguity caused by species variances (45).

It has been established that cell-culture-based assays considerably complement other technologies and are a more economical and effective option than conducting tests on novel medications and upcoming pharmaceuticals (46). Cell-based assays are actively contributing to research into the biological mechanisms, secondary interactions, and chemical activity of these studies, despite the fact that they are widely used in experimental settings for the goal of directly and indirectly evaluating nanotoxicity.

Due to its compliance with miniaturization and capacity to provide diverse sets of data, high-throughput screening (HTS) is being utilized to explore cell cultures in a variety of settings and to build a variety of cell-based assays for nanoparticle research (47).

2. Conclusion

Caco2-cells exhibit a variety of characteristics, it may perform as a crucial platform for pharmacokinetic parameters, cytotoxicity, and permeability research by minimizing the usage of animal models because it contains cytochrome P-450 enzymes, transporters, microvilli, and enterocytes that have characteristics with the human small intestine. This is due to the fact that it is a crucial technique for researching permeability and the transport mechanism. It is now clear that new 3D cell culture models have a lot of potential for drug safety and efficacy testing and disease modeling.

3. Acknowledgment

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4. Conflict Of Interest

The author declareس that there is no conflict of interest.

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زراعة خط الخلية في تطوير الأدوية وتطبيقها: مراجعة

الخلاصة

المقدمة: يأتي استخدام الاختبارات الحيوانية التقليدية لتحديد كيفية تأثير الأدوية على النظام البيولوجي مع العديد من التحديات. في السنوات الأخيرة، تم تقديم مجموعة متنوعة من التقنيات لتحقيق هذه الأهداف، واحدة من هذه التقنيات هي تقنية إنشاء خطوط الخلايا التي زادت بشكل كبير في فائدة وكفاءة أبحاث اكتشاف الأدوية. زراعة الخلايا هو المصطلح المستخدم لوصف إزالة الخلايا من حيوان أو نبات وزراعتها لاحقًا في بيئة معملية. يستخدم نموذج Caco-2 عادة في المراحل المبكرة من اكتشاف الأدوية لاتخاذ قرارات حول نفاذية و/أو امتصاص المواد الكيميائية المختبرة. من الواضح أن نماذج زراعة الخلايا ثلاثية الأبعاد الجديدة توفر إمكانات هائلة لنمذجة الأمراض وفعالية الأدوية وتقييم السلامة. ومع ذلك، أدت التحديات التي توفرها السمات المتأصلة في متغيرات الخلايا Caco-2 والطرق المشتركة بين المختبرات إلى تطوير بيانات غير قابلة للاختزال. **الاستنتاج:** هذه القيود لها تأثير على استقراء نتائج البحوث الخاضعة للتحقيقات السريرية على التداخلات بين الأدوية مع بعضها وتداخلات الادوية مع الأدوية العشبية

الكلمات المفتاحية : خط الخلية ، خلية Caco-2 ، آلية النقل ، دراسات النفاذية والسمية