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Review

Oral delivery of anticancer drugs: Challenges and opportunities

Kaushik Thanki [a], Rahul P. Gangwal [b], Abhay T. Sangamwar [b], Sanyog Jain [a,*]

[a] Centre for Pharmaceutical Nanotechnology, Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), SAS Nagar (Mohali), Phase X, Sector-67, Punjab 160062, India
[b] Department of Pharmacoinformatics, National Institute of Pharmaceutical Education and Research (NIPER), SAS Nagar (Mohali), Phase X, Sector-67, Punjab 160062, India

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ABSTRACT

The present report focuses on the various aspects of oral delivery of anticancer drugs. The significance of oral delivery in cancer therapeutics has been highlighted which principally includes improvement in quality of life of patients and reduced health care costs. Subsequently, the challenges incurred in the oral delivery of anticancer agents have been especially emphasized. Sincere efforts have been made to compile the various physicochemical properties of anticancer drugs from either literature or predicted *in silico via* GastroPlus™. The later section of the paper reviews various emerging trends to tackle the challenges associated with oral delivery of anticancer drugs. These invariably include efflux transporter based-, functional excipient- and nanocarrier based-approaches. The role of drug nanocrystals and various others such as polymer based- and lipid based-nanocarriers in the bioavailability enhancement along with their clinical outcomes has also been discussed exhaustively. Furthermore, an insight on the various absorption mechanisms of these nanocarriers across the gastrointestinal tract has also been highlighted.

Contents

1. Introduction

Cancer is defined as a complex series of disease condition caused by persistent tissue injury and host–environment interactions. The repeated exposure of carcinogens such as tobacco, ultraviolet light and infections leads to various genetic (mutations), epigenetic (loss of heterozygosity) and global transcriptome changes (*via* inflammation pathways) and is associated with increased cancer risk [1]. Owing to increased occurrence of cancer and worldwide prevalence during the last decade, it has posed a great challenge to the health care professionals. The latest WHO statistics suggests about 45% increase in the global cancer deaths by 2030, of which 70% would be

* Corresponding author.
E-mail addresses: sanyogjain@niper.ac.in, sanyogjain@rediffmail.com (S. Jain).

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contributed from developing countries like India [2]. With continuous upgradation in the field of science and technology, the need for addressing the practical problems associated with the drug therapies increased proportionately. The major portion of cancer therapy till the last couple of decades was based on parenteral route of administration [3,4]. However, looking at the quality of life and need of follow-up therapy after the diagnosis of the disease, oral route has gained major focus as compared to the parenteral route [4–6]. Oral route is considered as one of the most abundant and traditional ways of drug delivery; main advantage being greatest safety, convenience and patient compliance. The possibility of tailor-made design as per physicochemical properties of the drug substances further increases the attraction of the scientific community. However, diverse properties of drug substances, limitations in the choice of excipients and principally, physiological barriers pose great challenge for design and development of oral drug delivery system.

The use of oral anticancer therapy affects many clinically relevant aspects such as the following [7]:

1. An appropriate plasma drug concentration can be maintained to achieve a prolonged exposure of drugs to cancerous cells. This will increase the efficacy and decrease the side effects of the anticancer drugs.
2. Modulation of drug release from the dosage forms also provides an added advantage compared to that in other routes of administration.
3. It further facilitates the use of more chronic treatment regimens. This is especially important for cell cycle specific agents, especially those of predominantly cytostatic effect such as angiogenesis inhibitors and signal transduction inhibitors. For these agents, prolonged exposure to the drug may lead to pharmacodynamic advantages over intermittent intravenous administration.
4. Oral chemotherapy avoids the discomfort of injection and can be conducted at home. This approach may enhance the patient cooperation and their quality of life, which is an important issue and thus deserves high attention for any medical treatment.
5. The risks of infection and extravasations associated with intravenous infusion lines is avoided.
6. The treatment cost for the patient can be highly reduced due to avoidance of hospitalization, sterile manufacturing and trained personnel assistance.
7. Apart from the therapeutic applications, oral therapy can also be explored in the segment of prophylactics due to high level of ease in administration.

An interesting study has been carried out to evaluate the patient's preference for route of administration and it was found that almost 78.7% wanted themselves to be treated by oral route for recurring breast cancer disease, whereas nearly 2.7% preferred parenteral route while 18.6% landed with no preference [8]. Synchronizing with these results, the current scenario for development of new drug molecules has also rapidly shifted towards oral delivery. Approximately 20 molecules are already present in market for oral therapy of cancer, whereas a number of them are pipeline. This clearly indicates the developer's insight and intentions for oral delivery. Fig. 1 shows the list of drugs presently utilized for cancer therapy [4,9–11].

However, oral delivery of anticancer drugs is a great challenge owing to their peculiar physicochemical properties, and physiological barriers such as pre-systemic metabolism and gastrointestinal instability. Upon oral administration of such drugs, only a fraction of dose is available to systemic circulation for execution of therapeutic response *e.g.* oral bioavailability of paclitaxel, docetaxel, doxorubicin, tamoxifen, *etc.* is in the range of 5–20% [12–15]. Broadly, this could be attributed to low aqueous solubility, poor intestinal permeability, high level of P-glycoprotein (P-gp) efflux and pre-systemic metabolism. The P-gp efflux also has a key role in the execution of multidrug resistance in the tumor cells and thereby needs special consideration while designing the formulation of poor biopharmaceutical properties, as the amount which is required to achieve the therapeutic response might be very high ultimately leading to multidrug resistance.

Furthermore, cost of manufacturing novel formulations of the existing parenteral drugs and limited therapeutic window of the anticancer drugs leading to sub-therapeutic or toxic dose, also restricts the developability for oral route of administration [16]. However, recent advances in nanotechnology based drug delivery system posed potential advantages in overcoming these limitations. This includes polymeric nanoparticles, polymeric micelles, microemulsion, self-emulsifying drug delivery systems (SEDDS), carbon nanotubes, layersomes, liposomes, lipid–drug conjugates, nanocrystals, *etc.*

The therapeutic efficacy of the formulation depends upon its capability to deliver the drug at the right place and at the right time in amount adequate enough to yield a therapeutic response. Comparative therapeutic equivalence of oral and intravenous routes has been studied for wide variety of drugs and promising results were observed in most of the cases. Cyclophosphamide yields no statistical significant difference in the area under the plasma disappearance curve (AUC) and generated similar cytotoxic metabolic products upon administration through oral and parenteral routes thereby suggesting the therapeutic equivalence, irrespective of the route of delivery [17]. Paclitaxel in nanoparticulate dosage form administered by oral route had shown promising tumor reduction in animals compared to commercially available intravenous formulation at 50% reduced dose [18]. Co-administration of cyclosporin A further potentiated its oral bioavailability, due to inhibition of the P-gp efflux pump and CYP 3A4, both

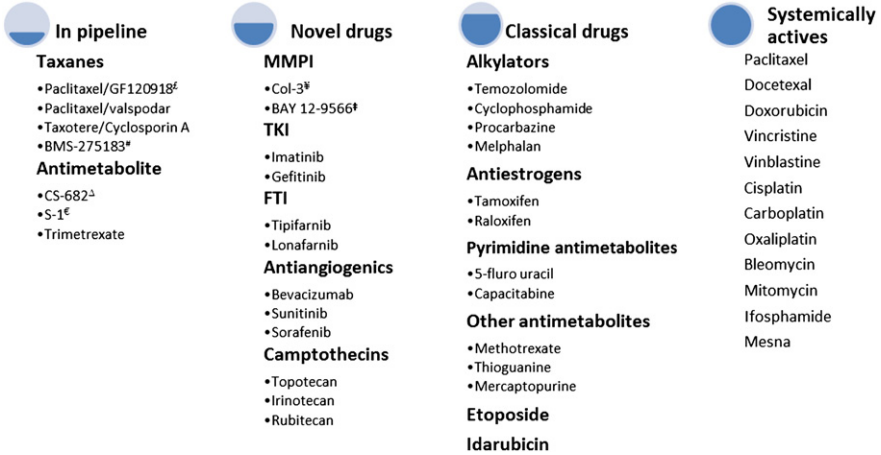

Fig. 1. Chemotherapeutic agents implemented to combat cancer. £P-gp modulator; #novel oral taxane; ΔDeoxycytidine-type antimetabolite; €Oral fluoropyrimidine; MMPImatrix metalloprotease inhibitors; ¥tetracycline analogue; ‡selective nonpeptide potent MMPI; TKItyrosine kinase inhibitor; FTIfarnesyl transferase inhibitor.