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REVIEW ON NOVEL EXTENDED RELEASE TABLETS

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Abstract:

There are approximately 35 million people infected by human immunodeficiency virus (HIV), with an estimated 2 million incident infections annually across the globe. While HIV infection was initially associated with high rates of morbidity and mortality, advances in therapy have transformed it into a chronic and manageable disease. To treat HIV infections a novel drug delivery system was designed like extended release tablets for controlled release. In addition, there is very strong evidence that those on antiretroviral therapy are much less likely to transmit infection to their partners. The success rates for maintaining viral suppression in treated patients has dramatically increased owing to the development of agents that are potent and well tolerated and can often be co-formulated into single pills for simplification. This review will outline advances in treatment over the last several years as well as new strategies that may shift the existing treatment paradigm in the near future.

Key Words: *HIV, Antiritroviral therapy,Controlled release medication*

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1.1 INTRODUCTION:

Oral controlled - release formulations for the small intestine and colon have received considerable attention in the past 25 years for a variety of reasons including pharmaceutical superiority and clinical benefits derived from the drug - release pattern that are not achieved with traditional immediate (or) sustained - release products[1]. By definition, colonic delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e. colon). The site-specific delivery of drugs to lower parts of the GI tract is advantageous for localized treatment of several colonic diseases, mainly inflammatory bowel disease (Crohn's disease and ulcerative colitis), irritable bowel syndrome, and colon cancer[2]. Other potential applications of colonic delivery include chronotherapy, prophylaxis of colon cancer and treatment of nicotine addiction. It has also gained increased importance not just for the delivery of drugs for the treatment of local diseases[4], but also potential site for the systemic delivery of therapeutic proteins and peptides which are being delivered by injections. These delivery systems when taken orally, allow drugs to release the drug from the delivery system once the delivery system arrives into the colon.

Colon targeted drug delivery would ensure direct treatment at the disease site, lower dosing and less systemic side effects. In addition to restricted therapy, the colon can also be utilized as a portal for the entry of drugs into the systemic circulation. For example, molecules that are degraded/poorly absorbed in the upper git, such as peptides and proteins, may be better absorbed from the more benign environment of the colon. Overall, there is less free fluid in the colon than in the small intestine and hence, dissolution could be problematic for poorly water-soluble drugs[3]. In such instances, the drug may need to be delivered in a pre-solubilized form, or delivery should be directed to the proximal colon, as a fluid gradient exists in the colon with more free water present in the proximal colon than in the distal colon. Aside from drug solubility, the stability of the drug in the colonic environment is a further factor that warrants attention. The drug could bind in a nonspecific manner to dietary residues, intestinal secretions, mucus or general faecal matter, thereby reducing the concentration of free drug. Moreover, the resident micro-flora could also affect colonic performance via degradation of the drug.

1.2 PHARMACEUTICAL APPROACHES FOR CDDS

Various pharmaceutical approaches that can be exploited for the development of colon targeted drug delivery systems are given below:

Approaches used for site specific drug delivery are –

a) Primary approaches for CDDS

- P^H sensitive polymer coating drug delivery to colon.
- Delayed (time controlled release system) release drug delivery to colon.
- Microbially triggered drug delivery to colon.

b) Newly developed approaches for CDDS

- Pressure controlled drug delivery system (PCDCS)
- Osmotic controlled drug delivery to colon (OROS – CT)
- Time clock system

a) PRIMARY APPROACHES

i) P^H Dependent systems:

The pH-dependent systems exploit the generally accepted view that pH of the human GIT increases progressively from the stomach (pH 1-2 which increase to 4 during digestion), small intestine (pH 6 - 7) at the site of digestion and it increases to 7-8 in the distal ileum. The gamma scintigraphy technique becomes most popular technique to investigate the gastrointestinal performance of pharmaceutical formulations[5]. The pH sensitive polymers (given in Table 4) which will produce delayed release and also give protection from gastric fluids.

1.3 NOVEL APPROACHES FOR CDDS

1.3.1 Pressure CDDS

It is due to peristalsis; higher pressures are encountered in the colon than in the small intestine. Takaya et al. developed pressure controlled colon-delivery capsules using ethyl cellulose, which is insoluble in water.[24]In such systems, drug release occurs followed by disintegration of a water-insoluble polymer capsule because of pressure in the lumen of the colon[6]. The thickness of the ethyl cellulose membrane is an important factor for the disintegration of the formulation. The system also depends on capsule size and density. Because of re absorption of water from the colon, the viscosity of luminal content is greater in the colon than in the small intestine. It is therefore being concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery

systems. In pressure, controlled ethyl cellulose single unit capsules the drug is in a liquid form. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to humans.

1.3.2 Osmotic Controlled Drug Delivery (ORDS-CT)

The OROS-CT (Alza Corporation) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable[7]. The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule, (Fig. 8). Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. An orifice is drilled through the membrane next to the drug layer. Immediately after the OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolves. Because of its drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water in the acidic aqueous environment of the stomach, and hence no drug is delivered. As the unit enters the small intestine, the coating dissolves in this higher pH environment (pH >7), water enters the unit, causing the osmotic push compartment to swell, and concomitantly creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semipermeable membrane. For treating ulcerative colitis, each push pull unit is designed with a 3 - 4 hr post gastric delay to prevent drug delivery in the small intestine. Drug release begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 hours in the colon or can deliver drug over a period as short as four hours. Recently, new phase transited systems have come which promise to be a good tool for targeting drugs to the colon[8]. Various in vitro / in vivo evaluation techniques have been developed and proposed to test the performance and stability of CDDS.These days the basic CDDS approaches are applied to formulate novel drug delivery systems Such as Multi-particulate systems, Microspheres, Liposomes, Microencapsulated particles etc.

1.4 INTRODUCTION OF HIV:

Human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome disease challenges to public health globally. AIDS is considered to be an epidemic according to estimates from the UNAIDS/WHO AIDS Epidemic Update, July 2008. Globally, there were an estimated 33 million people living with HIV in 2007. Moreover, in Sub-Saharan Africa remains most heavily affected by HIV, accounting for 67% of all people living with HIV and for 72% of AIDS deaths in 2007 and globally the percentage of women among people living with HIV has remained stable at 50% for several years. HIV-1 is the globally common infection while HIV-2 is more prevalent in West Africa, and takes a longer time to develop into immunodeficiency from infection than HIV-1. HIV infection in the human body results mainly from integration of the viral genome into the host cell for the purpose of cell replication, and AIDS is the advanced stage of the disease caused by HIV infection. The end stage of the disease may be characterized by a spectrum of diseases opportunistic infections (such as Pneumocystis carinii and Mycobacterium tuberculosis), dementia and cancer. Interestingly, HIV has been referred to as a ‘‘master regulator” of cellular gene expression as a means to augment expression of its own genome. The development of drugs for HIV infection has undergone substantial progress, currently various drugs are used as anti-retroviral therapy and has contributed significantly to improved patient/disease management.

When HIV infects a cell, a viral enzyme, reverse transcriptase copies the viral single stranded RNA genome into a double-stranded viral DNA. The viral DNA is then integrated into the host chromosomal DNA, which then allows host cellular processes, such as transcription and translation to reproduce the virus[9]. Reverse Transcriptase Inhibitors blocks the reverse transcriptase's enzymatic function and prevent completion of synthesis of the double-stranded viral DNA, thus preventing HIV from multiplying.

1.5 CLASSIFICATION OF ANTI VIRAL DRUGS:

1.Anti-Herpes virus

Idoxuridine, Acyclovir, Valacyclovir, Famciclovir, Ganciclovir, Foscarnet

2.Anti-Retrovirus

Nucleoside reverse transcriptase inhibitors (NRTIs)

Zidovudine (AZT), Didanosine, Zalcitabine, Stavudine, Lamivudine, Abacavir.

Nonnucleoside reverse transcriptase inhibitors (NNRTIs)

Nevirapine, Efavirenz, Delaviridine.

Protease inhibitors

Ritonavir, Indinavir,Nelfinavir, Saquinavir, Amprenavir,Lopinavir.

1. Anti-Influenza virus

Amantadine, Rimantadine

2. Nonselective antiviral drugs
Ribavirin, Adefovir dipivoxil, Interferon alpha.

1.6 Advantages and Limitations of Control Release Dosage Forms

- Reduction in frequency of drug administration
- Improved patient compliance
- Reduction in drug level fluctuation in blood
- Reduction in total drug usage when compared with conventional therapy
- Reduction in drug accumulation with chronic therapy
- Reduction in drug toxicity (local/systemic)
- Stabilization of medical condition (because of more uniform drug levels)

1.7 Disadvantages of Control Release Dosage Forms

- Decrease systemic availability
- Poor *invitro* – *invivo* correlation
- Increase risk of toxicity
- Retrieval of drug is difficult in case of toxicity, poisoning or hyper sensitivity reaction.

1.8 Mechanism based marketed product and their classification

S. No	Drug	Brand name	Company
1	Zolpidem Tartarate	Ambien CR	Sanofi-Aventis
2	Bupropion	Wellbutrin XL	GlaxoSmithKline
3	Levodopa and Benserazide	Modapar	Roche products, USA
4	Propranolol HCL	Inderal LA	Wyeth Inc.

1.9 CONCLUSION:

The controlled release drug delivery system aimed to release the drug at the desired rate over extended period of time to maintain the therapeutic level in blood. Nowadays, the oral route of administration for controlled release drug delivery system has received more attention due to its more flexibility, reduced dosing frequency and better patient compliance, we can have concluded that the controlled release drug delivery system is very helpful in increasing the efficiency of the dose as well as the patient compliance.

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