pH Dependent Drug Delivery System: Review

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The pH-dependent CTDDS exploit the generally accepted view that pH of the human GIT increases progressively from the stomach (pH 1-2 which increases 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 coating of pH-sensitive polymers to the tablets, capsules or pellets provide delayed release and protect the active drug from gastric fluid. The polymers used for colon targeting, how- ever, should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral of slightly alkaline pH of the terminal ileum and preferably at the ile-ocecal junction. These processes distribute the drug throughout the large intestine and improve the potential of colon targeted delivery systems. While this release pattern can be studied in-vitro, there is no real substitute for confirming reliable performance in vivo in man. The technique of gamma scintigraphy has become the most popular method to investigate the gastrointestinal performance of pharmaceutical dosage forms. The threshold pH commonly employed pH-sensitive polymers. The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. This review, mainly compares the primary approaches for CDDS (Colon Specific Drug Delivery) namely prodrugs, pH and time dependent systems, and microbially triggered systems, which achieved limited success and had limitations as compared with newer CDDS namely pressure controlled colonic delivery capsules, CODESTM, and osmotic controlled drug delivery which are unique in terms of achieving in vivo site specificity, and feasibility of manufacturing process.[10]

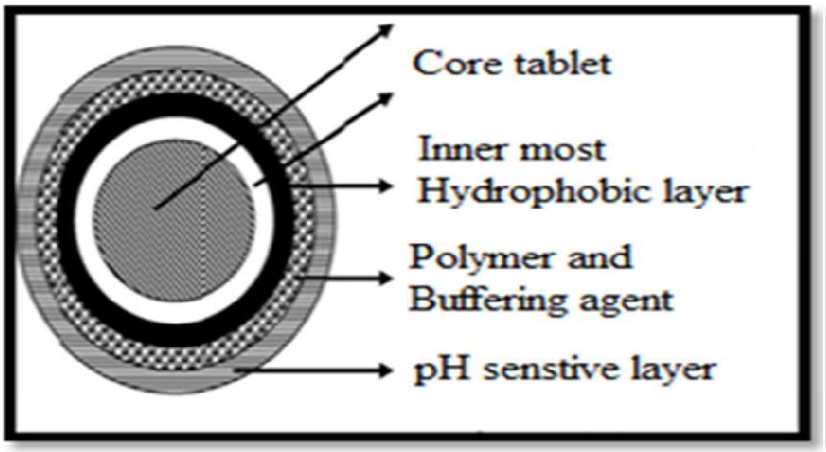


Fig no.1 pH dependent matrix tablet

Advantages-

- Decreased dose to be administered.
- decreased side effect.
- Improced drug utilization.
- Improved patient compliance.
- Lower daily cost to patient due to fewer dosage unit are required by the patient in therapy.
- Drug adapts to suit circadian rhythms of body functions or diseases.
- Drug targeting to specific site.
- Protection of mucosa from irritating drugs.
- Drug loss is prevented by extensive first pass metabolism.

pH in the colon

The pH of the GI tract is subject to both inter and intra subject variations. Diet, diseased state, and food intake influences the pH of the gastrointestinal fluid. The changes in the pH along the gastrointestinal tract have been used as a means for targeted colon drug delivery. Radio telemetry shows the highest pH (7.5±0.5) in the terminal ileum. On entry into the colon, the pH drops to 6.4±0.6. The pH in the mid colon is 6.6±0.8 and in the left colon 7.0±0.7. There is a fall in pH on entry into the colon due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides. For example lactose is fermented by the colonic bacteria to produce large amounts of lactic acid resulting in pH drop to about 5.0.

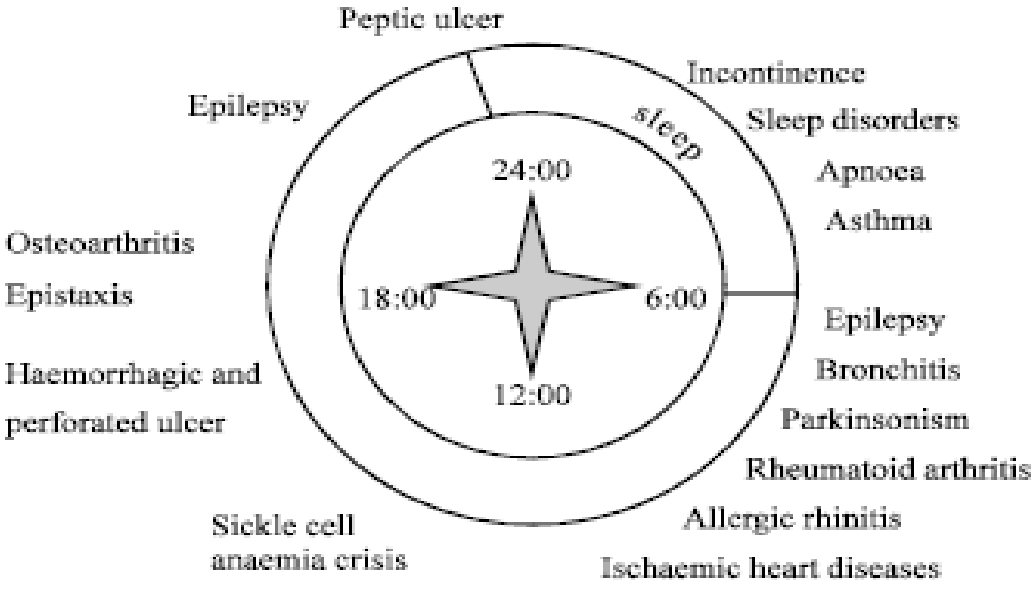
Approaches for pH dependent drug delivery-

- pH-sensitive Hydrogel-
- Enteric coating system-
    - ✓ Tablets-
    - ✓ Capsules-
- Multiple units-
    - ✓ pH sensitive gels-
    - ✓ pH activated drug delivery-
    - ✓ pH sensitive liposomes-
    - ✓ pH sensitive microspheres-

DISEASES TARGETING pH SENSITIVE DRUG DELIVERY:

This theory is based on the assumption of biological functions that display constancy over time. However, chronobiological studies have established circadian rhythm for almost all body functions, e.g., **heart rate**, **blood**

pressure, body temperature, plasma concentration of various hormones, gastric pH and renal function. It has become apparent that rhythmic processes are indispensable for the treatment of human diseases. Just as physiological functions vary over time, pathological states of disease have circadian rhythms. Epidemiological studies have documented the elevated risk of disease symptoms during the 24 h cycle.



Diseases known to display circadian rhythm

Anti-ulcer therapy: It is well established that patients with peptic ulcer disease often experience the greatest degree of pain near the time that they go to bed, as the rate of stomach acid secretion is highest at night. The timing of administration of ulcer medications has a significant impact on their therapeutic effect.

Anti-inflammatory therapy: In the case of individuals who suffer from rheumatoid arthritis and related painful joint disorders, the non-steroidal anti-inflammatory agents (NSAIDs) such as ibuprofen may be more effective at relieving pain, if the drug is administered at least 4 to 6 h before the pain reaches its peak. It will be more helpful if arthritis patients take the NSAIDs before bed time if they experience a particularly high level of discomfort in the morning.

Anti-asthma therapy: It has been estimated that symptoms of asthma occur 50 to 100 times more often at night than during the day. Many circadian-sensitive factors appear to contribute to the worsening of nocturnal asthmatic symptoms. For example, cortisol (an anti-inflammatory substance) levels were highest at the time of

awakening and lowest in the middle of the night and histamine (a mediator of bronchoconstriction) concentrations peaked at a level that coincided with the greatest degree of bronchoconstriction at 4:00 am. A research finding also reveals that theophylline absorption is slower at. The enhanced understanding of the chronobiological impact upon the pathology of asthma and the pharmacology and pharmacokinetics of the drugs used in its management, have led to new approaches to disease management and enhanced patient care.

Cardiovascular therapy: The differences in patterns of illness between day and night for cardiovascular disorders such as hypertension, angina, heart attack, sudden cardiac death and stroke have been documented. Medications have been formulated and dosing schedules established, in an attempt to provide appropriate concentration of a drug in the target area of the body when the drug is most needed. For example, it has often been found that the **blood pressure** of a hypertensive patient increases rapidly in the morning after awakening, typically peaks in the middle to late time of the day, decreases in the evening and is lowest while the patient sleeps at night. It may also be important to recognize that the risk of heart attack appears to be greatest during the early morning hours after awakening. Currently, there are antihypertensive products in the market that are chronotherapeutic medications with novel drug delivery systems, releasing drug during the vulnerable period of 6 am to noon upon administration of medications at 10 pm.

Chemotherapy: Antineoplastic drugs cause cytotoxic effectson healthy and diseased tissues. As would be expected, the biological rhythms of both healthy and tumor cells may influence the susceptibility of normal and malignant cells to these agents .It has been demonstrated that susceptibility rhythms to drugs may differ between healthy tissue and cancerous tissue. Therefore, the correct timing of drug treatment may reduce host toxicity, increase maximum drug tolerance and ultimately result in better tumor management. The pharmacologic and pharmacokinetic properties of the drug, rhythmic changes in DNA and RNA synthesis, RNA translational activity and mitotic activity may influence tumor cell susceptibility .It appears that the timing of drug administration in the treatment of cancer can have a significant impact upon treatment success.

Colonic drug therapy: The colon is also viewed as the preferred absorption site for oral administration of protein and peptide drugs, because of the relatively low proteolytic enzyme activities in the colon. In addition, to providing more effective therapy of colon related diseases such as irritable bowel syndrome, Inflammatory Bowel Disease (IBD) including Crohn’s disease and ulcerative colitis, colon specific delivery has the potential to address important unmet therapeutic needs including oral delivery of macromolecular drugs Therefore, it appears that targeted drug delivery with an appropriate release pattern could be crucial in providing effective therapy for this chronic disease

Chemical name abbreviation	Functional groups	Soluble above pH	Trade name (company)	Application form	Remarks
Cellulose acetate pthalate CAP USP 23/NF18	Acetyl, phthalyl	6	CAP (Eastman Comp.) Aquateric (Lehmann and voss)	Organic solution Aqueous dispersion (pseudolactices)	Sensitive to hydrolysis, 5-30% plasticizer required. Micronized powder ((0.05-3 µm)
Hydroxypropyl methyl cellulosephthalate HPMC USP23/NF18	Type 200731 Methoxy, hydroxypropoxy Phthalyl Type 220824 Methoxy, hydroxypropoxy, pthalate	5	HP 50, HP 55 (Syntapharm) HP 50 F, HP 55F (Syntapharm)	Organic solution Aqueous dispersion (pseudolactices)	Less sensitive to hydrolysis, plasticizer not essential Powder <20 µm, redispersible in water
Hdroxypropyyl methyl cellulose acetate succinate HPMCAS	Methoxy, hydroxypropoxy, Acetyl, succinyl	5	HPMCAS-L HPMCAS-M HMPCAS-H (Syntapharm)	Aqueous dispersion	Powder <5 µm Elastic properties, plasticizer not essential Slightly hygroscopic Notmicronized
Carboxymethyl ethyl cellulose CMEC (standard of Pharmaceutical Ingredients, Japan)	Carboxymethyl, ethoxy	5	Duodcell OQ Duodcell OQ (Lehmann and Voss)	Organic solution Aqueous dispersion	Micronized Stable, not senstive to moisture

Table No.1 Properties and applications of Ph dependent coating materials.

Conclusion:

For a drug labile to gastric fluid or irritating to gastric mucosa, this type of CrDDS has been developed to target the delivery of the drug only in the intestinal tract, not in the stomach. It is fabricated by coating a core tablet of the gastric fluid-sensitive drug with a combination of intestinal fluid-insoluble polymer, like ethyl cellulose and intestinal fluid-soluble polymer, like hydroxylmethyl cellulose phthalate

In the stomach, the coating membrane resists the degrading action of gastric fluid (pH<3) and the drug molecules are thus protected from the acidic degradation. After gastric emptying, the CrDDS travels to the small intestine and the intestinal fluid-soluble component in the coating membrane is dissolved away by the intestinal fluid (pH>7.5). This produces a microporous membrane of intestinal fluid-insoluble polymer to control the release of drug from the core tablet. The drug is thus delivered in a controlled manner in the intestine by a combination of drug dissolution in the core and diffusion through the pore channels. By adjusting the ratio of the intestinal fluid-soluble polymer to the intestinal fluid-insoluble polymer in the membrane, the rate of drug delivery can be regulated. Representative application of this type of CrDDS is in the oral controlled delivery of potassium chloride, which is highly irritating to gastric epithelium.