2. LITERATURE REVIEW

Oral route of administration has received the most attention as the most convenient and commonly used method of drug delivery. It is relatively safe route of drug administration, cost-effective manufacturing process, and it has more flexibility in dosage form design rather than the non-oral routes. Oral drug delivery systems can be classified into three major categories; immediate release preparations, control release preparations, and targeted release preparation. Oral controlled release is the most commonly used in pharmaceutical industry, and the sustained release formulation is the most common controlled release formulations. Sustained release formulations developed in order to maintained the optimum drug concentration and increasing the duration of therapeutic effect, by release a portion of drug immediately, and the remaining drug is released slowly over an extended period of time, normally over 12–18 h (Figure 2). The sustained release formulations reduce the frequency of drug administration, improve efficiency of treatment with less amount of drug, minimized side effects, reduce the drug level fluctuation in blood, and increased patient convenience and compliance (Collett and Moreton, 2002). The sustained release formulations provide commercial and industrial advantages such as product life-cycle extension, patent extension, market expansion and illustration of innovation. The limitations of sustained release formulations is the delaying in onset of drug action, possibility of dose dumping in the case of a poor formulation strategy, so if the drug reservoir of a sustained release formulation is damaged and release the drug all at once, the drug concentration may go above the toxic level. Furthermore, once the drug release begins, it is difficult to stop the release even if it is necessary. Not all drugs are suitable for formulating into sustained release dosage form. In addition, the cost of producing the controlled release formulation is higher than that of the conventional dosage forms.

Tablets are the most frequently used dosage form for oral administration because it is easy and convenient to use, it deliver an accurate dosage of the active ingredient, and can be packed in convenient portable package. It can be designed to protect unstable drugs, coloured or stamped to aid tablet recognition. Coated tablets can provide environmental protection and can modify the drug release.
2.1 **ANATOMY AND PHYSIOLOGY OF THE BLADDER**

The urinary bladder is located on the floor of the pelvic cavity. It is a muscular sac below the peritoneum and behind the pubic bones. In women, the bladder is inferior to the uterus; in men, the bladder is superior to the prostate gland. The bladder is a reservoir for accumulating urine, and it contracts to eliminate urine.

Sub-mucous is a thin layer of areolar tissue that loosely connects the muscular layer with the mucous layer, being itself intimately attached to the mucous layer. The innermost layer of the wall of the urinary bladder is the mucous membrane, which contains transitional epithelium tissue that can stretch without tearing the lining. The ability of this tissue to stretch is important because it contains variable volumes of liquid as the bladder is filled and emptied several times per day. Because it is only loosely attached to the strong and substantial muscular layer, the mucosa falls into many folds known as rugae when the bladder is empty or is only filled to a small extent. The other features inside of the bladder are the ureter orifices, the trigone, and the internal orifice of the urethra. The trigone is a smooth triangular region between the openings of the two ureters and the urethra. This area has a paler colour than the rest of the interior of the bladder and does not present any rugae even when the bladder is empty because this area is more tightly bound to its outer layer of bladder tissue. The points of the triangle are the openings of the two ureters and that of the urethra (Figure 3).
The detrusor muscle is the smooth muscle layer of the urinary bladder wall. It consists of three layers of smooth involuntary muscle fibres. Most of the fibres of the external layer are arranged longitudinally. Those of the middle layer are mostly arranged in a circular configuration, and the muscle fibres of the internal layer have a longitudinal arrangement. It is a muscle in the form of a sphere; when it contracts it becomes a smaller sphere, and its volume diminishes. Around the opening of the urethra, the muscle fibers of the detrusor form the internal urethral sphincter which is involuntary. When urine is released from the bladder it flows out via the neck of the bladder. The internal urethral sphincter is a sphincter (circular) muscle located at the neck of the bladder that helps to control the process of micturation. This involuntary muscle is formed from a thickening of the detrusor muscle and closes the urethra when the bladder has emptied. The bladder acts as a storage reservoir for urine, and the micturation is the process by which urine is expelled from the bladder.

Figure 3: Frontal section of female urinary bladder and urethra
2.2 **BLADDER DISORDER**

There are a number of different types of urinary incontinence (UI):

2.2.1 **STRESS URINARY INCONTINENCE**

It is an involuntary small leakage of urine on effort that increases the intra abdominal pressure such as, exertion, sneezing, coughing, during sexual intercourse and laughing. It is the most common type of urinary incontinence in younger women. Stress urinary incontinence also occurs in post-menopausal women due to age related physiological changes and due to a reduction in oestrogen levels and impairment to the contractability of the pelvic floor following labour and vaginal births.

2.2.2 **OVERFLOW INCONTINENCE OR VOIDING DIFFICULTY**

It occurs when there is an impediment to the normal smooth emptying of the bladder; it is more common in men. The most common cause of outflow obstruction is benign prostatic enlargement; other causes can be prostatic carcinoma and urethral stricture. Constipation can cause outflow obstruction in both men and women. Common symptoms suggestive of outflow obstruction are:

- Slow urine flow
- Hesitancy
- Inability to urinate (acute urinary retention)
- Urine stream that starts and stops
- Urgency frequency
- Urge incontinence
- Nocturia
- Continuous feeling of a full bladder

2.2.3 **MIXED INCONTINENCE**

It is not unusual for patients to present with a combination of urge and stress incontinence (Fantl, *et al.*, 1990; Ouslander, *et al.*, 1986). When both symptoms are present, the incontinence is called mixed UI. Mixed UI is common in women, especially older women. Often, however, one symptom (urge or stress) is more bothersome to the patient than the other. Identifying the most bothersome symptom is important in targeting diagnostic and therapeutic interventions.
2.2.4 Overactive Bladder

Overactive bladder is one of the most common bladder disorders. It is a syndrome characterized by urinary urgency, with or without urgency urinary incontinence which is usually associated with urinary frequency and nocturia (Abrams et al., 1998), or the involuntary loss of urine. OAB affects 12–17% of adults both men and women of all age in Europe and the United States (Thom, 2000; Milsom et al., 2001). It was stated that the complaint of UI increased with advanced age, especially among women (Malone-Lee, 2000). UI results in a loss of self-esteem and a decrease in ability to maintain an independent lifestyle. Dependence on caregivers for activities of daily life increases as incontinence worsens. Consequently, excursions outside the home, social interaction with friends and family, and sexual activity may be restricted or avoided entirely (Grimby et al., 1993; Noelker, 1987). It is objectively demonstrable as a common medical and social disability. The prevalence of UI among women and men between ages 70–97 was reported as 48% and 17%, respectively (Molander et al., 2002).

OAB is more common than diabetes mellitus (Thom, 2000), and it is a chronic condition that often requires long-term treatment to maintain control of symptoms. The smooth and striated muscles in the bladder, urethra, and external urethral sphincter are responsible for storage and periodically release of urine, in which the outlet should be closed and the bladder smooth muscle is quiescent during urine storage (Abrams and Andersson, 2007). When bladder volume reaches the micturition threshold, activation of a micturition center in the dorsolateral pons (the pontine micturition center) induces a bladder contraction and a reciprocal relaxation of the urethra, leading to bladder emptying. During voiding, sacral parasympathetic (pelvic) nerves provide an excitatory input (cholinergic and purinergic) to the bladder and inhibitory input (nitrergic) to the urethra (Hegde and Eglen, 1999). These peripheral systems are integrated by excitatory and inhibitory regulation at the levels of the spinal cord and the brain. Injury or diseases of the nervous system, as well as drugs and disorders of the peripheral organs, can produce lower urinary tract dysfunction.

2.2.5 Pathophysiology of OAB

The understanding of the pathophysiology of OAB is limited, and much of what is known about the clinical aetiology of the condition has been derived from epidemiological data. The mechanisms involved are complex and comprise both peripheral and central nervous system factors. Research into the pathogenesis of OAB is hampered by the fact that it is a symptom
based diagnosis, and consequently, studies in this field have focused on abnormalities of afferent signaling and the mechanisms underlying detrusor overactivity. Changes in afferent return and signal processing are presumed to be the basis of urgency. Regulation of normal micturition is complex and involves both spinal and supraspinal control mechanisms. The pontine micturition centre is the prime determinant of lower urinary tract function as it sets the volume at which the lower urinary tract switches from storage to voiding mode, thereby effectively determining maximum bladder capacity. The level of afferent activity arising from the bladder is the main factor causing the switch between these two phases.

### 2.2.6 Treatment of OAB

To treat OAB syndrome, the therapeutic targets are to facilitate of urine storage, which can be achieved by relaxing of bladder smooth muscles by modulating activity of ligand receptors. OAB symptoms increases with age and can have a neurogenic and/or myogenic aetiology (Harris, 1986). The financial implications of OAB and bladder problem control are considerable. The cost for treatment of urinary incontinence for individual aged patient in the US was estimated at US $ 26.3 billion in 1995 (Wagner and Hu, 1998). Despite the disturbing nature of OAB, many sufferers do not seek help for urinary symptoms because of embarrassment or because they are not aware that help is available (Shaw et al., 2001). Getsios et al. (2004) compare the economic cost of using extended-release formulation of oxybutynin and immediate-release of tolterodine tartrate for the treatment of OAB. They found out that the treatment with oxybutynin ER would reduce costs and provide better results than tolterodine tartrate IR over 1 year of treatment.

OAB is similar in men and women across age groups. It may be successfully managed in a variety of ways with 50% to 80% of patients responding to a triad of measures that integrates behavior modification, pelvic muscle physiotherapy and pharmacotherapy. Treatment options range from behavioral therapies to surgical interventions (Fantl et al., 1996). Table 1 shows the various marketed products for treatment of overactive bladder syndrome.

The medical treatment of urge urinary incontinence may involve bladder retraining, pelvic muscle rehabilitation, and therapy with drugs that inhibit detrusor contractions. Therapy with antimuscarinic (cholinergic) receptor antagonists has played a dominant role for many years, because these drugs block urinary bladder contractions (Andersson, 1993).
Acetylcholine activates muscarinic receptors on detrusor myocytes and is the main contractile transmitter. M3 receptors in the human detrusor are thought to be most important for detrusor contraction (Andersson and Wein, 2004). Evidence for this functional role comes from studies in M3 knockout mice. In the presence of carbachol, bladder strips from these mice had a maximal contractile response only 5% of that found in wild-type mice (Matsui et al., 2000). However, these mice have a nearly normal cystometric pattern due to the remaining purinergic activation mechanism. Acetylcholine causes contraction of detrusor muscle by stimulation of M3 receptors and minor M2 receptor-mediated contractions might also occur, acetylcholine also induces contraction indirectly by inhibiting the production of cyclic adenosine monophosphate (CAMP) and reversing the relaxation induced by β-adrenoceptors after stimulation by noradrenaline, inhibition of potassium channels might also be involved (Figure 4). Antimuscarinics drugs act at muscarinic receptors on detrusor smooth muscle cells to reduce spontaneous myocyte activity during the storage phase, which decrease the frequency and intensity of detrusor contractions (Hawthorn et al., 2000).

![Figure 4: Bladders demonstrate hypersensitivity to cholinergic agonists acting at muscarinic (M2 or M3) receptors.](image)

Tolterodine tartrate is the first antimuscarinic agent that was specifically developed to treat overactive bladder. Tolterodine tartrate is clinically efficacious at combined serum concentration of free tolterodine tartrate and its active metabolite. Evidence from studies conducted in humans and mice suggests that tolterodine tartrate does not readily cross the blood–brain barrier (Nilvebrant, 2000; Oki et al., 2007), and has little effect on central nervous system function.
function (Todorova et al., 2001). Yokoyama et al. (2005) studied the effects of tolterodine tartrate on an overactive bladder which depended on suppression of C-fiber bladder afferent activity in rats. They administered tolterodine tartrate intravenously or intravesically to rats with detrusor overactivity induced by cerebral artery occlusion with and without pretreatment with resiniferatoxin, a capsaicin analogue that induces C-fibre afferent desensitization. At low doses, tolterodine tartrate increased bladder capacity in untreated rats but was ineffective in those that had received resiniferatoxin. The authors concluded that tolterodine tartrate exerted an inhibitory effect on C-fibre bladder afferent nerves, thereby reducing detrusor activity and improving bladder capacity. It is reported that the tolterodine tartrate show antimuscarinic effect in rats even after treatment with resiniferatoxin (Hedlund et al., 2007). Cappon et al. (2008) studied the effect of oral tolterodine tartrate on the memory of the mice. They observed that the tested drug had no effect on memory in the mouse passive avoidance model and concluded that tolterodine tartrate does not disrupt cognitive function under the test conditions. Andersson (2011) studied the mechanisms of antimuscarinic drug in the treatment of OAB. He concludes that the recommended dose of antimuscarinics may decrease OAB symptoms and detrusor overactivity without affecting the voiding contraction, this due to the low drug plasma concentration, which is not enough to block the effect of acetyl choline during the voiding contraction. Athanasopoulos et al. (2011) studied the role of antimuscarinics in the management of men with symptoms of overactive bladder. They conclude the safety of antimuscarinics administered for the treatment of the OAB patients.

Table 1: Various marketed dosage for treatment of overactive bladder

<table>
<thead>
<tr>
<th>Active ingredients</th>
<th>Trade name</th>
<th>Dosage form (Dosage form)</th>
<th>Dose</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin chloride</td>
<td>Ditropan</td>
<td>Tablet, syrup, Solution</td>
<td>5 mg (two to three times a day), 5 mL of syrup contains 5 mg.</td>
<td>Ortho-McNeil Pharmaceuticals, Inc.</td>
</tr>
<tr>
<td>Oxybutynin chloride</td>
<td>Ditropan XL</td>
<td>Tablet (Extended release)</td>
<td>5 mg, 10 mg, or 15 mg once-a-day</td>
<td>Ortho-McNeil Pharmaceuticals, Inc.</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>Oxytrol</td>
<td>Patch (Extended release)</td>
<td>3.9 mg/patch Twice a week</td>
<td>Watson Pharmaceuticals</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>Gelnique</td>
<td>Gel (Extended release)</td>
<td>10%, once daily</td>
<td>Watson Pharmaceuticals</td>
</tr>
<tr>
<td>Oxybutynin chloride</td>
<td>Cystran</td>
<td>Tablet (Immediate release)</td>
<td>2.5-5 mg bid-tid</td>
<td>Intas Pharmaceuticals Ltd.</td>
</tr>
<tr>
<td>Active ingredients</td>
<td>Trade name</td>
<td>Dosage form</td>
<td>Dose</td>
<td>Company</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-----------------------------</td>
<td>---------------------------</td>
<td>-----------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Oxybutynin chloride</td>
<td>Nocturin</td>
<td>Tablet (Immediate release)</td>
<td>2.5-5 mg bid-tid</td>
<td>Elder Pharmaceuticals Pvt. Ltd.</td>
</tr>
<tr>
<td>Oxybutynin chloride</td>
<td>Oxyspas</td>
<td>Tablet (Immediate release)</td>
<td>2.5-5 mg bid-tid</td>
<td>Cipla</td>
</tr>
<tr>
<td>Oxybutynin chloride</td>
<td>Tropan</td>
<td>Tablet (Immediate release)</td>
<td>2.5-5 mg bid-tid</td>
<td>Sun Pharmaceuticals Industries Ltd.</td>
</tr>
<tr>
<td>Tolterodine tartrate</td>
<td>Detrusitol</td>
<td>Tablet (Immediate release)</td>
<td>2 mg twice daily</td>
<td>Pharmacia-Upjohn</td>
</tr>
<tr>
<td>Tolterodine tartrate</td>
<td>Detrol LA</td>
<td>Capsule (Extended release)</td>
<td>2 mg and 4 mg once daily</td>
<td>Pfizer Pvt. Ltd.</td>
</tr>
<tr>
<td>Tolterodine tartrate</td>
<td>Dezrolala</td>
<td>Capsule (Extended release)</td>
<td>2 mg and 4 mg once daily</td>
<td>Taj Pharmaceuticals Ltd.</td>
</tr>
<tr>
<td>Tolterodine tartrate</td>
<td>Dezrolala</td>
<td>Tablet (Immediate release)</td>
<td>1 mg bid</td>
<td>Taj Pharmaceuticals Ltd.</td>
</tr>
<tr>
<td>Tolterodine tartrate</td>
<td>Urotral</td>
<td>Tablet (Immediate release)</td>
<td>2 mg bid</td>
<td>Almirall Prodesfarma</td>
</tr>
<tr>
<td>Tolterodine tartrate</td>
<td>Urotral Neo</td>
<td>Capsule (Extended release)</td>
<td>4 mg once daily</td>
<td>Almirall Prodesfarma</td>
</tr>
<tr>
<td>Tolterodine tartrate</td>
<td>Flochek</td>
<td>Capsule (Extended release)</td>
<td>4 mg once daily</td>
<td>Alkem</td>
</tr>
<tr>
<td>Tolterodine tartrate</td>
<td>Roliten OD</td>
<td>Capsule (Extended release)</td>
<td>4 mg once daily</td>
<td>Ranbaxy</td>
</tr>
<tr>
<td>Tolterodine tartrate</td>
<td>Roliten</td>
<td>Tablet (Immediate release)</td>
<td>2 mg twice daily</td>
<td>Ranbaxy</td>
</tr>
<tr>
<td>Tolterodine tartrate and tamsulosin hydrochloride</td>
<td>Bapter</td>
<td>Capsule</td>
<td>4 mg + 0.4 mg once daily</td>
<td>Dr. Reddy's</td>
</tr>
<tr>
<td>Tolterodine tartrate</td>
<td>Terol LA</td>
<td>Capsule (Extended release)</td>
<td>4 mg once daily</td>
<td>Cipla</td>
</tr>
<tr>
<td>Tolterodine tartrate</td>
<td>Terol LA</td>
<td>Tablet (Immediate release)</td>
<td>2 mg twice daily</td>
<td>Cipla</td>
</tr>
<tr>
<td>Tolterodine tartrate</td>
<td>Tolter</td>
<td>Tablet (Immediate release)</td>
<td>2 mg twice daily</td>
<td>Zydus Cadilla</td>
</tr>
<tr>
<td>Tolterodine tartrate</td>
<td>Torq</td>
<td>Capsule (sustained release)</td>
<td>4 mg once daily</td>
<td>Dr. Reddy's</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>Vesicare</td>
<td>Tablet (Immediate release)</td>
<td>5-10 mg once daily</td>
<td>Yamanouchi Pharmaceutical Co.</td>
</tr>
<tr>
<td>Fesoterodine fumarate</td>
<td>Toviaz</td>
<td>Capsule (Extended release)</td>
<td>4 mg &amp; 8 mg once daily</td>
<td>Pfizer Pvt. Ltd</td>
</tr>
<tr>
<td>Trospium chloride</td>
<td>Sanctura</td>
<td>Capsule (Extended release)</td>
<td>20 mg once-daily</td>
<td>Indevus Pharmaceuticals</td>
</tr>
<tr>
<td>Derifenacin</td>
<td>Enablex</td>
<td>Tablet (extended release)</td>
<td>7.5-15 mg once-daily</td>
<td>Novartis</td>
</tr>
</tbody>
</table>
2.3 **DRUG DELIVERY SYSTEMS**

In pharmaceutical industry, novel drug delivery technologies represent a strategic tool for expanding drug markets. Such systems can be developed much faster at a lower cost compared to the development of a completely new chemical entity. These newer technologies have led to the rebirth of existing molecules which have resulted in increase in their market values along with extension in patent lives of such drugs. Drug delivery technologies also make delivery of difficult-to-deliver compounds possible and offer improved efficacy, safety, drug utilization and patient compliance to existing drugs. This further result in reducing side effects associated with higher doses of the drug. Different types of tablets dosage forms are being developed and the main reason behind that is to create a delivery system that is relatively simple and inexpensive to manufacture, provide the dosage form that is convenient from patient’s perspective and utilize an approach that is unlikely to add complexity during regulatory approval process.

2.3.1 **CONTROLLED DRUG DELIVERY SYSTEM**

Controlled drug delivery system can be developed by using a polymer, whether natural or synthetic which is combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. Controlled drug delivery system control and maintain the drug levels within a desired range to achieve more therapeutic effect and avoid overdosing (Brannon, 1997). The drug percentage, particle size, solubility and the type of the polymer, viscosity and particle size are the most important factors to be taken into account when developing a formulation based on hydrophilic matrices (Maderuelo et al., 2011).

2.3.2 **CONTROLLED RELEASE MECHANISMS AND APPROACHES**

Controlled drug delivery systems can be classified according to different criteria such as type of release (e.g. delayed, slow, prolonged, pulsed, repeat-action, etc.), the mechanism of release (e.g. diffusion, dissolution, etc.) or the type of technological system (Caramella et al., 1995).

Some of the important techniques that are used for extending drug release are as follow:

2.3.2.1 **Diffusion controlled release systems**

Diffusion occurs when the drug–polymer mixture is exposed to GI fluid, resulting in release of the drug from the system. In these systems water-insoluble polymer can be used to control the flow of water and the subsequent egress of dissolved drug from the dosage form. In
reservoir devices, a core of drug is coated with the polymer and, in a matrix system; the drug is dispersed throughout the matrix. Matrix materials may be plastics e.g. poly (methylacrylate), polyvinyl chloride or various other types of polymers such as cellulose derivatives or fatty compounds including carnauba wax, ethyl cellulose (EC) and Eudragit® RS100 (Siepmann et al., 1999). However cellulose derivatives are commonly used in the formulation of reservoir systems. Kreye et al. (2011) studied the drug release mechanisms of water soluble drug (theophylline and propranolol hydrochloride) from compressed lipid implants. The drug diffusion with constant diffusivities was found to be the dominant drug release mechanism. Cuppok et al. (2011) studied the drug release mechanisms of metoprolol succinate from various types of systems, coated pellets were prepared by casting or spraying aqueous dispersions of the Eudragit® NE polymer. Increasing Eudragit® NE content the films became more hydrophobic, resulting in decreased water permeability as well as water uptake rates and extents. The drug release from thin films was mainly controlled by pure diffusion.

(a) **Matrix diffusion control**

Matrix diffusion controlled systems involve dispersion of drug in either water-insoluble or a hydrophilic polymer (Jamzad et al., 2005). In these systems the drug release rate is controlled by the diffusion of drug molecules in the swollen polymer matrix (Colombo et al., 2000). Drug release from insoluble matrices involves penetration of fluid, followed by dissolution of the drug particles and diffusion through fluid filled pores. In case of soluble matrix containing swellable hydrophilic substances, the drug becomes available as the matrix swells or dissolves, and swollen matrix then undergoes surface erosion with little or no bulk erosion (Peppas and Khare, 1993). The surface area of the matrix decreased with the time, with a concomitant decrease in the drug release. The diffusion depends on the solubility of the drug in the polymer. The drug may either present below its solubility limit and dissolved in the polymer or present well above its solubility limit and dispersed in the polymer. Drug release by diffusion mechanism is depicted in figure 5.
(b) **Reservoir diffusion control**

Reservoir diffusion matrix system occurred by coating core of drug with the water insoluble polymer either by pan coating or by microencapsulating technique. The drug release mechanism through this system is controlled by diffusion of dissolution media through the membrane to the inside of the core, then dissolution of the drug and diffusion of the drug into the surrounding fluid. Materials used in such devices are hydroxypropyl cellulose, ethyl cellulose and polyvinyl acetate. The examples of reservoir diffusion products are Nico-400 (nicotinic acid) manufactured by Jones, Nitro-Bid (nitroglycerine) manufactured by noechst Marlo Rossuelt and Bronkodyl SR (theophylline) manufactured by Sanofi-Winthrop. Figure 6 shows the mechanism of drug release by reservoir diffusion.

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**Figure 5:** Schematic represent drug release by diffusion mechanism

**Figure 6:** Schematic represent drug release by reservoir diffusion mechanism
2.3.2.2 Dissolution–controlled system

In this system the rate of dissolution of the drug is controlled by slowly soluble polymers or by drug encapsulation. Dissolution controlled release can be obtained by slowing down the dissolution rate of a drug in the GI medium by incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness. Once the coating is dissolved, the drug becomes available for dissolution. By varying the thicknesses of the coat and its composition, the rate of drug release can be controlled. These products can be prepared as tablets or as encapsulated pellets. Fares et al. (2011) investigated the effect of inulin and poly (acrylic acid) in control the drug release rate, by enhancing the drug dissolution of poorly water-soluble drug. The increase of inulin content in the polymeric matrix increase the drug dissolution gradually until it reaches its maximum. The drug release from solid dosage can be controlled by using cyclodextrins, which enhance the solubility of the drugs and increase the dissolution rate of the drugs (Salústio et al., 2011).

(a) Matrix dissolution control

In this system, the drug is dispersed homogeneously in a rate controlling polymers. Hydrophilic drug can also be formulated as controlled release products by controlling their dissolution rate by using hydrophobic polymers such as waxes (beeswax, carnauba wax) and hydrogenated castor oil. Such systems can be prepared by dispersing the drug in the molten wax, congealing and granulating them (Varshosaz, 2006; Shoaib, 2010). The drug dissolution rate of the poorly water soluble drug increased with all water soluble excipients in the order of mannitol > lactose > maltitol > sorbitol > sodium chloride (Saharan et al., 2011).

(b) Reservoir dissolution control

In this system, the drug particles are coated or encapsulated by one of the several microencapsulation techniques with slowly dissolving materials like cellulose derivates, polyethylene glycols, polymethacrylates, waxes etc. The resulting reservoirs (coated beads, multiparticulate system, pellets) may be filled as such in hard gelatin capsules (Spansules) or compressed into tablets (Matsumoto et al., 2005). The common multi-particulate systems are microparticles (microspheres or microcapsules), nanoparticles (nanospheres or nanocapsules) and liposomes (Xing et al., 2003).
2.3.2.3 Erosion system

The release of drug from this system is controlled by the erosion rate of a carrier matrix. The rate of release is determined by the rate of erosion, e.g., polyethylene oxides (Kojima et al., 2008). Giunchedi et al. (1993) prepared of extended release erodible hydrophilic matrices containing a water insoluble drug (carbamazepine). These matrices appear to be subjected, during in vitro tests, both to a gelation and to erosion process. They are capable of releasing the drug at a nearly constant rate, until almost the entire drug content is released. Erodible matrix systems based on glyceryl monostearate and polyethylene glycol 6000 or poloxamer 188 were prepared to control on synchronized release of the five active components of herbal medicine. Buccodhesive erodible disks of cetylpyridinium chloride for treatment of oro-dental infections were prepared using different bioadhesive polymers (Ali et al. 2002). Di Carlo et al. (2002) studied the effects of chitosan on in-vitro release of ofloxacin from mucoadhesive erodible ocular inserts. The developed matrix formulation was showing erosion-controlled release mechanisms (Lu et al., 2007). Cahyadi et al. (2011) investigated the mechanism and rate of drug release of the hypromellose matrices. The drug release mechanism was due to a combination of diffusion and erosion. Viridén et al. (2011a) investigate the effect of different substituent heterogeneities of HPMC on the drug release from matrix tablets of the poorly soluble carbamazepine. The drug release was highly affected by the substituent heterogeneity of the polymers and the drug was mainly released by erosion.

2.3.2.4 Osmotic systems

Oral osmotic system, popularly known as ORAS®, based on principle of osmotic pressure to release the drug at constant rate. The rate of release of drug in this system is determined by the constant inflow of water across a semi-permeable membrane into a reservoir which contains an osmotic agent. The drug is either mixed with the agent or is located in the reservoir, in which the dosage form contains a small hole from which dissolved drug is pumped out due to osmotic pressure at a rate determined by the rate of entrance of water in the tablet. The advantage of this type of product is that the release is unaltered by the environment of the GIT and it relies simply on the passage of the water into the dosage form. Altering the osmotic agent and the size of the hole can modify the rate of release (Liu and Chea, 2006). The effect of orifices and the
concentration of osmotic agents on the rate of release of the active material were studied in ibuprofen tablets prepared by sodium chloride and polyethylene glycol 6000 as osmotic agents. It was observed that the release rate of ibuprofen was influenced by the concentration of osmotic agents (Özdemir and Sahin, 1997). Waterman et al. (2009) developed an osmotic tablet as controlled-release; extrudable core system to deliver high doses of low solubility drugs. The dosage form has been successfully control delivery of drug over a range of delivery rates even with 50% of the tablet being drug. Nifedipine and metoprolol tartrate extended release tablets were developed as sandwiched osmotic tablet system. This system composed of a middle push layer and attached drug layers of nifedipine and metoprolol. The system was stable and had a good sustained effect in comparison with the conventional product. The advantage of the sandwiched osmotic tablet system over the commercialized push–pull osmotic tablet system is its simplicity of preparation (Kumaravelrajan et al., 2010). Waterman et al. (2011) developed an osmotic oral capsule to control drug delivery at fixed delivery rates independent of the drug solubility or drug loading. Marucci et al. (2010) developed new mechanistic model of drug release by osmotic pumping and diffusion from pellets coated with a semi-permeable film developing pores created by the leaching of water-soluble compounds initially present in the coating pellets. The drug release was occurred through small pores created in the coating. The schematic diagram of osmotic pump system is represented in figure 7.

![Figure 7: Schematic diagram of osmotic pump system (Gaebler, 2007)](image-url)
2.3.2.5 Gastroretentive Drug Delivery Systems

Another controlled release technology which received an appreciable attention in the site specific drug delivery is gastroretentive systems. These systems have been developed to provide continuous, controlled administration of the drugs at the absorption site. Attempts have been made to retain the dosage form in the stomach by increasing the retention time by altered-density systems, gas-generating systems, mucoadhesive systems, and gastric-emptying delaying devices (Kagan et al., 2008). Gastroretentive system made of a matrix tablet coated with a permeable membrane on immersion in simulated gastric fluid expands for 18–20 h, allowing the release of the drug (e.g. chlopheniramine maleate or riboflavin phosphate). The coat was made of an elastic polymer (Eudragit® R), whereas Carbopol® acted as a strong binder to the swollen tablet, mainly due to cross-linked polyvinyl pyrrolidone. In this example, the addition of carbonates provided an alkaline microenvironment (optimal pH), enabling the jellification of Carbopol® providing buoyancy to the tablet (Deshpande et al., 1997). Expandable gastroretentive dosage forms have their size increased by swelling, prolonging their gastric retention times. After drug release, their dimensions are reduced with evacuation from the stomach. Gastric retention is enhanced by a substantial increase on the dimensions of the tablets with a high rigidity of the dosage form to withstand the peristalsis and mechanical contractility of the stomach (Klausner et al., 2003).

The swelling ability of some materials has been advantageous for the design of dosage forms to deliver drugs to the stomach (Brannon, 1997). By swelling some dosage forms have their density decreased below one promote floatation of the tablets in water. Gazzaniga et al. (2008) referred that swellable polymers undergo typical chain relaxation phenomena that coincide with a glassy rubbery transition. In the rubbery phase, these polymers may be subject to swelling, dissolution and erosion or, alternatively form an enduring gel barrier when cross-linked networks (hydrogels) are built. Other materials have been considered for instance, collagen can expand in the stomach after contact with the gastric fluids forming floating collagen sponges. These sponges can be produced by freeze-drying a solution of collagen containing a drug (e.g. riboflavin, captopril, and acyclovir). The dried product was mixed with hydroxypropyl methylcellulose (Groning et al., 2006). Tablets containing hydroxypropyl cellulose, hydroxyethyl cellulose or hydroxypropyl methylcelluloses form an outer hydrated layer of viscoelastic gel structure in the gastric fluid. This gel was able to entrap air increasing the matrix volume, thus decreasing the density (Baumgartner et al., 1998). Chueh et al. (1995) combined
the effect of floating with adhesion in a device designed to prolong the residence time of a tablet containing sotalol hydrochloride in the stomach. These effects were achieved by incorporating sodium carboxymethylcellulose, hydroxypropyl methylcellulose, ethyl cellulose and cross-linked polyvinyl pyrrolidone.

Buoyancy of a tablet can be achieved by entrapment of air in an agar gel network. The floating tablet of density of 0.67 controlled the release of theophylline but the retention in the stomach was further enhanced by the presence of food which significantly increased the retention time (Desai and Bolton, 1993). Similarly, diltiazem tablets have shown a higher hypotensive action when given to patients in a floating controlled release tablet (Gu et al., 1992). The use of a gas to decrease the density of the dosage form is an alternative to the previous strategy. Floating of dosage forms can be achieved by the inclusion of a gas generator agent in an inert matrix (Baumgartner et al., 2000). Sustained release verapamil hydrochloride has been delivered to patients as floating tablets produced from granules containing mixtures of a matrix former (hydroxypropyl methylcellulose, hydroxypropyl cellulose, ethyl cellulose or Carbopol®) together with sodium bicarbonate and anhydrous citric acid (Elkheshen et al., 2004). Mostafavi et al. (2011) developed and evaluated a prolonged release gastroretentive formulation of ciprofloxacin to be administered once daily. The pharmacokinetic parameters indicated that the developed formulation extended the pharmacokinetic profile.

2.3.2.6 Microencapsulation systems

It is a process in which very tiny droplets or particles of liquid or solid material are surrounded or coated with a continuous film of polymeric material. Pharmaceutical applications of microparticulate delivery systems have been studied extensively. Microencapsulation technology allows protection of the drug from the environment, stabilization of sensitive drug substances, elimination of incompatibilities, or masking of unpleasant taste. Using microencapsulation for development of controlled or prolonged release dosage forms has been increased. These microcapsules have a number of benefits, such as converting liquids to solids, separating reactive compounds, improved material handling properties. They play an important role as drug delivery systems; they improve bioavailability of conventional drugs and minimizing side effects. Microspheres can be used for different routes of administration like oral,
parenteral and pulmonary drug delivery. Microparticulate can be administered either as dry powder by inhalation, or in form of an aqueous suspension for parenteral administration. Active materials are encapsulated in a biocompatible or biodegradable polymer (gelatin, plastic, wax) forming particles with a diameter in the range of 1 to 1000 µm are then encapsulated in micron-sized capsules of barrier polymers (Li et al., 2008).

2.3.2.7 Ion exchange resins systems

Some drugs can be bound to ion exchange resins and, when ingested, the release of drug is determined by the ionic environment within the gastrointestinal tract, these determine the release of the drug from the system. Ion-exchange resins are also used as excipients in pharmaceutical formulations, such as tablets, capsules, and suspensions. In these uses the ion-exchange resin can have several different functions, including taste-masking, extended release, tablet disintegration, and improving the chemical stability of the active ingredients. The drug is released slowly by diffusion mechanism from the resins particle structure as shown in figure 8.

Examples of these types of products are Duromine® containing the basic drug phentermine complex onto an anionic resin and MS Contin (morphine sulphate) suspension which uses a polystyrene sulphonate resin. Kwon et al. (1992) studied the control release of proteins via ion exchange from Albumin-heparin and albumin microspheres which were prepared using ion exchange gels. The albumin-heparin microspheres enhanced ion exchange characteristics over albumin microspheres. A heterogeneous gel vehicles formulations as an ion exchange resins system was developed to transport nicotine across artificial and human skin membranes. Both strong and weak resins were used and the effects of resin bead size, the degree of cross-linking in the polymer, the medium in which the drug was bound, the drug concentration and the magnitude of the current were determined. The heterogeneous vehicles were shown to have advantages over comparable simple hydrogel vehicles in their versatility, in their capacities to store the drug and to control drug delivery rate (Conaghey et al., 1998). An ion exchange microsphere of indomethacin was developed as a drug delivery system to control the drug release rate through reduction of diffusion rate of the drug within the particle by impregnation of calcium alginate inside the microsphere porous (Chretien et al., 2004).
2.3.2.8 pH independent systems

In this system release of acidic or basic drug is controlled by mixing them with one or more buffering agents and coating with gastrointestinal fluid permeable film forming polymer. On permeation of the GI fluid in the system through the membrane, the buffering agents adjust the fluid inside to suitable constant pH, in which constant can be achieved rate of drug release. The duration of drug absorption after oral administration is mainly a function of drug related properties such as rate of absorption and clearance as well as residence time of the delivery system at the absorption site. This system is able to simulate dissolution of drugs, pH change and permeation of drugs through the epithelial cell membrane in the gastrointestinal tract. The pH dependent coatings make possible the design of dosage forms containing high levels of drugs, as alternatives to matrix or hydrogel systems using polymers dissolving at pH > 7 (e.g. Eudragit® FS) it is possible to prevent tablets or pellets from releasing drugs in the stomach or proximal small intestine (Vandamme et al., 2002). Tran et al. (2011) investigated the controlled pH-independent release of the pH dependent drug losartan potassium. The pH-independent of the drug from the sustained release tablet was achieved for 2h in gastric fluid (pH 1.2) and for 10h in intestinal fluid (pH 6.8). Körber et al. (2011) evaluated the strategies to set-off the very strong...
pH-dependent solubility of a weakly basic drug. Ethylcellulose/hydroxypropyl cellulose coated drug pellets was successfully control the drug release over 18 h.

2.3.3 DRUG RELEASE MECHANISM MODELING

The Mechanism of drug release elucidated by applying several equations that are reported in the literature to identify the fitting suitable mechanisms of drug release of the tested formulation with respect to the release data. The data can be evaluated according to the following equations:

1. **Zero-order model** (Donbrow *et al*., 1980)

\[ M_t = M_0 + K_0 t \]  

Where, \( M_t \) is the amount of drug dissolve in time \( t \), \( M_0 \) is the initial amount of drug in the solution, \( K_0 \) is the zero order release rate constant.

2. **First order model** (Merchant *et al*., 2006)

\[ \log C = \log C_0 + \frac{kt}{2.303} \]

Where, \( C \) = cumulative percent of drug release at time \( t \), \( C_0 \) = the initial concentration of drug and \( k \) = first order rate constant.

3. **Higuchi model** (Higuchi, 1961)

\[ \frac{M_t}{M_\infty} = K_h \sqrt{t} \]

Where \( M_t \) and \( M_\infty \) are cumulative amounts of drug released at time \( t \), and infinite time, respectively, \( K_h \) is the Higuchi rate constant and \( t \) is release time.

4. **Korsemeyer- Peppas equation** (Korsmeyer *et al*., 1983)

\[ \frac{M_t}{M_\infty} = K^n \]

Where, \( M_t \) and \( M_\infty \) are the absolute cumulative amount of drug released at time \( t \) and infinite time, respectively; \( k \) is the kinetic constant and ‘\( n \)’ is an exponent characterizing the diffusional mechanism. In cases of ‘\( n \)’ = 0.5 (pure diffusion controlled drug release) and if ‘\( n \)’ = 1 (Case II transport).

5. **Hixon-Crowells cube root of time equation** (Hixson and Crowell, 1931)

\[ M_0^{1/3} - M_t^{1/3} = k_3 t \]
Where $M_0$ is the initial amount of drug in the formulation, $M_t$ is the amount remaining at any time $t$ and $k_s$ is the constant incorporating the surface-volume relation.

### 2.4 Matrix systems

Matrix systems are considered as a simplest method for preparing sustained release tablets for an oral dosage form, in which matrix systems maintain and control the release of the drug in continuous manner by dissolution and or diffusion controlled mechanisms (Rowe, 1975). To control the release of the drugs, which are having different solubility properties, the drug is dispersed in inert swellable substances (hydrophilic polymers), non-swellable substances (hydrophobic polymers) or plastic materials in which the soluble drug was mixed with an inert hydrophobic polymer (non-interacting with the biological fluids) and then compressed into a tablet. Matrix tablets which were prepared by compressing granules to form matrices appeared in 1959 (British 808014). Introduction of commercial plastic matrix include the Duretter® (Sjogren, 1971) in which the drug release from the plastic matrix does not depended on the digestive juices condition (Rowe et al., 1975). During its transit GIT, the matrix tablet does not disintegrate as in conventional tablets, but it may remains intact and the porous matrix can be recovered in the stool after releasing the drug, the polymers used in these preparations were predominantly inert (insoluble polymers). The first polymers used for the preparation of matrix tablets were semi-synthetic polymers and lipophilic compounds.

To prepare extended release formulations, drug should have some of characteristics that make development of system suitable and rational as follow:

a) Drug has relatively small dose, so the dosage form will be easy for patient to swallow.

b) Drug with short elimination half-life (2-4 h).

c) Drug with high margin of safety, to prevent toxicity due to dose dumping or misuse.

d) Drug used in chronic treatment, for more convenient to patient to use single dose.

e) Drug has low molecular size, so drug will absorbed by passive diffusion.

#### 2.4.1 Advantages of Matrix Tablets

1. Easy to manufacture by using conventional manufacturing equipment.

2. Versatile, effective and low cost.
3. Can be made to release high molecular weight compounds.
4. Release kinetics profile can be tailored with modification.
5. Suitable for compound from low to high drug loading.

2.4.2 Disadvantages of Matrix Tablets
1. The drug release rates vary with the square root of time.
2. Release rate continuously diminishes due to an increase in diffusional resistance.
3. The remaining matrix must be removed after the drug has been released.

2.4.3 Classification of Matrix systems
Matrix tablets can be classified according to retardant material used as following:

2.4.3.1 Hydrophilic Matrix systems
Oral extended release preparations are prepared by mixing the active ingredients with hydrophilic polymer and compressing the mixture into tablets. Upon administration rapid dissolution of the drug is observed from the surface followed by formation of a viscous gel barrier due to hydration and gelation of the gum. Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance. Development of hydrophilic matrix systems can be prepared by using of one or combination of hydrophilic polymers, in which the mechanism of drug release is usually based on combination of diffusion and erosion processes. Hydroxypropylmethylcellulose (HPMC) is one of the most commonly used hydrophilic materials for development of hydrophilic matrix systems (Tiwari et al., 2003; Abdelkader et al., 2007). The rate of hydration increases with an increase in the hydroxypropyl content. The polymer material swells and the drug molecules begin to move out of the system by diffusion at a rate determined by the nature and composition of the polymer as well as formulation technology.

Natural polysaccharides are the highly preferred hydrophilic materials used for matrix tablets because they are biodegradable, nontoxic, safe, cost effective, have regulatory acceptance and easy available. Xanthan gum, which is a natural, biosynthetic, edible gum, has a greater drug release retarding property (Baumgartner et al., 2008). Guar gum is a nonionic polysaccharide gum which also extensively used for the development of matrix tablets (Fan et al., 2008; Varshosaz et al., 2006). Other natural polymers used for this purpose are alginites, chitosan, carageneen etc. Hydrophilic matrix tablets form gel when polymer interacts with water. This
interaction may lead to plasticization, dissolution, erosion or degradation of the polymer, which is responsible for achieving controlled release. Swelling of gel forming hydrophilic matrix tablets and erodible matrix tablets are the most important polymer behavior which is due to interaction of polymer with aqueous gastro-intestinal fluid, in which polymer is plasticized by macromolecular chain relaxation and volume expansion.

Drug release is governed by diffusion of the dissolved drug through the swollen gel layer and shows a burst effect, caused due to dissolution and leaching of drug particles present at the surface prior to formation of the release controlling gel. It has been reported that many drugs need to be administered at varying rates, and for some drugs, such as those used at the beginning of wound treatment, an initial burst provides immediate relief followed by prolonged release to promote gradual healing (Setterstrom et al., 1984). There is no relation between drug solubility and excipient percolation threshold in hydrophilic matrices (Fuertes et al., 2010). Ferrero et al. (2010) studied the mechanism of swelling polymer in compressed hydrophilic matrices made of cellulose ethers. They concluded that the polymer chain relaxation is not the rate-limiting step in the drug release process. The mechanism of drug release from swellable device is determined by the relative position of the rubber glass interface, the rate at which it penetrates the tablet, the diffusion coefficient of the drug and the erosion rate of the gel (Harland et al., 1988). Diffusion controlled release mechanism (Fickian) control drug release through the swollen gel layer when the penetration rate is high as compared to drug diffusion rate. Several parameters have been developed to characterize drug release from swelling controlled dosage from. Peppas and co-workers extensively studied diffusion and drug release from swellable tablets (Peppas, 1985; Ritger and Peppas, 1987). The release of drug from swellable tablets can be expressed by the following equation:

$$ \frac{M_t}{M_\infty} = k^n $$

Where $\frac{M_t}{M_\infty}$ the fractional of drug released is 'n' is the diffusion exponent, and $k$ is the pre-exponential factor. When the rate of solvent penetration is higher than the diffusion rate of dissolved drug through swollen gel layer, and $n = 0.5$ that express Fickian diffusion controlled release mechanisms. If the drug release governed by the penetration controlled release, in which the diffusion of the drug through the gel layer is fast as compared to the solvent penetration this
lead to zero-order release \((n = 1)\), this is also named as non-Fickian. Release profiles with intermediate \(n\)-values \((0.5 < n < 1)\) are classified as anomalous.

Polymers used in the preparation of hydrophilic matrices are divided into three main groups:

a) Cellulose derivatives: methylcellulose 400 and 4000 cPs; hydroxyethylcellulose; hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000 cPs; and sodium carboxymethylcellulose.

b) Non cellulose natural or semisynthetic polymers: agar, carob gum, alginates, molasses, polysaccharides of mannose and galactose, chitosan and modified starches.

c) Polymers of acrylic acid (corbopol 934) are the most used variety.

2.4.3.1.1 Hydroxypropyl methyl cellulose

Hydroxypropyl methylcellulose (HPMC) is a methylcellulose modified with a small amount of propylene glycol ether groups attached to the anhydroglucose of the cellulose. The dry product contains \((19-30\%)\) of methoxyl \((-OCH_3)\) groups and \(3-12\%\) of hydroxypropyl \((-OCH_2CHOHCH_3)\) groups. HPMC is a white or off-white odorless and flavorless powder. It is available in different grades that vary in properties like viscosity and extent of substitution, in which the viscosity depends on the length of the cellulose chain and the number of substituent on the polymeric backbone (Table 2). HPMC is soluble in cold water, glacial acetic acid, ethanol, methanol and propylene glycol, slightly soluble in acetone and practically insoluble in hot water, ethylene glycol and toluene. The viscosity depends on the degree of substitutions. HPMC is dissolved in a mixture of 10% methanol and 90% methylene chloride to form colloidal solutions. It is commonly used as hydrophilic polymer since the early 1960s (Pham and Lee, 1960). HPMC is a pH independent material and the drug release rates from HPMC matrix formulations are generally independent of processing variables such as compaction pressure, drug particle size, and the incorporation of a lubricant (Ford et al., 1985). It has been used as dispersant in the production of PVC and as thickener, stabilizer, emulsifier, water retention agent, film-forming agent, cosmetic and excipients. It is also used as a tablets binder (Chowhan, 1980) and as a film forming agent (Okhamafe and York, 1982). Chemical structure of HPMC is shown in figure 9.

HPMC is able to control drug release by acting as gelling agents in formulations. These properties are very important because they are responsible for the drug release by hydration, diffusion and erosion-resistant gel layer. It is reported that HPMC matrices can be used to develop sustained release formulations of different drugs such as salbutamol and ketoprofen.
The most important parameters for the drug release from tablets matrices are the penetration rate of solvent into the matrix. This parameter will be most effective for hydrophilic drugs. However, the erosion rate of the matrix system will be most effective for hydrophobic drugs. The penetration rate of medium to the matrix can controlled by changes in the interspaces volume of the matrix by the use of higher levels of materials such as lactose, which quickly rinses out of matrix system and leads to rapid release of the drug. Drug release of HPMC based controlled release tablets are controlled by diffusion through the gel layer. By proper selection of appropriate grade of HPMC polymer, the viscosity and erosion–dissolution characteristics of the gel layer can be controlled. For hydrophobic drugs the low viscous HPMC polymer grade is a suitable choice, since the erosion rate of the tablet matrix is the controlling factor for drug release.

The release rate of poorly soluble drug can be controlled by the rate of tablet erosion (Tahara et al., 1995). Huang et al. (2005) have suggested a hydroxypropyl methylcellulose-acetate maleate co-polymer to deliver drugs to the duodenum only, since the polymer was dissolving at $3 < \text{pH} < 3.7$. High concentrations of dissolved sugars can accelerate in vitro drug release in certain hydroxypropyl methylcellulose matrices (Williams et al., 2009). Further study to investigate the effects of combining sugar and salts commonly found in foods on the drug release behaviour of an HPMC matrix. The results show that the food salts can significantly reduce the concentration required for sugar effects on HPMC matrices (Williams et al., 2010a). Viriden et al. (2011) investigate the effect of the chemical heterogeneity of HPMC on the release of model drug substances from hydrophilic matrix tablets. They conclude that the drug release depending on the lipophilicity of the drug and the substituent heterogeneity of the HPMC used. Addition of tris(hydroxylmethyl) aminomethane as a buffering system for hydroxypropyl methylcellulose (HPMC) hydrophilic matrices containing a weak acid drug provided extended, diffusion-based release kinetics, without loss of matrix integrity at high buffer concentrations (Pygall et al., 2010). The matrix formulation with a lower concentration of HPMC and higher lactose concentration is more likely to perform poorly in the in-vivo environment (Ghimire et al., 2010). HPMC matrices containing a pregelatinized maize starch as diluents showed more drug retardation in compression to matrices containing lactose or MCC. This effect may be imparted through synergistic interactions between starch and HPMC (Levian and Rajabi-Siahboomi, 2004).
Figure 9: Chemical structure of HPMC

Table 2: HPMC different grades and viscosity range

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>HPMC grade</th>
<th>Viscosity range (mPa.s) at 25°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>40–60</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>75–130</td>
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<tr>
<td>6</td>
<td>2500</td>
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</tr>
<tr>
<td>7</td>
<td>4M</td>
<td>3500–5000</td>
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<td>8</td>
<td>7M</td>
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<td>15M</td>
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<td>25M</td>
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<td>40M</td>
<td>34000–46000</td>
</tr>
<tr>
<td>13</td>
<td>55M</td>
<td>46000–63000</td>
</tr>
<tr>
<td>14</td>
<td>70M</td>
<td>60000 Min</td>
</tr>
</tbody>
</table>
2.4.3.1.2 Natural gums polymers

Natural gums are translucent and amorphous substances produced by the plants. Usually pathological products, gums are produced when the plants are growing under unfavorable conditions or when injured. Gums are plant hydrocolloids and may be anionic or non ionic polysaccharides. On hydrolysis, gums yield sugar and salts of uronic acid (Tuovinen e al., 2003). Gums are hydrophilic in nature, cost-effective, safe, easily available, biodegradable, and nontoxic, hence are preferred for the development of matrices for drug delivery. Even the naturally occurring polysaccharides can be easily modified chemically and biochemically to impart desirable properties suitable for designing of drug delivery systems. In the past decade, a number of studies have been performed employing the use of the natural gums as release modifiers both for controlled release and delayed release of drugs through a variety of routes (Sinha and Kumria, 2001; Varshosaz 2006; Fan et al., 2008).

Controlled release technologies based on economical excipient and cost effective manufacturing processes provide an interesting option as generic products bioequivalent to high priced originator may be produced at low costs. From this point of view, the introduction of new excipients of safe natural origin onto the market is highly facilitating the registration of new drug products, and it is reducing the time and expense required for toxicological investigations. So due to the safety and the commercial usefulness of this category of excipients, pharmaceutical technologists world over are extensively exploiting the use of natural gums as release modifiers. However, the natural gums available for the said purpose are limited, and it is pertinent to explore the other gums which are having suitable characteristics to be utilized as a pharmaceutical aid. In the recent years a lot of attention has been laid on the development of modified drug delivery systems due to innumerable reasons.

a) Xanthan gum

Xanthan gum (XG) is high molecular weight extracellular polysaccharide produced by the fermentation of carbohydrate source with Xanthomonas campestris. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (Beta-D-gulucose residues) and a trisaccharide side chain of beta-D-mannose-beta-D-glucuronicacid-alpha-D-mannose attached with alternate glucose residues of the main chain (Bhardwaj et al., 2000; Katzbauer, 1998). Figure 10 shows the chemical structure of xanthan gum. The anionic character of this polymer is due to the presence of both glucuronic acid and pyruvic acid groups in the side
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chain (Kwon et al., 1996). XG showed a higher ability to retard the drug release than synthetic HPMC (Gohel et al., 2002). It contains glucose 37%, mannose 43.4%, glucuronic acid 19.5%, acetate 4.5%, and pyruvate 4.4%. It swells in gastric fluid to produce a highly viscous layer around the tablet through which the drug can slowly diffuse. This property makes it a useful ingredient for controlled release and sustained release (SR) applications. Its compatibility with a wide variety of ingredients makes it particularly effective in these applications as a hydrophilic polymer. XG has been used to develop and evaluate different model drugs as hydrophilic matrix for CR preparation e.g.: theophylline (Lu et al., 1991), cephalexin (Dhopeshwarkar et al., 1994), prednisolone (Watanabe et al., 1992), and indomethacin (Watanabe et al., 1993). XG consists of glucose, mannose, and glucuronic acid (Pai and Khan, 2002). It is widely used as a thickening agent in the food industry (Gwen et al., 1996), and in pharmacy it is used as a hydrocolloid to thicken, suspend, emulsify and stabilize water-based systems (Price, 1990). It is reported that XG can retards in-vitro drug release and provides time-independent release kinetics (Ingani and Moes, 1988; Baichwal and Staniforth, 1991; Lu et al., 1991; Dhopeshwarkar and Zatz, 1993; Saxena et al., 1993; Talukdar and Plaizier-Vercammen, 1993). Moreover, it can also work effectively in vivo and establish constant drug plasma levels (Lu et al., 1991). It has been reported that when XG mixed with starch, the stability and viscosity of gum get improved (Abdulmola et al., 1996; Alloncle and Doublier, 1991; Sudhakar et al., 1996). Swelling of XG matrix tablets was studied and a reciprocal relationship with salt concentration is reported, which is independent of the nature of the electrolyte, but it depend on the solubility of the drug. The drug release from XG matrix is regulated by its swelling behavior, so the release of an insoluble drug follows a direct relationship with swelling of the polymer matrix, while a reciprocal relationship is observed with soluble drugs. Swelling of the XG polymer matrix shows a square root of time dependence whereas drug release is almost time independent (Talukdar and Kinget, 1995). Mikac et al. (2010) studied the swelling dynamics of xanthan gum tablets at different pH and the effect in the drug release. They conclude that drug release is greatly influenced by changes in the xanthan molecular conformation, as reflected in changed thickness of the gel layer.
b) Lannea Woodier gum

Lannea Woodier gum or Odina gum (OG) is a new gum collected from the bark of *Lannea Woodier* or *Odina Woodier* Roxb., family *Anacardiaceae*. It is a large tree which locally known as Jingan, Kamlai tree; in Bengal known as Jeol trees, and in English it is called Rhus olina, which is common in deciduous forests of India (Kirtikar and Basu, 1935; Chauhan, 1999). The gum was investigated by Dhar and Mukherjee (1959) who reported that the gum containing arabinose, galactose, and galacturonic acid as constituent units. The structural composition of the gum and degradation has been reported earlier (Bhattacharyya and Rao, 1964). In ayurvedic medicine, it is reported the use of various parts of *Odina Woodier*. The leaves have been used in the treatment of elephantiasis of the legs (Kirtikar and Basu, 1935). Juice of green branches is used as an emetic in case of coma or insensibility. The bark extraction is used for vaginal trouble, curing ulcer and heart disease (Kiritkar and Basu, 1975). OG was indicated as a safe pharmaceutical excipient. Recently, Mukherjee *et al.* (2006) has evaluated the binding capability of the gum by comparing it with the standard starch paste as a tablet binder powdered bark. In this study, it was demonstrated that the gum provides desired hardness, binding and disintegration time to the formulation in quantities significantly lower than that of starch paste.

c) Boswellia gum

Boswellia gum (BG) is collected from the Boswellia tree (Figure11). The English name of this tree is frankincense; in Sanskrit it is known as Shallaki and in India known as Salai
guggul which comes from *Boswellia serrata*. Ru xiang is a Chinese name (*Boswellia carterii*). It is a tree that grows in Somalia and parts of Saudi Arabia and India; the tree native to hilly regions of India. The resin has a long tradition of use in Ayurvedic medicine. Boswellin is a standardized ethanol extract of boswellia gum which is available in the food store and contains 60 to 65 percent of boswellic acid and its derivatives. These are the primary active ingredients in the gum resin. The volatile oil contains pinene and phellandrene, among other ingredients, and imparts a distinctive fragrance, similar to that of frankincense. BG is pungent and bitter in taste, and warm in action.

Figure 11: Boswellia gum

BG is used as an effective pain-relieving, anti-inflammatory in the treatment of osteoarthritis, autoimmune inflammations such as rheumatoid arthritis, diarrhea, lung diseases (including asthma), boils, edema, pain, psoriasis, ulcerative colitis, bronchial asthma, and Crohn's disease (Safayhi *et al*., 1996; Singh and Atal, 1986). It works by affecting one of two classes of mediators of inflammation along the leukotriene pathway. Prostaglandins and leukotrienes are known collectively as eicosanoids, and they mediate pain and edema. In Ayurveda, it is used to reduce pain, swelling, mucus and inflammation in the lungs, intestines and joints. BG can be used as an alternative to NSAIDs and steroids, which does not causing any of common side effects of NSAIDs and steroids such as stomach bleeding, ulceration. Patients suffering from ulcerative colitis showed improvement after treatment with *Boswellia serrata* gum resin (Gupta *et al*., 1997). Gupta *et al.* (1998) studied also the effect of BG for the treatment of asthma. They carried out double blind study (placebo-controlled study) on 40 of asthma patients in Germany, and they showed marked improvement in the treated patients compared to the
control group. Also they studied effect of boswellia on ulcerative colitis patients. They observed an improvement in 82% of the patients.

Chinese study has shown that boswellia can be used to treat leukemia. It works by stimulation of leukemic cells to kill themselves, a phenomenon known as programmed cell death (Jing, et al., 1999). Gum resin of Boswellia serrata inhibit the synthesis of DNA, RNA and protein in human leukemia and significantly inhibit the cell growth of HL-60 cells (Shao et al., 1998). Oleo-gum-resin of boswellia serrata might benefit liver injury induced by carbon tetrachloride, paracetamol or thioacetamide (Jyothi et al., 2006). Boswellia gum in combination with HPMC in different ratios were used to develop colon-specific compression coated systems for delaying the drug release of 5-fluorouracil (Sinha et al., 2007a).

2.4.3.1.3 Acrylic acid Polymers

Acrylic acid is the simplest unsaturated carboxylic acid, which has double bond and carboxyl group CH₂=CHCOOH. The vinyl group is attached to the carbonyl carbon directly. Its systemic name is 2-propenoic acid. Acrylic acid has two reaction points or functional groups required for polymerization process. Purified (glacial) acrylic acid is a clear, colorless liquid with a characteristic acrid odor. It is miscible with water, alcohol and ether. Acrylic acid is produced from C₃ refinery. Acrylic acid undergoes the typical reactions of a carboxylic acid and forms acrylic esters-basic alkyl esters which are methyl, butyl, ethyl acrylate, and 2-ethylhexyl acrylate. Acrylic acid and its esters undergo the reactions of the double bond which readily combine with themselves or other monomers (e.g. amides, methacrylates, acrylonitrile, vinyl, styrene and butadiene) to form homopolymers or co-polymers which are used in the production of coatings, adhesives, elastomers, super absorbent polymers, flocculants, as well as fibres and plastics. Acrylate polymers show a wide range of properties dependent on the type of the monomers and reaction conditions (Rowe et al., 2009).

2.4.3.1.3.1 Carbopol® polymers

Carbopol® polymers are polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol. They are produced from primary polymer particles of about 0.2 to 6.0 micron average diameter. Figure 12 shows the chemical structure of Carbopol® polymers.
The flocculated agglomerates cannot be broken into the ultimate particles when produced. Each particle can be viewed as a network structure of polymer chains interconnected via cross-linking (Florence et al., 1994). The first prepared Carbopol® polymers were carbomers (Brown, US Patent, 1957). Since then, a number of extended release tablet formulations of carbomer matrices have been developed and patented (Goodrich, 1987). Carbopol® polymers essentially insoluble in water, hydrophilic in nature, cross-linked structure, so they absorb water, get hydrated and swell. These features make Carbopol® a potential candidate for use in controlled release drug delivery system (Carnali and Naser, 1992; Garcia-Gonzalez et al., 1994).

They swell in water up to 1000 times their original volume (and 10 times their original diameter) to form a gel when exposed to a pH environment above 4.0 to 6.0. The pKa of these polymers is 6.0 to 0.5. The carboxylate groups on the polymer backbone ionize, resulting in repulsion between the negative charges, which adds to the swelling of the polymer.

The glass transition temperature of Carbopol® polymers is 105°C in powder form. However, the glass transition temperature decreases significantly as the polymer comes into contact with water. The polymer chains start gyrating, and the radius of gyration becomes increasingly larger. Macroscopically, this phenomenon manifests itself as swelling. Carbopol® polymers have an average equivalent weight of 76 per carboxyl group.

Carbopol® polymers are available in various grades depending upon the degree of cross-linking and manufacturing conditions; each grade is having its use in pharmaceutical dosage forms (Alexander, 1986). Carbopol® 934P is cross-linked with allyl sucrose and is polymerized...
in solvent benzene. Carbopol® 71G, 971P and 974P are cross-linked with allyl penta erythritol and polymerized in ethyl acetate.

Polycarbophil is cross-linked polymer in divinyl glycol and polymerized in benzene. All the polymers fabricated in ethyl acetate are neutralized by 1-3% potassium hydroxide. Though Carbopol® 971P and Carbopol® 974P are manufactured by same process under similar conditions, the difference in them is that Carbopol® 971P has slightly lower level of cross-linking agent than Carbopol® 974P. Viscosity of different grade of Carbopol® polymers is presented in table 3.

Table 3: Viscosity range of different Carbopol® Polymers

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Carbopol® grade</th>
<th>Viscosity (cP) at 25°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Carbopol® 934</td>
<td>30500 – 39400</td>
</tr>
<tr>
<td>2</td>
<td>Carbopol® 934 P</td>
<td>29400 – 39400</td>
</tr>
<tr>
<td>3</td>
<td>Carbopol® 71 G</td>
<td>4000 – 11000</td>
</tr>
</tbody>
</table>

Carbopol® polymers are having different pharmaceutical application as:

- Controlled release of drugs. Carbopol® polymers offer consistent performance over a wide range of desired parameters (from pH-derived semi-enteric release to near zero-order drug dissolution kinetics) at lower concentrations than competitive systems.

- Bioadhesive polymer for buccal, ophthalmic, intestinal, nasal, vaginal, and rectal applications. Noveon AA-I USP polycarbophil is the recognized industry standard for bioadhesion.

- Thickening at very low concentrations (less than 1%) to produce a wide range of viscosities and flow properties in topical lotions, creams and gels, oral suspensions, and in transdermal gel reservoirs.

- Suspending agent of insoluble ingredients in oral suspensions and topicals.

- Emulsifying agent for topical oil-in-water systems permanently, even at elevated temperatures, with essentially no need for irritating surfactants.

2.4.3.1.3.2 Controlled-release applications of Carbopol® polymers

Carbopol® polymers have enjoyed success in controlled-release solid dosage formulations since the 1960s. Tablets containing Carbopol® 934 were developed as a prolonged
release formulation (Baun and Walker, 1971). The number of companies developing and commercializing controlled-release tablets using Carbopol® and Noveon polymers has increased significantly in recent years. Carbopol® polymers, variety of excipients and active drug ingredients were studied in tablet compressed by using both direct-compression and wet granulation methods (Durrani et al., 1992). Carbopol® polymers can be successfully formulated into a variety of different tablet forms, including the traditional swallowable tablets, chewable tablets, buccal tablets, sublingual tablets, effervescent tablets, and suppositories (Goodrich, 2003). These polymers provide controlled-release properties as well as good binding characteristics. Tablet formulations using Carbopol® polymers have been developed to demonstrate zero-order and near zero-order release kinetics (Choulis et al., 1976; Perez-Marcos et al., 1991). These polymers are effective at low concentrations (less than 10%) and feature extremely rapid and efficient gelation characteristics under both simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) test conditions. They also produce tablets of excellent hardness and low friability over a range of compression forces, as well as demonstrably longer dissolution times at lower concentrations than other controlled-release excipients. Greater formulating latitude in dosage forms is, therefore, possible using Carbopol® polymers as the functional controlled-release excipient.

Carbopol® 71G is the granular form of Carbopol® grade. It useful for developing controlled-release tablet formulations by direct compression technique with the following characteristics:

1. Low flowability tablets.
2. Good hardness tablets.
3. Good tablet friability.
4. Tablets with long drug release profiles.
5. Tablets Compression process with less dust and better handling characteristics.

Carbopol® 71G is a granular free flowing polymer grade that is produced by roll compaction of Carbopol® 971P (Kedar, 2009). The roll compaction process parameters are controlled to produce Carbopol® 71G which has about double bulk density of Carbopol® 971P. Carbopol® 71G has uniform particle size distribution having granules mostly between 40 and 80 mesh and also has uniform particle morphology. It is a good choice to be used as a release
literature review

retarding ingredient in any direct compression formulation. Combinations of Carbopol® 971P and Carbopol® 71G in 1:4 or 1:5 proportion represents another alternative to have overall lower polymer content in the formulation without affecting the flow significantly. Carbopol® 71G may also be combined with other powder grades of Carbopol® polymers or with other release retarding agents, such as HPMC, hydroxyethyl cellulose, or hydroxypropyl cellulose for a more robust formulation and to improve the flow and compressibility. The recommended grades for direct compression are Carbopol® 71G in concentrations of about 10 % to 30 % and Carbopol® 974P and Carbopol® 971P in concentrations from 3 % to 5 %. Tablets prepared by direct compression containing Carbopol® 71G show drug release slower than the drug release from tablets prepared by wet granulation either aqueous or non aqueous (Thapa et al., 2005). Carbamazepine tablets were prepared as SR formulations by wet granulation with HPMC and addition of Carbopol® 71G at low concentrations in the extra granular blend, to obtain controlled release properties (US. 6572889). Mortazavi and Aboofazeli (2003) have studied the effect of Carbopol® polymers on the release of propranolol HCl from matrices tablet; they have described wet granulation of propranolol blends and various carbomer grades using solution of povidone in chloroform as granulating agent. Aboofazeli and Mortazavi (2003) also have described the non aqueous granulation process for lithium carbonate SR enteric coated tablets and evaluated the effects of different Carbopol® polymer grades on the drug release profile. Saleki-Gerhardt and Keske (1999) used Carbopol® 974P to prepare an aqueous granulation of clarithromycin (US. 5919489). Jian (2004) developed tablets formulations for nifedipine by wet granulation process using Carbopol® 971P (US. 2004219210). Vaithiyalingam et al. (2002) described the fluidized bed granulation of blends containing ketoprofen, Carbopol® 971P and dicalcium phosphate using 0.8 % Carbopol® 971P dispersion. The controled release mucoadhesive tablet of eugenol for gingival application has also been prepared by using Carbopol® 934P and HPMC as polymers (Lohr et al., 2001). Pandey et al. (2010) prepared a control release bilayered buccal tablets of carvedilol using different ratio of Carbopol® 934P and HPMC K4M, in order to avoid the first pass effect.

2.4.3.2 Hydrophobic matrix systems

The drug is mixed with an inert or hydrophobic polymer and then compressed into a tablet to obtain controlled release. Sustained release is produced due to the dissolution of the drug which is diffused through network of channels that exist between compacted polymer
particles. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. In this matrix system, hydrophobic polymers are employed as matrix carrier, and the rate-controlling step for the drug release through these matrices is liquid penetration. The possible mechanism of release of drug in the matrices is diffusion. Hydrophobic matrix systems are not generally suitable for insoluble drug because the concentration gradient is too low to render adequate drug release. As such, depending on actual ingredient properties or formulation design, incomplete drug release within the gastrointestinal transit time is a potential risk and need to be delineated during the development.

Matrix systems providing programmable rates of delivery become more important. Constant rate delivery has always been one of the primary targets of controlled release system, especially for drug with narrow therapeutic index. In this system, the use of polymer is not essential to provide controlled drug release, although insoluble polymers have been used. As the term suggests, the primary rate-controlling components of hydrophobic matrix are water insoluble in nature. To modulate drug release, it may be necessary to incorporate soluble ingredients such as lactose into the formulation. The presence of insoluble ingredient in the formulations helps to maintaining the physical geometry of hydrophobic matrix during drug release. As such, diffusion of active ingredient from the system is the release mechanism (Kincl et al., 2004), and the corresponding release characteristic can be described by Higuchi equation known as square root of time release kinetic (Higuchi, 1963). The square root of time release profile is expected with a porous monolith, where the release from such system is proportional to the drug loading.

Many hydrophobic excipients (e.g., stearic acid, mono-, di- and tri-glycerides, glyceryl behenate, hydrogenated castor oil, ethyl cellulose, etc.) have been employed in preparing controlled release granules (Maki et al., 2006; Hayashi et al., 2007). Wax materials also have major applications in sustained-release systems, especially for highly water-soluble drugs e.g. Glyceryl behenate (Compritol® 888 ATO) (Hamdani et al., 2003; Abdelbarya and Tadros, 2008; Cortia et al., 2008). Pajander et al. (2006) studied the effect of the liquid penetration into both cylindrical and convex hydrophobic matrix tablets on the drug release. The cracking influences drug release by shortening the diffusion path and decreasing the tortuosity. The cylindrical
tablets are quite homogeneous in terms of density, but convex tablets have more porous areas at the domes of the tablet.

2.4.3.2.1 Glyceryl (di) behenate

Glyceryl (di) behenate (Compritol® 888 ATO) is a waxy fine white powder composed of spherical particles with a mean particle diameter of 50\(\mu\)m < \(d_{50} < 60\mu\)m. It has a low hydrophilic-lipophilic balance (HLB) and a low melting point (70°C). It has excellent tableting properties (mixing, flowability and compressibility) and is chemically inert and neutral in flavour. Glycerides are a family of excipients which have generated considerable interest for the preparation of oral dosage forms.

Glycerides represent a wide range of meltable excipients, which are composed of mixtures of glycerides and fatty acid esters of polyethylene glycol which, originally introduced as lubricant for tablets, which has recently had a wide application as a sustained-released excipient (Sutananta et al., 1995). Compritol® 888 ATO can be used as the principle sustained release agent in simple or multilayered tablets. It has been used for the preparation of controlled release formulations, since they possess some very interesting characteristics, i.e., chemical inertness against other materials and excellent flow properties. Barthelemy et al. (1999) had investigated the use of glyceryl behenate as a hot-melt coating agent to prolong the release of theophylline. Their study confirmed a satisfactory coating potential by this agent and a potential in sustaining the release of theophylline over an extended period of time. Compritol® 888 ATO has also been utilized as rate retarding material for sustained-release dosage form of diclofenac sodium (Mirghani et al., 2000). Obaidat and Obaidat (2001) have used glyceryl behenate as a matrix-forming agent to prepare matrix tablets to control the release of tramadol HCl. They showed that glyceryl behenate is an appropriate waxy material that can be used as a matrix-forming agent to control the release of a water-soluble drug. Lubricant performance of Compritol® 888 ATO in formulations prepared by classical blending or by hot melt coating procedure was studied. It reported an improvement in tablet lubricating property by hot melt coating process (Jannin et al., 2003). Compritol® 888 ATO has been used to design and develop matrix formulations to control drug release of freely water-soluble drug sodium ferulate to achieve a 24h release profile (Li et al., 2006). Unlike cellulose derivatives, which work by swelling in water, and eventually, disintegration of the matrix, the Compritol® 888 ATO based inert matrices might provide another solution for the formulation of sustained or controlled drug

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delivery system. Ghimire et al. (2011) investigated the erosion behaviour of tablets consisting of glyceryl behenate and HPMC manufactured by direct compression (DC), melt granulation (MG) and direct solidification (DS). Tablet erosion was affected by the preparation method and was found to decrease in the order of preparation method, DC > MG > DS tablets.

2.4.3.2.1.1 Advantages of Compritol® 888 ATO matrix:

1. It can be used for direct compression, wet, dry and melts granulation.
2. Drug release is pH-independent.
3. Drug release mechanism is by diffusion, that minimizing burst-out effect.
4. Inert, non-digestible, highly resistant to physiological conditions.

Compritol® 888 ATO matrix tablet does not swell or erode in water and therefore the rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of matrix tablets is diffusion. The lipid matrix is formed by the deformation of Compritol® 888 ATO during compression and, in some cases, by a partial melt. This creates an insoluble network structure throughout the tablet. The presence of hydrophilic ingredients in the tablet enables the creation of pores which facilitate water penetration and consequent diffusion of the active pharmaceutical ingredient (API). The diluents play a major role in the lipid matrix by generating the porous channels through which water penetrates into the otherwise insoluble structure. Therefore, it is important to select the right diluents to complement the lipid matrix (Zhang and Schwartz, 2000). Patel et al. (2008) used Compritol® 888 ATO to prepare floating matrices to control drug release of pH dependent soluble drug. They compared the drug release of tablets prepared by direct compression and tablets prepared by hot fusion method and they found out that matrices prepared by hot fusion was more effect in retarding and floating than direct compression matrices. Barakat et al. (2008a, 2008b) studied the effect of Compritol® 888 ATO and hydrophilic components on the release of carbamazepine from granules and tablet. The structural and thermal characterization of Compritol® 888 ATO was studied using X-ray, differential calorimetry and infrared spectroscopy (Brubach et al., 2007). Compritol® 888 ATO was used to develop controlled release matrix tablet formulation of acrivastine and pseudoephedrine (Gu, et al., 2004).

Hariharan et al. (2004) reported the effect of formulation composition on the physical characteristics and drug release behavior of controlled-release formulations made by roller...
compaction. They studied the effect of formulation components using substance and varying relative amounts of Compritol® 888 ATO. The longest release times were observed for formulations having higher concentrations of Compritol® 888 ATO; however the tablets with a high level of Compritol® 888 ATO showed the lowest values of crushing strength. Özyazıci et al. (2006) studied the swelling and relaxation properties of lipid matrix of metronidazole tablets. They found out that Compritol® 888 ATO matrix tablets prepared by hot fusion method showed a couple of drug release mechanism (fickian and relaxation). Compritol® 888 ATO was also used as a retardant material to prepare matrix tablets by physical mixture and solid dispersion methods. Tablets prepared by physical mixture gave higher drug release than tablets prepared by solid dispersion method. The drug release from tablets prepared by solid dispersion followed the diffusion controlled model described by Higuchi for inert porous matrix (Perez et al., 1993).

2.4.3.2.2 Ethyl cellulose

Ethyl cellulose (EC), chemical name is ethyl ether of cellulose, is prepared from wood pulp or cotton by treatment with alkali and ethylation of the alkali cellulose with ethyl chloride. EC is free flowing and white to light tan powder. The solubilities are characterized in terms of non-polar, polar, and hydrogen bonding components. EC is Practically insoluble in water, in glycerol and in propane-1,2-diol, but soluble in varying proportions in certain organic solvents, depending upon the ethoxyl content. EC containing less than 46-48% of ethoxyl groups is freely soluble in tetrahydrofuran, methyl acetate, chloroform, and aromatic hydrocarbon ethanol mixtures. EC containing 46-48% or more of ethoxyl groups is freely soluble in ethanol, methanol, toluene, chloroform, and ethyl acetate. EC is a water insoluble polymer used in controlled-release dosage forms to modulate the drug release from dosage forms with organic or aqueous coating techniques (Lin et al., 2001; Siepmann et al., 2007; Neau et al., 1999). It has different pharmaceutical applications including tablet coating and wet granulation binders. Although EC is considered insoluble, it can take up water; this is because of its hydrogen bonding capability with water due to the polarity difference between the oxygen atom and the ethyl group of the polymer (Joshi and Wilson, 1993; Agrawal et al., 2003). EC can also use as directly compressible excipient (Lin and Lin, 1998; Upadrashta et al., 1993; 1994; Katikaneni et al., 1995a; Crowley et al., 2004). The compaction characteristics of EC (Emeje et al., 2006) and the effects of various additives on the release properties of EC have been studied (Pather et al., 1998). EC, like other water insoluble polymers, is used in drug delivery systems, which create
channels through which drug leaches out, increase the wetting of the hydrophobic barriers of the matrix, or modify the barrier properties of the absorbing membrane. Chemical structure of ethyl cellulose is shown in figure 13.

![Chemical structure of ethyl cellulose](image)

**Figure 13: Chemical structure of ethyl cellulose (Shi et al., 2009)**

### 2.4.3.2.2.1 Ethyl Cellulose matrix

The effects of different viscosity grades of EC on drug release from sustained release tablets of a water-soluble drug with EC were studied. The results have shown marginal to moderate increase in the release rate, with the increase in viscosity grade; however, lower viscosity grades produced harder tablets (Katikaneni et al., 1995b). Neau et al. (1999) studied the drug release mechanism from EC matrix tablets to determine the best fitting drug release mechanism. Different ratio of EC was used to achieve a high and a low drug loading and to characterize the drug release mechanisms. At high drug loading the drug was released by a diffusion mechanism with a constant rate increased with an increase in aqueous solubility. At low drug loading, polymer relaxation also became a component for the release mechanism. Streubel et al. (2000) studied the pH independent release of a weakly basic drug from water insoluble EC matrix tablets. The release of verapamil hydrochloride from tablets composed of EC was found to be pH-independent. Ali et al. (2009) developed a pH and transit time controlled sigmoidal release polymeric matrix for colon-specific delivery of indomethacin by using EC in a hydrophilic polymer matrix to retard the initial release from formulations by reducing swelling of hydrophilic polymer. Physicochemical properties and drug release mechanism from EC matrix tablets was studied. Tablets were prepared by either direct compression or hot-melt extrusion (HME) of binary mixtures of water soluble drug (guaifenesin) and the polymer. The release rate was shown to be dependent on the EC particle size, compaction force and extrusion temperature (Crowley et al., 2004).
2.4.3.2.2 Ethyl cellulose as coating agents

Coated pellets are frequently used for oral controlled drug delivery (Fukumori, 1997; Ghebre-Sellassie, 1997). Compared to controlled release matrix pellets and mini-tablets, higher drug loadings can be generally achieved. Ethylcellulose is a suitable polymer for controlled release pellet coatings, since it is nontoxic, non-allergenic, non-irritant and a good film former. This polymer can be applied from organic solutions or aqueous dispersions (Banker, 1966; Eckersley and Rudin, 1990; Lecomte et al., 2004). The use of aqueous dispersions avoids toxicity and environmental concerns associated with organic solvents and decrease the viscosity of the coating formulation compared to organic solutions. Higher polymer contents can be also applied, resulting in shorter processing times. However, long term stability might be difficult to achieve, particularly upon storage under stress conditions (elevated temperature and relative humidity). If the polymer particles are not completely coalesced, the release rate might decrease with time due to ongoing film formation (Amighi and Moes, 1996; Wu and McGinity, 2000; Siepmann et al., 2006). Theophylline pellets coated with an aqueous EC dispersion was developed; the effect of curing and storage conditions of coated pellets on the drug release rate and the release mechanisms were studied. The results showed that the release mechanisms depend on the glass transition temperature of the EC, on the migration of the plasticizers and the pore former (Frohoff et al., 1999). The drug release mechanism from sustained release pellets coated with an ethylcellulose based was studied to determine the possible mechanisms for release include solution diffusion through the continuous polymer phase and/or plasticizer channels, diffusion through aqueous pores and osmotically driven release through aqueous pores. The results showed that as the coating thickness was increased, the rate of drug release decreased. Osmotic pressure of the medium was the major mechanism for drug release. It is also indicated that the plasticizer is important in terms of forming a continuous film (Ozturk et al., 1990). Arwidsson and Nicklasson (1990) have studied the suitable organic solvent in order to select suitable systems for a coating process applicable for a wide range of EC grades of different molecular weight. The results indicate that methylene chloride/ethanol (60:40, % w/w) is an advantageous solvent system for each of the polymer grades studied.

The release of metoclopramide hydrochloride (a water-soluble cationic drug) and diclofenac sodium (a sparingly soluble anionic drug) from pellets coated with ethylcellulose from aqueous ethylcellulose dispersion (Surelease®) at different coating levels was investigated.
The results have shown that the release rates of each drug decreased as the coating thickness of Surelease® increased. Despite its lower water solubility, diclofenac sodium was released slightly faster than metoclopramide hydrochloride at equivalent coating loads (Sadeghi et al., 2000). The prediction of drug release mechanisms from EC coated pellets of diltiazem HCl was also studied. The results indicate that the diltiazem HCl release from coated pellets containing small amounts of poly (vinyl alcohol)-poly (ethylene glycol) graft copolymer is primarily controlled by drug diffusion through the intact polymeric membranes, irrespective of the type of starter core (Muschert et al., 2009). Larsson et al. (2010) investigated the effect of ethanol in the dissolution medium on the drug release from films composed of ethyl cellulose and hydroxypropyl cellulose. The effect of ethanol on the drug release was dependent on the composition of the film. The swelling of EC in film was increased with increasing of ethanol concentration. Films with low HPC content showed more release. However, films with higher HPC content showed less water permeability and less drug release. The film thickness of ethyl cellulose played an important role in controlling the drug release rate from the tablets (Abraham et al., 2011).

2.4.4 Lipid Matrices

Hydrophobic wax matrix systems are being widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance (Goodhart et al., 1974). Waxes are one of the excipients being investigated for their use in controlled release pharmaceutical formulations (Cohen et al., 1984). They are used either as a matrix (Zhou et al., 1996) or as a coating polymer so as to sustain the release of the drug (Zhang et al., 2001). Lipophilic polymer was used as release modifiers to developed multiple-unit extended-release matrix of a hydrophilic drug using a one-step melt method as an alternative method for coating procedure (Gren and Nystrom, 1999). Lipids were used as carriers to achieve drug controlled release (Adeyeye and Price, 1991; Bodmeier et al., 1992; Maheshwari et al., 2003), in which drug is incorporated into lipid. Lipid can be used for taste masking (Robson et al., 2000a) and for stability improvement (Paradkar et al., 2003). Lipid excipients have been used for the preparation of sustained-release formulations for a long time. Methods of preparation include spray-chilling (Savolainen et al., 2003), hot-melt coating (Sinchaipanid et al., 2004), melt granulation (Hamdani et al., 2003) and molding (Khan and Craig, 2003; Mehuiys et al., 2004; 2005). All these methods require complete melting of the lipids during processing. The physical stability of lipids in solid dosage forms has been studied.
(Jannin et al., 2006). However, only a few studies have investigated the solid lipid extrusion process and its effect on the solid state of the processed lipids (Reitz and Kleinebudde, 2007a, b). The structure and morphology of extruded lipid matrices and their effect on drug release properties have not been studied. It is of special interest to investigate whether the outer or external surface of the cylindrical extrudate is equal to surfaces generated in downstream processes like cutting or milling. Due to friction in the extruder and/or in the die plate the temperature at the outer surface of the extrudate might be higher. This can result in a partial melting of the lipid and changes in the morphology due to recrystallization. Consequently, the exposure of incorporated drug particles might be different on the outer extrudate surface and new surfaces generated by cutting or milling.

Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are, therefore, more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized and used as a common carrier in various melt techniques. It contains wide group of chemicals such as glycerides, fatty acids, fatty alcohols and their esters. These are widely used as release retardant in the design of sustained release beads, tablets, suspensions, implants and microcapsules. The advantages of waxes include good stability at varying pH and moisture levels, well established safe application in human due to its non-swellable and water insoluble nature, minimal effect of food in GIT and no dose dumping (Obaidat and Obaidat, 2001). Lipid materials, commonly used in food products, have not only gained increased interest due to their attractive low cost and toxicity, but also their derivative abilities in a wide range of hydrophilicity-lipophilic properties. Waxy materials have major applications in sustained-release systems and the use of wax matrix appears to have several advantages such as being a multiple-unit system, chemical inertness against other materials, and ease of manufacturing with high reproducibility that can be obtained without special instrumentation, as well as low production cost (Otsuka et al., 1994; Sato et al., 1997). Moreover, as the matrix delivery system passes through the gastrointestinal tract, the active ingredient is slowly released and absorbed (Obaidat and Obaidat, 2001). Therefore, resistance to gastrointestinal motility has to be confirmed to maintain the expected-release profiles of lipid matrices (Horter and Dressman, 2001). Lipids are also preferable excipients for melt pelletisation. In this case, the product temperature is raised to the binder’s melting point by heating the jacket of the apparatus or by increasing the impeller
speed of a high-shear mixer. The binder melts during the process, promoting agglomeration or incorporating the drug in order to achieve a sustained drug release without any coating procedure (Voinovich et al., 2001; Thies and Kleinebudde, 2000; 2001).

2.4.4.1 Carnauba wax

Carnauba wax is obtained from the leaves of *Copernicia cerifera* Palma, in which leaves have a thick coating of wax, which can be harvested from the dried leaves. It contains mainly wax esters (85%), accompanied by small amounts of free acids and alcohols, hydrocarbons and resins. The wax esters constitute C\(_{16}\) to C\(_{20}\) fatty acids linked to C\(_{30}\) to C\(_{34}\) alcohols, giving C\(_{46}\) to C\(_{54}\) molecular species (Vandenburg and Wilder, 1970). The carnauba wax matrices were used either as capsules or as accompanying vehicles for the pigments in aqueous dispersions (Villalobos-Hernandez and Muller-Goymann, 2005). Further study discussed that due to partial presence of cinnamates carnauba wax show a synergistic effect to improve the sun protection factor (SPF) of cosmetic preparations (Villalobos-Hernandez and Muller-Goymann 2006). Solid lipid nanoparticles formulations prepared from carnauba wax have been proposed as suitable colloidal carriers for delivery of drugs with limited solubility (ketoprofen). Carnauba wax contained 5% of resins that allow almost no water to penetrate into the pores of the lipid structure. So the drug release from nanoparticles containing more carnauba wax was slow in comparison with nanoparticles containing beeswax (Kheradmandnia et al., 2010). Metronidazole lipid matrix granules using carnauba wax was prepared and the swelling and relaxation properties of lipid matrix were investigated. The carnauba wax matrix showed the lowest release rates; neither erosion nor swelling in matrix was observed, and the diffusion mechanism was pure Fickian (Özyazıcı et al., 2006).

Carnauba wax was used in combination with an acrylic polymer (Eudragit\(^\text{®} \) L100) to develop sustained release; a desirable release profile of diphenhydramine was achieved. Carnauba wax maintained the integrity of the matrix, whereas Eudragit\(^\text{®} \) L slowly eroded in the matrix as the drug was released (Huang et al., 1994). It was also used in the preparation of microspheres as sustained release formulations for oral use to target the ibuprofen by entrapping it into carnauba wax. The results showed that microspheres formulations prepared by melt dispersion of wax were spherical and smooth and had an extended release property (Ghaly and Sepulveda, 1996). Carnauba wax was also used to develop sustained release drug delivery system of venlafaxine hydrochloride and the drug release profile was investigated (Bhalekar et
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al., 2008). Its granules were used as binder to develop tablets. The tablets were evaluated for tensile strength and brittle fracture index (BFI). The tablets made with carnauba wax showed significantly lower in BFI in comparison to other binders (Uhumwangho et al., 2009). For transforming solids into fine particles, grinding is the most common method (Ghaly and Sepulveda, 1996). Carnauba wax is plastic in nature, for that it is difficult to grind. It can also be transformed by emulsification methods (Singh et al., 2007). Carnauba wax might be used for delivering highly water-soluble drugs like potassium citrate (Cao et al., 2007). Carnauba wax nanoparticles can induce strong cellular/humoral immune responses to HIV vaccine without inflammation (Arias et al., 2011).

2.4.4.2 Glyceryl monostearate

Glyceryl monostearate (GMS) has been introduced as lipid pelletisation aid and as an alternative for MCC; it is an organic molecule, insoluble in water, but with emulsifying and plastifying properties. GMS has been used as a waxy retardant polymer to form sustained-release matrices, including the formulation of pellets for tablets (Thomsen et al., 1993). The relationship between surface free energy, polarity and physical properties of spheroids particles prepared with and without GMS was studied. It was found that spheroids particles containing GMS has shown much higher porosities and lower crushing strengths than other formulations (Pinto et al., 1995).

Blanque et al. (1995) studied the effect of inclusion of GMS at levels of 16–32% into the formulation of pellets containing drugs of different solubility. No significant effect on the amount of water required to produce the best formulation or the steady state extrusion force for pellets produced was observed with a ram extruder and spheronizer. GMS was also used to developed pellets formulations for water-insoluble drugs (ranitidine) incorporating barium sulfate with and without MCC. This resulted in relatively spherical pellets of narrow size distribution. The pellets showed sufficient mechanical properties, and the drug was released within 15 min (Basit et al., 1999). An implantable delivery system based on GMS matrix was designed for the site-specific delivery of antibiotics for the prevention of surgical wound infection. The release of cefazolin was monitored from GMS matrixes implanted. The release of cefazolin from the GMS-based matrix followed Higuchi’s square root of time kinetics. A variety of GMS matrixes that would result in desired release rate or release duration (Allababidi et al., 1998).
Chatchawalsaisin *et al.* (2004) prepared pellets formulations of GMS using barium sulfate and diclofenec sodium as model drugs; the results showed that pellets were in acceptable spherical at drug contents between 10% and 90%. The porosity was dependent on the amount of GMS used in the formulations and demonstrated porosity levels of less than 10% even for high concentrations of GMS. The *in-vitro* dissolution from GMS formulations showed that after 3 hours 80% to 100% of the drug was released, thus exhibiting immediate release profiles. Further work reported that the drug release was only controlled by the solubility of the drug and not by the presence of GMS (Chatchawalsaisin *et al.*, 2005). The binary mixture of sodium valproate and glycerol monostearate was investigated. Results showed that the binder concentration was found to be one of the most important variables influencing the mean granule size and size distribution, and due to the solubility of the drug in the molten binder very low amounts of binder were necessary for the formation of pellets (Thies and Kleinebudde, 1999). The thermal behaviour of glycerides has been studied, particularly with a view to examine the relationship between preparation conditions and physical stability. It was noted that materials containing either glycerides tend to show an increase in tensile strength on storage (Sutananta *et al.*, 1994). Peh and Yuen (1995) reported that the inclusion of GMS retarded the drug release of theophylline in a pellet formulation. However Thomsen *et al.* (1994) reported that they could only achieve sustained release of this drug when they also included another wax with GMS in formulations made by melt granulation.

The mechanism of drug retardation from GMS matrix system was studied, and it was observed that the drug release from formulations is due to lipophilicity of the matrix. The rate of water penetration into the matrix decreased, and the drug release could be sustained (Peh *et al.*, 2000). Lu *et al.* (2007) have developed sustained release matrix systems using GMS to control drug release of herbal medicines. Newton *et al.* (2004) have shown that it is possible to make pellets for water insoluble drugs. The effect of HLB value of GMS had significant affect on various pharmaceutical properties of beads. The beads containing low HLB GMS showed faster drug release (Kambler *et al.*, 2010).

### 2.4.4.3 Stearic acid

Stearic acid (octadecanoic acid) \( \text{CH}_3 (\text{CH}_2)_{17} \text{COOH} \) is a long-chain fatty acid consisting of 18 carbon atoms without double bonds. Chemical structure of stearic acid is presented in figure 14. Stearic acid is widely used as a lubricant (Phadke *et al.*, 1994). More recently, such
excipients have been employed to produce solid fatty acid and implants containing insulin and reduced the resting blood glucose levels in diabetes rats (Wang, 1987; 1989; 1991). Kaewvichit and Tucker (1994) assessed the in vitro release of the protein bovine serum albumin from fatty acid compacts. The amount of drug released was affected by the particle size of drug and fatty acid. More release with increasing BSA particle size occurred only when stearic acid particle size was small. Release was anomalous as it deviated from the expected square root of time diffusion mechanism. Robson et al. (1999) investigate the effect of the dissolution medium on both the release rate and the physical integrity of the stearic acid-coated cefuroxime axetil microspheres. The release from the microspheres was found to be highly dependent on the media used. It is suggested that the release of the drug is dependent both on diffusion of media through the intact microspheres and changes in the physical integrity of the spheres as a result of a reaction with the surrounding medium. The produced stearic acid microspheres masked the bitter taste of the drug. Further study was carried out to understanding the mechanism of drug release and the effect of medium composition on drug release. Results indicated an interrelationship between medium composition, disintegration and release (Robson et al., 2000a, b).

Voinovich et al. (2000) prepared sustained-release pellets by melt pelletisation using stearic acid as a melting binder. They demonstrated that pellets based on the combination of stearic acid and lactose can be used to formulate sustained release pellets for theophylline. Stearic acid was used to develop controlled-release tablets of poorly-soluble drug (felodipine), tablets prepared by solid dispersion technique. The results showed that the drug release rate was extremely slow from the stearic acid tablets i.e. less than 15% was released after 4 hours. The degree of felodipine crystallinity and the ease of tablet disintegration played a more significant role on the drug release more than the matrix lipophilicity (Savolainen et al., 2002). Stearic acid as a binder was also used to prepare sustained release formulation for paracetamol by melt pelletisation method. The drug release kinetics of formulation was investigated. The drug release was controlled by drug diffusion and drug dissolution into dissolution medium (Grassi et al., 2003a). Stearic acid as a low melting binder was also used to develop a cylindrical sustained release dosage form of theophylline. The drug release was essentially slowed down by the increase of stearic acid in the matrix. And the drug release mechanism is initially ruled by dissolution, then diffusion (Grassi et al., 2003b). Sustained release capsule formulations were developed based on three components: drug, water-soluble polymer, and water-insoluble fatty
Stearic acid was selected as water-insoluble fatty acids. The results showed a diffusion-controlled release mechanism from these capsules (Desai et al., 2010). Killen and Corrigan, (2006) have studied the effect of the soluble filler lactose on drug release from stearic acid based compacts. The results showed higher drug release from drug-fatty acid systems with increase in lactose content in the range 10–50%. Özyazıcı et al. (2006) studied the swelling and relaxation properties and drug release mechanism of metronidazole lipid matrix granules using carnauba wax, beeswax, stearic acid, Cutina® HR, Precirol® ATO 5, and Compritol® ATO 888 by hot fusion method. There was erosion in stearic acid tablets and the drug release rate was the highest. Matrix systems can be prepared by direct compression or wet granulation methods. In addition, these matrices can also be prepared by solid dispersion and melt granulation methods.

![Chemical structure of stearic acid](image)

**Figure 14: Chemical structure of stearic acid**

### 2.5 Direct Compression Tablets

The compressed tablet is one of the most widely prescribed oral solid dosage forms today. Typically, the ingredients which comprise the tablet blend include the active pharmaceutical ingredient (API) together with various excipients which not only act as carriers for the drug compound, but which also enhance its therapeutic effect, or efficacy. Direct compression is a popular technique of tablet compression process, because it provides the shortest, most effective and least complex way to produce tablets. The manufacturer can blend an API with the excipient and the lubricant, followed by compression, which makes the product easy to process. No additional processing steps are required. Direct compression is suitable technique for moisture or heat sensitive ingredients, which would be contraindicated in wet granulation. Most of active ingredients tend to have poor compressibility, so suitable excipients of good flowability and compressibility should be selected for successful operation.

#### 2.5.1 Lactose for Direct Compression

Lactose one of the most common excipients used in pharmaceutical formulations, due to high stability, low hygroscopicity and relatively low cost. Lactose has good flowability and high compaction, which ensures rapid and uniform die-filling during the tablet compression process.
The flow of lactose is influenced by the particle shape, particle size and particle size distribution. These parameters can be controlled by milling, classification and agglomeration. Spray-dried lactose was the first excipient used successfully as filler-binder in direct compression of tablets (Rowe et al., 1996). It is still one of the most widely used excipients for direct compression. Lactopress® (spray-dried lactose) is prepared by spray-drying a suspension of fine alpha lactose monohydrate particles in a saturated aqueous solution of lactose. The final particles are spherical and contain approximately 85% alphanmonohydrate crystals and 15% amorphous lactose. The fine primary particles in the spray-dried lactose have a large surface area for bonding and these fine particles behave ductile. The betalactose present in the amorphous part also behaves ductile and contributes to the good compaction properties. Levian et al. (2004) studied the effect of excipients on the drug release from HPMC matrices tablets. The spray-dried lactose tablets showed the highest ejection forces, and faster drug release. Another study also showed that the drug release from the matrix tablets increased by the addition of water-soluble lactose which accelerated the drug release in a more pronounced manner (Kranz et al., 2006).

2.5.2 MICROCRYSTALLINE CELLULOSE

Microcrystalline cellulose (MCC) is a natural and ideal excipient used in pharmaceutical manufacturing. It is comprised of glucose units connected by a 1-4 beta glycosidic bond. These linear cellulose chains are bundled together as microfibril spiralled together in the walls of plant cell. Each microfibril exhibits a high degree of three-dimensional internal bonding resulting in a crystalline structure that is insoluble in water and resistant to reagents. There are, however, relatively weak segments of the microfibril with weaker internal bonding. These are called amorphous regions, but are more accurately called dislocations since microfibril containing single-phase structure. The crystalline region is isolated to produce MCC.

MCC is mainly used as dry binder in manufacturing of tablets as well as in wet granulation, and it is the most important excipient in the extrusion process (Newton, 2002). It is one of the best excipients used for direct compression (Lahdenpaa et al., 1997). Different grade of MCC are available; the most commonly used grade for direct compression is the MCC grade 102 (Avicel® PH 102). The reason for this preference is that many users expect segregation (and subsequent poor weight- and content-uniformity results) when combining fine active ingredients with coarse-grade excipients. Koo and Heng (2001) studied the effect of MCC different grade on the shape and shape distributions of pellets produced by Extrusion-Spheronization. Five MCC grades were physically characterized and used as spheronizing aid to form pellets by extrusion-
spheronization. It was found out that MCC grades with higher bulk densities, lower porosities and water retentive capacities required lower water contents to produce pellets of equivalent size. These MCC grades were also found to produce pellets of lower sphericity and wider shape distributions. The effect of MCC on the molecular and morphological properties of pellets prepared with two types of microcrystalline cellulose (MCC 101 and MCC 301) produced by an extrusion/spheronization process was investigated. The result indicated that MCC 101 was the best substance, with easy of handling and acceptable product properties (Fechner et al., 2003). Matrices containing microcrystalline cellulose as the sole diluents improve extended release of HPMC matrices (Williams et al., 2010b). The drug release from MCC pellets was predominantly controlled by pure diffusion and limited of drug solubility (Kranz at al., 2009).

MCC is incorporated in most formulations processed to prepare pellets via extrusion-spheronisation, since it provides the proper rheological properties to the wetted mass for successful extrusion and spheronisation (Shah et al., 1995). MCC has good binding properties that make it a golden standard in extrusion-spheronization process. Furthermore, it is able to absorb and retain a large quantity of water due to its large surface area and high internal porosity (Sonaglio et al., 1995). Table 4 presents the application of most MCC grade.

Table 4: Application of most MCC used grade

<table>
<thead>
<tr>
<th>MCC Grade</th>
<th>Diameter (µm)</th>
<th>Water content (&lt;%)</th>
<th>Bulk density (g/ml)</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avicel® PH-101</td>
<td>50</td>
<td>5%</td>
<td>0.29</td>
<td>Most popular grade, suited for all tableting processes, especially for wet granulation and globular granule production.</td>
</tr>
<tr>
<td>Avicel® PH-102</td>
<td>90</td>
<td>5%</td>
<td>0.31</td>
<td>Better flowability than PH101. Suited for direct compression and improves the liquidity of capsule fillings.</td>
</tr>
<tr>
<td>Avicel® PH-301</td>
<td>50</td>
<td>3%</td>
<td>0.32</td>
<td>Same quality as PH101, however, less moisture. Suited for tableting of water sensitive ingredients and processes in which moisture has to be avoided.</td>
</tr>
<tr>
<td>Avicel® PH-302</td>
<td>50</td>
<td>5%</td>
<td>0.38</td>
<td>Same particle size as PH101, but higher bulk density and better flowability.</td>
</tr>
<tr>
<td>Celldone® 105</td>
<td>90</td>
<td>5%</td>
<td>0.40</td>
<td>Same particle size as 102, but higher bulk density and better flowability.</td>
</tr>
</tbody>
</table>
2.6 HOT MELT GRANULATION TECHNIQUE

Using lipophilic waxes for preparing sustained release matrix tablets by hot-melt granulation technique has attracted more attention recently. Melt granulation technique (MG) has many advantages over other conventional wet granulation and roller compaction techniques. MG process is simple and rapid and may be performed in one step. This will decrease the number of process for tablets preparation and save operator time. MG is prepared by melting the wax by using heat to convert the wax into liquid in which active ingredients will dispersed easily (solid dispersion), so in this technique no need to use an organic or aqueous solvent to dissolve the binder as in conventional wet granulation. This will avoid the toxicity and flammability issue associated with the use of organic solvent. In case of aqueous solvents certain steps like drying for removal of solvent, hydrolysis of the drug and time required for drying is a major concern which can be avoided easily by using the melt granulation technique.

Hot melt technique can be used to prepare sustained release matrix to provide slow drug release. A further significant advantage of these techniques is that they are used for preparation tablets of moisture sensitive therapeutic compounds which are difficult to formulate by other technique due to moisture uptake from other excipients or during stress stability study. Selection of wax substances to be used as molten depending on melting point; relative low melting points waxes (50-80°C) are involved in this formulation. Melt granulation technology enhanced stability of moisture compound by minimizing the contact between moisture sensitive drug and water. The melt granulation process enhances compressibility of different pharmaceutical excipients such as lactose and microcrystalline cellulose.

Hot melt extruded technique (HME) was used to prepare floating tablet for gastroretentive controlled drug delivery system and for preparation of controlled-release matrix pellets. Many of hydrophobic excipients (e.g., stearic acid, mono-, di- and tri-glycerides, glyceryl behenate, hydrogenated castor oil, etc.) have been employed in preparing controlled release granules (Thies and Kleinebudde, 1999, Voinovich et al., 2000). The melt granulation can be used to prepare controlled release granules (Grassi et al., 2003a; Hamdani et al., 2002; Maejima et al., 1998; Zhang and Schwartz, 2003).

Solid dispersion technique is prepared by various methods like physical mixing, fusion method and solvent evaporation. Freeze drying technique is used to develop solid dispersion,
which an ideal method for poorly water soluble drugs. Solid dispersion technique is commonly used to increase solubility of poorly water-soluble drugs by increasing the dissolution rate of the drug (Patel et al., 2010). The concept of solid dispersion covers a wide range of systems (Chiou and Riegelman, 1971). The enhancement in the dissolution rate is obtained by one or combination of the following mechanisms: eutectic formation, increased surface area of the drug due to precipitation in the carrier, formation of true solid solution, improved wettability due to close contact with a hydrophilic carrier, precipitation as a metastable crystalline form or a decrease in substance crystallinity. The type of solid dispersion formed depends on both the carrier and drug combination and the method of manufacture (Serajuddin, 1999).

2.7 MULTIPARTICULATE SYSTEM

Oral modified release dosage forms can also be classified according to type of units as single unit dosage forms such as tablets and capsules, and multiple-unit dosage form such as pellets or beads. The first application of oral drug delivery system ‘Spansule’ was developed in the 1950s, and still used today, utilizes neutral particles which are coated and adapted to release material over a prolonged period of time. Such particles contain a sugar-based core in which therapeutic material may be incorporated directly or may be dusted or otherwise distributed over the particle surface. The particles are then coated with a suitable coating material such as a wax. Release of therapeutic material by disintegration of the coating is controlled by controlling the thickness of the coating or by varying the coating composition. This prolonged release system was marketed by SmithKline and French laboratories (Blythe, 1956 US. 2,738,303). Pellets provide many therapeutic advantages, over single units such as effectiveness and safety. The major advantages of multiparticulate controlled drug delivery systems compared to single unit dosage forms include the low intra- and inter-subject variability in gastric emptying times and their more homogeneous distribution within the contents of the gastro-intestinal tract. Moreover, the risk of dose dumping can significantly be reduced with multiparticulates compared to single unit dosage forms (Ghebre-Sellassie, 1989; Gandhi et al., 1999). Pellets are defined as spherical, free-flowing granules with a narrow size distribution, typically varying between 500 and 1500 µm. High shear granulation and pelletization have been widely used in the pharmaceutical industry and have many advantages over other techniques (Parikh, 1997). Different steps in the preparation of pellets are: nucleation, fragmentation, densification, exponential growth due to coalescence, and break up (Vonk et al., 1997). The pelletization is a multivariate process and the
product properties are sensitive to the change of the process variables, and it is important to optimize these critical parameters (Voinovich et al., 2000; 2001; Hamdani et al., 2002). Gómez-Carracedo et al. (2007, 2008) studied the influence of the procedure and conditions of the drying on the physical characteristics and drug release behaviour of MCC-Carbopol® pellets containing theophylline or ketoprofen. The drying procedure caused remarkable differences in pellet size and porosity of the pellet. Pore size appears as a critical factor for achieving controlled release. The greater pores leading to the faster drug release. Pellets are increasingly used to provide controlled-release dosage forms. For this purpose, they are either filled into hard gelatin capsules or they are compacted into tablets. Multiparticulate controlled release dosage forms can be classified into two systems: 1) reservoir system and 2) matrix system.

In the reservoir system, the drug-containing core is surrounded by a polymer membrane, which controls the release rate of the drug out of the device. Although coated pellets are widely used in the pharmaceutical industry, their preparation is often complex, time-consuming and costly. In the matrix system, the drug is embedded within a solid carrier material which controls the release rate of the drug out of the system. The production of controlled release matrix systems is generally much easier and the physicochemical nature of the matrix determines the drug release mechanisms and resulting release patterns. Various processes can be involved in the overall control of drug release, such as drug dissolution and diffusion, swelling and erosion of the matrix former, or a combination of two or more of these processes (Gandhi et al., 1999). The compressibility and compactability of the various types of pellets significantly influenced by the nature of the excipient and liquids used to prepare the pellet cores which affected the drug release from the tablets (Abraham et al., 2011).

Different types of polymers have been used to formed suitable matrix system, allowing to provide desired drug release kinetics, e.g. ethylcellulose (Goskonda et al., 1994), poly (vinylacetate) (Novoa et al., 2005), water-insoluble derivates of poly acrylic acid (Young et al., 2002), as well as hydroxypropyl methylcellulose and derivatives. Lipids were also used to form controlled drug delivery matrix systems, for example drug-loaded matrix pellets based on combinations of waxes, starches and maltodextrins have been prepared to control the drug release (Zhou et al. 1996). The additions of glycerol monostearate to microcrystalline cellulose-based pellets of ibuprofen, paracetamol, diclofenac sodium, and indomethacin were prepared by extrusion-spheronization. The result indicated that the drug release was not influenced by the presence of GMS or the method of incorporation of the drug into the formulation, the release was
only controlled by the solubility of the drug (Chatchawalsaisin et al., 2005). Gelucires were successfully used by to prepare controlled release matrices pellets (Montousse et al., 1999). Souto et al. (2005) studied the effect of two superdisintegrants (crosscarmellose sodium and sodium starch glycolate) in microcrystalline cellulose extrusion-spheronization pellets. Neither disintegrant had significant effect on the pellet morphology and flow properties. Drug dissolution rate was slightly higher in pellets prepared with sodium starch glycolate, probably because of higher swelling capacity.

The drug release mechanisms of pellets coated with aqueous ethyl cellulose was studied. The results indicated that the drug release from the pellets was primarily controlled by diffusion through the intact polymeric membranes, irrespective of the type of starter core and type of release medium (Muschert et al., 2009). Yadav et al. (2011) prepared two type of pellets, type I pellets of MCC to achieve more than 80% of drug release within 30 min and type II pellets of pellets coated with layer of HPMC and a rupturable layer of plasticized EC to burst release and a lag period of 6-8 h. A blend of the two types of pellets was successfully used to develop a pulsatile release product for glipizide.

2.7.1 METHODS USED FOR PELLET PREPARATION

Several methods are used for pellets preparation. The most popular methods being used are:

- Solution/suspension layering.
- Powder layering.
- Direct pelletisation using high shear mixers and fluid-bed granulators.
- Extrusion–spheronisation.

2.7.2 EXTRUSION–SPHERONISATION

Extrusion-spheronisation is an efficient technique to manufacture pellets of uniform size with high drug loading capacity. Pelletizations process improves the flowability of micron-sized granules and increased bulk density of the powder. It offers an alternative method for agglomerations of fine drug material into less cohesive larger units. Extrusion spheronization is a simple and fast procedure to produce spherical pellets. Extrusion spheronization process can be effectively produced multiparticulates for oral controlled drug delivery system.

The pellets produced by the extrusion spheronization offer advantages over conventional drug delivery system.
I. Therapeutic advantages:

- Less irritation of the gastro-intestinal tract.
- Lower risk of side effects due to dose dumping.
- Enhancement of bioavailability of drugs by uniformly dispersion of spheroids in the gastro-intestinal tract.

II. Technological advantages:

- Better flow properties less friable dosage form.
- Narrow particle size distribution and uniform packing.
- Ease of coating because of the spherical shape and low surface area to volume ratio.
- High loading capacity of active ingredient without producing extensively large particles.
- Different drugs can be blended and formulated in single unit dosage form.
- Improves the safety and efficiency of active ingredient.

2.7.2.1 Extrusion-spheronisation process involves in several preparation phases:

- Dry mixing of drug powder and excipient.
- Wetting of the powder mixture by the addition of a liquid binder.
- Extrusion the moistened mass through an extrusion screen to form cylindrical extrudates.
- Spheronization to round the rods into spherical granules with narrow size distribution.
- Drying the formed pellets to achieve the desired moisture content.
- Screening the dried pellets to obtain the desired size of pellets.

2.7.2.2 Equipment used in extrusions-pheronisation process

I. Granulation

It is the first step of an extrusion-spheronisation cycle in which the wet powder mass prepared by using different types of granulators to perform the mixing of the powder blend and the granulation liquid.

II. Extrusion

It is the second step of the process in which the wet mass transferred into the extruder to produce cylindrical long rods of uniform size and shape. The extruder based upon the type of feed mechanism used to transfer the mass towards the die, divided into three classes:
1) Screw feed extruder, which consists of one or two screws feeding the wet mass to an axial or radial extrusion screen (Figure 15)

![Diagram of Screw Feed Extruder](image15)

Figure 15: Schematic view of a screw extruder (A) Axial type, (B) radial type

2) Gravity feed extruder, which consists of cylindrical roll or gear roll, equipped with two counter rotating wheels of which one or both are perforated. The wet mass is fed between the two wheels and the extrudate is collected inside the extrusion wheels (Figure 16)

![Diagram of Gravity Feed Extruder](image16)

Figure 16: Schematic view of gravity-fed extruders (A) Roll extruder with one perforated roll, (B) Roll extruder with two perforated rolls
3) Piston feed extruder, the piston displace and forced the material through extrusion screen (Figure 17)

![Figure 17: Schematic view of piston-fed extruders](image)

### III. Spheronisation

It is the third step of the extrusions-spheronisation process, in which the cylinders rod will spheronised or rotated at higher speed by friction plate to broken up into smaller cylinders with a length equal to their diameter. The spheronizing time is usually 2–15 min, depending on the formulation characteristics. The size of the spheroids is mainly depending upon the diameter of circular die that modifies the diameter of cylindrical rods produced in extrusion stage. In the spheronisation process the cylinders rod pass through different stages starting from a cylinder over a cylinder with rounded edges, dumbbells and elliptical particles to eventually perfect spheres (Figure 18).

![Figure 18: Shape transitions during a spheronization process](image)

Different process parameters at each stage of the extrusion–spheronisation process are responsible for the pellet quality. Sinha et al. (2005) studied the influence of excipient variables on the pellet properties. Different grade of MCC and fillers was used to prepare pellets. Mean
pellet diameter did not vary among the Avicel® grades. However, lactose pellets showed the largest particle size. Avicel® PH 101 pellets showed more spherical pellets. Avicel® PH 302 pellets showed the highest drug release rate where as Avicel® PH 101 pellets showed the least. Further study indicates that the drying conditions influenced the mean size and the drug release of the pellets. The increasing of the drying temperature the drug release rate decreased. The freeze drying led to the highest drug release. Spheronization time and spheronization speed affected the shapes and friability of the pellets (Sinha et al., 2007b).

The mass formed for extrusion must possess inherent fluidity, permitting flow during extrusion and self-lubricating properties, as it passes through the die. The resultant strands of extrudates must not adhere to each other, and must exhibit plasticity such that the shape imposed by the die is maintained. The requirements for spheronisation of the cylindrical extrudate are as follows:

(a) The extrudate must possess sufficient mechanical strength when wet; yet it must be brittle enough to be broken down to short lengths in the spheroniser, but not so fragile that it disintegrates completely.

(b) The extrudate must be sufficiently plastic to enable the cylindrical rods to be rolled into spheres by the action of the friction plate in the spheroniser.

(c) The strands of the extrudates must not adhere to each other in order that particles do not aggregate during spheronization.

2.7.2.3 Some important parameter for pellet characterization:

- **Particle size distribution**

  The particle sizing determination is an important step because it has significant influence on the drug release (Husson et al., 1992). Particle size distribution can be determined by simple sieve analysis method using sieve shaker (Podzeck et al., 2008).

- **Sphericity factor**

  Sphericity of the pellets is one the most important characteristics. Various methods have been used to determine it. The sphericity factor estimates the amount by which the projected image of particles deviate from a circle and it is calculated by means of the projected area of the pellets and its circumference (Mezreb et al., 2004).
Bulk density and tapped density

Bulk and tapped density of pellets are important parameters. Pellets density can be affected by change in the formulation process which may affect on flowability of the prepared pellets.

Surface Morphology

Scanning electron microscopy is used to examine the surface morphology and cross section of pellets.

Tensile Strength

The tensile strength of the pellets is determined by using tensile apparatus, the pellets are strained until failure occurs. The load is recorded and the tensile strength is calculated applying the value for the failure load and the radius of the pellets (Santosh et al., 2004)

2.8 MICROSPHERES

Microparticles are the polymeric entities in the size range of 1-1000μm. Microparticles are divided into two types: 1) Microencapsules (reservoir systems) 2) Microspheres (matrix systems). Microspheres are matrix systems and spherical in shape, whereas microcapsules are encapsulated systems which may be spherical or non-spherical in shape. Microcapsules are small particles, which contain an active agent or core material surrounded by a coating or shell. Microcapsules, which are smaller than 1μm, are known as nanocapsules, whereas those that have diameter larger than 1000 μm are known as macrocapsules (Allen et al., 2005). There are several reasons for drugs encapsulation such as controls the drug release, mask taste, prevent drug degradation from atmospheric moisture or oxygen. Drug targets to ensure proper delivery as desired. These multi-unit dosage forms can be used for oral delivery, parenteral delivery and other routes of administration. Researchers have used both non-biodegradable and biodegradable polymers for preparation of microspheres. Selection of polymer depends on intended use of microsphere, physicochemical properties of the drug and method of preparation. Different microspheres have various rates controlling mechanism, like non-erodible mechanical barrier for diffusion controlled release, microporous membrane systems, water swellable and hydrogel systems, ion-exchange resin with polymer coating, etc.
2.8.1 Advantages of microspheres as Drug Delivery System

- Control and target drug delivery
- Protection of unstable and sensitive materials.
- Improving solubility, dispersibility and flowability.
- Self-life enhancement by providing protections from environment conditions like moisture, exposure to light etc.
- Reduced volatility of volatile components.
- Masking of odor or taste (Gao et al., 2006).
- Improving bioavailability.
- Drug targeting (Karrou et al., 2009).
- Improving the stability
- Limiting fluctuation within therapeutic range
- Protecting the drug against gastro-intestinal tract (Fatome et al., 1987).
- Conversion of liquid to pseudo solids, etc.

2.8.2 Techniques used for productions of microspheres

There are several methods of encapsulation and some of the important methods are coacervation, solvent evaporation, Interfacial polymerization, double emulsion, pan coating, centrifugal extrusion, spray drying, spray congealing, cross linking, wax coating (hot melt), etc.

2.8.2.1 Solvent evaporation and solvent extraction methods

Both hydrophilic and hydrophobic drugs can be encapsulated by solvent evaporation technique depends on the hydrophilicity or the hydrophobicity of drug (Jalil and Nixon, 1989; 1990b; Huang et al., 1997). The method suitability will dependent on high entrapment of the drug and high yield of desired of size microspheres. In order to achieve this properties a proper selection of the formulation components, solvent, liquid, manufacturing process, vehicle and stabilizer. For insoluble or poorly water-soluble drugs the oil-in-water (o/w) method is frequently used. A schematic representation the process is shown in figure 19.
The steps involved in preparation of microsphere by oil-in-water methods given below (Kamath and Park, 1994):

I. Dissolving of the selected polymer in an organic solvent.
II. Dissolving the hydrophobic drug in polymer solution.
III. Emulsification of the organic phase (dispersed phase) in an aqueous phase (continuous phase).
IV. Evaporation of the dispersed phase from continuous phase and transforming droplets of dispersed phase into solid particles.
V. Drying of microspheres to eliminate the residual solvent.

Oil-in-water methods may be not suitable for the hydrophilic drug due to either insolubility of the drug in the organic solvent, or due to diffusion of the drug into the continuous aqueous phase emulsion, and this will lead to loss of drug entrapment. For such drugs o/o emulsion systems may provide better drug loading in the microspheres (Mana et al., 2007). Other alternative methods/steps have been proposed for encapsulation of hydrophilic drugs as following:

a. O/w co-solvent method: when the drug is not soluble in the main organic solvent, a second solvent, called co-solvent, is necessary to dissolve the drug.

b. O/w dispersion method: the drug is dispersed in form of solid powder in the solution of polymer and organic solvent.

Figure 19: Schematic of microsphere preparation by solvent evaporation technique
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c. O/o non-aqueous solvent evaporation method: the aqueous phase is replaced by oil (such as mineral oil).

d. W/o/w double emulsion method: the aqueous solution of hydrophilic drug is emulsified with organic phase (w/o emulsion); this emulsion is then dispersed into a second aqueous solution forming a second emulsion (Ogawa et al., 1988).

Double emulsion method is suited technique to water soluble drugs, peptides, proteins and the vaccines. Natural as well as synthetic polymer can be used for this method. W/O/W double emulsions can achieve high protein entrapment efficiency and maintain a good bioactivity of protein (Meng et al., 2003). Zhang and Zhu (2004) developed a modified double emulsion technique to prepare bovine serum albumin loaded PLGA microspheres. Microsphere of smooth surface, high yield and entrapment efficiency could be produced successfully by introducing sodium chloride or glucose into the outer aqueous phase. Controlled release microspheres of zidovudine by double emulsion solvent diffusion method was developed with high entrapment efficiency (Das and Rao, 2007). Microsphere as controlled drug delivery systems of insulin in poly-e-caprolactone was developed by double emulsion solvent evaporation method (Mukerjee et al., 2007). A schematic diagram of the double emulsion process is shown in figure 20.

Figure 20: Schematic process for microsphere prepared by double emulsion technique (W/O/W)
2.8.2.2 Wax coating and hot-melt technique

In this technique, wax polymer is used to coat the core particles. Drug or other substance to be encapsulated is dissolved or dispersed in the molten wax, this waxy solution or suspension is dispersed by high speed mixing into a cold solution, like cold liquid paraffin. The mixture is agitated for at least one hour. The external phase (liquid paraffin) is then decanted and the microcapsules are washed with hexane and allowed to air-dry. These microcapsules can be successfully filled in capsules or compression as tablets (Jiménez-Castellanos et al., 1993). The polymers which having low melting point fabricated into microspheres by this technique easily. Mostly carnauba wax and beeswax can be used as the coating materials and these can be mixed in order to achieve desired characteristics. Beeswax microspheres of indomethacin showed controlled release (Gowda et al., 2009).

2.8.2.3 Spray drying and spray congealing

Spray drying technique are based on the drying of the polymer and drug in the air. Spray drying process depending upon the removal of the solvent; however spray congealing depending upon the cooling of solution. To prepare the microsphere by this technique the polymer is dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug will be then dispersed in the polymer solution under high speed homogenization. This dispersion solution will be then atomized in a hot air stream, which led to formation of small droplets and due to evaporation of the solvent microspheres particle will be formed. Microsphere particle in a size range 1-1000 μm will be collected by vacuum drying. The microsphere size is controlled by the rate of spraying, nozzle size, temperature and the feed rate of drug solution. Spray drying and spray congealing methods have been used for many years as microencapsulation techniques. In spray drying, evaporation is the basic mechanism, whereas in spray congealing it is that of a phase inversion from a liquid to a solid.

Spray drying is the most widely used in industrial due to flexibility and reproducibility. The main advantages of the process are feasibility of operation under aseptic conditions, ease of operation, can be used with both heat resistant and heat sensitive products, produce particle of uniform particle size, very useful methods to produce microsphere of very fine particles for pulmonary drug delivery. Huh et al. (2010) developed microsphere of fexofenadine HCl by spray drying method for nasal delivery. The microsphere showed higher of bioavailability and high drug loading efficiency. Da Silva et al. (2009) studied the effect of the spray drying process
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on the drug-polymer interactions and on the stability of microsphere. The result showed high levels of drug-loading efficiency and no affect on the stability of the microsphere components. Drug release from spray-dried microspheres is faster than drug release from microspheres prepared by emulsion solvent evaporation methods (Alhnan et al., 2011).

2.8.2.4 Coacervation

Two types of coacervation can be developed depending on macromolecule number: A) Simple coacervation, in which only one macromolecule is present, B) Complex coacervation, in which two or more of opposite charge macromolecules are present. In complex coacervation the process consists of three steps: 1) preparation of liquid phase, core material phase and coating material phase. 2) distribution of the polymer film on the core material. 3) rigidizing the coating usually by thermal, cross linking such as gluteraldehyde or desolvation techniques to form a microcapsule.

The process variables are critical to control the distribution of the polymer film, the particle size and agglomeration of the formed particles. Complex coacervation has been used as a microencapsulation technique to increase the oral drug absorption of low molecular weight heparins on the basis of charge compensation (Lamprecht et al., 2007). PLGA based microsphere of ciprofloxacin hydrochloride was prepared by using a reversed phase separation/coacervation method to control the drug release up to 6 weeks (Park et al., 2011).

2.8.2.5 Chemical and thermal cross-linking

The natural polymers include: gelatin, albumin, starch, chitosan and dextrin, are used to prepare microspheres by a cross-linking process. A water-in-oil emulsion is prepared, where the water phase is a solution of the polymer that contains the drug to be incorporated. The oil phase is a suitable vegetable oil or oil-organic solvent mixture containing an oil-soluble emulsifier. Once the desired w/o emulsion is formed, the water-soluble polymer is solidified by some kind of cross-linking process. This may involve thermal treatment or the addition of a chemical cross-linking agent such as gluteraldehyde to form a stable chemical cross-link (Thanoo et al., 1993).

Al-Kahtani et al. (2009) developed microsphere of chitosan-based pH-sensitive by emulsion crosslinking technique for controlled release of diclofenac sodium. The drug release influence by extent of cross-linking (Rokhade et al., 2009; Angadi et al., 2010). Table 5 presents the examples of drugs that have been encapsulated with the aforementioned methods.
<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Polymer</th>
<th>Method</th>
<th>Objective of study</th>
<th>Route of administration</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sodium alginate as the hydrophilic carrier</td>
<td>Modified emulsification method</td>
<td>Prolong release of isoniazid</td>
<td>Oral sustained drug delivery</td>
<td>Rastogi et al., 2007</td>
</tr>
<tr>
<td>2</td>
<td>Alginate (AL)-whey protein isolate (WPI)</td>
<td>Emulsification/ internal gelation technique</td>
<td>Retarding riboflavin release</td>
<td>Oral administration</td>
<td>Chen Subirade, 2006</td>
</tr>
<tr>
<td>3</td>
<td>Eudragit® RS PO and ethyl cellulose</td>
<td>Quasi-emulsion solvent diffusion</td>
<td>Sustained-release of nitrendipine</td>
<td>Oral administration</td>
<td>Cui et al., 2003</td>
</tr>
<tr>
<td>4</td>
<td>Eudragit® S</td>
<td>Emulsion solvent diffusion technique</td>
<td>Controlled-release drug delivery systems</td>
<td>Oral administration</td>
<td>Jain et al., 2005a</td>
</tr>
<tr>
<td>5</td>
<td>poly(lactic-co-glycolic acid) (PLGA)</td>
<td>S/O/O/W by freezing-induced phase separation</td>
<td>Protein drug delivery as sustained-release system</td>
<td>Parenteral administration</td>
<td>Yuan et al., 2009</td>
</tr>
<tr>
<td>6</td>
<td>Chitosan</td>
<td>SPG membrane emulsification technique and glutaraldehyde cross-linking</td>
<td>Oral delivery of insulin</td>
<td>Oral administration</td>
<td>Wei et al., 2010</td>
</tr>
<tr>
<td>7</td>
<td>Alginate matrix with chitosan and/or dextran sulphate</td>
<td>Ionotropic gelation</td>
<td>To increase insulin protection and to improve its release from microspheres</td>
<td>Oral administration</td>
<td>Martins et al., 2007</td>
</tr>
<tr>
<td>8</td>
<td>PLGA-PEG</td>
<td>Coacervation</td>
<td>To increase the core loading and release of teverelix</td>
<td>Oral administration</td>
<td>Mallardé et al., 2003</td>
</tr>
<tr>
<td>9</td>
<td>PLG</td>
<td>W/O/W</td>
<td>Oral delivery of propielaactone</td>
<td>Oral administration</td>
<td>Ramya et al., 2009</td>
</tr>
<tr>
<td>10</td>
<td>Poly(palmitoyl-L-hydroxyproline ester)</td>
<td>Solvent evaporation technique</td>
<td>Controlled delivery of rifampicin</td>
<td>Oral administration</td>
<td>Madhan et al., 1997</td>
</tr>
<tr>
<td>11</td>
<td>PVP + EC</td>
<td>Solvent diffusion-evaporation method</td>
<td>To improve the drug release of the poorly water-soluble drug (nifedipine)</td>
<td>Oral administration</td>
<td>Zhao et al., 2010</td>
</tr>
<tr>
<td>12</td>
<td>Chitosan/chondroitin sulfate complex</td>
<td>Emulsion-chemical crosslinking method</td>
<td>Controlled release of 5-fluorouracil</td>
<td>Oral administration</td>
<td>Huang et al., 2010</td>
</tr>
<tr>
<td>13</td>
<td>PLGA/PLA</td>
<td>Supercritical fluid processing (CriticalMix)</td>
<td>Sustained release of Human growth hormone</td>
<td>Parenteral administration</td>
<td>Jordan et al., 2010</td>
</tr>
</tbody>
</table>
2.8.3 Factors influencing properties of microspheres prepared by solvent evaporation method

Solvent evaporation methods are easy and commonly used methods used to prepare microsphere. Many factors can effect on the development of microsphere systems and on the properties of the resulting microsphere, such as size and size distribution of microspheres, rate of drug release and drug encapsulation efficiency.

2.8.3.1 Polymer

The biodegradability or biocompatibility is an essential property for the polymer used for pharmaceutical applications, in which polymer degraded into harmless components and not cause an adverse local or systemic response after administration. Lactic and glycolic acid polymers are one of the most commonly polymers used to develop drug delivery systems due to their safety and FDA approved applications in humans (Okada et al., 1989). Table 6 represents the most frequently used polymers in microspheres preparation.

Table 6: Most frequently polymers used form microspheres

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Polymer name</th>
<th>Polymer properties</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Poly(lactic acid)</td>
<td>Biodegradable and biocompatible</td>
<td>Smith and Hunneyball, 1986; Perez et al., 2001; Kidchob et al., 1998; Cui et al., 2005</td>
</tr>
<tr>
<td>2</td>
<td>Poly(lactic-co-glycolic acid)</td>
<td>Biodegradable and biocompatible</td>
<td>Anderson and Shive, 1997; Blanco and Alonso, 1998; Quaglia et al., 2003; De Rosa et al., 2005</td>
</tr>
<tr>
<td>3</td>
<td>poly(glycolic acid)</td>
<td>Biodegradable and biocompatible</td>
<td>Hazrati et al., 1989; Berkland et al., 2001</td>
</tr>
<tr>
<td>4</td>
<td>Chitosan</td>
<td>Natural polysaccharides</td>
<td>Kato et al., 2003; Sinha et al., 2004; Li et al., 2009; Li et al., 2010</td>
</tr>
<tr>
<td>5</td>
<td>Ethyl cellulose</td>
<td>Degradable, biocompatible</td>
<td>Zinatti et al., 1994;</td>
</tr>
<tr>
<td>Sr. No.</td>
<td>Polymer name</td>
<td>Polymer properties</td>
<td>References</td>
</tr>
<tr>
<td>--------</td>
<td>--------------------</td>
<td>----------------------------------------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>6</td>
<td>Sodium alginate</td>
<td>Natural polysaccharide and low cost</td>
<td>Yang <em>et al.</em>, 2001a; Shi <em>et al.</em>, 2009</td>
</tr>
<tr>
<td>7</td>
<td>Starch</td>
<td>Biodegradable</td>
<td>Bjoerk and Edman, 1990; Rose <em>et al.</em>, 2010; Ishida <em>et al.</em>, 2008</td>
</tr>
<tr>
<td>8</td>
<td>poly(methyl methacrylate)</td>
<td>Non-degradable, biocompatible, low cost</td>
<td>Maa and Hsu, 1997; Kempen <em>et al.</em>, 2006; Shi <em>et al.</em>, 2010</td>
</tr>
<tr>
<td>9</td>
<td>Poly (ethylene glycol)</td>
<td>Biodegradable and biocompatible</td>
<td>Nichols <em>et al.</em>, 2009; Wang <em>et al.</em>, 2010; Scott <em>et al.</em>, 2010</td>
</tr>
<tr>
<td>10</td>
<td>Dextran</td>
<td>polysaccharide</td>
<td>Hovgaard and Brondsted, 1995; Sajadi <em>et al.</em>, 2008</td>
</tr>
<tr>
<td>11</td>
<td>Eudragit® RS100</td>
<td>Poly(meth)acrylate, PH-dependent drug release</td>
<td>Trapani <em>et al.</em>, 2007; Nath <em>et al.</em>, 2011</td>
</tr>
<tr>
<td>12</td>
<td>Eudragit® RL100</td>
<td>Poly(meth)acrylate, PH-dependent drug release</td>
<td>Morishita <em>et al.</em>, 1993; Haznedar and Dortunc, 2004</td>
</tr>
</tbody>
</table>

2.8.3.2 Solvent

Suitable solvent should be selected to be used in preparation of microsphere by solvent evaporation, and it should meet the following criteria:

a. It should be able to dissolve the chosen polymer.

b. It should be poorly soluble in the continuous phase.

c. It should have a high volatility and a low boiling point.

d. It should have low toxicity.
The common solvents used in the preparation of microsphere are presented in Table 7.

Table 7: List of solvents commonly used for microsphere preparation by evaporation method

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Solvent name</th>
<th>Solvent boiling point °C</th>
<th>Solvent properties</th>
<th>Polymer used</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chloroform</td>
<td>61</td>
<td>Low solubility in water; higher toxicity than Dichloromethane</td>
<td>Poly(lactic acid)/ polyethylene glycol</td>
<td>Huang et al., 1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Polyhydroxybutyrate/ Polyhydroxybutyrate-hydroxyvalerate</td>
<td>Maia et al., 2004</td>
</tr>
<tr>
<td>2</td>
<td>Dichloromethane</td>
<td>39.7</td>
<td>Dissolution of most of the polymers, almost immiscible in water, high volatility and quite, low boiling temperature and high toxicity</td>
<td>Poly (D,L-lactide/glycolide)/ poly (D,L-lactide)</td>
<td>Herrmann and Bodmeier, 1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ethyl cellulose, Poly(D,L-lactic acid); Poly(DL -lactic-co-glycolic acid)</td>
<td>Poly(D,L -lactide-co-glycolide)</td>
<td>Yang et al., 2000a; 2000b</td>
</tr>
<tr>
<td>3</td>
<td>Ethyl acetate</td>
<td>77</td>
<td>Low toxicity, partially soluble in water, and very low vapour pressure</td>
<td>Poly(L-lactide)</td>
<td>Herrmann and Bodmeier, 1995</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Poly(D,L-lactide-co-glycolide)</td>
<td>Sah, 1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Poly(lactide)</td>
<td>Freytag et al., 2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Poly(D,L-lactide-co-glycolide)</td>
<td>Jang and Sah, 2011</td>
</tr>
<tr>
<td>4</td>
<td>Ethyl formate</td>
<td>54</td>
<td>Low toxicity and partially soluble in water</td>
<td>Poly(D,L-lactide-co-glycolide)</td>
<td>Sah, 2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Poly(D,L-lactide-co-glycolide)</td>
<td>Kim et al., 2007</td>
</tr>
<tr>
<td>5</td>
<td>Acetone</td>
<td>56.5</td>
<td>Low toxicity and extreme flammability</td>
<td>Eudragit® RS/ Eudragit® RL</td>
<td>Haznedar and Dortune, 2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Eudragit® S100</td>
<td>Paharia et al., 2007</td>
</tr>
<tr>
<td>6</td>
<td>Methanol</td>
<td>67.4</td>
<td>Miscible with water and cosolvent</td>
<td>Poly(lactide-co-glycolide)</td>
<td>Reithmeier et al., 2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Eudragit® S100</td>
<td>Rahman et al., 2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Poly (D,L-lactide/glycolide)</td>
<td>Kwak et al., 2010</td>
</tr>
</tbody>
</table>
Chloroform was frequently used earlier, but due to its toxicity and low vapour pressure, it was gradually replaced by methylene chloride. Methylene chloride is the most common solvent used for the encapsulation by solvent evaporation technique because of its high volatility, low boiling point and high immiscibility with water. This provides a high solvent evaporation rate and shortens the duration of fabrication of microspheres. However, this solvent is confirmed carcinogenic according to environmental protection agency data (EPA), and the researchers are making great efforts to find less toxic replacements. Ethyl acetate shows promising potential as a less toxic substitute of methylene chloride. But due to the partial miscibility of ethyl acetate in water, microspheres cannot form if the dispersed phase is introduced directly into the continuous phase. The sudden extraction of a big quantity of ethyl acetate from the dispersed phase makes the polymer precipitate into fibre-like agglomerates (Freytag et al., 2000). The microspheres prepared by methylene chloride are spherical and more uniform than microspheres prepared by ethyl acetate, in which particles appear to be partly collapsed, and as well the drug encapsulation efficiency reduces significantly compared to the microspheres made by methylene chloride which may be due to the high solubility of ethyl acetate in water leading to the loss of drug (Herrmann and Bodmeier et al., 1998).

2.8.3.3 Surfactant/stabilizer

The surfactant is frequently used for the dispersion of one phase in another immiscible phase and for the stabilization of obtained emulsion. It is added into continuous phase to reduce the surface tension of continuous phase, avoid the coalescence and agglomeration of drops and stabilize the emulsion. A suitable surfactant will be able to produce microspheres with regular size and a small size distribution, which provide predictable and stable drug release. Suitable surfactant should be selected according to the polarity of the two immiscible phases for the desired size of microspheres and the demand on the sphericity of microspheres. Surfactants may be amphiphilic; that means one part of the molecule has more affinity to polar solutes such as water (hydrophilic) and the other part has more affinity to non-polar solutes such as hydrocarbons (hydrophobic). When it is present in an emulsion, the surfactant covers the surface of drops with its hydrophobic part in the drop and its hydrophilic part in the water. Surfactant can be classified into four different types: anionic, cationic, amphoteric and non-ionic. The anionic surfactants release a negative charge in the aqueous solution. They have a relatively high HLB level because they are prone to be hydrophilic. The cationic surfactants, on the contrary, release a
positive charge in aqueous solution. The amphoteric surfactants behave as anionic in alkali pH and as cationic in acid pH. Non-ionic surfactants have no charge. Many hydrocolloids have also been successfully utilized as emulsifiers and emulsion stabilizers. The most commonly used surfactant for preparation of microsphere is presented in the table 8.

Table 8: The most commonly used surfactant for preparation of microsphere

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Surfactant name</th>
<th>Type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Polyvinyl alcohol</td>
<td>non-ionic</td>
<td>André- Abrant et al., 2001; Patil et al., 2004; Berchane et al., 2010; Ramakrishna et al., 2011</td>
</tr>
<tr>
<td>2</td>
<td>Tween</td>
<td>non-ionic</td>
<td>Yang et al., 2000a; Jain et al., 2006; Jordan et al., 2010</td>
</tr>
<tr>
<td>3</td>
<td>Span</td>
<td>non-ionic</td>
<td>Jalil and Nixon, 1990; Paharia et al., 2007; Raghavendra et al., 2008</td>
</tr>
<tr>
<td>4</td>
<td>Sodium dodecyl sulphate</td>
<td>anionic</td>
<td>Xu et al., 2009; Trivedi et al., 2008</td>
</tr>
<tr>
<td>5</td>
<td>Cetyltrimethyl ammonium bromide</td>
<td>cationic</td>
<td>Chatterjee et al., 2010; Kesavan et al., 2010</td>
</tr>
</tbody>
</table>

Poly vinyl alcohol gives the smallest microspheres (Jeffery et al., 1991). The increase of surfactant concentration reduces the size of microspheres and the microsphere size distribution became narrower (Yang et al., 2001b; Heiskanen et al., 2010). Surfactant can also effect on drug entrapment. For example tween 80 used to prepare cephalexin microsphere which showed the highest drug encapsulation efficiency (Chaisri et al., 2010)

2.8.3.4 Stirring

Stirring is the most straightforward processing step to generate droplets of the drug/matrix dispersion in the continuous extraction phase for subsequent solvent removal. In the simplest approach, extraction phase is filled into a vessel and agitated by an impeller. The drug/matrix dispersion is then added, drop wise or all at once, under agitation at a speed sufficient to reach the desired droplet size. The impeller speed is the main parameter for controlling the drug/matrix dispersion’s droplet size in the continuous phase. Increasing the mixing speed generally results in decreased microsphere mean size (Yang et al., 2001b; Sansdrap and Moes, 1993; Gabor et al., 1999; Mateovic et al., 2002). The spread of the microsphere size distribution was found to decrease with stirring speed (Berchane et al., 2006).
The rate of solvent removal by evaporation from the solidifying microspheres can be controlled by the temperature of the microsphere dispersion. Evaporation of the solvent can be facilitated by increasing temperatures of the continuous phase. To demonstrate the effect of temperature on the microsphere formulations, DCM and aqueous PVA solution was used as a continuous phase. The solvent evaporation process was done at various temperatures i.e. 5°C, 38°C and 42°C. The results showed that the PLGA microspheres were larger when prepared at higher temperatures (38 and 42°C), due to insufficient time to reduce droplet size. However, smaller particle sizes of microsphere were obtained at lower temperatures (5°C) (Yang et al., 2000; 2000b).

2.8.4 **Eudragit® Polymers**

Eudragit® polymers are copolymers derived from esters of acrylic and methacrylic acid. Physicochemical properties of different Eudragit® grade are determined by functional groups. Due to variation of solubility; Eudragit® polymers received lot of attentions for preparing modified dosage forms. Table 9 represents various grade of Eudragit®.

Table 9: Properties of various grade of Eudragit®

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Dissolution pH &amp; Application</th>
<th>Functional group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit® L 100-55</td>
<td>Targeted delivery in the duodenum.</td>
<td></td>
</tr>
<tr>
<td>Eudragit® L 30 D-55</td>
<td>pH dependent, soluble above pH 5.5 and targeted delivery in the duodenum.</td>
<td></td>
</tr>
<tr>
<td>Eudragit® L 100</td>
<td>pH dependent, soluble above pH 6.0 and targeted delivery in the jejunum.</td>
<td></td>
</tr>
<tr>
<td>Eudragit® S 100</td>
<td>pH dependent, soluble above pH 7.0 and targeted delivery in the ileum.</td>
<td></td>
</tr>
<tr>
<td>Eudragit® FS 30 D</td>
<td>pH dependent, soluble above pH 7.0</td>
<td></td>
</tr>
<tr>
<td>Eudragit® E 100</td>
<td>pH dependent, soluble in gastric fluid up to 5.0, swellable and permeable above pH 5.0</td>
<td></td>
</tr>
<tr>
<td>Eudragit® RL 100</td>
<td>pH independent, insoluble, high permeability</td>
<td></td>
</tr>
<tr>
<td>Eudragit® RS 100</td>
<td>pH independent, insoluble, low permeability</td>
<td></td>
</tr>
<tr>
<td>Eudragit® RD 100</td>
<td>pH independent for fast disintegrating films.</td>
<td></td>
</tr>
</tbody>
</table>

Eudragit® RL100 and RS100 are anionic copolymers of acrylic and methacrylic acid esters. The structures of Eudragit® RS100 and Eudragit® RL100 differ only in the extent of the
quaternary ammonium substitutions. Eudragit® RS100 containing less of the quaternary ammonium substitutions than Eudragit® RL100, which increase the hydrophilicity and water permeability of Eudragit® RL compare with Eudragit® RS. It is colourless, clear to cloudy granules with a faint amine-like odour. It is soluble in methanol, ethanol and isopropyl alcohol, as well as in acetone, ethyl acetate and methylene chloride. The ratio of the free carboxyl groups to the ester groups is approximately 1:2. The polymer is soluble in water above pH 6.0. But due to the lower content of free carboxyl groups, it dissolves less rapidly than other grade of Eudragit®. These polymers provide pH independent drug release that can be used for formulating the sustained release oral dosage forms. Structural formula of Eudragit® is shown in figure 21.

![Chemical structure of Eudragit®](image)

Figure 21: Chemical structure of Eudragit® (Wang et al., 2004)

Eudragit® S100 microspheres of roxithromycin were prepared by the emulsion solvent diffusion method to mask the bitter taste of the antibiotic. Among six deferent polymer (Eudragit® E100, Eudragit® L100-55, Eudragit® L100, Eudragit® S100 Hydroxypropylmethylcellulose phthalate HP-50 and HP-55) used to mask the unpleasant taste of roxithromycin, Eudragit® S100 was the best (Gao et al., 2006). Rahman et al. (2006) used Eudragit® S100 to coat the core microspheres of alginate prepared by the modified emulsification method in liquid paraffin and by cross-linking with calcium chloride by the solvent evaporation technique to prevent drug release in the stomach and small intestine. Eudragit® S100 was used to prepared microsphere of diloxanide furoate for colon delivery. Microsphere was prepared using emulsification–solvent evaporation method and conjugated with...
Con-A. It was found that the attachment of lectin to the Eudragit® microspheres significantly increases the mucoadhesiveness and also controls the release of drug in simulated GI fluids (Anande et al., 2008). Eudragit® coated pectin microspheres for colon targeting of 5-fluorouracil (FU) were prepared by emulsion dehydration method using different ratios. The result indicated that Eudragit®-coated pectin microspheres are promising controlled release carriers for colon-targeted delivery of FU (Paharia et al., 2007). Eudragit® S100 enteric-coated calcium pectinate microspheres were developed as colonic drug delivery. It was found that the Eudragit® S100 enteric coating was enabled maintenance of microsphere integrity until its expected arrival to colon and it improves the stability of microsphere during storage, avoiding morphologic changes observed for uncoated MS stored under ambient conditions coating (Maestrelli et al., 2008).

Sato et al. (2003) developed hollow microspheres or microballoons (MB) of riboflavin, aspirin, salicylic acid, ethoxybenzamide, and indomethacin using Eudragit® S100 as enteric polymer. Eudragit® S was used to develop floating microspheres of orlistat as an oral anti-obesity agent; calcium silicate was used as porous carrier; the results clearly indicated the controlled and sustained release of orlistat from developed gastro-retentive floating microspheres (Jain et al., 2006). It has been reported that Eudragit® S100 was selected to load insulin to microspheres for oral delivery, because Eudragit® S100 control the drug release at pH > 7, which make it suitable for oral delivery of acid labile enzymes (Jain et al., 2005). The effect of pH on the drug release from Eudragit® S100 microspheres were studied. The results showed drug leakage at pH below the polymer dissolution pH was highest with microspheres prepared at low theoretical drug loading and low surfactant concentrations. In vitro drug, release was found to be strongly pH-dependent; ibuprofen was retained in microspheres at pH 2.0 (<20% release within 4 h), whereas a higher leakage was observed at pH 5.5 and a nearly immediate drug release was obtained at pH 7.4 (Kietzmann et al., 2009). The influence of formulation parameters in the preparation of Eudragit® S100 microspheres for sustained release enzyme loaded was investigated. It was found out that the size of microspheres and the loading of protein in carrier was highly dependent on the solvent and stabilizer concentration for the preparation of Eudragit® S100 microspheres (Rawat et al., 2007).

Eudragit® RS100 microspheres of gentamicin were prepared by modified double emulsion method using factorial design study to target the antibiotics to the intracellular sites where the bacterium is found, and as being in a sustained manner, would permit to reduce the
Literature Review

number of doses and decrease drug toxicity (Singh et al., 2008). Horoz et al. (2006) studied the effects of the variations of dispersing agent types (aluminum tristearate and sucrose stearate) and concentration as well as polymer concentration on the Eudragit® RS100 microspheres prepared by the solvent-evaporation method. The aluminum tristearate and sucrose stearate were clearly effective on the average particle diameter and size distribution of microspheres. The microspheres were produced with high yield value and encapsulation efficiency. Aluminum tristearate retarded the drug release from microspheres because of its hydrophobic structure, while sucrose stearate with a high HLB value accelerated the drug release. The drug release mechanism from microparticles of Eudragit® RL and ethylcellulose binary mixture was studied. Poorly water-soluble drug nifedipine was loaded in the microsphere. Studies have indicated that nifedipine loading affected the nifedipine release kinetics/mechanism from microparticles (Huang et al., 2006). The preparation of Eudragit® microspheres containing acetazolamide using the solvent evaporation method was reported by Haznedar and Dortunc, (2004) in which Eudragit® RS and Eudragit® RL were used individually and in combination. The result showed that the drug release rate from microspheres were dependent on the type of polymer used. The drug release from Eudragit® RS microspheres was very slow whereas the release rates from Eudragit® RL microspheres were faster. Verma et al. (2010) developed Eudragit® RS100 and RL100 microsphere as sustained release formulation to deliver ketorolac tromethamine orally. The in-vivo studies showed drug sustained release without initial peak level that indicate the ability to reduce the dosing frequency and minimized drug side effect. Nanoparticle coating and encapsulation of silica particles with Eudragit® RL100 has been successfully described by Wang et al. (2004). Mateovic-Rojnik et al. (2005) studied the influence of various preparation temperatures: 10, 25, 35, and 40°C, on Eudragit® RS100 microsphere properties. The microsphere particle size particle size distribution increased with increase in temperature. At higher temperatures sphericity and surface smoothness of microsphere were improved.

2.8.5 Ethyl Cellulose Microspheres

Ethyl cellulose (EC) is a non-biodegradable and biocompatible polymer. It is one of the extensively used materials studied as encapsulating polymer for controlled release of different type of drugs. Several researchers have investigated the utilization of EC as a polymer to microencapsulate a drug by coacervation phase separation technique, emulsion solvent evaporation technique. EC microspheres of 5-fluorouracil was prepared, using three grades of
EC and using solvent evaporation technique. The drug loaded particles which were spherical in shape and were suitable for incorporating into a gel base. Drug release studies showed that acidic media provided a faster release rate than neutral media (Ghorab et al., 1990). EC microspheres of furosemide were developed by spherical crystallization technique. The results showed that by increasing EC concentration, the rate of furosemide release decreased and the drug release mechanism of furosemide from microsphere followed the Higuchi matrix model (Akbuga, 1991). Das and Rao (2006) developed sustained release microspheres formulations of zidovudine loaded in EC prepared by w/o/o double emulsion solvent diffusion method. Spherical, free flowing microspheres were obtained and in-vitro drug release profiles from microspheres of different polymer-drug ratios were best fitted to Higuchi model drug release mechanism.

An extended release microsphere formulation of diclofenac sodium was prepared using different proportions of EC as the retardant material to extend the release. The drug release study showed extended release beyond 24 h (Sajeev et al., 2002). Wu et al. (1994) studied the effect of the solvent, non-solvent pairs on the surface morphology and release behavior of EC microspheres; four solvent-non-solvent pairs were chosen to prepare EC microcapsules containing theophylline. The results showed that the surface morphology and release behavior of microcapsules were greatly affected by different solvent-non-solvent pairs. The surface of the microcapsules prepared from the system of high solubility parameter difference was smoother than those from the systems of low solubility parameter difference. The release rate of the drug from microcapsules decreased with increasing solubility parameter difference of the preparative system. The double-encapsulated microcapsules theophylline-loaded in EC were prepared to form core material and encapsulated to increase drug loading and regulate drug release rate. The result showed that the drug loss of the double-encapsulated microcapsules was 12.8%, less than that of microcapsules prepared by the o/w emulsion non-solvent addition method alone, and the drug release of the double-encapsulated microcapsules was to control for more time than the microcapsules prepared by o/w emulsion non-solvent addition method (Tsai et al., 2001). Shi et al. (2009) prepared ciprofloxacin hydrochloride loaded blending films of chitosan /ethyl cellulose microspheres. The drug was stable in the blended films and showed an extended release property.
Singh and Robinson (1988) studied the effect of non-ionic surfactants on release from EC microcapsules of captopril microcapsules. The results showed that the microcapsule formulations prepared with surfactant able to control drug release more than the microcapsules prepared without surfactant. Further studies for the effect of EC viscosity grade on the drug release rate from microcapsules was carried out, in which different viscosity grades of EC were used to prepare captopril microcapsules compressed tablets. The studies showed that the drug release was dependent on the core to wall ratio and the viscosity grade of the EC. Viscosity grade of greater than 100 c.p. was unsuitable for microencapsulation. The surface of the microcapsules prepared with 10 c.p. viscosity grade was comparatively more porous with larger size pores than 50 c.p. viscosity grade of EC. However, 300 c.p. viscosity grade showed incomplete wall formation. The tensile strength of microcapsules compressed tablets was increased as both the core to wall ratios and the viscosity of EC increased. The drug release rate from tableted microcapsules was significantly delayed (Singh and Robinson., 1990). Amri and Sfar (2008) studied the influence of EC with different viscosity grades on in vitro drug release of indomethacin from EC matrix tablets. Four viscosity grades of EC (7, 10, 50 and 100 cp) were studied. These results indicated that the release rates marginally increased with an increase in viscosity grade. The main explanation for the viscosity grade effect on release rates would be differences in tablet porosity. The resulted microspheres showed free flowing with excellent buoyancy and a biphasic controlled release pattern with 12 h (Mastiholimath et al., 2008).

Ethyl cellulose was used as retardant to developed extended release microsphere formulation of water soluble drug diclofenac sodium by w/o/o emulsion method. The drug release rate was affected by drug/polymer ratio and drug release was extended up to 6 h (Chella et al., 2010). Maravajhala et al. (2009) prepared niacin-ethyl cellulose microsphere by water-in-oil-in-oil double emulsion to control drug release. The drug release was controlled for 10 h. Acyclovir-loaded mucoadhesive microsphere using ethyl cellulose as matrix and Carbopol® as mucoadhesive polymer was prepared to improve the oral bioavailability of acyclovir. The result was indicated that the bioavailability of acyclovir was greatly improved due to the prolonged retention of microsphere in gastrointestinal tract (Tao et al., 2009). Rao et al. (2009) used the EC to develop floating microspheres formulations for the prolongation of gastric residence time of
rosiglitazone maleate. The results exhibited a prolonged drug release, remained buoyant for >12 hours.

2.9 ANIMAL MODELS IN OVERACTIVE BLADDER

A wide range of animal species have been used for lower urinary tract research studies. These include hamsters, mice, guinea-pigs, rats, rabbits, cats, dogs, pigs and non-human primates. Most animal models used to study OAB are induced models, whereby a relevant pathological challenge is experimentally applied to a healthy animal. Animal models that closely resemble the pathophysiology of human overactive bladder are important for evaluating novel therapeutics to treat the disorder.

OAB is a symptom-based diagnosis in which the conscious perception of urgency is the key to the diagnosis. There is no way of knowing for definite whether an animal is experiencing urgency, even if pseudo-affective changes in behaviour may suggest it. Animals cannot relate their symptoms to investigators, and consequently, it is not possible technically to create an animal model of OAB. Spontaneous hypertensive rat is a genetic model of multifactorial hypertension, which is considered to resemble human essential hypertension (McMurray et al., 2006). Mitobe et al. (2008) induced a non-invasive rat urinary hyperactive bladder model that is sensitive to anti-muscarinic drugs and without bladder inflammation to study the effect of the treatment on the therapeutics for OAB treatment.

2.10 DRUG PROFILE (TOLTERODINE TARTRATE)

Tolterodine tartrate is a white, crystalline powder. It is a new muscarinic receptor antagonist that is specifically developed for the treatment of urinary urge incontinence and other symptoms associated with an overactive bladder. The chemical name of tolterodine tartrate is (R)-N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate. The chemical formula of tolterodine tartrate is C_{26}H_{37}NO_{7} and the molecular weight is 475.6. The structural formula of tolterodine tartrate is shown in figure 22.
Solubility: Tolterodine tartrate solubility in water is 12 mg/ml. It is soluble in methanol, slightly soluble in ethanol, and practically insoluble in toluene.

Melting point: 210-215 °C

2.10.1 ANALYTICAL METHODS

➢ UV Spectrophotometric method

UV Method is a simple, rapid, precise, accurate and economical method used for analysis drugs in bulk and in pharmaceutical dosage form. Nanda et al. (2009) developed and validate an accurate and reproducible UV method for estimation of tolterodine tartrate in pharmaceutical dosage form.

➢ HPLC method

HPLC method for analysis of tolterodine tartrate in pharmaceutical dosage form was developed and validated for precision, recovery, ruggedness and robustness (Saxena et al., 2006).

2.10.2 DRUG CLASS AND MECHANISM

Tolterodine tartrate is used to treat bladder conditions that cause the feeling of having to urinate immediately, urinate too often, or the inability to control urination. It blocks muscarinic receptors, which can be found on the muscle cells of the bladder wall. Stimulation of these
receptors causes the bladder to contract and empty. When these receptors are blocked, the muscle of the bladder wall contracts less. The bladder can empty too often (urinary frequency) or unexpectedly (incontinence). This is thought to be due to the bladder wall contracting uncontrollably. This medication can dampen down these contractions and makes the bladder more stable. Tolterodine tartrate is used to relieve urinary difficulties, including frequent urination and inability to control urination. It is characterized by favorable tissue selectivity for the urinary bladder over salivary glands (Nilvebrant et al., 1997). Tolterodine tartrate showed to be more specific for the M₂ receptor. This drug also has less M₃ receptor activity with a direct correlation to lessen dry mouth. Large-scale of clinical trial demonstrated the efficacy and tolerability of tolterodine tartrate in 1,022 patients. Treated patients showed a 46% reduction in urge incontinence episodes compared with placebo, with significant improvements noted in frequency reduced by 15% and pad usage 36% reduction, with substantial improvement in volume voided per micturition 21% (Wein, 1998).

2.10.3 Pharmacology

2.10.3.1 Pharmacodynamics

Tolterodine tartrate is a competitive muscarinic receptor antagonist. Both urinary bladder contraction and salivation are mediated via cholinergic muscarinic receptors. After oral administration, tolterodine tartrate is metabolized in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically active metabolite. Both tolterodine tartrate and the 5-hydroxymethyl metabolite exhibit a high specificity for muscarinic receptors, since both show negligible activity or affinity for other neurotransmitter receptors and other potential cellular targets, such as calcium channels. Tolterodine tartrate has a pronounced effect on bladder function. Effects on urodynamic parameters before 1 and 5 hours after a single dose of tolterodine tartrate immediate release were determined in healthy volunteers. The main effects of tolterodine tartrate at 1 and 5 hours were an increase in residual urine, reflecting an incomplete emptying of the bladder, and a decrease in detrusor pressure. Tolterodine tartrate has shown more target-specification that possesses stronger selectivity for the urinary bladder than for the salivary glands and its appeared more potent in inhibiting detrusor instability than salivation (Stahl et al., 1995).
2.10.3.2 Pharmacokinetic

The pharmacokinetic profile of tolterodine tartrate after oral administration to humans is characterized by rapid absorption and a terminal half-life of 2–3 h. After oral administration of 14C-labeled tolterodine tartrate to mice and dogs, approximately equal amounts of radioactivity were recovered in the urine and feces. The maximum concentrations of tolterodine tartrate and its 5-hydroxymethyl metabolite are reported to be 2–3 ng/ml after oral administration of 2 mg dose. The terminal half-life of tolterodine tartrate was approximately 2 h in these species (Kankaanranta and Pahlman, 1997). Tolterodine tartrate exerted a marked inhibitory effect on bladder function within 2 hours after a single oral dose administration (Brynne et al., 1997). However, clinically noticeable decreases in voiding frequency and incontinence episodes do not occur immediately when behavioral aspects of patients are taken into account. Modification of voiding habits is a gradual process, and it takes a period of time for the patient to trust the enhanced control of the medication. Patients achieve approximately 70% of the maximum effects within 2 weeks of treatment initiation (Abrams et al., 1998). Optimal relief of OAB symptoms is achieved after 8 weeks of treatment (Millard et al., 1999). The pharmacokinetics of tolterodine tartrate are dependent in large part on the pharmacogenomics of the CYP2D6 and 3A4 isozymes, and protein binding is 96.3%.

I. Absorption

In a study with 14C-tolterodine tartrate solution in healthy volunteers who received a 5-mg oral dose, at least 77% of the radiolabeled dose was absorbed. Cmax and area under the concentration-time curve (AUC) determined after administration of tolterodine tartrate immediate release are dose-proportional over the range of 1 to 4 mg (Martindale, 2002).

II. Distribution

Tolterodine tartrate is highly bound to plasma proteins, primarily (alpha)1-acid glycoprotein. Unbound concentrations of tolterodine tartrate average 3.7% ± 0.13% over the concentration range achieved in clinical studies. The 5-hydroxymethyl metabolite is not extensively protein bound, with unbound fraction concentrations averaging 36% ± 4.0%. The blood to serum ratio of tolterodine tartrate and the 5-hydroxymethyl metabolite averages 0.6 and 0.8, respectively, indicate that these compounds do not distribute extensively into erythrocytes. The volume of distribution of tolterodine tartrate following administration of a 1.28 mg intravenous dose is 113 ± 26.7 l (Brynne et al., 1998).
III. Metabolism

Tolterodine tartrate is extensively metabolized by the liver following oral dosing. The primary metabolic route involves the oxidation of the 5-methyl group and is mediated by the cytochrome P450 2D6 (CYP2D6) and leads to the formation of a pharmacologically active 5-hydroxymethyl metabolite (Postlind et al., 1998). Further metabolism leads to formation of the 5-carboxylic acid and N-dealkylated 5-carboxylic acid metabolites, which account for 51% ± 14% and 29% ± 6.3% of the metabolites recovered in the urine, respectively. The metabolic profile of tolterodine tartrate in mice and dogs showed similarity to those of human (Brynne et al., 1997).

IV. Excretion

Following administration of a 5 mg oral dose of 14C-tolterodine tartrate solution to healthy volunteers, 77% of radioactivity was recovered in urine and 17% was recovered in feces in 7 days. Less than 1% (<2.5% in poor metabolizers) of the dose was recovered as intact tolterodine tartrate, and 5% to 14% (<1% in poor metabolizers) was recovered as the active 5-hydroxymethyl metabolite (Brynne et al., 1997).

V. Side Effects

Gastrointestinal side effects are reported with the use of tolterodine tartrate. Dry mouth is the most common and may occur in about 35% of patients. Constipation may occur in about 7% of individuals on the drug. About 5% of patients may experience abdominal pain and indigestion. Headaches occur in 7% of individuals. No serious adverse cardiac event attributed directly to tolterodine tartrate use has been documented in any of more than a few dozen well-conducted clinical trials. Central nervous system side effects are rare (Appell, 1997).

VI. Dosage and administration

The initial recommended dose of tolterodine tartrate tablets is 2 mg twice daily. The dose may be lowered to 1 mg twice daily based on individual response and tolerability.