Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2016, 8(5):229-242

Review Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Abuse resistant dosage forms: A redress to modified release dosage forms

P. Tripura Sundari*, M. Sumakanth and Soumya Reddy

RBVRR Women's College of Pharmacy, Barkatpura, Hyderabad 500027

ABSTRACT

During several years the usage of immediate releases formulations was a traditional mode of treatment for diseases. These formulations were supposed to release the drug without any delay after administration. But the problem with these formulations is they will not release the drug for prolonged periods of time and also the management of a chronic disease with conventional formulation are very difficult. To rectify this problem, modified release system had come into picture which will prolong the release of drug from the formulation for larger periods of time. They will also be helpful in maintaining the chronic disease very well with lesser no. of dose to be given per day which is fetched by the higher amount of drug loaded in the dosage form initially to prolong the release of drug. This high amount of drug in the dosage form lead to dose is dumping and misuse of drug especially in habit forming drugs. To keep a check on this misuse, abuse resistant dosage forms had come into the picture which gained good interest of researchers to develop various techniques. In this review article we had made an attempt to discuss some of the important issues of abuse resistant dosage forms.

Key words: Conventional dosage forms, Dose dumping, Drug abuse, Abuse resistance

---

INTRODUCTION

Progress of pharmaceutical preparations

During the past several decades, conventional drug dosage forms have been widely used for treatment of various conditions. These drug dosage forms typically provide an immediate or rapid medication release, and supply a given concentration or quantity of the drug to the body's systemic circulatory system without any rate control. Many problems are associated with conventional multiple dosing regimen of long acting therapy, such as systemic accumulation of the drug leading to side effects or toxicities, irregular profile of the plasma drug level, and poor patient compliance. To maintain the effective plasma drug concentration, frequent administration is required. Due to poor drug efficacy, the incidence of side effects, frequency of administration and patient compliance of these conventional drug preparations, many traditional drug dosage forms are undergoing replacement by second-generation, modified drug-release dosage forms fig. 1. Treatments of numerous diseases using traditional drug products are often [1,2] inconvenient and impractical if disease symptoms occur during the night or early morning.

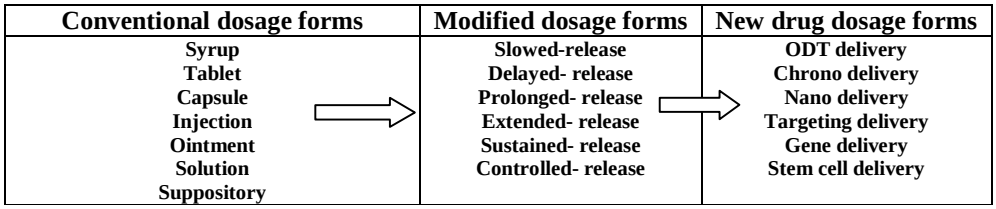

Fig.1 Development of New drug delivery systems

During the early 1990s, second-generation modified-release[3-5] drug preparations achieved continuous and constant-rate drug delivery, in which constant or sustained drug output minimize drug concentration "peak and valley" levels in the blood, so promoting drug efficacy and reducing adverse effects. Modified-release drug preparations are expected to provide reduced dosing frequency and improved patient compliance compared to conventional release preparations. Second-generation modified-release dosage forms include slowed-release, delayed-release, prolonged-release, extended-release, repeated-release, sustained-release, and controlled-release drug preparations.

Several controlled-release preparations [6-9] present numerous problems such as resistance and drug tolerance, and activation of the physiological system due to long-term constant drug concentrations in the blood and tissues. For example, many patients are required to upgrade their dosage regimen[10, 11] after one-year under treatment using transdermal clonidine patches. Arterial pressure in patients exceeds the pretreatment value during the 3–7 days following removal of their previous transdermal nitroglycerin patch. Moreover, modified-release dosage forms do not provide additional delivery at the time that symptoms are exacerbated. At other times of day, excessive plasma drug concentration may also cause adverse effects.[12-15] Long-term use of high-dose oral contraceptives can increase the risk of cardiovascular disease by modifying the low-density lipoprotein and high-density lipoprotein cholesterol levels, increasing triglyceride serum levels, reducing glucose tolerance, raising blood pressure, and promoting clotting mechanisms. Physiological tolerance may develop as an organism builds resistance to the effects of a drug substance after repeated exposures [16-18]. This indicates strongly that it is not always desirable to maintain constant blood levels of a drug over long periods. In most of the controlled release formulations, immediately upon placement in the release medium, an initial large bolus of drug is released before the release rate reaches a stable profile. This phenomenon is typically referred to as 'burst release' [19]. Burst release leads to higher initial drug delivery and also reduces the effective life time of the device.

Dose dumping:
Unintended, rapid drug release in a short period of time of the entire amount or a significant fraction of the drug contained in a modified release dosage form is often referred to as "dose dumping".[20-22]

Dose dumping can be defined either as the release of more than the usual fraction of drug or as the release of drug at a greater rate than the customary amount of drug per dosage interval, such that potentially adverse plasma levels may be reached.

Reasons for Dose dumping:
There are many reasons for dose dumping of an extended release dosage form like

- improper design of dosage form,
- drug excipient interactions,
- crushing or chewing by patient,
- Intake of food or alcohol of which dose dumping due to alcohol is of more concern.

Cases of Dose dumping:
Hydromorphone:
Dose dumping due to alcohol was initially identified in palladone capsules that contain hydromorphone used to treat pain. It is a potent narcotic with the dose of 12mg. Intake of about 240ml of 40% alcohol with the product increased the concentration of drug by about six times than that of intake with water. In one of the subjects studied, increase was found to be 16 times. Consumption of 8 ounces of 4% alcohol (2/3 glass of beer) with the product resulted in twice the concentration of hydromorphone when taken along with water. Risk of occurrence of fatal side effects may

be still higher with increasing doses. The manufacturer had voluntarily withdrawn it from the market. USFDA has given dissolution specifications to conduct dissolution study in the medium containing 0.1N HCl along with different alcohol concentrations for those products that are likely to undergo alcohol dose dumping.

Avinza® (morphine sulphate extended release capsules[23, 24]): in October 2005 Avinza received black box warning and label change due to an in vitro alcohol drug interaction.

Opana® (Oxymorphone[25,26]): in June 2006, the label included in vivo alcohol interaction data.

Other drugs which have the problem of dose dumping are Oxybutyrin chloride and Oxycodone with naloxone, Morphine IR[23,24], Codeine[25,26], Fentanyl[27], HydromorphoneIR[28,29], Propoxy phene IR[30,31,32,35], (dextropropoxyphene/paracetamol), Methadone[33], Meptazinol[31,34]

Dissolution Specifications for the drugs which are prone to have dose dumping in alcohol:
Dissolution should be conducted in 0.1N HCl containing 0 % alcohol, 0.1N HCl with 4% alcohol that resembles [35-37] beer, 20% alcohol (mixed drinks), and 40% alcohol (neat liquor). Dissolution can be conducted using [38-40] USP type I/type II apparatus by maintaining temperature at 37 $\pm 0.5^0$. Samples must be withdrawn for every 15min and the study must be continued up to 2hrs. The percentage of drug dissolved at every time interval is calculated. Depending on percentage of drug dissolved, products are identified as robust (does not dose dump), acceptable and unacceptable.

Approaches for avoiding Dose dumping:
Different techniques to obtain alcohol resistant forms:
Egalet's key technology[41] is an oral drug delivery system of capsules comprising a coat or shell and a drug release matrix. The drug is distributed throughout the drug release matrix, and is released over time as the coat and matrix are eroded within the gastrointestinal tract. By altering the composition of the shell and matrix, a variety of extended-release formulations can be produced. The technology offers a predictable and tailored pharmacokinetic profile, lacks a significant food effect and alcohol dose dumping, and can be used with a broad range of opioids and non-opioids.

Egalet's technology claims to be abuse resistant (neither crushable nor injectable and resistant to fast extraction) and does not experience alcohol-induced dumping.

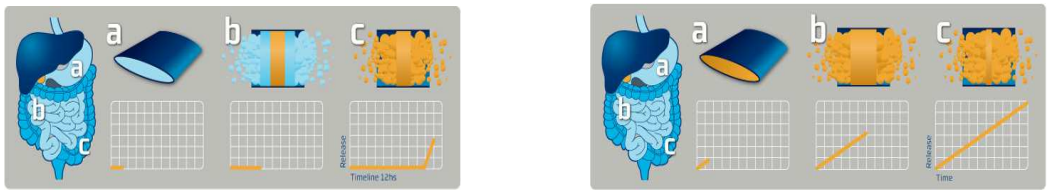

Fig 2: Egalet's technology

Table 1: Products developed based on Egalet's technology

Company Name	Compound	Abuse deterrent technology	Status
Alpharma (NYSE:ALO)	Embeda(morphine)	Extended-release formulation includes a sequestered pellet core of naltrexone	Registration
Pain Therapeutics (NASDAQ:PTIE)/ **King**(NYSE:KG)/**Durect**(NASDAQ:DRRX)	Remoxy(oxycodone)	Durect's Oradur technology consists of a high viscosity, liquid formulation in a hard gelatin capsule to prevent crushing or dissolving	Registration

Trigger Lock[42, 43] is a novel, proprietary and innovative delivery platform that enables the controlled release of narcotic and opioid analgesics while deterring their abuse.

The Trigger Lock technology platform is an adaptation of Micropump that takes advantage of one of Micropump's key characteristics. Because individual microparticles are so small, they effectively cannot be crushed. Crushing is a

common method for tampering with controlled release formulations. Trigger Lock has been designed to resist a number of commonly used methods employed to defeat controlled release systems.

Trigger lock successfully addresses the issues of opiod analgesics tempering:

- The sustained release microparticles are resistant to crushing: each micro particle retains its polymer coating which is virtually impervious to further crushing.
- Prevent misuse of scheduled drugs such as narcotic/opioid analgesics;
- The sustained release microparticles are resistant to crushing: each micro particle retains its polymer coating which is virtually impervious to further crushing.
- Trigger Lock preserves the bioavailability of the compound.
- Trigger Lock is compatible with different dosage forms.

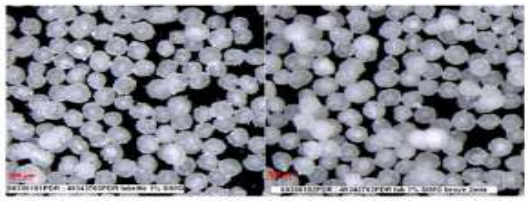

Fig 3: Trigger Lock technology

SOLIQS[44] **Technology:**

The melt extrusion *(Meltrex)* process, well-established in chemical engineering, has been adapted to the manufacture of pharmaceutical formulations in a single, continuous process. The active ingredients are mixed with, or in some cases dissolved in, the pharmaceutical polymer together with excipients if required and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The resulting tablets can have an innovative appearance, providing additional product protection, and the intermediates *(e.g. granules, powder)* can be further processed into conventional tablets.

Fig 4: SOLIQS Technology

The ORADUR® Sustained Release Gel Cap Technology[45-47]**:** ORADUR® can transform short-acting oral capsule dosage forms into sustained release oral products. Products based on ORADUR® technology can take the form of an easy to swallow gelatin capsule that uses a high-viscosity base component such as sucrose acetate isobutyrate (SAIB) to provide controlled release of active ingredient for a period of 12 to 24 hours of drug delivery. Oral dosage forms based on the ORADUR® gel-cap may also have the added benefit of being less prone to abuse (e.g., by crushing or alcohol or water extraction) than other controlled release dosage forms on the market today. ORADUR-based products can be manufactured by a simple process using conventional methods making them readily scalable. These properties have the potential to make ORADUR-based products an attractive option for pharmaceutical companies that seek to develop abuse deterrent oral products.

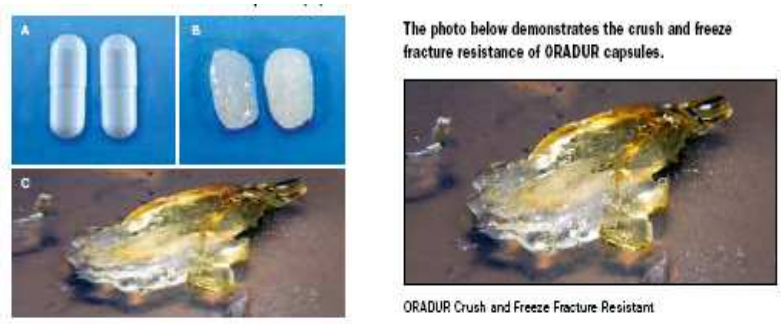

Fig 5: ORADUR Sustained release gel cap technology

The SABER™ Delivery System[44**]:**

The SABER™ Delivery System is a patented controlled-release technology that can be formulated for systemic or local administration of active agents via the parenteral or oral route. The SABER system uses a high-viscosity base component, such as sucrose acetate isobutyrate (SAIB), to provide controlled release of the drug. When the high viscosity SAIB is formulated with drug, biocompatible excipients and other additives, the resulting formulation is liquid enough to inject easily with standard syringes and needles. After injection of a SABER formulation, the excipients diffuse away, leaving a viscous depot. Depending on how it is formulated, the SABER system can successfully deliver therapeutic levels of a wide spectrum of drugs from one day to three months from a single injection.

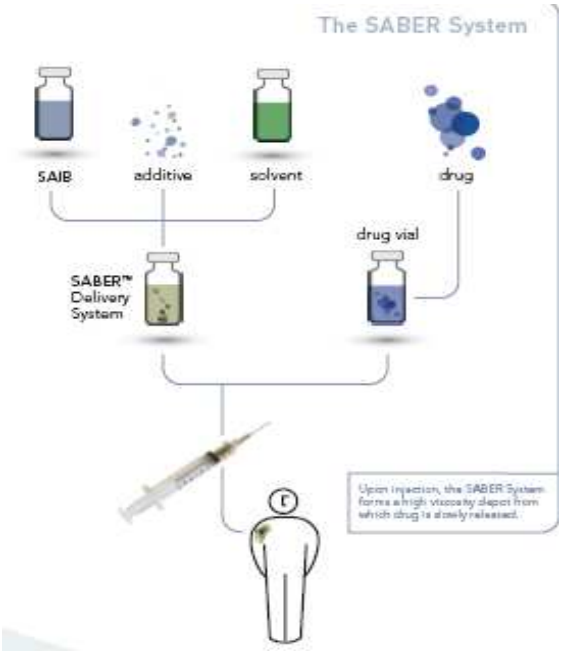

Fig 6: The SABER™ Delivery System

The Banner's Versatrol Technology[48**]:**

It offers controlled release formulations with the benefits of greater effectiveness in the treatment of chronic conditions by reducing side effects through minimizing peak plasma concentrations, and greater convenience leading to higher levels of patient compliance due to a simplified dosage schedule. In this technique, drug is incorporated in lipophilic or hydrophilic matrix and that is than incorporated in soft gelatin capsule shell. Technology is versatile because depending on physicochemical property of drug either emulsion/suspension can be developed. For lipophilic drugs suspension formulation is preferred while for hydrophilic drugs emulsion form is utilized. By applying combination of lipophilic and hydrophilic matrices desire release profile can be achieved.

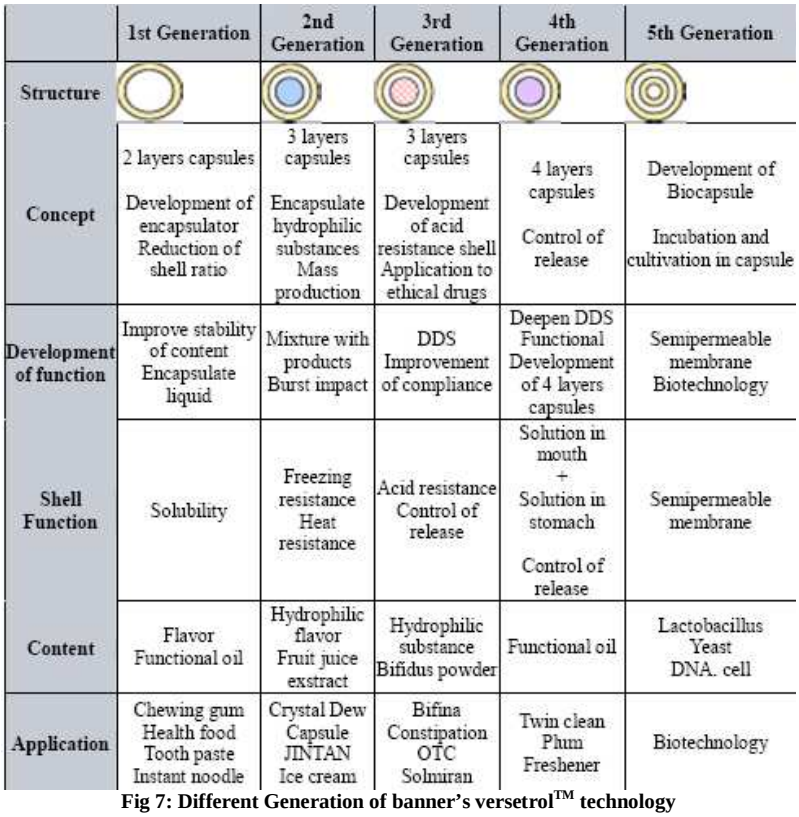

Fig 7: Different Generation of banner's versetrol™ technology

Patents filed on Abuse resistant techniques:

Table 2: Patents filed on Abuse resistant techniques

Sr. No.	Patent No.	Drug used	Technology	Polymers employed
1	US20110104266[49]	Acyclovir Metformin	Micro particulate formulation with modified release property	HPMC Ethyl cellulose Cellulose acetate Cellulose acetate butyrate Eudragit RS,RL,RS PO ,RL PO, NE 30 D
2	US20110177138[50]	Diltiazem HCL	Sustain release microgranules	Ethyl cellulose Cellulose acetate Cellulose acetate butyrate Eudragit RS 30D, RL 30D,RS PO ,RL PO, NE 30 D
3	EP2319499A1[51]	Hydromorphone Oxycodone + naloxone	Melt extrusion	Eudragit RSPO Ethyl Cellulose Hydroxypropyl cellulose Eudragit NE40D Ethyl cellulose
4	US20110223244[52]	duloxetine HCl, esomeprazole, mesalamine, lansoprazole, diclofenac sodium, valproic acid, aspirin, erythromycin, etc	Alcohol resistant Enteric coated pharmaceutical compositions	cellulose acetate phthalate, hypromellose phthalate, Eudragit S, and a mixture of Eudragit L 30 D-55 and Eudragit L 100-55.
5	US20100172989[53]	Hydrocodone Acetaminophen	Melt extrusion	Hydroxypropyl cellulose Eudragit RLPO
6	US20090155357[54]	analgesic, or a pharmaceutically acceptable salt	Modified release oral dosage form with therapeutic agent & alcohol resistant coating	cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), ethyl cellulose with less than 46.5% ethoxyl group, wax, or combination thereof.
7	US20070104789[55]	Hydromorphone	Gastro & ethanol resistant controlled release formulation	alginic acid, glyceryl monostearate, glyceryl palmitostearate, carnauba wax, microcrystalline wax, white wax, yellow wax, ethylcellulose with less than 46.5% of ethonyl groups, and any combination thereof.

Techniques used in Patents:

Patent No. 1: Micro particulate formulation[49]

The process consists of preparation of cores (uncoated micro-particles) of active pharmaceuticals by extrusion and spheronization. Secondly, reservoir micro-particles of AP are prepared by spraying in a fluidized air bed a solution or dispersion containing AP and other acceptable excipients. Preparing the final form of the drug by granulation or extrusion or spheronization of the reservoir microparticles of AP which can be coated with acceptable polymers.

Patent No. 2: Sustain release microgarnules preparation[50]

Firstly microgranules are prepared. Then mounting dispersion is prepared to spray on the surface of microgranules. Mounting dispersion is the dispersion in which the active principles will be dissolved or suspended. The AP is applied to granules in a conventional way by spraying in a FBR and finally the microgranules are dried in FBD.

Patent No. 5 & 7: Melt extrusion[53, 55]

Melt Extrusion:

General steps for melt extrusion method:

- Screening
- Blending
- Extrusion
- Cooling
- Pelletizing
- Screening

The materials screened are blended with ambient temperature and then blended material is extruded and processed in strands when the extruder was set on specific rotation. Strands were cooled and cooled strands were cut into the pellets.

Patent No. 6: Gastro & ethanol resistant controlled release formulation[54]

The first step of the process for the preparation of the composition with controlled release of hydromorphone is anhydrous granulation of hydromorphone and dried pharmaceutically acceptable auxiliary substances. The plastic mixture obtained in the process of anhydrous granulation is formed into granules or pellet cores by common pharmaceutical technological processes such as extruding and spheronizing methods.

Pellet cores or granules prepared by means of anhydrous granulation may be coated with gastro-resistant and ethanol-resistant coating and then filled into capsules or bags or compressed into tablets under addition of dried pharmaceutically acceptable auxiliary substances.

Polymers employed in abuse resistant techniques:

Hydroxy Propyl Methyl Cellulose (HPMC):

It is also known as Hypromellose. Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder. Hypromellose[56, 57] is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating,and as a matrix for use in extended release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades[58-60] may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%. Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lowerviscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Examples of film-coating materials that are commercially available include Any Coat C, Spectracel, Pharmacoat, and the Methocel E Premium LV series. Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose[61-63] produces aqueous solutions of greater clarity, with fewer undissolved fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. It is also used commercially in liquid nasal formulations at a concentration of 0.1%. Hypromellose [64-67] is used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or

agglomerating, thus inhibiting the formation of sediments. In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Cellulose acetate butyrate: Thermoplastic polymer
Cellulose Acetate Butyrate (CAB), commonly known as butyrate, is resistant [68,69] to ultraviolet rays, has lower moisture absorption than acetate and has extremely high impact strength. It is an amorphous[70, 71], transparent thermoplastic polymer. When cellulose is esterified with both acetyl and butyryl radicals to form the mixed ester, cellulose acetate butyrate, many of the desirable properties of both esters are obtained. It is used in

- Osmotic drug delivery
- Pharmaceutical excipient
- Tableting, especially for sustained release
- Taste-masking
- Used in preparation of microballons and micro capsules

Cellulose acetate phthalate
Cellulose acetate phthalate is a hygroscopic, white to off-white, free flowing powder, granule, or flake. It is tasteless and odorless, or might have a slight odor of acetic acid.

Cellulose acetate phthalate (CAP) [72, 73] is used as an enteric film coating material, or as a matrix binder for tablets and capsules. Such coatings resist prolonged contact with the strongly acidic gastric fluid, but dissolve in the mildly acidic or neutral intestinal environment. Cellulose acetate phthalate is commonly applied to solid-dosage forms either by coating from organic or aqueous solvent systems, or by direct compression. Concentrations generally used are 0.5–9.0% of the core weight. The addition of plasticizers improves the water resistance of this coating material, and formulations using such plasticizers are more effective than when cellulose acetate phthalate is used alone. Cellulose acetate phthalate[74,75] is compatible with many plasticizers, including acetylated monoglyceride; butyl phthalybutyl glycolate; dibutyl tartrate; diethyl phthalate; dimethyl phthalate; ethyl phthalylethyl glycolate; glycerin; propylene glycol; triacetin; triacetin citrate; and tripropionin. It is also used in combination with other coating agents such as ethyl cellulose, in drug controlledrelease preparations. Therapeutically, cellulose acetate phthalate has recently been reported to exhibit experimental microbicidal activity against sexually transmitted disease pathogens, such as the HIV-1 retrovirus.

Ethylcellulose
It is an inert, hydrophobic polymer[76-79] and is essentially tasteless, odorless, colorless, noncaloric, and physiologically inert. It has been extensively used as a pharmaceutical vehicle in a number of dosage forms. It has been used as a coating material[80, 81] for tablets and granules, as a tablet binder, in preparing microcapsules and microspheres, and also as film- and matrix-forming material for sustained-release dosage forms.

EUDRAGIT® polymers
These are copolymers[82] derived from esters of acrylic and methacrylic acid, whose physicochemical properties are determined by functional groups (R). EUDRAGIT® polymers are available in a wide range of different physical forms (aqueous dispersion, organic solution granules and powders).

A distinction is made between
1. Poly(meth)acrylates; soluble in digestive fluids by salt formation EUDRAGIT® L, S, FS and E polymers with acidic or alkaline groups enable pH-dependent release of the active ingredient. **Applications:** from simple taste masking through gastric resistance to controlled drug release in all sections of the intestine
2. Poly(meth)acrylates; insoluble but permeable in digestive fluids EUDRAGIT® RL and RS polymers with alkaline and EUDRAGIT® NE polymers with neutral groups enable controlled time release of the active ingredient by pH-independent swelling. **Applications:** delayed and sustained drug release.

Advantages of Eudragits:
- pH-dependent drug release
- Protection of sensitive actives
- Taste and odor masking

- Moisture protection
- Economical application
- Smooth and glossy surfaces, good color coating
- Gastro and alcohol resistance.

EUDRAGIT® RS PO & EUDRAGIT® RL PO is a copolymer[83-86]of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups. The ammonium groups are present as salts and make the polymers permeable.

Physical properties: It is a solid substance in form of white powder[87] with a faint amine-like odour.

Targeted Drug Release Area: Time controlled release, pH independent, Suitable for matrix structures.

Table 4: List of Eudragit polymers

Eudragit polymer	Availability (Product form)	Dissolution Properties
RS PO	White powder, faint amine-like odour.	Insoluble ,Low permeability, pH dependent swelling
RL PO	White powder, faint amine-like odour.	Insoluble ,High permeability, pH dependent swelling
RL 30 D	30% Aq. Dispersion. It is milky white liquid of low viscosity with a faint characteristic odour.	pH dependent swelling
RL 12,5	12.5% Organic solution It is a light yellow liquid of low viscosity, clear to slightly cloudy with a characteristic odour of the solvents.	Organic solution
RS100	Granules It is is a solid substance in form of colourless, clear to cloudy granules with a faint amine-like odour.	Insoluble
RL100	Granules It is is a solid substance in form of colourless, clear to cloudy granules with a faint amine-like odour.	Insoluble
RS 30 D	30% Aq. Dispersion It is milky white liquid of low viscosity with a faint characteristic odour.	pH dependent swelling
NE 30 D	30% Aq. Dispersion. It is milky white liquid of low viscosity with a faint characteristic odour.	Insoluble, low permeability No plasticizer required
NE 40 D	40% Aq. Dispersion. It is milky white liquid of low viscosity with a faint characteristic odour.	pH dependent swelling No plasticizer required
NM 30 D	30% Aq. Dispersion. It is milky white liquid of low viscosity with a faint characteristic odour.	Highly flexible No plasticizer required

Hydroxypropyl cellulose:
Hydroxypropyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder. Hydroxypropyl cellulose[88] is widely used in oral and topical pharmaceutical formulations. In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder, film-coating and extended-release-matrix former. Concentrations of hydroxypropyl cellulose of 2–6% w/w may be used as a binder in either wet-granulation or dry, direct compression tableting processes. Concentrations of 15–35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release. The release rate of a drug increases with decreasing viscosity of hydroxypropyl cellulose. The addition of an anionic surfactant similarly increases the viscosity of hydroxypropyl cellulose and hence decreases the release rate of a drug. Blends of hydroxypropyl cellulose and other cellulosic polymers have been used to improve wet granulation characteristics and tableting characteristics, as well as to achieve better control and manipulation of the rate of drug release.As an alternative technology to wet granulation, dry granulation and direct compression of hydroxypropyl cellulose formulations have been reported to exhibit acceptable tableting and flow characteristics for application in extended-release matrix tablets. Typically, a 5% w/w solution of hydroxypropyl cellulose may be used to film-coat tablets. Aqueous solutions containing hydroxypropyl cellulose together with an amount of methyl cellulose or ethanolic solutions have been used. Stearic acid or palmitic acid may be added to ethanolic hydroxypropyl cellulose solutions as plasticizers. Environmental concerns have limited the use of ethanol in film coating solutions. A low-substituted hydroxypropyl cellulose is used as a tablet disintegrant.

Hydroxypropyl cellulose is also used in microencapsulation processes and as a thickening agent. In topical formulations, hydroxypropyl cellulose is used in transdermal patches and ophthalmic preparations. Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer.

Hydroxy Propyl Methyl Cellulose Pthalate (HPMCP):
Hypromellose phthalate[89] occurs as white to slightly off-white, free flowing flakes or as a granular powder. It is odorless or with a slightly acidic odor and has a barely detectable taste. Hypromellose phthalate is widely used in oral pharmaceutical formulations as an enteric coating material for tablets or granules. Hypromellose phthalate is insoluble in gastric fluid but will swell and dissolve rapidly in the upper intestine. Generally, concentrations of 5–10% of hypromellose phthalate are employed with the material being dissolved in either a dichloromethane : ethanol (50 : 50) or an ethanol : water (80 : 20) solvent mixture.

Hypromellose phthalate[90]can normally be applied to tablets and granules without the addition of a plasticizer or other film formers, using established coating techniques. However, the addition of a small amount of plasticizer or water can avoid film cracking problems; many commonly used plasticizers, such as diacetin, triacetin, diethyl and dibutyl phthalate, castor oil, acetyl monoglyceride, and polyethylene glycols, are compatible with hypromellose phthalate. Tablets coated with hypromellose phthalate disintegrate more rapidly than tablets coated with cellulose acetate phthalate. Hypromellose phthalate can be applied to tablet surfaces using a dispersion of the micronized hypromellose phthalate powder in an aqueous dispersion of a suitable plasticizer such as triacetin, triethyl citrate, or diethyl tartrate together with a wetting agent. Hypromellose phthalate may be used alone or in combination with other soluble or insoluble binders in the preparation of granules with sustained drug-release properties; the release rate is pH-dependent. Since hypromellose phthalate is tasteless and insoluble in saliva, it can also be used as a coating to mask the unpleasant taste of some tablet formulations. Hypromellose phthalate has also been co-precipitated with a poorly soluble drug to improve dissolution characteristics.

Waxes:
Different types of waxes are used in pharmaceuticals like yellow wax, white wax, Carnauba Cream Wax, micro crystalline wax etc.

Yellow wax:
It is available as Yellow or light brown pieces or plates with a fine-grained matt, noncrystalline fracture and a faint characteristic odor. The wax becomes soft and pliable when warmed. The PhEur 6.0 describes yellow wax as the wax obtained by melting the walls of the honeycomb made by the honeybee, Apis mellifera, with hot water and removing foreign matter.

Yellow wax is used in food, cosmetics, and confectionery products. Its main use is in topical pharmaceutical formulations, where it is used at a concentration of 5–20%, as a stiffening agent in ointments and creams. Yellow wax is also employed in emulsions because it enables water to be incorporated into water-in-oil emulsions. In some oral formulations yellow wax is used as a polishing agent for sugar-coated tablets. It is also used in sustained-release formulations. Yellow wax coatings can be used to affect the release rate of drug from ion-exchange resin beads, and yellow wax has also been used in multiparticulate controlled-release dosage forms of chlorphenamine maleate. Yellow wax forms soap with borax.

White wax:
White wax [91, 92] consists of tasteless, white or slightly yellow-colored sheets or fine granules with some translucence. Its odor is similar to that of yellow wax but is less intense.

White wax is a chemically bleached form of yellow wax and is used in similar applications: for example, to increase the consistency of creams and ointments, and to stabilize water-in-oil emulsions. White wax is used to polish sugar-coated tablets and to adjust the melting point of suppositories. White wax is also used as a film coating in sustained-release tablets. White beeswax microspheres may be used in oral dosage forms to retard the absorption of an active ingredient from the stomach, allowing the majority of absorption to occur in the intestinal tract. Wax coatings can also be used to affect the release of drug from ion-exchange resin beads.

Carnauba Cream Wax:
Carnauba wax [93] occurs as a light brown- to pale yellow-colored powder, flakes, or irregular lumps of a hard, brittle wax. It has a characteristic bland odor and practically no taste. It is free from rancidity. Various types and grades are available commercially.

Carnauba wax [94] is widely used in cosmetics, certain foods, and pharmaceutical formulations. Cosmetically, carnauba wax is commonly used in lip balms. Carnauba wax is the hardest and highest-melting of the waxes commonly used in pharmaceutical formulations and is used primarily as a 10% w/v aqueous emulsion to polish sugar-coated tablets. Aqueous emulsions may be prepared by mixing carnauba wax with an ethanolamine compound and oleic acid. The carnauba wax coating produces tablets of good luster without rubbing. Carnauba wax may also be used in powder form to polish sugarcoated tablets. Carnauba wax [95] (10–50% w/w) is also used alone or with other excipients such as hypromellose, hydroxypropyl cellulose, alginate/ pectin-gelatin, Eudragit, and stearyl alcohol to produce sustained release solid-dosage formulations. Carnauba wax has been experimentally investigated for use in producing microparticles in a novel hot air coating (HAC) process developed as an alternative to conventional spray-congealing techniques. In addition, carnauba wax has been used to produce gel beads for intragastric floating drug delivery and has been investigated for use in nanoparticulate sunscreen formulations.

Micro crystalline wax:
Microcrystalline wax [96] occurs as odorless and tasteless waxy lumps or flakes containing small irregularly shaped crystals. It may vary in color from white to yellow, amber, brown, or black depending on the grade of material; pharmaceutical grades are usually white or yellow Microcrystalline wax is used mainly as a stiffening agent in topical creams and ointments.

Microcrystalline wax [97] is used mainly as a stiffening agent in topical creams and ointments. The wax is used to modify the crystal structure of other waxes (particularly paraffin wax) present in a mixture so that changes in crystal structure, usually exhibited over a period of time, do not occur. Microcrystalline wax also minimizes the sweating or bleeding of oils from blends of oils and waxes. Microcrystalline wax generally has a higher melting point than paraffin wax, and higher viscosity when molten, thereby increasing the consistency of creams and ointments when incorporated into such formulations. Microcrystalline wax [98, 99] is also used in oral controlled-release matrix pellet formulations for various active compounds and as a tablet- and capsule-coating agent. In controlled-release systems, microcrystalline wax coatings can also be used to affect the release of drug from ion-exchange resin beads. Microcrystalline wax is also used in confectionery, cosmetics, and food products.

CONCLUSION

The development of dosage forms which are resistant to dose dumping will definitely increase the efficiency of modified release dosage forms and the present scenario is alarming us to develop the dosage forms which are resistant to burst release and especially to alcohol dose dumping. The technologies described above are trying to form niche in the modern release techniques. The technologies available till date are not satisfactory to compensate the need for the development of these dosage forms for all the drugs and also still more polymers to be explored towards their use in developing alcohol resistant dosage forms.

REFERENCES

[1] Shargel L, Wu-Pong S., Yu A. Applied Biopharmaceutics & Pharmacokinetics Mc.Donalds publisher, 5th edition McGraw-Hill, **2005,**
[2] Allen L.V., Popovich N.G., Ansel H.C. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems 9th edition, Lippincott Williams & Wilkins, **2010**
[3] Münzel T, x Heitzer T, Brockhoff C. *Am. J. Cardiol.*, **1998**, 81 (1), 30A–40A.
[4] Flaherty J.T, Nitrate tolerance. A review of the evidence Drugs, **1989**, 37,523–550.
[5] Berner B., John V.A. *Clin. Pharmacokinet*. **1994**, 26,121–134.
[6] Coudert B, Focan C, Donato di Paola E, Levi F. *Eur. J. Cancer*, **2002**, 38, S50–S53.
[7] Fazio G, Ferrara F, Barbaro G, Alessandro G, Ferrro G, Novo G, Novo S. *Curr. Pharm. Des*. **2010**, 16,3490–3496.
[8] Peper A. Intermittent adaptation. A theory of drug tolerance, dependence and addiction Pharmacopsychiatry, **2009**, 42 (1),S129–S143.

[9] Syed a, et al *Int J of Biopharm & Tox res*, **2011**, 1(1), 24
[10] Susijit S, Mishra B, Biswal P, Panda O, Mahapatra S.K, Jana G. K, *Drug Invention Today* **2010**,2,130-133.
[11] Gupta A, Mishra A.K, Gupta .V, Bansal .P, Singh R, *Int J Pharm & Bio Arch* **2010**, 1(1), 1 – 10
[12] Lachmann L, Herbert A, Liberman, Joseph L.K, The theory and practice of Industrial Pharmacy,293-303.
[13] Allen L.V., Popovich N.G., Ansel H.C, Ansel`s Pharmaceutical dosage forms & drug delivery systems, Lippincot William and wilkins, eighth edition, 227-260.
[14] Macheras, P. Symillides, M. Georgiacodis M. *Int J Pharm*, **1989**, 52(3), 249-253.
[15] Aulton`s Pharmaceutics, The design & manufacture of medicines,Biopharmaceutics and pharmacokinetics, A Treatise, second edition, Valabh Prakashan, 315-384
[16] Shalin A. Modi, P. D. Gaikwad,V. H. Bankar, S. P. *Int J Pharm Res Dev*, **2011**, 2, (12).
[17] Stephen P. M. and Alger, In Vitro Release and Dissolution TestingFocus Group Alcohol dose dumping for extended release solid oral dosage products paper presented at AAPS , Nov. 11,**2009**, Los Angles, USA.
[18] Robert J. M, Ajaz S. H, Awareness Topic: Mitigating the Risks of Ethanol Induced Dose Dumping from Oral Sustained/Controlled Release Dosage Forms U.S. Department of Health and Human Services, Food and Drug Administration, CDER, U.S. Government Printing Office: Washington, DC, **2005.**
[19] Hendeles L, Wubbena P, Weinberger M. *Lancet*. **1984**, 22, 1471.
[20] Reddy NM, Mazur AK, Sampath S, Osian A, Sood BM, Ravi A, Nori D, *Cancers Medical Dosimetry*, **2008**, 33(1), 55–61.
[21] Aleksandra K, Ian G T, *International Journal of Pharmaceutics*, **2003**, 251(1–2), 67–78.
[22] Darwish M, Bond M, Tracewell W, Robertson P, *The Journal of Pain*, **2012**, 13(4), S76.
[23] Johnson F et al. J Pain. Johnson F, Wagner G, Sun S, Stauffer J. *The Journal of Pain* **2008**, 9,330-336.
[24] Fiske W et al. Poster presented at the American Pain Society. **2008**. Poster #241.
[25] Sathyan G, Sivakumar K, Thipphawong J., *Curr Med ResOpin*., **2008**,24(1),297-305.
[26] Brown J, Setnik B, Lee K, Cleveland JM, Roland CL, Wase L, Webster L., *J Pain Res*. **2011**, 4,373-84.
[27] Sokolowska M, Romach R, Schuller S, Sun F, Johnson J, Stauffer G, Wagner E, *The Journal of Pain* , **2007**, 8(4), S39 -S39 .
[28] Cudworth A G, Barber H E, and Calvey T N, *Br J Clin Pharmacol*. **1975**, 2(1),65-67.
[29] Linnoila, Hakkinen S, *ClinPhrramcolTher*,**1973**, 15(4), 368-373.
[30] Lichtor j. L, Zacny j, Apfelbaum j. L., lane b. S., Rupani g., Thisted r. A., Dohr c., Korttila k., *Br J Anaesth* **1991**,67(5),579-584.
[31] Rush CR, *Alcohol Clin ExpRes*. **2001**, 25(1),9-17.
[32] Girre C, Hirschhorn M, Bertaux L, Palombo S, Dellatolas F, Ngo R, Moreno M, Fournier P. E. ,EurJ ClinPharmacol. Enhancement of propoxyphene bioavailability by ethanol, **1991**, 41(2),147-152
[33] Ali NA, Marshall EM, Allen DF, Richens A, *Br J Clin Pharmacol* **1985**, 20, 631–637
[34] Sellers EM, Hamilton CA, Kaplan HL, Degani NC, Foltz RL., *Br J Clin Pharmacol* **1985**,19,398-401.
[35] Cushman P et al, *Drug Alcohol Dep*, **1978**, 3,35-42.
[36] Tedeschi G, Smith AT, Richens A. *Hum Toxicol* **1984**, 3(1),37-43.
[37] Gossinger H, Hruby K, Haubenstock A, *Lancet*, **1982**, 2(8294),384.
[38] Om A., Lawrence X. Yu, Dale P. Conner, and Barbara M. Davit, *AAPS J*. **2011**, 13(3), 328–335.
[39] Beatrice S, King Pharmaceuticals, Alcohol and Opioid Interactions: A critical Review of the Worldwide Literature, available from http://www.thci.org/Opioid/nov08docs/setnik.pdf.
[40] Robert J. M, Ajaz S. H, Awareness Topic: Mitigating the Risks of Ethanol Induced Dose Dumping from Oral Sustained/Controlled Release Dosage Forms U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), U.S. Government Printing Office, Washington, DC, **2005.**
[41] Egalet innovators in pain management [home page on internet].
Available from http://www.egalet.dk/index.dsp?area=7
[42] Trigger lock by Flamel technologies [home page on internet].
Available from http://www.flamel.com/wp-conte nt/uploads/2011/07/
[43] Flamel-Technologies, Dr Laury T., New trends in Drug abuse deterrence: LOCKTAb® formulations to address drug misuse and abuse, **2010.**
[44] Elan Drug Technologies: Advances in solid dose oral drug delivery home page on internet].
Available from http://www.ondrugdelivery.com/publications/Oral%**202010**/Elan.pdf
[45] ORADUR™ oral delivery technology [home page on internet].
Available from http://www.durect.com/pdf/ORADUR_Brochure_**July2010**.pdf
[46] DURECT corporation [home page on internet].

Available from http://www.durect.com/pdf/oradur_brochure_**20080107**.pdf
[47] DURECT: ORADUR® Technology [home page on internet].
Available from http://www.durect.com/wt/durect/page_name/oradur
[48] R. Weidman, K. Barham, Development of a Novel Abuse-Resistant Extended Release (ER) Formulation of Compound Z, Banner Pharmacaps, Inc. [home page on internet].
Available from http://www.aapsj.org/abstracts/AM_**2011**/R6180.pdf
[49] Liversidge, Gary, Manser, David, Shah, Hardik, Ruddy, Stephen B., Rekhi, Gurvinder Singh. Inventor, Elan Pharma International Limited Assignee. Alcohol Resistant Enteric Pharmaceutical Compositions. United States Patent 20110223244. **2011** Sept 15.
[50] Muhuri, Goutam Inventor, Alpharma Inc. Assignee Alcohol Resistant Pharmaceutical Formulations. United States Patent 20090155357. **2009** June18.
[51] Donald Spector Inventor Diehl Servilla LLC Assignee. Gastro-resistant and ethanol-resistant controlled-release formulations comprising hydromorphone. United States Patent 20070104789. **2007** May10.
[52] Florence Guimberteau, Frédéric Dargelas Inventors. Flamel Technologies Assignee. Micro particulate formulation with modified release property. United States patent US20110104266. **2011** Jan 11.
[53] Catherine Herry, Laury Trichard Inventors. Ethypharm Assignee. United States Patent US20110177138. **2009** Oct 2.
[54] Kathleen Helen Danagher Inventor. Euro-Celtique S.A. Assignee. Extrusion Technology for Hydromorphone Oxycodone + naloxone. European Patent 2319499A1. **2011**May 11.
[55] Wolfgang Roth, Alexander Burst, Martina Zietsch, Wei Liu, Sandeep Dutta Inventors: Abbott Laboratories, Abbott GmbH & Co. KG Assignees. Sustain release microgranules. United States Patent US20100172989. **2009** Dec 4.
[56] Banker G et al. *Drug Dev Ind Pharm* **1981**, 7, 693–716.
[57] Hardy JG et al. *J Pharm Pharmacol* **1982**, 34, 91P.
[58] Hogan JE. *Drug Dev Ind Pharm* **1989**, 15, 975–999.
[59] Shah AC et al. *J Control Release* **1989**, 9, 169–175.
[60] Wilson HC, Cuff GW. *J Pharm Sci* **1989**, 78, 582–584.
[61] Dahl TC et al. *J Control Release* **1990**, 14, 1–10.
[62] Mehuys E, Remon J.P, Korst A, Van Bortel L, Mols R, Augustijns P, Porter C, Vervaet C. *J Cont Rel* , **2005**,107(3),523-536.
[63] Manish G., Lee A. H., Janet B., Bridget O'M., Fiona J. M., Alexander B. M., Howard N.E. *J Cont Rel*, **2010**, 147(1, 1), 70-75.
[64] Makoto I, Kenichi A, Minoru H, Masao K, *Int J Pharm*, **2008**, 359(1–2), 46-52.
[65] Siepmann J, Peppas N.A, *Adv Drug Del Rev*, **2001**,48(2–3), 139-157.
[66] Sadeghi F et al. *Drug Dev Ind Pharm* **2001**, 27(5), 419–430.
[67] Maria A. Frohoff-Hülsmann, Annemarie S, Bernhard C. L, *Int J Pharm*, **1999**,177(1), 69-82.
[68] Yasunori M, Kanako O, Shigeru Y, Tsuneji N, Kozo T, *Int J Pharm.*, **2003**, 258 (1–2, 4), 21-29.
[69] Yuya T., Nguyen T., Truong G., Fumi N., Masahiro F., Masao K., *Polymer Degradation and Stability* , **2010**, 95, (8), 1406-1413.
[70] Gheorghe F, Marieta C, Elisabetta E, Rita C, Claudio N, Enea M, *Biomaterials*, **2005**, 26 (20), 4337-4347.
[71] Gheorghe F, Marieta C, Elisabetta E, Rita C, Claudio N, Enea M, *Eur J Pharm and Biopharm*, **2007**, 66(1), 11-20.
[72] Prasad Rao J, Kurt E. G., *Progress in Polymer Science*, **2011**, 36(7), 887-913.
[73] Maharaj I et al. *J Pharm Sci* **1984**, 73, 39–42.
[74] Beyger JW, Nairn JG. *J Pharm Sci* **1986**, 75,573–578.
[75] Lin SY, Kawashima Y. *Pharm Res* **1987**, 4, 70–74.
[76] Pujiang S, Li Y., Li Z, *Carbohydrate Polymers*, **2008**,72(3), 490-499.
[77] Porter SC, *Drug Dev Ind Pharm* **1989**, 15(10), 1495–1521.
[78] Pollock D, Sheskey P. *Pharm Technol* **1996**, 20(9), 120–130.
[79] Katikaneni P et al. *Int J Pharm* **1995,** 123, 119–125.
[80] Michael M, Britta S, Anke F, Sakae O, Mark T, Shawn K, James W, *Int J Pharm*, **2004**, 269(2), 509-522.
[81] Sakellariou P, Rowe R.C, White E.F.T, *Intl J Pharm*, **1986**, 34(1–2), 93-103.
[82] Shan-Yang Lin, Chau-Jen Lee, Yih-Yih Lin, *J Cont Rel*, **1995**,33(3), 375-381.
[83] Abbaspour M.R, Sadeghi F, Afrasiabi Garekani H, *Eur J Pharm Biopharm*, **2007**, 67(1), 260-267.
[84] Oth M.P, Moës A.J, *Int J Pharm*, **1989**, 55(2–3),157-164.
[85] Dourado F, Bastos M, Mota M, Gama F.M., *J Biotech*, **2002**, 99(2),121-131.

[86] Haznedar S, Dortunç B, *J Pharm*, **2004**,269(1, 9),131-140.
[87] Shan-Yang Lin, Ching-Li Cheng, Ren-Ing Perng *Eur J Pharm Sci*, **1994**,1(6), 313-322.
[88] Rosario P, Marinella F, Guido De G, *et al.*, *I J Pharm*, **2001**, 218(1–2), 27-42.
[89] Francis L, Balakrishnan A, Sanosh K.P, Marsano E, *Materials Research Bulletin*, **2010**,45(8), 989-992.
[90] Hyuk K, Jung Hwan P, In Woo C, Jung Hyun K, *J Cont Rel*, **2003**, 89(2),225-233.
[91] Torres D, García-Encina G, Seijo B, Vila Jato J.L. *I J Pharm*, **1995**,121(2)239-243.
[92] Gowda, D.V. Vikas K. G., Shuaib Khan M, Afifa B, *Int J PharmTech Res*., **2011**, 3(4), 2199-2207.
[93] Monica C. Chuong, Luca Palugan, Tiffany M. Su, Claudelle Busano, Ronald Lee, Giustino Di Pretoro, and Anee Shah, *AAPS PharmSciTech*. **2010**, 11(4), 1650–1661
[94] Curtis L. W, Aristippos G, Raquel A. S, *Food Science and Technology*, **1998**,31(3),279-285.
[95] Villalobos-Hernández J.R, Müller-Goymann C.C, *Int J Pharm*, **2006**, 322(1–2),161-170.
[96] Soheila K, Ebrahim V.F, Mohsen N.i, Fatemeh A. *Nanotechnology, Biology and medicine*, **2010,** 6(6),753-759.
[97] Zhou F, Vervaet C, Remon J.P., *Int J Pharm*, **1997**,147(1),23-30.
[98] De Brabander C, Vervaet C, Görtz J.P, Remon J.P, Berlo J.A, *Int J Pharm*, **2000**,208(1–2),81-86.
[99] De Brabander C, Vervaet C, Fiermans L, J.P, *Int J Pharm*, **2000**,199(2),195-203.