Multiparticulate modified release formulation drug delivery system for cardiovascular drugs: A review

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ABSTRACT:

Cardiovascular diseases such as Ischemic heart disease and stroke are the two most common causes of death worldwide. Extensive drug development activities are being done to develop drug delivery technologies using drugs effective for cardiovascular diseases & alike. The intent of this review article is to capture advances in drug delivery systems for cardiovascular drugs. In order to obtain adequate or required concentrations of the active agents in a continuous fashion and to minimize the dose dumping; modified release pellet dosage forms are being developed and are more preferred over immediate release dosage forms. The USP defines modified-release dosage form as the dosage form for which the drug release characteristics (i.e. the time and location of drug release) are chosen to accomplish convenience or therapeutic objectives not offered by conventional dosage forms, such as immediate-release dosage forms. The USP defines two types of modified-release dosage forms: delayed-release and extended-release. Generally, most of the cardiovascular drugs have relatively short plasma half-life and extensive first pass metabolism; different successful attempts have been made for developing the sustained release pellet dosage forms for different cardiovascular drugs. The drug therapy or treatments with these drugs are usually chronic, so it is more critical that the treatment should be given in coordination to the biological rhythm in order to optimize the desired effects of the drugs. Many significant Chronotherapeutic techniques have been designed, developed and even patented. Using these techniques like MICROSPHERE® by Flamel Technology CONTIN®, physico-chemical modification of the active pharmaceutical ingredient (API), OROS®, CODAS®, CEFORM®, DIFFUCAPS®, chronomodulating infusion pumps, TIMERx®, three-dimensional printing, controlled-release (CR) erodible polymer and CR microchip strategies, different cardiovascular pellet dosage forms are already developed. Many patent applications are already granted and many more are published in order to provide an implicit basis for the development of the modified release pellet dosage forms of the cardiovascular drugs.

Keywords: Pelletization, Sustained release, controlled release, Chronotherapeutic, Cardiovascular drugs,

INTRODUCTION

Presently, with any dosage form, the basic goal of therapy is to achieve a steadfast blood or tissue level that is pharmacologically efficacious and nontoxic for prolonged period of time. The design of exact dosage regimens is an important element in achieving this target. Thus basic aim in dosage form design is to optimize the delivery of medication so as to achieve a measure of control of the therapeutic effect in the face of uncertain fluctuations in the in-vivo environment in which the drug

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release take place and also to minimize the local & systemic side effects produced by that particular dosage forms. In modified release dosage forms, the therapeutic agents will be automatically delivered at the predetermined rates over a long period of time. Now as the frequency of drug administration is lessened, patient compliance is improved, blood level oscillation characteristic of multiple dosing of conventional dosage forms is even reduced & also in these dosage forms, the amount of the drug administered can also be reduced [1]. Pellets are small spherical solid masses consisting of a highly purified drug (with or without excipients) made by spheronization or Wurster technique. They are generally had a purpose of giving a continuous release of drugs over a long period of time [2]. Presently, pellets are of high concern to the pharmaceutical industry for a variety of benefits as these products offers both flexibility in dosage form design and development and also utilized to ameliorate the safety and efficacy of efficacious agents. However, the single most important factor responsible for wide spread of pelletized products is the popularity of controlled release technology in the delivery of drugs [3].

For the sustained release composition of pellets, the core of the pellet may contain: as exemplified below,

A therapeutically efficacious medicament in very appropriate proportion;  
0.5 to 50% by weight of a water soluble polymer;  
1 to 25% by weight of a water-insoluble polymer applied in an aqueous latex dispersion and subsequently the water is removed; and as per calculation, the sum of all the three i.e. the medicament, the water soluble polymer and the water insoluble polymer is equal to less than 100%.

The diameter of the particle ranges from 0.8 to 1.2 mm. also, generally the water-soluble polymer used is hydroxypropyl methylcellulose and water-insoluble polymer used is ethyl cellulose. The diluent, in general terms, comprise of 20% to 40% of weight of total composition and is microcrystalline cellulose or maltodextrin. The surfactant ranges from 0.5% to 2% by weight of the total composition and is sodium lauryl sulfate [5].

The variety and purview of cardiovascular drugs have increased immensely in the past few decades and new drug entities are being approved annually. In the 1950s, effective oral diuretics became available. These drugs dramatically changed the treatment of heart failure and hypertension. In the mid-1960s a class of agents called beta blockers was discovered. This led to major changes in physicians’ ability to treat patients with hypertension or angina pectoris. Calcium channel blockers and ACE inhibitors became widely used in the 1980s, and they, too, have allowed patients with hypertension, heart

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**Fig 1:** Different Pelletization techniques [4]
failure, and coronary artery disease to be treated more efficiently. The development and use of thrombolytic, the “clot busters,” have revolutionized our ability to treat patients having a heart attack [6].

**Table 1**: Cardiovascular drugs can be divided into several categories, each of which is discussed below [6]:

<table>
<thead>
<tr>
<th>Therapeutic Drug Categories</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs to treat angina</td>
<td>Beta blockers, calcium channel blockers, nitrates</td>
</tr>
<tr>
<td>Drugs to treat blood clot disorders</td>
<td>Anticoagulants</td>
</tr>
<tr>
<td>Drugs to treat heart failure</td>
<td>ACE inhibitors, combination drugs, diuretics, digitalis drugs</td>
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</table>

Currently, many cardiovascular drugs or their pharmacologically accepted derivatives, salts or stereoisomers are available in sustained and controlled release dosage forms. Mainly some are diltiazem hydrochloride, propranolol, isosorbide dinitrate, nifedipine, nitroglycerin, verapamil hydrochloride, dipyridamole, glipizide, enalapril maleate, carvedilol phosphate, metoprolol succinate, disopyramide, procainamide hydrochloride, felodipine & carvedilol phosphate.

There are numerous techniques available and exemplified in literatures to manufacture pellets as a dosage from, the skill lies in selection of process, composition, control parameters to achieve desired drug release profile.
Fig 3: Circulation through the heart [8].

PELLETIZATION TECHNIQUE

Dry Mixing
During the first step, uniform blend should be made by mixing dry powders in an appropriate mixer for a particular period of time because uneven distribution of mixture can lead to localized over wetting during early stages of granulation and due to these unevenly wetted surfaces, size distribution of pellets would highly alter. Thus, uniform distribution of particles before preparation of granulating fluid is highly necessary for monotonous pellets [9].

Granulation
The major differences in the this step, as compared to typical granulations for compression, are the amount of granulating fluid required to develop pellets uniformity and Sphericocity and the mixing time required for the same are much more higher than granulation intended for tabletting [9].

Four different procedures of granulation were applied, keeping different shear forces, like planetary mixer, high-shear mixer and twin-screw extruder with two different screw assemblies and results were obtained. It was found that by applying higher shear forces needed higher water content which was necessary for successful development of pellets. This observation was contrasting against the conventional granulation and was explained well by the crystallite-gel-model [10].

The melt Pelletization technique was implanted using 10-1 high shear mixer and ternary mixtures of Stearic acid as a melting binder, anhydrous lactose as a filler and theophylline as a model drug for preparing sustained release pellets. It was found that the pellet size fraction of 2000 µm exhibited zero-order release [11].

Fig. 4 [12]: three different types of impeller blades characterized by different angles of inclination of the plane blades (60°, α; 30°, β; 45°, γ), deflector (φ) used in screening study.

The doehlert matrix was applied for the optimization of process variables and quality control of pellets characteristics [11],[12].

The characterization of the surface smoothness of the pellets was studied by determining the shape parameters like circularity, roundness and elongation and also the fractional dimension by wet granulation method using...
rotary processor. It was found that by increasing the time and intensity of spheronization process, the variability in Sphericity of pellets rather than elongation parameter was solved.[13].

The surface free energies between the drug and the excipients could also be a factor in wet granulation technique. If the spreading coefficient of the binder over substrate is positive or higher, it resulted in dense, non-friable pellets but if coefficient is negative, then porous, loose textured pellets were formed.[14].

The self-emulsifying pellets composed of oil to surfactant ratio of 1:4 (w/w) were found to be improved version of all formulations designed and prepared by wet granulation technique.[15].

Extrusion:
This is a third step, which converts the wetted mass into rod-shaped particles. On basis of variety of extrusion zones, different screw extruders are available. The primary extrusion process variables are the feed rate, die opening and die length. Also, heat buildup is of important concern.[9].

The impeller design and massing time[11], [12], the extruder screen and spheronizer speed also[16], [17] played a very significant role in developing pellet quality. The study was performed using the instrumented basket extruder. By just modifying the perforation method in impeller of different extruders, the concentration of the excipients β lactose and dicalcium phosphate are highly increased in case of high and low water soluble drugs, respectively.

The formulation variable like moisture content was of significant concern in formulation of pellets as by maintaining their optimum level, agglomeration tendencies of extrudates were reduced. This could be done by using the two different kinds of extruders’ i.e. twin-screw extruder and rotary ring die press because in case of twin-screw extruder, the moisture content was higher as the hold of particle size was also observed.[18].

Spheronization:
This is the fourth step, relatively done on simple equipment principled on frictional forces having different disks installed, helped to convert the extrudates into spheres or pellets[9].

Flow Chart 1: Extrusion/Spheronization process[9].

<table>
<thead>
<tr>
<th>Process</th>
<th>Equipment Type</th>
<th>Fluid type</th>
<th>Fluid level</th>
<th>Die Diameter</th>
<th>Die length</th>
<th>Residence time</th>
<th>Disk speed</th>
<th>Charge</th>
<th>Temperature</th>
<th>Time</th>
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<tbody>
<tr>
<td>Dry Mixing</td>
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<tr>
<td>Granulation</td>
<td>Equipment Type</td>
<td>Fluid type</td>
<td>Fluid level</td>
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<tr>
<td>Extrusion</td>
<td>Equipment Type</td>
<td>Die Diameter</td>
<td>Die length</td>
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<tr>
<td>Spheronization</td>
<td>Equipment Type</td>
<td>Residence time</td>
<td>Disk speed</td>
<td>Charge</td>
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<td></td>
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<tr>
<td>Drying</td>
<td>Equipment Type</td>
<td>Temperature</td>
<td>Time</td>
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It was found that a combination of speeds ranging from 1000 to 2000 rpm and residence times between 5 and 15 min may be used to produce spheroids with a modal fraction in a size range of 0.7–1.0 mm. On increasing a spheronation speed and residence time to comparatively higher limits, the size of the spheroids could be reduced \[19\].

Also, study has been made in which the physical characteristics like the pellet size, density, porosity, mechanical strength, residual moisture after drying and shape were determined after five different formulations of pellets were prepared using a sound statistical plan keeping different ratios of drug and fillers \[20\].

It was also found that using the ram extruder, the mixtures containing fine particle size (18.0 \(\mu m\)) will form good spheres at either 33 or 37\% water content, but the mixtures containing the coarse particle size (118.0 \(\mu m\)) will only form controlled size spheres at 33\% moisture content. The results were found to be equivalent for both 1.0 and 1.5 mm extrudates \[21\].

Spheroids of uniform size and shape could be developed while using mixture of macrocrystalline cellulose, lactose (with median diameter of either 18 or 117 \(\mu m\)) and water if only cylinder extruder is used but not if ram extruder was used \[22\].

**Wurster Technology:**

**Definition:** The Wurster fluid-bed process is recognized by the pharmaceutical industry as the technology for precision application of a film coating onto particulate materials such as powders, crystals, or granules. The technology can be used to encapsulate solid materials with diameters ranging from near 20\(\mu m\) to several centimeters.

Film coating processes require evaporative removal of an organic solvent or aqueous vehicle as the film coat is deposited. The speed of a film coat application is related to the drying capacity of the process. Fluid-bed film coating processes have a greater drying capacity than other coating systems due to a relatively high fluidizing air volume that is used to both circulate particles and evaporate the coating vehicle. This increased drying capacity translates to more efficient film coat application.

Coating possibilities are almost unlimited including the ability to place a hydrophilic coating on a hydrophobic core, or a water-based coating on a water-soluble core. Film coat properties or product performance can be optimized with changes made to the coating formulation, processing conditions, or the use of multiple coating layers.

**Working principle:** The Wurster process is well suited to uniformly coat or microencapsulate individual particles. The technology is characterized by the location of a spray nozzle at the bottom of a fluidized bed of solid particles. The particles are moved with a fluidizing air stream that is designed to induce a cyclic particle flow upward past the spray nozzle. The nozzle sprays atomized droplets of coating solution or suspension.
concurrently with particle flow. Passing particles move upward into an expansion chamber as droplets deposit on their surfaces. The expansion chamber reduces air velocity to allow particles to circulate back to the coating chamber. It also allows particles to further separate from one another temporarily and minimize the potential for particle agglomeration and accretion. The organic solvent or aqueous coating vehicle is evaporated as the particles move into and through the expansion chamber to leave non-volatile coat formulation ingredients on the particle surface as part of the developing film coat. Process parameters are set for optimal vehicle removal and film coat characteristics. This batch process is continued until each particle is coated uniformly to the desired coat percentage or film thickness.

In a similar way, the Wurster fluid-bed process can be used to apply a hot melt coating such as a wax. The wax is heated to a molten state and sprayed in the same manner as a solution or suspension. Process parameters are adjusted to congeal molten wax droplets on the surfaces of the circulating particles.

**Fig 6: Working of Wurster Fluid bed machine**

**CHARACTERIZATION OF SUSTAINED RELEASE PELLET DOSAGE FORMS**

*Emulsion droplet size determination* [23]. These tests is only for Self Emulsifying (SE) pellets and for Self Emulsifying Drug Delivery System (SEDDS) (without drug) were agitated gently in distilled water with magnetic stirrer. Samples were withdrawn after 30 min and passed through 0.45 µm micropore filters. Now the droplet size of the resultant emulsion was measured using Laser diffractometry.

Size distribution and shape evaluation of the pellets [23]. In order to determine the size distribution, take an appropriate amount of produced pellets vibrate by hands for 5 min using a set of ASTM Standard Sieves. For shape evaluation, pellets of size in microns were taken under a microscope with an optical zoom of 40x0.17 and an eye piece of 10x22.

*Disintegration test of pellets* [23]. Using a disintegration apparatus, pellets were taken in de-ionized water at 37°C. The 0.3mg pellet samples from each formulation were tested (n=3) and endpoint was measured at time when no obvious particles were present on the sieve in each of disintegration basket.

*Crushing strength of pellets* [23]. Applying a force using a tablet hardness tester of 10-kg load cell on 10 pellets of each formulation individually, the crushing strength of the pellets was analyzed. This force is then converted into surface tensile strength using the below mentioned equation:

$$\sigma_{f(s)} = \frac{0.4F}{\pi R^2}$$

Where $\sigma_{f(s)}$ is a surface tensile strength (Pa), $F$ is a crushing force (N) and $R$ is the radius (m).

*Pharmacokinetic data analysis* [23] From the individual plasma concentration and time profiles, the peak plasma concentration ($C_{max}$)
and the time for their occurrence ($T_{\text{max}}$) were calculated. As per linear trapezoidal rule, the area under concentration-time curve (AUC) was estimated. The relative bioavailability ($F$) of pellets and liquid Drug Delivery System to the conventional tablets (reference) was calculated using equation:

$$F = \frac{\text{AUC}_{\text{test}} \times 100}{\text{AUC}_{\text{reference}}}$$

**In-vitro dissolution Test.** This test used to carry out as per the apparatus and other conditions mentioned in respective monographs of drugs in pharmacopoeias and the dissolution medium was chosen as per the nature of the drug. Generally paddle apparatus are used and temperature of 37 ± 0.5 $^\circ$C.

**Roundness** [24]. The roundness of the prepared pellets was calculated using the following equation:

$$\text{Roundness} = \frac{4\pi A}{P^2}$$

$A$ – Area occupies by a single pellet image

$P$ – Pellet’s perimeter.

**Sieve Analysis** [24]. Sieve analysis was performed using a nest of U.S. Standard Sieves between Nos. 8 and 35. The average diameter was calculated using the equation below:

$$d_{\text{avg}} = \frac{\sum \text{MO} \times \%\text{retained}}{100}$$

Where MO is defined as the mean sieve opening for each sequential pair of sieves in the nest of sieves. % retained is the mass of pellets retained on the sieve in that pair that has the smaller aperture, expressed as a percentage of the total mass of pellets in the sieve analysis. The entire mass of each bead batch experienced sieve analysis. Yield is defined as the percentage of pellets found in the 14/20 meshcut. Only the pellets in this meshcut were used in further studies to minimize pellet size effects on characteristics.

**Internal & external morphologies** [24]. The internal and external morphologies of the pellets were investigated using a Model S-530 scanning electron microscope (SEM) (Hitachi, Tokyo, Japan) at 10 kV. Pellets were mounted on aluminum studs as a whole pellet, or after being sliced in half, and then sputtercoated with gold for approximately 1 min. The images of the pellets were viewed at 50×magnification.

**Moisture Analysis** [24]. Using halogen moisture analyzer, moisture analysis was performed in triplicate. For each batch of pellets, a sample of approximately 1 g was accurately weighed and then heated to and maintained at 105$^\circ$C. The mass was recorded every 5 min to ensure that the mass was consistent at 10 and 15 min. The moisture content, calculated as the difference between the initial mass and the mass at 15 min divided by the initial mass, was expressed as a percentage.

**Statistical analysis** [24] this analysis was performed with the help of different software’s available and various parameters like Area under Curve (AUC), Maximum concentration ($C_{\text{max}}$), etc. were calculated.

**Content uniformity** [25] this test can be performed using spectrophotometer taking 100 mg of the prepared dosage units in 100 ml of distilled water. Then filtering the resultant solution, the content of the drug can be measured.

**Stability Studies** [26] coated pellets were stored at room temperature (25 $^\circ$C and 60%RH) and under stress conditions (40 $^\circ$C and 75%RH). Drug released from the pellets was measured after 1, 2, 3 and 6 months.
**Image Analysis** ([27]) this is an excellent method for checking the robustness and also for estimating the mean pellet size and coating thickness. It checks the coating thickness with an accuracy of ±1.2 µm.

![Image Analysis](image)

**Fig. 7** ([28]): Image analysis of the surface of the pellets

Based on the research made on the chronopharmacology and chrono-pharmaceutical of cardiovascular diseases, it is found that functions made by heart in form of heart rates, blood pressure show 24 hours of variation. A clear diurnal oscillation is also seen in cardiovascular diseases such as acute myocardial infarction, strokes and arrhythmia. Since most of these disorders can induce fatal or severe outcomes, it is important to elucidate the precise mechanism of the onset of these diseases. This circadian occurrence is believed to be tightly associated with an internal clock ([29]).

**EXAMPLES OF CHRONOPHARMACEUTICAL TECHNOLOGIES**

Currently key technologies in chronopharmaceutics includes: CONTIN®, physico-chemical modification of the active pharmaceutical ingredient (API), OROS®, CODAS®, CEFORM®, DIFFUCAPS®, chronomodulating infusion pumps, TIMERx®, three-dimensional printing, controlled-release (CR) erodible polymer and CR microchip strategies ([29]).

**Fig 8: The Circadian pattern of diseases** ([30]).

**Table 2: Common onset of cardiovascular diseases** ([29]).

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Common Onset</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Fibrillation</td>
<td>Morning/night</td>
<td></td>
</tr>
<tr>
<td>Ventricular</td>
<td>Morning</td>
<td></td>
</tr>
<tr>
<td>Tachycardia/fibrillation</td>
<td>Morning</td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>Early morning</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>Early Morning</td>
<td></td>
</tr>
<tr>
<td>Cerebral Infarction</td>
<td>Morning</td>
<td></td>
</tr>
<tr>
<td>Subarachnoidal haemorrhage</td>
<td>Daytime</td>
<td></td>
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</tbody>
</table>

**CONTIN® TECHNOLOGY**

In this technology, molecular coordination complexes are formed between a cellulose polymer and a non-polar solid aliphatic alcohol optionally substituted with an aliphatic group by solvating the polymer with a volatile polar solvent and reacting the solvated
cellulose polymer directly with the aliphatic alcohol, preferably as a melt. This constitutes the complex having utility as a matrix in controlled release formulations since it has a uniform porosity (semi permeable matrixes) which may be varied\(^\text{[29]}\). E.g.\(^\text{[31]}\): Evening administration of Uniphyl\(^\text{®}\) (anhydrous theophylline) tablets represented a rational dosing schedule for patients with asthma who often exhibit increased bronchoconstriction in the morning. Hokunalin\(^\text{®}\) tape (Tulobuterol) represented a CONTIN\(^\text{®}\) Transdermal chrono delivery technology.

**OROS\(^\text{®}\) TECHNOLOGY**

OROS\(^\text{®}\) technology\(^\text{[32]}\) uses an osmotic mechanism to provide pre-programmed, controlled drug delivery to the gastrointestinal tract. The dosage form comprises a wall that defines a compartment. The active drug is housed in a reservoir, surrounded by a semi-permeable membrane/wall (e.g. cellulose esters, cellulose ethers and cellulose ester–ethers) and formulated into a tablet. The tablet is divided into two layers, an active drug layer and a layer of osmotically active agents (e.g. poly(ethylene oxide)) comprising means for changing from a non-dispersible viscosity to a dispersible viscosity when contacted by fluid that enters the dosage form.

E.g.\(^\text{[31]}\): OROS\(^\text{®}\) Delayed Push–Pull System, also known as controlled onset extended release (COER) was used to design Covera-HSR, a novel anti-hypertensive product\(^\text{[31]}\).

**CODAS\(^\text{®}\) TECHNOLOGY**

The Chronotherapeutic Oral Drug Absorption System (CODAS\(^\text{®}\))\(^\text{[34]}\) is a multi-particular system which is designed for bedtime drug dosing, incorporating a 4–5 h delay in drug delivery. This delay is introduced by the level of non-enteric release-controlling polymer applied to drug loaded beads.

![Fig 9](image1.png) Delivery systems used in Chronotherapeutic antihypertensive agents.

For example, water from the gastrointestinal tract diffuses through the membrane at a controlled rate into the tablet core, causing the drug to be released in solution or suspension at a predetermined rate. This creates a 'pump' effect that pushes the active drug through a hole in the tablet. This technology, especially the OROS\(^\text{®}\) Delayed Push–Pullk System, also known as controlled onset extended release (COER) was used to design Covera-HSR, a novel anti-hypertensive product\(^\text{[31]}\).

![Fig 10](image2.png) Delivery systems used in Chronotherapeutic antihypertensive agents.
The release controlling polymer is a combination of water soluble and water insoluble polymers. As water from the gastrointestinal tract comes into contact with the polymer coated beads, the water soluble polymer slowly dissolves and the drug diffuses through the resulting pores in the coating. e.g. [31]: The CODAS®- verapamil extended release Capsules (Verelan® PM) as ChrDDS actually provided enhanced BP reduction during the morning period when compared with other time intervals of the 24-h dosing period.

**CEFORM® TECHNOLOGY**

The CEFORM® technology [35] allows the production of uniformly sized and shaped microspheres of pharmaceutical compounds. This chrono pharmaceutical Drug Delivery (ChrDDS) approach is based on “melt-spinning”, which means subjecting solid feedstock i.e. biodegradable polymer/bioactive agents combinations to the combination of temperature, thermal gradients, mechanical forces, flow, and flow rates during processing. The microspheres obtained are almost perfectly spherical, having a diameter that is typically 150–180 nm, and allow for high drug content. The microspheres can be used in a wide variety of dosage forms, including tablets, capsules, suspensions, effervescent tablets, and sachets. The microspheres may be coated for controlled release either with an enteric coating or combined into a fast/ slow release combination. e.g. [31]: Cardizem® LA, 1-day diltiazem formulation as ChrDDS.

**DIFFUCAPS® TECHNOLOGY**

In the DIFFUCAPS® technology [36], a unit dosage form, such as a capsule for delivering drugs into the body in a circadian release fashion, comprises of one or more populations of drug-containing particles (beads, pellets, granules, etc.). Each bead population exhibits a pre-designed rapid or sustained release profile with or without a predetermined lag time of 3–5 h. The active core of the dosage form may comprise an inert particle or an acidic or alkaline buffer crystal (e.g. cellulose ethers), which is coated with an API-containing film-forming formulation and preferably a water-soluble film forming composition (e.g. hydroxyl propyl methyl cellulose, poly vinyl pyrrolidone) to form a water-soluble/dispersible particle. The active core may be prepared by granulating and milling and/or by extrusion and spherization of a polymer composition containing the API. e.g. [31]: Propranolol-containing ChrDDS (InnopranR XL) for the management of hypertension.

**CHRONOMODULATING INFUSION PUMPS**

Externally and internally controlled systems across a range of technologies including pre-programmed systems, as well as systems that are sensitive to modulated enzymatic or hydrolytic degradation, pH, magnetic fields, ultrasound, electric fields, temperature, light and mechanical stimulation have been reviewed in detail elsewhere [37]. To our knowledge infusion pumps on the market that have been referred to as chronomodulating for drug delivery application include the Melodie®, programmable Synchromed®, Panomat® V5 infusion, and the Rhythmic® pumps. The portable pumps are usually characterized by a light weigh (300–500 g) for easy portability and precision in drug delivery.

**MICROPUMP DRUG DELIVERY SYSTEM** [38, 39] was also developed in which the microparticles after dispersing in the stomach passes into the small intestine...
(absorbed 75% of all drugs), where every single particle would behave as an independent delivery system, releases the drug at an adjustable rate and over an extended period of time (up to 24 hours).

Micro pump used to develop extremely precise pharmacokinetic profiles of single or combination of drugs, in various dosage forms like capsule, sachet, pill or liquid. In even includes Trigger Lock™ which is tamper resistant controlled release formulation of narcotics. For children, there is LiquiTime™ as extended release formulation for those who found problems in engulfing tablets or capsules.

Over Micropump-based products successfully tested in human clinical trials:

- Coreg CR® (Carvedilol CR)
- Aspirin SR
- Genvir™ (acyclovir SR)
- Metformin XL
- Lansoprazole SR
- Omeprazole XL
- Co-amoxyclav XR

**TIMERX® TECHNOLOGY**

The TIMERx® technology (hydrophilic system) [40] combines primarily Xanthun and locust bean gums mixed with dextrose. The physical interaction between these components works to form a strong, binding gel in the presence of water. Drug release is controlled by the rate of water penetration from the gastrointestinal tract into the TIMERx® gum matrix, which expands to form a gel and subsequently releases the active drug substance. This system can precisely control the release of the active drug substance in a tablet by varying the proportion of the gums, together with the third component, the tablet coating and the tablet manufacturing process. e.g. [31]: An oral, CR opioid analgesic oxymorphone.

**THREE-DIMENSIONAL PRINTING®**

Three dimensional printing® (3DP) is a novel technique used in the fabrication of complex oral dosage delivery pharmaceuticals based on solid freeform fabrication methods. It is possible to engineer devices with complicated internal geometries, varying densities, diffusivities, and chemicals [41]. Different types of complex oral drug delivery devices have been fabricated using the 3DP process: immediate-extended release tablets, pulse release, breakaway tablets, and dual pulsatory tablets. The enteric dual pulsatory tablets were constructed of one continuous enteric excipient phase into which diclofenac sodium was printed into two separated areas. These samples showed two pulses of release during in vitro with a lag time between pulses of about 4 h. This technology is the basis of the Their Form® technology. The latter is a micro fabrication process that works in a manner very similar to an “ink-jet” printer. It is a fully integrated computer-aided development and manufacturing process.

**OTHER CR ERODIBLE POLYMERS**

Erodible polymers have been designed in different forms (e.g. tablets, capsules, microparticles) for ChrDDS applications. For example, Ross et al. [42] reported the development of a chrono pharmaceutical capsule drug delivery system. The drug formulation is sealed inside the insoluble
capsule body by an erodible tablet (ET) that is composed of an insoluble (e.g. dibasic calcium phosphate) and gel-forming (e.g. hydroxypropyl methyl cellulose) excipient.

CONTROLLED-RELEASE MICROCHIP

An alternative method to achieve pulsatile or chronopharmaceutical drug release involves using microfabrication technology. Santini et al. [41] reported a solid-state silicon microchip that can provide controlled release of single or multiple chemical substances on demand. The release mechanism was based on the electrochemical dissolution of thin anode membranes covering micro reservoirs filled with chemicals in solid, liquid or gel form. This technology has the potential to be used in the design of ChrDDS with a better control over drug release kinetic in order to match biological requirement over a versatile period of time.

Thus the major objective of chronotherapy for the cardiovascular diseases is to deliver the drug in higher concentrations during the time of greatest need, typically during the early morning hours, and in lesser concentrations when need is less, such as during the late evenings and early sleep hours. This can be achieved by controlled absorption of propranolol from dosage form varying in circadian rhythm fashion following administration of a single dosage form at bedtime, thus minimizing potential risks of a stroke and/or heart attack and enhancing patient compliance and therapeutic efficacy, while reducing cost of treatment.

Table 3 [31]: Various Patent in the field of Chronotherapy.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Devices</th>
<th>US Patent Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Implantable electromechanically driven device</td>
<td>4003379</td>
</tr>
</tbody>
</table>

New Advances of Cardiovascular Drugs into Sustained Release Pellet Dosage Forms

1) Five Different Formulations of Sustained Release Propranolol Pellets [28]. Pellets were manufactured using five different forms of propranolol like free base & propranolol Maleate at a particular mass or as a particular number of moles. The formulation of propranolol free base form (PF) in mass consisted of 5% of particular propranolol form, 20% Carbopol and 75% of Avicel and to convert mass to moles, this 5% of free propranolol is converted to moles and then masses corresponding to the same number of moles of propranolol hydrochloride (PH) and propranolol Maleate (PM) were calculated.

The formulation for PH in moles consisted of 5.70% PH, 20% Carbopol, and 74.30% Avicel and for PM fixed as moles, 7.24% PM, 20% Carbopol, and 72.76% Avicel. Here at first, PF is manufactured using Sodium Chloride and PH by precipitation. PM is also synthesized.
using PF, Maleic Acid, THF and MTBE. Then, microenvironment pH estimation is done using a 1 g sample of pellet batch using 5 ml of pH 6.8 0.05 M phosphate buffer using Accumet Model AB15 Basic pH meter.

By using the different grades of EUDRAGIT, the amount of water needed to prepare the wet mass, also varies. In case of Eudragit RS, the water needed is more than other grades. Eudragit RL PO compare with Eudragit RS PO resulted in pellets with high crushing strength [43].

Precipitates were formed of Propranolol solutions using near neutral phosphate-buffered Carbopol dispersions in the same medium. These precipitates were filtered with a 0.22 µm filter and then appropriate dilution, was measured using the UV-Visible spectrophotometer. Five different pellet formulations were prepared to study each form present at a particular mass or as a particular number of moles.

Formerly, the mixing of powder was done in a Kitchen Aid Model KSSS planetary mixer for 10min. Then mixture was converted to wetted mass by adding Calcium Chloride aqueous solution. This wetted mass was immediately fed into a Model EXDS-60 radial twin-screw extruder having a 1.5mm screen at a speed of 20 rpm. Then, extrudates were transferred to Q230 Marumerizer consisted of hatched groove pattern plate, operated for 10min at 860 rpm and at last, the pellets were air dried for 2 h and oven dried at least overnight at 40°C.

Pellet characterization is done using HB43 halogen moisture analyzer and sieve analysis was performed using a nest of U.S. Standard Sieves between Nos. 8 and 35. Force of detachment tests were performed using a Chatillon LTC force gauge and two 3 in. diameter GF8 peel strength grips. The wetted mass was applied on grips and then grips were moved closer to a 1mm gap. After removing excess of wetted mass from periphery of grips, the grips were slowly pulled apart and the force of detachment was measured at the time the grips were separated.

Statistical analysis was also performed using Sigma Stat version 3.1 and thus different models were made with different passing criteria.

2) SUSTAINED RELEASE PROPRANOLOL PELLETS [16,26] were manufactured by classical coating pan procedure using the factorial design. The core material used, at first, was 700 g sucrose, with EUDRAGIT® NE30D dispersion spraying was done continuously onto the falling particles with the application of the dusting powder containing a mixture of lactose, polyvinylpyrrolidone and propranolol. These pellets were coated then with EUDRAGIT® RS in acetone/isopropanol mixture in a coating plan and dried in steam of hot air. Now, to complete evaluation requirements, the dissolution studies were done using the USP XXIII rotating basket method at 37°C and 100 rpm. Content uniformity data was also obtained using 100 mg of each prepared batches spectrophotometrically.

Separate two factors, three levels full factorial design was made which provided an empirical second order polynomial model used for prediction of the effect of formulation variables on the dissolution characteristics. In this mathematical approach, each experimental response $Y$ can be represented by a quadratic equation of the response surface:

$$Y = b_o + b_1X_1 + b_2X_2 + b_{11}X_1^2 + b_{22}X_2^2 + b_{12}X_1X_2$$
Table 4: independent variables: factors and levels for full factorial design

<table>
<thead>
<tr>
<th>Factors</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasticizer concentration</td>
<td>-1 0 1</td>
</tr>
<tr>
<td>(%w/w) (X1)</td>
<td>10 28 46</td>
</tr>
<tr>
<td>Volume of coating</td>
<td>80 200 320</td>
</tr>
<tr>
<td>(ml/100 g pellets) (X2)</td>
<td></td>
</tr>
</tbody>
</table>

Table 5: dependent variables and the constraints used

<table>
<thead>
<tr>
<th>Dependent variables</th>
<th>Constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y1</td>
<td>10 ≤ Y1 ≤ 20</td>
</tr>
<tr>
<td>Cumulative % dissolved in 1 h</td>
<td></td>
</tr>
<tr>
<td>Y2</td>
<td>45 ≤ Y1 ≤ 65</td>
</tr>
<tr>
<td>Cumulative % dissolved in 6 h</td>
<td></td>
</tr>
<tr>
<td>Y3</td>
<td>80 ≤ Y1 ≤ 100</td>
</tr>
<tr>
<td>Cumulative % dissolved in 12 h</td>
<td></td>
</tr>
</tbody>
</table>

Also, four different ratios with different grades of the Hydroxy propyl methylcellulose-HPMC K4M, HPMC K15M, and HPMC K100M matrices at similar drug, in preparation of the controlled release pellets and studies were conducted regarding the effect of the polymer content on the dissolution rates and also about the effect of the changes in the surface area of the particles by varying the polymer content [44].

3) METOPROLOL SUCCINATE USP PELLET was formed using the technologies in chronopharmaceutics which are approved by FDA for the market. The pellets were prepared by the multiple layering of a polymer coat on a salt core, followed by drug layering and an outer polymer coat. Commercially available salts (different anion containing salts of organic and inorganic acids) were milled using multimill at medium speed, knives forward, sifted and fractions between 425 and 850 µm were taken. These salt cores coated with EUDRAGIT®NE30D using 2%w/w Tween 80 as plasticizer and 5% glyceryl monostearate as a glidant in fluid bed processor for optimum film formation.

Layering of Metoprolol succinate is done on these coated salt cores as a suspension of 70% in the size range of 710-850 µm, Kollidon 30 and 1% Aerosil 200 was sprayed onto the cores to achieve a weight gain of 100% w/w. these drug layered pellets were further coated with EUDRAGIT® RS30D with talc at 50%w/w of polymer tri-ethyl citrate at 20% w/w of polymer as glidant and plasticizer respectively.

To confirm the regular drug release from the formulation, Drug release studies were performed as Dissolution Test using USP I Apparatus at 37°C and 100 rpm using different media including water, 0.1 N HCl and phosphate buffer pH 6.8 EP and samples were checked using Waters Alliance 2695 separation module with Waters 2487 dual wavelength detector.

Clinical investigations were carried out using Beloc-zok® as a reference formulation on healthy human subjects under fasting conditions and different pharmacokinetic parameters were determined. Metoprolol
succinate levels from the plasma were also determined by validated analytical HPLC method using LC-MS/MS by different system suitability parameters. The statistical analysis of blood plasma concentration levels of metoprolol succinate was also performed computing all necessary pharmacokinetic parameters using LinMix procedures of WinNonlin Enterprise® version 4.1 software applications. Then in vitro-in vivo correlation was studied for metoprolol succinate by the numerical deconvolution method based on trapezoidal formula which uses unit impulse response (UIR) of the body system as weighing function and this was taken from available pharmacokinetic data of the drug obtained after scaling up the dose of used 100 mg Metoprolol Tartrate corresponding to 95 mg Metoprolol Succinate [45].

Chronopharmacokinetics have been implicated on many cardiovascular drug delivery systems and drugs are propranolol, organic nitrates, nifedipine, etc. Here biological rhythms were taken into account and studies were conducted as a basis of drug treatment [46].

Different strategies have also been designed as per the circadian rhythms of the patient and then the treatment is given in order to prevent the sudden catastrophic cardiac events [47].

4) Multiple drug pellets were also prepared which are having both immediate as well as sustained release of cardiovascular drugs. At first, uncoated pellets were formed using the uniform blend of solid components i.e. 83% (w/w) Nicotinic Acid (NA) and Microcrystalline Cellulose (MCC) mixture wetted with the HPMC E5 aqueous solution used as binder. This mass is passed through the extruder and then spheronizer to form pellets which were dried at 40°C for 12 h in hot air oven. After preparing the outer coating solution using 3% (w/w) Ethyl cellulose, PVP (in ratios of 5:1 and 2:1) to 95% (v/v) alcohol, subcoating was done in a fluidized bed coater with specific technical parameters. Then preparation of Simvastatin wet milled suspension was done using Simvastatin, Magnesium oxide and HPMCE5 aqueous solution grinded and removed from the Basket dispersing mill after 30 minutes. Layering of this suspension was done on the sub coated pellets in fluidized bed coater.

In vitro dissolution testing were performed for both drugs i.e. Nicotinic Acid and Simvastatin using USP31-NH26 Apparatus 1 (basket) at 100 rpm in 900 ml solution at 37 ± 0.5°C and data was successfully evaluated. Drug content analysis of both the drugs in a formulation was done according to US Pharmacopoeia. Using the scanning electron microscope, the surface and the cross section of the pellets were also examined after application of gold coating. Stability testing was also performed under stress conditions and the content and related substances of SIM in the compound pellets were analyzed [27].

Also, another study was also performed preparing granules of a model drug dimenhydrinate (DMH) using the same ethylcellulose (EC) by a solid dispersion technique. It was found that as ethyl cellulose was increased, the drug release rate was also decreased and drug kinetics was showing zero order kinetics [49].

5) Floating Drug Formulation was prepared filling ten granules pellets with Verapamil (V), in a dose of 40 mg, in a gelatin capsule. These pellets were prepared by the wet granulation of powder mixture, spheronization of granulated mass and coating of the cores with a sustained release film.
Pellet core contents (%):
Verapamil hydrochloride 20.0
Sodium hydrocarbonate 20.4
Microcrystalline cellulose 43.72
Lactose 12.08
Povidone K-30 3.80

At first, the powder mixture was wetted with 95 g of 40% ethanol and extruded through a metal sieve. The granulate were formed, and then were dried in a blow dryer. These granulate were spheronized in a Caleva Model 120 apparatus. Wet cores were dried and separated into fractions. Pellets of 1.25-1.6 mm were designated for the coating process. Coating mixture consisted of Eudragit NE 30D, Eudragit L-30D 55, triethyl citrate, talcum, distilled water and coating was done in a Uni-Glatt Apparatus. Conventional tablets, Staveran 40 mg was used as a reference drug.

In vitro drug release tests were performed by measuring the release rate of Verapamil from Floating drug formulation and Staveran using the Ph Eur paddle apparatus, Pharma Test Model PTWS-3. The concentration of Verapamil was determined in the samples spectrophotometrically at 278 nm. For a given pellet formulation, this test was repeated five times.

The results obtained are presented in the figure:

Fig 12: In vitro verapamil release from floating drug formulation 40 mg and Staveran 40 mg (n = 5)

In-vivo studies or bioavailability studies were also performed in a group of 12 Caucasian volunteers, six men and six women, aged 20-38 years, weighing from 50 to 94 kg, and height ranging from 155 to 185 cm and results were obtained using HPLC with fluorescence detection.

Pharmacokinetic parameters were also calculated using Topfit version 2.0 and statistical analysis was also conducted using Statgraphics plus Software [50].

In one study it was found that pellets prepared using the Eudragit RS 30 D was 20% (w:w), based on the dry weight of polymer, for all pellet formulations, got plasticized with increasing concentrations of either Triethyl citrate (TEC) or Acetyl tributyl citrate (ATBC). Prior to the breakage point on the stress-strain curve, elastic deformation was found as the major deformation pattern and all pellets exhibited brittle fracture under the diametral load [51].

6) The Self-Emulsifying Drug Delivery System (Sedds) of Nitrendipine was also made by first preparing the liquid SEDDS and then converting this liquid into a self-emulsifying (SE) pellets. The composition of liquid SEDDS was:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>% (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miglyol® 812</td>
<td>28.13</td>
</tr>
<tr>
<td>Cremophor® RH 40</td>
<td>37.50</td>
</tr>
<tr>
<td>Tween 80</td>
<td>18.75</td>
</tr>
<tr>
<td>Transcutol® P</td>
<td>9.37</td>
</tr>
</tbody>
</table>

Here, formerly, Miglyol® 812 (MCT, caprylic/capric triglyceride), Cremophor® RH 40 (PEG-40 hydrogenated castor oil), Tween
80 and Transcutol® P (diethylene glycol monoethyl ether) were mixed with a magnetic stirrer. Then Nitrendipine (NTD) was dissolved in this blank SEDDS to form an isotropic mixture and it was cooled at room temperature.

The compositions of the liquid SEDDS and SE pellets are mentioned in table. Here, only in case of formulation 1 (F.1), the content of 30% SEDDS was directly added into Avicel® PH 101 (MCC) resulted into a poor flowable powder, so water is added to form a wet mass. Now, in all other four formulations i.e. F.2, F.3, F.4 and F.5, at first 30% SEDDS was mixed into SYLOID® 244 FP or in a mixture of SYLOID® 244 FP and Kollidon® CL-SF using a kneader until whole lot of powder was adsorbed with fine flowability. After this, the adsorbed mixtures were blended with Avicel® PH 101 and FLOWLAC® 100 for further 5 minutes, followed by addition of water to form a suitable wetted mass. Then this mass was passed through the extruder, extrudates formed were spheronized in a radial plate spheronizer having cross-hatch frictional plate to form pellets which were at last dried in an oven.

Table 7: Composition of the SE pellets

<table>
<thead>
<tr>
<th>Ingredients % (w/w)</th>
<th>F.1</th>
<th>F.2</th>
<th>F.3</th>
<th>F.4</th>
<th>F.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEDDS</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Kollidon® CL-SF</td>
<td>-</td>
<td>-</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>SYLOID® 244 FP</td>
<td>-</td>
<td>15</td>
<td>15</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Avicel® PH 101</td>
<td>70</td>
<td>55</td>
<td>40</td>
<td>50</td>
<td>35</td>
</tr>
<tr>
<td>FLOWLAC® 100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>15</td>
</tr>
</tbody>
</table>

Similarly, self-micro emulsifying drug delivery system (SMEDDS) was also designed for the oral bioavailability enhancement of the poor water soluble drug Simvastatin in beagle dogs. It was found that the release rate of the drug from this formulation was also increased and the absorption of the simvastatin acid from SMEDDS form was resulted in about 1.5-fold increase in bioavailability compared with the conventional tablet (Zocor®) [52]. The characterization of the SMEDDS could also be done by droplet size and zeta-potential determination and cloud point measurement [53].

By using the fixed level of 5.66% w/w of the coenzyme Q10, four different formulations were prepared of self-emulsifying drug delivery systems and then characterized. Two oils (Myvacet 9-45 and Captex-200), two emulsifiers (Labrafac CM-10 and Labrasol) and a cosurfactant (lauroglycol) were used to prepare the whole formulation [54].

7) HALLOYSITE55 [56] is defined as a two-layered aluminosilicate, and is chemically similar to kaolin, which however, has a stacked plate-like structure. It is an unusual clay mineral, having a hollow tubular structure in the submicron range. DILTIAZEM HYDROCHLORIDE, a calcium channel blocker or propranolol Hydrochloride, a well-known beta blocker were coated with this...
Hallo site forming a Sustained Release formulation.

Fig. 14: Schematic representation of proposed binding patterns of the cationic linear PEI polymer to Halloysite when (i) dilute and (ii) more concentrated aqueous solutions are used.

Dissolution studies were performed subjecting formulations to McIlvaine’s buffer; pH 6.8 or 3.2, using baskets rotated at 100 rpm and was assayed by UV spectroscopy at a particular wavelength.

Fig 15: Dissolution of diltiazem HCl from drug loaded Halloysite at pH 3.2 and 6.8 for 8 h at 37 °C, compared to free drug at pH 6.8.

In one study, sugar starter cores were coated with the drug Diltiazem Hydrochloride and hydroxypropyl methylcellulose (HPMC) in a fluidized bed coater. These drug layered starter cores were then coated with aqueous ethylcellulose dispersion with small amounts of poly (vinyl alcohol) (PVA)–poly(ethylene glycol) (PEG) -graft-copolymer. After performing long term stability studies and studies related to drug release, it was concluded that small amounts of PVA-PEG-graft-copolymer to aqueous ethylcellulose dispersion to provide long term stability even under stress conditions. Also, as per the studies, it could be concluded that the presence of only 5% PVA–PEG-graft-copolymer is not sufficient to provide appropriate film formation during coating/curing and to avoid structural changes within the film coatings during storage, irrespective of the initial drug loading and type of plasticizer [57].

8) ISOSORBIDE-5-MONONITRATE (5-ISMN) [58] is one of the major active metabolites of isosorbide dinitrate (ISDN), which is mainly indicated for the treatment of stable and unstable angina pectoris, acute myocardial infarction, and heart failure. It offers several therapeutic advantages over other organic nitrates, such as good oral absorption and 5-ISMN was cleared...
from the body almost exclusively by metabolism and its clearance is about 120 ml/min (Stockis et al., 2002).

Fig. 17: Charge transfer complex diagrammatic sketch between 5-ISMN and PVC.

The main formulations at different research stages:

**Table 8:** The main formulations at different research stages:

<table>
<thead>
<tr>
<th>Formulation</th>
<th>5-ISMN (w/w)</th>
<th>MCC (w/w)</th>
<th>PVP K30</th>
<th>HPMCE5 (w/w)</th>
<th>10%HPMC solution (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15%</td>
<td>76%</td>
<td>-</td>
<td>-</td>
<td>9%</td>
</tr>
<tr>
<td>2</td>
<td>16%</td>
<td>67%</td>
<td>6%</td>
<td>-</td>
<td>11%</td>
</tr>
<tr>
<td>3</td>
<td>15%</td>
<td>65%</td>
<td>13%</td>
<td>-</td>
<td>7%</td>
</tr>
<tr>
<td>4</td>
<td>18%</td>
<td>60%</td>
<td>-</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>5</td>
<td>15%</td>
<td>38%</td>
<td>-</td>
<td>40%</td>
<td>7%</td>
</tr>
</tbody>
</table>

In above all formulations stated, at first the pellets were prepared by mixing 5-ISMN, MCC with PVP or HPMC, a 10% HPMC aqueous solution was used as the adhesive and added to prepare the wetted mass. Then, mass was converted into cylindrical strips in extruder and then by increasing the speed, they are spheronized into pellets. These drug loaded pellets were passed through the appropriate sized sieve to obtain a narrow particle size range.

These drug loaded pellets of 300 g then sub coated with materials ((1) ethyl cellulose (EC):PVPK30=5:1 (w/w); (2) EC: diethyl phthalate (DEP):PVPK30 = 5:1:1 (w/w/w)), were added to 95% (v/v) alcohol with an EC content of 3% (w/w), in a fluidized bed coater with a bottom spray.

Eudragit®NE30D is an aqueous polymer dispersion composed of methyl methacrylate and ethyl acrylate monomers in a ratio of 2:1. Here, Eudragit®NE30D was used on two occasions: (1) Eudragit®NE30D was used to control the drug release rate by its permeability and (2) a portion of isosorbide-5-mononitrate (accounted for 20% of the content of pellets) as the immediate-release fraction was added to the Eudragit®NE30D aqueous dispersion. Distilled water to 10% (w/w) based on the dry polymer weight was taken and Eudragit®NE30D aqueous dispersion was diluted in it. The prepared sub coated pellets
were coated with Eudragit®NE30D. As per the film formation temperature of Eudragit®NE30D, the temperature was set at 20 °C. After the outer coating process, pellets were cured at 40 °C for at least 24 h to form an intact film.

As for evaluation, a dissolution test was performed using the USP XXXIII apparatus 1 (basket) at 50 rpm in 500 ml purified water at 37 ±0.5 °C and samples were examined in HPLC. Microscope and scanning electron microscope (SEM) studies and stability studies were also performed.

RELATED PATENTS OF CARDIOVASCULAR SUSTAINED RELEASE PELLET DOSAGE FORMS

1) Timed, Sustained release multi-particulate Dosage forms of Propranolol. (Patent No. AU2002/330211 B2) [69]

The present invention provides a timed, sustained release multi-particulate dosage form comprising a propranolol core having a first membrane of a sustained release polymer and a second membrane of a mixture of water insoluble polymer and the enteric polymer (2nd or outer coating), wherein the water insoluble polymer and the enteric polymer may be present at a weight ratio of from 10:1 to 1:2, and the total weight of the coatings is 10 to 60 weight % based on the total weight of the coated beads.

As per chronotherapy, when administered orally at bedtime, the dosage form comprising one or more bead populations delivers the drug in lesser concentrations during the time of least need and in higher concentrations during the time of greatest need. It takes about 12 hours after administration to reach Tmax.

Here, timed sustained release (TSR) beads comprise of A core particle comprising propranolol or a pharmaceutically acceptable salt thereof; each dosage form contains a total of from 80mg to 160mg propranolol or its salt. It also contains polymeric binder which is converted into an immediate release (IR) bead by granulation and milling or by extrusion/spheronization; A first membrane comprising ethylcellulose plasticized solution or suspension surrounding said core to sustain drug release; and A second outer membrane comprising a mixture of ethyl cellulose and enteric polymers selected from the group consisting of esters of cellulose, polyvinyl acetate phthalate, pH-sensitive methacrylic acid-methylmethacrylate co-polymers, shellac and their derivatives and it is hydroxypropyl methylcellulose phthalate providing a Timed, sustained release (TSR) capsules.

This dosage form is tested in a USP type II apparatus at 50 rpm using a 2-stage dissolution medium i.e. 1st 2 hours in 700 ml 0.1 HCl at 37 °C and then in a pH of 6.8 obtained by the addition of 200 ml of pH modifier which exhibit a dissolution profile corresponding to the mentioned pattern:

<table>
<thead>
<tr>
<th>Time Duration (hours)</th>
<th>% of Total Propranolol Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 2</td>
<td>0-20</td>
</tr>
<tr>
<td>After 4</td>
<td>5-35</td>
</tr>
<tr>
<td>After 6</td>
<td>10-60</td>
</tr>
<tr>
<td>After 10</td>
<td>40-90</td>
</tr>
<tr>
<td>After 16</td>
<td>Not less than 60</td>
</tr>
</tbody>
</table>

2) Method to prepare microparticles containing Metoprolol (Patent No. EP 1 370 245 B1) [69]

Metoprolol is a selective beta-blocker and its structure is:
By using the continuous fluidized bed granulation process having integrated microparticle selecting system, the spherical, free-flowing, homogenous microparticles can be formed. No particle should exceed the size of 250 µm. At first, granulation liquid medium consisting of solid content between 15 weight % and 60 weight % in which percentage weight of metoprolol in form of metoprolol succinate or metoprolol fumarate is 90-100%.

This liquid in solution, suspension or in emulsion form, is sprayed in Fluidized bed with bottom up flow of air or inert gas. With the continuous application of this granulation liquid and excessive heat change results into the formation of layers over the core and microparticle is formed.

These microparticles are selectively isolated as per the desired size distribution from the lot using the countercurrent gravity classifier or by zigzag classifier which are having a perfect command over grain size.

After that, the controlled release coating can be done on metoprolol microparticles using the polymers after dissolving in water or any other organic solvents like ethyl alcohol, isopropyl alcohol and/or methylene chloride using the coating pan or more likely Fluidized bed. This controlled release microparticles of metoprolol can be used for the prophylaxis of cardiovascular diseases.

3) Controlled release pharmaceutical composition containing Carvedilol. (Patent No. EP 1 928 431 B1)\cite{61}

Carvedilol is a non-selective, α and α₁ adrenoreceptor antagonist which is used for the long-term treatment of essential hypertension and angina pectoris. The β-adrenoreceptor antagonistic effect of the compound inhibits the development of reflex tachycardia and the α₁ adrenoreceptor antagonistic effect causes vasodilatation. This drug is also having the antioxidant activity. Its structure is:

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{carvedilol.png}
\caption{Carvedilol}
\end{figure}

A controlled release formulation containing the carvedilol is designed here in layered pellet form in which the core consists of 5-50 weight % solid organic acid preferably succinic acid and also one or more 5-50 weight % auxiliary agents most preferably microcrystalline cellulose and optionally dimethylpolysiloxane.

On this core, the layering of enteric coating polymer can be done more preferably methacrylic acid-ethyl acrylate copolymer, a drug carvedilol with other additional auxiliary agents like propylene glycol, triethylcitrate or...
polyethylene glycol as softeners or optionally antiahesive agents like talc or dimethylpolysiloxane.

Carvedilol along with it also contains water soluble binding agents like hydroxypropylmethyl cellulose and polyethylene glycol. Then these solid particles can be converted into tablet or hard gelatin capsule dosage forms with appropriate use of other useful excipients. For the purpose of evaluation of these prepared pellets, in vitro dissolution test can also be performed using PhEUR I (basket) at 100 rpm on 37°C with the use of dual mode of dissolution media as for 0-24 hours, A/ as phosphate buffer with pH 6.8 can be used and for 0-2 hours, B/ as 0.1 M hydrochloric acid can be used. High Performance Liquid Chromatography (HPLC) can be used for analysis of active ingredient.

The similarity factor can be calculated through:

\[ F_2 = 50 \log \left\{ 100 \left[ 1 + \frac{1}{n} \sum_{t=1}^{n} \left( \frac{R_t - T_t}{T_t} \right)^2 \right] \right\} \]

Wherein \( R_t \) and \( T_t \) are the measured dissolution rates of the compared pharmaceutical compositions (Reference and Test) at \( t \) moment. Also, the dissolution of the two compositions are seen similar if \( F_2 > 50 \).

The dissolution rates of the controlled release pellets containing carvedilol can be as follows:

F\(_2\) = 63.81.

<table>
<thead>
<tr>
<th>Dissolution time (hours)</th>
<th>Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hour</td>
<td></td>
</tr>
<tr>
<td>2 hours</td>
<td></td>
</tr>
<tr>
<td>4 hours</td>
<td></td>
</tr>
<tr>
<td>6 hours</td>
<td></td>
</tr>
<tr>
<td>8 hours</td>
<td></td>
</tr>
<tr>
<td>12 hours</td>
<td></td>
</tr>
<tr>
<td>16 hours</td>
<td></td>
</tr>
<tr>
<td>24 hours</td>
<td></td>
</tr>
</tbody>
</table>


Diltiazem controlled release formulation can be formed by coating a biologically inactive core such as non-pariel sugar particles, sugar spheres, starch granules, clay particles or other particles which can be coated with 20-50% by weight of enteric polymer membrane coated core with a pharmacologically active drug Diltiazem, polysorbate 80, acetyltributyl citrate as plasticizer along with a polymer binder and 50% to 80% by weight of delayed pulse polymer membrane coated pellets comprising a polymer membrane coated core forming first layer as mentioned above and second layer made of acrylic and methacrylic acid esters with a content of ammonium groups, apolymer membrane through which the contents of first layer are permeable.

Evaluation of these dosage units can be done through in vitro dissolution test in 0.1N HCl using USP Type II apparatus at 37°C and 100 rpm giving results as shown below:

<table>
<thead>
<tr>
<th>Time Taken (hours)</th>
<th>Drug Release (% of total diltiazem)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 6</td>
<td>0-15</td>
</tr>
<tr>
<td>After 12</td>
<td>10-30</td>
</tr>
<tr>
<td>After 18</td>
<td>25-65</td>
</tr>
<tr>
<td>After 24</td>
<td>Not less than 70</td>
</tr>
</tbody>
</table>

5) Long Acting Nicardipine Hydrochloride Formulation (Patent No. US005198226A) \[^{64}\]

Fig. 21: Nicardipine
Where;
R1 is –NO2, --CF3 or halo;
R2 is alkyl or –CH2CH2OCH3; and
R6 is hydrogen or alkyl; and
R3 is alkyl, alkylenoxyalkyl, haloalkyl,
optionally substituted phenyl alkyl, optionally
substituted naphthyl alkyl, or

\[ \text{R}^4 \text{A} \text{R}^5 \]

In which;
A is alkylene;
R4 is alkyl, alkoxy, or optionally substitutes
phenyl or phenyl alkyl; and
R5 is hydrogen or alkyl;
And the pharmaceutically acceptable salt
thereof.

The long acting sustained release Nicardipine
hydrochloride formulation with smooth,
spherical and non-rugose surfaces can be
formed without taking any core particle. Dry
powder can be blended of the active
pharmaceutical ingredient along with the
excipients like diluent; the pH dependent
binder, a copolymer of methacrylic acid and
methacrylic or acrylic acid ethyl esters, can be
added in dry powder mixture or in preparing
wetting solution with purified water or in both
and then the wetted mass can be formed by
mixing the aqueous binding solution with dry
powder mixture. This wetted mass can be
passed through the extruder and then the rod
shaped segments can be passed through the
spheronizer to convert into spherical particles
having an area radius to circumference radius
ratio of 0.85 to 1.0 and diameters of about 0.7-
1.0 mm and comprising about 10-25 weight %
Nicardipine hydrochloride and about 5-25
weight % of a polymethacrylate which is
substantially insoluble below pH 4.5, and then
dried. The preferred composition for non-
amorphous Nicardipine hydrochloride is:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicardipine HCl</td>
<td>20</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>20</td>
</tr>
<tr>
<td>Maize starch</td>
<td>20</td>
</tr>
<tr>
<td>Lactose</td>
<td>29</td>
</tr>
<tr>
<td>Eudragit L</td>
<td>11</td>
</tr>
</tbody>
</table>

This prepared dosage form can be incorporated
into an inert pharmaceutical carrier i.e. hard
gelatin capsule.

6) Extended Release Pharmaceutical
formulations (Patent no. EP 0 396 425 B1)

Extended release isosorbide-5-monomonitrate
dosage form is developed. At first the core
material is prepared containing the inert
spherical substrate particles like sugar spheres
and non-toxic plastic resin beads (15-40 % by
weight). Now the isosorbide-5-monomonitrate
drug(4-85 %)-binder(0.5-4%) solution is
sprayed on these core particles in a coating
pan and dried. Then coating layer of talc (4-20%
) is done so that the product is classified by
size to recover particles having sizes from -10+60 mesh, U.S. Standard mesh size.

These immediate release particles are coated
with the dissolution modifying system
containing plasticizers (0.01-5%) like diethyl
phthalate, diethyl sebacate, triethyl citrate,
crotonic acid, propylene glycol, castor oil,
citric acid esters, dibutyl phthalate, dibutyl
sebacate and their mixtures and film-forming
agents (0.5-25%) from the class of
hydroxypropylmethyl cellulose and other
porosity modifying agents (up to 25%) to form
an extended release particles.

For evaluation, in vitro dissolution test can be
performed in accordance with U.S.
Pharmacopoeia XXI apparatus II by paddle method, in a 7.5 pH phosphate buffer and the results should match the following profile:

Table 13:

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>% Drug Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 1 hour</td>
<td>Less than 30%</td>
</tr>
<tr>
<td>After 8 hours</td>
<td>Less than 75%</td>
</tr>
<tr>
<td>After 16 hours</td>
<td>Not less than 100%</td>
</tr>
</tbody>
</table>

CONCLUSION:

It can be concluded that the newer approach in making the cardiovascular sustained and controlled release pellet dosage forms taking into account chronopharmaceutics is much more advantageous than other conventional oral dosage forms. Also, this approach can also be incorporated in other drugs of cardiovascular and even in other pharmacological classes of drugs to develop a new efficacious medicinal product.

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