

FORMULATION AND EVALUATE A PULSATILE COMPRESSION-COATED TABLET OF NEBIVOLOL FOR TIME- CONTROLLED DRUG RELEASE

DINESH S A^{1,*} and Dr. P. SRIRAMCHARAN, Ph.D.,¹

1(*) Department of Pharmaceutics.
P.S.V. College of Pharmaceutical Science and Research, Krishnagiri-
635108, Tamil Nadu, India.
Corresponding author Gmail: dineshsakgi@gmail.com

ABSTRACT

Cardiovascular events such as myocardial infarction, angina pectoris, and sudden cardiac death exhibit a distinct circadian rhythm, frequently peaking during the early morning hours upon awakening. This study aimed to design, formulate, and evaluate a chronotherapeutic, **time-controlled pulsatile compression-coated tablet system** of **Nebivolol Hydrochloride** to delay drug release, thereby providing peak plasma concentration precisely when the physiological surge occurs.

Keywords:

Nebivolol Hydrochloride, Pulsatile Drug Delivery, Compression-Coated Tablet, Chronotherapeutics, Lag Time, Burst Release.

1.Introduction

Disease may modify the temporal (biological rhythm) structure of the human body, resulting in major changes in therapy response. Despite the fact that continuous release systems have been developed, The biological systems have become more evolved, and they are less sensitive to those type of release system. In certain cases, such as the timed administration of hormones and certain medications, sustained and controlled release devices are ineffective. This requirement was met by the Pulsatile drug delivery system. Pulsatile or chronomodulated drug release refers to a technique in which a drug is released abruptly after a predetermined lag period or a discrepancy based on disease states circadian rhythms (Many human body functions, including metabolism, behaviour, sleep patterns, and hormone production, are governed by the circadian rhythm) during this time lag, no drug is released from the system and the product has a sigmoidal drug release profile, which includes a period of no release (lag time) before a rapid and full drug release (Figure 1). This delivery system is more appropriate for the drug such as Proteins and peptides which are highly metabolically degraded .

In the case of long-term care, drug resistance can develop along with the ADR but in case of chronomodulated drug delivery system the chances of the ADR, drug resistance is very less since here the desired concentration of the drug is released from the device and it provides the optimal drug concentration at a specific time point is available. This approach works well with drugs that have a lot of first-pass metabolism and those that are targeted to particular parts of the intestine. The plasma peak is obtained at an optimum moment, the amount of doses per day can be decreased, it is with saturable first pass metabolism, and tolerance development can also be prevented by developing the Pulsatile system for precise colonic delivery.

Theoretically, therapy with modified release dosage forms and zero order drug release results in regulated and steady drug levels in plasma throughout the day. Single unit systems and multiparticulate systems are the two types of Pulsatile drug delivery systems. Because of benefits such as predictable gastric emptying, lower risk of dose dumping, versatility in release patterns, and improved bioavailability, multiparticulate drug delivery systems are favoured over single unit dosage types.[10] Minitabs are a multiparticulate device that is filled inside a capsule, demonstrating the advantages of tableting within a capsule. These minitabs can be programmed to deliver the medication at various points in the gastrointestinal tract. Minitabs come in a variety of sizes to address the issue of drug loading, with diameters ranging from 1.5 to 4 mm. On the minitabs, additional layering can be done to monitor the release at different rates

2. Materials and Methods

2.1 Ingredient List

1. Nebivolol

Nebivolol is a pharmaceutical active ingredient belonging to the class of beta-1 adrenergic receptor blockers. It is primarily used in the treatment of hypertension (high blood pressure). Nebivolol reduces heart rate and the force of cardiac contraction by selectively blocking beta-1 adrenergic receptors. It also promotes vasodilation through the nitric oxide pathway, which helps reduce peripheral vascular resistance. In pharmaceutical formulation development, the physicochemical properties of nebivolol, including its solubility, stability, and compatibility with excipients, must be evaluated to achieve the desired drug release, content uniformity, and bioavailability. The selection of suitable excipients depends on the intended dosage form, such as tablets, capsules, or other pharmaceutical delivery systems.

2. Propylene Glycol

Propylene glycol is a clear, colourless, odourless, and hygroscopic liquid widely used in pharmaceutical formulations as a solvent, cosolvent, humectant, and vehicle. It can improve the solubility of certain active pharmaceutical ingredients and help maintain uniform distribution of dissolved substances within a formulation. Propylene glycol is used in oral, topical, and selected parenteral products, subject to appropriate grade and concentration requirements. It may also help maintain moisture and improve the processing characteristics of certain formulations. During formulation development, its concentration must be optimized according to the drug's solubility, the intended route of administration, and patient safety requirements. Excessive exposure can cause adverse effects, particularly in vulnerable patient populations, so its use must comply with applicable pharmaceutical standards.

3. Polyethylene Glycol (PEG)

Polyethylene glycol (PEG) is a family of water-soluble polymers available in different molecular weights and physical forms, ranging from liquids to waxy solids. It is widely used in pharmaceutical manufacturing as a solvent, cosolvent, carrier, lubricant, binder, plasticizer, and base for various dosage forms. Depending on its molecular weight and concentration, PEG can influence drug solubility, viscosity, moisture retention, and drug-release characteristics. In pharmaceutical formulations, the appropriate grade of PEG is selected based on the desired functional properties and the compatibility of the active ingredient with the excipient. PEG may be incorporated into liquid, semisolid, and solid dosage forms. Formulation scientists must evaluate its physical and chemical compatibility, stability, and potential effects on dissolution and drug absorption before selecting it for a finished pharmaceutical product.

4. Methanol

Methanol is a volatile, colourless, flammable organic solvent that is used in certain laboratory procedures, analytical testing methods, chemical synthesis, and pharmaceutical manufacturing processes. It has the ability to dissolve various organic compounds and may be used during research, extraction, or analytical sample preparation. However, methanol is highly toxic and can cause serious poisoning, including metabolic acidosis, visual impairment, blindness, and death following significant exposure. For this reason, it is generally not suitable as a direct ingredient in finished oral pharmaceutical products. If methanol is used during manufacturing, its removal and control as a residual solvent must be assessed according to applicable regulatory requirements and the relevant ICH residual-solvent guidance. Appropriate ventilation, protective equipment, storage controls, and fire-safety measures are essential when handling methanol.

5. Tween 80 (Polysorbate 80)

Tween 80, also known as polysorbate 80, is a nonionic surfactant and emulsifying agent commonly used in pharmaceutical formulations. It helps reduce interfacial tension between oil and water, allowing the formation and stabilization of emulsions and dispersions. Tween 80 can also improve the wetting of poorly water-soluble drug particles and assist in solubilizing certain active ingredients. Depending on the formulation, it may be used in oral, topical, ophthalmic, and selected parenteral products, provided the appropriate pharmaceutical grade and concentration are selected. Its effectiveness depends on the concentration, the nature of the oil phase, and the properties of the other formulation components. During development, compatibility, oxidation stability, potential degradation products, and the effects of the surfactant on drug release and product quality should be carefully evaluated.

6. Castor Oil

Castor oil is a vegetable oil obtained from the seeds of the castor plant (*Ricinus communis*). It consists predominantly of triglycerides containing ricinoleic acid and has been used in pharmaceutical and cosmetic applications. Depending on its grade and intended application, castor oil may function as an oily vehicle, emollient, lubricant, or component of an oil-based formulation. In pharmaceutical development, it may be considered for formulations requiring an oil phase or for improving the solubilization of certain lipophilic substances. However, its suitability depends on the drug's physicochemical properties, the intended route of administration, and the quality specifications of the oil. The pharmaceutical grade must be appropriately characterized, and tests for identity, purity, oxidation, and stability should be conducted. Compatibility with

surfactants and other excipients should also be assessed to prevent phase separation or changes in product performance.

7. Capmul MCM

Capmul MCM is a trade name associated with medium-chain mono- and diglycerides, commonly used as lipid-based pharmaceutical excipients. Depending on the specific grade, it may serve as an oily vehicle, solubilizing agent, wetting agent, or component of self-emulsifying drug delivery systems. Lipid-based excipients such as Capmul MCM can help incorporate poorly water-soluble active ingredients into an oil phase and may support the formation of fine oil-in-water dispersions when combined with suitable surfactants and cosolvents. Such systems can be investigated to improve drug dispersion and potentially enhance oral absorption for selected compounds. The precise composition and functional characteristics vary by grade, so the manufacturer's technical documentation should be consulted. Compatibility, drug loading, emulsification behaviour, dilution stability, and in-vitro dissolution should be evaluated before selecting the material for a pharmaceutical formulation.

8. Avicel

Avicel is a commercial brand of microcrystalline cellulose (MCC), a purified cellulose-based excipient widely used in pharmaceutical manufacturing. Depending on the grade, it functions primarily as a diluent, binder, compression aid, and carrier in tablet and capsule formulations. Microcrystalline cellulose has good compressibility, which supports the production of tablets with suitable mechanical strength. It can also contribute to powder flow and content uniformity when used with appropriate formulation and manufacturing techniques. Different Avicel grades are available with varying particle sizes and physical properties, allowing formulators to select a material suitable for direct compression, wet granulation, or other manufacturing processes. The chosen grade must be evaluated for compatibility with the active pharmaceutical ingredient, moisture sensitivity, blend uniformity, tablet hardness, friability, and dissolution performance. Its suitability should be established through formulation trials and finished-product testing.

9. Crospovidone

Crospovidone is a cross-linked synthetic polymer of N-vinyl-2-pyrrolidone that is widely used as a superdisintegrant in solid oral dosage forms. Its main function is to help tablets and capsules break apart rapidly when they come into contact with aqueous fluids. This action facilitates the dispersion of the dosage form into smaller particles, which can support drug dissolution when the active ingredient has suitable solubility characteristics. Crospovidone is commonly incorporated into tablet formulations through intragranular addition, extragranular addition, or a combination of both methods. Its effectiveness depends on the grade, concentration, particle characteristics, tablet hardness, and manufacturing conditions. It generally has good compatibility with many pharmaceutical ingredients, but the optimal concentration and method of incorporation must be established experimentally. Formulation testing should include disintegration time, dissolution, friability, and stability to confirm that the excipient performs as intended.

2.2 List of Used Instruments

The pharmaceutical formulation was developed using Nebivolol as the active pharmaceutical ingredient (API), along with selected excipients, including propylene glycol, polyethylene glycol (PEG), Tween 80 (polysorbate 80), castor oil, Capmul MCM, Avicel (microcrystalline cellulose), and crospovidone. Nebivolol

was selected as the active ingredient for its antihypertensive activity, while propylene glycol and polyethylene glycol were considered as potential solvents or carriers, depending on the selected grade and formulation requirements. Tween 80 was used as a surfactant to improve wetting and support the formation of a stable dispersion, whereas castor oil and Capmul MCM were considered as lipid-based excipients to support the solubilization of the drug. Avicel was included as a potential diluent and binder to improve powder handling and tablet formation, while crospovidone was selected as a superdisintegrant to promote tablet disintegration and facilitate drug release. Methanol, if required, should be restricted to an appropriately justified analytical or manufacturing process and controlled as a residual solvent because of its toxicity. The suitability and concentration of each ingredient must be established through drug–excipient compatibility studies, solubility testing, formulation optimization, and stability evaluation. The final formulation should undergo appropriate quality-control tests, including drug-content analysis, disintegration, dissolution, and stability studies, to assess its quality, safety, and performance.

3.FORMULATION OF LIQUID SOLID COMPACTS PULSATILE COMPRESSED COATED

TABLET:

A weighed amount of Nebivolol and a liquid vehicle (propylene glycol) are mixed together using a sonication process to achieve a homogeneous combination. The obtained liquid mixture is homogenized at 100 RPM in a prescribed amount of carrier material (Avicel) to guarantee that the liquid medication is uniformly spread throughout the carrier. The required amount of coating ingredient (Aerosil) is next weighed and mixed together uniformly. The prepared powder mixture is spread as a homogeneous layer on the surface of a mortar and allowed to stand for 5 minutes to allow complete absorption of the drug medication into the internal structure of carrier and coating components. Add the required amount of disintegrants (Crosspovidone) to the aforementioned mixture to create a final liquisolid system. The resultant liquisolid system was crushed into a tablet using an 8mm tablet punch in a tablet compression machine. The weighted ethyl cellulose coating granules were then inserted in a 16mm die cavity, the previously crushed tablet was kept centrally, and the pulsatile core tablet was compressed. It should be noted that the tablet's compression force, weight fluctuation, and hardness should all be changed depending on the situation. The formulation and optimization strategy for the Nebivolol solid liquid pulsatile coated tablet are shown in Table

4 Precompression parameter

4.1 Angle of repose:

Angle of repose is used to calculate the frictional forces present in a mixture of grains and pellets. It can be calculated by setting the funnel to a certain height and passing the mixture through it under the influence of gravity, which will form a pile. After forming a sharp edge on the pile, the height of the pile is measured, the surface of the pile is measured, and the angle of repose is calculated using the formula

$$\theta = \tan^{-1}(h/r)$$

θ = angle of repose; h = height of pile; r = radius of pile

4.2 Density:

Weigh the granules or pellets (W) accurately and pour into an empty graduated cylinder. The volume of the cylinder (V₀) was measured for bulk density, and then the cylinder was tapped 100 times on a wooden surface and the volume of the cylinder (V_f) was measured for tap density

Post compression evaluation

SL.No:	Flow character	Angle of repose	Hausner's ratio	Carr's index	References
1.	Excellent	<20	1.00-1.11	≤10	55, 56
2.	Good	20-30	1.12-1.18	11-15	
3.	Fair	----	1.19-1.25	16-20	
4.	Passable	30-34	1.26-1.34	21-25	
5.	Poor	----	1.35-1.45	26-31	
6.	Very poor	>35	1.46-1.59	32-37	
7.	Very very poor	----	>1.6	>38	

4.3 Hausner's ratio:

The ratio of tapped density to bulk density is known as Hausner's ratio. The better the flow property, the lower the value of Hausner's ratio. The following formula is used to compute the ratio. It assesses the powder's ability to be compressed.

4.4 Carr's index:

The percentage compressibility (Carr's index) was determined by multiplying the difference between tapped density and bulk density by 100. It assesses the interparticulate interaction between particle. All the precompression parameter and its limits are shown

5 Post Compression Parameter

5.1 Weight variation:

Weigh each of the 20 tablets. The formula must be used to calculate the average weight and the % weight variance. Individual tablets were then weighed and correlated to an average weight. The weight variation test is passed if the comparative variation is within the I.P limits

Weight variation percentage deviation of tablets

Sl.no	Average weight	Percentage deviation
	Tablet (mg)	

1.	130 or less	10%
2.	130-324	7.5%
3.	More than 324	5%

5.2 Thickness & diameter:

Measure the thickness, width, and measurements of 20 tablets or capsules at random from each batch with vernier callipers, and the average thickness is computed from mean standard deviations

Friability:

20 tablets (W₁) are weighed individually, then put on the Roche friabilator and spun for 100 revolutions at 25RPM. For the % friability from the formula, the tablets are reweighed (W₂). According to IP limits [93], the percentage friability shall not exceed 1%.

$$\% \text{Percentage friability} = \frac{(W_2 - W_1)}{W_1} \times 100$$

W₁ = Initial weight of pellets; W₂ = Final weight of pellets

Hardness:

Crushing strength is determined by subjecting the produced tablets to the force required to break them. The test is carried out in a Pfizer hardness tester. The IP limit should be in the region of 4-6 kg/cm²[93].

Surface morphology:

The tablet should be devoid of fractures, depressions, pinholes, and other flaws, and the colour and punch should be consistent and smooth. Scanning electron microscopy (SEM) and Transmission electron Microscopy (TEM) are used to examine the form and surface morphology of the Solid lipid composite for spherical shape and smoothness by placing a sample on a double-sided carbon adhesive pad and visualising it under SEM [94].

Drug content:

Choose 20 triturate tablets at random and pulverise them with a mortar and pestle. 10mg of it was ingested and mixed with 100ml of pH 6.8 phosphate buffer for around 10 minutes while stirring. After that, the solution was filtered through a 0.45µm membrane filter, diluted appropriately, and the absorbance was measured using a UV visible spectrophotometer with

phosphate buffer as a blank. Pick ten capsules at random and test each one according to the instructions. According to the IP limit, it should fall between 85 and 115 percent. In a 100ml volumetric flask, place 100mg of sample and add distilled water to make the volume up to 100ml. The suspension was then vigorously shaken and left at room temperature for 24 hours. After 24 hours, the supernatant layer was centrifuged and the drug content was determined using a UV Visible spectrophotometer set to 280nm [95, 96].

Wetting time

It is determined by the tablet's internal structure and the excipients' hydrophilicity. It's wetting time. In a petri plate (internal diameter 6.5 cm) holding 6ml of water, a piece of double-folded tissue paper was inserted. The tablet was placed on the paper, and the time it took for the tablet to completely wet was recorded in seconds. The procedure was somewhat altered by keeping the water at 37 degrees Celsius

Swelling & erosion:

Under typical settings, tablets are placed in a pH7.4 phosphate buffer that is fastened to a dissolution equipment. Tablets were carefully taken from the medium and placed on tissue paper at varied time intervals, and the weight of the swelled matrix was measured before being dried in a vacuum oven at 450°C for 3 hours. Finally, the formula is used to determine percent swelling and percent erosion. [98].

$$\% \text{Swelling} = \frac{S}{R} \times 100 ; \% \text{Erosion} = \frac{T-R}{T} \times 100$$

T = Initial weight of tablet matrix at time “0”; S = Weight of swollen matrix of tablet at time “t”; R = Weight of dry eroded matrix at time “t”

Disintegration time:

6 tablets should be placed in the disintegration apparatus's tube. The tube is submerged in phosphate saline buffer (pH 6.8), and the time it takes for the pills to dissolve must be recorded [97]. Coated tablets take 60 minutes to dissolve, uncoated tablets take 30 minutes to dissolve, and capsules take 45 minutes to dissolve.

***Invitro* dissolution studies:**

Under typical settings at room temperature, tablets are put into a six station USP Type II dissolution test device with 900ml of phosphate buffer saline (pH7.4). Every 5 minutes, aliquots

are extracted and a new volume of buffer is delivered. In a UV visible spectrophotometer, the absorbances of aliquots were evaluated at 280nm. Samples are collected at different time intervals to measure the % of drug release in each interval, and the same amount of buffer is administered to maintain sink conditions, as determined by measuring absorbance. Time in hours on the x-axis and cumulative percent drug release on the y-axis were shown in a graph for the cumulative percent invitro drug release experiments [98-100].

Stability Studies :

The optimal pulsatile compression coated tablet was used in this study (CT3). Each formulation was divided into two batches and stored for three months at $25^{\circ}\text{C} \pm 2^{\circ}\text{C} / 60\% \text{ RH} \pm 5\% \text{ RH}$; $40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \text{ RH} \pm 5\% \text{ RH}$. At the 8th hour, each sample from both storage conditions was evaluated and quantified to determine Hardness (Kg/cm²), Weight variation (mg), percent Drug content, and percent CDR. The findings of each formulation were tabulated after they were tested for repeatability

Conclusion:

Pulsatile drug delivery systems represent a significant advancement in drug delivery technology, offering precise control over drug release kinetics and enhancing therapeutic outcomes. As research progresses, these systems hold promise for optimizing therapy across diverse disease conditions. However, challenges remain, including manufacturing reproducibility, formulation complexity, and in vivo variability. Despite these challenges, recent advancements in technology, such as chronopharmaceuticals and smart polymers, have revolutionized the field, enabling more targeted and effective drug delivery[16].

In conclusion, the development of pulsatile drug delivery systems, particularly the optimized formulation CT 3, shows promising results in terms of physicochemical properties and controlled release profiles. Stability studies confirm the robustness of these systems, indicating their potential for commercialization. Future research should focus on long-term stability assessments, in vivo evaluations, and clinical trials to validate their therapeutic efficacy fully. Ultimately, pulsatile drug delivery systems offer exciting opportunities for personalized medicine and improved patient outcomes across various therapeutic areas.

RESULT AND CONCLUSION :

Because of patient compliance and the cost of therapy, the oral route is the most popular form of drug delivery among the many routes of drug delivery. However, knowing the exact whereabouts of drugs in the body after oral administration requires knowledge of gastrointestinal problems. Physiology (TGI). Drug absorption from the GIT is a complex procedure because it is difficult to isolate and identify the system within the expected ranges of the GIT, and absorption varies depending on GIT conditions [13].

For some diseases with symptoms of circadian rhythms, such as cardiovascular disease, arthritis,

bronchial asthma, cancer, duodenal ulcer, diabetes and neurological diseases, it is important to give the maximum amount of the drug at the time the symptoms appear, with a delay time that controls drug release. Since, for example, myocardial infarction and cardiac arrest from morning to noon are more likely in cardiovascular diseases, the best antihypertensive and / or antianginal drugs should be administered in the morning [4, 5]. (PDDS) are best for treating these disorders because they are characterized by a slow initial release of the drug, followed by a quick and complete release of the drug after a short period of time. Most PDDSs are reservoir systems with a barrier layer that dissolves, erodes, or degrades over time, allowing the drug to be rapidly released from the reservoir. In the colon. In previous work, we used tablet and capsule technology to generate time-controlled pulsing formulations for various drugs [6, 7].

Nebivolol is bound to 98% of proteins and is mainly metabolized in the liver (via CYP2D6) with a half-life of approximately 10 hours. A large amount of Nebivolol passes through the kidneys and stool. The half-life of Nebivolol was 12 hours in extensive metabolizers of CYP2D6 and 19 hours in poor metabolizers. In CYP2D6 metabolizers with low metabolism, the bioavailability of Nebivolol is very high (96%); while in major metabolizers it is only about 12%. The drug must be administered quickly into the systemic circulation to improve solubility, dissolution and bioavailability without going through first pass metabolism. It should also be given early in the morning if there is an increased risk of high blood pressure [8]. Therefore, it is important to develop Nebivolol as a gastro retentive polymer-coated Pulsatile tablet consisting of a liquid solid compound that enhances the release and bioavailability of Nebivolol at the required time by delaying the drug release and releasing the maximum amount at the time that hypertension is present, whereby the release of the drug can be controlled by the delay time.

Reference:

1. Tei H, Okamura H, Shigeyoshi Y, Fukuhara C, Ozawa K, Hirose M. Circadian oscillation of a mammalian homologue of the *Drosophila* period gene. *Nature* 1997; 389:512-6.
2. Motta R, Jose L, Vila J. Design of new Multiparticulate system for potential site-specific and controlled drug delivery to the colonic region. *J Contr Rel* 1998; 55:67-7.
3. Radadia Ashwinbhai Arjanbhai, Satyajit sahoo. New hope in hypertension. *World journal of pharmaceutical and medical research*. 2019; 5(11): 31-42.
4. Martin RJ, Banks-Schlegel S. Chronobiology of asthma. *Am J Respir Crit Care Med* 1998; 158:1002-7.
5. Sangalli ME, Maroni A, Zema L, Busetti C, Giordano F, Gazzaniga A. In vitro and in vivo evaluation of an oral system for time and/or site-specific drug delivery. *J Control Release* 2001;73:103-10.
6. Bruguierolle B, Labrecque G. Rhythmic pattern in pain and their chronotherapy. *Adv Drug Deliv. Rev* 2007;59:883-95.
7. Richard JM, Susan BS. Chronobiology of asthma. *Am J Resp Crit Care Med*. 1998;158:1002-7.
8. Gazzaniga A, Maroni A, Sangalli ME, Zema L. Time-controlled oral delivery systems for colon targeting. *Exp Opin. Drug Deliv* 2006;5:583-97.
9. Mohamad A, Dashevsky A. pH-independent pulsatile drug delivery system based on hard gelatin capsules and coated with aqueous dispersion Aquacoat ECD. *Eur J Pharm Biopharm* 2006;64:173-9.
10. Khan Z, Pillay V, Choonara YE, Du Toit LC. Drug delivery technologies for chronotherapeutic applications. *Pharm Dev Technol* 2009;14:602-12.
11. Roy P, Shahiwala A. Multiparticulate formulation approach to pulsatile drug delivery: Current perspectives. *J Control Release*. 2009;4(134):74–80.
12. Kumar Babu Pasupuleti, Venkatachalam A, Bhaskar Reddy Kesavan, Formulation And In Vitro–In Vivo Pharmacokinetic Evaluation Of Cardiovascular Drug-Loaded Pulsatile Drug Delivery Systems. *Innovare Academic Science* 2021; 0975-7058
13. Anil A, Thomas L, Sudheer P. Liquisolid compacts: an innovative approach for dissolution enhancement. *Int J Pharm Pharm Sci*. 2018; 10:1-7.
14. Fahmy RH, Kassem MA. Enhancement of famotidine dissolution rate through liquidsolid tablets formulation: In vitro and in vivo evaluation. *Eur. J. Pharm. Biopharm.*, 2008;69(3): 993-1003.
15. Dalvi PB, Ingale PR. Liquisolid technique: an approach for enhancement of solubility. *World J Pharm Sci*. 2014; 3:434-46.

16. Bhalla A, Singh R, Sachdev A, D'Cruz S, Duseja A. Circadian pattern in cerebro vascular disorders. *Neurol India*. 2002;50:526–7
17. Sateesh Kumar Vemula. A Novel Approach to Flurbiprofen Pulsatile Colonic Release: Formulation and Pharmacokinetics of Double-Compression-Coated Mini-Tablets. *AAPS PharmSciTech*. 2015;16(6):1465-73.
18. Sungthongjeen S, Puttipipakhachorn S, Paeratakul O, Dasheysky A, Bodmeier R. Development of Pulsatile Release Tablets with swelling and rupturable layers. *J. Control. Release*. 2004; 95(2):147-59.
19. Patel BB, Shah CN. Recent research on liquid solid technology for solubility enhancement-a review. *Int J Adv Pharm* 2016; 5:1-7.
20. Morta R, Jose L, Vila J. Design of new multiparticulate system for potential site-specific and controlled drug delivery to the colonic region. *J Contr Rel* 1998; 55:67-77.
21. Sanjayamitra PVSS, Ganesh GNK. Dissolution and solubility enhancement strategies: current and novel prospectives. *J Crit Rev* 2018;5:1-10.
22. Spireas S, Bolton M. Liquisolid systems and methods of preparing same, U. S. Patent 5 968, 550; 1999.
23. Javadzadeh Y, Jafari-Navimipour B, Nokhodchi A. Liquisolid technique for dissolution rate enhancement of a high dose water-insoluble drug (carbamazepine). *International Journal of Pharmaceutics* 2007; 341 (1-2): 26–34.
24. Susmit S, Diggikar, Tanaji D, Nandgude, Sushikumar S, Poddar. Formulation of modified release pellets of montelukast sodium. *Research journal of pharmacy and development* 2018;11(1):31-7.
25. Amitha shetty, Paneer selvam, Maya Sharma, Smitha shetty. Formulation and evaluation of chronomodulated drug delivery system containing captopril and hydrochlorthiazide; *Journal of pharma research* 2019; 8(7): 468-77.
26. Senthilnathan B, Aviyankavasireddy, Kausalya J, Suba V. Design and development of pulsatile drug delivery of Glibeclamide using Pulsincap technology. *International journal of Pharmtech Research* 2012; 4(4):1606-13.
27. Lemmer B. Chronopharmacokinetic: implications for drug treatment. *J. Pharm. Pharmacol*. 1999; 51(3):887–90.
28. Liberman, Lachman, Schwartz. *Pharmaceutical Dosage Forms: Tablet*, 2nd edn, vol.-2, CBS publishers, New Delhi, 1990; 201-338.
29. J. Reddy, M. Jyothsna, M. Saleem, C. Chetty, Review on: pulsatile drug delivery systems. *J. Pharm. Sci. Res.*, 2009;1: 109-15.
30. V. Belgamwar, M. Gaikwad, G. Patil, S. Surana. Pulsatile drug delivery system, *Asian J. Pharm*. 2008;2:141-5.
31. M. Rajput, R. Sharma, S. Kumar, F. Jamil, N. Sissodia, S. Sharma/ Pulsatile drug delivery system: a review, *Int. J. Res. Pharm. Bio. Sci.*, 2012;3:118-24.
32. Madhavi AV, Brahma Reddy DR, Venugopal M, Srihari N, Chenniah P, Koteswarao P, Formulation and Evaluation of Pulsatile Drug Delivery System of Zafirlukast. *Journal of Drug Delivery and Therapeutics*. 2020; 10(2):122-128
33. Patil AS, Dandagi PM, Masthiholimath VS, Gadad AP, Najwade BK. Development and characterization of chronomodulated drug delivery system of captopril. *Int J Pharm Investig*. 2011;1:227–33.

