European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 7, Issue 4, 2020

FORMULATION DEVELOPMENT OF MODIFIED RELEASE DOSAGE FORM OF ANTIHYPERTENSIVE DRUG

Raosaheb S Shendge[1], Kishor S Salunkhe[2], Kashid Girish

[1]Associate professor, Pharmaceutics Dept.
Sanjivani College of Pharmaceutical Education and Research, Kopargaon, 423603,Maharashtra,India.
shendgerajan@gmail.com
[2]Professor, Pharmaceutics Dept.
Sanjivani College of Pharmaceutical Education and Research ,Kopargaon,, 423603,Maharashtra,India.
[3]Assistant professor, Pharmaceutical chemistry Dept.
Sanjivani College of Pharmaceutical Education and Research Kopargaon,423603,Maharashtra,India.

ABSTRACT
Changed delivery dosage structures have been created to deliver drug to the aspect of the body where it will be ingested, to streamline dosing plans, and to guarantee that centralization of drug is kept up over a fitting time interval. Drugs that are not innately dependable require various every day dosing to accomplish the ideal therapeutic impacts. Numerous day by day dosing is regularly badly designed and can bring about missed doses, made-up doses and patient rebellious with therapeutic routine. Blood levels of drugs from conventional prompt delivery dosage structures taken more than once every day following distinct timetable normally demonstrate consecutive pinnacles and troughs (valleys) related with each dose. Intended to deliver their prescription in controlled way, at a pre-decided rate, span and area in the body to accomplish and keep up optimum therapeutic blood levels of drug.
Keywords: Drugs, Propranolol Hydrochloride, Bulk density, Matrix tablets

INTRODUCTION

Oral delivery of drugs is the most best course of drug delivery because of the simplicity of organization, tolerant consistence and adaptability in definition, and so forth. A significant number of the drug delivery frameworks accessible in the market are oral drug delivery type frameworks. Around half of the drug delivery frameworks accessible in the market are oral drug delivery frameworks and verifiably as well, oral drug organization has been the overwhelming course for drug delivery. It doesn't represent the sterility issue and insignificant danger of harm at the site of organization. Pharmaceutical items intended for oral delivery are chiefly prompt delivery type or conventional drug delivery frameworks, which are intended for guaranteed arrival of drug for fast assimilation. Drugs with short half-life require successive organization, which expands odds of missing dose of drug prompting helpless patient consistence.

A regular peak valley plasma focus time profile is acquired which makes fulfillment of consistent state condition troublesome. The fluctuating drug levels may prompt precipitation of unfavorable impacts

particularly of a drug with little therapeutic list, at whatever point overmedication happens. So as to conquer the downsides of conventional drug delivery frameworks, a few specialized progressions have prompted the advancement of controlled drug delivery framework that could change technique for prescription and give various therapeutic advantages. The oral course of organization is the most favored course because of adaptability in dosage structure, plan and patient consistence. In any case, here one needs to mull over, the different pH that the dosage structure would experience during its travel, the gastro intestinal motility, the chemical framework and its effect on the drug and the dosage structure. Most of oral supported delivery frameworks depend on disintegration, dispersion or a blend of the two components, to produce moderate arrival of drug to the gastrointestinal tract.

Hypothetically and desirably a continued delivery gadget, should deliver the drug by a zero-request measure which would bring about a blood-level time profile like that after intravenous steady rate imbuement. Plasma drug fixation profiles for conventional tablet or container detailing, a continued delivery plan, and a zero request supported delivery definition. Supported delivery comprises any dosage structure that gives medicine over an all-encompassing time or indicates that the framework can give some genuine therapeutic control whether this is of a temporal sort, spatial nature or both. Supported delivery framework by and large don't achieve zero request type discharge and ordinarily attempt to copy zero request discharge by giving drug in a moderate first request. Rehash activity tablet are an elective strategy for supported delivery in which various doses of drug are an elective technique for continued delivery, in which, numerous doses are contained inside a dosage structure and each dose is delivered at an intermittent interval.

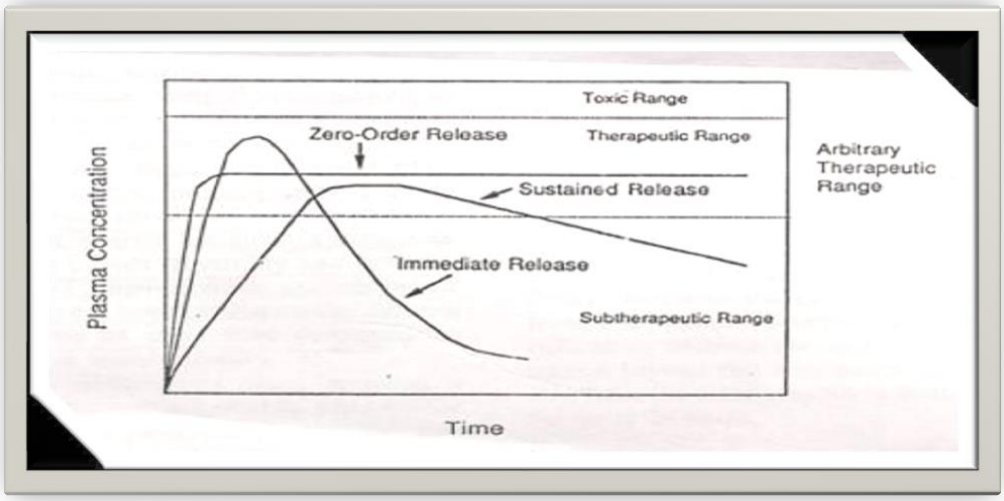

Figure 1Plasma Concentration-profiles Vs Time (sustained release formulationand zero order formulation)

The controlled delivery frameworks for oral use are generally strong and dependent on disintegration or dissemination or a mix of both the instruments in the control of delivery pace of drug. As of late, significant consideration has been centered around hydrophilic polymers in the plan of oral controlled drug delivery frameworks as a result of their adaptability to get an alluring drug discharge profile, cost-adequacy, and expansive administrative acknowledgment. Cardiovascular diseases are one of the dangerous diseases of humanity and hypertension is the most widely recognized cardiovascular sickness, which requires consistent observing. Control of hypertension inverts the danger of congestive heart disappointment; though the danger of coronary ailment isn't switched quickly. It is a lot of basic to control the hypertension and keep up adequate blood course to heart to decrease the dreariness and make the patient to lead a close to typical life.

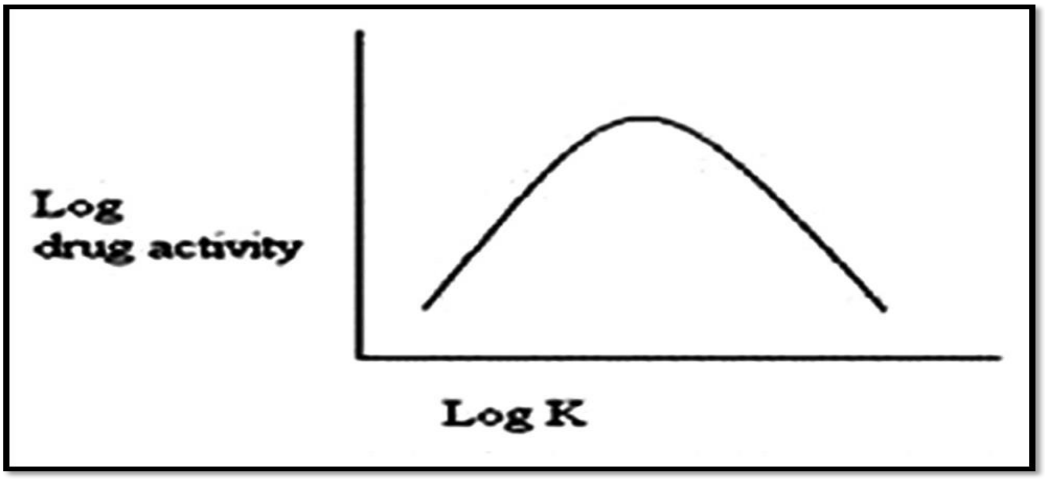

Figure 2: A relationship between drug action and partition coefficient

Hypertension is characterized as a systolic blood pressure (SBP) =140 mmHg and a diastolic blood pressure (DBP) = 90 mmHg for people as long as 60 years old and for subjects with diabetes mellitus or recognizable hypercholesterolemia and as a SBP = 160 mmHg and a DBP = 90 mmHg for people of 60 years and more seasoned without diabetes mellitus or natural hypercholesterolemia. Hypertension is a danger factor for myocardial localized necrosis, stroke, congestive cardiovascular breakdown, end stage renal infection, and fringe vascular malady. The World Health Organization announced that problematic blood pressure (SBP > 115 mmHg) is liable for 62% of all cerebro vascular diseases and 49% of all ischemic heart diseases5.One way to deal with the assembling of controlled delivery dosage structures is the immediate pressure of mixes of drug, retardant material and added substances to frame a tablet in which drug is inserted in a framework center of the retardant. Then again, retardant drug mixes might be granulated preceding pressure. Grid tablets are viewed as the financially achievable controlled activity dosage structures. The goal of the current examination was to Formulation and assessment of oral controlled delivery dosage type of Antihypertensive operator. Propranolol hydrochloride was defined as an oral controlled delivery dosage structure utilizing different polymers like HPMCK4, Guargum, MCC and PVPK90.

LITRATURE REVIEW

Muhammad Ali Sheraz, et al (2016) suggested that Amlodipine (AD) is a calcium channel blocker that is predominantly utilized in the treatment of hypertension and angina. In any case, most recent discoveries have uncovered that its adequacy isn't just restricted to the treatment of cardiovascular diseases as it has appeared to have cancer prevention agent movement and assumes a significant part in apoptosis. Along these lines, it is additionally utilized in the therapy of cerebrovascular stroke, neurodegenerative diseases, leukemia, bosom malignancy, etc either alone or in mix with different drugs. Promotion is a photosensitive drug and requires security from light. Various specialists have attempted to plan different conventional and nonconventional dosage types of AD. This audit features all the definitions that have been created to accomplish most extreme dependability with the ideal therapeutic activity for the delivery of AD, for example, quick dissolving tablets, drifting tablets, layered tablets, single-pill blends, cases, oral and transdermal movies, suspensions, emulsions, muco cement microspheres, gels, transdermal patches, and liposomal plans.

SudhirKarna et al.,(2015) indicated that the cost and difficulties associated with promoting new drug substances have expanded, with corresponding acknowledgment of the therapeutic focal points of controlled drug delivery, more noteworthy consideration has been centered around advancement of continued or controlled delivery drug delivery frameworks (DDS). For some, ailment expresses, a considerable number of therapeutically powerful mixes as of now exist. The viability of these drugs is frequently restricted by reactions or need to regulate the compound in a moral setting. The objective in planning supported drug delivery is to lessen the recurrence of dosing or to build the adequacy of the drug by limitation at the site of activity, decreasing the dose required or giving uniform drug delivery. The plan of oral supported delivery DDS relies upon different factors, for example, physicochemical properties of drug, sort of delivery framework, infection being dealt with, and patient condition, and treatment length, presence of food, gastrointestinal motility, and co-organization of different drugs.

PROPOSED METHODLOGY

MATERIALS AND METHODS

Propranolol Hydrochloride was gotten as sample from Yarrow chem Products, Mumbai. Guargum, Hydroxy propyl methyl cellulose K4M, Talc and Magnesium stearate were acquired from S d fine-chem restricted, Mumbai. Microcrystalline cellulose was acquired. PVPK90 was acquired from Lobachemie.

The formula for preparation of matrix tablets:

Preparation of matrix tablets:

Matrix tablets containing Propranolol were set up by direct pressure strategy utilizing changing proportions of various polymers. All the ingredients were weighed precisely and blended. Propranolol was first blended in with the polymer and legitimately compressible microcrystalline cellulose for 15 min to acquire uniform blend. At that point the blend is gone through 60# sifter. At long last, the blend is mixed with powder and magnesium stearate.

Pre-compression parameters

Bulk Density

Both tapped density (TD) and bulk density (BD) was determined. An amount of 10 gm of powder blend from every formula, previously shaken to break any agglomerates shaped, was acquainted in with 100 ml estimating chamber. After that the underlying volume was noted and the chamber was permitted to fall under its own load on to a hard surface from the stature of 2.5 cm at second intervals. Tapping was proceeded until no further change in volume was noted. Mass thickness (BD) and Tapped thickness (TD) were determined utilizing the accompanying equations.

$$BD = \frac{\text{Weight of the powder blend}}{\text{Untapped Volume of the packing}}$$

$$TD = \frac{\text{Weight of the powder blend}}{\text{Tapped Volume of the packing}}$$

Carr's Compressibility Index:

% Carr's Index can be calculated by using the followingformula

Carr's Index (%) = ×100

Angle of repose:
Angle of repose (θ) can be calculated from the followingFormulawhere

tanθ=h/r

h=height of pile and r=radius of the base of pile

Hausner's ratio:
Hausner ratio is an indirect index of ease of measuring the powder flow. It is calculated by the following formula

Hausner's ratio= Tapped Density / Bulk Density

Post-compression parameters
a) Friability test: Recently weighed 15 tablets were taken in Roche friabilator and the friability was checked at 20 rpm for 5 minutes.
b)Hardness test: Hardness of the tablets was tried utilizing the "Monsanto" hardness tester. The physical properties of the tablets are appeared.
c)Uniformity of weight: Average weight of the tablet was calculated by weighing 25 tablets individually and alltogether.
d)Drug content uniformity of the tablets:
Twenty tablets were weighed and powdered. The amount proportional to 150mg of Propranolol HCl was weighed precisely and taken in 100ml volumetric flask. The volume was made up to 200 ml with pH 6.8 and sifted. From this, 1ml was pipetted into 20 ml volumetric flasks and the volume made with pH 6.8. The absorbance was estimated at the 289 nm by utilizing pH 6.8 as a blank.
e) *In-vitro* dissolution studies:
Disintegration of the tablets was completed on USP XXIII disintegration type II mechanical assembly utilizing paddle. The disintegration medium comprised of 800 ml of pH 1.2 support (0.1N HCl) for initial two hours and the phosphate cradle pH 6.8 from 4-11 hours kept up and the temperature of the medium was set at 37±0.5^{o} C. The rotational speed of the oar was set at 100 rpm. 10 ml of test was pulled back at volume of new medium was supplanted. The pulled back examples were weakened to 20ml with pH 6.8, separated and broke down on UV spectrophotometer at 289 nm utilizing pH 6.8 as a blank. Rate total drug discharge was determined.
f) Stability studies:

Transient security considers were performed at temperature 40±2°Cover a time of a quarter of a year on the matrix tablet formulation adequate number of tablets were pressed in golden shaded screw topped containers and kept in solidness chamber kept up at 40±2°C.

g) Kinetics of Drug Release:

The combined measure of Propranolol hydrochloride delivered from controlled delivered matrix tablets at various time intervals was fitted to zero-request, first request energy, Higuchi's model and Korsmeyer'speppas models.

h) Swelling and erosion study:

Swelling and erosion considers were performed utilizing the strategy portrayed Weighed tablets (H1) were taken on recently weighed watch glass and put in a level base disintegration vessel, containing phosphate cushion (pH 6.8) at 370 C. At one hourly time intervals (1-12 hours) tablets were pulled back and abundance measure of water was eliminated from the tablet by utilizing smudging paper and weighed (H3) on a solitary dish balance.

RESULTS AND DISCUSSION:

Physical characterization of the tablets:

All the formulations were set up as indicated by the Formula. The readied matrix tablets were assessed for different physical properties as shown. All the clumps were delivered under comparable conditions to abstain from handling factors. All the formulations were assessed for different physical boundaries, for example, weight variety, thickness, hardness, friability and drug content. Hardness of tablets extended from 3.9 + 0.18 to 5.8 + 0.14 kg/cm2, thickness of tablets were found inside the scope of 3.12 + 0.085 to 3.65 + 0.66mm. The rate friability of the apparent multitude of formulations was in the middle of 0.45 + 0.09 to 1.05 + 0.35 percent. The estimations of hardness test and percent friability shows great dealing with property of arranged tablets. The drug content consistency in the tablets was inside the range from 99.43 + 2.80 to 101.39 + 0.97 %

Table No.1: Ingredients used in the formulation

Ingredients mg	F1	F2	F3	F4	F5	F6	F7
Prppranolol HCL	40	40	40	40	40	40	40
Guargum	160	180	200	-	-	-	80
$HPCMCK_4$	-	-	-	160	180	200	80
MCC	122	102	82	122	102	82	122
$PVPK_{90}$	20	20	20	20	20	20	20
Mg.sterate	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4

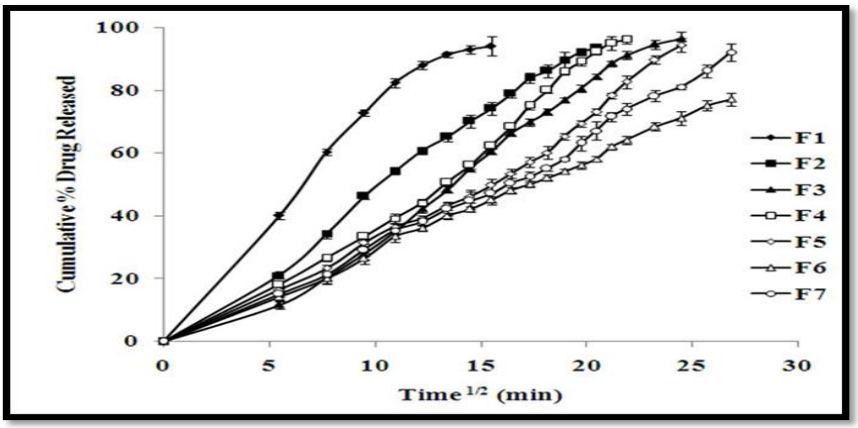

Figure 3: Higuchi plot for cumulative percent Propranolol hydrochloride released *vs.* square root of time (mean ± SD, *n* = 3) from different formulations

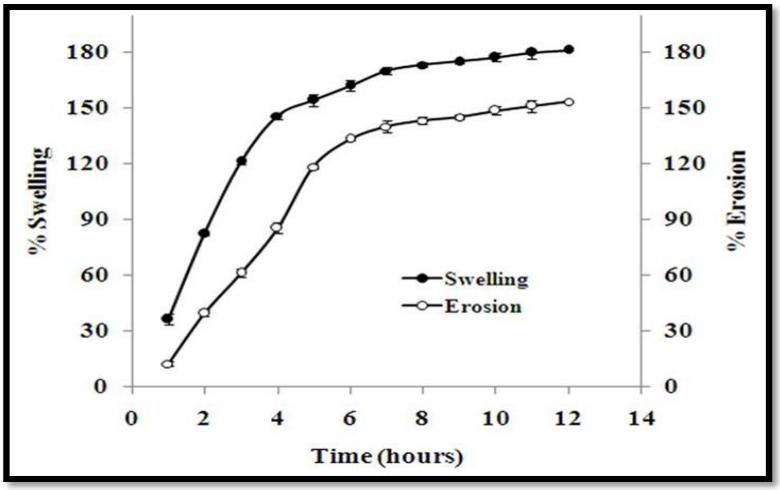

Figure4: Swelling and Erosion behavior of optimized formulation of matrix tablet. Data are represented as mean ± SD, *n*=3)

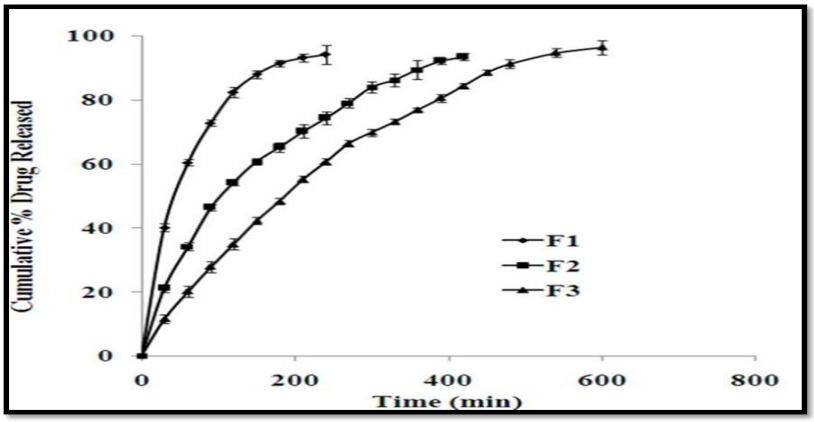

Figure 5: Cumulative % Propranolol hydrochloride released *vs.* time (mean ± *SD*, *n* = 3) from formulations F4, F5, F6, F7

Table No.2Kinetics of Drug Release from Propranolol hydrochloride Matrix Tablets

Formulations	Drug release kinetics, Coefficient of determination 'r²'			Korsmeyer Model	Higuchi rate constant (K_2)	Release exponent (n)	$t_{50\%}$ (hour)
	Zero Order	First Order	Higuchi Equation				
F1	0.961	0.913	0.962	0.995	6.278	0.575	0.73
F2	0.943	0.911	0.993	0.995	4.769	0.545	1.71
F3	0.916	0.814	0.984	0.999	4.510	0.537	3.21
F4	0.944	0.931	0.982	0.991	4.787	0.590	2.68
F5	0.899	0.809	0.980	0.986	3.885	0.665	3.63
F6	0.952	0.948	0.997	0.998	2.932	0.799	4.63
F7	0.937	0.924	0.991	0.997	3.465	0.540	4.04

FT-IR Study

FT-IR study recommended that there was no association between the unadulterated drug, polymers and their mix utilized in the examination. The infrared range was taken in the Perkin-Elmer FT-IR (range RX) by checking the upgraded formulation in potassium bromide plates. The example of unadulterated drug (Propranolol HCl), unadulterated polymers and the advanced formulation (F7) were filtered.

Statistical analysis

The information were introduced as mean ± standard deviation. The drug discharge information was exposed to one path investigation of variance(one way ANOVA) trailed by Holm-Sidak test for different correlation examination ($p<0.05$) to see if critical distinction was available between the formulations or not.

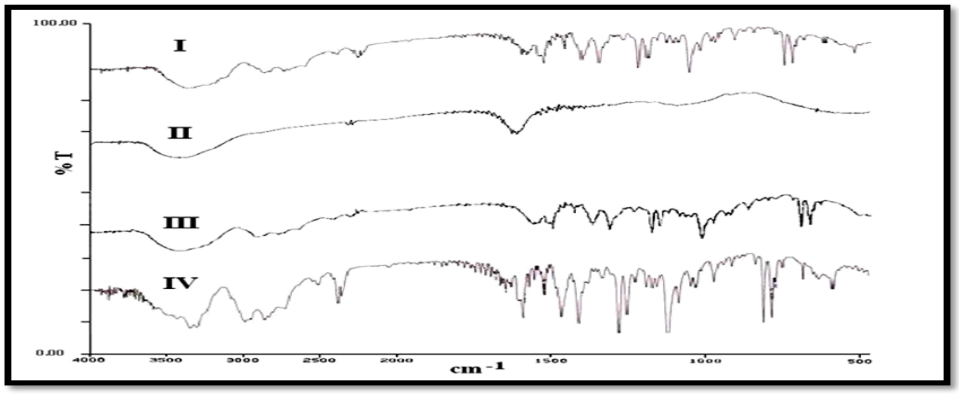

Figure 6FT-IR spectra of pure Propranolol hydrochloride (I), HPMC (II), ethyl cellulose (III), and Optimized formulation F7

CONCLUSIONS

Propranolol HCl continued delivery matrix tablets were effectively formulated utilizing the blends of normal gum, for example, gum karaya with electrolytes for delivery of drug over an all-encompassing timeframe. Past investigations have indicated that normal gums like thickener, guar gum, karaya gum and sodium alginate alone in the tablets can't productively control the drug discharge for delayed timeframe. This examination demonstrates that the blend of hydrophilic characteristic gum and electrolytes with optimum focuses prompted delayed arrival of the drug up to 12 hrs. A significant element of this framework is the potential for creating steady drug discharge. The physical boundaries were acceptable and acquired inside IP indicated limits. The FT-IR considers uncovered the nonattendance of drug-polymer cooperation. The streamlined formulation PKE8 had the option to control the drug discharge as long as 12 hours. The formulated continued delivery tablets can diminish, the recurrence of drug organization and it can diminish the plasma drug variance and it can improve the patient consistence. In this investigation it was likewise discovered that the grouping of polymer have additionally an enormous impact on drug discharge rates, by expanding the measure of polymer, drug discharge rate can be diminished to a high worth.

REFERENCES

1. S.Vidyadhara etal.,(2017) Formulation and Evaluation of Sustained Release matrix tablets of Propranolol HCl with Gum Karaya.
2. Senthil K K et al.,(2012)Formulation of Oral controlled release dosage form of Anti-hypertensive agent.
3. SudhirKarna et al.,(2015)Formulation Approaches for sustained release dosage forms.
4. P. N. Murthy, et al.,(2008) Comparative Study of Propranolol hydrochloride Release from Matrix Tablets with Kollidon or Hydroxy Propyl Methyl Cellulose.
5. MadhusmrutiKhandai etal.,(2010) Development of propranololhydrochloride matrix tablets: An investigation on effects of combination hydrophilic and hydrophobic matrix formers using multiple comparison analysis.
6. B.S. Kuchekaretal., Formulation and Evaluation of Sustained Release Matrix Tablet
   Gupta BP etal., (2010) Osmotically controlled drug delivery system with associated drugs.
7. R. N. Saha, et al.,(2001) A comparative study of controlled release matrix tablets of Diclofenac Sodium, Ciprofloxacin Hydrochloride, and Theophylline. Drug Delivery.
8. Kamboj S,etal.,(2009) Matrix Tablets: An Important Tool for Oral Controlled-Release Dosage Forms, Pharmainfo.
9. S. C. Sweetman, (2009)the Complete Drug Reference, Royal Pharmaceutical Society.
10. N. M. Sanghavi,etal.,(1998) Matrix tablets of propranolol hydrochloride. Indian Drugs.
11. Punna RR, etal.,(2008)Controlled Release Matrix Tablets of Zidovudine: Effect of Formulation Variables on the *In Vitro*Drug Release Kinetics. An Official Journal of the American Association of Pharmaceutical Scientists.
12. Jha AK, etal.,(2009) “Formulation and Invitro Evaluation of sustained release matrix tablets of Metoprololsuccinate using hydrophilic polymers”.
13. Walle T et.al,(1978) The predictable relationship between plasmalevels and dose during chronic propranolol therapy.
14. Ambeth Kumar, V., Malathi, S., Venkatesan, R., Ramalakshmi, K., Vengatesan, K., Ding, W., & Kumar, A. (2020). Exploration of an innovative geometric parameter based on performance enhancement for foot print recognitionJournal of Intelligent & Fuzzy Systems(Preprint), 1–16.

15. Vengatesan, K., Kumar, A., Karuppuchamy, V., Shaktivel, R., & Singhal, A. (2019). Face Recognition of Identical Twins Based On Support Vector Machine Classifier. In 2019 Third International conference on I-SMAC (IoT in Social, Mobile, Analytics and Cloud)(I-SMAC) (pp. 577–580).
16. Kumar, A., Kumar, P., Srivastava, A., Kumar, V., Vengatesan, K., & Singhal, A. (2020). Comparative Analysis of Data Mining Techniques to Predict Heart Disease for Diabetic Patients. In International Conference on Advances in Computing and Data Sciences (pp. 507–518).
17. Parashar T, et.al,(2013) Novel Oral Sustained Release Technology: A Concise Review. Int J Res & Development in Pharm and Life Sci.