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Optimization and Evaluation of Novel Oral Self-Emulsifying Drug Delivery System Carvedilol Tablet Formulations

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ABSTRACT

Carvedilol is a potential antihypertensive drug and classified under class –II as per Bio Pharmaceutical Classification (BCS) system and also possess low bioavailability. The aim of the study was to develop carvedilol self-emulsifying ER tablets to improve bioavailability.

Solid – SEDDS was prepared by using spray drying technology. The excipients used were. Labrafil M2125, Oleic acid, Cremophor RH40, Polyethylene glycol 400, HPMC E5 and Neusilin UFL2 were used to prepare formulations. The optimal solid-SEDDS formulation had particle size in the range of 86.64±2.6µm, loading efficiency 99.86% and 63% drug dissolved in 10 min and reached 100% in 60 min. The pharmacokinetic studies were revealed that bioavailability was increased by 3.4 folds compared to pure drug. Optimized ER formulation extended drug release up to 24hrs with first order kinetics. Thus, the optimized formulation may provide a useful solid dosage form for extended release of poorly soluble and low bioavailable drugs.

The optimized formation was showed first order drug release and followed Non-Fickian Model and above 85% drug release was observed. Conventional matrix tablets also developed and evaluated. Optimized formulation extended drug up to 12 hrs and met innovator specification.

1. INTRODUCTION

1.1 From decades, acute and chronic diseases/illness are being treated with a number of pharmaceutical dosage forms like tablets, capsules, pills, creams, liquid systems, ointments and injections etc. Extended-release formulations are available over long period for oral administration. After administration of extended-release tablet/capsule the drug or API is released slowly for a period of 24hours. The formulation helps out to evade side effects which are usually observed with conventional dosage form possibly shows peaks and troughs in plasma level vs time curves of drug. The extended-release systems have various advantages: like maintains drug concentration blood with in safety level, minimize toxicity, improved stability by giving protective

coatings for dosage form to avoid hydrolysis and reduce degradative changes in gastrointestinal tract, reduced drug accumulation, systemic as well as local side effects, lessen drug accumulation by way of chronic dosing, improves patient compliance and proper medication adherence. Disadvantages: Dose dumping, difficulty in accurate dose adjustment, less in vivo and invitro correlation, retrievals of the active is difficult once administered, difficult dose adjustment of drugs. Extended drug release formulations are of two types: controlled release and sustained release. A sustained release system is extremely popular because of ease of fabrication and less dose dumping problems and is to change pharmacokinetic parameters of drugs by using novel approaches in dosage form design. Sustained release drug delivery principally prolongs the drug action with high expectedness and reproducible results.

1.2 Sustained Release Drug Delivery:

The oral controlled release formulations have several advantages over a conventional system viz. increased patient compliance, reduced dosing frequency, discriminating pharmacological activity and reduced side effects. These systems show significant therapeutic effect. The CR system gives prolonged delivery of active moieties at active site or maintains plasma drug levels in therapeutic range. In addition, by comparing rate of drug administration with rate of drug elimination, a steady state drug levels in plasma can be achieved. The most of SR systems shows 1st 3 order kinetics where drug level in plasma is more after administration and diminishes exponentially. Figure 1.1 clearly depicts plasma drugs levels upon administrations of IR and CR formulations.

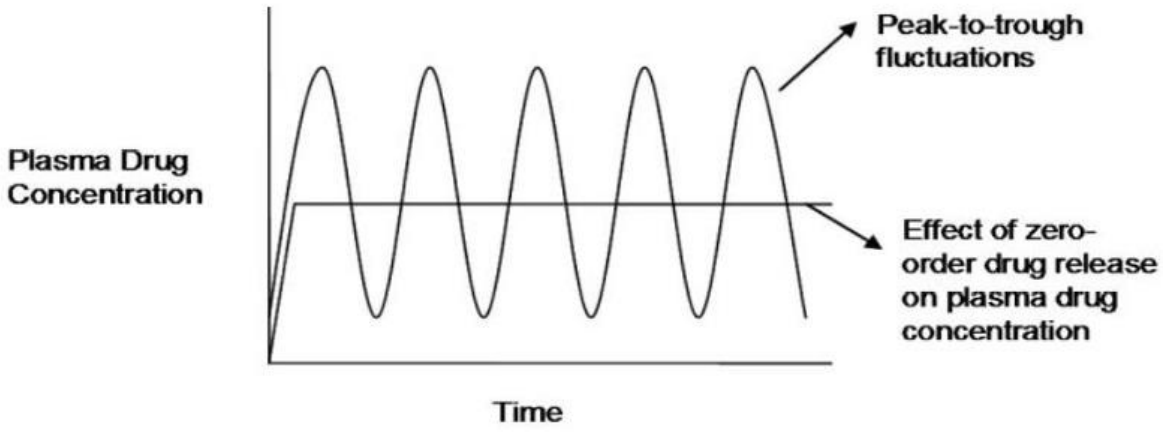

Figure 1.1: Plasma drug level versus time course of conventional and sustained or controlled release formulations[6].

1.3 Sustained drug release perfectly shows zero order drug release with extended time of drug release usually greater than 12 hours. Several studies are carried out for development of DDS easy to give zero or near zero order release kinetics. From many years, the geometric principles have been considered to change drug release pattern from a nonlinear manner to zero or near zero order. The researchers have tried to control drug release way of DDS by altering the geometry of drug delivery devices by using optimization techniques e.g., geometries like cylindrical, spherical, a holed cylinder and bi-convex. The need of changing the geometry of devices is to give a constant and stable surface area to get zero order release kinetics. Pharmaceutical polymers

are crucial in development of multilayered matrix devices and their characters are also important factors for performance of the devices.

The polymers mainly in use are hydrophilic polymers, while the hydrophilic polymers are swollen or non-swollen, porous or non-porous to an erodible or non-erodible. The functional mechanism of a polymer is swelling, erosion and dissolution. Some studies revealed that the drug release from monolithic hydrophilic matrices gives time dependent drug release profile and which is controlled by polymeric swelling. The function of geometric technology in development of controlled drug delivery systems, is focusing on different types of polymers and its key role in geometrically modified systems.

1.4 Multi-layered Tablets: Multilayered systems like (bi-layered and tri layered tablets etc.) are turns into as a major class of CR devices. These are advantageous over conventional tablet systems. The multilayered tablets have enormous benefits, to prevent drug interactions in multi drug dosage forms and also excipients which modify drug release profiles; an immediate drug release pattern is acquired by a disintegrating monolithic matrix to attain a quick peak plasma drug level. Further, plasma level was sustained by erodible matrix delivers same or second drug in controlled manner, swellable matrices are better in manage and normalize the release profile by hold up the initial release of drug to achieve zero order release profiles.

1.5 Multi layered tablets usually contain, a core layer which is surrounded polymeric barrier layers composed up of swellable hydrophilic polymers e.g. hydroxyl propyl methyl cellulose and polyethylene oxide and/or hydrophobic polymers e.g. EC and stearic acid. The barrier layers reduce interaction of active core with GI contents or by reducing the surface of device for drug release and with control of solvent penetration rate and initial burst release of the drug. As time goes, the swollen barrier layer(s) undergo erosion and increase in the surface area allows drug to release extensively. Usually, a constant drug release profile can be achieved when both of the barrier layers are hydrophilic in nature and core drug layer should be hydrophobic, the additional factors also taken into account to get zero order release patterns..

1.6 Different models of tri-layer tablets and their composition were shown in figure 1.2 and Table 1.1

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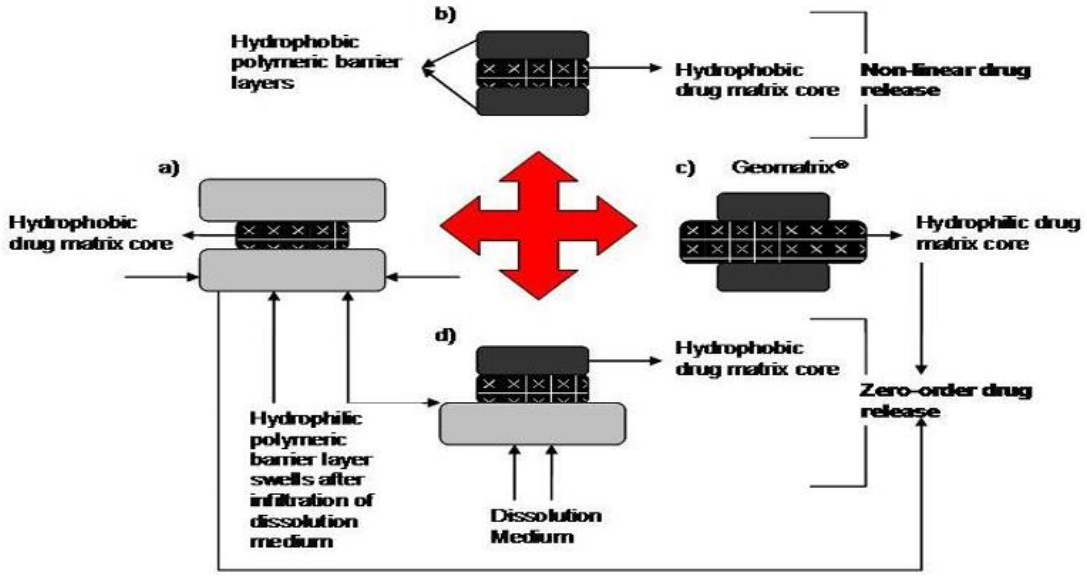

Figure 1.2: Various models of multi-layered tablets

Table 1.1: The polymers influence the release characteristics of multilayered tablets.

Drug containing layer	Barrier layer	Type of the tablet	Drug release pattern
Drug and Hydrophilic polymer	Hydrophilic polymer	Bi layered	Extended Release
Drug and Hydrophilic polymer	Hydrophobic polymer	Bi layered	Drug release Retarded up to less Extent
Drug and Hydrophobic polymer	Hydrophilic polymer	Tri layered	Zero order
Drug and Hydrophobic polymer	Hydrophobic polymer	Tri layered	Non-linear
Drug and Hydrophobic polymer	Both Hydrophilic and hydrophobic polymers	Tri layered	Zero order
Drug and Hydrophilic polymer	Hydrophobic polymer	Tri layered	Zero order

1.7 Factors influencing Drug Release from Multi-layered Tablets:

The multilayered system initially swells, as gel and slowly erodes. The effect of polymers on release of venlafaxine HCl. The blend of hydrophilic & swellable polymers like HPMC K100M and Polyox in barrier layer and cellulose acetate propionate (hydrophobic) was used in core layer that contain venlafaxine HCl. Bi layered and tri-layered tablets were prepared by covering one side of core layer in case of bi layered and two sides were covered to prepare trilayerd tablets. The covering layer was composed of Hydrophilic polymeric blend and resulted layer have the swelling ability. The release profiles showed that the drug release was retarded in case of multi-layer tablets than a core tablet. It may because of rapid swelling and expansion of

drug layer when contacted with dissolution medium. Generally, HPMC matrices shows deliberate drug release compared to matrices made up of CAP, as they give a more strong and solid barrier. Novel specialized polymers can be efficiently used to get zero order release profile.

The behavior of diffusional layered matrices for sustained as well as zero order release was well explained in following research work. Layered tablets made up of a drug layer contains hydrophobic material; composed of pseudoephedrine HCl 24% w/w, carnauba wax 40% w/w and soluble filler, lactose. Barrier layers of the tablet were made up of either Methocel K4M or Methocel K100M or a hydrophobic polymer. Total 3 types of layered matrix systems were developed. First one was fabricated as 2 hydrophilic barrier layers, second one was made with both hydrophobic and hydrophilic layers. Third one consists two barrier layers which are hydrophobic in nature. The results depicted that the most attractive release profiles were achieved with 1st and 2nd type of matrices. In the first type, drug release mechanism was combination of swelling and erosion. The influence of viscosity and concentration of polymer on release surface was seen in this study. These factors ultimately control the diffusion path length as well as diffusion coefficient. These mechanical or chemical characters of polymers inherently change the geometry.

1.8 Tri-Layered Tablets: Tri-layered tablet is mainly composed of middle drug layer, which is covered with two polymeric or restrictive barrier layers. By incorporating drug in barrier layers can achieve various release profiles. Factors influencing the drug release from tri-layered systems are matrix erosion, concentration gradient, surface area of drug release. Drug Release Profiles Achievable by Triple-Layered Tablets: A triple-layered tablet can give immediate as well as sustained release of drug. An initial burst followed with a sustained or controlled release of drug. These release patterns are most useful in designing a dosage form for drugs having large min values and also have good therapeutic efficacy. The drug release profile of conventional tablet and Versa tab (patented technology) compared in figure 1.3.

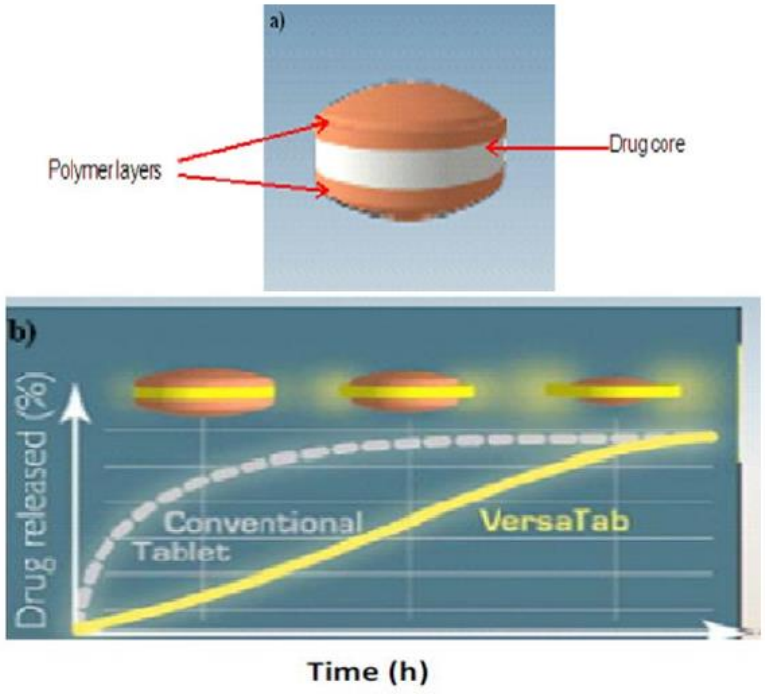

Figure 1.3: Drug release profiles of a conventional tablet and versatab (trilayer tablet)

The CR multi-layered tablet containing the drug, naproxen and its sodium salt developed and it includes delayed drug release layer containing naproxen and an 8 immediate drug release layer contains naproxen sodium. This tablet was designed to get a punctual therapeutic effect maintained for 24 hours. A multi-layer/tri-layered system that contains a sustained release core matrix of NSAID and two covering layers contain histamine (H2) receptor antagonist. Sustained release of the antagonist from first layer and a rapid release of H2 antagonist from second layer were achieved. So, this technique can be used to treat osteoarthritic patients who are more susceptible to GI adverse effects induced by a NSAID.

1.9 Selection of polymers in designing a controlled release formulation:

Polymers are basically natural or synthetic, high molecular weight macromolecules composed of repeating monomer units linked by covalent chemical bond. Classification of Polymers: Polymers are versatile in nature and few characters can be modifiable by using some chemical approaches. So, polymers can be classified in many aspects like source or characteristics. They can be classified as following on basis of source

Natural polymers: proteins - collagen, keratin, albumin etc. carbohydrates - starch, cellulose etc.

Synthetics polymers: poly ethylene oxide, poly-esters, poly-amides etc.

On basis of bio-response towards polymer

Non-biodegradable hydrophobic polymers: polyvinylchloride, polyethylene vinyl acetate **Biodegradable polymers:** polyglycolide, polylactic acid, polycaprolactone. Based on polymerisation method:

Addition polymers: alkene polymer ¬ Condensation polymers: polyester, polyamides etc. Based on heating:

Thermo plastic: - polyethylene, polypropylene, Teflon etc.

Thermo sets: - phenolic, urea resin etc.

Based on interaction with water

Hydrophilic polymers: Cellulose derivatives: Hydroxy ethyl cellulose, Hydroxypropyl methylcellulose (HPMC) 25, 100, 400, & 1500cps, Sodium carboxy methyl cellulose Methyl cellulose 400 & 4000cps.

Natural Non –cellulose and artificial polymers: Agar-agar, gums, alginates, Molasses, polysaccharides of mannose & Galactose, chitoson, modified starch.

Acrylate based Polymers: Carbopol Hydrophilic Matrices:

Hydrophilic matrices are compressed blends of drug and hydrophilic polymer(s). The general mechanism the release of drug from a hydrophilic matrix is hydration of tablet and form a viscous or mucilaginous gel barrier. The formed gel fills the gaps and reduces porosity of the tablet leads to retardation of the entry of medium. The conc. of the polymer in the hydrated gel layer is about 90% w/w of the core. Drug release rapidly occurs from the surface by diffusion/erosion or from the hydrated gel layer.

Approaches for development of extended-release systems containing poorly soluble and low bio-available drugs

The oral route is considered as a simplest and traditional route of drug administration. Not surprisingly, this route is complex and tough on possibly 50% of currently marketed drugs due to two reasons. Firstly, owing to their low solubility, high hydrophobicity and low permeability and secondly, they have to cross a number

of barriers to reach systemic circulation. Therefore, this makes the drug candidates poor bioavailable. Hence there is every need to produce such a formulation which is suitable to improve the drug solubility as well as bioavailability.

One such idea to solve these problems is to produce lipid systems. These are at present in investigation to enhance bioavailability of BCS class -II and IV drug. Lipid formulations are a simple approach to administer the drugs with vehicles like oils, surfactants, liposomes, emulsions/ dispersions, solid lipid nanoparticles and SEDDS. Lack of knowledge on these systems as to how they function to improve solubility and bioavailability makes them less commercia l.

A recent popular approach called SEDDS have shown reasonably great promise in improving oral bioavailability of hydrophobic drugs and a success in offering inherent stability. In brief SEDDS formulation involves solubilising drug(s) in oil(s) and then mixing/blending with other solubilising agents. Conventional SEDDS are normally in liquid form leading to some disadvantages like follows

- low stability
- low portability
- low drug loading
- cost of production being high and
- chance of drug precipitation
- GI irritation (surfactant level - (30-60%)

An alternative approach is to solidify the conventional liquid SEDDS into powders or nanoparticles so as to increase the choices of dosage forms like SE tablets, SE pellets etc..

The advantages of SEDDS are as follows

- Improved solubility and enhanced bioavailability
- Low production cost
- Ease of process control,
- Highly stable and give reproducible results
- More patient compliance

SEDDS are isotropic mixtures which emulsify with the physiological fluid in GI environment producing droplets ranging from few (SMEDDS) to hundred nanometres (SEDDS). For example, Humberstone et al., 1997, developed SEDDS formulation loaded with Tipranavir (TPV), an anti-HIV with a resultant double increase in bioavailability in rats. The bioavailability of coenzyme Q10 was increased to 150% when formulated as SEDDS using polyglycolyzed glycerides explained by Kommuru et al., 2001. A number of examples demonstrate enhanced bioavailability of drug candidates when formulated as SEDDS.

Studies have been carried out for evaluating a set of SEDDS formulations and their definite functions and also characteristic potential to emulsify explained by Gao et al., 2003 and Kang et al., 2004. Enhanced quantitative interpretation of how properties of a certain self-emulsifying formulation communicate with the bioenvironment in the body to allow oral absorption could assist in modifying SEDDS formulation for improving bioavailability. In spite of the fact that a remarkable quantity of information is present in some other fields regarding the function of emulsions, pharmaceutical formulations have not been predominantly studied concerning the basic functions of emulsion and their properties. Specific analysis and optimization of the function of emulsions covering a large set of formulation parameters by virtue of their experimental design has not been extensively explored. The impact of different formulation components on the performance of SEDDS in 26 vivo is defectively explained. Various types of oils and their characteristics with various surfactants combined at different ratios may affect the performance in-vivo.

Presently there is no information available for formulating a drug with definite properties in SEDDS. Hence it is obligatory to examine the influence of various components with a quantitative and statistical model and analysed approach. An additional fact is that there is a little information about the mechanism of how SEDDS work to increase the general oral bioavailability of a lipophilic drug. Proposed mechanisms accounting for the functioning of SEDDS in the GI tract environment involves increased dissolution of drug in the lumen

GI contents which is due to variations in the composition and character of colloidal environment of the GI tract fluid and improved absorption of the drug due to increased permeability (for example opening of tight junctions or any mechanical or chemical changes at cellular level) and lymphatic transport. Suggested mechanism is that the extent of the lipid components is being digested which affects the drug solubilisation in the lumen. During the process of degradation by the digestive enzymes, the rate of drug release from the oil droplets is another proposed mechanism.

Therefore, it is obligatory to explore the rate at which the self-emulsifying lipidic formulation is digested, the release rate in addition to extent of drug transport across the intestinal monolayer to account for the functioning of the formulation in the GI tract. Knowledge from these mechanisms can be used as quantitative expressions that can be assimilated into pharmacokinetic models to predict the oral bioavailability. To specify and elaborate the challenges involved in the oral delivery of lipophilic drugs it is important to demonstrate an overview of the present technologies. Oral delivery of lipophilic drugs: Around 40% of new APIs are lipophilic, showing complications in attaining bioavailability with oral formulations.

The factors responsible for poor oral absorption of lipophilic drugs are its slow or incomplete dissolution or precipitation in the GI lumen. As a result, lipophilic drugs need to be administered in such a delivery system that minimizes the complications of bioavailability. Oral DDS for hydrophobic drugs: According to BCS, class -II & class -IV drugs have poor aqueous solubility. Hence these drugs are eliminated from the biological environment either as metabolites or unchanged forms. For increasing the oral bioavailability of

a lipophilic drug one usual approach is to use a carrier that can simply increase the amount and time of dispersed drug in the GI fluid. Therefore, to increase the amount of drug that is administered orally and to minimize drug precipitation or elimination, excipients should be selected that can increase the solubilization of lipophilic drugs.

The drug delivery systems that can modify solubilization of the drug in-vivo will be explored in the successive sections. Overview of technologies: Excipients (as mentioned above) are used as solubilising agents in oral dosage forms. They can be pH modifiers, surfactants, water soluble and insoluble organic solvents, triglycerides (medium chain), phospholipids, cyclodextrins etc. Solid dosage forms like tablets and capsules cover a major part of trade.

Despite that, there are liquid oral formulations such as solutions or syrups that are filled into capsules (both soft and hard gelatin). Lipophilic drugs can be solubilised in both water-soluble organic solvent and also solvent mixtures containing both aqueous and organic solvents. Commercially accessible organic solvents are ethanol, propylene glycol, glycerine, PEG 400, non-ionic surfactants etc. For example, an HIV protease inhibitor, ritonavir has aqueous solubility of 1µg/ml with two weak basic groups of low pKa values 1.8 and 2.6 limiting the use of a pH modifier solvent with the drug in the formulations. Another approach for improving solubilisation of lipophilic drugs include the use of water insoluble solvents such as oils like hydrogenated soyabean oil, peanut oil, oleic acid, hydrogenated vegetable oils, MCT and LCT, beeswax and vitamin E etc. Usually, these types of solvents are used to encapsulate drugs in gelatine capsules.

CHAPTER 2

LITERATURE SURVEY

1. Marc Afilalo et al., (2013) conducted several studies to establish effective treatment with extended-release tapentadol dosage forms. The ER formulation of tapentadol i.e. 100 to 250mg once in a day is alleviate pains related to osteoarthritis, lower back and DPN and it shows equal effects to oxycodone CR systems i.e. 20-50mg orally once a day. Tapentadol ER treatment has more advantages than oxycodone CR like better gastrointestinal tolerability and compliance with therapy.
2. Nalini Vadivelu et al., (2011) have studied on Tapentadol extended release; as per preliminary trials formulation showed advantages above CR formulations of an opioid, improved GI tolerability, reduced vomiting and nausea sensation occur by oxycodone C.R. It is a broad-spectrum analgesic compared to opioid drug. Because of polymorphism, accumulation of drug, interactions of drugs alter PK profiles of tapentadol. Studies should not be conducted in hepatic and renal failure patients; pregnancy and older people. There is a need of testing in several pains associated in cancer, neuro and cancer related pains.
3. Varma et al., (2010) have developed losartan potassium SR matrices with hydrophilic polymers like HPMC K4M and Carbopol 934P. They concluded that the release rate was retarted by using such polymers.

4. Deshmukh et al., (2009) have made an attempt on the effect of hydrophilic gums such as guar gum verified in polymeric marices containing metoprolol succinate and it was found that release process was lowered with raise in polymer level.
5. Larsson et al., (2009) has investigated the critical polymer properties of HPMC matrix tablets for swelling and polymer release. On basis of the study, HPMC matrices were characterized chemically and chemically and interrelated with unloaded HPMC matrices. Several factors like MW, rheological behaviour and gyration were adjusted in specific range, it results weak interrelation beween release of polymer and swelling.
6. Regina Kleinert et al., (2008) studied on efficacy of TAP with a single dose in post operative pain. Several clinical reports were also suggested same. As per heir 46 suggestions, more effective, CNS acting having less side effects with early onset of action. In case of successive dosings, everything is to be evaluated.
7. Ravi et al., (2008) developed oral controlled release (CR) matrix tablets of zidovudine (AZT) using HPMC, EC and cabopol-971P. Polymer level, ratio and hardness affects the rate of drug release.
8. Tzschentke et al., (2007) in their review explained the use of Tapentadol as an analgesic with a dual mechanism. It shows moderate activity as MOR agonist and potent NE reuptake inhibitor. Metabolic activation is not necessary for active form of tapentadol. Because of dual mechanism, tapentadol is an efficient broad-spectrum analgesic can be used for acute and chronic pain models with an improved tolerability.
9. Varshosaz et al., (2006) developed tapentadol SR matrices using guar and xanthan gums or combination with HPMC. Matrices prepared with xantham gum retards drug release in a great way but when it is mixed with HPMC showed more retardation capacity.
10. Sandip et al., (2003) prepared tramadol matrices using both hydrophilic and hydrophobic materials. In this work, level of polymer HPMC and HCO, EC on drug release was thoroughly studies but interestingly results reveals the negative effect of waxes on drug release was seen and not completed in 12 hours.
11. Silvina et al., (2002) have formulated diclofenac - HPMC matrices and studied relation with MCC, lactose and starch levels to achieve 00 release. All factors showed significant effect on rate and order of drug release.
12. Kommuru et al., (2001) have formulated coenzyme Q10 self-emulsifying systems using poly glycolyzed glycerides as an emulsifying agent and estimated its bioavailability in beagle dogs. Lipid system was developed by using Captex-200 and Myvacet9-45 as oil phase and Labrasol and Labrafac CM-10 as emulsifying agents and Lauroglycol is used as co-surfactant. Total 4 formulaion were developed with fixed drug level i.e. 5.66% w/w. The results showed positive context in improvement of bioavailability of Co-Q10 and proved that SEDDS are promising solution for poorly soluble and available drugs.
13. Bok Ki Kang et al., (2004) developed SMEDDS to enhance bioavailability of simvastatin which is a poorly soluble in nature. The solubility of simvastatin was estimated and self-emulsification region was determined by constructing pseudo ternary phase diagrams. Laser diffraction method used to

determine globule size and distribution patterns. Drug release studies showed a great effect of SEDDS in dissolution of simavastatin and it also more than simple tablet formulation. The bioavailability of simavasatin found to increase by 1.5folds when compared with conventional formulation.

14. Wei wu et al., (2006) developed SMEDDS for silymarin to enhance oral bioavailability. Drug release studies were done by dialysis method. Solution, suspension and SMEDDS containing silybin were distinguished with respect of pharmacokinetic and dynamic properties in rabbits. Drug plasma concentrations were analysed by using Bio-Analytical technique by RP-HPLC. Both suspension and solution were failed in absorption studies by showing negligible amounts of drug in blood even after 4 hours upon oral administration. But SMEDDS showed 2 Cmax values which is a feature of enterohepatic circulation.
15. Patel et al., (2007) have made an attempt to develop SMEDDS of 10 poorly soluble drugs varying physicochemical parameters. solubility of drugs estimated in long and medium chain fatty acid containing oils and emulsifying agents having HLB < 10 and HLB > 12. Globule size and surface charge were analysed in presence and absence of drug. From results, it was observed that all formulations given less globule size and not affected by dispersion medium properties but zeta potential was varied with loaded drugs. Drug release studies were performed by reverse mode dialysis technique which is par than conventional technique and results were interesting and proved formation of miscelles during dispersion. Dissolution studies stated that the solubilization capacity of SEDDS will be changed from acidic to above neutral pH. Finally, a conclusion was made that efficacy of the formulation is not only depends on components but also affected by loaded drugs.
16. Ahmed Abdulla et al., (2008) developed a pellet form of SE system for low soluble drugs. Based on preliminary trials, basic composition of SE system was selected as lipid phase consists a mixture of MCGs and solutol HS15. The pelletization was done by using extruder and spheronizer by mixing liquid SEDDS mixture with MCC. The formed pellets were evaluated for morphology and physical strength. USP-Physiological media was employed for dissolution studies to assess the effect of digestion of efficacy of the formulation. Finally, it was concluded that extrusion/spheronization is an appropriate method for production of SE pellets with greatest drug loading capacity and in other side efficacy of formulation was affected by digestion of formulation components.
17. Amit Kala et al., (2008) developed Nimodipine self -emulsifying drug delivery system which has showed globule size less than 180nm. Invitro drug release studies revealed that optimized SEDDS able to deliver total amount of drug without influence of pH of medium. A comparative study was done for drug in oil, suspension, micellar dispersion and SEDDS for determination of pharmacokinetic parameters in rabbits. Results showed that optimized formulation was effectively improved bioavailability of nimodipine compared to conventional system.
18. Eman Atef et al., (2008) developed SE system containing phenytoin and results were showed a positive outcome result and proved to be better than conventional system like tablet or marketed suspension.

19. Tao Yi et al., (2008) developed nimodipine SE system and evaluated is bioavailability in rabbits. Optimized SEDDS chiefly contains ethyl oleate as oil phase, Labrasol as co-surfactant and Cremophor RH40 as surfactant and liquid system is adsorbed on to dextran used as a solid carrier by using spray drying technique. Developed solid-SEDDS were characterized for solid state using Scanning electron microscopy, Differential canning Calometry and powder XRD. Results revealed that both liquid and solid SEDDS showed similar values of pharmacokinetic parameters like AUC and Cmax and they are 2.6 and 6.6 folds more than the conventional system. The results recommended that developed solid SEDDS was a promising alternative to solve the problems with liquid form of SEDDS.
20. Ying Chen et al., (2008) formulated a SE lipid formulation containing vinpocetine. The formulation was optimized with an oil phase-ethyl oleate 15%w/w, a surfactant – solutolHS-50%w/w, co-solvent – transcutolP-35%w/w. 49 From studies it was revealed that dissolution rate and BA (1.72 folds) of vinpocetine was greatly improved by SE lipid system compared to conventional formulation and also reveals that employing SMEDDS significantly improved vinpocetine absorption.
21. Pradeep Patil et al., (2009) have formulated SNES of felodipine for the improved the dissolution rate and extended release. Gelled SNES containing felodipine encased in a hydrophobic GEL coat can serve as an alternative for conventional extended-release formulations. They concluded that the formulation-dependent extended release of felodipine was achieved and the release profile of felodipine can be manipulated as required by varying the contents of release enhancer and gelling agent in such composition.
22. Vilasinee Hirunpanich et al., (2009) have studied the effect of various vehicles like ethyl docosahexaenoate on BA of cyclosporine-A. The combined oral administration of CsA and DHA-EE, exhibited large AUC and Cmax which were raised by 2folds but improvement was dose dependent. Formulation was optimized with a ratio 53.30/6.50/35.90/3.30 %w/w of alcohol, Tween20, H2O and DHA-EE. The system with DHA-ME showed average particle size of 50 nm and appears transparent and found to be stable and similar to the control formulation which was consists of vit-E. The relative BA (Fr) of drug with DHA ME showed 114.3% compared with Neoral, but BA (Fr) of drug with VE-ME was found to be only 60.50%. So, results recommended that DHA-EE improves BA of drugs which are poorly soluble in water.
23. Prabagar Balkrishnan et al., (2009) have developed dexiboprofen solid SEDDS using spray drying technique. In his study, Aerosil 200 was used as an adsorbant. Optimized solid-SEDDS subjected for SEM, DSC and XRD analysis. The surface morphology of powder particles was smooth and individual with retained self-dispersing abilities. From thermal as well as diffraction analysis, it was found that drug is homogeneously dispersed in molecular state. Dissolution studies reveled that drug is release rapidly with SE based formulation when compared to conventional one.
24. Thao Do Thi et al., (2009) developed a micro-emulsion forming system which comprises an active moiety; a lipophilic vehicle; a surfactant and co-surfactant 50 mixture. The composition also contains a polymeric matrix which is not ionised at GI conditions and added to self-emulsifying system. after administration of formulation orally this system was expected to form a gelled polymeric matrix and drug release was prolonged by diffusion process.

25. Vikas Agarwal et al., (2009) reported the effects of adsorbants on powder flow dynamics of developed solid SEDDS containing griseofulvin. Several adsorbants were used in this study, varying ratios of mixture of adsorbants like silicon dioxide, magnesium aluminium silicate and calcium silicate. Dissolution behavior of drug from solid-SEDDS was depending on the pore length in adsorbent as well as nuclei formation at the interface of oil/adsorbent. Drug release rate was directly proportional to surface area and not affected by type of an adsorbant.
26. Alaa Kassem et al., (2010) formulated self-nanoemulsified formulations of clotrimazole with different ratios of oleic acid, coconut oil, Tween20, PEG200, n butanol. They concluded that the globule size, turbidity parameter and rapid drug release were acceptable and increased bioavailability profile of clotrimazole was achieved.
27. Ashish Deshmukh et al., have developed SE system of Furosemide and Captex 500 and Cremophore EL used as oil and surfactant respectively in 20:80 ratio. Dissolution studies of SMEDDS form of Furosemide was compared to marketed formulation of furosemide i.e., LASIXO 40mg tablet, SMEDDS showed complete and faster pH independent dissolution profile, it suggesting that oral bioavailability of furosemide may improve the with reduced dose and variability.
28. Maulik Patel et al., (2010) did an attempt on formulation and evaluation of SMEDDS of lovastatin. Sunflower oil (oil), Acrysol K140 (surfactants), Capmul MCM C8 (co-surfactant) and PEG 400 (co-solvent) were used for the preparation of SMEDDS formulations by simple mixing at 40ºc. Droplet size was obtained between 25 to 40 nanometers. Drug release was up to 92% in one hour.
29. Vikrant Wankhade et al., (2010) developed SNEDDS containing Gliclazide. Drug solubility is determined in oil as well as surfactant phase as it is an important factor in development of lipid based system. Pseudo-ternary phase diagrams were constructed to screen surfactants and co-surfactants to know the emulsifying 51 ability for oils and nano emulsifying area also identified. Results depicted that optimized formulation gives nano emulsion with less than 55%w/w surfactant composition with a size range of 146.5nm. the dissolution was completed within 20min.
30. Bhupinder Singh et al., (2011) developed liquid self-nanoemulsified formulations of carvedilol using capmul PG8, cremophore EL, transcutol HP and evaluated for emulsifying parameters, size and drug release. Results showed positive outcome with respect to bioavailability.
31. Jing Han et al., (2011) have formulated and evaluated the in-vitro properties developed self -nano emulsifying system containing paclitaxel. Solubility and compatibility were tested to select proper compositions to develop SNEDDS. Ternary plots were developed to identify nano emulsifying region which is finalized as Cremophor EL-60%w/w, PEG400-20%w/w and isopropyl myristate 20%w/w. dissolution test reveals that drug release was almost completed in 4hrs from SNEDDS. Finally, it suggested that optimized SNEDDS was potential alternative to conventional formulation for oral administration.
32. Akhlaquer et al., (2012) have formulated sertraline loaded SNEDDS to surmount the troubles related with poor aqueous solubility, sensitive to liver enzymes. Primary selection was done to choose proper combinations of ingredients. An optimized one composed of oil (25.42 %), surfactant (49.72 %), and co-surfactant (24.86 %) was exhibited a mean globule size and percentage transmittance of 63.5 nm

and 82.43 %, respectively. TEM studies showed that particles were spherical in shape. A marked difference was observed with optimized formulation compared to drug suspension.

CHAPTER 3

3.1 OBJECTIVES OF THE WORK

Part 1: Development of carvedilol self-emulsifying extended-release drug delivery system Need for the study: Carvedilol is popularly employed drug in various cardiovascular disorders.

But the greatest drawback encountered with the conventional tablet dosage forms are,

• Low water solubility (0.01mg/ml in water)

• Extensive first pass metabolism

• Absolute oral bioavailability is ~ 15-25%

Hence to overcome these problems the drug may be designed in form solid self-emulsifying dosage form to improve the bioavailability by augmenting its dissolution and bypassing hepatic first-pass effect.

3.2 Aim

The aim of the present study was to prepare and evaluate solid self-emulsifying drug delivery of Carvedilol by spray drying technique to improve dissolution and bioavailability.

3.3 Objective

The objective of current work was to design solid self-emulsifying dosage form of carvedilol by taking into consideration it's physical, chemical and pharmacokinetic properties and was proposed to investigate the following:

1. To carry out preformulation studies such as solubility, method development.

2. To characterize liquid SEDDS

3. To prepare solid SEDDS by spray drying method

4. Development of SR matrices.

3.4 Plan of Work

The plan of work for this study was designed in such a way that to get a stable and efficient formulation.

The investigation essentially consists of the following steps:

• Solubility studies

. • Selection of excipients.

• Development of UV method for the estimation of carvedilol

• API – excipients Compatibility studies.

- Preparation of liquid SEDDS.
- Determination of globule size and distribution
- Determination of zeta potential
- Measurement of emulsification time.
- Preparation of solid SEDDS by spray drying technique
- Optimization studies
- Invitro dissolution studies.
- Release kinetics.

CHAPTER 4

MATERIALS AND METHODS

4.1 List of Materials used:

Table 4.1: List of Materials used.

S.No.	Material	Source
1.	Carvedilol	Gift sample from Dr. Reddys laboratories
2.	Capryol PGMC	Gattefosse
3.	Captex 355	Abitech corporation
4.	Capmul GMO 50	Abitech corporation
5.	Oleic acid	s.d. Fine chemicals
6.	Lauroglycol 90	Gattefosse
7.	Labrafil M 2125 CS	Gattefosse
8.	Gelucire 44/14	Gattefosse
9.	Cremophor EL	Gattefosse
10.	Cremophor RH 40	Gattefosse
11.	Tween 20	s.d. Fine chemicals
12.	polyethyleneglycol	s.d. Fine chemicals
13.	propyleneglycol	s.d. Fine chemicals
14.	Transcutol P	Gattefosse
15.	Aerosil 200	Sri SJS Pharma
16.	Neusilin UFL2	AET Labs
17.	HPMC K200M	Dr. Reddys laboratories
18.	HPMCK100M	Dr. Reddys laboratories
19.	Talc	Qualikems fine che pvt Ltd
20.	Magnesium stearate	Sri SJS Pharma

4.1.1 Carvedilol

Description: Carvedilol is indicated for treatment of congestive heart failure (CHF) mainly acts by blocking alpha-1, beta-1 and beta-2 adrenergic receptors.

Chemical name: [3-(9H-carbazol-4-yloxy)-2-hydroxypropyl] [2-(2methoxyphenoxy) ethyl] amine

Structure:

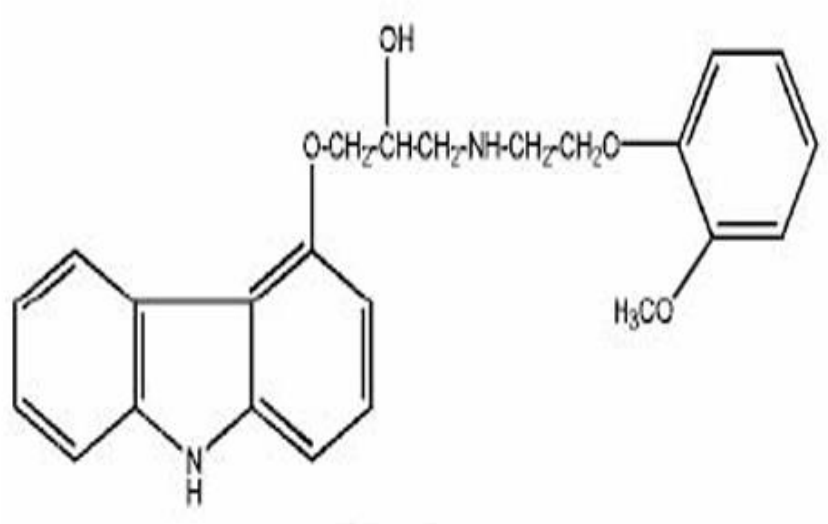

Fig 4.1: Structure of carvedilol

Molecular formula: C24H26N2O4

MW: 406.5

state: Solid

Solubility: 0.01mg/ml and 22.7mg/ml in water and ethanol respectively

Melting point: 114.5 ·C

Indications: used to treat mild-moderate heart failure (myopathic or ischemic)

Mechanism of action: Carvedilol is subsisted as a racemic mixture i.e. R and S forms. R (-) forms show beta receptor blocking activity (nonselective) and S (-) form shows Adreno receptor blocking activity. It reduces heart rate, contractility and vascular resistance as well as myocardial O2 demand.

Pharmacokinetics Absorption: It is rapidly absorbed orally but bioavailability is only 15-25%.

Distribution Volume of distribution: 115 L

Protein Binding: >98%

Metabolism: Liver metabolism

Excretion: very less quantity excreted in urine

T1/2: 7-10 hours

4.2 Equipment's used

Table 4.2: List of Equipment's used.

Equipment name	Manufacturer	Model
Digital weighing balance	Shimadzu	AY220
Rotary tablet machine	Ridhi pharma	--
Dissolution test apparatus-II	Electrolab	TDT-06 T
Digital pH meter	Analab	PHCAL10
UV-Spectrophotometer	Elico	SL 159
Fourier transformer infrared spectroscopy	Bruker	Alpha
HPLC	Waters	2489
Zetasizer	Malvern	ZS90
Spray dryer	Techno Search	SPD-D-111

4.3 METHODOLOGY

Solvent Development

Solvent / Medium

Methanol

(alternatively: methanol: water, pH 6.8 phosphate buffer, or 0.1 N HCl depending on study)

λmax (Maximum Absorption)

241 nm (most commonly reported for carvedilol in methanol)

4.3 Preparation of Standard Solutions

Stock Solution

- Weigh **10 mg of carvedilol**
- Dissolve in methanol and make up to **100 mL**
- Concentration = **100 µg/mL**

Table 4.3: Readings of standard curve of Carvedilol.

Concentration (µg/mL)	Absorbance (at 241 nm)
2	**0.112**
4	**0.225**
6	**0.336**
8	**0.447**
10	**0.558**

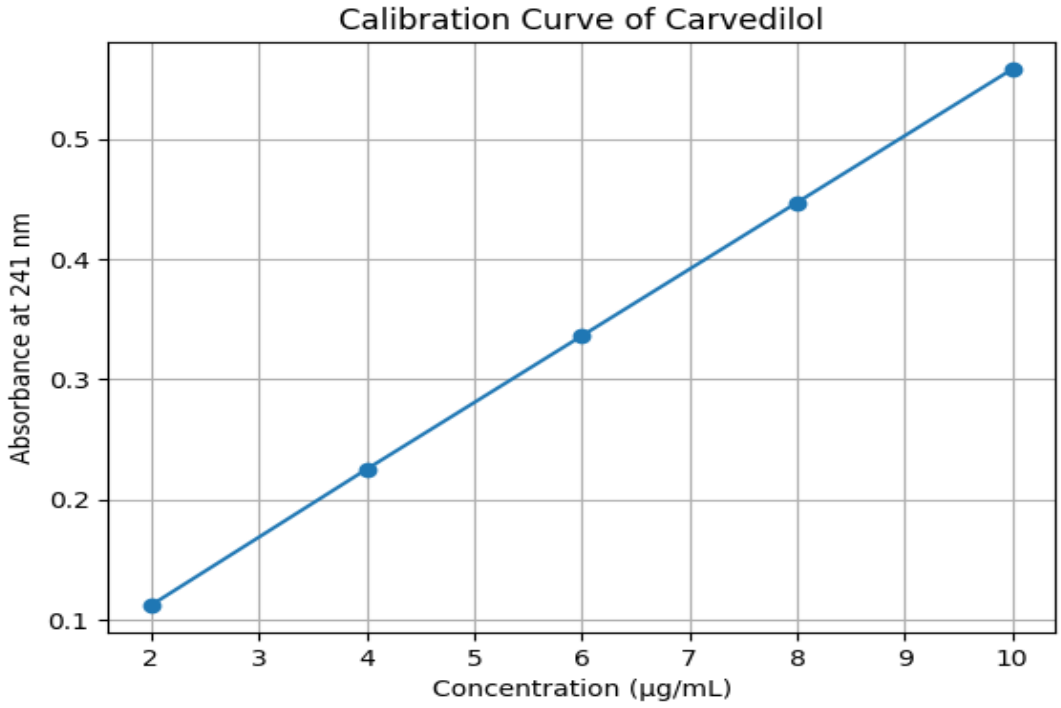

Figure 4.2: Calliberation curve of Carvedilol.

Calibration Curve

- **X-axis:** Concentration (µg/mL)
- **Y-axis:** Absorbance
- A straight line should be obtained.

Regression Equation (Example)

$$A = 0.055C + 0.002$$

Where:

- A = Absorbance

- *C* = Concentration (µg/mL)

Correlation Coefficient

- **$R^2 \approx 0.999$** → indicates excellent linearity

4.4 IR spectra of carvedilol

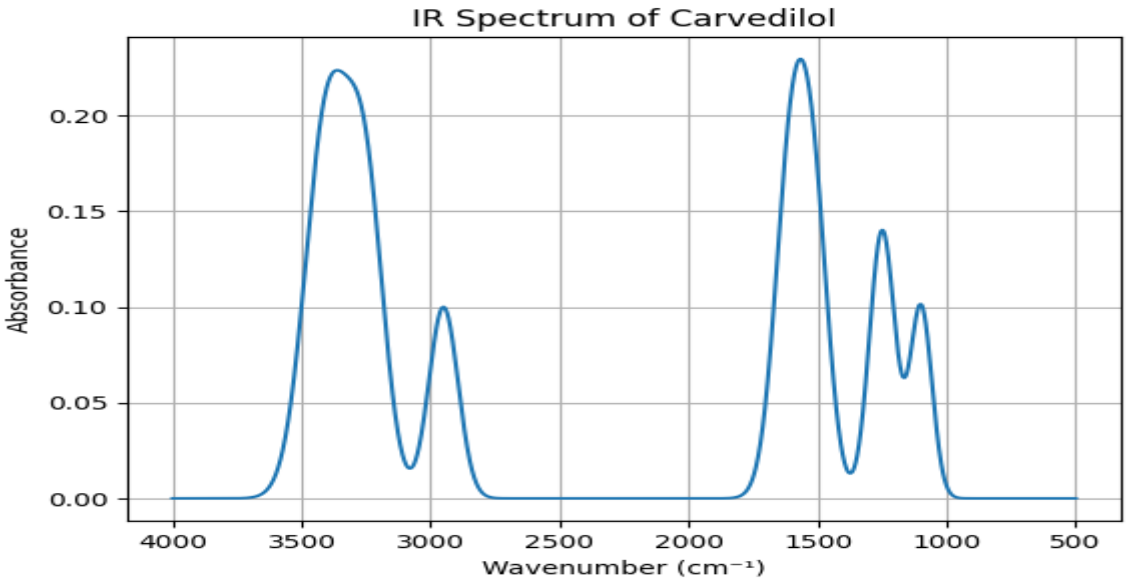

Figure 4.3: IR spectra of Carvedilol.

4.5: **Solubility**

Carvedilol is a poorly water-soluble drug and is classified as a **BCS Class II drug** (low solubility, high permeability).

Table 4.4: Solubility Profile of Carvedilol.

Solvent / Medium	**Solubility**
Water	Practically insoluble (< 0.1 mg/mL)
Methanol	Soluble
Ethanol	Soluble
Acetone	Freely soluble
Chloroform	Soluble
0.1 N HCl	Slightly soluble (pH-dependent)
Phosphate buffer pH 6.8	Poorly soluble

4.6 A. Liquid SEDDS Composition

Table 4.5: Formulation Table.

S.NO	DRUG/EXCIPIENTS	FUNCTION	QTY (%) F1	F2	F3
1.	Carvedilol	Drug	5	5	5
2.	Capryol PGMC	Oil phase	30	35	40
3.	Captex 355	Co-oil	20	22	24
4.	Cremophor RH 40	Surfactant	40	43	46
5.	Transcutol P	Co-surfactant	20	24	28
6.	Lauroglycol 90	Solubilizer	Q. S	Q. S	Q. S

(Oil: Surfactant: Co-surfactant = 1: 2: 1)

B. Solid SEDDS Tablet Composition

Table 4.6: Formulation Table.

S.NO	DRUG/EXCIPIENTS	FUNCTION	QTY (%) F1	F2	F3
1.	Liquid SEDDS	Drug-loaded system	Eq.to dose	Eq.to dose	Eq.to dose
2.	Neusilin UFL2	Adsorbent	150	152	154
3.	Aerosil 200	Glidant/adsorbent	20	21	22
4.	HPMC K200M	Binder/Matrix polymer	60	62	64
5.	HPMC K100M	Release modifier	40	43	46
6.	Talc	Lubricant	10	12	14
7.	Magnesium stearate	Lubricant	5	6	7

4.7 Procedure for Preparation

Step 1: Preparation of Liquid SEDDS

1. Accurately weigh **oil (Capryol PGMC, Captex 355)**.
2. Add **surfactant (Cremophor RH 40)** and mix thoroughly.

3. Add **co-surfactant (Transcutol P)**.
4. Add **Carvedilol** slowly with continuous stirring.
5. Sonicate or stir until a **clear isotropic mixture** is obtained.

Step 2: Preparation of Solid SEDDS (Adsorption Method)

1. Take **Neusilin UFL2** in a mortar.
2. Add liquid SEDDS dropwise.
3. Mix until a **free-flowing powder** is formed.
4. Add **Aerosil 200** to improve flow.

Step 3: Blending

1. Add **HPMC K200M and HPMC K100M**.
2. Mix uniformly for 10–15 minutes.
3. Add **Talc and Magnesium stearate**.
4. Perform final blending (2–3 min).

Step 4: Compression

1. Compress the blend using a **tablet compression machine**.
2. Use suitable punch size (e.g., 8–10 mm).
3. Adjust hardness (4–6 kg/cm²).

4.8 Evaluation Parameters

Pre-compression:

- Angle of repose
- Bulk density
- Carr's index

Post-compression:

- Hardness
- Friability
- Disintegration time
- Drug content
- In-vitro dissolution

CHAPTER 5

RESULT AND DISCUSSION

5.1 PRE-COMPRESSION PARAMETERS

5.2. Angle of Repose (θ)

- Allow powder to flow through a funnel forming a cone.
- Measure height (h) and radius (r).

Formula:

$$\theta = tan^{-1}\left(\frac{h}{r}\right)$$

Table 5.1: Angle of Repose Values.

S.NO	ANGLE	FLOW PROPERTY
1.	< 25°	Excellent
2.	25–30°	Good
3.	30–40°	Passable
4.	> 40°	Poor

Result: F3 Formulation was found to be 28 which shows good flowable property.

5.3 **Bulk Density (ρ b)**

Purpose: Packing ability of powder

Formula:

$$\rho_b = \frac{M}{V_b}$$

Where:

M = mass of powder

Vb = bulk volume

Result: The bulk density of powder(F3) was found to be

5.4 Tapped Density (ρt)

$$\rho_t = \frac{M}{V_t}$$

Where:

Vt = tapped volume

Result: The tapped density of powder(F3) was found to be

5.5 Carr's Index (%)

Purpose: Compressibility indicator

$$Carr's\ Index = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

Table 5.2: Carr's Index (%) Values.

S.NO	% COMPRESSIBILITY	FLOW
1.	5–15%	Excellent
2.	16–20%	Good
3.	21–25%	Fair
4.	> 25%	Flow

Result: The Carr's Index **(%)** of powder(F3) was found to be

5.6 POST-COMPRESSION PARAMETERS

5.7 Hardness

Purpose: Mechanical strength of tablets

Method: Monsanto/Pfizer hardness tester

Result: The **Hardness** of tablet (F3) was found to be 5.5kg/cm^2.

5.8 Friability

Purpose: Resistance to abrasion

Method:

- Use Roche friabilator
- 100 revolutions at 25 rpm

Formula:

$$\%F = \frac{W_1 - W_2}{W_1} \times 100$$

Result: The **Friability** of tablet (F3) was found to be 0.91%.

5.9 Disintegration Time

Preparation of Medium

- Use distilled water or simulated gastric fluid
- Maintain temperature at 37 ± 2°C

Sample Placement

- Place 6 tablets in the tubes of the basket assembly
- Add discs if required

Operation

- Immerse basket in medium
- Operate apparatus at 28–32 cycles per minute

Observation

- Observe tablets at regular intervals

End Point

- Tablet is considered disintegrated when:
- No solid mass remains except fragments of coating or matrix

Result: The **Disintegration Time** of tablet (F3) was found to be 1 hours 15 min.

5.10 In-vitro Dissolution

Apparatus: USP Type II (Paddle)

Dissolution medium:

First 2 hrs: 0.1 N HCl (pH 1.2)

Then: Phosphate buffer (pH 6.8)

Volume: 900 mL

Temperature: 37 ± 0.5°C

Rotation speed: 50–75 rpm (commonly 50 rpm)

1. Preparation of Medium

- Fill dissolution vessel with 900 mL of 0.1 N HCl
- Maintain temperature at 37°C

2. Tablet Placement

- Place one tablet in each vessel
- Start paddle rotation

3. Sampling Schedule

- Withdraw 5 mL samples at time intervals:
- 0.5, 1, 2, 4, 6, 8, 10, 12 hours
- Replace with equal volume of fresh medium

4. Medium Change (Extended Release)

- After 2 hours, replace medium with pH 6.8 phosphate buffer
  Simulates intestinal conditions

5. Analysis

- Filter samples (Whatman filter paper)
- Measure absorbance using UV spectrophotometer
- Λ max for Carvedilol ≈ 241nm.

6. Calculation

$$\%Drug\ Release = \frac{Amount\ of\ drug\ released}{Total\ drug} \times 100$$

Table 5.3: Dissolution Data table of ER SEDDS of Carvedilol tablets.

S.NO	F3 TIME(HOUR)	% DRUG RELEASED
2.	1	38%
3.	2	49%
4.	4	61%
5.	6	69%
6.	8	75%
7.	10	78%
8.	12	83%

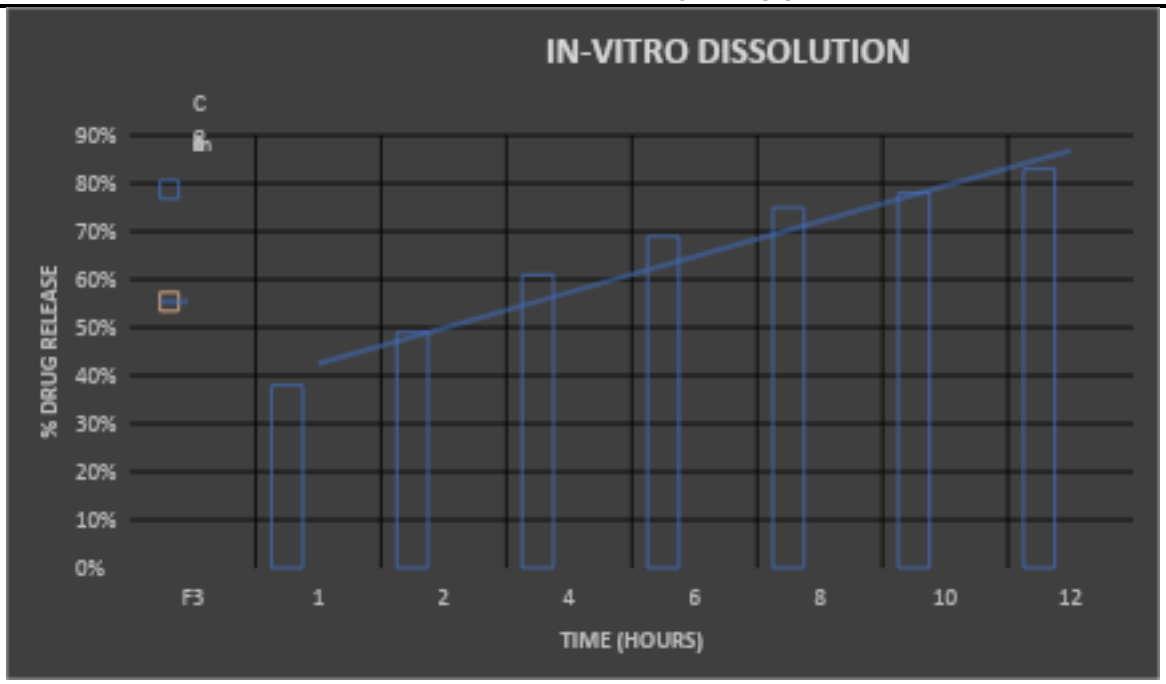

Figure 5.1: In-vitro Dissolution Profile of Carvedilol SEDDDS Tablets(F3).

5.11 Kinetic modals for Carvedilol SEDDDS Tablets(F3).

For, Carvedilol SEDDDS Tablets(F3) the drug release kinetics are usually analysed using standard mathematical models applied to dissolution data. The most common models used in microsphere studies are:

- **Zero-order kinetics**
- **First-order kinetics**
- **Higuchi diffusion model**
- **Korsmeyer–Peppas model**
- **Hixson–Crowell model**

These models help determine drug release mechanism (diffusion, erosion, or swelling).

Kinetic Models for **Carvedilol SEDDDS Tablets(F3).**

1. Zero-Order Kinetics

Zero-order kinetics describes a system where the drug release rate is constant and independent of drug concentration.

Equation

$Q_t = Q_0 + K_0 t$

Were

Q_t = amount of drug released at time t

Q0=Initial amount of drug

Ko=zero order rate constant

Graph: It shows graph between cumulative percentage drug release VS time.

Interpretation: Its straight line indicates control drug release.

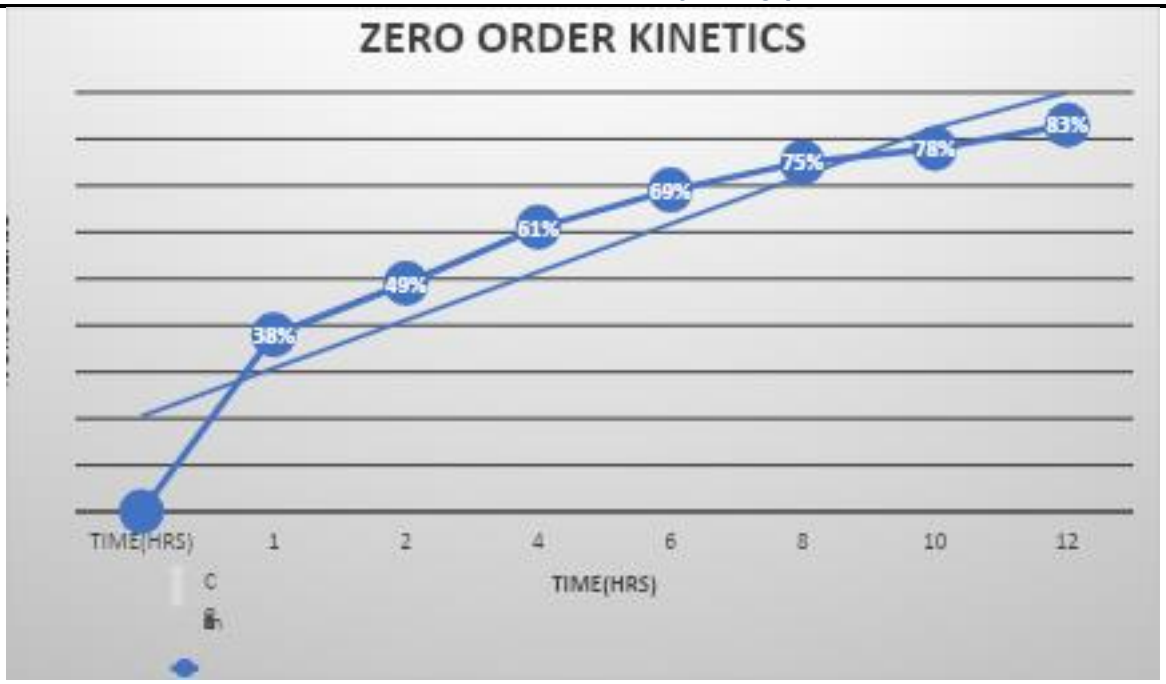

Figure 5.2: Zero order kinetics of F3.

2. First-Order Kinetics

In first-order kinetics, drug release rate depends on the remaining drug concentration in the dosage form.

Equation

\Log (Q_0 - Q_t) = \log Q_0 - \frac {K_1 t} {2.303}

Were

K_1 = first-order rate constant

Graph: Log % drug remaining vs time

Interpretation: Release rate decreases with time

Table 5.4: First order release kinetics data.

S.NO	TIME	% RELEASE(Q)	% REMAINING (100-Q)	LOG (100-Q)
1.	1	38%	62	1.792
2.	2	49%	51	1.708
3.	4	61%	39	1.591
4.	6	69%	31	1.491
5.	8	75%	25	1.398
6.	10	78%	22	1.342
7.	12	83%	17	1.230

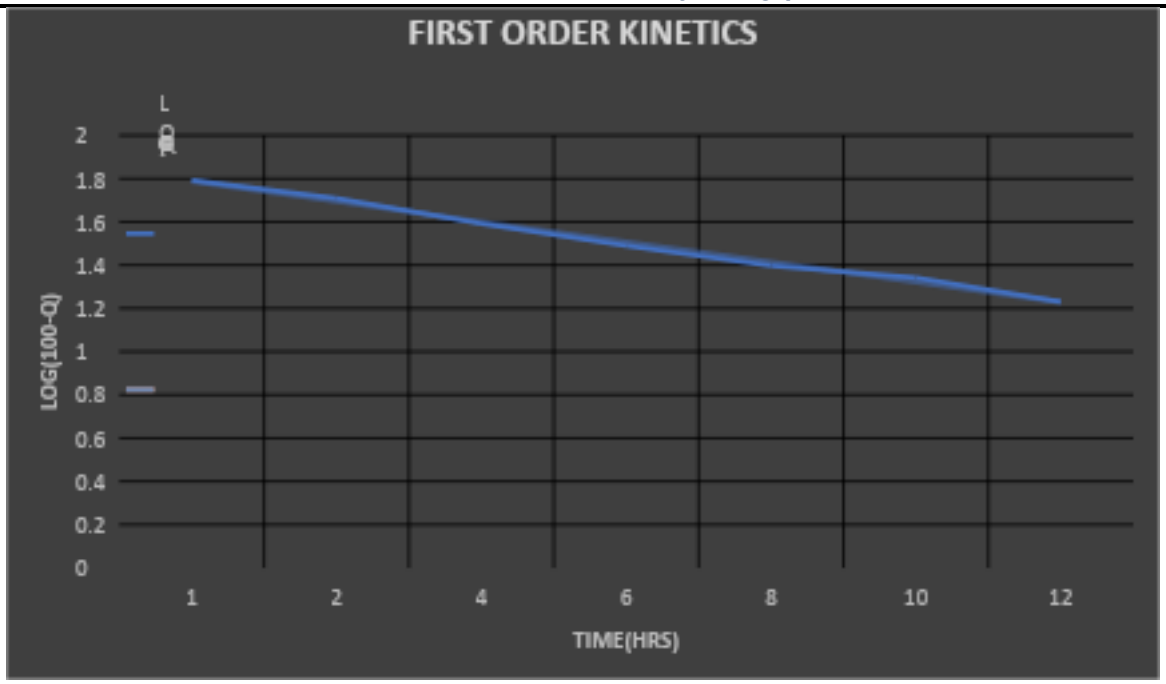

Figure 5.3: First order kinetics of F3.

3.Higuchi Model

The Higuchi model describes drug release by diffusion from a polymer matrix system.

Equation

Q = K_H t^ {1/2}

Where

Q = cumulative amount of drug released
K_H = Higuchi constant

Graph: Cumulative % drug release vs √time

Interpretation: Indicates diffusion-controlled release.

Table 5.5: Higuchi Model Data Release Kinetics.

S.NO	√T(TIME)	% REMAINING
1.	1.000	38%
2.	1.414	49%
3.	2.000	61%
4.	2.449	69%
5.	2.828	75%
6.	3.162	78%
7.	3.464	83%

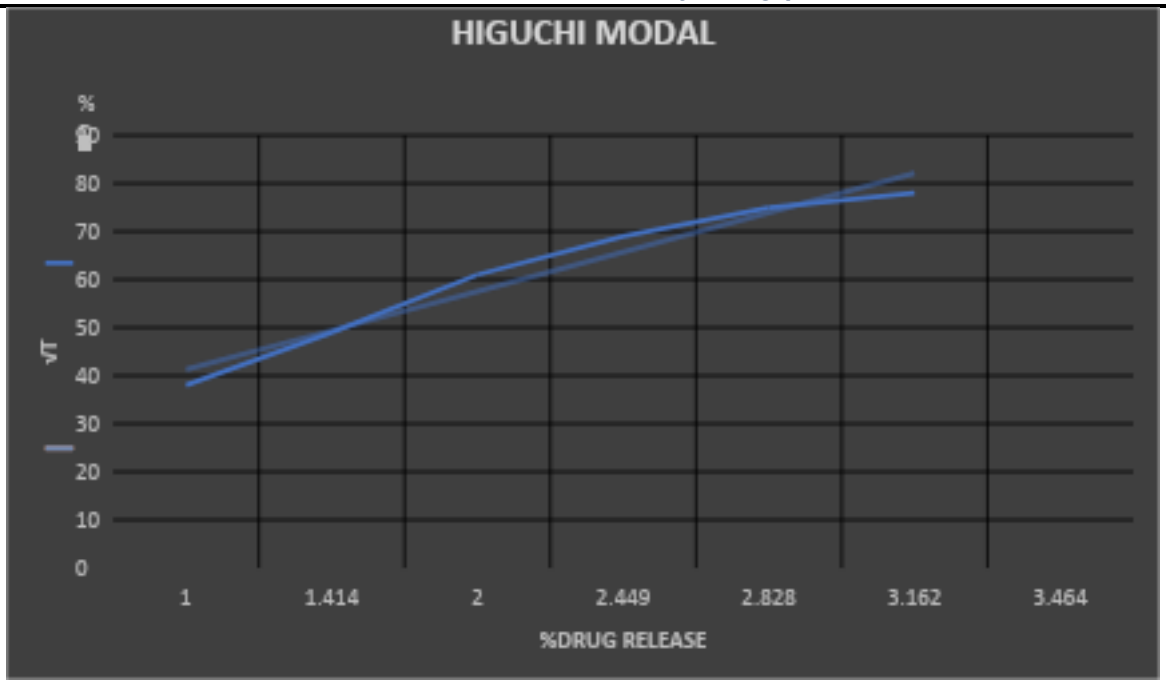

Figure 5.4: Higuchi Modal kinetics of F3.

4. Korsmeyer–Peppas Model

It is used when the drug release mechanism is complex or not well known.

Equation

\Frac {Mt} {M_\infty} = K t^n

Where

M_t/M_\infty = fraction of drug released
K = release constant
n = release exponent

Table 5.6: Interpretation of n.

N VALUE	MECHANISM
n ≤ 0.45	**Fickian diffusion**
0.45–0.89	**Non-Fickian diffusion**
0.89	**Case II transport**
>0.89	**Super Case II transport**

Table 5.7: Korsmeyer–Peppas Model release kinetics data.

S.NO	TIME	LOG (TIME)	% RELEASE	LOG(Q)
1.	1	0.000	38%	1.580
2.	2	0.301	49%	1.690
3.	4	0.602	61%	1.785
4.	6	0.778	69%	1.839

5.	8	0.903	75%	1.875
6.	10	1.000	78%	1.892
7.	12	1.079	83%	1.919

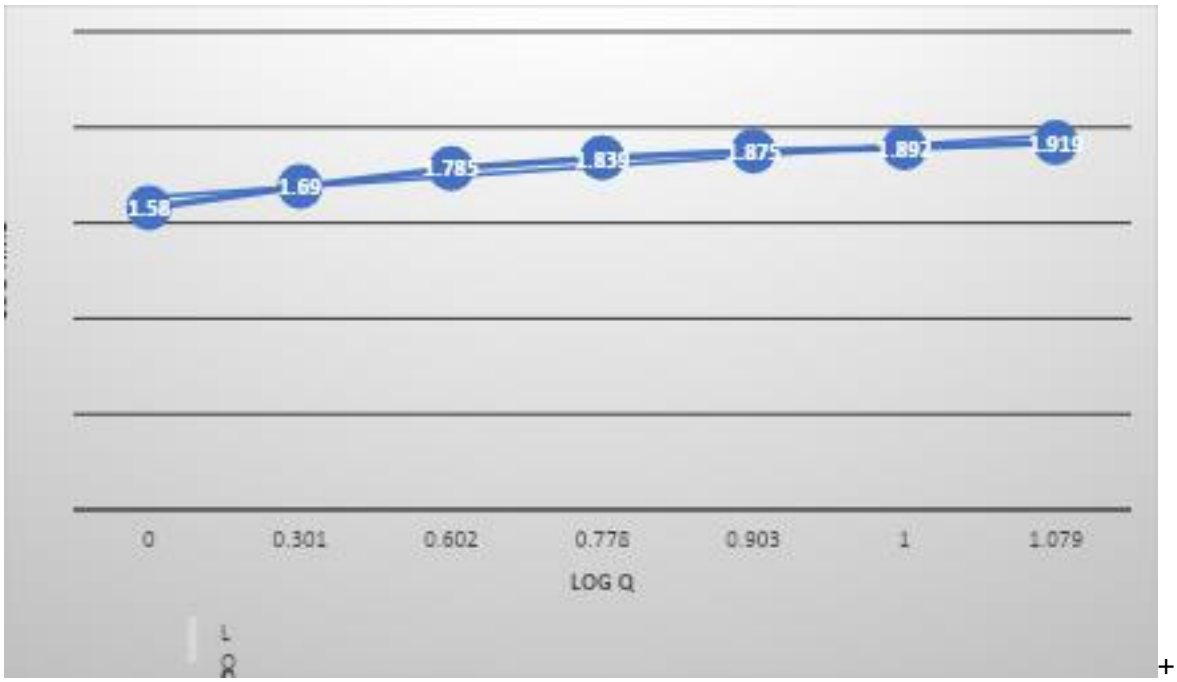

Figure 5.5: Korsmeyer–Peppas Model release kinetics data of F3.

5.Hixson–Crowell Model

It is Used when drug release occurs due to change in particle size and surface area.

Equation

Q_0^ {1/3} - Q_t^ {1/3} = K_{HC} t

Graph: Cube root of % drug remaining vs time

Interpretation: Indicates erosion or dissolution of microspheres

Table 5.8: Typical Result Pattern for Carvedilol ER Tablets.

Model	Mechanism	Graph
Zero order	**Constant release**	**% Release vs Time**
First order	**Concentration dependent**	**log % remaining vs Time**
Higuchi	**Diffusion**	**% Release vs √Time**
Koresmeyer-peppas	**Diffusion + polymer relaxation**	**Log % Release vs Log Time**
Hixson -=Crowell	**Surface erosion**	**Cube root plot**

Table 5.9: Hixson–Crowell Model Data Release Kinetics.

S.NO	TIME	% REMAINING (100−Q)	Cube Root (100−Q) ^ (1/3)
1.	1	62	3.96
2.	2	51	3.71
3.	4	39	3.39
4.	6	31	3.41
5.	8	25	2.92
6.	10	22	2.80
7.	12	17	2.57

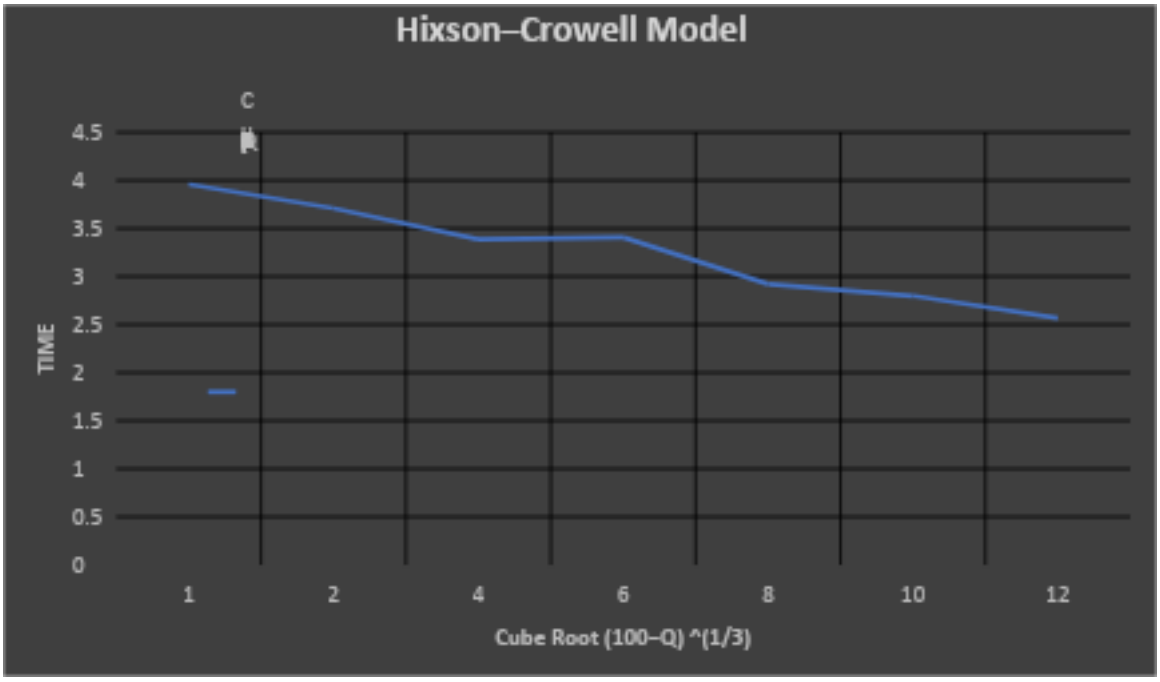

Figure 5.6: Hixson-Crowell Model release kinetics data of F3.

CHAPTER 6

RESULT AND DISCUSSION

The extended release (ER) solid self-emulsifying drug delivery system (SEDDS) tablets of Carvedilol were successfully prepared and evaluated for both pre-compression and post-compression parameters. Among all formulations, F3 showed the most satisfactory performance and was selected as the optimized formulation. The angle of repose for F3 was found to be 28°, indicating good flow properties of the powder blend, which ensured uniform die filling during compression. The bulk density and tapped density values suggested acceptable packing ability and compressibility of the formulation. Carr's Index further confirmed good flow behavior of the powder mixture, demonstrating suitability for tablet manufacturing.

Post-compression evaluation revealed that the tablets possessed adequate mechanical strength and integrity. The hardness of formulation F3 was found to be 5.5 kg/cm², indicating sufficient resistance to handling and transportation. Friability was observed to be 0.91%, which was within the pharmacopeial limit of less than 1%, confirming good resistance to abrasion. The disintegration time of 1 hour and 15 minutes indicated the sustained release nature of the matrix tablets prepared using HPMC K200M and HPMC K100M polymers.

In-vitro dissolution studies demonstrated a controlled and prolonged release profile of Carvedilol from the SEDDS tablets. The formulation released 38% drug within 1 hour and gradually extended the release up to 83% at 12 hours. This sustained release behavior may be attributed to the hydrophilic matrix system formed by HPMC polymers, which controlled drug diffusion and erosion. The dissolution profile confirmed the suitability of the formulation for extended drug delivery.

Drug release kinetic studies indicated that the release mechanism followed diffusion-controlled behavior. The Higuchi model showed good correlation, suggesting diffusion as the dominant release mechanism. Korsmeyer–Peppas analysis indicated a combination of diffusion and polymer relaxation mechanisms governing drug release. Overall, the optimized F3 formulation demonstrated satisfactory pharmaceutical properties, sustained drug release, and suitable release kinetics, making it a promising ER SEDDS formulation for Carvedilol delivery.

CHAPTER 7

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