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EVALUATION AND STABILITY STUDIES OFDEVELOPEDFORMULATION OF LIQUISOLID DRUG CARVEDILOL

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Abstract

This article raises the possibility that prolonged release devices can be manufactured by optimizing the Liquisolid technology is utilized to decrease the rate of pharmaceutical dissolution.. The present investigation utilized PEG 400 as the liquid medium for dispersing carvedilol. The liquid medicine was subsequently combined with a binary mixture of carrier-coating materials (Avicel PH-102) while being continuously mixed in a mortar. With the help of the tablet compression machine, the final mixture was compressed. There was an effort to determine the carvedilol release profile from liquisolid compacts by varying the drug content, loading factor, and heat treatment. A comparison was made between the rate of carvedilol release from matrix tablets and liquisolid compacts. Any changes in crystallinity or the creation of drug-excipient structures were studied using X-ray crystallography and dynamic scanning calorimetry (DSC). The retardation properties of carvedilol tablets made using the liquisolid process were found to be higher than those of matrix tablets. The results of this study show that hydroxypropyl methylcellulose (HPMC) has a significant impact in maintaining the drug release from liquisolid tablets. Additionally, the results demonstrated that wet granulation significantly affected the release rate of carvedilol from liquisolid compacts, decreasing the drug release rate. The drug's hardness and dissolving profile were unaffected by age, as demonstrated by the fact that the liquid-solid tablets were maintained at 400C and 75% relative humidity for three months. The bulk of the liquisolid formulations followed the zero-order release pattern, according to the kinetics investigations. Infrared spectroscopy and differential scanning calorimetry (DSC) ruled out the development of complexes or changes in crystallinity during the production of liquisolid formulations.

Keywords;Liquisolid compact, Carrier particle, Dispersion Technology, Solubilization, Crystallinity ect.

1. Introduction

The rate of dissolution in the gastrointestinal tract is widely used to limit the rate of oral absorption for the class II medication Carvedilol, which is poorly soluble but highly permeable.[1]Solubility and dissolving behavior, together with permeability, are important factors that determine the oral bioavailability of a medication. The development of pharmacological dosage forms is hindered by the poor solubility rate of these medications in water.[2]. Dissolving these medications in the gastrointestinal tract is a common method for controlling their oral absorption [3]. As a result, medication dispersion is crucial for absorption. Some methods for improving the solubility of drugs that are insoluble in water include decreasing the particle size, using a surfactant as a solubilizing agent, creating a drug complex with a hydrophilic carrier, taking a pro-drug stance, and finally, formulating the drug as a solid solution in order to decrease crystallinity and increase the solubility rate. Using Liquisolid compacts is the most promising approach for increasing dissolution[4].

Liquisolid technology, which is sometimes referred to as technique for the dispersion of liquids, is a formulation strategy that is utilized to improve the solubility and dissolution of pharmaceuticals that are not very water-soluble [5]. This process transforms a liquid drug or a drug that has been dissolved in a non-volatile liquid solvent into a powder that is either dry and free-flowing. In most cases, this procedure entails combining the drug solution with a powder combination that is comprised of a particular adsorbent and a coating substance. Among its many benefits are enhanced drug solubility, faster dissolution, more drug load, and more formulation design freedom [6].These characteristics make liquidsolid technology a promising option.

Patients with hypertension (high blood pressure), congestive heart failure (CHF), or left ventricular dysfunction (LVD) after a heart attack may find relief with the use of beta-blockers like carvedilol [7]. The action of carvedilol is based on its ability to inhibit the action of specific neurotransmitters known as beta-adrenergic receptors. Because of its non-selective beta-blocking action, it inhibits the beta-1 and beta-2 adrenergic receptors [8]. Additionally, it has the ability to inhibit alpha-1 receptors. Reduced cardiac workload, slower heart rate, and dilated blood vessels are the results of Carvedilol's ability to inhibit these receptors, which in turn lowers blood pressure and improves cardiac function. Carvedilol has a bioavailability of about 25–35% once it has been absorbed from the GI tract. Its reduced systemic availability is due to its substantial first-pass metabolism in the liver[9].The medicine binds well to proteins, especially albumin. It takes a lot of water to dissolve Carvedilol. Its solubility in water is low; at

25°C, it dissolves about 2.9 mg/mL, according to reports . Carvedilol is not easily soluble, which makes it difficult to create effective dosage forms. Carvedilol dosages range from 6.25 mg to 50 mg daily, tailor-made for each patient based on their unique medical needs. The current research aims to improve carvedilol's solubility through the creation of a liquisolid compact formulation. This formulation will then be compressed into tablet dosage form and tested for quality characteristics.

2. Liquisolid Technology provides a solution Form [10]

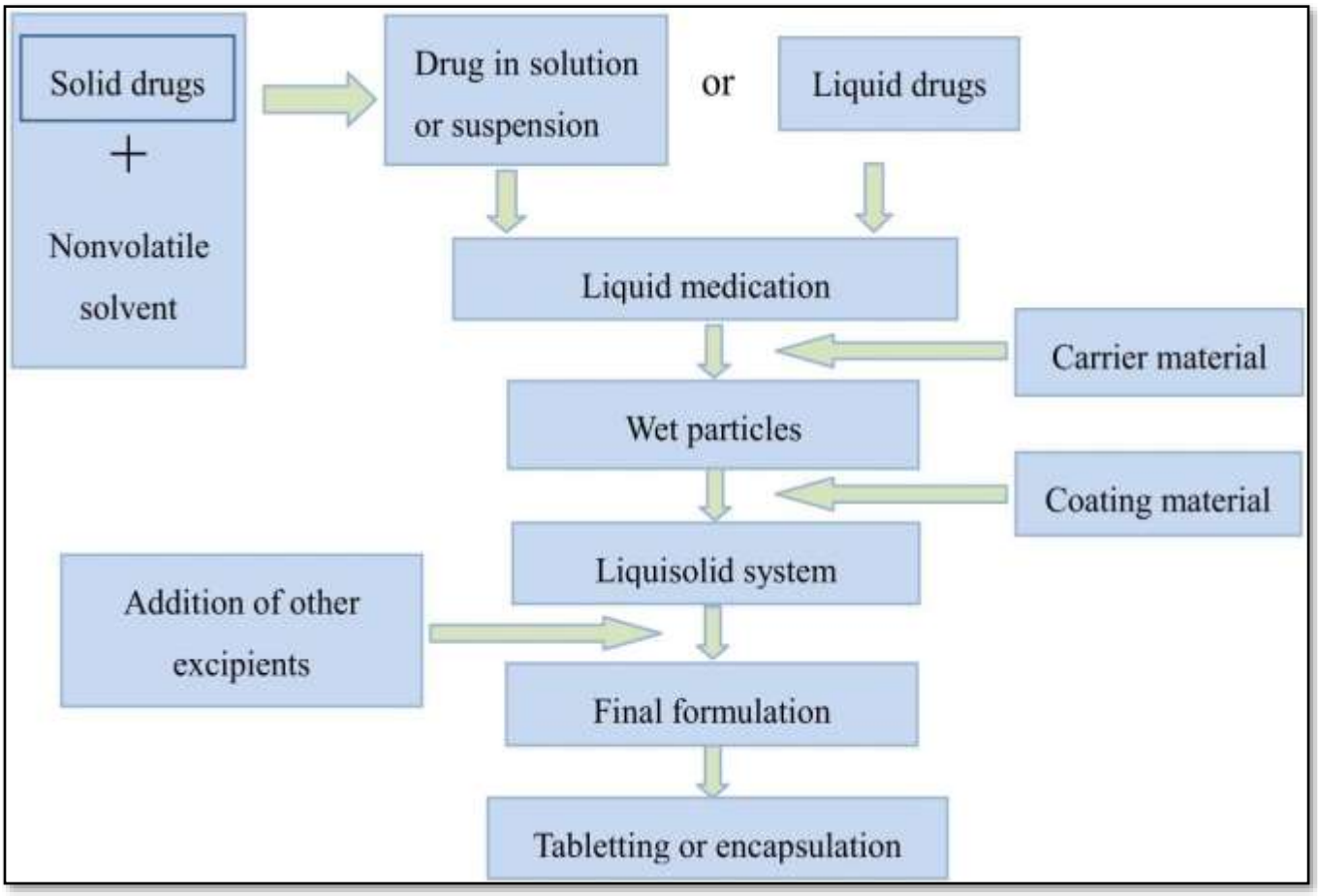


Fig.1 Flow chart represent the formulation of Liquisolid Technology

3. EvaluationofLiquisolid developedFormulation[11]

1. Appearance

Thetabletswerewhitetooffwhiteincolorandroundbiconvexinshape.Thetabletswereuncoatedandexhibitedplainsurface onbothsides.

2. Weight variationtest

Twentytabletsweretakenrandomly.Individualweightof20tabletswasfoundtobewithin5.0%oftheaverageweight.This means that the weight variation test was successful for these liquisolid pills.

3. Contentuniformitytest

The test was performedfor the optimized formulation and the average assay (initial) was foundto be 101%. The every individual tablet has an assay within the range of 94 to 105% (as perguidelines criterionisrangewithin85to115%ofthemeanvalue).

4. Friability,hardnessanddisintegrationoftablets

Hardness, friability and disintegration time of the formulated tablet is shown in table 1. Thetablets were found to have passed the acceptable hardness friability and disintegrationg time. Thetabletsshoweduniformityinweight,drugcontent,thicknessanddiameter.

Table1.Disintegration, hardness, and friability of both traditional and liquisolid tablets[12]

BatchCode	Crushingstrengthkg/cm^2	%Friability	Disintegrationtime(sec)
PEG	7.0	0.112	80
PG	6.5	0.198	70
Tween80	6.0	0.214	75
Cardivas	7.5	0.010	70
ConventionalTablet	7.5	0.240	60
R1	5.0	0.872	90
R2	6.5	0.215	76
R3	7.0	0.219	60
R4	7.0	0.115	84
R5	6.5	0.129	62

5. InvitroDissolution kineticsStudies of Liquisolid Formulation[13]

Liquisolid tablets containing PEG400 showed a relatively better release profile as comparedto Cardivas. Liquisolid tablets release carvedilol more than 75% within the first 10 min of thedissolution. The comparative dissolution profile of carvedilol in various formulations is shownin Fig.2. One possible explanation for the increased carvedilol release from PEG-based

tablets is that the medication is already present in a molecularly dispersed (solubilized) form. This might be because a large portion of the medication is already present in a molecularly distributed form in the PEG.

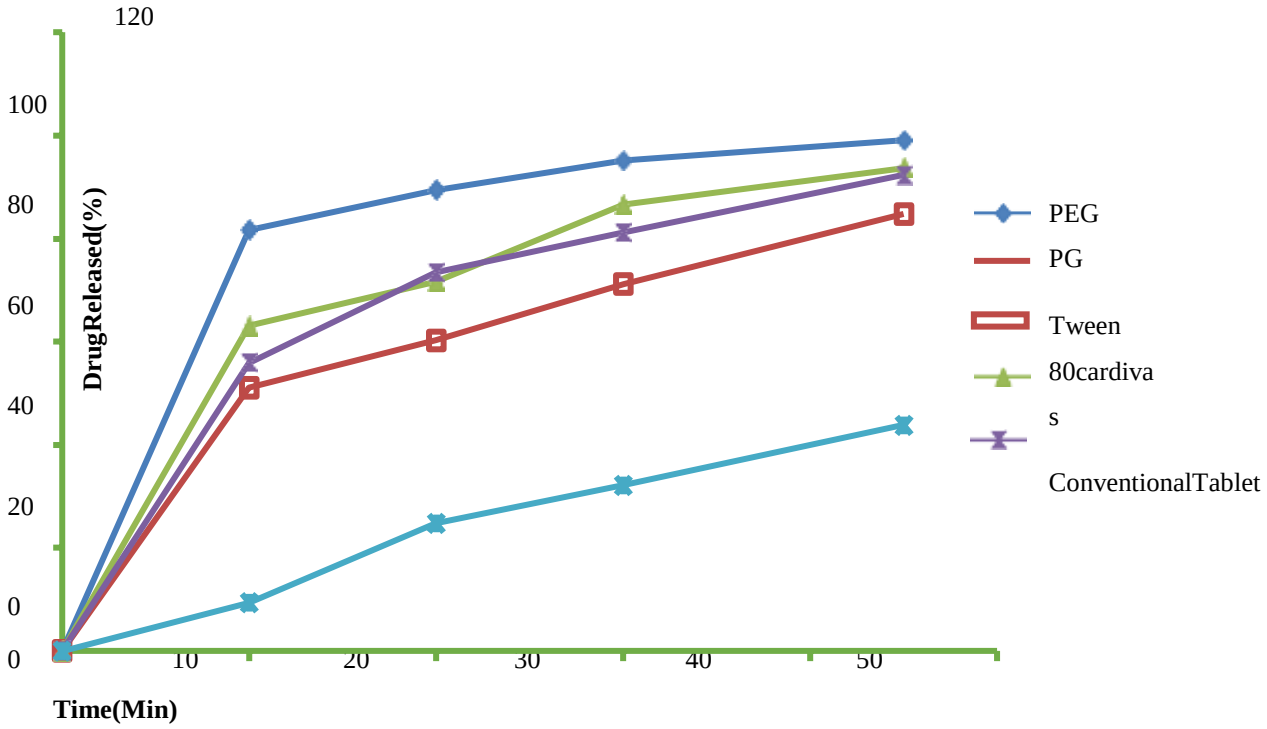


Fig.2.Carvedilol liquisolid pills dissolved in various liquids in vitro

In order to understand the effect of excipient ratio on dissolution profile of carvedilol thesebatches were planned. The blend used for compression into tablets was also evaluated for Carr'sindex.Thecorrespondingvalues ofCiare shownintable 3.

Table3.Civalues fordifferentliquisolidblends[14]

BatchCode	R1	R2	R3	R4	R5
Ci(%)	31.81	35.33	21.43	25	20

R1beinghighestamountofPEGcontainingtabletshowedhighdissolutionofcarvedilolhowever as expected the corresponding blend showed poor flow as exhibited by higher values ofCi. Therefore it is a prerequisite to understand that the tablet should contain higher quantity ofliquid (PEG) while maintaining decent flow of blend, to avoid weight variation andcontent nonuniformity. On the contrary R4 showed almost similar kind of dissolution profile with acceptableCi value. Thus there will be minimal chances of weigh variation and content non uniformity.ThereforeR4wasfinalizedasafinaloptimizedformulation.Thesameformulationwassubjectedtofurtherevaluationandstabilitystudies.

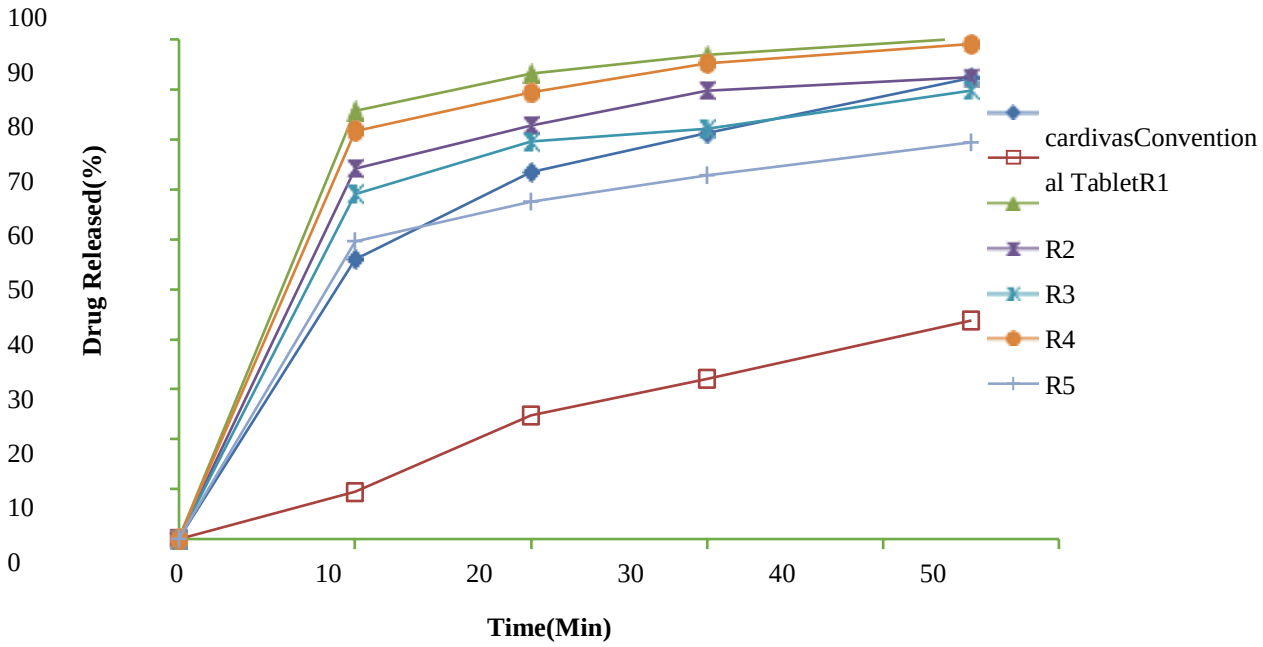
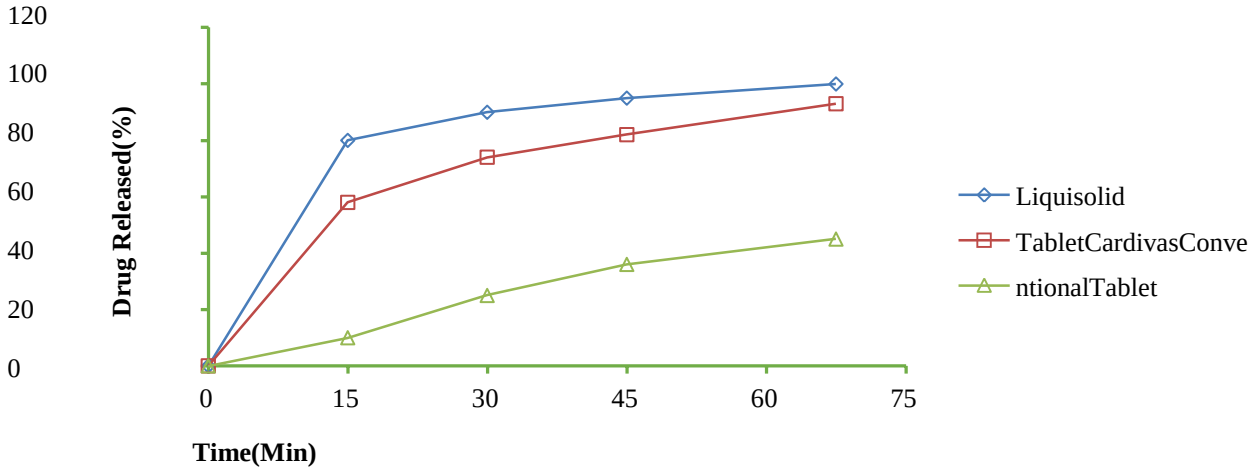


Fig. 3Effect ofcarriertocoatingmaterialratioondissolutionprofileofcarvedilol

6.InvitromultimediaDissolution of Liquisolid Formulation[15]

Theformulationisexpected tofacedifferentpHandenvironmental conditions.Therefore,dissolution studies were planned in dissolution media having different pH. Since the carvedilolhas pH dependant solubility it is expected to have a different release profile as shown in fig 4.16.Through thesestudiesitcleartounderstandthatthedevelopedformulationhasimproveddissolutionascomparedtoconventionalandmarketedone atallpH conditions.



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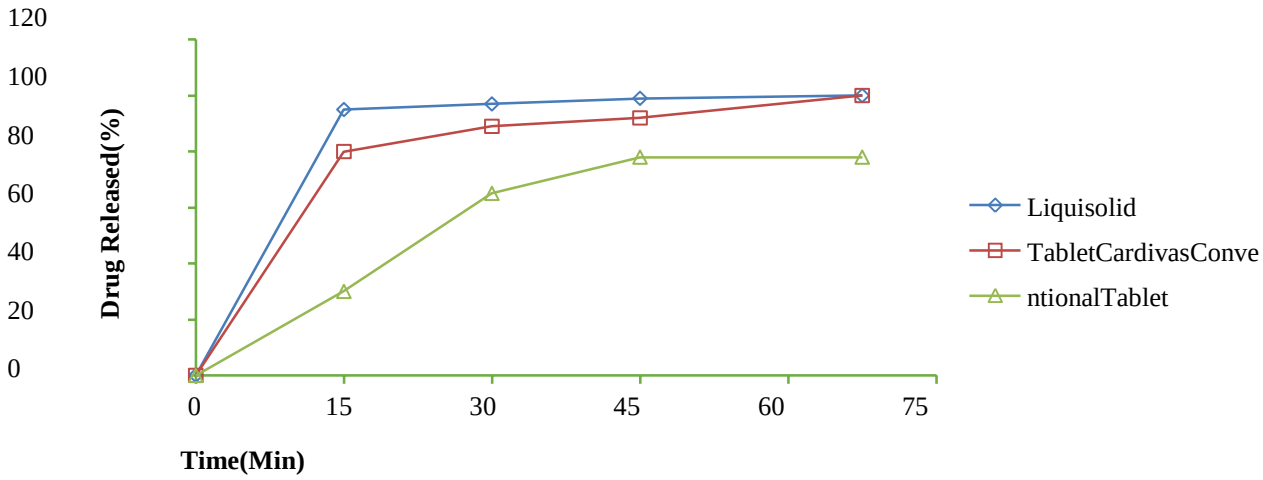

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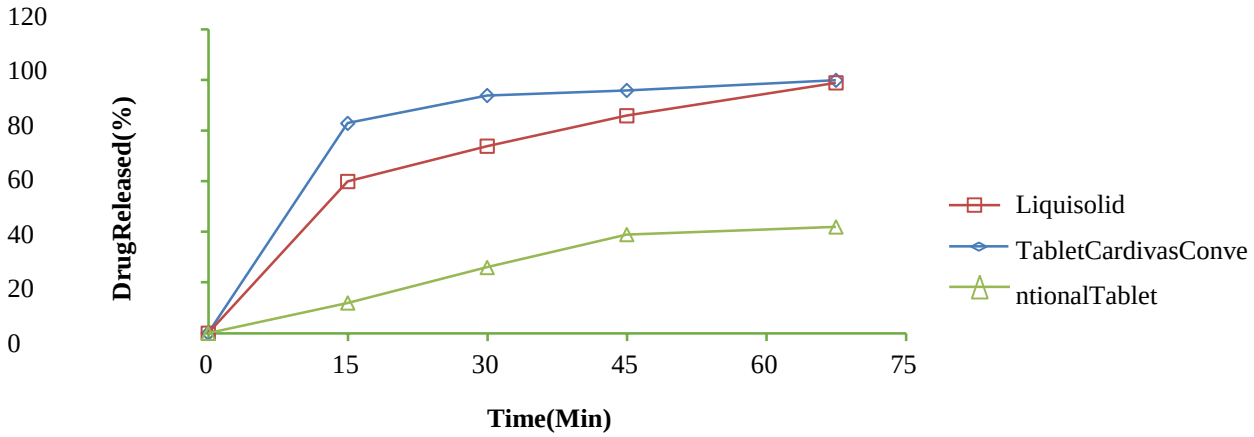


(c)

Fig 4.. Carvedilol release profiles in pH a: 1.2,b: 4.5 and c: 6.8

7 .Thermalmethod of analysis of Carvedilol Formulation[16,17]

Often, solubility of a substance is dependent on melting point via latent heat of fusion. Latentheat of fusion is the heat released by the substance during melting or fusion.A high latent heat of fusion and a low melting point are typical properties of crystals with strong bonds, whereas the opposite is true for those with weak links. In order to dissolve a drug crystal in a solvent, its structure has to be disrupted. Consequently, a low solubility is typically indicated by a high melting point.

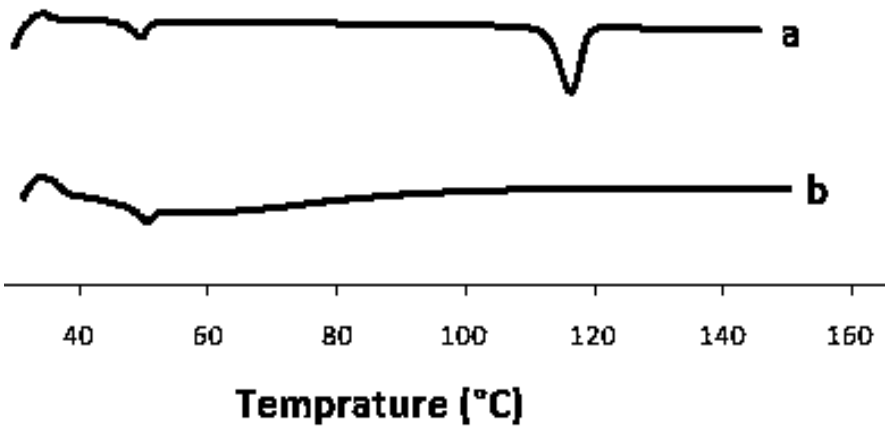


Fig. 5 DSCofa:neatcarvedilolandb:liquisolidformulation

For the purpose of predicting the physicochemical interaction between the formulation components, a DSC study was conducted, as seen in Figure 5. A sharp endothermic peak around 118^0C was observed in the thermogram of pure carvedilol, which is a result of the drug melting. Thus, indicating crystalline anhydrous state.Liquisolid formulation's DSC thermogram masked the characteristic melting peak of carvedilolindicating complete solubilization of carvedilol and interaction between carvedilol and excipients.

8. PowderedX-raydiffraction studies of Liquisolid Formulation[18,19]

Fig.6revealedxraydiffractionpatternofneatcarvedilolandliquisolidformulation.It is possible that the variation in relative integrated intensities of the peaks observed in the two samples is due to the interaction between carvedilol and PEG 400.Thepercentcrystallinityforcarvedilolandliquisolidformulation(R4)wasfoundtobe34.4and 6.4respectively.

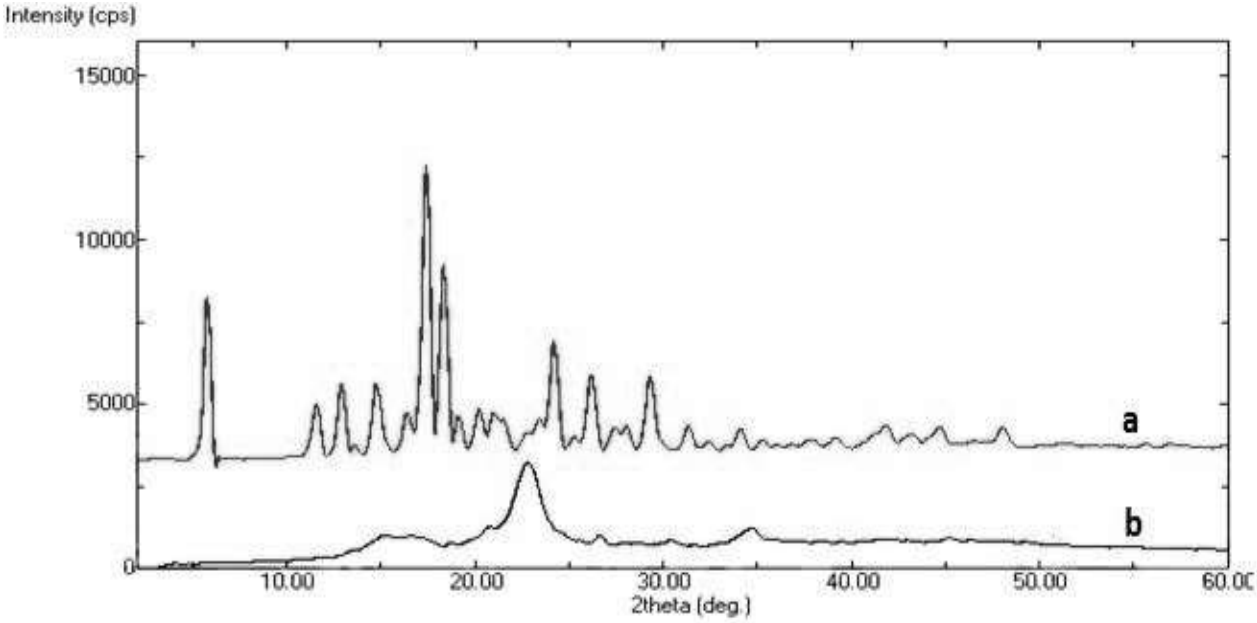


Fig.6. XRDofa:neatcarvediloland b:liquisolidtablet

4.Stabilitystudies of Carvedilol Liquisolid Formulation[20]

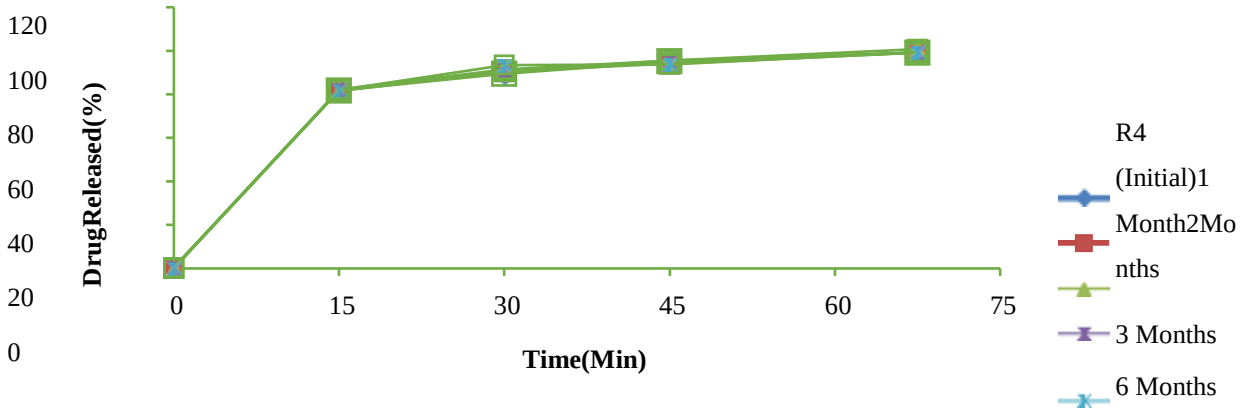
Stability analyses were conducted on the optimized formulation R4. The assay, friability, hardness, disintegration, and dissolution pattern were determined to be satisfactory. Based on these criteria, a satisfactory stability study was conducted and it was determined that the formulation remained stable during storage. Given that the formulation remained stable under accelerated settings, it may be assumed that the formulation will also remain stable for a duration of two years under normal storage conditions.

Table 2.Evidence on the stability of carvedilol liquisolid tablets (R4)

Storagecondition	**Time(months)**	**Assay(%)**	**Friability(%)**	**Disintegration (seconds)**	**Hardness(kg/cm^2)**
25ºC/60%RH	0	101	0.111	80	7.0
25ºC/60%RH	1	100	0.183	60	7.5
25ºC/60%RH	2	101	0.165	90	8.0
25ºC/60%RH	3	99.5	0.176	95	6.5
25ºC/60%RH	6	101.2	0.125	97	7.5
30ºC/65%RH	1	100	0.190	89	7.5
30ºC/65%RH	2	99.9	0.272	83	6.0
30ºC/65%RH	3	99.3	0.369	98	8.5

30ºC/65%RH	6	102	0.128	96	7.0
40ºC/75%RH	1	99	0.210	87	6.5
40ºC/75%RH	2	103	0.309	69	7.0
40ºC/75%RH	3	99.9	0.343	95	6.5
40ºC/75%RH	6	101	0.323	98	5.0

The stability statistics were displayed in Table 2. According to ICH criteria, the pills remained stable while stored. The drug content of the formulation remained unchanged, and there was no change observed in the dissolving profile.



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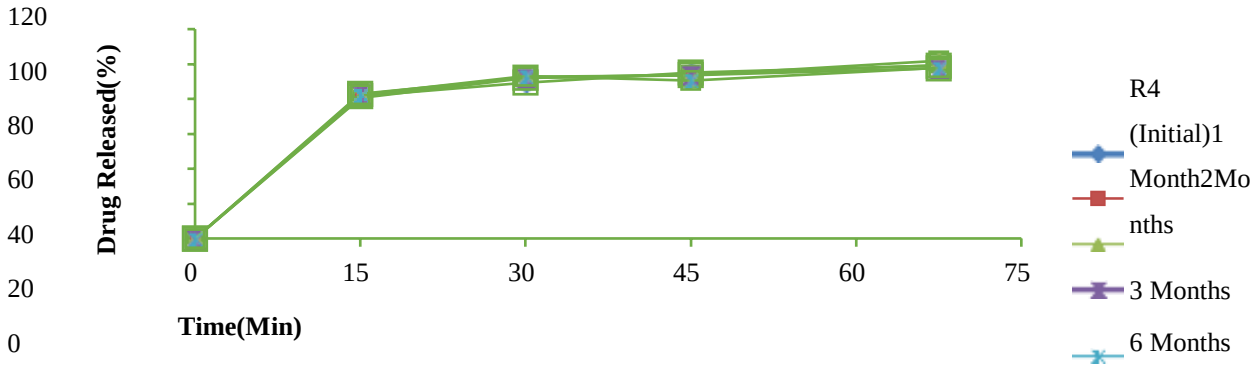

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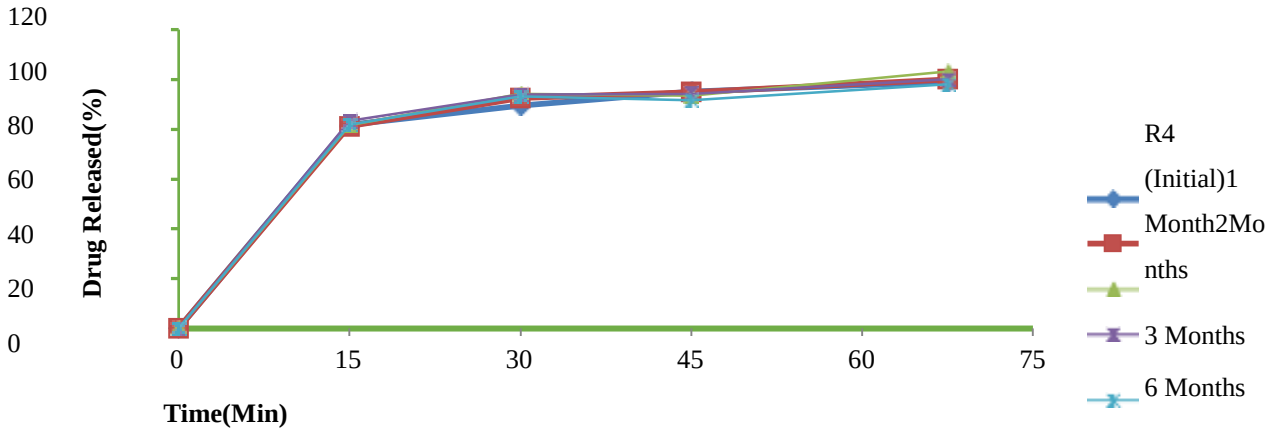

(c)

Fig. 7Carvedilol liquisolid formulation's dissolution profile at a: 25°C/60% RH, b: 30°C/65% RH, and c: 40°C/75% RH in storage

5.Result and Discussion

In conclusion, the liquisolid compact approach proved to be a successful means of enhancing the solubility and dissolving rate of the cardiovascular disease medication carvedilol, which is not very water-soluble. Characterization investigations revealed that the liquisolid compacts that were created were had good compressibility, flow, and compatibility with Carvedilol. Studies on drug solubility in vitro showed that liquisolid compacts significantly outperformed the standard tablet in terms of medication release. The liquisolid formulation increases the surface area and improves the wetting qualities, which in turn enhances the drug solubility in the compacts. This finding may lead to better patient outcomes in cardiovascular therapy by increasing Carvedilol's bioavailability and therapeutic effectiveness.Carvedilol and other medications with low water solubility can be effectively increased in their solubility using the liquisolid compact technology, according to this study's results. The results of this study shown that the liquisolid compacts technique may be utilized in an efficient manner for the manufacturing of sustained release (SR) matrix tablets containing the medication carvedilol, which is weakly water soluble. PEG 400 was utilized as the liquid vehicle in this application. Based on the findings of the previous study, we can also draw the conclusion that the use of microcrystalline cellulose (Avicel) in conjunction with Aerosil as a coating material resulted in improved SR of carvedilol. The liquisolid compact formulation should be further validated for its applicability and performance by in vivo pharmacokinetic evaluations and stability tests in future investigations.

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