Evaluation And Stability Studies Of Developed Formulation Of Liquisolid Drug Metoprolol Succinate

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Abstract
Optimisation of liquisolid technology to decrease drug dissolving rate is suggested as a potential route for the production of prolonged release devices in this article. Polyethylene glycol 400 was the liquid medium used to disperse metoprolol succinate in this experiment. After that, the drug was mixed with a binary mixture of carrier-coating materials (Avicel PH-102) in a mortar while it was being mixed constantly. The last step was to compress the mixture using the tablet compression machine. The goal was to find out how different drug contents, loading factors, and heat treatments affected the release profile of metoprolol succinate from liquisolid compacts. The release rates of metoprolol succinate from liquisolid compacts and matrix tablets were compared. Metoprolol succinate tablets produced by the liquisolid method outperformed matrix tablets in terms of retardation. This study's findings highlight the importance of hydroxypropyl methylcellulose (HPMC) in liquisolid tablet drug release maintenance. Furthermore, the results showed that the drug release rate of metoprolol succinate from liquisolid compacts was dramatically reduced by wet granulation. The drug's dissolving profile and hardness remained unchanged with age, as shown by the three months of storage of the liquid-solid tablets at 400C and 75% relative humidity. The kinetics experiments showed that most of the liquisolid formulations followed a zero-order release pattern. 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, HPMC, Humidity, Crystallinity,Avicel, Beta blocker,DSC ect.

1. Introduction

Metoprolol succinate, a class II medicine, is very permeable despite being weakly soluble; this property makes it ideal for limiting the rate of oral absorption.[1] Factors that influence the oral bioavailability of a medicine include its solubility, dissolving behavior, and permeability. The low rate of solubility of these drugs in water is a barrier to the creation of pharmacological dose forms.[2]. To regulate their absorption from the mouth, these drugs are often dissolved in the digestive system [3]. Consequently, absorption relies on medicine dispersion. Reducing particle size, using a surfactant as a solubilizing agent, forming a drug complex with a hydrophilic carrier, advocating for the drug, and finally, formulating the drug as a solid solution to decrease crystallinity and increase the solubility rate are some methods for improving the solubility of drugs that are insoluble in water. To increase solubility, the most effective method is to use Liquisolid compacts [4]. Pharmaceuticals that are not very water-soluble can have their solubility and dissolution improved using a formulation method known as liquid-liquid dispersion technology or liquid-solid technology. Adsorbing the medicine onto appropriate carrier particles, also called "carrier particles" or "carrier powder" [5], allows it to be delivered. This method turns a medication that is either dissolved in a non-volatile liquid solvent or is already in a liquid state into a dry, free-flowing powder. The medication solution is typically mixed with a powder mixture of an adsorbent and a coating material during this process. The several benefits it provides—such as higher drug solubility, dissolving rate, drug load, and formulation design flexibility—make it a promising approach to solving the solubility problems of pharmaceuticals that are not very water-soluble [6].Given these features, liquid-solid technology seems like a good bet. After a heart attack, beta-blockers such as metoprolol succinate may help patients with hypertension, left ventricular dysfunction, or congestive heart failure [7]. Inhibiting the function of certain neurotransmitters called beta-adrenergic receptors is the basis of metoprolol succinate's action. Not only does it inhibit beta-1 and beta-2 adrenergic receptors, but it does it in a non-selective manner [8]. Alpha-1 receptors can also be inhibited by it. By blocking these receptors, Metoprolol succinate reduces blood pressure and enhances cardiac performance by reducing cardiac effort, slowing the heart rate, and widening blood vessels. When absorbed from the gastrointestinal tract, metoprolol succinate has a bioavailability of around 25-35%. Its high rate of first-pass hepatic metabolism causes its decreased systemic availability [9].Albumin is one of the proteins that the medication interacts to effectively. Metoprolol succinate is very water-soluble. Reports indicate that it dissolves around 2.9 mg/mL in water at 25°C, indicating a low solubility. Developing a liquisolid

compact formulation of metoprolol succinate is the current focus of this study. The next step is to compress the mixture into tablet dosage form and evaluate its quality attributes.

2. **Liquisolid Technology provides a solution by either[10]**
Improving Release Rates: It enhances the release rates of poorly absorbed drugs.
Controlled Release: Achieving sustained-release profiles with zero-order release kinetics.
Additionally, it serves as a photoprotective system for photosensitive drugs and can modulate the drug microenvironmental pH

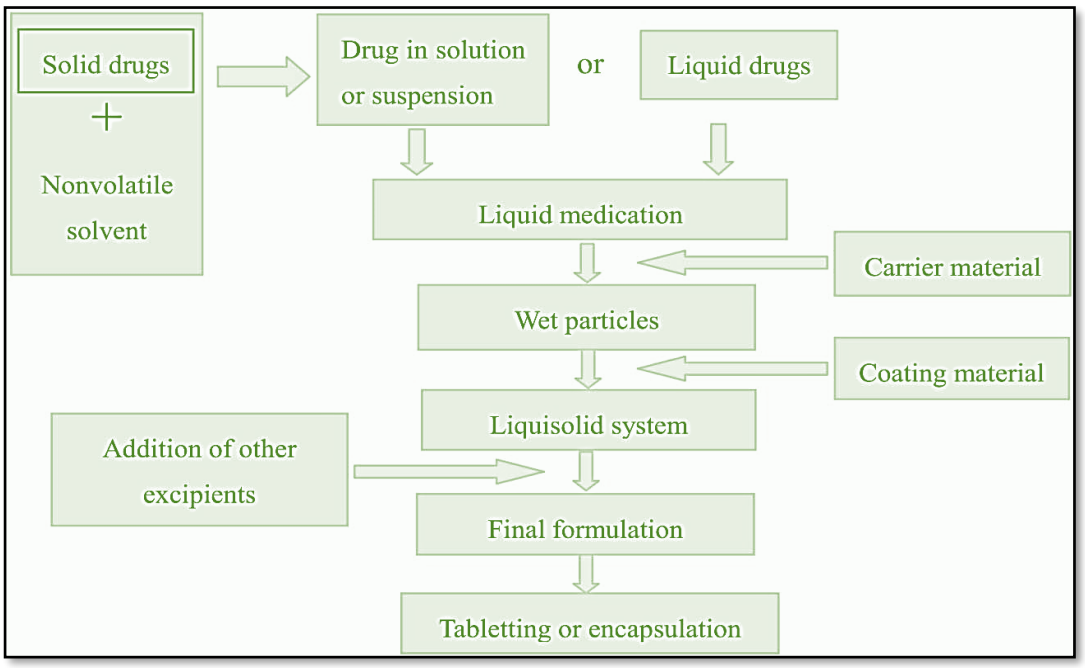


Fig.1 Flow chart represent the formulation of Liquisolid Technology

2 Evaluation of Liquisolid developed Formulation[11]

1. Appearance
The pills had a round biconvex form and a white to off-white tint. The pills had a smooth, uncoated surface on both sides.

2. Weight variation test
A random sample of twenty pills was taken. Each of the twenty tablets had a weight that was within five percent of the mean. The results showed that these liquisolid tablets passed the test for weight variation.

3. Content uniformity test
The optimized formulation was tested, and the initial average assay yielded a value of 101%. According to the criteria, each tablet must have an assay that falls between 94.5 and 105% of the mean value.

4. Friability, hardness and disintegration of tablets
Table 1 displays the formulated tablet's hardness, friability, and disintegration time. It was determined that the tablets met the required standards for hardness, friability, and disintegration time. There was no variation in the tablets' diameter, thickness, weight, or medication content.

Table 1. Hardness, friability and disintegration for liquisolid tablets and conventional tablets[12]

Batch Code	Crushing strength kg/cm^2	% Friability	Disintegration time (sec)
PEG	7.0	0.112	80
PG	6.5	0.198	70
Tween 80	6.0	0.214	75
Cardivas	7.5	0.010	70
Conventional Tablet	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. Investigations of Liquisolid Formulation Dissolution Kinetics in a Laboratory Setting[13]
When compared to Cardivas, the release profile of liquidsolid pills containing PEG400 was noticeably superior. Upon dissolving, liquidsolid pills release around 75% of their metoprolol succinate content in the first ten minutes. Figure 2 shows the solubility profiles of metoprolol succinate in different formulations. One possible explanation for the increased release of metoprolol succinate from PEG-based tablets is that the medication is already present in a molecularly dispersed (solubilized) form in the compound. The existence of the medication in a molecularly distributed state in PEG may be the reason behind this.

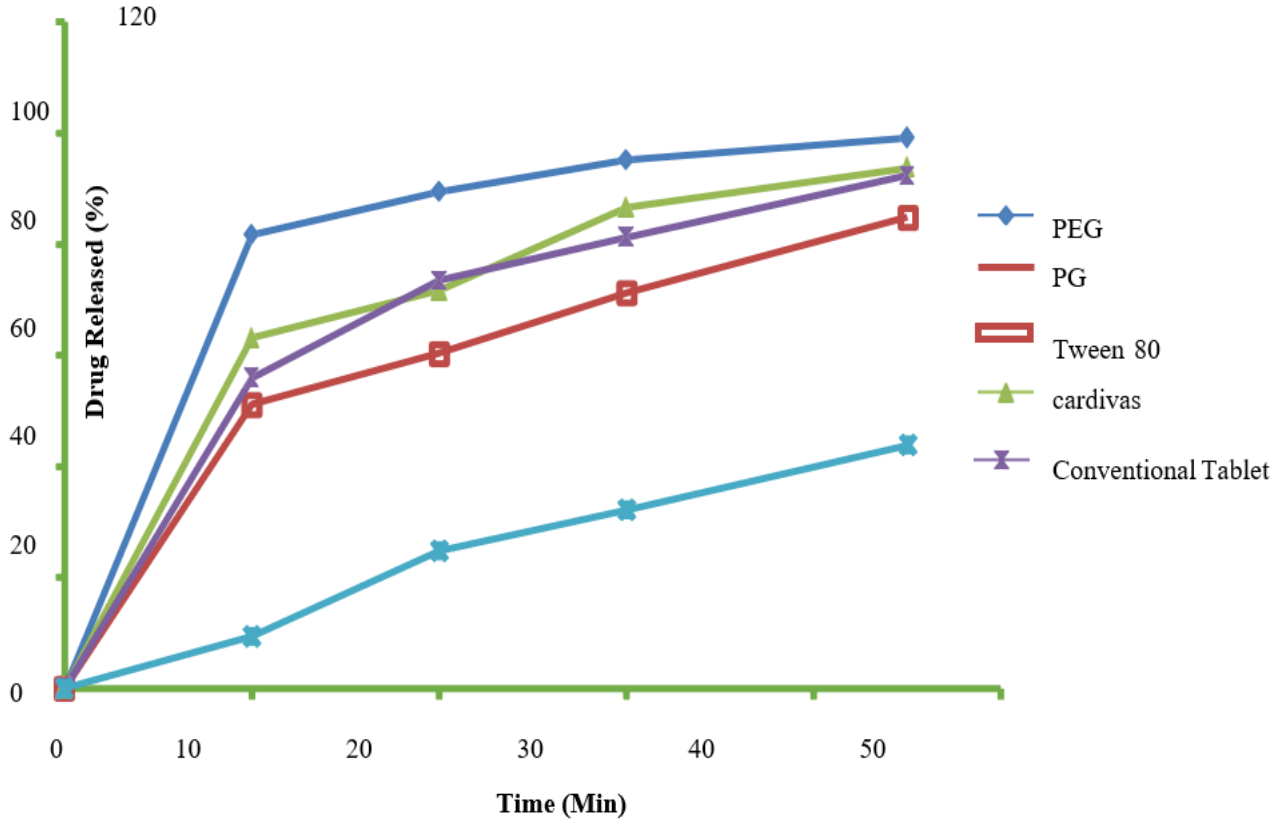


Fig.2.The in vitro dissolving characteristics of several liquid-solid tablets contain metoprolol succinate

In order to understand the effect of excipient ratio on dissolution profile of metoprolol succinate these batches were planned. The blend used for compression into tablets was also evaluated for Carr's index. The corresponding values of Ci are shown in table 3.

Table 3. Ci values for different liquisolid blends[14]

Batch Code	R1	R2	R3	R4	R5
Ci (%)	30.71	33.22	20.63	30	25

Despite the fact that the maximum feasible concentration of PEG in R1 was responsible for the quick dissolution of metoprolol succinate, the matching blend displayed poor flow due to the higher Ci values that were found. This was something that was anticipated. It is essential to be aware of the fact that the tablet requires a bigger quantity of liquid (PEG) while keeping a sufficient flow of the mixture in order to prevent weight variation and content non-uniformity. This is because the amount of liquid required for the tablet is higher. R4 on the other hand displayed a dissolution profile that was substantially equivalent to that of R3 and had a Ci value that was satisfactory. R4 also had a Ci value that was satisfactory. As a consequence of this, there will be very little room for changes in weight and substance that are not fully consistent. This will be the case because of the lack of opportunities. Due to this, it was concluded that R4 was the most effective formulation that could possibly be used. The same formulation was put through several rounds of testing in order to evaluate whether or not it was effective and maintain its stability.

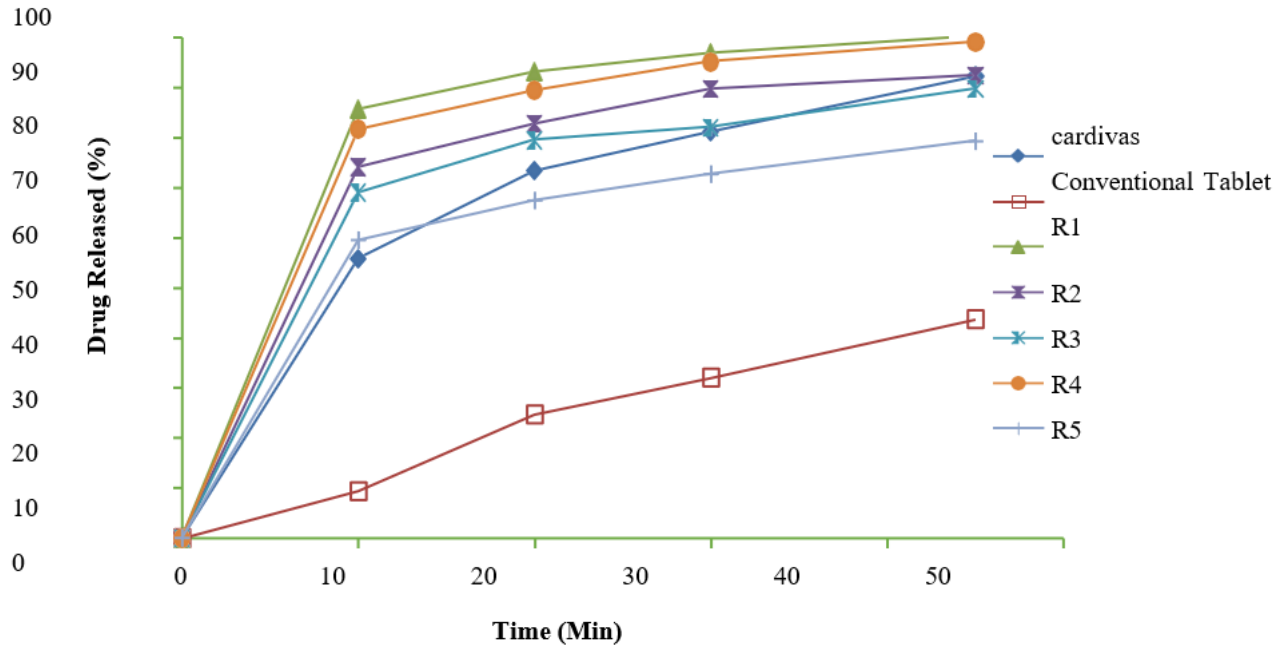
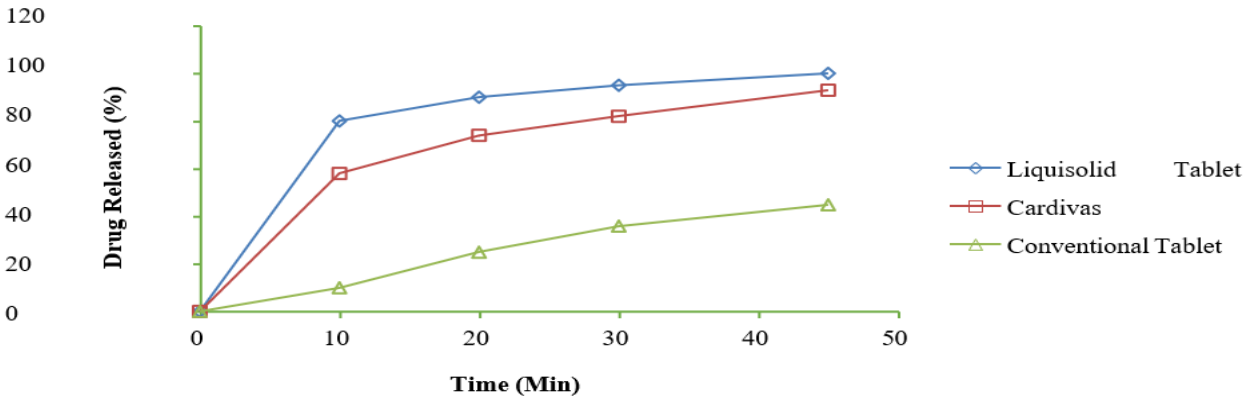


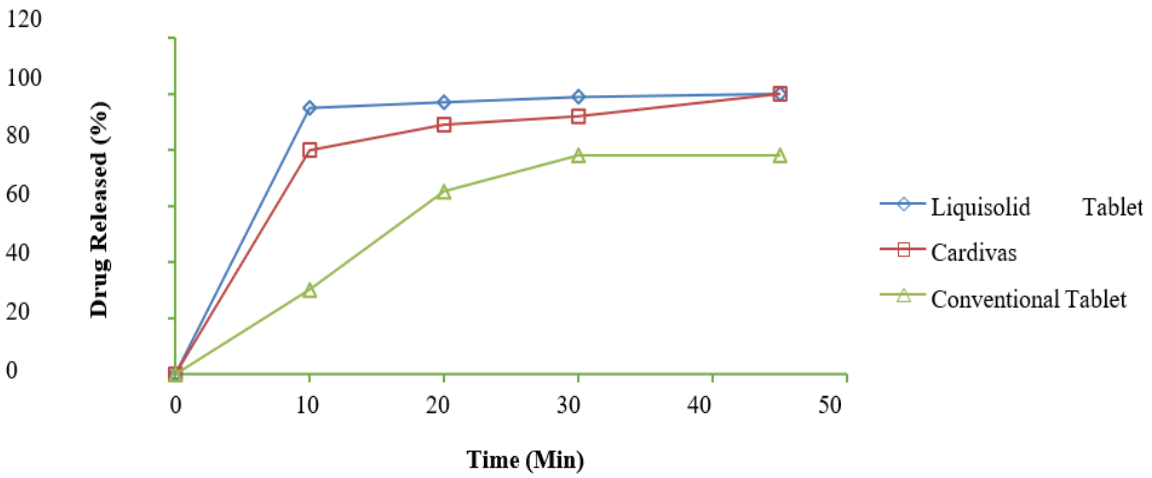
Fig. 3 Effect of carrier to coating material ratio on metoprolol succinate

6. **Experimental settings How Liquisolid Formulations Dissolve [15]**

Various ambient and pH variables are anticipated to be encountered by the formulation. As a result, experiments involving dissolution were set up using dissolution media with varying pH levels. Figure 4. shows that the release profile of metoprolol succinate will be altered due to its pH-dependent solubility. It is evident from these investigations that the created formulation outperforms the conventional and commercially available ones in terms of solubility, regardless of the pH level.



(a)



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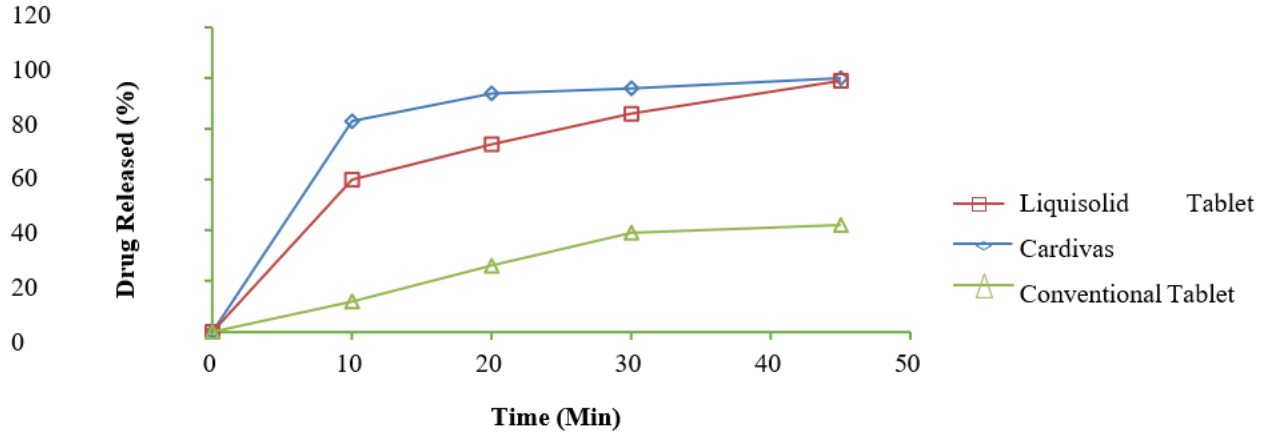

(c)

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

7. Metoprolol succinate formulation analysis using thermal methods[16,17]

Frequently, a substance's solubility is dictated by its melting point in relation to its latent heat of fusion. A substance's latent heat of fusion is the amount of heat it releases when it melts or fuses. In general, the melting point and latent heat of fusion are both low in crystals with weak bonds and high in crystals with strong 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.

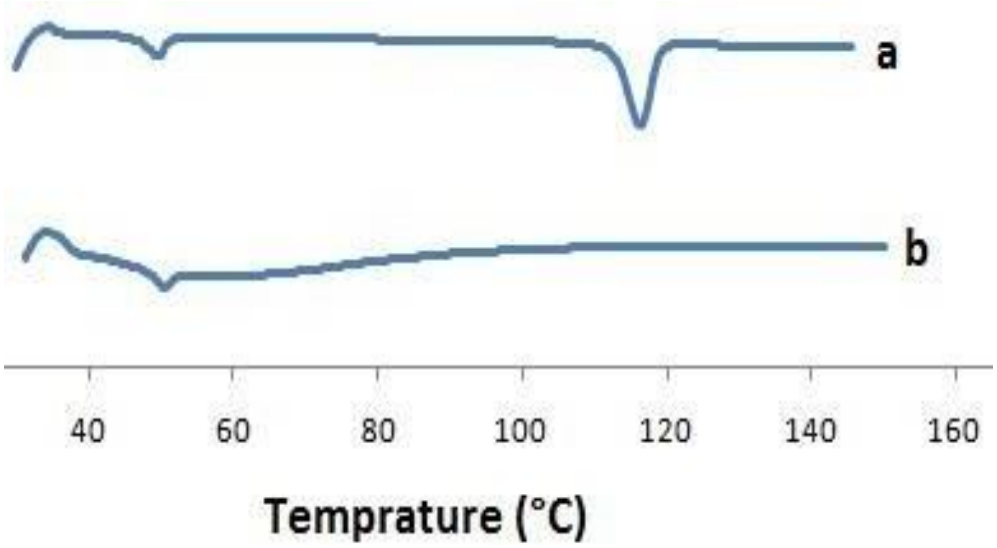

Fig. 5 DSC of a: neat metoprolol succinate and b: liquisolid formulation

DSC study as shown in fig. was used to predict the physicochemical interaction between the formulation components. The thermogram of pure metoprolol succinate showed sharp endothermic peak at 118^0C due to drug melting. Thus, indicating crystalline anhydrous state. Liquisolid formulation's DSC thermogram masked the characteristic melting peak of metoprolol succinate indicating complete solubilization of metoprolol succinate and interaction between metoprolol succinate and excipients.

8. Powdered X- ray diffraction studies of Liquisolid Formulation[18,19]

Figure 6 shows the x-ray diffraction pattern of the neat and liquisolid formulations of metoprolol succinate. Potentially attributable to the interaction between metoprolol succinate and PEG 400, there were some variations in the relative integrated intensities of each peak between the two samples. The percentage of crystallinity for the liquisolid formulation (R4) and metoprolol succinate was determined to be 6.4 and 34.4 percent, respectively.

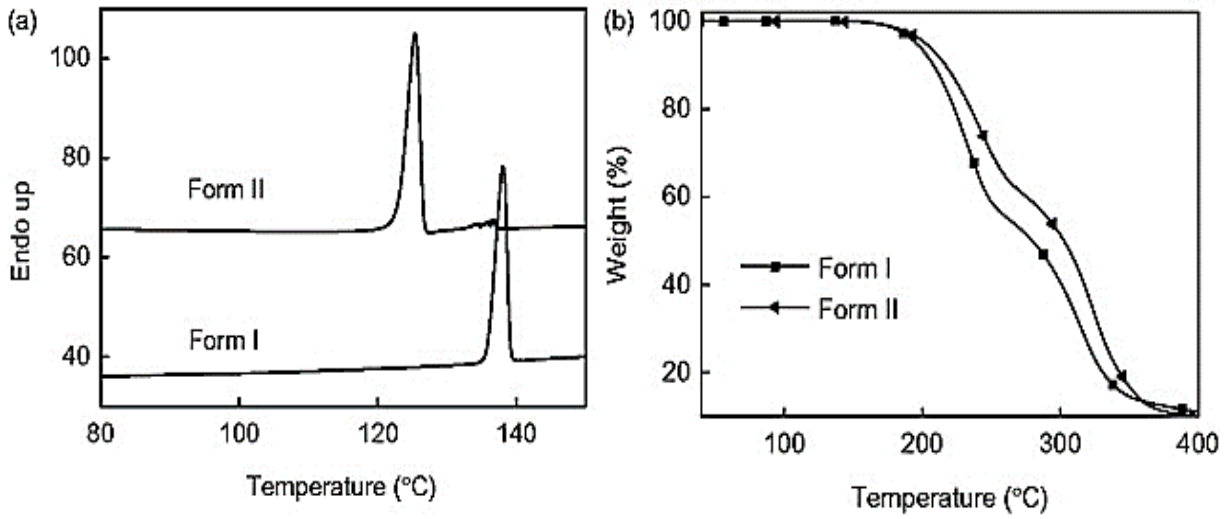

Fig. 6. XRD of : form I neat metoprolol succinate and II: liquisolid tablet

4.Stability studies of Metoprolol succinate Liquisolid Formulation[20]

In order to determine the substance's stability, stability tests were performed on the formulation R4, which had been appropriately tuned. After the test was finished, it was discovered that the friability, hardness, disintegration, and dissolution pattern were all satisfactory according to the results.

This was the conclusion reached after the test was finished. In accordance with the findings of a successful stability study that was carried out in regard to these requirements, it was discovered that the formulation remained stable after being stored. It is possible to make an assumption regarding the stability of the formulation and, as a consequence, its shelf life over a period of two years in real time. This is due to the fact that the formulation was demonstrated to be stable under accelerated settings. It was discovered that the formulation was stable at accelerated settings, which is the reason for this consequence.

Table 2. Stability data of metoprolol succinate liquisolid tablets (R4)

Storage condition	Time (months)	Assay (%)	Friability (%)	Disintegration (seconds)	Hardness (kg/cm^2)
25 ºC/ 60% RH	0	101	0.111	80	7.0
25 ºC/ 60% RH	1	100	0.183	60	7.5
25 ºC/ 60% RH	2	101	0.165	90	8.0
25 ºC/ 60% RH	3	99.5	0.176	95	6.5
25 ºC/ 60% RH	6	101.2	0.125	97	7.5
30 ºC/ 65% RH	1	100	0.190	89	7.5
30 ºC/ 65% RH	2	99.9	0.272	83	6.0
30 ºC/ 65% RH	3	99.3	0.369	98	8.5
30 ºC/ 65% RH	6	102	0.128	96	7.0
40 ºC/ 75% RH	1	99	0.210	87	6.5
40 ºC/ 75% RH	2	103	0.309	69	7.0
40 ºC/ 75% RH	3	99.9	0.343	95	6.5
40 ºC/ 75% RH	6	101	0.323	98	5.0

The findings on stability were presented in Table 2. According to the rules established by the ICH, the tablets were found to be stable after being stored. Both the dissolving profile and the drug content of the formulation were determined to have remained same, and there was no substantial change in either of these aspects.

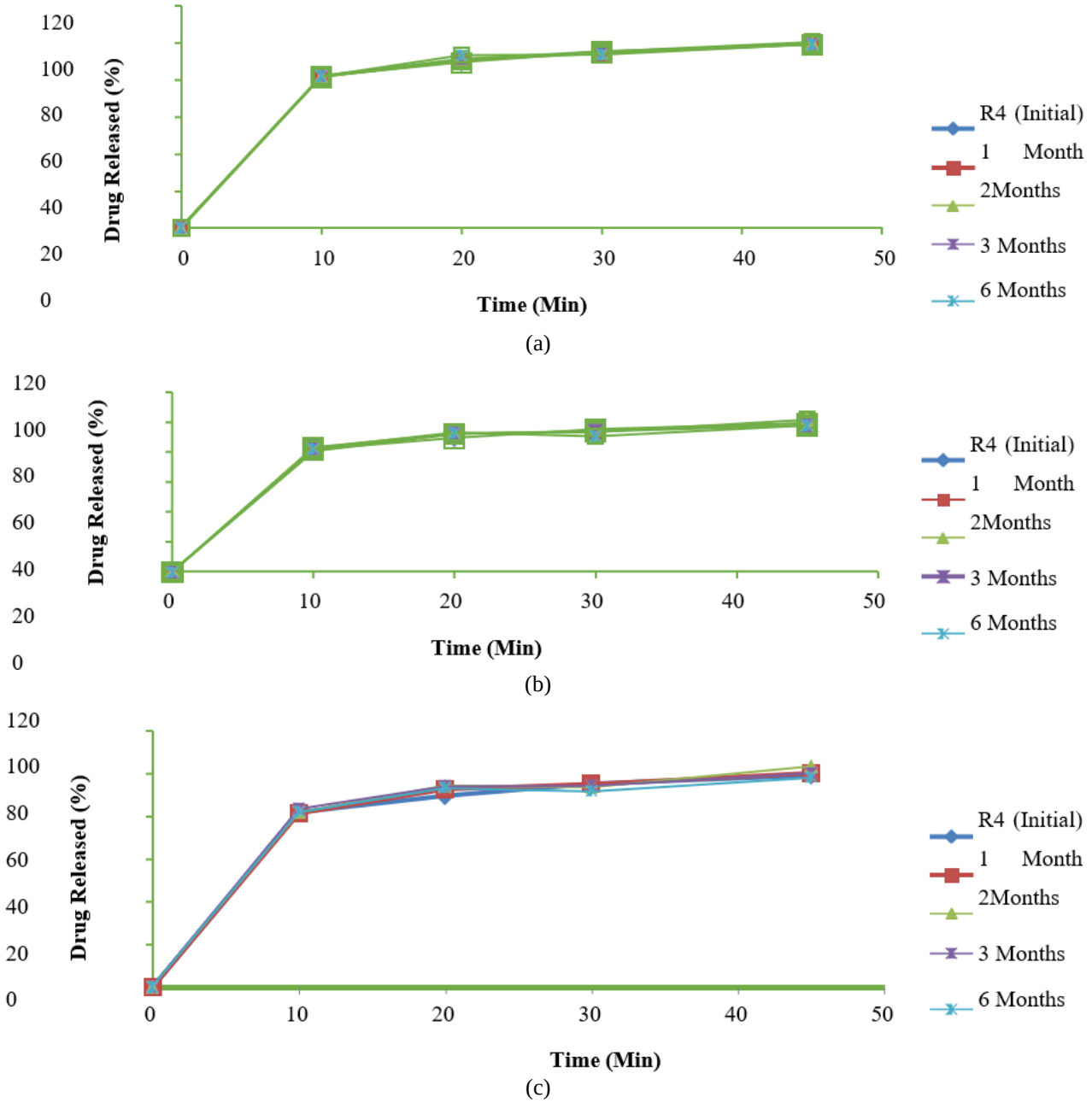

Fig. 7 Metoprolol succinate liquisolid formulation is stored, the dissolution profile for the formulation at a: 25°C/60% RH, b:30°C/65%RH and c: 40°C/75%RH

5.Result and Discussion

Metoprolol succinate is a treatment for cardiovascular disease; however, it is not very water-soluble. The liquisolid compact approach proved an excellent way to boost its solubility and dissolving rate. The created liquisolid compacts showed excellent compressibility, flow, and compatibility with Metoprolol succinate in the characterization investigations. When compared to the conventional tablet, liquisolid compacts demonstrated a considerable improvement in drug release, according to in vitro studies on drug solubility. The medication is more soluble in the compacts thanks to the liquisolid formulation's increased surface area and better wetting properties. This discovery has the potential to improve cardiovascular therapy patient outcomes by raising the bioavailability and therapeutic efficacy of Metoprolol succinate.The results of this investigation show that the liquisolid compact technology may successfully increase the solubility of drugs with low water solubility, such as metoprolol succinate. The study's findings suggest that the liquisolid compacts method could be effectively used to make sustained release (SR) matrix tablets with the water-insoluble medicine metoprolol succinate. For this purpose, PEG 400 served as the liquid carrier. The prolonged release profile of carvediol from this tablet is supported by the fact that the zero-order model is the best fit for drug release profiles when fitting models. Following from the prior study's conclusions, we can say that coating metoprolol succinate with Aerosil and microcrystalline cellulose (Avicel) improved its SR. Future research should conduct stability testing and in vivo pharmacokinetic evaluations to further validate the application and performance of the liquisolid compact formulation.

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Conflict of Interests
The authors have no conflict of interests.

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