Section A-Research paper
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Telmisartan Liquisolid Compact Formulation Development for Enhanced Aqueous Solubility

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Abstract

Solubility enhancement strategies play a vital role in formulating effective drug products that ensure optimal absorption, bioavailability, and therapeutic outcomes. A comprehensive understanding of aqueous solubility is crucial for the successful development of oral solid formulations with improved therapeutic outcomes. Various approaches are applied in formulation development for solubility enhancement of poorly aqueous soluble drugs in which the development of the liquisolid compact is a promising approach for improving the solubility, dissolution and bioavailability of poorly soluble drugs. With their versatility and potential benefits, they have gained attention as a valuable tool in the formulation of oral solid dosage forms. Furthermore, liquisolid compacts can be conveniently compressed into tablets or filled into capsules, making them suitable for oral administration. Considering these advantages, this study aims to enhance the solubility of Telmisartan by developing liquisolid compacts using Polyethylene Glycol (PEG), Microcrystalline Cellulose (MCC), Colloidal Silica and Crosspovidone as excipients. The six formulations were developed with varying excipients concentrations and evaluated for invitro dissolution studies, indicating Telmisartan's aqueous solubility enhancement in the developed compacts. The excipients drug instruction was studied with the FTIR spectra and DSC and XRD were also performed to evaluate changes after formulation development. The drug release profile of the optimized formulation was also compared with the marketed formulation which shows promising results. These findings highlight the potential of liquisolid compacts in enhancing the solubility and dissolution of Telmisartan, contributing to the formulation of effective drug products.

Keywords :

liquisolid compacts, Solubility enhancement, Poorly aqueous soluble, Telmisartan, formulation development

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1. Introduction

Solubility enhancement for drugs is a critical aspect of pharmaceutical development. Many drugs possess poor aqueous solubility, which can hinder their bioavailability and therapeutic effectiveness.[1] Various approaches are employed to improve drug solubility, including particle size reduction, solid dispersion techniques, complexation and the use of surfactants or

co-solvents. [2] These methods aim to increase the surface area available for dissolution, promote drug-polymer interactions and enhance molecular dispersion in the formulation. Additionally, techniques like nanosizing, amorphous solid dispersions, lipid-based formulation and liquisolid compact development have shown promise in enhancing drug solubility. The aqueous solubility plays a pivotal role in the development of oral solid dosage forms. It determines the rate and extent of drug dissolution in the gastrointestinal tract, influencing the drug's bioavailability and therapeutic efficacyPoorly soluble drugs often exhibit low absorption, resulting in reduced efficacy or the need for higher doses. Various formulation strategies are used to improve the solubility and the dissolution rate. Liquisolid compact is one of the most promising approache for poorly aqueous soluble drugs to enhance the solubility. [3]

Liquisolid compacts, also known as powder-liquid compacts or liquid-loaded compacts were introduced to overcome the limitations of poorly soluble drugs and enhance their dissolution and bioavailability. [4] Liquisolid compacts are prepared by converting liquid drugs or drug solutions into a free-flowing powder form by incorporating them into a powder blend consisting of an inert carrier material, such as a solid excipient and a coating material. The liquid drug is absorbed within the powder matrix, resulting in the formation of a cohesive solid compact. [5] The coating material helps to maintain the integrity of the compact and prevents drug leakage. The liquid drug present in the compact spreads on the surface of the carrier material, significantly increasing the effective surface area available for dissolution. This leads to improved drug release and absorption, thereby enhancing bioavailability.[6] Liquisolid compacts also offer flexibility in drug formulation. By adjusting the amounts of carrier material and coating material, the drug loading and release properties can be tailored to specific requirements. Additionally, the technique allows the use of hydrophilic or lipophilic liquid drugs, expanding the range of drugs that can be formulated. [7]

Telmisartan is a class of angiotensin II receptor blockers (ARBs), primarily used for the treatment of hypertension (high blood pressure) and to reduce the risk of cardiovascular events in patients with cardiovascular diseases. Telmisartan works by selectively blocking the angiotensin II receptor, which helps to relax blood vessels and lower blood pressure. It is generally well-tolerated and has a favourable safety profile but the aqueous solubility profile is poor. It is a white to off white crystalline power, practically insoluble in water, but freely soluble in organic solvents. [8] The effected dose is 40-80 mg once daily, but in some case 20 mg is also sufficient to achieve the targeted blood pressure. Elimination half life is approx 24 hours with a clearance of approx 800ml/minute. Absorbed quickly from gut with varying degree and average bioavailability is about 50%. Plasma protein binding is about 99.5%. Because of poor aqueous solubility the absorption of drug from GIT fluid is governed by its solubility. To overcome this barrier various techniques are employed to enhance the solubility. The present study focuses on the enhancement of dissolution for Telmisartan using the liquisolid technique.

2. Materials and methods

2.1 Materials

Drug Telmisartan IP was obtained as gift sample from Unichem Pharmaceuticals Laboratory, Baddi. Polyethylene glycol 400 (PEG 400), Propylene glycol were purchased from SD fine Chem Ltd. Microcrystalline Cellulose (MCC), Colloidal Silica, Crosspovidone were purchased from Ankit Traders, Delhi. All other chemicals were purchased from Merk Pvt. Ltd. and Marketed formulation of Telmisartan were procured locally.

2.2 Preformulation studies

Drug Identification & Melting Point determination was carried and compared with the standard parameters as per the monograph. [9] Melting Point was measured by

capillary tube method. The FTIR spectra of Telmisartan and excipients were generated by using FTIR Spectrophotometer (Shimadzu) in rage of 400-4000/cm by KBr disc method and compare with the standard spectra to know compatibility of drug and excipients.

2.3 Solubility studies

For solubility studies the saturated solution of drug was prepared in the different solvent by adding excess of drug to the selected solvent and Shaked with orbital shaker for specific time and kept for 48 hours and then filtered with the help of filter paper for removal of excess amount of the drug. [10] The solution was suitably diluted and analyses with help of UV spectrophotometer at 298 nm for concentration of drug.

2.4 Liquid load factor calculation

The liquid load factor (LLF) in liquisolid compacts is a parameter that quantifies the amount of liquid medication that can be incorporated into the formulation. It is calculated using the following equation:

$$LLF = (Q/MR) \times (1 / ?c)$$

Where, LLF is the liquid load factor, Q is the amount of liquid medication (in grams) required to achieve the desired drug dose, MR is the ratio of the weight of the powdered drug formulation to the amount of liquid medication required (Q) and ?c is the apparent porosity of the powdered drug formulation. [11]

S. No.	Solvent	Solubility (mg/ml)
1	Distilled water	0.023
2	0.1 N HCL	0.549
3	0.1 N NaOH	0.643
4	PEG 400	5.700
5	Propylene glycol	3.100

Table No. 1. Solubility of Telmisartan in different Vehicles

Formulation Variables	F1	F2	F3	F4	F5	F6
Telmisartan (gm)	10	10	10	10	10	10
polyethylene glycol (PEG) (gm)	10	10	20	20	30	30
microcrystalline cellulose (MCC) (gm)	50	60	50	60	50	60
Crosspovidone (gm)	5	5	5	5	5	5
colloidal silica (gm)	5	6	5	6	5	6

Table No. 2. Formulation Matrix of Telmisartan Liquisolid Compact

2.5 Liquisolid Compact preparation

Liquisolid compacts of Telmisartan were prepared by using Polyethylene Glycol (PEG) as non volatile solvent (liquid vehicle), Microcrystalline Cellulose (MCC) as carrier and Colloidal Silica as coating material along with Crosspovidone as disintegrant by trituration method. [12]

2.6 Flow behaviour studies of compact

The flow behaviour of the developed compact was analysed

by determination of Angle of Repose, Bulk & Tapped Density, Carr's index and Hausner's Ratio with standard methods.

2.7 In Vitro dissolution studies

In vitro dissolution studies were conducted to know the release pattern from the compact, using the USP paddle method. The experiments took place in 900 mL of 0.1 N HCl (pH 1.2) at a temperature of

37.5 ± 0.5?C. Stirring was maintained at a rate of 75 ± 1 rpm. At specific time intervals (5, 10, 15, 20, 30, 40, 50, and 60 minutes), 5 mL samples were collected and filtered, Subsequently, the samples were subjected to analysis at a wavelength of 298 nm using a UV-visible spectrophotometer. To calculate the drug release from each formulation, the average of three determinations was employed. Dissolution profile was also compared with the marketed formulation. [14]

2.8 Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) thermograms provide valuable information about the thermal behaviour of the formulation and can offer insights into the compatibility, stability and physical changes occurring within the system. It helps in identify potential interactions

Formulation	F1	F2	F3	F4	F5	F6
% Production Yield	92.3	95.2	93.2	94.1	90.6	94.3
Drug Content	72.3	75.2	82.5	80.0	84.1	83.2

Table No. 3. Drug content & Percentage production yield of Telmisartan Liquisolid Compact

Parameter	F1	F2	F3	F4	F5	F6
Bulk density (gm/ml)	0.32	0.32	0.30	0.29	0.34	0.29
Tapped density (gm/ml)	0.38	0.39	0.36	0.33	0.38	0.32
Carr's index (%)	15.7	17.9	16.6	12.1	10.5	9.3
Hausner's Ratio	1.1	1.2	1.2	1.13	1.1	1.1
Angle of repose	22.1	22.3	24.0	24.6	21.4	21.2

Table No. 4. Flow Behaviour Parameters of Telmisartan Liquisolid Compact

between the drug and excipients present in the liquisolid compact. [15] By analyzing the thermogram, any shifts or changes in the characteristic peaks of the drug or excipients can be observed. This can indicate the presence of drug-excipient interactions, such as melting point depression, eutectic formation, or crystalline transformations.

2.9 X-ray diffraction (XRD)

X-ray diffraction (XRD) provides valuable information about the crystalline structure, crystallographic phases and physical characteristics of the components present in the formulation. XRD spectra are used to identify the presence of specific crystalline phases in the liquisolid compact formulation. [15] By analyzing the diffraction pattern obtained from the sample, the peaks can be matched to known reference patterns in databases to determine the crystalline phases present. This helps in confirming the identity of the drug and excipients and identifying any changes in the crystalline stru cture due to formulation processes or interactions.

Time (Min)	Percentage drug release in 900 ml of 0.1N HCL					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	10.01 ± 0.02	12.04 ±0.02	15.20 ±0.03	10.30 ±0.01	17.20 ±0.02	16.00 ±0.02
10	24.29 ±0.02	28.10 ±0.02	22.01 ±0.04	18.32 ±0.03	30.0 ±0.03	20.04 ±0.02
15	28.12 ±0.03	32.01 ±0.03	28.32 ±0.01	26.89 ±0.02	42.18 ±0.01	26.32 ±0.01
20	37.16 ±0.01	38.50 ±0.01	37.02 ±0.04	36.41 ±0.03	53.02 ±0.02	35.27 ±0.03
30	47.20 ±0.04	50.01 ±0.01	45.65 ±0.01	40.03 ±0.02	65.64 ±0.02	50.22 ±0.02
40	55.54 ±0.03	58.03 ±0.03	62.25 ±0.01	52.14 ±0.01	77.23 ±0.02	64.00 ±0.01
50	62.32 ±0.02	66.87 ±0.01	78.41 ±0.03	66.23 ±0.02	82.51 ±0.02	71.02 ±0.02
60	70.21 ±.01	73.28 ±0.03	85.60 ±0.04	72.05 ±0.04	93.60 ±0.03	86.04 ±0.04

n = 3 ± standard daviation

Table No. 5. In- Vitro Release of Telmisartan Liquisolid Compacts

Time (Min)	Percentage drug release in 900 ml of 0.1N HCL		
	Pure drug	Marketed formulation	F5
0	0	0	0
5	10.02 ±0.01	16.02 ±0.02	17.20 ±0.004
10	32.01 ±0.01	20.50 ±0.01	30.0 ±0.03
15	47.02 ±0.03	26.50 ±0.02	42.18 ±0.01
20	60.03 ±0.02	34.09 ±0.02	53.02 ±0.02
30	99.27 ±0.01	48.06 ±0.04	65.64 ±0.02
40	-	53.02 ±0.03	77.23 ±0.02
50	-	61.08 ±0.04	82.51 ±0.02
60	-	71.05 ±0.03	93.60 ±0.03

Table No. 6. In- Vitro Release comparison of Telmisartan Liquisolid Compacts with marketed formulation

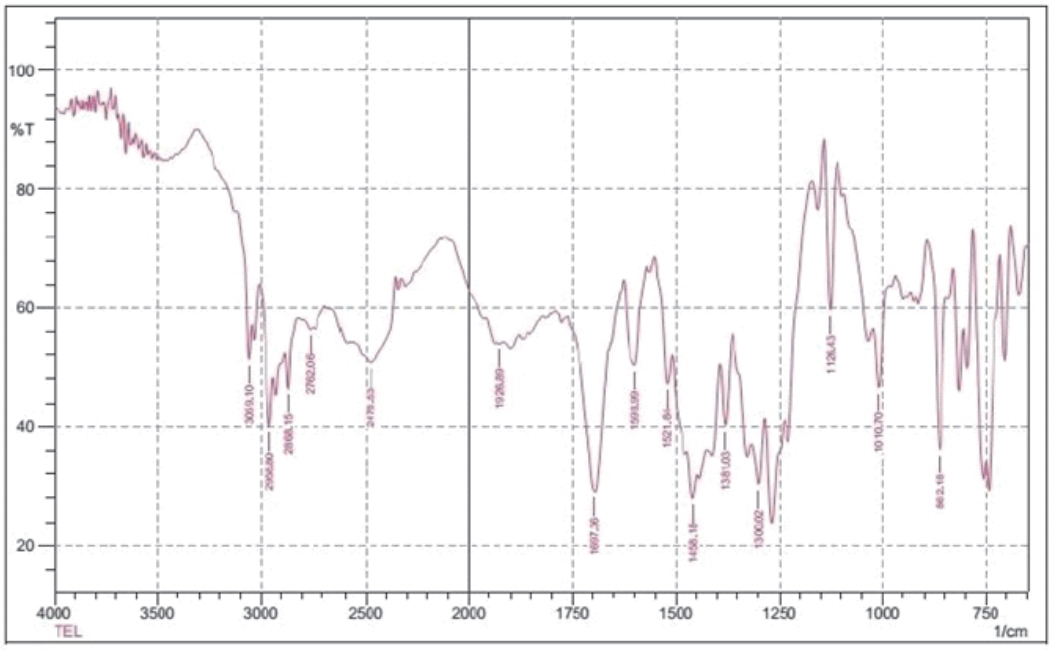

Figure No.1. FITR Spectra of Telmisartan

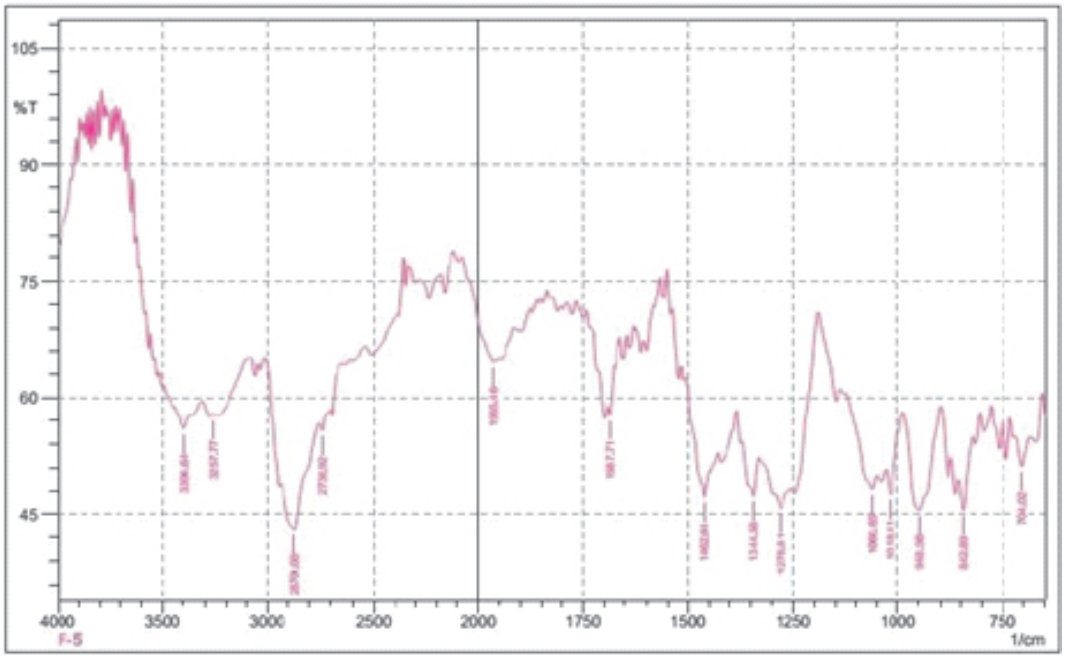

Figure No.2. FITR Spectra of Telmisartan with Excipients

3. Results and Discussion

3.1 Preformulation studies

Telmisartan procured as a gift sample was physically characterized as per monograph for its organoleptic properties and melting point. It was found to be White, odourless, bitter power having the melting point of 2660C. FTIR spectra of Telmisartan was similar with the standard spectra (Figure 1) and all reference peaks was visible in the FTIR spectra of Telmisartan with excipients shows in figure 2

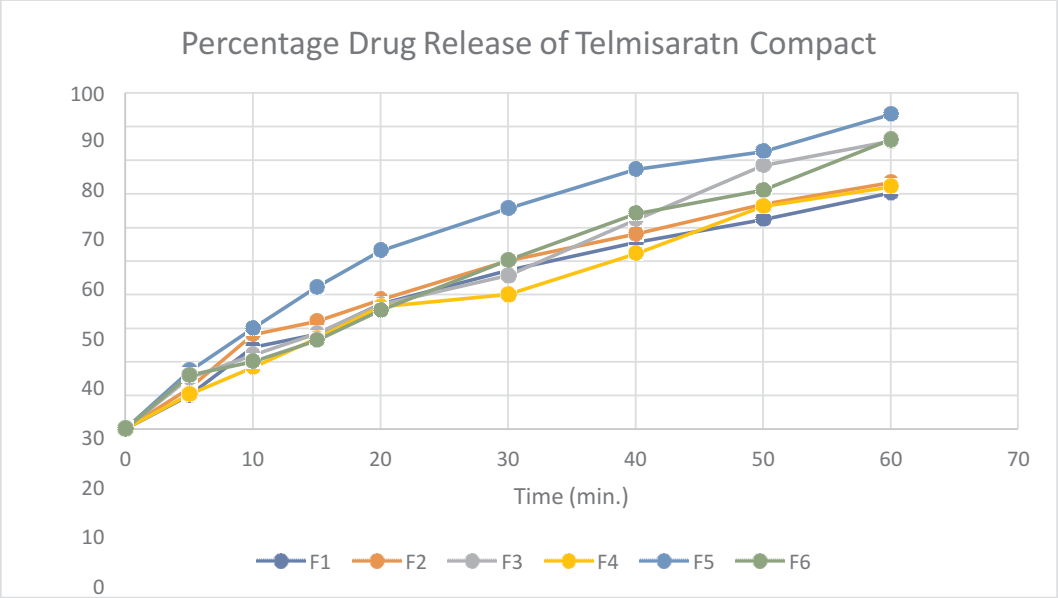

Figure No. 3. In-vitro Release of Telmisartan compact

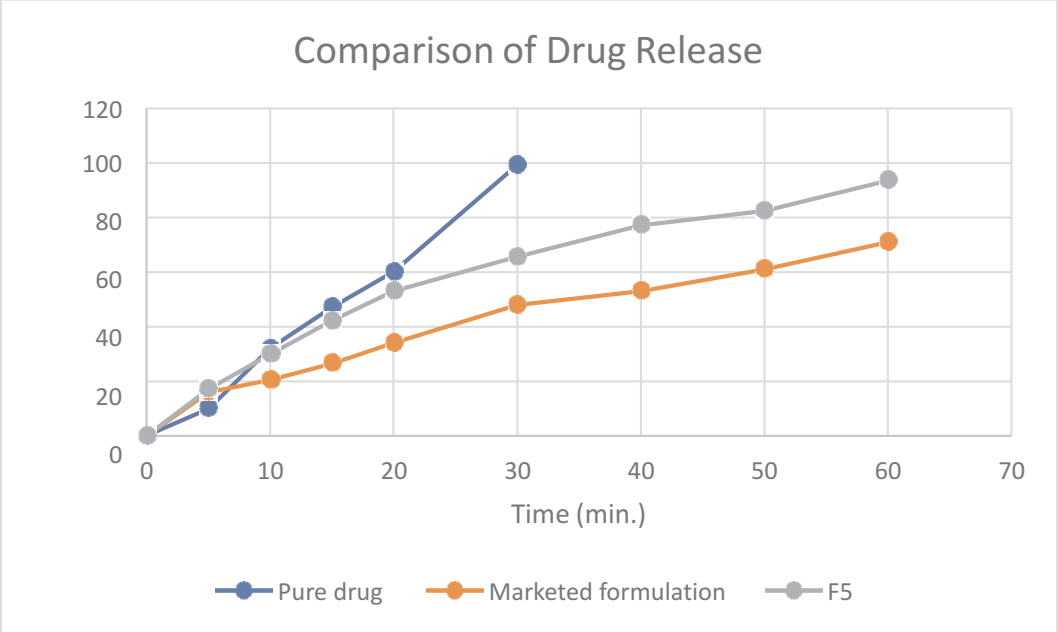

Figure No. 4. Comparison of In-vitro Release of Telmisartan compact with marketed formulation

3.2 Solubility studies

Solubility is one of most important parameter formulation development process. It affects the selection of suitable excipients, solvents and manufacturing techniques required to develop a stable and effective dosage form. For Liquisolid compact development the solubility of the drug candidate must be evaluated to in different non-volatile solvent for appropriate selection of vehicle to achieve the good bioavailability profile. The solubility of Telmisartan in different solvent are shown in table no. 1. On the basis of solubility data Polyethylene glycol 400 (PEG 400) was selected as vehicle for formulation development.

3.3 Liquid load factor

The liquid load factor provides an indication of the ability of the liquisolid compact formulation to incorporate the desired amount of liquid medication while maintaining the

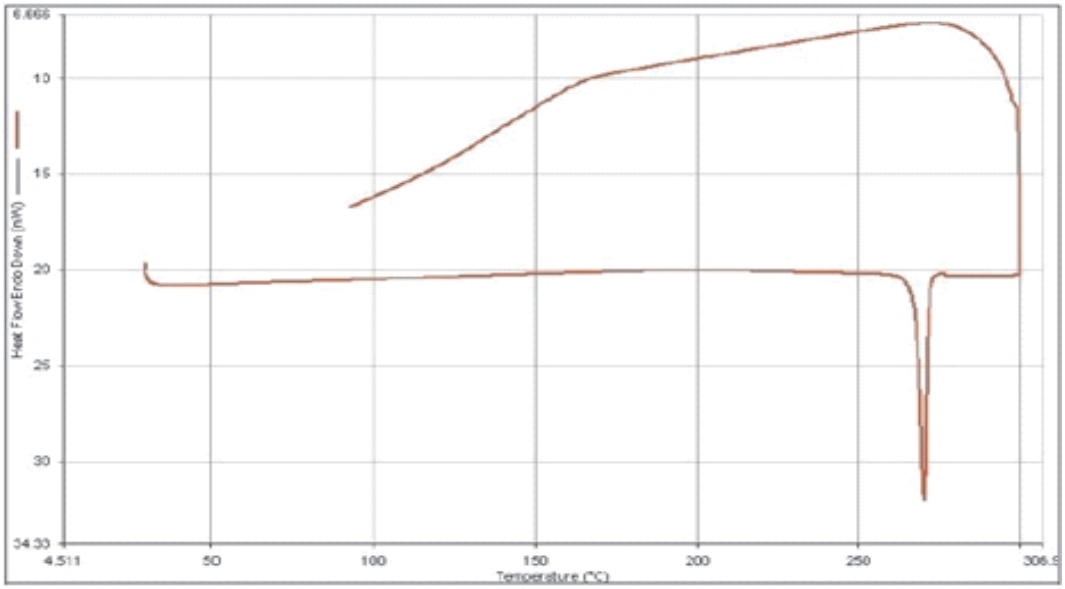

Figure No. 5. DSC Thermogram of Telmisartan

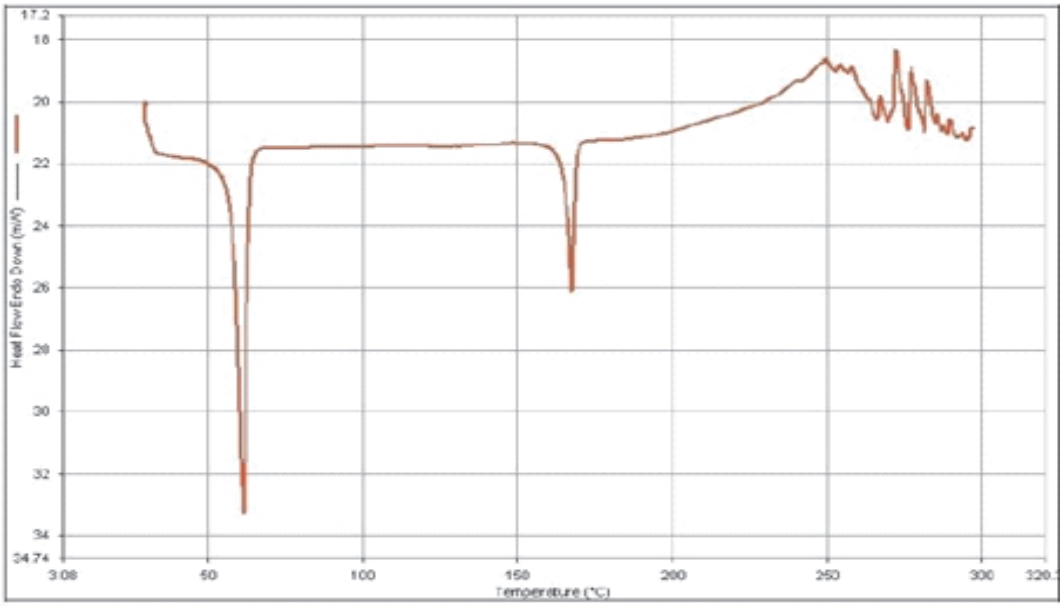

Figure No. 6. DSC Thermogram of Formulation F5

required flow and compressibility properties. It helps in optimizing the formulation design and dosage form development for liquisolid compacts. The liquid load factor was calculated by using the different ratios of selected carrier and coating material using Polyethylene glycol as a solvent (vehicle). The liquid load factor was found to be 0.198 with the ratio of 1:10.

3.4 Preparation of Liquisolid Compact

Liquisolid compacts of Telmisartan were prepared as per formulation matrix shown in Table no. 2 by using different ratios of Polyethylene Glycol (PEG) & Microcrystalline Cellulose (MCC) as per as liquid load factor along with Crosspovidone as disintegrant by trituration method. Total six formulations were prepared (F1 to F6) as per matrix and further evaluated for optimisation. The percentage practical yield was found to be 90.6 to 94.3% and the drug contained was found to be in range of 80.0 to 84.1 % as Shown in table no. 3.

3.5 Flow behaviour studies of compact

The flow behaviour of the developed compacts were analysed by determination of Angle of Repose, Bulk &

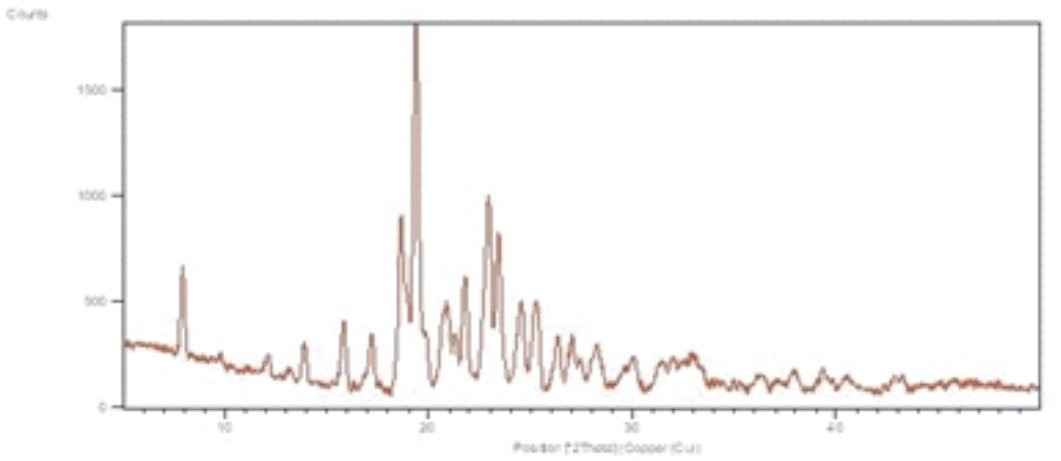

Figure No. 7. XRD Spectra of Telmisartan

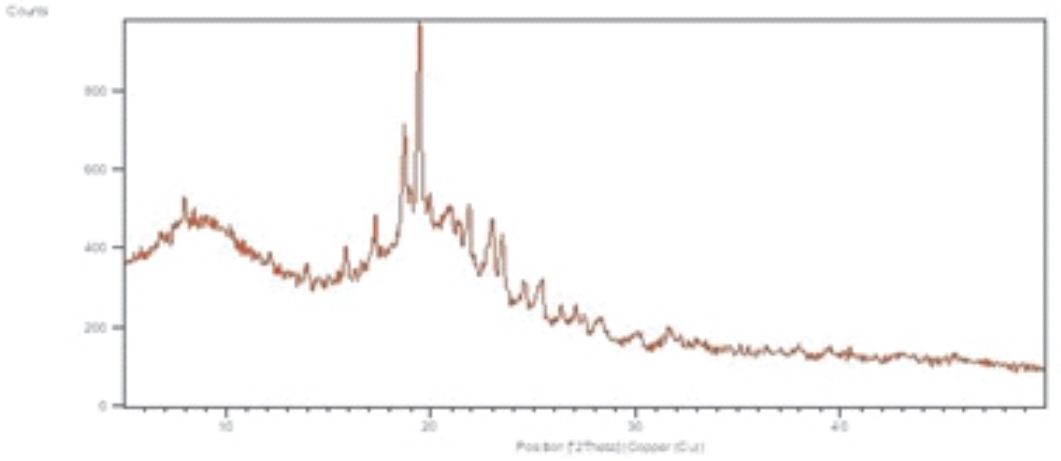

Figure No. 8. XRD Spectra of Formulation F5

Tapped Density, Carr's index and Hausner's Ratio shown in table no 4. Developed telmisartan compacts have good flow properties.

3.6 In Vitro dissolution studies

The in vitro dissolution studies were conducted using the USP paddle method in 900 mL of

0.1 N HCl (pH 1.2) at a temperature of 37.5 ± 0.5?C. The results indicate that the release of the drug from the compacts began at 5 minutes and within 60 minutes, a range of 70.00% to 93.28% of the drug was observed in the dissolution media (Table No. 5). The release pattern of all six formulations is depicted in Figure No. 3. The F5 formulation, which exhibited the highest release, was compared with a marketed formulation of Telmisartan known for its favourable in-vitro drug release profile (Table No. 6). This comparison is illustrated in Figure 4.

3.7 Differential scanning calorimetry (DSC)

DSC thermograms can provide insights into the compatibility between the drug and excipients used in the liquisolid compact formulation. By analyzing the melting points and enthalpy changes of the components individually and in the formulated mixture, potential interactions or incompatibilities can be identified. Incompatible interactions may result in the appearance of new peaks, disappearance of existing peaks, or shifts in peak temperatures. The DSC thermogram of Telmisartan shown in Figure no. 5 the sharp peak at 266.45 in the formulation represents no drug excipient interaction as it is similar to melting point of Telmisartan(Figure no. 6).

3.8 X-ray diffraction (XRD)

XRD can assess the compatibility between the drug and excipients in the liquisolid compact formulation. The

Changes in the diffraction pattern or peak intensities can indicate the occurrence of drug-excipient interactions, such as solid-state reactions, crystalline transformations, or formation of new phases (Figure no.7). figure no. 8 represents the XRD spectra of liquisolid compact, which indicate that conversion of amorphous form of Telmisartan from its crystalline structure.

4. Conclusion

This research article focused on the development of Telmisartan liquisolid compact formulations to enhance its aqueous solubility. The six such formulation F1 to F6 was prepared during the study by using Polyethylene Glycol (PEG) as liquid vehicle, Microcrystalline Cellulose (MCC) as carrier and Colloidal Silica as coating material along with Crosspovidone as disintegrants. All the compacts formulation shows the good feasibility and the release of the drug from the compacts commenced at 5 minutes, with a significant percentage of drug release (ranging from 70.00% to 93.28%) observed within 60 minutes. These results indicate that the liquisolid technique can effectively enhance the dissolution of Telmisartan. Overall the findings of this study suggest that the liquisolid technique holds great promise for improving the aqueous solubility and dissolution of Telmisartan. Further studies can be conducted to explore the potential application of liquisolid compacts in optimizing drug delivery systems for other poorly soluble drugs.

5. Conflict of Intrust

The authors declare that there is no conflict of interest regarding the publication of paper.

6. References

1. Pradeep C, Venugopalaiah H, Praveen P, Gnanaprakash K, Gobinath M. 2013. Liquisolid Systems - An Emerging Strategy For Solubilization & Dissolution Rate Enhancement of BCS Class-II Drugs. International Journal of Pharmacy Review & Research, 3(2):56-66.
2. Y. Kawabata, K. Wada, M. Nakatani, S. Yamada, and S. Onoue. 2011. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications, International Journal of Pharmaceutics,420 (1): 1-10.
3. Lu Mei et al. 2017. Liquisolid technique and its applications in pharmaceutics, Asian Journal of Pharmaceutical Sciences, 12 :115-23.
4. A. D. Sarvkare et al. 2017. Liquisolid Technology: A review, Int. J. Pham. Sci. and Research, 8(7), 2768-75
5. Spireas S. 2002. Liquisolid Systems and Methods of Preparing Same; U.S. Patent 6423339 B1.
6. Geethika et al. 2015. Liquisolid compact technology: A review, Indo. A. J. of Pharmceutical Sciences, 2(3): 684-91.
7. U. B. Patel et al. 2017. Liquisolid compacts : A review, Int. J. Adv. in Pharmceutics 6(7),110-13.
8. W. Wienen, M. Entzeroth, J. C. A. Van Meel et al. 2000. A review on telmisartan: a novel, long-acting angiotensin II-receptor antagonist, Cardiovascular Drug Reviews, vol. 18(2), 127-156.
9. M. Kaur, R. Bala and S. Arora. 2013. Liquisolid technology: A review, Int. J. Adv. in Pharm. Sciences 4 ,98-104.
10. P. R. Kamble, K. S. Shaikh, and P. D. Chaudhari. 2014. Application of liquisolid technology for enhancing solubility and dissolution of rosuvastatin, Advanced Pharmaceutical Bulletin, 4(2), 197-204.
11. B. Bonthagarala et al. 2019. Quality-by-Design based development and characterization of pioglitazone loaded liquisolid compact tablets with improved biopharmaceutical attributes, Journal of Drug Delivery Science and Technology 51, 345-55.
12. Spireas, S. Sadu. 1998. Enhancement of prednisolone dissolution properties using Liquid -solid compacts, Int. J. Pharm. 166, 177-188
13. S. A. Tayel, I. I. Soliman, and D. Louis. 2008. Improvement of dissolution properties of Carbamazepine through application of the liquisolid tablet technique, European Journal of Pharmaceutics and Biopharmaceutics,69(1), 342-347.
14. N. Tiong and A. A. Elkordy. 2009. Effects of liquisolid formulations on dissolution of naproxen, European Journal of Pharmaceuticsand Biopharmaceutics, 73(3), 373-384.
15. J. L. Ford and T. E. Mann. 2012.Fast-Scan DSC and its role in pharmaceutical physical form characterisation and selection, Advanced Drug Delivery Reviews, 64(5), 422-430.