Ind. J. Pharm. Edu. Res., 2024; 58(4):1198-1204.
https://www.ijper.org

Original Article

Development and Characterization of Liquisolid Compact to Improve Dissolution of an Antihypertensive Drug

Arvinder Kaur[1,*], Sachin Verma[1], Deepa Bagur Paramesh[1], Nawaz Mahammad[2]

[1]Department of Pharmaceutics, KLE College of Pharmacy (Constituent Unit of KLE Academy of Higher Education and Research, Belagavi), Bengaluru, Karnataka, INDIA.
[2]Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education, Anantapur, Andhra Pradesh, INDIA.

ABSTRACT

Background: The goal of the current research was to use the straight forward, scalable, and economical Liquisolid compact to improve the dissolution profile of the poorly soluble medication Ramipril. **Objectives:** Utilising various polymers and liquid vehicles, the study's objective was to develop and characterise Liquisolid compact. **Materials and Methods:** Ramipril liquisolid were formulated using Propylene glycol and PEG 400 as liquid vehicle, MCC as a carrier, Aerosil 200 as a coating material. By using differential scanning calorimetry, the crystallinity of the newly developed drug formulation and the interactions between excipients were investigated. No interaction between the medication and excipients was established by FTIR tests. **Results:** The friability, hardness, weight variation, disintegration test, and *in vitro* dissolution investigations of all formed systems were evaluated for post-compression parameters. The optimized F9 formulation showed better results *in vitro* dissolution of 97.91% at 60 min, when compared with the marketed which showed 77.28% at 60 min. **Conclusion:** The drug release rates from liquisolid compacts were substantially higher than those from commercial formulations, which points to a potential strategy for speeding up the breakdown of medications that aren't very water-soluble.

Keywords: Ramipril, Liquisolid, Dissolution enhancement, Immediate drug release, FT-IR.

Correspondence:
Mrs. Arvinder Kaur
Department of Pharmaceutics, KLE College of Pharmacy (Constituent Unit of KLE Academy of Higher Education and Research, Belagavi), Bengaluru, Karnataka, INDIA.
Email: Kaurarvinder@outlook.com

Received: 27-06-2023;
Revised:18-01-2024;
Accepted: 20-08-2024.

INTRODUCTION

Liquisolid technology is a novel approach to improving the bioavailability and solubility of medications that are not readily soluble.[1,2] Using this method, the drug is combined with a carrier substance and a liquid non-volatile solvent to create a non-adherent, free-flowing, and compressible powder.[3-5]

In order to prepare a medication solution, suspension, or emulsion, liquidsolid systems often consist of non-volatile solvents (or just the drug).[2,4,7] The medicine is carried inside the liquid system during preparation because these solvents do not evaporate, and the resultant solid product is subsequently distributed throughout by the liquid system.[6-8]

Liquisolid system is a novel drug delivery system that has several advantages over conventional drug delivery systems. Here are several advantages of liquisolid system:

Improved drug solubility: Liquisolid systems make poorly water-soluble medications more soluble and more quickly dissolve by transforming them into a powder that is free-flowing and easily wettable.

Enhanced bioavailability: Liquisolid systems can improve a drug's bioavailability by expanding its surface area and speeding up its disintegration.

Customized drug release: Depending on the requirements of the medicine and the desired therapeutic effect, liquisolid systems can be created to release drugs in a controlled manner, either right away or over a lengthy period of time.

Increased patient compliance: By lowering the number of doses needed each day, lowering the chance of adverse effects, and offering a more practical and user-friendly dosage form, liquidsolid systems can increase patient compliance.

Cost-effective: In comparison to other drug delivery methods, liquidsolid systems are more affordable since they can be produced using standard tools and procedures.[9-12]

Overall, using liquisolid systems is an approach that shows promise for enhancing the effectiveness and security of drug delivery systems.[13,14]

Ramipril is of BCS class II which is an antihypertensive drug. Less than 2.2 mg/mL of ramipril were reported to be soluble in water. Following oral administration, the medication is quickly

DOI: 10.5530/ijper.58.4.132

Copyright Information :
Copyright Author (s) 2024 Distributed under Creative Commons CC-BY 4.0

Publishing Partner : EManuscript Tech. [www.emanuscript.in]

absorbed, with a bioavailability of about 27%. In order to increase the drug's bioavailability, the dissolution rate in the stomach must be increased. With the support of liquisolid compact technology, the extant study aimed to enhance ramipril's dissolution.

MATERIALS AND METHODS

Ramipril was received as a gift sample from Dr. Reddy Laboratories Pvt. Ltd., Hyderabad, India. PEG 400 [SPECTROCHEM Pvt. Ltd., Mumbai], Propylene glycol [Loba Chemicals, Mumbai] Aerosil 200 [HiMedia Laboratories Pvt. Ltd., Nashik], Microcrystalline Cellulose [Fine-Chem Ltd., Tarapur], PVP K30 [Loba Chemie Pvt. Ltd., Tarapur]. Marketed product of Ramipril 5 mg [Cipla Pvt. Ltd., Solan] was procured from pharmacy.

Solubility Studies

Ramipril was subjected to a shake flask method solubility investigation in a variety of solvents, including propylene glycol and polyethylene glycol 400. Every volumetric flask carrying 1 mL of solvent both Propylene glycol and PEG 400 also contained an excess amount of medication. Using rotatory shaker, for 48 hr solutions were prepared at room temperature. UV spectrophotometer set to 210 nm was used to measure the medication concentration in each solution.[15,16]

Preparation of Liquisolid Compact

A 20 mL glass beaker was filled with the exact calculated amount of liquid vehicle and medication, and it was thoroughly mixed. The resultant mixture was added to the suitable quantum of carrier and coating materials Table 1. There were three steps in the mixing procedure.In first, system was mixed for around a minute at a mixing rate of one rotation per second to equally distribute liquid medication throughout the powder. In second, a mortar's surface was coated with a uniform layer of the liquid/powder mixture, which was then let to stand for around 5 min to allow the drug solution to permeate the powder particles. In third step, using an aluminium spatula to scrape the powder from the mortar's surface. The mixture was then mixed in a mortar with Carrier: Coating material [20:1]. The produced liquisolid system was then given a final addition of 5% (w/w) disintegrant.[17-19,21,23]

Formulation Design of LSC

Precompression Studies of Liquisolid Compact

Angle of Repose

The surface of a powder pile can only be angled away from the horizontal plane at this maximum angle Table 2. From a height of 4 cm above the base, a funnel was used to release 10 g of powder. The diameter of the base and pile height were measured, and the formula used;[19-21]

$$\tan \theta = h/r$$

$$\theta = \tan\text{-}1\ (h/r)$$

Where, θ=angle of repose, h=height, r=radius.

Bulk Density: Powder was cautiously poured into a graduated cylinder here after being correctly weighed Table 2. The bulk volume was then determined in millilitres by directly measuring it from cylinder's mark. The following formula is used to determine bulk density;

Bulk density=Powder's weight/Bulk volume

Tapped Density: The same measuring cylinder was placed into the tap density equipment after the bulk volume measurement Table 2.

Tapped density=Powder's weight/Tapped Volume.

Carr's Index: It is among the most popular crucial factors in characterising the nature of granules and powders Table 2. The following equation can be used to compute it:

Carr's index=[(Tapped density-Bulk density)/Tapped density] ×100

Hausner's Ratio: When analysing flow characteristics of granules and powders, Hausner's ratio is a crucial factor Table 2. The following equation can be used to compute this;

Hausner's ratio=Tapped density/Bulk density

IR spectra analysis: The majority of molecules absorb light in the infrared range, which is the basis for FTIR (Figure 1a). The bonds in the molecule are directly related to this absorption. Wave numbers used to measure frequency ranges often fall between 4000 and 400 cm^{-1} (Figure1b).

DSC: Thermograms of Ramipril and liquisolid compact were captured on DSC, after scanning thermal behaviour of the samples was examined (Figure 2).

Post Compression Studies

Weight variation: Using 20 liquisolid compact tablets, the weight variation test was conducted Table 3.[16,22-25]

Hardness: The mean hardness of three manufactured liquisolid tablet was computed using the Pfizer hardness tester Table 3.

Friability: For the purpose of determining friability, a Roche type apparatus was utilised and the drum was revolved at 25 rpm for 4 min Table 3.

% friability=mass loss x 100/initial mass

Table 1: Liquisolid tablet formulation of Ramipril.

Formulation	Ramipril (mg)	PEG 400 (%) w/w	PG (%) w/w	MCC (mg)	Aerosil 200 (mg)	PVP K30 (%) w/w	L_f
F1	5	10	-	150	7.5	5	0.33
F2	5	10	-	200	10	5	0.25
F3	5	15	-	200	10	5	0.166
F4	5	15	-	225	11.25	5	0.148
F5	5	20	-	200	10	5	0.125
F6	5	20	-	225	11.25	5	0.111
F7	5	20	-	250	12.5	5	0.10
F8	5	-	20	175	8.75	5	0.142
F9	5	-	20	200	10	5	0.125
F10	5	-	20	225	11.25	5	0.111
F12	5	-	20	250	12.5	5	0.10

Excipient Ratio, R=Q/q. Q=carrier's weight, q=coating material's weight. Excipient ratio was maintained at 20. L_f=W/Q. W=weight of liquid medication.

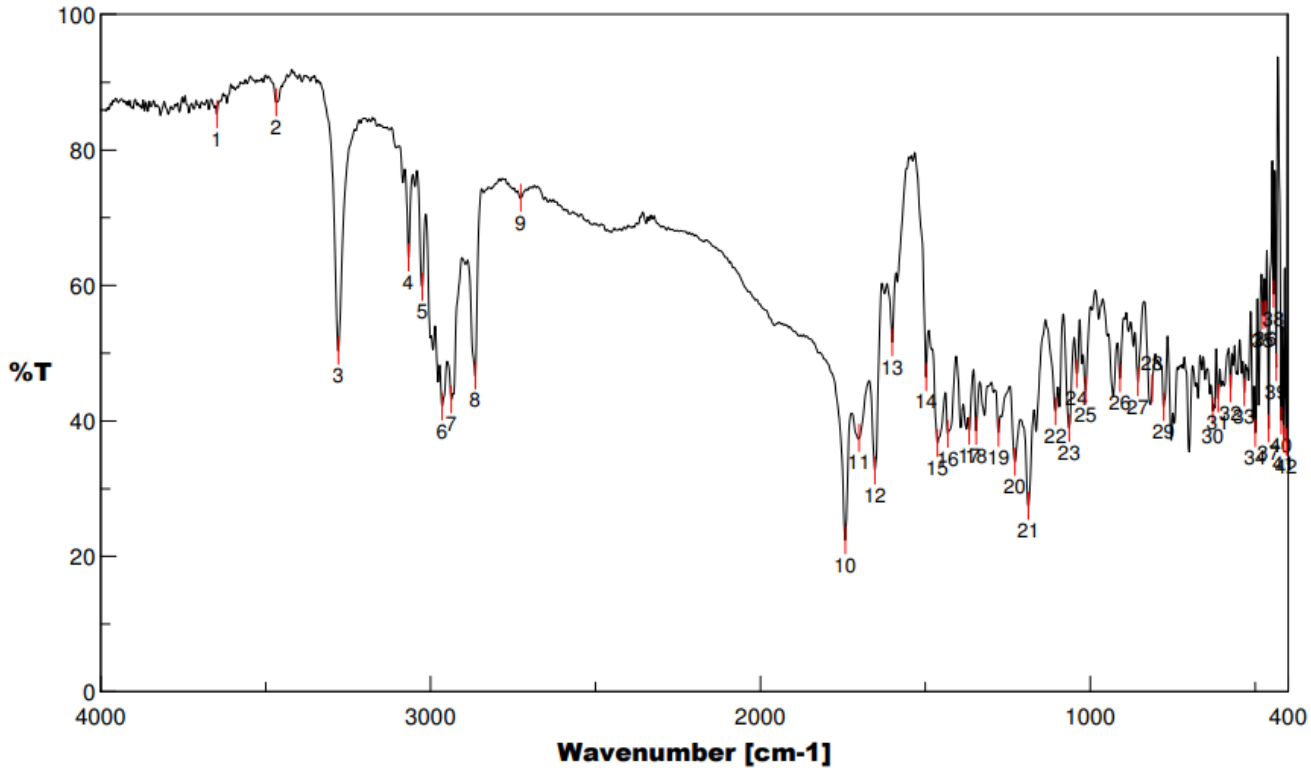

Figure 1a: FT-IR of Ramipril.

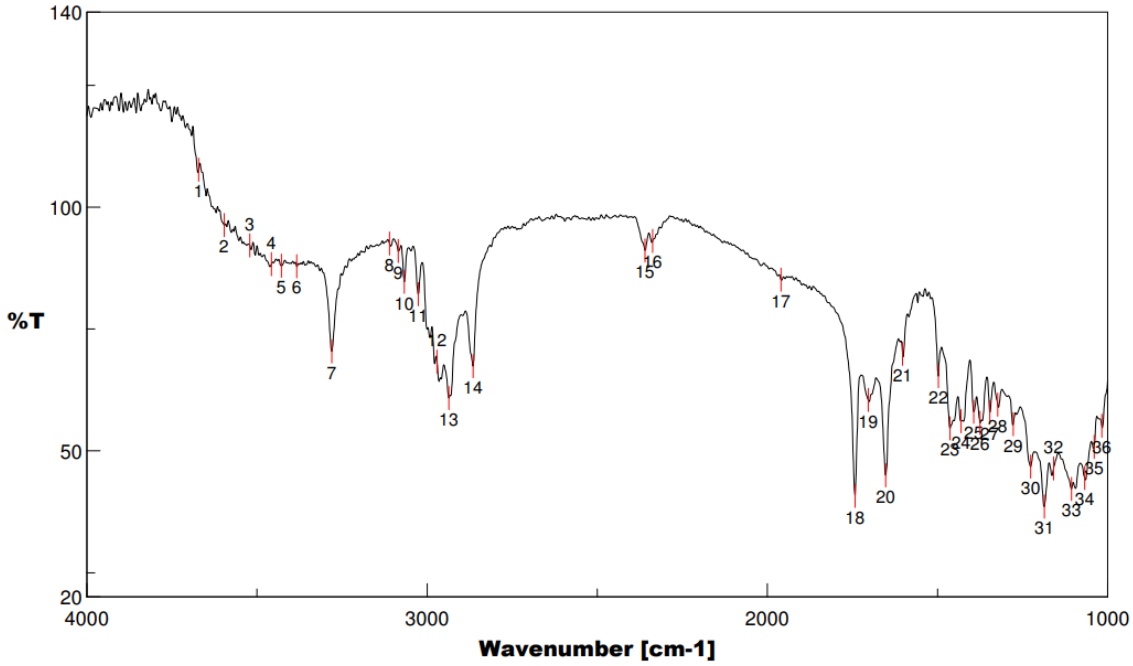

Figure 1b: FT-IR of physical mixture.

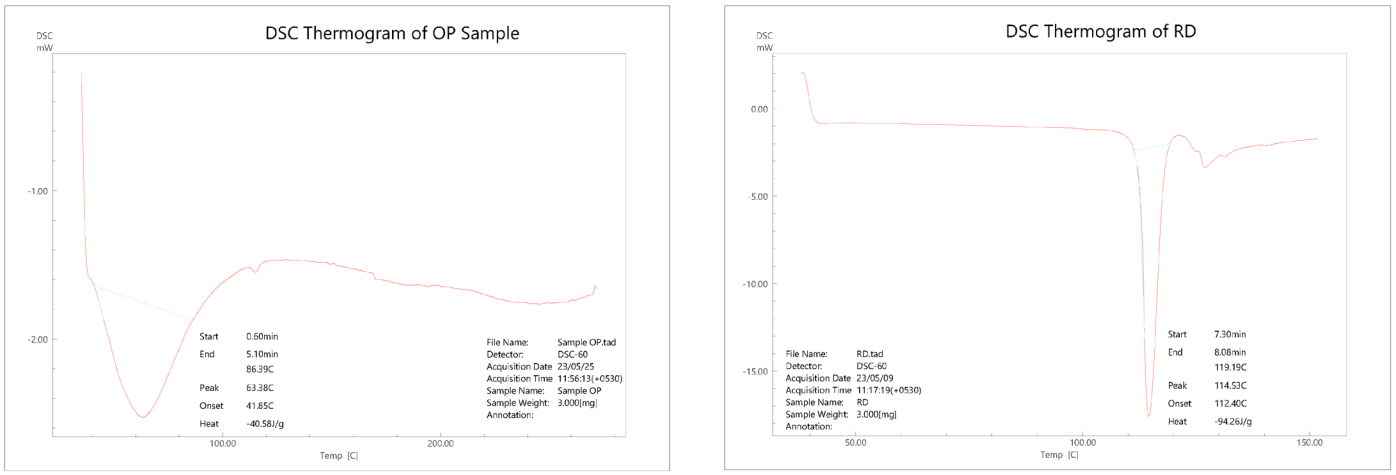

Figure 2: Ramipril Dsc Thermogram And F9 Formulation Dsc Thermogram.

Drug content

The term "drug content uniformity" describes how evenly the active component is distributed throughout a pharmaceutical dosage form, such as tablets or capsules Table 3.

Disintegration test

Using the tablet disintegration device, the disintegration test was conducted for six tablets from each formulation at 37°C in distilled water. As there is no trace of the tablets on the screen, they were deemed entirely destroyed. Low compression pressures should be used to provide the desired tablet hardness so that the compressed tablet allows for simultaneous drug dissolution and quick disintegration Table 3.

In vitro dissolution studies

Utilising the USP-I dissolution test device, an *in vitro* dissolving profile of tablets and liquisolid compacts was produced. Dissolution investigations were conducted at 37°C for 75 rpm using 0.1 N HCl and distilled water upto 500 mL media. 5 mL samples were taken every 10 min up to 60 min. To keep the washbasin situation constant, the dissolution medium was changed out for 5 mL to maintain sink condition. Filtered and sent to spectrophotometric analysis were the samples that had been withheld.

Table 2: Flow properties.

Formulation	Angle Of Repose (°)	Observation	Bulk Density (Gm/Ml)	Tapped Density (gm/mL)	Carr's Index (%)	Hausner's Ratio
F1	41.27±0.3478	Poor	-	-	-	-
F2	43.32±0.4538	Poor	-	-	-	-
F3	42.57±0.4428	Poor	-	-	-	-
F4	48.46±0.5682	Poor	-	-	-	-
F5	45.45±0.0874	Poor	-	-	-	-
F6	46.67±0.5676	Poor	-	-	-	-
F7	43.59±0.6742	Poor	-	-	-	-
F8	29.94±0.2402	Excellent	0.553±0.0057	0.656±0.0057	12.986±1.875	1.186±0.0115
F9	31.51±1.0678	Good	0.583±0.0115	0.640±0.0264	9.863±1.148	1.096±0.0251
F10	31.86±0.2990	Good	0.566±0.0251	0.636±0.0208	10.826±1.815	1.12±0.02
F11	32.23±0.4410	Good	0.563±0.0057	0.640±0.0100	11.953±2.211	1.133±0.030

N=3.

Table 3: Post compression studies of LSC.

Formulation	Thickness (mm)	Weight Variation (mg)	Hardness (kg/cm^2)	Friability (%)	Disintegration Time (min)	Uniformity Content (%)
F8	3.34±0.07	217.33±1.1547	4.3±0.2645	0.5733±0.1150	3.73±0.0436	98.78±0.765
F9	3.79±0.017	247.33±1.1257	4.53±0.2081	0.7566±0.0550	3.10±0.0543	99.45±0.257
F10	3.72±0.118	268.33±1.5275	4.3±0.2645	0.5366±0.1450	3.48±0.0567	99.18±0.542
F11	3.79±0.119	296.33±1.2575	4.43±0.3055	0.8366±0.0416	3.66±0.0621	97.57±0.387

N=3.

Table 4: *In vitro* dissolution studies.

Time (min)	F8 (%)	F9 (%)	F10 (%)	F11(%)	M (%)
0	0	0	0	0	0
10	16.576	21.106	14.356	15.096	13.616
20	36.294	38.227	26.521	29.335	27.408
30	48.651	53.104	44.779	46.266	35.307
40	59.996	72.302	64.997	60.567	50.772
50	77.580	88.563	79.773	77.426	60.491
60	92.416	97.916	94.59	93.416	77.928

F8 -F11 Liquisolid formulation, M=Marketed product.

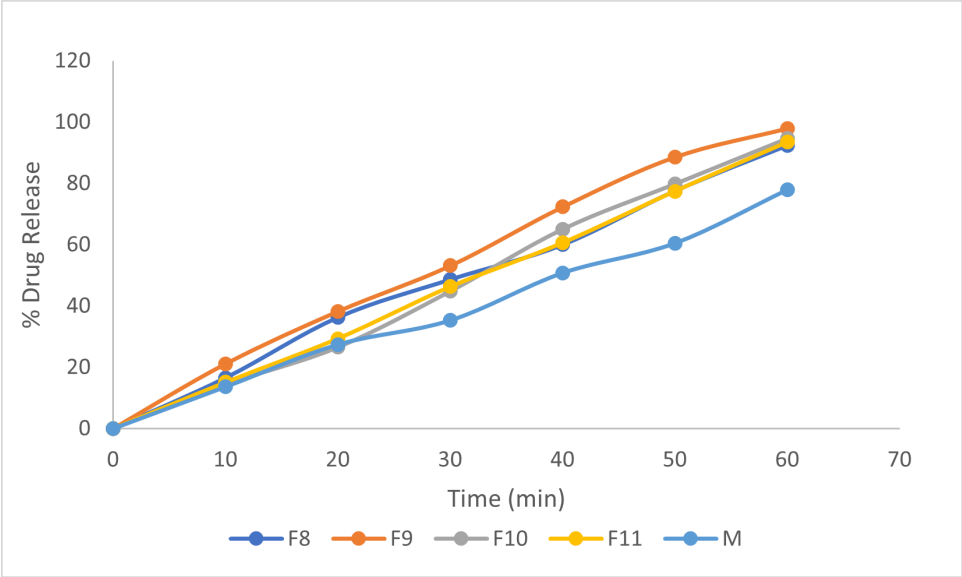

Figure 3: Lsc Dissolution Study (F8-F11) And Marketed (M).

RESULTS AND DISCUSSION

Solubility Studies

All of the Ramipril solution standard curves, followed Beer's law at concentration range of 1-10 µg/mL was linear. Ramipril's solubility in Propylene glycol (13.28 w/w) and PEG 400 (9.56 w/w) was determined.

IR spectra analysis

Samples of pure ramipril and physical mixture was subjected to FT-IR spectroscopic analysis and their spectra are shown in Figure 1a and 1b.

Characteristics peak of aromatic N-H stretching, O-H stretching, C=O stretching at 3468 cm^{-1}, 3279 cm^{-1}, 1742 cm^{-1} appeared respectively.

The Ramipril physical mixture's IR spectrum had all of the reference peaks that can be seen in the IR spectra of ramipril.

DSC

DSC was used to assess the potential interaction in an excipient and pharmacological core in a liquisolid compact. Ramipril in its purest form has distinguishing peak around 114.53°C, which is a key sign of the drug's crystalline composition. Additionally, the thermal behaviour of the liquisolid system (Figure 2) demonstrates the moving of the peak. It suggests that the drug's crystalline nature entirely transforms into an amorphous form, which causes a noticeable variation in the endothermic peak of the resulting liquisolid compact.

Flow properties

Angle of repose

The angle of repose which is a gauge of the internal friction or cohesion of the particles, will have a high if the powder is cohesive and a low if it is not Table 2.

Here, F1-F7 by using PEG 400 angle of repose was found to be higher than 40°. So, further these formulations were not taken for an evaluation. F8-F11 using Propylene Glycol shows good flow properties.

Post Compression Studies

In vitro dissolution studies

Significantly better dissolving rate was shown by liquidsolid compact. Liquisolid compacts appear to have a much faster rate of medication disintegration than traditional tablets. in vitro dissolution studies shown in Table 4 provide a comparison between liquisolid compact and marketed formulation. Comparing a traditional tablet to Liquisolid compact F9, the former produced a highest level of dissolution (0.1 N HCl). Has maximum dissolution rate as, it shows 97.91% release in 60 min. From F8-F11 by Figure 3 we can see that drug release gradually increases in time interval of 10-60 min. The medication dissolves at a faster rate now. The drug's improved water solubility and surface area for dissolution.

CONCLUSION

The study proved that liquisolid technique can be an alluring approach for progressing the dissolution profile of BCS class II drugs. The best formulation of liquisolid tablets among all batches made is F9, which has propylene glycol at drug concentrations of 20% w/w. This formulation has a quicker disintegration time, a

better dissolution profile, and acceptable tablet characteristics. It was look for that propylene glycol was a good liquid vehicle for creating Ramipril liquisolid compacts. There were no any interactions between Propylene glycol and drug according to DSC thermogram. The dissolution of Ramipril was significantly increased in liquisolid formulation compared to the marketed product.

ACKNOWLEDGEMENT

The authors are thankful to KLE College of Pharmacy, Bangalore for helping in procuring the drug sample and for the guidance in performing the instrument work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DCT: Directly Compressible Tablet; **LSC:** Liquid Solid Compact; **PEG:** Polyethylene Glycol.

SUMMARY

The study likely demonstrates improved dissolution rates for the antihypertensive drug when formulated as a liquisolid compact, potentially leading to enhanced bioavailability and therapeutic efficacy.

REFERENCES

1. Narender Thakur, Sukhbir Lal Khokra, Dharmesh Sharma, Naseeb Singh Thakur, Rahul Purohit, Vikrant Arya. A review on pharmaceutical applications of liquisolid technique. American journal of Pharmatech research. 2011;1(3);2249-3387.
2. Nokhodchi A, Aliakbar R, Desai S, Javadzadeh Y. Liquisolid Compacts. The effect of co solvent and HPMC on Theophylline release. Colloid Surf B Biointerfaces. 2010;79:262-9.
3. Nokhodchi A, Javadzadeh Y, Mosaelrezaei L. Liquisolid technique for sustaining the drug release from Compacts. J Pharm Pharmacol 2007;59:A19-20.
4. Darwish IAE, El-Kama AH. Dissolution enhancement of Glibenclamide using Liquisolid tablet technology. Act Pharm 2001;51:173-81.
5. Gubbi S, Jarag R. Liquisolid technique for enhancement of dissolution properties of Bromhexine Hydrochloride. Res J Pharm and Tech 2009;2:382-8.
6. Nokhodchi A, CM Hentzschel, Leopord CS. Drug release from Liquisolid system: speed it up, slow it down. Expert Opin Drug Del 2011;8:191-205.
7. Spireas S, Jarowski CI, B Rohera. Powdered Solution Technology: Principles and Mechanism. Pharm Res 1992;9:1351-8.
8. B. Vraníková and J. Gajdziok. Liquisolid systems and aspects influencing their research and development. Acta Pharm. 2013;63:447-65.
9. S. Spireas, S.M. Bolton, Liquisolid systems and methods of preparing same, US Patent. 1999
10. C. Lipinski, Poor aqueous solubility-an industry wide problem in drug discovery, Am. Pharm. Rev. 2002;5:82-5
11. Amol S. Deshmukh, Vinod G. Mahale, Vijay R. Mahajan. Liquisolid Compact Techniques: A Review. Research Journal of Pharmaceutical Dosage Forms and Technology. 2014;6(3):161-6.
12. Nilesh P. Kala, Divyesh H. Shastri, and Pragna K. Shelat. Design and Characterization of Buccoadhesive Liquisolid System of an Antihypertensive Drug. Journal of Drug Delivery. 2015;574247.
13. El-Say KM, Samy AM, Fetouh MI. Formulation and Evaluation of Rofecoxib Liquisolid Tablets. International Journal of Pharmaceutical Sciences Review and Research. 2010;3:135-42.
14. Ngiik Tiong, Amal A. Elkordy. Effects of liquisolid formulations on dissolution of naproxen. European Journal of Pharmaceutics and Biopharmaceutics. 2009;73:373-84.
15. Sandip Vajir, Vishal Sahu, Nilesh Ghuge, B.V.Bakde. Liquisolid compact: a new technique for enhancement of drug dissolution. International journal of pharmaceutical research and development. 2011;4(3):302-6.
16. Mei Lu, Haonan Xing, Jingzheng Jiang, Xiao Chen, Tianzhi Yang, Dongkai Wang, *et al.* Liquisolid technique and its applications in pharmaceutics. asian journal of pharmaceutical sciences. 2017;12:115-23.
17. Kala N. P., Shaikh M. T., Shastri D. H., Shelat P. K A Review on Liquisolid Systems. Journal of Drug Delivery and Therapeutics. 2014;4(3):25-33.
18. Remeth Jacky Dias, Kailas Krishnat Mali, Vishwajeet Sampatrao Ghorpade, Vijay Daulatrao Havaldar, Vishal Ramesh Mohite. Formulation and Evaluation of Carbamazepine Liquisolid Compacts Using Novel Carriers. Indian Journal of Pharmaceutical Education and Research. 2017;51:S69-78.
19. Manali D. Prajapata, Shital B. Butania, Mukesh C. Gohel. Liquisolid: A promising technique to improve dissolution efficiency and bioavailability of poorly water soluble nimodipine. Journal of Drug Delivery Science and Technology. 2019;53(44):101135.
20. Naveen Chella, Nalini Shastri and Tadikonda Rama Rao. Use of the liquisolid compact technique for improvement of the dissolution rate of valsartan. Acta Pharmaceutica Sinica B. 2012;2(5):502-8.
21. Indian Pharmacopoeia. The controller of Publications, Ministry of Health and Welfare, New Delhi: 1996.
22. N. Jaipakdee, E. Limpongsa, B-o. Sripanidkulchai, P. Piyachaturawat, Preparation of *Curcuma comosa* tablets using liquisolid techniques: *In vitro* and *in vivo* evaluation, International Journal of Pharmaceutics. 2018;553(1-2):157-68.
23. Gubbi S, Jarag R. Liquisolid technique for enhancement of dissolution properties of bromhexine hydrochloride. Research Journal of Pharmacy and Technology. 2009;2(2):382-6.
24. Nawaz Mahammed, Harshini Yadav, Ashok Thulluru, Narahari Narayana, Saravanakumar, Anna Balaji, *et al.* Formulation and Evaluation of Clopidogrel Bisulphate Tablets by Liquisolid Compact Technique. Research J. Pharm. and Tech 2020;13(5):2427-34.
25. E. Bhavya, M.D. Dhere. Liquisolid Compacts Technique of Poor Water-Soluble Drugs: An Overview. Research Journal of Pharmacy and Technology 2021;14(10):5569-2.

Cite this article: Kaur A, Verma S, Paramesh DB, Mahammad N. Development and Characterization of Liquisolid Compact to Improve Dissolution of an Antihypertensive Drug. Indian J of Pharmaceutical Education and Research. 2024;58(4):1198-204.