IJPSR (2020), Volume 11, Issue 6 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 18 July 2019; received in revised form, 07 October 2019; accepted, 22 October 2019; published 01 June 2020

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION PROFILE OF EPLERENONE BY LIQUISOLID COMPACTS USING NOVEL EXCIPIENTS

G. Narender Naik [*1] and R. Shyam Sunder [2]

Jyothishmathi Institute of Pharmaceutical Sciences [1], Karimnagar - 505527, Telangana, India.
University Institute of Chemical Technology [2], Osmania University, Hyderabad - 500007, Telangana, India.

Keywords:

BCS-Class II drug, Liquisolid compact, Non-volatile liquid, Carrier, Coating material.

Correspondence to Author:
G. Narender Naik

Assistant Professor,
Jyothishmathi Institute of Pharmaceutical Sciences, Karimnagar - 505527, Telangana, India.

E-mail: skyrowhruday29@gmail.com

ABSTRACT: Eplerenone is a poorly soluble drug that belongs to class II biopharmaceutical classification system. It is a selective aldosterone receptor antagonist, which binds to the mineralocorticoid receptor and blocks the binding of aldosterone, thereby decreases the sodium resorption and subsequently increasing water outflow. This leads to a decrease in blood pressure and used in congestive heart failure. The aim of the present study was to improve the solubility, dissolution and permeability properties of Eplerenone by liquisolid compacts, thereby enhancing oral bioavailability. Different formulations of Liquisolid were developed by dissolving the drug in mixture of Transcutol HP: Capmul MCM and Cremophor EL: Capmul MCM (Non-volatile liquid; 1:1 ratio), converting this liquid medication using carriers as fujicalin and neusilin and coating material as syloid FP 244. The results showed that Liquisolid formulation exhibited significantly higher drug dissolution rate compared to pure drug as well as marketed formulation. The plasma concentration-time profile of healthy Wister rats indicated that the oral bioavailability of optimized formulation has been significantly improved compared to pure drug and marketed formulation. The enhanced bioavailability might be due to increased wetting properties of drug and permeability of the drug due to lipophilic properties of solvent used for wetting. This study can conclude that Liquisolid technique is a promising alternative method for improving the bioavailability of class-II drugs.

INTRODUCTION: Nowadays, the synthesis of poorly soluble drugs increasing steadily [1]. Around 75% of the new drug candidates are poorly water-soluble [2], therefore, there is great interest in developing techniques to improve the solubility and the dissolution rate of drugs [3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(6).2892-98

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(6).2892-98

BCS Class II drugs pose challenging problems in their pharmaceutical product development process because of their low solubility and dissolution rates.

Therapeutic effectiveness of a drug depends up on the bioavailability and ultimately up on the solubility and dissolution rates of drug molecules [4, 5]. Solubility and dissolution rate are the important parameters to achieve the desired concentration of drug in systemic circulation for pharmacological response to be shown [6, 7]. The dissolution rate is one of the rate-determining step in the drug absorption [8, 9].

The challenge for these poorly soluble drugs /class –II drugs is to enhance the solubility and dissolution profile by several techniques such as micronization [10], solid dispersions [11], salt formation [12], micellar solubilization [13], hydrotrophy [14], inclusion complexes [15], lyophilisation [16], co solvency [17,] *etc*. Despite the availability, these techniques are suffering from one or two drawbacks like reduced micromeritics or altered stability and still need further development to overcome them.

One of the novels and most promising techniques for promoting dissolution is the formation of liquisolid compacts among all. Liquisolid compacts promotes dissolution rate of water-insoluble drugs to a greater extent and also enhances the drug flow property [18]. The liquisolid compaction technology is described by Spire as liquid medication may be transformed into a free-flowing, readily compressible, and apparently dry powder by simple physical blending with selected excipients named the carrier and coating material [19]. When the drug is dissolved in the liquid vehicle and incorporated into a carrier material which has a porous surface and closely matted fibres in its interior as cellulose, where both absorption and adsorption mechanism takes place; *i.e.*, initially the liquid is absorbed in the internal structure of carrier and after the saturation process, adsorption of the liquid on to the internal and external surfaces of the porous carrier particles takes place. And where the coating material posses high adsorptive property and large specific surface area that gives the desirable flow characteristic and also increases the wetting property. Thus, due to significantly increased wetting properties and surface area of drug available for dissolution [20]. So, liquisolid compacts of water-insoluble substances may be expected to enhancement of drug release and consequently, improved Oral bioavailability [21].

Eplerenone is a class II drug, aldosterone receptor antagonist approved by Food and drug administration on September 27, 2002 and October 7, 2003 with therapeutic applications as antihypertensive and can also be used as monotherapy for initial management of uncomplicated hypertension [22, 23]. In this study Eplerenone was taken as a model drug, dissolution enhancement was done by liquisolid compaction technology using combination of nonvolatile liquids and novel carriers to improve its oral bioavailability [24].

MATERIALS AND METHODS:

Materials: Gift sample Eplerenone received from Dr Reddy's Laboratories Ltd. Miyapur, Hyderabad, Telangana, India. The following materials were gifted by Abitec Corp, Mumbai, India and were used as received: Captex355 (Glyceryltricaprylate), Captex 200 (Propylene glycol dicaprylocaprate), Transcutol HP and Cremophor EL. Labrafil M 2125CS (Linoleyl macrogol-6 glycerides), Labrafil 1944CS, Lauroglycol 90 (Propylene glycol mono-laurate), PlurolOleique (Polyglyceryl-3 dioleate), Capmul MCM (Glycerylmonocaprylate), Capmul C8, Acconon C-80 (Polyoxyethylene 80 coconut glycerides) were received as gift sample from Gattefosse, India. Tween 80, PEG 400, and PG were purchased from SD Fine Chemicals, India. Fujicalin (Dibasic calcium phosphate anhydrous) and Neusilin (Magnesium aluminometasilicate) obtained as gift sample from Fuji Chemical Industry Co. Ltd., Japan.

Methods:

Saturation Solubility Studies: Eplerenone Saturation solubility studies done in different non-volatile solvents and followed by combination of solvents in which drug is shown to have maximum solubility was estimated by conducting saturation solubility studies. 10 mL Solvent was taken in a series of vials and an excess amount of drug added and subjected to continuous shaking using a rotary shaker for 48 h at room temperature. Then each solution was centrifuged, filtered through Whatman filter paper no. 42 and clear supernatants were analyzed for drug content and solubility using UV-spectrophotometer at 245 nm.

Selection of Coating, Carrier Materials & Preparation of Liquisolid Compacts: Novel carriers fujicalin (dibasic calcium phosphate anhydrous) and neusilin (magnesium alumina-metasilicate) were selected as carriers, Syloid FP 244 as coating material and carrier to coating ratio was varied from 5:1 to 10:1. From the saturation solubility studies it was observed that the drug is having maximum solubility in Transcutol HP: Capmul MCM and Cremophore: Capmul MCM when used in combination at the ratio of 1:1.

Hence, the solvent system has been used as non-volatile vehicle. The liquid medication was prepared at 25% w/w and 50% w/w drug concentration by adding the weighed quantity of drug to the required quantity of previously mixed liquid vehicle. The resultant liquid medication was incorporated into carrier and coating material by admixing in a mortar to get freely flowable non-adherent powder. The total quantity of each formulation was adjusted to 500 mg to get uniform weight for each formulation with Avicel pH 102. The liquid/powder admixtures were then evaluated for their micromeritics, uniformity of drug content and *in-vitro* dissolution.

***In-vitro* Drug Release Studies:** Dissolution studies of all the prepared formulations were performed using USP Dissolution apparatus II using 1000 mL of 0.1 N HCl. The temperature and speed of rotation maintained were 37 ± 0.5 °C and 50 rpm, respectively. 5 mL samples were collected and the equal volume of fresh dissolution medium was replaced at predetermined time points and analyzed using UV-spectrophotometer at 245 nm.

***In-vivo* Evaluation for Pharmacokinetic Parameters:** The study protocol (JIPS/IAEC/ 2018/01) was prepared and approved by the Institutional Ethics Committee of the institution (reg. no.:7970/PO/Re/S/76/ CPCSEA). The *in-vivo* pharmacokinetic study was conducted in white Wistar rats. Animals were fed with standard diet throughout the study as there was no impact of diet on drug absorption. 18 rats weighing 210-260 g were divided into 3 groups of six in each. Group 1 was administered with pure drug, group 2 was administered with marketed formulation (Eptus 25 mg) and group 3 was administered with optimum formulation at 2 mg/kg dose through oral route. Blood samples were collected from retro orbital vein at predetermined time points up to 8 h and were centrifuged at 5000 rpm for 5 min. Plasma was collected and stored at -20 °C until analyzed. The plasma samples were analyzed using RP-HPLC, and plasma drug concentrations were determined using standard calibration curve. All possible pharmacokinetic parameters (AUC, C_{max}, T_{max}, $t_{1/2}$) were calculated for each formulation and each subject. Relative bioavailability of optimized formulation was done comparatively with pure drug and marketed formulation.

RESULTS AND DISCUSSION:

Saturation Solubility Studies: Saturation solubility studies in different solvents were performed and the results obtained are represented as a bar graph in **Fig. 1**. Among all the solvents tested, Eplerenone was found to be higher in Cremophore EL (6.2 mg/ml), Transcutol HP (5.6 mg/ml), Capmul MCM (4.5 mg/ml) compared to other solvents.

Saturation solubility of the drug was also estimated in the combination of these solvent mixtures at the ratio of 1:1 to check the synergistic effect. It was found that the solubility of drug was increased to 7.5 mg/mL within the solvent blend of Cremophore EL: Capmul MCM and it was further increased to 8.2 mg/mL with the solvent blend of Transcutol HP: Capmul MCM.

Hence, the solvent blend consisting of Transcutol HP: Capmul MCM and Cremophore EL: Capmul MCM was selected as non-volatile liquid vehicle to improve the dissolution rate of drug.

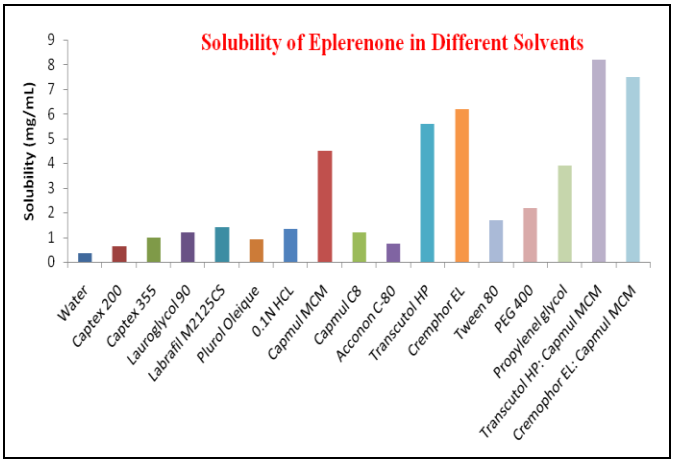

FIG. 1: SATURATION SOLUBILITY OF EPLERENONE IN DIFFERENT SOLVENTS

Formulation of Liquisolid Compacts: Composition of various formulations of liquisolid compacts are represented in **Table 1**.

Micromeritics and Drug Content Uniformity of Liquisolid Formulations: Flow properties of all the formulations were evaluated and the results are shown in **Table 2**. Values of angle of repose (32.4 ± 0.4 - 40.1 ± 0.2), carr's index (13.14 ± 0.2 - 18.66 ± 0.3) and Hausner's ratio (<1.24) in all the formulations corresponding to good flow. The flowability of Eplerenone liquisolid formulations was enhanced compared with pure drug.

TABLE 1: COMPOSITION OF LIQUISOLID COMPACTS OF EPLERENONE

Ingredient Name	F1	F2	F3	F4	F5	F6	F7	F8
Drug	25	25	25	25	25	25	25	25
Transcutol HP	12.5	37.5	12.5	37.5	12.5	37.5	12.5	37.5
Capmul MCM	12.5	37.5	12.5	37.5	12.5	37.5	12.5	37.5
Cremophor EL	NA	NA	NA	NA	NA	NA	NA	NA
Fujicalin	150	300	150	300	NA	NA	NA	NA
Neusilin	NA	NA	NA	NA	140	280	140	280
Syloid FP	15	30	30	60	14	28	28	56
Avicel PH 102	285	70	270	40	296	92	282	64
Total Unit Weight (mg)	500	500	500	500	500	500	500	500
Non Volatile Vehicle	Transcutol HP: Capmul MCM (1:1)							
% w/w of Liquid Medication	50	25	50	25	50	25	50	25
Ratio of Carrier to Coating Material (R)	10	10	10	10	10	10	10	10
Loading Factor (Lf)	0.333	0.333	0.333	0.333	0.357	0.357	0.357	0.357
Ingredient Name	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**
Drug	25	25	25	25	25	25	25	25
Transcutol HP	NA	NA	NA	NA	NA	NA	NA	NA
Capmul MCM	12.5	37.5	12.5	37.5	12.5	37.5	12.5	37.5
Cremophor EL	12.5	37.5	12.5	37.5	12.5	37.5	12.5	37.5
Fujicalin	160	320	160	320	NA	NA	NA	NA
Neusilin	NA	NA	NA	NA	170	330	170	330
Syloid FP	16	32	32	64	17	33	34	66
Avicel PH 102	274	48	258	16	263	37	246	4
Total Unit Weight (mg)	500	500	500	500	500	500	500	500
Non Volatile Vehicle	Capmul MCM : Cremophor EL (1:1)							
% w/w of Liquid Medication	50	25	50	25	50	25	50	25
Ratio of Carrier to Coating Material (R)	10	10	10	10	10	10	10	10
Loading Factor (Lf)	0.313	0.313	0.313	0.313	0.294	0.303	0.294	0.303

TABLE 2: MICROMERITICS AND DRUG CONTENT UNIFORMITY OF LIQUISOLID FORMULATIONS

Formulation	Angle of Repose	Carr's Index	Hausner's Ratio	Drug Content (%)
F1	38.2 ± 0.6	18.66 ± 0.3	1.22 ± 0.6	98.4 ± 0.5
F2	36.3 ± 0.2	18.03 ± 0.6	1.22 ± 0.6	97.5 ± 0.2
F3	32.4 ± 0.4	17.46 ± 0.5	1.21 ± 0.7	98.8 ± 0.4
F4	40.1 ± 0.2	17.20 ± 0.6	1.20 ± 0.8	97.2 ± 0.3
F5	34.6 ± 0.3	16.34 ± 0.7	1.19 ± 0.8	99.4 ± 0.3
F6	33.8 ± 0.6	15.17 ± 0.5	1.17 ± 0.2	99.9 ± 0.4
F7	38.5 ± 0.3	14.38 ± 0.2	1.16 ± 0.7	100.1 ± 0.2
F8	39.8 ± 0.6	13.14 ± 0.7	1.15 ± 0.6	99.9 ± 0.3
F9	34.7 ± 0.6	16.90 ± 0.5	1.20 ± 0.5	99.7 ± 0.5
F10	38.2 ± 0.7	16.12 ± 0.2	1.19 ± 0.6	99.4 ± 0.2
F11	33.9 ± 0.5	15.86 ± 0.6	1.18 ± 0.2	100.2 ± 0.3
F12	39.6 ± 0.2	15.10 ± 0.3	1.17 ± 0.7	99.2 ± 0.1
F13	38.1 ± 0.7	14.28 ± 0.2	1.16 ± 0.2	99.9 ± 0.3
F14	32.4 ± 0.4	13.54 ± 0.6	1.15 ± 0.5	102.1 ± 0.2
F15	37.2 ± 0.5	14.37 ± 0.5	1.16 ± 0.4	100.7 ± 0.5
F16	39.8 ± 0.3	15.16 ± 0.3	1.17 ± 0.7	99.2 ± 0.2

***In-vitro* Drug Release Profile of Liquisolid Formulations:** *In-vitro* drug release of liquisolid formulation was estimated using USP Type II apparatus. The dissolution profile of formulations prepared with fujicalin is shown in **Fig. 2** & **4**, prepared with neusilin is shown in **Fig. 3** & **5**. Formulation (F14) containing 25% of drug in liquid medication, neusilin as a carrier to coating ratio of 10:1 has shown fastest drug release (100% release in 15 min) when compared to other

formulations, pure drug (25.6% release in 30 minutes) and marketed formulation (91.2% release in 30 min). The comparative dissolution profile of pure drug, marketed formulation and optimized formulation has shown in **Fig. 6**. The improved dissolution rate of optimized formulation might be achieved due to higher amount of liquid vehicle, hydrophilic properties attributed by carrier materials and higher surface area provided by Syloid244FP. Hence, F14 was selected as optimized formulation for evaluating its pharmacokinetic parameters.

TABLE 3: *IN-VITRO* DRUG RELEASE PROFILE OF PURE DRUG, LIQUISOLID FORMULATIONS, AND MARKETED FORMULATIONS

Time (min)	% Drug Release																	
	Pure Drug	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	Marketed
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	3.4	28.4	52.3	41.4	58.5	56.2	70.5	52.4	64.5	45.3	62.7	51.9	65.6	64.2	75.6	58.6	70.2	20.2
10	5.2	41.5	61.3	61.5	68.5	63.6	91.6	69.5	89.8	58.6	79.9	66.4	76.4	88.9	98.6	78.5	96.5	31.2
15	8.5	52.6	69.4	68.5	79.5	76.5	95.6	79.6	94.6	64.6	89.5	74.7	83.6	93.5	100.1	85.6	98.5	48.5
20	13.5	68.4	82.5	77.5	85.6	85.4	98.6	91.2	100.1	72.9	94.6	82.6	89.7	99.8	100.1	92.3	100.2	67.8
25	18.9	78.2	88.5	82.5	89.6	90.3	100.1	96.6	100.2	83.6	100.2	91.2	93.6	100.2	100.2	98.6	100.2	79.8
30	25.6	91.2	92.6	92.5	99.6	99.9	100.1	99.9	100.1	96.5	100.1	99.7	100.1	100.1	100.1	100.1	100.1	91.2

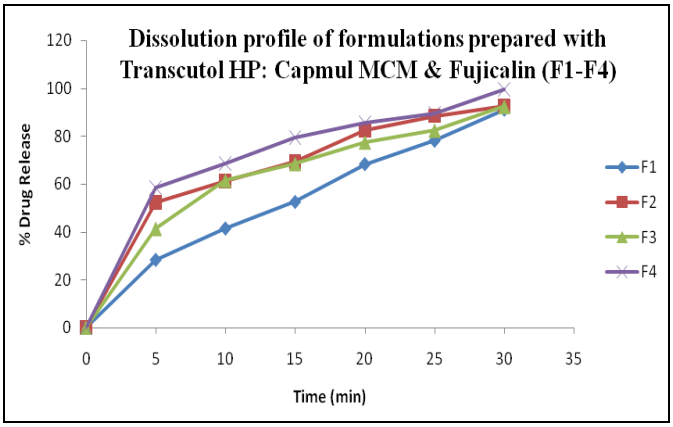

FIG. 2: DISSOLUTION PROFILE OF LIQUISOLID FORMULATIONS (F1 TO F4) PREPARED WITH FUJICALIN

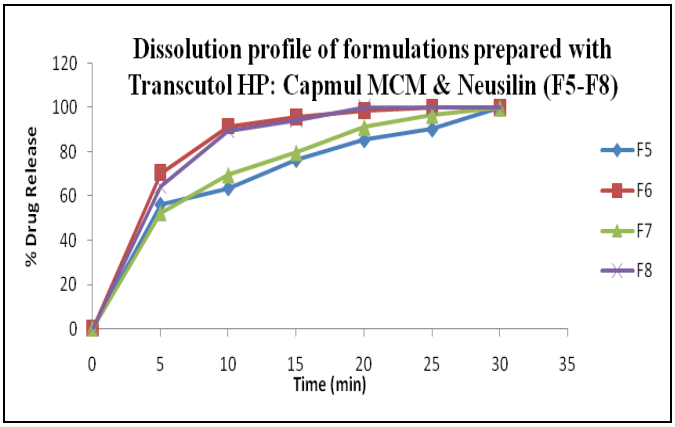

FIG. 3: DISSOLUTION PROFILE OF LIQUISOLID FORMULATIONS (F5 TO F8) PREPARED WITH NEUSILIN

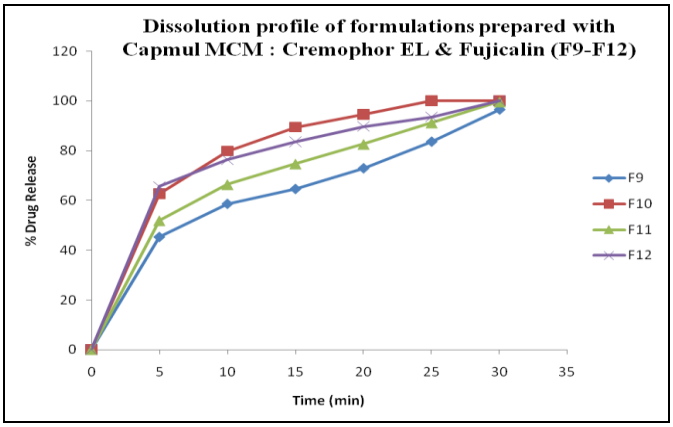

FIG. 4: DISSOLUTION PROFILE OF LIQUISOLID FORMULATIONS (F9 TO F12) PREPARED WITH FUJICALIN

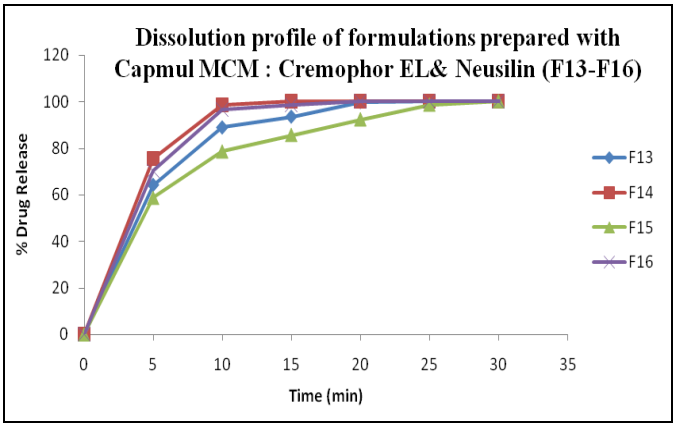

FIG. 5: DISSOLUTION PROFILE OF LIQUISOLID FORMULATIONS (F13 TO F16) PREPARED WITH NEUSILIN

***In-vivo* Studies:** *In-vivo* studies conducted in Wistar rats revealed that the bioavailability of optimized formulation is high compared to pure drug and marketed products. The plasma concentration-time profile is given in **Table 4** and shown in **Fig. 7**. The pharmacokinetic parameters are calculated and listed in **Table 5**.

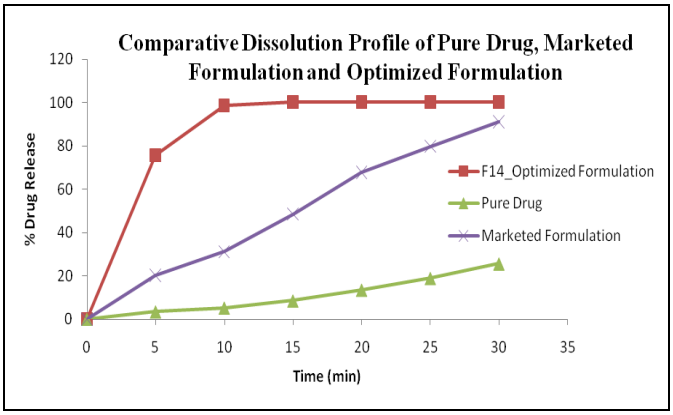

FIG. 6: COMPARATIVE DISSOLUTION PROFILE OF PURE DRUG MARKETED AND OPTIMIZED FORMULATIONS

TABLE 4: PLASMA CONCENTRATION VALUES OF PURE DRUG, OPTIMIZED FORMULATION AND MARKETED PRODUCT

Time (h)	Plasma Concentration (ng/mL)		
	Pure Drug	F14	Marketed
0	0	0	0
0.5	984.5	1325.8	1012.3
0.75	1123.5	1926.5	1326.4
1	1434.5	2354.6	1756.8
1.5	1000.82	1642.75	1225.68
2	619.29	1016.51	758.43
3	301.44	494.79	369.17
4	115.42	189.45	141.35
6	27.35	44.89	33.49
8	4.01	6.58	4.91

TABLE 5: CALCULATED PHARMACOKINETIC PARAMETERS OF PURE DRUG, MARKETED AND OPTIMIZED FORMULATION

Parameter	Units	Optimized	Marketed	Pure Drug
Elimination rate constant (k)	1/h	0.83	0.83	0.83
Half life ($t_{1/2}$)	h	0.834	0.834	0.834
T_{max}	h	1	1	1
C_{max}	ng/ml	2354.6	1756.8	1434.5
AUC	ng/ml*h	4320.84	3204.76	2686.15
Relative BA of Optimized with Pure Drug			160.86	
Relative BA of Optimized with Marketed Drug			134.82	

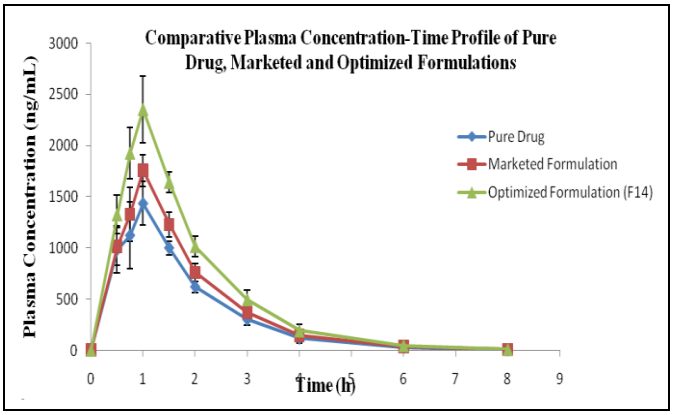

FIG. 7: COMPARATIVE PHARMACOKINETIC PROFILE OF PURE DRUG, MARKETED AND OPTIMIZED FORMULATION

CONCLUSION: From the results of in vivo pharmacokinetic evaluation conducted in rats, it was observed that the oral bioavailability of optimized formulation was found to be significantly higher than marketed and pure drug. Hence, it can be concluded that the liquisolid approach using a combination of solvents and novel carriers is promising technique to improve the bioavailability of poorly soluble drugs such as Eplerenone.

ACKNOWLEDGEMENT: Authors would like to thank Abitec corp, Gattefosse and fuji chemical industry for providing gift samples for successful completion of this research work.

CONFLICT OF INTEREST: The authors do not have any conflict of interest.

REFERENCES:

1. Rokade M, Khandagale P and Phadtare D: Liquisolid compact techniques. Int J of Current Pharma Research 2018; 10(4): 1-5.
2. Di L, Fish PV and Mano T: Bridging solubility between drug discovery and development. Drug Discov Today 2012; 17: 486-95.
3. Kawabata Y, Wada K, Nakatani M, Yamada S and Onoue: Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications. IJP 2011; 420: 1-10.
4. Ashwini A, Garud and Shahal RR: Formulation and optimization of liquisolid tablets of olmesartan medoxomil using 32 factorial design. Int J of Pharm Sci and Res 2017; 8(11): 4682-93.
5. Siju VV and Soniwala M: Review on the development of liquisolid compact using an experimental design. Int J of Pharma Sci Review and Research 2017; 43(1): 173-77.
6. Korni R and Voodikala S: Liquisolid technique: an approach to enhance the dissolution rate of olanzapine. Indian J of Pharmaceutical Sciences 2018; 80(6): 1003-10.
7. Gavali SM and Sharad S: Liquisolid compact: a new technique for enhancement of drug dissolution. Int J of Research in Pharmacy and Chemistry 2011; 1(3): 2231-81.
8. Brahamankar DM: A text book of Biopharmaceutics and pharmacokinetics. Vallabah Prakashan Publisher, ed 2015.
9. Yalkowsky and Samuel H: A text book of Techniques of solubilisation of drugs, Marcel dekker 12: 122-37.
10. Chen T, Zhang M, Bhandari B and Yang Z: Micronization and nanosizing of particles for an enhanced quality of food. Food journal 2017; (6): 993-001.
11. Jafar E: Preparation, characterization and dissolution of solid dispersion of diclofenac sodium using eudragit E-100; J of Applied Pharma Science 2013; 3(08): 167-70.

12. Makary P: Principles of salt formation. Uk J of Pharma and Biosciences 2014; 2(4): 1-4.
13. Durga P and Rambhau D: Micellar solubilization in the formulation development of poorly soluble naproxen. Pharmaceutical Regulatory Affairs 2013; 2(1): 1-12.
14. Kate BA and Bagade MY: Solubility enhancement of telmisartan using mixed hydrotropy. Asian J of Biomedical and Pharma Sciences 2015; 5(50): 37-39.
15. Carneiro SB and Duarte FÍC: Cyclodextrin–drug inclusion complexes: *in-vivo* and *in-vitro* approaches. Int J Mol Sci 2019; 20: 642.
16. Nireesha GR and Divya L: Lyophillzation- review. Int J of Novel Trends in Pharm Sciences 2013; 3(4): 87-98.
17. Mbah CJ, Umegboa NL and Nwodo NJ: Pharmacokinetic features of nimodipine: effects of cosolvents and surfactants. J of Chemical and Pharmaceutical Research 2018; 10(9): 116-20.
18. Utsav SP and Patel KC: Liquisolid technique for poorly soluble drugs. J of Scientific and Innovative Research 2013; 2(1): 145-59.
19. Kulkarni AS, Aloorkar NH, Mane MS and Gaja JB: Liquiosolid system: a review. Int J of Pharmaceutical Sciences and Nanotechnology 2010; 3(1): 795-02.
20. Burra S and Yamsani M: The liquisolid technique: an overview Braz. J Pharm Sci 2011; 47(3): 475-82.
21. Naik GN and Sunder RS: A promising technique to improve the solubility by liquisolid compaction technology. J of Drug Delivery & Therapeutics 2018; 8(5): 56-61.
22. www.drugbank.ca
23. www.rxlist.com
24. Mei Lu Haonan Xing Jingzheng Jiang Xiao Chen: Liquisolid technique and its applications in pharmaceutics. Asian J of Pharmaceutical Sciences 2017; 12: 115-23.

How to cite this article:
Naik GN and Sunder RS: Enhancement of solubility and dissolution profile of eplerenone by liquisolid compacts using novel excipients. Int J Pharm Sci & Res 2020; 11(6): 2892-98. doi: 10.13040/IJPSR.0975-8232.11(6).2892-98.