European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 9, Issue 7, Summer 2022

Impact, Improvement Of Solubility On Drug Belonging To BCS-II And Their Formulation For Oral Delivery

N. Madhavi[1] , V.T. Iswariya[2]

[1, 2] - Department of pharmaceutics, CMR College of pharmacy, Telangana, Hyderabad

ABSTRACT

The present study aimed to enhance the dissolution rate of a poorly water-soluble drug, haloperidol by adopting liquisolid compact technique and formulating it into an orodispersible system. Haloperidol is widely used neuroleptic which is a butyrophenone. Though well absorbed after oral dosing, there is a first pass metabolism leading to a reduced bioavailability of the drug (60- 70%). Therefore the present investigation is concerned with development orally disintegrating tablet of haloperidol. Different formulations of liquisolid compacts of drug were formulated by varying the concentration of drug solution from 10- 30%w/v. Avicel 102 and Aerosil 200 was used as carrier and coating material respectively. Crospovidone and SSG in the ratio of 1:1were added to the formulation for faster disintegration. Prior to the compression of orodispersible tablets all batches of liquisolid compacts were subjected to pre-compression evaluations and the results were found to be satisfactory. Further, the prepared powder blends were directly compressed into orodispersible liquisolid tablets. These tablets were evaluated for the post-compression parameters. Liquisolid tablet (F2) demonstrated a significantly higher drug release rate than those of marketed tablet, which may be due to enhanced wetting properties and effective surface area of the drug. The results of the kinetic study revealed that the formulation followed first-order kinetics with a dissolution-controlled release pattern. In conclusion the liquisolid compacts technique can be a promising alternative for the formulation of water-insoluble drugs by combining the liquisolid technology and orodispersible system can be used to improve the dissolution rate of poorly water-soluble drugs.

Keywords: Poorly water-soluble drug, liquisolid technique, orally disintegrating tablet

INTRODUCTION

The poor dissolution rate of water-insoluble drugs is still a substantial problem confronting the pharmaceutical industry. There are several methods used to increase the solubility of drugs, of those liquid-solid compact technique is a new and promising addition towards such a novel aim, that the solubility of the insoluble drug moiety is increased by the aid of non- volatile solvents and hence increasing the dissolution and bioavailability. Oral drug administration has been one of the most convenient and widely accepted routes of delivery for most of the therapeutic agents. It is one of the most extensively used routes of administration because of its obvious advantages of ease of administration, improved patient compliance, and convenience. The enhancement of oral bioavailability

of poorly water- soluble drugs remains one of the most challenging aspects of drug development. A simplest and easiest way of administering drug is through oral route.

The oral dosage forms have many advantages over other types of dosage forms like greater stability, accurate dosage, smaller bulk and easy production is possible. The formulation of poorly soluble compounds for oral delivery at present is one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry. Nearly 40% of identified potential new drug by pharmaceutical industry are poorly water soluble. Poor water-soluble compounds show decreased release rate & poor bioavailability. So large dose is required to produce desirable effect but that may lead to toxicity of the drug. So best option for increasing release rate is improvement of the solubility through formulation approaches. A variety of formulation strategies have been explored to overcome the poor aqueous solubility of drugs, including micronization, nano crystalization, cyclodextrin inclusion, co-crystallization, micelle solubilization, solid dispersion, liquisolid technique, and encapsulation in nanoparticles.[1,2]

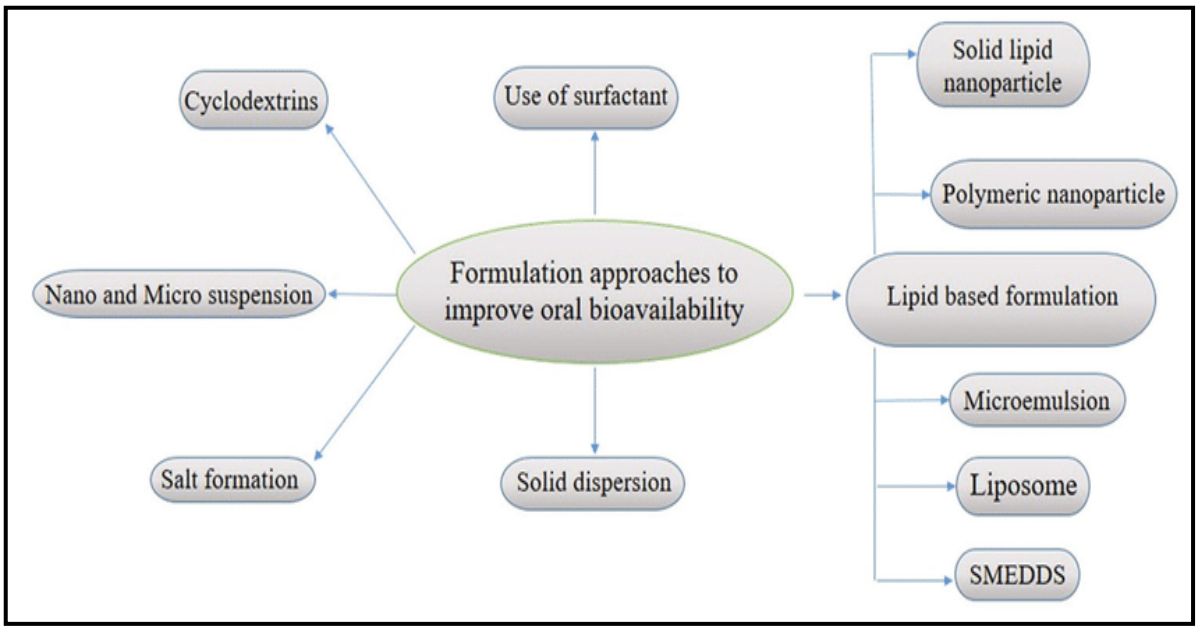


Figure1: Pictorial representation of various methods to improve drug solubility

Pharmaceutical engineering involves all sorts of dispersion systems, including suspension system, colloidal system and solution system, in which a drug can be dispersed by itself or in a solid matter, a semisolid matter, a solvent or nanoparticles. Among these, solid dispersion, lipid-based dispersion and liquisolid dispersion are well-developed and more commonly used pharmaceutical dispersion techniques. Liquisolid system as a viable alternative to the conventionally used dispersion techniques for dissolution and bioavailability improvement has received considerable attention in recent years [3].

LIQUISOLID SYSTEM

Over the years, various solid dosage formulation techniques, to enhance the dissolution of poorly

soluble substances, have been introduced with different degrees of success. Liquisolidtechnique is a new and promising method that can change the dissolution rate of drugs. It has been used to enhance dissolution rate of poorly water-soluble drugs especially those belonging to the biopharmaceutical classification system (BCS) class II and IV, dissolve slowly, poorly and irregularly, and hence pose serious delivery challenges, like incomplete release from the dosage form, poor bioavailability, increased food effect, and high inter- patient variability. The new 'liquisolid'' technique may be applied to formulate liquid medications (i.e., oily liquid drugs and solutions, suspensions or emulsions of water-insolublesolid drugs carried in non-volatile liquid vehicles) into powders suitable for tableting or encapsulation. Since, the liquisolid tablets contain a solution of the drug in suitable solvent; the drug surface available for dissolution is tremendously increased. Due to significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display enhanced drug release characteristics and, consequently, improved oral bioavailability. In this case, even though the drug is in a solid dosage form, it is held within the powder substrate in solution or, in a solubilized, almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties. [4-6]

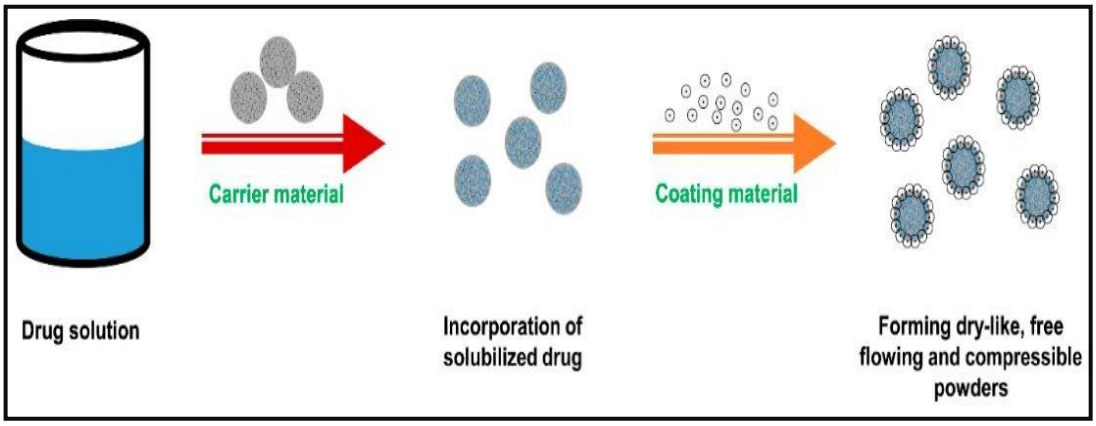


Figure 2: Various stages to form compressible powders in the liqui-solid system

MATERIALS AND METHODS

MATERIALS

Haloperidol was obtained as a gift sample from Rhyme Organics and Chemicals Ltd, Hyderabad. Propylene glycol,microcrystalline cellulose 102, aerosol200 were purchased from Sigmaldrich, India. Sodium starch glycolate, crospovidone, magnesium stearate, asparatame,mannitol were obtained from Saanvi drugs Ltd, Hyderabad.

METHODS

Construction of calibration curve for Haloperidol

The calibration curve for haloperidol was constructed in phosphate buffer pH 6.8. Various

concentrations of 5, 10, 15, 20, 25, 30, 35µg/ml were made against blank buffer solution of pH 6.8 [7-8].

Formulation design of orodispersible liquisolid tablets

It includes two techniques i.e., formulation of liquisolid compact of haloperidol and conversion of prepared compacts into orodispersible tablets. Since the solubility of haloperidol was very less in water we have dissolved the haloperidol in a non-volatile solventand then converted to solid dosage form with the help of a carrier and coating material addedto it. The drug will be retained as a liquid in the soluble state within the product but outer partwill be serves as a solid due to the presence of carrier and coating material [9-10].

Preparation of liquisolid compacts

Here PG was selected as a non-volatile solvent. MCC and Aerosil200 were used as carrier and coating material respectively. Now the amount of carrier and coating material for the specific batches were determined by using spirea's equation. For the preparation of liquisolid compacts the drug is dissolved in non-volatile solvent (PG) and this drug solution was added to the calculated amount of carrier material and triturated well. The preparation was kept aside for one min in order to complete absorption of liquefied drug in to the porous carrier material.Then weighed amount of coating material was added and triturated slowly for five another minutes for the complete absorption of coating material over the porous carrier material so as to convert the mixture to free flowing powder. To these four batches of liquisolid compacts prepared with varying ratios of carrier and coating material superdisintegrants, crospovidone and SSG should be added to obtain a faster disintegration once they are compressed [11-13].

Results and Discussions:

PRECOMPRESSION EVALUATIONS

To four batches of liquisolid compacts prepared, the other excipients for the tablet formulations were added. Which included crospovidone & SSG-7.5mg (superdisintegrants), Aspartame-5% (sweetening agent), Mannitol (diluent), and Magnesium stearate1% (glidant). These prepared powder blends were subjected to precompression evaluations such as angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio to determine the flow property of the prepared powder blend. Results were reported in Table 1

Preparation of Orodispersible Liquisolid Tablets Of Haloperidol:

The formulas of four different batches of liquisolid oral dispersables were given in Table 1.

Batches F1-F4, were prepared using 10, 20 and 30% concentration of drug solutions respectively. The formulated four batches of liquisolid compact powder blend containing 2mg of Haloperidol were directly compressed into tablets by using rotary tablet punching machine [14-17].

Table 1: Formulation composition of liquisolid tablets

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**
Haloperidol	2.0	2.0	2.0	2.0
Propylene glycol	10.0	20.0	6.6	20.0
MCC102	76.92	173	58.40	185.1
Aerosol 200	15.3	8.65	1.94	5.2
SSG	7.5	7.5	7.5	7.5
Crospovidone	7.5	7.5	7.5	7.5
Mg sterate	2.5	2.5	2.5	2.5
Asparatame	5	5	5	5
Mannitol	36.3	23.8	17.6	15.2
Total weight	250mg	250mg	250mg	250mg

POST COMPRESSION EVALUATIONS

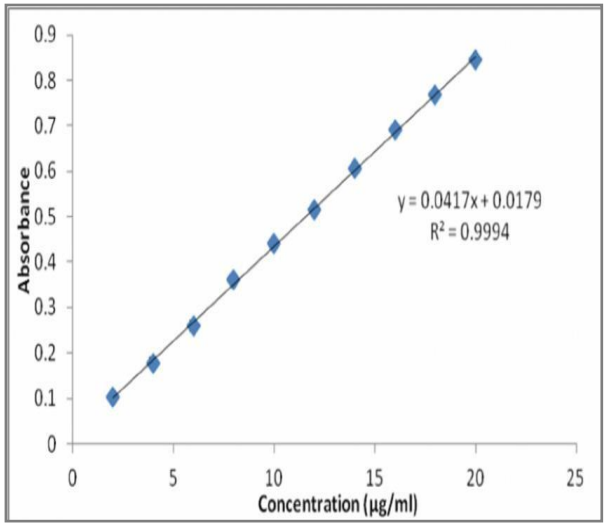
General appearance, Thickness and diameter, Tablet hardness, Friability test, Weight variation test, Wetting time, Water absorption ratio, In-vitro disintegration time, Drug content determination, *In vitro* drug release study

Drug release kinetics

To determine the release mechanism from formulation, the regression coefficients of various kinetic models were performed, including zero-order, first order, higuchi and Hixson-Crowell.

CALIBRATION CURVE OF HALOPERIDOL

The λmax was found to occur at 248 nm. A regression equation was derived from the plot, which was used for the estimation of haloperidol in phosphate buffer solution of pH 6.8±0.5 The method obeyed Beer's law in concentration range of 5-50µg/mLand is suitable



for the estimation of haloperidol from different sample solutions.

Figure 3: Calibration curve of Haloperidol in phosphate buffer pH 6.8.

The correlation coefficient value (R) was found to be 0.999 indicating a positive correlation between the concentration of haloperidol and the corresponding absorbance values. The regression line describes the relation between the concentration and absorbance was as follows. Y= 0.0417X + 0.0179

PRE-COMPRESSION EVALUATIONS

From the results of precompression evaluation study given in table 2 it was concluded that allthe prepared batches were in the specified limits. Then the prepared powder blends were subjected to compression for formulating orodispersible liquisolid tablets.

Table 2: Pre compression parameters of the prepared haloperidol orally disintegrating tablets

Formulation code	Bulk density (g/cc)	Tapped density(g/cc)	Carr's index	Hausner's ratio	Angle of repose(θ)
F1	0.314±0.023	0.379±0.016	16.15±0.045	1.2±0.025	26.5±0.25

F2	0.323±0.341	0.363±0.024	11.01±0.012	1.12±0.120	25.4±0.32
F3	0.332±0.121	0.384±0.018	13.54±0.022	1.15±0.203	27.30±0.17
F4	0.343±0.025	0.403±0.020	14.88±0.026	1.17±0.025	26.3±0.43

Each value represents mean value of ±s.d (n=3)

RESULTS OF POST COMPRESSION PARAMETERS

Table 3: Evaluation data of the prepared haloperidol orally disintegrating tablets

Formulation code	Thickness(mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation(%)	Drug content	Disintegration time (sec)	Wetting time(sec)
F1	3.4±0.023	3.6±0.052	0.229±0.120	1.2	95±0.4	38±2.5	73.5±2.0
F2	3.2±0.012	3.3±0.012	0.386±0.458	0.8	98.5±0.5	25±1.0	73.5±2.0
F3	3.1±0.032	3.2±0.058	0.284±0.250	1.4	98±0.8	31±1.4	62.2±2.3
F4	3.3±0.120	3.3±0.078	0.453±0.59	0.9	93.5±0.3	34±2.0	69.8±1.3

Each value represents mean value of ±s.d (n=3)

None of the test formulations had a percentage loss in tablet weights greater than 0.7 percent, indicating that all of the selected haloperidol tablets were had acceptable friability. Mean thickness of tablets were found to be uniform in all the formulations. The thickness varied from 2.9-3.4 mm was acceptable. The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness in the range of 3.0-3.6 kg/cm^2. The weight variation in the tablets was ranged from 0.7-1.4. Drug content was observed to vary from 93%-98%. The wetting time and water absorption ratio of the prepared Haloperidolliquisolid tablets were shown in the Table 3. Wetting time was ranged from 58-85.4 sec and water absorption ratio from 62.4-91.2%. The lesser wetting time and higher water absorption ratio was displayed by liquisolid tablets in comparison to other prepared DCTs in lab may bedue to increased hydrophilicity of haloperidol tablet as haloperidol was

converted into a liquisolid compact. The non-volatile solvents employed in liquisolid system formulations reduce interfacial tension between the dissolution medium and the tablet/powder, making it easier to wet the final solid dosage form the disintegration time of the tablets were ranged from 25-67 sec for the prepared tablets. The faster wetting time facilitates the faster disintegration of the tablets. These results of fast disintegration can be attributed to the two superdisintegrants used crospovidone and SSG (7.5mg) in the ratio 1:1 which was optimized.Of all the 12 batches LS2 exhibited the shorter disintegration time of 25 sec.

IN VITRO DISSOLUTION STUDY

Table 4: values of *in vitro* dissolution profile of haloperidol oraldispersable tablet

S.No	**Time (hr)**	**%CDR the haloperidol tablet**			
1		**F1**	**F2**	**F3**	**F4**
2	0	0	0	0	0
3	1	41.13	56.0	55.44	18.80
4	2	16.4	66.5	28.99	38.58
5	4	47.60	71.62	50.12	65.36
6	6	82.57	79.0	83.21	82.75
7	8	86.21	84.7	88.56	86.76
8	10	88.68	92.1.2	89.48	90.73

Each value represents mean value of ±s.d (n=3)

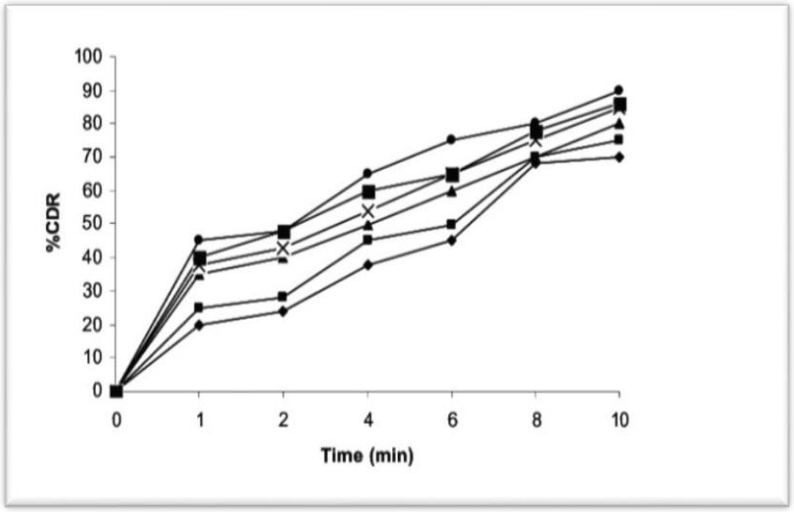


Figure 7: *In vitro* dissolution profile of haloperidol liquisolid tablet

Dissolution studies were conducted for all the 4 batches (F1-F4), from the results it was found that F2 formulation with a carrier to coating material ratio of 20:1 with 10% drug solution exhibited better dissolution rate (92.1%) compared to other batches. The control of pH deviation on drug release can be reduced by using liquisolid technology. When compared to marketed tablets and directly compressed tablets, the dissolution rate of liquisolid tablets is more and less affected by pH deviation on drug release. Drug photostability in solid dosage forms can be enhanced by this method. Liquisolid technology can be applied in probiotics. Dissolution of drugs can be improved by liquisolid technique: Dissolution rate of low dose insoluble drugs such as haloperidol, Prednisolone can be enhanced by the use of the liquisolid technique. Incorporation of high dose water-insoluble drugs: by employing few additives such as PVP, HPMC and polyethylene glycol 35000, large dose, poorly soluble could be incorporated into liquisolid systems. This may be due to the fact that, these additives have the capability to increase the liquid uptake nature of carrier and coating materials and also by using modern carriers with augmented effective surface and greater absorption capacity.

Drug release kinetics

The release data obtained from the optimized formulation F2 were fitted in to various models. The regression value (R2) was compared for zero order and first order which was found to be 0.4214 and 0.9212respectively. The R2 value of Higuchi and HixsonCrowell

were found to be 0.4982 and 0.7117 respectively. Thus we can conclude that the release kinetics follows first order, dissolution controlled pattern.

Table 5: Release kinetics of optimized formulation

Formulation code	Zero-order	First order	Higuchi model	Hixson Crowell model.
	R^2	R^2	R^2	R^2
Formulation (F2)	0.4214	0.9212	0.4982	0.7117

Comparison of optimized formulation of haloperidol and conventional marketed formulation

The *in-vitro* drug release profile of the optimized formulation (F2) was compared with the marketed formulation of Haloperidol. From the results it was found that liquisolid tablet formulation F2 exhibited better dissolution profile than those of marketed formulation. To confirm highest solubility was not only due to another directly compressed tablet. From the results of comparison study, the F2 batch had a better dissolution rate of 98.1% when compared with the DCTs (DH) of Haloperidol which was only 43.2%. Hence it can be concluded that the increased dissolution rate of F2 formulation may be attributed due to the adopted liquisolid technique. Another reason for the enhanced release of Haloperidol from the orodispersible liquisolid tablets may be due to the presence of non-volatile liquid vehicle (PG), where the drug still remains in dissolved state. Which aid the wettability and hence the disintegration of the prepared tablets. That is the surface area of Haloperidol available in orodispersible liquisolid tablets for dissolution is much greater than that of the other directly compressed compacts.

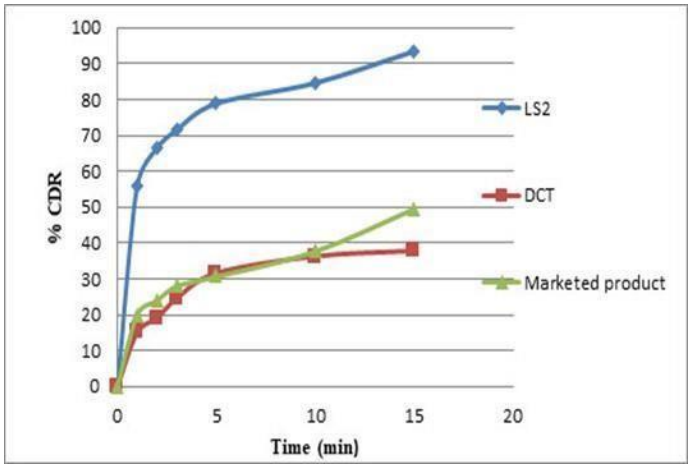


Figure 8: Comparison of *in-vitro* dissolution profile optimized formulation against marketed formulation

Drug release kinetics

The release data obtained from the optimized formulation F2 were fitted in to various models. The regression value (R2) was compared for zero order and first order which was found to be 0.4214 and 0.9212respectively. The R2 value of Higuchi and Hixson Crowell were found to be 0.4982 and 0.7117 respectively. Thus we can conclude that the release kinetics follows first order, dissolution controlled pattern.

Table 6: Release kinetics of optimized formulation

Formulation code	Zero-order	First order	Higuchi model	Hixson Crowell model
	R^2	R^2	R^2	R^2
F2	0.4214	0.9212	0.4982	0.7117

STABILITY STUDIES

Accelerated stability studies for the optimized tablet (formulation two) were carried out at a temperature of 40 ±2 ˚C and 75±5% RH for a period of 45 days. Tablets were evaluated for physical appearance, hardness, disintegration time, wetting time, water absorption ratio, % drug content and in-vitro drug release. From the results it was seen that the tablets have not shown any significant difference during its storage period. Hence, we can conclude that

tablets of liquisolid batch two were stable

CONCLUSION

From the results obtained, it was concluded that among four formulations of liquisolid orodispersible tablets prepared, the tablet formulated with 10% drug solution with carrier to coating material ratio of 20:1 (F2) was selected as the best formulation, in terms of faster disintegration time, superior dissolution profile, and acceptable tablet properties. The comparison study showed that the tablet formulate by adopting liquisolid technique gave a far better drug release rate than that of a conventional marketed product. The enhanced dissolution rate of Haloperidol in liquisolid tablets improves the solubility and hence bioavailability of the drug. Hence this study proved that liquisolid technique can be an enticing approach for improving the dissolution profile of drugs having high dose requirements and low water solubility. Liquisolid technique is a new and promising method used to enhance dissolution rate of poorly water-soluble drugs (BCS Class II and IV Drugs). Since, the liquisolid tablets contain a solution of the drug in suitable solvent, the drug surface available for dissolution and wetting property of the drug tremendously increases. So the liquisolid tablets show an enhanced drug release characteristics and, consequently, improvedoral bioavailability.

REFERENCES

1. ferences Alonzo, D.E., Zhang, G.G., Zhou, D., Gao, Y., Taylor, L.S., 2010. Understanding the behavior of amorphous pharmaceutical systems duringdissolution. Pharm. Res. 27, 608–618.
2. Avachat, A.M., Parpani, S.S., 2015. Formulation and development of bicontinuous nanostructured liquid crystalline particles of efavirenz. Colloids Surf., B 126, 87– 97..
3. Burra, S., Yamsani, M., Vobalaboina, V., 2011. The liquisolid technique: anoverview. Brazil. J. Pharm. Sci. 47, 475–482.
4. Kulkarni, A. S., Aloorkar, N. H., Mane, M. S. &Gaja, J. B. Liquisolid Systems : A review. International Journal of Pharmaceutical Sciences and Nanotechnology : 3, 795–802 (2010).
5. Pathak, A., Goyal, R., Agrawal, P., Rajput, S. &Tiwari, G. a review on liquisolid technology.World Journal of Pharmaceutical research. 1, 500–512 (2012).
6. Vijaykumar Nagabandi,T.Ramarao.,K.N.Jayaveera. LIQUISOLID Compacts: A Novel Approach to Enhance Bioavailability of Poorly Soluble Drugs. International Journal of

Pharmacy and Biological Sciences1,89-102 (2011).

7. U.V.S.Sara. Development and Validation of UV Spectrophotometric Method for the Estimation of Haloperidol | Journal of Pharmaceutical Research International [Internet]. Journal of Pharmaceutical Research International. 2014 [cited 2021 Sep24]
8. Yasir and U. V. S. Sara, Development and Validation of UV SpectrophotometricMethod for the Estimation of Haloperidol, British Journal of Pharmaceutical Research, 2014; 4(11): 1407-1415
9. K. Rajesh., R. Rajalakshmi., J. Umamaheswari&C.K. Ashok Kumar. liquisolid technique a novel approach to enhancesolubility and bioavailability.International Journal of Biopharmaceutics2, 8– 13 (2011).
10. Dokoumetzidis, A. & Macheras, P. A century of dissolution research: from Noyes and Whitney to the biopharmaceutics classification system. International journal ofpharmaceutics321, 1– 11 (2006).
11. Hooper P, Lasher J, Alexander KS, Baki G. A new modified wetting test and an alternative disintegration test for orally disintegrating tablets. J Pharm Biomed Anal. 2016 Feb 20;120:391–6.
12. Akinlade, B., Elkordy, A. a, Essa, E. a & Elhagar, S. Liquisolid systems to improve the dissolution of furosemide. Scientia pharmaceutica78, 325–44 (2010).
13. Pradeep yala., S. Srinivasan., k. Mahalingan., siddalingappa zalaki .solubilityenhancement of a model etoricoxib drug using liquisolid compacts International Journal of Biological & Pharmaceutical Research. 3, 577–585 (2012).
14. Barmpalexis, P.; Grypioti, A.; Eleftheriadis, G.K.; Fatouros, D.G. Development of a new aprepitant liquisolid formulation with the aid of artificial neural networks and genetic programming. AAPS PharmSciTech 2018, 19, 741–752.
15. Vraníková B, Gajdziok J, Vetchý D. Modern Evaluation of Liquisolid Systems with Varying Amounts of Liquid Phase Prepared Using Two Different Methods. 2015
16. Kapure VJ, Pande VV, Deshmukh PK. Dissolution Enhancement of Rosuvastatin Calcium by Liquisolid Compact Technique. J Pharm (Cairo). 2013;2013:315902.
17. Fahmy RH, Kassem MA. Enhancement of famotidine dissolution rate through liquisolid tablets formulation: in vitro and in vivo evaluation. Eur J Pharm Biopharm. 2008 Aug;69(3):993–1003.