Asian Journal of Pharmaceutical Education and Research
Vol -10, Issue-1, January- March 2021
ISSN:2278 7496

RESEARCH ARTICLE Impact Factor: 7.014

INCREASED THE DISSOLUTION RATE AND SOLUBILITY OF CLOPIDOGREL BISULFATE ORODISPERSIBLE TABLETS

Ritu Sahu*, Swati Saxena, Dr. Sarang Jain

Rajeev Gandhi college of Pharmacy, Bhopal, India, 462042

*Corresponding Author's E mail: ritusahu5836@gmail.com

Received 22 Nov. 2020; Revised 26 Nov. 2020; Accepted 12 Dec. 2020, Available online 10 January 2021.

Cite this article as: Sahu R, Saxena S, Jain S. Increased the Dissolution Rate and Solubility of Clopidogrel Bisulfate orodispersible tablets. Asian Journal of Pharmaceutical Education and Research. 2021; 10(1): 96-109.
https://dx.doi.org/10.38164/AJPER/10.1.2021.96-109

ABSTRACT

The purpose of the present investigation was to increase the solubility and dissolution rate of clopidogrel bisulphate orodispersible tablets by optimization of drug: polymer ratio. Solid dispersions formulated to improve solubility & dissolution rate of poorly soluble drug clopidogrel bisulfate by physical mixture method. The prepared solid dispersions were characterized by solubility determination, drug content, and *in vitro* dissolution stability studies. The results revealed that solid dispersions shown improvement in solubility and dissolution characteristics than the physical mixtures and pure drug. The reasons for increase in solubility and dissolution rate is decrease in particle size, increased surface area, amorphous state of the drug in solid dispersions, absence of aggregation and increased wetting of drug molecules. Formulation F7 was selected for optimization. The drug release of optimized formulation follows the Higuchi kinetic model, and the mechanism is found to be non-Fickian/anomalous according to Korsmeyer–Peppas. First order was maximum i.e. 0.997 hence indicating drug release from formulation was found to follow First order release kinetics.

Keywords: Orodispersible tablets, Clopidogrel bisulfate, Solid dispersions, Solubility, Dissolution rate.

INTRODUCTION

Solubility enhancement of poorly water-soluble drugs is a crucial issue to improve solubility and bioavailability. Numerous attempts to improve the dissolution behavior have been made by using solid dispersions of drugs with polymers, inclusion complexes with cyclodextrins, liposomes, emulsions, and microemulsions [1].

Clopidogrel bisulfate (CB) (S-methyl 2-(2-chlorophenyl-6,7-dihydrothieno [3,2-c]pyridine-5(4)-acetatesulfate) is a thienopiridine antiplatelet drug (Figure 1b). It is an antithrombotic agent that inhibits

adenosine diphosphate-mediated platelet aggregation by selectively and irreversibly blocking platelet purinergic P2Y12 receptors [2,3]. Clopidogrel bisulfate is practically insoluble in water at neutral pH, but freely soluble at pH 1. It also dissolves freely in methanol, sparingly in methylene chloride, and is practically insoluble in ethyl ether [4].

Development of formulation and validation of the dissolution method for poorly water soluble drugs has been a challenge in the pharmaceutical industry and for scientists, especially for drugs which belong to Biopharmaceutical Classification System (BCS) II or IV groups, like acetylsalicylic acid and clopidogrel bisulfate, with low solubility and/or permeability. Low solubility and dissolution rate are usually a limiting factor for oral drug absorption of these substances and consequently affect the bioavailability and therapeutic efficacy of the drug [5, 6]. Formulations of solid dispersions (SD) were often used to increase the solubility and dissolution rate of low solubility drugs [7-9]. A solid dispersion is a dispersion of one or more active ingredients in a hydrophilic inert carrier matrix at solid state. Two basic procedures used to prepare solid dispersions are solvent evaporation and melting methods. Increasing the aqueous solubility and dissolution of poorly water soluble drugs is of therapeutic importance. For this reason, the rational of the present study was the preparation of solid dispersion of clopidogrel bisulphate by optimization of drug: polymer ratio to overcome limited dissolution rate and formulation difficulties.

MATERIALS AND METHODS

Material

Clopidogrel bisulphate was received as gift sample from Cadila pharmaceuticals, Gujarat. All other chemicals used were of analytical grade and were used as received.

Experimental

Preformulation studies

The solubility of the drug sample was carried out in different solvents (Methanol, Purified water, 0.1N HCl, Acetate buffer pH4.5 and Phosphate buffer pH6.8) according to the United States Pharmacopoeia. Melting point of the drug sample was evaluated. Solubility can be determined by saturating the drug with different solvents used in Solubility studies in a vial. Then vial was tightly closed, agitated at constant temperature for 24hrs in Rotary Mechanical Shaker. The amount of drug in solution is determined periodically by filtering samples through whatsman filter paper and assayed by using U.V – Visible Spectrophotometer at 249 nm. The results are then compared with those given in the United States Pharmacopoeia [10-15].

Preparation of physical mixture

All the ingredients were weighed accurately and passed through sieve no. 85 in order to obtain powder of fine particle size with narrow size distribution. The physical mixtures of drug with carrier PEG 4000 was prepared indifferent concentration by slightly grinding the drug and carrier in mortar for 2 min. The drug: PEG 4000 ratio which was taken as 1:1, 1:2, and 1:3 respectively. Then the resultant powder was passed through sieve no 85 and was stored in desiccator for 2-6 hrs to carry out further analysis. The prepared physical mixture was subjected to spectrophotometric method [16].

Preparation of solid dispersion of clopidogrel bisulfate

For the preparation of clopidogrel bisulfate-PEG 4000 solid dispersion by conventional method, PEG 4000 was weighed and a measured amount of clopidogrel bisulfate was added and stirred, sample was pulverized with use of a pestle and mortar and sieved through a 400-mm mesh. 10mg of clopidogrel bisulfate - PEG 4000 powder (containing 75mg of clopidogrel bisulfate and 225mg of PEG 4000) and was used for further investigations [17].

Evaluation of dispersion

Percentage drug content

For the determination of clopidogrel bisulfate content, dispersion equivalent to 10 mg of clopidogrel bisulfate, were weighed and extracted with 10 ml of methanol by mechanical mixing for 5min followed by centrifugation at 10,000 rpm for 5 min on a centrifuge. The supernant was filtered through 0.45µ membrane filter, and the filtered solutions were suitably diluted and analyzed for clopidogrel bisulfate at 230 nm using a validated UV spectrophotometric method [17].

Formulation development of orodispersible tablets of clopidogrel bisulfate

All ingredients were passed through #60 sieve. Then required quantity of all ingredients were weighed for a batch size of 100 tablets and mixed uniformly in a mortar except talc and magnesium stearate. Finally, magnesium stearate and talc were added as lubricant and mixed for 5 min. This uniformly mixed blend was compressed in to tablets containing 75 mg drug using 9 mm flat face surface punches on a Rimek-1 rotary tablet machine by direct compression method. Total weight of tablet was kept 250mg [18].

Table 1: Formulation development of orodispersible tablets of Clopidogrel bisulfate

F. Ingredients (mg)	F1	F2	F3	F4	F5	F6	F6	F8	F9
Clopidogrel bisulfate solid dispersion (Equivalent to 75mg)	300	300	300	300	300	300	300	300	300
SSG	5	10	15	-	-	-	-	-	-
CP	-	-	-	5	10	15			
CCS	-	-	-	-	-	-	5	10	15
Talc	5	5	5	5	5	5	5	5	5
Mg. Srearate	5	5	5	5	5	5	5	5	5
Lactose	28	23	18	28	23	18	28	23	18
Citric acid	5	5	5	5	5	5	5	5	5
Mannitol	2	2	2	2	2	2	2	2	2
Total wt.	350	350	350	350	350	350	350	350	350

Evaluations of powder blend (precompression parameters)

The powder mix was evaluated for various flow properties such as bulk density and tapped density, Hausner's ratio, and Carr's index.

Bulk density and tapped density

The powder weighing 5g from each formula was introduced into a 25mL measuring cylinder. It was initially shaken lightly to break agglomerates that may have formed. The initial volume was noted, and the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5cm at 2 to 3 second intervals. The tapping was continued until a constant volume was observed [19]. Then LBD (Loose bulk density) and TBD (Tapped bulk density) were calculated using the following formulas:

LBD=Weight of powder/volume of the packing

TBD= Weight of powder/ tapped volume of the packing

Compressibility index and Hausner's ratio

The following formula was used to determine the compressibility index of powder [20]:

Carr's compressibility index (Carr's index) = (TBD − LBD) × 100 TBD

Hausner's ratio was calculated by the following formula:

Hausner's ratio = Tapped density/ Bulk density

Evaluation of tablet (post compression evaluation)

Thickness and Hardness

Thickness of tablet was determined by using vernier caliper and Hardness of crushing strength of the tablets was measured using a Monsanto hardness tester three tablets from each formulation batch were tested randomly and the average reading noted [21].

Weight Variation

Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight [22].

Friability

Twenty tablets were weighed and placed in a Roche friabilator. Twenty reweighed tablets were rotated at 25 rpm for 4 min. The tablets were then deducted and reweighed and the percentage of weight loss was calculated [22]. The percentage friability of the tablets was measured as per the following formula,

Friability = Initial weight-Final weight × 100 Initial weight

In-vitro disintegration time

Tablet was placed in a beaker containing 20mL of phosphate buffer solution, pH 7.4 at 37±0.5 °C. Time for complete disintegration of the tablet was measured in triplicate[23]. Drug content Five tablets from each formulation were weighed individually and crushed to fine powder. The powder equivalent to 75mg of clopidogrel bisulfate was introduced into 100mL volumetric flask and extracted using pH 6.8 phosphate buffer. This solution obtained was filtered, and filter was suitably diluted with pH 6.8 phosphate buffer and the solution was analyzed by measuring the absorbance at 220nm by UV visible spectrophotometer using p the blank [24].

In-vitro dissolution study

In vitro release of clopidogrel bisulfate from tablets was monitored by using 900 mL of simulated intestinal fluid, SIF (USP phosphate buffer solution, pH 7.4) at 37±0.5 using programmable dissolution tester 5 mL Aliquots were withdrawn at one minute time intervals and were replenished immediately with the same volume of fresh buffer medium. Aliquots, following suitable dilutions, were analyzed by spectrophotometrically at 220 nm [25].

RESULTS AND DISCUSSION

Clopidogrel bisulphate is a BCS class-II drug having low solubility and high permeability. Thus, it was challenging to enhance the solubility of clopidogrel bisulphate particles in an aqueous solution. Initially solubility study was carried out by taking drug in different solvents. The solubility of clopidogrel in different solvents was given in table 2.

Table 2: Solubility determination of clopidogrel bisulfate in various solvent

Solvents	Results of Solubility
Methanol	Soluble
Ethanol	Freely soluble
Chloroform	Sparingly soluble
Distilled water	Sparingly soluble
6.8 pH phosphate buffer	Soluble
0.1 N HCl	Soluble
0.1 N NaOH	Sparingly soluble

The clopidogrel bisulfate was melted at 156-157°C, which is identical to the melting point of pure clopidogrel bisulfate as stated in USP.

The UV scan of standard solutions between 200-400 nm showed the absorption maxima at 246 nm. The method was shown linear in mentioned concentration having line equation 0.019x + 0.009 with correlation coefficient of 0.999 recovery values for clopidogrel bisulfate ranged from 98% to 100%.

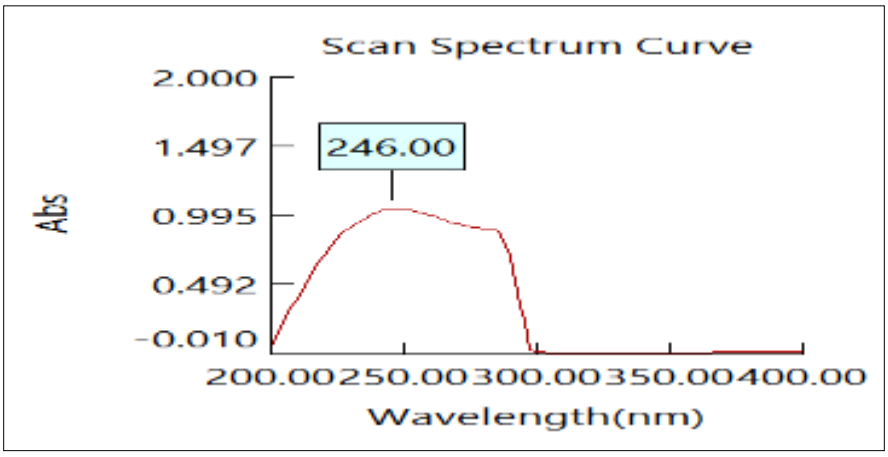

Figure 1: UV-visible absorption maxima of clopidogrel bisulfate

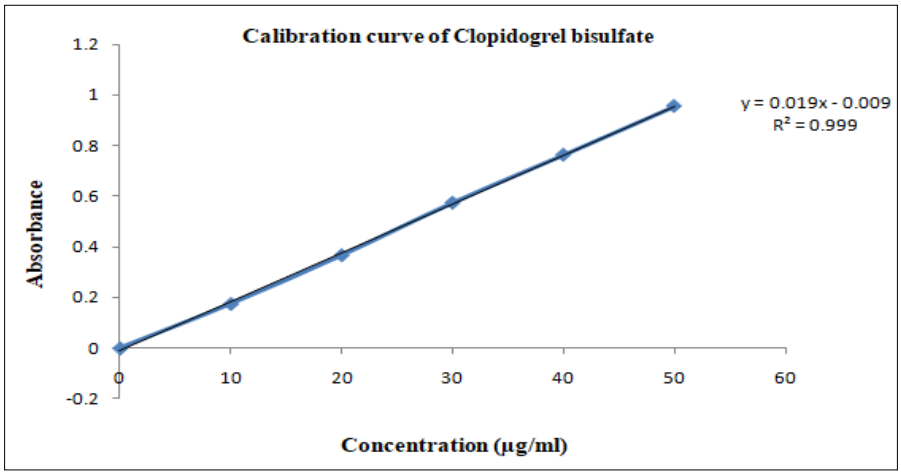

Figure 2: Calibration curve of clopidogrel bisulfate

From the study the results showed that the drug polymer ratio 1:3 that contain PEG 4000 as carrier gave the best release in comparison with other formula and the formula shows a maximum cumulative percentage drug release of 100 % within 10 minutes, drug polymer ratio 1:3 was considered as the selected formula because it had the higher dissolution rate in comparison with other formula.

Table 3 : Percentage cumulative drug release of physical mixture

Parameter	% Solubility enhancement Drug: PEG 400			
	1:1	**1:2**	**1:3**	**Pure Drug**
Absorbance	0.148	0.198	0.256	0.092
% Solubility Enhancement	160.87	215.22	278.26	----

The present study has shown that drug content of solid dispersions of clopidogrel bisulfate was found to be 9.92 mg.

Table 4 : Results of drug content

Formulation	Label claim	Amount found*	Label claim (%)
Solid dispersion	10 mg	9.92	99.20±0.21

*****Average of three determinations±SD

Bulk density and tapped density of all formulations was shown in the table-5. The mean bulk density of powders was found to be in the range from 0.311 to 0.318 gm/ml. The mean tapped density of powders was found to be in the range from 0.415 to 0.428 gm/ml. Carr's Index is a measure of the propensity of a powder to be compressed. Also, the flowability of a system is represented by its Hausner's ratio. The results showed that most formulas exhibited good flowability. The results of Carr's index, Hausner's ratio showed that the formulations F1-F9 are passable and formulations had good flow properties.

Table 5: Results of pre-compression parameters of all formulations

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	0.311	0.415	25.06	1.334
F2	0.315	0.422	25.36	1.340
F3	0.316	0.419	24.58	1.326
F4	0.318	0.425	25.18	1.336
F5	0.322	0.428	24.77	1.329
F6	0.314	0.423	25.77	1.347
F7	0.315	0.424	25.71	1.346
F8	0.312	0.423	26.24	1.356
F9	0.318	0.421	24.47	1.324

As shown in table 6, thicknesses of all tablet formulations are ranged from 2.22 to 2.24 mm, and tablets with less thickness may attribute to less density of powder blends. The hardness of all formulations F1 to F12 managed from 3.2±0.2 to 3.5±0.2 kg/cm^2 with good mechanical strength. The hardness of the tablets might have been increased in an account of the increase in contact area among powder particles. Weight variation test of all tablets ranged from 348±2 to 356±6 %. So, they were within limits of I.P. Friability results indicates that the friability of formulations was between 0.548±0.008 to 0.856±0.005% which is considered that, the formulations are physically stable to mechanical shocks during handling. The drug content of formulation ranged from 97.89±0.65 to 99.98±0.23%.

Table 6: Results of post-compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
F1	3.4±0.1	0.742±0.002	355±3	2.2±0.2	98.85±0.45
F2	3.3±0.2	0.623±0.006	350±5	2.3±0.2	98.95±0.23
F3	3.5±0.2	0.548±0.008	352±4	2.1±0.1	98.65±0.74
F4	3.4±0.2	0.856±0.005	348±7	2.2±0.1	97.89±0.65
F5	3.4±0.2	0.658±0.007	345±5	2.3±0.2	98.85±0.32
F6	3.2±0.2	0.556±0.006	356±6	2.4±0.2	98.65±0.41
F7	3.3±0.1	0.741±0.008	351±4	2.3±0.2	99.98±0.23
F8	3.4±0.1	0.723±0.009	354±1	2.4±0.2	99.02±0.14
F9	3.3±0.1	0.814±0.007	348±2	2.3±0.2	98.56±0.25

All tablets disintegrated rapidly as per USP disintegration test. The disintegration time was dependent on the concentration and type of disintegrant used and as the disintegration is rapid they are considered suitable for immediate release tablets.

Table 7: Results of *in vitro* disintegration time of all formulations

S. No.	Formulation code	Disintegration Time* (Sec.)
1.	F1	105±4
2.	F2	99±5
3.	F3	98±3
4.	F4	102±2
5.	F5	95±4
6.	F6	98±5
7.	F7	65±2
8.	F8	79±4
9.	F9	83±2

N=3 mean±S.D

The dissolution data of the various formulations of tablets were fitted into the various kinetic models and their regression values used to assess the best fit. The higher the R^2 value (i.e the more linear the graph), the better the fit of the dissolution profile to that kinetic model. Various release kinetics models were

applied to determine the release of the drug and to evaluate the best fit model. Formulation F7 was selected for optimization. The drug release of optimized formulation follows the Higuchi kinetic model, and the mechanism is found to be non-Fickian/anomalous according to Korsmeyer–Peppas. First order was maximum i.e. 0.997 hence indicating drug release from formulation was found to follow First order release kinetics.

Table 8: *In-vitro* drug release data for optimized formulation F7

Time (min)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1	0	33.23	1.522	66.77	1.825
2	1.414	0.301	65.58	1.817	34.42	1.537
5	2.236	0.698	89.98	1.954	10.02	1.001
10	3.162	1	98.95	1.995	1.05	0.021

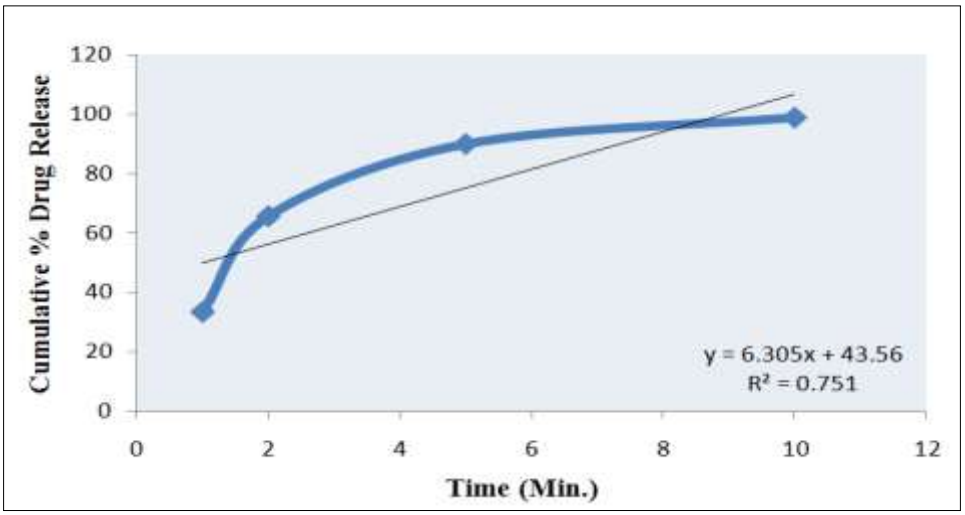

Figure 1: Zero order release Kinetics of formulation F7

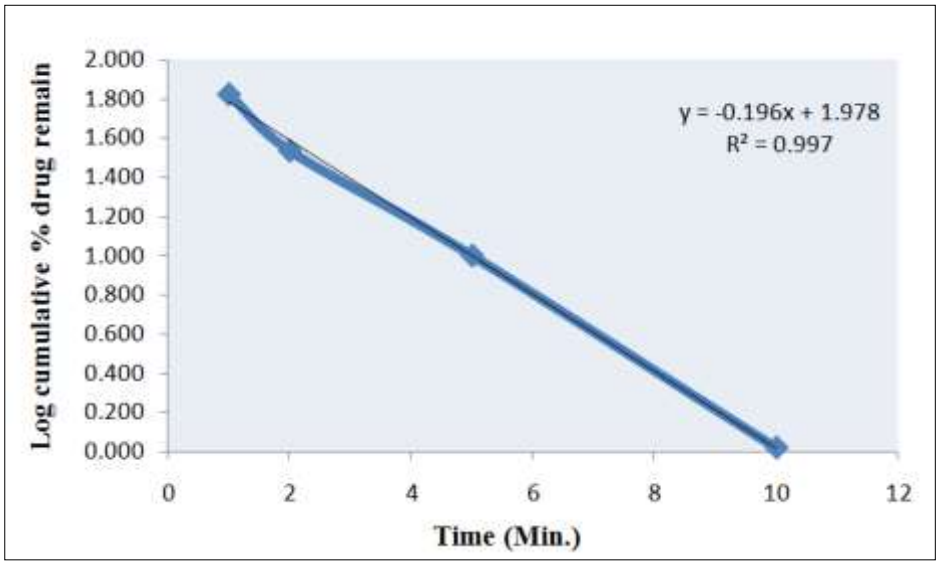

Figure 8.5: Graph of first order release kinetics of formulation F7

Table 9: Regression analysis data

Batch	Zero Order	First Order
	R^2	R^2
F7	0.751	0.997

Understanding the physicochemical properties of a drug is crucial for determining the most effective strategy for enhancing dissolution. Typically, the greatest enhancement in the dissolution of poorly soluble compounds is made by changing the dissolution medium to increase compound solubility. Surfactants and pH changes are very effective ways to increase solubility. The choice of a medium, like any other experimental conditions for dissolution testing should be linked to appropriate physiological characteristics which are similar to those of the gastrointestinal tract [26]. The most common dissolution medium is dilute hydrochloric acid, however other media commonly used include buffers at physiological pH and stimulated gastric or intestinal. Results clearly indicated the improvement in the dissolution of clopidogrel was due to its primary particles suspended in the dissolution medium had the drug particles in a state of molecular dispersion. In contrary, there was a limited surface area of the plain drug exposed to the dissolution medium in solid dispersion and the marketed tablets, because of the hydrophobic nature of the drug particles. However, the higher dissolution rates observed in clopidogrel bisulphate orodispersible tablets could be related to a considerably larger surface area of the dispersed drug particles exposed to the dissolution medium [27].

The dissolution profile results showed a significant difference in the dissolution profile of the drug, from the percent drug release profiles it was observed that it is possible to establish dissolution test parameters,

which could be used as an alternative to food and drug administration FDA dissolution test for clopidogrel tablets.

CONCLUSIONS

The present study has shown that solid dispersions of clopidogrel bisulfate enhanced solubility as compared to pure and physical mixture with PEG 4000 as carrier. Optimized formulation prepared showed significant improvement in solubility as well as dissolution characteristics which may significantly improve its oral bioavailability. Overall, this research work presents a very simple but effective technique for dissolution enhancement using very common polymers. Further in vivo studies are required to confirm the applicability of these polymers in formulation technology.

REFERENCES

1. Sahoo N, Kakran M, Shaal L, Li L, Muller R, Pal M, et al. Preparation and characterization of quercetin nanocrystals. J Pharm Sci 2011; 100 (6): 2379-90.
2. Bali DE, Osman MA, El Maghraby GM. Enhancement of dissolution rate and intestinal stability of clopidogrel hydrogen sulfate. Eur J Drug Metab Pharmacokinet. 2016; 41: 807-818.
3. Evaluation of medicines for Human Use. European Medicines Agency, 2009. Doc. Ref EMEA/661461/2009.
4. Singh A, Worku ZA, Van der Mooter G. Polymeric Delivery Systems for Poorly Soluble Drugs. In Encyclopedia of Pharmaceutical Science and Technology, 4th ed.; Swarbrick, J., Ed.; CRC Press: London, UK; New York, NY, USA, 2013; Volume IV.
5. Krstic, M, Razic S, Vasiljevic D, Spasojevic D, Ibric, S. Application of experimental design in the examination of the dissolution rate of carbamazepine from formulations. Characterization of the optimal formulation by DSC, TGA, FT-IR and PXRD analysis. J. Serb. Chem. Soc. 2015; 80: 209–222.
6. Mogal, S.A.; Gurjar, P.N.; Yamgar, D.S. Solid dispersion or improving solubility of some poorly soluble drugs. Pharm. Lett. 2012; 4: 1574–1586.
7. Sotthivirata S, McKelveya C, Moser J, Rege B, Xu W, Zhang D. Development of amorphous solid dispersion formulations of a poorly water-soluble drug, MK-0364. Int J Pharm. 2013; 452: 73–81.
8. Vasconcelos V, Marques S, Das Neves J, Sarmento B. Amorphous solid dispersions: Rational selection of manufacturing process. Adv Drug Deliv Rev. 2016; 100: 85-101.
9. Krsti M, Duris J, Petrovic O, Lazarevic N, Cvijic S, Ibric S. Application of the melt granulation technique in development of lipid matrix tablets with immediate release of carbamazepine. J Drug Deliv Sci Technol. 2017; 39: 467-474.
10. Gibson, Pharmaceutical preformulation and formulation.HIS Health group, Englewood, 2001.

11. Wells J, Pharmaceutical preformulation Ellis Horwood Limited, 1988.
12. Ravin L. J, Radebaugh G.W. "Preformulation" chapter 75 in Remington's pharmaceutical.
13. British Pharmacopeia, London; The stationary office 2000.
14. Pharmacopeia. India, the drug controller of publications, 1996.
15. United States Pharmacopeia/National formulary (USP 25/NF 20).
16. Jassim ZE, Hussein AA. Formulation and evaluation of clopidogrel tablet incorporating drug nanoparticles. Int J Pharm Sci. 2014; 838-851.
17. Kaza R, Raju YP, Nagaraju R, Dissolution enhancement of valsartan using natural polymers by solid dispersion technique, Der Pharmacia Lettre. 2013; 126-134.
18. Bhargav E, Reddy CSP, Sowmya C, Haranath C, Khan AA, Rajesh K et al. Formulation and Optimization of Piroxicam Orodispersible Tablets by Central Composite Design. J Young Pharm. 2017; 9(2):187-191.
19. Elkhodairy KA, Hassan MA, Afifi SA. Formulation and Optimization of Orodispersible tablets of Flutamide. Saudi Pharm J. 2014;22: 53–61.
20. Puttewar TY, Kshirsagar MD, Chandewar AV, Chikhale RV. Formulation and evaluation of orodispersible tablet of taste masked Doxylamine Succinate using ion exchange resin. J King Saud Univ Sci 2010; 22: 229-240.
21. Prasanth VV, Sarkar S, Tribedi S, Mathappan R, Mathew ST. Formulation and Evaluation of Orodispersible Tablets of Salbutamol Sulphate. Res Rev J Pharm Pharma Sci. 2013;2(3):26-36.
22. Dange Y, Randive D, Bhinge S, Bhutkar M, Wadkar G. Formulation and Evaluation of Gastroretentive Floating tablets of Candesartan Celexetil by Direct Compression. Indian Drugs.2017;54(03):23-27.
23. Pahwa R, Piplani M, Garg VK, Rao R, Lamba HS. Formulation and Evaluation of Orally Disintegrating Tablets: Comparison of Natural and Synthetic Superdisintegrants. Der Pharmacia Lettre. 2011;3(2):407-418.
24. Bucktowar K, Bucktowar S, Bucktowar M, Bholoa LD, Ganesh NS. Formulation and Evaluation of Fast Dissolving Tablets of Paracetamol using Ocimum basilicum Seed Mucilage as Superdisintegrant. Int Res J Pharm Bio Sci. 2017; 4(1): 44-55.
25. Dave V, Yadav RB, Ahuja R, Yadav S. Formulation design and optimization of novel fast dissolving tablet of Chlorpheniramine maleate by using lyophilization techniques. , Bulletin Facult Pharmacy Cairo Univ. 2017;55:31–39.
26. Qureshi S. Dissolution-drug dissolution testing: selecting a dissolution medium for solid oral products. American Pharma Rev. 2009;12(1):18.

27. Nokhodchi A, Javadzadeh Y, Siahi-Shadbad MR, Barzegar-Jalali M. The effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts. J Pharm Pharm Sci. 2005;8(1):18–25.