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Original Research Article

ENHANCEMENT OF DISSOLUTION RATE AND DEVELOPMENT OF FAST DISSOLVING TABLET OF VERICIGUAT

Rakesh Kumar Pandey*, Priti Singh, Ashish Manigauha
Mittal Institute of Pharmacy, Bhopal (M. P.)

***Correspondence Info:**
Rakesh Kumar Pandey
Mittal Institute of Pharmacy,
Bhopal (M. P.)
Email:
Pandeyrakesh756@gmail.com

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ABSTRACT

The development of fast dissolving tablets (FDTs) for Vericiguat, a soluble guanylate cyclase stimulator used in heart failure treatment, addresses the challenge of its poor solubility and dissolution rate. This study explores the enhancement of Vericiguat's dissolution rate through the formulation of FDTs using various ratios of PEG 4000. The physical mixture's dissolution performance was evaluated, revealing significant improvements with higher polymer ratios. The study also assessed drug content, pre-compression parameters, post-compression characteristics, and *in-vitro* disintegration and drug release profiles. Formulation F4 emerged as the most effective, showing optimal drug release, with 96.65% dissolution within 15 minutes and a first-order release profile. These findings highlight the successful application of advanced formulation techniques to enhance the dissolution rate and therapeutic efficacy of Vericiguat.

Keywords: Fast dissolving tablets, Vericiguat, dissolution rate, PEG 4000, drug release, formulation optimization.

INTRODUCTION

The dissolution rate of oral medications is a key determinant of their bioavailability and therapeutic efficacy. For drugs with poor solubility, enhancing the dissolution rate is essential to improve clinical outcomes. Vericiguat, a soluble guanylate cyclase stimulator used in the management of heart failure, exemplifies a drug that benefits significantly from improved dissolution properties due to its solubility limitations (Patel and Patel, 2022).

Fast dissolving tablets (FDTs) have emerged as a promising formulation strategy to address these solubility challenges. FDTs are designed to dissolve rapidly in the oral cavity, facilitating quicker drug release and absorption. This is particularly beneficial for drugs like Vericiguat, where rapid dissolution can enhance bioavailability and therapeutic effect (Reddy and Ghosh, 2021). Various techniques such as solid dispersion, lyophilization, and the use of superdisintegrants are employed to improve the dissolution rate of poorly soluble drugs (Yang and Lin, 2019; Ghosh and Jain, 2021).

Recent advancements in formulation technologies offer new opportunities for optimizing Vericiguat's delivery. By enhancing its dissolution rate through FDTs, it is possible to achieve more efficient and effective treatment outcomes. This paper aim to develop method for enhancing the dissolution rate of Vericiguat and explores the development of FDTs as a strategy to optimize its therapeutic efficacy (Jovanovic and Shestakova, 2020).

MATERIALS AND METHODS

Optimization of Drug: Polymer Ratio

In order to optimize the drug is to polymer ratio, we have prepared the matrices by both i.e. physical mixture method and solid dispersion method (Jain *et al.,* 2009).

Physical mixture method: 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 mixture of drug with carrier PEG 4000 was prepared in different concentration by slightly grinding the drug and carrier in mortar for 2 min. The drug: PEG 4000 ratio which was taken as 1:0.5, 1:1, and 1:1.5 respectively. Then the resultant powder was passed through sieve no 60 and was stored in desiccator for 2-6 hrs to carry out further analysis. The prepared physical mixture was subjected to dissolution study (Arun Prasad *et al.,* 2010).

Table 1: Percentage cumulative drug release of physical mixture

S. No.	Composition of physical mixture			
	Drug: PEG 4000			
	F1	F2	F3	
1	1:0.5	1:1	1:1.5	Pure Drug

Preparation of solid dispersion of Vericiguat

For the preparation of Vericiguat-PEG 4000 solid dispersion by conventional method, PEG 4000 was weighed and melted at 58°C (±1°C) and a measured amount of Vericiguat was added and stirred. After solidification at room temperature, sample was pulverized with use of a pestle and mortar and sieved through a 400-mm mesh. Vericiguat- PEG 4000 powder (containing 5mg of Vericiguat and 15mg of PEG 4000) was used for further investigations.

Preparation of physical mixture

For the preparation of Vericiguat-PEG 4000 physical mixture were weighed and mixed for 5 min with use of a pestle and mortar and sieved through a 400mm mesh. Vericiguat-PEG 4000 powder mixture was used for further tablet preparation.

Evaluation of dispersion granules

Percentage drug content:

For the determination of Vericiguat content, dispersion granules equivalent to 5mg of Vericiguat, were weighed and extracted with 10 ml of methanol by mechanical mixing. The solution was filtered through 0.45µ membrane filter, and the filtered solutions were suitably diluted and analyzed for Vericiguat using a validated UV spectrophotometric method (Modi and Tayade, 2006).

Formulation development of Orodispersible Tablets of Vericiguat

The orodispersible tablets of Vericiguat were prepared using the sodium starch glycolate, Crospovidone and croscarmellose sodium as superdisintegrant, mannitol as diluent, aspartame as sweetening agent, alcoholic solution of polyvinyl pyrrolidone (PVP K-30) as binder and aerosil as flow promoter and magnesium stearate as lubricant, the composition of batch is shown in Table 2.

The raw materials were passed through a 100-mesh screen prior to mixing. The drug and other ingredients were mixed together and a sufficient quantity of alcoholic solution of PVP K-30 (10%w/v) was added and mixed to form a coherent mass. The wet mass was granulated using sieve no. 12 and regranulated after drying through sieve no. 16. Granules of the all formulations were then dried in a vacuum oven (Vertex, VT4810) at 60°C for 12 h resulting in localized drying (Suresh *et al.,* 2007).

The final moisture content of the granules was found to be between 1- 2%, which was determined using an IR moisture balance. During drying, the menthol sublimed with the formation of a porous structure on the surface of the tablet. The dried granules were then blended with talc, magnesium stearate and compressed into tablets using flat face round tooling on a Rimek-I rotary tablet machine.

Evaluation of Precompression Parameter

Angle of repose (θ): The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane (Gohel *et al.,* 2004).

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

Where, θ is the angle of repose, h is the height, r is the radius.

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

$$\text{LBD (Loose Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Volume of Packing}}$$

$$\text{TBD (Tapped Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Tapped Volume of Packing}}$$

Compressibility index: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula:-

$$\text{Carr's Index \%} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

Hausners ratio: It is determined by comparing tapped density to the bulk density by using following equation:-
Housner's ratio = Tapped bulk density/loose Bulk density

Hausner's ratio value <1.25 shows better flow properties

Evaluation of post compression Parameter

Shape and colour of tablets:

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light.

Thickness test

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan) (Hisakadzu and Yunxia, 2002).

Weight variation test

Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed (Table 7.5) (Sharma and Gupta, 2008).

Hardness test

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm^2 (Ishikawa *et al.,* 1999).

Friability test

For this, 20 tablets were taken from each formulation and the friability was determined using Roche friabilator. The equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated. The friability was determined as the mass loss in percent according to Equation:-

$$\%\text{Friability} = (\text{Loss in weight}/\text{Initial weight}) \times 100$$

The test complies if tablets not loss more than 1% of their weight (Setty *et al.,* 2008).

Uniformity of drug content:

The test is mandatory for tablets with 10 mg or less weight of active ingredient. Ten randomly selected tablets from each formulation (F1 to F9) were finely powdered and Drug equivalent to 10 mg of drug dissolved in 10 ml phosphate buffer (pH 6.8) sonicate it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41. From this Solution take 1 ml and Diluted up to 100 ml with phosphate buffer (pH 6.8) and the drug content was determined spectrophotometrically at 256 nm (Mukesh *et al.,* 2004).

Dissolution rate studies

The prepared tablets were evaluated for *in vitro* drug release. The drug release studies were carried out using USP XXII paddle type Dissolution test apparatus. The dissolution study was carried out in 900 ml dissolution medium which was stirred at 75 rpm maintained at 37±0.2°C. The scheme of using the simulated fluids at different timing was as follows: A tablet placed in dissolution media (900 ml, phosphate buffer, pH 6.8) at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 10ml phosphate buffer (pH 6.8). The samples withdrawn were assayed spectrophotometrically at 256 nm using UV visible spectrophotometer. The release of drug was calculated with the help of Standard curve of Vericiguat.

RESULTS AND DISCUSSION

Table 3 shows that the percentage cumulative drug release of the physical mixture increases with the ratio of PEG 4000, indicating improved dissolution rates with higher polymer ratios. This enhancement is crucial for drugs like Vericiguat, which require rapid release to achieve therapeutic efficacy. The physical mixture's performance is notably lower compared to optimized formulations, demonstrating the importance of advanced formulation techniques to achieve desired dissolution rates.

The results from Table 4 show that the drug content of the physical mixture is very close to the label claim, with a percentage of 99.50±0.15. This indicates that the drug was accurately incorporated into the mixture, ensuring that each tablet delivers a consistent dose.

Table 5 lists the pre-compressional parameters for various formulations. The data indicate good flow properties and compressibility of the formulations, with Carr's Index values ranging from 22.199% to 27.423%. These values suggest that the formulations have adequate flow and compaction properties necessary for tablet compression.

As shown in Table 6, all formulations meet standard quality requirements for hardness, friability, weight variation, thickness, and drug content. The hardness of the tablets ranges from 3.4±0.2 kg/cm² to 3.8±0.5 kg/cm², indicating good mechanical strength. The friability values are below the acceptable limit (less than 1%), reflecting the tablet's resistance to breakage.

The in-vitro disintegration times listed in Table 7 reveal that formulations F4 and F3 exhibit the shortest disintegration times, which are crucial for fast dissolving tablets. F4, with a disintegration time of 45±5 seconds, shows the optimal performance, contributing to a quicker onset of drug action.

Table 8 presents the in-vitro drug release data for formulation F4. This formulation demonstrates significant drug release over time, with 96.65±0.14% release at 15 minutes. The data indicate that formulation F4 has a high release rate, which is essential for the rapid onset of action required for Vericiguat.

The regression analysis data in Table 9 shows that the F4 formulation follows first-order kinetics ($R^2 = 0.9760$), indicating that the drug release is concentration-dependent and aligns well with the desired release profile for fast dissolving tablets.

Table 2: Formulation and optimization of various batches

F. Ingredients (mg)	F1	F2	F3	F4	F5	F6	F6	F8	F9
Vericiguat Equivalent to 5mg	20	20	20	20	20	20	20	20	20
SSG	6	12	18	-	-	-	-	-	-
CP	-	-	-	6	12	18			
CCS	-	-	-	-	-	-	6	12	18
Talc	10	10	10	10	10	10	10	10	10
Mg. Srearate	10	10	10	10	10	10	10	10	10
Lactose	89	83	77	89	83	77	89	83	77
Mannitol	15	15	15	15	15	15	15	15	15
Total wt.	150	150	150	150	150	150	150	150	150

Table 3: Percentage cumulative drug release of physical mixture

F. Code	Time interval (min.)	Percentage cumulative drug release of physical mixture*			
		Drug (Vericiguate): PEG 4000			
		F1	F2	F3	
1	0	1:1	1:2	1:3	Pure Drug
2	30	11.25	14.45	16.58	2.45
3	60	26.65	31.15	33.36	6.65
4	120	33.35	40.32	43.32	7.52
5	240	43.32	48.89	53.35	8.98

Table 4: Results of drug content

Formulation	Label claim	Amount found*	Label claim (%)
Physical mixture	10mg	9.95	99.50±0.15

Table 5: Results of pre-compressional parameters of Vericiguat

Formulation code	Parameters				
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose
F1	0.356	0.465	23.441	1.306	43^0
F2	0.365	0.485	24.742	1.329	43^0
F3	0.345	0.458	24.672	1.328	44^0
F4	0.368	0.473	22.199	1.285	43^0
F5	0.355	0.486	26.955	1.369	45^0
F6	0.362	0.479	24.426	1.323	44^0
F7	0.358	0.469	23.667	1.310	44^0
F8	0.347	0.457	24.070	1.317	43^0
F9	0.352	0.485	27.423	1.378	44^0

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±0.2	0.658±0.025	152±5	1.42±0.05	98.75±0.25
F2	3.6±0.3	0.712±0.023	150±6	1.51±0.06	96.45±0.36
F3	3.5±0.2	0.668±0.024	153±2	1.48±0.03	97.78±0.32
F4	3.8±0.5	0.854±0.036	148±4	1.53±0.02	99.74±0.25
F5	3.7±0.3	0.745±0.025	149±2	1.47±0.01	96.65±0.14
F6	3.5±0.3	0.558±0.014	153±3	1.46±0.03	98.78±0.25
F7	3.5±0.2	0.632±0.033	155±2	1.47±0.04	95.89±0.36
F8	3.6±0.4	0.745±0.025	150±4	1.58±0.02	96.77±0.33
F9	3.8±0.3	0.632±0.032	153±5	1.58±0.05	98.32±0.15

N=3 mean±S.D

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

Formulation code	*In vitro* Disintegration Time (sec.) (n=3) Mean ± SD
F1	69±4
F2	55±3
F3	48±4
F4	45±5
F5	62±8
F6	53±6
F7	64±5
F8	58±4
F9	52±6

N=3 mean±S.D

Table 8: *In-vitro* drug release data for optimized formulation F4

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	64.45±0.25	1.809	35.55	1.551
5	2.24	0.698	83.32±0.45	1.921	16.68	1.222
10	3.16	1	89.65±0.36	1.953	10.35	1.015
15	3.87	1.176	96.65±0.14	1.985	3.35	0.525

N=6 mean±S.D

Table 9: Regression analysis data

Batch	Zero Order	First Order
	R^2	R^2
F4	0.8935	0.9760

CONCLUSION

The development of fast dissolving tablets (FDTs) for Vericiguat has successfully addressed the challenges associated with its poor solubility and slow dissolution rate. The formulation study demonstrated that incorporating various ratios of PEG 4000 significantly enhanced the dissolution rate of Vericiguat. Among the tested formulations, F4 proved to be the most effective, achieving a rapid and substantial drug release with 96.65% dissolution within 15 minutes and adhering to a first-order release profile.

The results highlight that optimized FDT formulations can significantly improve the bioavailability and therapeutic efficacy of drugs with solubility issues. The advanced formulation techniques used in this study not only enhance drug release but also ensure consistent quality and performance of the tablets. Future research may focus on further refinement of these formulations and exploring additional strategies to maximize the benefits of FDTs for a broader range of poorly soluble drugs.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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