Research Article

Comparision of Different Solubility Enhancement Techniques for Clopidogrel

Degala. Vishwanayani, Dr. P.Tripura Sundari*
Department Of Pharmaceutics, RBVRR Women's College of Pharmacy, Osmania university, Hyderabad, Telangana, India.
***Corresponding author's E-mail:** vishwanayani.degala@gmail.com

Received: 21-04-2021; **Revised:** 25-06-2021; **Accepted:** 03-07-2021; **Published on:** 15-07-2021.

ABSTRACT

The present study is aimed to formulate and evaluate various formulations to enhance the solubility of poorly aqueous soluble drug Clopidogrel. For this we have selected different techniques like solid dispersion, Nanosuspension and cyclodextrin complexes. As a part of it we prepared solid dispersions of drug employing PVPk30 and PEG 4000. Beta cyclodextrin complexes are prepared by kneading and solvent evaporation methods. Whereas nanosuspension are prepared by employing polaxomer as polymer. The prepared formulations were evaluated for drug Content and drug release studies.

Keywords: Solubility enhancement techniques, Clopidogrel, Anti-platelet, BCS-II.

QUICK RESPONSE CODE →

DOI:
10.47583/ijpsrr.2021.v69i01.005

DOI link: http://dx.doi.org/10.47583/ijpsrr.2021.v69i01.005

INTRODUCTION

The aim of this study is to formulate and evaluate the Comparison of different solubility enhancement techniques for Clopidogrel.

Clopidogrel is an anti-platelet drug, used to reduce the risk of myocardial infarction, peripheral vascular disease and stroke, it belongs to class Thienopyridine. Clopidogrel is a prodrug; it should be activated for the pharmacological action. So, it is metabolized to active form by carboxylesterase-I and the active form is the platelet inhibitor, which binds to P2Y12 adenosine diphosphate receptor of the platelets and it results in reduced ADP-Mediated activation of the glycoprotein IIb/IIIa complex1. Due to poor solubility and high permeability of the drug clopidogrel, it belongs to BCS Class II, so we need to improve the solubility and bioavailability of poorly soluble drug clopidogrel by various solubility enhancement techniques such as solid dispersions, Nanosuspensions, Complex formations and Microspheres etc. Solubility is a physiochemical factor affecting the drug absorption and therapeutic effectiveness. So based on the solubility parameter the formulation development would lead to be failure if it's poorly aqueous soluble. The low dissolution rate and low aqueous solubility of drug in the aqueous GI fluids leads to inadequate bioavailability. Several methods have been introduced to overcome the problem. For the enhancement of solubility and dissolution rate of the poorly soluble drugs, various commercial methods are available such as liquisolid, in which drug is in the solution state or the dissolved drug is absorbed over the insoluble carriers[2-3]. To improve the wettability and solubility of the poorly soluble drugs methods such as Micronization, Nanonization, complex formation, permeation enhancer and solid dispersion can be utilized to improve the bioavailability of the poorly water soluble drugs. Oral route of drug administration is said to be most convenient and easy way of administration. For many drugs it is problematic to deliver the drug through oral route, because of many reasons due to limited drug absorption because of poor bioavailability and ultimately upon the drug solubility. So solubility is an important parameter to achieve the desired concentration of drug in systemic circulation for the pharmacological response[3].

MATERIALS AND METHODOLOGY

Materials

The following materials were used: Clopidogrel – API (Aurobindo Pharma LTD), PVPk30, PVA, PEG4000, acetone, methanol, ß-Cyclodextrin (Evonik), Poloxamer (BASF),

METHODS

Formulation of solid dispersion by solvent evaporation method

Clopidogrel, PVP and PEG 4000 were made in different ratios of drug and polymer. Clopidogrel was taken in a china dish and methanol was added to it, when the drug is completely dissolved, the polymer is added to the drug solution. Then the solution was triturated or stirred till the entire solvent is evaporated. Then the drug powder was sieved through 60mesh sieve[2-8].

Formulation of Cyclodextrin complexes by solvent evaporation method

Complex forming agents are prepared by different ratios using ß-cyclodextrin as complexing agent. Clopidogrel was taken in a china dish and methanol was added to it, when

the drug is completely dissolved, ß-CD is added to the drug solution. Then the solution was triturated or stirred till the entire solvent is evaporated. Then the drug powder was sieved through 60mesh sieve and sample was analysized by UV apparatus.

Formulation ß-CD complexes by Kneading method

Complex forming agents are prepared by different ratios using ß-cyclodextrin as complexing agent. In this method the drug and ß-CD are dissolved with little amount of methanol till form into a paste. The kneaded mass is then triturated and sieved[5-9].

Formulation of Nanosuspension

Nanosuspensions are prepared by anti-solvent precipitation method. The drug was dissolved in methanol to form organic solution. The stabilizers (PVP, PVA and Poloxamer) were separately dissolved in distilled water to form aqueous solution. After that organic solution containing drug added by means of syringe drop by drop to the aqueous solution with stirring for about 2hours maintained at temperature of 30-40°c to get aqueous suspension[10].

Evaluations of Solid Dispersions, Nano Suspensions and ß-Cyclodextrin Comlexes

Drug content

10mg product was taken to this 10 ml of methanol was added. The dispersion was stirred thoroughly. Then the dispersion was filtered through whatman filter paper, the clear filtrate is further diluted and concentration of drug was measured U.V spectrophotometrically[11-13].

In vitro Drug Release Studies

The in vitro drug release of clopidogrel formulations was determined by dissolution apparatus using USP II. Accurately weighed clopidogrel formulations of 100mg equivalent weight particles are placed in capsules and kept in 900ml buffer in each basket and rpm is set to 50. The dissolution studies were carried out by withdrawing 5ml of sample at equal intervals of time intervals of time and maintain sink conditions with equal volume of buffer. The samples were analyzed by UV apparatus. Whereas for Nanosuspensions the drug equivalent to 1ml was taken into the dialysis bag and sealed. This sealed dialysis bag was then suspended into the dissolution basket containing 900ml of phosphate buffer solution of 0.1NHCL the temperature of 37± 2°C, and stirred at a constant speed of 100rpm. Aliquots were collected at each hour upto6 hours and the same was replaced with the fresh buffer. The drug content was determined spectrophotometrically by measuring the absorbance at 210nm using the same buffer solution as the blank[14-17].

RESULTS AND DISCUSSION

Characterization and Evaluations of Different Solubility Enhancement Techniques

Table 1: Solid dispersion by Solvent Evaporation method by using PVP k30and PEG4000 as carriers

Formulation code	Drug:polymer ratio	Drug (clopidogrel) in mg	Polymer in mg
K1	1:1	100	100
K2	1:2	100	200
K3	1:3	100	300
K4	2:1	200	100
K5	3:1	300	100
P1	1:1	100	100
P2	1:2	100	200
P3	1:3	100	300
P4	1:4	100	400
P5	1:5	100	500
P6	2:1	100	100

Table 1.1: Percentage of Drug content for Solid Dispersion

Formulation code	K1	K2	K3	K4	K5	P1	P2	P3	P4	P5	P6
%DC	48	59	65	56	53	51	59	67	70	82	60

Table 2: ß-CD by Solvent Evaporation method and kneading method

Formulation code	Drug : polymer ratio	Drug (clopidogrel) in mg	ß-CD in mg
C1	1:1	100	100
C2	1:2	100	200
C3	1:3	100	300
C4	1:4	100	400
C5	2:1	200	100
Ck1	1:1	100	100
Ck2	1:2	100	200
Ck3	1:3	100	300
Ck4	1:4	100	400
Ck5	2:1	200	100

Table 2.1: Percentage of Drug content for ß-CD

Formulation code	C1	C2	C3	C4	C5	Ck1	Ck2	Ck3	Ck4	Ck5
%DC	82	88	94	99	78	83	89	97	98	80

Table 3: Nanosuspension by Polymer precipitation method

Formulation code	Drug : polymer ratio	Drug (clopidogrel) in mg	ß-CD in mg
N1	1:1	100	100
N2	1:2	100	200
N3	1:3	100	300
N4	2:1	200	100

Table 3.1: Percentage of Drug content for Nanosuspension

Formulation code	N1	N2	N3	N4
%DC	71	76	80	68

Drug Content: The percentage of Drug Content of each of the formulations is given in the table. It can be seen that percentage of drug content was found to be in the range of 48 to 99% of drug content, from all the formulations, It shows that, higher ratios of all formulations gave good %DC.

***In vitro* drug release studies**

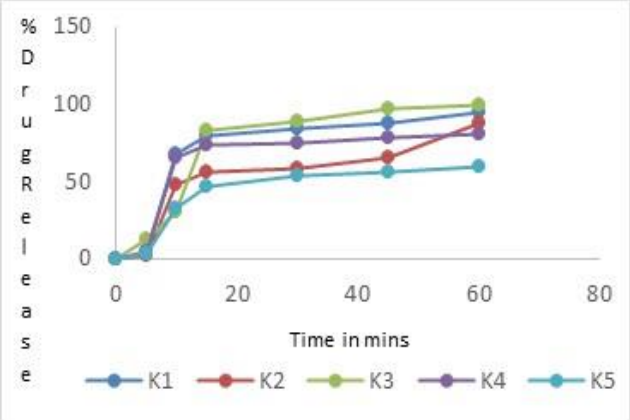

Figure 1: %Drug Release for solid dispersion with PVP k30

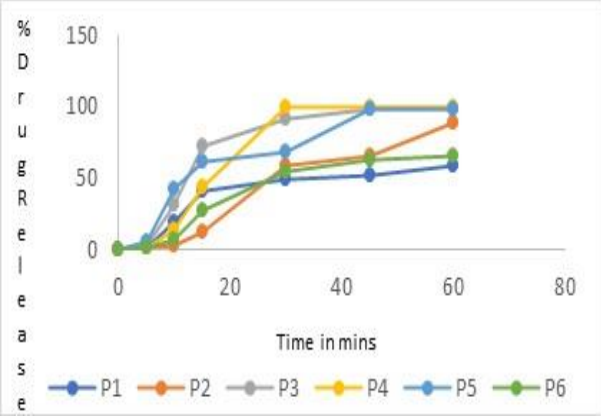

Figure 2: %Drug Release for solid dispersion with PEG 4000

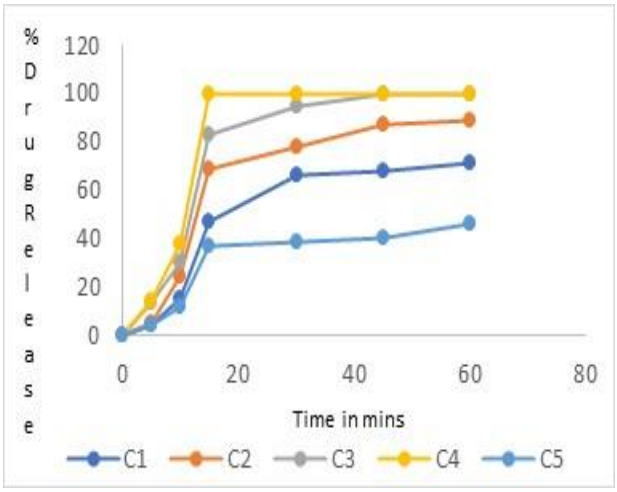

Figure 3: % Drug release for ß-Cyclodextrin by solvent evaporation method

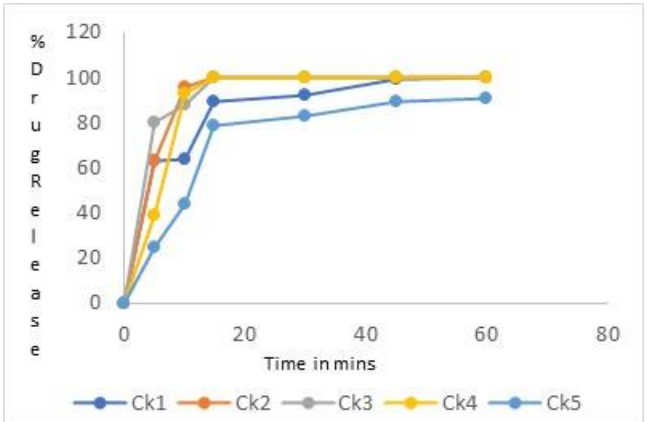

Figure 4: % Drug release for ß-Cyclodextrin by kneading method

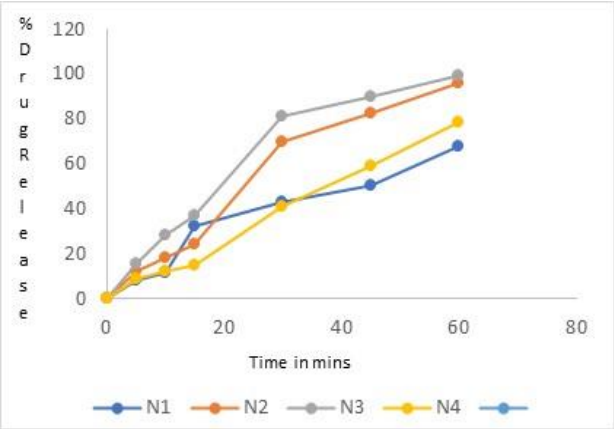

Figure 5: % Drug release for Nanosuspension

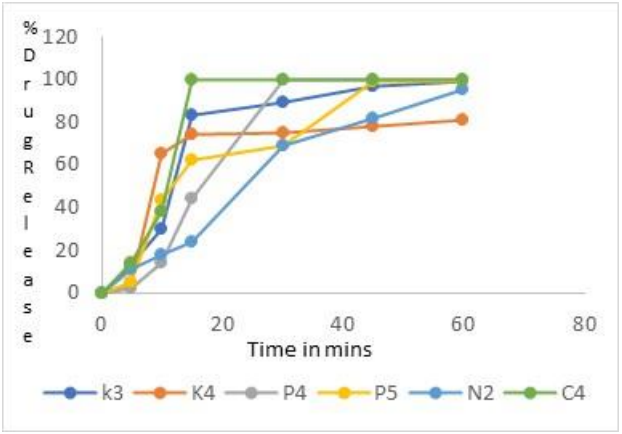

Figure 6: Comparison of different solubility enhancement techniques

The release profiles from all the clopidogrel formulations were studied and compared with each other. It shows that drug release from all formulations increases as the polymer concentration increases. All the formulations shows good release profiles as compared to each method of formulation , fig:4 has shown highest %DR i.e 100% within 15 mins.

DISCUSSION AND CONCLUSION

In the present study the formulations namely Solid dispersion, Nanosuspension and Complex formation were utilized to improve the solubility of Clopidogrel. In each method, polymer concentrations were taken as variable. The polymers used for solid dispersion are PVPk30 and PEG4000, For Complex formation the complexing agent used is ß-Cyclodextrin, Whereas for Nanosuspension are prepared by employing poloxamer, the solvent used was methanol. After preparation of all the formulations were evaluated for drug content and %DR studies. For SD with PVPk30 the %DR was found to be 59 to 99% within 60 mins, whereas drug Content was found to be 48 to 65%. For SD with PEG 4000 the %DR was found to be 52 to 99% within 45mins, drug Content was found to be 51 to 82% . For ß-CD by solvent evaporation method the %DR was 37 to 100% within 15 mins in kneading method the it shows 79 to 100 in 15mins, drug Content was found to be 78 to 99% in kneading method it shows 83 to 98%. For Nanosuspensions the %DR was found to be 67 to 99% within 60mins, drug content was found to be 71 to 80%.

All of these techniques are said to be the promising techniques which enhances the dissolution rate of the drug so all these techniques can be easily employed for poorly soluble drugs to enhance the solubility of the drug.

CONCLUSION

Various techniques like solid dispersion, cyclodextrins and Nanosuspension were tried to enhance the solubility of clopidogrel. All the techniques employed in the present study were promising to enhance the solubility of the drug, when compared to all techniques employed in the present study ß-Cyclodextrin technique is showing the better results that is 100% drug release within 15mins.

Acknowledgement: The authors wish to thank Dr. Sumakanth. This work was supported in part by a grant from RBVRR WOMENS COLLEGE OF PHARMACY.

REFERENCES

1. Eman Abd- Elhakeem, Mahmoud HM, Teaima. Bioavailability enhanced clopidogrel loaded solid SNEEDS: Development and Invitro or invivo characterization. Journal of drug delivery science and technology December 2018; 1773-2247: 604.
2. Xingwang Zhang, Huijic xing. Pharmaceutical dispersion techniques for dissolution and bioavailability enhancement of poorly water soluble drugs. ISRN Pharmaceutics June 2018; 10030074: 1-2.
3. Ketan, Savjvja. T, Anuradha, Gajjar. K. Drug solubility : Importance and enhancement techniques. ISRN Pharmaceutics July 5, 2012; 10: 4-5.
4. Sharma. and Sharma. C. P. Preparation and characterization of solid dispersion of carvediol with pvpk30. Research in pharmaceutical sciences February 2010; 5(1): 49-56.
5. Laxmi raj. A, Shravan kumar. Y. Preparation and evaluation of solid dispersion of Nebivolol using solvent evaporation method. International journal of pharmaceutical sciences and drug research July 2018; 10(4): 322-328.
6. Fakhar ul Hassnain, Sajid Bashir, Muhammad Asad. Formulation and characterization of solid dispersion of Nisoldipine by solvent evaporation method. Journal of pharmacy and alternative medicine January 2012; 2: 21-23.
7. Arun raj, Nadiya. K. K, Jyothi Harindran. Enhancement of bioavailability of clopidogrel using different solubility enhancement techniques. Journal of pharmaceutical sciences January 2016; 7(2): 25-27.
8. Christopher vimalson, Parimalakrishnan. S, Nithyananda, Sockalingam. Solid dispersion technique to enhance the solubility and dissolution of febuxostat an bcs class II drug. International journal of applied Pharmaceutics January 2019; 11(1): 241.
9. Ghosh. A, Biswas. S, Ghosh. T. Preparation and Evaluation of silymarin ß-Cyclodextrin molecular inclusion complexes. Journal of young pharmacists, Jul-Sep 2011; 3(3): 205-210.

10. Pankaj verma, Sandeep Singh, Hemachaudary. Formulation, characterization and Invitro evaluation of Nanosuspension formulation of clopidogrel using solvent antisolvent technique. Indo American journal of pharmaceutical sciences February 2017;10(5): 433-441.

11. Ganesan Poovi, Vinothini rami. Development characterization and solubility enhancement of comparative dissolution study of second generation of solid dispersions and microspheres for poorly water soluble drug. Asian journal of pharmaceutical sciences October 2015; 10(5): 4433-441.

12. Batra. V, Satish Shirolkar, Paresh Mahaparak, Kasture P. V. Formulation and evaluation of solid dispersion of glipizide for solubility and dissolution rate enhancement. Indian journal of pharmaceutical education October 2008; 42(4): 371-376.

13. Sandip sapkal, Vaibhav, Raj thence, Rahul ashok darakhe. Formulation and characterization of solid dispersion of Etorcoxib using natural polymers. Turkish journal of pharmaceutical sciences December 2018; 10.42741: 1-10.

14. Govindarajulu Geetha, Poojitha, Ashad Khan. Nanosuspensions: Types of nanosuspensions, methods and various applications. International journal of pharma research and review September 2014; 9(3): 30-37.

15. Sundar devendiran, Pamu Divya, Dhanaraju. MD. Design, formulation and evaluation of Nanosuspension for drug delivery of celecoxib. International journal of pharmaceutical research March 2019; 11(1): 139-144.

16. Rupali shid, Shashikant, Niksh, Santosh. Formulation and Evaluation of Nanosuspension formulation for drug delivery of Simvastastin. International journal of pharmaceutical sciences and Nanotechnology May 2014; 7(2): 2459-2475.

17. Bobe.KR, Subramanya. Cr, Sarasija suresh, Dinanath Galkwad. Formulation and Evaluation of solid dispersion of Atorvastatin with various carriers. International journal of comprehensive pharmacy January 2011; 2(01): 1-3.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.