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Formulation, development and evaluation of solid dispersions for enhancement of solubility and dissolution rate of clopidogrel bisulfate

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ABSTRACT

Clopidogrel is a thienopyridine class inhibitor of P2Y12 adenosine 5′-diphosphate (ADP) platelet receptors and used to inhibit blood clots in coronary artery disease, peripheral vascular disease and cerebrovascular disease. Clopidogrel is a pro-drug of carboxyl clopidogrel activated in the liver by cytochrome P450 and CYP2C19 enzyme. The active metabolite has an elimination half-life of about 7-8 h and acts by forming a disulfide bridge with the platelet ADP receptor. In the present study, solid dispersions of Clopidogrel were prepared by physical trituration method to increase its water solubility. Hydrophilic carriers such as polyethylene glycol 4000 were used in the ratio of 1:1, 1:2, 1:4 and 1: (drug to carrier ratio). Percentage assay of different formulation was determined by U.V. Vis Spectroscopy. Further fast dissolving tablets of Clopidogrel were prepared and evaluated. The percentage assay of different formulation was in range of 97.85±0.32 to 99.98±0.21%. The maximum percentage assay (99.98±0.21%) and less disintegration time (99.98±0.21 sec.) were found to be formulation F4 in Fast dissolving tablets. The optimized formulation of batch F4 subjected to further *in vitro* drug release. The *in vitro* drug release studies of the enhanced detailing was subjected to integrity of fit test by linear regression analysis as indicated by zero order, first order kinetic Higuchi and peppas release equation, in order to decide the mechanism of drug release. At the point when the regression coefficient values of were looked at, it was watched that 'r' values of first order was most extreme i.e. 0.997 consequently showing drug release from plans was found to take after first order kinetics.

Keywords: Clopidogrel, Solid dispersions, Physical trituration, Solvent evaporation, Kneading method.

INTRODUCTION

Solubility is a major physicochemical factor which affecting absorption / onset of action of drug and its therapeutic potency. If medication having poorly aqueous solubility they can face problem in dosage form design as well as successful therapeutic action. The drug candidate's poor dissolution rate and aqueous solubility affects the oral bioavailability of the drug[1]. One of the key

factors affecting dosage type production is the increase of the solubility and degradation rate of drugs. Several techniques have been used to eradicate the issue of weak solubility. Different approaches are available, such as liquisolid, in which drug molecules are adsorbed over or loaded into inert carrier molecules, for problems of solubility and dissolution rate of poorly soluble drugs.[2]. Various surfactants of different charges also helpful in improve wettability and solubility of various hydrophobic drug formulations[3]. Another approach i.e. drug micronization is unsuitable method because product after micronization has been agglomerated. The solid dispersion is also one of the methods to formulate solid dispersions because of its more effective, simplicity of preparation, not require expensive instruments and ease of optimization[4]. In solid dispersion techniques, whereby the active moiety were dispersed in an inert carrier molecules or polymer, usually with a view to enhancing solubility, dissolution rate and oral bioavailability[5]. Solid dispersion of drug in a water soluble polymer has been shown to be one of the most promising strategies to improve solubility[6]. Polyethylene glycols (PEG) are polymers of ethylene oxide, with a molecular weight (MW) usually falling in the range 200-300000. For the manufacture of solid dispersions and solutions, PEGs with molecular weights of in the range of 1500 to 20 000 are usually employed. As the MW increases, so does the viscosity. They are most commonly used because of their good solubility in water and in many organic solvents, low melting points (under 65°C), ability to solubilize some compounds, and improvement of compound wettability. The relatively low melting point is advantageous for the manufacture of solid dispersions by the melting method. PEG 8000 is a hydrophilic polymer that has been used in the preparation of solid dispersion systems. It is a chemically stable polymer with a melting point of 61°C and it also exhibits a low viscosity in the molten state which allows it to be used as a carrier for the preparation of solid dispersion by fusion method[7]. It enhances solubility by reducing particle aggregation, eliminating crystallinity, increasing wettability and dispersibility and altering the surface properties of drug particles[8]. Clopidogrel is a thienopyridine class inhibitor of P2Y12 adenosine 5′-diphosphate (ADP) platelet receptors and used to inhibit blood clots in coronary artery disease, peripheral vascular disease and cerebrovascular disease. Clopidogrel is a pro-drug of carboxyl clopidogrel activated in the liver by cytochrome P450 and CYP2C19 enzyme[9]. The main objective of this work was to investigate the possibility of improving the solubility and dissolution rate of Clopidogrel by preparing SDs with various water-soluble polymers such as PEG 4000, the prepared SDs were evaluated for % practical yield, drug content, *in vitro* dissolution rate studies and interactions between the drug and polymer using IR spectral studies.

MATERIALS AND METHODS

Material

Clopidogrel was received as a gift sample from Pharmaceutical Company. The polymers and PEG 4000 were purchased from Sigma–Aldrich, Mumbai. All other materials and reagents were of analytical grade.

Method

Determination of λmax

Accurately weighed 10 mg of Clopidogrel separately and dissolved in 10 ml of methanol in 10 ml of separate volumetric flask and prepared suitable dilution to make it to a concentration of 10 µg/ml make adequate of sample with concentration range of 10-50µg/ml Clopidogrel and calculate the spectrum of this solution was run in 200-400 nm range in U.V spectrophotometer (Labindia UV 3000+).

Calibration curve of Clopidogrel:

10mg of Clopidogrel was weighed accurately and transferred to 10 ml volumetric flask, and the volume was adjusted to the mark with methanol to give a stock solution of 1000 ppm or µg/ml. From stock solutions of Clopidogrel 1 ml was taken and diluted up to 10 ml. from this solution 1.0, 2.0, 3.0, 4.0 and 5.0 ml solutions were transferred to 10ml volumetric flasks and make up the volume up to 10 ml with methanol separately to gives standard drug solution of 10, 20, 30, 40, 50 µg/ml concentration.

Preparation of solid dispersions

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[10].

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 1:1, 1:2, and 1:3 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.

Preparation of tablets of Clopidogrel

Fast dissolving tablets of Clopidogrel (2mg) were prepared by direct compression method after incorporating different superdisintegrants such as, croscarmellose sodium (Ac-Di-Sol) 10, 15, and 20 mg, crospovidone in different concentrations 10, 15, and 20 mg for optimization of best formulation. The ingredients given below were weighed and mixed in geometric progression in a

dry and clean mortar. Then the ingredients were passed through mesh 60. Magnesium stearate (6mg) as lubricant and talc (5 mg) as glidant and Microcrystalline cellulose as bulking agent (29, 24, 19mg) were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included Angle of repose, Bulk density, Tap density, Carr's index and Hausner's ratio. The Blend was compressed on 8 mm (diameter) fat punches on a 'Rime mini press 16 station rotary compression machine. Six formulations of Clopidogrel granules were prepared and each formulation contained one of the three disintegrant in different concentration[11]. Each tablet weighing 200 mg was obtained. Composition of tablets is mentioned in Table 1.

Table 1: Composition of Clopidogrel fast dissolving tablets

Ingredients (mg)	Formulation code					
	F1	F2	F3	F4	F5	F6
Equivalent to 75 mg Clopidogrel	150	150	150	150	150	150
Sodium Starch glycolate	10	15	20	-	-	-
Croscarmellose sodium	_	_	_	10	15	20
Microcrystalline cellulose	29	24	19	29	24	19
Talc	5	5	5	5	5	5
Magnesium stearate	6	6	6	6	6	6
Total weight	200	200	200	200	200	200

Evaluation of Pre-compression Parameter[12-15]

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.

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

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

Car's

Compressibility index: Percent compressibility of powder mix was determined by Car's compressibility index, calculated by using following formula (Newman, 1995; Wells, 1998): -

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

Hauser's 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[16-20]

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) [18].

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 No.6.5).

Hardness test

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm^2.

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 [19]. 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:-

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

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 F6) 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 244.0 nm.

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 [20]. The scheme of using the simulated fluids at different timing was as follows: A tablet placed in dissolution media (900 ml) 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 244.0 nm using UV visible spectrophotometer. The release of drug was calculated with the help of standard curve of Clopidogrel.

RESULTS AND DISCUSSION

Table 2: Percentage cumulative drug release of physical mixture

F. Code	Time interval (min.)	Percentage cumulative drug release of physical mixture* Drug: PEG 4000			
		F1	F2	F3	
1	0	1:1	1:2	1:3	Pure Drug
2	30	9.96	14.56	11.65	0.45
3	60	14.65	39.98	35.65	2.36
4	120	26.65	55.65	48.89	4.85
5	240	39.98	62.32	53.32	7.95

On the basis of percentage cumulative drug release study, it was concluded that solid dispersion is better option in spite of pure drug. The study revealed that physical mixture shows a sudden bursting effect and erratic pattern in their release mechanism therefore the solid dispersion was best alternate. At higher polymer ratio i.e. at 1:2 (Drug: PEG 4000) the drug release was truly more which can further optimize to get better results. Therefore 1:2 ratios were found to be superior and were used for further evaluation purpose.

Pre-compressional parameters

Table 2: Results of pre-compressional parameters of Clopidogrel

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	0.38	0.49	22.449	1.289
F2	0.39	0.48	18.750	1.231
F3	0.36	0.46	21.739	1.278
F4	0.35	0.48	27.083	1.371
F5	0.34	0.45	24.444	1.324
F6	0.36	0.47	23.404	1.306

Post-Compression parameters

Table 3: Results of Post-Compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)	Disintegration Time (sec.) (n=3)
F1	2.8±0.1	0.89±0.12	Passes	2.1±0.2	98.89±0.32	68±5
F2	2.6±0.2	0.85±0.14	Passes	2.1±0.1	98.89±0.45	55±4
F3	2.9±0.4	0.69±0.25	Passes	2.2±0.3	99.12±0.65	45±6
F4	2.8±0.3	0.74±0.23	Passes	2.2±0.4	99.98±0.21	33±4
F5	2.6±0.2	0.85±0.25	Passes	2.1±0.2	98.78±0.14	48±5
F6	2.7±0.1	0.65±0.21	Passes	2.3±0.3	97.85±0.32	43±2

Release kinetics of Clopidogrel mouth dissolving tablets

Table 4: *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	48.89	1.524	66.55	1.823
5	2.24	0.698	75.65	1.745	44.35	1.647
10	3.16	1	98.85	1.878	24.44	1.388

Table 5: Regression analysis data

Batch	Zero Order	First Order
	R^2	R^2
F4	0.989	0.997

Percentage assay of different formulation was determined by U.V. Vis Spectroscopy. The percentage assay of different formulation was in range of 97.85±0.32 to 99.98±0.21%. The maximum percentage assay (99.98±0.21%) and less disintegration time (99.98±0.21 sec.) were found to be formulation F4 in Fast dissolving tablets. The optimized formulation of batch F4 subjected to further *in vitro* drug release. The *in vitro* drug release studies of the enhanced detailing was subjected to integrity of fit test by linear regression analysis as indicated by zero order, first order kinetic Higuchi and peppas release equation, in order to decide the mechanism of drug release. At the point when the regression coefficient values of were looked at, it was watched that 'r' values of first order was most extreme i.e. 0.997 consequently showing drug release from plans was found to take after first order kinetics.

Conclusion

Finally, based on the above study, Fast dissolving tablets of Clopidogrel were conveniently formulated by direct compression method. The *in vitro* dissolution studies showed that Clopidogrel

tablets formulation F4 showed maximum 99.98±0.21% over a period of 10 min. Overall the results of the enhanced dissolution rate studies indicated greater dissolution rate of Clopidogrel from fast dissolving tablets.

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