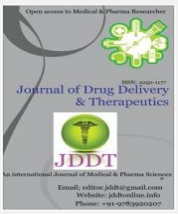
Available online on 25.12.2017 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research



Open Access Research Article

SOLUBILITY ENHANCEMENT OF CLOPIDOGREL BISULFATE BY SOLID DISPERSION TECHNIQUE USING CARBOXYMETHYLCELLULOSE SODIUM AND XANTHAN GUM

Urvashi Sharma, Ankur Joshi, Narendra Vyas, Sapna Malviya, Anil Kharia

Modern Institute of Pharmaceutical Sciences, Indore (M.P.), India - 453111

E-mail address: urvashi.ekta12@gmail.com

ABSTRACT

Solid dispersions formulated to improve solubility & dissolution rate of poorly soluble drug clopidogrel bisulfate. Physical mixtures & solid dispersions of clopidogrel bisulfate were prepared with carboxymethylcellulose sodium and xanthan gum in the weight ratios of 1:1, 1:3 and 1:5 using kneading method. The prepared solid dispersions were characterized by solubility determination, drug content, *In Vitro* dissolution and accelerated 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. It was also observed that solid dispersions of drug with both carriers showed increased dissolution rate in the ratio of 1:5 (Drug: Carrier) in comparison to pure drug and found to be stable during stability studies.

Cite this article as: Sharma U, Joshi A, Vyas N, Malviya S, Kharia A, Solubility enhancement of clopidogrel bisulfate by solid dispersion technique using carboxymethylcellulose sodium and xanthan gum, Journal of Drug Delivery and Therapeutics. 2017; 7(7):35-37

INTRODUCTION:

Solubility behavior of a drug is one of the important determinants of its bioavailability as the rate and extent of dissolution of the active ingredient from any dosage form often determines the rate and extent of absorption of the drugs[1]. About 40% of new chemical entities currently discovered are poorly water soluble. Solubility enhancement is important parameters which should be considered in formulation development of drug with poor aqueous solubility. For improvement of solubility and dissolution, numerous techniques are available. But, solid dispersion is the most promising method to formulators because of its ease of preparation, ease of optimization, and reproducibility [2]. This may be achieved by incorporating the drug in a hydrophilic carrier material obtaining products called solid dispersions [3].Clopidogrel bisulfate is practically insoluble in water, results in poor dissolution and poor bioavailability (50%), used as potent anti-platelet drug, indicated for the prevention of atherothrombotic events in patients with acute coronary syndromes. Also used for the prevention of vascular thrombotic events in patients at risk. Thus increasing the aqueous solubility and dissolution is of therapeutic importance [4]. Literature survey revealed that certain hydrophilic swellable polymers such as carboxymethylcellulose sodium (NaCMC) and xanthan gum had been used for their potential to form solid dispersions [3]. For this reason, the rational of the present study was the preparation of solid dispersion of clopidogrel bisulfate using carboxymethylcellulose sodium and xanthan gum to overcome limited dissolution rate and formulation difficulties.

MATERIALS AND METHODS:

Materials

Clopidogrel bisulfate was received as gift sample from Ipca Laboratories, Indore. Polymers (Carboxymethyl cellulose sodium and Xanthan gum) and all other ingredients were of analytical grade.

Methods

Preparation of physical mixture

Physical mixtures of clopidogrel bisulfate with carriers (carboxymethylcellulose sodium and xanthan gum) in were prepared by taking drug and carriers in ratio of 1:1, 1:3, 1:5 and pulverized by light triturating for 5 m in mortar till a homogenous mixture was obtained. This

mixture was passed through sieve no.80 for uniform size and stored in desiccators for further use[1].

Preparation of solid dispersion

Solid dispersions of clopidogrel bisulfate with NaCMC and xanthan gum were prepared by kneading method in ratio of 1:1, 1:3 and 1:5. In this method, accurately weighed quantity of clopidogrel bisulfate and selected carriers were transferred into a mortar and methanol was added to the mixture and triturated to form paste for 30 m. Then the mixture was dried at 50°C in the hot air oven until to get constant weight. The dried mass was pulverized to fine powder, sieved through sieve no.80. The prepared solid dispersion formulations were stored in desiccator for further studies [5].

Characterization of solid dispersions

Determination of equillibrium solubility

Solubility studies were performed according to the method reported by Higuchi and Connors. In solubility study, excess of formulations (drug, PMs and SDs) were added to 10 ml of distilled water in a stoppered conical flasks and subjected to shaking for 8 h at 37±1°C and kept for 24 h after shaking to achieve equilibrium. 2 ml aliquots were withdrawn, filtered and after appropriate dilution with distilled water, filtrate was analyzed at 220nm against blank. Readings were taken in triplicate and observations were recorded in table 1.

Drug content

Solid dispersions equivalent to 10mg of clopidogrel bisulfate were weighed accurately and dissolved in the 10ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 220nm using UV spectrophotometer and observations were recorded (table 1).

Dissolution rate studies

The dissolution studies were carried out using dissolution apparatus (Rotating Paddle type) at a speed of 50 rpm. Accurately weighed amount of drug, PMs and SDs immersed in a pH 2.0 HCl buffer as dissolution medium at 37±0.5°C. The dissolution was carried out for 1 h and aliquot of 5ml was withdrawn at adequate intervals. The filtered samples were suitably diluted, assayed at 220nm and cumulative percentage of the drug dissolved from the formulations was calculated (Table 2, 3).

Stability studies

The selected solid dispersions of clopidogrel bisulfate with NaCMC (FS3) and xanthan gum (FS6) were subjected to accelerated stability study as per ICH guidelines. The formulations were filled in 10ml glass vials. The vials were plugged, sealed and kept at different temperature conditions such as room temperature (25°C) and 40±2°C/75±5% RH using dessicator containing calcium chloride, for a period of 1 month. At definite time intervals, the samples were visually examined for any physical change. The drug content and dissolution rate was estimated after one month[1].

RESULTS AND DISCUSSION:

Determination of Equilibrium Solubility

Solubility of clopidogrel bisulfate was found to enhance in solid dispersion and physical mixture. The formulation prepared with carboxymethylcellulose sodium as carrier showed greater solubility as compared to xanthan gum and result was best in case of formulation FS3 and FS6 which is in the ratio of 1:5 (Table 1).

Table 1: Saturation Solubility Study and Drug Content of Various Formulations

S.No.	Formulation Code	Saturation Solubility at 37±1°C in water (µg/ml)	Percentage Solubility Enhancement (%)	% Drug Content
1	Pure Drug	9.94±0.01	-	
2	FS1	15.49±0.17	155.84	88.58±0.12
3	FS2	17.15±0.09	172.53	96.34±0.25
4	FS3	19.67±0.24	197.89	99.55±0.19
5	FS4	14.72±0.40	148.09	86.52±0.35
6	FS5	16.21±0.14	163.07	94.73±0.19
7	FS6	18.99±0.32	191.05	98.97±0.41
8	FP1	11.63±0.36	117.00	82.54±0.24
9	FP2	13.81±0.07	138.93	92.43±0.15
10	FP3	14.19±0.22	142.75	97.62±0.08
11	FP4	11.03±0.18	110.96	81.69±0.16
12	FP5	12.74±0.41	128.17	91.50±0.26
13	FP6	13.95±0.36	140.34	96.38±0.23

Drug Content

The drug content of prepared formulations of clopidogrel bisulfate with carboxymethylcellulose sodium (NaCMC) was observed to be varying from 88.58±0.12 to 99.55±0.19% and for solid dispersions with xanthan gum, it was found to be in range of 86.52±0.35 to 98.97±0.41% (Table 1).

Dissolution Rate Studies

Solid dispersion of clopidogrel bisulfate showed a significant increase in the dissolution rate than the

corresponding physical mixtures and pure drug. The dissolution rate increased on increasing the amount of polymers and maximum drug release was shown by FS3 (SDs with NaCMC 93.37±0.11%) and FS6 (SDs with Xanthan Gum 92.25±0.15%) as shown in Table 2, 3.

Table 2: Cumulative % Drug Release of Solid Dispersion and Physical Mixture with Carboxymethylcellulose Sodium

Time(m)	Drug	FS1	FS2	FS3	FP1	FP2	FP3
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
10	2.67±0.11	6.98±0.29	8.65±0.21	10.35±0.12	4.67±0.18	5.19±0.27	5.95±0.21
20	5.89±0.25	17.83±0.69	22.50±0.15	25.87±0.54	10.85±0.23	12.36±0.29	15.58±0.34
30	12.46±0.10	29.56±0.21	38.07±0.82	43.20±0.09	19.15±0.93	24.22±0.16	27.94±0.26
40	20.08±0.17	41.83±0.92	50.19±0.27	57.15±0.36	31.09±0.24	36.80±0.41	40.98±0.17
50	27.92±0.47	65.95±0.17	74.42±0.12	77.82±0.22	48.81±0.35	51.69±0.23	62.82±0.43
60	38.17±0.23	81.35±0.10	88.25±0.32	93.37±0.11	60.67±0.08	69.34±0.75	78.59±0.18

Table 3: Cumulative % Drug Release of Solid Dispersion and Physical Mixture with Xanthan Gum

Time	Drug	FS4	FS5	FS6	FP4	FP5	FP6
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
10	2.67±0.11	6.05±0.12	8.12±0.25	9.87±0.18	4.15±0.11	4.85±0.34	5.36±0.22
20	5.89±0.25	15.21±0.35	20.75±0.11	24.72±0.57	9.52±0.23	11.77±0.42	13.84±0.83
30	12.46±0.10	28.89±0.41	37.71±0.91	42.96±0.23	18.65±0.16	21.46±0.13	23.02±0.19
40	20.08±0.17	41.54±0.18	51.74±0.09	56.89±0.42	30.81±0.10	34.75±0.75	38.90±0.15
50	27.92±0.47	60.33±0.16	72.00±0.21	76.14±0.29	46.73±0.08	50.39±0.17	59.14±0.93
60	38.17±0.23	79.99±0.23	87.05±0.17	92.25±0.15	59.32±0.35	67.50±0.21	76.59±0.09

Stability Studies

The selected formulations FS3 and FS6 showed physical stability at room temperature (25°C) and at 40°C for a period of 1 month i.e no change in colour, no sign of caking. The results of chemical stability studies are showed in the table. This indicated that formulations were physically and chemically stable.

Table 4: Drug Content and Cumulative % Drug Release of Solid Dispersion for Stability Study

Formulation Code	Stability Parameters	Initial	15 Days		30 Days	
			25°C	40 °C	25°C	40 °C
FS3	% Drug Content	99.55±0.19	98.82±0.32	98.27±0.47	97.51±0.12	97.18±0.23
	Cumulative % Drug Release	93.37±0.11	93.30±0.27	93.35±0.36	93.19±0.13	93.24±0.09
FS6	% Drug Content	98.97±0.41	97.65±0.11	97.17±0.25	96.49±0.68	96.07±0.36
	Cumulative % Drug Release	92.25±0.15	92.18±0.31	92.20±0.24	92.09±0.17	91.97±0.44

CONCLUSION:

The present study has shown that solid dispersions of clopidogrel bisulfate prepared by kneading method enhanced solubility as compared to pure and physical mixture with water soluble carriers i.e. carboxymethylcellulose sodium and xanthan gum. This might be due to amorphous state of the drug in solid dispersions, wettability improvement, reduction in particle size and increase in the effective surface area over which the drug distribution increases. The results of study demonstrated the suitability of selected polymer xanthan gum and NaCMC in the preparation of solid dispersions as effective carrier for increasing solubility. As these swellable polymers are regularly used in conventional solid dose preparations and herbal polymer is readily available at low cost, this ensures about the availability, feasibility in use and cost effectiveness of the formulations. 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. Satle A, Agrawal S, Solubility enhancement potential of tamarind seed polysaccharide as a Solubilizer, IJCPR, 2012, 67-73.
2. Dalvi P, Gerange A. Ingale P, Solid dispersion: strategy to enhance solubility. Journal of Drug Delivery and Therapeutics, 2015; 5(2):20-28. doi:10.22270/jddt.v5i2.1060
3. Kaur J, Aggarwal G, Singh G, Rana AC, Self-emulsifying drug delivery systems: formulation and biopharmaceutic evaluation of an investigational lipophilic compound, IJPS, 2014, 47-53.
4. Jassim ZE, Hussein AA, Formulation and Evaluation of. Clopidogrel tablet incorporating drug nanoparticles, IJPS, 2014, 838-851.
5. Kaza R, Raju YP, Nagaraju R, Dissolution enhancement of valsartan using natural polymers. by solid dispersion technique, Der Pharmacia Lettre, 2013, 126-134.