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Design, development and *In vitro* characterization of Clopidogrel bisulfate floating drug delivery system

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ABSTRACT

Floating drug delivery is an alternative route for systemic drug delivery which minimizes the absorption and increase the bioavailability. Orally Clopidogrel bisulfate has a short elimination half-life (7-8 hrs.), low oral bioavailability (50%) undergoes extensive first pass metabolism (85%) and frequent high doses (75 mg) are required to maintain the therapeutic level as a result, dose development toxic effect. The purpose of this research work was to formulation and evaluation of floating drug delivery system of Clopidogrel bisulfate using various polymers such as Agar, SCMC, and Eudragit RS-100 with different proportions by wet granulation technique. The FTIR study revealed no physical or chemical interactions between Clopidogrel bisulphate and excipients. Partition co efficient present in between 2-6 for this drug so it is suitable for the floating tablets. The prepared formulations were evaluated for different physicochemical characteristics like thickness, hardness, drug content, percentage drug content, friability, and weight variation. The result of dissolution studies shows that formulation, F8 (Agar-20mg, SCMC-10mg and Eudragit RS-100-20mg) showed maximum release of 99.25 % in 12hrs, whereas F1 (Agar-50mg) showed minimum release of 96.26% in 8hrs. Based on the drug release and physicochemical values obtained the formulation F8 is considered as an optimized formulation which shows higher percentage of drug release of 98.82 % in 11 hr. The developed floating tablets increase the therapeutic efficacy and reduced toxic effect of Clopidogrel bisulfate.

Key words: Clopidogrel bisulfate, Agar, SCMC, and Eudragit RS-100, floating drug delivery system.

INTRODUCTION

Oral route of drug delivery is the feasible pathway of drug delivery because of easy administration, patient obedience and flexibility in the formulations. It is evident that novel drug delivery dosage forms are retained in the stomach for longer period of time that is existed in academic and industrial research groups. As different attempts has prepared to develop GRDDS. FDDSTEchnology¹ benefits drugs that have narrow window of assimilation in the stomach and upper GI tract and these systems remained in the stomach for hours and then progressively increase the GRT of the drugs [1, 2]. By this we can improve drug bio available

nature, decreases wastage of drug and increases solubility of drugs which are low soluble in high pH environment. Floating drug delivery system is known as hydrodynamically balanced systems. It is having low bulk density that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the gastric juice of the stomach without affecting gastric emptying rate for a prolonged period of time. This leads to an increased gastric retention time and a better control of the fluctuaions in plasma drug concentration. FDDS has density <1 that of gastric fluids which remains float in the stomach and doesn't shows any affect on the GER for prolonged period of time. Hence the drug is released slowly from the system at desired level while

the system is buoyant on the gastric contents. This result shows an increase in GRT and better control of the drug levels in the plasma [3].

Fig. 1: Floating tablet in the Stomach [3]

Floating DDS is divided into 2 types. They are Non-effervescent system and Effervescent system. After swallowing this type of system bulges through the imbibitions of gastric fluid that leads to prevent their exit from the stomach. After oral administration of the non-effervescent system into the gastric fluid it swells and holds particular shape and density of <1 within the outer gelatinous layer. Non-effervescent system is further classified into four subtypes,

1. Colloidal gel barrier system
2. Microporous compartment system
3. Multiparticulate system (Floating beads)
4. Hollow microspheres (Microballons)

Clopidogrel bisulfate has short biological half life of 7-8 hours and eliminated rapidly and undergoes hepatic first pass metabolism. Controlled release formulation is need for clopidogrel bisulfate for better Anti- platelet action and enhance clinical efficacy, to reduce toxic effects. The objective of present research work was to design, development and *In vitro* characterization of Clopidogrel bisulfate Floating Tablets by using various polymers such as Agar, SCMC, and Eudragit RS-100 by wet granulation method [5].

MATERIALS AND METHOD:

Clopidogrel bisulfate was obtained as a gift sample from Aurabindo Pharma pvt.ltd, Hyderabad. Agar, SCMC, and Eudragit RS-100 was purchased from local market and Lactose, Magnesium stearate, Talc was bought from S.D. Fine Chem (Mumbai). All other materials used were of pharmacopoeial grade.

Drug-polymer compatibility studies by FTIR:

Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy). FTIR spectra of Clopidogrel bisulfate, Agar, SCMC, and Eudragit RS-100 and the combination of drug and polymers were showing no significant interaction between drug and polymers [9].

Preparation of floating tablets:

The total ingredients were weighed accurately as per the formulation code. Clopidogrel bisulphate, Eudragit, Agar and Sodiumcarboxymethylcellulose was passed through #40 mesh sieve and collected in a bag. All materials were loaded in a mixer and mixed for 15 minutes. PVP K-30 granulating solution was prepared by adding 10mg in 10ml of distilled water. (I.e. 1mg/ml).

The granules were prepared by wet granulation process by the following process. The binder solution was added to the ingredients and mixes it well until obtaining dough mass. Wet mass was dried at 50-55°C by using tray dryer for 5-6 hours, until preferred LOD is obtained. Dried granules was passed through #16 mesh sieve and over sized granules passed through 2.0mm multi mill at normal speed in ahead path. Finally milled granules was passed through #16 mesh size and laden in a 2 cone blender. Talc was passed through #40 meshes and it was further mixed with other contents of 2 cone blender and mixed for 10 minutes. Blended material was weighed down in a hopper and compresses the powder into tablets by using (cad mach) compression machine with (9mm) standard flat punches. Check for weight variation, hardness, friability, thickness to reach the parameters. Collect the tablets in a cleaned double poly bag indicating the product and batch number [5].

Characterization of tablets

Weight uniformity

A total of 20 tablets were weighed individually, average weight was calculated and the individual tablet weights were compared with the average weight. The tablets meet the USP test if not more than two tablets are outside the percentage limit and if no tablets differs by more than two times the percentage limit.

Crushing strength

The crushing strengths of the tablets were determined individually with the Monsanto hardness tester. Three tablets were used and the mean crushing strength was calculated and expressed in kg/cm^2

Friability test

The friability of tablets was determined using Roche friabilator. Six tablets (6) were initially weighed (W_0) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again (W). The % friability was then calculated by the following equation [6].

$$\%F = (1 - W/W_0) \times 100$$

% Friability of tablets $<1\%$ are considered as acceptable.

Fig.2: FTIR Spectra for pure Drug (Clopidogrel bisulphate)

Fig. 3: FTIR studies of Agar with Clopidogrel bisulphate

Fig. 4: FTIR studies of Eudragit RS-100 with Clopidogrel bisulphate

Fig. 4: FTIR studies of Eudragit RS-100 with Clopidogrel bisulphate

Table 1: Formulae of Clopidogrel bisulphate floating tablets (mg)

S.No	Ingredients	CB1	CB2	CB3	CB4	CB5	CB6	CB7	CB8	CB9
1	Clopidogrel bisulfate	98	98	98	98	98	98	98	98	98
2	Agar	50	-	-	25	-	25	10	20	20
3	SCMC	-	50	-	25	25	-	20	10	20
4	Eudragit RS-100	-	-	50	-	25	25	20	20	10
5	Talc	2	2	2	2	2	2	2	2	2
6	Sodium bicarbonate	23	23	23	23	23	23	23	23	23
7	Mannitol	75	75	75	75	75	75	75	75	75
8	Sodium lauryl sulphate	2	2	2	2	2	2	2	2	2
Total Weight		250	250	250	250	250	250	250	250	250

Table 2: Physicochemical parameters of tablets

Formulation Code	Weight Variation (mg)	Thickness (mm)	Hardness (Kg/cm ³)	Friability (%)	Drug content (%)
CB1	248±0.13	3.60±0.03	4.06±0.11	0.76±0.04	98.44±0.36
CB2	252±0.45	3.54±0.31	4.02±0.07	0.69±0.02	99.74±0.51
CB3	248±0.16	3.53±0.23	3.98±0.14	0.87±0.05	99.66±0.46
CB4	251±0.21	3.52±0.08	4.00±0.16	0.74±0.01	98.56±0.65
CB5	248±0.17	3.33±0.16	4.09±0.04	0.84±0.03	99.57±0.30
CB6	249±0.32	3.36±0.12	4.03±0.12	0.89±0.04	98.45±0.55
CB7	247±0.25	3.45±0.15	3.99±0.16	0.80±0.05	98.35±0.45
CB8	249±0.15	3.42±0.10	3.98±0.15	0.79±0.03	99.85±0.25
CB9	249±0.20	3.48±0.21	4.05±0.14	0.78±0.04	98.39±0.75

Drug content

A total of 10 tablets were weighed and powdered. The quantity of powder equivalent to 100 mg of clopidogrel bisulfate was dissolved in 100 ml of 0.1 N HCl. Then the solution was filtered, diluted suitably and analyzed using an ultra violet (UV) visible spectrophotometer at 270.5 nm [13].

Table 3: *In-vitro* buoyancy studies for drug tablets

S.No	Floating lag time	Floating log time
1	7	>8
2	5	>8
3	7	>8
4	6	>8
5	7	>8
6	6	>8
7	7	>8
8	7	>8
9	7	>8

In-vitro buoyancy studies

The *in-vitro* buoyancy was determined by floating lag-time method as per the method described by Rosa *et al.* The tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and the duration of the time the tablet constantly floats on the dissolution medium was noted as the total floating time respectively [4].

'0'seconds

'15' seconds

At '70' secs

After '130' secs

Fig.6: *In-vitro* Buoyancy study of Formulation-8(F8)

CB1-CB4

Swelling index studies

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in 100 ml beaker of 0.1 N HCl and after 1, 2, 3, 4 and 5 h each, beaker containing tablet was withdrawn, blotted with tissue paper to remove the excess water and weighed on the analytical balance. Swelling index was calculated by using the following formula [12].

Swelling index = $\frac{[\text{Wet weight of tablet} - \text{Dry weight of tablet}]}{\text{Dry weight of tablet}} \times 100$

In-vitro drug release studies

Clopidogrel bisulfate drug release studies from different formulated tablets were performed by using USP Type II apparatus in 900 ml of 0.1 N HCl as the dissolution medium, with rpm of 50 and the bath was maintained at a temperature of $37 \pm 0.5^\circ\text{C}$. Samples were withdrawn at regular intervals of time and these were replaced with an equivalent volume of the fresh dissolution media. The withdrawn samples were analyzed after suitable dilutions at a wavelength of 270.5 nm using UV spectrophotometer. The cumulative percentage drug release was calculated using slope obtained from the standard curve [7].

Kinetic modeling of drug release

The dissolution data was fitted to popular release models such as zero-order, first-order, and Higuchi and Peppas-Korsmeyer equation models. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics.

CB5 - CB9

Fig. 7: Prepared Clopidogrel bisulphate floating tablets with different batches

The mechanism of drug release from the matrix systems was studied by using Higuchi equation and Peppas's-Korsmeyer equation. Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the zero order release kinetics equation: $Q_t = Q_0 + K_0 t$; Where Q_t is the amount of drug dissolved in time t , Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and K_0 is the zero order release constant expressed in units of concentration/time.

The release of the drug, which followed first order kinetics, can be expressed by the first order release kinetics equation: $\log C = \log C_0 - Kt/2.303$; where C_0 is the initial concentration of drug, k is the first order rate constant and t is the time. Higuchi equation defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time and can be expressed as $Q = K_H t^{1/2}$; Where, K_H is the release rate constant. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent. In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by Peppas and Korsmeyer equation: $M_t/M_\infty = K t^n$; Where M_t/M_∞ is a fraction of drug released at time t , K is the release rate constant and n is the release exponent. In this model, the value of n characterizes the release mechanism of drug. For the case of cylindrical tablets, $n = 0.45$ corresponds to a Fickian diffusion mechanism, $0.45 < n < 0.89$ to non-Fickian transport, $n = 0.89$ to Case II (relaxation) transport, and $n > 0.89$ to super Case II transport [11].

RESULTS AND DISCUSSION

The flow properties and the derived properties evaluated for all the nine formulations were proved to be within the limits showing good flow properties. The physical properties like tapped density, bulk density, angle of repose, compressibility index and Hausner's ratio of all the formulations were complied with standard specification. The difference in the hardness of the prepared tablets ranges from 3.98 ± 0.14 to 4.09 ± 0.04 KP released by the course of action of diffusion. The thickness of the tablet was observed by using digital vernier caliper and found to be in the range from 3.48 ± 0.21 to 3.60 ± 0.03 .

The Weight variation of the prepared tablets was bringing into within the range of 247 ± 0.25 to 252 ± 0.45 . The strength of the prepared tablets was tested by using Roche Friabilator. The friability of all the formulations was observed within the range of 0.69 ± 0.02 to 0.80 ± 0.05 . The drug content of all the formulations was observed within the range of 98.35 ± 0.45 to 99.85 ± 0.25 . The *In vitro* drug release study were conducted using 0.1N Hcl as dissolution medium and the results tabulated as and also represented graphically by taking Time (hrs) on X-axis and Cumulative percentage drug release on Y-axis. In formulation CB1 the Drug tablet were prepared with 98mg drug and 50mg Agar, they shown drug release of 96.26 in P.B.S at the end of 8 hour. In formulation CB2 the Drug tablet were prepared with 98mg drug and 50mg SCMC, they shown drug release of 98.65 in P.B.S at the end of 9 hour. In formulation CB3 the

Table 4: *In-vitro* Drug release studies of Clopidogrel bisulphate floating tablets

Time (h)	CB1	CB2	CB3	CB4	CB5	CB6	CB7	CB8	CB9
1	10.38±0.12	11.18±0.23	6.78±0.23	7.98±0.21	8.38±0.15	9.98±0.12	10.78±0.25	11.97±0.32	10.48±0.24
2	19.16±0.21	21.56±0.14	12.37±0.25	13.57±0.12	12.37±0.25	14.37±0.13	15.57±0.34	16.77±0.30	12.77±0.34
3	29.54±0.11	31.14±0.16	25.25±0.31	22.76±0.14	21.16±0.26	22.76±0.18	23.55±0.32	25.95±0.24	18.76±0.26
4	39.90±0.13	38.73±0.18	37.38±0.34	29.14±0.15	27.55±0.17	28.74±0.28	33.54±0.23	38.73±0.35	31.54±0.28
5	57.67±0.15	44.72±0.10	55.56±0.16	38.73±0.17	32.74±0.26	32.34±0.30	37.13±0.25	41.12±0.26	38.73±0.21
6	65.42±0.23	58.62±0.15	73.46±0.12	48.51±0.25	40.53±0.16	38.56±0.35	43.52±0.32	49.51±0.28	46.31±0.29
7	83.56±0.24	70.26±0.17	85.78±0.19	59.29±0.23	55.56±0.19	44.72±0.32	55.51±0.19	55.50±0.35	49.91±0.30
8	96.26±0.18	83.45±0.13	93.48±0.20	72.67±0.24	67.48±0.18	69.46±0.19	62.68±0.27	69.47±0.23	65.08±0.20
9	-	98.65±0.24	97.45±0.22	88.62±0.25	76.66±0.13	83.85±0.26	77.86±0.20	81.05±0.12	78.66±0.35
10	-	-	-	97.02±0.27	86.64±0.15	97.65±0.23	86.24±0.23	87.44±0.15	84.65±0.28
11	-	-	-	-	-	-	-	98.82±0.25	-

Fig 8: *In-vitro* Drug release studies of Clopidogrel bisulphate floating tablets

Comparison of all formulations of Clopidogrel bisulfate tablets revealed the fact the developed formulation F8 showed comparable release characteristics, thus it may have fair clinical efficacy

Drug tablet were prepared with 98mg drug and 50mg Eudragit, they shown drug release of 97.45 in P.B.S at the end of 9 hour.

In formulation CB4 the Drug tablet were prepared with 98mg drug, 25mg Agar and 25mg SCMC, they shown drug release of 97.02 in P.B.S at the end of tenth hour. In formulation CB5 the Drug tablet were prepared with 98mg drug, 25mg SCMC and 25mg Eudragit, they shown drug release of 98.22 in P.B.S at the end of 11 hour. In formulation CB6 the Drug tablet were prepared with 98mg drug, 25mg Agar and 25mg Eudragit, they shown drug release of 97.65 in P.B.S at the end of tenth hour. In formulation CB7 the Drug tablet were prepared with 98mg drug, 10mg Agar, and 20mg SCMC and 20mg Eudragit, they shown drug release of 98.22 in P.B.S at the end of 11 hour. In formulation CB8 the Drug tablet were prepared with 98mg drug, 20mg Agar, and 10mg SCMC and 20mg Eudragit, they shown drug release of 99.82 in P.B.S at the end of 12 hour. In formulation CB9 the Drug tablet were prepared with 98mg drug, 20mg Agar, and 20mg SCMC and 10mg Eudragit, they shown drug release of 98.62 in P.B.S at the end of 11 hour. Among all the formulations (CB1-CB9), CB8 formulation shows superior drug release which is obtained in the graph

***In vitro* release kinetics:**

Data of *In vitro* drug release were fitted into dissimilar equations and kinetic models used to elucidate the release kinetics of drug from controlled release tablet. The kinetic models used are zero-order equation, Higuchi's model and Peppas's models. The obtained outcome in these formulations were plotted and are as follows i.e. Cumulative % release of drug V_{ss} of t (Higuchi's) and Log cumulative percentage drug release $V_{slog t}$ (Peppas's). To know the method of drug release drug release from tablet, the release of drug data was fit into Higuchi's models. To find out the method of drug release drug release, the *In-vitro* dissolution data of each formulation with dissimilar kinetic drug release equations namely Zero order $Q = K_0t$; Higuchi's $Q = K_H t^{1/2}$ and Peppas's $F = K_m t^n$. The correlation coefficient values (R) indicate the kinetic of drug release was zero order and the method of drug release indicates the super case-II transport (both diffusion and corrosion occurs). The stability studies were conceded according to ICH guidelines for the optimized formulation i.e. CB8 under accelerated stability studies ($40 \pm 2^\circ\text{C}/75 \pm 5\%\text{RH}$). A stability study has not shown any significant changes during the period of 3 months.

CONCLUSION

The prepared floating tablets of Clopidogrel bisulfate using different proportions of Agar, SCMC, and Eudragit RS-100 had shown good promising results for

all the evaluated parameters. It was concluded that SCMC and Eudragit RS-100 of moderate level useful for preparation of control release floating tablet formulation. The developed floating tablets increase the therapeutic efficacy and reduced toxic effect of Clopidogrel bisulfate.

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