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Original Article

Design and Characterization of Bilayered Floating Tablets of Clopidogrel Bisulfate and Aspirin using Natural Gums

Manasa Reddy Devarapalli, Latha Kukati Latha*, Naseeb Basha Shaik, Shailaja Thoudoju, Saleha Fatima, Arshiya Sheerin, Mohammed Atif Mujtaba, Shashanka Bhukya, Gaikwad Sushmitha
Department of Pharmaceutics, G. Pulla Reddy College of Pharmacy, Hyderabad, Telangana, INDIA.

ABSTRACT

Objectives: In present investigation, an attempt was made to develop bilayered floating tablets of clopidogrel bisulfate and aspirin using natural gums as release retarded material. Clopidogrel bisulfate and aspirin are anti-platelet agents. **Methodology:** Clopidogrel bisulfate is a suitable candidate for formulating as gastro retentive dosage form as it has absorption window in stomach and solubility in the acidic pH. Sodium bicarbonate and citric acid were used to get desired floating properties. The effect of formulation variables on floating properties and drug release were investigated. **Results:** The tablets so designed were evaluated and found to have acceptable physicochemical properties, floating lag time, floating time and drug release. Among all the bilayered formulations, CBXA with susutained.release layer containing xanthan gum (2 ratio with drug), sodium bicarbonate (15% w/w) and citric acid (1.2% w/w) and immediate release layer containing sodium bicarbonate (10% w/w) and guar gum (4% w/w) has shown optimum results. Sustained release layer has shown dissolution of 99.03±0.42 % in 12 hrs whereas immediate release layer has shown 99.4±0.44 % in 30mins.CBXA has shown optimum floating properties with *in vitro* floating lag time of 4 min and floating time of >12 hr. *In vivo* buoyancy study revealed that the floating time of CBXA was greater than 6 hr. The *in vitro* release data of optimized formulation was treated with mathematical equations and was evident that drug release followed zero order kinetics with case II transport mechanism. **Conclusion:** Based on the results it can be found that bilayered floating tablets of clopidogrel bisulfate and aspirin containing xanthan gum provides a better approach for sustained release and improved bioavailability.

Key words: Clopidogrel bisulfate, Bilayered floating tablets, Susutained release layer, Immediate release layer and Bioavailability.

Correspondence

Dr. K Latha, M. Pharm,

Professor, Department of Pharmaceutics, G. Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad-28, Telangana, INDIA.

Phone: +91 9848630966

Email: lathakukatil@gmail.com

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INTRODUCTION

Concept of novel drug delivery system arose to overcome certain aspect related to physicochemical properties of drug and the related formulations. The important physiological factor which is responsible for the reduction in efficacy of oral formulations is gastric residence time (GRT). GRT considerably affects the bioavailability of the drug. Variable and short gastric emptying time results in incomplete drug release from oral formulations which leads to reduction in efficacy of the administered dose. GRT is affected by both the fasting as well as fed states of the stomach.

Gastroretentive systems are designed so that they are retained in the upper part of the gastrointestinal (GI) tract for several hours thereby prolong the gastric residence time of drugs. Floating systems or dynamically controlled systems are low-density systems that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. This results in an increase in gastric retention time and a better control of fluctuation in plasma drug concentration.[1-4]

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. Following oral administration, it is well absorbed with bioavailability of about only 50% due to poor water solubility. The main side effects of the drug are gastric bleeding and clopidogrel drug resistance during chronic treatment. A sustained release floating clopidogrel formulation may be desired for several reasons, such as improving the bioavailability and to minimize the side effects of the drug such as gastric bleeding and to prevent the development of drug resistance wherefore to improve patient compliance.

Acetylsalicylic acid as an anti-inflammatory and anti-rheumatic agent may be due to inhibition of synthesis and release of prostaglandins. Acetylsalicylic acid appears to produce analgesia by virtue of both a peripheral and CNS effect. Peripherally, acetylsalicylic acid acts by inhibiting the synthesis and release of prostaglandins. Acetylsalicylic acid directly and irreversibly inhibits the activity of both types of cyclooxygenase (COX-1 and COX-2) to decrease the formation of precursors of prostaglandins and thromboxane from arachidonic acid.[5-8]

The aim of the present study was to formulate and to characterize floating tablets of clopidogrel bisulphate and aspirin using the natural polymers such as guar gum, karaya gum, locust bean gum, xanthun gum, sodium bicarbonate, citric acid and PVPK-30 with increased bioavailability and sustained release.

MATERIALS AND METHODS

Materials

Clopidogrel bisulphate, aspirin, guar gum, karaya gum, locust bean gum, xanthun gum, sodium bicarbonate, citric acid and PVPK-30.

Experimental methods

Preparation of formulation

Development of bilayered floating tablets of clopidogrel bisulfate and aspirin were prepared using natural gums as release retarded material. Two layers such as immediate release (IR) layer and sustained release (SR) layer were formulated separately using different concentration of polymers in different ratios. After optimization of individual layers by *in-vitro* studies, bilayer tablets were prepared using optimized formula. Bilayer tablets were prepared on rotary tablet compression machine. First the extended release tablets were pre-compressed on compression machine manually and the immediate release layer was loaded on top of pre-compressed layer and punched.

Evaluation parameters

Pre compression parameters

All the flow properties were studied such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose.

Post compression parameters

Bilayered floating tablets were evaluated for hardness, weight variation, friability and content uniformity. Sustained release floating layer was also evaluated for.

Lag time

The *in vitro* buoyancy was determined by the lag time. The tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time required for a tablet to rise to the surface for floating was determined as the lag time.

Floating time

The tablets were placed in a 100 ml glass beaker containing 0.1 N HCl. The time required for which the tablet remained floating on the surface of medium was determined as floating time.

Swelling index

The swelling index of tablets was determined in 0.1 N HCl at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation. Determinations were made in triplicate.

$$\% \text{ Swelling Index} = \frac{W_t - W_0}{W_t} \times 100$$

Where, W_0 is the initial weight of tablet, W_t is the weight of the tablet at time.

RESULTS AND DISCUSSIONS

Analytical method development for clopidogrel bisulfate and aspirin

Scan for absorption maxima (λ_{max}) of clopidogrel bisulfate and aspirin

The analytical method development for clopidogrel bisulfate and aspirin were performed for the determination of absorption maxima using 10 µg/ml of standard solution on a double beam spectrophotometer against 0.1N HCl as the blank.

Drug-excipients compatibility study by FTIR

From IR spectra shown in the Figure 1, 2 and 3 the peaks representing the pure drugs were similar in all the graphs suggesting that there are no interactions and the pure drugs were not altered functionally.

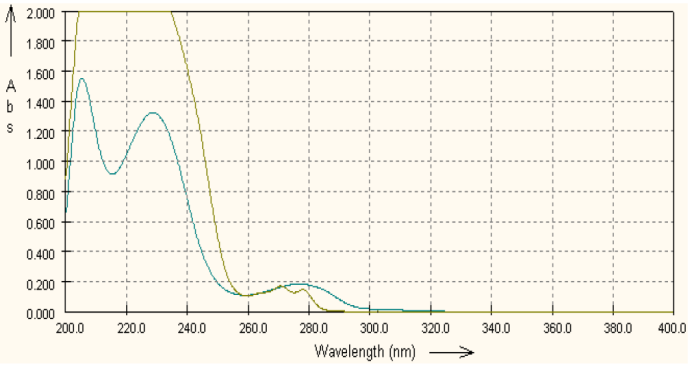

Figure 1: Spectral scan of clopidogrel bisulfate and aspirin.

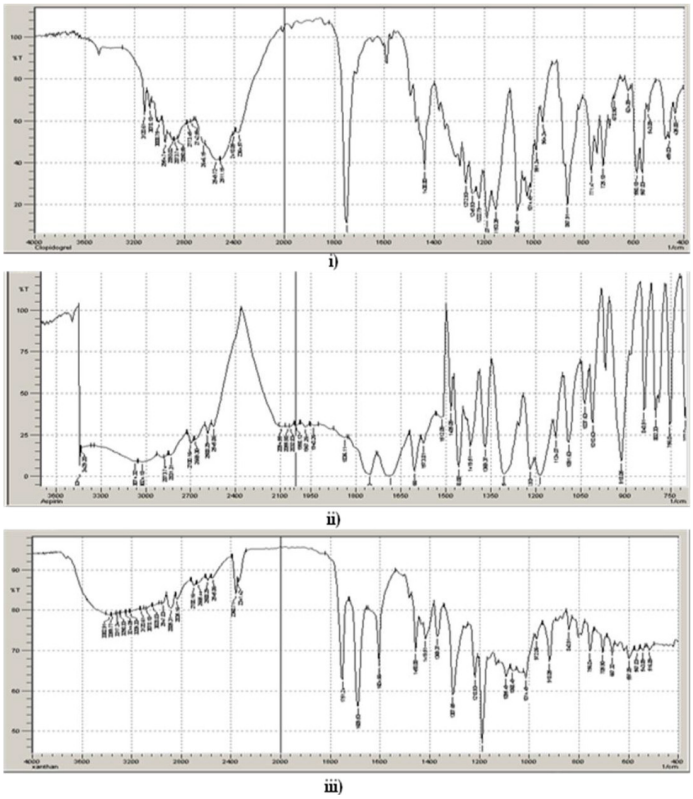

Figure 2: FTIR spectra of i) Clopidogrel bisulfate ii) Xanthan gum iii) Clopidogrel bisulfate +Xanthan gum.

Pre compression parameters

It was found that the Angle of repose, Hausner's ratio and Carr's index of clopidogrel bisulfate and the its powder blends were in the range of 44.92 to 53.3°, 1.32 to 1.46 gm/cm^3 and 22.46 to 29.67 % respectively as shown in the Table 1. This indicates that they do not possess required flow characteristics for direct compression.[8] Hence sustained release clopidogrel bisulfate layer was prepared by using .wet.granulation. Whereas aspirin has shown angle of repose, hausner's ratio and Carr's index values of 31.2°, 1.15 gm/cm^3 and 13.38 % respectively. This indicates that aspirin have enough flow properties for direct compression.

From Table 2 Angle of repose, Hausner's ratio and Carr's Index was found in the range of 30.21-38.9°, 0.66-0.79 gm/cm^3 and 8.9-14.9% which indicates that granules of all the formulations possess good flow properties.[8]

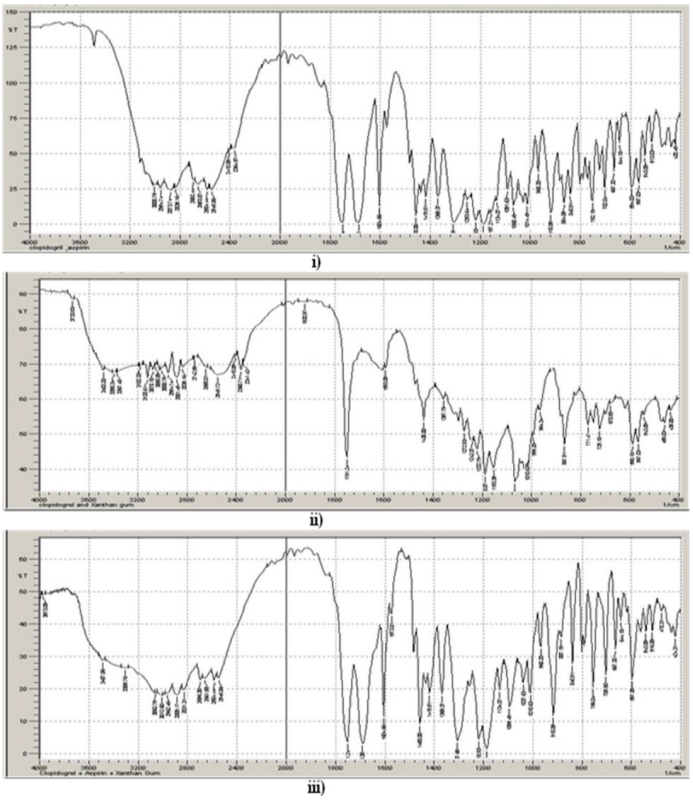

Figure 3: FTIR spectra of i) Aspirin ii) Clopidogrel bisulfate + Aspirin iii) Clopidogrel bisulfate + Aspirin +xanthan gum.

EVALUATION OF TABLETS

Prepared floating tablets were evaluated for physiochemical properties.

The hardness of clopidogrel bisulfate sustained release tablets was found to be in the range of 6.7 to 7.05 kg/cm^2. The thickness of the tablets was found to be in the range of 4.08 to 4.18 mm. Weight variation, friability and drug content were in the range of 385 to 400 mg, 0.1 to 0.52 % and 94 to 99.3 % respectively as shown in the Table 3. Thus all the parameters of the tablets were within compendial standards.[8]

The hardness of clopidogrel bisulfate sustained release tablets was found to be in the range of 6.78 to 7.12 kg/cm^2. The thickness of the tablets was found to be in the range of 4 to 4.17 mm. Weight variation, friability and drug content were in the range of 378 to 392 mg, 0.1 to 0.43 % and 94 to 99.6 % respectively as shown in the Table 4. Thus all the parameters of the tablets were within compendial standards.[9-11]

The hardness of aspirin immediate release tablets was found to be in the range of 3 to 3.2 kg/cm^2. The thickness of the tablets was found to be in the range of 2.08 to 2.24 mm. Weight variation, friability and drug content were in the range of 242 to 249 mg, 0.38 to 0.68 % and 95.86 to 98.1 % respectively. All the formulations have shown disintegration

Table 1: Pre compression parameters of the powder blends.

Ingredients	Angle of repose	Hausner's ratio	Carr's index (%)
Clopidogrel bisulfate	53.3±0.54	1.40±0.093	29.67±0.22
CB+ karaya gum	44.92±0.13	1.32±0.041	22.46±0.15
CB+ xanthan gum	50±0.49	1.46±0.027	24.1±0.17
Aspirin	31.265±3.9	1.15±0.035	13.38±0.33

Table 2: Pre compression parameters of the granules.

CODE	Angle of repose	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio	Carr's Index (%)
CBK1	32.05±0.12	0.75±0.016	0.84±0.02	1.12±0.05	10.93±0.09
CBK2	37.26±0.19	0.73±0.063	0.80±0.014	1.01±0.016	12.32±0.014
CBK3	30.21±0.22	0.79±0.034	0.86±0.04	1.09±0.053	11.15±0.018
CBK4	36.74±0.37	0.73±0.023	0.84±0.014	1.15±0.055	10.27±0.025
CBK5	38.63±0.18	0.71±0.07	0.79±0.015	1.11±0.049	11.285±0.07
CBK6	37.06±0.05	0.7±0.05	0.75±0.056	1.07±0.079	13.38±0.082
CBK7	34.33±0.27	0.73±0.022	0.78±0.01	1.07±0.033	14.65±0.031
CBK8	35.54±0.44	0.79±0.09	0.84±0.09	1.05±0.012	9.785±0.047
CBK9	37.95±0.96	0.72±0.06	0.79±0.03	1.09±0.05	11.345±0.07
CBK10	37.36±0.43	0.71±0.011	0.74±0.073	1.03±0.01	13.88±0.014
CBK11	36.26±0.34	0.68±0.51	0.77±0.8	1.13±0.12	11.55±0.23
CBX1	36.63±0.18	0.7±0.025	0.75±0.012	1.06±0.034	8.9±0.14
CBX2	36.36±0.72	0.72±0.033	0.81±0.018	1.12±0.038	10.65±0.23
CBX3	37.27±0.8	0.75±0.065	0.78±0.05	1.03±0.022	11.39±0.07
CBX4	38.63±0.97	0.66±0.03	0.71±0.07	1.08±0.05	10.57±0.51
CBX5	36.55±0.14	0.66±0.062	0.7±0.024	1.06±0.09	13.78±0.27
CBX6	37.67±0.56	0.68±0.09	0.74±0.013	1.09±0.063	11.84±0.19
CBX7	38.92±0.42	0.75±0.023	0.83±0.045	1.1±0.035	14.89±0.15
CBX8	38.47±0.69	0.67±0.094	0.74±0.015	1.1±0.023	14.37±0.055
CBX9	35.76±0.3	0.72±0.089	0.80±0.03	1.12±0.05	13.39±0.038
CBX10	38.95±0.42	0.76±0.033	0.87±0.056	1.14±0.049	11.33±0.16
CBX11	37.15±0.57	0.7±0.01	0.78±0.012	1.1±0.037	11.75±0.12
CBX12	38.32±0.48	0.68±0.081	0.72±0.014	1.05±0.022	9.65±0.037
CBX13	37.49±0.32	0.75±0.016	0.84±0.02	1.11±0.05	10.95±0.09

Note: All the values are expressed as Mean ±SD, n = 3

Table 3: Physiochemical evaluations of clopidogrel bisulfate matrix tablets.

Code	Hardness (kg/cm²)[a]	Thickness (mm)[b]	Weight variation (%)[c]	Friability (%)[d]	Drug content (%)[e]
CBK1	6.77±0.26	4.1±0.056	389±3.1	0.25±0.07	98±0.9
CBK2	6.94±0.25	4.13±0.059	398±0.2	0.37±0.011	98.7±0.18
CBK3	6.26±0.23	4.02±0.091	400±-0.1	0.39±0.018	99.3±0.94
CBK4	7.05±0.25	4.19±0.063	387±0.96	0.3±0.017	95.3±0.91
CBK5	7±0.16	4.08±0.08	399±0.17	0.34±0.098	95.3±0.82
CBK6	7.03±0.15	4.09±0.044	385±1.35	0.52±0.04	95.3±0.9
CBK7	6.96±0.27	4.2±0.055	392±1.7	0.14±0.018	96±0.88
CBK8	6.95±0.26	4.18±0.067	395±0.8	0.27±0.019	99.6±0.97
CBK9	7±0.26	4.05±0.08	386±1.2	0.32±0.036	94±0.84
CBK10	7.05±0.16	4.03±0.074	391±0.57	0.3±0.019	98±0.94
CBK11	6.99±0.22	4.08±0.068	393±0.15	0.16±0.032	97.3±0.8

Note: All the values are expressed as Mean ±SD. a, b: n=5, c: n=20, d, e: n=10

Table 4: Physiochemical evaluations of clopidogrel bisulfate matrix tablets.

Code	Hardness (kg/cm²)[a]	Thickness (mm)[b]	Weight variation (%)[c]	Friability (%)[d]	Drug content (%)[e]
CBX1	6.97±0.01	4.1±0.017	385±0.021	0.4±0.019	98.9±0.14
CBX2	7.04±0.025	4.07±0.02	381±0.028	0.32±0.037	99.3±0.94
CBX3	7.05±0.022	4.01±0.06	388±0.053	0.23±0.017	97.3±1.9
CBX4	7.07±0.013	4.06±0.024	391±0.027	0.43±0.018	95.3±0.9
CBX5	7.02±0.023	4.03±0.062	397±0.073	0.31±0.036	94±0.81
CBX6	7±0.024	4.11±0.039	384±0.051	0.14±0.018	97.3±0.94
CBX7	6.78±0.019	4.05±0.023	383±0.077	0.39±0.017	97.3±0.19
CBX8	6.96±0.019	4.1±0.034	394±0.015	0.15±0.098	99.3±0.9
CBX9	7.2±0.068	4.12±0.046	380±0.03	0.24±0.019	97.3±1.4
CBX10	7.04±0.023	4.04±0.033	387±0.078	0.17±0.01	95.6±0.37
CBX11	6.95±0.022	4.17±0.05	378±0.02	0.1±0.02	97.6±0.32
CBX12	7.12±0.013	4.08±0.037	392±0.034	0.28±0.054	96.7±0.47
CBX13	7.02±0.02	4.15±0.016	384±0.02	0.26±0.05	95.3±0.68

Note: All the values are expressed as Mean ±SD. a, b: *n*=5, c: *n*=20, d, e: *n*=10

Table 5: Physiochemical evaluations of immediate release tablets.

Code	Hardness (kg/cm²)[a]	Thickness (mm)[b]	Weight variation (%)[c]	Friability (%)[d]	Drug content (%)[e]	Disintegration (Mins)[f]
A1	3.2±0.017	2.1±0.045	243±0.87	0.45±0.016	97.84±0.45	5
A2	3.14±0.029	2.15±0.061	247±0.71	0.38±0.028	95.86±0.57	3
A3	3±0.021	2.08±0.086	242±-0.68	0.58±0.018	97.6±0.90	1
A4	3.07±0.013	2.24±0.021	249±0.26	0.68±0.06	96.06±0.91	2
A5	3.12±0.031	2.17±0.016	248±0.17	0.42±0.014	98.14±0.22	4
A6	3.17±0.024	2.13±0.02	243±0.5	0.54±0.017	97.45±0.55	6
A7	3.11±0.019	2.19±0.03	243±0.26	0.65±0.06	96.13±0.56	6
A8	3.09±0.013	2.17±0.041	247±0.15	0.52±0.016	97.06±0.42	4
A9	3.21±0.068	2.13±0.016	245±0.53	0.48±0.08	97.8±0.51	5

Note: All the values are expressed as Mean ±SD. a, b: *n*=5, c: *n*=20, d, e: *n*=10, f: *n*=6

Table 6: Physiochemical evaluations of bilayered floating tablets.

Code	Hardness (kg/cm²)[a]	Thickness (mm)[b]	Weight variation (%)[c]	Friability (%)[d]	Drug content (%)[e]
CBKA	6.4±0.23	5.89±0.15	648±0.7	0.16±0.4	97.6±0.41
CBXA	6.34±0.19	5.77±0.2	643±0.6	0.23±0.6	98.96±0.6

Note: All the values are expressed as Mean ±SD. a, b: n=5, c: n=20, d, e: n=10

Table 7: Floating lag time and floating time of sustained release tablets (Karaya gum).

CODE	Floating lag time (min.)	Floating time (hrs)
CBK1	35	6
CBK2	38	10
CBK3	47	8
CBK4	51	10
CBK5	41	NO INTEGRITY
CBK6	33	NO INTEGRITY
CBK7	20	11
CBK8	5	NO INTEGRITY
CBK9	2	NO INTEGRITY
CBK10	21	>12
CBK11	11	8

Table 8: Floating lag time and floating time of sustained release tablets (Xanthan gum).

CODE	Floating lag time (mins)	Floating time (hrs)
CBX1	28	8
CBX2	28	10
CBX3	40	11
CBX4	43	10
CBX5	39	NO INTEGRITY
CBX6	25	NO INTEGRITY
CBX7	17	9
CBX8	4	11
CBX9	3	NO INTEGRITY
CBX10	19	10
CBX11	3	NO INTEGRITY
CBX12	7	>12
CBX13	6	NO INTEGRITY

less than 6 mins as shown in the Table 5. Among all the formulations A3 have shown less disintegration time. Thus all the parameters of the tablets were within compendial standards.

The hardness of bilayered floating tablets was found to be in the range of 6.34 to 6.4 kg/cm^2. The thickness of the tablets was found to be in the range of 5.77 to 5.89 mm. Weight variation, friability and drug content were in the range of 643 to 648 mg, 0.16 to 0.23 % and 97.6 to 98.96 % respectively as shown in the Table 6. Thus all the parameters of the tablets were within compendial standards.

In vitro buoyancy

Buoyancy test was conducted for the formulations CBK1 to CBK11. Among these formulations CBK7, CBK8, CBK9, CBK10, CBK11 have shown lag time less than 30 min as shown in the Table 7.

Buoyancy test was conducted for the formulations CBK1 to CBK11 and CBX1 to CBX13 as shown in the Table 8.

Buoyancy test was conducted for the formulations CBK1 to CBK11 and CBX1 to CBX13.Among these formulations CBK7, CBK8, CBK9, CBK10, CBK11, CBX1, CBX2, CBX6, CBX7, CBX8, CBX9, CBX10, CBX11, CBX12, CBX13 have shown lag time less than 30 mins. But,

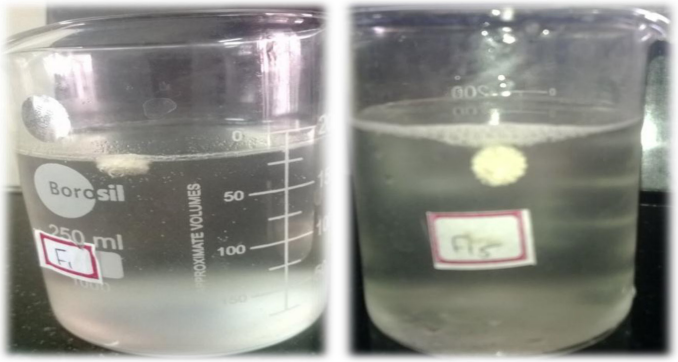

Figure 4: *In-vitro* buoyancy of optimized formulation.

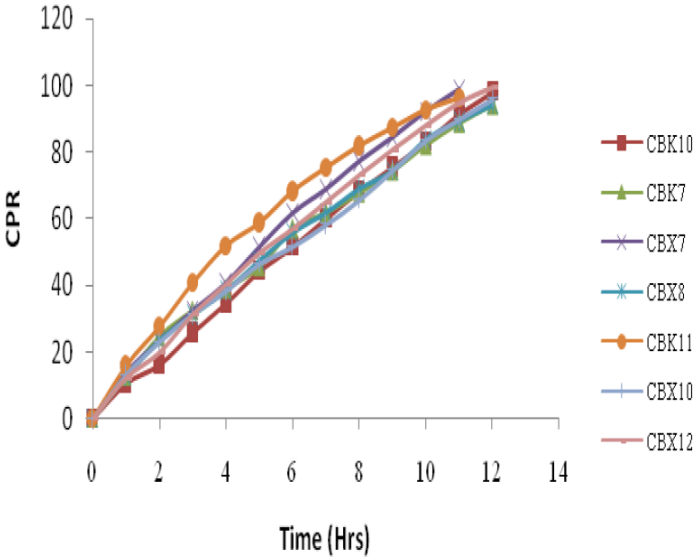

Figure 5: Dissolution profiles of different formulations.

formulations CBK8, CBK9, CBX6, CBX9, CBX11, CBX13 have lost integrity though they have shown floating lag time less than 30 mins. So, formulations CBK7, CBK10, CBK11, CBX1, CBX2, CBX7, CBX8, CBX10, CBX12 were selected and subjected to dissolution studies for optimization. Figure 4 indicates *in vitro* buoyancy of CBX12

In vitro drug dissolution testing of floating table

It was observed that increasing the amount of karaya gum in the formulation, resulted in slower rate and decreased amount of drug release from the tablet. This slow release is because of the formation of more thick gel like structure around karaya gum that delays release from tablet matrix and retarding further penetration of dissolution medium, prolong the drug release. Among all the formulations CBK10 has shown maximum drug release i.e. 98% over a period of 12 h as shown in the Table 9 and Figure 5, 6 and 7.

It was observed that increasing the amount of gum in the formulation, resulted in slower rate and decreased amount of drug release from the tablet. Comparison between xanthan gum and karaya gum based tablets, release of drug from xanthan gum based tablet was found to be more slowly compared to karaya gum based tablet. This slow release is because of the formation of more thick gel like structure around the matrix of xanthan gum compared to karaya gum that delays release from tablet matrix and retarding further penetration of dissolution medium, prolong

Table 9: Dissolution profiles of sustained release matrix tablets (Karaya gum).

TIME (hrs)	%Drug release						
	CBK1	CBK2	CBK3	CBX4	CBK7	CBK10	CBK11
1	13.8±0.96	15.6±0.21	13.2±0.13	10.2±0.74	12.6±0.54	10.5±0.4	15.9±0.49
2	25.8±0.79	29.4±0.62	24.6±0.74	18.6±0.18	24.6±0.85	16.1±0.14	27.5±1.7
3	38.4±0.06	43.2±0.77	31.8±0.74	28.2±0.13	32.4±0.69	25.8±0.16	40.68±1.2
4	51±0.83	54±0.64	39±0.18	36.6±0.68	39±0.84	34.6±0.25	51.8±0.7
5	60.6±0.67	63.6±0.4	47.4±0.53	45.7±0.43	45.6±0.39	44.2±2.38	58.6±0.83
6	67.2±0.35	69.6±0.96	56.4±0.31	54.6±0.29	57±0.85	51.5±0.35	68.1±0.04
7	83.4±0.56	75±0.61	61.8±0.27	60.6±0.48	61.8±0.81	60.1±0.02	75.2±0.37
8	90.6±0.37	81.6±0.29	67.8±0.45	66.6±0.97	67.8±0.54	68.3±0.19	81.8±0.15
9	96.1±0.88	86.4±0.71	75.6±0.32	72.6±0.83	74.4±0.69	75.5±0.11	87.2±0.1
10	-	91.8±0.42	83.4±0.19	77.4±0.28	82.2.±0.5	83.1.±0.13	92.5±0.09
11	-	96.6±0.42	89.4±0.2	81.6±0.57	88.8±0.69	91.5±0.48	96±0.26
12	-	-	95.4±0.46	84.6±0.24	94.2.±0.24	98.±0.24	-

Note: All the values are expressed as mean± SD, n=3

Table 10: Dissolution profiles of sustained release matrix tablets (Xanthan gum).

TIME (hrs)	%Drug release							
	CBX1	CBX2	CBX3	CBKX4	CBX7	CBX8	CBX10	CBX12
1	12.6±0.38	12.1±0.95	9.71±0.63	7.3±0.12	13.8±2.5	12.6±0.84	13.2±0.43	12.2±0.04
2	23.4±0.46	23.4±0.63	17.4±54	13.8±0.75	23.4±0.85	23.4±0.84	23±0.03	19.8±0.3
3	35.3±0.39	31.3±0.07	25.8±0.25	20.1±0.62	32.4±1.69	31.2±0.00	31.4±0.44	31.3±0.3
4	46.7±0.98	40.2±0.32	33.1±0.32	26.4±0.55	40.8±1.7	38.4±1.69	38.3±0.73	40.3±0.28
5	56.4±0.54	48.6±0.15	40.2±0.66	31.5±0.81	51.6±0.39	47.4±2.55	46.4±0.26	49.6±0.51
6	64.2±0.78	55.8±0.64	47.41±0.85	37.2±0.42	61.8±0.54	55.8±0.85	51.6±0.5	56.84±0.19
7	73.3±0.24	62.4±0.41	54.67±0.3	45.6±0.13	69±0.84	61.8±0.85	58.2±0.21	64.9±0.2
8	81.1±0.77	69.8±0.2	60.9±0.57	50.1±0.27	77.4±0.54	69±0.85	65.6±0.2	73±0.14
9	89.4±0.72	75.6±0.62	67.8±0.38	56.4±0.78	84.6±0.85	74.4±1.7	74.5±0.39	80.7±0.47
10	97.2±0.5	82.2±0.57	72.6±0.22	63.8±0.95	92.4±0.69	83.8±1.7	83.5±0.67	87.9±0.27
11	-	89.4±0.77	77.3±0.91	66.7±0.77	99±0.84	89.4±0.85	89.9±0.16	94.7±0.26
12	-	94.1±0.16	82.2±0.71	72.7±0.12	-	94.2±0.85	95.9±0.1	99.3±0.08

Note: All the values are expressed as mean± SD, *n*=3

the drug release.[11] Among all the xanthan gum based formulations, CBX12 has shown the maximum drug release of 99.3% over a period of 12 as shown in the Table 10.

Among all the formulations of immediate release aspirin layer formulation A4 with 5% sodium bicarbonate and 3% guar gum was optimized as it has shown release within 30 mins[12] as shown in the Table 11.

In bilayered tablet, Sustained release matrix layer with 1:2 ratio of clopidogrel bisulfate: xanthan gum has shown 99.03±0.42 release in 12 hrs whereas immediate release layer with 5% sodium bicarbonate and 3% guar gum has shown 99.4±0.44 % release within 30 min[13-16] as Table 12 and Figure 8.

Drug release kinetics

Model dependent Method: Drug release profiles of all the formulations into zero order release model, first order release model, Higuchi model and korsmeyer-peppas model as the Table 13.

Based on the results of model dependent kinetic analysis of dissolution profiles of formulation CBXA, it was found that the release of the drug

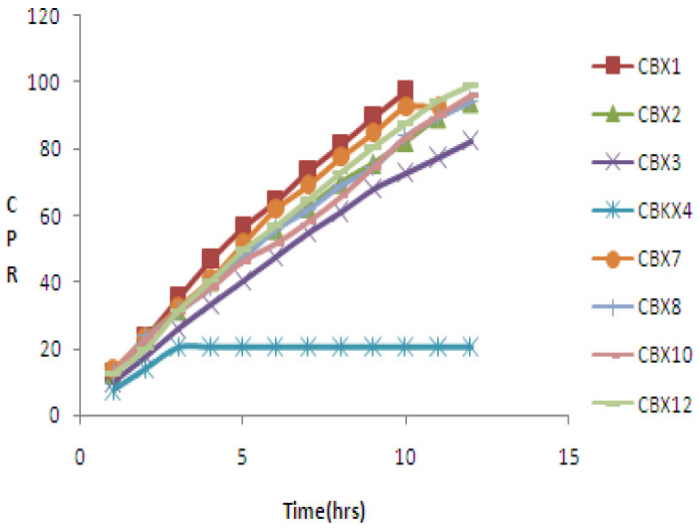

Figure 6: Dissolution profiles of different formulations.

Table 11: Dissolution profiles of immediate release tablets.

TIME (hrs)	%Drug release							
	A4	A5	A6	A7	A8	A9	CBX10	CBX12
5	23.1±0.54	15.7±0.9	14.2±0.18	24.5±0.36	24.5±0.36	15.2±0.54	13.2±0.43	12.2±0.04
10	41.1±0.36	28.3±0.72	23.7±0.36	38.4±0.54	38.4±0.54	29.2±0.18	23±0.03	19.8±0.3
15	57.2±0.72	43.9±0.36	38.9±1.2	51.3±0.36	30.38±0.7	44±0.18	31.4±0.44	31.3±0.3
20	72.3±0.18	56±0.18	47.5±0.36	63.7±0.18	41.5±0.54	56.7±0.36	38.3±0.73	40.3±0.28
25	85±0.72	67.2±0.18	54.4±0.00	73.8±0.39	50±0.36	66.9±0.72	46.4±0.26	49.6±0.51
30	95.6±0.9	79.7±0.36	64.7±0.9	92±0.54	59.7±0.00	77.6±0.36	51.6±0.5	56.84±0.19
40	-	95.5±0.72	74.3±0.7	99.6±0.36	76.6±0.7	96.1±0.5	58.2±0.21	64.9±0.2
50	-	-	89±0.18	-	94.6±0.18	-	65.6±0.2	73±0.14
60	-	-	97.7±0.54	-	-	-	74.5±0.39	80.7±0.47

Note: All the values are expressed as mean± SD, n=3

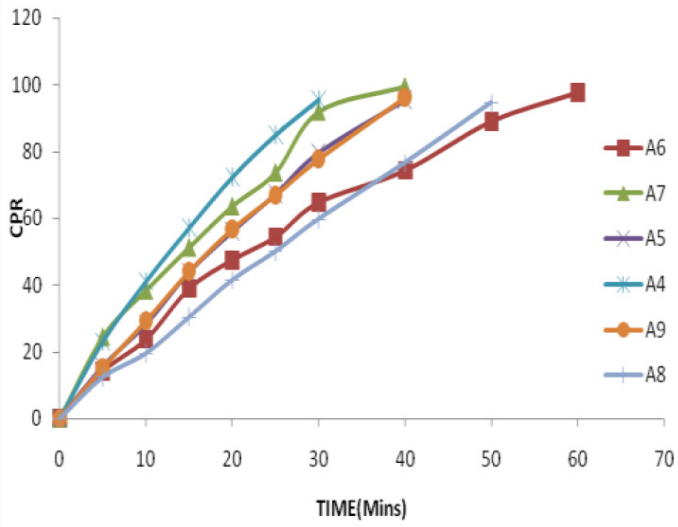

Figure 7: Dissolution profiles of different immediate release formulations.

Table 12: Dissolution profiles of optimized bilayered tablet.

Time (Hrs)	% Drug release of sustained release matrix layer	Time (Min.)	% Drug release of immediate release layer
1	14±0.28	5	26.04±0.4
2	22.4±0.07	10	48±0.95
3	30.5±0.6	15	62.8±0.6
4	37.1±0.03	20	77.7±0.7
5	46.4±0.09	25	89.3±0.17
6	54.4±0.5	30	99.4±0.44
7	61.2±0.08	-	-
8	68.9±0.37	-	-
9	75.6±0.1	-	-
10	84.7±1.6	-	-
11	92.5±0.46	-	-
12	99.03±0.42	-	-

Note: All the values are expressed as mean± SD, *n*=3

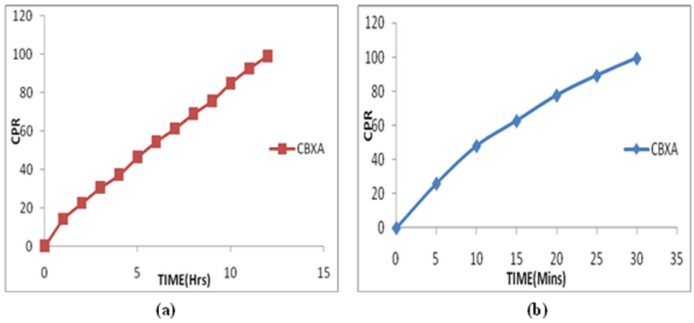

Figure 8: Dissolution profiles of CBXA a) Sustain release b) Immediate release.

from these formulations followed zero order kinetics and mechanism of release was found to be case II transport as shown in the Table 14. Indicates model dependant kinetics of CBX12.

In vivo Buoyancy Study

In vivo buoyancy study was performed on healthy rabbit. The animal dose was calculated using dose translation based on Body Surface Area (BSA). From the obtained results it was observed bilayered floating tablets (CBXA) remained in the gastric region for 6 hr of administration indicating good retention of the tablets in the stomach region.

Figure 9 indicates position of bilayered floating tablet at different time intervals. *In vivo* floating time was greater than 6 hrs as shown in the Figure 9 i, ii, iii, iv whereas after 6 hrs floating ability of tablet was lost as shown in the Figure 9 v.

STABILITY STUDIES

Optimized formulation was subjected for stability studies. Based on the results it can be concluded that, optimized tablets were stable during accelerated stability studies, with insignificant change in the floating lag time, floating time, drug content and *in vitro* drug release characteristics as shown in the Figure 10.

CONCLUSION

Bilayered floating matrix tablets of clopidogrel bisulfate and aspirin can be formulated as an approach to increase gastric residence time and thereby improving its bioavailability. Sustained release matrix layer of clopidogrel bisulfate was been prepared using guar gum, karaya gum,

Table 13: Model dependent kinetics of sustained release formulations.

CODE	Zero order	First order	Higuchi	Korsmeyer-Peppas		Release Mechanism
	R^2	R^2	R^2	R^2	n	
CBK1	0.991	0.82	0.99	0.98	0.89	Case II transport
CBK2	0.951	0.79	0.99	0.93	0.74	Anomalous transport
CBK3	0.991	0.55	0.91	0.83	0.71	Anomalous transport
CBK4	0.980	0.76	0.97	0.95	0.77	Anomalous transport
CBK7	0.998	0.9	0.91	0.98	0.78	Anomalous transport
CBK10	0.998	0.84	0.97	0.96	0.61	Anomalous transport
CBK11	0.992	0.93	0.94	0.99	0.78	Anomalous transport
CBX1	0.989	0.97	0.71	0.95	1.75	Super case II transport
CBX2	0.992	0.92	0.94	0.99	0.539	Anomalous transport
CBX3	0.993	0.97	0.95	0.97	1.18	Super case II transport
CBX4	0.997	0.98	0.82	0.93	1.37	Super case II transport
CBX7	0.994	0.78	0.98	0.85	1.34	Super case II transport
CBX8	0.991	0.81	0.98	0.87	1.87	Super case II transport
CBX10	0.994	0.86	0.97	0.89	1.48	Super case II transport
CBX12	0.993	0.97	0.84	0.88	1.57	Super case II transport

Table 14: Model dependent kinetic analysis of optimized bilayered formulation

CODE	Zero order	First order	Higuchi	Korsmeyer- Peppas		Release Mechanism
	R^2	R^2	R^2	R^2	n	
CBKA	0.991	0.871	0.98	0.972	0.73	Anomalous transport
CBXA	0.999	0.925	0.91	0.993	0.89	Case II transport

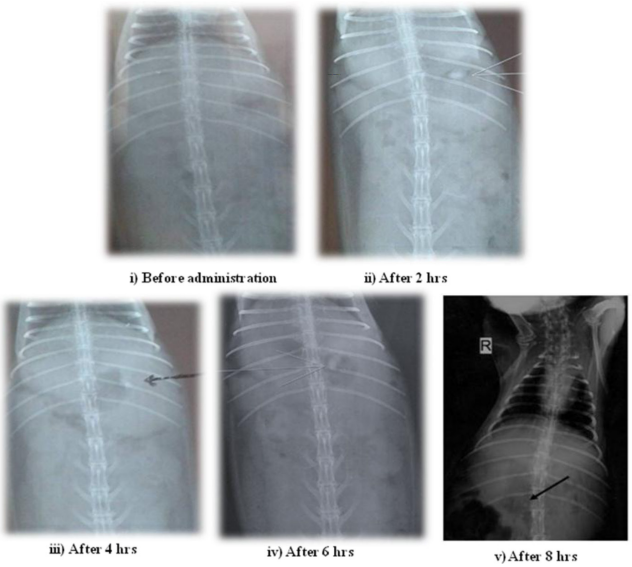

Figure 9: X-ray photographs of GIT of rabbit at different time intervals after administration of bilayered floating tablet.

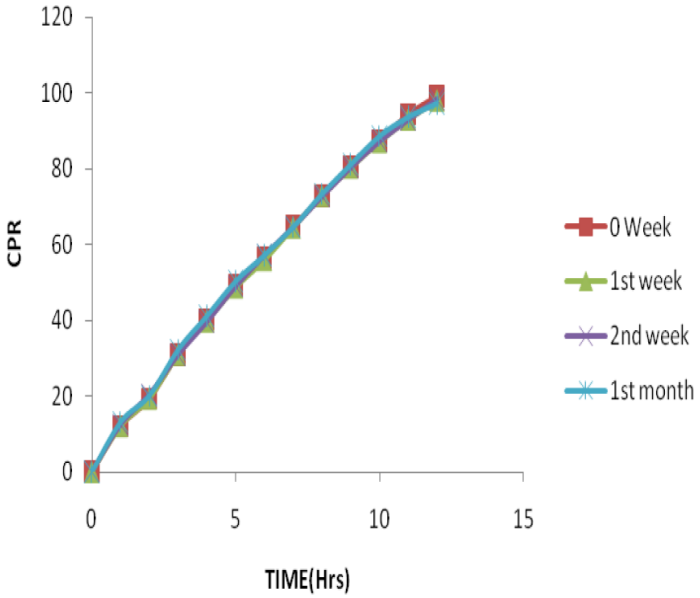

Figure 10: Percentage drug release of optimized formulation during ASS.

locust bean gum and xanthan gum as rate control polymers, sodium bicarbonate and citric acid as gas generating agents. Immediate release layer of aspirin have been prepared using sodium bicarbonate as disintegrant and PVP K-30, guar gum and gum acacia as binders. Among all the bilayered formulations, CBXA with susutained release layer containing xanthan gum (2 ratio with drug), sodium bicarbonate (15% w/w) and citric acid (1.2% w/w) and immediate release layer containing sodium bicarbonate (10% w/w) and guar gum (4% w/w) has shown optimum results. Sustained release layer has shown dissolution of 99.03±0.42 % in 12 hr whereas immediate release layer has shown 99.4±0.44 % in 30min. CBXA has shown optimum floating properties with *in vitro* floating lag time of 4 min and floating time of >12 hr. *In vivo* buoyancy study revealed that floating time is greater than 6 hr. Based on the results of model dependent kinetic analysis of CBXA, it was found that the release of the drug followed zero order kinetics and mechanism of release was found to be case II transport.

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CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

ABBREVIATIONS

GRT: Gastric Residence Time; **GI tract:** Gastro Intestinal; **COX:** CycloOxygenase; **IR:** Immediate Release; **SR:** Sustained Release; **FTIR:** Fourier Transfer InfraRed; **BSA:** Body Surface Area.

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