CHAPTER 5

SINGLE UNIT GASTRORETENTIVE CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

5.1. Introduction

Bioavailability of several drugs has been found to be poor and variable even when administered as extended/ controlled release formulations. In situ and in vivo experiments conducted on dogs have revealed that increased residence time in the stomach has the potential to increase overall bioavailability of celecoxib, a drug with extremely poor solubility [Paulson et al., 2001]; and of acyclovir, a drug with narrow absorption window in the upper GIT and poor solubility in the lower GIT (from the intestine) [Krasny et al., 1981]. Appropriately designed gastroretentive controlled release formulations, with floating and/ or mucoadhesive properties, are ideal intervention for such drugs [Rubinstein and Friend, 1994; Singh and Kim, 2000].

Buoyant drug delivery systems may be prepared with natural polysaccharides (e.g. alginate, chitosan, guar gum, etc) or swellable semi-synthetic polymers (e.g. HPMC) and in some cases, synthetic polymers (e.g. carbopol and polycarbophil) with or without effervescent components [Rubinstein and Friend, 1994; Tahara et al., 1995; Velasco et al., 1999; Bhardwaj et al., 2000; Li et al., 2002; Jacob et al., 2006]. At pH below 3, hydration of alginic acid leads to the formation of a high viscosity 'acid gel', which is highly buoyant in the presence of entrapped gas and capable of creating a diffusion barrier that can efficiently control drug release [Stockwell, 1986; Inouye et al., 1988; Efentakis and Koutlis, 2001; Tønnesen and Karlsen; 2002]. In the recent past, gas forming matrix based tablets employing different polymers have been developed and evaluated for controlled delivery of calcium [Li et al., 2001], amoxicillin [Tokumura and Machida, 2006], captopril [Rahman et al., 2006], phenoporlamine hydrochloride [Xu et al., 2006], and metoprolol tartrate [Narendra et al., 2006].

As a part of overall objective of designing gastroretentive controlled release formulations of two candidate drugs, an attempt was made to fabricate and evaluate gas generating floating

controlled release tablets of celecoxib and acyclovir, which have been presented in this chapter. Various types of polymers used for the formulations include sodium alginate, guar gum, xanthan gum, carbopol 934P NF, polycarbophil (Noveon AA1) and HPMC of various viscosity grades (15, 4000, 15000 and 1 lac cps). Gas generating agents used were anhydrous citric acid, sodium bicarbonate and calcium carbonate. Fabricated tablets were evaluated for physical properties, drug content, floating characters and in vitro drug release. Effects of type and proportion of polymers (alone or in combination), type and proportion of floating agents and hardness were evaluated on floating characteristics, drug release kinetics, swelling, disintegration and mucoadhesive characters of the designed formulations. Batch reproducibility, stability on storage and the effect of storage conditions on the characters were also investigated for selected formulations.

5.2. Experimental section

5.2.1. Materials

Drugs, polymers, excipients and chemicals/ reagents used in the studies were obtained from the same sources as mentioned in the Chapters 3 and 4.

5.2.2. Equipments

Formulations were compressed in single-punch/ single-station tablet compression machine (Cadmach, Ahmedabad). In vitro release studies were carried out in USP dissolution apparatus (USP XXIII) type 2 (Electrolab, Mumbai). UV-visible-NIR spectrophotometer (*Jasco*, Japan) was used for analysis. Water bath shaker (MAC, New Delhi) with thermostatic temperature control was employed for floating studies.

5.2.3. Analytical method

UV-visible spectrophotometric method described in Chapter 3 was employed for the analysis of celecoxib and acyclovir in formulation and in vitro release studies samples.

5.2.4. Preparation of floating tablets

Matrix embedded buoyant gas generating SU-GR-CRDFs were prepared by dry blending and direct compression. All the ingredients, including drug, polymer(s), floating agent(s) and manufacturing additives were initially dried in a tray drier at 55 °C for half an hour and individually passed through sieve # 80 before use. Required quantities of respective ingredients were weighed, uniformly blended and compressed into tablets. To study the impact of various parameters on physical characteristics, floating behaviour and in vitro release profiles, different formulations were prepared as discussed in the following sections.

Single polymer based and double polymer type systems were designed for both celecoxib and acyclovir.

5.2.4.1. Preparation of celecoxib tablets

(a) Single polymer based tablets

Effect of polymer type: Tablets using different types of polymer with fixed drug to polymer ratio (1:0.5), drug to total floating agent ratio (1:1) and sodium bicarbonate to anhydrous citric acid ratio (3:1) were prepared. Different polymers used included sodium alginate, guar gum, HPMC-15cps, carbopol and polycarbophil. The compositions and characteristics of this category of formulations are given in Table 5.1.

Table 5.1: Composition and characteristics of floating tablets of celecoxib prepared using different types of polymers

Formulation Code	**CA-21-31-1X**	**CG-21-31-1X**	**CH1-21-31-1X**	**CC-21-31-1X**	**CP-21-31-1X**
Composition (mg/tab)					
Celecoxib	200	200	200	200	200
Sodium alginate	100	-	-	-	-
Guar gum	-	100	-	-	-
HPMC 15 cps	-	-	100	-	-
Carbopol	-	-	-	100	-
Polycarbophil	-	-	-	-	100
Sodium bicarbonate	150	150	150	150	150
Anhydrous citric acid	50	50	50	50	50
Weight (mg/tab)*	505	505	505	505	505
Hardness (kg/cm^2)	7±0.5	7±0.5	7±0.5	7±0.5	7±0.5
Floating Behaviour					
Buoyancy (Lag time to float)	Semifloat within 3 min; 12-17 min (core)	6-7 min	30 min	Semifloat after 45 min; sinks after 3-4 h	Poor (settled at bottom)
Portion floating and duration of floating	Core (beyond 24 h)	Core (6-6.5 min); fragments (3.5-4 h)	Core (2 h); fragments (7-8 h)	NA	NA
Swelling (after 12 h)	3 times	ϕ	ϕ	2 times	ϕ
Disintegration/ Erosion	Insignificant	Significant surface erosion & complete fragmentation in 15 min	Significant surface erosion & complete fragmentation in 2 h	Low	Significant surface erosion & complete fragmentation in 1 hr

* Includes 1 % w/w of manufacturing additives; NA- Not applicable; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

Effect of viscosity of polymer: To study the effect of viscosity of the polymer on floating and drug release kinetics from designed tablets, HPMC of different viscosity (15 cps, 4000 cps, 15000 cps and 1 lac cps) was employed. Proportion of drug, polymer and floating agents were kept same as above. The compositions and characteristics of these tablets are presented in Table 5.2.

Table 5.2: Composition and characteristics of floating tablets of celecoxib prepared using HPMC of different viscosity

Formulation Code	CH1-21-31-1X	CH2-21-31-1X	CH3-21-31-1X	CH4-21-31-1X
Composition (mg/tab)				
Celecoxib	200	200	200	200
HPMC 15 cps	100	-	-	-
HPMC 4000 cps	-	100	-	-
HPMC 15000 cps	-	-	100	-
HPMC 1 lac cps	-	-	-	100
Sodium bicarbonate	150	150	150	150
Anhydrous citric acid	50	50	50	50
Weight (mg/tab)*	505	505	505	505
Hardness (kg/cm^2)	7±0.5	7±0.5	7±0.5	7±0.5
Floating Behaviour				
Buoyancy (Lag time to float)	30 min	35 min	40 min	Poor (settled at bottom)
Portion floating and duration of floating	Core (2 h); fragments (7-8 h)	Core (2.25 h); fragments (7-8 h)	Core (2.5 h); fragments (4 h)	NA
Swelling (after 12 h)	ϕ	ϕ	ϕ	ϕ
Disintegration/ Erosion	Significant surface erosion & complete fragmentation in 2 h	Significant surface erosion & complete fragmentation in 2.25 h	Significant surface erosion & complete fragmentation in 2.5 h	Significant surface erosion & complete fragmentation in 3 h

* Includes 1 % w/w of manufacturing additives; NA- Not applicable; ϕ-Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

Effect of proportion of polymer: To study the effect of polymer proportion, tablets were manufactured with varying drug to polymer ratio. The composition and characteristics of designed sodium alginate and carbopol based tablets are given in Table 5.3 and 5.4 respectively.

Table 5.3: Composition and characteristics of floating tablets of celecoxib prepared using varying proportion of sodium alginate

Formulation Code	CA-2,0.5-31-1X	CA-2,0.75-31-1X	CA-21-31-1X	CA-22-31-1X
Composition (mg/tab)				
Celecoxib	200	200	200	200
Sodium alginate	50	75	100	200
Sodium bicarbonate	150	150	150	150
Anhydrous citric acid	50	50	50	50
Weight (mg/tab)*	454.5	479.8	505	606
Hardness (kg/cm^2)	7±0.5	7±0.5	7±0.5	7±0.5
Floating Behaviour				
Buoyancy (Lag time to float)	Semifloat within 2 min; 5-8 min (core)	Semifloat within 3 min; 10-12 min (core)	Semifloat within 3 min; 12-17 min (core)	Semifloat within 1.5 min; 5.5-6 min
Portion floating and duration of floating	Core (2 min) ; few fragments (10-12 h)	Core (beyond 24 h)	Core (beyond 24 h)	Core (beyond 24 h)
Swelling (after 12 h)	ϕ	2 times	3 times	4 times
Disintegration/ Erosion	Initial surface erosion & fragmentation within 2 min	Initial surface erosion	Little surface erosion till the core floats	Insignificant

* Includes 1 % w/w of manufacturing additives; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

Table 5.4: Composition and characteristics of floating tablets of celecoxib prepared using varying proportion of carbopol

Formulation Code	CC-2,0.5-31-1X	CC-21-31-1X	CC-22-31-1X
Composition (mg/tab)			
Celecoxib	200	200	200
Carbopol	50	100	200
Sodium bicarbonate	150	150	150
Anhydrous citric acid	50	50	50
Weight (mg/tab)*	454.5	505	606
Hardness (kg/cm^2)	7±0.5	7±0.5	7±0.5
Floating Behaviour			
Buoyancy (Lag time to float)	Semifloat after 30 min	Semifloat after 45 min; sinks after 3-4 h	Semifloat after 1 hr; sinks after 2 h
Portion floating and duration of floating	NA	NA	NA
Swelling (after 12 h)	2 times	2 times	ϕ
Disintegration/ Erosion	Negligible; splits into two halves in 12 h	Little surface erosion	Significant surface erosion & complete fragmentation in 2 h

* Includes 1 % w/w of manufacturing additives; NA- Not applicable; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

In these formulations, drug to total floating agent ratio and sodium bicarbonate to anhydrous citric acid ratio were kept constant at 1:1 and 3:1 respectively. Tablets were manufactured at drug to sodium alginate ratios of 1:0.25 [CA-2,0.5-31-1X], 1:0.375 [CA-2,0.75-31-1X], 1:0.5 [CA-21-31-1X] and 1:1 [CA-22-31-1X]. Similarly, carbopol based tablets were prepared with varying drug to carbopol ratios of 1:0.25 [CC-2,0.5-31-1X], 1:0.5 [CC-21-31-1X] and 1:1 [CC-22-31-1X].

Effect of nature and proportion of gas generating agent: Sodium alginate based celecoxib tablets, without citric acid at fixed drug to polymer ratio (1:1) were prepared using varying proportion of either sodium bicarbonate or calcium carbonate as the floating agent. Tablets at drug to base ratios of 1:1 and 1:0.75 were manufactured as per the composition given in Table 5.5.

Table 5.5: Composition and characteristics of sodium alginate based floating tablets of celecoxib prepared using sodium bicarbonate or calcium carbonate as floating agent

Formulation Code	CA-22-sbc-2	CA-22-sbc-1.5	CA-22-cc-2	CA-22-cc-1.5
Composition (mg/tab)				
Celecoxib	200	200	200	200
Sodium alginate	200	200	200	200
Sodium bicarbonate	200	150	-	
Calcium carbonate	-	-	200	150
Weight (mg/tab)*	606	555.5	606	555.5
Hardness (kg/cm^2)	5±0.5	5±0.5	5±0.5	5±0.5
Floating Behaviour				
Buoyancy (Lag time to float)	10-11 min	19-20 min	20-22 min	28-30 min
Portion floating and duration of floating	Core (beyond 24 h)	Core (beyond 24 h)	Core (beyond 24 h)	Core (beyond 24 h)
Swelling (after 12 h)	2-3 times	2-3 times	2-3 times	2-3 times
Disintegration/ Erosion	Initial surface erosion till the core floats	Initial surface erosion till the core floats	Insignificant	Initial surface erosion till the core floats

* Includes 1 % w/w of manufacturing additives

Effect of sodium bicarbonate to citric acid ratio as floating agent mixture: Tablets at drug to sodium alginate ratio of 1:0.5 and drug to total floating agent ratio of 1:1 were prepared with varying sodium bicarbonate and anhydrous citric acid ratio. Tablets were manufactured at sodium bicarbonate to anhydrous citric acid ratios of 1:1 [CA-21-11-1X], 2:1 [CA-21-21-1X] and 3:1 [CA-21-31-1X] as per compositions given in Table 5.6.

Table 5.6: Composition and characteristics of sodium alginate based floating tablets of celecoxib prepared using varying sodium bicarbonate to anhydrous citric acid ratio

Formulation Code	**CA-21-11-1X**	**CA-21-21-1X**	**CA-21-31-1X**
Composition (mg/tab)			
Celecoxib	200	200	200
Sodium alginate	100	100	100
Sodium bicarbonate	100	133.3	150
Anhydrous citric acid	100	66.7	50
Weight (mg/tab)*	505	505	505
Hardness (kg/cm^2)	7±0.5	7±0.5	7±0.5
Floating Behaviour			
Buoyancy (Lag time to float)	Fragments float within 1 min; 6-8 min (core)	Fragments float within 2 min; 8-12 min (core)	Semifloat within 3 min; 12-17 min (core)
Portion floating and duration of floating	Core & some fragments (6-8 h)	Core & some fragments (8-11 h)	Core (beyond 24 h)
Swelling (after 12 h)	1.5 times	2 times	3 times
Disintegration/ Erosion	Significant surface erosion till the core floats	Surface erosion till the core floats	Little surface erosion till the core floats

* Includes 1 % w/w of manufacturing additives

Table 5.7: Composition and characteristics of sodium alginate based floating tablets of celecoxib prepared using varying amount of floating agent

Formulation Code	**CA-21-31-X/2**	**CA-21-31-1X**	**CA-21-31-1.33X**	**CA-21-31-1.5X**	**CA-21-31-2X**
Composition (mg/tab)					
Celecoxib	200	200	200	200	200
Sodium alginate	100	100	100	100	100
Sodium bicarbonate	75	150	200	225	300
Anhydrous citric acid	25	50	66.7	75	100
Weight (mg/tab)*	404	505	572.4	606	707
Hardness (kg/cm^2)	7±0.5	7±0.5	7±0.5	7±0.5	7±0.5
Floating Behaviour					
Buoyancy (Lag time to float)	Semifloat within few seconds; 2-3 min (core)	Semifloat within 3 min; 12-17 min (core)	Semifloat within 4 min; 21-24 min (core)	Semifloat within 3-4 min; 24-25 min (core)	Semifloat within 3-4 min; 25-26 min (core)
Portion floating and duration of floating	Core (beyond 24 h)	Core (beyond 24 h)	Core & few fragments (22-23 h)	Core & some fragments (12-13 h)	Core & many fragments (9-10 h)
Swelling (after 12 h)	2 times	3 times	2.5 times	ϕ	ϕ
Disintegration/ Erosion	Insignificant	Little surface erosion till the core floats	Initial surface erosion	Initial surface erosion till the core floats	Significant surface erosion till the core floats

* Includes 1 % w/w of manufacturing additives; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

Effect of total amount of floating agent: Sodium alginate based tablets at fixed drug to polymer ratio (1:0.5) and sodium bicarbonate to anhydrous citric acid ratio (3:1) with varying total amount of floating agent (sodium bicarbonate + anhydrous citric acid) were prepared. Formulations containing drug to total floating agent ratios of 1:0.5 [CA-21-31-X/2], 1:1 [CA-21-31-1X], 1:1.33 [CA-21-31-1.33X], 1:1.5 [CA-21-31-1.5X] and 1:2 [CA-21-31-2X] were manufactured. The compositions and characteristics of these tablets are given in Table 5.7.

Effect of absence of floating agent: Formulations were prepared without floating agent using sodium alginate, HPMC-15 cps, and carbopol at fixed drug to polymer ratio (1:0.5) to study the effect on release kinetics. The compositions and characteristics of tablets prepared without floating agent are given in Table 5.8.

Table 5.8: Composition and characteristics of tablets of celecoxib prepared using different polymers without floating agent

Formulation Code	**CA-21**	**CH1-21**	**CC-21**
Composition (mg/tab)			
Celecoxib	200	200	200
Sodium alginate	100	-	-
Guar gum	-	-	100
HPMC 15 cps	-	100	-
Weight (mg/tab)*	303	303	303
Hardness (kg/cm^2)	7±0.5	7±0.5	7±0.5
Floating Behaviour			
Buoyancy (Lag time to float)	Never floated	Never floated	Never floated
Portion floating and duration of floating	NA	NA	NA
Swelling (after 12 h)	3 times	2 times	2 times
Disintegration/ Erosion	Low; laminated	Negligible	Slow (17 h)

* Includes 1 % w/w of manufacturing additives; NA- Not applicable

Table 5.9: Composition and characteristics of sodium alginate based floating tablets of celecoxib having different hardness

Formulation Code	**CA-21-31-1X**	**CA-21-31-1X-L**	**CA-22-31-1X**	**CA-22-31-1X-L**
Composition (mg/tab)				
Celecoxib	200	200	200	200
Sodium alginate	100	100	200	200
Sodium bicarbonate	150	150	150	150
Anhydrous citric acid	50	50	50	50
Weight (mg/tab)*	505	505	606	606
Hardness (kg/cm^2)	7±0.5	4±0.5	7±0.5	4±0.5
Floating Behaviour				
Buoyancy (Lag time to float)	Semifloat within 3 min; 12-17 min (core)	Semifloat immediately; 2-4 min (core)	Semifloat within 1.5 min; 5.5-6 min (core)	Semifloat within 1 min; 4.5-5 min (core)
Portion floating and duration of floating	Core (beyond 24 h)	Smaller core & many fragments (10-11 h)	Core (beyond 24 h)	Core & some fragments (16-17 h)
Swelling (after 12 h)	3 times	ϕ	4 times	3-3.5 times
Disintegration/ Erosion	Little surface erosion till the core floats	Very fast erosion & fragmentation initially	Insignificant	Initial surface erosion till the core floats

* Includes 1 % w/w of manufacturing additives; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

Effect of hardness: Sodium alginate based tablets at fixed drug to total floating agent ratio (1:1), sodium bicarbonate to anhydrous citric acid ratio (3:1) and drug to sodium alginate ratio (1:0.5 or 1:1), were prepared in which hardness was decreased from the normally maintained value of 7±0.5 kg/cm^2 to a lower level of 4±0.5 kg/cm^2 as per compositions given in Table 5.9.

(b) Double polymer type tablets

Effect of polymer type: Double polymer (sodium alginate and another polymer in equal proportion) based tablets were prepared at fixed drug to total polymer ratio (1:0.5), drug to total floating agent ratio (1:1) and sodium bicarbonate to anhydrous citric acid ratio (3:1) with different type of second polymer in the matrix. Different polymers used included guar gum, HPMC-15cps, carbopol and polycarbophil. The compositions and characteristics of designed double polymer type tablets of celecoxib are presented in Table 5.10.

Table 5.10: Composition and characteristics of double polymer type sodium alginate floating tablets of celecoxib having different type of second polymer

Formulation Code	**CAG-21-11-31-1X**	**CAH1-21-11-31-1X**	**CAC-21-11-31-1X**	**CAP-21-11-31-1X**
Composition (mg/tab)				
Celecoxib	200	200	200	200
Sodium alginate	50	50	50	50
Guar gum	50	-	-	-
HPMC 15 cps	-	50	-	-
Carbopol	-	-	50	-
Polycarbophil	-	-	-	50
Sodium bicarbonate	150	150	150	150
Anhydrous citric acid	50	50	50	50
Weight (mg/tab)*	505	505	505	505
Hardness (kg/cm^2)	7±0.5	7±0.5	7±0.5	7±0.5
Floating Behaviour				
Buoyancy (Lag time to float)	5-6 min	6-9 min	6 min	30-45 min
Portion floating and duration of floating	Core (10 min); fragments (9-10 h)	Core (2.25 h); fragments (10-11 h)	Core (10 min)	Core (15 min); fragments (12-13 h)
Swelling (after 12 h)	ϕ	ϕ	ϕ	ϕ
Disintegration/ Erosion	Significant surface erosion & complete fragmentation in 10 min	Significant surface erosion & complete fragmentation in 2.5 h	Significant surface erosion & complete fragmentation in 10 min	Significant surface erosion & complete fragmentation in 15 min

* Includes 1 % w/w of manufacturing additives; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

Effect of viscosity of polymer: Sodium alginate and HPMC double polymer tablets were prepared with fixed drug to total polymer ratio (1:0.5), first polymer to second polymer ratio (1:1), drug to total floating agent ratio (1:1) and sodium bicarbonate to anhydrous citric acid

ratio (3:1) using different viscosity of HPMC namely 15 cps, 4000 cps, 15000 cps and 1 lac cps. Compositions and characteristics of these formulations are given in Table 5.11.

Table 5.11: Composition and characteristics of double polymer type sodium alginate floating tablets of celecoxib having different viscosity grade HPMC as second polymer

Formulation Code	**CAH1-21-11-31-1X**	**CAH2-21-11-311X**	**CAH3-21-11-31-1X**	**CAH4-21-11-31-1X**
Composition (mg/tab)				
Celecoxib	200	200	200	200
Sodium alginate	50	50	50	50
HPMC-15 cps	50	-	-	-
HPMC-4000 cps	-	50	-	-
HPMC-15000 cps	-	-	50	-
HPMC-1 lac cps	-	-	-	50
Sodium bicarbonate	150	150	150	150
Anhydrous citric acid	50	50	50	50
Weight (mg/tab)*	505	505	505	505
Hardness (kg/cm^2)	7±0.5	7±0.5	7±0.5	7±0.5
Floating Behaviour				
Buoyancy (Lag time to float)	6-9 min	10-11 min	25-30 min	35-40 min
Portion floating and duration of floating	Core (2.25 h); fragments (10-11 h)	Core (2 h 49-50 min); fragments (9 h)	Core (2.5 h); fragments (6 h)	Core (1 h)
Swelling (after 12 h)	ϕ	ϕ	ϕ	ϕ
Disintegration/ Erosion	Significant surface erosion & complete fragmentation in 2.5 h	Significant surface erosion & complete fragmentation in 3 h	Significant surface erosion & complete fragmentation in 3.5 h	Significant surface erosion & complete fragmentation in 4 h

* Includes 1 % w/w of manufacturing additives; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

Effect of hardness: Sodium alginate and guar gum based tablets were prepared in which other variables were kept constant as above, but hardness was varied. Formulations were prepared at hardness of 8±0.5, 6.0±0.5 and 4.0±0.5 kg/cm^2 respectively as per composition given in Table 5.12.

Table 5.12: Composition and characteristics of double polymer type sodium alginate and gaur gum based floating tablets of celecoxib having different hardness

Formulation Code	**CAG-21-11-31-X/2-H**	**CAG-21-11-31-X/2-M**	**CAG-21-11-31-X/2-L**
Composition (mg/tab)			
Celecoxib	200	200	200
Guar gum	50	50	50
Sodium alginate	50	50	50
Sodium bicarbonate	75	75	75
Anhydrous citric acid	25	25	25
Weight (mg/tab)*	404	404	404
Hardness (kg/cm^2)	8±0.5	6.0±0.5	4.0±0.5
Floating Behaviour			
Buoyancy (Lag time to float)	1 min	2-3 min	9-11 min
Portion floating and duration of floating	Core (beyond 24 h)	Core & fragments (10-11 h)	Core & fragments (10-11 h)
Swelling (after 12 h)	2-3 times	ϕ	ϕ
Disintegration/ Erosion	Insignificant	Significant surface erosion initially	Significant surface erosion initially

* Includes 1 % w/w of manufacturing additives; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

5.2.4.2. Preparation of acyclovir tablets

(a) Single polymer based tablets

Effect of polymer type: Acyclovir tablets with fixed drug to polymer ratio (1:0.5), drug to total floating agent ratio (1:1) and sodium bicarbonate to anhydrous citric acid ratio (3:1) were prepared using different types of polymer. Different polymers used included sodium alginate, guar gum, HPMC-15cps, carbopol and polycarbophil. The composition and characteristics of acyclovir tablets prepared using different types of polymer is listed in Table 5.13.

Table 5.13: Composition and characteristics of floating tablets of acyclovir prepared using different types of polymers

Formulation Code	AA-21-31-1X	AG-21-31-1X	AH1-21-31-1X	AC-21-31-1X	AP-21-31-1X
Composition (mg/tab)					
Acyclovir	200	200	200	200	200
Sodium alginate	100	-	-	-	-
Guar gum	-	100	-	-	-
HPMC 15 cps	-	-	100	-	-
Carbopol	-	-	-	100	-
Polycarbophil	-	-	-	-	100
Sodium bicarbonate	150	150	150	150	150
Anhydrous citric acid	50	50	50	50	50
Weight (mg/tab)*	505	505	505	505	505
Hardness (kg/cm^2)	7±0.5	7±0.5	7±0.5	7±0.5	7±0.5
Floating Behaviour					
Buoyancy (Lag time to float)	28-30 sec	3-3.5 min	10-12 min	45-50 min	Poor (settled at bottom)
Portion floating and duration of floating	Core & many fragments (1.5 h)	Core & many fragments (40-45 min)	Core & many fragments (45 min)	Core (2 h)	NA
Swelling (after 12 h)	ϕ	ϕ	ϕ	ϕ	ϕ
Disintegration/ Erosion	High erosion & completely disintegration in 1.5 h	High erosion & complete disintegration in 40-45 min	High erosion & complete disintegration in 55 min	High erosion & complete fragmentation in 2 h	High erosion & complete fragmentation in 2 h

* Includes 1 % w/w of manufacturing additives; NA- Not applicable; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

Effect of viscosity of polymer: Formulations with different viscosity grade HPMC (15, 4000, 15000 and 1 lac cps) were prepared at 1:0.5 drug to polymer, 1:1 drug to total floating agent and 3:1 sodium bicarbonate to anhydrous citric acid ratio [Table 5.14].

Effect of proportion of polymer: Sodium alginate based tablets were prepared in which drug to total floating agent ratio and sodium bicarbonate to anhydrous citric acid ratio were kept constant as 1:1 and 3:1 respectively, but proportion of sodium alginate was varied. Tablets were manufactured at drug to sodium alginate ratios of 1:0.25 [AA-2,0.5-31-1X], 1:0.5 [AA-21-31-1X] and 1:1 [AA-22-31-1X] as per the composition given in Table 5.15.

Similarly, effect of proportion of polycarbophil and carbopol respectively was studied by making tablets with other variables fixed as above, but varying drug to polymer ratios of 1:0.5 and 1:1 as per the compositions given in Table 5.16.

Table 5.14: Composition and characteristics of floating tablets of acyclovir prepared using HPMC of different viscosity

Formulation Code	**AH1-21-31-1X**	**AH2-21-31-1X**	**AH3-21-31-1X**	**AH4-21-31-1X**
Composition (mg/tab)				
Acyclovir	200	200	200	200
HPMC 15 cps	100	-	-	-
HPMC 4000 cps	-	100	-	-
HPMC 15000 cps	-	-	100	-
HPMC 1 lac cps	-	-	-	100
Sodium bicarbonate	150	150	150	150
Anhydrous citric acid	50	50	50	50
Weight (mg/tab)*	505	505	505	505
Hardness (kg/cm^2)	7±0.5	7±0.5	7±0.5	7±0.5
Floating Behaviour				
Buoyancy (Lag time to float)	10-12 min	45-50 sec	50-55 sec	55-60 sec
Portion floating and duration of floating	Core & many fragments (45 min)	Core & many fragments (2 h)	Core & many fragments (2.5 h)	Core & many fragments (2.5 h)
Swelling (after 12 h)	ϕ	ϕ	ϕ	ϕ
Disintegration/ Erosion	High erosion & complete disintegration in 55 min	High erosion & complete disintegration in 2 h	High erosion & complete disintegration in 2.5 h	High erosion & complete disintegration in 2.5 h

* Includes 1 % w/w of manufacturing additives; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

Table 5.15: Composition and characteristics of floating tablets of acyclovir prepared using varying proportion of sodium alginate

Formulation Code	**AA-2,0.5-31-1X**	**AA-21-31-1X**	**AA-22-31-1X**
Composition (mg/tab)			
Acyclovir	200	200	200
Sodium alginate	50	100	200
Polycarbophil			
Sodium bicarbonate	150	150	150
Anhydrous citric acid	50	50	50
Weight (mg/tab)*	454.5	505	606
Hardness (kg/cm^2)	7±0.5	7±0.5	7±0.5
Floating Behaviour			
Buoyancy (Lag time to float)	25-29 sec	28-30 sec	1 min
Portion floating and duration of floating	Core & many fragments (50 min)	Core & many fragments (2 h 50 min)	Core & some fragments (12-13 h)
Swelling (after 12 h)	ϕ	ϕ	ϕ
Disintegration/ Erosion	High erosion & complete disintegration in 50 min	High erosion & complete disintegration in 1.5 h	High surface erosion till the core floats

* Includes 1 % w/w of manufacturing additives; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

Table 5.16: Composition and characteristics of floating tablets of acyclovir prepared using varying proportion of polycarbophil or carbopol

Formulation Code	AP-21-31-1X	AP22-31-1X	AC-21-31-1X	AC-22-31-1X
Composition (mg/tab)				
Acyclovir	200	200	200	200
Guar gum	-	-	-	-
Carbopol	100	200	100	200
Sodium bicarbonate	150	150	150	150
Anhydrous citric acid	50	50	50	50
Weight (mg/tab)*	505	606	505	606
Hardness (kg/cm^2)	7±0.5	7±0.5	7±0.5	7±0.5
Floating Behaviour				
Buoyancy (Lag time to float)	Poor (settled)	Poor (settled)	45-50 min	60 min
Portion floating and duration of floating	NA	NA	Core (2 h)	Core (2.5 h)
Swelling (after 12 h)	ϕ	ϕ	ϕ	ϕ
Disintegration/ Erosion	High erosion & complete fragmentation in 2 h	High erosion & complete fragmentation in 3 h	High erosion & complete fragmentation in 2 h	High erosion & complete fragmentation in 2.5 h

* Includes 1 % w/w of manufacturing additives; NA- Not applicable; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

Effect of total amount of floating agent: Sodium alginate based tablets at fixed drug to polymer ratio and sodium bicarbonate to anhydrous citric acid ratio (3:1) were prepared having varying amount of total floating agent. Formulations containing drug to total floating agent ratios of 1:0.5 [AA-21-31-X/2], 1:1 [AA-21-31-1X] and 1:2 [AA-21-31-2X] were manufactured at drug to polymer ratio of 1:0.5. Similar formulations [AA-22-31-X/2, AA-22-31-1X and AA-22-31-2X] were prepared at drug to polymer ratio of 1:1. The compositions and characteristics of designed formulations are given in Table 5.17.

Table 5.17: Composition and characteristics of sodium alginate based floating tablets of acyclovir prepared using varying amount of floating agent

Formulation Code	AA-21-31-X/2	AA-21-31-1X	AA-21-31-2X	AA-22-31-X/2	AA-22-31-1X	AA-22-31-2X
Composition (mg/tab)						
Acyclovir	200	200	200	200	200	200
Sodium alginate	100	100	100	200	200	200
Sodium bicarbonate	75	150	300	75	150	300
Anhydrous citric acid	25	50	100	25	50	100
Weight (mg/tab)*	404	505	707	505	606	808
Hardness (kg/cm^2)	7±0.5	7±0.5	7±0.5	7±0.5	7±0.5	7±0.5
Floating Behaviour						
Buoyancy (Lag time to float)	2 sec	28-30 sec	3 min	30 sec	1 min	4-5 min
Portion floating and duration of floating	Core (beyond 24 h)	Core & many fragments (1.5 h)	Core & many fragments (45-50 min)	Core (beyond 24 h)	Core & some fragments (12-13 h)	Core & many fragments (1.5 h)
Swelling (after 12 h)	2 times	ϕ	ϕ	2 times	ϕ	ϕ
Disintegration/	Significant	High erosion	High erosion	Little surface	High surface	Complete

Erosion	surface erosion till the core floats	& completely disintegration in 1.5 h	& completely disintegration in 45-50 min	erosion till the core floats	erosion till the core floats	fragmentation in 1.5 h

* Includes 1 % w/w of manufacturing additives; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

In addition, carbopol and HMPC-4000 cps based tablets were also prepared at drug to polymer ratio of 1:0.5 with drug to total floating agent ratio varied as 1:0.5 and 1:1. Compositions and characteristics of these formulations are given in Table 5.18.

Table 5.18: Composition and characteristics of carbopol or HPMC-4000cps based floating tablets of acyclovir prepared using varying amount of floating agent

Formulation Code	**AC-21-31-X/2**	**AC-21-31-1X**	**AH2-21-31-X/2**	**AH2-21-31-1X**
Composition (mg/tab)				
Acyclovir	200	200	200	200
Carbopol	100	100	-	-
Polycarbophil	-	-	-	-
HPMC- 4000 cps	-	-	100	100
Sodium bicarbonate	75	150	75	150
Anhydrous citric acid	25	50	25	50
Weight (mg/tab)*	404	505	404	505
Hardness (kg/cm^2)	7±0.5	7±0.5	8±0.5	8±0.5
Floating Behaviour				
Buoyancy (Lag time to float)	5-15 min	45-50 min	23-27 sec	2-3 min
Portion floating and duration of floating	Core (2-2.5 hr)	Core (2 h)	Core & many fragments (10-11 h)	Core & many fragments (7-8 h)
Swelling (after 12 h)	ϕ	ϕ	ϕ	ϕ
Disintegration/ Erosion	High erosion & complete disintegration in 2-2.5 h	High erosion & complete fragmentation in 2 h	High surface erosion till the core floats	High surface erosion till the core floats

* Includes 1 % w/w of manufacturing additives; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

Effect of hardness: Sodium alginate based tablets at fixed drug to sodium alginate ratio (1:1), drug to total floating agent ratio (1:0.5 or 1:1) and sodium bicarbonate to anhydrous citric acid ratio (3:1) were prepared at two hardness levels of 8±0.5 kg/cm^2 and 6±0.5 kg/cm^2. The compositions and characteristics of these formulations are listed in Table 5.19.

Table 5.19: Composition and characteristics of sodium alginate based floating tablets of acyclovir prepared using different hardness

Formulation Code	**AA-22-31- X/2-H**	**AA-22-31- X/2-L**	**AA-22-31-1X-H**	**AA-22-31-1X-L**
Composition (mg/tab)				
Acyclovir	200	200	200	200
Sodium alginate	200	200	200	200
Sodium bicarbonate	75	75	150	150
Anhydrous citric acid	25	25	50	50
Weight (mg/tab)*	505	505	606	606
Hardness (kg/cm^2)	8±0.5	6±0.5	8±0.5	6±0.5
Floating Behaviour				
Buoyancy (Lag time to float)	45-60 sec	10-15 sec	2-3 min	30 sec
Portion floating and duration of floating	Core (beyond 24 h)	Core (24 h)	Core & some fragments (13-14 h)	Core & fragments (3-4 h)

Swelling (after 12 h)	2.5 times	1.5 times	ϕ	ϕ
Disintegration/ Erosion	Insignificant	Surface erosion till the core floats	Significant surface erosion till the core floats	Very high surface erosion till the core floats

* Includes 1 % w/w of manufacturing additives; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

Effect of absence of floating agent: Sodium alginate and HPMC-4000 cps based tablets, without floating agent, at fixed drug to polymer ratio (1:0.5) were also prepared and their compositions & characteristics are given in Table 5.20.

Table 5.20: Composition and characteristics of single polymer based tablets of acyclovir prepared using different polymers without floating agent

Formulation Code	**AA-21**	**AH2-21**
Composition (mg/tab)		
Acyclovir	200	200
Sodium alginate	100	-
HPMC 4000 cps	-	100
Weight (mg/tab)*	303	303
Hardness (kg/cm^2)	7±0.5	7±0.5
Floating Behaviour		
Buoyancy (Lag time to float)	Never floated	Never floated
Portion floating and duration of floating	NA	NA
Swelling (after 12 h)	Negligible	Negligible
Disintegration/ Erosion	Low	Insignificant

* Includes 1 % w/w of manufacturing additives; NA- Not applicable

(b) Double polymer type tablets

Effect of polymer type: Double polymer (sodium alginate as polymer one) based tablets were prepared in which drug to total polymer ratio (1:0.5), first polymer (sodium alginate) to second polymer ratio (1:1), drug to total floating agent ratio (1:1) and sodium bicarbonate to anhydrous citric acid ratio (3:1) was kept constant, but type of second polymer was varied. Different polymers used included guar gum, HPMC-15cps, carbopol and polycarbophil. Their compositions and characteristics are given in Table 5.21.

Effect of viscosity of polymer: Double polymer type acyclovir tablets using sodium alginate and HPMC were prepared at drug to polymer ratio of 1:0.5, drug to floating agent ratio of 1:1 and sodium bicarbonate to anhydrous citric acid ratio of 3:1 using HPMC of varying viscosity (15, 4000, 15000 and 1 lac cps). Compositions and characteristics of these formulations are given in Table 5.22.

Effect of different polymer combinations: Double polymer type acyclovir tablets were prepared using different polymer combinations as per compositions given in Table 5.23. Polymer combinations employed included polycarbophil & guar gum, carbopol & guar gum, carbopol & polycarbophil and polycarbophil & xanthan gum. In all these formulations

drug to polymer ratio, first polymer to second polymer ratio, drug to floating agent ratio and sodium bicarbonate to anhydrous citric acid ratio was kept constant at 1:0.5, 1:1, 1:1 and 3:1 respectively.

Table 5.21: Composition and characteristics of double polymer type sodium alginate floating tablets of acyclovir having different types of second polymer

Formulation Code	AAG-21-11-31-1X	AAH1-21-11-31-1X	AAC-21-11-31-1X	AAP-21-11-31-1X
Composition (mg/tab)				
Acyclovir	200	200	200	200
Sodium alginate	50	50	50	50
Guar gum	50	-	100	100
HPMC-15 cps	-	50	-	-
Carbopol	-	-	50	-
Polycarbophil	-	-	-	50
Sodium bicarbonate	150	150	150	150
Anhydrous citric acid	50	50	50	50
Weight (mg/tab)*	505	505	505	505
Hardness (kg/cm^2)	7±0.5	7±0.5	7±0.5	7±0.5
Floating Behaviour				
Buoyancy (Lag time to float)	1 min	3.5-4 min	5 min	15 min
Portion floating and duration of floating	Core & many fragments (54 min)	Core & many fragments (7-8 h)	Core & some fragments (12 h)	Core & some fragments (7-8 h)
Swelling (after 12 h)	ϕ	ϕ	ϕ	ϕ
Disintegration/ Erosion	Very high surface erosion & complete disintegration in 55 min	High surface erosion till the core floats	High surface erosion till the core floats	High surface erosion till the core floats

* Includes 1 % w/w of manufacturing additives; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

Table 5.22: Composition and characteristics of double polymer type sodium alginate floating tablets of acyclovir having different viscosity grade HPMC as second polymer

Formulation Code	AAH1-21-11-31-1X	AAH2-21-11-31-1X	AAH3-21-11-31-1X	AAH4-21-11-31-1X
Composition (mg/tab)				
Acyclovir	200	200	200	200
Sodium alginate	50	50	50	50
HPMC-15 cps	50	-	-	-
HPMC-4000 cps	-	50	-	-
HPMC-15000 cps	-	-	50	-
HPMC-1 lac cps	-	-	-	50
Sodium bicarbonate	150	150	150	150
Anhydrous citric acid	50	50	50	50
Weight (mg/tab)*	505	505	505	505
Hardness (kg/cm^2)	7±0.5	7±0.5	7±0.5	7±0.5
Floating Behaviour				
Buoyancy (Lag time to float)	3.5-4 min	2 min	40 sec	55 sec
Portion floating and duration of floating	Core & some fragments (7-8 h)	Core & some fragments (7-8 h)	Core & many fragments (54 min)	Core & many fragments (49 min)
Swelling (after 12 h)	ϕ	ϕ	ϕ	ϕ
Disintegration/ Erosion	Very high surface erosion till the core floats	Very high surface erosion till the core floats	High erosion & complete disintegration in 55 min	High erosion & complete disintegration in 50 min

* Includes 1 % w/w of manufacturing additives; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

Table 5.23: Composition and characteristics of double polymer type floating tablets of acyclovir having different polymer combinations

Formulation Code	APG-21-11-31-1X	ACG-21-11-31-1X	ACP-21-11-31-1X	APZ-21-11-31-1X
Composition (mg/tab)				
Acyclovir	200	200	200	200
Guar gum	50	50	-	-
Xanthan gum	-	-	-	50
Carbopol	-	50	50	-
Polycarbophil	50	-	50	50
Sodium bicarbonate	150	150	150	150
Anhydrous citric acid	50	50	50	50
Weight (mg/tab)*	505	505	505	505
Hardness (kg/cm^2)	7±0.5	7±0.5	7±0.5	7±0.5
Floating Behaviour				
Buoyancy (Lag time to float)	7 min	5 min	2 min	9-11 min
Portion floating and duration of floating	Core & some fragments (10-11 h)	Core & few fragments (11-11.5 h)	Core & many fragments (1.5 h)	Core & few fragments (13-14 h)
Swelling (after 12 h)	ϕ	ϕ	ϕ	ϕ
Disintegration/ Erosion	High surface erosion till the core floats	Significant surface erosion till the core floats	High erosion & complete disintegration in 1.5 h	Significant surface erosion till the core floats

* Includes 1 % w/w of manufacturing additives; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

Effect of proportion of polymer: Double polymer tablets of acyclovir with sodium alginate and guar gum were prepared to study the effect of proportion of total polymer in the matrix. Tablets were manufactured at drug to total polymer ratios of 1:0.5 and 1:1 as per compositions given in Table 5.24. Similarly, formulations were prepared using polycarbophil and guar gum at drug to total polymer ratios of 1:0.5 and 1:1. The compositions and characteristics of these tablets are given in Table 5.24.

Table 5.24: Composition and characteristics of double polymer type floating tablets of acyclovir prepared using varying total polymer proportion

Formulation Code	AAG-21-11-31-1X	AAG-22-11-31-1X	APG-21-11-31-1X	APG-22-11-31-1X
Composition (mg/tab)				
Acyclovir	200	200	200	200
Sodium alginate	50	100	-	-
Polycarbophil	-	-	50	100
Gaur gum	50	100	50	100
Polycarbophil	-	-	50	50
Sodium bicarbonate	150	150	150	150
Anhydrous citric acid	50	50	50	50
Weight (mg/tab)*	505	606	505	606
Hardness (kg/cm^2)	7±0.5	7±0.5	7±0.5	7±0.5
Floating Behaviour				
Buoyancy (Lag time to float)	1 min	2-2.5 min	7 min	1 min

Portion floating and duration of floating	Core & many fragments (54 min)	Core & many fragments (2 h)	Core & some fragments (10-11 h)	Core (13-14 h)
Swelling (after 12 h)	ϕ	ϕ	ϕ	Negligible
Disintegration/ Erosion	Very high surface erosion & complete disintegration in 55 min	High surface erosion	High surface erosion till the core floats	Little surface erosion till the core floats

* Includes 1 % w/w of manufacturing additives; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

Effect of total amount of floating agent: Sodium alginate and HPMC-15 cps or sodium alginate and HPMC-4000 cps double polymer type tablets at fixed drug to total polymer ratio (1:0.5) and sodium bicarbonate to anhydrous citric acid ratio (3:1) were prepared using different amount of total floating agent. Formulations were manufactured at drug to total floating agent ratios of 1:0.5 and 1:1 for both categories of formulations. The compositions and characteristics of formulations prepared in this series are presented in Table 5.25.

Table 5.25: Composition and characteristics of double polymer type floating tablets of acyclovir prepared using varying amount of floating agent

Formulation Code	**AAH1-21-11-31-X/2**	**AAH1-21-11-31-1X**	**AAH2-21-11-31-X/2**	**AAH2-21-11-31-1X**
Composition (mg/tab)				
Acyclovir	200	200	200	200
Sodium alginate	50	50	50	50
HPMC-15 cps	50	50	-	-
HPMC-4000 cps	-	-	50	50
Sodium bicarbonate	75	150	75	150
Anhydrous citric acid	25	50	25	50
Weight (mg/tab)*	404	505	404	505
Hardness (kg/cm^2)	7±0.5	7±0.5	7±0.5	7±0.5
Floating Behaviour				
Buoyancy (Lag time to float)	60-70 sec	3.5-4 min	45-50 sec	2 min
Portion floating and duration of floating	Core & some fragments (11-11.5 h)	Core & some fragments (7-8 h)	Core & few fragments (15-16 h)	Core & some fragments (7-8 h)
Swelling (after 12 h)	ϕ	ϕ	ϕ	ϕ
Disintegration/ Erosion	Significant surface erosion till the core floats	Very high surface erosion till the core floats	Very high surface erosion till the core floats	Very high surface erosion till the core floats

* Includes 1 % w/w of manufacturing additives; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

Effect of hardness: Sodium alginate and HPMC-15 cps based and polycarbophil and guar gum based double polymer type tablets of acyclovir were prepared at two hardness levels. Formulations were prepared at hardness of 8±0.5 and 6.0±0.5 kg/cm^2 for both types of formulations as per compositions given in Table 5.26. In these formulations drug to polymer ratio, first polymer to second polymer ratio, drug to floating agent ratio and sodium bicarbonate to anhydrous citric acid ratio was kept constant at 1:0.5, 1:1, 1:1 and 3:1 respectively.

Effect of absence of floating agent: Various double polymer tablets including sodium alginate and HPMC-15 cps based, carbopol and guar gum based and polycarbophil and guar gum based, without floating agent, at fixed drug to total polymer ratio (1:0.5) were also prepared and their compositions & characteristics are given in Table 5.27.

Table 5.26: Composition and characteristics of double polymer type floating tablets of acyclovir prepared using different hardness

Formulation Code	AAH1-21-11-31-1X-H	AAH1-21-11-31-1X-L	APG-21-11-31-1X-H	APG-21-11-31-1X-L
Composition (mg/tab)				
Acyclovir	200	200	200	200
Sodium alginate	50	50	-	-
HPMC-15 cps	50	50	-	-
Polycarbophil	-	-	50	50
Gaur gum	-	-	50	50
Sodium bicarbonate	150	150	150	150
Anhydrous citric acid	50	50	50	50
Weight (mg/tab)*	505	505	505	505
Hardness (kg/cm^2)	8±0.5	6±0.5	8±0.5	6±0.5
Floating Behaviour				
Buoyancy (Lag time to float)	4.5-5 min	2-3 min	3 min	2 min
Portion floating and duration of floating	Core & some fragments (10-11h)	Core & many fragments (1.5 h)	Core & few fragments (13-14 h)	Core & some fragments (7-8 h)
Swelling (after 12 h)	ϕ	ϕ	ϕ	ϕ
Disintegration/ Erosion	Significant surface erosion till the core floats	Very high erosion & complete disintegration in 1.5 h	Significant surface erosion till the core floats	High surface erosion till the core floats

* Includes 1 % w/w of manufacturing additives; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

Table 5.27: Composition and characteristics of double polymer type tablets of acyclovir prepared using different polymers without floating agent

Formulation Code	AAH1-21-11	ACG-21-11	APG-21-11
Composition (mg/tab)			
Acyclovir	200	200	200
Sodium alginate	50	-	-
Guar gum	-	50	50
HPMC 15 cps	50	-	-
HPMC 4000 cps	-	-	-
Carbopol	-	50	-
Polycarbophil	-	-	50
Weight (mg/tab)*	303	303	303
Hardness (kg/cm^2)	7±0.5	7±0.5	7±0.5
Floating Behaviour			
Buoyancy (Lag time to float)	Never floated	Never floated	Never floated
Portion floating and duration of floating	NA	NA	NA
Swelling (after 12 h)	ϕ	Negligible	2 times
Disintegration/ Erosion	Low; laminated in 1 hr	Insignificant	Insignificant

* Includes 1 % w/w of manufacturing additives; NA- Not applicable; ϕ- Tablets fragmented/ disintegrated completely within 12 h and so no observable swelling after 12 h

5.2.4.3. Placebo tablets

To compare, mucoadhesiveness of some selected formulations, placebo tablets containing 500 mg of single polymer [namely sodium alginate, guar gum, HPMC-15 cps, HPMC-4000 cps, HPMC-15000 cps, HPMC-1 lac cps, carbopol 934P NF and polycarbophil (Noveon AA 1)] were also prepared by dry blending followed with direct compression.

5.2.5. Physicochemical characterization of designed tablets

Developed formulations were subjected to the following physicochemical characterization studies.

Appearance: Tablets were observed for their colour, surface texture and dimensions. For each batch of formulations manufactured, six tablets were selected randomly. Diameter and thickness of each tablet was measured using a Vernier calliper and result calculated as average value with standard deviation for three batches.

Hardness: Six tablets were selected at random from each batch of all the formulations prepared and hardness was measured using Monsanto (standard type) tablet hardness tester. The results were expressed as average with standard deviation for three batches.

Weight variation: Weight of 20 tablets was taken individually and % weight variation was measured on average weight basis.

Friability: For determining friability, twenty tablets were selected randomly from each batch of manufactured formulations, dedusted and weighed. The weighed tablets were placed inside the plastic disc of Roche friabilator and the lid tightly secured. The disc was rotated for 4 minutes at the rate of 25 rotations per min. At the end of the procedure, tablets were taken out, dusted and weighed. The result was expressed as average % weight loss.

Drug content uniformity: Twenty tablets were selected randomly from each batch manufactured, weighed, crushed, and total contents were thoroughly mixed in a mortar-pestle. Aliquot quantity of the powder equivalent to 10 mg of the drug was taken in 100 ml volumetric flask in triplicate for drug content estimation. Further procedure employed for determining the drug content in designed formulations of celecoxib and acyclovir was as that mentioned in section 3.2.6 of Chapter 3.

Mucoadhesiveness: Mucoadhesive property of polymeric placebo tablets and some of the selected celecoxib & acyclovir tablets was determined on goat stomach and intestinal mucosa. For this, an in-house fabricated modified pan balance apparatus comprising of teflon blocks was used. The left hand side pan of the balance was replaced with a hanging

circular teflon block kept in contact with another stationary circular teflon block of identical dimension placed in a beaker containing simulated gastric pH media (0.1 N HCl with 1.0 % w/v SLS and 0.1 N HCl for celecoxib and acyclovir tablets respectively). The pan was balanced in such a way that under no weight condition, the left hand side teflon block just touched the stationary block. Freshly excised goat stomach/ ileum lining (preserved in physiological salt solution) was mounted on the lower teflon block and properly secured with nylon thread. Precaution was taken to prevent any damage to the mucin layer on the mucosal surface of the lining. Each tablet was fixed to the upper teflon block with the aid of adhesive araldite, and then placed on the lower block touching the mucosal surface of the tissue, and the two blocks were held tightly together for 30 mins (equilibration time) so as to provide sufficient time for the preparation to interact with the mucin layer of the tissue in each case. Then, on the right hand side, pan weights were increased carefully so as to avoid any mechanical jerk. Mucoadhesiveness (g/cm^2) of different types of tablets was determined as the weight (g) required per unit surface area (cm^2) to detach tablet and closely held tissue.

Floating: Two tablets from each batch of manufactured formulations were selected randomly and weighed individually. Each tablet was dropped in a beaker, containing 200 ml of 0.1 N HCl with 1.0 % w/v of SLS (in case of celecoxib tablets) or 0.1 N HCl (in case of acyclovir tablets), mounted on thermostatic water bath shaker kept at 37.0±0.5 °C for 24 h. The lag time to float i.e. the time taken for the tablets to float and the total duration for which the tablet floated were recorded. These parameters were also recorded during the 24 h in vitro release studies.

Swelling/ disintegration: The rate and extent of swelling and the disintegration & fragmentation behaviour was observed visually during the 24 h in vitro release studies. Surface erosion, if any, and rate and extent of fragmentation were observed for formulations of both the drugs.

5.2.6. In vitro release studies

In vitro release studies were carried out in USP dissolution apparatus (USP 2000) type 2 (paddle method) at a stirring speed of 75 rpm, containing 900 ml of the dissolution media (0.1 N HCl with 1.0 % SLS in case of celecoxib and 0.1 N HCl in case of acyclovir respectively) kept at 37.0±0.5 °C. A 10 ml sample was collected and replaced with fresh media at different time intervals and analyzed. The release studies were continued up to complete drug release or for a maximum period of 24 h.

5.2.6.1. Characterization of the release kinetics

Release data, of the designed matrix based tablets of both drugs, was fitted into zero order, first order or Higuchi's square root model release kinetics equation. Correlation coefficient ('r' value) for each fit was calculated to determine best fit and type of release kinetics for the respective formulation. Since these model fail to account for the impact of swelling (upon hydration) and gradual erosion of the matrix on the release kinetics, the release data was also fitted according to the exponential equation (1), which is often used to describe the drug release behaviour from polymeric matrix systems [Ritger and Peppas, 1987; Kim, 2000; Hakim and Jalil, 2001]:

$$M_t/M_\infty = K.t^n \qquad (1)$$

Here, M_t is the cumulative drug release at time t; M_∞ is the cumulative drug release at infinite time; M_t/M_∞ is the fractional drug release at time t; K is the release rate constant incorporating the structural and geometric characteristics of the device and properties of the polymeric system and the drug; and n is the diffusional exponent indicative of the release mechanism, which depends on and is used to characterize the transport mechanism. Relationship between values of n and types of release mechanism are presented in Appendix A-1 [Ritger and Peppas, 1987; Kim, 2000; Hakim and Jalil, 2001].

This concept has been applied to characterize the release from hydrogel based delivery [Peppas and Khare, 1993]; xanthan gum and HPMC based matrices [Talukder et al., 1996]; alginate compressed matrices [Giunchedi et al., 2000]; ethyl cellulose based matrices [Sajeev and Saha, 2001; Saha et al., 2001; Agrawal et al., 2003]; plastic, hydrophobic and hydrophilic polymer based matrix tablets [Reza et al., 2003]; pH-sensitive anionic hydrogels [Kim et al., 2003]; and from lithium carbonate based matrix tablets [Emami et al., 2004; Emami and Tavakoli, 2004].

By fitting release data in equation (1), the n values for different formulations were calculated to identify the type of release mechanism. Using the slope and intercept value of the regression plot various parameters like, diffusional exponent, release rate constant and time for release of fixed percentage of the drug from different types of formulations were calculated and compared.

5.2.7. Batch reproducibility

To study batch variation during manufacturing of the designed tablets, three batches of each formulation were manufactured and their physical and in vitro release characteristics were evaluated, as described earlier.

5.2.8. Stability studies

Real time stability studies of some selected formulations were carried at ambient conditions. The prepared tablets were wrapped in waxed paper, followed by aluminum foil and packaged in resealable polythene bags and stored in carton boxes in laboratory cupboards. At fixed interval of time (0, 3, 6, 9 and 12 months), tablets were analyzed for appearance, hardness, drug content (drug stability), in vitro release profile, floating and disintegration/ swelling characteristics to study the impact of storage on these variables.

5.3. Results and discussion

5.3.1. Physicochemical characterization of designed tablets

All the designed tablets were 12 mm in diameter, smooth in texture and cylindrical in shape with biconvex surface. Tablets employing natural polymers like, sodium alginate, guar gum and xanthan gum were off white in colour, while those made from synthetic polymers like, carbopol, polycarbophil and HPMC were white in colour. Thickness of the designed tablets ranged from 1.38±0.01 to 3.95±0.02 mm depending on the total weight and bulk density of the designed tablets, and hardness of the tablets. The average normal hardness of most of the designed tablets of both the drugs was 7±0.5 kg/ cm^2. The hardness was changed to 4±0.5 to 6±0.5 or 8±0.5 kg/ cm^2 in some formulations purposely to study the effect of hardness on floating behaviour and release kinetics. Weight variation and friability, for all the designed tablets, was not more than ±3.0 % w/w and less than 0.5 % w/w respectively, indicating dry blending and direct compression to be an acceptable method for manufacturing good quality matrix based tablets for either of the drugs. The drug content of all the developed formulations was found to vary between 95 % to 105 % of the label claim, further indicating the reliability and reproducibility of the manufacturing process. The results of important physicochemical parameters of designed tablets of celecoxib and acyclovir are presented in Tables 5.1 to 5.12 and Tables 5.13 to 5.27 respectively, along with their compositions and characteristics.

5.3.2. Mucoadhesive property

Results of mucoadhesive studies, conducted for placebo tablets and some formulations of celecoxib and acyclovir, are presented in Table 5.28. Each placebo tablet had a fixed

diameter of 12 mm and thickness ranging from 2.21±0.01 to 2.60±0.02 mm. Out of the placebo tablets of different polymers investigated, HPMC-15 cps showed maximum mucoadhesiveness with stomach mucosal layer (192.84±3.68 g/cm^2), followed by carbopol (187.52±3.06 g/cm^2), guar gum (176.02±3.24 g/cm^2), HPMC-4000 cps (173.38±3.14 g/cm^2), polycarbophil (170.72±2.90 g/cm^2), HPMC-15000 cps (153.02±2.56 g/cm^2), HPMC-1 lac cps (126.50±2.48 g/cm^2) and finally sodium alginate (115.88±2.62 g/cm^2). All these placebo tablets showed lower mucoadhesiveness with intestinal mucosal layer when compared to that on stomach mucosal layer with carbopol showing maximum mucoadhesiveness of 174.26±2.78 g/cm^2 and sodium alginate showing minimum mucoadhesiveness of 99.96±2.36 g/cm^2 on the intestinal mucosa [Table 5.28]. The probable reason for higher mucoadhesiveness with stomach mucosa may be because of thicker mucin layer compared to intestinal mucosa.

Table 5.28: Mucoadhesive property of placebo tablets and some selected tablets of celecoxib and acyclovir respectively

Formulations	Code	Mucoadhesiveness (g/cm^2) on stomach mucosal layer	Mucoadhesiveness (g/cm^2) on intestinal mucosal layer
Placebo Tablets	Sodium alginate	115.88±2.62	99.96±2.36
	Gaur gum	176.02±3.24	162.76±2.82
	HPMC-15 cps	192.84±3.68	171.60±3.58
	HPMC-4000 cps	173.38±3.14	164.52±2.86
	HPMC-15000 cps	153.02±2.56	142.76±2.62
	HPMC-1 lac cps	126.50±2.48	107.92±2.24
	Carbopol	187.52±3.06	174.26±2.78
	Polycarbophil	170.72±2.90	149.50±2.38
Celecoxib Tablets	CA-21-11-1X	12.38±0.66	15.04±0.78
	CA-21-21-1X	13.26±0.62	16.80±0.90
	CA-2,0.5-31-1X	12.38±0.68	19.46±0.96
	CA-21-31-1X	15.92±0.80	20.34±1.04
	CA-22-31-1X	20.58±1.02	26.76±1.26
	CA-24-31-1X	33.62±1.18	39.80±1.56
	CG-21-31-1X	50.42±1.58	55.72±1.66
	CH1-21-31-1X	ϕ	ϕ
	CH2-21-31-1X	ϕ	ϕ
	CH3-21-31-1X	ϕ	ϕ
	CH4-21-31-1X	ϕ	ϕ
	CC-2,0.5-31-1X	55.72±1.44	60.16±1.62
	CC-21-31-1X	61.04±1.76	69.00±1.80
	CC-22-31-1X	65.46±1.78	74.30±1.90
	CP-21-31-1X	55.72±1.62	60.14±1.74
	CAH1-21-11-31-1X	56.62±1.84	62.80±2.02
	CAH2-21-11-31-1X	48.66±1.50	53.08±1.60
	CAH3-21-11-31-1X	33.62±1.36	37.16±1.42
	CAH4-21-11-31-1X	ϕ	ϕ
Acyclovir Tablets	AA-2,0.5-31-1X	14.16±0.62	17.70±0.76
	AA-21-31-1X	15.92±0.66	19.46±0.82
	AA-22-31-1X	20.34±0.96	24.76±1.18
	AA-24-31-1X	26.54±1.24	31.84±1.32
	AH1-21-31-1X	ϕ	ϕ
	AH2-21-31-1X	ϕ	ϕ
	AH3-21-31-1X	ϕ	ϕ

AH4-21-31-1X	ϕ	ϕ
AC-22-31-1X	82.26±1.92	86.68±1.98
AAH1-21-11-31-1X	21.22±0.72	24.76±0.80
AAH2-21-11-31-1X	15.04±0.60	18.58±0.68
AAH3-21-11-31-1X	10.62±0.42	13.26±0.58
AAH4-21-11-31-1X	ϕ	ϕ

ϕ- No mucoadhesiveness observed due to rapid erosion/ fragmentation and detachment

Designed tablets of celecoxib were found to have much lower mucoadhesive property than pure placebo tablets. This could be because of lower amount of total polymer present and presence of gas generating agents (combination of sodium bicarbonate & citric acid), which made the tablets fragmentable and thus, detachable. HPMC based formulations showed no mucoadhesiveness at all because rapid erosion & fragmentation in these formulations resulted in a detachment of the main core of these tablets. However, the eroded/ fragmented surface was still found sticking to the mucosal surface. Sodium alginate based preparations showed overall poorer mucoadhesive property. However, an increase in the stoichiometric ratio of base to acid in the formulation resulted in slight increase in the mucoadhesiveness. CA-21-11-1X with base to acid ratio of 1:1 showed lowest mucoadhesive property (12.38±0.66 and 15.04±0.78 g/cm^2 respectively in stomach and intestine) due to maximum & fastest erosion/ fragmentation, followed by CA-21-21-1X with base to acid ratio of 2:1 (13.26±0.62 and 16.80±0.90 g/cm^2 respectively in stomach and intestine) and maximum in case of CA-21-31-1X with base to acid ratio of 3:1 (15.92±0.80 and 20.34±1.04 g/cm^2 respectively in stomach and intestine) due to relatively lesser and slower erosion/ fragmentation.

Increasing the relative proportion of polymer in the tablet resulted in increase in mucoadhesiveness. The formulation CA-2,0.5-31-1X having lowest relative amount of polymer showed minimum mucoadhesiveness of 12.38±0.68 and 19.46±0.96 g/cm^2 respectively in stomach and intestine, while CA-24-31-1X having highest relative amount of polymer showed maximum mucoadhesiveness of 33.62±1.18 and 39.80±1.56 g/cm^2 respectively in stomach and intestine.

Carbopol based preparations showed highest mucoadhesiveness amongst the single polymer based formulations tested and increasing the relative proportion of polymer in this series resulted in higher mucoadhesiveness. The mucoadhesiveness in stomach and intestine of CC-2,0.5-31-1X (with drug to polymer ratio of 1:0.25) was found to be 55.72±1.44 and 60.16±1.62 g/cm^2 respectively, while for CC-22-31-1X (with drug to polymer ratio of 1:1) it was significantly higher with a value of 65.46±1.78 and 74.30±1.90 g/cm^2 respectively. In stomach and intestinal lining, guar gum based formulation CG-21-31-1X showed

mucoadhesiveness of 50.42±1.58 and 55.72±1.66 g/cm^2 respectively, while polycarbophil based formulation CP-21-31-1X showed mucoadhesiveness of 55.72±1.62 g/cm^2 and 60.14±1.74 g/cm^2 respectively.

HPMC, when used in combination with sodium alginate, gave good mucoadhesive property. In the presence of sodium alginate, the erosion of HPMC was drastically decreased due to the ability of sodium alginate to form acid gel, which enhanced intactness of the preparations. Lower viscosity grade HPMC showed better mucoadhesiveness than higher viscosity grade in combination with sodium alginate. CAH1-21-11-31-X and CAH3-21-11-31-X showed mucoadhesiveness of 56.62±1.84 & 62.80±2.02 g/cm^2 and 33.62±1.36 & 37.16±1.42 g/cm^2 respectively in the stomach and intestinal mucosa. CAH4-21-11-31-X, made with 1 lac cps viscosity HPMC showed no mucoadhesiveness at all [Table 5.28].

Similar results were obtained with tablets of acyclovir. Acyclovir formulations showed slightly lesser mucoadhesive property than similar formula of celecoxib probably due to faster and higher degree of fragmentation because of higher solubility of acyclovir. Only in case of carbopol formulation prepared at drug to polymer ratio of 1:1, an opposite impact was observed. This could be because these formulations were not fragmentable in nature, whereas other polymer based formulations of acyclovir were fragmentable. AC-22-31-1X showed higher mucoadhesiveness of 82.26±1.92 and 86.68±1.98 g/cm^2 respectively in the stomach and intestinal mucosal layer, while CC-22-31-1X showed mucoadhesiveness of 65.46±1.78 and 74.30±1.90 g/cm^2 respectively [Table 5.28].

5.3.3. Floating characteristics, in vitro release behaviour and release characterization

In general, acyclovir tablets [e.g. AA-21-31-1X; Table 5.13] though took lower lag time to float, but were more fragmentable and showed faster release as compared to celecoxib tablets [e.g. CA-21-31-1X; Table 5.1]. Since acyclovir (amphoteric drug) has relatively good solubility in acidic media compared to celecoxib (weakly acidic drug) the matrix containing acyclovir permitted faster penetration/ entry of the dissolution media into the matrix system due to wicking action of the drug. This in return caused quicker initiation of the reaction between the organic acid and base (when used in combination) or between base and acidic media. This resulted in faster generation of CO_2 and made the tablets more buoyant. Tablets containing combination of base and acid [e.g. CA-22-31-1X; Table 5.3] took lesser time to float than those containing only base [e.g. CA-22-sbc-2; Table 5.5] because intimate contact between an acid and a base ensured faster and more quantum of CO_2 generation, whereas dissolution media (0.1 N HCl) took some time to penetrate and

slowly react with the base when no acid was present in the formula. Lower amount of floating agent [e.g. AA-22-31-X/2; Table 5.17] resulted in more intact tablets with slower and more prolonged release, in which the core continued to float for longer period of time (24 h in many cases), while higher amount of floating agent [e.g. AA-22-31-2X; Table 5.17] resulted in higher erosion & fragmentation of the matrix and faster disintegration. Also, lowering the hardness led to quicker floating but higher initial surface erosion/ fragmentation and lesser controlled release behaviour [e.g. AA-22-31-1X-H and AA-22-31-1X-L; Table 5.19]. Therefore, hardness in most of the formulations was maintained at 7±0.5 kg/cm^2.

In these studies, in which mostly hydrophilic, gel-forming polymer(s) were employed, there was always a lag time for a perfect gel barrier to form. Till that perfect gel barrier was formed, higher rate of erosion was observed resulting in high initial drug release. This character was more prominent when higher amount of floating agent was used. The in vitro release profile obtained for the manufactured formulations could be directly linked to their erosion, fragmentation and disintegration behaviour.

In case of both celecoxib and acyclovir, sodium alginate alone gave very buoyant tablets with very low lag time to float and longer floating durations (beyond 24 h). At gastric acid pH (< 3), hydration of insoluble alginic acid lead to the formation of a high viscosity 'acid gel', which was highly buoyant in the presence of entrapped gas and capable of creating a diffusion barrier that could efficiently control drug release. Therefore sodium alginate based systems resulted in initial faster release, followed by a very slow release corresponding to the lag time for sodium alginate to form a perfect gel in acidic media. Lower amount of polymer and very hard formulations of carbopol gave very controlled and prolonged release. Probably at higher polymer proportion carbopol by virtue of its swelling property created burst effect. Guar gum, polycarbophil and HPMC based matrix formulations were found to have poor controlled release characteristics due to the inability of these polymers to form efficient gel barrier in the presence of effervescent ingredients in acidic media.

In case of double polymer type systems, including sodium alginate along with these polymers (otherwise showing poor control on release) helped in retarding the release. In case of acyclovir, HPMC alone or in combination with sodium alginate gave tablets that took less time to float, but they disintegrated quickly. Some formulations of polycarbophil and guar gum (double polymer) also floated very well in an intact manner. Double polymer system with lower amount of floating agent also showed more controlled drug release.

Formulations without floating agents, prepared maintaining other variables to be constant, released the drug in more prolonged and controlled manner.

Floating, swelling and disintegration property of each category of formulations are further discussed in detail in the following sections and presented in Tables 5.1 to 5.12 for celecoxib tablets and Tables 5.13 to 5.27 for acyclovir tablets. Plots of cumulative percentage release versus time for various matrix based formulations are shown in Figures 5.1 to 5.12 for celecoxib and Figures 5.13 to 5.26 for acyclovir. Results of cumulative percentage release and release characterization of celecoxib tablets are presented in Tables 5.29 to 5.42, with the release characterization data for all the formulations enlisted in Tables 5.30 and 5.37. Results of cumulative percentage release and release characterization of acyclovir tablets are presented in Tables 5.43 to 5.58, with the corresponding release characterization data for all the designed formulations enlisted in Tables 5.44 and 5.52.

5.3.3.1. Evaluation of celecoxib tablets

(a) Single polymer based tablets

Effect of polymer type: Sodium alginate, alone gave highly buoyant tablets with very low lag time to float & longer duration of floating (beyond 24 h), and resulted in very intact, non-disintegrating type of tablets. Other polymers like carbopol, HPMC-15 cps, polycarbophil and guar gum, when used alone showed inferior floating behaviour (in terms of buoyancy & duration of floating) and higher tendency to fragment/ disintegrate [Table 5.1]. CA-21-31-1X (sodium alginate based tablet) floated in 12-17 min and continued floating beyond 24 h with approximately 3 times swelling in 12 h. CG-21-31-1X (guar gum based tablet) floated in 6-7 min, but continued to float for just 6-6.5 min and completely fragmented within 15 min, while CH1-21-31-1X (HPMC-15 cps based tablet) floated in 30 min, continued to float for 2 h and completely fragmented within 2 h. On the other hand, carbopol based formulation [CC-21-31-1X] became semi-float only after 45 min, remained in that state for 3-4 h and showed 2 times swelling at 12 h, while CP-21-31-1X (polycarbophil based tablet) was settled at the bottom throughout and fragmented completely in 1 h [Table 5.1].

In case of single polymer type celecoxib tablets, sodium alginate based system [CA-21-31-1X] showed initial fast release (due to significant surface erosion in the beginning) followed by a very slow and sustained release (once the polymer formed a perfect gel barrier in acidic media) with a cumulative release of only 53.99±1.18 % in 24 h. Carbopol based system [CC-21-31-1X] also prolonged the release to 24 h with a cumulative

release of 96.80±1.09 %. On the other hand, guar gum, HPMC-15 cps and polycarbophil based formulations showed very high cumulative release (84.23±0.90 %, 67.19±0.85 % and 47.79±0.92 % respectively) of the drug in the first one hour itself and the entire dose was released within 6-9 h [Table 5.29; Figure 5.1].

Formulations, CA-21-31-1X, CG-21-31-1X and CH1-21-31-1X followed quasi-Fickian (0.1084 = n = 0.2972) type of release transport. In case of CA-21-31-1X the K and $t_{60\%}$ values were obtained as 21.74 $h^{-0.2972}$ and 30.44 h respectively. CC-21-31-1X followed case II/ supercase II (n=1.0234) transport with K and $t_{60\%}$ values of 7.38 $h^{-1.0234}$ and 7.75 h respectively. CP-21-31-1X showed first order release and followed anamolous (n=0.5574) transport with K and $t_{60\%}$ values of 47.79 $h^{-0.5574}$ and 1.50 h respectively. CG-21-31-1X and CH1-21-31-1X showed first order release with very high K values and very low $t_{60\%}$ values respectively [Table 5.30].

Table 5.29: Cumulative percentage drug release from floating tablets of celecoxib to study the effect of polymer type

Time (h)	Cumulative percentage released [a]				
	CA-21-31-1X	**CG-21-31-1X**	**CH1-21-31-1X**	**CC-21-31-1X**	**CP-21-31-1X**
1	15.01±1.29	84.23±0.90	67.19±0.85	8.94±0.45	47.79±0.92
2	25.29±1.35	90.80±1.05	78.91±1.16	14.53±0.93	70.33±1.25
3	30.87±1.52	95.54±1.88	84.49±1.58	23.09±1.34	81.75±1.17
6	38.65±1.78	101.07±1.14	92.54±1.05	49.52±0.92	91.61±1.10
9	42.51±1.22	-	99.03±1.67	66.07±1.04	100.33±1.74
12	46.23±1.08	-	-	76.48±1.93	-
15	49.02±1.56	-	-	85.08±1.74	-
18	50.36±1.33	-	-	90.07±1.69	-
24	53.99±1.18	-	-	96.80±1.09	-

[a]: Mean and S.D. of three batches with duplicate determination per batch

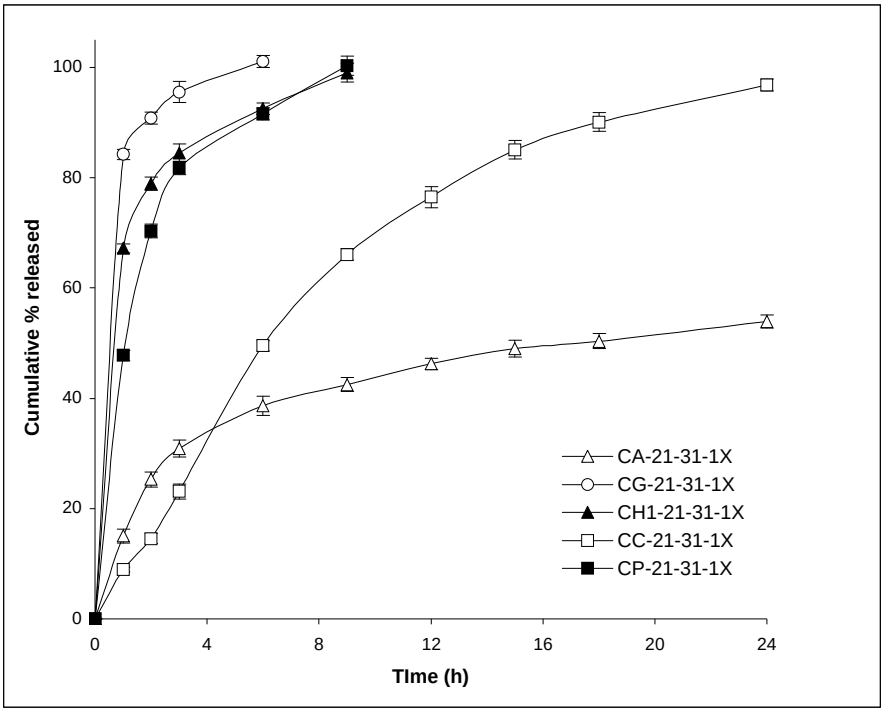

Figure 5.1: In vitro release from floating tablets of celecoxib to study the effect of polymer type [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Table 5.30: In vitro release rate parameters of floating tablets of celecoxib

Formulation code	Correlation coefficient				Release rate constant [a] [K (h^{-n})]	Release exponent[b] [n]	Mechanism of release	Time for 60 % drug release [c] $t_{60\%}$ (h)
	Zero order	First order	Higuchi's model	Ritger-Peppas model				
(a) Effect of polymer type								
CA-21-31-1X	0.8657	0.9134	0.9676	0.9921	21.74	0.2972	Quasi-Fickian	30.44
CG-21-31-1X	0.6900	0.9589	0.8875	0.9999	84.23	0.1084	Quasi-Fickian	-
CH1-21-31-1X	0.7292	0.9754	0.9030	1.0000	67.19	0.2320	Quasi-Fickian	0.61
CC-21-31-1X	0.9498	0.9960	0.9835	0.9967	7.38	1.0234	Case II/ Supercase II	7.75
CP-21-31-1X	0.8245	0.9746	0.9579	1.0000	47.79	0.5574	Anamolous	1.50
(b) Effect of different viscosity grade HPMC								
CH1-21-31-1X	0.7292	0.9754	0.9030	0.9999	67.19	0.2320	Quasi-Fickian	0.61
CH2-21-31-1X	0.7548	0.9428	0.9184	0.9999	65.49	0.2086	Quasi-Fickian	0.66
CH3-21-31-1X	0.7653	0.9707	0.9251	0.9999	62.94	0.2165	Quasi-Fickian	1.11
CH4-21-31-1X	0.7686	0.9778	0.9192	0.9999	58.24	0.2838	Quasi-Fickian	0.80
(c) Effect of proportion of sodium alginate								
CA-2,0.5-31-1X	0.9226	0.9426	0.9921	0.9951	31.30	0.4876	Fickian	3.80
CA-2,0.75-31-1X	0.8912	0.9904	0.9784	0.9945	23.38	0.5818	Anamolous	5.05
CA-21-31-1X	0.8657	0.9134	0.9676	0.9921	21.74	0.2972	Quasi-Fickian	30.44
CA-22-31-1X	0.8343	0.8697	0.9474	0.9975	16.98	0.2239	Quasi-Fickian	280.54
(d) Effect of proportion of carbopol								
CC-2,0.5-31-1X	0.9881	0.9323	0.9242	0.9692	3.42	0.9455	Case II/ zero order	20.71
CC-21-31-1X	0.9498	0.9960	0.9835	0.9967	7.38	1.0234	Case II/ Supercase II	7.75
CC-22-31-1X	0.8928	0.9901	0.9719	0.9999	32.57	0.7882	Anamolous	2.17
(e) Effect of sodium bicarbonate or calcium carbonate alone as floating agent								
CA-22-sbc-2	0.8088	0.9075	0.9369	0.9986	35.45	0.2940	Quasi-Fickian	5.99
CA-22-sbc-1.5	0.8594	0.8939	0.9620	0.9981	15.42	0.2730	Quasi-Fickian	145.10
CA-22-cc-2	0.8181	0.8882	0.9429	0.9964	29.83	0.2653	Quasi-Fickian	13.93
CA-22-cc-1.5	0.8527	0.8814	0.9588	0.9977	13.16	0.2758	Quasi-Fickian	244.86
(f) Effect varying sodium bicarbonate to citric acid ratio								
CA-21-11-1X	0.8521	0.9742	0.9621	0.9978	34.28	0.3845	Quasi-Fickian	4.29
CA-21-21-1X	0.8822	0.9394	0.9768	0.9971	23.13	0.3360	Quasi-Fickian	17.07
CA-21-31-1X	0.8657	0.9134	0.9676	0.9921	21.74	0.2972	Quasi-Fickian	30.44

[a]: Release rate constant (based on Ritger-Peppas model; for data fitted up to 60 % of drug released); [b]: Release exponent, indicative of the mechanism of release (based on Ritger-Peppas model); [c]: Time for 60 % ($t_{60\%}$) of the drug release (based on Ritger-Peppas model)

Effect of viscosity of polymer: HPMC based tablets took relatively longer time to become afloat (30-40 min). The lag to float was found to increase as the viscosity grade of HPMC was increased with no floating observed in case of tablets made of HPMC-1 lac cps. These tablets showed high surface erosion, complete fragmentation in 2-3 h and no observable swelling at 12 h [Table 5.2]. In case of HPMC based celecoxib tablets, all formulations showed very poor release behaviour, releasing 58.24±1.31 to 67.19± 0.85 % of the drug in first one hour itself and extending the release up to 9-12 h. Increasing the viscosity of HPMC did not significantly retard the release [Table 5.31; Figure 5.2].

Table 5.31: Cumulative percentage drug release from floating tablets of celecoxib to study the effect of different viscosity grade HPMC

Time (h)	Cumulative percentage released [a]			
	CH1-21-31-1X	**CH2-21-31-1X**	**CH3-21-31-1X**	**CH4-21-31-1X**
1	67.19± 0.85	65.49±1.19	62.94±0.66	58.24±1.31
2	78.91±1.16	75.68±1.05	73.13±1.57	70.90±1.08
3	84.49±1.58	83.26±1.43	82.78±1.15	78.60±1.49
6	92.54±1.05	91.91±1.13	90.48±1.64	88.12±1.38
9	99.03±1.67	100.24±1.24	99.17±1.06	94.60±1.72
12	-	-	-	99.14±1.25

[a]: Mean and S.D. of three batches with duplicate determination per batch

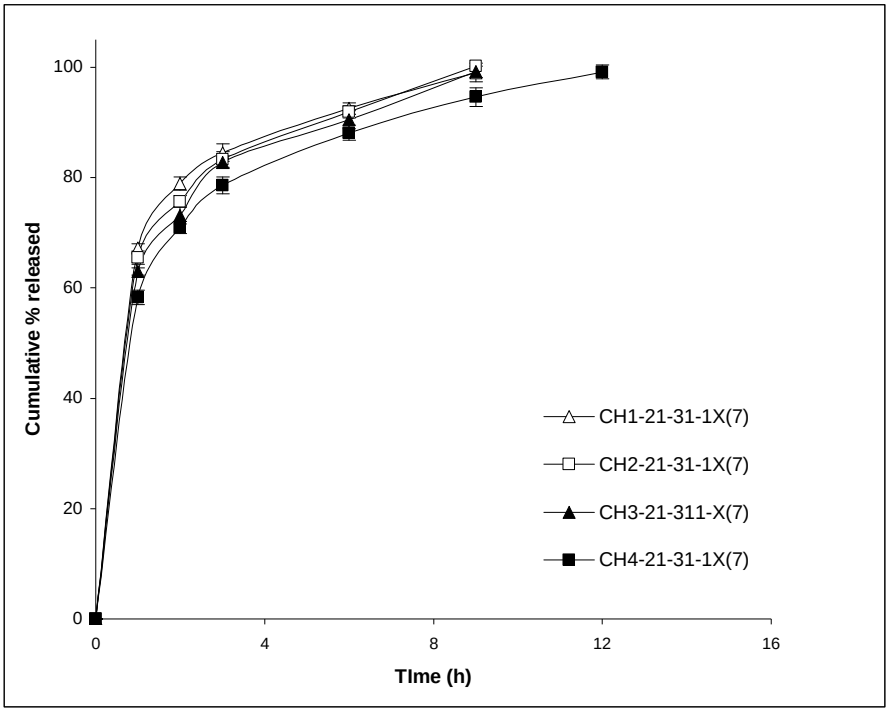

Figure 5.2: In vitro release from floating tablets of celecoxib to study the effect of different viscosity grade HPMC [Data presented is mean ± SD of release studies on products of three batches in duplicate]

This was probably due to the generation of CO_2 by the effervescent components present in the tablet, which lead to high surface erosion and disintegration of the matrix. All HPMC based tablets were found to follow first order release with quasi-Fickian (0.2086 = n = 0.2838) release transport and very high K values (58.24 $h^{-0.2838}$ to 67.19 $h^{-0.2320}$) and very low $t_{60\%}$ values (0.61-1.11 h) [Table 5.30].

Effect of proportion of polymer: In case of sodium alginate based tablets of celecoxib, on varying the drug to polymer (sodium alginate) ratio (1:0.25, 1:0.375, 1:0.5 and 1:1), lag time to float increased with higher relative proportion of the polymer probably due to increase in tablet weight. CA-2,0.5-31-1X, CA-2,0.75-31-1X and CA-21-31-1X floated in 5-8 min, 10-12 min and 12-17 min respectively. In case of CA-22-31-1X, the tablets floated within 6 min indicating that at a drug to polymer ratio of 1:1, a perfect gel barrier was formed due to hydration of polymer, which was able to entrap the gas generated within the matrix more efficiently resulting in intact core that lifted quickly and remained afloat for more than 24 h. At lowest proportion of sodium alginate (1:0.25), the tablets formed incomplete gel barrier and highly disintegrating type of tablets with extremely low duration of floating of the core (as low as 2 min) and the fragments (as low as 10-12 h). For drug to polymer ratio of 1:0.375 and above, the core floated for more than 24 h. Core of the tablets with highest polymer proportion (1:1) was most swellable (4 times) and lowest polymer proportion was non-swellable due to complete fragmentation [Table 5.3].

Increasing the polymer proportion in the matrix resulted in retardation of the release. In case of sodium alginate based tablets containing drug to polymer ratio of 1:0.25 [CA-2,0.5-31-1X], complete release was observed in 15 h. On the other hand, at higher polymer proportions the release was extended beyond 24 h. CA-2,0.75-31-1X, CA-21-31-1X and CA-22-31-1X released 94.08±1.27 %, 53.99±1.18 % and 35.12±1.92 % drug respectively in 24 h [Table 5.32; Figure 5.3].

CA-2,0.5-31-1X and CA-2,0.75-31-1X, containing lower amount of sodium alginate, showed Fickian (n=0.4876) and anamolous (n=0.5818) transports respectively, with K and $t_{60\%}$ values of 31.30 $h^{-0.4876}$ and 3.80 h; and 23.38 $h^{-0.5818}$ and 5.05 h respectively. On the other hand, higher polymer proportions showed quasi-Fickian (n=0.2239) transport. CA-22-31-1X, containing highest amount of sodium alginate, showed slowest release with K and $t_{60\%}$ values of 16.98 $h^{-0.2239}$ and 280.54 h respectively [Table 5.30].

Table 5.32: Cumulative percentage drug release from floating tablets of celecoxib to study the effect of proportion of sodium alginate

Time (h)	Cumulative percentage released [a]			
	CA-2,0.5-31-1X	CA-2,0.75-31-1X	CA-21-31-1X	CA-22-31-1X
1	28.16±1.04	22.16±0.96	15.01±1.29	14.20±0.58
2	43.05±1.19	34.15±1.05	25.29±1.35	19.80±0.94
3	55.15±1.45	46.06±1.23	30.87±1.52	22.16±1.03
6	74.15±1.68	65.37±1.48	38.65±1.78	25.13±1.25
9	85.24±1.50	74.24±1.62	42.51±1.22	27.25±1.43
12	93.66±1.57	82.66±1.00	46.23±1.08	29.48±1.33
15	99.64±1.77	87.64±1.55	49.02±1.56	30.79±1.16
18	-	89.86±1.34	50.36±1.33	32.83±1.75
24	-	94.08±1.27	53.99±1.18	35.12±1.92

[a]: Mean and S.D. of three batches with duplicate determination per batch

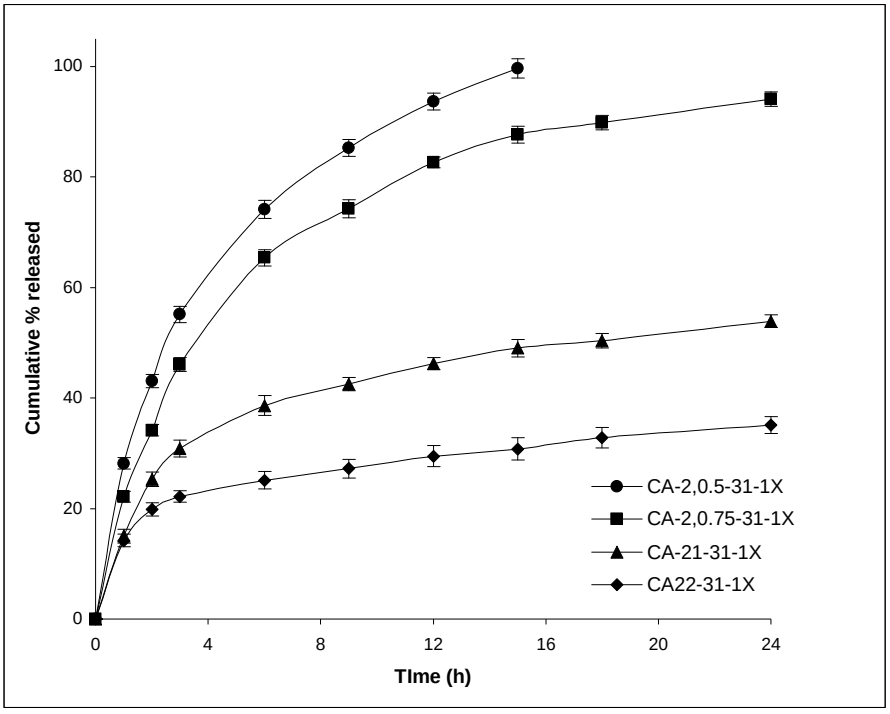

Figure 5.3: In vitro release from floating tablets of celecoxib to study the effect of proportion of sodium alginate [Data presented is mean ± SD of release studies on products of three batches in duplicate]

In case of carbopol based tablets, increasing the proportion of carbopol resulted in fragmentation & breaking of tablets and deterioration in the floating behaviour due to poor gel barrier forming capacity of carbopol in acidic medium and burst effect. Low swelling (2 times) was observed for all tablets after 12 h, except for CC-22-31-1X, which disintegrated completely by that time [Table 5.4].

In these tablets, upon increasing the proportion of carbopol, a faster and less prolonged release was observed. CC-2,0.5-31-1X and CC-21-31-1X released only 86.95± 1.21% and 96.80± 1.09 % in 24 h, while CC-22-31-1X released the entire dose in just 9 h. Carbopol, a weakly acidic polymer, shows negligible gel strength in acidic media and by virtue of being highly hydrophilic in nature would have wicked the media into the matrix very quickly when used at higher proportion, resulting in fragmentable tablets with faster release [Table 5.33; Figure 5.4].

Table 5.33: Cumulative percentage drug release from floating tablets of celecoxib to study the effect of proportion of carbopol

Time (h)	Cumulative percentage released [a]		
	CC-2,0.5-31-1X	CC-21-31-1X	CC-22-31-1X
1	3.89± 0.77	8.94± 0.45	25.22± 0.89
2	8.37± 0.46	14.53± 0.93	56.25±1.36
3	9.13± 0.71	23.09± 1.34	77.43± 1.13
6	14.41± 0.89	49.52± 0.92	91.28± 1.88
9	22.37± 1.15	66.07± 1.04	100.72± 1.86
12	32.92± 1.32	76.48± 1.93	-
15	50.92± 1.77	85.08± 1.74	-
18	65.09± 1.98	90.07± 1.69	-
24	86.95± 1.21	96.80± 1.09	-

[a]: Mean and S.D. of three batches with duplicate determination per batch

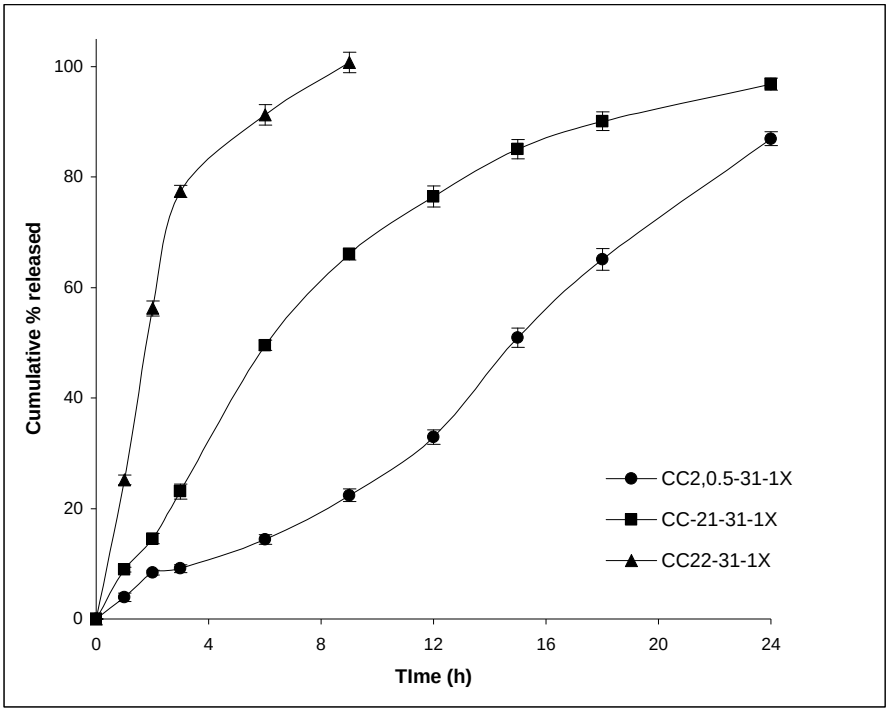

Figure 5.4: In vitro release from floating tablets of celecoxib to study the effect of proportion of carbopol [Data presented is mean ± SD of release studies on products of three batches in duplicate]

CC-2,0.5-31-1X showed more significant r value for zero order release model, while CC-21-31-1X and CC-22-31-1X followed first order release model. As per power equation, CC-2,0.5-31-1X showed case II (n=0.9455) transport with K and $t_{60\%}$ values of 3.42 $h^{-0.9455}$ and 20.71 h respectively. CC-21-31-1X followed case II/ supercase II (n=1.0234) transport with K and $t_{60\%}$ values of 7.38 $h^{-1.0234}$ and 7.75 h respectively and CC-22-31-1X followed anamolous (n=0.7882) transport with K and $t_{60\%}$ values of 32.57 $h^{-0.7882}$ and 2.17 h respectively [Table 5.30].

Effect of nature and proportion of gas generating agent: The tablets designed with sodium bicarbonate without citric acid in the matrix of designed sodium alginate based celecoxib tablets took more time to become afloat. But once they became afloat, they floated beyond 24 h and showed negligible/ no erosion, with the core intact throughout the release studies. Replacing sodium bicarbonate with calcium carbonate resulted in systems that took more time to float indicating that calcium carbonate takes more time to react with the acidic media to generate CO_2. Increasing the total amount of floating agent (either sodium bicarbonate or calcium carbonate) decreased the lag time to come up. CA-22-sbc-2 floated in 10-11 min, while CA-22-sbc-1.5 took 19-20 min to float. Similarly, CA-22-cc-2 floated in 20-22 min, while CA-22-cc-1.5 took 28-30 min to float. All the formulations showed approximately similar extent of swelling (2-3 times) [Table 5.5].

Sodium alginate based tablets without citric acid showed very slow and prolonged release, with very low release in 24 h. Increasing the total amount of floating agent resulted in faster and higher release when either of the base alone was used as floating agent. CA-22-sbc-2 (drug to sodium bicarbonate ratio of 1:1) released 75.69±1.18 %, while CA-22-sbc-1.5 (drug to sodium bicarbonate ratio of 1:0.75) released only 36.29±1.32 % drug in 24 h. Similarly, CA-22-cc-2 (1:1 ratio of drug to calcium carbonate) released 63.07±1.22 %, while CA-22-cc-1.5 (1:0.75 ratio of drug to calcium carbonate) released only 30.68±1.26 % in 24 h [Table 5.34; Figure 5.5].

All the formulations followed quasi-Fickian transport with n value ranging from 0.2653 [CA-22-cc-2] to 0.2940 [CA-22-sbc-2]. CA-22-sbc-2 showed K and $t_{60\%}$ values of 35.45 $h^{-0.2940}$ and 5.99 h respectively. On the other hand, in case of CA-22-sbc-1.5, these values were obtained as 15.42 $h^{-0.2730}$ and 145.10 h respectively. Using calcium carbonate in

place of sodium bicarbonate showed similar results with lower K values and higher $t_{60\%}$ values. The K and $t_{60\%}$ values were obtained as 29.83 $h^{-0.2653}$ and 13.16 $h^{-0.2758}$; and 13.93 h and 244.86 h respectively for CA-22-cc-2 and CA-22-cc-1.5 [Table 5.30].

Table 5.34: Cumulative percentage drug release from floating tablets of celecoxib to study the effect of sodium bicarbonate or calcium carbonate alone as floating agent

Time (h)	Cumulative percentage released [a]			
	CA-22-sbc-2	CA-22-sbc-1.5	CA-22-cc-2	CA-22-cc-1.5
1	31.73±1.26	15.76±0.86	26.02±1.15	13.97±0.79
2	43.19±1.11	18.60±0.92	35.06±1.42	15.72±1.02
3	49.45±1.46	21.01±1.09	40.55±1.82	17.96±1.15
6	59.81±1.77	24.90±1.24	48.68±1.18	21.66±1.16
9	65.29±1.82	27.40±1.36	54.18±1.27	24.13±1.19
12	68.02±1.31	30.98±1.05	57.72±1.66	26.06±1.05
15	71.56±1.55	32.75±1.12	59.86±1.92	28.45±1.27
18	73.6±1.67	34.08±1.24	61.59±1.08	29.53±1.16
24	75.69±1.18	36.29±1.32	63.07±1.22	30.68±1.26

[a]: Mean and S.D. of three batches with duplicate determination per batch

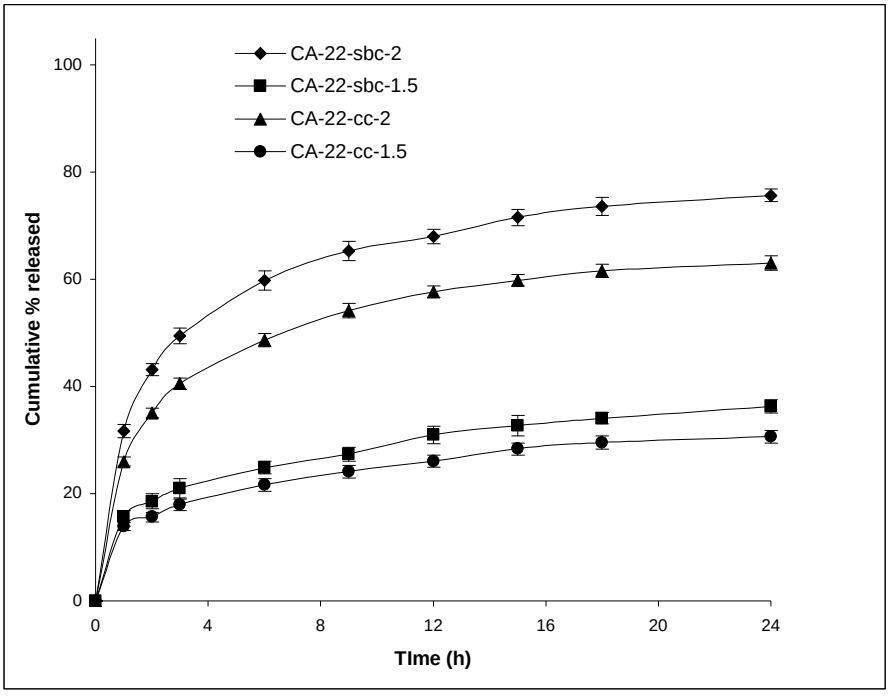

Figure 5.5: In vitro release from floating tablets of celecoxib to study the effect of sodium bicarbonate or calcium carbonate alone as floating agent [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Effect of sodium bicarbonate to citric acid ratio as floating agent mixture: In case of sodium alginate based tablets of celecoxib, on varying the ratio of sodium bicarbonate to anhydrous citric acid from 1:1 to 3:1, lag time to float increased but duration of floating also increased. CA21-11-1X, CA21-21-1X and CA21-31-1X floated in 6-8, 8-12 and 12-17 min

respectively and floated for 6-8 h, 8-11 h and more than 24 h respectively. Higher proportion of acid in the acid-base mix lead to disintegration and fragmentation of the tablets. Tablets containing base to acid ratios of 1:1 and 2:1 showed higher rate of erosion and complete fragmentation/ disintegration, but formulations with base to acid ratio of 3:1 remained more or less intact till the end of the release. Swelling at 12 hours was more prominently observed in case of tablets with base to acid ratio of 3:1 than at other ratios due to better intactness of the tablets [Table 5.6]. In case of these formulations, on varying the ratio of sodium bicarbonate to anhydrous citric acid from 1:1 to 3:1, higher initial release (in first hour) and faster overall release was observed in case of 1:1 systems, followed by 2:1 and then 3:1 systems. CA-21-11-1X, CA-21-21-1X and CA-21-31-1X released 30.98±1.26 %, 20.57±1.27 % and 15.01±1.29 % respectively in 1 h and 91.63±1.56 %, 63.18±1.78 % and 53.99±1.18 % respectively in 24 h [Table 5.35; Figure 5.6].

Table 5.35: Cumulative percentage drug release from floating tablets of celecoxib to study the effect of varying sodium bicarbonate to anhydrous citric acid ratio

Time (h)	**Cumulative percentage released** [a]		
	CA-21-11-1X	**CA-21-21-1X**	**CA-21-31-1X**
1	30.98±1.26	20.57±1.27	15.01±1.29
2	44.29±1.56	28.25±1.84	25.29±1.35
3	53.16±1.08	34.30±1.61	30.87±1.52
6	67.86±1.69	42.90±1.52	38.65±1.78
9	75.90±1.54	48.82±1.01	42.51±1.22
12	81.39±1.26	53.95±1.88	46.23±1.08
15	84.57±1.15	57.09±1.34	49.02±1.56
18	87.28±1.89	59.70±1.59	50.36±1.33
24	91.63±1.56	63.18±1.78	53.99±1.18

[a]: Mean and S.D. of three batches with duplicate determination per batch

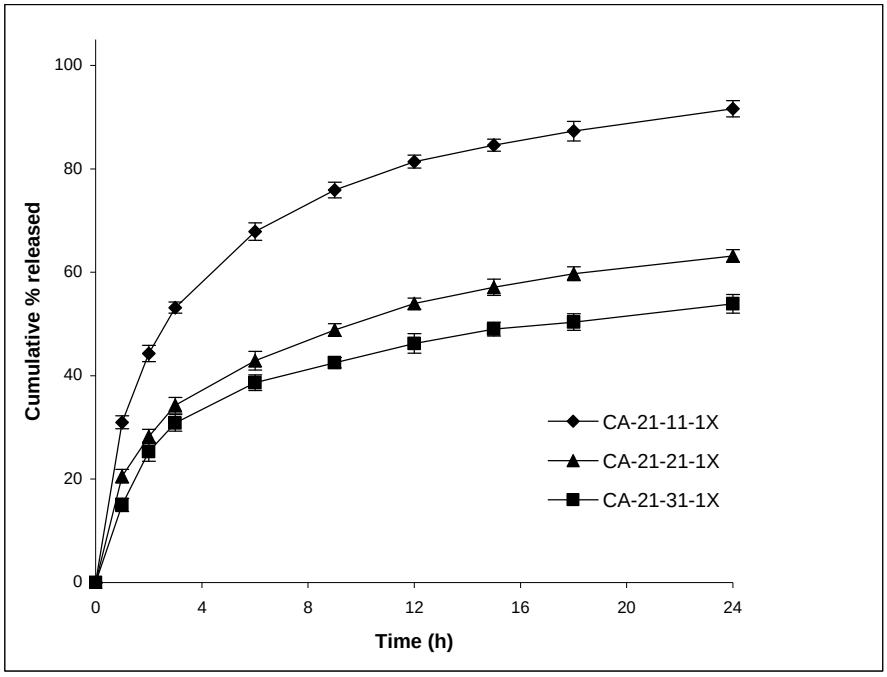

Figure 5.6: In vitro release from floating tablets of celecoxib to study the effect of varying sodium bicarbonate to anhydrous citric acid ratio [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Formulations in this category obtained most significant r value for either first order or Higuchi's type of release and showed Fickian/ quasi-Fickian type of release transport mechanism. In case of CA-21-11-1X, CA-21-21-1X and CA-21-31-1X the obtained n values were 0.3845, 0.3360 and 0.2972 respectively. In case of CA-21-11-1X the obtained K and $t_{60\%}$ values were 34.28 $h^{-0.3845}$ and 4.29 h respectively. In case of CA-21-21-1X the obtained these values were 23.13 $h^{-0.3360}$ and 17.07 h, while for CA-21-31-1X the obtained values were 21.74 $h^{-0.2972}$ and 30.44 h respectively [Table 5.30].

Effect of total amount of floating agent: Lesser amount of total floating agent in the matrix resulted in more intact tablets in which the core continued to float for longer period of time. On the other hand, higher amount of floating agent resulted in higher erosion, more fragments and faster disintegration. At fixed celecoxib to sodium alginate ratio of 1:0.5, reducing the total amount of floating agent decreased the lag time to float. CA-21-31-X/2 took least time of 2-3 min to float, whereas CA-21-31-2X (with highest amount of floating agent) took 25-26 min to float. Increase in the amount of floating agent resulted in increased swelling of the core (at 12 h of release studies) up to drug to total floating agent ratio of 1:1. Further increase in this ratio to 1:1.33, 1:1.5 or 1:2 led to high fragmentation/ disintegration and thus, no observable swelling at 12 h [Table 5.7].

In case of sodium alginate based celecoxib tablets prepared at fixed drug to polymer ratio of 1:0.5, increasing the total amount of floating agent resulted in faster and more complete release. CA21-31-2X, CA21-31-1.5X and CA21-31-1.33X extended the release to 12 h, 15 h and 24 h respectively, while CA21-31-1X and CA21-31-X/2 released only 53.99±1.18 % and 39.03±0.99 % respectively in 24 h [Table 5.36; Figure 5.7].

Table 5.36: Cumulative percentage drug release from sodium alginate based floating tablets of celecoxib to study the effect of varying amount of floating agent

Time (h)	Cumulative percentage released [a]				
	CA-21-31-X/2	CA-21-31-1X	CA-21-31-1.33X	CA-21-31-1.5X	CA-21-31-2X
1	8.04±1.06	15.01±1.29	28.05±1.09	33.99±1.08	52.02±1.31
2	13.98±1.31	25.29±1.35	48.15±1.48	57.61±1.24	68.20±1.19
3	17.51±1.24	30.87±1.52	59.20±1.29	66.38±1.43	78.58±1.07
6	25.14±1.44	38.65±1.78	71.88±1.48	78.29±1.18	93.64±1.29
9	29.69±1.37	42.51±1.22	78.36±1.24	86.45±1.66	97.73±1.70
12	32.76±1.22	46.23±1.08	83.98±1.57	93.82±1.54	100.63±1.49
15	35.05±1.09	49.02±1.56	88.75±1.63	99.91±1.28	-
18	36.86±1.07	50.36±1.33	93.64±1.49	-	-
24	39.03±0.99	53.99±1.18	101.88±1.37	-	-

[a]: Mean and S.D. of three batches with duplicate determination per batch

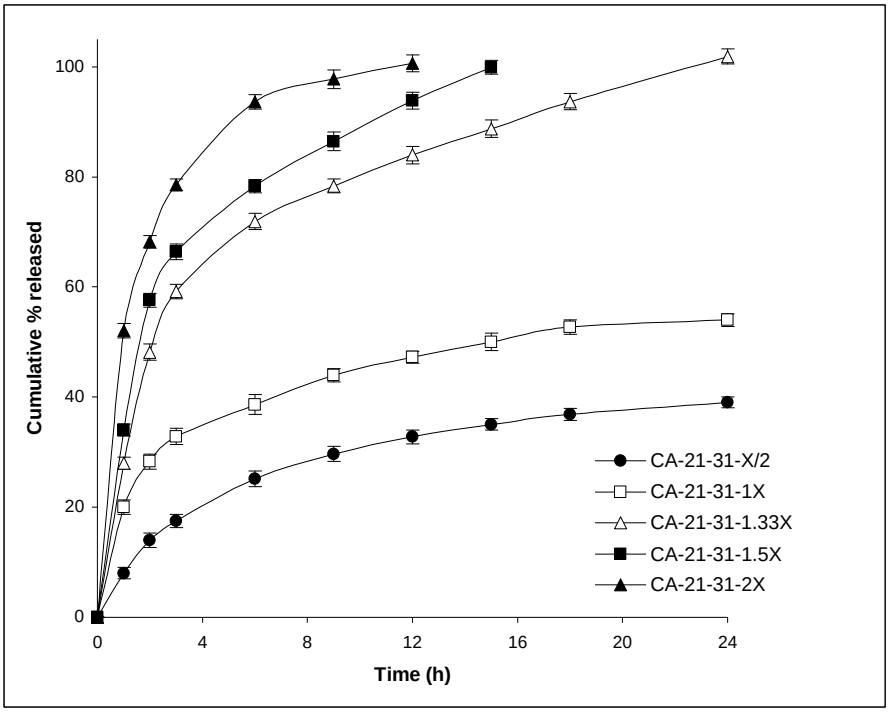

Figure 5.7: In vitro release from floating tablets of celecoxib to study the effect of varying amount of floating agent [Data presented is mean ± SD of release studies on products of three batches in duplicate]

The release mechanism was found to be quasi-Fickian in all cases except for CA21-31-1.33X, which showed Fickian/ anamolous type of release transport. CA21-31-X/2, containing least amount of floating agent, showed slowest release with K and $t_{60\%}$ values of 11.11 $h^{-0.4207}$ and 55.06 h respectively; while CA21-31-2X, containing highest amount of floating agent, showed fastest release with K and $t_{60\%}$ values of 52.02 $h^{-0.3907}$ and 1.44 h respectively [Table 5.37].

Effect of absence of floating agent: All the formulations prepared without any floating agent were non-floatable, with relatively low/ negligible erosion and disintegration. CC-21 and CH1-21 showed 2 times swelling, while CA-21 showed 3 time swelling [Table 5.8]. These formulations released extremely low amounts of drug when compared to similar formula with floating agent. CA-21 and CC-21 released only 12.26±0.87 % and 6.26±0.47 % respectively in 24 h. A cumulative release of 43.53±1.17 % in 24 h was observed in case of HPMC-15 cps based tablets (CH1-21) [Table 5.38; Figure 5.8]. Sodium alginate and HPMC-15 cps based tablets showed anamolous release transport, with n=0.6024 in case of CA-21 and n=0.8811 in case of CH1-21. CC-21 showed a Fickian (n=0.4760) type of release transport. Other release kinetics parameters of these tablets are presented in Table 5.37.

Table 5.37: In vitro release rate parameters of floating tablets of celecoxib

Formulation code	Correlation coefficient				Release rate constant [a] [K (h^{-n})]	Release exponent [b] [n]	Mechanism of release	Time for 60 % drug release [c] $t_{60\%}$ (h)
	Zero order	First order	Higuchi's model	Ritger-Peppas model				
(a) Effect of amount of floating agent								
CA-21-31-X/2	0.9099	0.9333	0.9862	0.9900	11.11	0.4207	Quasi-Fickian	55.06
CA-21-31-1X	0.8657	0.9134	0.9676	0.9921	21.74	0.2972	Quasi-Fickian	30.44
CA-21-31-1.33X	0.8666	0.9847	0.9667	0.9999	33.82	0.5095	Fickian/ Anamolous	3.08
CA-21-31-1.5X	0.8654	0.8995	0.9675	0.9999	45.22	0.3495	Quasi-Fickian	2.25
CA-21-31-2X	0.7988	0.9948	0.9392	0.9999	52.02	0.3907	Quasi-Fickian	1.44
(b) Effect of absence of floating agent								
CA-21	0.9719	0.9763	0.9973	0.9988	2.13	0.6024	Anamolous	254.64
CH1-21	0.9586	0.9741	0.9807	0.9771	3.32	0.8811	Anamolous	26.71
CC-21	0.9490	0.9513	0.9887	0.9843	1.29	0.4760	Fickian	3191.50
(c) Effect of hardness in single polymer based tablets								
CA-21-31-1X	0.8657	0.9134	0.9676	0.9921	21.74	0.2972	Quasi-Fickian	30.44
CA-21-31-1X-L	0.8530	0.9926	0.9659	0.9999	39.22	0.7026	Anamolous	1.83
CA-22-31-1X	0.8343	0.8697	0.9474	0.9975	16.98	0.2239	Quasi-Fickian	280.54
CA-22-31-1X-L	0.8955	0.9932	0.9818	0.9991	36.66	0.4012	Quasi-Fickian	3.42
(d) Effect of polymer type in double polymer based sodium alginate tablets								
CAG-21-11-31-1X	0.8171	0.9753	0.9476	0.9999	45.16	0.5145	Anamolous	1.74
CAH1-21-11-31-1X	0.7132	0.9472	0.8818	0.9998	64.45	0.3214	Quasi-Fickian	0.80
CAC-21-11-31-1X	0.7745	0.9606	0.9148	0.9997	56.10	0.2654	Quasi-Fickian	1.29
CAP-21-11-31-1X	0.8466	0.9451	0.9583	0.9999	40.81	0.5452	Anamolous	2.03
(e) Effect of HPMC viscosity in double polymer based sodium alginate tablets								
CAH1-21-11-31-1X	0.7292	0.9754	0.9030	0.9998	67.19	0.2320	Quasi-Fickian	0.61
CAH2-21-11-31-1X	0.7548	0.9428	0.9184	0.9998	65.49	0.2086	Quasi-Fickian	0.66
CAH3-21-11-31-1X	0.7653	0.9707	0.9251	0.9997	62.49	0.2165	Quasi-Fickian	0.80
CAH4-21-11-31-1X	0.7686	0.9778	0.9192	0.9999	58.24	0.2838	Quasi-Fickian	1.11
(f) Effect of hardness in double polymer based tablets								
CAG-21-11-31-X/2-H	0.9140	0.9570	0.9857	0.9866	18.13	0.3440	Quasi-Fickian	32.43
CAG-21-11-31-X/2-M	0.9005	0.9263	0.9845	0.9999	28.73	0.7763	Anamolous	2.58
CAG-21-11-31-X/2-L	0.8609	0.9855	0.9704	0.9999	36.55	0.6229	Anamolous	2.22

[a]: Release rate constant (based on Ritger-Peppas model; for data fitted up to 60 % of drug released); [b]: Release exponent, indicative of the mechanism of release (based on Ritger-Peppas model); [c]: Time for 60 % ($t_{60\%}$) of the drug release (based on Ritger-Peppas model)

Table 5.38: Cumulative percentage drug release from floating tablets of celecoxib to study the effect of absence of floating agent

Time (h)	Cumulative percentage released [a]		
	CA-21	CH1-21	CC-21
1	2.64±0.25	1.32±0.02	1.15±0.09
2	3.23±0.36	4.95±0.21	1.71±0.24
3	4.03±0.39	8.65±0.66	2.31±0.45
6	6.07±0.35	20.05±0.57	2.89±0.41
9	7.84±0.51	27.32±0.66	4.13±0.56
12	8.70±0.52	33.74±0.71	4.22±0.43
15	9.92±0.64	36.55±0.83	4.41±0.52
18	10.60±0.66	38.85±0.88	4.65±0.38
24	12.26±0.87	43.53±1.17	6.26±0.47

[a]: Mean and S.D. of three batches with duplicate determination per batch

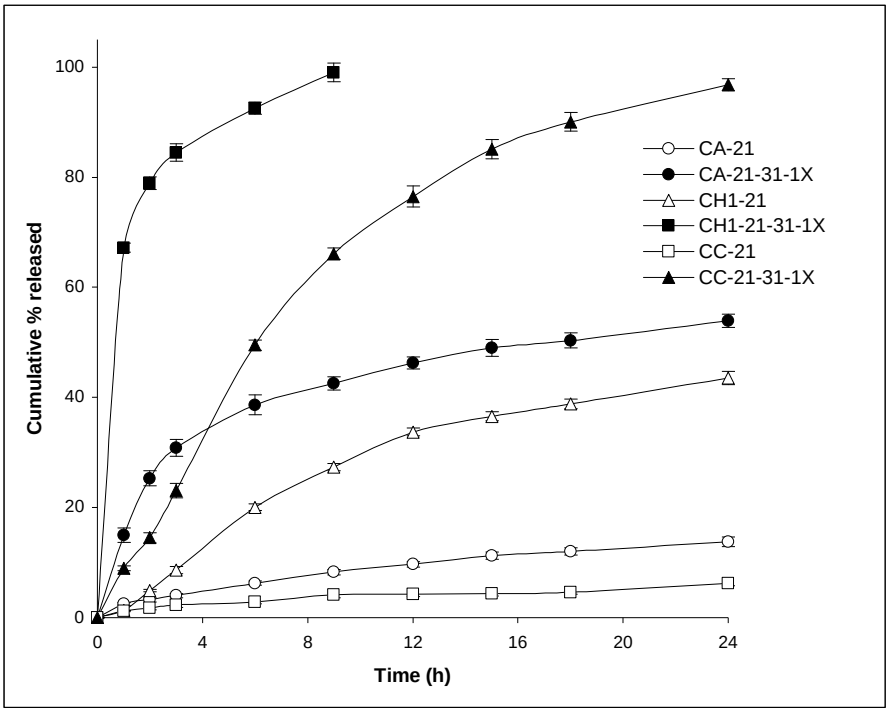

Figure 5.8: In vitro release from single polymer based tablets of celecoxib prepared without floating agent in comparison to similar formula with floating agent [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Effect of hardness: Tablets with same formula, but lesser hardness resulted in tablets that took lesser time to float, but were less intact due to disintegration and floated for shorter duration. Tablets with lower hardness (4±0.5 kg/cm^2) showed very high initial erosion and core disintegrated very quickly into multiple fragments/ granules. In case of sodium alginate based tablets containing drug to sodium alginate ratio of 1:0.5, CA-21-31-1X at higher

hardness of 7±0.5 kg/cm^2 was afloat within 12-17 min and floated for more than 24 h with a swelling of 3 times at 12 h. Whereas, CA-21-31-1X-L at lower hardness of 4±0.5 kg/cm^2, though was afloat in just 2-4 min but floated for only 10-11 h with complete disintegration at the end of 12 h. Similarly in case of sodium alginate based tablets containing drug to sodium alginate ratio of 1:1, CA-22-31-1X was afloat in 6 min and floated for more than 24 h with a swelling of 4 times at 12 h. On the other hand, CA-22-31-1X-L floated in 4.5-5 min but duration of floating was reduced to 16-17 h with a swelling of 3-3.5 times at 12 h [Table 5.9]. Formulations CA-21-31-1X and CA-21-31-1X-L prolonged the release beyond 24 h (with only 53.99±1.18 % in 24 h) and up to 12 h respectively [Table 5.39; Figure 5.9] with corresponding n values of 0.2972 (quasi-Fickian) and 0.7026 (anamolous) [Tables 5.37].

Table 5.39: Cumulative percentage drug release from floating tablets of celecoxib to study the effect of hardness

Time (h)	Cumulative percentage released [a]			
	CA-21-31-1X	CA-21-31-1X-L	CA-22-31-1X	CA-22-31-1X-L
1	15.01±1.29	39.22±1.17	14.20±0.58	35.04±1.45
2	25.29±1.35	63.83±1.51	19.80±0.94	48.07±1.28
3	30.87±1.52	72.84±1.28	22.16±1.03	57.59±1.67
6	38.65±1.78	87.03±1.47	25.13±1.25	74.91±1.92
9	42.51±1.22	96.40±1.53	27.25±1.43	85.19±1.54
12	46.23±1.08	101.49±1.06	29.48±1.33	91.41±1.06
15	49.02±1.56	-	30.79±1.16	96.84±1.21
18	50.36±1.33	-	32.83±1.75	101.84±1.09
24	53.99±1.18	-	35.12±1.92	-

[a]: Mean and S.D. of three batches with duplicate determination per batch

CA-21-31-1X showed slow release with K and $t_{60\%}$ values of 21.74 $h^{-0.2972}$ and 30.44 h respectively, while CA-21-31-1X-L showed faster release with K and $t_{60\%}$ values of 39.22 $h^{-0.7026}$ and 1.83 h respectively. At drug to polymer ratio of 1:1, value of n was 0.2239 and 0.4012 respectively for CA-22-31-1X and CA-22-31-1X-L. Formulation CA-22-31-1X prolonged the release beyond 24 h with K and $t_{60\%}$ values of 16.98 $h^{-0.2239}$ and 280.54 h respectively. On the other hand, CA-22-31-1X-L prolonged the release to 18 h with K and $t_{60\%}$ values of 36.66 $h^{-0.4012}$ and 3.42 h respectively [Table 5.37].

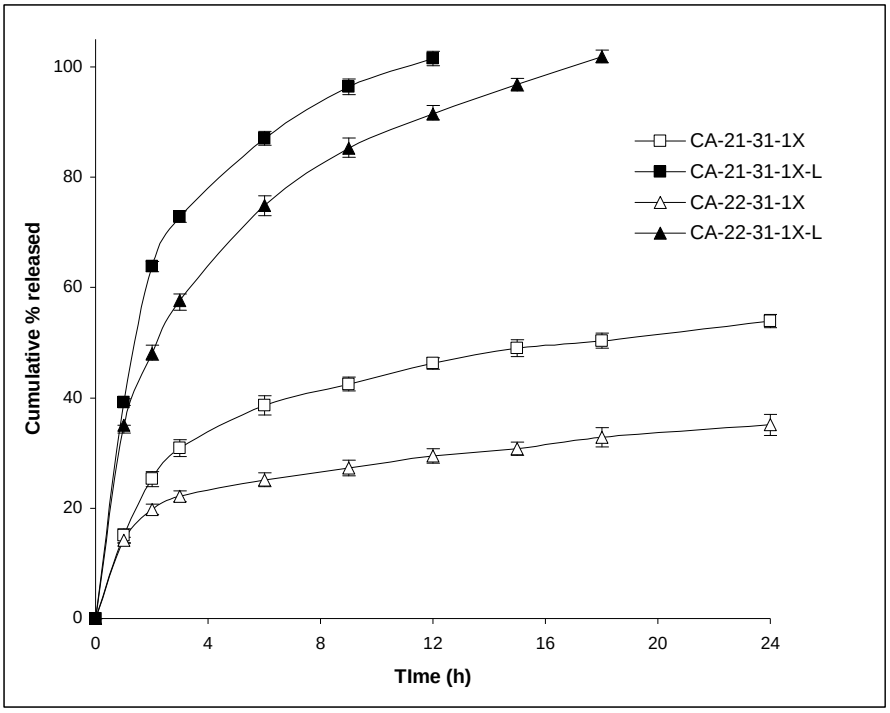

Figure 5.9: In vitro release from floating tablets of celecoxib to study the effect of hardness [Data presented is mean ± SD of release studies on products of three batches in duplicate]

(b) Double polymer type tablets

Effect of polymer type: In case of double polymer type tablets of celecoxib with sodium alginate as one of the polymers along with another polymer, there was an improvement in lag time to float in comparison to tablets made with single polymer. However, none of these floated for more than 9-13 h with all tablets showing high degree of fragmentation/ disintegration [Table 5.10]. The celecoxib release, from double polymer type tablets of sodium alginate with other polymers, was better extended in comparison to tablets of these polymers when used alone. The drug release was extended up to 12-15 h in case of these tablets with high initial release of 40.81±1.28 to 64.45±1.25 % in first one hour [Table 5.40; Figure 5.10].

CAG-21-11-31-1X showed anamolous (n=0.5145) release transport with K and $t_{60\%}$ values of 45.16 $h^{-0.5145}$ and 1.74 h respectively. CAH1-21-11-31-X showed quasi-Fickian (n=0.3214) release transport with K and $t_{60\%}$ values of 64.45 $h^{-0.3214}$ and 0.80 h respectively. CAC-21-11-31-X showed quasi-Fickian (n=0.2654) release transport with K and $t_{60\%}$ values of 56.10 $h^{-0.2654}$ and 1.29 h respectively and CAP-21-11-31-X followed anamolous (n=0.5452) release transport with K and $t_{60\%}$ values of 40.81 $h^{-0.5452}$ and 2.03 h respectively [Table 5.37].

Table 5.40: Cumulative percentage drug release from double polymer type sodium alginate floating tablets of celecoxib to study the effect of second polymer type

Time (h)	Cumulative percentage released [a]			
	CAG-21-11-31-1X	CAH1-21-11-31-1X	CAC-21-11-31-1X	CAP-21-11-31-1X
1	45.16±1.36	64.45±1.25	56.10± 0.96	40.81±1.28
2	64.51±1.48	80.53±1.32	67.43±1.05	59.55±1.31
3	79.25±1.81	85.42±1.58	76.23±1.54	69.08±1.03
6	87.43±1.67	91.03±1.73	83.33±1.32	78.05±1.79
9	94.36±1.54	96.56±1.11	89.54±1.14	85.60±1.81
12	100.07±1.41	101.44±1.47	95.46±1.88	93.62±1.74
15	-	-	99.40±1.69	99.45±1.11

[a]: Mean and S.D. of three batches with duplicate determination per batch

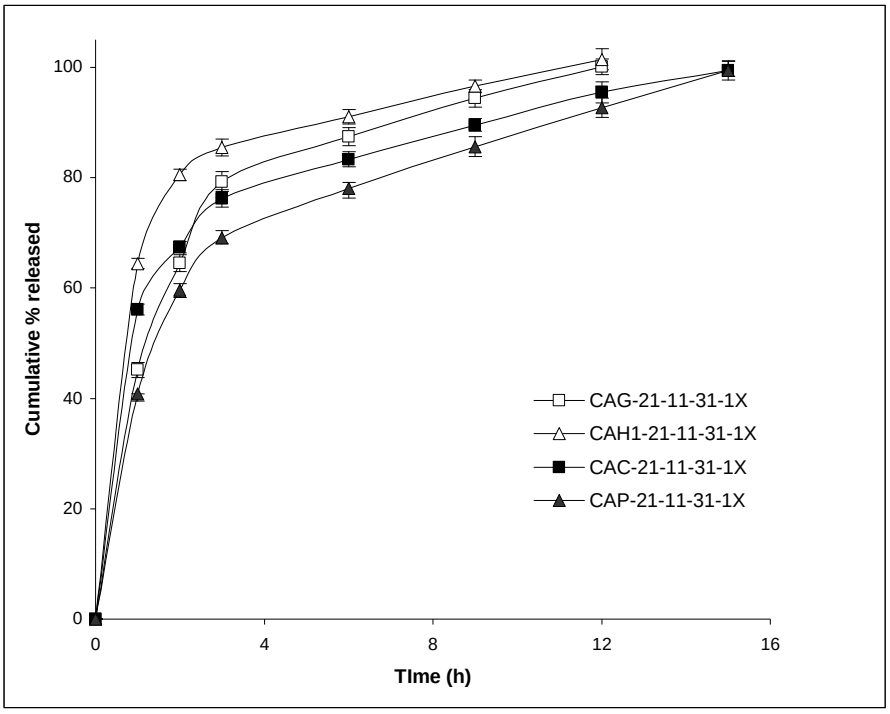

Figure 5.10: In vitro release from double polymer type sodium alginate floating tablets of celecoxib to study the effect of second polymer type [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Effect of viscosity of polymer: Celecoxib double polymer type tablets of sodium alginate with HPMC of varying viscosity showed inverse relationship between duration of floating and HPMC viscosity. Lag time to float increased with increase in viscosity of HPMC. CAH1-21-11-31-1X (with HPMC-15 cps) took least time (6-9 min) to come up, while CAH4-21-11-31-1X (containing HPMC-1 lac cps) took 35-40 min to float. Fragmentation

of these tablets relatively decreased with increase in viscosity with all the formulations fragmenting completely within 2.5-4 h and so, no observable swelling at 12 h [Table 5.11]. In this category of tablets, increase in viscosity of HPMC resulted in more prolonged release. CAH1-21-11-31-1X (containing HPMC-15 cps) released 64.45±1.25 % in first hour and extended the release up to 12 h, while CAH4-21-11-31-X (containing HPMC-1 lac cps) released 41.40±1.29 % in first hour and extended the release up to 18 h. Increase in viscosity resulted in more prolonged release [Table 5.41; Figure 5.11].

Table 5.41: Cumulative percentage drug release from double polymer type sodium alginate floating tablets of celecoxib to study the effect of different viscosity grade HPMC as second polymer

Time (h)	Cumulative percentage released [a]			
	CAH1-21-11-31-1X	CAH2-21-11-31-1X	CAH3-21-11-31-1X	CAH4-21-11-31-1X
1	67.19±0.85	65.49±1.19	62.94± 0.66	58.24±1.31
2	78.91±1.16	75.68±1.05	73.13±1.57	70.90±1.08
3	84.49±1.58	83.26±1.43	82.78±1.15	78.60±1.49
6	92.54±1.05	91.91±1.13	90.48±1.64	88.12±1.38
9	99.03±1.67	100.24±1.24	99.17±1.06	94.60±1.72
12	-	-	-	99.14±1.25

[a]: Mean and S.D. of three batches with duplicate determination per batch

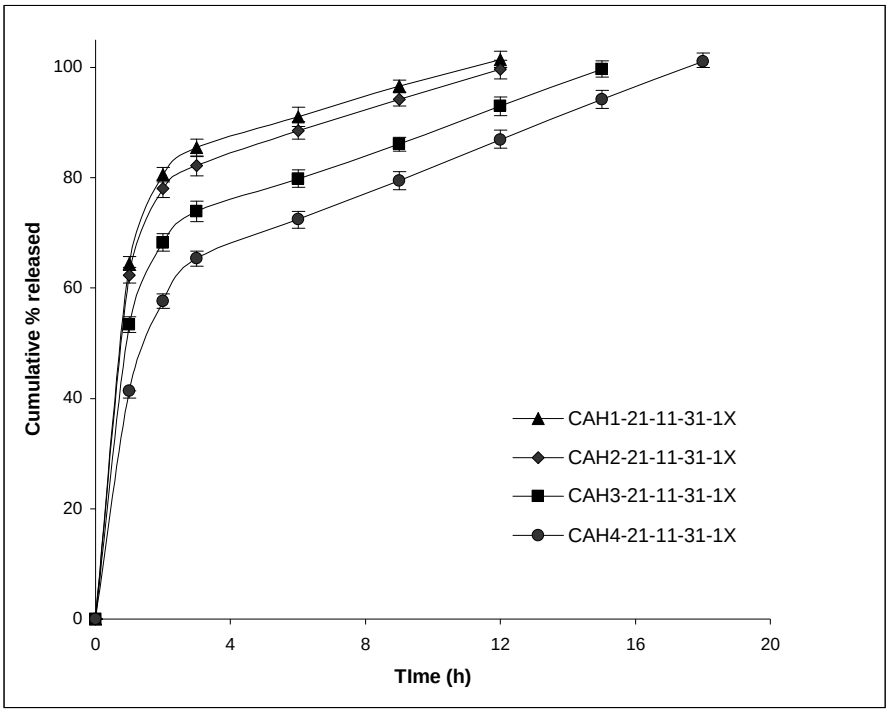

Figure 5.11: In vitro release from double polymer type sodium alginate floating tablets of celecoxib to study the effect of different viscosity grade HPMC as second polymer [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Including sodium alginate in HPMC based tablets, increased the n value and made the release mechanism more of Fickian type. CAH1-21-11-31-X showed quasi-Fickian (n=0.3214) release transport with K and $t_{60\%}$ values of 64.45 $h^{-0.3214}$ and 0.80 h respectively, while CAH4-21-11-31-X showed Fickian (n=0.4777) type of release transport with K and $t_{60\%}$ values of 41.40 $h^{-0.4777}$ and 2.17 h respectively [Table 5.37].

Effect of hardness: In case of sodium alginate and guar gum based double polymer tablets, on decreasing the hardness, lag time to float increased and duration of floating decreased. CAG-21-11-31-X/2-H (hardness 8±0.5 kg/cm^2) was afloat in just 1 min and continued to float for more than 24 h, while CAG-21-11-31-X/2-M (hardness 6±0.5 kg/cm^2) and CAG-21-11-31-X/2-L (hardness 4±0.5 kg/cm^2) took 2-3 min and 9-11 min respectively to float and remained afloat for 10-11 h. Upon decreasing the hardness, the initial erosion was higher but the core remained intact till the end of release [Table 5.12].

Sodium alginate and guar gum based tablets with hardness of 8±0.5 kg/cm^2 [CAG-21-11-31-X/2-H] showed quasi-Fickian (n=0.3440) type of release transport and extended the release to 24 h with K and $t_{60\%}$ values of 18.13 $h^{-0.3440}$ and 32.43 h respectively [Table 5.42; Figure 5.12]. Whereas, CAG-21-11-31-X/2-M and CA-G21-11-31-X/2-L showed anamolous type of release transport and extended the release to 12 h and showed very little difference in their release profiles. CAG-21-11-31-X/2-M obtained slightly lower K value and higher $t_{60\%}$ value than CA-G21-11-31-X/2-L [Table 5.37].

Table 5.42: Cumulative percentage drug release from double polymer type sodium alginate and gaur gum based floating tablets of celecoxib to study effect of hardness

Time (h)	Cumulative percentage released [a]		
	CAG-21-11-31-X/2-H	CAG-21-11-31-X/2-M	CAG-21-11-31-X/2-L
1	16.79±0.95	33.74±1.51	43.74±1.33
2	21.66±1.18	49.20±1.73	56.28±1.45
3	29.36±1.25	67.40±1.82	72.45±1.57
6	33.23±1.36	76.44±1.69	82.84±1.60
9	37.65±1.48	89.41±1.53	93.16±1.68
12	41.30±1.33	99.65±1.47	100.01±1.49
15	45.38±1.27	-	-
18	49.34±1.39	-	-
24	55.80±1.24	-	-

[a]: Mean and S.D. of three batches with duplicate determination per batch

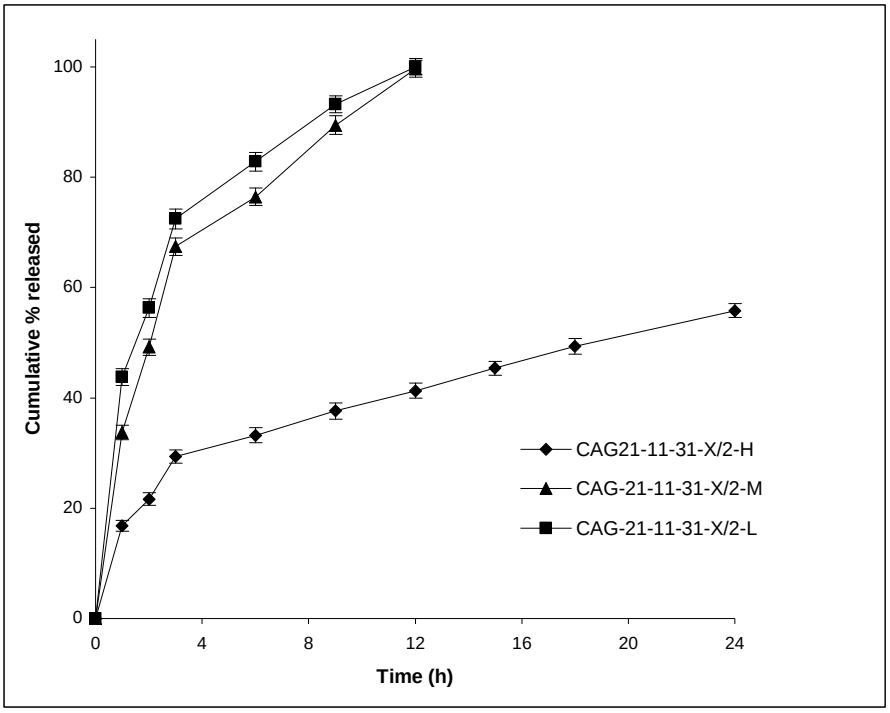

Figure 5.12: In vitro release from double polymer type sodium alginate and gaur gum based floating tablets of celecoxib to study effect of hardness [Data presented is mean ± SD of release studies on products of three batches in duplicate]

5.3.3.2. Evaluation of acyclovir tablets

(a) Single polymer based tablets

Effect of polymer type: In case of acyclovir tablets prepared with different types of polymers, tablets made of sodium alginate [AA-21-31-1X], guar gum [AG-21-31-1X] and HPMC-15 cps [AH1-21-31-1X] took 28-30 sec, 3-3.5 min and 10-12 min to float respectively. Whereas tablets made of carbopol [AC-21-31-1X] took 45-50 min to float and tablets of polycarbophil did not float at all. All the formulations showed high tendency to fragment with all tablets disintegrating completely in 40 min to 2 h [Table 5.13]. Higher solubility of acyclovir in acidic media probably resulted in very quick penetration of the media into the formulation matrix causing CO_2 generation due to acid/ base reaction and fragmentation of matrix base [Table 5.13].

At fixed drug to polymer ratio (1:0.5), formulations of the all polymers employed showed poor controlled release characteristics. Formulations AA-21-31-1X, AG-21-31-1X and AH1-21-31-1X released the entire dose in 1-2 h. On the other hand, AP-21-31-1X and AC-21-31-1X prolonged the release to 3 h and 6 h respectively [Table 5.43; Figure 5.13]. Carbopol based tablets [AC21-31-X] followed quasi-Fickian (n=0.3622) transport with K and $t_{60\%}$ values of 66.50 $h^{-0.3622}$ and 0.75 h respectively [Table 5.44].

Table 5.43: Cumulative percentage drug release from floating tablets of acyclovir to study the effect of polymer type

Time (h)	Cumulative percentage released [a]				
	AA-21-31-1X	**AG-21-31-1X**	**AH1-21-31-1X**	**AC-21-31-1X**	**AP-21-31-1X**
1	88.60± 1.84	102.3±1.21	100.34±1.14	66.50±1.63	82.05±1.77
2	101.40± 1.10	-	-	85.48±1.13	92.44±1.28
3	-	-	-	96.27±1.80	99.56±1.11
6	-	-	-	99.37±1.20	-

[a]: Mean and S.D. of three batches with duplicate determination per batch

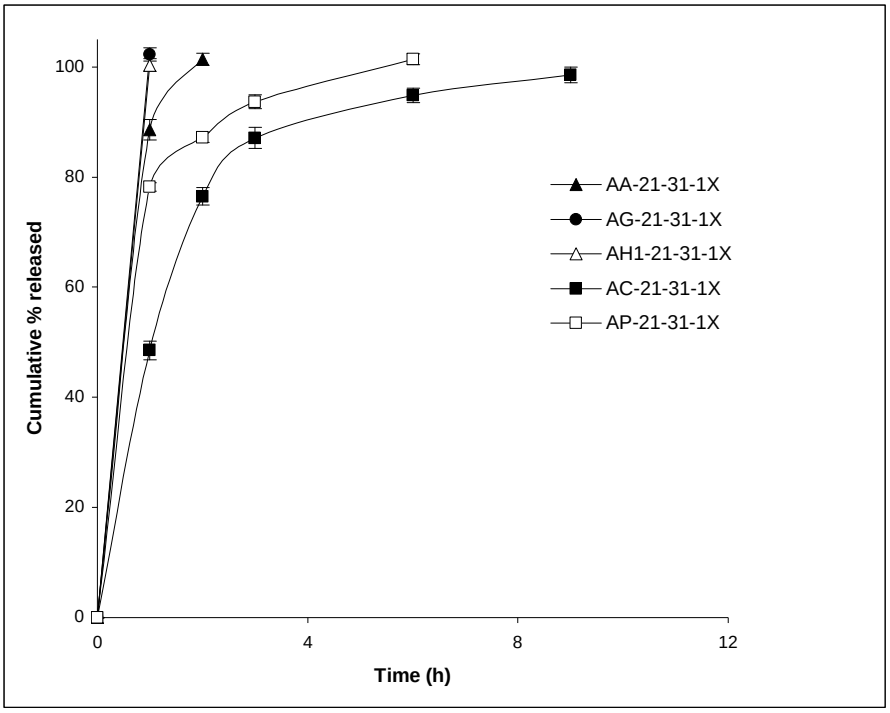

Figure 5.13: In vitro release from floating tablets of acyclovir to study the effect of polymer type [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Effect of viscosity of polymer: In case of acyclovir tablets made of different viscosity of HPMC, HPMC-15 cps based formulations took 10-12 min to float. Other viscosity grades of HPMC produced very buoyant tablets, which floated in less than one minute. But all these formulations were highly fragmentable, non-swellable and duration of floating was less than 2.5 h. With increase in viscosity grade, there was a slight improvement in the non-disintegrating behaviour with duration of floating increasing from 45 min in case of HPMC-15 cps [AH1-21-31-1X] to 2.5 h in case of HPMC-1 lac cps [AH4-21-31-1X] [Table 5.14].

Table 5.44: In vitro release rate parameters of floating tablets of acyclovir

Formulation code	Correlation coefficient				Release rate constant [a] [K (h^{-n})]	Release exponent [b] [n]	Mechanism of release	Time for 60 % drug release [c] $t_{60\%}$ (h)
	Zero order	First order	Higuchi's model	Ritger-Peppas model				
(a) Effect of polymer type								
AA-21-31-1X	0.9181	-	0.9851	1.0000	88.60	0.1947	Quasi-Fickian	0.14
AC-21-31-1X	0.7645	0.9877	0.9345	0.9999	66.50	0.3622	Quasi-Fickian	0.75
AP-21-31-1X	0.8630	0.9764	0.9681	1.0000	82.05	0.1720	Quasi-Fickian	0.16
(b) Effect of different viscosity grade HPMC								
AH2-21-31-1X	0.8784	0.9993	0.9758	0.9999	79.50	0.2555	Quasi-Fickian	0.33
AH3-21-31-1X	0.8949	0.9962	0.9830	0.9999	75.28	0.2765	Quasi-Fickian	0.44
AH4-21-31-1X	0.9106	0.9583	0.9891	0.9999	71.30	0.3228	Quasi-Fickian	0.59
(c) Effect of proportion of sodium alginate								
AA-21-31-1X	0.9181	-	0.9851	1.0000	88.60	0.1947	Quasi-Fickian	0.14
AA-22-31-1X	0.7502	0.9654	0.8961	1.0000	63.12	0.1775	Quasi-Fickian	0.75
(d) Effect of proportion of polycarbophil or carbopol								
AP-21-31-1X	0.8630	0.9764	0.9681	1.0000	82.05	0.1720	Quasi-Fickian	0.16
AP22-31-1X	0.8081	0.9935	0.9492	0.9999	50.80	0.7750	Anamolous	1.24
AC-21-31-1X	0.7645	0.9877	0.9345	0.9999	66.50	0.3622	Quasi-Fickian	0.75
AC-22-31-1X	0.7822	0.9861	0.9338	0.9999	48.52	0.6569	Anamolou	1.38
(d) Effect of amount of floating agent in sodium alginate based tablets								
AA-21-31-X/2	0.8952	0.9759	0.9732	0.9858	37.48	0.2513	Quasi-Fickian	6.50
AA-21-31-1X	0.9181	-	0.9851	1.0000	88.60	0.1947	Quasi-Fickian	0.14
AA22-31-X/2	0.9468	0.9962	0.9933	0.9998	14.12	0.6654	Anamolous	8.79
AA-22-31-1X	0.7502	0.9654	0.8961	1.0000	63.12	0.1775	Quasi-Fickian	0.75
AA22-31-2X	0.9541	0.9684	0.9976	1.0000	76.80	0.3734	Quasi-Fickian	0.52
(e) Effect of amount of floating agent in carbopol or HPMC-4000cps based tablets								
AC-21-31-X/2	0.9198	0.9844	0.9909	0.9999	67.29	0.4709	Fickian	0.78
AC-21-31-1X	0.7645	0.9877	0.9345	0.9999	66.50	0.3622	Quasi-Fickian	0.75
AH2-21-31-X/2	0.6950	0.9248	0.8671	0.9999	70.05	0.1724	Quasi-Fickian	0.41
AH2-21-31-1X	0.6805	0.9384	0.8712	0.9999	50.70	0.1602	Quasi-Fickian	2.86
(f) Effect of hardness in sodium alginate based tablets								
AA-22-31- X/2-H	0.9919	0.9908	0.9697	0.9870	1.97	1.2736	Supercase II	14.65
AA-22-31- X/2-L	0.9268	0.9948	0.9928	0.9984	23.39	0.5017	Fickian/ Anamolous	6.54
AA-22-31-1X-H	0.7830	0.9195	0.9156	0.9999	56.31	0.2580	Quasi-Fickian	1.28
AA-22-31-1X-L	0.6672	0.9526	0.8731	1.0000	86.31	0.1273	Quasi-Fickian	-

[a]: Release rate constant (based on Ritger-Peppas model; for data fitted up to 60 % of drug released); [b]: Release exponent, indicative of the mechanism of release (based on Ritger-Peppas model); [c]: Time for 60 % ($t_{60\%}$) of the drug release (based on Ritger-Peppas model)

HPMC-15 cps, 4000 cps, 15000 cps and 1 lac cps based tablets at drug to polymer ratio of 1:0.5 showed extremely poor controlled release characteristics. AH1-21-31-X (made with HPMC-15 cps) released the entire dose in just 1 h, while other viscosity grades of HPMC extended the release till 3 h with more than 71.30±1.13 % drug release in first one hour [Table 5.45; Figure 5.14]. All of the formulations in this category followed quasi-Fickian (0.2555 = n = 0.3228) release transport and showed very high K values (71.30 $h^{-0.3228}$ to 79.50 $h^{-0.2555}$) [Table 5.44].

Table 5.45: Cumulative percentage drug release from floating tablets of acyclovir to study the effect of different viscosity grade HPMC

Time (h)	Cumulative percentage released [a]			
	AH1-21-31-1X	AH2-21-31-1X	AH3-21-31-1X	AH4-21-31-1X
1	100.34±1.14	79.50±1.40	75.28±1.21	71.30±1.13
2	-	94.90±1.05	91.18±1.34	89.18±1.47
3	-	100.94±1.24	100.01±1.19	99.59±1.55

[a]: Mean and S.D. of three batches with duplicate determination per batch

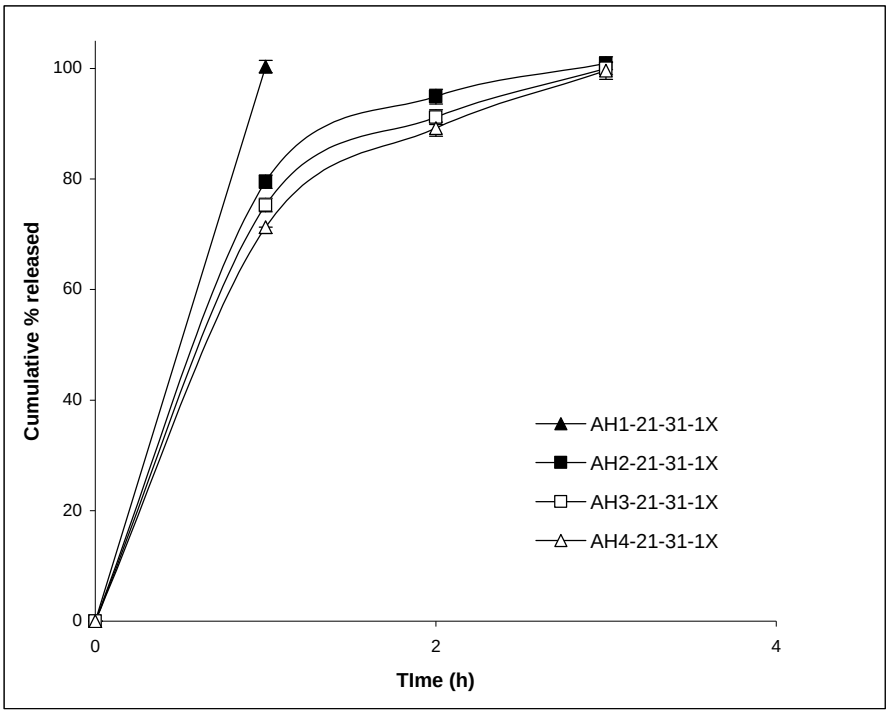

Figure 5.14: In vitro release from floating tablets of acyclovir to study the effect of different viscosity grade HPMC [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Effect of proportion of polymer: In case of sodium alginate based tablets of acyclovir with varying drug to polymer ratio (1:0.25, 1:0.5 and 1:1), the lag time to float was found to be 25-29 sec, 28-30 sec and 1 min respectively for AA-2,0.5-31-1X, AA-21-31-1X and

AA-22-31-1X. Increasing the polymer proportion (1:1) resulted in very intact core which floated for 12-13 h [AA-22-31-1X]. On the other hand at lower polymer proportion (1:0.25), very high degree of surface erosion and disintegration was observed, resulting in very low duration of floating of the core with tablet AA-2,0.5-31-1X floating for only 50 min. Duration of floating increased due to intactness of the tablet and slower disintegration in case of higher polymer proportion [Table 5.15]. Increasing the sodium alginate proportion resulted in retardation of the release of acyclovir [Table 5.46; Figure 5.15].

Table 5.46: Cumulative percentage drug release from floating tablets of acyclovir to study the effect of proportion of sodium alginate

Time (h)	Cumulative percentage released [a]		
	AA-2,0.5-31-1X	AA-21-31-1X	AA-22-31-1X
1	99.95±1.28	88.60±1.84	63.12±1.52
2	-	101.40±1.10	71.39±1.73
3	-	-	76.63±1.59
6	-	-	84.29±1.62
9	-	-	91.55±1.54
12	-	-	96.71±1.68
15	-	-	100.61±1.39

[a]: Mean and S.D. of three batches with duplicate determination per batch

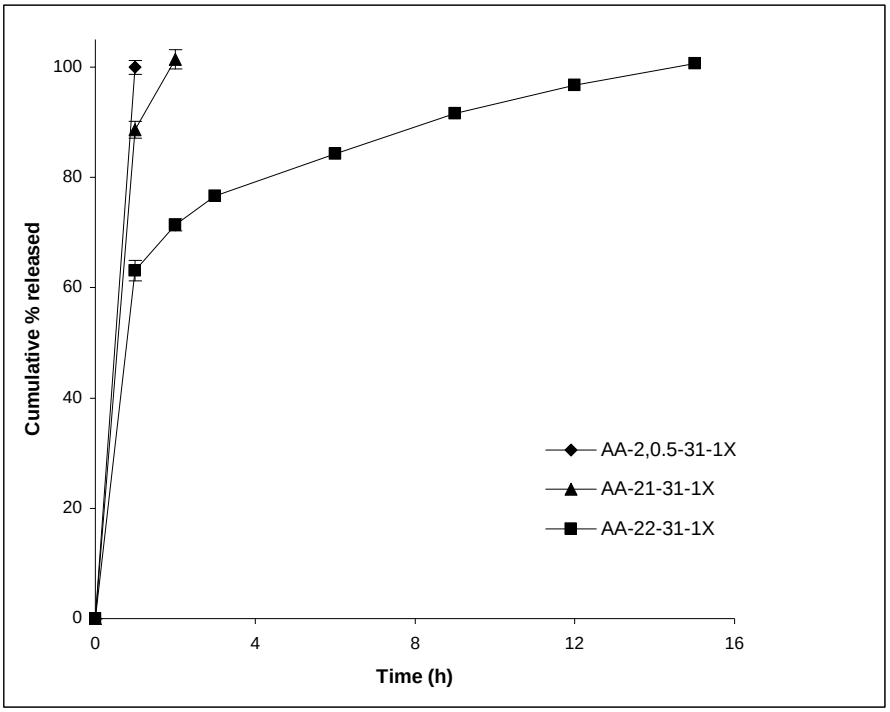

Figure 5.15: In vitro release from floating tablets of acyclovir to study the effect of proportion of sodium alginate [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Formulations AA2,0.5-31-1X and AA-21-31-1X showed very fast and complete release in 1 h and 2 h respectively. Whereas, AA22-31-1X released 63.12±1.52 % in first hour and extended the release up to 15 h. The mechanism of release transport followed in case of AA22-31-1X was quasi-Fickian (n=0.1775) with K and $t_{60\%}$ values obtained as 63.12 $h^{-0.1775}$ and 0.75 h respectively [Table 5.44].

In case of carbopol or polycarbophil based tablets, increasing the proportion of polymer did not improve floating characteristics, increase swelling or retard fragmentation [Table 5.16]. While polycarbophil based tablets did not float, the carbopol based tablets [AC-21-31-1X and AC-22-31-1X] showed a lag time to float as 45-50 min & 60 min and duration of floating as 2 h & 2.5 h respectively [Table 5.16]. In case of polycarbophil based tablets, AG-21-31-1X and AG-22-31-1X showed complete release in 3 h and 6 h with quasi-Fickian and anamolous type of release transport respectively [Table 5.47; Figure 5.16].

Table 5.47: Cumulative percentage drug release from floating tablets of acyclovir to study the effect of proportion of polycarbophil or carbopol

Time (h)	Cumulative percentage released [a]			
	AP-21-31-1X	AP22-31-1X	AC-21-31-1X	AC-22-31-1X
1	82.05±1.77	50.80±1.92	66.50±1.63	48.52±1.73
2	92.44±1.28	86.93±1.81	85.48±1.13	76.50±1.60
3	99.56±1.11	94.36±1.66	96.27±1.80	87.08±1.91
6	-	100.11±1.17	99.37±1.20	94.83±1.33
9	-		-	98.55±1.41

[a]: Mean and S.D. of three batches with duplicate determination per batch

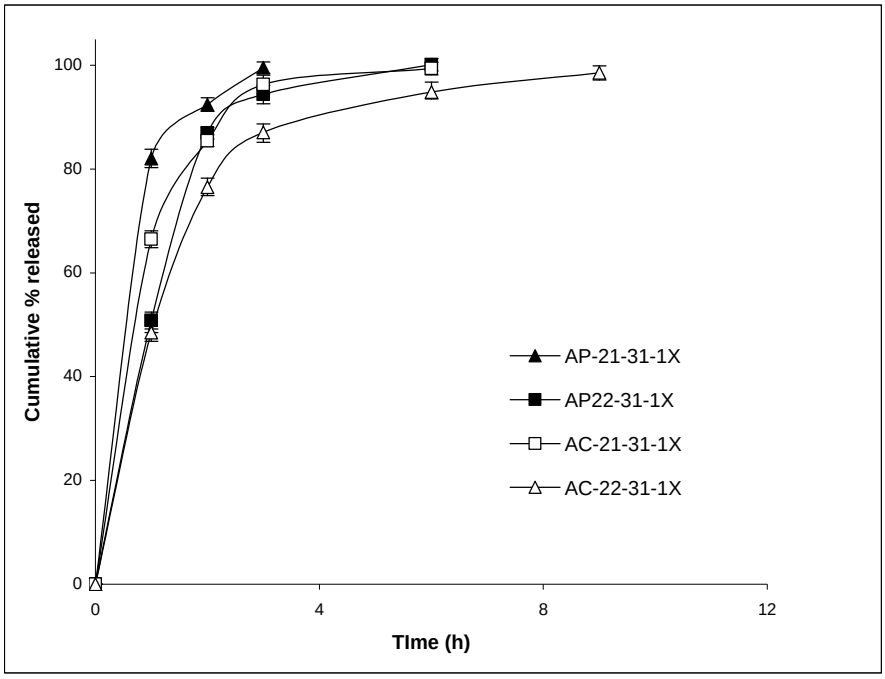

Figure 5.16: In vitro release from floating tablets of acyclovir to study the effect of proportion of polycarbophil or carbopol [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Similarly in case of carbopol based tablets, AC-21-31-1X followed quasi-Fickian (n=0.3622) transport, prolonged the release to 6 h with K and $t_{60\%}$ values of 66.50 $h^{-0.3622}$ and 0.75 h respectively. On the other hand, AC-22-31-1X (with higher polymer proportion) followed anamolous (n=0.6569) transport prolonged the release to 9 h with K and $t_{60\%}$ values of 48.52 $h^{-0.6569}$ and 1.38 h [Table 5.44].

Effect of total amount of floating agent: Lower drug to floating ratio of (1:0.5) resulted in more intact tablets, in which the core took less to float (due to lesser weight) and continued to float for longer period of time (more than 24 h in some cases) at both 1:0.5 and 1:1 drug to polymer ratios. On the other hand, higher amount of floating agents resulted in higher erosion, more fragments and faster disintegration.

In case of sodium alginate based tablets prepared at drug to polymer ratio of 1:0.5, AA-21-31-X/2 with least amount of floating agent, took only 2 sec to become afloat, floated for more than 24 h, and showed a swelling of 2 times in 12 h. On the other hand, AA-21-31-2X with highest amount of floating agent became afloat in 3 min and floated for just 45-50 min with no swelling at 12 h [Table 5.17]. Similarly at drug to sodium alginate ratio of 1:1, AA22-31- X/2 took 30 sec to float, floated for more than 24 h, and showed a swelling of 2 times in 12 h. AA22-31-2X with double the amount of floating agent took 4-5 min to float and floated for just 1.5 h without any swelling at 12 h [Table 5.17]. In case of HPMC-4000 cps and carbopol based formulations, similar results were obtained. AH2-21-31-X/2 and AH2-21-31-X floated in 23-27 sec and 2-3 min; and floated for 10-11 h and 7-8 h respectively. AC-21-31-X/2 and AC-21-31-X floated in 5-15 min and 45-50 min respectively and the duration of floating was just 2-2.5 h [Table 5.18].

Lesser amount of floating agent in the tablet matrix of acyclovir resulted in more intact tablets, lesser surface erosion and thus, lesser initial release and slower overall release. At drug (acyclovir) to sodium alginate ratios of 1:0.5 and 1:1, increasing the total amount of floating agent resulted in faster and higher initial release with more pronounced effect at lower polymer proportion (1:0.5 ratio) [Table 5.48; Figure 5.17]. At drug to polymer ratio of 1:0.5, no change in release mechanism (quasi-Fickian) was observed, but higher floating agent ratio resulted in lower n value. AA-21-31-X/2, with n= 0.2513, prolonged the release beyond 24 h with K and $t_{60\%}$ values of 37.48 $h^{-0.2513}$ and 6.50 h respectively [Table 5.44]. AA-21-31-1X and AA-21-31-2X showed very rapid release in 2 h and 1 h respectively

[Table 5.48; Figure 5.17]. Similar effects were observed for sodium alginate based tablets prepared at drug to polymer ratio of 1:1 with duration of release extended beyond 24 h (88.11±1.89 % in 24 h) in case of AA-22-31-X/2, up to 15 h in case of AA-22-31-1X and up to only 2 h in case of AA-22-31-2X [Table 5.48; Figure 5.17]. The faster rate of drug release at higher total floating agent proportion could be attributed to the burst effect mediated by the in situ CO_2 formed within the matrix.

Table 5.48: Cumulative percentage drug release from sodium alginate based floating tablets of acyclovir to study the effect of amount of floating agent

Time (h)	Cumulative percentage released [a]					
	AA-21-31-X/2	AA-21-31-1X	AA-21-31-2X	AA-22-31-X/2	AA-22-31-1X	AA-22-31-2X
1	41.66±1.77	88.60±1.84	100.41±1.40	16.10±0.98	63.12±1.52	76.80±1.50
2	45.79±1.81	101.40±1.10	-	22.39±1.06	71.39±1.73	99.49±1.43
3	48.07±0.99	-	-	29.22±1.83	76.63±1.59	-
6	57.48±1.50	-	-	47.07±1.15	84.29±1.62	-
9	66.68±1.83	-	-	60.48±1.97	91.55±1.54	-
12	74.89±1.45	-	-	70.69±1.38	96.71±1.68	-
15	81.68±1.53	-	-	78.04±1.19	100.61±1.39	-
18	87.54±1.48	-	-	83.08±1.35	-	-
24	96.25±1.14	-	-	88.11±1.89	-	-

[a]: Mean and S.D. of three batches with duplicate determination per batch

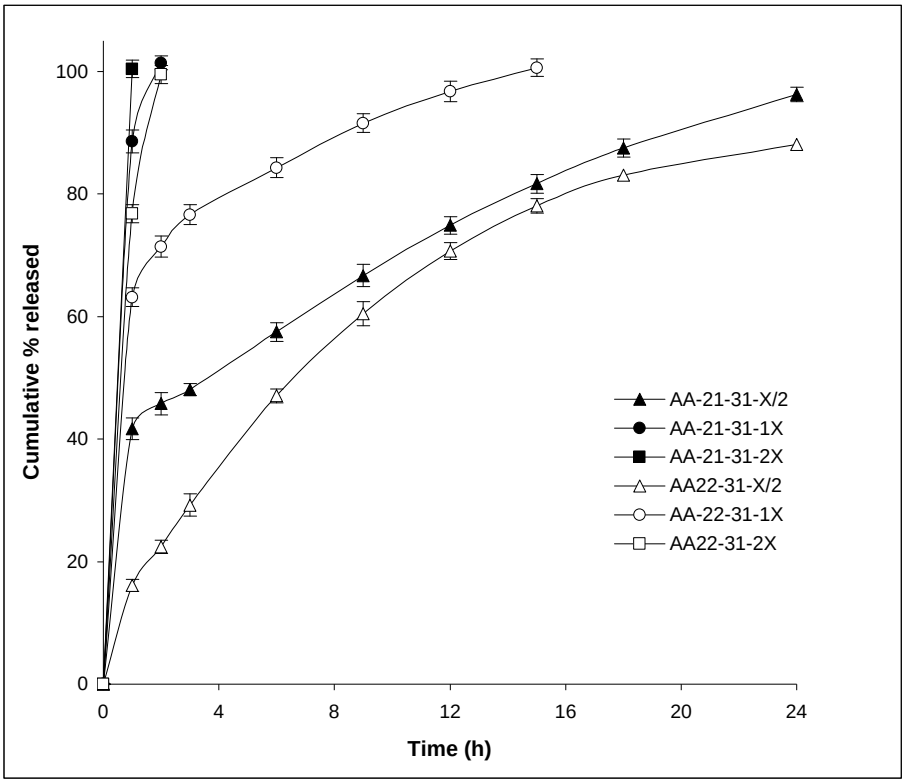

Figure 5.17: In vitro release from sodium alginate based floating tablets of acyclovir to study the effect of amount of floating agent [Data presented is mean ± SD of release studies on products of three batches in duplicate]

In case of HPMC-4000 cps based formulations, similar results were obtained with AH2-21-31-X/2 and AH2-21-31-X extending the release to 12 h and 9 h respectively [Table 5.49; Figure 5.18]. Both formulations showed quasi-Fickian type of release transport. Carbopol based formulations AC-21-31-X/2 and AC-21-31-X, extended the release to 3 h and 6 h respectively with more than 65 % drug release in the first hour and insignificant difference in release kinetics between the two. These formulations showed quasi-Fickian/ Fickian type of release transport [Table 5.44].

Table 5.49: Cumulative percentage drug release from carbopol or HPMC-4000cps based floating tablets of acyclovir to study the effect of amount of floating agent

Time	Cumulative percentage released [a]			
(h)	AC-21-31-X/2	AC-21-31-1X	AH2-21-31-X/2	AH2-21-31-1X
1	67.29±1.25	66.50±1.63	70.05±1.59	73.31±1.38
2	93.26±1.17	85.48±1.13	78.95±1.37	85.41±1.49
3	99.43±1.02	96.27±1.80	84.18±1.58	90.08±1.62
6	-	99.37±1.20	90.25±1.24	95.16±1.29
9	-	-	95.09±1.61	99.98±1.37
12	-	-	100.47±1.40	-

[a]: Mean and S.D. of three batches with duplicate determination per batch

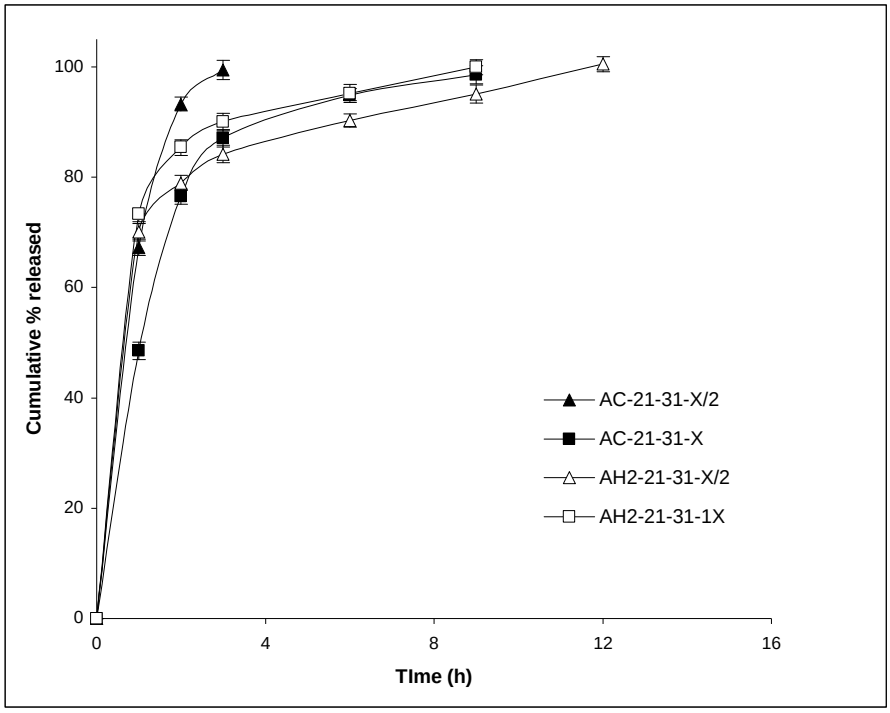

Figure 5.18: In vitro release from carbopol or HPMC-4000 cps based floating tablets of acyclovir to study the effect of amount of floating agent [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Effect of hardness: Upon increasing the hardness (from 6±0.5 kg/cm^2 to 8±0.5 kg/cm^2), the lag time to float slightly increased and at the same time, duration of floating increased drastically and tendency to fragment decreased. In case of sodium alginate based tablets prepared at drug to total floating agent ratio of 1:0.5, the lag time to float increased from 10-15 sec at lower hardness [AA-22-31-X/2-L] to 45-60 sec at higher hardness [AA-22-31-X/2-H] but at the same time both formulations were found to float for more than 24 h. Insignificant surface erosion was observed in case of AA-22-31-X/2-H (at 8±0.5 kg/cm^2 hardness) [Table 5.19]. Similarly in case of tablets prepared at drug to total floating agent ratio of 1:1, the lag time to float increased from 30 sec [AA-22-31-1X-L] to 2-3 min [AA-22-31-1X-H] with duration of floating of 13-14 h and 3-4 h respectively [Table 5.19].

Tablets with same formula, but lesser hardness resulted in faster and less controlled release of acyclovir in case of sodium alginate based tablets. At drug to total floating agent ratio of 1:0.5, AA-22-31-X/2-H and AA-22-31-X/2-L extended the release to beyond 24 h, with release of 80.15±1.39 % and 96.89±1.55 % respectively [Table 5.50; Figure 5.19]. The two formulations showed supercase II (n=1.2736) and Fickian/ anamolous (n=0.5017) release

transport respectively. AA-22-31-X/2-H showed slower release with K and $t_{60\%}$ values of 1.97 $h^{-1.2736}$ and 14.65 h respectively, while AA-22-31- X/2-L showed faster release with K and $t_{60\%}$ values of 23.39 $h^{-0.5017}$ and 3.94 h respectively [Table 5.44].

Table 5.50: Cumulative percentage drug release from sodium alginate based floating tablets of acyclovir to study the effect of hardness

Time (h)	Cumulative percentage released [a]			
	AA-22-31- X/2-H	AA-22-31- X/2-L	AA-22-31-1X-H	AA-22-31-1X-L
1	0.80±0.02	21.21±1.18	56.31±1.28	86.31±1.93
2	3.84±0.11	32.49±1.25	67.33±1.53	94.27±1.28
3	8.37±0.34	41.65±1.46	71.78±1.48	96.42±1.48
6	26.06±0.59	57.54±1.37	78.38±1.37	100.55±1.36
9	36.28±1.22	69.88±1.58	84.68±1.96	-
12	44.18±1.65	78.51±1.44	92.04±1.36	-
15	56.71±1.58	85.53±1.79	99.40±1.85	-
18	69.24±1.71	90.29±1.68	-	-
24	80.15±1.39	96.89±1.55	-	-

[a]: Mean and S.D. of three batches with duplicate determination per batch

At drug to total floating agent ratio of 1:1, AA-22-31-1X-H and AA-22-31-1X-L extended the release to 15 h and 6 h respectively with initial first hour release of 56.31±1.28 % and 86.31±1.93 % respectively [Table 5.50; Figure 5.19]. For this category of formulations, decrease in the hardness did not result in alteration of release mechanism (0.1273 = n = 0.2580; quasi-Fickian), but caused an increase in the release rate. AA-22-31-1X-H showed slower release with K and $t_{60\%}$ values of 56.31 $h^{-0.2580}$ and 1.28 h respectively, while AA-22-31-1X-L showed faster release with K and $t_{60\%}$ values of 86.31 $h^{-0.1273}$ and 0.06 h respectively [Table 5.44].

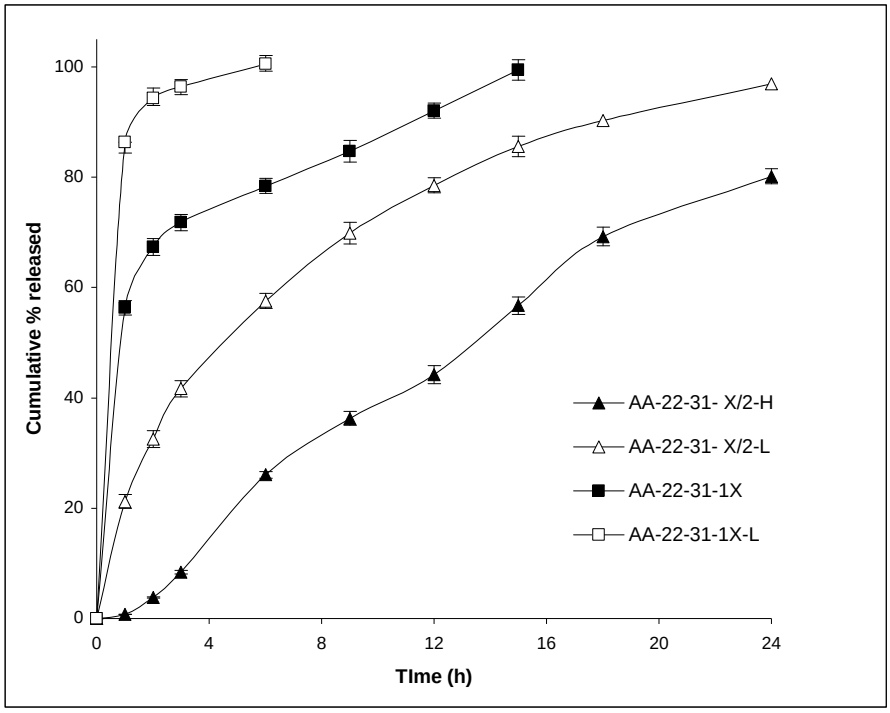

Figure 5.19: In vitro release from sodium alginate based floating tablets of acyclovir to study the effect of hardness [Data presented is mean ± SD of release studies on products of three batches in duplicate]

(b) Double polymer type tablets

Effect of polymer type: In case of double polymer type tablets of acyclovir, sodium alginate in combination with other polymer produced tablets that had shorter lag time to float with longer duration of floating and were more intact, non-disintegrating type of systems compared to formulations of corresponding single polymer. In case of sodium alginate and guar gum based tablets [AAG-21-11-31-1X], the lag time to float was found to be 1 min, which floated for just 54 min till they disintegrated completely. AAH1-21-11-31-1X and AAP-21-11-31-1X floated in 3.5-4 min and 15 min respectively and in both case the duration of floating was found to be 7-8 h. On the other hand, AAC-21-11-31-1X took 5 min to become afloat and continued to float for 12 h [Table 5.21]. When polymers like, HPMC-15 cps, carbopol and polycarbophil (which did not control acyclovir release when used alone in floating tablets) were used in combination with sodium alginate, better control and more retardation of the release [Table 5.51; Figure 5.20]. Only guar gum-sodium alginate based tablets [AAG-21-11-31-1X] released entire dose in 1 h. Tablets prepared using sodium alginate in combination with HPMC-15 cps [AAH1-21-11-31-1X] and polycarbophil [AAP-21-11-31-1X] extended the release up to 9 h, while carbopol [AAC-21-11-31-1X] extended the release up to 15 h. The release mechanism was found to

be quasi-Fickian (n=0.1666). The K and $t_{60\%}$ value in case of AAC-21-11-31-1X was obtained as 63.13 $h^{-0.1666}$ and 0.74 h respectively [Table 5.52].

Table 5.51: Cumulative percentage drug release from double polymer type sodium alginate floating tablets of acyclovir to study the effect of second polymer

Time (h)	Cumulative percentage released [a]			
	AAG-21-11-31-1X	AAH1-21-11-31-1X	AAC-21-11-31-1X	AAP-21-11-31-1X
1	101.28±1.61	74.28±1.58	63.13±1.27	73.10±1.14
2	-	80.37±1.16	70.86±1.18	79.16±1.69
3	-	86.71±1.34	77.27±1.72	83.73±1.48
6	-	95.82±1.57	87.49±1.19	94.94±1.55
9	-	100.53±1.69	93.27±1.28	100.90±1.32
12	-	-	97.65±1.53	-
15	-	-	101.57±1.11	-

[a]: Mean and S.D. of three batches with duplicate determination per batch

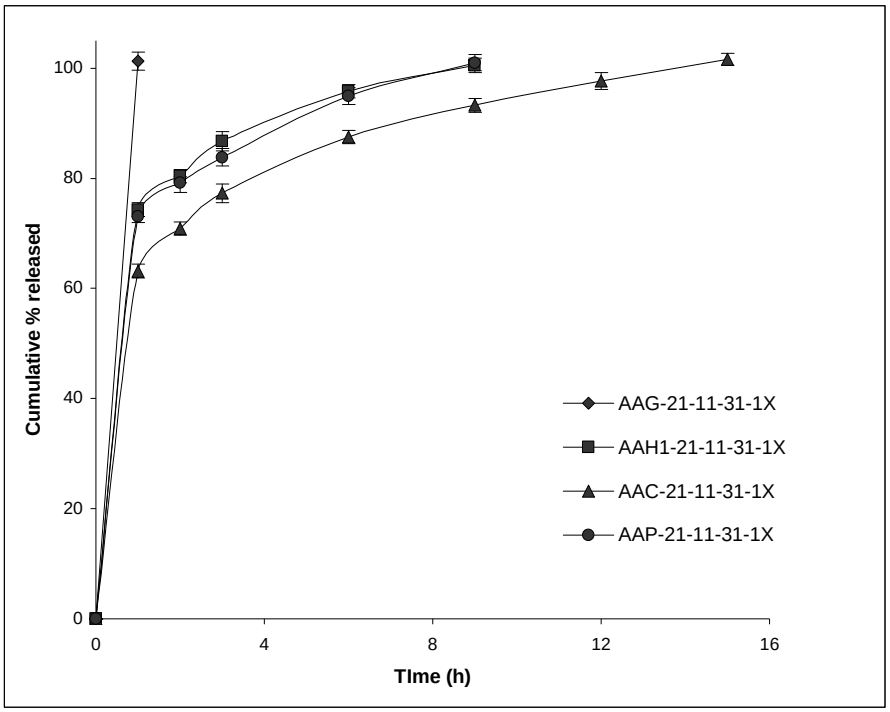

Figure 5.20: In vitro release from double polymer type sodium alginate floating tablets of acyclovir to study the effect of second polymer [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Table 5.52: In vitro release rate parameters of floating tablets of acyclovir

Formulation code	Correlation coefficient				Release rate constant [a] [K (h^{-n})]	Release exponent [b] [n]	Mechanism of release	Time for 60 % drug release [c] $t_{60\%}$ (h)
	Zero order	First order	Higuchi's model	Ritger-Peppas model				
(a) Effect of polymer type in double polymer type sodium alginate tablets								
AAH1-21-11-31-1X	0.7055	0.9546	0.8861	0.9999	70.58	0.1874	Quasi-Fickian	0.42
AAC-21-11-31-1X	0.7532	0.9764	0.8999	0.9999	63.13	0.1666	Quasi-Fickian	0.74
AAP-21-11-31-1X	0.7214	0.9499	0.8953	0.9999	73.10	0.1149	Quasi-Fickian	0.18
(b) Effect of HPMC viscosity in double polymer type sodium alginate tablets								
AAH1-21-11-31-1X	0.7055	0.9546	0.8861	0.9999	70.58	0.1874	Quasi-Fickian	0.42
AAH2-21-11-31-1X	0.6707	0.9162	0.8650	0.9999	71.24	0.1361	Quasi-Fickian	0.28
(c) Effect of different polymer combination in double polymer type tablets								
APG-21-11-31-1X	0.7035	0.9479	0.8744	0.9999	69.16	0.1774	Quasi-Fickian	0.45
ACG-21-11-31-1X	0.9316	0.9907	0.9963	0.9999	35.85	0.3960	Quasi-Fickian	3.67
ACP-21-11-31-1X	0.9499	0.9781	0.9965	0.9999	77.85	0.3491	Quasi-Fickian	0.47
APZ-21-11-31-1X	0.8767	0.9864	0.9738	0.9999	31.37	0.6923	Anamolous	2.55
(d) Effect of total polymer proportion in double polymer type tablets								
AAG-22-11-31-1X	0.8111	0.9698	0.9393	0.9999	88.15	0.1121	Quasi-Fickian	0.03
APG-21-11-31-1X	0.7035	0.9479	0.8744	0.9999	69.16	0.1774	Quasi-Fickian	0.45
APG-22-11-31-1X	0.9878	0.9179	0.9877	0.9998	12.79	0.8015	Anamolous	6.88
(e) Effect of amount of floating agent in double polymer type tablets								
AAH1-21-11-31-X/2	0.7364	0.9521	0.8233	0.9999	54.83	0.3493	Quasi-Fickian	1.29
AAH1-21-11-31-1X	0.7055	0.9546	0.8861	0.9999	70.58	0.1874	Quasi-Fickian	0.42
AAH2-21-11-31-X/2	0.7099	0.9474	0.8733	0.9999	68.53	0.1124	Quasi-Fickian	0.31
AAH2-21-11-31-1X	0.7030	0.9466	0.8806	0.9999	76.06	0.1092	Quasi-Fickian	0.18
(f) Effect of hardness in double polymer type tablets								
AAH1-21-11-31-1X-H	0.7734	0.9345	0.9137	1.0000	61.85	0.1509	Quasi-Fickian	0.82
AAH1-21-11-31-1X-L	0.9274	-	0.9890	0.9999	85.89	0.2355	Quasi-Fickian	0.22
APG-21-11-31-1X-H	0.9522	0.9858	0.9984	0.9999	30.52	0.4076	Quasi-Fickian	5.25
APG-21-11-31-1X-L	0.7102	0.9723	0.8915	1.0000	76.12	0.1238	Quasi-Fickian	0.15
(g) Effect of absence of floating agent								
AA-21	0.9087	0.9899	0.9875	0.9958	26.84	0.4565	Fickian/ Case I	5.83
AH2-21	0.9522	0.9765	0.9970	0.9985	18.02	0.5919	Anamolous	7.63
AAH1-21-11	0.8774	0.9738	0.9758	0.9999	34.93	0.6320	Anamolous	2.35
ACG-21-11	0.9728	0.9973	0.9956	0.9953	11.34	0.6452	Anamolous	13.24
APG-21-11	0.9757	0.9972	0.9954	0.9963	11.33	0.6503	Anamolous	12.98

[a]: Release rate constant (based on Ritger-Peppas model; for data fitted up to 60 % of drug released); [b]: Release exponent, indicative of the mechanism of release (based on Ritger-Peppas model); [c]: Time for 60 % ($t_{60\%}$) of the drug release (based on Ritger-Peppas model)

Effect of viscosity of polymer: In case of sodium alginate and HPMC (of varying viscosity) based double polymer tablets of acyclovir, AAH1-21-11-31-1X and AAH2-21-11-31-1X floated within 3.5-4 min & 2 min respectively and both showed very high initial surface erosion with duration of floating of 7-8 h. On the other hand, AAH3-21-11-31-X and AAH4-21-11-31-X showed a lag to float of less than 1 min, but the duration of floating was also less than 1 h in both case within which they disintegrated completely [Table 5.22].

The in vitro release profile of this category of formulations was found to show very fast release with rate of release increasing with increase in viscosity due to rapid disintegration of the matrix at higher viscosity of HPMC [Table 5.53; Figure 5.21].

Table 5.53: Cumulative percentage drug release from double polymer type sodium alginate floating tablets of acyclovir to study the effect of viscosity of HPMC as second polymer

Time (h)	Cumulative percentage released [a]			
	AAH1-21-11-31-1X	AAH2-21-11-31-1X	AAH3-21-11-31-1X	AAH4-21-11-31-1X
1	74.28±1.58	79.87±1.24	101.64±1.21	100.30±1.26
2	80.37±1.16	83.58±1.35	-	-
3	86.71±1.34	88.32±1.48	-	-
6	95.82±1.57	95.55±1.64	-	-
9	100.53±1.69	101.06±1.60	-	-

[a]: Mean and S.D. of three batches with duplicate determination per batch

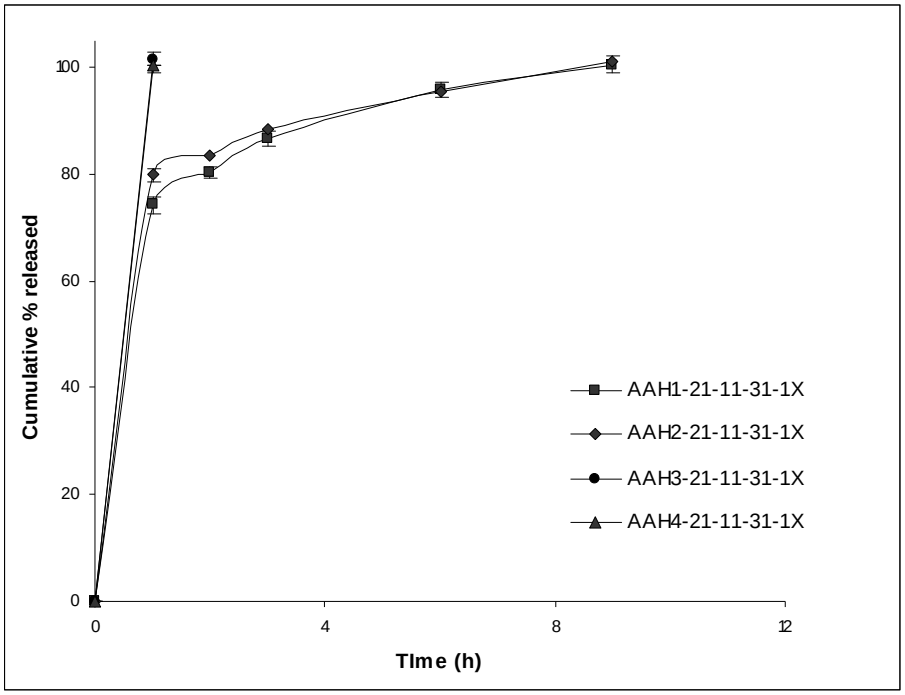

Figure 5.21: In vitro release from double polymer type sodium alginate floating tablets of acyclovir to study the effect of viscosity of HPMC as second polymer [Data presented is mean ± SD of release studies on products of three batches in duplicate]

AAH1-21-11-31-1X and AAH2-21-11-31-1X showed quasi-Fickian type of release transport, releasing more than 70 % of the dose in 1 h, and prolonged the release to 9 h, while AAH3-21-11-31-X and AAH4-21-11-31-X released the entire dose in 1 h. Tablets containing HPMC-15 cps and 4000 cps, though extended the release up to 9 h, possessed very high rate of release (~ 70.0 h^{-n}) and very low $t_{60\%}$ value [Table 5.52].

Effect of different polymer combinations: In case of double polymer type tablets of acyclovir designed without sodium alginate, varying floating characteristics and disintegration behaviour was observed [Table 5.23]. While ACP-21-11-31-1X floated within 2 min, its tablets disintegrated completely in 1.5 h. ACG-21-11-31-1X and APG-21-11-31-1X floated for 9 h with a lag time to float of 5 min and 7 min respectively. The duration of floating in case of APZ-21-11-31-1X was observed as 13-14 h, but this formulation took 9-11 min to become afloat [Table 5.23].

In this series of formulations, carbopol and polycarbophil based tablets [ACP-21-11-31-1X] followed quasi-Fickian type of release transport with complete release within 2 h. On the other hand, polycarbophil and xanthan gum based tablets [APZ-21-11-31-1X] followed anamolous type of release transport and showed maximum extension of release of 15 h with K and $t_{60\%}$ values of 31.37 $h^{-0.6923}$ and 2.55 h respectively. Formulations ACG-21-11-31-1X and APG-21-11-31-1X extended the release up to 12 h with 36.31±0.89 % and 66.51±1.55 % release in just one hour [Tables 5.52 and 5.54; Figure 5.22].

Table 5.54: Cumulative percentage drug release from double polymer type floating tablets of acyclovir to study the effect of various polymer combinations

Time (h)	Cumulative percentage released [a]			
	APG-21-11-31-1X	ACG-21-11-31-1X	ACP-21-11-31-1X	APZ-21-11-31-1X
1	66.51±1.55	36.31±0.89	77.85±1.68	36.96±1.23
2	78.21±1.39	47.37±1.13	99.16±1.34	50.70±1.38
3	84.04±1.49	55.00±1.37	-	67.13±1.46
6	89.81±1.67	73.06±1.62	-	78.02±1.52
9	94.21±1.38	88.27±1.25	-	85.97±1.51
12	99.58±1.57	100.01±1.27	-	93.88±1.38
15	-	-	-	100.27±1.37

[a]: Mean and S.D. of three batches with duplicate determination per batch

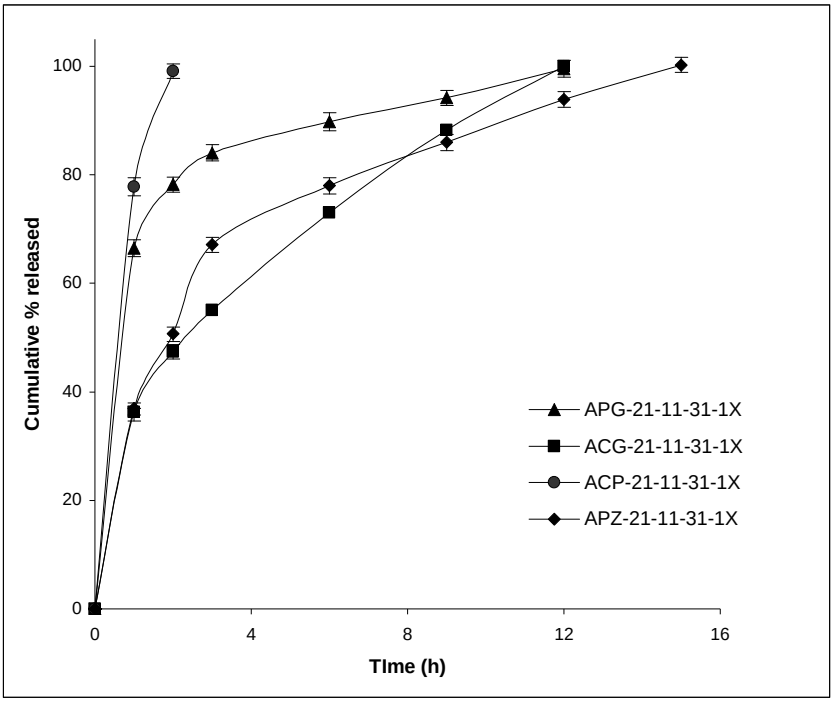

Figure 5.22: In vitro release from double polymer type floating tablets of acyclovir to study the effect of various polymer combinations [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Effect of proportion of polymer: In case of sodium alginate and guar gum based double polymer formulations, increasing the polymer proportion had a negative impact on buoyancy, but a positive effect on duration of floating and intactness of tablets. While AAG-21-11-31-1X (drug to total polymer ratio of 1:0.5) floated in just 1 min and continued to float for just 54 min (till it disintegrated completely), AAG-22-11-31-1X (drug to total polymer ratio of 1:1) floated in 2-2.5 min and continued to float for 2 h, till it disintegrated completely [Table 5.24]. Whereas in case of polycarbophil and guar gum based double polymer tablets, increasing the polymer proportion had positive impact on buoyancy, duration of floating and intactness of tablets. In this case, APG-21-11-31-1X (1:0.5 ratio) floated in 7 min and continued to float for 10-11 h (till it disintegrated completely) and APG-22-11-31-1X (1:1 ratio) floated in just 1 min and continued to float for 13-14 h, by which time the tablet had disintegrated [Table 5.24].

In case of sodium alginate and guar gum based double polymer tablets, AAG-21-11-31-1X released the entire dose in just 1 h, whereas doubling the total quantity of polymer caused extended release of 3 h [AAG-22-11-31-1X]. The release transport for this formulation was quasi-Fickian with very high K value and low $t_{60\%}$ value [Table 5.55; Figure 5.23]. In case of polycarbophil and guar gum based tablets, increase in polymer proportion prolonged the

release from 12 h [APG-21-11-31-1X] to 15 h [APG-22-11-31-1X] with drastic reduction in initial release (in first hour) from 66.51±1.55 % to 15.51±0.89 %. APG-22-11-31-1X followed anamolous (n=0.8015) type of release transport, whereas APG-21-11-31-1X followed quasi-Fickian (n=0.1774) type of release transport. APG-22-11-31-X (at drug to polymer ratio of 1:1) showed K and $t_{60\%}$ values of 12.79 $h^{-0.1774}$ and 6.88 h respectively [Table 5.52].

Table 5.55: Cumulative percentage drug release from double polymer type floating tablets of acyclovir to study the effect of total polymer proportion

Time (h)	Cumulative percentage released [a]			
	AAG-21-11-31-1X	AAG-22-11-31-1X	APG-21-11-31-1X	APG-22-11-31-1X
1	101.28±1.61	92.64±1.29	66.51±1.55	15.51±0.89
2		95.27±1.37	78.21±1.39	22.27±1.02
3		99.70±1.48	84.04±1.49	31.05±1.26
6			89.81±1.67	53.00±1.36
9			94.21±1.38	75.05±1.42
12			99.58±1.57	87.28±1.51
15				99.19±1.37
24				

[a]: Mean and S.D. of three batches with duplicate determination per batch

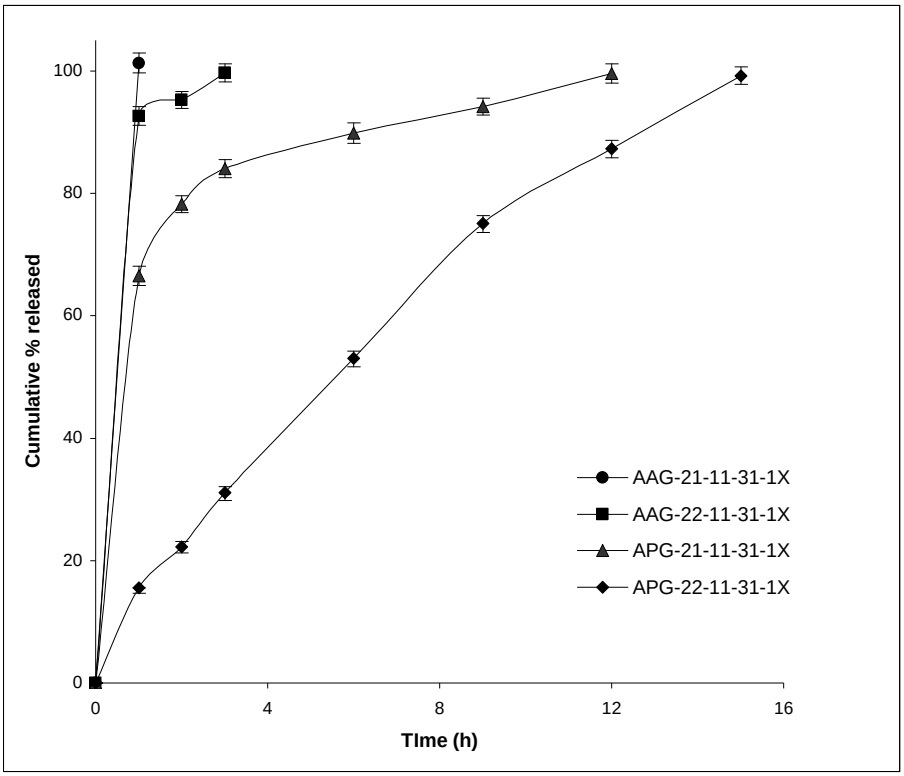

Figure 5.23: In vitro release from double polymer type floating tablets of acyclovir to study the effect of total polymer proportion [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Effect of total amount of floating agent: In case of sodium alginate and HPMC-15 cps based double polymer tablets, AAH1-21-11-31-1X showed a lag time to float of 3.5-4 min and remained afloat for 7-8 h. Upon reducing the floating agent to one-half [AAH1-21-11-31-X/2], the buoyancy was increased with a lag time to float decreasing to 60-70 sec and duration of floating increasing to 11-11.5 h [Table 5.25]. Similar effect was observed in case of sodium alginate and HPMC-4000 cps based tablets. AAH2-21-11-31-1X 2 showed a lag time to float of 2 min and remained afloat for 7-8 h, while AAH2-21-11-31-X/2 became afloat in 45-50 sec and the duration of floating was found to be 15-16 h [Table 5.25].

Decreasing the amount of floating agent was found to have a positive impact on extension of the release. In case of sodium alginate and HPMC-15 cps based tablets, release was extended from 9 h [in case of AAH1-21-11-31-1X] to 12 h [in case of AAH1-21-11-31-X/2] upon reducing the total amount of floating agent to half [Table 5.56; Figure 5.24]. Both the formulations showed quasi-Fickian type of release transport. For AAH1-21-11-31-X/2, the K and $t_{60\%}$ values were obtained as 54.83 $h^{-0.3493}$ and 1.29 h respectively [Table 5.52]. Similarly in case of sodium alginate and HPMC-4000 cps based tablets, quasi-Fickian type of release transport was observed and the duration of release was extended from 9 h [in case of AAH2-21-11-31-1X] to 18 h [in case of AAH2-21-11-31-X/2] with very high initial release of 79.87±1.24 % and 67.99±1.54 % respectively [Tables 5.52 and 5.56; Figure 5.24].

Table 5.56: Cumulative percentage drug release from double polymer type floating tablets of acyclovir to study the effect of amount of floating agent

Time (h)	Cumulative percentage released [a]			
	AAH1-21-11-31-X/2	**AAH1-21-11-31-1X**	**AAH2-21-11-31-X/2**	**AAH2-21-11-31-1X**
1	61.10±1.24	74.28±1.58	67.99±1.54	79.87±1.24
2	65.40±1.35	80.37±1.16	74.08±1.29	83.58±1.35
3	69.84±1.48	86.71±1.34	77.54±1.34	88.32±1.48
6	80.47±1.64	95.82±1.57	84.13±1.56	95.55±1.64
9	89.84±1.56	100.53±1.69	88.88±1.85	101.06±1.60
12	99.25±1.71	-	93.27±1.47	-
15	-	-	96.45±1.29	-
18	-	-	101.17±1.64	-

[a]: Mean and S.D. of three batches with duplicate determination per batch

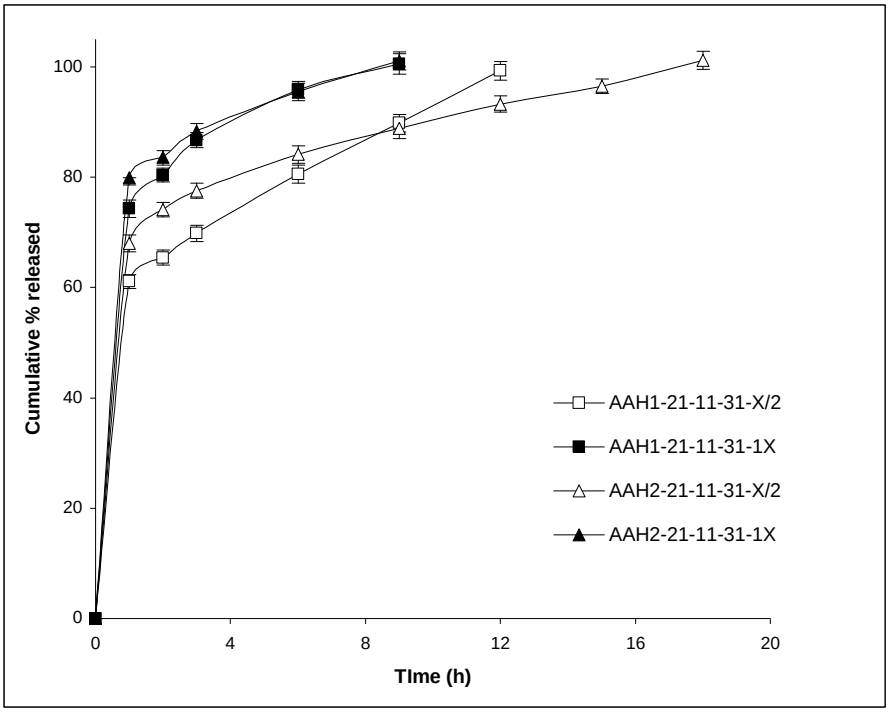

Figure 5.24: In vitro release from double polymer type floating tablets of acyclovir to study the effect of amount of floating agent [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Effect of hardness: For sodium alginate and HPMC-15 cps based double polymer tablets, decrease in hardness decreased the lag time to float and also duration of floating due to rapid disintegration of tablet at lower hardness. AAH1-21-11-31-1X-H (with hardness of 8±0.5 kg/cm^2) and AAH1-21-11-31-1X-L (with hardness of 6±0.5 kg/cm^2) showed a lag time to float of 4.5-5 min and 2-3 min respectively and remained afloat for 10-11 h and 1.5 h respectively [Table 5.26]. Similarly in case of polycarbophil and guar gum based double polymer tablets, APG-21-11-31-1X-H (hardness of 8±0.5 kg/cm^2) floated in 3 min and continued to float for 13-14 h, while APG-21-11-31-1X-L (hardness of 6±0.5 kg/cm^2) floated in 2 min and remained afloat for 7-8 h [Table 5.25].

Lower hardness resulted in faster and less controlled release of acyclovir in both the categories of formulations manufactured. In cases of sodium alginate and HPMC-15 cps based tablets, extension of release was decreased from 12 h [AAH1-21-11-31-1X-H] to 2 h [AAH1-21-11-31-1X-L] [Table 5.57; Figure 5.25]. Both the formulations followed quasi-Fickian type of release transport and lower K value and higher $t_{60\%}$ value were obtained for AAH1-21-11-31-1X-H [Table 5.52]. Similarly, in case of polycarbophil and guar gum based tablets, APG-21-11-31-1X-H and APG-21-11-31-1X-L extended the release to 15 h and 9 h respectively [Table 5.57; Figure 5.25]. Both the formulations

followed quasi-Fickian (0.1238 = n = 0.4076) type of release transport. Upon increasing the hardness, value of n increased while release rate constant K decreased with corresponding increase in $t_{60\%}$ value [Table 5.52].

Table 5.57: Cumulative percentage drug release from double polymer type floating tablets of acyclovir to study the effect of hardness

Time (h)	Cumulative percentage released [a]			
	AAH1-21-11-31-1X-H	AAH1-21-11-31-1X-L	APG-21-11-31-1X-H	APG-21-11-31-1X-L
1	64.59±1.48	85.89±1.28	31.58±1.34	67.34±1.53
2	68.67±1.38	101.12±1.47	40.54±1.82	82.94±1.21
3	73.00±1.54	-	47.65±1.34	87.20±1.58
6	82.32±1.49	-	63.41±1.81	93.52±1.71
9	91.64±1.37	-	78.79±1.73	99.12±1.59
12	100.72±1.44	-	91.35±1.61	-
15	-	-	101.31±1.24	-
18	-	-	-	-
24	-	-	-	-

[a]: Mean and S.D. of three batches with duplicate determination per batch

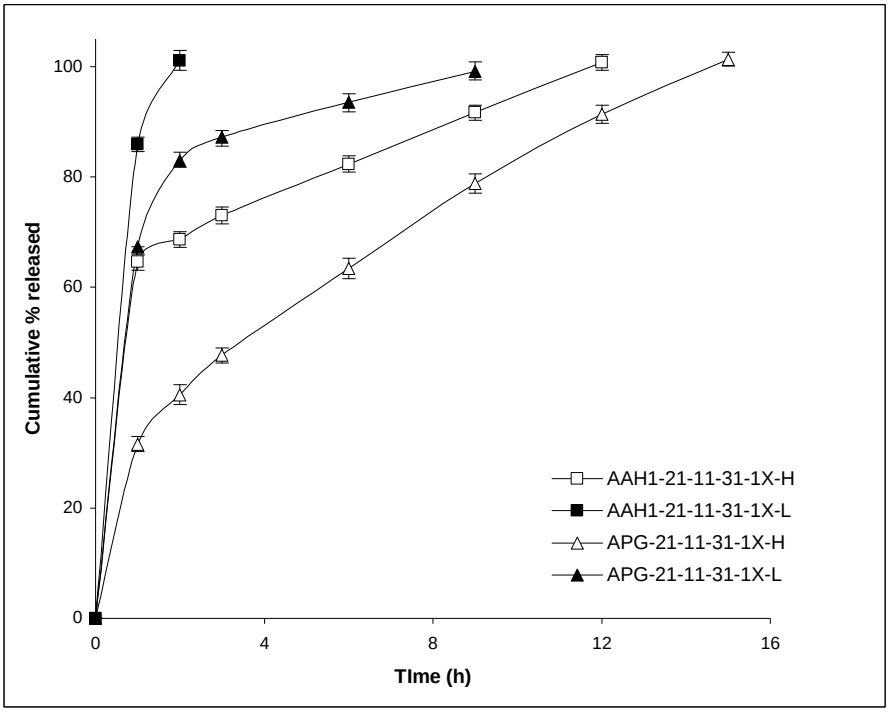

Figure 5.25: In vitro release from double polymer type floating tablets of acyclovir to study the effect of hardness [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Effect of absence of floating agent: Both single polymer based tablets of acyclovir [AA-21 and AH2-21] were non-floatable, with insignificant/ low surface erosion. However, they

showed faster disintegration than that shown by similar formulations of celecoxib, which can be directly attributed to the higher solubility of acyclovir in the dissolution media [Table 5.20]. These formulations released the drug slowly in a more prolonged manner when compared to similar formula with floating agent. AA-21 and AH2-21 extended the release beyond 24 h with cumulative release of 96.30±1.02 % and 97.90±1.01 % respectively in 24 h [Table 5.58; Figure 5.26]. AA-21 showed highest r value for first order release, while for AH2-21 highest r value was obtained for Higuchi's release model. The n, K and $t_{60\%}$ values were obtained as 0.4565, 26.84 $h^{-0.4565}$ and 5.83 h respectively for AA-21 and 0.5919, 18.02 $h^{-0.5919}$ and 7.63 h respectively for AH2-21 [Table 5.52].

Table 5.58: Cumulative percentage drug release from tablets of acyclovir prepared using different polymers without floating agent

Time (h)	Cumulative percentage released [a]				
	AA-21	AH2-21	AAH1-21-11	ACG-21-11	APG-21-11
1	27.96±0.97	19.50±0.89	34.07±1.63	12.33±0.88	12.53±0.91
2	36.22±1.04	26.57±1.34	54.13±1.97	17.75±1.51	17.90±1.10
3	45.52±1.37	35.53±1.01	69.94±1.13	22.02±1.12	22.10±1.02
6	60.22±1.29	52.33±1.83	87.03±1.09	38.65±1.18	38.91±1.45
9	73.27±1.36	65.42±1.36	94.41±1.81	48.57±1.01	48.03±1.23
12	78.90±1.91	73.41±1.25	99.60±1.47	52.83±1.40	56.14±1.72
15	82.30±1.13	80.59±1.30	-	65.01±1.64	66.28±1.88
18	88.78±1.24	92.97±1.85	-	71.64±1.52	73.38±1.61
24	96.30±1.02	97.90±1.01	-	81.00±1.12	83.03±1.27

[a]: Mean and S.D. of three batches with duplicate determination per batch

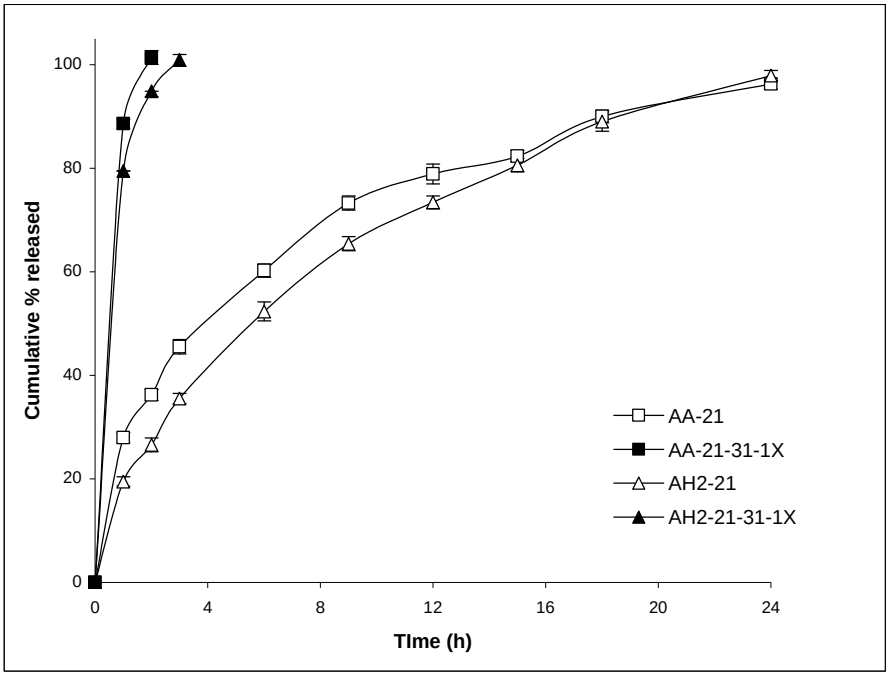

Figure 5.26: In vitro release from single polymer based tablets of acyclovir prepared without floating agent in comparison to similar formula with floating agent [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Double polymer type tablets without floating agent were also found to be non-floatable, with relatively low/ insignificant surface erosion. AAH1-21-11 disintegrated completely in 11 h, while the rest of the tablets were available as small left over lump at the end of 24 h. Except for APG-21-11, which showed swelling of 2 times at 12 h, rest of the formulations showed no swelling [Table 5.27]. ACG-21-11 and APG-21-11 released only 81.00±1.12 % and 83.03±1.27 % respectively in 24 h, while AAH1-21-11 released the entire dose in 12 h [Table 5.58; Figure 5.27]. ACG-21-11 and APG-21-11 showed highest r value for first order release, while AAH1-21-11 obtained highest r value for Higuchi's release model. All the formulations showed anamolous (0.6320 = n = 0.6503) type of release transport. Most extended release was obtained in case of ACG-21-11 with K and $t_{60\%}$ values of 11.34 $h^{-0.6452}$ and 13.24 h respectively. Fastest release was observed in case of AAH1-21-11 with K and $t_{60\%}$ values of 34.93 $h^{-0.6320}$ and 2.35 h respectively [Table 5.52].

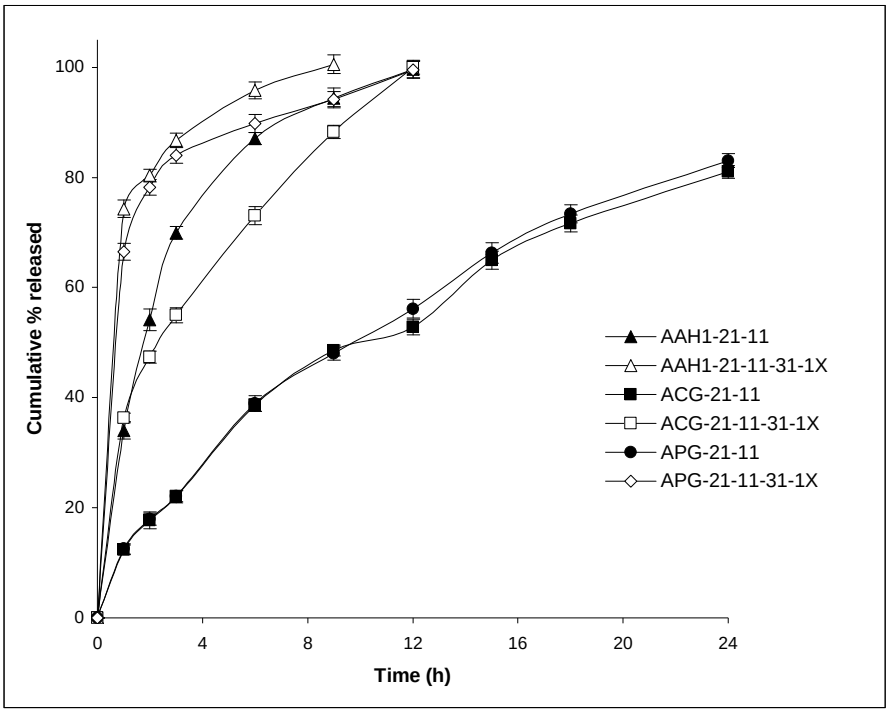

Figure 5.27: In vitro release from double polymer type tablets of acyclovir prepared without floating agent in comparison to similar formula with floating agent [Data presented is mean ± SD of release studies on products of three batches in duplicate]

5.3.4. Formulation optimization

Based on various studies presented in preceding sections, it can be agreed on that an ideal floating gastroretentive CR tablet of a drug should start floating immediately on coming in contact with GI fluid with controlled release of the drug for 12-15 h and continue to float throughout the duration of the release. To obtain formulation with above mentioned characteristics, it is essential to optimize the polymer type and proportion in the matrix. The polymer should be able to form gel barrier briskly in the acidic media to ensure entrapment of CO_2 generated by the gas generating agent. The gel barrier should facilitate penetration of dissolution fluid and at the same time, control the release of the drug from the matrix core. An optimum hardness of such a tablet would permit formulation to be intact and non-disintegrating and at the same time, allow sufficient porosity for imbibing dissolution media at fast rate to ensure minimum possible lag time. Floating agent composition and amount should be able to balance between buoyancy and fragmentation due to burst effect.

In this study in case of celecoxib tablets, 1:0.5 drug to floating agent ratio ensured good buoyancy & floating behaviour and prolonged release in polymeric matrix capable of forming efficient gel barrier. Celecoxib being poorly soluble in acidic media, required lower polymer proportion (drug to polymer ratio of 1:0.5) and a combination (1:1) of lyophilic polymer (guar gum) with lyophobic polymer (sodium alginate) to ensure complete release within 12-15 h in acidic media. Combining all the attributes, the most appropriately designed formulation of celecoxib was CAG-21-11-31-X/2-M (with hardness of 6 ± 0.5 kg/cm^2). This formulation floated in just 2-3 min, extended the drug release up to 12 h and continued to float till the end of the release. Since the initial release in first hour was approximately 30 %, loading dose in the formulation can be avoided [Table 5.40; Figure 5.12]. The release kinetics was found to be Higuchi's square root kinetics with anamolous type of release transport [Table 5.37].

When acyclovir having good solubility in acidic media was the candidate drug, polymer proportion also had to be increased (drug to polymer ratio of 1:1) to ensure adequate retardation of drug release. In addition higher proportion of lyophobic polymer in the polymer mix (sodium alginate to guar gum or polycarbophil ratio of 3:1) was desired. Keeping this in view, sodium alginate and guar gum based tablets and sodium alginate and polycarbophil based tablets with half the amount of floating agent and hardness in the range 7-8 kg/cm^2 were manufactured. The compositions and characteristics of above formulations are presented in Table 5.59. The formulations AAG-22-31-31-X/2 and AAP-22-31-31-X/2 floated in just 10-20 sec and 1 min respectively and remained afloat till the end of release [Table 5.59]. AAG-22-31-31-X/2 and AAP-22-31-31-X/2 prolonged the release to 15 h and

18 h respectively [Table 5.60; Figure 5.28] and followed a near-zero order release with supercase II type of release transport [Table 5.61]. In case of AAG-22-31-31-X/2 the K and $t_{60\%}$ values were obtained as 3.39 $h^{-1.2823}$ and 9.41 h respectively. For AAP-22-31-31-X/2 the K and $t_{60\%}$ values were 3.46 $h^{-1.3517}$ and 8.25 h respectively [Table 5.61].

Table 5.59: Composition and characteristics of tablets of acyclovir with optimized floating and release characteristics

Formulation Code	AAG-22-31-31-X/2	AAP-22-31-31-X/2
Composition (mg/tab)		
Acyclovir	200	200
Sodium alginate	150	150
Guar gum	50	-
Polycarbophil	-	50
Sodium bicarbonate	75	75
Anhydrous citric acid	25	25
Weight (mg/tab)*	505	505
Hardness (kg/cm^2)	7±0.5	8±0.5
Floating Behaviour		
Buoyancy (Lag time to float)	10-20 sec	1 min
Portion floating and duration of floating	Core (13-14 h)	Core (16-17 h)
Swelling (after 12 h)	2.5 times	1.5 times
Disintegration/ Erosion	Low	Low

* Includes 1 % w/w of manufacturing additives

Table 5.60: Cumulative percentage drug release from floating tablets of acyclovir with optimized floating and release characteristics

Time (h)	Cumulative percentage released [a]	
	AAG-22-31-31-X/2	AAP-22-31-31-X/2
1	2.53±1.34	01.81±0.26
2	7.33±1.29	08.16±0.58
3	15.29±1.41	16.66±1.01
6	37.24±1.38	41.52±1.47
9	56.97±1.47	63.00±1.58
12	74.98±1.53	78.527±1.64
15	100.96±1.37	91.96±1.37
18	-	100.94±1.25

[a]: Mean and S.D. of three batches with duplicate determination per batch

Table 5.61: In vitro release rate parameters of floating tablets of acyclovir with optimized floating and release characteristics

Formulation code	Correlation coefficient				Release rate constant [a] [K (h^{-n})]	Release exponent [b] [n]	Mechanism of release	Time for 60 % drug release [c] $t_{60\%}$ (h)
	Zero order	First order	Higuchi's model	Ritger-Peppas model				
AAG-22-31-31-X/2	0.9981	0.9840	0.9460	0.9944	3.39	1.2823	Supercase II	9.41
AAP-22-31-31-X/2	0.9908	0.9739	0.9699	0.9956	3.46	1.3517	Supercase II	8.25

[a]: Release rate constant (based on Ritger-Peppas model; for data fitted up to 60 % of drug released); [b]: Release exponent, indicative of the mechanism of release (based on Ritger-Peppas model); [c]: Time for 60 % ($t_{60\%}$) of the drug release (based on Ritger-Peppas model)

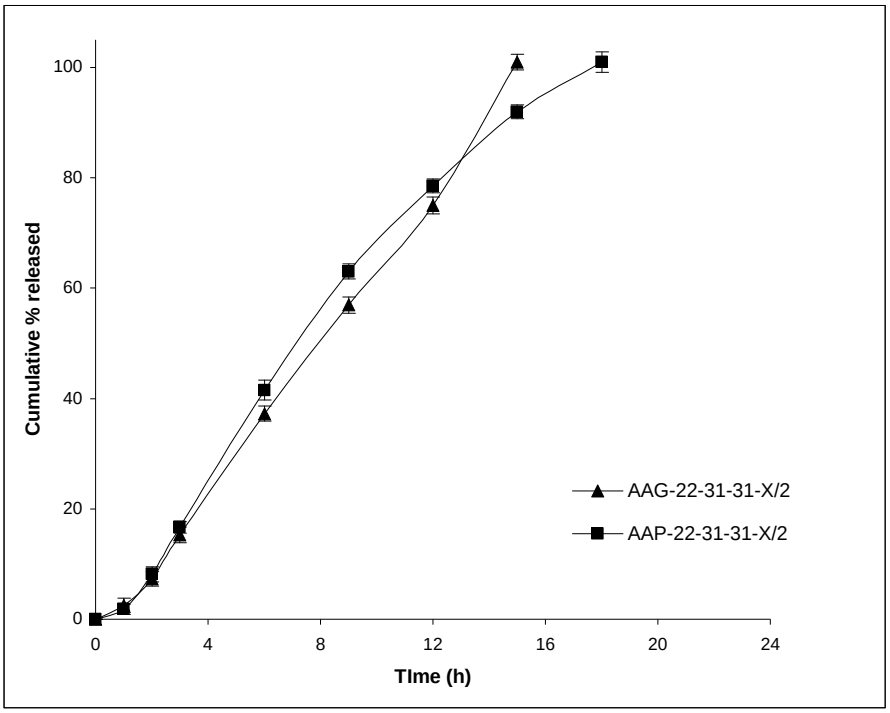

Figure 5.28: In vitro release from floating tablets of acyclovir with optimized floating and release characteristics [Data presented is mean ± SD of release studies on products of three batches in duplicate]

5.3.5. Batch reproducibility

Batch to batch variation and reproducibility of the manufacturing process was studied based on evaluation of the physical properties and release characteristics of drug from three batches of each formulation. Low values of weight variation, friability, low standard deviation of drug content determination and reproducibility of floating behaviour indicated absence of significant batch-to-batch variation. Low value of standard deviation of the cumulative release data at different time points obtained from replicate release studies of samples from different batches further indicated no significant batch to batch variation. The manufacturing was required to be carried out at lower relative humidity conditions to avoid premature reaction between base and acid in the matrix.

5.3.6. Stability studies

Real time stability studies revealed that there was no significant difference in the physical attributes, drug content, in vitro release profile and floating characteristics of the designed formulations upon proper storage till a span of 12 months for both the drugs. But these tablets were very sensitive to the type of packing done. Improperly packed (without a

trilayered system) formulations did not show much difference in the drug content but showed deviation in other physical attributes like, discolouration of tablets, change in hardness, buoyancy as well as in vitro release characteristics. Properly packed formulations retained all their characters beyond 12 months.

5.4. Conclusions

Designed formulations of celecoxib and acyclovir were found to possess good appearance, uniform drug content, very low weight variation, low friability and optimal hardness. Some of the selected formulations of both the drugs were found to possess good mucoadhesive property as well. In general, acyclovir tablets, though, took lower lag time to float but showed faster release as compared to celecoxib tablets. Tablets containing combination of base and acid took lesser time to float than those containing only base. Lower amount of floating agent resulted in more intact tablets with slower and more prolonged duration of floating as well as release. Tablets with same formula, but lesser hardness took less time to float, but showed higher initial surface erosion/ fragmentation and lesser controlled release behaviour.

In case of both celecoxib and acyclovir, sodium alginate, alone gave very buoyant tablets with very low lag time to float and longer floating durations. These systems showed initial fast release, followed by a very slow release. Lower amount of polymer and very hard formulations of carbopol gave very controlled and prolonged release, but poor floating ability. Guar gum, polycarbophil and HPMC based matrix formulations were found to have poor controlled release characteristics. In case of double polymer type systems, including sodium alginate along with these polymers, otherwise showing poor control on release, helped in enhancing floating ability as well as retarding the release. Some formulations of polycarbophil and guar gum (double polymer) also floated very well and showed prolonged release. Double polymer system with lower amount of floating agent also showed good floating behaviour and more controlled drug release. Formulations without floating agents were non-floatable and released the drug in more prolonged and controlled manner. A variety of release mechanisms were observed for these tablet formulations of both the drugs, with acyclovir showing quasi-Fickian type of release transport in most of the cases.

No significant difference was observed in the physical properties, floating behaviour and release profile of different batches of the developed formulations, thus suggesting this technique to be an acceptable method for manufacturing good quality, reproducible, floating controlled release tablets of both celecoxib and acyclovir. Initial burst effect was seen for

many formulations, suggesting no need of adding loading dose to these products. However, it was observed that failure to maintain hardness and low humidity condition during manufacturing could alter the floating and release behaviour of the designed systems. These tablets were very sensitive to packaging and moisture, but upon proper storage, all the designed formulations were found to be stable even after 12 months.

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