CHAPTER 6

MULTIPLE UNIT GASTRORETENTIVE CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

6.1. Introduction

Most gastroretentive systems are single unit devices that show variable bioavailability and therapeutic efficacy due to the inherent problem of disintegration of the device in the stomach earlier or later than expected or decrease in gastroretention time due to their sudden emptying into the intestine. Multiple unit systems can be designed to overcome such problems of single unit systems, show a more predictable release profile and insignificant impairing of performance. In addition, multiple unit formulations allow co-administration of units with different release profiles or different drugs, or units containing incompatible substances [Singh and Kim, 2000]. They show less inter and intra subject variability as well as a decreased risk of dose dumping [Whitehead et al., 1998]. The subunits of the multiple particulate dosage spread into the GIT and distribute uniformly within the gastric content as soon as the outer hard gelatin capsule shell dissolutes, hence drug release occurs over a large area avoiding high local drug concentrations [Whitehead et al., 1998; Singh and Kim, 2000].

Floating multiple unit systems may be in the form of microspheres (i.e. matrix based systems) or microcapsules, prepared using natural, semi-synthetic or synthetic polymers. Employing natural or semi-synthetic polymers eliminates the drawback of high toxicity associated with most of the synthetic polymers [Kakoulides et al., 1998; Al-Musa et al., 1999]. Alginate can play a significant role in the design of these floating multiple unit controlled release dosage forms. Alginates easily gel at low pH and also in the presence of a divalent cation. Alginate gelation takes place when divalent cations (usually Ca^{2+}), interact ionically with blocks of guluronic acid residues, resulting in formation of three-dimensional network which is usually described as ‘egg-box’ structure [Grant et al., 1973]. The ability of alginate to form two types of gel dependent on pH, i.e., an acid gel and an ionotropic gel, gives the polymer unique properties, unmatched with other neutral macromolecules [Efentakis and Koutlis, 2001;

Tønnesen and Karlsen; 2002]. Both of these properties of alginate have been exploited in the present work to obtain different types of multiple unit controlled release products.

In this chapter, work on design and evaluation of different types of multiple unit floating controlled release formulations, namely microcapsules and calcium alginate beads, of celecoxib and acyclovir have been presented. Polymers employed for microcapsule based formulations, include sodium alginate (as the gel forming matrix of the core) and polyvinyl pyrrolidone (PVP) K-30 as the granulating agent; and ethyl cellulose (EC)-10 cps, PVP K-90, and polyethylene glycol (PEG)-6000 in different combinations as the coating material. Calcium alginate beads of both the drugs were prepared through ionic cross-linking. Designed formulations were evaluated for physical properties, drug content, floating behaviour and in vitro drug release. For microcapsule based formulations, effects of proportion of floating agent in the core, ratio of base to acid in the core, ratio of hydrophobic to hydrophilic polymer in the coating solution and core to coat ratio on floating behaviour and in vitro drug release kinetics were investigated. For bead based formulations, effect of various process and formulation parameters were studied. The effect of drug property on the release kinetics and floating behaviour was also seen for both categories of formulations. Batch reproducibility, stability on storage and the effect of packaging on the performance of these multiple unit formulations were also investigated.

6.2. Experimental section

6.2.1. Materials

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

6.2.2. Equipments

Formulations were prepared using thermostatic magnetic stirrers (MAC, New Delhi; REMI, Mumbai; Tempo Industrial Co., Mumbai). For drying the final products, Vacuum rotary evaporator (Buchitype), Atlantis, New Delhi and MAXI-Dry Lyo, Heto Lab Equipment, Denmark were employed. In vitro release studies were carried out in USP dissolution apparatus (USP XXIII) type 2 (Electrolab, Mumbai). UV-visible-NIR spectrophotometer (*Jasco*, Tokyo, Japan, model V-570) was used for all the analysis. Water bath shaker (MAC, New Delhi) was employed for floating studies as mentioned in the previous chapter.

6.2.3. Analytical method

UV-visible spectrophotometric method as described in Chapter 3 was employed for the analysis of celecoxib and acyclovir.

6.2.4. Preparation of floating multiple unit systems

Microencapsulation and ionic cross-linking technique was employed for preparing microcapsules and calcium alginate beads respectively of celecoxib and acyclovir.

6.2.4.1. Microencapsulated systems

The method for preparing microencapsulated product of both the drugs is shown in Figure 6.1. For the preparation of microencapsulated products, each ingredient was dried at 55 °C in tray dryer and passed through sieve # 200. Required amount of sieved drug, sodium alginate (gel forming polymer), sodium bicarbonate and citric acid (gas generating agents) were mixed. The mixture was granulated with 3.0 % w/v of PVP K-30 solution prepared in isopropyl alcohol (IPA) by passing the wet mass through sieve # 80. Wet granules were dried at 55 °C in tray dryer. Dried core granules/ microspheres, passed through sieve # 80 and retained on sieve # 100, were used for microencapsulation [Figure 6.1].

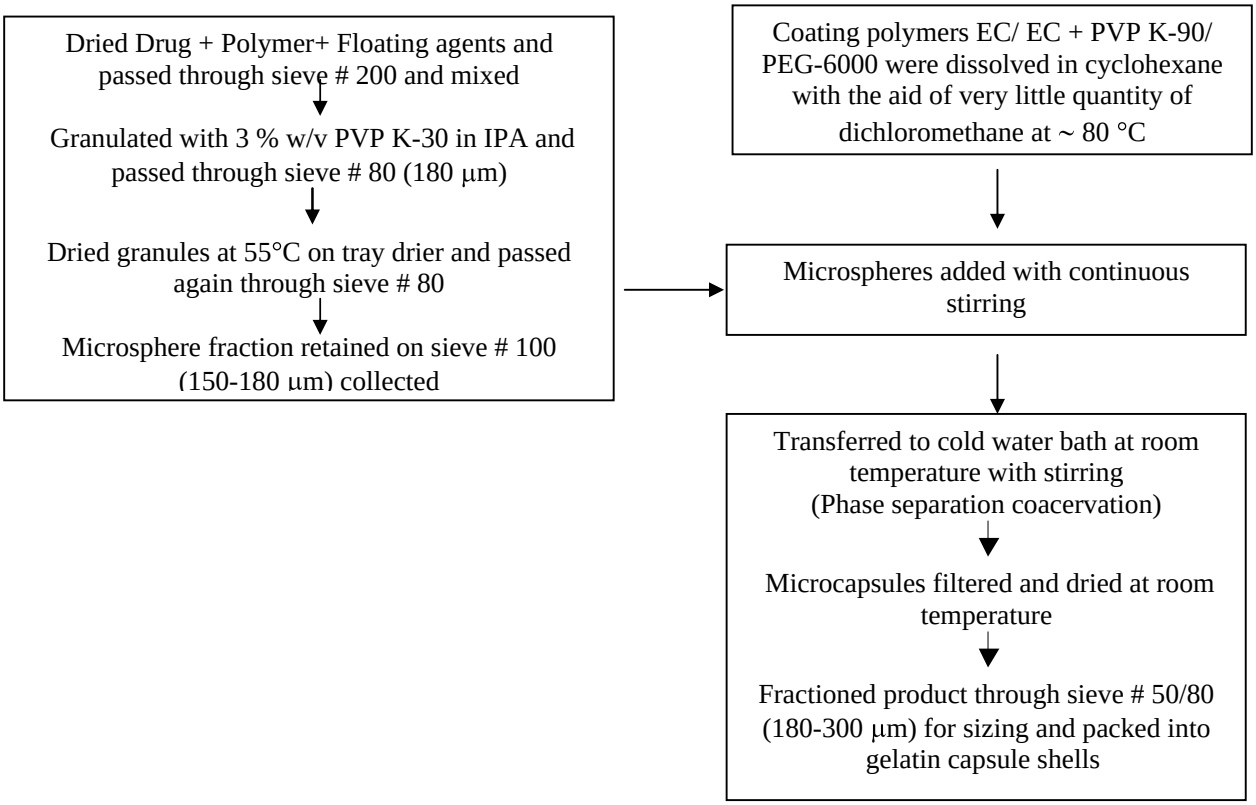

Figure 6.1: Flow chart for preparing microcapsule based formulations of celecoxib and acyclovir

Required amounts of the granules and the coating polymer(s) (EC-10 cps either alone or in combination with PVP K-90 or PEG-6000) were weighed. Coating polymers were dissolved in cyclohexane with the help of little quantity of dichloro methane with continuous stirring at 80 °C in glass a beaker with a teflon bead mounted on a thermostatic magnetic stirrer to make a 2.0 % w/w polymeric solution. Dichloro methane (1part per 100 parts by weight of cyclohexane) was used to remove the turbidity of the polymeric solution. To this polymeric solution, core granules/ microspheres prepared earlier were added with continuous stirring. The stirring was continued for 30 seconds at 80 °C and then immediately transferred under stirring to an ice-cold water bath mounted on separate magnetic stirrer resulting in phase separation coacervation and encapsulation of the core. Stirring was continued for 6-7 minutes until the microencapsulated product temperature fell below 10 °C. Supernatant was decanted and microcapsules were filtered and air dried at room temperature. The dried microcapsules were fractioned between sieve # 50/ 80 to obtain final product in the size range of 180-300 μm. Aliquot of the sized products were filled into gelatin capsule shells and stored. Compositions of uncoated granules of celecoxib and acyclovir are shown in Table 6.1. Compositions of various microencapsulated products of celecoxib and acyclovir coated with EC alone or in combination with PVP K-90 or PEG-6000 are presented in Tables 6.2 and 6.3 respectively.

Table 6.1: Composition of sodium alginate uncoated granules used as core for preparing microencapsulated products of celecoxib and acyclovir

Core code	**Core composition (in g)**					**Drug content*** (mg/100mg of formulation)
	Drug (Celecoxib/ Acyclovir)	Sodium alginate	Sodium bicarbonate	Anhydrous citric acid	Granulating agent (3 % w/v PVP K-30 in IPA)	
(a) Celecoxib microspheres						
Cele(21-0.5)	2.0	2.0	0.67	0.33	q.s.	38.45±0.34
Cele(31)	2.0	2.0	1.5	0.5	q.s.	31.58±0.20
(b) Acyclovir microspheres						
Acyclo(21-0.5)	2.0	2.0	0.67	0.33	q.s.	38.57±0.29
Acyclo(31-0.5)	2.0	2.0	0.75	0.25	q.s.	38.71±0.19
Acyclo(31)	2.0	2.0	1.5	0.5	q.s.	31.89±0.21

PVP- Polyvinyl pyrrolidone; IPA- Isopropyl alcohol; q.s.- Quantity sufficient

* Mean ± Standard deviation

Table 6.2: Composition of microencapsulated products of celecoxib

Formulation Code	Core to coat ratio	Core		Coat composition			Relative ratio [EC:PVP or EC:PEG in the coat]
		Code	Amount (g)	EC	PVP	PEG	
(a) Coated with EC alone							
Cele(21-0.5)-EC-61	6:1	Cele(21-0.5)	2.0	0.33	-	-	-
Cele(21-0.5)-EC-41	4:1	Cele(21-0.5)	2.0	0.50	-	-	-
Cele(31)-EC-41	4:1	Cele(31)	2.0	0.50	-	-	-
(b) Coated with EC & PVP							
Cele(21-0.5)-EC-PVP(1:3)21	2:1	Cele(21-0.5)	2.0	0.25	0.75	-	1:3
Cele(21-0.5)-EC-PVP(1:2)21	2:1	Cele(21-0.5)	2.0	0.33	0.66	-	1:2
Cele(21-0.5)-EC-PVP(1:1)21	2:1	Cele(21-0.5)	2.0	0.50	0.50	-	1:1
Cele(21-0.5)-EC-PVP(1:0.5)21	2:1	Cele(21-0.5)	2.0	0.66	0.33	-	1:0.5
Cele(21-0.5)-EC-PVP(1:3)31	3:1	Cele(21-0.5)	2.0	0.17	0.51	-	1:3
Cele(21-0.5)-EC-PVP(1:2)31	3:1	Cele(21-0.5)	2.0	0.22	0.44	-	1:2
Cele(21-0.5)-EC-PVP(1:1)31	3:1	Cele(21-0.5)	2.0	0.33	0.33	-	1:1
Cele(21-0.5)-EC-PVP(1:0.5)31	3:1	Cele(21-0.5)	2.0	0.44	0.22	-	1:0.5
Cele(31)-EC-PVP(1:3)21	2:1	Cele(31)	2.0	0.25	0.75	-	1:3
Cele(31)-EC-PVP(1:2)21	2:1	Cele(31)	2.0	0.33	0.66	-	1:2
Cele(31)-EC-PVP(1:1)21	2:1	Cele(31)	2.0	0.50	0.50	-	1:1
Cele(31)-EC-PVP(1:0.5)21	2:1	Cele(31)	2.0	0.66	0.33	-	1:0.5
(c) Coated with EC & PEG							
Cele(21-0.5)-EC-PEG(1:3)21	2:1	Cele(21-0.5)	2.0	0.25	-	0.75	1:3
Cele(21-0.5)-EC-PEG(1:2)21	2:1	Cele(21-0.5)	2.0	0.33	-	0.66	1:2
Cele(21-0.5)-EC-PEG(1:1)21	2:1	Cele(21-0.5)	2.0	0.50	-	0.50	1:1
Cele(21-0.5)-EC-PEG(1:0.5)21	2:1	Cele(21-0.5)	2.0	0.66	-	0.33	1:0.5
Cele(21-0.5)-EC-PEG(1:3)31	3:1	Cele(21-0.5)	2.0	0.17	-	0.51	1:3
Cele(21-0.5)-EC-PEG(1:2)31	3:1	Cele(21-0.5)	2.0	0.22	-	0.44	1:2
Cele(21-0.5)-EC-PEG(1:1)31	3:1	Cele(21-0.5)	2.0	0.33	-	0.33	1:1
Cele(21-0.5)-EC-PEG(1:0.5)31	3:1	Cele(21-0.5)	2.0	0.44	-	0.22	1:0.5

EC- Ethyl cellulose 10 cps; PVP- Polyvinyl pyrrolidone K-90; PEG- Poly ethylene glycol 6000 mol. wt.

Table 6.3: Composition of microencapsulated products of acyclovir

Formulation Code	Core to coat ratio	Core		Coat composition			Relative ratio of [EC:PVP or EC:PEG in the coat]
		Code	Amount (g)	EC	PVP	PEG	
(a) Coated with EC alone							
Acyclo(21-0.5)-EC-61	6:1	Acyclo(21-0.5)	2.0	0.33	-	-	-
Acyclo(21-0.5)-EC-41	4:1	Acyclo(21-0.5)	2.0	0.50	-	-	-
Acyclo(31-0.5)-EC-41	4:1	Acyclo(31-0.5)	2.0	0.50	-	-	-
Acyclo(31)-EC-41	4:1	Acyclo(31)	2.0	0.50	-	-	-
(b) Coated with EC & PVP							
Acyclo(21-0.5)-EC-PVP(1:3)21	2:1	Acyclo(21-0.5)	2.0	0.25	0.75	-	1:3
Acyclo(21-0.5)-EC-PVP(1:2)21	2:1	Acyclo(21-0.5)	2.0	0.33	0.66	-	1:2
Acyclo(21-0.5)-EC-PVP(1:1)21	2:1	Acyclo(21-0.5)	2.0	0.50	0.50	-	1:1
Acyclo(21-0.5)-EC-PVP(1:0.5)21	2:1	Acyclo(21-0.5)	2.0	0.66	0.33	-	1:0.5
Acyclo(21-0.5)-EC-PVP(1:3)31	3:1	Acyclo(21-0.5)	2.0	0.17	0.51	-	1:3
Acyclo(21-0.5)-EC-PVP(1:2)31	3:1	Acyclo(21-0.5)	2.0	0.22	0.44	-	1:2
Acyclo(21-0.5)-EC-PVP(1:1)31	3:1	Acyclo(21-0.5)	2.0	0.33	0.33	-	1:1
Acyclo(21-0.5)-EC-PVP(1:0.5)31	3:1	Acyclo(21-0.5)	2.0	0.44	0.22	-	1:0.5
Acyclo(31-0.5)-EC-PVP(1:1)21	2:1	Acyclo(31)	2.0	0.50	0.50	-	1:1
Acyclo(31-0.5)-EC-PVP(1:0.5)21	2:1	Acyclo(31)	2.0	0.66	0.33	-	1:0.5
Acyclo(31)-EC-PVP(1:1)21	2:1	Acyclo(31)	2.0	0.50	0.50	-	1:1
Acyclo(31)-EC-PVP(1:0.5)21	2:1	Acyclo(31)	2.0	0.66	0.33	-	1:0.5
(c) Coated with EC & PEG							
Acyclo(21-0.5)-EC-PEG(1:3)21	2:1	Acyclo(21-0.5)	2.0	0.25	-	0.75	1:3
Acyclo(21-0.5)-EC-PEG(1:2)21	2:1	Acyclo(21-0.5)	2.0	0.33	-	0.66	1:2
Acyclo(21-0.5)-EC-PEG(1:1)21	2:1	Acyclo(21-0.5)	2.0	0.50	-	0.50	1:1
Acyclo(21-0.5)-EC-PEG(1:0.5)21	2:1	Acyclo(21-0.5)	2.0	0.66	-	0.33	1:0.5
Acyclo(21-0.5)-EC-PEG(1:3)31	3:1	Acyclo(21-0.5)	2.0	0.17	-	0.51	1:3
Acyclo(21-0.5)-EC-PEG(1:2)31	3:1	Acyclo(21-0.5)	2.0	0.22	-	0.44	1:2
Acyclo(21-0.5)-EC-PEG(1:1)31	3:1	Acyclo(21-0.5)	2.0	0.33	-	0.33	1:1
Acyclo(21-0.5)-EC-PEG(1:0.5)31	3:1	Acyclo(21-0.5)	2.0	0.44	-	0.22	1:0.5

EC- Ethyl cellulose 10 cps; PVP- Polyvinyl pyrrolidone K-90; PEG- Poly ethylene glycol 6000 mol. wt.

6.2.4.2. Calcium alginate beads

Porous beads of calcium alginate for both drugs were prepared by in situ ionic cross-linking technique using sodium alginate and calcium chloride [Figure 6.2]. Various formulation parameters like, proportion of calcium alginate, concentration of surface active agent, curing conditions and effect of drying technique (vacuum drying versus freeze drying) on the floating characteristics (lag time to float and total duration of floating) and release kinetics of the drug were evaluated. Effects of presence of gas generating agent (sodium bicarbonate) and drug property on the floating character and release kinetics were also studied.

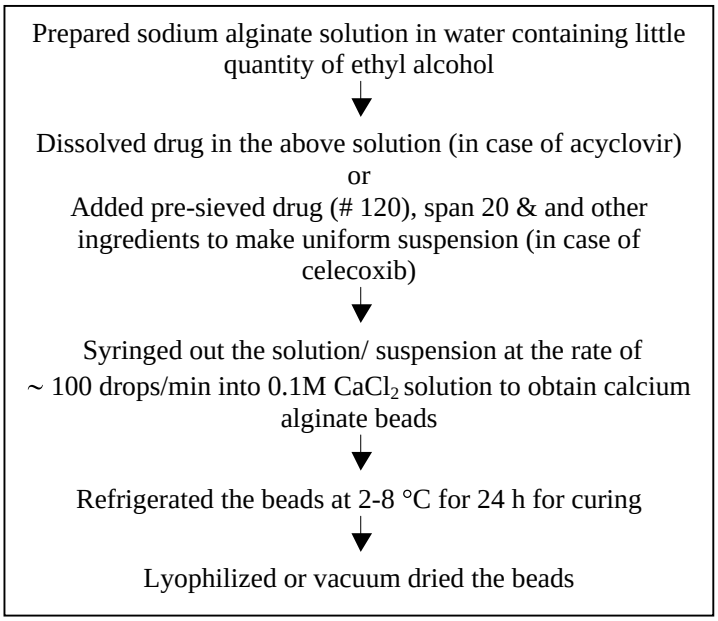

Figure 6.2: Flow chart for preparing calcium alginate bead based formulations of celecoxib and acyclovir

Calcium alginate beads of celecoxib: To prepare calcium alginate beads of celecoxib, 1.5 % w/v sodium alginate solution was prepared in purified water containing 2.0 % v/v of ethyl alcohol. The stock solution of sodium alginate was allowed to stand in well-enclosed glass flask with intermittent shaking for 12 hours to ensure optimal hydration. Calcium chloride ($CaCl_2$) solution (1.5 % w/v) was prepared in purified water and refrigerated for about 30 minutes before use. Freshly sieved (# 120) dried celecoxib, span 20 (wetting agent) and other ingredients were uniformly dispersed in 100 ml of sodium alginate solution on a magnetic stirrer for about 20 minutes. 300 ml of refrigerated $CaCl_2$ solution was taken in a 500 ml beaker maintained in stirring condition on a cold water bath fitted magnetic stirrer. The sodium alginate drug mixture was dropped into the cold $CaCl_2$ solution from a height of

20 cm (above $CaCl_2$ solution surface) using a glass syringe fitted with 22 gauge × 1 inch stainless steel needle at a rate of 5 ml/min or ~ 100 drops/min. The calcium alginate beads formed due to ionic cross-linking were allowed to cure for 24 h at 2-8 °C in a refrigerator. After 24 hours, supernatant was decanted and beads were filtered and washed with isopropyl alcohol (IPA) to remove residual water content. The beads were either frozen and lyophilized at - 110 °C for 6-8 h at 1 mbar to obtain dry and porous beads or vacuum dried using rotary vacuum evaporator at 100 rpm. The beads obtained were sized (using sieve # 16 and 20) and packed into gelatin capsule shells for in vitro release studies [Figure 6.2]. Effects of sodium bicarbonate in the formulation, concentration of span 20 and drying technique (freeze drying versus vacuum drying) on floating characteristics and release kinetics were studied. The strength of the sodium alginate solution was varied from 0.5 % w/v to 1.5 % w/v to study the impact of polymer proportion in the formulation on floating and release kinetics of designed products. Compositions of calcium alginate beads of celecoxib are presented in Table 6.4.

Table 6.4: Composition of calcium alginate beads of celecoxib and acyclovir

Formulation Code	**Drying technique employed**	**Composition (g)**			
		Drug (Celecoxib/ Acyclovir)	Sodium alginate[a]	Sodium bicarbonate	Span 20
(a) Celecoxib products					
Cele-A(1.5)-V-0.25	Vacuum dried	1.0	1.5	-	0.25
Cele-A(1.5)-sbc(1.0)-V-0.25	Vacuum dried	1.0	1.5	1.0	0.25
Cele-A(1.5)-F-0.25	Lyophilized	1.0	1.5	-	0.25
Cele-A(1.5)-sbc(1.0)-F-0.25	Lyophilized	1.0	1.5	1.0	0.25
Cele-A(0.5)-F-0.75	Lyophilized	1.0	0.5	-	0.75
Cele-A(0.75)-F-0.75	Lyophilized	1.0	0.75	-	0.75
Cele-A(1.0)-F-0.75	Lyophilized	1.0	1.0	-	0.75
Cele-A(1.5)-F-0.75	Lyophilized	1.0	1.5	-	0.75
(b) Acyclovir products					
Acyclo-A(0.75)-F	Lyophilized	1.0	0.75	-	-
Acyclo-A(1.0)-F	Lyophilized	1.0	1.0	-	-
Acyclo-A(1.5)-F	Lyophilized	1.0	1.5	-	-
Acyclo-A(2.0)-F	Lyophilized	1.0	2.0	-	-
Acyclo-A(2.5)-F	Lyophilized	1.0	2.5	-	-
Acyclo-A(3.0)-F	Lyophilized	1.0	3.0	-	-

[a]: 100ml of specified % w/v solution prepared in distilled water

Calcium alginate beads of acyclovir: To prepare calcium alginate beads of acyclovir, 3.0 % w/v sodium alginate solution was prepared in purified water containing 4.0 % v/v of ethyl alcohol. Further processing done was exactly similar to the procedure employed for preparing calcium alginate beads of celecoxib, except that in this case drug was dissolved in sodium alginate solution and no other formulation additives like, span 20 or sodium bicarbonate was added. Various concentrations varying from 0.75 % w/v to 3.0 % w/v of sodium alginate was used to study the effect of strength of the sodium alginate solution on floating characteristics and drug release kinetics of designed beads. Compositions of calcium alginate beads of acyclovir are also presented in Table 6.4.

6.2.5. Physicochemical characterization of designed formulations

Developed formulations were subjected to the following physicochemical characterization studies.

Appearance and micromeritics: Products were observed for their colour, surface texture, shape, size range and flow. Sieve analysis (using sieve # 50 and 80 for microencapsulated products and sieve # 16 and 20 calcium bead based products) was employed to determine size range. The ease of fall and entry into the capsule shell gave a rough estimate of the flow of the products.

Drug content uniformity: To determine drug content uniformity, samples of microcapsules/ beads were taken from three different locations from the container of each batch of all the formulations manufactured. Samples of each formulation were crushed and the contents were thoroughly mixed in a mortar-pestle. Aliquot amount of the crushed microcapsules/ beads 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.

Floating: Two hard gelatin capsules, filled with MU-GR-CRDFs, were randomly selected from each of the batches of all the designed formulations and weighed individually. Each capsule was dropped in a beaker containing 200 ml of 0.1 N HCl with 1 % w/v of SLS (in case of celecoxib products) or 0.1 N HCl (in case of acyclovir products) mounted on a thermostatic water bath shaker kept at 37.0±0.5 °C. In addition to lag time to float and duration of floating, fraction of the multiple unit microcapsules/ beads floating was also observed. These parameters were also recorded during the 24 h in vitro release studies.

State of microcapsules/ beads after release from capsule shell: During the 24 h in vitro release studies, the state of the microcapsules/ beads (i.e. whether they are released as free entities, agglomerates or bigger lumps), once the gelatin shell dissolves, was observed.

Swelling: The rate and extent of swelling, if any, was observed visually during the 24 h in vitro release studies carried out at 37.0±0.5 °C in chosen dissolution media for formulations of both the drugs.

Adhesiveness: During in vitro release studies, tendency of the free, agglomerated or clumped microcapsules/ beads to stick tenaciously to the paddle and or dissolution flask was observed indicating adhesive property of the designed formulations.

6.2.6. In vitro release studies

The in vitro release studies were carried out for designed microcapsules or beads of celecoxib and acyclovir as per the procedure given in section 5.2.7 of Chapter 5.

6.2.6.1. Characterization of the release kinetics

Different kinetic equations were applied to interpret the release models from matrix based free granules, microencapsulated matrix based granules and calcium alginate bead based formulations of both the drugs as done for the formulations in the previous chapter. Similarly, the release data were also fitted according to the exponential Eq. (1) as described in the Chapter 5. Values of release exponent and the corresponding release mechanism for swellable and non-swellable spherical matrix systems are presented in Appendix A-1 [Ritger and Peppas, 1987; Kim, 2000; Hakim and Jalil, 2001]. In the case of polydisperse spherical systems, the values of n may be lower than expected, and Ritger and Peppas (1987) computed values of n as low as 0.3 for Fickan transport. Soppimath and colleagues reported further reduction of n values for nifedipine loaded hydrogel microspheres [Soppimath et al., 2000; Soppimath et al., 2001a; Soppimath et al., 2001b].

This concept of characterization has been applied to poly (methyl methacrylate/ methacrylic acid) microspheres based system of azidothymidine [Esbun, 1998], calcium alginate microparticles based delivery [Acartüerk and Takka; 1999a; Acartüerk and Takka; 1999b], ethyl cellulose microcapsules [Sajeev et al., 2002] and hollow microspheres of cardiovascular drugs [Soppimath et al., 2001a].

In this study, n values for different formulations were calculated to identify the drug release mechanism. Diffusional exponent, release rate constant and time for release of fixed percentage of the drug from the formulation were also calculated for comparing different formulations in a similar way as done in Chapter 5.

6.2.7. Batch reproducibility

To study batch variation in design formulations, at least three batches of each formulation were manufactured and evaluated for their physicochemical characteristics and in vitro release profile as described earlier in this chapter.

6.2.8. Stability studies

Real time stability studies of some selected formulations were carried at ambient conditions. Formulations were wrapped in waxed paper and aluminum foil, which were packaged in resealable polythene bags and stored in carton boxes in laboratory cupboards. Triplicate samples were withdrawn at predetermined time intervals (0, 3, 6, 9 and 12 months) and analyzed for physical attributes, drug content, floating behaviour and in vitro release kinetics (as per the respective procedures described in earlier sections of this chapter).

6.3. Results and discussion

6.3.1. Physicochemical characterization of designed formulations

Designed MU-GR-CRDFs of both the drugs possessed excellent physicochemical and floating characteristics. The details are discussed in the following text and presented in Table 6.5 for microencapsulated products of celecoxib, Table 6.6 for microencapsulated products of acyclovir and Table 6.7 for calcium alginate beads of celecoxib and acyclovir.

6.3.1.1. Microencapsulated system

Uncoated granules of both the drugs were off white in colour, slightly rough to touch and somewhat irregular in shape. They ranged in size from 150 to 180 µm and possessed good flow property. The granules floated from zero time, continued to float till the entire duration of their release and had a tendency to swell in acidic media. They were of sticky nature and formed agglomerates (into one capsular lump) during release studies. The granules encapsulated with EC or EC + PVP/ PEG were more spherical in shape with smoother texture, better flow property and increased particle size (180 to 300 µm). An increase in the proportion of ethyl cellulose (EC), hydrophobic polymer, in the coat, enhanced the dispersity of the microcapsules conferring better tendency to float as individual units. However, the rate of swelling was slightly decreased in microcapsules with higher EC proportion in the coat. Entrapment efficiency, for microencapsulated products, ranged from about 90-95 % for both the drugs [Tables 6.5 and 6.6 in case of celecoxib and acyclovir respectively]. The drug content per 100 mg of the formulation varied from 20.64±0.09 to 31.02±0.05 mg in case of

microcapsules of celecoxib [Table 6.5] and 20.89±0.14 to 31.39±0.04 mg in case of acyclovir products [Table 6.6].

Table 6.5: Physical characteristics of microencapsulated products of celecoxib

Formulation Code	**Drug content*** (mg/100mg of formulation)	**Entrapment efficiency*** (%)
(a) Coated with EC alone		
Cele(21-0.5)-EC-61	31.02±0.05	90.48±0.15
Cele(21-0.5)-EC-41	29.73±0.07	92.91±0.22
Cele(31)-EC-41	25.13±0.19	94.24±0.71
(b) Coated with EC & PVP		
Cele(21-0.5)-EC-PVP(1:3)21	24.67±0.15	92.51±0.56
Cele(21-0.5)-EC-PVP(1:2)21	24.63±0.13	92.36±0.49
Cele(21-0.5)-EC-PVP(1:1)21	24.51±0.11	91.91±0.41
Cele(21-0.5)-EC-PVP(1:0.5)21	24.38±0.08	91.43±0.30
Cele(21-0.5)-EC-PVP(1:3)31	27.89±0.11	92.97±0.37
Cele(21-0.5)-EC-PVP(1:2)31	27.61±0.10	92.03±0.33
Cele(21-0.5)-EC-PVP(1:1)31	27.43±0.08	91.43±0.27
Cele(21-0.5)-EC-PVP(1:0.5)31	27.28±0.06	90.93±0.20
Cele(31)-EC-PVP(1:3)21	21.01±0.15	94.55±0.68
Cele(31)-EC-PVP(1:2)21	20.97±0.12	94.37±0.54
Cele(31)-EC-PVP(1:1)21	20.83±0.10	93.74±0.45
Cele(31)-EC-PVP(1:0.5)21	20.64±0.09	92.88±0.41
(c) Coated with EC & PEG		
Cele(21-0.5)-EC-PEG(1:3)21	25.11±0.14	94.16±0.53
Cele(21-0.5)-EC-PEG(1:2)21	24.97±0.12	93.64±0.45
Cele(21-0.5)-EC-PEG(1:1)21	24.61±0.11	92.29±0.42
Cele(21-0.5)-EC-PEG(1:0.5)21	24.49±0.09	91.84±0.34
Cele(21-0.5)-EC-PEG(1:3)31	28.15±0.12	93.83±0.40
Cele(21-0.5)-EC-PEG(1:2)31	27.85±0.10	92.83±0.33
Cele(21-0.5)-EC-PEG(1:1)31	27.78±0.09	92.60±0.30
Cele(21-0.5)-EC-PEG(1:0.5)31	27.73±0.07	92.43±0.23

* Mean ± Standard deviation

Table 6.6: Physical characteristics of microencapsulated products of acyclovir

Formulation Code	Drug content* (mg/100mg of formulation)	Entrapment efficiency* (%)
(a) Coated with EC alone		
Acyclo(21-0.5)-EC-61	31.39±0.04	91.55±0.12
Acyclo(21-0.5)-EC-41	30.09±0.06	94.03±0.19
Acyclo(31-0.5)-EC-41	30.36±0.09	94.88±0.28
Acyclo(31)-EC-41	25.30±0.15	94.88±0.56
(b) Coated with EC & PVP		
Acyclo(21-0.5)-EC-PVP(1:3)21	24.32±0.17	91.20±0.64
Acyclo(21-0.5)-EC-PVP(1:2)21	24.58±0.14	92.18±0.53
Acyclo(21-0.5)-EC-PVP(1:1)21	24.79±0.10	92.96±0.38
Acyclo(21-0.5)-EC-PVP(1:0.5)21	24.04±0.08	90.15±0.30
Acyclo(21-0.5)-EC-PVP(1:3)31	27.75±0.12	92.50±0.40
Acyclo(21-0.5)-EC-PVP(1:2)31	28.01±0.13	93.37±0.43
Acyclo(21-0.5)-EC-PVP(1:1)31	28.15±0.14	93.83±0.47
Acyclo(21-0.5)-EC-PVP(1:0.5)31	28.33±0.11	94.43±0.37
Acyclo(31-0.5)-EC-PVP(1:1)21	25.03±0.11	93.87±0.41
Acyclo(31-0.5)-EC-PVP(1:0.5)21	25.14±0.10	94.28±0.38
Acyclo(31)-EC-PVP(1:1)21	20.89±0.14	94.01±0.63
Acyclo(31)-EC-PVP(1:0.5)21	21.09±0.11	94.91±0.50
(c) Coated with EC & PEG		
Acyclo(21-0.5)-EC-PEG(1:3)21	24.74±0.13	92.78±0.49
Acyclo(21-0.5)-EC-PEG(1:2)21	24.91±0.11	93.41±0.41
Acyclo(21-0.5)-EC-PEG(1:1)21	25.08±0.09	94.05±0.34
Acyclo(21-0.5)-EC-PEG(1:0.5)21	25.12±0.10	94.20±0.38
Acyclo(21-0.5)-EC-PEG(1:3)31	27.73±0.16	92.43±0.53
Acyclo(21-0.5)-EC-PEG(1:2)31	27.89±0.13	92.97±0.43
Acyclo(21-0.5)-EC-PEG(1:1)31	28.01±0.11	93.37±0.37
Acyclo(21-0.5)-EC-PEG(1:0.5)31	28.17±0.09	93.90±0.30

* Mean ± Standard deviation

6.3.1.2. Calcium alginate beads

Most of the bead based formulations of both the drugs were smooth, spherical and had a size range of 850 to 1180 µm with good flow property. The beads were found to be non swellable in acidic media and non sticky in nature. Entrapment efficiency ranged from about 75-92 % for the designed formulations in case of both the drugs. The drug content per 100 mg of the formulation varied from 22.34±0.34 to 36.58±0.17 mg in case of celecoxib beads and 22.04±0.07 to 48.84±0.21 mg in case of acyclovir beads [Table 6.7].

Calcium alginate beads of celecoxib: Physical attributes of designed calcium alginate beads were influenced by various process and formulation parameters like, mode of drying the products, presence of sodium bicarbonate in the formula, proportion of wetting agent (span 20) and proportion of release rate controlling polymer (calcium alginate). Vacuum dried beads were off white in colour, opaque, slightly larger in diameter and non floatable, whereas freeze dried beads were white, translucent and floatable in nature. Inclusion of sodium bicarbonate in the composition resulted in slightly bigger sized and non floatable beads. On increasing the proportion of span 20 in the formula, entrapment efficiency increased from 79.04±0.81 % in case of Cele-A(1.5)-F-0.25) to 83.75±0.36 % in case of Cele-A(1.5)-F-0.75), but fraction floating decreased from approx. 50 % to 40 % [Table 6.7]. Lower proportions of sodium alginate in the composition resulted in irregular, fibrous, oblong/ oval beads with poorer flow property and floating characteristics. Fraction floating from zero time up to the end of release increased from < 10 % in case of Cele-A(0.5)-F-0.75 containing lowest polymer proportion to approx. 40 % in case of Cele-A(1.5)-F-0.75 containing highest polymer proportion [Table 6.7].

Table 6.7: Physical characteristics of calcium alginate beads of celecoxib and acyclovir

Formulation Code	**Appearance**			**Drug content*** (mg/100mg of formulation)	**Entrapment efficiency*** (%)	**Fraction floating** (%)
	Colour	Surface texture	Shape			
(a) Celecoxib products						
Cele-A(1.5)-V-0.25	off white; opaque	smooth	spherical	27.70±0.31	75.55±0.85	0
Cele-A(1.5)-sbc(1.0)-V-0.25	off white; opaque	smooth	spherical	22.34±0.34	83.27±1.27	0
Cele-A(1.5)-F-0.25	white; transluscent	smooth	spherical	31.00±0.25	84.55±0.68	~50
Cele-A(1.5)-sbc(1.0)-F-0.25	white; transluscent	smooth	spherical	24.63±0.27	91.80±1.01	0
Cele-A(0.5)-F-0.75	white	irregular; fibrous	oblong	36.58±0.17	82.03±0.38	<10
Cele-A(0.75)-F-0.75	white	irregular; fibrous	oval	35.07±0.15	87.28±0.37	~20
Cele-A(1.0)-F-0.75	white; transluscent	smooth	spherical	32.15±0.13	87.93±0.36	~25
Cele-A(1.5)-F-0.75	white; transluscent	smooth	spherical	27.46±0.10	88.62±0.32	~40
(b) Acyclovir products						
Acyclo-A(0.75)-F	white	Irregular; fibrous	oval	48.84±0.21	84.92±0.37	<10
Acyclo-A(1.0)-F	white; transluscent	smooth	spherical	42.92±0.17	85.19±0.34	~10
Acyclo-A(1.5)-F	white; transluscent	smooth	spherical	34.10±0.13	84.48±0.32	~20
Acyclo-A(2.0)-F	white; transluscent	smooth	spherical	29.61±0.10	87.93±0.30	~30
Acyclo-A(2.5)-F	white; transluscent	smooth	spherical	25.17±0.09	87.14±0.31	~40
Acyclo-A(3.0)-F	white; transluscent	smooth	spherical	22.04±0.07	87.16±0.28	~50

* Mean ± Standard deviation

Calcium alginate beads of acyclovir: As in case of beads of celecoxib, lower sodium alginate proportion in calcium alginate beads of acyclovir resulted in irregular, fibrous, oval beads with poorer flow property and floatability. Upon increasing the proportion of sodium alginate in the formula, improvement in appearance, flow and floatability of the beads was observed. Fraction floating from zero time up to the end of release increased from < 10 % in case of Acyclo-A(0.75)-F containing lowest polymer proportion to approx. 50 % in case of Acyclo-A(3.0)-F containing highest polymer proportion [Table 6.7].

6.3.2. In vitro release studies and release kinetics characterization of microencapsulated system

In general, microencapsulated products of celecoxib showed more controlled and prolonged release (beyond 24 h) in all the cases, while designed microcapsules of acyclovir prolonged the drug release to different extent, ranging from as low as 2 h (in case of uncoated granules) to beyond 24 h in some cases. This was probably due to very poor solubility of celecoxib and relatively very high solubility of acyclovir in the acidic dissolution media.

Results of cumulative percentage release from uncoated granules of celecoxib and acyclovir are presented in Table 6.8 with the corresponding release characterization data (i.e., calculated r value for different types of release models and n, K & $t_{60\%}$ values of drug release) enlisted in Table 6.9. The cumulative percentage release versus time profile is presented in Figure 6.3 for celecoxib and Figure 6.4 for acyclovir. Results of cumulative percentage release from microencapsulated celecoxib products are presented in Tables 6.10, 6.12 to 6.18 and from microencapsulated acyclovir products are presented in Tables 6.19, 6.21 to 6.27 with the corresponding release characterization data of all these products enlisted in Table 6.11 for celecoxib and in Table 6.20 for acyclovir. Plots of cumulative percentage release versus time for various MU-GR-CRDFs are shown in Figures 6.5 to 6.12 for microencapsulated celecoxib products and Figures 6.13 to 6.21 for microencapsulated acyclovir products.

6.3.2.1. Optimization of core composition for microencapsulated products of celecoxib and acyclovir

Core composition of celecoxib products

Two types of core (uncoated granules) were prepared for celecoxib with drug to total floating agent ratio of 1:0.5 and 1:1, and sodium bicarbonate to citric acid ratio as 2:1 and 3:1. Cele(21-0.5)-uncoated granules of celecoxib (at drug to total floating agent ratio of 1:0.5 and sodium bicarbonate to citric acid of 2:1) once released from the gelatin shell formed loose agglomerates or mesh-like structure. The drug release from these granules were relatively

faster with a cumulative release of 56.10±5.37 % in 24 h. Whereas, Cele(31)-uncoated granules (drug to total floating agent ratio of 1:1 and sodium bicarbonate to citric acid of 3:1) were totally agglomerated into one lump (capsular shape), with a cumulative release of only 27.20±2.88 % in 24 h [Table 6.8; Figure 6.3]. Decreasing the base to acid ratio from 3:1 [Cele(31)-uncoated granules] to 2:1 [Cele(21-0.5)-uncoated granules] resulted in faster rate of drug release due to faster rate of CO_2 generation in aqueous media with base to acid ratio of 2:1.

When the release data was fitted into zero order, first order and Higuchi's model, best correlation coefficient (r value) for the best fit line was obtained for Higuchi's model for both the granules [Table 6.9]. According to power equation [Ritger and Peppas, 1987], Cele(21-0.5)-uncoated granule followed quasi-Fickian (n=0.1703) transport with K and $t_{60\%}$ values of 23.88 $h^{-0.1703}$ and 81.58 h respectively. Cele(31)-uncoated granules also followed quasi-Fickian (n=0.3636) transport, with obtained K and $t_{60\%}$ values of 10.24 $h^{-0.3636}$ and 129.55 h respectively [Table 6.9].

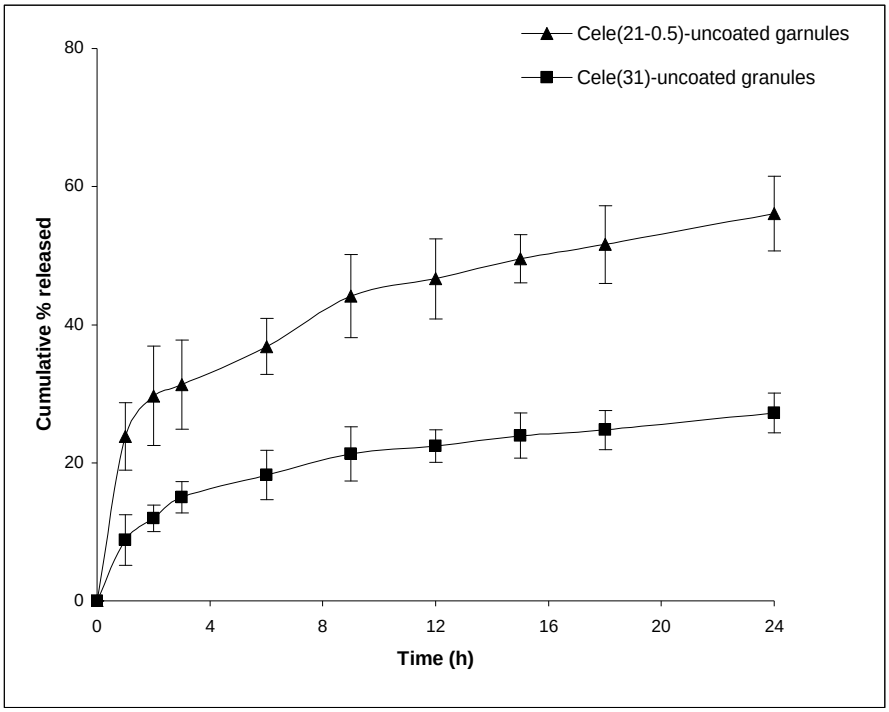

Figure 6.3: In vitro release from sodium alginate uncoated celecoxib granules to study the effect of core composition [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Table 6.8: Cumulative percentage drug release from sodium alginate uncoated granules of celecoxib and acyclovir

Time (h)	Cumulative percentage released[a]				
	Uncoated granules of celecoxib		Uncoated granules of acyclovir		
	Cele(21-0.5)	Cele(31)	Acyclo(21-0.5)	Acyclo(31-0.5)	Acyclo(31)
1	23.85±4.88	8.81±3.67	85.30±2.83	15.78±1.71	35.60±1.25
2	29.70±7.21	11.96±1.93	100.20±2.23	31.12±2.03	73.16±3.99
3	31.33±6.46	15.03±2.27	-	52.36±1.13	88.22±2.95
6	36.85±4.03	18.25±3.56	-	72.71±1.69	95.75±2.38
9	44.14±6.03	21.31±3.94	-	87.07±2.72	100.39±1.30
12	46.64±5.78	22.42±2.33	-	102.73±1.87	-
15	49.55±3.48	23.94±3.28	-	-	-
18	51.62±5.65	24.75±2.82	-	-	-
24	56.10±5.37	27.20±2.88	-	-	-

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

Table 6.9: In vitro release rate parameters of sodium alginate uncoated granules of celecoxib and acyclovir

Core 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				
Uncoated granules of celecoxib								
Cele(21-0.5)	0.8601	0.9191	0.9617	0.9953	23.88	0.1703	Quasi-Fickian	81.58
Cele(31)	0.8657	0.8912	0.9756	0.9812	10.24	0.3636	Quasi-Fickian	129.55
Uncoated granules of acyclovir								
Acyclo(21-0.5)	0.9267	-	0.9887	0.9999	85.30	0.2323	Quasi-Fickian	0.22
Acyclo(31-0.5)	0.9758	0.9968	0.9899	0.9998	18.18	0.7700	Anamolous	4.71
Acyclo(31)	0.8145	0.9787	0.9415	0.9999	35.60	1.0393	Supercase II	1.65

[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)

Core composition of acyclovir products

All the three types of uncoated granules were totally agglomerated into one lump (capsular shape) once released from the gelatin shell. Acyclo(21-0.5)-uncoated granule, Acyclo(31)-uncoated granule and Acyclo(31-0.5)-uncoated granule extended the drug release to 2 h, 9 h and 12 h respectively. Keeping drug to total floating agent ratio constant at 1:0.5 and decreasing sodium bicarbonate to citric acid from 3:1 [Acyclo(31-0.5)-uncoated granules] to 2:1 [Acyclo(21-0.5)-uncoated granules] caused faster release due to a quicker reaction between the acid and base resulting in faster production of CO_2 in the matrix core. Keeping sodium bicarbonate to citric acid ratio constant at 3:1 and increasing the drug to total floating agent proportion from 1:0.5 [Acyclo(31-0.5)-uncoated granules] to 1:1 [Acyclo(31)-uncoated granules], a faster rate of drug release was observed due to more generation of carbon dioxide resulting in micro disintegration of core matrix containing fairly soluble acyclovir in acidic media [Table 6.8; Figure 6.4].

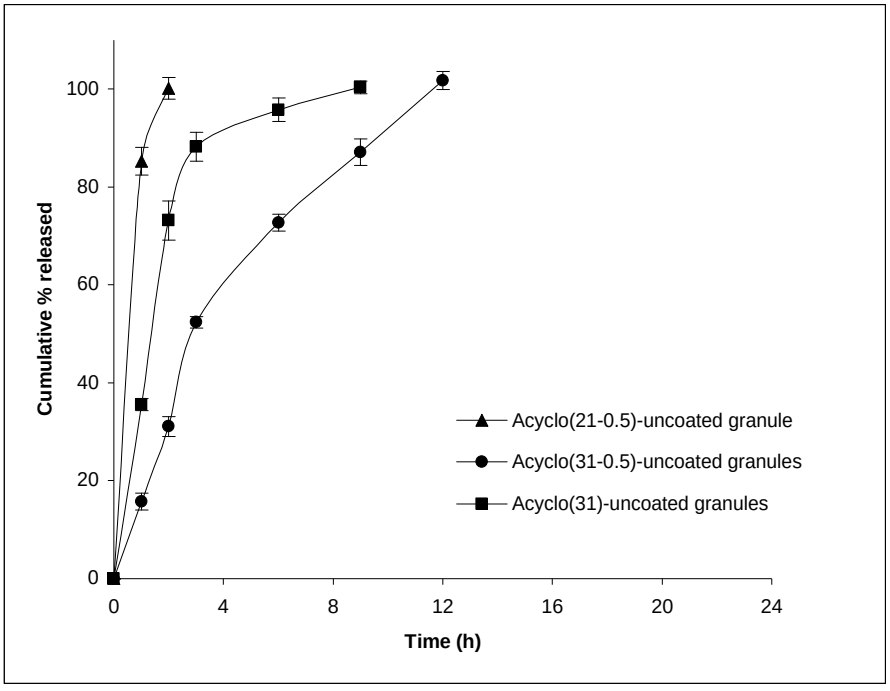

Figure 6.4: In vitro release from sodium alginate uncoated acyclovir granules to study the effect of core composition [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Acyclo(21-0.5)-uncoated granules showed more significant r value for Higuch's model, while Acyclo(31-0.5) and Acyclo(31) uncoated granules showed more significant r value for first order release model [Table 6.9]. Keeping drug to total floating agent ratio constant at 1:0.5 and changing the base to acid ratio from 2:1 to 3:1, release mechanism changed from quasi-Fickian (n=0.2323) to anamolous (n=0.7700). The corresponding K and $t_{60\%}$ values for Acyclo(21-0.5)-uncoated granules changed from 85.30 $h^{-0.2323}$ and 0.22 h respectively to 18.18 $h^{-0.7700}$ and 4.71 h respectively in case of Acyclo(31-0.5)-uncoated granules. Keeping base to acid ratio constant at 3:1, but doubling the amount of total floating agent resulted in supercase II transport (n=1.0393) with the release rate constant increasing from 18.18 $h^{-0.7700}$ in case of Acyclo(31-0.5)-uncoated granules to 35.60 $h^{-1.0393}$ in case of Acyclo(31)-uncoated granules. A $t_{60\%}$ value of 1.65 h was obtained in case of Acyclo(31)-uncoated granules. Higher amount of floating agent in the core matrix lead to more generation of gas, resulting in higher release rate constant and supercase II type of release transport [Table 6.9].

6.3.2.2. Sodium alginate based microencapsulated products of celecoxib

For designing microencapsulated products of celecoxib, the uncoated granule of Cele(21-0.5) was used because of its faster drug release profile. Cele(31)-uncoated granules were used only for studying the effect of formulation variables. Coating the granules with hydrophobic or its combination with hydrophilic polymer system, made the granules less clumped and altered the rate and extent of release, depending upon the composition of the coat. The release rate and the mechanism of release from the designed microcapsules were influenced by the type of core used, core to coat ratio, proportion of hydrophobic polymer in the coat and type of hydrophilic polymer in the coat. These parameters have been discussed in detail in the following sections.

Effect of coating with varying amount of EC alone: Coating with EC alone significantly retarded the drug release from Cele(21-0.5) granules. The release rate was further retarded with decrease in core to coat ratio from 6:1 [Cele(21-0.5)-EC-61] to 4:1 [Cele(21-0.5)-EC-41]. Cele(21-0.5)-EC-61 and Cele(21-0.5)-EC-41 released only 31.25±1.61 % and 24.40±1.29 % drug in 24 h respectively, as compared to 56.10±5.37 % in 24 h in case of uncoated granules [Table 6.10; Figure 6.5]. EC coated products also followed quasi-Fickian type of release transport with n value increasing with increase in proportion of coat from n=0.2270 at core to coat ratio of 6:1 to n=0.2843 in case of core to coat ratio of 4:1. In case of Cele(21-0.5)-EC-61, the K and $t_{60\%}$ values obtained were 15.28 $h^{-0.2270}$ and 414.17 h respectively, whereas for Cele(21-0.5)-EC-41, the values were 9.78 $h^{-0.2843}$ and 590.71 h respectively [Table 6.11].

Table 6.10: Cumulative percentage drug release from microencapsulated granules of celecoxib coated with EC alone

Time (h)	Cumulative percentage released [a]		
	Cele(21-0.5)-EC-61	**Cele(21-0.5)-EC-41**	**Cele(31)-EC-41**
1	16.34±1.25	11.49±0.51	7.23±0.78
2	18.06±1.96	11.67±1.08	11.81±1.25
3	19.58±1.01	13.59±1.42	14.77±0.90
6	22.67±1.48	16.59±1.17	16.77±0.89
9	24.65±1.92	18.03±1.63	21.59±1.22
12	27.33±1.93	20.34±1.68	24.81±1.53
15	28.22±2.33	20.70±1.74	28.68±1.41
18	29.87±1.16	21.84±1.42	32.36±1.74
24	31.25±1.61	24.40±1.29	36.16±1.73

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

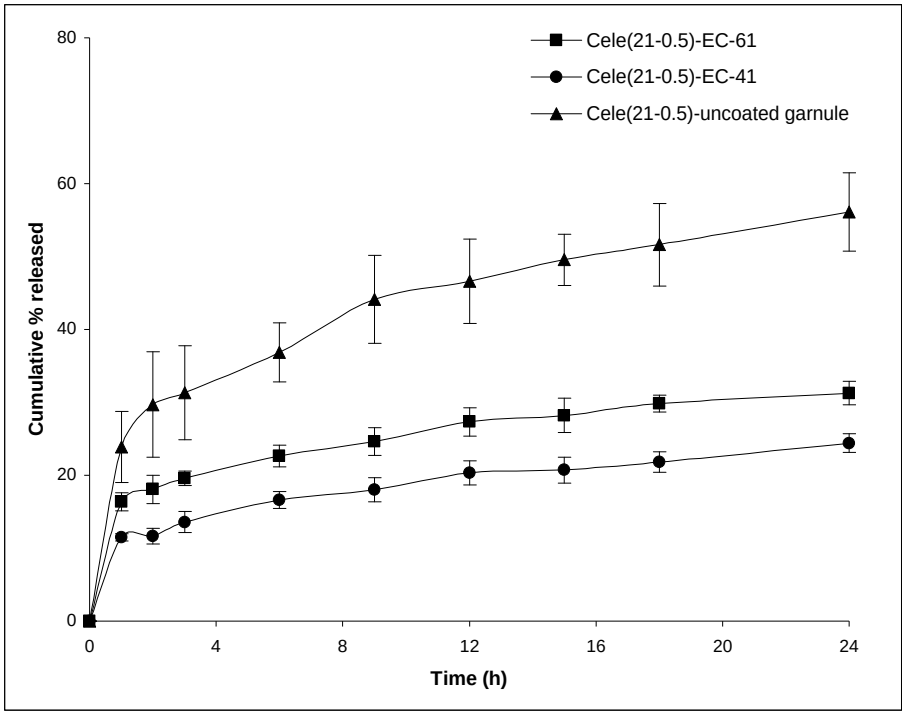

Figure 6.5: In vitro release from Cele(21-0.5) microencapsulated granules of celecoxib to study the effect of coating with varying amount of EC [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Table 6.11: In vitro release rate parameters of microencapsulated products 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) Coated with EC alone								
Cele(21-0.5)-EC-61	0.8163	0.8503	0.9339	0.9978	15.28	0.2270	Quasi-Fickian	414.17
Cele(21-0.5)-EC-41	0.8588	0.8812	0.9579	0.9969	9.78	0.2843	Quasi-Fickian	590.71
Cele(31)-EC-41	0.9631	0.9843	0.9984	0.9994	7.96	0.5552	Anamolous	37.99
(b) Coated with EC & PVP								
Cele(21-0.5)-EC-PVP(1:3)21	0.7501	0.8159	0.8886	0.9953	28.36	0.1703	Quasi-Fickian	81.58
Cele(21-0.5)-EC-PVP(1:2)21	0.7354	0.8007	0.8755	0.9886	28.71	0.1533	Quasi-Fickian	122.46
Cele(21-0.5)-EC-PVP(1:1)21	0.7138	0.7725	0.8554	0.9937	26.08	0.1520	Quasi-Fickian	240.10
Cele(21-0.5)-EC-PVP(1:0.5)21	0.8159	0.8482	0.9354	0.9982	14.76	0.2290	Quasi-Fickian	456.75
Cele(21-0.5)-EC-PVP(1:3)31	0.8138	0.8803	0.9330	0.9981	26.41	0.2200	Quasi-Fickian	41.69
Cele(21-0.5)-EC-PVP(1:2)31	0.8315	0.8789	0.9444	0.9940	20.80	0.2317	Quasi-Fickian	96.70
Cele(21-0.5)-EC-PVP(1:1)31	0.8837	0.9126	0.9681	0.9873	12.62	0.2975	Quasi-Fickian	188.53
Cele(21-0.5)-EC-PVP(1:0.5)31	0.9271	0.9438	0.9890	0.9898	8.63	0.3715	Quasi-Fickian	184.68
Cele(31)-EC-PVP (1:3)21	0.9084	0.9711	0.9907	0.9884	17.30	0.4879	Fickian/ Anamolous	12.79
Cele(31)-EC-PVP (1:2)21	0.9078	0.9572	0.9886	0.9929	14.13	0.5322	Anamolous	15.13
Cele(31)-EC-PVP (1:1)21	0.8920	0.9336	0.9803	0.9751	13.68	0.5023	Anamolous	18.98
Cele(31)-EC-PVP (1:0.5)21	0.8856	0.9232	0.9765	0.9682	12.40	0.5093	Anamolous	22.09
(c) Coated with EC & PEG								
Cele(21-0.5)-EC-PEG(1:3)21	0.7339	0.8190	0.8783	0.9966	35.39	0.1554	Quasi-Fickian	29.89
Cele(21-0.5)-EC-PEG(1:2)21	0.8071	0.8747	0.9272	0.9966	27.57	0.1990	Quasi-Fickian	49.83
Cele(21-0.5)-EC-PEG(1:1)21	0.8155	0.8630	0.9334	0.9978	20.17	0.2261	Quasi-Fickian	124.10
Cele(21-0.5)-EC-PEG(1:0.5)21	0.8188	0.8806	0.9349	0.9873	12.62	0.2975	Quasi-Fickian	188.46
Cele(21-0.5)-EC-PEG(1:3)31	0.7369	0.8701	0.8802	0.9975	46.27	0.1506	Quasi-Fickian	5.62
Cele(21-0.5)-EC-PEG(1:2)31	0.7347	0.8253	0.8779	0.9975	36.59	0.1545	Quasi-Fickian	24.55
Cele(21-0.5)-EC-PEG(1:1)31	0.8060	0.8675	0.9266	0.9943	25.75	0.1979	Quasi-Fickian	71.77
Cele(21-0.5)-EC-PEG(1:0.5)31	0.8158	0.8652	0.9336	0.9978	20.83	0.2265	Quasi-Fickian	106.78

[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 core to coat ratio: Keeping other parameters constant and changing only the core to coat ratio from 2:1 to 3:1, there was an enhancement in release rate and cumulative % released in 24 h [Table 6.12; Figure 6.6].

Table 6.12: Cumulative percentage drug release from microencapsulated granules [Cele(21-0.5)] of celecoxib to study the effect of core to coat ratio at fixed EC: PVP or EC:PEG ratio (1:3) in the coat

Time (h)	Cumulative percentage released [a]			
	Cele(21-0.5)-EC-PVP(1:3)21	Cele(21-0.5)-EC-PVP(1:3)31	Cele(21-0.5)-EC-PEG(1:3)21	Cele(21-0.5)-EC-PEG(1:3)31
1	29.25±1.56	26.97±0.81	34.77±0.98	45.18±1.35
2	32.57±1.77	30.42±1.32	39.66±1.20	51.58±1.38
3	33.69±2.42	34.31±1.30	41.67±1.14	54.22±1.03
6	37.65±1.37	39.25±1.85	46.67±1.60	60.75±1.30
9	41.13±1.06	42.52±1.86	50.55±1.46	64.89±1.94
12	43.98±1.42	44.95±1.68	51.34±1.24	66.88±1.81
15	45.31±2.00	47.74±1.24	53.20±1.67	69.89±1.63
18	46.07±1.65	50.46±1.37	56.20±1.46	73.12±1.71
24	48.83±1.21	53.37±0.94	58.10±1.31	75.66±1.50

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

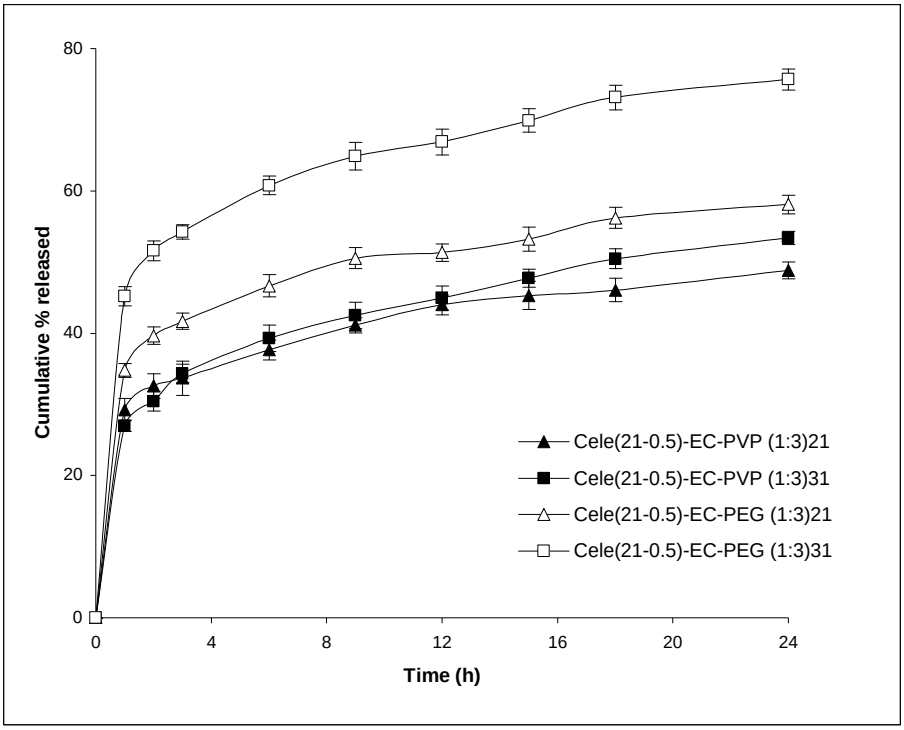

Figure 6.6: In vitro release from microencapsulated Cele(21-0.5) granules of celecoxib to study the effect of core to coat ratio at fixed EC: PVP or EC:PEG ratio (1:3) in the coat [Data presented is mean ± SD of release studies on products of three batches in duplicate]

At fixed EC: PVP ratio of 1:3 in the coat, when core to coat ratio of 2:1 [Cele(21-0.5)-EC-PVP(1:3)21] was increased to 3:1 [Cele(21-0.5)-EC-PVP(1:3)31], the drug release was marginally increased from 48.83±1.21 % to 53.37±0.94 % respectively in 24 h. But in case of EC: PEG (1:3) coat, increasing the core to coat ratio form 2:1 to 3:1 as in case of Cele(21-0.5)-EC-PEG(1:3)21 and Cele(21-0.5)-EC-PEG(1:3)31, the drug release was significantly increased from 58.10±1.31 % to 75.66±1.50 % respectively in 24 h. The mechanism of release in all the formulations was found to be quasi-Fickian [Table 6.11].

Effect of coat composition (varying EC: PVP ratio): Granules, coated with only EC (hydrophobic polymer), released the drug in a more prolonged manner than granules coated with a combination of EC and PVP K-30 (hydrophilic polymer). Including a hydrophilic polymer significantly increased the release of celecoxib at all core to coat ratios and core composition. As the proportion of PVP K-30 was increased in the coat, there was a corresponding increase in the release rate and cumulative % released in 24 h.

In case of Cele(21-0.5) coated products prepared at core to coat ratio of 2:1, Cele(21-0.5)-EC-PVP(1:3)21, Cele(21-0.5)-EC-PVP(1:2)21, Cele(21-0.5)-EC-PVP(1:1)21 and Cele(21-0.5)-EC-PVP(1:0.5)21 released 48.83±1.21 %, 47.20±0.89%, 42.92±1.42 % and 30.62±1.58 % respectively in 24 h [Table 6.13; Figure 6.7]. At core to coat ratio of 3:1, Cele(21-0.5)-EC-PVP(1:3)31, Cele(21-0.5)-EC-PVP(1:2)31, Cele(21-0.5)-EC-PVP(1:1)31 and Cele(21-0.5)-EC-PVP(1:0.5)31 released 53.37±0.94 %, 43.23±1.82 %, 33.12±1.69 % and 28.09±0.93 % respectively in 24 h [Table 6.14; Figure 6.8].

Table 6.13: Cumulative percentage drug release from microencapsulated granules [Cele(21-0.5)] of celecoxib to study the effect of coat composition (varying EC: PVP ratio) at core to coat ratio of 2:1

Time (h)	Cumulative percentage released [a]			
	Cele(21-0.5)-EC-PVP(1:3)21	Cele(21-0.5)-EC-PVP(1:2)21	Cele(21-0.5)-EC-PVP(1:1)21	Cele(21-0.5)-EC-PVP(1:0.5)21
1	29.25±1.56	29.08±1.68	27.07±1.95	15.31±1.11
2	32.57±1.77	32.43±1.63	29.08±2.59	17.11±1.47
3	33.69±2.42	34.41±1.34	31.34±1.65	18.92±1.52
6	37.65±1.37	36.68±1.30	33.81±2.17	22.83±1.09
9	41.13±1.06	38.88±1.94	35.89±1.09	24.52±1.69
12	43.98±1.42	42.20±2.32	37.17±2.19	26.00±1.97
15	45.31±2.00	43.53±1.51	39.62±1.75	27.38±1.83
18	46.07±1.65	45.63±1.37	40.88±1.96	28.23±2.01
24	48.83±1.21	47.20±0.89	42.92±1.42	30.62±1.58

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

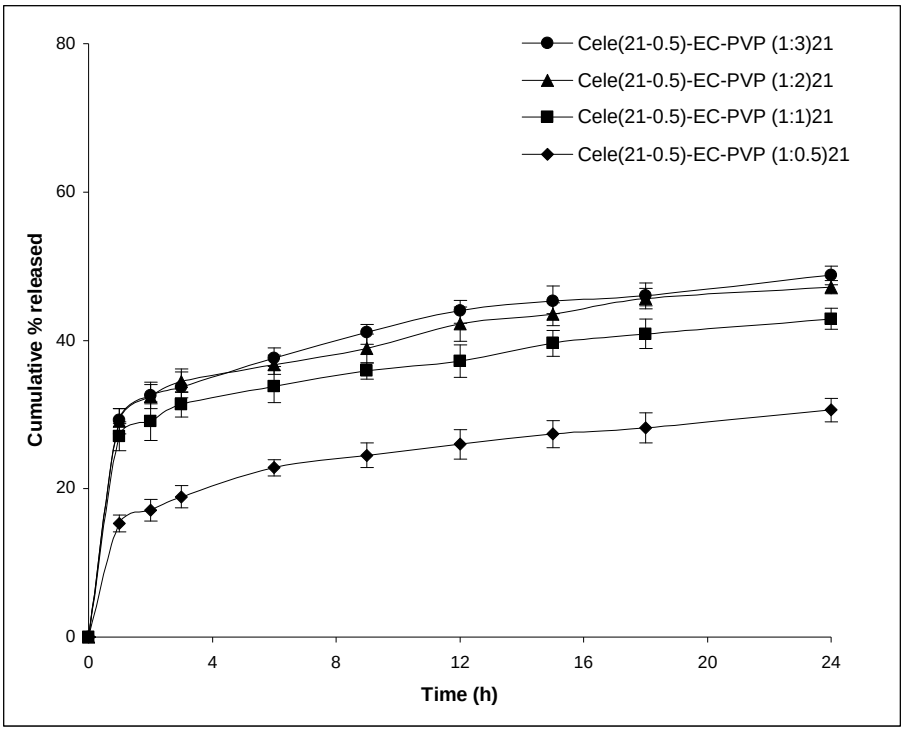

Figure 6.7: In vitro release from microencapsulated Cele(21-0.5) granules to study the effect of coat composition (varying EC: PVP ratio) at core to coat ratio of 2:1 [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Table 6.14: Cumulative percentage drug release from microencapsulated granules [Cele(21-0.5)] of celecoxib to study the effect of coat composition (varying EC: PVP ratio) at core to coat ratio of 3:1

Time	Cumulative percentage released [a]			
(h)	Cele(21-0.5)-EC-PVP(1:3)31	Cele(21-0.5)-EC-PVP(1:2)31	Cele(21-0.5)-EC-PVP(1:1)31	Cele(21-0.5)-EC-PVP(1:0.5)31
1	26.97±0.81	20.26±1.88	14.32±1.10	8.46±1.18
2	30.42±1.32	24.61±1.82	15.41±1.00	11.54±1.88
3	34.31±1.30	27.07±1.78	18.45±1.52	12.92±1.68
6	39.25±1.85	31.38±1.07	21.11±1.73	16.69±1.09
9	42.52±1.86	33.50±1.18	22.98±1.64	18.74±1.08
12	44.95±1.68	35.99±1.09	24.97±1.34	20.08±1.67
15	47.74±1.24	40.18±2.09	29.57±1.82	24.24±1.91
18	50.46±1.37	41.61±1.88	30.47±1.74	27.21±1.41
24	53.37±0.94	43.23±1.82	33.12±1.69	28.09±0.93

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

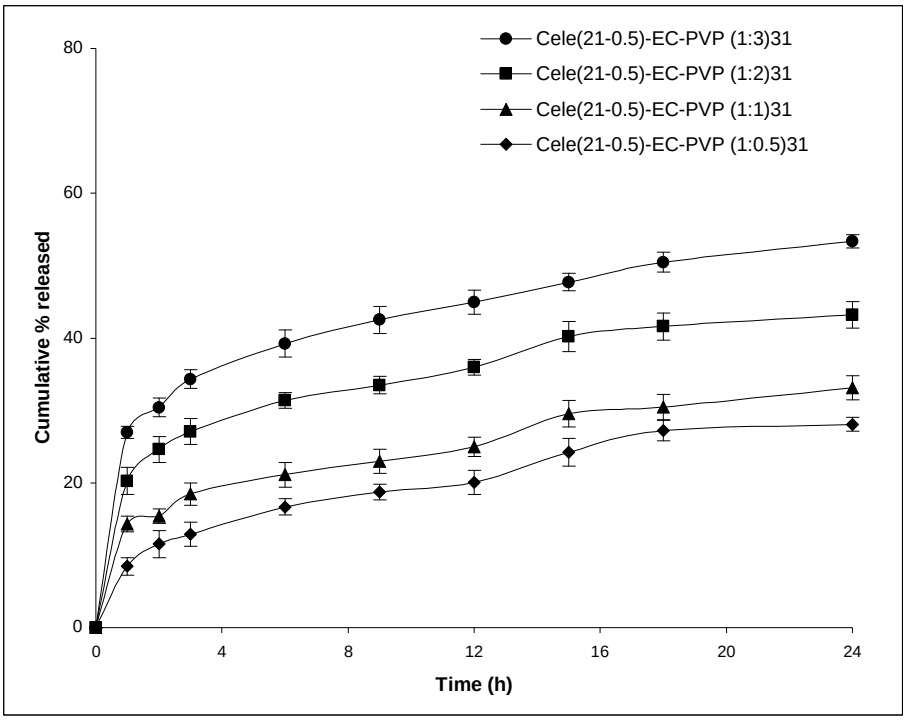

Figure 6.8: In vitro release from microencapsulated Cele(21-0.5) granules to study the effect of coat composition (varying EC: PVP ratio) at core to coat ratio of 3:1 [Data presented is mean ± SD of release studies on products of three batches in duplicate]

For microencapsulated Cele(21-0.5) products at all core to coat ratios, the release data fitted best in Higuchi's square root model with more significant r values. Higher PVP proportion in the coat resulted in lower r values as compared to granules coated with higher content of EC. In case of EC-PVP coated products, all the formulations followed quasi-Fickian transport. Products coated with higher proportion of EC showed closer proximity to Fickian release and slower rate of drug release. At core to coat ratio of 2:1, Cele(21-0.5)-EC-PVP(1:3)21 with highest relative proportion of PVP in the coat, showed n, K and $t_{60\%}$ values of 0.1703, 28.36 $h^{-0.1703}$ and 81.58 h respectively. On the other hand, Cele(21-0.5)-EC-PVP(1:0.5)21 with lowest PVP proportion in the coat, showed values of 0.2290, 14.76 $h^{-0.2290}$ and 456.75 h respectively [Table 6.11]. Similarly, at core to coat ratio of 3:1 [Cele(21-0.5)-EC-PVP(1:3)31] the obtained n, K and $t_{60\%}$ values were 0.2200, 26.41 $h^{-0.2200}$ and 41.69 h respectively, while for Cele(21-0.5)-EC-PVP(1:0.5)31 the obtained n, K and $t_{60\%}$ values were found to be 0.3715, 8.63 $h^{-0.3715}$ and 184.68 h respectively [Table 6.11].

Coating Cele(31) granules with EC alone at core to coat ratio of 4:1 did not alter significantly the drug release up to 9 h, but showed a much higher cumulative % release in 24 h (36.16±1.73 %) as compared to uncoated granules (27.20±2.88 %) [Tables 6.8 and 6.10;

Figure 6.9]. This can be attributed to the effect of coating, which resulted in granules that were free and non-agglomerating in nature, increasing the overall exposed surface area for release.

Upon microencapsulating Cele(31) granules at fixed core to coat ratio of 2:1 with varying proportion of EC and PVP in the coat, relatively faster rate of drug release was observed post 1 h in comparison to similar products obtained using Cele(21-0.5) granules. In these products also rate of release decreased with increase in relative proportion of EC in coat with highest cumulative release of 62.16±1.10 % in case of Cele(31)-EC-PVP(1:3)21 and a lowest of 48.94±1.69 % in case of Cele(31)-EC-PVP(1:0.5)21 in 24 h [Table 6.15; Figure 6.9]. In case of microencapsulated Cele(31) products at core to coat ratio of 2:1 also, high r values were obtained for Higuchi's model. Encapsulating the granules with a coating polymer changed the nature of release mechanism from quasi-Fickian to Fickian or anamolous depending upon the coat composition [Table 6.11]. Granules encapsulated with EC alone showed anamolous release mechanism, indicating the role of polymer relaxation, in addition to Fickian diffusion during drug release. As the proportion of EC was decreased in the coat (ratio of EC: PVP from 1:0.5 to 1:3), role of polymer relaxation was observed to diminish and almost became negligible at EC: PVP ratio of 1:3. In case of Cele(31)-EC-41 the n, K and $t_{60\%}$ values were obtained as 0.5552, 7.96 $h^{-0.5552}$ and 37.99 h respectively. The n, K and $t_{60\%}$ values were obtained as 0.4879, 17.30 $h^{-0.4879}$ and 12.79 h respectively in case of Cele(31)-EC:PVP(1:3)21 and as 0.5093, 12.40 $h^{-0.5093}$ and 22.09 h respectively in case of Cele(31)-EC:PVP(1:0.5)21 [Table 6.11].

Table 6.15: Cumulative percentage drug release from microencapsulated granules [Cele(31)] of celecoxib to study the effect of coat composition (varying EC: PVP ratio) at core to coat ratio of 2:1

Time (h)	Cumulative percentage released [a]			
	Cele(31)-EC-PVP(1:3)21	Cele(31)-EC-PVP(1:2)21	Cele(31)-EC-PVP(1:1)21	Cele(31)-EC-PVP(1:0.5)21
1	15.73±1.42	11.96±0.62	10.41±1.62	8.41±1.45
2	22.35±1.59	19.40±1.34	17.14±1.58	15.14±1.33
3	29.60±1.64	24.72±1.26	22.53±1.81	20.53±1.91
6	36.82±1.44	31.96±1.28	30.31±1.57	28.31±1.20
9	44.14±1.63	37.68±1.14	35.54±1.46	33.54±1.98
12	48.61±1.48	43.78±1.08	41.03±1.29	39.03±1.78
15	52.64±1.03	49.15±1.45	47.44±1.69	42.44±1.82
18	56.63±1.48	52.03±1.88	49.78±1.34	45.78±1.22
24	62.16±1.10	56.68±1.38	52.94±1.05	48.94±1.69

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

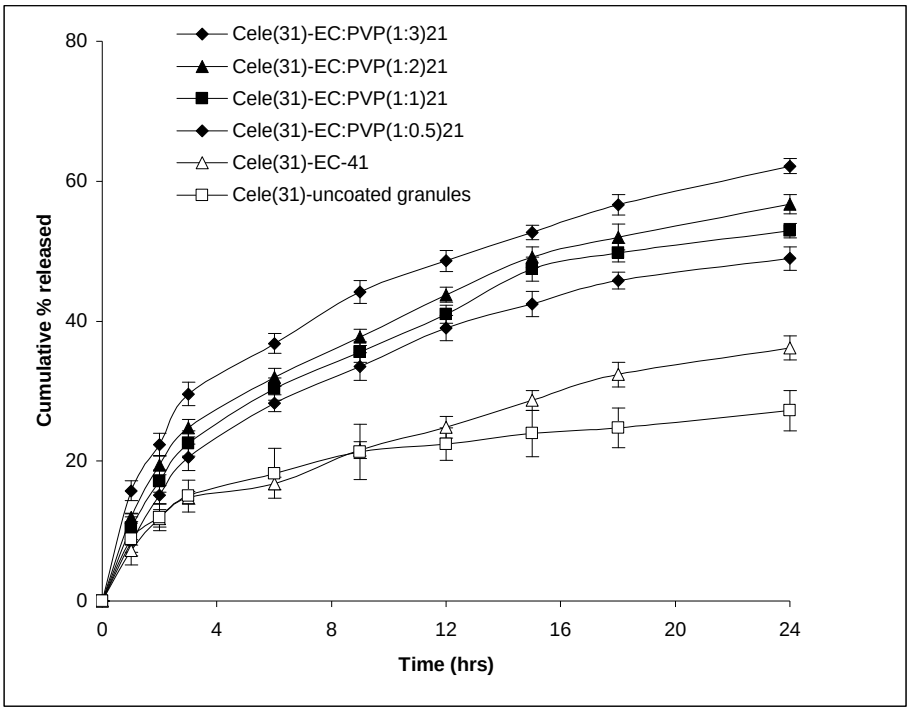

Figure 6.9: In vitro release from microencapsulated Cele(31) granules of celecoxib to study the effects of coating with EC alone and EC & PVP combination in varying ratio [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Effect of coat composition (varying EC: PEG ratio): Similar effect as above was observed in case of granules coated with EC and PEG-6000. As the proportion of hydrophilic polymer PEG-6000 was increased in the coat, there was a corresponding increase in the release rate and cumulative % released in 24 h and this effect was more prominently observed at core to coat ratio of 2:1 when compared to 3:1. At core to coat ratio of 2:1, Cele(21-0.5)-EC-PEG(1:3)21, Cele(21-0.5)-EC-PEG(1:2)21, Cele(21-0.5)-EC-PEG(1:1)21 and Cele(21-0.5)-EC-PEG(1:0.5)21 released 58.10±1.31 %, 53.16±1.30 %, 51.00±1.64 % and 41.14±1.50 % respectively in 24 h [Table 6.16; Figure 6.10]. Similarly at core to coat ratio of 3:1, Cele(21-0.5)-EC-PEG(1:3)31, Cele(21-0.5)-EC-PEG(1:2)31, Cele(21-0.5)-EC-PEG(1:1)31 and Cele(21-0.5)-EC-PEG(1:0.5)31 released 75.66±1.50 %, 59.97±1.37 %, 49.49±1.11 % and 42.54±1.80 % respectively in 24 h [Table 6.17; Figure 6.11].

The drug release data of these products showed best fit to Higuchi's model, with an increase in the r value as the proportion of EC increased in the coat. Encapsulating the granules in EC-PEG polymer system, did not alter the release mechanism significantly. Uncoated as well as the encapsulated products followed quasi-Fickian transport, with a slight increase in the n value and significant decrease in release rate constant with increase in proportion of EC in the coat. At core to coat ratio of 3:1, release rate constant was much higher than at core to coat

ratio of 2:1 for all EC: PEG ratio in the coat. For products at core to coat ratio of 2:1, n, K and $t_{60\%}$ values were obtained as 0.1554, 35.39 $h^{-0.1554}$ and 29.89 h respectively in case Cele(21-0.5)-EC-PEG(1:3)21 (containing least amount of EC in the coat), whereas in case of Cele(21-0.5)-EC-PEG(1:0.5)21 (containing highest amount of EC in the coat), n, K and $t_{60\%}$ values obtained were 0.2975, 12.62 $h^{-0.2975}$ and 188.46 h respectively [Table 6.11]. Similarly, for products at core to coat ratio of 3:1, Cele(21-0.5)-EC-PEG(1:3)31 obtained n, K and $t_{60\%}$ values of 0.1506, 46.27 $h^{-0.1506}$ and 5.62 h respectively, while Cele(21-0.5)-EC-PEG(1:0.5)31 obtained n, K and $t_{60\%}$ values of 0.2265, 20.83 $h^{-0.2265}$ and 106.78 h respectively [Table 6.11].

Table 6.16: Cumulative percentage drug release from microencapsulated granules [Cele(21-0.5)] of celecoxib to study the effect of coat composition (varying EC: PEG ratio) at core to coat ratio of 2:1

Time	Cumulative percentage released [a]			
(h)	Cele(21-0.5)-EC-PEG(1:3)21	Cele(21-0.5)-EC-PEG(1:2)21	Cele(21-0.5)-EC-PEG(1:1)21	Cele(21-0.5)-EC-PEG(1:0.5)21
1	34.77±0.98	26.14±1.12	23.93±1.31	21.55±0.90
2	39.66±1.20	32.21±1.87	30.10±1.88	23.83±1.70
3	41.67±1.14	34.43±1.81	32.33±1.90	25.82±1.90
6	46.67±1.60	38.92±1.63	36.81±1.86	29.87±1.64
9	50.55±1.46	41.83±1.42	39.74±1.73	32.46±1.75
12	51.34±1.24	44.02±1.37	41.96±1.56	35.99±1.34
15	53.20±1.67	46.98±1.39	44.31±1.80	37.17±1.65
18	56.20±1.46	49.90±1.60	47.78±1.41	39.33±1.42
24	58.10±1.31	53.16±1.30	51.00±1.64	41.14±1.50

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

Table 6.17: Cumulative percentage drug release from microencapsulated granules [Cele(21-0.5)] of celecoxib to study the effect of coat composition (varying EC: PEG ratio) at core to coat ratio of 3:1

Time	Cumulative percentage released [a]			
(h)	Cele(21-0.5)-EC-PEG(1:3)31	Cele(21-0.5)-EC-PEG(1:2)31	Cele(21-0.5)-EC-PEG(1:1)31	Cele(21-0.5)-EC-PEG(1:0.5)31
1	45.18±1.35	36.18±1.04	24.31±1.62	22.27±1.43
2	51.58±1.38	41.12±1.81	30.05±1.00	24.62±1.90
3	54.22±1.03	43.14±1.76	32.13±2.01	26.68±1.43
6	60.75±1.30	48.25±1.82	36.30±1.20	30.88±1.71
9	64.89±1.94	51.09±1.64	39.03±1.30	33.56±2.54
12	66.88±1.81	52.95±1.53	41.10±1.80	37.21±1.15
15	69.89±1.63	55.36±1.58	43.62±1.52	38.43±1.92
18	73.12±1.71	58.20±1.46	46.50±1.06	40.66±1.64
24	75.66±1.50	59.97±1.37	49.49±1.11	42.54±1.80

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

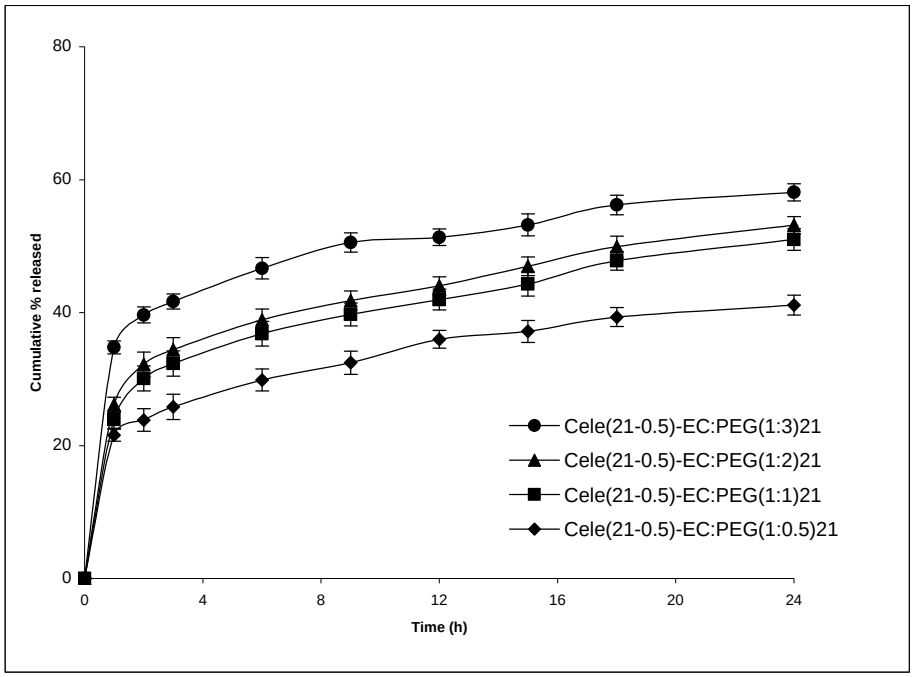

Figure 6.10: In vitro release from microencapsulated Cele(21-0.5) granules of celecoxib to study the effect of coat composition (varying EC: PEG ratio) at core to coat ratio of 2:1 [Data presented is mean ± SD of release studies on products of three batches in duplicate]

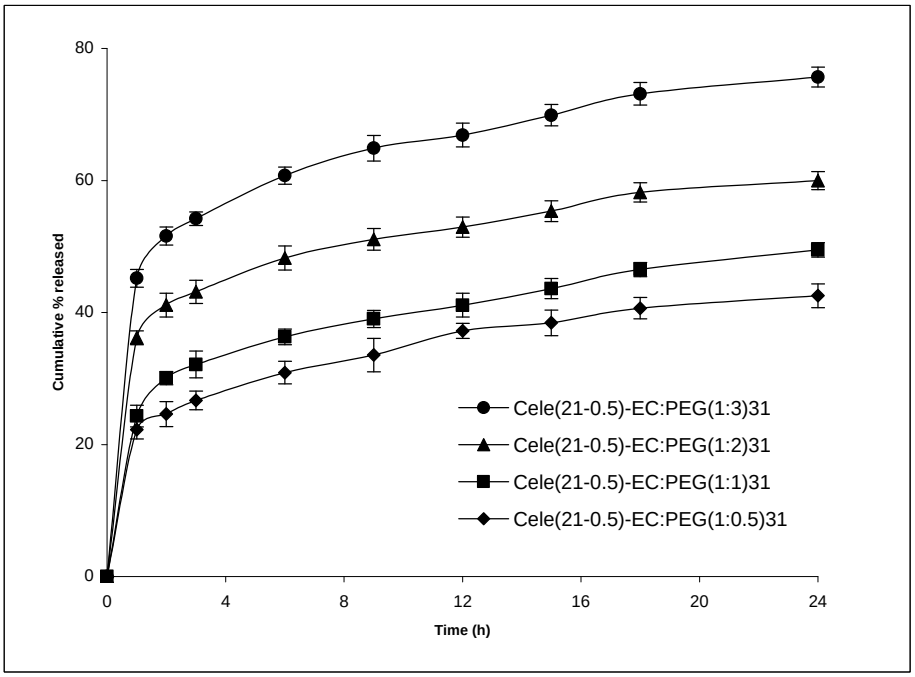

Figure 6.11: In vitro release from microencapsulated Cele(21-0.5) granules of celecoxib to study the effect of coat composition (varying EC: PEG ratio) at core to coat ratio of 3:1 [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Effect of type of hydrophilic polymer type in the coat: Keeping core to coat ratio and hydrophobic to hydrophilic polymer ratio constant, coating Cele(21-0.5) granule with EC-PEG combination resulted in a much faster release and higher cumulative % released in 24 h as compared to that coated with EC-PVP combination, with 48.83±1.21 % for Cele(21-0.5)-EC-PVP(1:3)21] and 58.10±1.31 % [for Cele(21-0.5)-EC-PEG(1:3)21] of drug release in 24 h [Table 6.18; Figure 6.12].

Table 6.18: Cumulative percentage drug release from microencapsulated granules [Cele(21-0.5)] of celecoxib to study the effect of type of hydrophilic polymer in the coat at core to coat ratio (2:1) and two levels of hydrophobic to hydrophilic polymer ratio in the coat

Time (h)	Cumulative percentage released [a]			
	Cele(21-0.5)-EC-PVP(1:3)21	Cele(21-0.5)-EC-PEG(1:3)21	Cele(21-0.5)-EC-PVP(1:0.5)21	Cele(21-0.5)-EC-PEG(1:0.5)21
1	29.25±1.56	34.77±0.98	15.31±1.11	21.55±0.90
2	32.57±1.77	39.66±1.20	17.11±1.47	23.83±1.70
3	33.69±2.42	41.67±1.14	18.92±1.52	25.82±1.90
6	37.65±1.37	46.67±1.60	22.83±1.09	29.87±1.64
9	41.13±1.06	50.55±1.46	24.52±1.69	32.46±1.75
12	43.98±1.42	51.34±1.24	26.00±1.97	35.99±1.34
15	45.31±2.00	53.20±1.67	27.38±1.83	37.17±1.65
18	46.07±1.65	56.20±1.46	28.23±2.01	39.33±1.42
24	48.83±1.21	58.10±1.31	30.62±1.58	41.14±1.50

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

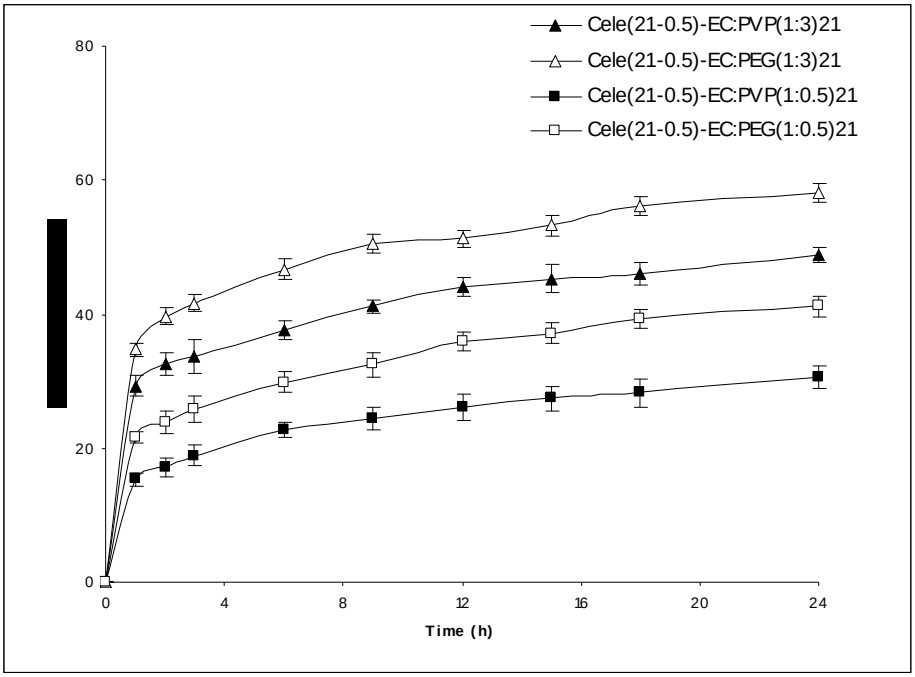

Figure 6.12: In vitro release from microencapsulated Cele(21-0.5) granules of celecoxib to study the effect of type of hydrophilic polymer in the coat at fixed core composition, core to coat ratio (2:1) and two levels of hydrophobic to hydrophilic polymer ratio in the coat [Data presented is mean ± SD of release studies on products of three batches in duplicate]

At higher proportion of EC in the coat (1:0.5), cumulative % drug release in 24 h was 30.62±1.58 % and 41.14±1.50 % respectively in case of Cele(21-0.5)-EC-PVP(1:0.5)21 and Cele(21-0.5)-EC-PEG(1:0.5)21. Release characterization parameters for these formulations are presented in Table 6.11.

6.3.3.3. Sodium alginate based microencapsulated products of acyclovir

For designing microencapsulated products of acyclovir, three different granular cores Acyclo(21-0.5), Acyclo(31-0.5) and Acyclo(31) were employed. As discussed earlier, Acyclo(21-0.5)-uncoated granules of acyclovir showed very rapid drug release kinetics with complete release in 2 h. The primary challenge in this case was to design microencapsulated products for the drug with controlled drug release kinetics and better extension of release profile. Products using other two cores Acyclo(31-0.5) and Acyclo(31) were prepared for comparison purpose. The in vitro release behavior was impacted by parameters like, composition of the inner core, core to coat ratio and coat composition.

Effect of coating with varying amount of EC alone: Granules, coated with EC alone, released the drug in a more controlled fashion and for extended period than uncoated granules as shown in Figure 6.13. While Acyclo(21-0.5)-uncoated granules released the complete dose in just 2 h, Acyclo(21-0.5)-EC-61 and Acyclo(21-0.5)-EC-41 prolonged the release beyond 24 h with 80.44±1.20 % and 68.64±1.02 % cumulative drug release respectively in 24 h [Table 6.19; Figure 6.13]. In case of products with different base to acid ratio in the core (2:1 or 3:1), Acyclo(21-0.5)-EC-41 released 47.74±1.54 % in 6 h and only 68.64±1.02 % in 24 h, while Acyclo(31-0.5)-EC-41 released as low as 41.53±1.41 % in 6 h and as high as 96.52±0.93 % in 24 h [Table 6.19; Figure 6.14].

Table 6.19: Cumulative percentage drug release from microencapsulated granules of acyclovir coated with EC alone

Time (h)	Cumulative percentage released [a]			
	Acyclo(21-0.5)-EC-61	Acyclo(21-0.5)-EC-41	Acyclo(31-0.5)-EC-41	Acyclo(31)-EC-41
1	53.49±1.30	25.00±1.30	10.30±1.07	19.30±1.31
2	60.00±1.20	30.59±1.70	19.52±1.54	24.09±1.15
3	62.64±1.50	39.24±1.50	29.26±1.09	36.49±1.02
6	71.54±1.60	47.74±1.54	41.53±1.41	47.73±1.78
9	74.16±1.40	57.27±1.64	60.08±1.72	63.61±1.28
12	77.27±1.20	63.90±1.25	75.23±1.35	76.90±1.70
15	78.59±2.10	67.04±1.75	85.47±1.03	86.24±1.34
18	79.86±1.50	68.56±1.91	91.97±1.32	96.14±1.21
24	80.44±1.20	68.64±1.02	96.52±0.93	100.24±0.94

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

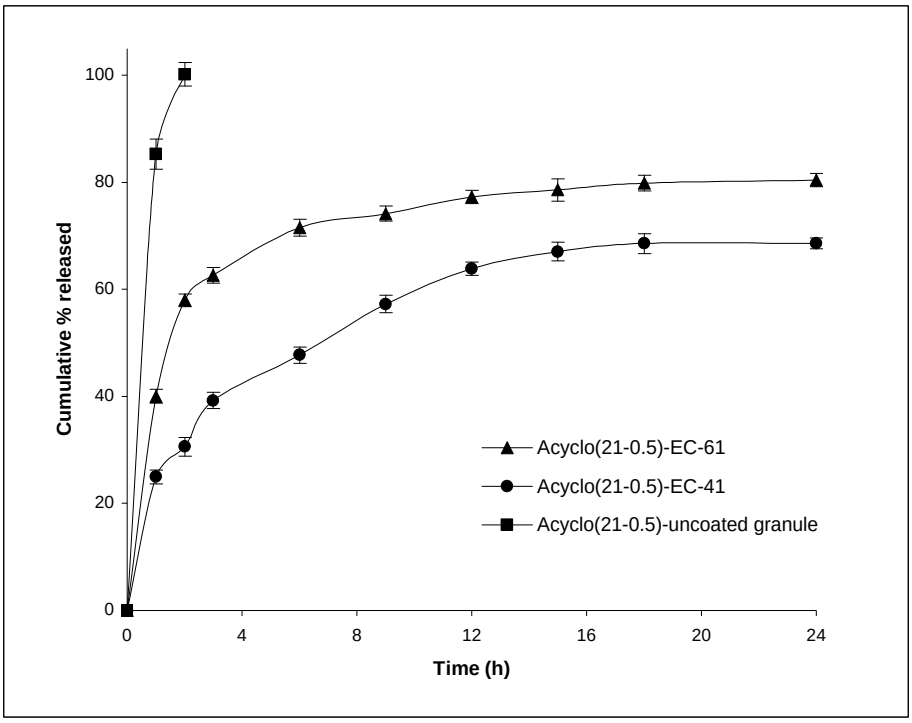

Figure 6.13: In vitro release from Acyclo(21-0.5) microencapsulated granules of acyclovir to study the effect of coating with varying amount of EC [Data presented is mean ± SD of release studies on products of three batches in duplicate]

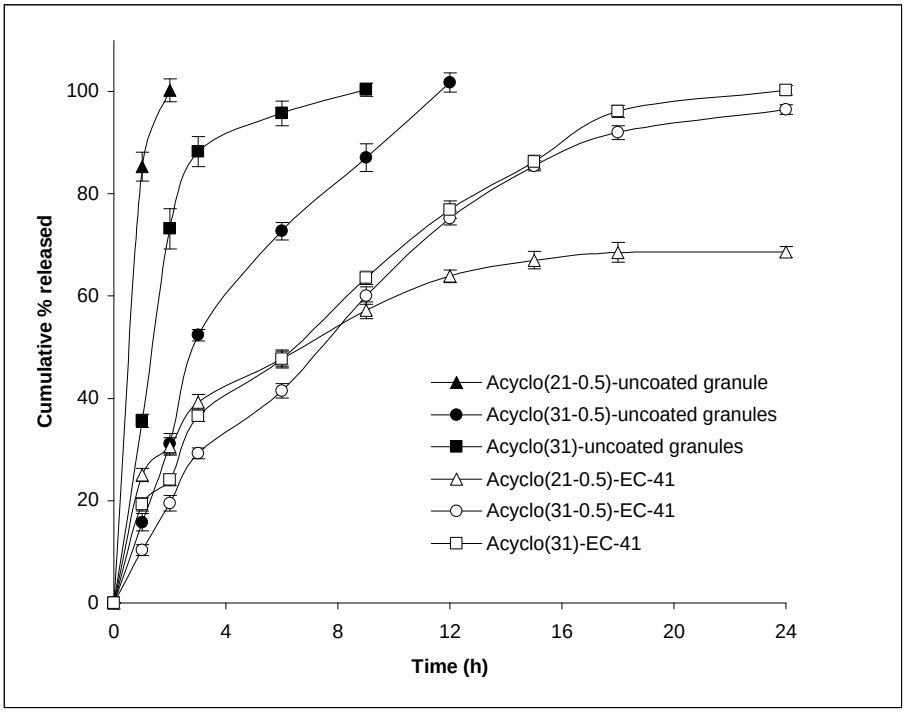

Figure 6.14: In vitro release from sodium alginate based uncoated and EC coated acyclovir granules to study the effect of core composition [Data presented is mean ± SD of release studies on products of three batches in duplicate]

In case of Acyclo(21-0.5)-EC-61 and Acyclo(21-0.5)-EC-41, the n value was obtained as 0.1059 and 0.3924 respectively. The corresponding K and $t_{60\%}$ value was obtained as 55.75 $h^{-0.1059}$ and 2.00 h for Acyclo(21-0.5)-EC-61 and 24.13 $h^{-0.3924}$ and 10.19 h for Acyclo(21-0.5)-EC-41. The mechanism of release was found to be quasi-Fickian in case of EC coated granules of Acyclo(21-0.5) and anamolous in case of Acyclo(31-0.5) and Acyclo(31) granules [Table 6.20].

Effect of core to coat ratio: Faster and higher release was observed for core to coat ratio of 3:1 as compared to 2:1 in case of both EC-PVP and EC-PEG coat at hydrophobic to hydrophilic polymer ratio of 1:1. At 1:1 EC to PVP ratio in the coat at 2:1 core to coat ratio [Acyclo(21-0.5)-EC-PVP(1:1)21], the release was extended beyond 24 h (93.05±1.30 % in 24 h), while at core to coat ratio of 3:1 [Acyclo(21-0.5)-EC-PVP(1:1)31], relatively higher release of 97.60±1.23 % was observed in 24 h. Similarly at fixed EC: PEG ratio of 1:1 in the coat, Acyclo(21-0.5)-EC-PEG(1:1)21 extended the release to beyond 24 h with 95.20±1.40 % drug release in 24 h, while Acyclo(21-0.5)-EC-PEG(1:1)31 showed 100.30±1.54 % release within 15 h [Table 6.21; Figure 6.15]. The mechanism of release in case of products coated with EC-PVP at core to coat ratio of 2:1 & 3:1 was found to be anamolous (n=0.5665) in case of Acyclo(21-0.5)-EC-PVP(1:1)21 and quasi-Fickian (n=0.3528) in case of Acyclo(21-0.5)-EC-PVP(1:1)31. The corresponding release rate constant was $25.70^{-0.5665}$ and $35.43^{-0.3528}$ respectively [Table 6.20]. The n value in case of EC-PEG coated products at 2:1 & 3:1 core to coat ratio was found to be 0.3838 and 0.5779 indicating quasi-Fickian and anamolous release kinetics respectively. The corresponding $t_{60\%}$ for the two products was 4.52 h and 1.78 h respectively [Table 6.20].

In case of microencapsulated Acyclo(21-0.5) products prepared at core to coat ratio of 2:1, coats containing only EC or high proportion of EC i.e. at EC:PVP ratio of 1:0.5 resulted in products with quasi-Fickian type of release mechanism. Upon increasing proportion of PVP in the coat, anamolous/ supercase II type of release mechanism and faster release and higher release rate constants were obtained [Table 6.20]. While for microencapsulated Acyclo(21-0.5) products prepared at core to coat ratio of 3:1, slower release and Fickian/ quasi-Fickian type of release mechanism was observed at EC:PVP ratios of 1:0.5 and 1:1 in the coat. Faster release and anamolous transport was obtained when proportion of PVP was increased in the coat [Table 6.20].

Table 6.20: In vitro release rate parameters of microencapsulated products 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) Coated with EC alone								
Acyclo(21-0.5)-EC-61	0.6735	0.8238	0.8377	0.9999	55.75	0.1059	Quasi-Fickian	2.00
Acyclo(21-0.5)-EC-41	0.8650	0.9239	0.9678	0.9933	24.13	0.3924	Quasi-Fickian	10.19
Acyclo(31-0.5)-EC-41	0.9619	0.9928	0.9863	0.9934	11.16	0.7448	Anamolous	9.57
Acyclo(31)-EC-41	0.9581	0.9639	0.9947	0.9682	16.98	0.6003	Anamolous	8.19
(b) Coated with EC & PVP								
Acyclo(21-0.5)-EC-PVP(1:3)21	0.7443	0.9877	0.9045	0.9999	52.19	0.5962	Anamolous	1.26
Acyclo(21-0.5)-EC-PVP(1:2)21	0.8531	0.9792	0.9534	0.9999	22.85	1.0549	Supercase II	2.50
Acyclo(21-0.5)-EC-PVP(1:1)21	0.8669	0.9775	0.9666	0.9946	25.70	0.5665	Anamolous	4.47
Acyclo(21-0.5)-EC-PVP(1:0.5)21	0.8193	0.8869	0.9408	0.9863	30.68	0.2414	Quasi-Fickian	16.09
Acyclo(21-0.5)-EC-PVP(1:3)31	0.8837	0.9400	0.9803	0.9999	36.81	0.5505	Anamolous	2.43
Acyclo(21-0.5)-EC-PVP(1:2)31	0.8653	0.9711	0.9657	0.9999	32.10	0.6191	Anamolous	2.75
Acyclo(21-0.5)-EC-PVP(1:1)31	0.8870	0.9918	0.9774	0.9722	35.43	0.3528	Quasi-Fickian	4.45
Acyclo(21-0.5)-EC-PVP(1:0.5)31	0.9420	0.9967	0.9963	0.9989	22.10	0.4719	Fickian (case I)	8.30
Acyclo(31-0.5)-EC-PVP(1:1)21	0.9470	0.9721	0.9874	0.9820	20.63	0.4882	Fickian/ Anamolous	8.90
Acyclo(31-0.5)-EC-PVP(1:0.5)21	0.9595	0.9604	0.9891	0.9956	18.35	0.5094	Anamolous	10.24
Acyclo(31)-EC-PVP(1:1)21	0.8339	0.9750	0.9514	0.9999	40.09	0.5065	Anamolous	2.22
Acyclo(31)-EC-PVP(1:0.5)21	0.9285	0.9852	0.9885	0.9325	24.64	0.5912	Anamolous	4.51
(c) Coated with EC & PEG								
Acyclo(21-0.5)-EC-PEG(1:3)21	0.8790	0.9534	0.9829	0.9999	47.49	0.3676	Quasi-Fickian	1.89
Acyclo(21-0.5)-EC-PEG(1:2)21	0.8868	0.9240	0.9772	0.9999	40.98	0.3302	Quasi-Fickian	3.17
Acyclo(21-0.5)-EC-PEG(1:1)21	0.8721	0.9875	0.9712	0.9943	33.64	0.3838	Quasi-Fickian	4.52
Acyclo(21-0.5)-EC-PEG(1:0.5)21	0.8980	0.9768	0.9816	0.9689	27.25	0.3985	Quasi-Fickian	7.25
Acyclo(21-0.5)-EC-PEG(1:3)31	0.8236	0.9977	0.9585	0.9999	53.30	0.3220	Quasi-Fickian	1.44
Acyclo(21-0.5)-EC-PEG(1:2)31	0.8412	0.9985	0.9616	0.9999	47.06	0.3792	Quasi-Fickian	1.90
Acyclo(21-0.5)-EC-PEG(1:1)31	0.8222	0.9837	0.9463	0.9999	42.96	0.5779	Anamolous	1.78
Acyclo(21-0.5)-EC-PEG(1:0.5)31	0.8980	0.9775	0.9792	0.9999	39.52	0.3257	Quasi-Fickian	3.60

[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 6.21: Cumulative percentage drug release from microencapsulated granules [Acyclo(21-0.5)] of acyclovir to study the effect of core to coat ratio at fixed EC: PVP or EC:PEG ratio (1:1) in the coat

Time	Cumulative percentage released [a]			
(h)	Acyclo(21-0.5)-EC-PVP(1:1)21	Acyclo(21-0.5)-EC-PVP(1:1)31	Acyclo(21-0.5)-EC-PEG(1:1)21	Acyclo(21-0.5)-EC PEG(1:1)31
1	23.84±1.23	30.40±1.34	37.73±1.98	42.96±1.50
2	37.16±1.02	43.73±1.64	44.62±1.70	64.12±1.84
3	49.71±1.64	55.09±2.10	49.95±1.57	71.73±2.01
6	69.93±1.81	65.34±1.84	67.56±1.89	86.41±1.88
9	75.04±1.06	71.74±1.56	76.02±1.43	90.67±1.83
12	80.06±1.10	83.35±1.98	84.10±1.82	97.40±1.94
15	81.77±1.52	90.08±1.54	88.47±1.57	100.30±1.54
18	86.09±1.93	95.34±1.29	93.94±2.00	-
24	93.05±1.30	97.60±1.23	95.20±1.40	-

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

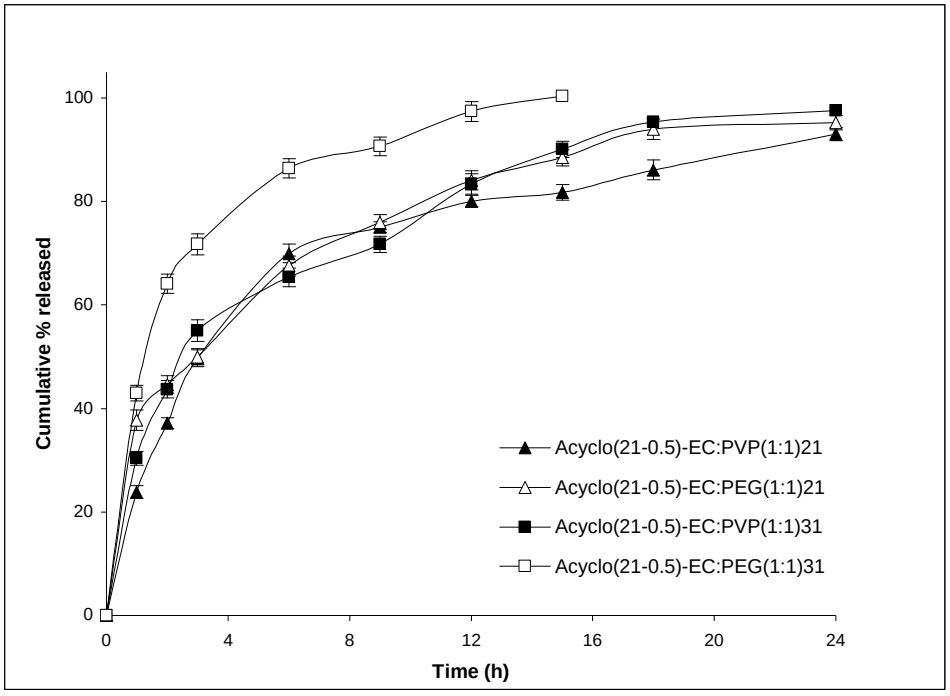

Figure 6.15: In vitro release from microencapsulated Acyclo(21-0.5) granules of acyclovir to study the effect of core to coat ratio at fixed EC: PVP or EC: PEG ratio (1:1) in the coat [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Effect of coat composition (varying EC: PVP ratio): Acyclovir has good solubility in acidic media and its granules coated with EC alone (hydrophobic polymer), released the drug in a more controlled fashion than granules coated with a combination of EC and PVP (coat with hydrophilic content). Increasing the proportion of PVP significantly accelerated the release of acyclovir at all core to coat ratios and core compositions.

In case of Acyclo(21-0.5) granules coated at core to coat ratio of 2:1, Acyclo(21-0.5)-EC-PVP(1:3)21 showed a high initial release of 52.19±1.11 % in 1 h and extended the release up to 12 h. Acyclo(21-0.5)-EC-PVP(1:2)21 and Acyclo(21-0.5)-EC-PVP(1:1)21, with EC: PVP ratio of 1:2 & 1:1 respectively, extended the release to 15 h and beyond 24 h. Whereas, Acyclo(21-0.5)-EC-PVP(1:0.5)21 released only 63.20±1.72 % in 24 h [Table 6.22; Figure 6.16]. Similarly on increasing the proportion of core as in products with core to coat ratio of 3:1, Acyclo(21-0.5)-EC-PVP(1:3)31 showed a relatively lower initial release of 36.51±1.68 % in 1 h and extended the release up to 12 h. Acyclo(21-0.5)-EC-PVP(1:2)31 extended the release to 18 h. On the other hand, Acyclo(21-0.5)-EC-PVP(1:1)31 and Acyclo(21-0.5)-EC-PVP(1:0.5)31 released 97.60±1.23 % and 91.99±1.51 % respectively in 24 h [Table 6.23; Figure 6.17].

Table 6.22: Cumulative percentage drug release from microencapsulated granules [Acyclo(21-0.5)] of acyclovir to study the effect of coat composition (varying EC: PVP ratio) at core to coat ratio of 2:1

Time	Cumulative percentage released [a]			
(h)	Acyclo(21-0.5)-EC-PVP(1:3)21	Acyclo(21-0.5)-EC-PVP(1:2)21	Acyclo(21-0.5)-EC-PVP(1:1)21	Acyclo(21-0.5)-EC-PVP(1:0.5)21
1	52.19±1.11	25.24±1.60	23.84±1.23	19.40±1.51
2	78.90±1.42	47.47±1.10	37.16±1.02	34.70±1.24
3	85.60±1.71	72.81±1.34	49.71±1.64	40.70±1.65
6	95.60±1.41	90.76±1.35	69.93±1.81	49.80±1.45
9	98.60±1.71	97.21±1.65	75.04±1.06	53.60±1.33
12	100.30±1.24	99.86±1.85	80.06±1.10	55.30±1.47
15	-	100.79±1.81	81.77±1.52	57.41±1.21
18	-	-	86.09±1.93	60.80±1.80
24	-	-	93.05±1.30	63.20±1.72

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

Table 6.23: Cumulative percentage drug release from microencapsulated granules [Acyclo(21-0.5)] of acyclovir to study the effect of coat composition (varying EC: PVP ratio) at core to coat ratio of 3:1

Time	Cumulative percentage released [a]			
(h)	Acyclo(21-0.5)-EC-PVP(1:3)31	Acyclo(21-0.5)-EC-PVP(1:2)31	Acyclo(21-0.5)-EC-PVP(1:1)31	Acyclo(21-0.5)-EC-PVP(1:0.5)31
1	36.51±1.68	30.95±1.25	30.40±1.34	18.32±1.50
2	53.92±1.90	49.31±1.75	43.73±1.64	31.04±1.80
3	67.40±1.62	63.37±1.94	55.09±2.10	36.70±1.60
6	85.27±1.23	81.45±1.72	65.34±1.84	50.75±1.30
9	92.52±1.47	87.89±1.68	71.74±1.56	63.20±1.64
12	99.81±1.39	93.29±1.53	83.35±1.98	68.64±1.97
15	-	97.60±1.76	90.08±1.54	79.69±1.58
18	-	99.73±1.41	95.34±1.29	85.41±2.01
24	-	-	97.60±1.23	91.99±1.51

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

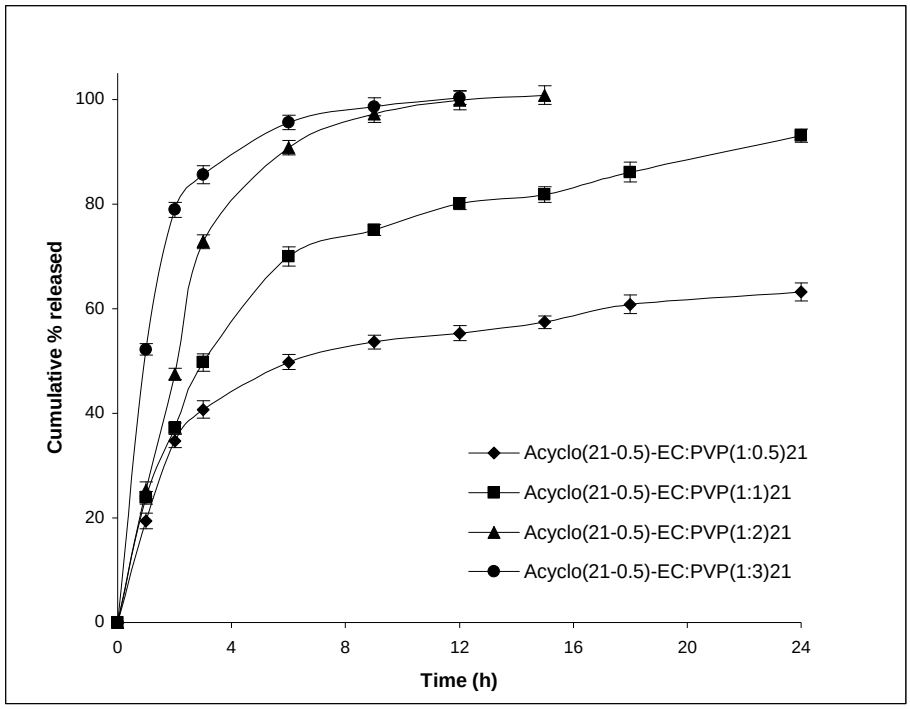

Figure 6.16: In vitro release from microencapsulated Acyclo(21-0.5) granules of acyclovir to study the effect of coat composition (varying EC: PVP ratio) at core to coat ratio of 2:1 [Data presented is mean ± SD of release studies on products of three batches in duplicate]

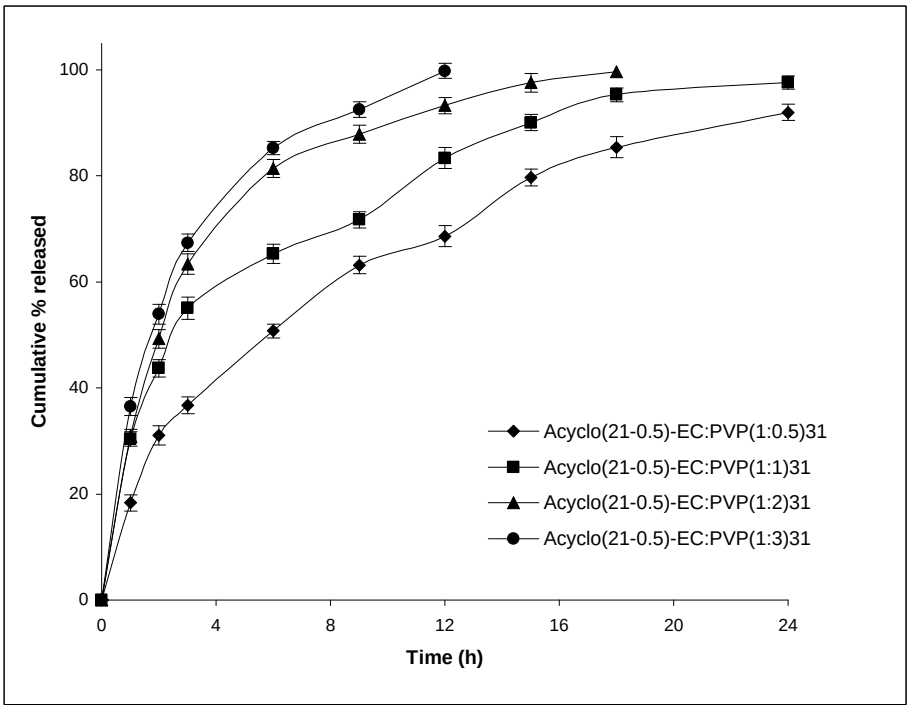

Figure 6.17: In vitro release from microencapsulated Acyclo(21-0.5) granules of acyclovir to study the effect of coat composition (varying EC: PVP ratio) at core to coat ratio of 3:1 [Data presented is mean ± SD of release studies on products of three batches in duplicate]

At core to coat ratio of 2:1, Acyclo(21-0.5)-EC-PVP(1:3)21 with least amount of EC in the coat showed fastest release kinetics with n, K and $t_{60\%}$ values of 0.5962, 52.19 $h^{-0.5962}$ and 1.26 h respectively, whereas in case of Acyclo(21-0.5)-EC-PVP(1:0.5)21 with highest amount of EC in the coat, the values were obtained as 0.2414, 30.68 $h^{-0.2414}$ and 16.09 h respectively [Table 6.20]. At core to coat ratio of 3:1 for Acyclo(21-0.5)-EC-PVP(1:3)31 the n, K and $t_{60\%}$ values were found to be 0.5505, 36.81 $h^{-0.5505}$ and 2.43 h respectively, while in case of Acyclo(21-0.5)-EC-PVP(1:0.5)31 the values were obtained as 0.4719, 22.10 $h^{-0.4719}$ and 8.30 h respectively [Table 6.20].

Similar effects were observed in case of Acyclo(31-0.5) and Acyclo(31) coated granules [Table 6.24; Figure 6.18]. Upon decreasing the proportion of PVP in the coat, there was corresponding retardation of drug release. The mechanism of release in this category of products was found to be anamolous with faster release in case of Acyclo(31) coated granules than for Acyclo(31-0.5) coated granules. Release characterization parameters for this category of formulations are enlisted in Table 6.20.

Table 6.24: Cumulative percentage drug release from microencapsulated granules [Acyclo(31-0.5) & Acyclo(31)] of acyclovir to study the effect of coat composition (varying EC: PVP ratio) at core to coat ratio of 2:1

Time	**Cumulative percentage released** [a]			
(h)	**Acyclo(31-0.5)-EC-PVP(1:1)21**	**Acyclo(31-0.5)-EC-PVP(1:0.5)21**	**Acyclo(31)-EC-PVP(1:1)21**	**Acyclo(31)-EC-PVP(1:0.5)21**
1	15.38±1.42	14.04±1.33	40.09±1.75	20.31±1.08
2	30.21±1.38	26.74±2.01	56.95±1.16	33.87±1.18
3	38.43±1.07	35.60±1.26	74.28±1.39	54.55±1.10
6	47.13±1.03	45.67±1.98	83.97±1.23	67.36±1.39
9	64.10±0.87	57.36±1.17	88.65±1.16	81.43±1.24
12	83.70±1.31	77.35±1.77	94.60±1.07	90.16±1.54
15	94.42±1.75	90.36±1.60	100.37±0.99	97.22±1.92
18	99.35±1.67	95.37±1.97	-	101.02±0.73
24	-	99.55±1.51	-	-

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

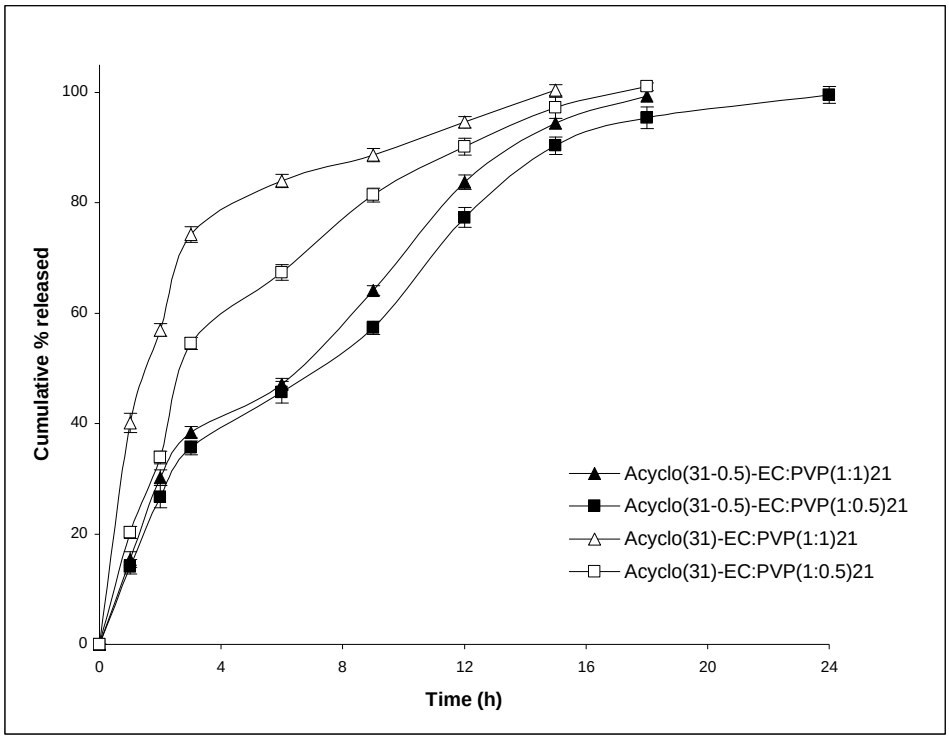

Figure 6.18: In vitro release from microencapsulated Acyclo(31-0.5) and Acyclo(31) granules of acyclovir to study the effect of coating with EC & PVP combination in varying ratio [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Effect of coat composition (varying EC: PEG ratio): As the proportion of PEG was increased in the coat there was a corresponding enhancement in the release rate. This effect was more prominently observed at core to coat ratio of 2:1 than in case of 3:1 [Table 6.25; Figure 6.19].

Table 6.25: Cumulative percentage drug release from microencapsulated granules [Acyclo(21-0.5)] of acyclovir to study the effect of coat composition (varying EC: PEG ratio) at core to coat ratio of 2:1

Time	Cumulative percentage released [a]			
(h)	Acyclo(21-0.5)-EC-PEG(1:3)21	Acyclo(21-0.5)-EC-PEG(1:2)21	Acyclo(21-0.5)-EC-PEG(1:1)21	Acyclo(21-0.5)-EC-PEG(1:0.5)21
1	47.49±1.53	42.71±1.07	37.73±1.98	25.10±1.34
2	61.27±1.39	51.52±2.03	44.62±1.70	33.60±1.87
3	68.42±1.20	58.90±1.85	49.95±1.57	45.60±1.50
6	91.91±1.50	72.50±1.27	67.56±1.89	57.80±1.10
9	99.86±1.76	81.50±1.57	76.02±1.43	62.30±1.97
12	-	89.30±1.29	84.10±1.82	67.44±1.76
15	-	99.23±1.64	88.47±1.57	78.70±1.28
18	-	-	93.94±2.00	82.04±2.01
24	-	-	95.20±1.40	85.23±1.60

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

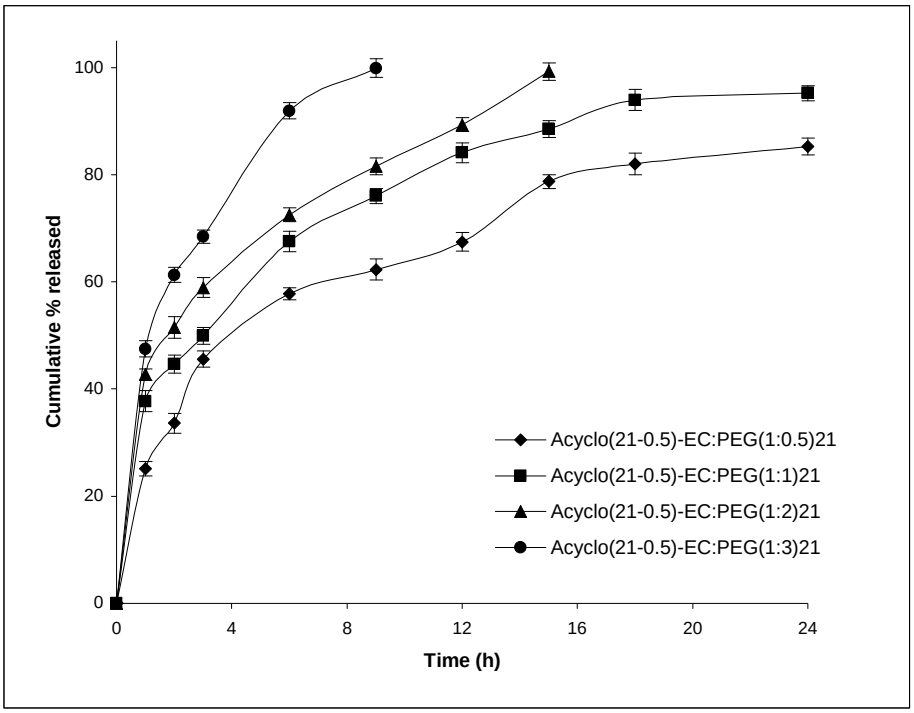

Figure 6.19: In vitro release from microencapsulated Acyclo(21-0.5) granules of acyclovir to study the effect of coat composition (varying EC: PEG ratio) at core to coat ratio of 2:1 [Data presented is mean ± SD of release studies on products of three batches in duplicate]

At core to coat ratio of 2:1, Acyclo(21-0.5)-EC-PEG(1:3)21 (with one part of EC to 3 parts of PEG in the coat) and Acyclo(21-0.5)-EC-PEG(1:2)21 (with one part of EC to 2 parts of PEG in the coat) extended the release to 9 h and 15 h respectively, while Acyclo (21-0.5)-EC-PEG(1:1)21 and Acyclo(21-0.5)-EC-PEG(1:0.5)21 extended the release beyond 24 h with 95.20±1.40 % and 85.23±1.60 % in 24 h respectively. Similar results were obtained at core to coat ratio of 3:1. Acyclo(21-0.5)-EC-PEG(1:3)31, Acyclo(21-0.5)-EC-PEG(1:2)31, Acyclo(21-0.5)-EC-PEG(1:1)31 and Acyclo(21-0.5)-EC-PEG(1:0.5)31 extended the release to 9 h, 12 h, 15 h and 18 h respectively [Table 6.26; Figure 6.20].

The release data for formulations in this category prepared at core to coat ratio of 2:1 showed best fit to Higuchi's model, while formulations prepared at core to coat ratio of 3:1 showed best fit to first order release model in most of the cases. At both core to coat ratios, quasi-Fickian type of release mechanism was observed in all cases, with an exception of Acyclo(21-0.5)-EC-PEG(1:1)31, which showed anamolous type of release. For products at core to coat ratio of 2:1, Acyclo(21-0.5)-EC-PEG(1:3)21 showed fastest release with K value of 47.49 $h^{-0.3676}$ and $t_{60\%}$ value of 1.89 h. Whereas, Acyclo(21-0.5)-EC-PEG(1:0.5)21 showed slowest release with K value of 27.25 $h^{-0.3985}$ and $t_{60\%}$ value of 7.25 h. The n value of this category of products ranged from 0.3302 to 0.3985 indicating quasi-Fickian release

mechanism. For products at core to coat ratio of 3:1, Acyclo(21-0.5)-EC-PEG(1:3)31 showed fastest release with n, K and $t_{60\%}$ values of 0.3220, 53.30 $h^{-0.3220}$ and 1.44 h respectively. On the other hand, Acyclo(21-0.5)-EC-PEG(1:0.5)31 showed slowest release with n, K and $t_{60\%}$ values of 0.3257, 39.52 $h^{-0.3257}$ and 3.60 h respectively [Table 6.20].

Table 6.26: Cumulative percentage drug release from microencapsulated granules [Acyclo(21-0.5)] of acyclovir to study the effect of coat composition (varying EC: PEG ratio) at core to coat ratio of 3:1

Time (h)	Cumulative percentage released [a]			
	Acyclo(21-0.5)-EC PEG(1:3)31	Acyclo(21-0.5)-EC PEG(1:2)31	Acyclo(21-0.5)-EC PEG(1:1)31	Acyclo(21-0.5)-EC PEG(1:0.5)31
1	53.30±1.66	47.06±1.18	42.96±1.50	42.91±1.43
2	66.62±1.87	61.21±1.08	64.12±1.84	49.53±2.01
3	82.30±1.08	73.46±1.62	71.73±2.01	56.52±1.84
6	96.80±1.82	93.76±1.09	86.41±1.88	68.19±1.68
9	100.20±1.06	98.61±1.17	90.67±1.83	78.60±1.90
12	-	101.30±1.56	97.40±1.94	89.50±1.57
15	-	-	100.30±1.54	96.30±1.94
18	-	-	-	100.30±1.35

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

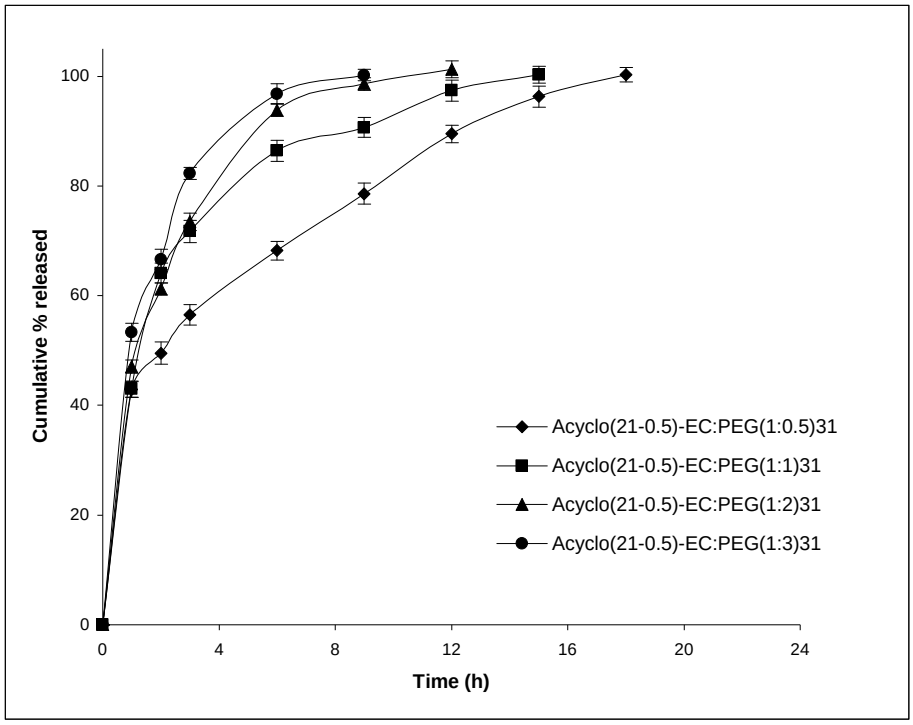

Figure 6.20: In vitro release from microencapsulated Acyclo(21-0.5) granules of acyclovir to study the effect of coat composition (varying EC:PEG ratio) at core to coat ratio of 3:1 [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Effect of type of hydrophilic polymer in the coat: At core to coat ratio of 2:1 and hydrophobic to hydrophilic polymer ratio of 1:0.5, coating Acyclo(21-0.5) granules with EC-PEG combination resulted in a much faster release and a higher cumulative drug release at 24 h as compared to that coated with EC-PVP combination [Table 6.27; Figure 6.21].

Table 6.27: Cumulative percentage drug release from microencapsulated granules [Acyclo(21-0.5)] of acyclovir to study the effect of type of hydrophilic polymer in the coat at core to coat ratio (2:1) and two levels of hydrophobic to hydrophilic polymer ratio in the coat

Time	Cumulative percentage released [a]			
(h)	Acyclo(21-0.5)-EC-PVP(1:3)21	Acyclo(21-0.5)-EC-PEG(1:3)21	Acyclo(21-0.5)-EC-PVP(1:0.5)21	Acyclo(21-0.5)-EC-PEG(1:0.5)21
1	52.19±1.11	47.49±1.53	19.40±1.51	25.10±1.34
2	78.90±1.42	61.27±1.39	34.70±1.24	33.60±1.87
3	85.60±1.71	68.42±1.20	40.70±1.65	45.60±1.50
6	95.60±1.41	91.91±1.50	49.80±1.45	57.80±1.10
9	98.60±1.71	99.86±1.76	53.60±1.33	62.30±1.97
12	100.30±1.24	-	55.30±1.47	67.44±1.76
15	-	-	57.41±1.21	78.70±1.28
18	-	-	60.80±1.80	82.04±2.01
24	-	-	63.20±1.72	85.23±1.60

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

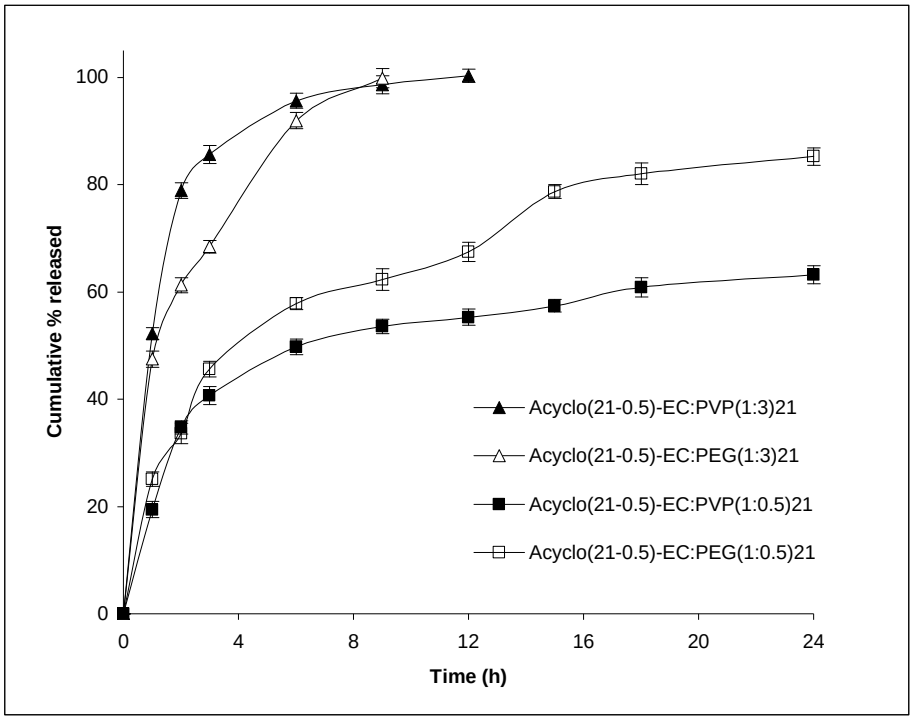

Figure 6.21: In vitro release from microencapsulated Acyclo(21-0.5) granules of acyclovir to study the effect of hydrophilic polymer in the coat at fixed core composition, core to coat ratio (2:1) and two levels of hydrophobic to hydrophilic polymer ratio in the coat [Data presented is mean ± SD of release studies on products of three batches in duplicate]

However at the same core to coat ratio (2:1), but higher hydrophobic to hydrophilic polymer ratio (1:3), this effect was not observed. Acyclo(21-0.5)-EC-PEG(1:3)21 and Acyclo(21-0.5)-EC-PVP(1:3)21 extended the release to 9 and 12 h respectively, in which faster and higher drug release was observed in case of EC-PVP coated Acyclo(21-0.5) granules up to 6 h. This could be because of higher degree of agglomeration observed in case of Acyclo(21-0.5)-EC-PEG(1:3)21 as compared to Acyclo(21-0.5)-EC-PVP(1:3)21. Release characterization parameters are as already mentioned in the preceding paragraphs and the results are presented in Table 6.20.

6.3.4. In vitro release studies and release kinetics characterization of calcium alginate beads

In case of calcium alginate beads, results of cumulative percentage release are presented in Tables 6.28, 6.30 and 6.31 for celecoxib and in Table 6.32 for acyclovir with the corresponding release characterization data of all these products enlisted in Table 6.29. Plots of cumulative percentage release versus time for various calcium alginate beads based MU-GR-CRDFs are shown in Figures 6.22 to 6.24 (calcium alginate beads of celecoxib) and Figure 6.25 (calcium alginate beads of acyclovir).

6.3.4.1. Calcium alginate beads of celecoxib

The in vitro release profile of celecoxib from calcium alginate beads was influenced by various parameters like, mode of drying, inclusion of sodium bicarbonate in the formula, proportion of span 20 and proportion of sodium alginate. The effect of these parameters on the release kinetics is discussed in the following sections.

Effect of vacuum drying versus freeze drying: Freeze dried beads showed a faster and higher cumulative % release in 24 h than vacuum dried beads. This was probably due to increased porosity in case of lyophilized products. At fixed drug to sodium alginate ratio of 1:1.5 and drug to span 20 ratio of 1:0.25, vacuum dried beads Cele-A(1.5)-V-0.25 released 30.13±1.12 % in 24 h, whereas freeze dried beads Cele-A(1.5)-F-0.25 released 44.18±0.91 % in 24 h [Table 6.28; Figure 6.22].

Vacuum dried product, without sodium bicarbonate, showed higher n value than its corresponding freeze dried product. In case of formulation Cele-A(1.5)-V-0.25 the obtained n, K and $t_{60\%}$ values were 0.7138, 3.37 $h^{-0.7138}$ and 56.56 h respectively. On the other hand for Cele-A(1.5)-F-0.25 the obtained n, K and $t_{60\%}$ values were obtained as 0.5658, 6.88 $h^{-0.5658}$ and 45.99 h respectively [Table 6.29].

Table 6.28: Cumulative percentage drug release from calcium alginate beads of celecoxib to study the effects of vacuum drying versus freeze drying and presence of sodium bicarbonate

Time (h)	Cumulative percentage released [a]			
	Cele-A(1.5)-V-0.25	Cele-A(1.5)-sbc(1.0)-V-0.25	Cele-A(1.5)-F-0.25	Cele-A(1.5)-sbc(1.0)-F-0.25
1	5.66±1.36	7.98±1.88	8.70±0.88	9.60±0.87
2	6.07±1.61	9.97±1.17	11.16±0.97	12.61±0.79
3	6.43±1.39	12.85±1.71	12.13±1.02	15.90±1.01
6	12.37±1.16	15.86±1.19	18.13±1.19	24.08±0.99
9	14.58±1.47	17.90±1.28	22.95±1.28	31.81±1.08
12	22.55±1.57	24.77±1.40	27.30±1.17	39.65±1.54
15	24.69±1.39	28.31±1.52	31.81±1.23	45.93±1.41
18	26.84±1.80	31.06±1.01	35.70±1.01	51.35±1.21
24	30.13±1.12	36.99±1.12	44.18±0.91	56.88±1.06

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

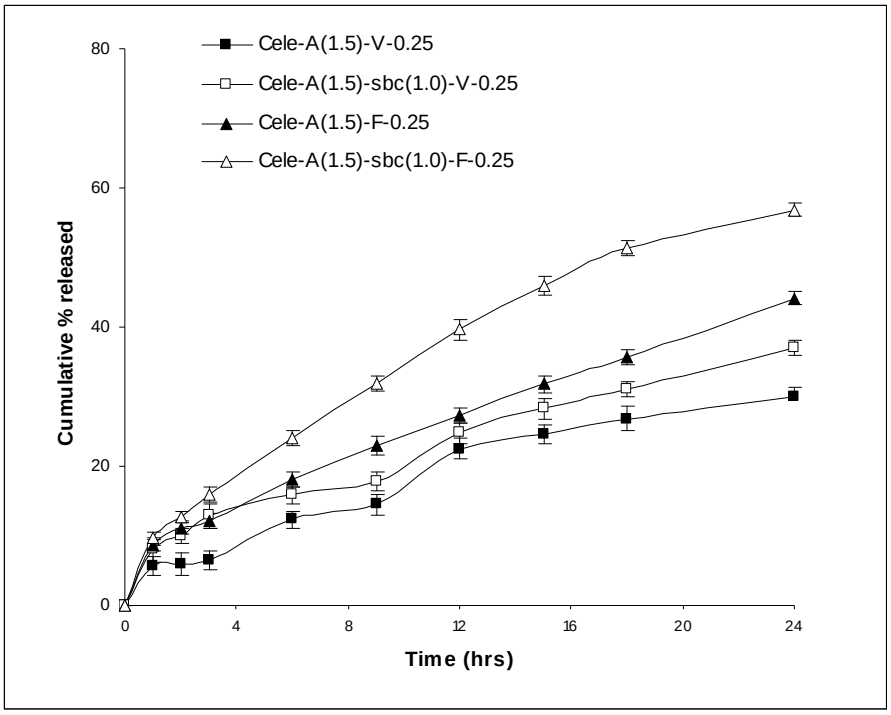

Figure 6.22: In vitro release from calcium alginate beads of celecoxib to study the effects of vacuum drying versus freeze drying and presence of sodium bicarbonate [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Table 6.29: In vitro release rate parameters of calcium alginate beads of celecoxib and acyclovir

Core 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) Celecoxib products								
Cele-A(1.5)-V-0.25	0.9747	0.9813	0.9830	0.9884	3.37	0.7138	Anamolous	56.56
Cele-A(1.5)-sbc(1.0)-V-0.25	0.9748	0.9855	0.9915	0.9852	6.76	0.5170	Anamolous	68.21
Cele-A(1.5)-F-0.25	0.9835	0.9932	0.9930	0.9944	6.88	0.5658	Anamolous	45.99
Cele-A(1.5)-sbc(1.0)-F-0.25	0.9772	0.9934	0.9944	0.9986	8.05	0.6278	Anamolous	24.51
Cele-A(0.5)-F-0.75	0.9657	0.9936	0.9993	0.9991	12.22	0.5492	Anamolous	18.13
Cele-A(0.75)-F-0.75	0.9673	0.9912	0.9988	0.9983	10.43	0.5625	Anamolous	22.42
Cele-A(1.0)-F-0.75	0.9631	0.9856	0.9986	0.9966	9.51	0.5528	Anamolous	28.01
Cele-A(1.5)-F-0.75	0.9712	0.9888	0.9989	0.9989	8.87	0.5333	Anamolous	36.04
(b) Acyclovir products								
Acyclo-A(0.75)-F	0.9104	0.9889	0.9938	0.9999	37.06	0.7086	Anamolous	1.97
Acyclo-A(1.0)-F	0.8944	0.9609	0.9869	0.9999	37.55	0.5770	Anamolous	2.25
Acyclo-A(1.5)-F	0.9410	0.9978	0.9961	0.9999	25.75	0.5216	Anamolous	5.06
Acyclo-A(2.0)-F	0.9429	0.9939	0.9977	0.9995	25.94	0.4267	Quasi-Fickian/ Fickian	7.13
Acyclo-A(2.5)-F	0.9417	0.9893	0.9971	0.9973	25.49	0.4020	Quasi-Fickian	8.41
Acyclo-A(3.0)-F	0.9289	0.9912	0.9936	0.9967	24.77	0.3868	Quasi-Fickian	9.84

[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 presence of sodium bicarbonate: Presence of sodium bicarbonate in the formula (at fixed drug to sodium alginate ratio of 1:1.5, drug to sodium bicarbonate ratio of 1:1 and drug to span 20 ratio of 1:0.25) increased the drug release rate from the beads and overall release in 24 h [Table 6.28; Figure 6.22]. This was probably due to incomplete conversion of sodium alginate (water soluble polymer) to calcium alginate (water insoluble and rate controlling polymer) during curing process due to the presence of sodium bicarbonate. In case of formulation with sodium bicarbonate, Cele-A(1.5)-sbc(1.0)-V-0.25 obtained n, K and $t_{60\%}$ values of 0.5170, 6.76 h^{-n} and 68.21 h respectively, while Cele-A(1.5)-sbc(1.0)-F-0.25 obtained these values as 0.6278, 8.05 h^{-n} and 24.51 h respectively [Table 6.29].

Effect of proportion of span 20: Keeping other parameters constant, upon increasing the proportion of span 20 in the formula, a faster and higher release was observed. This was as expected because a wetting agent usually enhances release rate, especially in case of water insoluble drugs like, celecoxib [Table 6.30; Figure 6.23]. At drug to sodium alginate ratio of 1:1.5, Cele-A(1.5)-F-0.25 (with drug to span 20 ratio of 1:0.25) and Cele-A(1.5)-F-0.75 (with drug to span 20 ratio of 1:0.75) released 44.18±0.91 % and 48.56±1.04 % respectively in 24 h [Table 6.30].

Table 6.30: Cumulative percentage drug release from freeze dried calcium alginate beads of celecoxib to study the effect of proportion of span 20

Time (h)	**Cumulative percentage released** [a]	
	Cele-A(1.5)-F-0.25	**Cele-A(1.5)-F-0.75**
1	8.70±0.88	9.99±0.98
2	11.16±0.97	13.32±1.07
3	12.13±1.02	15.40±1.36
6	18.13±1.19	22.89±1.57
9	22.95±1.28	28.43±1.39
12	27.30±1.17	33.02±1.16
15	31.81±1.23	37.61±1.22
18	35.70±1.01	42.18±1.47
24	44.18±0.91	48.56±1.04

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

Increase in the proportion of wetting agent in the formula resulted in higher K value and lower $t_{60\%}$ value. For Cele-A(1.5)-F-0.75 the n, K and $t_{60\%}$ values were obtained as 0.5333, 8.87 $h^{-0.5333}$ and 36.04 h respectively and for Cele-A(1.5)-F-0.25 these values were obtained as 0.5658, 6.88$h^{-0.5658}$ and 45.99 h [Table 6.29].

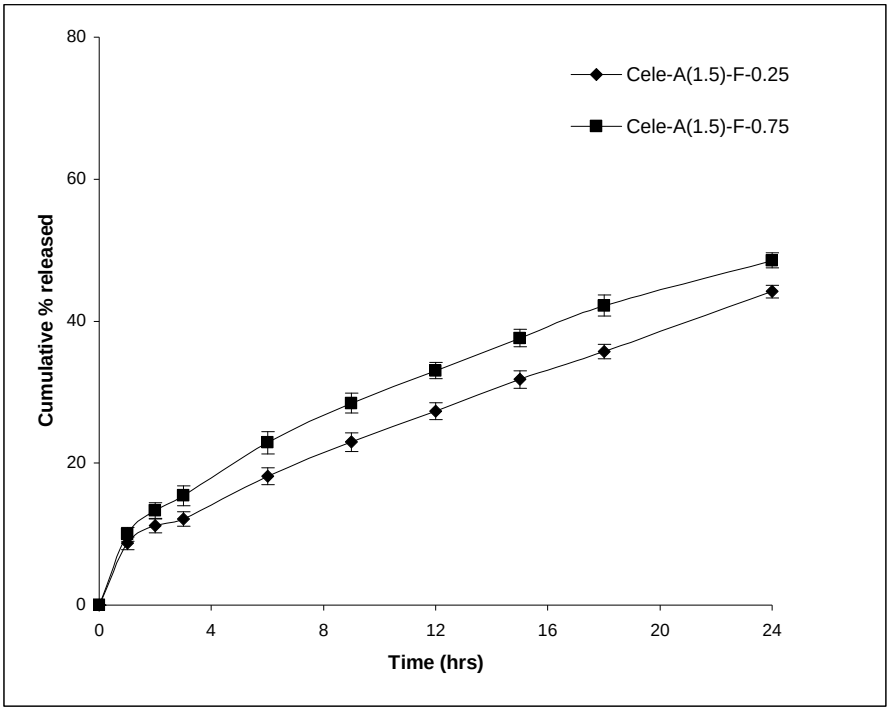

Figure 6.23: In vitro release from freeze dried calcium alginate beads of celecoxib to study the effect of proportion of span 20 at drug to sodium alginate ratio of 1:1.5 [Data presented is mean ± SD of release studies on products of three batches in duplicate]

Effect of proportion of sodium alginate: Increase in the relative proportion (corresponding to drug) of sodium alginate from 0.5 to 1.5 in the formula resulted in lower K value and higher $t_{60\%}$ value. This is because higher proportion of sodium alginate would have resulted in formation of higher amount of rate controlling polymer (calcium alginate), resulting in corresponding retardation in the release rate [Table 6.31; Figure 6.24]. For these formulations, n value varied between 0.5333 [Cele-A(1.5)-F-0.75)] and 0.5625 [Cele-A(0.75)-F-0.75]. Fastest release was observed in case of Cele-A(0.5)-F-0.75 with K and $t_{60\%}$ value of 12.22 $h^{-0.5492}$ and 18.13 h respectively with a cumulative release of 67.57±1.11 % in 24 h; and slowest release was observed in case of Cele-A(1.5)-F-0.75 with K and $t_{60\%}$ value of 8.87 $h^{-0.5333}$ and 36.04 h respectively with a cumulative release of only 48.56±1.04 % in 24 h. The release mechanism was found to be anamolous in case of all the formulations prepared in this category [Tables 6.29 and 6.31].

Table 6.31: Cumulative percentage drug release from freeze dried calcium alginate beads of celecoxib to study the effect of proportion of sodium alginate

Time (h)	Cumulative percentage released [a]			
	Cele-A(0.5)-F-0.75	Cele-A(0.75)-F-0.75	Cele-A(1.0)-F-0.75	Cele-A(1.5)-F-0.75
1	13.52±0.91	11.55±1.00	10.85±0.89	9.99±0.98
2	17.72±1.01	15.41±1.13	14.09±0.91	13.32±1.07
3	22.09±1.26	18.53±1.07	16.27±1.09	15.40±1.36
6	34.12±1.13	30.03±1.39	27.24±1.06	22.89±1.57
9	40.84±1.02	36.56±1.01	32.86±1.22	28.43±1.39
12	47.27±1.33	42.31±1.35	38.23±1.11	33.02±1.16
15	53.75±1.42	47.99±1.36	42.55±1.43	37.61±1.22
18	59.55±1.59	53.25±1.12	46.43±1.54	42.18±1.47
24	67.57±1.11	60.32±1.03	53.19±1.15	48.56±1.04

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

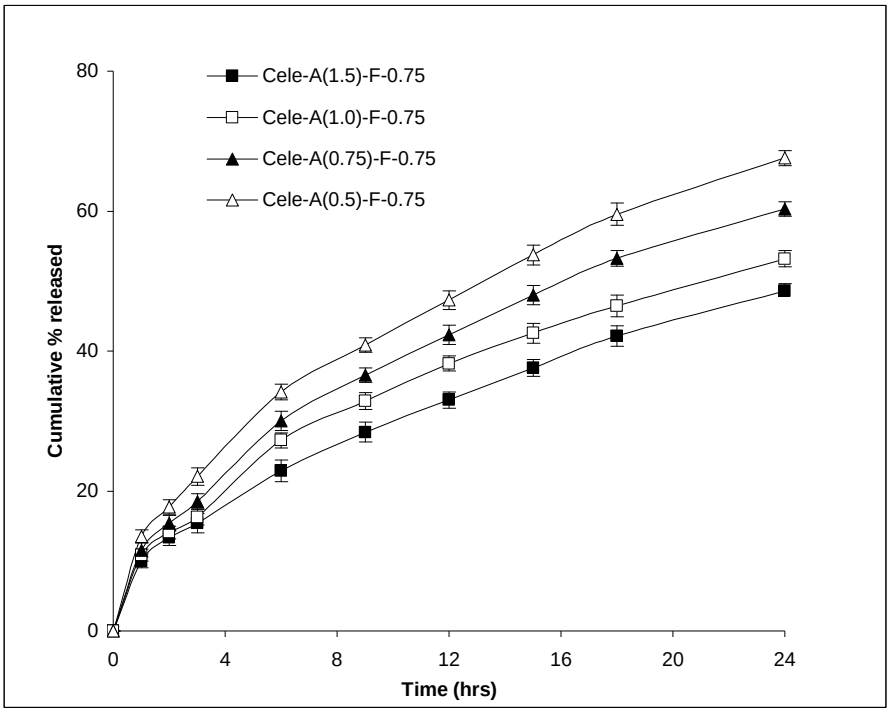

Figure 6.24: In vitro release from freeze dried calcium alginate beads of celecoxib to study the effect of proportion of sodium alginate [Data presented is mean ± SD of release studies on products of three batches in duplicate]

6.3.4.2. Calcium alginate beads of acyclovir

Effect of proportion of sodium alginate: On increasing the proportion of sodium alginate in the formula, a corresponding decrease in the release was observed due to formation of higher proportion of rate controlling polymer calcium alginate in the beads. Acyclo-A(0.75)-F, Acyclo-A(1.0)-F, Acyclo-A(1.5)-F, Acyclo-A(2.0)-F, Acyclo-A(2.5)-F and Acyclo-A(3.0)-F

extended the release of acyclovir to 6 h, 9 h, 18 h, 24 h, beyond 24 h (95.01±1.07 % in 24 h) and beyond 24 h (85.28±1.23 % in 24 h) respectively [Table 6.32; Figure 6.25].

Except for Acyclo-A(1.5)-F, which showed highest r value for first order release model, other bead based formulations of acyclovir showed highest r value for Higuchi's model. On increasing the proportion of calcium alginate (rate-controlling polymer), the release transport changed from anamolous to Fickian to quasi-Fickian and resulted in lower release rates. The change in release transport could be attributed to the physicochemical property of the drug. Acyclovir, being highly soluble in acidic media, showed higher wicking action of the media. Calcium alginate, though negligibly swellable and relaxable in acidic media showed significant extent of polymer relaxation due to higher proportion of lyophilic agent (acyclovir) at lower polymer proportion and little/ no polymer relaxation at higher polymer proportion due to higher rigidity and lesser wicking action of the drug. Acyclo-A(0.75)-F with lowest polymer proportion, showed anamolous transport (n=0.7086) and had fastest release with K and $t_{60\%}$ value of 37.06 $h^{-0.7086}$ and 1.97 h respectively. Acyclo-A(2.0)-F with intermediate polymer proportion, showed quasi-Fickian/ Fickian transport (n=0.4267) and intermediate release rate with K and $t_{60\%}$ value of 25.94 $h^{-0.4267}$ and 7.13 h respectively. On the other hand, Acyclo-A(3.0)-F with highest polymer proportion, showed quasi-Fickian transport (n=0.3868) and slowest release with K and $t_{60\%}$ value of 24.77 $h^{-0.3868}$ and 9.84 h respectively [Table 6.29].

Table 6.32: Cumulative percentage drug release from freeze dried calcium alginate beads of acyclovir to study the effect of proportion of sodium alginate

Time (h)	Cumulative percentage released [a]					
	Acyclo-A(0.75)-F	**Acyclo-A(1.0)-F**	**Acyclo-A(1.5)-F**	**Acyclo-A(2.0)-F**	**Acyclo-A(2.5)-F**	**Acyclo-A(3.0)-F**
1	47.12±1.13	42.39±1.09	23.44±0.94	22.26±0.92	21.58±0.93	20.90±0.83
2	60.57±1.44	56.01±1.63	36.86±1.91	35.15±1.94	34.34±1.32	33.08±1.73
3	80.73±1.72	70.77±1.54	45.90±1.52	41.13±1.79	38.54±1.02	36.94±1.27
6	100.12±1.53	95.25±1.43	65.46±1.78	55.30±1.76	52.55±1.74	49.09±1.26
9	-	99.95±1.15	76.53±1.56	66.77±1.22	61.97±1.20	58.75±1.98
12	-	-	84.94±1.48	76.56±1.93	72.90±1.96	69.29±1.96
15	-	-	91.27±1.51	83.39±1.88	79.27±1.42	74.17±1.86
18	-	-	100.08±1.03	90.57±1.76	85.84±1.85	80.21±1.51
24	-	-	-	101.05±0.95	95.01±1.07	85.28±1.23

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

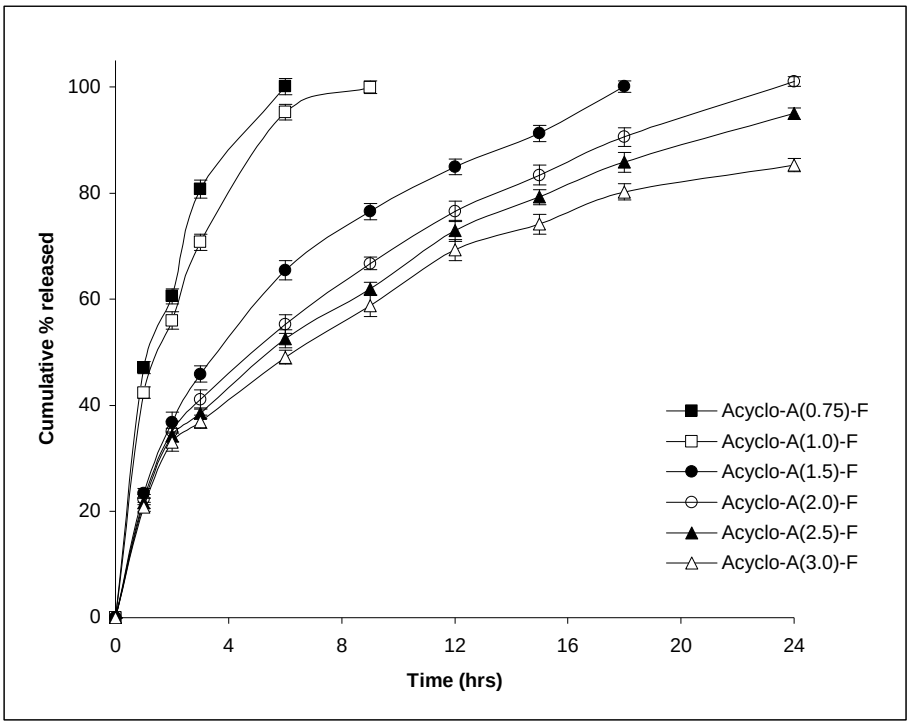

Figure 6.25: In vitro release from freeze dried calcium alginate beads of acyclovir to study the effect of proportion of sodium alginate [Data presented is mean ± SD of release studies on products of three batches in duplicate]

6.3.4. Batch reproducibility

No significant difference was observed in physical properties and release characteristics of drug from three batches of each of the designed formulations. There was insignificant batch-to-batch variation with respect to the size range, drug content, entrapment efficiency and floating behaviour of various formulations. Release profile of different batches of the developed formulations also showed low value of standard deviation of the cumulative release data at different time points obtained from replicate release studies of samples from different batches (as discussed in previous sections of this chapter). Only in case of uncoated matrix based granules meant for microencapsulation for both the drugs, a little higher values of standard deviation were observed during release studies. This indicated that the methods, both microencapsulation technique and ionic cross-linking technique, employed are acceptable methods for manufacturing good quality multiple unit gastroretentive controlled release drug delivery systems for celecoxib and acyclovir.

6.3.5. 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 upon proper storage up to 12 months of storage for all types of formulations for both the drugs. Sodium alginate based beads and their microencapsulated products were more sensitive to the type of packing done. Improperly packed (without a trilayered system) formulations did not show much deviation in their physical attributes as well as drug content, but resulted in diminishing floating behaviour i.e. more fraction of the product became non-floating with storage and the drug release also became significantly slower. Calcium alginate beads were not so sensitive to packing. A single layered system was able to protect the formulations and retain the floating and release characteristics even after 12 months.

6.4. Conclusions

Designed microencapsulated formulations of celecoxib and acyclovir were found to possess good appearance, spherical shape, uniform size (180-300 μm), good flow property, uniform drug content, high entrapment efficiency and good buoyancy. They floated immediately and continued to float beyond 24 h in case of celecoxib products and till the end of complete drug release in case of acyclovir products. Microencapsulated products of celecoxib were unable to release the entire dose within 24 h, whereas acyclovir microcapsules released the drug at a faster rate and prolonged the release to different extent with complete release within 24 h. In general, increasing the proportion of hydrophilic polymer in the coating mixture increased the rate of release for all core to coat ratios. Also upon increasing total quantity of core with respect to the coat quantity, formulations with faster release were obtained. Most of the microcapsules of celecoxib followed quasi-Fickian release, while microcapsules of acyclovir followed variety of release mechanisms.

Designed calcium alginate beads of celecoxib and acyclovir were spherical in nature with very good flow with a size range of 850-1180 μm. Freeze dried products showed good floating characteristics as well as better release compared to vacuum dried products. A limitation with bead based formulation was that only a fraction floated in all the cases. Products containing sodium bicarbonate showed higher and more complete release, but lacked floating property. Decreasing the amount of calcium alginate increased the rate of release and decreased the duration of release in case of both celecoxib and acyclovir. All celecoxib calcium alginate beads extended the release beyond 24 h, while acyclovir beads extended the release from 6 to

24 h or beyond. Most of the beads of celecoxib followed anamolous release, while beads of acyclovir followed variety of release mechanisms.

No significant difference was observed in the physical properties and release profiles of different batches of the developed formulations, thus suggesting these techniques to be reproducible for manufacturing good quality multiple unit CR systems. Initial burst effect was seen for most of the formulations, suggesting no need of adding loading dose to the product. But in case of celecoxib multiple unit formulations, none of the product could release complete amount of the drug in 24 h, indicating that some intervention need to be done to ensure entire release, although performance of these formulations in vivo and overall bioavailability of the drug are likely to be much better. As soon as these multiple unit systems will sink in the GI fluid or ultimately get emptied into the lower part of the GIT, the neutral pH of the small intestine is likely to convert the gelled polymer matrix to freely soluble system and more leachable or penetratable system in case of microencapsulated and calcium alginate based products of celecoxib. This is expected to result in complete release and better extend of absorption of the drug in vivo from the designed formulation. Microenacpsulated products were more sensitive to packaging. Upon proper storage, all the designed formulations were stable for more than 12 months.

6.5. References

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