CHAPTER 4

PREFORMULATION STUDIES

4.1. Introduction

Preformulation studies provide valuable information on physicochemical properties of a drug substance which influence decision of dosage form, choice of additives and predict bioavailability. Thorough and adequate understanding of the physicochemical properties of the drug substance minimizes problems in later stages of drug development, reduces drug development costs, and decreases the time to bring product to the market. The objectives of preformulation studies are to choose the correct form of the drug substance, evaluate and understand its pharmaceutically significant physicochemical properties, estimate its stability in bulk or in combination with excipients on exposure to various common stresses, and aids in finalizing formulation development strategy. This strategy specifies probable formulation ingredients/ microenvironment, processing methodology, analytical methods, etc., which are prerequisites for development of an optimal drug delivery system [Connors et al., 1986; Fiese and Hagen, 1987; Ravin and Radebaugh, 1990; Carstensen, 1996; Carstensen, 2000a; Grimm, 2000]. Important physical properties of the drug that have a bearing on the formulation manufacturing and/ or the optimum oral bioavailability of the drug from the formulations include physical form of the drug, crystallinity, polymorphism, particle size distribution, surface characteristics, porosity, density, melting point, vapour pressure, solubility, partition coefficient (log P), pK_a (negative logarithm of acid dissociation constant), hygroscopicity, and compactability [Carstensen, 1996; Carstensen, 2000a]. Knowledge of solubility in different media and the drug stability in those media help us in choosing appropriate media for dissolution testing [Ravin and Radebaugh, 1990].

Early predictions of drug stability as well as drug-excipient incompatibility are also vital in dosage form design and development to avoid costly material wastage and time delays. Excipients are generally considered inert additives included in drug formulation to help in the manufacturing, administration or absorption, but they can have a tremendous impact on the stability of the drug in the dosage form and ultimate pharmacological availability of a drug substance [Jackson et al., 2000; Manoj and Anbazhagan, 2004]. The magnitude of this

effect depends on the characteristics of the drug and on the quantity and properties of the excipients [Carstensen, 2000b; Mc Daid et al., 2003]. Carrying out stability studies for establishing credible shelf-life for the final pharmaceutical products is also essential from regulatory perspective [US FDA, 1987; Willig and Stoker, 1997; ICH, 2003]. Shelf life of a pharmaceutical product is influenced by factors like, stability of the active ingredient alone, stability of the active ingredient in the presence of additive/ excipients, manufacturing process employed, choice of dosage form, type of container closure-liner system used and environmental conditions encountered during shipment, storage & handling [Vadas, 1990].

Celecoxib and acyclovir are two well-established drugs with several oral formulations in the market. Acyclovir also has many topical as well as injectable preparations available in the Indian as well as international market. A good amount of information is available on their physicochemical properties, formulations, stability profile and degradation products [Martindale, 1999; AHFS, 2001; Micromedex, 2002; Searle/ Pfizer, 2005; Medline Plus, 2006].

In this chapter, results of some preformulation studies carried on celecoxib and acyclovir are presented. As the present research work focused at formulating controlled release gastroretentive drug delivery systems for these candidate drugs, dissolution media, simulating gastric fluid (having a pH of 1.2), had to be optimized in which the respective drugs should be stable as well as sufficiently soluble, to be able to maintain a sink condition. Solubility studies were carried out in 0.1 N HCl alone and 0.1 N HCl in combination with various co-solvents and surfactants at different concentrations. Stability of each drug was investigated in the respective dissolution media studied and in solvent system employed for drug analysis. Effects of potential formulation excipients, other reagents and chemicals were studied on the UV absorbency and on stability of the drug. Stability of the drugs was studied alone and in the presence of common formulation additives in solid state under controlled (25± 2 ºC; 60±5 % RH) and accelerated (40±2 ºC; 75±5 % RH) storage conditions.

4.2. Experimental section

4.2.1. Chemicals

Celecoxib and acyclovir were obtained as gift samples as already mentioned in the previous chapter. Spectroscopic grade hydrochloric acid (HCl) and analytical grade sodium lauryl sulphate (SLS) were purchased as mentioned earlier. High quality TDW was prepared using

our in-house glass distillation unit. And all other chemicals/ polymers/ excipients used in the studies were either of pharmaceutical grade or analytical grade and were either purchased or obtained as gift samples from IPCA Labs, Mumbai and Signet, Mumbai.

4.2.2. Equipments

UV-visible-NIR spectrophotometer (*Jasco*, Tokyo, Japan, model V-570), as mentioned in chapter 3 was used for UV analysis. Water bath shaker (MAC, New Delhi) with thermostatic temperature control was employed for solubility studies. For carrying out accelerated stability studies, temperature and humidity control chamber (MAC model) having thermostatic temperature control unit, digital temperature recorder and relative humidity recorder was used.

4.2.3. Characterization of bulk drugs

The gifted drugs, celecoxib and acyclovir, were characterized by various in-house (IPCA Labs, Mumbai) and official tests of identification [USP, 2006] respectively. The IR spectrums, obtained using IR spectrophotometer, were compared with those of the standard.

4.2.4. Optimization of dissolution media

0.1 N HCl solution (pH 1.2) alone or in combination with ethyl alcohol/ surfactants was studied to optimize the dissolution media so as to maintain a sink condition. Solubility studies were carried out in hexaplate at 25 ºC by shaking excess of drug in a stoppered volumetric flask containing approximately 10 ml of solvent system investigated. In case of celecoxib, solubility was determined in 0.1 N HCl alone, 0.1 N HCl with 1.0 % v/v polyoxyethylene sorbitan monooleate (Tween 80), and 0.1 N HCl with 1.0 % w/v SLS respectively. For acyclovir, solubility was determined in 0.1 N HCl alone and TDW respectively.

4.2.5. Stability studies in dissolution media

Stability of both the drugs was investigated in solvent systems showing appropriate solubility. For this, 100 µg/ml stock solution of respective drugs was prepared in solvent system. Appropriate dilution was made to prepare 10 µg/ml solution and analyzed at zero-time. The rest of the solutions were divided into three parts, tightly sealed and stored at controlled (25±2 ºC; 60±5 % RH), ambient (bench-top), and accelerated (40±2 ºC; 75±5 % RH) storage conditions. Samples were withdrawn at 12, 24 and 48 h, appropriately diluted, and analyzed.

4.2.6. Drug-excipient stability studies in solid admixture

Stability of the drugs was studied alone and in the presence of common formulation

additives in solid state under controlled and accelerated storage conditions. Physical admixtures of each drug and excipients, previously passed through sieve # 100, were prepared in the ratio of 1:1 or 1:0.5. The excipients used for the study included: citric acid, sodium bicarbonate, calcium carbonate, sodium alginate, guar gum, gelatin, HPMC (15, 4000, 15000 and 1 lac cps), EC 10 cps, CMC, carbopol 934P NF, polycarbophil (Noveon AA1) and PVP K-30. To ensure uniform blending, drug and excipients were thoroughly blended and the mix was again passed through sieve # 100. Drugs alone and their mixtures were filled in clean dry 5 ml neutral glass vials (Borosil) and stored in both closed as well as open vials under controlled and accelerated storage conditions. Samples were withdrawn, in triplicate, at predetermined time intervals (0, 2, 7, 14, 21, 28, 35, 42, 49, 56, 64, 70, 90 days), examined visually for any physical change in appearance and analyzed after suitable dilution for drug content. Stability study data were analyzed and degradation rate constant (K_{deg}) and $T_{90\%}$ (time taken for the drug content to reduce to 90%) of the drug alone and in the presence of various excipients/ additives at controlled and accelerated storage conditions were calculated.

4.3. Results and discussion

4.3.1. Characterization of bulk drugs

Celecoxib: Supplied celecoxib passed various in-house tests of identification and analysis. The determined melting point was 157 ºC and the IR spectrum of the sample was found to be comparable with that of the standard.

Acyclovir: Supplied acyclovir passed various tests of identification and analysis as per USP-2006. The determined melting point was 256 ºC and the IR spectrum of the sample was found to be comparable with that of the standard.

4.3.2. Optimization of dissolution media

Celecoxib: Solubility studies carried out at 25 ºC revealed that celecoxib being a weakly acidic drug with a pK_a of 11.1 is almost insoluble in 0.1 N HCl, but shows approximately 75 to100 times enhancement in solubility in the presence of surfactants. Solubility of celecoxib was found to be 5.18±0.29, 381.99±1.24 and 500.39±2.67 µg/ml in 0.1 N HCl, 0.1 N HCl with 1.0 % v/v Tween 80 and 0.1 N HCl with 1.0 % w/v SLS respectively. The results of solubility studies are presented in Table 4.1.

Table 4.1: Solubility data of celecoxib at 25 °C

Media	Solubility ± SD[a] (µg/ml)
0.1 N HCl	5.18±0.29
0.1 N HCl with 1.0 % v/v Tween 80	381.99±1.24
0.1 N HCl with 1.0 % w/v SLS	500.39±2.67

[a]: Average of six samples with standard deviation; SLS- Sodium lauryl sulphate

Since celecoxib showed appropriate solubility (for maintaining sink condition) in simulated gastric pH aqueous media (0.1 N HCl) only in the presence of surfactants, 0.1 N HCl containing 1.0 % v/v Tween 80 or 1.0 % w/v SLS were narrowed down for stability studies.

Acyclovir: Acyclovir being an amphoteric drug with pK_a values of 2.27 and 9.25 is expected to have higher solubility in acidic pH. Solubility of acyclovir in TDW was found to be 2.23±0.82 mg/ml. In 0.1 N HCl, the solubility was found to be 12.27±1.26 mg/ml, showing nearly a 6-fold increase in solubility. Based on this, 0.1 N HCl alone was selected for stability studies in case of acyclovir. The results of solubility studies are presented in Table 4.2.

Table 4.2: Solubility data of acyclovir at 25 °C

Media	Solubility ± SD[a] (mg/ml)
Triple distilled water (TDW)	2.23±0.82
0.1 N HCl	12.27±1.26

[a]: Average of six samples with standard deviation

4.3.3. Stability studies in dissolution media

Celecoxib: Stability studies of celecoxib in the selected solvent systems revealed that it is not very stable in 0.1 N HCl with 1.0 % v/v Tween 80, but is quite stable in 0.1 N HCl with 1.0 % w/v SLS. Overlay of the scan of 10 µg/ml celecoxib in the solvent systems (employed for stability studies) at zero-time and at 12 h, 24 h and 48 h of storage at controlled, ambient, and accelerated conditions revealed that there was a slight depreciation in absorbency profile in 0.1 N HCl with 1.0 % v/v Tween 80 after 24 h. On the other hand, spectras did not show any deviation (no change in absorbency) up to 48 h from that at zero-time when solvent system employed was 0.1 N HCl with 1.0 % w/v SLS under all the three storage conditions.

Acyclovir: Stability studies of acyclovir in 0.1 N HCl revealed that it is quite stable in 0.1 N HCl. Overlay of the scan of 10 µg/ml acyclovir in 0.1 N HCl at zero-time and at 12 h, 24 h and 48 h of storage at controlled, ambient and accelerated conditions revealed no deviation from that at zero-time.

4.3.4. Drug-excipient stability studies in solid admixture

Both the drugs were white in colour and when blended with the excipients, the appearance was changed depending upon the colour/ nature of the excipient [Tables 4.3 to 4.6]. In case of storage in both controlled as well as accelerated condition, there was no significant change in the physical characteristics of the drug in the presence of the excipient in closed as well as open container, except for admixtures with citric acid, gelatin and PVP.

Table 4.3: Results of physical compatibility of celecoxib with different excipients at controlled storage condition (25±2 °C and 60±5 % RH)

Drug/ Drug + Excipient	**Observed physical appearance**			
	0 day	**3 weeks**	**10 weeks**	**20 weeks**
Drug alone				
Cele-C	white powder	white powder	white powder	white powder
Cele-O	white powder	white powder	white powder	white powder
Drug + Excipient				
Citric acid-C	white powder	white powder	white powder	white powder
Citric acid-O	white powder	white powder	white powder	white powder
Sodium bicarbonate-C	white powder	white powder	white powder	white powder
Sodium bicarbonate-O	white powder	white powder	white powder	white powder
Guar gum-C	off white powder	off white powder	off white powder	off white powder
Guar gum-O	off white powder	off white powder	off white powder	off white powder
Sodium alginate-C	buff coloured powder	buff coloured powder	buff coloured powder	buff coloured powder
Sodium alginate-O	buff coloured powder	buff coloured powder	buff coloured powder	buff coloured powder
Carbopol-C	white powder	white powder	white powder	white powder
Carbopol-O	white powder	white powder	white powder	white powder
Polycarbophil-C	white flaky powder	white flaky powder	white flaky powder	white flaky powder
Polycarbophil-O	white flaky powder	white flaky powder	white flaky powder	white flaky powder
PVP K-30-C	off white powder	off white powder	off white powder	off white powder
PVP K-30-O	off white powder	off white powder	off white powder	off white powder
Ethyl cellulose-10cps-C	white powder	white powder	white powder	white powder
Ethyl cellulose-10cps-O	white powder	white powder	white powder	white powder
CMC-C	white powder	white powder	white powder	white powder
CMC-O	white powder	white powder	white powder	white powder
HPMC 15 cps-C	white powder	white powder	white powder	white powder
HPMC 15 cps-O	white powder	white powder	white powder	white powder
HPMC 4K cps-C	white powder	white powder	white powder	white powder
HPMC 4K cps-O	white powder	white powder	white powder	white powder
HPMC 15K cps-C	white powder	white powder	white powder	white powder
HPMC 15K cps-O	white powder	white powder	white powder	white powder
HPMC 1 lac cps-C	white powder	white powder	white powder	white powder

HPMC 1 lac cps-O	white powder	white powder	white powder	white powder
Gelatin-C	buff coloured powder	buff coloured powder	buff coloured powder	buff coloured powder
Gelatin-O	buff coloured powder	buff coloured powder	buff coloured powder	buff coloured powder

Cele- celecoxib; O- open; C- closed; PVP- polyvinyl pyrrolidone; CMC- carboxy methyl cellulose; HPMC- Hydroxy propyl methyl cellulose

Table 4.4: Results of physical compatibility of acyclovir with different excipients at controlled storage condition (25±2 °C and 60±5 % RH)

Drug/ Drug + Excipient	**Observed physical appearance**			
	0 day	**3 weeks**	**10 weeks**	**20 weeks**
Drug alone				
Acyclo-C	white powder	white powder	white powder	white powder
Acyclo-O	white powder	white powder	white powder	white powder
Drug + Excipient				
Citric acid-C	white powder	white powder	white powder	white powder
Citric acid-O	white powder	white powder	white powder	white powder
Sodium bicarbonate-C	white powder	white powder	white powder	white powder
Sodium bicarbonate-O	white powder	white powder	white powder	white powder
Guar gum-C	off white powder	off white powder	off white powder	off white powder
Guar gum-O	off white powder	off white powder	off white powder	off white powder
Sodium alginate-C	buff coloured powder	buff coloured powder	buff coloured powder	buff coloured powder
Sodium alginate-O	buff coloured powder	buff coloured powder	buff coloured powder	buff coloured powder
Carbopol-C	white powder	white powder	white powder	white powder
Carbopol-O	white powder	white powder	white powder	white powder
Polycarbophil-C	white flaky powder	white flaky powder	white flaky powder	white flaky powder
Polycarbophil-O	white flaky powder	white flaky powder	white flaky powder	white flaky powder
PVP K-30-C	off white powder	off white powder	off white powder	off white powder
PVP K-30-O	off white powder	off white powder	off white powder	off white powder
Ethyl cellulose-10cps-C	white powder	white powder	white powder	white powder
Ethyl cellulose-10cps-O	white powder	white powder	white powder	white powder
CMC-C	white powder	white powder	white powder	white powder
CMC-O	white powder	white powder	white powder	white powder
HPMC 15 cps-C	white powder	white powder	white powder	white powder
HPMC 15 cps-O	white powder	white powder	white powder	white powder
HPMC 4K cps-C	white powder	white powder	white powder	white powder
HPMC 4K cps-O	white powder	white powder	white powder	white powder
HPMC 15K cps-C	white powder	white powder	white powder	white powder
HPMC 15K cps-O	white powder	white powder	white powder	white powder
HPMC 1 lac cps-C	white powder	white powder	white powder	white powder
HPMC 1 lac cps-O	white powder	white powder	white powder	white powder
Gelatin-C	buff coloured powder	buff coloured powder	buff coloured powder	buff coloured powder
Gelatin-O	buff coloured	buff coloured	buff coloured	buff coloured

	powder	powder	powder	powder

Acyclo- acyclovir; O- open; C- closed; PVP- polyvinyl pyrrolidone; CMC- carboxy methyl cellulose; HPMC- Hydroxy propyl methyl cellulose

These admixtures showed globulation when kept in an open container under accelerated condition within one month of storage [Tables 4.5 and 4.6]. Under controlled storage condition, rate of degradation of both the drugs were very low when compared to that observed in accelerated condition.

Table 4.5: Results of physical compatibility of celecoxib with different excipients at accelerated storage condition (40±2 ℃ and 75±5 % RH)

Drug/ Drug + Excipient	**Observed physical appearance**			
	0 day	**3 weeks**	**10 weeks**	**20 weeks**
Drug alone				
Cele-C	white powder	White powder	white powder	white powder
Cele-O	white powder	White powder	white powder	white powder
Drug + Excipient				
Citric acid-C	white powder	White powder	white powder	white powder
Citric acid-O	white powder	white globular mass	white globular mass	white globular mass
Sodium bicarbonate-C	white powder	White powder	white powder	white powder
Sodium bicarbonate-O	white powder	White powder	white powder	white powder
Guar gum-C	off white powder	off white powder	off white powder	off white powder
Guar gum-O	off white powder	off white powder	off white powder	off white powder
Sodium alginate-C	buff coloured powder	buff coloured powder	buff coloured powder	buff coloured powder
Sodium alginate-O	buff coloured powder	buff coloured powder	buff coloured powder	buff coloured powder
Carbopol-C	white powder	white powder	white powder	white powder
Carbopol-O	white powder	white powder	white powder	white powder
Polycarbophil-C	white flaky powder	white flaky powder	white flaky powder	white flaky powder
Polycarbophil-O	white flaky powder	white flaky powder	white flaky powder	white flaky powder
PVP K-30-C	off white powder	off white powder	off white powder	off white powder
PVP K-30-O	off white powder	off white globular mass	off white globular mass	off white globular mass
Ethyl cellulose-10cps-C	white powder	white powder	white powder	white powder
Ethyl cellulose-10cps-O	white powder	white powder	white powder	white powder
CMC-C	white powder	white powder	white powder	white powder
CMC-O	white powder	white powder	white powder	white powder
HPMC 15 cps-C	white powder	white powder	white powder	white powder
HPMC 15 cps-O	white powder	white powder	white powder	white powder
HPMC 4K cps-C	white powder	white powder	white powder	white powder

HPMC 4K cps-O	white powder	white powder	white powder	white powder
HPMC 15K cps-C	white powder	white powder	white powder	white powder
HPMC 15K cps-O	white powder	white powder	white powder	white powder
HPMC 1 lac cps-C	white powder	white powder	white powder	white powder
HPMC 1 lac cps-O	white powder	white powder	white powder	white powder
Gelatin-C	buff coloured powder	buff coloured powder	buff coloured powder	buff coloured powder
Gelatin-O	buff coloured powder	buff coloured globular mass	buff coloured globular mass	buff coloured globular mass

Cele- celecoxib; O- open; C- closed; PVP- polyvinyl pyrrolidone; CMC- carboxy methyl cellulose; HPMC- Hydroxy propyl methyl cellulose

Table 4.6: Results of physical compatibility of acyclovir with different excipients at accelerated storage condition (40±2 °C and 75±5 % RH)

Drug/ Drug + Excipient	**Observed physical appearance**			
	0 day	**3 weeks**	**10 weeks**	**20 weeks**
Drug alone				
Acyclo-C	white powder	white powder	white powder	white powder
Acyclo-O	white powder	white powder	white powder	white powder
Drug + Excipient				
Citric acid-C	white powder	white powder	white powder	white powder
Citric acid-O	white powder	white globular mass	white globular mass	white globular mass
Sodium bicarbonate-C	white powder	white powder	white powder	white powder
Sodium bicarbonate-O	white powder	white powder	white powder	white powder
Guar gum-C	off white powder	off white powder	off white powder	off white powder
Guar gum-O	off white powder	off white powder	off white powder	off white powder
Sodium alginate-C	buff coloured powder	buff coloured powder	buff coloured powder	buff coloured powder
Sodium alginate-O	buff coloured powder	buff coloured powder	buff coloured powder	buff coloured powder
Carbopol-C	white powder	white powder	white powder	white powder
Carbopol-O	white powder	white powder	white powder	white powder
Polycarbophil-C	white flaky powder	white flaky powder	white flaky powder	white flaky powder
Polycarbophil-O	white flaky powder	white flaky powder	white flaky powder	white flaky powder
PVP K-30-C	off white powder	off white powder	off white powder	off white powder
PVP K-30-O	off white powder	off white globular mass	off white globular mass	off white globular mass
Ethyl cellulose-10cps-C	white powder	white powder	white powder	white powder
Ethyl cellulose-10cps-O	white powder	white powder	white powder	white powder
CMC-C	white powder	white powder	white powder	white powder
CMC-O	white powder	white powder	white powder	white powder
HPMC 15 cps-C	white powder	white powder	white powder	white powder
HPMC 15 cps-O	white powder	white powder	white powder	white powder
HPMC 4K cps-C	white powder	white powder	white powder	white powder

HPMC 4K cps-O	white powder	white powder	white powder	white powder
HPMC 15K cps-C	white powder	white powder	white powder	white powder
HPMC 15K cps-O	white powder	white powder	white powder	white powder
HPMC 1 lac cps-C	white powder	white powder	white powder	white powder
HPMC 1 lac cps-O	white powder	white powder	white powder	white powder
Gelatin-C	buff coloured powder	buff coloured powder	buff coloured powder	buff coloured powder
Gelatin-O	buff coloured powder	buff coloured globular mass	buff coloured globular mass	buff coloured globular mass

Acyclo- acyclovir; O- open; C- closed; PVP- polyvinyl pyrrolidone; CMC- carboxy methyl cellulose; HPMC- Hydroxy propyl methyl cellulose

Also, drug/ drug-excipient admixtures stored in open vials showed faster rate of degradation when compared to the same samples stored in closed vials. Based on the results of stability studies, it was concluded that these drugs in solid form, alone or in combination with chosen excipients, follow a first order degradation pattern. The observed degradation rate constants and $T_{90\%}$ at controlled and accelerated storage conditions, both for open and closed state, of various polymers/ excipients employed are enlisted in Tables 4.7 and 4.8.

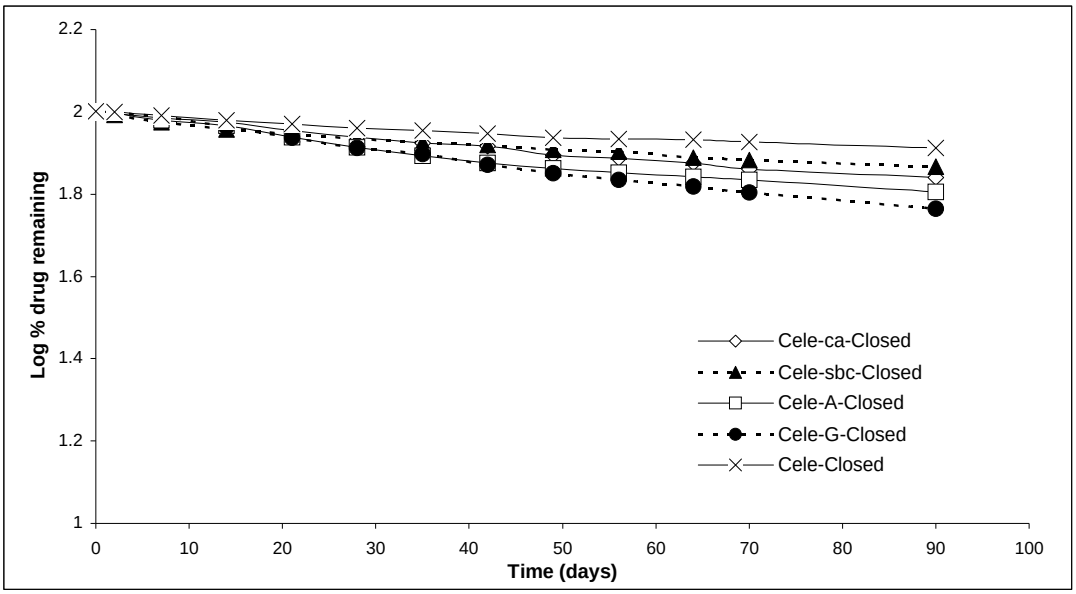
Table 4.7: Observed degradation rate constants obtained for celecoxib from drug-excipient compatibility study

Drug/ Drug + Excipient	**Controlled storage condition (25±2 °C and 60±5 % RH)**		**Accelerated storage condition (40±2 °C and 75±5 % RH)**	
	$K_{deg} \times 10^4$ (day^{-1})	$T_{90\%}$ (months)	$K_{deg} \times 10^4$ (day^{-1})	$T_{90\%}$ (months)
Drug alone				
Cele-C	0.46	75.9	2.34	15.1
Cele-O	0.61	57.9	3.01	11.7
Drug + Excipient				
Citric acid-C	0.54	65.2	4.32	8.1
Citric acid-O	0.71	49.8	4.71	7.5
Sodium bicarbonate-C	0.68	51.6	3.38	10.4
Sodium bicarbonate-O	1.11	31.6	4.24	8.3
Guar gum-C	0.88	40.0	6.39	5.5
Guar gum-O	1.10	32.1	6.61	5.3
Sodium alginate-C	0.89	39.3	5.32	6.6
Sodium alginate-O	1.15	30.7	5.72	6.1
Carbopol-C	0.78	44.8	4.55	7.7
Carbopol-O	1.02	34.7	4.86	7.2
Polycarbophil-C	0.60	58.6	3.24	10.8
Polycarbophil-O	0.85	41.5	3.47	10.1
PVP K-30-C	0.60	58.2	2.86	12.3
PVP K-30-O	0.77	45.9	3.29	10.7
Ethyl cellulose-10cps-C	0.48	73.5	2.52	13.9
Ethyl cellulose-10cps-O	0.69	51.1	3.20	11.0

CMC-C	0.90	38.9	5.55	6.3
CMC-O	0.91	38.7	5.77	6.1
HPMC 15 cps-C	0.50	70.7	2.39	14.7
HPMC 15 cps-O	0.71	49.5	3.19	11.0
HPMC 4K cps-C	0.52	67.8	2.37	14.9
HPMC 4K cps-O	0.68	51.7	3.30	10.7
HPMC 15K cps-C	0.57	61.3	2.43	14.4
HPMC 15K cps-O	0.66	53.2	3.39	10.4
HPMC 1 lac cps-C	0.48	73.5	2.42	14.5
HPMC 1 lac cps-O	0.65	54.0	3.39	10.4
Gelatin-C	1.09	32.1	4.80	7.3
Gelatin-O	1.30	26.9	5.31	6.6

Cele- celecoxib; O- open; C- closed; PVP- polyvinyl pyrrolidone; CMC- carboxy methyl cellulose; HPMC- Hydroxy propyl methyl cellulose; K_{deg}- Degradation rate constant

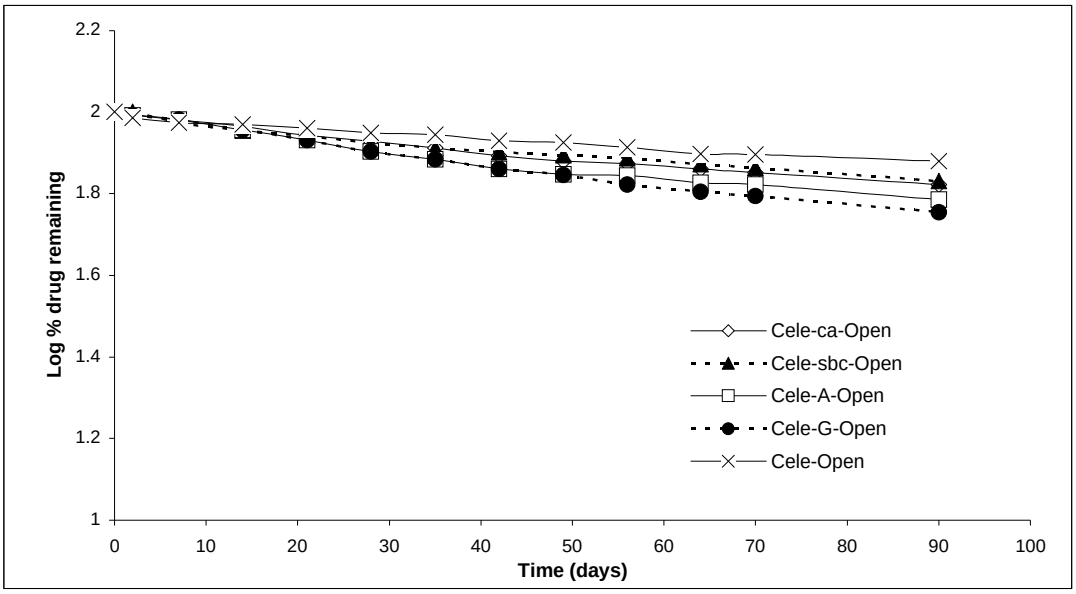
Celecoxib: Under controlled storage condition, the first order degradation rate constant (K_{deg}) for celecoxib in solid state in the absence of any excipient was found to be 0.46×10^{-4} day^{-1} in closed container and 0.61×10^{-4} day^{-1} in open container, with corresponding $T_{90\%}$ values of 75.9 and 57.9 months respectively [Table 4.7]. Under accelerated condition, celecoxib alone showed a K_{deg} of 2.34×10^{-4} day^{-1} and 3.01×10^{-4} day^{-1} respectively in closed and open container. The corresponding $T_{90\%}$ value was 15.1 and 11.7 months respectively [Table 4.7]. Comparative log percentage drug content remaining versus time profiles for celecoxib, alone and in the presence of excipients, at 40±2 °C and 75±5 % RH are presented in Figures 4.1a to 4.3b.



Cele- celecoxib; ca- citric acid; sbc- sodium bicarbonate; A- sodium alginate; G- guar gum

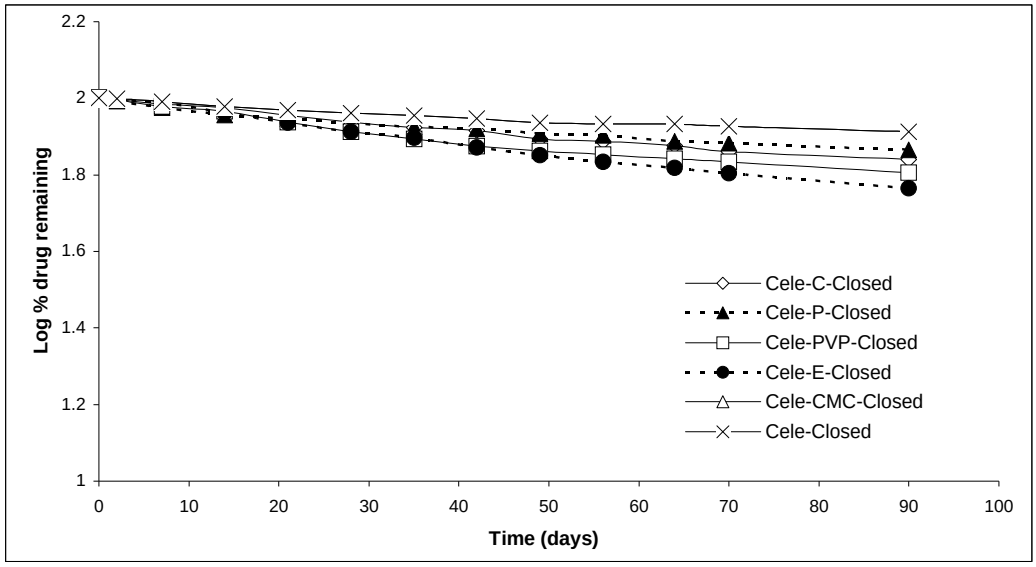
Figure 4.1a: Stability profiles of celecoxib, alone and in the presence of excipients, in closed container at 40±2 °C and 75±5 % RH

Under controlled storage condition, the observed K_{deg} in the presence of various excipients selected for the study varied from 0.48×10^{-4} day^{-1} (in the presence of EC 10 cps & HPMC 1 lac cps) with $T_{90\%}$ value of 73.5 months to 1.09×10^{-4} day^{-1} (in the presence of gelatin) with $T_{90\%}$ value of 32.1 months in the closed container. In the open container, K_{deg} varied from 0.65×10^{-4} day^{-1} (in the presence of HPMC 1 lac cps) with $T_{90\%}$ value of 54.0 months to 1.30×10^{-4} day^{-1} (in the presence of gelatin) with $T_{90\%}$ value of 26.9 months [Table 4.7]. Under accelerated storage condition, the observed K_{deg} in the presence of various excipients selected for the study varied from 2.37×10^{-4} day^{-1} (in the presence of HPMC 4000 cps) with $T_{90\%}$ value of 14.9 months to 6.39×10^{-4} day^{-1} (in the presence of guar gum) with $T_{90\%}$ value of 5.5 months in the closed container. In the open container, K_{deg} varied from 3.19×10^{-4} day^{-1} (in the presence of HPMC 15 cps) with $T_{90\%}$ value of 11.0 months to 6.61×10^{-4} day^{-1} (in the presence of guar gum) with $T_{90\%}$ value of 5.3 months respectively [Table 4.7].



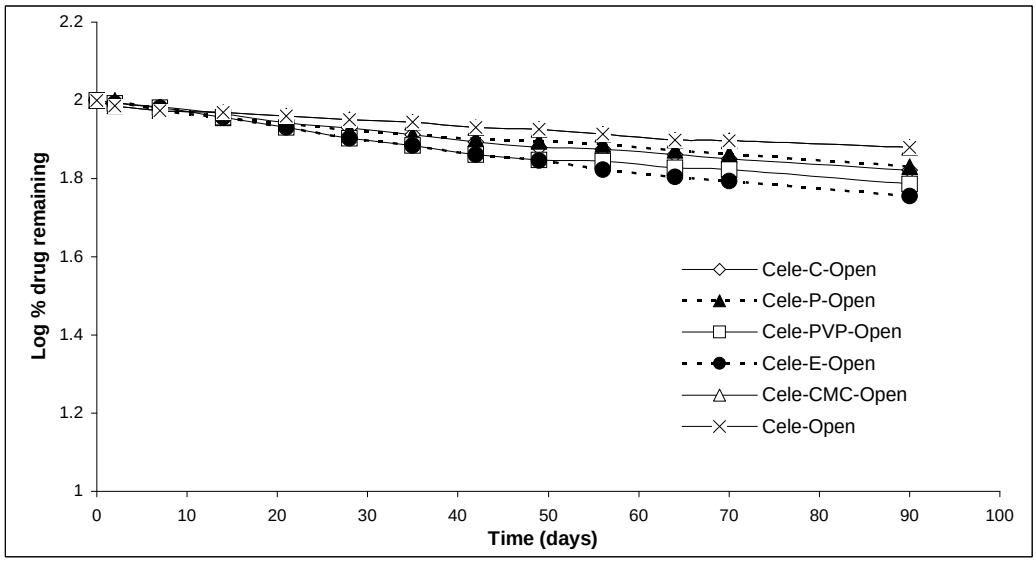
Cele- celecoxib; ca- citric acid; sbc- sodium bicarbonate; A- sodium alginate; G- guar gum

Figure 4.1b: Stability profiles of celecoxib, alone and in the presence of excipients, in open container at 40±2 °C and 75±5 % RH



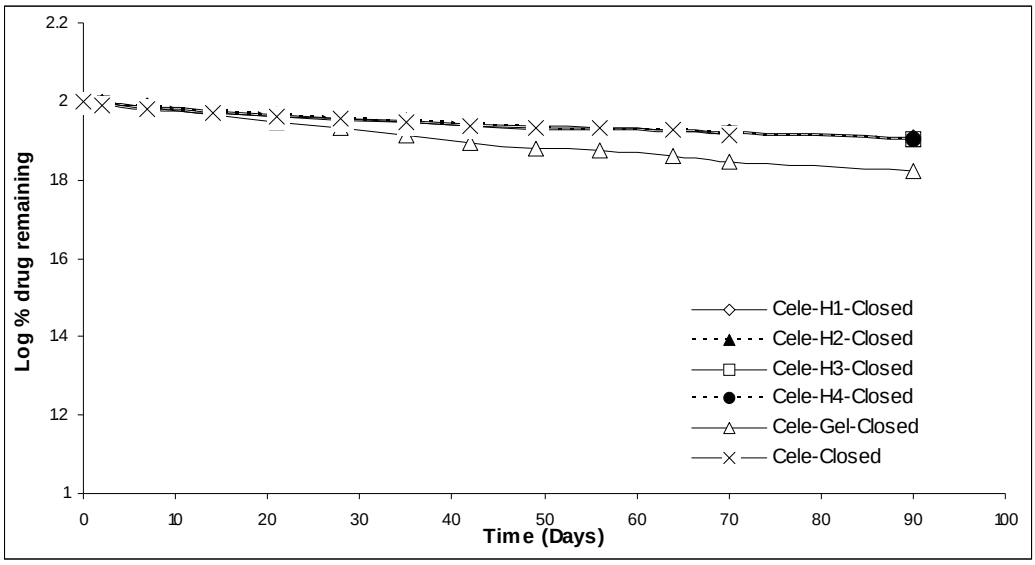
Cele- celecoxib; C- carbopol 934P NF; P- polycarbophil; PVP- polyvinyl pyrrolidone K-30; E- ethyl cellulose 10 cps; CMC- carboxy methyl cellulose

Figure 4.2a: Stability profiles of celecoxib, alone and in the presence of excipients, in closed container at 40±2 °C and 75±5 % RH



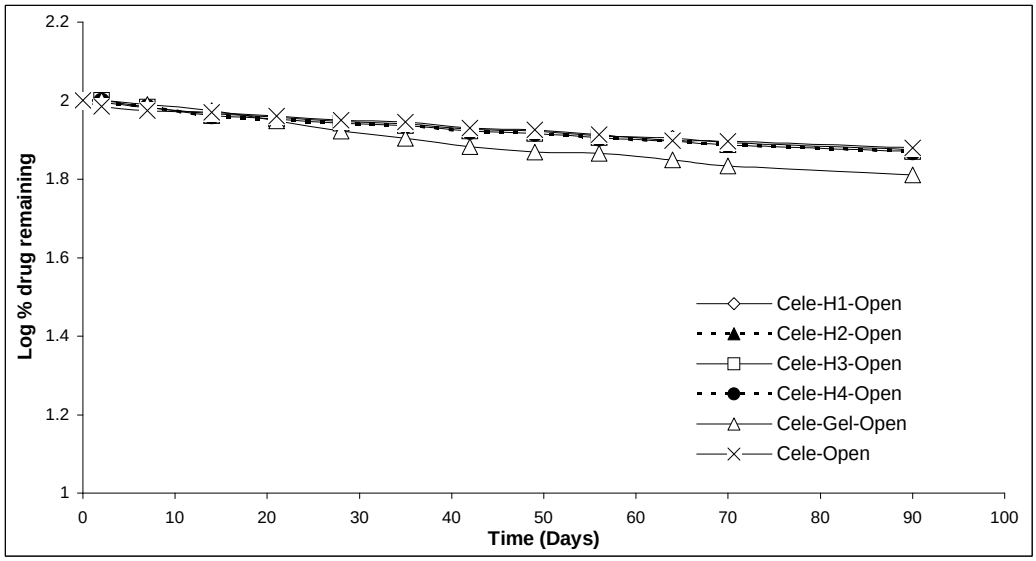
Cele- celecoxib; C- carbopol 934P NF; P- polycarbophil; PVP- polyvinyl pyrrolidone K-30; E- ethyl cellulose 10 cps; CMC- carboxy methyl cellulose

Figure 4.2b: Stability profiles of celecoxib, alone and in the presence of excipients, in open container at 40±2 °C and 75±5 % RH



Cele- celecoxib; H1- HPMC 15 cps; H2- HPMC 4K cps; H3- HPMC 15K cps; H4- HPMC 1 lac cps; Gel- gelatin

Figure 4.3a: Stability profiles of celecoxib, alone and in the presence of excipients, in closed container at 40±2 °C and 75±5 % RH



Cele- celecoxib; H1- HPMC 15 cps; H2- HPMC 4K cps; H3- HPMC 15K cps; H4- HPMC 1 lac cps; Gel- gelatin

Figure 4.3b: Stability profiles of celecoxib, alone and in the presence of excipients, in open container at 40±2 °C and 75±5 % RH

Acyclovir: At 25±2 ºC and 60±5 % RH, K_{deg} for acyclovir in solid state in the absence of any excipient was found to be 0.50×10^{-4} day^{-1} in closed container and 0.61×10^{-4} day^{-1} in

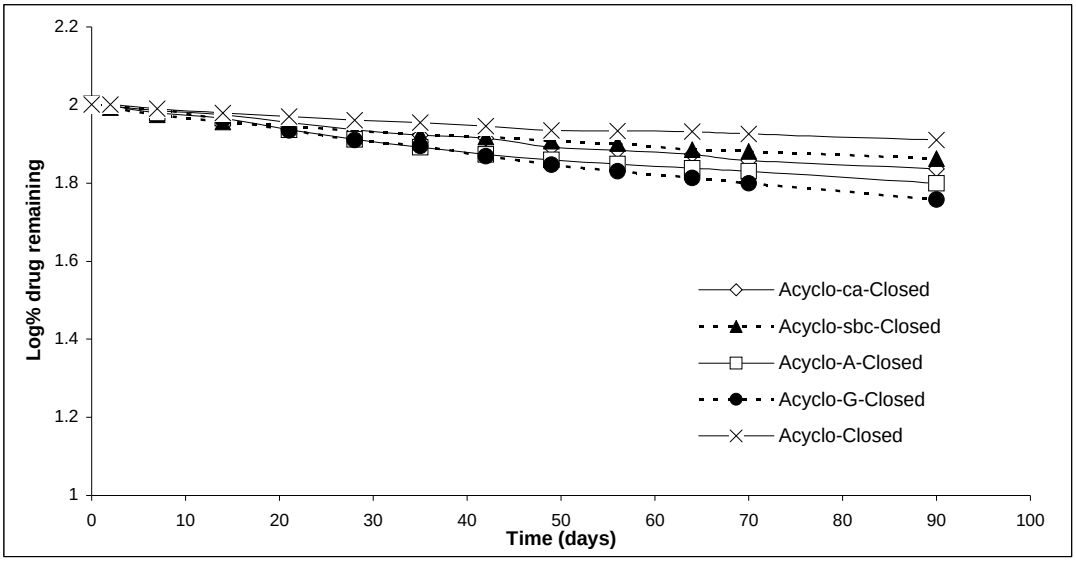
open container, with corresponding $T_{90\%}$ values of 70.2 and 57.3 months respectively [Table 4.8]. On the other hand, at 40±2 ºC and 75±5 % RH, K_{deg} for acyclovir in solid state in the absence of any excipient was found to be 2.40×10^{-4} day^{-1} in closed container and 3.10×10^{-4} day^{-1} in open container, with corresponding $T_{90\%}$ values of 14.7 and 11.3 months respectively [Table 4.8]. Under controlled storage condition, the observed K_{deg} in the presence of various excipients selected for the study varied from 0.52×10^{-4} day^{-1} (in the presence of EC 10 cps and HPMC 15000 cps & 1 lac cps) with corresponding $T_{90\%}$ value of 67.5 months in each case to 0.96×10^{-4} day^{-1} (in the presence of gelatin) with $T_{90\%}$ value of 36.4 months in the closed container [Table 4.8]. In open container, K_{deg} varied from 0.65×10^{-4} day^{-1} (in the presence of EC 10 cps & HPMC 4000 cps) with $T_{90\%}$ value of 54.5 months to 1.31×10^{-4} day^{-1} (in the presence of gelatin) with $T_{90\%}$ value of 26.8 months respectively [Table 4.8]. Under accelerated storage condition, the observed K_{deg} in the presence of various excipients selected for the study varied from 2.42×10^{-4} day^{-1} (in the presence of HPMC 15 & 4000 cps) with $T_{90\%}$ value of 14.5 months to 6.59×10^{-4} day^{-1} (in the presence of guar gum) with $T_{90\%}$ value of 5.3 months in the closed container. In open container, K_{deg} varied from 3.23×10^{-4} day^{-1} (in the presence of HPMC 15 cps) with $T_{90\%}$ value of 10.9 months to 6.83×10^{-4} day^{-1} (in the presence of guar gum) with $T_{90\%}$ value of 5.2 months respectively [Table 4.8]. Comparative log percentage drug content remaining versus time profiles for acyclovir, alone and in the presence of excipients, at 40±2 ºC and 75±5 % RH are presented in Figures 4.4a to 4.6b.

Table 4.8: Observed degradation rate constants obtained for acyclovir from drug-excipient compatibility study

Drug/ Drug + Excipient	**Controlled storage condition (25±2 °C and 60±5 % RH)**		**Accelerated storage condition (40±2 °C and 75±5 % RH)**	
	$K_{deg} \times 10^4$ (day^{-1})	$T_{90\%}$ (months)	$K_{deg} \times 10^4$ (day^{-1})	$T_{90\%}$ (months)
Drug alone				
Acyclo-C	0.50	70.2	2.40	14.7
Acyclo-O	0.61	57.3	3.10	11.3
Drug + Excipient				
Citric acid-C	0.87	40.6	4.45	7.9
Citric acid-O	1.12	31.3	4.85	7.2
Sodium bicarbonate-C	0.74	47.3	3.48	10.1
Sodium bicarbonate-O	0.94	37.5	4.36	8.1
Guar gum-C	0.77	45.5	6.59	5.3
Guar gum-O	0.99	35.3	6.83	5.2

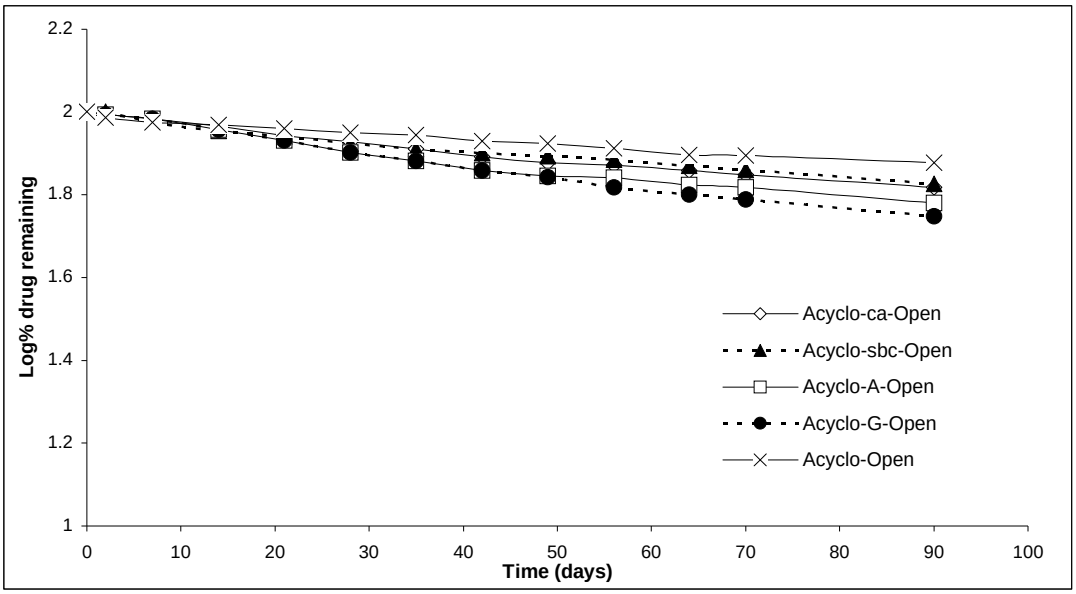
Sodium alginate-C	0.93	37.7	5.48	6.4
Sodium alginate-O	1.10	31.8	5.90	6.0
Carbopol-C	0.80	43.9	4.68	7.5
Carbopol-O	0.84	41.5	4.75	7.4
Polycarbophil-C	0.78	44.7	3.33	10.7
Polycarbophil-O	0.96	36.7	3.72	9.4
PVP K-30-C	0.78	44.5	3.06	11.5
PVP K-30-O	0.94	37.5	3.38	10.4
Ethyl cellulose-10cps-C	0.52	67.5	2.59	13.6
Ethyl cellulose-10cps-O	0.65	54.5	3.28	10.7
CMC-C	0.94	37.2	5.71	6.2
CMC-O	1.05	33.6	5.93	5.9
HPMC 15 cps-C	0.57	61.9	2.42	14.5
HPMC 15 cps-O	0.67	52.6	3.23	10.9
HPMC 4K cps-C	0.53	65.9	2.42	14.5
HPMC 4K cps-O	0.65	54.5	3.34	10.5
HPMC 15K cps-C	0.52	67.5	2.46	14.3
HPMC 15K cps-O	0.66	53.7	3.44	10.2
HPMC 1 lac cps-C	0.52	67.5	2.45	14.3
HPMC 1 lac cps-O	0.66	53.3	3.44	10.2
Gelatin-C	0.96	36.4	4.87	7.2
Gelatin-O	1.31	26.8	5.38	6.5

Acyclo- acyclovir; O- open; C- closed; PVP- polyvinyl pyrrolidone; CMC- carboxy methyl cellulose; HPMC- Hydroxy propyl methyl cellulose; K_{deg}- Degradation rate constant



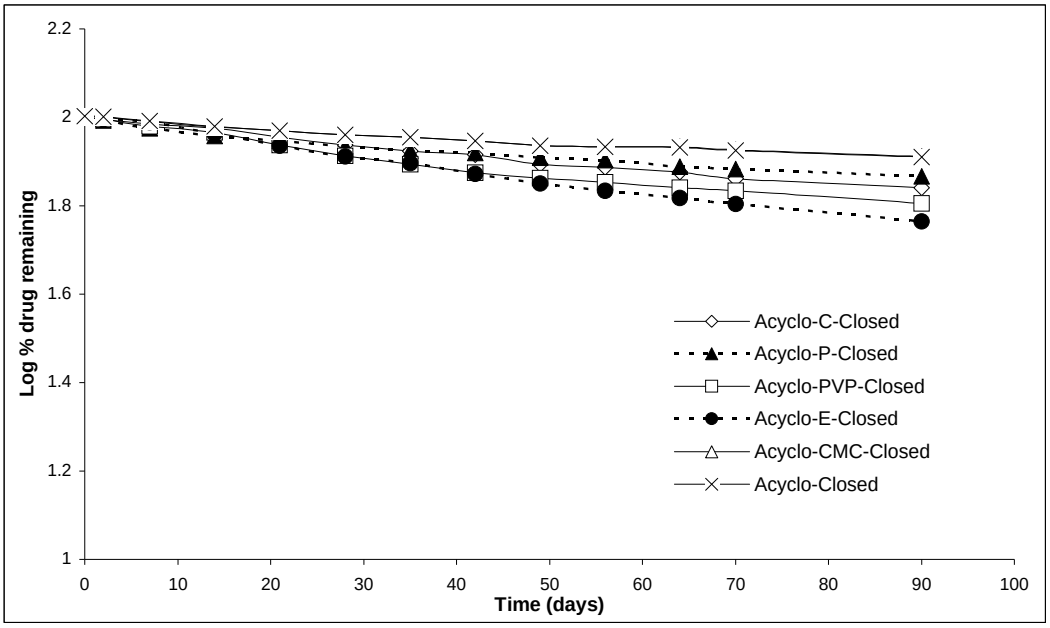
Acyclo- acyclovir; ca- citric acid; sbc- sodium bicarbonate; A- sodium alginate; G- guar gum

Figure 4.4a: Stability profiles of acyclovir, alone and in the presence of excipients, in closed container at 40±2 °C and 75±5 % RH



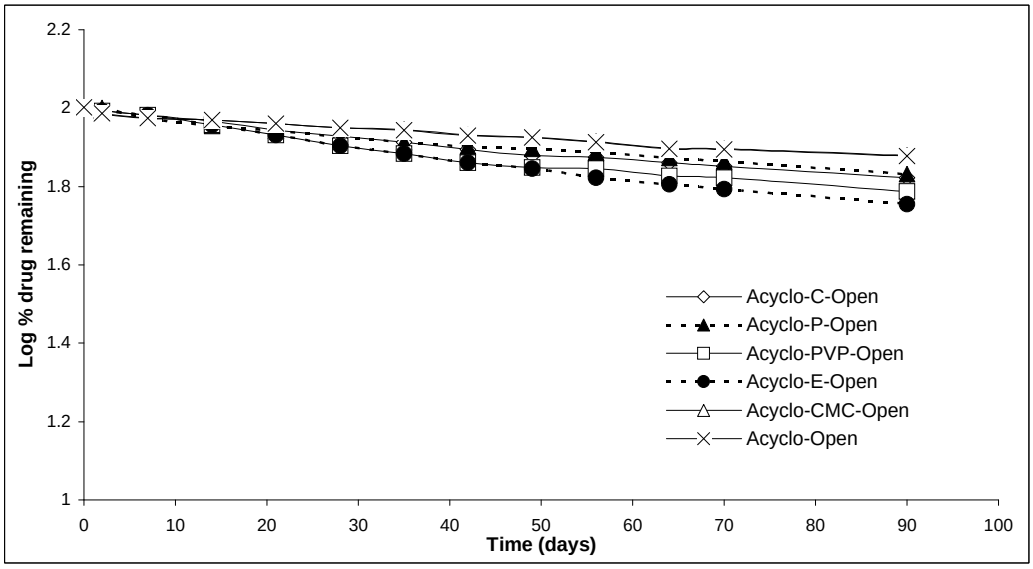
Acyclo- acyclovir; ca- citric acid; sbc- sodium bicarbonate; A- sodium alginate; G- guar gum

Figure 4.4b: Stability profiles of acyclovir, alone and in the presence of excipients, in open container at 40±2 °C and 75±5 % RH



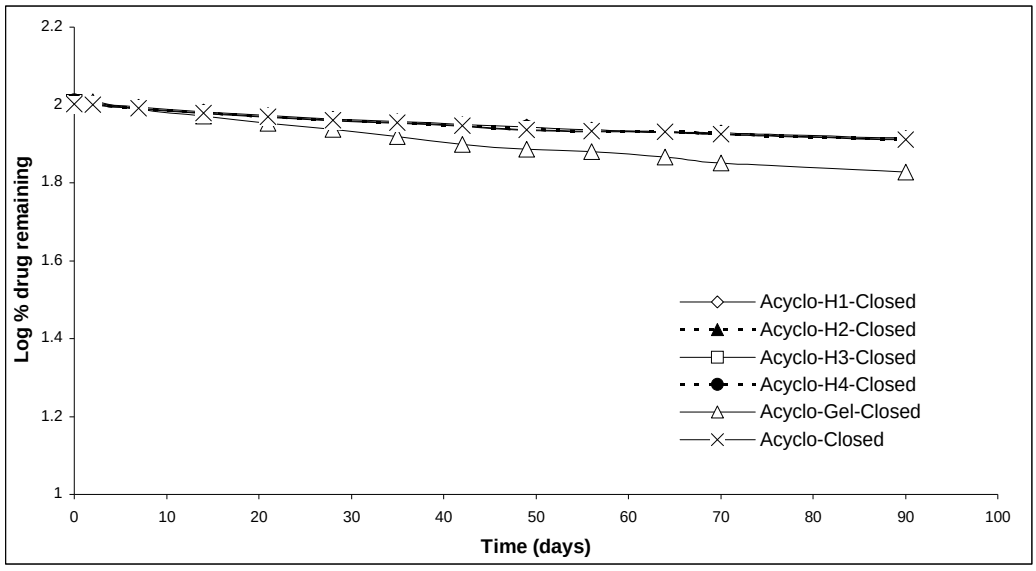
Acyclo- acyclovir; C- carbopol 934P NF; P- polycarbophil; PVP- polyvinyl pyrrolidone K-30; E- ethyl cellulose 10 cps; CMC- carboxy methyl cellulose

Figure 4.5a: Stability profiles of acyclovir, alone and in the presence of excipients, in closed container at 40±2 °C and 75±5% RH



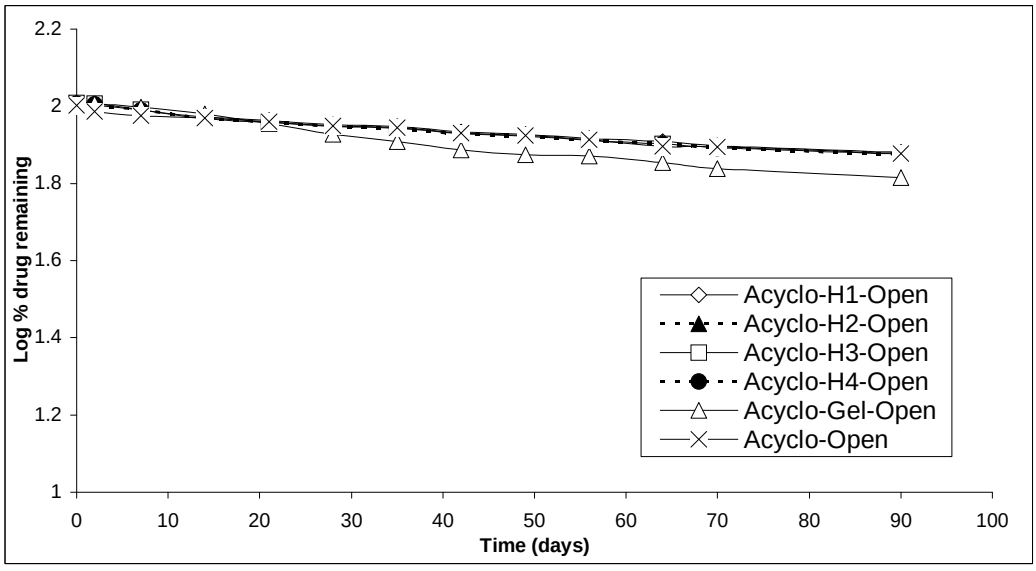
Acyclo- acyclovir; C- carbopol 934P NF; P- polycarbophil; PVP- polyvinyl pyrrolidone K-30; E- ethyl cellulose 10 cps; CMC- carboxy methyl cellulose

Figure 4.5b: Stability profiles of acyclovir, alone and in the presence of excipients, in open container at 40±2 °C and 75±5 % RH



Acyclo- acyclovir; H1- HPMC 15 cps; H2- HPMC 4K cps; H3- HPMC 15K cps; H4- HPMC 1 lac cps; Gel- gelatin

Figure 4.6a: Stability profiles of acyclovir, alone and in the presence of excipients, in closed container at 40±2 °C and 75±5 % RH



Acyclo- acyclovir; H1- HPMC 15 cps; H2- HPMC 4K cps; H3- HPMC 15K cps; H4- HPMC 1 lac cps; Gel- gelatin

Figure 4.6b: Stability profiles of acyclovir, alone and in the presence of excipients, in open container at 40±2 °C and 75±5 % RH

Both the drugs were found to be most compatible with HPMC of various viscosity grades, EC and PVP; followed by polycarbophil, sodium bicarbonate, citric acid and carbopol. However, in the presence of natural polymers like, sodium alginate, CMC, guar gum and gelatin, both drugs showed marginal degradation [Tables 4.7 and 4.8]. In general, excipients obtained from natural source or having hygroscopic character showed marginally increased degradation effect in open containers, whereas hydrophobic excipients did not show such effect. Open condition, as expected, resulted in faster chemical degradation and physical change (in few cases) than closed condition.

4.4. Conclusions

Based on the preformulation studies done, it can be concluded that celecoxib has poor solubility in triple distilled water and 0.1 N HCl, but solubility can be enhanced to great extent with 1.0 % v/v Tween 80 (about 75 times) as well as with 1.0 % w/v SLS (about 100 times). On the other hand, acyclovir has very good solubility in 0.1 N HCl, which is about 6 times more when compared to TDW. Both celecoxib and acyclovir showed good bench top stability in 0.1 N HCl with 1.0 % w/v SLS and 0.1 N HCl respectively. Based on the solubility and stability profiles of celecoxib and acyclovir, 0.1 N HCl with 1.0 % w/v SLS and 0.1 N HCl were respectively finalized as dissolution media for celecoxib and acyclovir. Stability studies revealed that celecoxib as well as acyclovir, alone or in combination with various excipients, in solid state showed negligible to marginal degradation of first order kinetics. Drugs were stable in the presence of HPMC of various viscosity grades, EC and PVP; and showed marginal degradation in the presence of sodium alginate, CMC, guar gum and gelatin. Excipients obtained from natural source or having hygroscopic character showed marginally higher rate of drug degradation and some physical change when stored in accelerated condition in open containers, whereas hydrophobic excipients did not show such effect. Drug-excipients interaction studies did not reveal any serious deleterious effect of the excipients on the drug stability.

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