STABILITY STUDIES OF OPTIMIZED EXTENDED RELEASE ACECLOFENAC MICROPARTICLE FORMULATIONS

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Abstract : Aceclofenac is one of the well tolerated COX-2 inhibitor and often the drug of choice in the treatment of osteoarthritis, rheumatic arthritis and other related conditions. However, because of its short half life (2- 4 hrs) it requires dosing of 100mg twice daily. Missing of dose, which is often common, would cause in consistence drug level in the blood, which would in turn reflect therapeutic outcome. Five types of stability generally recognised are physical, chemical, microbiological, therapeutic and toxicological stability. The Final formulation results of stability testing indicated no significant changes in any of the formulations with respect to physical appearance, drug content as well as drug release profile It has been reported that more than 50% of patient fail to take medicine as advised. Extended release formulations are the tools useful promoting, medication adherence and improve therapeutic outcome. Medication adherence in chronic conditions like arthritis improves the quality of life of the patients.

IndexTerms - **Aceclofenac, Extended release, stability testing, osteoarthritis and Medication adherence.**

I. INTRODUCTION

From pharmaceutical point of view, stability may be technically defined as capability of particular formulation, in a specified container and closure system, to retain same characteristics during the shelf life. A drug product during shelf life is said to be stable, if it fulfils the requirements of at least 90% of the stated therapeutic activity, stated concentrations of the active constituents etc. Also it should not produce any discolouration, precipitation, develop unacceptable odour, should not develop toxicity. Five types of stability generally recognised are physical, chemical, microbiological, therapeutic and toxicological stability.

Decomposition or degradation of the pharmaceutical formulations may develop due to environmental factors like temperature, radiation, light air, humidity etc. and due to interaction with other chemical constituent/excipients in formulation or due to nature of container. This decomposition may lead to (a) reduction in the therapeutic activity, (b) formation of toxic products, (c) formation of in-elegant product and (d) the product becomes unacceptable. Hence it is necessary to perform stability testing to find out the extent of deterioration or degradation and to ensure that the degradation has not exceeded acceptable level, assuring safety and efficacy of the pharmaceuticals.

1.2. Methods

The stability studies for the selected formulations were carried out as per ICH "Q1A" guidelines (Table 1). Based on results of *in-vitro* and *in-vivo* evaluation Optimized formulations (viz. AECM, AEUM) were selected for stability studies. The samples were subjected to long term and accelerated stability testing as per ICH guidelines. During stability testing the samples were evaluated for physical appearance, drug content and drug release profile at predetermined time intervals for microparticles and additionally particle size analysis was also carried out.

Table 1.Final product Composition of optimized condition Aceclofenac ethylcellulose micro particles (AECM) using aerosil as dispersing Agent

Composition	Final product (code AECM)
Aceclofenc	0.200 (g)
Ethyl cellulose	0.600 (g)
Aerosil	0.100 (g)
Dichloromethane	14 (ml)
Acetone	06 (ml)
Aqueous Phase (milli Q water containing 0.12 % w/v Tween 80	150 (ml)
RPM	1100
viscosity of oil phase(VOP) mpas	0.8

Table 2. Final product Composition of optimized condition Aceclofenac eudragit RSPO micro particles (AEUM) using aerosil as dispersing Agent

Composition	Final product (code AEUM)
Aceclofenc	0.200 (g)
Eudragit RSPO	0.500 (g)
Aerosil	0.100 (g)
Dichloromethane	14 (ml)
Acetone	06 (ml)
Aqueous Phase (milli Q water containing 0.12 % w/w SDS	150 (ml)
RPM	800
viscosity of oil phase(VOP) mpas	0.6

Both the formulations were subjected to long term and accelerated stability testing as per ICH guidelines. During stability testing the samples were evaluated for physical appearance, drug content and drug release profile at predetermined time intervals. The results of stability testing indicated no significant changes in any of the formulations with respect to physical appearance, drug content as well as drug release profile.

Table 3. Recommended stability storage conditions for various drug products as per ICH guidelines

S. No	Product	Accelerated Stability conditions	Intermediate Stability conditions	Long term Stability conditions
1	Solid oral dosage forms, solids for reconstitution, dry and lyophilised powders in vials.	40 °C/ 75 % RH	30 °C/ 80 % RH	25 °C/ 80 % RH
2	Liquids in glass bottles, vials or sealed glass ampoules which provide an impermeable barrier to water loss	40 °C/ ambient humidity	30 °C/ ambient humidity	25 °C/ ambient humidity
3	Drug products in semi-permeable and permeable containers, large volume parenterals (LVP), small volume parenterals (SVP), ophthalmics, optics and nasal sprays packaged in semi-permeable containers such as plastic bags, semi-rigid plastic containers, ampoules, vials or bottles with or without droppers. Applicators which may be susceptible to water loss.	40 °C/ 15 % RH	30 °C/ 40 % RH	25 °C/ 40 % RH
4	Drug products intended to be stored in refrigerator temperatures (incl. lyophilised powders, biological preparations, enzymes. hormonal preparations)	25 °C/ 60 % RH or 25 °C/ ambient humidity for liquid products	5 ± 3 °C/ With monitoring but not control of humidity	
5	Stability storage conditions for drug products to be intended to be stored in freezer temperature	5 ± 3 °C/ ambient humidity		-15 ± 5 °C
6	Stability storage conditions for some inhalation products	Additional storage conditions may apply to inhalation powders and suspension inhalation alcohols when significant change in aerodynamic particle size distribution or in dose constant uniformity occurs at accelerated stability conditions (40 °C/75 % RH) conditions being satisfied.		

The accelerated and long term stability studies of the prepared microsphere formulations were carried out as per the ICH guidelines. The observations of long-term storage condition and accelerated storage condition are shown in Tables 2. The microspheres formulations chosen were stored at 25 ± 2^0 C and 60 ± 5% RH for a period of 9 months for long term stability studies and for accelerated stability studies they were stored at 40 ± 2^0 C and 75 ± 5% RH for a period of 6 months. The stored samples were tested for their drug content and for any physical change. The testing was carried out at 2 months interval for accelerated storage condition and at 3-month intervals for a period of 9 months for long-term storage condition. The formulations were stable for the 9-month period in long-term storage temperatures of 25 ± 2^0 C and 60 ± 5% RH. The drug content of the microspheres formulations did not vary to a large extent. No changes in the morphology of microspheres were noticed during the storage time and the microspheres formulations were stable at the accelerated storage conditions.

Results and discussion

The results of the stability studies are furnished in the (Tables .2 & .3 and Figs 1 & 2.)

No visible physical changes (colour and cake formation) were observed in any of the products during storage periods. The percentage drug content and release profiles were found to be satisfactory and within the limits. No significant changes ($P<0.05$) were observed in percentage drug content as well as drug release profile before and after storage (Table. 4 & 5).

Table 4.Results of stability studies in accelerated storage Condition (40 ± 2^{0}C and 75 ± 5% RH) of Aceclofenac formulations.

Microparticle Formulations	Drug remaining (%)				Physical change			
	Months				Months			
	0	2	4	6	0	2	4	6
AECM	100.00	98.66±0.17	97.35±0.12	96.33±0.23	–	–	–	–
AEUM	100.00	98.68±0.14	97.52±0.21	96.98±0.19	–	–	–	–

(–) **Stands for No physical change**

Table 5. Results of stability studies in long time storage condition (25 ± 2^{0}C and 60 ± 5% RH) of Aceclofenac formulations
(–) Stands for No physical change

Micro particle Formulations	Drug remaining (%)					Physical change			
	Months					Months			
	0	3	6	9	12	0	3	6	9
AECM	100.00	98.56±0.21	97.86±0.18	97.32±0.14	96.90±0.12	–	–	–	–
AEUM	100.00	98.65±0.15	97.62±0.19	96.94±0.23	96.10±0.14	–	–	–	–

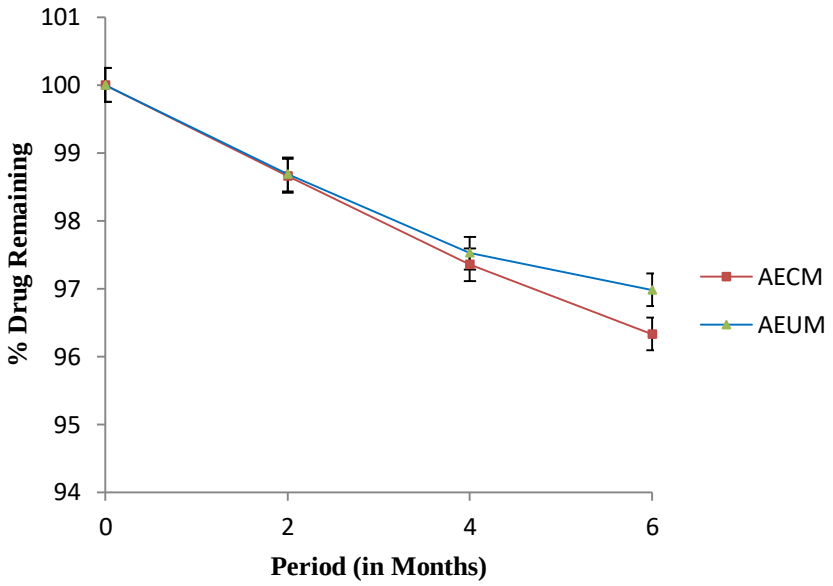

Figure.1: Plot of % drug content vs. time optimized Aceclofenac microparticle formulations (AECM & AEUM) subjected to accelerated stability study as per ICH guidelines (6 months at 40°C ± 2°C; 75 ± 5 % RH)

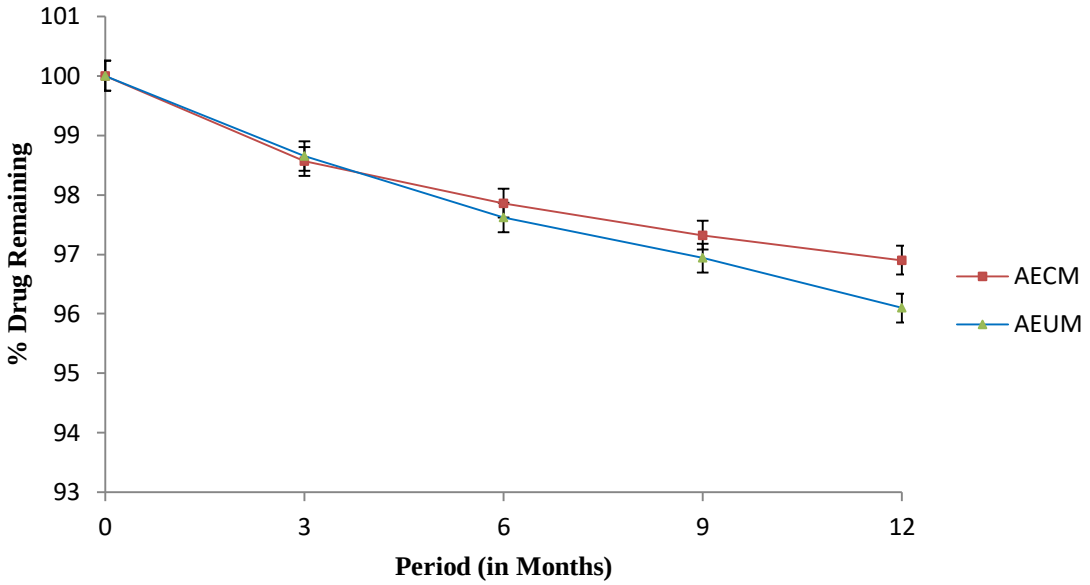

Figure .2: Plot of % drug content vs. time (in month) optimized microparticle formulations (AECM & AEUM) subjected to long term stability study as per ICH guidelines (9 months at 25°C ± 2°C; 60 ± 5 % RH)

CONCLUSION

The results of stability testing indicated that the formulations were likely to be stable under proposed storage conditions without any significant deviations in their properties.

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